SUGAR MODIFICATION TECHNOLOGIES

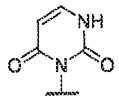
CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application No. 63/574186, filed April 3, 2024, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] Modified sugars are useful for many purposes, including for preparing nucleosides, nucleotides, oligonucleotides, etc.

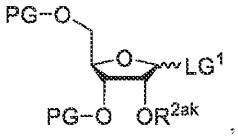
SUMMARY

[0003] Many compounds include sugars. For example, natural nucleic acids include sugars in their backbones. For many uses, such as in compounds (e.g., nucleosides, phosphoramidites, nucleotides, and nucleic acids) as research tools, therapeutics, etc., the typical sugars in natural DNA and RNA are often modified to provide improved properties, activities, etc. For example, many modified sugars have 2'-modifications which are groups having different structures and/or arranged differently compared to the 2'-H and 2'-OH in the typical DNA and RNA sugars. In some embodiments, a 2'-modification is 2'-OR^{2ak} wherein R^{2ak} is optionally substituted C_{1-6} aliphatic. In some embodiments, the present disclosure provides technologies (e.g., compounds (e.g., reagents and products), compositions (e.g., crude product compositions, purified product compositions and reaction systems), and methods) for preparing modified sugars, e.g., those comprising 2'-OR^{2ak} (e.g., 2'-OMe) modifications, and compounds, such as nucleosides, nucleotides, nucleic acids (e.g., oligonucleotides) comprising such modified sugars. In some embodiments, a compound comprises, instead of an optionally protected A, T, C, G or U nucleobases, an optionally protected nucleobase other than A, T, C, G and U. In some embodiments, a compound comprises  (N3U). In some embodiments, a compound is a nucleoside comprising a 2'-OR^{2ak} modified sugar and an optionally protected non-natural nucleobase. In some embodiments, a compound is a nucleoside comprising a 2'-OR^{2ak} modified sugar and an optionally protected or substituted N3U. In some embodiments, a compound is a phosphoramidite comprising such a nucleoside. In some embodiments, a compound is an oligonucleotide comprising such a nucleoside.

[0004] Among other things, the present disclosure encompasses the recognition of the source of a problem with many technologies for preparing modified sugars, nucleosides, phosphoramidites, oligonucleotides, nucleic acids, etc. In some embodiments, the present disclosure encompasses the

recognition that challenges associated with preparing compounds, e.g., oligonucleotides, phosphoramidites, nucleosides, and sugars, comprising 2'–OR^{2ak} modifications and/or unnatural nucleobases include lengthy synthetic routes, low yields, low efficiency, generation of by-products, unstable reagents, etc. In some embodiments, the present disclosure provides methods for addressing these challenges.

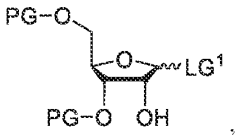
[0005] In some embodiments, the present disclosure provides a method for preparing a compound of formula P-2:



P-2

or a salt thereof,

comprising reacting a compound of formula P-1:



P-1

or a salt thereof with an alkylating agent, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

LG^1 is a leaving group, or is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-SOR^{LG}$, $-OSOR^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$, wherein each R^{LG} is independently R;

each PG is independently a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

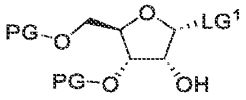
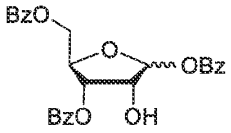
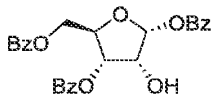
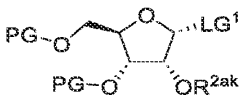
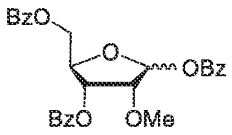
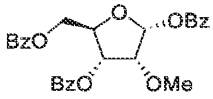
each R' is independently –R, –C(O)R, –C(O)OR, or $-S(O)_2R$;

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:

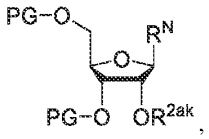
two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[0006] Various alkylating reagents can be assessed and utilized in accordance with the present disclosure. In some embodiments, an alkylating agent is a compound having the structure of $(R^{2ak})_3OY$ or a salt thereof, where each R^{2ak} is independently as described herein, and Y is a counterion. For example, in some embodiments, Y is BF^-. Among other things, provided technologies can utilize alkylating reagents, e.g., reagents comprising $[(R^{2ak})_3O]^+$ such as trialkyloxonium (e.g., Me_3OBF_4 and Et_3OBF_4), that are more stable and safer than reference technologies, e.g., those utilizing CH_2N_2.

[0007] In some embodiments, a compound of formula P-1 has the structure of . In some embodiments, a compound of formula P-1 is . In some embodiments, a compound of formula P-1 is . In some embodiments, a compound of formula P-2 is . In some embodiments, a compound of formula P-2 is . In some embodiments, a compound of formula P-2 is .

[0008] Those skilled in the art appreciate that compounds of formula P-2 are useful for various purposes. Among other things, a compound of P-2 or a salt thereof can react with a nucleophile such that LG^1 is replaced with another moiety to provide a new compound. In some embodiments, a nucleophile comprises a nucleophilic atom, e.g., carbon, oxygen, nitrogen, and sulfur. In some embodiments, in a reaction a nucleophilic atom forms a bond with the carbon atom to which LG^1 is attached and LG^1 is removed. For example, in some embodiments, a nucleophilic is a nitrogen atom. In some embodiments, a nucleophilic compound reacts a compound of formula P-2 or a salt thereof to form a nucleoside or a salt thereof.

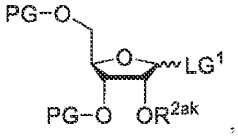
[0009] In some embodiments, the present disclosure provides method for preparing a compound of formula P-3:



P-3

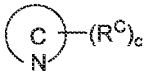
or a salt thereof,

comprising reacting a compound of formula P-2:



P-2

or a salt thereof with a compound of formula P-A:

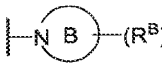


P-A

or a salt thereof, wherein:

each PG is independently a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R^*;

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

each of Ring B and Ring C is independently an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each of R^B and R^C is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R^*)_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each of b and c is independently 0-5;

LG^1 is a leaving group;

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_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5

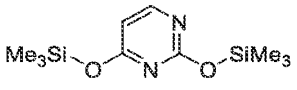
heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; or

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:

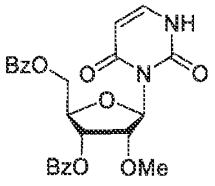
two R groups are optionally and independently taken together to form a covalent bond; or:

two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[0010] In some embodiments, Ring C is an optionally substituted nucleobase ring or a tautomer thereof. For example, in some embodiments, a compound of formula P-A is



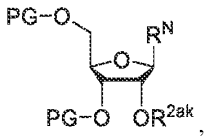
. In some embodiments, a compound of formula P-3 is



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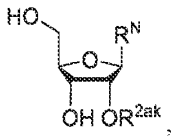
[0011] In some embodiments, the present disclosure provides technologies for preparing compounds, e.g., nucleosides, comprising –OH groups. For example, in some embodiments, the present disclosure provides a method, comprising:

converting a compound of formula P-3:



P-3

or a salt thereof, into a compound of formula P-4:



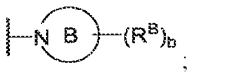
,

P-4

or a salt thereof, wherein:

each PG is independently a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

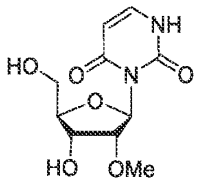
each R' is independently $-R$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R is independently $-H$, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; or

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:

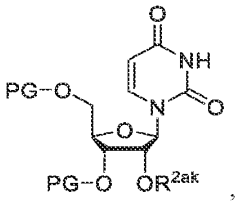
two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.



[0012] For example, in some embodiments, a compound of formula P-4 is .

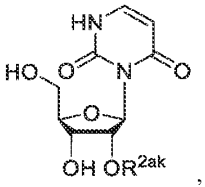
[0013] In some embodiments, the present disclosure provides methods for converting one nucleoside to another. In some embodiments, the present disclosure provides a method, comprising:

converting a compound of formula P-3-E:



P-3-E

or a salt thereof, into a compound of formula P-4-1:



P-4-1

or a salt thereof, wherein:

each PG is independently a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

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_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; or

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

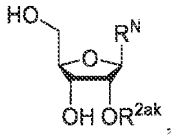
having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or:

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

two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[0014] In some embodiments, hydroxy groups are converted into other groups, e.g., $-O-PG^P$ as described herein. In some embodiments, hydroxy groups in compounds are protected, e.g., for further reactions. In some embodiments, the present disclosure provides a method, comprising:

reacting a compound of formula P-4:



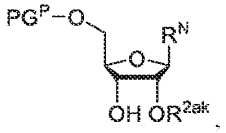
P-4

or a salt thereof, with a protecting agent or a compound of formula P-B:

$PG\text{-}LG^2$,

P-B

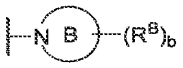
or a salt thereof, to provide a compound of formula P-5:



P-5

or a salt thereof, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

LG^2 is a leaving group, or is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-SOR^{LG}$, $-OSOR^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$, wherein each R^{LG} is independently R;

PG^P is a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

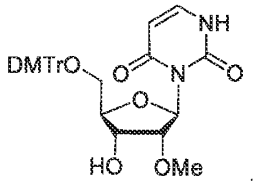
each R' is independently −R, −C(O)R, −C(O)OR, or $-S(O)_2R$;

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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

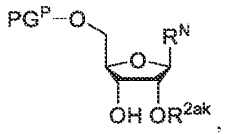
[0015] Various technologies are available and can be utilized to protect hydroxy groups in accordance with the present disclosure. For example, in some embodiments, DMTr is utilized to protect 5'-OH in phosphoramidites for oligonucleotide synthesis. In some embodiments, a compound of formula P-5 is



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[0016] Protected nucleosides, e.g., those having the structure of formula P-5 or salts thereof, are useful for many purposes, e.g., for manufacturing phosphoramidites. In some embodiments, the present disclosure provides a method, comprising:

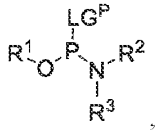
reacting a compound having the structure of formula P-5:



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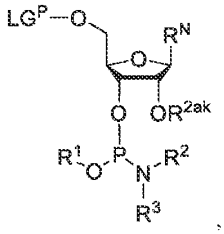
P-5

or a salt thereof with a compound having the structure of formula AX:



AX

or a salt thereof, to provide a compound of formula PMT:

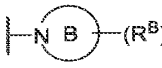


PMT

or a salt thereof, wherein:

PG^P is a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

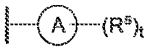
Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

LG^P is $-Cl$, $-Br$, or $-I$;

each of R^1, R^2, and R^3 is independently R', or two or three of R^1, R^2, and R^3 are taken together with their intervening atoms to form ;

Ring A is an optionally substituted 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

t is 0-5;

each R^s is independently $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-N_3$, $-NO$, $-NO_2$, $-L^s-R^{s11}$, $-L^s-OR^{s11}$, $-L^s-SR^{s11}$, $-L^s-S(O)_2R^{s11}$, $-L^s-N(R^{s11})_2$, $-O-L^s-OR^{s11}$, $-O-L^s-SR^{s11}$, $-O-L^s-N(R^{s11})_2$, $-C(R^{s11})_3$ or $-L^s-Si(R^{s11})_3$;

each R^{s11} is independently R';

each L^s is independently L;

each L is independently a covalent bond, or a bivalent, optionally substituted group selected from C_{1-10} aliphatic and C_{1-10} heteroaliphatic group having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, wherein one or more methylene units of L are optionally and independently replaced by −Cy−, −O−, −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)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −SC(O)−, or −C(O)O−;

−Cy− is an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[0017] In some embodiments, compounds of present disclosure, e.g., phosphoramidites having the structure of formula PMT or salts thereof, are useful for, e.g., manufacturing oligonucleotides.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0018] Technologies of the present disclosure may be understood more readily by reference to the following detailed description of certain embodiments.

DEFINITIONS

[0019] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M. B. and

March, J., John Wiley & Sons, New York: 2001.

[0020] As used herein in the present disclosure, unless otherwise clear from context, (i) the term "a" or "an" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; (iii) the terms "comprising", "comprise", "including" (whether used with "not limited to" or not), and "include" (whether used with "not limited to" or not) may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; (iv) the term "another" may be understood to mean at least an additional/second one or more; (v) the terms "about" and "approximately" may be understood to permit standard variation as would be understood by those of ordinary skill in the art; and (vi) where ranges are provided, endpoints are included. Unless otherwise clear from context, isomers of compounds are included. As those skilled in the art, compounds may be provided, administered, or delivered in various forms, e.g., salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, esters, prodrugs and tautomers.

[0021] Aliphatic: As used herein, "aliphatic" means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation (but not aromatic), or a substituted or unsubstituted monocyclic, bicyclic, or polycyclic hydrocarbon ring that is completely saturated or that contains one or more units of unsaturation (but not aromatic), or combinations thereof. In some embodiments, aliphatic groups contain 1-50 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-20 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-9 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-7 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1, 2, 3, or 4 aliphatic carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0022] Alkenyl: As used herein, the term "alkenyl" refers to an aliphatic group, as defined herein, having one or more double bonds.

[0023] Alkyl: As used herein, the term "alkyl" is given its ordinary meaning in the art and may include saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In some embodiments, alkyl has 1-100 carbon atoms. In certain embodiments, a straight chain or branched chain alkyl has about 1-20 carbon atoms in its backbone (e.g., C_1-C_{20} for straight chain, C_2-C_{20} for branched chain), and alternatively, about 1-10. In some embodiments, cycloalkyl rings have from

about 3-10 carbon atoms in their ring structure where such rings are monocyclic, bicyclic, or polycyclic, and alternatively about 5, 6 or 7 carbons in the ring structure. In some embodiments, an alkyl group may be a lower alkyl group, wherein a lower alkyl group comprises 1-4 carbon atoms (e.g., C_1-C_4 for straight chain lower alkyls).

[0024] Alkynyl: As used herein, the term "alkynyl" refers to an aliphatic group, as defined herein, having one or more triple bonds.

[0025] Animal: As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans, at any stage of development. In some embodiments, "animal" refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish and/or worms. In some embodiments, an animal may be a transgenic animal, a genetically-engineered animal and/or a clone.

[0026] Aryl: The term "aryl", as used herein, used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic, bicyclic or polycyclic ring systems having a total of five to thirty ring members, wherein at least one ring in the system is aromatic. In some embodiments, an aryl group is a monocyclic, bicyclic or polycyclic ring system having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, and wherein each ring in the system contains 3 to 7 ring members. In some embodiments, each monocyclic ring unit is aromatic. In some embodiments, an aryl group is a biaryl group. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but is not limited to, phenyl, biphenyl, naphthyl, binaphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, or tetrahydronaphthyl, and the like.

[0027] Chirally controlled oligonucleotide composition: The terms "chirally controlled oligonucleotide composition", "chirally controlled nucleic acid composition", and the like, as used herein, refers to a composition that comprises a plurality of oligonucleotides (or nucleic acids) which share 1) a common base sequence, 2) a common pattern of backbone linkages, and 3) a common pattern of backbone phosphorus modifications, wherein the plurality of oligonucleotides share the same stereochemistry at one or more chiral internucleotidic linkages (chirally controlled internucleotidic linkages), and the level of the plurality of oligonucleotides in the composition is pre-determined. In some embodiments, each chiral internucleotidic linkage is a chiral controlled internucleotidic linkage, and the composition is a completely chirally controlled oligonucleotide composition. In some embodiments, not

all chiral internucleotidic linkages are chiral controlled internucleotidic linkages, and the composition is a partially chirally controlled oligonucleotide composition. In some embodiments, a chirally controlled oligonucleotide composition comprises predetermined levels of individual oligonucleotide or nucleic acids types. In some embodiments, oligonucleotides of a plurality share the same constitution and may be optionally in various forms (e.g., acid, basic, and salt forms).

[0028] Comparable: The term "comparable" is used herein to describe two (or more) sets of conditions or circumstances that are sufficiently similar to one another to permit comparison of results obtained or phenomena observed. In some embodiments, comparable sets of conditions or circumstances are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will appreciate that sets of conditions are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under the different sets of conditions or circumstances are caused by or indicative of the variation in those features that are varied.

[0029] Cycloaliphatic: The term "cycloaliphatic," "carbocycle," "carbocyclyl," "carbocyclic radical," and "carbocyclic ring," are used interchangeably, and as used herein, refer to saturated or partially unsaturated, but non-aromatic, cyclic aliphatic monocyclic, bicyclic, or polycyclic ring systems, as described herein, having, unless otherwise specified, from 3 to 30 ring members. Cycloaliphatic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, norbornyl, adamantyl, and cyclooctadienyl. In some embodiments, a cycloaliphatic group has 3–6 carbons. In some embodiments, a cycloaliphatic group is saturated and is cycloalkyl. The term "cycloaliphatic" may also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as decahydronaphthyl or tetrahydronaphthyl. In some embodiments, a cycloaliphatic group is bicyclic. In some embodiments, a cycloaliphatic group is tricyclic. In some embodiments, a cycloaliphatic group is polycyclic. In some embodiments, "cycloaliphatic" refers to C_3-C_6 monocyclic hydrocarbon, or C_8-C_{10} bicyclic or polycyclic hydrocarbon, that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule, or a C_9-C_{16} polycyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule.

[0030] Heteroaliphatic: The term "heteroaliphatic", as used herein, is given its ordinary meaning in the art and refers to aliphatic groups as described herein in which one or more carbon atoms are independently replaced with one or more heteroatoms (e.g., oxygen, nitrogen, sulfur, silicon, phosphorus, and the like). In some embodiments, one or more units selected from C, CH, CH_2, and CH_3 are

independently replaced by one or more heteroatoms (including oxidized and/or substituted forms thereof). In some embodiments, a heteroaliphatic group is heteroalkyl. In some embodiments, a heteroaliphatic group is heteroalkenyl.

[0031] Heteroalkyl: The term "heteroalkyl", as used herein, is given its ordinary meaning in the art and refers to alkyl groups as described herein in which one or more carbon atoms are independently replaced with one or more heteroatoms (e.g., oxygen, nitrogen, sulfur, silicon, phosphorus, and the like). Examples of heteroalkyl groups include alkoxy, poly(ethylene glycol)-, alkyl-substituted amino, tetrahydrofuranyl, piperidinyl and morpholinyl.

[0032] Heteroaryl: The terms "heteroaryl" and "heteroar–", as used herein, used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to monocyclic, bicyclic or polycyclic ring systems having a total of five to thirty ring members, wherein at least one ring in the system is aromatic and at least one aromatic ring atom is a heteroatom. In some embodiments, a heteroaryl group is a group having 5 to 10 ring atoms (i.e., monocyclic, bicyclic or polycyclic), in some embodiments 5, 6, 9, or 10 ring atoms. In some embodiments, each monocyclic ring unit is aromatic. In some embodiments, a heteroaryl group has 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. In some embodiments, a heteroaryl is a heterobiaryl group, such as bipyridyl and the like. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Non-limiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be monocyclic, bicyclic or polycyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl group, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0033] Heteroatom: The term "heteroatom", as used herein, means an atom that is not carbon or hydrogen. In some embodiments, a heteroatom is boron, oxygen, sulfur, nitrogen, phosphorus, or silicon (including oxidized forms of nitrogen, sulfur, phosphorus, or silicon; charged forms of nitrogen (e.g., quaternized forms and forms as in iminium groups), phosphorus, sulfur, oxygen; etc.). In some

embodiments, a heteroatom is silicon, phosphorus, oxygen, sulfur or nitrogen. In some embodiments, a heteroatom is silicon, oxygen, sulfur or nitrogen. In some embodiments, a heteroatom is oxygen, sulfur or nitrogen.

[0034] Heterocycle: As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring", as used herein, are used interchangeably and refer to a monocyclic, bicyclic or polycyclic ring moiety (e.g., 3-30 membered) that is saturated or partially unsaturated and has one or more heteroatom ring atoms. In some embodiments, a heterocyclyl group is a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur and nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in N-substituted pyrrolidinyl). A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3H-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be monocyclic, bicyclic or polycyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0035] Optionally Substituted: As described herein, compounds of the disclosure may contain optionally substituted, substituted and/or unsubstituted moieties. In general, the term "substituted," means that one or more hydrogens of the designated moiety are independently replaced with a substituent. Unless otherwise indicated, an "optionally substituted" group may independently have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with two or more substituents, the substituents may be either the same or different at every position. In some embodiments, an optionally substituted group is unsubstituted. In some embodiments, an optionally substituted group is substituted. Various substituents are described below.

[0036] Monovalent substituents are independently halogen; $-(CH_2)_{0-4}R^{\circ}$; $-(CH_2)_{0-4}OR^{\circ}$; $-O(CH_2)_{0-4}R^{\circ}$, $-O-(CH_2)_{0-4}C(O)OR^{\circ}$; $-(CH_2)_{0-4}CH(OR^{\circ})_2$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°;

–$(CH_2)_{0-4}O(CH_2)_{0-1}$Ph which may be substituted with R°; –CH=CHPh, which may be substituted with R°; –$(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; –NO_2; –CN; –N_3; -$(CH_2)_{0-4}N(R°)_2$; –$(CH_2)_{0-4}N(R°)C(O)R°$; –$N(R°)C(S)R°$; –$(CH_2)_{0-4}N(R°)C(O)N(R°)_2$; –$N(R°)C(S)N(R°)_2$; –$(CH_2)_{0-4}N(R°)C(O)OR°$; –$N(R°)N(R°)C(O)R°$; –$N(R°)N(R°)C(O)N(R°)_2$; –$N(R°)N(R°)C(O)OR°$; –$(CH_2)_{0-4}C(O)R°$; –$C(S)R°$; –$(CH_2)_{0-4}C(O)OR°$; –$(CH_2)_{0-4}C(O)SR°$; –$(CH_2)_{0-4}C(O)OSi(R°)_3$; –$(CH_2)_{0-4}OC(O)R°$; –$OC(O)(CH_2)_{0-4}SR°$, –$SC(S)SR°$, –$(CH_2)_{0-4}SC(O)R°$; –$(CH_2)_{0-4}C(O)N(R°)_2$; –$C(S)N(R°)_2$; –$C(S)SR°$; –$SC(S)SR°$, -$(CH_2)_{0-4}OC(O)N(R°)_2$; -$C(O)N(OR°)R°$; –$C(O)C(O)R°$; –$C(O)CH_2C(O)R°$; –$C(NOR°)R°$; -$(CH_2)_{0-4}SSR°$; –$(CH_2)_{0-4}S(O)_2R°$; –$(CH_2)_{0-4}S(O)_2OR°$; –$(CH_2)_{0-4}OS(O)_2R°$; –$S(O)_2N(R°)_2$; -$(CH_2)_{0-4}S(O)R°$; –$N(R°)S(O)_2N(R°)_2$; –$N(R°)S(O)_2R°$; –$N(OR°)R°$; –$C(NH)N(R°)_2$; –$Si(R°)_3$; –$OSi(R°)_3$; –$P(R°)_2$; –$P(OR°)_2$; –$OP(R°)_2$; –$OP(OR°)_2$; –$N(R°)P(R°)_2$; –$B(R°)_2$; –$OB(R°)_2$; –$P(O)(R°)_2$; –$OP(O)(R°)_2$; –$N(R°)P(O)(R°)_2$; –($C_{1-4}$ straight or branched alkylene)O–$N(R°)_2$; or –(C_{1-4} straight or branched alkylene)C(O)O–$N(R°)_2$; wherein each R° may be independently substituted as defined below and is independently hydrogen, C_{1-10} (e.g., C_{1-6}, and C_{1-4}) aliphatic, C_{1-10} (e.g., C_{1-8}, C_{1-6}, and C_{1-4}) heteroaliphatic having 1-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, 6-10 (e.g., 6 and 10) membered aryl, 5-10 (e.g., 5-9, 5-6, 5, 6, 9 and 10) membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur, –CH_2–(C_{6-10} (e.g., C_6 and C_{10}) aryl), –$O(CH_2)_{0-1}$(C_{6-10} (e.g., C_6 and C_{10}) aryl), –CH_2–(5-10 (e.g., 5-9, 5-6, 5, 6, 9, and 10) membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur), –$O(CH_2)_{0-1}$(5-10 (e.g., 5-9, 5-6, 5, 6, 9 and 10) membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur), a 3-10 (e.g., 3-6, 5-6, 3, 4, 5, 6, 7, 8, 9 and 10) membered, monocyclic, bicyclic, or polycyclic, saturated, or partially unsaturated ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-10 (e.g., 3-6, 5-6, 3, 4, 5, 6, 7, 8, 9 and 10) membered, monocyclic, bicyclic, or polycyclic, saturated, partially unsaturated or aromatic ring (for aromatic ring, 5-10 (e.g., 5-9, 5-6, 5, 6, 9 and 10) membered) having 0-5 heteroatoms independently selected from nitrogen, oxygen, sulfur, silicon and phosphorus, which may be substituted as defined below.

[0037] Monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, –$(CH_2)_{0-2}R^•$, –(halo$R^•$), –$(CH_2)_{0-2}OH$, –$(CH_2)_{0-2}OR^•$, –$(CH_2)_{0-2}CH(OR^•)_2$; –O(halo$R^•$), –CN, –N_3, –$(CH_2)_{0-2}C(O)R^•$, –$(CH_2)_{0-2}C(O)OH$, –$(CH_2)_{0-2}C(O)OR^•$, –$(CH_2)_{0-2}SR^•$, –$(CH_2)_{0-2}SH$, –$(CH_2)_{0-2}NH_2$, –$(CH_2)_{0-2}NHR^•$, –$(CH_2)_{0-2}NR^•_2$, –NO_2, –$SiR^•_3$, –$OSiR^•_3$, -$C(O)SR^•$, –(C_{1-4} straight or branched alkylene)$C(O)OR^•$, or –$SSR^•$ wherein each $R^•$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is

independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3-6 (e.g., 3-5, 5-6, 3, 4, 5 and 6)-membered saturated, partially unsaturated, or aromatic ring (for aromatic ring, 5- or 6-membered) having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Divalent substituents on a saturated carbon atom of R° are independently =O or =S.

[0038] Divalent substituents are independently the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 3-6 (e.g., 3-5, 5-6, 3, 4, 5 and 6)-membered saturated, partially unsaturated, or aromatic ring (for aromatic ring, 5- or 6-membered) having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group are independently $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 3-6 (e.g., 3-5, 5-6, 3, 4, 5 and 6)-membered saturated, partially unsaturated, or aromatic ring (for aromatic ring, 5- or 6-membered) having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0039] Substituents on the aliphatic group of R^* are independently halogen, $-R^\bullet$, -(halo$R^\bullet$), $-OH$, $-OR^\bullet$, -O(halo$R^\bullet$), $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3-6 (e.g., 3-5, 5-6, 3, 4, 5 and 6)-membered saturated, partially unsaturated, or aromatic ring (for aromatic ring, 5- or 6-membered) having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0040] Substituents on a substitutable nitrogen are independently $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 3-6 (e.g., 3-5, 5-6, 3, 4, 5 and 6)-membered saturated, partially unsaturated, or aromatic ring (for aromatic ring, 5- or 6-membered) having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12 (e.g., 3-10, 3-6, 5-10, 5-6, 3, 4, 5, 6, 7, 8, 9 and 10) membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0041] Substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, -(halo$R^\bullet$), $-OH$, $-OR^\bullet$, -O(halo$R^\bullet$), $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 3-6 (e.g., 3-5, 5-6, 3, 4, 5 and 6)-membered

saturated, partially unsaturated, or aromatic ring (for aromatic ring, 5- or 6-membered) having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0042] Partially unsaturated: As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0043] Pharmaceutical composition: As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, an active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0044] Pharmaceutically acceptable: As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0045] Pharmaceutically acceptable carrier: As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and

suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0046] Pharmaceutically acceptable salt: The term "pharmaceutically acceptable salt", as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, i.e., salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). In some embodiments, pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts, which are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. In some embodiments, pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, a provided compound comprises one or more acidic groups, and a pharmaceutically acceptable salt is an alkali, alkaline earth metal, or ammonium (e.g., an ammonium salt of $N(R)_3$, wherein each R is independently defined and described in the present disclosure) salt. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. In some embodiments, a pharmaceutically acceptable salt is a sodium salt. In some embodiments, a pharmaceutically acceptable salt is a potassium salt. In some embodiments, a pharmaceutically acceptable salt is a calcium salt. In some embodiments, pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl

sulfonate. In some embodiments, a provided compound comprises two or more acid groups. In some embodiments, a pharmaceutically acceptable salt, or generally a salt, of such a compound comprises two or more cations, which can be the same or different. In some embodiments, in a pharmaceutically acceptable salt (or generally, a salt), all ionizable hydrogen (e.g., in an aqueous solution with a pKa no more than about 11, 10, 9, 8, 7, 6, 5, 4, 3, or 2; in some embodiments, no more than about 7; in some embodiments, no more than about 6; in some embodiments, no more than about 5; in some embodiments, no more than about 4; in some embodiments, no more than about 3) in the acidic groups are replaced with cations.

[0047] Protecting group: The term "protecting group," as used herein, is well known in the art and includes those described in detail in Protecting Groups in Organic Synthesis, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Also included are those protecting groups specially adapted for nucleoside and nucleotide chemistry described in Current Protocols in Nucleic Acid Chemistry, edited by Serge L. Beaucage et al. 06/2012, the entirety of Chapter 2 is incorporated herein by reference. Suitable amino–protecting groups include methyl carbamate, ethyl carbamante, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–t–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–t–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)ethyl carbamate (Bpoc), 1–(3,5–di–t–butylphenyl)–1–methylethyl carbamate (t–Bumeoc), 2–(2'– and 4'–pyridyl)ethyl carbamate (Pyoc), 2–(N,N–dicyclohexylcarboxamido)ethyl carbamate, t–butyl carbamate (BOC), 1–adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1–isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4–nitrocinnamyl carbamate (Noc), 8–quinolyl carbamate, N–hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), p–methoxybenzyl carbamate (Moz), p–nitobenzyl carbamate, p–bromobenzyl carbamate, p–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(p–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, m–chloro–p–acyloxybenzyl carbamate, p–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (Tcroc), m–nitrophenyl carbamate, 3,5–

dimethoxybenzyl carbamate, o–nitrobenzyl carbamate, 3,4–dimethoxy–6–nitrobenzyl carbamate, phenyl(o–nitrophenyl)methyl carbamate, phenothiazinyl–(10)–carbonyl derivative, N'–p–toluenesulfonylaminocarbonyl derivative, N'–phenylaminothiocarbonyl derivative, t–amyl carbamate, S–benzyl thiocarbamate, p–cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p–decyloxybenzyl carbamate, 2,2–dimethoxycarbonylvinyl carbamate, o–(N,N–dimethylcarboxamido)benzyl carbamate, 1,1–dimethyl–3–(N,N–dimethylcarboxamido)propyl carbamate, 1,1–dimethylpropynyl carbamate, di(2–pyridyl)methyl carbamate, 2–furanylmethyl carbamate, 2–iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, p–(p'–methoxyphenylazo)benzyl carbamate, 1–methylcyclobutyl carbamate, 1–methylcyclohexyl carbamate, 1–methyl–1–cyclopropylmethyl carbamate, 1–methyl–1–(3,5–dimethoxyphenyl)ethyl carbamate, 1–methyl–1–(p–phenylazophenyl)ethyl carbamate, 1–methyl–1–phenylethyl carbamate, 1–methyl–1–(4–pyridyl)ethyl carbamate, phenyl carbamate, p–(phenylazo)benzyl carbamate, 2,4,6–tri–t–butylphenyl carbamate, 4–(trimethylammonium)benzyl carbamate, 2,4,6–trimethylbenzyl carbamate, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, N–benzoylphenylalanyl derivative, benzamide, p–phenylbenzamide, o–nitophenylacetamide, o–nitrophenoxyacetamide, acetoacetamide, (N'–dithiobenzyloxycarbonylamino)acetamide, 3–(p–hydroxyphenyl)propanamide, 3–(o–nitrophenyl)propanamide, 2–methyl–2–(o–nitrophenoxy)propanamide, 2–methyl–2–(o–phenylazophenoxy)propanamide, 4–chlorobutanamide, 3–methyl–3–nitrobutanamide, o–nitrocinnamide, N–acetylmethionine derivative, o–nitrobenzamide, o–(benzoyloxymethyl)benzamide, 4,5–diphenyl–3–oxazolin–2–one, N–phthalimide, N–dithiasuccinimide (Dts), N–2,3–diphenylmaleimide, N–2,5–dimethylpyrrole, N–1,1,4,4–tetramethyldisilylazacyclopentane adduct (STABASE), 5–substituted 1,3–dimethyl–1,3,5–triazacyclohexan–2–one, 5–substituted 1,3–dibenzyl–1,3,5–triazacyclohexan–2–one, 1–substituted 3,5–dinitro–4–pyridone, N–methylamine, N–allylamine, N–[2–(trimethylsilyl)ethoxy]methylamine (SEM), N–3–acetoxypropylamine, N–(1–isopropyl–4–nitro–2–oxo–3–pyrolin–3–yl)amine, quaternary ammonium salts, N–benzylamine, N–di(4–methoxyphenyl)methylamine, N–5–dibenzosuberylamine, N–triphenylmethylamine (Tr), N–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), N–9–phenylfluorenylamine (PhF), N–2,7–dichloro–9–fluorenylmethyleneamine, N–ferrocenylmethylamine (Fcm), N–2–picolylamine N'–oxide, N–1,1–dimethylthiomethyleneamine, N–benzylideneamine, N–p–methoxybenzylideneamine, N–diphenylmethyleneamine, N–[(2–pyridyl)mesityl]methyleneamine, N–(N',N'–dimethylaminomethylene)amine, N,N'–isopropylidenediamine, N–p–nitrobenzylideneamine, N–salicylideneamine, N–5–chlorosalicylideneamine, N–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, N–cyclohexylideneamine, N–(5,5–dimethyl–3–oxo–1–

cyclohexenyl)amine, N–borane derivative, N–diphenylborinic acid derivative, N–[phenyl(pentacarbonylchromium– or tungsten)carbonyl]amine, N–copper chelate, N–zinc chelate, N–nitroamine, N–nitrosoamine, amine N–oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o–nitrobenzenesulfenamide (Nps), 2,4–dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2–nitro–4–methoxybenzenesulfenamide, triphenylmethylsulfenamide, 3–nitropyridinesulfenamide (Npys), p–toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,–trimethyl–4–methoxybenzenesulfonamide (Mtr), 2,4,6–trimethoxybenzenesulfonamide (Mtb), 2,6–dimethyl–4–methoxybenzenesulfonamide (Pme), 2,3,5,6–tetramethyl–4–methoxybenzenesulfonamide (Mte), 4–methoxybenzenesulfonamide (Mbs), 2,4,6–trimethylbenzenesulfonamide (Mts), 2,6–dimethoxy–4–methylbenzenesulfonamide (iMds), 2,2,5,7,8–pentamethylchroman–6–sulfonamide (Pmc), methanesulfonamide (Ms), β–trimethylsilylethanesulfonamide (SES), 9–anthracenesulfonamide, 4–(4',8'–dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0048] Suitably protected carboxylic acids further include, but are not limited to, silyl–, alkyl–, alkenyl–, aryl–, and arylalkyl–protected carboxylic acids. Examples of suitable silyl groups include trimethylsilyl, triethylsilyl, t–butyldimethylsilyl, t–butyldiphenylsilyl, triisopropylsilyl, and the like. Examples of suitable alkyl groups include methyl, benzyl, p–methoxybenzyl, 3,4–dimethoxybenzyl, trityl, t–butyl, tetrahydropyran–2–yl. Examples of suitable alkenyl groups include allyl. Examples of suitable aryl groups include optionally substituted phenyl, biphenyl, or naphthyl. Examples of suitable arylalkyl groups include optionally substituted benzyl (e.g., p–methoxybenzyl (MPM), 3,4–dimethoxybenzyl, o–nitrobenzyl, p–nitrobenzyl, p–halobenzyl, 2,6–dichlorobenzyl, p–cyanobenzyl), and 2– and 4–picolyl.

[0049] Suitable hydroxy protecting groups include methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), t–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), p–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (p–AOM), guaiacolmethyl (GUM), t–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyranyl, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyranyl, 4–methoxytetrahydrothiopyranyl S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–

ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, t–butyl, allyl, p–chlorophenyl, p–methoxyphenyl, 2,4–dinitrophenyl, benzyl, p–methoxybenzyl, 3,4–dimethoxybenzyl, o–nitrobenzyl, p–nitrobenzyl, p–halobenzyl, 2,6–dichlorobenzyl, p–cyanobenzyl, p–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl N–oxido, diphenylmethyl, p,p'–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl, α–naphthyldiphenylmethyl, p–methoxyphenyldiphenylmethyl, di(p–methoxyphenyl)phenylmethyl, tri(p–methoxyphenyl)methyl, 4–(4'–bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4',4''–tris(levulinoyloxypbenyl)methyl, 4,4',4''–tris(benzoyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4',4''–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1'–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodithiolan–2–yl, benzisothiazolyl S,S–dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylthexylsilyl, t–butyldimethylsilyl (TBDMS), t–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–p–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), t–butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, p–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, p–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate, alkyl allyl carbonate, alkyl p–nitrophenyl carbonate, alkyl benzyl carbonate, alkyl p–methoxybenzyl carbonate, alkyl 3,4–dimethoxybenzyl carbonate, alkyl o–nitrobenzyl carbonate, alkyl p–nitrobenzyl carbonate, alkyl S–benzyl thiocarbonate, 4–ethoxy–1–napththyl carbonate, methyl dithiocarbonate, 2–iodobenzoate, 4–azidobutyrate, 4–nitro–4–methylpentanoate, o–(dibromomethyl)benzoate, 2–formylbenzenesulfonate, 2–(methylthiomethoxy)ethyl, 4–(methylthiomethoxy)butyrate, 2–(methylthiomethoxymethyl)benzoate, 2,6–dichloro–4–methylphenoxyacetate, 2,6–dichloro–4–(1,1,3,3–tetramethylbutyl)phenoxyacetate, 2,4–bis(1,1–dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (E)–2–methyl–2–butenoate, o–(methoxycarbonyl)benzoate, α–naphthoate, nitrate, alkyl N,N,N',N'–tetramethylphosphorodiamidate, alkyl N–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). For protecting 1,2– or 1,3–diols, the protecting groups include methylene acetal, ethylidene acetal, 1–t–butylethylidene ketal, 1–phenylethylidene ketal, (4–methoxyphenyl)ethylidene acetal, 2,2,2–

trichloroethylidene acetal, acetonide, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal, benzylidene acetal, p–methoxybenzylidene acetal, 2,4–dimethoxybenzylidene acetal, 3,4–dimethoxybenzylidene acetal, 2–nitrobenzylidene acetal, methoxymethylene acetal, ethoxymethylene acetal, dimethoxymethylene ortho ester, 1–methoxyethylidene ortho ester, 1–ethoxyethylidine ortho ester, 1,2–dimethoxyethylidene ortho ester, α–methoxybenzylidene ortho ester, 1–(N,N–dimethylamino)ethylidene derivative, α–(N,N'–dimethylamino)benzylidene derivative, 2–oxacyclopentylidene ortho ester, di–t–butylsilylene group (DTBS), 1,3–(1,1,3,3–tetraisopropyldisiloxanylidene) derivative (TIPDS), tetra–t–butoxydisiloxane–1,3–diylidene derivative (TBDS), cyclic carbonates, cyclic boronates, ethyl boronate, and phenyl boronate.

[0050] In some embodiments, a hydroxy protecting group is acetyl, t-butyl, tbutoxymethyl, methoxymethyl, tetrahydropyranyl, 1 -ethoxyethyl, 1 -(2-chloroethoxy)ethyl, 2- trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, benzoyl, p-phenylbenzoyl, 2,6- dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl (trityl), 4,4'-dimethoxytrityl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triphenylsilyl, triisopropylsilyl, benzoylformate, chloroacetyl, trichloroacetyl, trifiuoroacetyl, pivaloyl, 9- fluorenylmethyl carbonate, mesylate, tosylate, triflate, trityl, monomethoxytrityl (MMTr), 4,4'-dimethoxytrityl (DMTr) and 4,4',4"-trimethoxytrityl (TMTr), 2-cyanoethyl (CE or Cne), 2-(trimethylsilyl)ethyl (TSE), 2-(2-nitrophenyl)ethyl, 2-(4-cyanophenyl)ethyl 2-(4-nitrophenyl)ethyl (NPE), 2-(4-nitrophenylsulfonyl)ethyl, 3,5-dichlorophenyl, 2,4-dimethylphenyl, 2-nitrophenyl, 4-nitrophenyl, 2,4,6-trimethylphenyl, 2-(2-nitrophenyl)ethyl, butylthiocarbonyl, 4,4',4"-tris(benzoyloxy)trityl, diphenylcarbamoyl, levulinyl, 2-(dibromomethyl)benzoyl (Dbmb), 2-(isopropylthiomethoxymethyl)benzoyl (Ptmt), 9-phenylxanthen-9-yl (pixyl) or 9-(p-methoxyphenyl)xanthine-9-yl (MOX). In some embodiments, each of the hydroxy protecting groups is, independently selected from acetyl, benzyl, t- butyldimethylsilyl, t-butyldiphenylsilyl and 4,4'-dimethoxytrityl. In some embodiments, the hydroxy protecting group is selected from the group consisting of trityl, monomethoxytrityl and 4,4'-dimethoxytrityl group. In some embodiments a protecting group is 2-cyanoethyl (CE or Cne), 2-trimethylsilylethyl, 2-nitroethyl, 2-sulfonylethyl, methyl, benzyl, o-nitrobenzyl, 2-(p-nitrophenyl)ethyl (NPE or Npe), 2-phenylethyl, 3-(N-tert-butylcarboxamido)-1-propyl, 4-oxopentyl, 4-methylthio-1-butyl, 2-cyano-1,1-dimethylethyl, 4-N-methylaminobutyl, 3-(2-pyridyl)-1-propyl, 2-[N-methyl-N-(2-pyridyl)]aminoethyl, 2-(N-formyl,N-methyl)aminoethyl, or 4-[N-methyl-N-(2,2,2-trifluoroacetyl)amino]butyl.

[0051] Subject: As used herein, the term "subject" or "test subject" refers to any organism to which a compound or composition is administered in accordance with the present disclosure e.g., for experimental, diagnostic, prophylactic and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; etc.) and

plants. In some embodiments, a subject is a human. In some embodiments, a subject may be suffering from and/or susceptible to a disease, disorder and/or condition.

[0052] Substantially: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological and/or chemical arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and/or chemical phenomena.

[0053] Susceptible to: An individual who is "susceptible to" a disease, disorder and/or condition is one who has a higher risk of developing the disease, disorder and/or condition than does a member of the general public. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition is predisposed to have that disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may not have been diagnosed with the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may exhibit symptoms of the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder and/or condition may not exhibit symptoms of the disease, disorder and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[0054] Therapeutic agent: As used herein, the term "therapeutic agent" in general refers to any agent that elicits a desired effect (e.g., a desired biological, clinical, or pharmacological effect) when administered to a subject. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, an appropriate population is a population of subjects suffering from and/or susceptible to a disease, disorder or condition. In some embodiments, an appropriate population is a population of model organisms. In some embodiments, an appropriate population may be defined by one or more criterion such as age group, gender, genetic background, preexisting clinical conditions, prior exposure to therapy. In some embodiments, a therapeutic agent is a substance that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms or features of a disease, disorder, and/or condition in a subject when administered to the subject in an effective amount. In some embodiments, a "therapeutic agent" is an agent that has been or is required to be approved by a government agency before it can be marketed for administration to humans. In some embodiments, a "therapeutic agent" is an agent for which a medical prescription is required for administration to humans.

In some embodiments, a therapeutic agent is a provided compound.

[0055] Therapeutically effective amount: As used herein, the term "therapeutically effective amount" means an amount of a substance (e.g., a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, etc. For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

[0056] Treat: As used herein, the term "treat," "treatment," or "treating" refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0057] Unsaturated: The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0058] As those skilled in the art will appreciate, methods and compositions described herein relating to provided compounds generally also apply to pharmaceutically acceptable salts of such compounds.

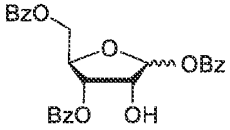
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0059] Among other things, the present disclosure provides technologies (e.g., compounds, and methods) for preparing various compounds, e.g., modified sugars, nucleosides, nucleotides, phosphoramidites, and oligonucleotides. For example, in some embodiments, provided technologies are particularly useful in preparing 2'-OR^{2ak} modified sugars, and nucleosides comprising 2'-OR^{2ak} and optionally protected or substituted non-natural nucleobases, and phosphoramidites and oligonucleotides comprising such nucleosides. Among other things, provided technologies can avoid utilization of certain

unstable reagents, provide shorter synthetic routes, and/or higher yields and/or efficiency as described herein. Certain embodiments are described below as examples.

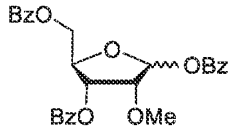
Compounds

[0060] In some embodiments, compounds of the present disclosure are compounds of formula P-1 or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. Various technologies are available for preparing such compounds and can be utilized in accordance with the present disclosure. In some embodiments, a compound of formula P-1 is



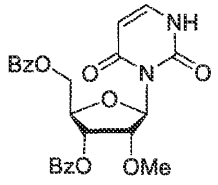
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[0061] In some embodiments, compounds of the present disclosure are compounds of formula P-2 or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds. In some embodiments, a compound of formula P-2 is



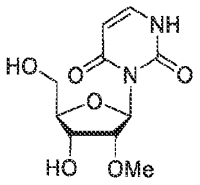
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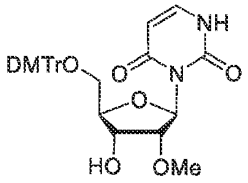
[0062] In some embodiments, compounds of the present disclosure are compounds of formula P-3 or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds. In some embodiments, a compound of formula P-3 is



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[0063] In some embodiments, compounds of the present disclosure are compounds of formula P-4 or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds. In some embodiments, a compound of

formula P-4 is .

[0064] In some embodiments, compounds of the present disclosure are compounds of formula P-5 or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds. In some embodiments, a compound of formula P-5 is .

[0065] In some embodiments, compounds of the present disclosure are compounds of formula PMT or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds.

[0066] In some embodiments, compounds of the present disclosure are compounds of formula AX or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds.

[0067] In some embodiments, compounds of the present disclosure are compounds of formula P-A or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds.

[0068] In some embodiments, compounds of the present disclosure are compounds of formula P-B or salts thereof. In some embodiments, the present disclosure provides compositions comprising such compounds. In some embodiments, the present disclosure provides methods for preparing such compounds and compositions comprising such compounds.

[0069] Formulae of the present disclosure comprise various variables. Certain embodiments of certain variables and compounds are described below as examples.

R^{2ak}

[0070] Certain embodiments for R^{2ak} are described below. In some embodiments, R^{2ak} is C_{1-6} aliphatic. In some embodiments, R^{2ak} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{2ak} is

C_{1-6} alkyl. In some embodiments, R^{2ak} is optionally substituted ethyl. In some embodiments, R^{2ak} is ethyl. In some embodiments, R^{2ak} is optionally substituted methyl. In some embodiments, R^{2ak} is methyl.

PG

[0071] Certain embodiments for PG are described below. In some embodiments, PG is a protecting group. Various suitable hydroxy protecting group are available and can be utilized in accordance with the present disclosure.

[0072] In some embodiments, PG is R^P as described herein. In some embodiments, PG is $-C(O)R^P$ wherein R^P is as described herein. In some embodiments, PG is $-Si(R^P)_3$ wherein each R^P is independently as described herein. In some embodiments, PG is $-Si(R^P)_3$ wherein each R^P is independently as described herein but is not $-H$. In some embodiments, PG is $-Si(R^P)_3$ wherein each R^P is independently an optionally substituted group selected from C_{1-6} aliphatic and C_{6-14} aryl. In some embodiments, PG is $-Si(R^P)_3$ wherein each R^P is independently an optionally substituted group selected from C_{1-6} aliphatic and C_{6-10} aryl. In some embodiments, PG is $-Si(R^P)_3$ wherein each R^P is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl.

[0073] In some embodiments, R^P is not $-H$. In some embodiments, R^P is R as described herein but is not $-H$. In some embodiments, R^P is an optionally substituted group selected from C_{1-6} aliphatic and phenyl. For example, in some embodiments, PG is $-C(O)R^P$ wherein R^P is optionally substituted C_{1-6} aliphatic. In some embodiments, PG is $-C(O)R^P$ wherein R^P is optionally substituted phenyl. In some embodiments, PG is $-C(O)Ph$.

[0074] In some embodiments, PG groups within a compound are different. In some embodiments, they are the same. For example, in some embodiments, each PG is Bz.

PG^P

[0075] In some embodiments, PG^P is PG as described herein. In some embodiments, PG is a protecting group. Various suitable hydroxy protecting group are available and can be utilized in accordance with the present disclosure.

[0076] In some embodiments, PG^P is a protecting group for oligonucleotide synthesis. In some embodiments, PG^P is $-C(O)R^P$ wherein R^P is as described herein. In some embodiments, PG^P is $-DMTr$.

R^P

[0077] Certain embodiments for R^P are described below. In some embodiments, R^P is $-H$. In some embodiments, R^P is R' as described herein but is not $-H$. In some embodiments, R^P is R as described herein but is not $-H$. In some embodiments, R^P is an optionally substituted group selected from C_{1-6} aliphatic and C_{6-14} aryl. In some embodiments, R^P is optionally substituted C_{1-6} aliphatic. In some embodiments, R^P is optionally substituted C_{1-6} alkyl. In some embodiments, R^P is optionally substituted phenyl. In some embodiments, R^P is optionally substituted naphthyl.

LG^1

[0078] Certain embodiments for LG^1 are described below. In some embodiments, LG^1 is a leaving group. Various leaving groups are available and can be utilized in accordance with the present disclosure.

[0079] In some embodiments, LG^1 is $-O-PG$ wherein PG is as described herein.

[0080] In some embodiments, LG^1 is halogen. In some embodiments, LG^1 is $-Cl$. In some embodiments, LG^1 is $-Br$. In some embodiments, LG^1 is $-I$.

[0081] In some embodiments, LG^1 is R^{LG}, wherein R^{LG} is R as described herein but is not $-H$.

[0082] In some embodiments, LG^1 is $-OR^{LG}$ wherein R^{LG} is as described herein. In some embodiments, R^{LG} is not $-H$. In some embodiments, R^{LG} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{LG} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{LG} is not substituted. In some embodiments, R^{LG} is $-OMe$.

[0083] In some embodiments, LG^1 is $-C(O)R^{LG}$ wherein R^{LG} is as described herein.

[0084] In some embodiments, LG^1 is $-OC(O)-R^{LG}$, wherein R^{LG} is as described herein. For example, in some embodiments, LG^1 is $-OC(O)-R^{LG}$, wherein R^{LG} is optionally substituted C_{1-6} aliphatic. In some embodiments, LG^1 is $-OC(O)-R^{LG}$, wherein R^{LG} is optionally substituted phenyl. In some embodiments, LG^1 is Bz.

[0085] In some embodiments, LG^1 is $-C(O)OR^{LG}$ wherein R^{LG} is as described herein. In some embodiments, LG^1 is $-C(O)N(R^{LG})_2$ wherein R^{LG} is as described herein. In some embodiments, LG^1 is $-OC(O)N(R^{LG})_2$ wherein R^{LG} is as described herein. In some embodiments, LG^1 is $-SOR^{LG}$ wherein R^{LG} is as described herein. In some embodiments, LG^1 is $-OSOR^{LG}$ wherein R^{LG} is as described herein. In some embodiments, LG^1 is $-S(O)_2R^{LG}$ wherein R^{LG} is as described herein. In some embodiments, LG^1 is $-OS(O)_2R^{LG}$ wherein R^{LG} is as described herein.

LG^2

[0086] In some embodiments, LG^2 is a leaving group. Various leaving groups are available and can be utilized in accordance with the present disclosure.

[0087] In some embodiments, LG^2 is LG^1 as described herein.

[0088] In some embodiments, LG^2 is halogen. In some embodiments, LG^2 is $-Cl$. In some embodiments, LG^2 is $-Br$. In some embodiments, LG^2 is $-I$.

R^{LG}

[0089] Certain embodiments for R^{LG} are described below. In some embodiments, R^{LG} is R as described herein but is not $-H$. In some embodiments, R^{LG} is $-H$. In some embodiments, R^{LG} is an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, R^{LG} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{LG} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{LG} is C_{1-6} alkyl.

[0090] In some embodiments, R^{LG} is optionally substituted C_{6-14} aryl. In some embodiments, R^{LG} is optionally substituted naphthyl. In some embodiments, R^{LG} is optionally substituted phenyl. In some embodiments, R^{LG} is phenyl.

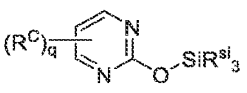
Ring C

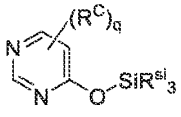
[0091] In some embodiments, Ring C is an optionally substituted 5-14 (e.g., 5-10, 5, 6, 9, or 10) membered ring having 0-6 (e.g., 0, 1-6, 1-4, 1, 2, 3, 4, 5 and 6) heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom. In some embodiments, Ring C is an optionally substituted 5-10 membered ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom. In some embodiments, Ring C is an optionally substituted 5-10 membered ring having 1-4 nitrogen atoms. In some embodiments, Ring C is monocyclic. In some embodiments, Ring C is monocyclic and has one heteroatom in addition to the nitrogen atom. In some embodiments, the one heteroatom is nitrogen. In some embodiments, Ring C is monocyclic and is 5-membered. In some embodiments, Ring C is monocyclic and is 6-membered. In some embodiments, Ring C is bicyclic. In some embodiments, Ring C is bicyclic and is 9-membered. In some embodiments, Ring C is bicyclic and is 10-membered. In some embodiments, a monocyclic ring unit is 5-membered. In some embodiments, a monocyclic ring unit is 6-membered. In some embodiments, a monocyclic ring unit is saturated. In some embodiments, a monocyclic ring unit is partially unsaturated. In some embodiments, a monocyclic ring unit is aromatic. In some embodiments, Ring C is saturated. In some embodiments, Ring C is partially unsaturated. In some embodiments, Ring C is aromatic.

[0092] In some embodiments, Ring C has no additional heteroatoms. In some embodiments, Ring C has 1-6 additional heteroatoms. In some embodiments, Ring C has one additional heteroatom. In some embodiments, Ring C has two additional heteroatoms. In some embodiments, Ring C has three additional heteroatoms. In some embodiments, Ring C has four additional heteroatoms. In some embodiments, Ring C has five additional heteroatoms. In some embodiments, Ring C has six additional heteroatoms. In some embodiments, each additional heteroatom is nitrogen.

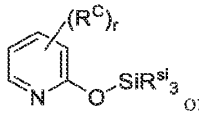
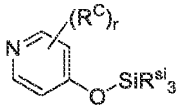
[0093] In some embodiments, Ring C is an optionally substituted ring of a nucleobase. In some embodiments, Ring C is an optionally substituted ring of A, T, C, G and U. In some embodiments, Ring C is an optionally substituted ring of a nucleobase which nucleobase is other than A, T, C, G and U.

[0094] In some embodiments, a compound of formula P-A is or comprises an optionally substituted nucleobase or a tautomer thereof. In some embodiments, a compound of formula P-A is an optionally substituted or protected nucleobase selected from A, T, C, G, U and tautomers thereof. In some embodiments, a compound of formula P-A is a protected nucleobase selected from A, T, C, G, and U.

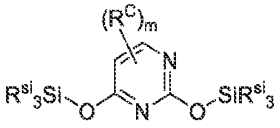
[0095] In some embodiments, a compound of formula P-A has a structure of 

or a salt thereof, wherein q is 0-3. In some embodiments, a compound of formula P-A has a structure of  or a salt thereof, wherein q is 0-3.

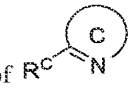
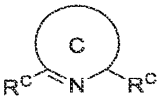
[0096] In some embodiments, q is 0. In some embodiments, q is 1. In some embodiments, q is 2. In some embodiments, q is 3.

[0097] In some embodiments, a compound of formula P-A has a structure of  or a salt thereof, wherein r is 0-4. In some embodiments, a compound of formula P-A has a structure of  or a salt thereof, wherein r is 0-4.

[0098] In some embodiments, r is 0. In some embodiments, r is 1-4. In some embodiments, r is 1. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4.

[0099] In some embodiments, a compound of formula P-A has a structure of  or a salt thereof, wherein m is 0-2.

[00100] In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

[00101] In some embodiments, a compound of formula P-A has a structure of  or a salt thereof. In some embodiments, a compound of formula P-A has a structure of  or a salt thereof.

R^C

[00102] In some embodiments, R^C is a protecting group. In some embodiments, R^C is a hydroxy protecting group. Various protecting group are available and can be utilized in accordance with the present disclosure.

[00103] In some embodiments, R^C is R as described herein. In some embodiments, R^C is –H. In some embodiments, R^C is not –H. For example, in some embodiments, R^C is R wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R^C is R wherein R is optionally substituted C_{1-6} alkyl. In some

embodiments, R^C is R wherein R is C_{1-6} alkyl. In some embodiments, R^C is R wherein R is methyl.

[00104] In some embodiments, R^C is –OR wherein R is as described herein. In some embodiments, R^C is –OH.

[00105] In some embodiments, R^C is $-OSi(R^{si})_3$ wherein each of R^{si} is independently as described herein. In some embodiments, each of R^{si} is not –H. In some embodiments, each R^{si} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, each R^{si} is independently an optionally substituted group selected from C_{1-6} alkyl and phenyl.

[00106] In some embodiments, R^C is halogen. In some embodiments, R^C is –F. In some embodiments, R^C is –Cl. In some embodiments, R^C is –Br. In some embodiments, R^C is –I. In some embodiments, R^C is –CN. In some embodiments, R^C is $-NO_2$.

[00107] In some embodiments, R^C is $-N(R')_2$ wherein each R` is independently as described herein. In some embodiments, $R^C$ is $-NH_2$. In some embodiments, $R^C$ is a protected amino group. In some embodiments, $R^C$ is –NH(R`).

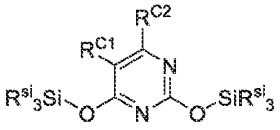
[00108] In some embodiments, R^C is –C(O)R wherein R is as described herein.

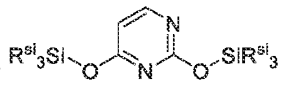
[00109] In some embodiments, R^C is –C(O)OR wherein R is as described herein. For example, in some embodiments, R is not –H. In some embodiments, R is optionally substituted C_{1-6} aliphatic.

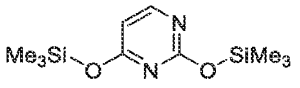
[00110] In some embodiments, R^C is $-S(O)_2R$ wherein R is as described herein. For example, in some embodiments, R is not –H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted phenyl.

[00111] In some embodiments, an occurrence of R^C is bonded to the nitrogen atom. In some embodiments, an occurrence of R^C is bonded to the nitrogen atom and is –H.

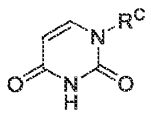
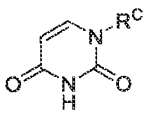
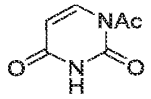
[00112] In some embodiments, each R^C is independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic. In some embodiments, each R^C is independently –H.

[00113] In some embodiments, a compound of formula P-A has a structure of 

or a salt thereof, wherein R^{C1} and R^{C2} are each independently R^C. In some embodiments, R^{C1} and R^{C2} are each independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic. In some embodiments, a compound of formula P-A has a structure of 

or a salt thereof. In some embodiments, a compound of formula P-A has a structure of 

. In some embodiments, a compound of formula P-A has a structure of


. In some embodiments, a compound of formula P-A has a structure of 
wherein R^C is –C(O)R. In some embodiments, a compound of formula P-A has a structure of 
.

c

[00114] In some embodiments, c is 0. In some embodiments, c is 1-5. In some embodiments, c is 1. In some embodiments, c is 2. In some embodiments, c is 3. In some embodiments, c is 4. In some embodiments, c is 5.

R^{C1}

[00115] As defined herein, R^{C1} is R^C as described herein. For example, in some embodiments, R^{C1} is –H. In some embodiments, R^{C1} is halogen, e.g., –F, –Cl, –Br or –I. In some embodiments, R^{C1} is –CN. In some embodiments, R^{C1} is $-NO_2$. In some embodiments, R^{C1} is R but is not –H. In some embodiments, R^{C1} is optionally substituted C_{1-10} aliphatic. In some embodiments, R^{C1} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{C1} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{C1} is optionally substituted C_{1-3} alkyl. In some embodiments, each substituent is independently selected from halogen, –CN, R^s, $-OR^s$, $-N(R^s)_2$, $-C(O)OR^s$, $-C(O)N(R^s)_2$, and $-S(O)_2N(R^s)_2$, wherein each R^s is independently –H, C_1-C_6 aliphatic or C_1-C_6 haloaliphatic. In some embodiments, R^{C1} is C_{1-6} aliphatic. In some embodiments, R^{C1} is C_{1-6} alkyl. In some embodiments, R^{C1} is C_{1-3} alkyl. In some embodiments, R^{C1} is methyl. In some embodiments, R^{C1} is halogen substituted methyl. In some embodiments, R^{C1} is $-CF_3$. In some embodiments, R^{C1} is halogen substituted ethyl. In some embodiments, R^{C1} is ethyl. In some embodiments, R^{C1} is halogen substituted propyl. In some embodiments, R^{C1} is propyl. In some embodiments, R^{C1} is halogen substituted isopropyl. In some embodiments, R^{C1} is isopropyl. In some embodiments, R^{C1} is optionally substituted alkenyl. In some embodiments, R^{C1} is optionally substituted alkynyl. In some embodiments, R^{C1} is –C≡CH.

[00116] In some embodiments, R^{C1} and R^2 are the same. In some embodiments, R^{C1} is –H and R^{C2} is not –H. In some embodiments, R^{C2} is –H and R^{C2} is not –H.

R^{C2}

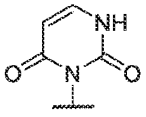
[00117] As defined herein, R^{C2} is R^C as described herein. For example, in some embodiments, R^{C2} is –H. In some embodiments, R^{C2} is halogen, e.g., –F, –Cl, –Br or –I. In some embodiments, R^{C2} is –CN. In some embodiments, R^{C2} is $-NO_2$. In some embodiments, R^{C2} is R but is not –H. In some embodiments, R^{C2} is optionally substituted C_{2-10} aliphatic. In some embodiments, R^{C2} is optionally substituted C_{2-6}

aliphatic. In some embodiments, R^{C2} is optionally substituted C_{2-6} alkyl. In some embodiments, R^{C2} is optionally substituted C_{2-3} alkyl. In some embodiments, each substituent is independently selected from halogen, −CN, R^s, $-OR^s$, $-N(R^s)_2$, $-C(O)OR^s$, $-C(O)N(R^s)_2$, and $-S(O)_2N(R^s)_2$, wherein each R^s is independently −H, C_{2-6} aliphatic or C_{2-6} haloaliphatic. In some embodiments, R^{C2} is C_{2-6} aliphatic. In some embodiments, R^{C2} is C_{2-6} alkyl. In some embodiments, R^{C2} is C_{2-3} alkyl. In some embodiments, R^{C2} is methyl. In some embodiments, R^{C2} is halogen substituted methyl. In some embodiments, R^{C2} is $-CF_3$. In some embodiments, R^{C2} is halogen substituted ethyl. In some embodiments, R^{C2} is ethyl. In some embodiments, R^{C2} is halogen substituted propyl. In some embodiments, R^{C2} is propyl. In some embodiments, R^{C2} is halogen substituted isopropyl. In some embodiments, R^{C2} is isopropyl. In some embodiments, R^{C2} is optionally substituted alkenyl. In some embodiments, R^{C2} is optionally substituted alkynyl. In some embodiments, R^{C2} is −C≡CH.

R^{si}

[00118] As defined herein, R^{si} is R as described herein. In some embodiments, R^{si} is −H. In some embodiments, each R^{si} is not −H. In some embodiments, each R^{si} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, each R^{si} is independently an optionally substituted group selected from C_{1-6} alkyl and phenyl. In some embodiments, each R^{si} is independently C_{1-6} alkyl or phenyl. In some embodiments, each R^{si} is independently methyl, ethyl or t-butyl. In some embodiments, each R^{si} is methyl.

R^N

[00119] In some embodiments, R^N is or comprises an optionally substituted nucleobase or a tautomer thereof. In some embodiments, R^N is an optionally substituted or protected nucleobase selected from A, T, C, G, U and tautomers thereof. In some embodiments, R^N is a protected nucleobase selected from A, T, C, G and U. In some embodiments, R^N is an optionally protected nucleobase which nucleobase is not A, T, C, G or U. In some embodiments, R^N is .

Ring B

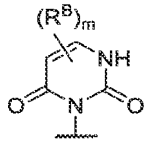
[00120] In some embodiments, Ring B is an optionally substituted ring of a nucleobase. In some embodiments, Ring B is an optionally substituted ring of A, T, C, G or U. In some embodiments, Ring B is an optionally substituted ring of a nucleobase other than A, T, C, G and U.

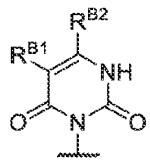
[00121] As defined herein, Ring B is an optionally substituted 3-14 (e.g., 5-14, 5-10, 6-14, 6-10, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14) membered ring having, in addition to the nitrogen atom, 0-6 (e.g., 0, 1-6, 1-4, 1, 2, 3, 4, 5 and 6) heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, Ring B is an optionally substituted 4-14 membered ring having, in addition to the nitrogen

atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, Ring B is an optionally substituted 5-14 membered ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom. In some embodiments, Ring B is an optionally substituted 5-10 membered ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom. In some embodiments, Ring B is an optionally substituted 5-10 membered ring having 1-4 nitrogen atoms.

[00122] In some embodiments, Ring B is an optionally substituted 5-10 membered ring having 1-4 nitrogen atoms. In some embodiments, Ring B is monocyclic. In some embodiments, Ring B is monocyclic and has one heteroatom in addition to the nitrogen atom. In some embodiments, the one heteroatom is nitrogen. In some embodiments, Ring B is monocyclic and is 5-membered. In some embodiments, Ring B is monocyclic and is 6-membered. In some embodiments, Ring B is bicyclic. In some embodiments, Ring B is bicyclic and is 9-membered. In some embodiments, Ring B is bicyclic and is 10-membered. In some embodiments, a monocyclic ring unit is 5-membered. In some embodiments, a monocyclic ring unit is 6-membered. In some embodiments, a monocyclic ring unit is saturated. In some embodiments, a monocyclic ring unit is partially unsaturated. In some embodiments, a monocyclic ring unit is aromatic. In some embodiments, Ring B is saturated. In some embodiments, Ring B is partially unsaturated. In some embodiments, Ring B is aromatic.

[00123] In some embodiments, Ring B has no additional heteroatoms. In some embodiments, Ring B has 1-6 additional heteroatoms. In some embodiments, Ring B has one additional heteroatom. In some embodiments, Ring B has two additional heteroatoms. In some embodiments, Ring B has three additional heteroatoms. In some embodiments, Ring B has four additional heteroatoms. In some embodiments, Ring B has five additional heteroatoms. In some embodiments, Ring B has six additional heteroatoms. In some embodiments, each additional heteroatom is nitrogen.

[00124] In some embodiments, R^N is , wherein m is 0-2. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2. In some embodiments, each R^B is independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic.

[00125] In some embodiments, R^N is , wherein R^{B1} and R^{B2} are each independently R^B. In some embodiments, R^{B1} and R^{B2} are each independently hydrogen, halogen, or optionally substituted C_1.

$_{1\text{-}6}$ aliphatic.

R^B

[00126] In some embodiments, R^B is a protecting group. In some embodiments, R^B is a hydroxy protecting group. Various protecting group are available and can be utilized in accordance with the present disclosure.

[00127] In some embodiments, R^B is R as described herein. In some embodiments, R^B is −H. In some embodiments, R^B is not −H. For example, in some embodiments, R^B is R wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R^B is R wherein R is optionally substituted C_{1-6} alkyl. In some embodiments, R^B is R wherein R is C_{1-6} alkyl. In some embodiments, R^B is R wherein R is methyl.

[00128] In some embodiments, R^B is −OR wherein R is as described herein. In some embodiments, R^B is −OH.

[00129] In some embodiments, R^B is $-OSi(R^{si})_3$ wherein each of R^{si} is independently as described herein. In some embodiments, each of R^{si} is not −H. In some embodiments, each R^{si} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, each R^{si} is independently an optionally substituted group selected from C_{1-6} alkyl and phenyl.

[00130] In some embodiments, R^B is halogen. In some embodiments, R^B is −F. In some embodiments, R^B is −Cl. In some embodiments, R^B is −Br. In some embodiments, R^B is −I. In some embodiments, R^B is −CN. In some embodiments, R^B is $-NO_2$.

[00131] In some embodiments, R^B is $-N(R')_2$ wherein each R' is independently as described herein. In some embodiments, R^B is $-NH_2$. In some embodiments, R^B is a protected amino group. In some embodiments, R^B is −NH(R').

[00132] In some embodiments, R^B is −C(O)R wherein R is as described herein.

[00133] In some embodiments, R^B is −C(O)OR wherein R is as described herein. For example, in some embodiments, R is not −H. In some embodiments, R is optionally substituted C_{1-6} aliphatic.

[00134] In some embodiments, R^B is $-S(O)_2R$ wherein R is as described herein. For example, in some embodiments, R is not −H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted phenyl.

[00135] In some embodiments, an occurrence of R^B is bonded to the nitrogen atom. In some embodiments, an occurrence of R^B is bonded to the nitrogen atom and is −H.

[00136] In some embodiments, each R^B is independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic. In some embodiments, each R^B is independently −H.

b

[00137] In some embodiments, b is 0. In some embodiments, b is 1-5. In some embodiments, b is 1. In some embodiments, b is 2. In some embodiments, b is 3. In some embodiments, b is 4. In some

embodiments, b is 5.

R^{B1}

[00138] As defined herein, R^{B1} is R^B as described herein. For example, in some embodiments, R^{B1} is −H. In some embodiments, R^{B1} is halogen. In some embodiments, R^{B1} is −F. In some embodiments, R^{B1} is −Cl. In some embodiments, R^{B1} is −Br. In some embodiments, R^{B1} is −I. In some embodiments, R^{B1} is −CN. In some embodiments, R^{B1} is $-NO_2$. In some embodiments, R^{B1} is R but is not −H. In some embodiments, R^{B1} is optionally substituted C_{1-10} aliphatic. In some embodiments, R^{B1} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{B1} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{B1} is optionally substituted C_{1-3} alkyl. In some embodiments, each substituent is independently selected from halogen, −CN, R^s, $-OR^s$, $-N(R^s)_2$, $-C(O)OR^s$, $-C(O)N(R^s)_2$, and $-S(O)_2N(R^s)_2$, wherein each R^s is independently −H, C_1-C_6 aliphatic or C_1-C_6 haloaliphatic. In some embodiments, R^{B1} is C_{1-6} aliphatic. In some embodiments, R^{B1} is C_{1-6} alkyl. In some embodiments, R^{B1} is C_{1-3} alkyl. In some embodiments, R^{B1} is methyl. In some embodiments, R^{B1} is halogen substituted methyl. In some embodiments, R^{B1} is $-CF_3$. In some embodiments, R^{B1} is halogen substituted ethyl. In some embodiments, R^{B1} is ethyl. In some embodiments, R^{B1} is halogen substituted propyl. In some embodiments, R^{B1} is propyl. In some embodiments, R^{B1} is halogen substituted isopropyl. In some embodiments, R^{B1} is isopropyl. In some embodiments, R^{B1} is optionally substituted alkenyl. In some embodiments, R^{B1} is optionally substituted alkynyl. In some embodiments, R^{B1} is −C≡CH.

[00139] In some embodiments, R^{B1} and R^2 are the same. In some embodiments, R^{B1} is −H and R^{B2} is not −H. In some embodiments, R^{B2} is −H and R^{B2} is not −H.

R^{B2}

[00140] As defined herein, R^{B2} is R^B as described herein. For example, in some embodiments, R^{B2} is −H. In some embodiments, R^{B2} is halogen. In some embodiments, R^{B2} is −F. In some embodiments, R^{B2} is −Cl. In some embodiments, R^{B2} is −Br. In some embodiments, R^{B2} is −I. In some embodiments, R^{B2} is −CN. In some embodiments, R^{B2} is $-NO_2$. In some embodiments, R^{B2} is R but is not −H. In some embodiments, R^{B2} is optionally substituted C_{2-10} aliphatic. In some embodiments, R^{B2} is optionally substituted C_{2-6} aliphatic. In some embodiments, R^{B2} is optionally substituted C_{2-6} alkyl. In some embodiments, R^{B2} is optionally substituted C_{2-3} alkyl. In some embodiments, each substituent is independently selected from halogen, −CN, R^s, $-OR^s$, $-N(R^s)_2$, $-C(O)OR^s$, $-C(O)N(R^s)_2$, and $-S(O)_2N(R^s)_2$, wherein each R^s is independently −H, C_{2-6} aliphatic or C_{2-6} haloaliphatic. In some embodiments, R^{B2} is C_{2-6} aliphatic. In some embodiments, R^{B2} is C_{2-6} alkyl. In some embodiments, R^{B2} is C_{2-3} alkyl. In some embodiments, R^{B2} is methyl. In some embodiments, R^{B2} is halogen substituted methyl. In some embodiments, R^{B2} is $-CF_3$. In some embodiments, R^{B2} is halogen substituted ethyl. In some embodiments, R^{B2} is ethyl. In some embodiments, R^{B2} is halogen substituted propyl. In some

embodiments, R^{B2} is propyl. In some embodiments, R^{B2} is halogen substituted isopropyl. In some embodiments, R^{B2} is isopropyl. In some embodiments, R^{B2} is optionally substituted alkenyl. In some embodiments, R^{B2} is optionally substituted alkynyl. In some embodiments, R^{B2} is $-C\equiv CH$.

R^1

[00141] In some embodiments, R^1 is R` as described herein and is not −H. In some embodiments, R^1 is R as described herein. In some embodiments, R^1 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^1 is optionally substituted methyl. In some embodiments, R^1 is optionally substituted ethyl. In some embodiments, R^1 is optionally substituted ethyl, wherein the methylene unit boned to the oxygen is optionally monosubstituted, and the methyl is substituted with an electron-withdrawing group, e.g., −CN. Certain electron-withdrawing groups are described in US 10167309, US 11643657, US 11718638, US 11608355 or US 20230089442, the electron-withdrawing groups of each of which are incorporated herein by reference. In some embodiments, R^1 is $-CH_2CH_2CN$.

R^2

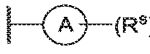
[00142] In some embodiments, R^2 is R` as described herein and is not −H. In some embodiments, R^2 is R as described herein. In some embodiments, R^2 is not −H. In some embodiments, R^2 is optionally substituted C_{1-10} aliphatic. In some embodiments, R^2 is optionally substituted C_{1-10} alkyl. In some embodiments, R^2 is C_{1-6} aliphatic. In some embodiments, R^2 is C_{1-6} alkyl. In some embodiments, R^2 is isopropyl.

R^3

[00143] In some embodiments, R^3 is R` as described herein and is not −H. In some embodiments, R^3 is R as described herein. In some embodiments, R^3 is not −H. In some embodiments, R^3 is optionally substituted C_{1-10} aliphatic. In some embodiments, R^3 is optionally substituted C_{1-10} alkyl. In some embodiments, R^3 is C_{1-6} aliphatic. In some embodiments, R^3 is C_{1-6} alkyl. In some embodiments, R^3 is isopropyl.

[00144] In some embodiments, R^2 and R^3 are the same. In some embodiments, R^2 and R^3 are different.

[00145] In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is $-P(OCH_2CH_2CN)N[CH(CH_3)_2]_2$.

[00146] In some embodiments, two or three of R^1, R^2, and R^3 are taken together with their intervening atoms to form  wherein each variable is independently as described herein. In some embodiments, R^1 and R^2 are taken together with their intervening atoms to form a ring as described herein. In some embodiments, R^2 and R^3 are taken together with their intervening atoms to from a ring as described herein. In some embodiments, R^1, R^2 and R^3 are taken together with their intervening atoms to form a ring as described herein.

Ring A

[00147] As defined herein, Ring A is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 3-15, 3-14, 3-10, 5-10, 3-7 and 3-6) membered ring having 0-10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 0-5, and 1-5) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, Ring A is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 3-15, 3-14, 3-10, 5-10, 3-7 and 3-6) membered ring having 0-10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 0-5, and 1-5) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, Ring A has no additional heteroatoms. In some embodiments, Ring A has 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 additional heteroatoms.

[00148] In some embodiments, Ring A is not substituted (as appreciated by those skilled in the art, not including R^s). In some embodiments, Ring A is substituted (as appreciated by those skilled in the art, not including R^s).

[00149] In some embodiments, Ring A is monocyclic. In some embodiments, Ring A is bicyclic. In some embodiments, Ring A is polycyclic. In some embodiments, each monocyclic ring unit is independently an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 3-8, 3-7, 3-6, 4-6, 5-6 and 5-8) membered ring having 0-5 (e.g., 1, 2, 3, 4, 5, 1-5, 1-4 and 1-2) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur and 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-5 and 1-4) carbon atoms. In some embodiments, each monocyclic ring unit is independently an optionally substituted 4-10 (e.g., 4, 5, 6, 7, 8, 9, 10, 5-7, 5-6) membered ring having 0-5 (e.g., 1, 2, 3, 4, 5, 1-5, 1-4 and 1-2) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur and 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-5 and 1-4) carbon atoms. In some embodiments, each monocyclic ring unit is independently an optionally substituted 3-10 membered. In some embodiments, each monocyclic ring unit is independently an optionally substituted 3-7 membered. In some embodiments, each monocyclic ring unit is independently an optionally substituted 4-6 membered. In some embodiments, each monocyclic ring unit is independently an optionally substituted 5-6 membered. In some embodiments, each monocyclic ring unit is independently an optionally substituted 5-membered. In some embodiments, a monocyclic ring unit is an optionally substituted saturated ring. In some embodiments, a monocyclic ring unit is an optionally substituted partially unsaturated ring. In some embodiments, a monocyclic ring unit is an optionally substituted aromatic ring. In some embodiments, a monocyclic ring unit is an optionally substituted phenyl ring. In some embodiments, a monocyclic ring unit is an optionally substituted 5-membered heteroaromatic having 1-4 (e.g., 1, 2, 3, 4, 1-3 and 1-2) heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, a monocyclic ring unit is an optionally substituted 6-membered heteroaromatic having 1-4 (e.g., 1, 2, 3, 4,

1-3 and 1-2) heteroatoms independently selected from nitrogen, oxygen and sulfur. Each monocyclic ring unit is independently optionally substituted. In some embodiments, a monocyclic ring unit is unsaturated. In some embodiments, a monocyclic ring unit is saturated.

[00150] In some embodiments, a monocyclic ring unit comprising the nitrogen atom to which R^2 and R^3 are bond is an optionally substituted saturated 4-10 (e.g., 4-8, 4-6, 4, 5, 6, 7, 8, 9 and 10) membered ring having 0-2 heteroatoms in addition to the nitrogen atom independently selected from nitrogen, oxygen and sulfur. In some embodiments, a monocyclic ring unit comprising the nitrogen atom to which R^2 and R^3 are bond is an optionally substituted saturated 4-10 (e.g., 4-8, 4-6, 4, 5, 6, 7, 8, 9 and 10) membered ring having no heteroatoms in addition to the nitrogen atom independently selected from nitrogen, oxygen and sulfur. In some embodiments, it is 4-membered. In some embodiments, it is 5-membered. In some embodiments, it is 6-membered. In some embodiments, it is 7-membered. In some embodiments, it is 8-membered.

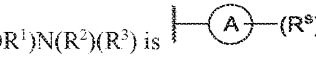
[00151] In some embodiments, Ring A is an optionally substituted saturated ring. In some embodiments, Ring A is an optionally substituted partially unsaturated ring. In some embodiments, Ring A is an optionally substituted aromatic ring.

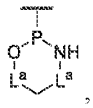
[00152] In some embodiments, Ring A is an optionally substituted monocyclic 3-10 (e.g., 3-6, 5-10, 5-6, 3, 4, 5, 6, 7, 8, 9 and 10) membered, monocyclic, bicyclic or polycyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, Ring A is an optionally substituted bicyclic or polycyclic 6-20 (e.g., 6-15, 6-10, 8-20, 8-15, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20) membered, monocyclic, bicyclic or polycyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, Ring A is 3-9, 3-8, 3-7, 3-6, 4-10, 4-9, 4-8, 4-7, 4-6, 5-10, 5-9, 5-8, 5-7, 5-6, or 3, 4, 5, 6, 7, 8, 9, or 10-membered. In some embodiments, Ring A is 3-9 membered. In some embodiments, Ring A is 3-7 membered. In some embodiments, Ring A is 4-10 membered. In some embodiments, Ring A is 4-7 membered. In some embodiments, Ring A is 5-10 membered. In some embodiments, Ring A is 5-7 membered. In some embodiments, Ring A is 3-membered. In some embodiments, Ring A is 4-membered. In some embodiments, Ring A is 5-membered. In some embodiments, Ring A is 6-membered. In some embodiments, Ring A is 7-membered. In some embodiments, Ring A is 8-membered. In some embodiments, Ring A is 9-membered. In some embodiments, Ring A is 10-membered. In some embodiments, Ring A is 11-membered. In some embodiments, Ring A is 12-membered. In some embodiments, Ring A is monocyclic. In some embodiments, Ring A is bicyclic. In some embodiments, Ring A is an optionally substituted bicyclic 7-12 membered ring. In some embodiments, Ring A is an optionally substituted bicyclic 8-10 membered ring. In some embodiments, Ring A is an optionally substituted bicyclic 7-membered ring. In some embodiments, Ring A is an optionally substituted bicyclic

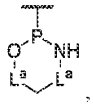
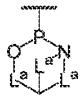
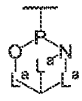
8-membered ring. In some embodiments, Ring A is an optionally substituted bicyclic 9-membered ring. In some embodiments, Ring A is an optionally substituted bicyclic 10-membered ring. In some embodiments, Ring A is polycyclic. In some embodiments, Ring A has no additional heteroatoms. In some embodiments, Ring A has 0-6, e.g., 0, 1-6, 1-5, 1-3, or 1, 2, 3, 4, 5, or 6 additional heteroatoms. In some embodiments, Ring A comprises one or more aromatic ring. In some embodiments, Ring A is bicyclic or polycyclic, and each monocyclic ring unit is independently 3-10 (e.g., 3-9, 3-8, 3-7, 3-6, 4-10, 4-9, 4-8, 4-7, 4-6, 5-10, 5-9, 5-8, 5-7, 5-6, or 3, 4, 5, 6, 7, 8, 9, or 10) membered, saturated, partially unsaturated or aromatic and having 0-5 (e.g., 0, 1-5, 1-3, 1, 2, 3, 4, or 5) heteroatoms. In some embodiments, a monocyclic ring unit is saturated. In some embodiments, a monocyclic ring unit is partially unsaturated. In some embodiments, a monocyclic ring unit is aromatic. In some embodiments, a monocyclic ring unit is heteroaromatic. Those skilled in the art appreciate that intervening atom(s), e.g., of groups taken together to form a ring, are typically atoms on the shortest path connecting such groups if multiple paths exist.

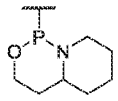
[00153] In some embodiments, a monocyclic ring unit comprising the phosphorus, nitrogen and oxygen atoms is saturated. In some embodiments, a monocyclic ring unit comprising the phosphorus, nitrogen and oxygen atoms is partially saturated. In some embodiments, it is 4-membered. In some embodiments, it is 5-membered. In some embodiments, it is 6-membered. In some embodiments, it is 7-membered. In some embodiments, it has one or more additional heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, the phosphorus, nitrogen and oxygen atoms are the only heteroatoms in that monocyclic ring unit.

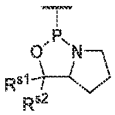
[00154] In some embodiments, a monocyclic ring unit comprising the nitrogen atom to which R^2 and R^3 are bond is an optionally substituted partially unsaturated 4-10 (e.g., 4-8, 4-6, 4, 5, 6, 7, 8, 9 and 10) membered ring having 0-2 heteroatoms in addition to the nitrogen atom independently selected from nitrogen, oxygen and sulfur. In some embodiments, a monocyclic ring unit comprising the nitrogen atom to which R^2 and R^3 are bond is an optionally substituted partially unsaturated 4-10 (e.g., 4-8, 4-6, 4, 5, 6, 7, 8, 9 and 10) membered ring having no heteroatoms in addition to the nitrogen atom independently selected from nitrogen, oxygen and sulfur. In some embodiments, it is 4-membered. In some embodiments, it is 5-membered. In some embodiments, it is 6-membered. In some embodiments, it is 7-membered. In some embodiments, it is 8-membered.

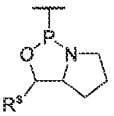
[00155] In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is , wherein Ring A is bonded to the rest of the compound at a phosphorus atom.

[00156] In some embodiments, Ring A comprises optionally substituted , wherein each L^a is

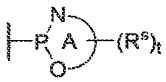
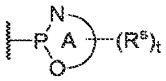
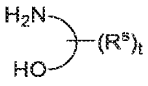
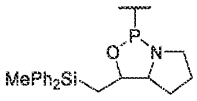
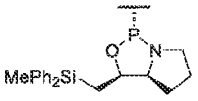
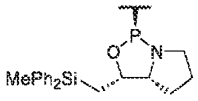
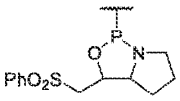
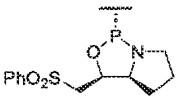
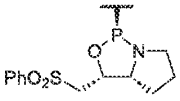
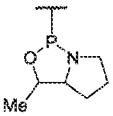
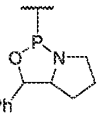
independently a covalent bond or a bivalent C_{1-5} aliphatic group wherein one or more methylene units of each L^a are optionally and independently replaced by –O–, –S–, or –NH. In some embodiments, Ring A is optionally substituted , wherein each L^a is independently a covalent bond or a bivalent C_{1-5} aliphatic group wherein one or more methylene units of each L^a are optionally and independently replaced by –O–, –S–, or –NH. In some embodiments, Ring A comprises optionally substituted , wherein each L^a is independently a covalent bond or a bivalent C_{1-5} aliphatic group wherein one or more methylene units of each L^a are optionally and independently replaced by –O–, –S–, or –NH. In some embodiments, Ring A is optionally substituted , wherein each L^a is independently a covalent bond or a bivalent C_{1-5} aliphatic group wherein one or more methylene units of each L^a are optionally and independently replaced by –O–, –S–, or –NH. In some embodiments, L^a is a covalent bond. In some embodiments, L^a is not a covalent bond. In some embodiments, L^a is $–CH_2–$. In some embodiments, L^a is $–(CH_2)_2–$. In some embodiments, L^a is $–(CH_2)_3–$. In some embodiments, L^a is $–(CH_2)_4–$. In some embodiments, L^a is $–(CH_2)_5–$. In some embodiments, a methylene unit is replaced with –O–. In some embodiments, a methylene unit is replaced with –S–. In some embodiments, a methylene unit is replaced with –NH–.

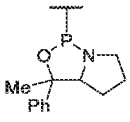
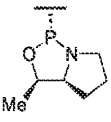
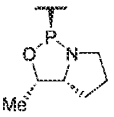
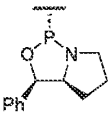
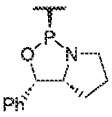
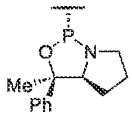
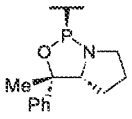
[00157] In some embodiments, Ring A is optionally substituted . In some embodiments, Ring A is optionally substituted . In some embodiments, Ring A is optionally substituted .

[00158] In some embodiments, an occurrence of R^s is bonded to a carbon atom bonded to the oxygen of $–P(OR^1)N(R^2)(R^3)$. In some embodiments, $–P(OR^1)N(R^2)(R^3)$ is , wherein each of R^{s1} and

R^{s2} is independently R^s as described herein. In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is .

[00159] In some embodiments, one of R^{s1} and R^{s2} is $-H$. In some embodiments, R^{s1} and R^{s2} are independently not $-H$. In some embodiments, R^{s1} is R as described herein. In some embodiments, R^{s1} is not hydrogen. In some embodiments, R^{s1} is hydrogen. In some embodiments, R^{s1} is hydrogen and R^{s2} is not hydrogen. In some embodiments, R^{s1} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{s1} is methyl. In some embodiments, R^{s1} is optionally substituted phenyl. In some embodiments, R^{s1} is phenyl. In some embodiments, R^{s2} is R as described herein. In some embodiments, R^{s2} is not hydrogen. In some embodiments, R^{s2} is hydrogen. In some embodiments, R^{s2} is optionally substituted C_{1-6} aliphatic. In some embodiments, wherein R^{s2} is methyl. In some embodiments, R^{s2} is optionally substituted phenyl. In some embodiments, wherein R^{s2} is phenyl.

[00160] In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is  wherein each variable is independently as described herein. In some embodiments,  is of such a structure that  is a chiral auxiliary, e.g., described in US 10167309, US 11643657, US 11718638, US 11608355 or US 20230089442, the chiral auxiliaries of each of which are incorporated herein by reference. For example, in some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In

some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is . In some embodiments, it is .

t

[00161] In some embodiments, t is 0. In some embodiments, t is 1-5. In some embodiments, t is 1. In some embodiments, t is 2. In some embodiments, t is 3. In some embodiments, t is 4. In some embodiments, t is 5.

R^s

[00162] In some embodiments, R^s is −F. In some embodiments, R^s is −Cl. In some embodiments, R^s is −Br. In some embodiments, R^s is −I. In some embodiments, R^s is −CN. In some embodiments, R^s is $-N_3$. In some embodiments, R^s is −NO. In some embodiments, R^s is $-NO_2$.

[00163] In some embodiments, R^s is $-L^s-R^{s11}$ wherein each of L^s and R^{s11} is independently as described herein. In some embodiments, R^s is R^{s11} as described herein.

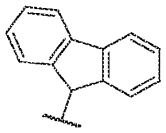
[00164] In some embodiments, R^s is R' as described herein. For example, in some embodiments, R' is −C(O)R wherein R is as described herein. In some embodiments, R' is $-CO_2R$ wherein R is as described herein. In some embodiments, R' is $-S(O)_2R$ wherein R is as described herein. In some embodiments, R is C_{1-6} aliphatic. In some embodiments, R is C_{1-6} alkyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R^s is $-S(O)_2R$ wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, R^s is $-S(O)_2Me$. In some embodiments, R^s is $-S(O)_2t$-Bu. In some embodiments, R^s is $-S(O)_2R$ wherein R is optionally substituted phenyl. In some embodiments, R^s is $-S(O)_2Ph$.

[00165] In some embodiments, R^s is R as described herein. For example, in some embodiments, R is not −H. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is methyl. In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl.

[00166] In some embodiments, R^s is $-L^s-OR^{s11}$ wherein each of L^s and R^{s11} is independently as described herein. In some embodiments, R^s is $-OR^{s11}$ wherein R^{s11} is as described herein. In some embodiments, R^s is $-CH_2OR^{s11}$ wherein R^{s11} is as described herein.

[00167] In some embodiments, R^s is $-L^s-SR^{s1}$ wherein each of L^s and R^{s1} is independently as described herein. In some embodiments, R^s is $-SR^{s1}$ wherein R^{s1} is as described herein. In some embodiments, R^s is $-CH_2SR^{s1}$ wherein R^{s1} is as described herein.

[00168] In some embodiments, R^s is $-L^s-N(R^{s1})_2$ wherein each of L^s and R^{s1} is independently as described herein. In some embodiments, R^s is $-N(R^{s1})_2$ wherein each of L^s and R^{s1} is independently as described herein. In some embodiments, R^s is $-CH_2N(R^{s1})_2$ wherein each of L^s and R^{s1} is independently as described herein.

[00169] In some embodiments, R^s is $-C(R^{s1})_3$ wherein each R^{s1} is independently as described herein. In some embodiments, R^s is $-CH(R^{s1})_2$ wherein each R^{s1} is independently as described herein. In some embodiments, two or more R^{s1} are taken together with the carbon atom to which they are attached to form an optionally substituted 3-20 (e.g., 3-15, 3-10, 3-6, 5-10, 5-6, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20) membered ring having 0-10 (e.g., 0, 1-10, 1-5, 1-4, 1-3, 1-2, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, R^s is optionally substituted .

[00170] In some embodiments, R^s is $-L^s-Si(R^{s1})_3$ wherein each R^{s1} is independently as described herein. In some embodiments, each R^{s1} is independently R` as described herein and is not –H. In some embodiments, each R^{s1} is independently R as described herein and is not –H. In some embodiments, at least one R^{s1} is optionally substituted C_{1-10} aliphatic. In some embodiments, at least one R^{s1} is optionally substituted C_{1-10} alkyl. In some embodiments, at least one R^{s1} is methyl. In some embodiments, at least one R^{s1} is optionally substituted phenyl. In some embodiments, at least one R^{s1} is phenyl. In some embodiments, each R^{s1} is independently an optionally substituted group selected from C_{1-10} aliphatic and 6-10 membered aryl. In some embodiments, each R^{s1} is independently an optionally substituted group selected from C_{1-10} alkyl and 6-10 membered aryl. In some embodiments, each R^{s1} is independently an optionally substituted group selected from C_{1-6} alkyl and 6-10 phenyl. In some embodiments, R^{s1} is $-SiPh_2Me$.

R^{sl}

[00171] As defined herein, R^{sl} is R^s as described herein. In some embodiments, R^{sl} is R as described herein. In some embodiments, R^{sl} is –H. In some embodiments, R^{sl} is not –H. In some embodiments, R^{sl} is C_{1-6} aliphatic. In some embodiments, R^{sl} is C_{1-6} alkyl. In some embodiments, R^{sl} is optionally substituted 6-10 membered aryl. In some embodiments, R^{sl} is optionally substituted phenyl. In some embodiments, R^{sl} is phenyl. In some embodiments, R^{sl} is $-CH_2-Si(R^{s1})_3$ wherein each R^{s1} is

independently R but is not −H. In some embodiments, each R^{s11} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, R^{s1} is $-CH_2-SiMePh_2$. In some embodiments, R^{s1} is $-CH_2-S(O)_2R^{s11}$, wherein R^{s11} is independently R but is not −H. In some embodiments, R^{s11} is an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, R^{s11} is optionally substituted phenyl. In some embodiments, R^{s11} is phenyl. In some embodiments, R^{s1} is $-CH_2-S(O)_2Ph$. In some embodiments, R^{s11} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{s11} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{s11} is t-butyl.

[00172] In some embodiments, R^{s1} and R^{s2} are the same. In some embodiments, R^{s1} and R^{s2} are different. In some embodiments, R^{s1} is not −H and R^{s2} is −H. In some embodiments, R^{s1} is −H and R^{s2} is not −H.

R^{s2}

[00173] As defined herein, R^{s2} is R^s as described herein. In some embodiments, R^{s2} is R as described herein. In some embodiments, R^{s2} is −H. In some embodiments, R^{s2} is not −H. In some embodiments, R^{s2} is C_{1-6} aliphatic. In some embodiments, R^{s2} is C_{1-6} alkyl. In some embodiments, R^{s2} is optionally substituted 6-10 membered aryl. In some embodiments, R^{s2} is optionally substituted phenyl. In some embodiments, R^{s2} is phenyl. In some embodiments, R^{s2} is $-CH_2-Si(R^{s11})_3$ wherein each R^{s11} is independently R but is not −H. In some embodiments, each R^{s11} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, R^{s2} is $-CH_2-SiMePh_2$. In some embodiments, R^{s2} is $-CH_2-S(O)_2R^{s11}$, wherein R^{s11} is independently R but is not −H. In some embodiments, R^{s11} is an optionally substituted group selected from C_{1-6} aliphatic and phenyl. In some embodiments, R^{s11} is optionally substituted phenyl. In some embodiments, R^{s11} is phenyl. In some embodiments, R^{s2} is $-CH_2-S(O)_2Ph$. In some embodiments, R^{s11} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{s11} is optionally substituted C_{1-6} alkyl. In some embodiments, R^{s11} is t-butyl.

R^{s11}

[00174] As used herein, R^{s11} is R' as described herein. For example, in some embodiments, R' is R as described herein. In some embodiments, R' is −C(O)R wherein R is as described herein. In some embodiments, R' is $-CO_2R$ wherein R is as described herein. In some embodiments, R' is $-S(O)_2R$ wherein R is as described herein. R^{s11} is −H. In some embodiments, R^{s11} is not −H. In some embodiments, two or more R^{s11} on the same atom are taken together with their intervening atom(s) to form an optionally substituted 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. Certain embodiments of rings are described herein.

L^s

[00175] As used herein, L^s is L as described herein. For example, in some embodiments, L is a covalent bond. In some embodiments, L is optionally substituted $-CH_2-$. In some embodiments, L is

$-CH_2-$. In some embodiments, L is monosubstituted $-CH_2-$.

L

[00176] Certain embodiments for L are described below. Various variables, e.g., L^s, can be L, and embodiments for L can also be applied to such variables that can be L.

[00177] In some embodiments, L is a covalent bond. In some embodiments, L is a bivalent, optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) aliphatic group wherein one or more methylene units of L are optionally and independently replaced by –Cy–, –O–, –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)–, $-S(O)_2-$, $-S(O)_2N(R')-$, –SC(O)–, or –C(O)O–. In some embodiments, L is a bivalent, optionally substituted C_{1-6} aliphatic group wherein one or more methylene units of L are optionally and independently replaced by –Cy–, –O–, –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)–, $-S(O)_2-$, $-S(O)_2N(R')-$, –SC(O)–, or –C(O)O–. In some embodiments, L is a bivalent, optionally substituted C_{1-5} aliphatic group wherein one or more methylene units of L are optionally and independently replaced by –Cy–, –O–, –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)–, $-S(O)_2-$, $-S(O)_2N(R')-$, –SC(O)–, or –C(O)O–. In some embodiments, each methylene unit are replaced. In some embodiments, at least one methylene unit is not replaced. In some embodiments, L comprises at least one chain carbon atom. In some embodiments, L is –O–. In some embodiments, L is –S–. In some embodiments, L is –N(R')–. In some embodiments, L is –C(O)–.

[00178] In some embodiments, no methylene unit is replaced. In some embodiments, L is a bivalent, optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) aliphatic group. In some embodiments, L is optionally substituted C_{1-6} aliphatic group. In some embodiments, L is bivalent, optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) alkylene. In some embodiments, L is optionally substituted C_{1-6} alkylene. In some embodiments, L is linear. In some embodiments, L is branched. In some embodiments, L is substituted. In some embodiments, L is not substituted.

[00179] In some embodiments, L is a bivalent, optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) heteroaliphatic group having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, wherein one or more methylene units of L are optionally and independently replaced by –Cy–, –O–, –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)–, $-S(O)_2-$, $-S(O)_2N(R')-$, –SC(O)–, or –C(O)O–. In some embodiments, L is a bivalent, optionally substituted C_{1-6} heteroaliphatic group having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, wherein one or more methylene units of L are optionally and independently replaced by –Cy–, –O–, –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')−, −SC(O)−, or −C(O)O−. In some embodiments, L is linear. In some embodiments, L is branched. In some embodiments, L is substituted. In some embodiments, L is not substituted.

[00180] In some embodiments, a methylene unit is replaced by −Cy− as described herein.

Cy

[00181] As used herein, −Cy− is an optionally substituted bivalent 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 3-15, 3-14, 3-10, 5-10, 3-7 and 3-6) membered ring having 0-10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 0-5, and 1-5) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen and sulfur. In some embodiments, −Cy− is an optionally substituted bivalent 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 3-15, 3-14, 3-10, 5-10, 3-7 and 3-6) membered ring having 0-10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 0-5, and 1-5) heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, −Cy− is monocyclic. In some embodiments, −Cy− is bicyclic. In some embodiments, −Cy− is polycyclic. In some embodiments, each monocyclic ring unit is independently an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 3-8, 3-7, 3-6 and 5-8) membered ring having 0-5 (e.g., 1, 2, 3, 4, 5, 1-5, 1-4 and 1-2) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur and 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-5 and 1-4) carbon atoms. In some embodiments, a monocyclic ring unit is an optionally substituted saturated ring. In some embodiments, a monocyclic ring unit is an optionally substituted partially unsaturated ring. In some embodiments, a monocyclic ring unit is an optionally substituted aromatic ring. In some embodiments, a monocyclic ring unit is an optionally substituted phenyl ring. In some embodiments, a monocyclic ring unit is an optionally substituted 5-membered heteroaromatic having 1-4 (e.g., 1, 2, 3, 4, 1-3 and 1-2) heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, a monocyclic ring unit is an optionally substituted 6-membered heteroaromatic having 1-4 (e.g., 1, 2, 3, 4, 1-3 and 1-2) heteroatoms independently selected from nitrogen, oxygen and sulfur. Each monocyclic ring unit is independently optionally substituted. In some embodiments, a monocyclic ring unit is unsaturated. In some embodiments, a monocyclic ring unit is saturated. In some embodiments, −Cy− is an optionally substituted saturated ring. In some embodiments, −Cy− is an optionally substituted partially unsaturated ring. In some embodiments, −Cy− is an optionally substituted aromatic ring.

[00182] In some embodiments, −Cy− is an optionally substituted bivalent 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, or 10) membered monocyclic cycloaliphatic ring. In some embodiments, −Cy− is an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, or 10) membered monocyclic cycloalkyl ring. In some embodiments, −Cy− is an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, or 10) membered

monocyclic heteroaliphatic ring having 1-5 heteroatoms. In some embodiments, –Cy– is an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, or 10) membered monocyclic heteroalkyl ring having 1-5 heteroatoms. In some embodiments, –Cy– is an optionally substituted bivalent 5-15 (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) membered bicyclic or polycyclic cycloaliphatic group. In some embodiments, –Cy– is an optionally substituted bivalent 5-15 (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) membered bicyclic or polycyclic cycloalkyl group. In some embodiments, –Cy– is an optionally substituted 5-15 (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) membered bicyclic or polycyclic heteroaliphatic ring having 1-5 heteroatoms. In some embodiments, –Cy– is an optionally substituted 5-15 (e.g., 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) membered bicyclic or polycyclic heterocyclyl ring having 1-5 heteroatoms. In some embodiments, a cycloaliphatic, cycloalkyl, heteroaliphatic or heteroalkyl ring is 3-membered. In some embodiments, it is 4-membered. In some embodiments, it is 5-membered. In some embodiments, it is 6-membered. In some embodiments, it is 7-membered. In some embodiments, it is 8-membered. In some embodiments, it is 9-membered. In some embodiments, it is 10-membered. In some embodiments, it is 11-membered. In some embodiments, it is 12-membered. In some embodiments, –Cy– is optionally substituted phenylene. In some embodiments, –Cy– is an optionally substituted bivalent 10-membered bicyclic aryl ring. In some embodiments, –Cy– is an optionally substituted 5-membered heteroaryl ring having 1-4 heteroatoms. In some embodiments, –Cy– is an optionally substituted 6-membered heteroaryl ring having 1-4 heteroatoms. In some embodiments, –Cy– is an optionally substituted 9-membered bicyclic heteroaryl ring having 1-5 heteroatoms. In some embodiments, –Cy– is an optionally substituted 10-membered bicyclic heteroaryl ring having 1-5 heteroatoms. In some embodiments, a heteroaliphatic, heterocyclyl or heteroaryl ring contains no more than 1 heteroatom. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen and sulfur.

[00183] In some embodiments, –Cy– is an optionally substituted 4-7 membered ring having 0-3 heteroatoms. In some embodiments, –Cy– is an optionally substituted phenyl ring. In some embodiments, an aryl ring is substituted. In some embodiments, it is substituted with one or more halogen. In some embodiments, it is substituted with one or more –F. In some embodiments, it is not substituted. In some embodiments, –Cy– is an optionally substituted 5-membered heteroaryl ring having 1-3 heteroatoms. In some embodiments, a heteroatom is nitrogen. In some embodiments, a heteroatom is oxygen. In some embodiments, a heteroatom is sulfur.

R'

[00184] Certain embodiments for R' are described below. Various variables, e.g., R^p, can be R', and embodiments for R' can also be applied to such variables that can be R'.

[00185] In some embodiments, R' is R as described herein. In some embodiments, R' is –H. In some embodiments, R' is not –H.

[00186] In some embodiments, R' is −C(O)R wherein R is as described herein. In some embodiments, R' is −C(O)OR wherein R is as described herein. In some embodiments, R' is $-S(O)_2R$ wherein R is as described herein. In some embodiments, as described herein, R is not −H.

[00187] In some embodiments, two or more R' are taken together with their intervening atom(s) to form an optionally substituted 3-20 (e.g., 3-15, 3-10, 3-6, 5-10, 5-6, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20) membered ring having 0-10 (e.g., 0, 1-10, 1-5, 1-4, 1-3, 1-2, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, two or more R' on the same atom are taken together with the atom to which they are attached to form an optionally substituted 3-20 (e.g., 3-15, 3-10, 3-6, 5-10, 5-6, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20) membered ring having 0-10 (e.g., 0, 1-10, 1-5, 1-4, 1-3, 1-2, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, two R' on the same atom are taken together with the atom to which they are attached to form an optionally substituted 3-20 (e.g., 3-15, 3-10, 3-6, 5-10, 5-6, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20) membered ring having 0-10 (e.g., 0, 1-10, 1-5, 1-4, 1-3, 1-2, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur.

[00188] In some embodiments, each R' is independently −R, −C(O)R, −C(O)OR, or $-S(O)_2R$, or two or more R' on the same atom are taken together with the atom to which they are attached to form an optionally substituted 3-20 membered ring having 0-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur.

[00189] In some embodiments, two R' are taken together with their intervening atom(s) to form a ring as described herein. In some embodiments, there is one intervening atom (the atom to which the two R' are attached to). In some embodiments, there are two intervening atoms. In some embodiments, there are three intervening atoms. In some embodiments, there are four intervening atoms. In some embodiments, the number of intervening atoms are no more than 4.

Ring

[00190] Compounds of the present disclosure may contain various rings. In some embodiments, a variable, e.g., R or a variable that can be R, can be of a ring as described herein. In some embodiments, two variables, e.g., two R' groups, may be taken together with their intervening atom(s) to form a ring as described herein. In some embodiments, a ring is monovalent. In some embodiments, a ring is bivalent. In some embodiments, a ring can be polyvalent. Rings are optionally substituted. In some embodiments, a ring is unsubstituted. In some embodiments, a ring is substituted. In some embodiments, no more than two groups (e.g., two R groups) are taken together with their intervening atom(s), the number of which is 1, 2, 3 or 4, to form a ring as described herein. In some embodiments, the number of intervening atom(s)

is 1. In some embodiments, the number of intervening atoms is 2. In some embodiments, the number of intervening atoms is 3. In some embodiments, the number of intervening atoms is 4. In some embodiments, the number of intervening atoms are no more than 4.

[00191] Certain embodiments and features of rings are described below as examples.

[00192] In some embodiments, a ring is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 3-15, 3-14, 3-10, 5-10, 3-7 and 3-6) membered ring having 0-10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 0-5 and 1-5) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen and sulfur. In some embodiments, a ring is an optionally substituted 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 3-15, 3-14, 3-10, 5-10, 3-7 and 3-6) membered ring having 0-10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 0-5 and 1-5) heteroatoms independently selected from oxygen, nitrogen, and sulfur. In some embodiments, a ring is monocyclic. In some embodiments, a ring is bicyclic. In some embodiments, a ring is polycyclic.

[00193] In some embodiments, each monocyclic ring unit is independently an optionally substituted 3-10 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 3-8, 3-7, 3-6 and 5-8) membered ring having 0-5 (e.g., 1, 2, 3, 4, 5, 1-5, 1-4 and 1-2) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur and 1-10 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-5 and 1-4) carbon atoms. In some embodiments, a monocyclic ring unit is an optionally substituted saturated ring. In some embodiments, a monocyclic ring unit is an optionally substituted partially unsaturated ring. In some embodiments, a monocyclic ring unit is an optionally substituted aromatic ring. In some embodiments, a monocyclic ring unit is an optionally substituted phenyl ring. In some embodiments, a monocyclic ring unit is an optionally substituted 5-membered heteroaromatic having 1-4 (e.g., 1, 2, 3, 4, 1-3 and 1-2) heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, a monocyclic ring unit is an optionally substituted 6-membered heteroaromatic having 1-4 (e.g., 1, 2, 3, 4, 1-3 and 1-2) heteroatoms independently selected from nitrogen, oxygen and sulfur. Each monocyclic ring unit is independently optionally substituted. In some embodiments, a monocyclic ring unit is unsaturated. In some embodiments, a monocyclic ring unit is saturated.

[00194] In some embodiments, a ring is an optionally substituted saturated ring. In some embodiments, a ring is an optionally substituted partially unsaturated ring. In some embodiments, a ring is an optionally substituted aromatic ring.

[00195] In some embodiments, a ring is an optionally substituted 3-10 membered, monocyclic, bicyclic or polycyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, a ring is 3-9, 3-8, 3-7, 3-6, 4-10, 4-9, 4-8, 4-7, 4-6, 5-10, 5-9, 5-8, 5-7, 5-6, or 3, 4, 5, 6, 7, 8, 9, or 10-membered. In some embodiments, a ring is 3-9 membered. In some

embodiments, a ring is 3-7 membered. In some embodiments, a ring is 4-10 membered. In some embodiments, a ring is 4-7 membered. In some embodiments, a ring is 5-10 membered. In some embodiments, a ring is 5-7 membered. In some embodiments, a ring is 3-membered. In some embodiments, a ring is 4-membered. In some embodiments, a ring is 5-membered. In some embodiments, a ring is 6-membered. In some embodiments, a ring is 7-membered. In some embodiments, a ring is 8-membered. In some embodiments, a ring is 9-membered. In some embodiments, a ring is 10-membered. In some embodiments, a ring is monocyclic. In some embodiments, a ring is bicyclic. In some embodiments, a ring is polycyclic. In some embodiments, a ring has no heteroatoms. In some embodiments, a ring has 1-6, e.g., 1-5, 1-3, or 1, 2, 3, 4, 5, or 6 heteroatoms. In some embodiments, a ring formed by two or more groups taken together with their intervening atom(s) has no heteroatoms in addition to those in the intervening atom(s). In some embodiments, a ring formed by two or more groups taken together with their intervening atom(s) has 1-6, e.g., 1-5, 1-3, or 1, 2, 3, 4, 5, or 6 heteroatoms in addition to those in the intervening atom(s). In some embodiments, a ring is saturated. In some embodiments, a ring is partially unsaturated. In some embodiments, a ring comprises one or more aromatic ring. In some embodiments, a ring is bicyclic or polycyclic, and each monocyclic ring unit is independently 3-10 (e.g., 3-9, 3-8, 3-7, 3-6, 4-10, 4-9, 4-8, 4-7, 4-6, 5-10, 5-9, 5-8, 5-7, 5-6, or 3, 4, 5, 6, 7, 8, 9, or 10) membered, saturated, partially unsaturated or aromatic and having 0-5 (e.g., 0, 1-5, 1-3, 1, 2, 3, 4, or 5) heteroatoms. In some embodiments, each heteroatom is independently selected from nitrogen, oxygen and sulfur. In some embodiments, a monocyclic ring unit is saturated. In some embodiments, a monocyclic ring unit is partially unsaturated. In some embodiments, a monocyclic ring unit is aromatic. In some embodiments, a monocyclic ring unit is heteroaromatic. Those skilled in the art appreciate that intervening atom(s), e.g., of groups taken together to form a ring, are typically atoms on the shortest path connecting such groups if multiple paths exist. In some embodiments, the number of intervening atom(s) are about or no more than about 1, 2, 3, 4 or 5.

[00196] In some embodiments, a ring has one or more heteroatoms. In some embodiments, a ring comprises a nitrogen atom. In some embodiments, a ring comprises an oxygen atom. In some embodiments, a ring comprises a sulfur atom.

R

[00197] Various variables in the present disclosure can independently be R. Certain embodiments for R are described below as examples. Those skilled in the art reading the present disclosure appreciate that embodiments that are described for a variable that can be R and fall within the definition of R can be embodiments for R as well. Those skilled in the art reading the present disclosure further appreciate that embodiments for R, e.g., those described for R and those described for a variable that can be R and within

the definition of R, can be embodiments for a variable that can be R.

[00198] In some embodiments, each R is independently –H, or an optionally substituted group selected from C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) aliphatic, C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) heteroaliphatic having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-14} aryl, C_{6-14} arylaliphatic, C_{6-14} arylheteroaliphatic having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, 5-14 (e.g., 5, 6, 9, 10 and 14) membered heteroaryl having 1-6 (e.g., 1-5, 1-4, 1, 2, 3, 4, 5 and 6) heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, and 3-15 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 3-10, 3-7, 4-10 and 4-6) membered heterocyclyl having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) 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 R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-20 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 3-15, 3-14, 3-10, 5-10, 3-7 and 3-6) membered ring having 0-10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1-10, 0-5 and 1-5) heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, wherein the number of intervening atom(s) of the two R groups taken together to form a covalent bond or ring is about or no more than about 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5). Various features of rings are described herein.

[00199] two R groups are optionally and independently taken together to form a covalent bond; or:

[00200] two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

[00201] In some embodiments, R is –H. In some embodiments, R is not –H. In some embodiments, R is optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) aliphatic. In some embodiments, R is optionally substituted C_{1-8} aliphatic. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) alkyl. In some embodiments, R is optionally substituted C_{1-8} alkyl. In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is optionally substituted $-CH_2-C_{3-6}$ cycloaliphatic. In some embodiments, R is optionally substituted $-CH_2-C_{3-6}$ cycloaliphatic. In some embodiments, R is optionally substituted $-CH_2-C_{3-6}$ cycloalkyl. In some embodiments, R is methyl. In some embodiments, R is ethyl. In some embodiments, R is isopropyl. In some embodiments, R is $-CF_3$. In some embodiments, R is $-CH_2CF_3$. In some embodiments, R is butyl. In some embodiments, R is t-butyl.

[00202] In some embodiments, R is optionally substituted 3-10 membered (e.g., 3-9, 3-8, 3-7, 3-6, 5-7, 4, 5, 6, 7, 8, 9 and 10) cycloaliphatic. In some embodiments, R is optionally substituted C_{3-10} cycloalkyl. In some embodiments, R is optionally substituted cyclopropyl. In some embodiments, R is optionally substituted cyclobutyl. In some embodiments, R is optionally substituted cyclopentyl. In some embodiments, R is optionally substituted cyclohexyl.

[00203] In some embodiments, R is optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) heteroaliphatic having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, R is optionally substituted C_{1-6} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5 and C_6) heteroaliphatic having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, R is optionally substituted C_{1-10} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9 and C_{10}) heteroaliphatic having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from oxygen, nitrogen and sulfur. In some embodiments, R is optionally substituted C_{1-6} (e.g., C_{1-6}, C_{2-8}, C_1, C_2, C_3, C_4, C_5 and C_6) heteroaliphatic having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from oxygen, nitrogen and sulfur. In some embodiments, R is optionally substituted C_{1-6} heteroaliphatic having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur C_{1-6} heteroaliphatic having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted C_{1-6} heteroaliphatic having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur C_{1-6} heteroaliphatic having 1 heteroatom independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is heteroalkyl.

[00204] In some embodiments, R is optionally substituted 3-15 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 3-10, 3-7, 4-10 and 4-6) membered heterocyclic ring having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, R is optionally substituted 3-15 (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 3-10, 3-7, 4-10 and 4-6) membered heterocyclic ring having 1-5 (e.g., 1-4, 1-3, 1-2, 1, 2, 3, 4 and 5) heteroatoms independently selected from oxygen, nitrogen and sulfur. In some embodiments, R is optionally substituted 3-10 (e.g., 3-9, 3-8, 3-7, 3-6, 5-7, 4, 5, 6, 7, 8, 9 and 10) membered heterocyclyl having 1-4 (e.g., 1-2, 1, 2, 3 and 4) heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 3-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 3-membered heterocyclyl having one heteroatom independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 4-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally

substituted 5-membered heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 6-membered heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 7-membered heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 8-membered heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 9-membered heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 10-membered heterocyclyl having 1-3 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, there is one carbon atom in a heterocyclyl ring. In some embodiments, there are two or more (e.g., 2-14, 2-9, 2-6, 2-4, 3-10, 3-5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14) carbon atoms in a heterocyclyl ring.

[00205] In some embodiments, R is optionally substituted phenyl. In some embodiments, R is phenyl. In some embodiments, R is optionally substituted naphthyl. In some embodiments, R is optionally substituted 1-naphthyl. In some embodiments, R is optionally substituted 2-naphthyl. In some embodiments, R is naphthyl.

[00206] In some embodiments, R is optionally substituted 5-14 (e.g., 5, 6, 9, 10 and 14) membered heteroaryl having 1-6 (e.g., 1-5, 1-4, 1, 2, 3, 4, 5 and 6) heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur. In some embodiments, R is optionally substituted 5-14 (e.g., 5, 6, 9, 10 and 14) membered heteroaryl having 1-6 (e.g., 1-5, 1-4, 1, 2, 3, 4, 5 and 6) heteroatoms independently selected from oxygen, nitrogen and sulfur. In some embodiments, R is optionally substituted 5-10 (e.g., 5, 6, 9 and 10) membered heteroaryl having 1-6 (e.g., 1-5, 1-4, 1, 2, 3, 4, 5 and 6) heteroatoms independently selected from oxygen, nitrogen and sulfur. In some embodiments, R is optionally substituted 5-10 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, a heteroaryl ring is monocyclic and is 5-membered. In some embodiments, a heteroaryl ring is monocyclic and is 6-membered. In some embodiments, a heteroaryl ring is bicyclic and is 9-membered. In some embodiments, a heteroaryl ring is bicyclic and is 10-membered. In some embodiments, a heteroaryl ring is tricyclic and is 14-membered. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 5-membered heteroaryl having 1 heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted 6-membered heteroaryl having 1 heteroatom selected from nitrogen, oxygen and sulfur. In some

embodiments, R is optionally substituted bicyclic 8-10 membered aromatic ring having 1-6 heteroatoms nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted bicyclic 9-membered aromatic ring having 1-6 heteroatoms nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted bicyclic 10-membered aromatic ring having 1-6 heteroatoms nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted bicyclic 9-membered aromatic ring having 1 heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, R is optionally substituted bicyclic 10-membered aromatic ring having 1 heteroatom nitrogen, oxygen and sulfur. In some embodiments, at least one heteroatom is nitrogen. In some embodiments, at least one heteroatom is oxygen. In some embodiments, at least one heteroatom is sulfur. In some embodiments, each heteroatom is the same. In some embodiments, at least one heteroatom is different from another heteroatom.

[00207] As described herein, various groups may be optionally substituted. Substituents are routinely utilized in chemistry including in development of various therapeutics. Many substituents can be utilized in accordance with the present disclosure. In some embodiments, an optionally substituted group is unsubstituted. In some embodiments, an optionally substituted group is substituted. Substituents are preferably those that result in the formation of compounds for a desired property, activity, use, etc., as described herein. In some embodiments, compounds are stable for therapeutic use as described herein. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a substituent is a hydrocarbon group. In some embodiments, a substituent comprises a heteroatom. In some embodiments, a substituent comprises multiple heteroatoms. In some embodiments, each atom in a substituent is independently selected from hydrogen, carbon, halogen, nitrogen, oxygen, sulfur, phosphorus and silicon. In some embodiments, each atom in a substituent is independently selected from hydrogen, carbon, halogen, nitrogen, oxygen, and sulfur. In some embodiments, each atom in a substituent is independently selected from hydrogen, carbon, fluorine, chlorine, bromine, iodine, nitrogen, oxygen, and sulfur. In some embodiments, the total number of carbon and non-halogen heteroatom(s) in a substituent is about or no more than about 1; in some embodiments, it is no more than about 2; in some embodiments, it is no more than about 3; in some embodiments, it is no more than about 4; in some embodiments, it is no more than about 5; in some embodiments, it is no more than about 6; in some embodiments, it is no more than about 7; in some embodiments, it is no more than about 8; in some embodiments, it is no more than about 9; in some embodiments, it is no more than about 10; in some embodiments, it is no more than about 11; in some embodiments, it is no more than about 12; in some embodiments, it is no more than about 13; in some embodiments, it is no more than about 14; in some embodiments, it is no more than about 15; in some embodiments, it is no more than about 20. In some embodiments, the total number of carbon and non-

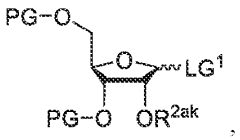
halogen heteroatom(s) in each substituent is independently no more than about 20. In some embodiments, the total number of carbon and non-halogen heteroatom(s) in each substituent is independently no more than about 15. In some embodiments, the total number of carbon and non-halogen heteroatom(s) in each substituent is independently no more than about 10. In some embodiments, the total number of carbon and non-halogen heteroatom(s) in each substituent is independently no more than about 6.

[00208] In some embodiments, a compound, e.g., sugar, nucleoside, nucleotide, phosphoramidite and oligonucleotide, comprises 5'-modification. In some embodiments, a compound is a compound of formula P-1, P-2, P-3, P-4 or P-5, but one or both of the 5'-H are substituted as described herein. In some embodiments, both are substituted. In some embodiments, only one is substituted. In some embodiments, a 5'-substituent is selected from halogen, C_{1-4} alkyl and $-O-(C_{1-4}$ alkyl). In some embodiments, each 5'-substituent is independently selected from halogen, C_{1-4} alkyl and $-O-(C_{1-4}$ alkyl). In some embodiments, each 5'-substituent is independently C_{1-4} alkyl. In some embodiments, a 5'-substituent is methyl. In some embodiments, each 5'-substituent is methyl. In some embodiments, the present disclosure provides technologies for preparing compounds comprising 5'-modifications. In some embodiments, methods are similar or the same as the corresponding methods for compounds of formula P-2, P-3, P-4 or P-5 or salts thereof, except that the corresponding compounds with 5'-modifications are utilized.

[00209] Among other things, the present disclosure provides methods for preparing various compounds, e.g., those of formula P-2, P-3, P-4, P-5, PMT, etc. or salts thereof. Certain methods are described below as examples.

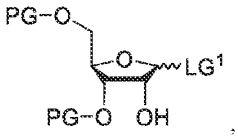
Preparation of Compounds of Formula P-2

[00210] In some embodiments, the present disclosure provides technologies for preparation 2'-OR^{2ak} modified sugars. In some embodiments, provided technologies comprise alkylating sugars comprising 2'-OH. In some embodiments, provided technologies comprise contacting a sugar comprising 2'-OH with an alkylating agent, wherein the other hydroxy group(s) of the sugar are protected (e.g., by PG as described herein). In some embodiments, the present disclosure provides a method for preparing a compound of formula P-2:



P-2

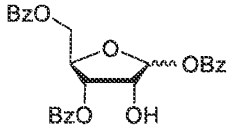
or a salt thereof, comprising reacting a compound of formula P-1:



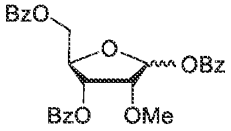
P-1

or a salt thereof with an alkylating agent, wherein each variable is independently as described herein.

[00211] As described herein, provided methods are useful for introducing various 2'-modifications. For example, in some embodiments, a 2'-modification is 2'-OR^{2ak} wherein R^{2ak} is as described herein. In some embodiments, R^{2ak} is methyl. In some embodiments, PG is a hydroxy protecting group. Various such protecting group are available and can be utilized in accordance with the present disclosure. In some embodiments, PG is –C(O)R wherein R is as described herein. For example, in some embodiments, PG is Bz. In some embodiments, LG^1 is a leaving group, e.g., –Cl, –Br, –I and –OC(O)R. Those skilled in the art reading the present disclosure appreciate and many leaving groups can be utilized in accordance with the present disclosure. In some embodiments, a compound of formula P-1 is



. In some embodiments, a compound of formula P-2 is



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[00212] Various alkylating agents can be utilized in accordance with the present disclosure to incorporate R^{2ak} which is optionally substituted C_{1-6} aliphatic as described herein. For example, in some embodiments, an alkylating agent is a halide. In some embodiments, an alkylating agent is a compound having the structure of R^{2ak}–LG^A or a salt thereof, wherein LG^A is a leaving group such as –Cl, –Br or –I, and R^{2ak} is as described herein. In some embodiments, an alkylating agent is $(R^{2ak})_3OY$ wherein Y is a counterion and each R^{2ak} is independently as described herein. In some embodiments, each R^{2ak} is the same. Various counterions are reported and can be utilized in accordance with the present disclosure. For example, in some embodiments, Y is BF_4^-.

[00213] In some embodiments, R^{2ak} is methyl. In some embodiments, an alkylating agent is methylating agent. In some embodiments, a methylating agent is selected from CH_3I, dimethyl sulfate, dimethyl carbonate, $N(CH_3)_4X$, CH_3OTf, diazomethane, methyl fluorosulfonate, and $(CH_3)_3OY$, wherein X and Y are each independently a suitable counterion. In some embodiments, methylation agent is selected from CH_3I, dimethyl sulfate, CH_3OTf, methyl fluorosulfonate, and $(CH_3)_3OY$, wherein X and Y are each independently a counterion. In some embodiments, a methylation agent is $(CH_3)_3OY$. In some

embodiments, it is $(CH_3)_3OBF_4$. Those skilled in the art reading the present disclosure appreciate that similar alkylating agents can be utilized to incorporate other R^{2ak} as methylating agents to incorporate methyl.

[00214] In some embodiments, reacting a compound of formula P-1 or a salt thereof and an alkylating agent is performed in the presence of a base, for example, when the reacting can generate an acid or a compound in the reaction system is acidic. In some embodiments, a base is non-nucleophilic or less nucleophilic, and/or more sterically hindered, than 2'-OH in a compound of formula P-1 or a salt thereof, so that an alkylating agent selectively reacts with the 2'-OH instead of a base. For example, in some embodiments, a base is a proton scavenger such as 1,8-bis(dimethylamino)naphthalene.

[00215] Various solvent systems can be assessed and utilized in accordance with the present disclosure. In some embodiments, a method is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%. In some embodiments, it is v%. In some embodiments, it is wt%. In some embodiments, the percentage of a solvent compound in a solvent system is about or at least about 10%. In some embodiments, it is about or at least about 20%. In some embodiments, it is about or at least about 30%. In some embodiments, it is about or at least about 40%. In some embodiments, it is about or at least about 50%. In some embodiments, it is about or at least about 60%. In some embodiments, it is about or at least about 70%. In some embodiments, it is about or at least about 80%. In some embodiments, it is about or at least about 90%. In some embodiments, it is about or at least about 95%. In some embodiments, the percentage is about 100%. In some embodiments, a solvent system consists of a single solvent compound.

[00216] In some embodiments, a solvent compound has a polarity index lower than dimethylformamide (about 6.4).

[00217] In some embodiments, a solvent compound is a halogenated solvent. In some embodiments, a solvent compound is C_{1-3} alkane substituted with halogen. In some embodiments, a solvent compound is C_{1-3} alkane substituted with two or more halogen. In some embodiments, a solvent compound is C_{1-3} alkane substituted with two or more −Cl. In some embodiments, a solvent compound is dichloromethane. In some embodiments, a solvent compound is 1,2-dichloroethane (DCE).

[00218] In some embodiments, a solvent compound is a compound has the structure of R^a-O-R^b, wherein R^a and R^b are each independently selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic, or R^a and R^b are taken together with the oxygen atom to which they are attached to form a 3-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen. In some embodiments, a solvent compound is R^a−C(O)−OR^b wherein each of R^a and R^b is independently as described herein.

[00219] In some embodiments, R^a is C_{1-6} aliphatic. In some embodiments, R^b is C_{1-6} alkyl. In some embodiments, each R^a and R^b is independently C_{1-6} alkyl. In some embodiments, R^a and R^b are taken together with the oxygen atom to which they are attached to form a 4-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen. In some embodiments, R^a and R^b are taken together with the oxygen atom to which they are attached to form a 6- membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

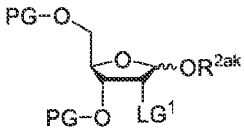
[00220] In some embodiments, a solvent compound is 1,4-dioxne. In some embodiments, a solvent compound is EtOAc.

[00221] A solvent compound is typically a liquid under reaction conditions. In some embodiments, a solvent compound is a liquid at about 298 K and about 1 atm.

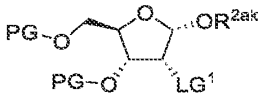
[00222] In some embodiments, the method is carried out in dichloromethane. In some embodiments, wherein the method is carried out in 1,2-dichloroethane (DCE). In some embodiments, the method is carried out in EtOAc. In some embodiments, the method is carried out in 1,4-dioxane.

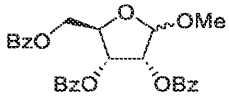
[00223] As demonstrated herein, in some embodiments, under certain conditions certain solvent systems, e.g., 1,4-dioxane (which may be referred to as dioxane) and EtOAc, provide better yields and/or crude purities compared to certain other solvent systems, e.g., DMF, MeCN, etc.

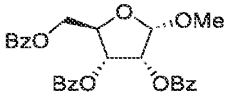
[00224] In some embodiments, a method for preparing a compound of formula P-2 or a salt thereof may produce a second product. For example, in some embodiments, a second product is a compound of formula P-2':



P-2'

or a salt thereof, wherein each variable is independently as described herein. In some embodiments, a compound of formula P-2' has the structure of 

. In some embodiments, a compound of formula P-2' is 

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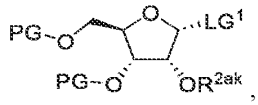
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[00225] In some embodiments, a method selectively produces a compound of formula P-2 or a salt

thereof over a compound of formula P-2' or a salt thereof. In some embodiments, the ratio of a compound of formula P-2 or a salt thereof over a compound of formula P-2' or a salt thereof is about or at least about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100. In some embodiments, it is at about or at least about 1.5. In some embodiments, it is at about or at least about 5. In some embodiments, it is at about or at least about 10. In some embodiments, it is at about or at least about 15. In some embodiments, it is at about or at least about 20. In some embodiments, it is at about or at least about 50. In some embodiments, it is at about or at least about 100. In some embodiments, a compound of formula P-2' or a salt thereof is not observed when assessed. For example, in some embodiments, a compound of formula P-2' or a salt thereof is not detected when assessed using HPLC using UV detection.

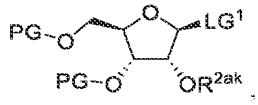
[00226] In some embodiments, the present disclosure provides a composition comprising a compound of formula P-2 or a salt thereof, a compound of formula P-2' or a salt thereof, and optionally a compound of formula P-1 or a salt thereof. In some embodiments, the ratio of a compound of formula P-2 or a salt thereof over a compound of formula P-2' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100 as described herein.

[00227] In some embodiments, a method produces a compound of formula P-2 or a salt thereof, wherein the compound of formula P-2 or a salt thereof is a compound has the structure of formula P-2A:

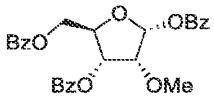


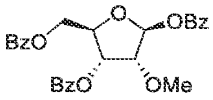
P-2A

or a salt thereof, wherein each variable is independently as described herein. In some embodiments, a method produces a compound of formula P-2 or a salt thereof, wherein the compound of formula P-2 or a salt thereof is a compound has the structure of formula P-2B:



P-2B

or a salt thereof, wherein each variable is independently as described herein. In some embodiments, a compound of P-2A is 

. In some embodiments, a compound of P-2B is 

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[00228] In some embodiments, a method selectively produces a compound of formula P-2A or a salt thereof over a compound of formula P-2B or a salt thereof. In some embodiments, the ratio of a compound of formula P-2A or a salt thereof over a compound of formula P-2B or a salt thereof is about or at least about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100. In some embodiments, it is at about or at least about 1.5. In some embodiments, it is at about or at least about 2. In some embodiments, it is at about or at least about 3. In some embodiments, it is at about or at least about 5. In some embodiments, it is at about or at least about 10. In some embodiments, it is at about or at least about 15. In some embodiments, it is at about or at least about 20. In some embodiments, it is at about or at least about 50. In some embodiments, it is at about or at least about 100. In some embodiments, a compound of formula P-2B or a salt thereof is not observed when assessed. For example, in some embodiments, a compound of formula P-2B or a salt thereof is not detected when assessed using HPLC using UV detection.

[00229] In some embodiments, the present disclosure provides a composition comprising a compound of formula P-2A or a salt thereof, a compound of formula P-2B or a salt thereof, and optionally a compound of formula P-1 or a salt thereof. In some embodiments, the ratio of a compound of formula P-2A or a salt thereof over a compound of formula P-2B or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100 as described herein.

[00230] Various temperatures can be utilized and assessed for provided methods in accordance with the present disclosure. In some embodiments, a reaction is performed at certain temperature or a range thereof. In some embodiments, temperature increases or decreases, typically within a range for a reaction or a method. For example, in some embodiments, for a method for preparing a compound of formula P-2 or a salt thereof, a reaction is performed at about 20-50 °C, e.g., about 20-40, 25-50, 25, 30, 33 and 35 °C. In some embodiments, a reaction, e.g., between a compound of formula P-1 or a salt thereof and an alkylating agent as described herein, is performed at about 20 °C. In some embodiments, it is performed at about 25 °C. In some embodiments, it is performed at about 30 °C. In some embodiments, it is performed at about 33 °C. In some embodiments, it is performed at about 35 °C.

[00231] Reactions may be performed for various periods of time, e.g., in view of conversion, yield, formation of by-product, efficiency, etc. For example, in some embodiments, reaction time for a method is about 1-24 hours. In some embodiments, a reaction time is about 5 hours. In some embodiments, it is about 6 hours. In some embodiments, it is about 10 hours. In some embodiments, it is about 12 hours.

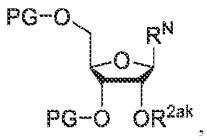
[00232] Among other things, it is observed that concentration of a compound, e.g., a compound of formula P-1 or a salt thereof, can impact reaction rate, conversion, yield, crude purity, formation of by-product, etc. In some embodiments, a concentration of a compound of formula P-1 or a salt thereof is about 1 gram per about 1-50 (e.g., about 1-40, 10-40, 10-30, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17,

18, 19, 20, 35, 30, 35, 40 and 55) mL solvent. In some embodiments, a concentration of a compound of formula P-1 or a salt thereof is about or at least about 1-2000 (e.g., about 5-2000, 10-2000, 50-2000, 10-1000, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 125, 150, 200, 250, 300, 400, 500, 600, 700, 800, 900, 1000, 1500 and 2000) mg/mL. In some embodiments, it is about 20 mg/mL. In some embodiments, it is about 25 mg/mL. In some embodiments, it is about 30 mg/mL. In some embodiments, it is about 50 mg/mL. In some embodiments, it is about 100 mg/mL. In some embodiments, it is about 1000 mg/mL. In some embodiments, a concentration of a compound of formula P-1 or a salt thereof is about or at least about 1-3000 (e.g., about 1-2500, 10-2000, 50-2000, 10-1000, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 125, 150, 200, 250, 300, 400, 500, 600, 700, 800, 900, 1000, 1500 and 2000) mM. In some embodiments, it is about $4 * 10^{-2}$ M. In some embodiments, it is about $5 * 10^{-2}$ M. In some embodiments, it is about $7 * 10^{-2}$ M. In some embodiments, it is about $10 * 10^{-2}$ M. In some embodiments, it is about 0.10-0.15 M. In some embodiments, it is about 0.2 M. In some embodiments, it is about 1 M. In some embodiments, it is about 2 M.

Preparation of Compounds of Formula P-3

[00233] In some embodiments, the present disclosure provides methods for preparing compounds comprising various 1'-groups. In some embodiments, a compound of P-2 or a salt thereof reacts with a nucleophile such that LG^1 is replaced with another moiety to provide a new compound. In some embodiments, a nucleophile comprises a nucleophilic atom, e.g., carbon, oxygen, nitrogen, and sulfur. In some embodiments, in a reaction a nucleophilic atom forms a bond with the carbon atom to which LG^1 is attached and LG^1 is removed. For example, in some embodiments, a nucleophilic is a nitrogen atom. In some embodiments, a nucleophilic compound reacts a compound of formula P-2 or a salt thereof to form a nucleoside or a salt thereof. In some embodiments, the present disclosure provides methods for preparing nucleosides comprising 2'-OR^{2ak} modifications. In some embodiments, nucleosides comprises non-natural nucleobases. In some embodiments, nucleobases of nucleosides are not A, T, C, G or U, or protected forms thereof.

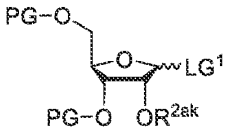
[00234] For example, in some embodiments, the present disclosure provides a method for preparing a compound of formula P-3:



P-3

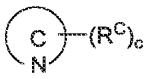
or a salt thereof,

comprising reacting a compound of formula P-2:



P-2

or a salt thereof with a compound of formula P-A:



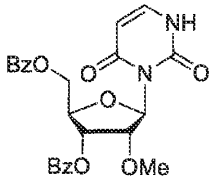
P-A

or a salt thereof, wherein each variable is independently as described herein.

[00235] In some embodiments, a compound of formula P-3 is a protected nucleoside, e.g., the 3'- and 5'-OH protected with Bz, and the nucleobase optionally protected for oligonucleotide synthesis.

[00236] In some embodiments, LG^1 is a leaving group as described herein. In some embodiments, LG^1 is $-OC(O)R$ wherein R is as described herein. In some embodiments, LG^1 is $-OBz$. In some embodiments, LG^1 is $-OR$ wherein R is as described herein and is not $-H$. In some embodiments, LG^1 is $-OR$ wherein R is optionally substituted C_{1-6} aliphatic. In some embodiments, LG^1 is $-OMe$.

[00237] In some embodiments, a compound of P-A is an optionally substituted or protected nucleobase. In some embodiments, a nucleobase is a natural nucleobase. In some embodiments, a nucleobase is other than A, T, C, G or U. In some embodiments, a compound of P-A is an optionally protected nucleobase which is other than A, T, C, G, or U. In some embodiments, protection is suitable of oligonucleotide synthesis. Various protecting technologies for oligonucleotide synthesis are available (e.g., see WO 2021/071858, WO 2022/099159, WO 2023/049475 and WO 2023/201095, the entirety of each of which is incorporated herein by reference) and can be utilized in accordance with the present disclosure.

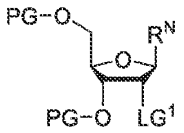
[00238] In some embodiments, a compound of formula P-3 is  .

[00239] Various solvent systems can be assessed and utilized in accordance with the present disclosure. In some embodiments, a method is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%. In some embodiments, it is v%. In some embodiments, it is wt%. In some embodiments, the percentage of a solvent compound in a solvent system is about or at least about 10%. In some embodiments, it is about or

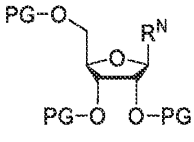
at least about 20%. In some embodiments, it is about or at least about 30%. In some embodiments, it is about or at least about 40%. In some embodiments, it is about or at least about 50%. In some embodiments, it is about or at least about 60%. In some embodiments, it is about or at least about 70%. In some embodiments, it is about or at least about 80%. In some embodiments, it is about or at least about 90%. In some embodiments, it is about or at least about 95%. In some embodiments, the percentage is about 100%. In some embodiments, a solvent system consists of a single solvent compound.

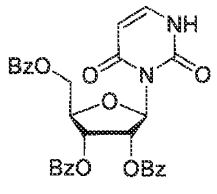
[00240] In some embodiments, a solvent compound is R^a–C(O)–OR^b wherein each of R^a and R^b is independently as described herein. In some embodiments, R^a is C_{1-6} aliphatic. In some embodiments, R^b is C_{1-6} alkyl. In some embodiments, each R^a and R^b is independently C_{1-6} alkyl. In some embodiments, R^a is methyl. In some embodiments, R^b is methyl. In some embodiments, R^b is ethyl. In some embodiments, a solvent compound is EtOAc. In some embodiments, a method is carried out in EtOAc.

[00241] In some embodiments, a method for preparing a compound of formula P-3 or a salt thereof may produce one or more additional products. For example, in some embodiments, an additional product is a compound of formula P-3':

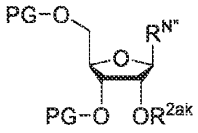


P-3'

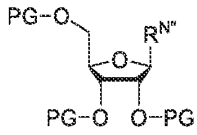
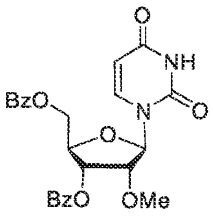
or a salt thereof, wherein each variable is independently as described herein. In some embodiments, an additional product is a compound having the structure of 

or a slat thereof. In some embodiments, a compound of formula P-3' has the structure of 

. In some embodiments, an additional product is a compound of formula P-3'':



P-3''

or a salt thereof, wherein $R^{N"}$ is R^N but is different from R^N in a product of formula P-3 or a salt thereof, and each other variable is independently as described herein. In some embodiments, an additional product is a compound having the structure of  wherein each variable is independently as described herein. In some embodiments, a compound of formula P-3" has the structure of .

[00242] In some embodiments, the present disclosure provides a composition comprising a compound of formula P-3 or a salt thereof (may be referred to as compound 3C), and a compound of formula P-3' or a salt thereof (may be referred to as compound 3D) or a compound of formula P-3" or a salt thereof (may be referred to as compound 3E). In some embodiments, a composition comprises compound 3C and compound 3D. In some embodiments, a composition comprises compound 3C and compound 3E. In some embodiments, a composition comprises compound 3C, compound 3D and compound 3E.

[00243] In some embodiments, a method selectively produces a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof. In some embodiments, the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100. In some embodiments, it is at about or at least about 5. In some embodiments, it is at about or at least about 10. In some embodiments, it is at about or at least about 15. In some embodiments, it is at about or at least about 20. In some embodiments, it is at about or at least about 50. In some embodiments, it is at about or at least about 100. In some embodiments, a compound of formula P-3' or a salt thereof is not observed when assessed. For example, in some embodiments, a compound of formula P-3' or a salt thereof is not detected when assessed using HPLC using UV detection.

[00244] In some embodiments, a method selectively produces a compound of formula P-3 or a salt thereof over a compound of formula P-3" or a salt thereof. In some embodiments, the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3" or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100. In some embodiments, it is at about or at least about 5. In some embodiments, it is at about or at least about 10. In some embodiments, it is at about or at least about 15. In some embodiments, it is at about or at least about 20.

In some embodiments, it is at about or at least about 50. In some embodiments, it is at about or at least about 100. In some embodiments, a compound of formula P-3" or a salt thereof is not observed when assessed. For example, in some embodiments, a compound of formula P-3" or a salt thereof is not detected when assessed using HPLC using UV detection.

[00245] In some embodiments, a method selectively produces a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof as described herein, and selectively produces a compound of formula P-3 or a salt thereof over a compound of formula P-3" or a salt thereof.

[00246] In some embodiments, the present disclosure provides a composition comprising a compound of formula P-3 or a salt thereof, and a compound of formula P-3' or a salt thereof or a compound of formula P-3" or a salt thereof. In some embodiments, the present disclosure provides a composition comprising a compound of formula P-3 or a salt thereof, and a compound of formula P-3' or a salt thereof. In some embodiments, the present disclosure provides a composition comprising a compound of formula P-3 or a salt thereof, and a compound of formula P-3" or a salt thereof. In some embodiments, the present disclosure provides a composition comprising a compound of formula P-3 or a salt thereof, a compound of formula P-3' or a salt thereof, and a compound of formula P-3" or a salt thereof. In some embodiments, the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100 as described herein, and/or the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3" or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100 as described herein.

[00247] In some embodiments, a reaction is performed in the presence of a Lewis acid. In some embodiments, a reaction is performed in the presence of a boron Lewis acid. In some embodiments, a reaction is performed in the presence of BF_3. In some embodiments, a reaction is performed in the presence of $BF_3 \cdot Et_2O$.

[00248] Various temperatures can be utilized and assessed for provided methods in accordance with the present disclosure. In some embodiments, a reaction is performed at certain temperature or a range thereof. In some embodiments, temperature increases or decreases, typically within a range for a reaction or a method. For example, in some embodiments, for a method for preparing a compound of formula P-3 or a salt thereof, a reaction is performed at about -50-50 °C, e.g., about -20-25, -10-25, 0-30 and 0-25 °C. In some embodiments, a method comprises a temperature of about 0-25 °C. In some embodiments, a method comprises a temperature increase from about 0 °C to, e.g., about 25 °C. In some embodiments, a method comprises a temperature increase from about -20 °C to about 25 °C. In some embodiments, a method comprises a temperature increase from about -10 °C to about 25 °C.

[00249] Reactions may be performed for various periods of time, e.g., in view of conversion, yield,

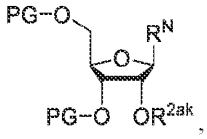
formation of by-product, efficiency, etc. For example, in some embodiments, reaction time for a method is about 1-24 hours. In some embodiments, a reaction time is about 5 hours. In some embodiments, it is about 6 hours. In some embodiments, it is about 10 hours. In some embodiments, it is about 12 hours.

Preparation of Compounds of Formula P-4

[00250] In some embodiments, the present disclosure provides technologies for preparing compounds, e.g., nucleosides, comprising sugars with free hydroxy groups. In some embodiments, protected hydroxy groups are de-protected. Various technologies are available for de-protection and can be utilized in accordance with the present disclosure.

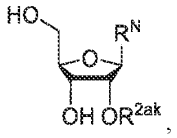
[00251] In some embodiments, the present disclosure provides a method, comprising:

converting a compound of formula P-3:



P-3

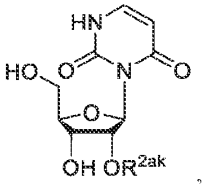
or a salt thereof, into a compound of formula P-4:



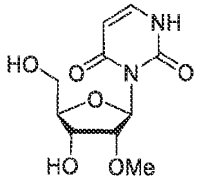
P-4

or a salt thereof, wherein each variable is independently as described herein.

[00252] In some embodiments, a compound of formula P-4 or a salt thereof is a compound of formula P-4-1:



P-4-1

or a salt thereof. In some embodiments, a compound of formula P-4 or P-4-1 is .

[00253] In some embodiments, converting is carried out in the presence of a base. In some embodiments, converting is carried out in the presence of methoxide. In some embodiments, converting is carried out in the presence of NaOH. In some embodiments, converting is carried out in the presence of NaOMe.

[00254] Various solvent systems can be assessed and utilized in accordance with the present disclosure. In some embodiments, a method is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%. In some embodiments, it is v%. In some embodiments, it is wt%. In some embodiments, the percentage of a solvent compound in a solvent system is about or at least about 10%. In some embodiments, it is about or at least about 20%. In some embodiments, it is about or at least about 30%. In some embodiments, it is about or at least about 40%. In some embodiments, it is about or at least about 50%. In some embodiments, it is about or at least about 60%. In some embodiments, it is about or at least about 70%. In some embodiments, it is about or at least about 80%. In some embodiments, it is about or at least about 90%. In some embodiments, it is about or at least about 95%. In some embodiments, the percentage is about 100%. In some embodiments, a solvent system consists of a single solvent compound. In some embodiments, a solvent compound is an alcohol. In some embodiments, a solvent compound is a compound having the structure of R^a–OH, wherein R^a is selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic. In some embodiments, R^a is C_{1-6} alkyl. In some embodiments, a solvent compound is MeOH. In some embodiments, converting is carried out in MeOH.

[00255] Various temperatures can be utilized and assessed for provided methods in accordance with the present disclosure. In some embodiments, a reaction is performed at certain temperature or a range thereof. In some embodiments, temperature increases or decreases, typically within a range for a reaction or a method. For example, in some embodiments, for a method for preparing a compound of formula P-2 or a salt thereof, a reaction is performed at about 20-50 °C, e.g., about 20-40, 25-50, 25, 30, 33 and 35 °C. In some embodiments, a reaction, e.g., between a compound of formula P-1 or a salt thereof and an alkylating agent as described herein, is performed at about 20 °C. In some embodiments, it is performed at about 25 °C. In some embodiments, it is performed at about 30 °C. In some embodiments, it is performed at about 33 °C. In some embodiments, it is performed at about 35 °C.

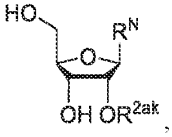
[00256] Reactions may be performed for various periods of time, e.g., in view of conversion, yield, formation of by-product, efficiency, etc. For example, in some embodiments, reaction time for a method is about 1-24 hours. In some embodiments, a reaction time is about 5 hours. In some embodiments, it is about 6 hours. In some embodiments, it is about 10 hours. In some embodiments, it is about 12 hours.

Preparation of Compounds of Formula P-5

[00257] In some embodiments, the present disclosure provides technologies for preparing compounds, e.g., nucleosides, comprising sugars with free hydroxy groups and protected hydroxy groups. In some embodiments, the present disclosure provides technologies for preparing protected nucleosides. Various technologies are available for protecting hydroxy groups including for oligonucleotide manufacturing and can be utilized in accordance with the present disclosure.

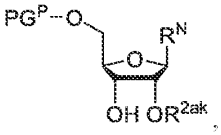
[00258] In some embodiments, the present disclosure provides a method, comprising:

reacting a compound of formula P-4:



P-4

or a salt thereof, with a protecting agent to provide a compound of formula P-5:

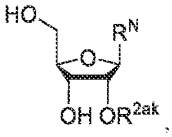


P-5

or a salt thereof, wherein each variable is independently as described herein.

[00259] In some embodiments, the present disclosure provides a method, comprising:

reacting a compound of formula P-4:



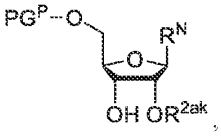
P-4

or a salt thereof, with a compound of formula P-B:

$PG\text{-}LG^2$,

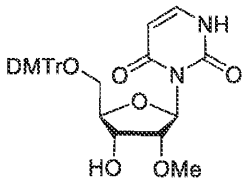
P-B

or a salt thereof, to provide a compound of formula P-5:



P-5

or a salt thereof, wherein each variable is independently as described herein.



[00260] In some embodiments, a compound of formula P-5 is .

[00261] In some embodiments, a protecting agent is a compound of formula P-B or a salt thereof. In some embodiments, PG^P is a protecting group suitable for oligonucleotide synthesis. In some embodiments, PG^P is DMTr. In some embodiments, a compound of formula P-B is DMTr-Cl.

[00262] In some embodiments, reacting is carried out in the presence of a base. In some embodiments, reacting is carried out in the presence of methoxide. In some embodiments, reacting is carried out in the presence of NaOH. In some embodiments, reacting is carried out in the presence of NaOMe.

[00263] Various solvent systems can be assessed and utilized in accordance with the present disclosure. In some embodiments, a method is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%. In some embodiments, it is v%. In some embodiments, it is wt%. In some embodiments, the percentage of a solvent compound in a solvent system is about or at least about 10%. In some embodiments, it is about or at least about 20%. In some embodiments, it is about or at least about 30%. In some embodiments, it is about or at least about 40%. In some embodiments, it is about or at least about 50%. In some embodiments, it is about or at least about 60%. In some embodiments, it is about or at least about 70%. In some embodiments, it is about or at least about 80%. In some embodiments, it is about or at least about 90%. In some embodiments, it is about or at least about 95%. In some embodiments, the percentage is about 100%. In some embodiments, a solvent system consists of a single solvent compound. In some embodiments, a solvent compound is an alcohol. In some embodiments, a solvent compound is a compound having the structure of R^a–OH, wherein R^a is selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic. In some embodiments, R^a is C_{1-6} alkyl. In some embodiments, a solvent compound is MeOH. In some embodiments, converting is carried out in MeOH.

[00264] Various temperatures can be utilized and assessed for provided methods in accordance with the present disclosure. In some embodiments, a reaction is performed at certain temperature or a range thereof. In some embodiments, temperature increases or decreases, typically within a range for a reaction or a method. For example, in some embodiments, for a method for preparing a compound of formula P-2 or a salt thereof, a reaction is performed at about 20-50 °C, e.g., about 20-40, 25-50, 25, 30, 33 and 35 °C. In some embodiments, a reaction, e.g., between a compound of formula P-1 or a salt thereof and an alkylating

agent as described herein, is performed at about 20 °C. In some embodiments, it is performed at about 25 °C. In some embodiments, it is performed at about 30 °C. In some embodiments, it is performed at about 33 °C. In some embodiments, it is performed at about 35 °C.

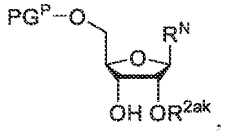
[00265] Reactions may be performed for various periods of time, e.g., in view of conversion, yield, formation of by-product, efficiency, etc. For example, in some embodiments, reaction time for a method is about 1-24 hours. In some embodiments, it is about 2 hours. In some embodiments, a reaction time is about 5 hours. In some embodiments, it is about 6 hours. In some embodiments, it is about 10 hours. In some embodiments, it is about 12 hours.

Preparation of Phosphoramidites

[00266] Provided compounds are useful for many purposes. For example, compounds of formula P-5 are useful for preparing various phosphoramidites, which, among other things, can be utilized for manufacturing oligonucleotides for various purposes. Certain useful methods for preparing phosphoramidites, uses of phosphoramidites (e.g., for manufacturing oligonucleotides) and technologies for manufacturing oligonucleotides are described in US 9982257, US 20170037399, US 20180216108, US 20180216107, US 9598458, WO 2017/062862, WO 2018/067973, WO 2017/160741, WO 2017/192679, WO 2017/210647, WO 2018/098264, WO 2018/022473, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/032612, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2018/223056, WO 2018/223073, WO 2018/223081, WO 2018/237194, WO 2019/032607, WO 2019/055951, WO 2019/075357, WO 2019/200185, WO 2019/217784, WO 2019/032612, WO 2020/191252, WO 2021/071858, WO 2022/099159, WO 2023/049475 and WO 2023/201095, the entirety of each of which is incorporated herein by reference.

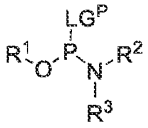
[00267] In some embodiments, the present disclosure provides a method, comprising:

reacting a compound having the structure of formula P-5:



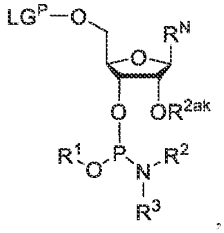
P-5

or a salt thereof with a compound having the structure of formula AX:



AX

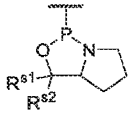
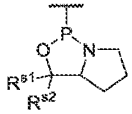
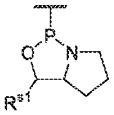
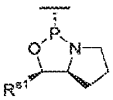
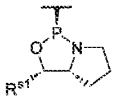
or a salt thereof, to provide a compound of formula PMT:



PMT

or a salt thereof, wherein each variable is independently as described herein.

[00268] In some embodiments, LG^P is −Cl. In some embodiments, LG^P is −Br. In some embodiments, LG^P is −I.

[00269] In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is $-P(OCH_2CH_2CN)N[CH(CH_3)_2]_2$. In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is , wherein each R^{s1} and R^{s2} is independently R^s as described herein. In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is , wherein each R^{s1} and R^{s2} is independently R as described herein. In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is  wherein R^{s1} is as described herein. In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is  wherein R^{s1} is as described herein. In some embodiments, $-P(OR^1)N(R^2)(R^3)$ is  wherein R^{s1} is as described herein. In some embodiments, R^{s1} is $-CH_2-Si(R^{s11})_3$ wherein each R^{s11} is independently R but is not −H. In some embodiments, In some embodiments, R^{s1} is $-CH_2-SiMePh_2$. In some embodiments, R^{s1} is $-CH_2-S(O)_2R^{s11}$, wherein R^{s11} is independently R but is not −H. In some embodiments, R^{s1} is $-CH_2-S(O)_2Ph$.

Purity

[00270] In some embodiments, a compound, e.g., a product compound prepared from a provided method, has a purity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or more. In some embodiments, a product has a purity of 80% or more. In some embodiments, a compound has a purity of 85% or more. In some embodiments, a compound has a purity of 90% or more. In some embodiments, a compound has a purity of 91% or more. In some embodiments, a compound has a purity of 92% or more. In some embodiments, a compound has a purity of 93% or more. In some embodiments, a compound has a purity of 94% or more. In some embodiments, a compound has a purity of 95% or more. In some embodiments, a compound has a purity of 96% or more. In some embodiments, a compound has a purity of 97% or more. In some embodiments, a compound has a purity of 98% or more. In some embodiments, a compound has a purity of 99% or more. In some embodiments, a compound has a purity of 99.5% or more. In some embodiments, a compound has a purity of 99.9% or more. In some embodiments, an impurity is a stereoisomer of a compound. In some embodiments, an impurity is a diastereomer of a compound. In some embodiments, a purity is weight %. In some embodiments, a purity is mol%. In some embodiments, purity is peak area %. Various technologies can be utilized to assess purity, e.g., HPLC coupled with various detection technologies and qNMR.

[00271] In some embodiments, a product comprises one or more chiral elements, e.g., chiral centers. In some embodiments, a product has a stereopurity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or more. In some embodiments, a product has an enantiomeric purity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or more. In some embodiments, a product has a diastereomeric purity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or more. In some embodiments, a percentage is about or at least about 80%. In some embodiments, a percentage is about or at least about 85%. In some embodiments, a percentage is about or at least about 90%. In some embodiments, a percentage is about or at least about 95%.

[00272] In some embodiments, a product is formed selectively over another product, e.g., a by-product and a stereoisomer. In some embodiments, ratio of a product over another product is 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100. In some embodiments, it is about or at least about 1.5. In some embodiments, it is about or at least about 2. In some embodiments, it is about or at least about 5. In some embodiments, it is about or at least about 10. In some embodiments, it is about or at least about 20. In some embodiments, it is about or at least about 50. In some embodiments, it is about or at least about 100.

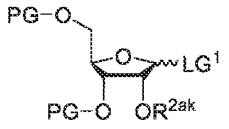
Scale

[00273] In some embodiments, a provided method provides a compound at a scale of about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, or 1000 mmol, or about or at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 500, or 1000 mol. In some embodiments, it is about 1-2000, 50-2000, or 100-2000 mmol. In some embodiments, it is about 1-1000, 1-500, 10-1000 or 1-100 mol.

[00274] In some embodiments, a provided method is carried out at a scale of about or greater than about 10 mmol of a nucleoside product. In some embodiments, a provided method is carried out at a scale of about or greater than about 20 mmol of a nucleoside product. In some embodiments, a provided method is carried out at a scale of about or greater than about 50 mmol of a nucleoside product. In some embodiments, a provided method is carried out at a scale of about or greater than about 100 mmol of a nucleoside product. In some embodiments, a provided method is carried out at a scale of about or greater than about 150 mmol of a nucleoside product. In some embodiments, a provided method is carried out at a scale of about or greater than about 200 mmol of a nucleoside product.

[00275] Among other things, the present disclosure provides the following Embodiments:

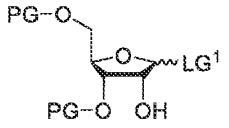
1. A method for preparing a compound of formula P-2:



P-2

or a salt thereof,

comprising reacting a compound of formula P-1:



P-1

or a salt thereof with an alkylating agent, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

LG^1 is a leaving group, or is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$, wherein each R^{LG} is independently R;

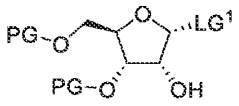
each PG is independently a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R';

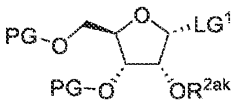
each R' is independently –R, –C(O)R, –C(O)OR, or $-S(O)_2R$;

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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

2. The method of Embodiment 1, wherein a compound of formula P-1 is .

3. The method of any one of Embodiments 1-2, wherein a compound of formula P-2 is .

4. The method of any one of Embodiments 1-3, wherein R^{2ak} is C_{1-6} alkyl.

5. The method of any one of Embodiments 1-4, wherein the alkylating agent is $(R^{2ak})_3OY$, wherein Y is a counter ion.

6. The method of any one of Embodiments 1-5, wherein R^{2ak} is ethyl.

7. The method of any one of Embodiments 1-6, wherein Y is BF_4.

8. The method of any one of Embodiments 1-3, wherein R^{2ak} is methyl.

9. The method of Embodiment 8, wherein the alkylating agent is a methylating agent.

10. The method of Embodiment 9, wherein the methylating agent is selected from CH_3I, dimethyl sulfate, dimethyl carbonate, $N(CH_3)_4X$, CH_3OTf, diazomethane, methyl fluorosulfonate, and $(CH_3)_3OY$, wherein X and Y are each independently a counterion.

11. The method of Embodiment 9, wherein the methylation agent is selected from CH_3I, dimethyl sulfate, CH_3OTf, methyl fluorosulfonate, and $(CH_3)_3OY$, wherein X and Y are each independently a counterion.

12. The method of Embodiment 9, wherein the methylating agent is $(CH_3)_3OY$.

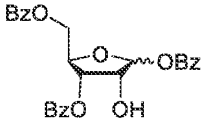
13. The method of Embodiment 9, wherein the methylating agent is $(CH_3)_3OBF_4$.

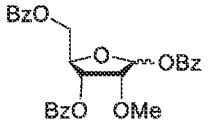
14. The method of any one of Embodiments 1-13, wherein the reacting is carried out in the presence

of a base.

15. The method of any one of Embodiments 1-13, wherein the reacting is carried out in the presence of a non-nucleophilic base.

16. The method of any one of Embodiments 1-13, wherein the reacting is carried out in the presence of .

17. The method of any one of Embodiments 1-5 and 7-16, wherein the compound of formula P-1 is .

18. The method of any one of Embodiments 1-5 and 7-16 and , wherein the compound of formula P-2 is .

19. The method of any one of Embodiments 1-16, wherein LG^1 is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$.

20. The method of any one of Embodiments 1-16, wherein LG^1 is halogen.

21. The method of any one of Embodiments 1-16, wherein LG^1 is $-Cl$.

22. The method of any one of Embodiments 1-16, wherein LG^1 is $-Br$.

23. The method of any one of Embodiments 1-16, wherein LG^1 is $-I$.

24. The method of any one of Embodiments 1-16, wherein LG^1 is $-OR^{LG}$.

25. The method of any one of Embodiments 1-16, wherein LG^1 is $-OR^{LG}$ wherein R^{LG} is C_{1-6} aliphatic.

26. The method of any one of Embodiments 1-16, wherein LG^1 is $-OMe$.

27. The method of any one of Embodiments 1-16, wherein LG^1 is $-OC(O)R^{LG}$.

28. The method of any one of Embodiments 1-16, wherein LG^1 is $-OC(O)R^{LG}$ and R^{LG} is optionally substituted C_{6-14} aryl.

29. The method of any one of Embodiments 1-16, wherein LG^1 is $-OC(O)R^{LG}$ and R^{LG} is optionally substituted phenyl.

30. The method of any one of Embodiments 1-16, wherein LG^1 is $-OC(O)Ph$.

31. The method of any one of Embodiments 1-30, wherein each PG is independently a protecting group;

32. The method of any one of Embodiments 1-30, wherein each PG is independently R^p, $-C(O)R^p$, or

$-Si(R^p)_3$.

33. The method of any one of Embodiments 1-30, wherein each PG is independently R^p, $-C(O)R^p$, or $-Si(R^p)_3$, wherein R^p is not $-H$.

34. The method of any one of Embodiments 1-30, wherein each occurrence of PG is independently $-C(O)R^p$, wherein R^p is optionally substituted C_{6-14} aryl.

35. The method of any one of Embodiments 1-30, wherein each occurrence of PG is independently $-C(O)R^p$, wherein R^p is optionally substituted phenyl.

36. The method of any one of Embodiments 1-30, wherein each occurrence of PG is $-C(O)Ph$.

37. The method of any one of Embodiments 1-36, wherein the reacting is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%.

38. The method of Embodiment 37, wherein the solvent compound has a polarity index lower than dimethylformamide (about 6.4).

39. The method of Embodiment 37, wherein the solvent compound is C_{1-3} alkane substituted with halogen.

40. The method of Embodiment 37, wherein the solvent compound is C_{1-3} alkane substituted with two or more halogen.

41. The method of Embodiment 37, wherein the solvent compound is C_{1-3} alkane substituted with two or more $-Cl$.

42. The method of Embodiment 37, wherein the solvent compound has the structure of R^a-O-R^b, wherein R^a and R^b are each independently selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic, or R^a and R^b are taken together with the oxygen atom to which they are attached to form a 3-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

43. The method of Embodiment 42, wherein each R^a and R^b is independently C_{1-6} alkyl.

44. The method of Embodiment 42, wherein R^a and R^b are taken together with the oxygen atom to which they are attached to form a 4-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

45. The method of Embodiment 42, wherein R^a and R^b are taken together with the oxygen atom to which they are attached to form a 6- membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

46. The method of Embodiment 37, wherein the solvent compound is $R^a-C(O)-OR^b$, wherein R^a and R^b are each independently selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic, or R^a and R^b are taken together with the oxygen atom to which they are attached to form a 3-10 membered ring having 0-2

additional heteroatoms independently selected from oxygen and nitrogen.

47. The method of Embodiment 46, wherein each R^a and R^b is independently C_{1-6} alkyl.

48. The method of Embodiment 37, wherein the solvent compound is dichloromethane.

49. The method of Embodiment 37, wherein the solvent compound is 1,2-dichloroethane (DCE).

50. The method of Embodiment 37, wherein the solvent compound is EtOAc.

51. The method of Embodiment 37, wherein the solvent compound is 1,4-dioxane.

52. The method of any one of Embodiments 37-47, wherein the solvent compound is a liquid at about 298 K and about 1 atm.

53. The method of Embodiment any one of Embodiments 37-52, wherein the percentage is v%.

54. The method of Embodiment any one of Embodiments 37-53, wherein the percentage is about or at least about 95% v%.

55. The method of Embodiment any one of Embodiments 37-54, wherein the percentage is about 100%.

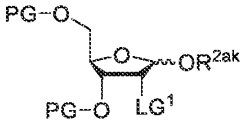
56. The method of any one of Embodiments 1-36, wherein the reacting is carried out in dichloromethane.

57. The method of any one of Embodiments 1-36, wherein the reacting is carried out in 1,2-dichloroethane (DCE).

58. The method of any one of Embodiments 1-36, wherein the reacting is carried out in EtOAc.

59. The method of any one of Embodiments 1-36, wherein the reacting is carried out in 1,4-dioxane.

60. The method of any one of Embodiments 1-59, wherein the method produces a compound of formula P-2':



P-2'

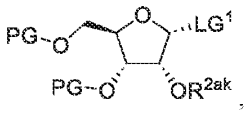
or a salt thereof.

61. The method of any one of Embodiments 1-60, wherein the method produces a compound of formula P-2 or a salt thereof over a compound of formula P-2' or a salt thereof.

62. The method of Embodiment 61, wherein the ratio of a compound of formula P-2 or a salt thereof over a compound of formula P-2' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

63. The method of Embodiment 62, wherein the ratio is about or at least about 10.

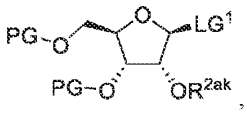
64. The method of any one of Embodiments 1-63, wherein the method produces a compound of formula P-2A:



P-2A

or a salt thereof.

65. The method of any one of Embodiments 1-64, wherein the method produces a compound of formula P-2B:



P-2B

or a salt thereof.

66. The method of any one of Embodiments 1-65, wherein the method selectively produces a compound of formula P-2A or a salt thereof over a compound of formula P-2B or a salt thereof.

67. The method of Embodiment 66, wherein the ratio of a compound of formula P-2A or a salt thereof over a compound of formula P-2B or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

68. The method of Embodiment 67, wherein the ratio is about or at least about 2.

69. The method of any one of Embodiments 1-68, wherein the reacting is performed at about 20-50 °C.

70. The method of any one of Embodiments 1-68, wherein the reacting is performed at about 20 °C.

71. The method of any one of Embodiments 1-68, wherein the reacting is performed at about 25 °C.

72. The method of any one of Embodiments 1-68, wherein the reacting is performed at about 35 °C.

73. The method of any one of Embodiments 1-72, wherein the concentration of the compound of formula P-1 or a salt thereof is about 1-2000 mg/mL.

74. The method of any one of Embodiments 1-72, wherein the concentration of the compound of formula P-1 or a salt thereof is about 20, 25, 50, 100 or 1000 mg/mL.

75. The method of any one of Embodiments 1-74, wherein the concentration of the compound of formula P-1 or a salt thereof is about 1-3000 mmol.

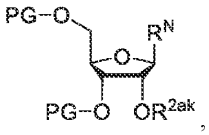
76. The method of any one of Embodiments 1-74, wherein the concentration of the compound of formula P-1 or a salt thereof is about $4 * 10^{-2}$, $5 * 10^{-2}$, $7 * 10^{-2}$, $10 * 10^{-2}$, 0.1 or 0.2 M.

77. The method of any one of Embodiments 1-74, wherein the concentration of the compound of formula P-1 or a salt thereof is about 0.05-0.2 M.

78. The method of any one of Embodiments 1-74, wherein the concentration of the compound of

formula P-1 or a salt thereof is about 0.1-0.2 M.

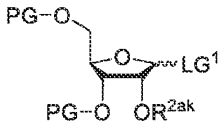
79. A method for preparing a compound of formula P-3:



P-3

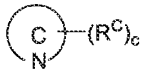
or a salt thereof,

comprising reacting a compound of formula P-2:



P-2

or a salt thereof with a compound of formula P-A:

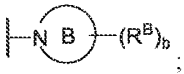


P-A

or a salt thereof, wherein:

each PG is independently a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

each of Ring B and Ring C is independently an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each of R^B and R^C is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each of b and c is independently 0-5;

LG^1 is a leaving group;

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_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus

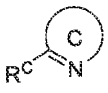
and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; or

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:

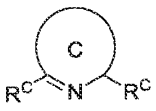
two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

80. The method of Embodiment 79, wherein the compound of formula P-A has a structure of



or a salt thereof.

81. The method of Embodiment 79, wherein the compound of formula P-A has a structure of



or a salt thereof.

82. The method of any one of Embodiments 79-81, wherein Ring C is an optionally substituted 5-14 membered ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom.

83. The method of any one of Embodiments 79-81, wherein Ring C is an optionally substituted 5-10 membered ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom.

84. The method of any one of Embodiments 79-81, wherein Ring C is an optionally substituted 5-10 membered ring having 1-4 nitrogen atoms.

85. The method of any one of Embodiments 82-84, wherein Ring C is monocyclic and is 5-membered.

86. The method of any one of Embodiments 82-84, wherein Ring C is monocyclic and is 6-membered.

87. The method of any one of Embodiments 82-84, wherein Ring C is bicyclic and is 9-membered.

88. The method of any one of Embodiments 82-84, wherein Ring C is bicyclic and is 10-membered.

89. The method of any one of Embodiments 87-88, wherein a monocyclic ring unit is 5-membered.

90. The method of any one of Embodiments 87-88, wherein a monocyclic ring unit is 6-membered.

91. The method of any one of Embodiments 87-90, wherein a monocyclic ring unit is saturated.

92. The method of any one of Embodiments 87-90, wherein a monocyclic ring unit is partially unsaturated.

93. The method of any one of Embodiments 87-90, wherein a monocyclic ring unit is aromatic.

94. The method of any one of Embodiments 79 and 82-88, wherein Ring C is saturated.

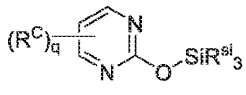
95. The method of any one of Embodiments 79-88, wherein Ring C is partially unsaturated.

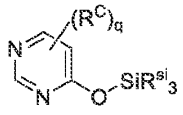
96. The method of any one of Embodiments 79-88, wherein Ring C is aromatic.

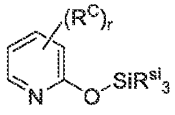
97. The method of any one of Embodiments 79-82, wherein the compound of formula P-A is or comprises an optionally substituted nucleobase or a tautomer thereof.

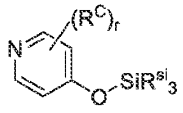
98. The method of any one of Embodiments 79-82, wherein the compound of formula P-A is an optionally substituted or protected nucleobase selected from A, T, C, G, U and tautomers thereof.

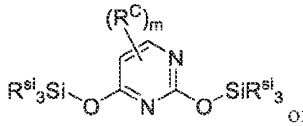
99. The method of any one of Embodiments 79-82, wherein the compound of formula P-A is a protected nucleobase selected from A, T, C, G, and U.

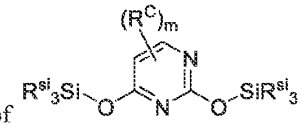
100. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein q is 0-3.

101. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein q is 0-3.

102. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein r is 0-4.

103. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein r is 0-4.

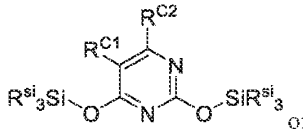
104. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein m is 0-2.

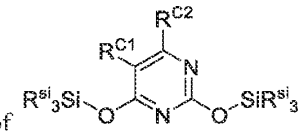
105. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein m is 0-2 and each R^C is independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic.

106. The method of any one of Embodiments 79-105, wherein each R^C is independently R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$.

107. The method of any one of Embodiments 79-105, wherein each R^C is independently R, $-OR'$, $-OSi(R^{si})_3$, $-N(R')_2$, or $-S(O)_2R$.

108. The method of any one of Embodiments 79-105, wherein each R^C is $-H$.

109. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein R^{C1} and R^{C2} are each independently R^C.

110. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein R^{C1} and R^{C2} are each independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic.

111. The method of any one of Embodiments 109-110, wherein R^{C1} is hydrogen.

112. The method of any one of Embodiments 109-110, wherein R^{C1} is halogen.

113. The method of Embodiment 112, wherein R^{C1} is $-F$.

114. The method of Embodiment 112, wherein R^{C1} is $-Cl$.

115. The method of Embodiment 112, wherein R^{C1} is $-Br$.

116. The method of Embodiment 112, wherein R^{C1} is $-I$.

117. The method of any one of Embodiments 109-110, wherein R^{C1} is optionally substituted C_{1-10} aliphatic.

118. The method of any one of Embodiments 109-110, wherein R^{C1} is optionally substituted C_{1-6} aliphatic.

119. The method of any one of Embodiments 109-110, wherein R^{C1} is optionally substituted C_{1-6} alkyl.

120. The method of any one of Embodiments 109-110, wherein R^{C1} is optionally substituted C_{1-3} alkyl.

121. The method of any one of Embodiments 117-121, wherein each substituent is independently selected from halogen, $-CN$, R^s, $-OR^s$, $-N(R^s)_2$, $-C(O)OR^s$, $-C(O)N(R^s)_2$, and $-S(O)_2N(R^s)_2$, wherein each

R^s is independently −H, C_1-C_6 aliphatic or C_1-C_6 haloaliphatic.

122. The method of any one of Embodiments 109-110, wherein R^{C1} is C_{1-6} alkyl.

123. The method of any one of Embodiments 109-110, wherein R^{C1} is C_{1-3} alkyl.

124. The method of any one of Embodiments 109-110, wherein R^{C1} is halogen substituted methyl.

125. The method of any one of Embodiments 109-110, wherein R^{C1} is methyl.

126. The method of any one of Embodiments 109-110, wherein R^{C1} is halogen substituted ethyl.

127. The method of any one of Embodiments 109-110, wherein R^{C1} is ethyl.

128. The method of any one of Embodiments 109-110, wherein R^{C1} is halogen substituted propyl.

129. The method of any one of Embodiments 109-110, wherein R^{C1} is propyl.

130. The method of any one of Embodiments 109-110, wherein R^{C1} is halogen substituted isopropyl.

131. The method of any one of Embodiments 109-110, wherein R^{C1} is isopropyl.

132. The method of any one of Embodiments 109-131, wherein R^{C2} is hydrogen.

133. The method of any one of Embodiments 109-131, wherein R^{C2} is halogen.

134. The method of Embodiment 133, wherein R^{C2} is −F.

135. The method of Embodiment 133, wherein R^{C2} is −Cl.

136. The method of Embodiment 133, wherein R^{C2} is −Br.

137. The method of Embodiment 133, wherein R^{C2} is −I.

138. The method of any one of Embodiments 109-131, wherein R^{C2} is optionally substituted C_{1-10} aliphatic.

139. The method of any one of Embodiments 109-131, wherein R^{C2} is optionally substituted C_{1-6} aliphatic.

140. The method of any one of Embodiments 109-131, wherein R^{C2} is optionally substituted C_{1-6} alkyl.

141. The method of any one of Embodiments 109-131, wherein R^{C2} is optionally substituted C_{1-3} alkyl.

142. The method of any one of Embodiments 109-141, wherein each substituent is independently selected from halogen, −CN, R^s, −OR^s, −$N(R^s)_2$, −$C(O)OR^s$, −$C(O)N(R^s)_2$, and −$S(O)_2N(R^s)_2$, wherein each R^s is independently −H, C_1-C_6 aliphatic or C_1-C_6 haloaliphatic.

143. The method of any one of Embodiments 109-131, wherein R^{C2} is C_{1-6} alkyl.

144. The method of any one of Embodiments 109-131, wherein R^{C2} is C_{1-3} alkyl.

145. The method of any one of Embodiments 109-131, wherein R^{C2} is halogen substituted methyl.

146. The method of any one of Embodiments 109-131, wherein R^{C2} is methyl.

147. The method of any one of Embodiments 109-131, wherein R^{C2} is halogen substituted ethyl.

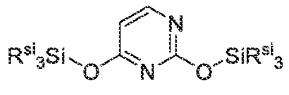
148. The method of any one of Embodiments 109-131, wherein R^{C2} is ethyl.

149. The method of any one of Embodiments 109-131, wherein R^{C2} is halogen substituted propyl.

150. The method of any one of Embodiments 109-131, wherein R^{C2} is propyl.

151. The method of any one of Embodiments 109-131, wherein R^{C2} is halogen substituted isopropyl.

152. The method of any one of Embodiments 109-131, wherein R^{C2} is isopropyl.

153. The method of any one of Embodiments 79-82, wherein the compound of formula P-A has a structure of  or a salt thereof.

154. The method of any one of Embodiments 79-153, wherein each R^{si} is not –H.

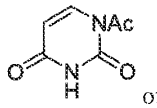
155. The method of any one of Embodiments 79-153, wherein each R^{si} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl.

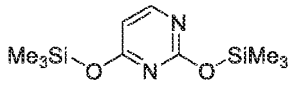
156. The method of any one of Embodiments 79-153, wherein each R^{si} is independently an optionally substituted group selected from C_{1-6} alkyl and phenyl.

157. The method of any one of Embodiments 79-153, wherein each R^{si} is independently C_{1-6} alkyl or phenyl.

158. The method of any one of Embodiments 79-153, wherein each R^{si} is independently methyl, ethyl or t-butyl.

159. The method of any one of Embodiments 79-153, wherein each R^{si} is methyl.

160. The method of any one of Embodiments 79-153, wherein the compound of formula P-A has a structure of  or a salt thereof

161. The method of any one of Embodiments 79-153, wherein the compound of formula P-A has a structure of  or a salt thereof.

162. The method of any one of Embodiments 79-161, wherein LG^1 is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$.

163. The method of any one of Embodiments 79-161, wherein LG^1 is halogen.

164. The method of any one of Embodiments 79-161, wherein LG^1 is –Cl.

165. The method of any one of Embodiments 79-161, wherein LG^1 is –Br.

166. The method of any one of Embodiments 79-161, wherein LG^1 is –I.

167. The method of any one of Embodiments 79-161, wherein LG^1 is $-OC(O)R^{LG}$.

168. The method of any one of Embodiments 79-161, wherein LG^1 is $-OC(O)R^{LG}$ and R^{LG} is optionally substituted C_{6-14} aryl.

169. The method of any one of Embodiments 79-161, wherein LG^1 is $-OC(O)R^{LG}$ and R^{LG} is optionally

substituted phenyl.

170. The method of any one of Embodiments 79-161, wherein LG^1 is –OC(O)Ph.

171. The method of any one of Embodiments 79-161, wherein the method is reacting out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%.

172. The method of any one of Embodiments 79-171, wherein the solvent compound is R^a–C(O)–OR^b, wherein R^a and R^b are each independently selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic, or R^a and R^b are taken together with the oxygen atom to which they are attached to form a 3-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

173. The method of Embodiment 172, wherein each R^a and R^b is independently C_{1-6} alkyl.

174. The method of Embodiment 172, wherein the solvent compound is EtOAc.

175. The method of any one of Embodiments 172, wherein the solvent compound is a liquid at about 298 K and about 1 atm.

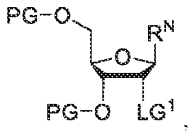
176. The method of any one of Embodiments 79-175, wherein the percentage is v%.

177. The method of any one of Embodiments 79-176, wherein the percentage is about or at least about 95% v%.

178. The method of Embodiment any one of Embodiments 79-177, wherein the percentage is about 100%.

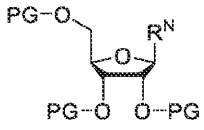
179. The method of Embodiment any one of Embodiments 79-177, wherein the reacting is carried out in EtOAc.

180. The method of any one of Embodiments 79-179, wherein the method produces a compound of formula P-3':



P-3'

or a salt thereof.

181. The method of Embodiment 180, wherein the compound of formula P-3' is a compound having the structure of 

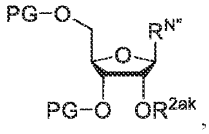
182. The method of any one of Embodiments 79-181, wherein the method selectively produces a

compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof.

183. The method of Embodiment 182, wherein the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

184. The method of Embodiment 183, wherein the ratio is about or at least about 2.

185. The method of any one of Embodiments 79-184, wherein the method produces a compound of formula P-3":



P-3"

or a salt thereof, wherein $R^{N"}$ is R^N but is different from R^N in a compound of formula P-3 or a salt thereof.

186. The method of any one of Embodiments 79-185, wherein the method selectively produces a compound of formula P-3 or a salt thereof over a compound of formula P-3" or a salt thereof.

187. The method of Embodiment 186, wherein the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

188. The method of Embodiment 187, wherein the ratio is about or at least about 2.

189. The method of Embodiment any one of Embodiments 79-188, wherein the reaction is performed in the presence of a Lewis acid.

190. The method of Embodiment any one of Embodiments 79-188, wherein the reaction is performed in the presence of a boron Lewis acid.

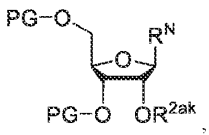
191. The method of Embodiment any one of Embodiments 79-188, wherein the reaction is performed in the presence of BF_3.

192. The method of Embodiment any one of Embodiments 79-188, wherein the reaction is performed in the presence of $BF_3 \cdot Et_2O$.

193. The method of any one of Embodiments 1-78, further comprises a method of one of Embodiments 79-192.

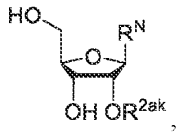
194. A method, comprising:

converting a compound of formula P-3:



P-3

or a salt thereof, into a compound of formula P-4:

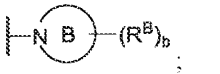


P-4

or a salt thereof, wherein:

each PG is independently a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

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_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; or

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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently

selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

195. The method of Embodiment 194, wherein each PG is independently a protecting group;

196. The method of Embodiment 194, wherein each PG is independently R^P, $-C(O)R^P$, or $-Si(R^P)_3$.

197. The method of Embodiment 194, wherein each PG is independently R^P, $-C(O)R^P$, or $-Si(R^P)_3$, wherein R^P is not $-H$.

198. The method of Embodiment 194, wherein each occurrence of PG is independently $-C(O)R^P$, wherein R^P is optionally substituted C_{6-14} aryl.

199. The method of Embodiment 194, wherein each occurrence of PG is independently $-C(O)R^P$, wherein R^P is optionally substituted phenyl.

200. The method of Embodiment 194, wherein each occurrence of PG is $-C(O)Ph$.

201. The method of any one of Embodiments 194-200, comprises deprotecting a compound of formula P-3 or a salt thereof.

202. The method of any one of Embodiments 194-201, wherein the converting is carried out in the presence of a base.

203. The method of any one of Embodiments 194-201, wherein the converting is carried out in the presence of methoxide.

204. The method of any one of Embodiments 194-201, wherein the converting is carried out in the presence of NaOH.

205. The method of any one of Embodiments 194-201, wherein the converting is carried out in the presence of NaOMe.

206. The method of any one of Embodiments 194-205, wherein the converting is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%.

207. The method of any one of Embodiments 194-206, wherein the solvent compound is an alcohol.

208. The method of any one of Embodiments 194-206, wherein the solvent compound is a compound having the structure of R^a-OH, wherein R^a is selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic.

209. The method of Embodiment 208, wherein R^a is C_{1-6} alkyl.

210. The method of Embodiment 208, wherein the solvent compound is MeOH.

211. The method of any one of Embodiments 194-210, wherein the percentage is v%.

212. The method of any one of Embodiments 194-210, wherein the percentage is about or at least about 95% v%.

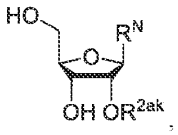
213. The method of Embodiment any one of Embodiments 194-210, wherein the percentage is about 100%.

214. The method of Embodiment any one of Embodiments 194-210, wherein the converting is carried out in MeOH.

215. The method of any one of Embodiments 1-193, further comprises a method of one of Embodiments 194-214.

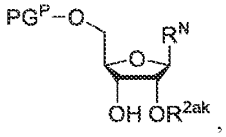
216. A method, comprising:

reacting a compound of formula P-4:



P-4

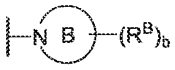
or a salt thereof, with a protecting agent to provide a compound of formula P-5:



P-5

or a salt thereof, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

PG^P is a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R';

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,

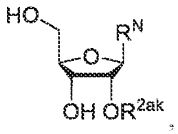
and 3-30 membered heterocyclyl having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or:

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

two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

217. A method, comprising:

reacting a compound of formula P-4:



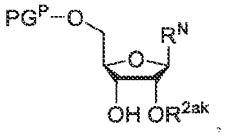
P-4

or a salt thereof, with a compound of formula P-B:

$PG\text{-}LG^2$,

P-B

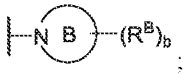
or a salt thereof, to provide a compound of formula P-5:



P-5

or a salt thereof, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

LG^2 is a leaving group, or is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$, wherein each R^{LG} is independently R;

PG^P is a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R';

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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

218. The method of any one of Embodiments 216-217, wherein the reacting is performed in the presence of a base.

219. The method of any one of Embodiments 216-217, wherein the reacting is performed in the presence of pyridine.

220. The method of any one of Embodiments 217-219, wherein LG^2 is halogen.

221. The method of Embodiment 220, wherein LG^2 is –Cl.

222. The method of any one of Embodiments 216-221, wherein PG^P is a protecting group for oligonucleotide synthesis.

223. The method of any one of Embodiments 216-221, wherein PG^P is $-C(O)R^p$.

224. The method of any one of Embodiments 216-223, wherein PG^P is –DMTr.

225. The method of any one of Embodiments 79-224, wherein R^{2ak} is C_{1-6} alkyl.

226. The method of any one of Embodiments 79-225, wherein R^{2ak} is methyl.

227. The method of any one of Embodiments 79-226, wherein R^N is or comprises an optionally substituted nucleobase or a tautomer thereof.

228. The method of any one of Embodiments 79-226, wherein R^N is an optionally substituted or protected nucleobase selected from A, T, C, G, U and tautomers thereof.

229. The method of any one of Embodiments 79-226, wherein R^N is a protected nucleobase selected from A, T, C, G and U.

230. The method of any one of Embodiments 79-226, wherein Ring B is an optionally substituted 4-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from

nitrogen, oxygen and sulfur.

231. The method of Embodiment 230, wherein Ring B is an optionally substituted 5-14 membered ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom.

232. The method of Embodiment 230, wherein Ring B is an optionally substituted 5-10 membered ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom.

233. The method of Embodiment 230, wherein Ring B is an optionally substituted 5-10 membered ring having 1-4 nitrogen atoms.

234. The method of any one of Embodiments 231-233, wherein Ring B is monocyclic and is 5-membered.

235. The method of any one of Embodiments 231-233, wherein Ring B is monocyclic and is 6-membered.

236. The method of any one of Embodiments 231-233, wherein Ring B is bicyclic and is 9-membered.

237. The method of any one of Embodiments 231-233, wherein Ring B is bicyclic and is 10-membered.

238. The method of any one of Embodiments 236-237, wherein a monocyclic ring unit is 5-membered.

239. The method of any one of Embodiments 236-237, wherein a monocyclic ring unit is 6-membered.

240. The method of any one of Embodiments 236-239, wherein a monocyclic ring unit is saturated.

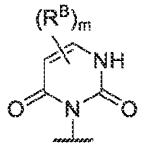
241. The method of any one of Embodiments 236-239, wherein a monocyclic ring unit is partially unsaturated.

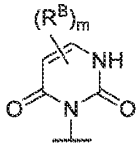
242. The method of any one of Embodiments 236-239, wherein a monocyclic ring unit is aromatic.

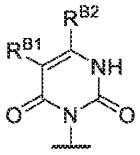
243. The method of any one of Embodiments 231-237, wherein Ring B is saturated.

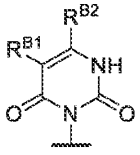
244. The method of any one of Embodiments 231-237, wherein Ring B is partially unsaturated.

245. The method of any one of Embodiments 231-237, wherein Ring B is aromatic.

246. The method of any one of Embodiments 79-226, wherein R^N is , wherein m is 0-2.

247. The method of any one of Embodiments 79-226, wherein R^N is , wherein m is 0-2 and each R^B is independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic.

248. The method of any one of Embodiments 79-226, wherein R^N is , wherein R^{B1} and R^{B2} are each independently R^B.

249. The method of any one of Embodiments 79-226, wherein R^N is , wherein R^{B1} and R^{B2} are each independently R^B, and R^B is independently hydrogen, halogen, or optionally substituted C_{1-10} aliphatic.

250. The method of any one of Embodiments 248-249, wherein R^{B1} is hydrogen.

251. The method of any one of Embodiments 248-249, wherein R^{B1} is halogen.

252. The method of Embodiment 251, wherein R^{B1} is −F.

253. The method of Embodiment 251, wherein R^{B1} is −Cl.

254. The method of Embodiment 251, wherein R^{B1} is −Br.

255. The method of Embodiment 251, wherein R^{B1} is −I.

256. The method of any one of Embodiments 248-249, wherein R^{B1} is optionally substituted C_{1-10} aliphatic.

257. The method of any one of Embodiments 248-249, wherein R^{B1} is optionally substituted C_{1-6} aliphatic.

258. The method of any one of Embodiments 248-249, wherein R^{B1} is optionally substituted C_{1-6} alkyl.

259. The method of any one of Embodiments 248-249, wherein R^{B1} is optionally substituted C_{1-3} alkyl.

260. The method of any one of Embodiments 256-260, wherein each substituent is independently selected from halogen, −CN, R^s, −OR^s, −$N(R^s)_2$, −$C(O)OR^s$, −$C(O)N(R^s)_2$, and −$S(O)_2N(R^s)_2$, wherein each R^s is independently −H, C_1-C_6 aliphatic or C_1-C_6 haloaliphatic.

261. The method of any one of Embodiments 248-249, wherein R^{B1} is C_{1-6} alkyl.

262. The method of any one of Embodiments 248-249, wherein R^{B1} is C_{1-3} alkyl.

263. The method of any one of Embodiments 248-249, wherein R^{B1} is halogen substituted methyl.

264. The method of any one of Embodiments 248-249, wherein R^{B1} is methyl.

265. The method of any one of Embodiments 248-249, wherein R^{B1} is halogen substituted ethyl.

266. The method of any one of Embodiments 248-249, wherein R^{B1} is ethyl.

267. The method of any one of Embodiments 248-249, wherein R^{B1} is halogen substituted propyl.

268. The method of any one of Embodiments 248-249, wherein R^{B1} is propyl.

269. The method of any one of Embodiments 248-249, wherein R^{B1} is halogen substituted isopropyl.

270. The method of any one of Embodiments 248-249, wherein R^{B1} is isopropyl.

271. The method of any one of Embodiments 248-270, wherein R^{B2} is hydrogen.

272. The method of any one of Embodiments 248-270, wherein R^{B2} is halogen.

273. The method of Embodiment 272, wherein R^{B2} is −F.

274. The method of Embodiment 272, wherein R^{B2} is −Cl.

275. The method of Embodiment 272, wherein R^{B2} is −Br.

276. The method of Embodiment 272, wherein R^{B2} is −I.

277. The method of any one of Embodiments 248-270, wherein R^{B2} is optionally substituted C_{1-10} aliphatic.

278. The method of any one of Embodiments 248-270, wherein R^{B2} is optionally substituted C_{1-6} aliphatic.

279. The method of any one of Embodiments 248-270, wherein R^{B2} is optionally substituted C_{1-6} alkyl.

280. The method of any one of Embodiments 248-270, wherein R^{B2} is optionally substituted C_{1-3} alkyl.

281. The method of any one of Embodiments 248-280, wherein each substituent is independently selected from halogen, −CN, R^s, −OR^s, −$N(R^s)_2$, −$C(O)OR^s$, −$C(O)N(R^s)_2$, and −$S(O)_2N(R^s)_2$, wherein each R^s is independently −H, C_1-C_6 aliphatic or C_1-C_6 haloaliphatic.

282. The method of any one of Embodiments 248-270, wherein R^{B2} is C_{1-6} alkyl.

283. The method of any one of Embodiments 248-270, wherein R^{B2} is C_{1-3} alkyl.

284. The method of any one of Embodiments 248-270, wherein R^{B2} is halogen substituted methyl.

285. The method of any one of Embodiments 248-270, wherein R^{B2} is methyl.

286. The method of any one of Embodiments 248-270, wherein R^{B2} is halogen substituted ethyl.

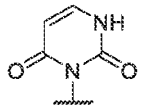
287. The method of any one of Embodiments 248-270, wherein R^{B2} is ethyl.

288. The method of any one of Embodiments 248-270, wherein R^{B2} is halogen substituted propyl.

289. The method of any one of Embodiments 248-270, wherein R^{B2} is propyl.

290. The method of any one of Embodiments 248-270, wherein R^{B2} is halogen substituted isopropyl.

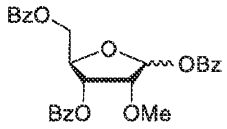
291. The method of any one of Embodiments 248-270, wherein R^{B2} is isopropyl.

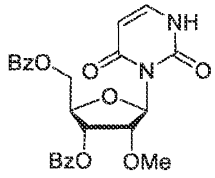
292. The method of any one of Embodiments 79-226, wherein R^N is 

.

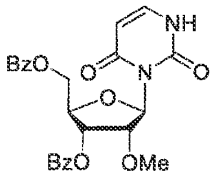
293. The method of any one of Embodiments 1-215, further comprises a method of one of Embodiments 216-292.

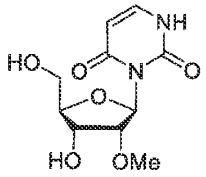
294. The method of any one of Embodiments 79, 161 and 171-192, wherein the compound of formula

P-2 is 

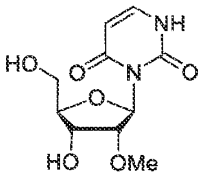
295. The method of any one of Embodiments 79, 161, 171-192, and 295, wherein the compound of formula P-3 is 

296. The method of any one of Embodiments 1-18, comprising a method of any one of Embodiments 294-295.

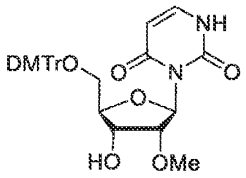
297. The method of any one of Embodiments 194 and 201-214, wherein the compound of formula P-3 is 

298. The method of any one of Embodiments 194, 201-214 and 297, wherein the compound of formula P-4 is 

299. The method of any one of Embodiments 1-18 and 294-296, comprising a method of any one of Embodiments 297-298.

300. The method of any one of Embodiments 217-221, wherein the compound of formula P-4 is 

301. The method of any one of Embodiments 217-221 and 300, wherein the compound of formula P-5

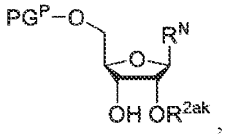
is  .

302. The method of any one of Embodiments 217-221 and 300-301, wherein the compound of formula P-B is DMTr-Cl.

303. The method of any one of Embodiments 1-18 and 294-299, comprising a method of any one of Embodiments 300-302.

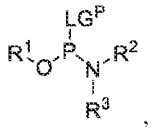
304. The method of any one of the preceding Embodiments, comprising:

reacting a compound having the structure of formula P-5:



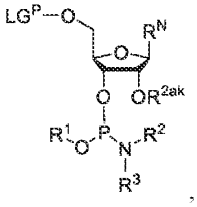
P-5

or a salt thereof with a compound having the structure of formula AX:



AX

or a salt thereof, to provide a compound of formula PMT:

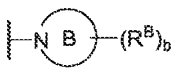


PMT

or a salt thereof, wherein:

PG^P is a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is  ;

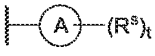
each Ring B is independently an optionally substituted ring selected from a 3-14 membered heterocyclyl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom, and a 5-14 membered heteroaryl ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom;

each R^B is independently a protecting group, R, −OR, $-OSi(R^{si})_3$, halogen, −CN, $-NO_2$, $-N(R')_2$, −C(O)R, −C(O)OR, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

LG^P is −Cl, −Br, or −I;

each of R^1, R^2, and R^3 is independently R', or two or three of R^1, R^2, and R^3 are taken together with their intervening atoms to form ;

Ring A is an optionally substituted 3-20 membered ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

t is 0-5;

each R^s is independently −F, −Cl, −Br, −I, −CN, $-N_3$, −NO, $-NO_2$, $-L^s-R^{s11}$, $-L^s-OR^{s11}$, $-L^s-SR^{s11}$, $-L^s-S(O)_2R^{s11}$, $-L^s-N(R^{s11})_2$, $-O-L^s-OR^{s11}$, $-O-L^s-SR^{s11}$, $-O-L^s-N(R^{s11})_2$, $-C(R^{s11})_3$ or $-L^s-Si(R^{s11})_3$;

each R^{s11} is independently R';

each L^s is independently L;

each L is independently a covalent bond, or a bivalent, optionally substituted group selected from C_{1-10} aliphatic and C_{1-10} heteroaliphatic group having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, wherein one or more methylene units of L are optionally and independently replaced by −Cy−, −O−, −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)−, $-S(O)_2-$, $-S(O)_2N(R')-$, −SC(O)−, or −C(O)O−;

−Cy− is an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

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

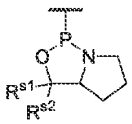
each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10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

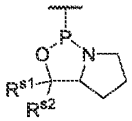
sulfur, phosphorus and silicon; or:

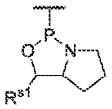
two R groups are optionally and independently taken together to form a covalent bond; or:

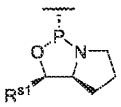
two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

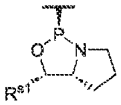
305. The method of Embodiment 304, wherein $-P(OR^1)N(R^2)(R^3)$ is $-P(OCH_2CH_2CN)N[CH(CH_3)_2]_2$.

306. The method of Embodiment 304, wherein $-P(OR^1)N(R^2)(R^3)$ is , wherein each R^{s1} and R^{s2} is independently R^s.

307. The method of Embodiment 304, wherein $-P(OR^1)N(R^2)(R^3)$ is , wherein each R^{s1} and R^{s2} is independently R.

308. The method of Embodiment 304, wherein $-P(OR^1)N(R^2)(R^3)$ is .

309. The method of Embodiment 304, wherein $-P(OR^1)N(R^2)(R^3)$ is .

310. The method of Embodiment 304, wherein $-P(OR^1)N(R^2)(R^3)$ is .

311. The method of any one of Embodiments 306-310 wherein R^{s1} is $-CH_2-Si(R^{s11})_3$, wherein each R^{s11} is independently R but is not $-H$.

312. The method of Embodiment 311, wherein each R^{s11} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl.

313. The method of Embodiment 311, wherein R^{s1} is $-CH_2-SiMePh_2$.

314. The method of any one of Embodiments 306-310 wherein R^{s1} is $-CH_2-S(O)_2R^{s11}$, wherein R^{s11} is independently R but is not $-H$.

315. The method of Embodiment 314, wherein R^{s11} is an optionally substituted group selected from C_{1-6} aliphatic and phenyl.

316. The method of Embodiment 314, wherein R^{s11} is optionally substituted phenyl.

317. The method of Embodiment 314, wherein R^{s11} is phenyl.

318. The method of Embodiment 314, wherein R^{sli} is optionally substituted C_{1-6} aliphatic.

319. The method of Embodiment 314, wherein R^{sli} is optionally substituted C_{1-6} alkyl.

320. The method of Embodiment 314, wherein R^{sli} is t-butyl.

321. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 10 mmol of the product.

322. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 20 mmol of the product.

323. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 50 mmol of the product.

324. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 100 mmol of the product.

325. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 150 mmol of the product.

326. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 200 mmol of the product.

327. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 500 mmol of the product.

328. The method of any one of Embodiment 1-320, wherein the method is carried out at a scale of about or greater than about 1000 mmol of the product.

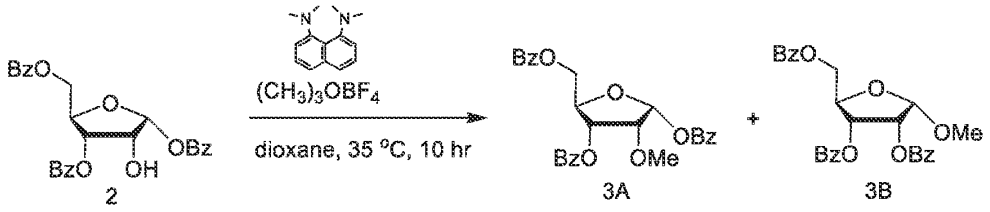
EXEMPLIFICATION

[00276] Non-limiting examples are provided below. A person of ordinary skill in the art appreciates that other technologies, e.g., compounds, compositions, methods, etc., may also be utilized in the present technologies in accordance with the present disclosure.

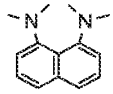
[00277] As described herein, provided technologies can provide a number of advantages, e.g., fewer steps, higher yield, higher crude purity, higher selectivity, higher safety, higher efficiency, and lower cost. Various advantages are demonstrated in Examples below.

[00278] Example 1. Preparation of modified sugars.

[00279] Among other things, the present disclosure provides technologies for preparing modified sugars, e.g., those comprising 2'-OR^{2ak} modifications as described herein. Various technologies for preparing (2R,3R,4R,5R)-5-((benzoyloxy)methyl)-3-methoxytetrahydrofuran-2,4-diyl dibenzoate (3A) are presented below as examples.



[00280] Various conditions are assessed for preparing 3A. In some embodiments, a compound of formula P-2', 3B, was also observed. In some embodiments, certain conditions, e.g., using EtOAc or dioxane as solvent, provides higher yields of 3A. In some embodiments, certain conditions, e.g., using dioxane as solvent, provides higher selectivity for 3A over 3B. In some embodiments, under certain conditions 3B was not observed. Percentage is area % of all peaks (HPLC separation followed by UV detection at 220 nm). In some embodiments, a UV wavelength for detection is 220 nm.

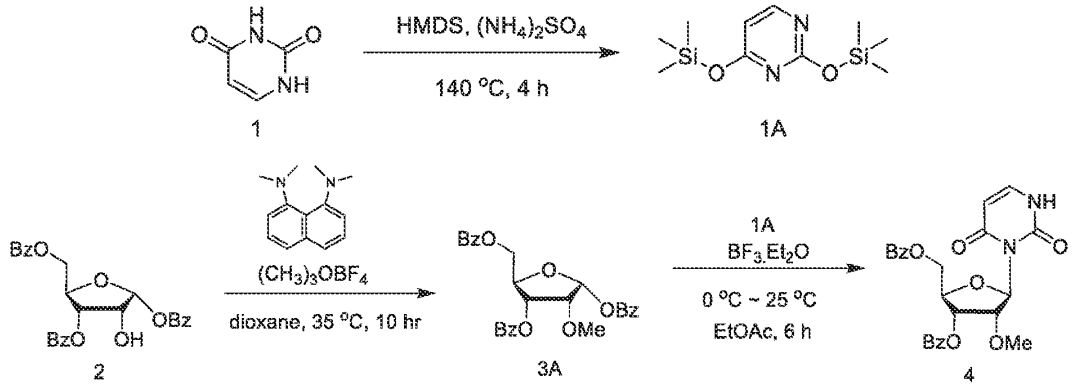
Solvent (volume)	MeCN (40ML)	DMF (40ML)	EtOAc (40ML)	Dioxane (40ML)
1g Compound 2  (3eq.) $(CH_3)_3OBF_4$ (3eq.) 25 °C, 6 h	2:19% 3A: 2.5%	2:100% 3A: 0%*	2: 29%; 3A: 46% 3B: 3%	2: 17%; 3A:40% 3B: 0%

	Solvent (volume)	DCE (10 mL)	THF (10 mL)
33°C 5 h 10 mL	1g Compound 2  (3eq.) $(CH_3)_3OBF_4$ (3eq.)	2: 1% 3A: 15% 3B: 10%	2: 100% 3A: 0%* 3B: 0%
33°C 12 h 20 mL	1g Compound 2  (3eq.) $(CH_3)_3OBF_4$ (3eq.)	2: 6% 3A: 24% 3B: 5%	2: 100% 3A: 0%* 3B: 0%

* No 3A observed under specified test conditions.

[00281] Example 2. Preparation of nucleosides.

[00282] Modified sugars are useful for many applications, e.g., for manufacturing nucleosides comprising modified sugars. A preparation of 3-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-254) is presented below as an example.



[00283] Step 1. For four batches: To a solution of pyrimidine-2,4(1H,3H)-dione (1) (25 g, 223.04 mmol) in HMDS (500 mL) was added $(NH_4)_2SO_4$ (2.95 g, 22.30 mmol, 1.67 mL). The mixture was stirred at 140 °C for 4 hr. TLC indicated compound 1 was consumed completely and one new spot formed. Cool the reaction mixture to 25 °C. The reaction mixture was concentrated under reduced pressure to remove HMDS to afford 2,4-bis((trimethylsilyl)oxy)pyrimidine (1A) (200 g, crude) as a colorless oil, which is directly used for next step.

[00284] Step 2. For four batches: To a solution of (2R,3R,4S,5R)-5-((benzoyloxy)methyl)-3-hydroxytetrahydrofuran-2,4-diyl dibenzoate (2, CAS#2224-41-5) (50 g, 108.12 mmol) in dioxane (1000 mL) was added N^1,N^1,N^8,N^8-tetramethylnaphthalene-1,8-diamine (69.51 g, 324.36 mmol), trimethyloxonium tetrafluoroborate (47.98 g, 324.36 mmol), then the mixture was stirred at 35 °C for 10 hr. LCMS showed compound 2 was consumed completely and desired mass was detected. Four batches was combined together, and the mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 15: 1) to afford (2R,3R,4R,5R)-5-((benzoyloxy)methyl)-3-methoxytetrahydrofuran-2,4-diyl dibenzoate (3A) (153 g, 74.3% yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.12 - 8.00 (m, 6H), 7.73 - 7.65 (m, 3H), 7.58 - 7.46 (m, 6H), 6.70 (d, J = 4.2 Hz, 1H), 5.74-5.72 (m, 1H), 4.86- 4.85 (m, 1H), 4.56 (d, J = 4.4 Hz, 2H), 4.40-4.37 (m, 1H), 3.39 (s, 3H); LCMS: ($M+Na^+$): 499.

[00285] Step 3. For three batches: To a solution of compound 3A (51 g, 107.04 mmol) in EtOAc (800 mL) at -20 °C was added compound 1A (41.17 g, 160.55 mmol) and $BF_3.Et_2O$ (197.49 g, 1.39 mol, 171.13 mL) under N_2. The mixture was stirred at 0 ~ 25 °C for 6 hr. LCMS showed compound 3A was consumed completely and desired mass was detected. Four batches were combined together, and the reaction mixture was adjusted to pH = 7 by sat. $NaHCO_3$ at 0 °C, and then extracted with EtOAc (300 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1) to give ((2R,3R,4R,5R)-3-(benzoyloxy)-5-(2,6-dioxo-3,6-dihydropyrimidin-

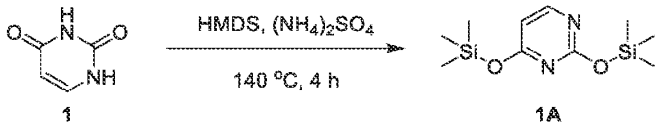
1(2H)-yl)-4-methoxytetrahydrofuran-2-yl)methyl benzoate (4) (123 g, 82.6% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 11.41 - 11.19 (m, 1H), 8.03 - 7.93 (m, 4H), 7.71 - 7.60 (m, 2H), 7.56 - 7.43 (m, 5H), 6.31 (d, J = 2.4 Hz, 1H), 5.72 (t, J = 7.2 Hz, 1H), 5.64 (d, J = 7.6 Hz, 1H), 4.66 - 4.53 (m, 2H), 4.53 - 4.43 (m, 2H), 3.24 (s, 3H); LCMS: ($M+Na^+$): 489.2, purity: 98.88%.

[00286] Step 4. For four batches: To a solution of compound 4 (30.78 g, 65.99 mmol) in MeOH (500 mL) was added NaOMe (10.69 g, 197.97 mmol) at 25 °C for 12 hr. LCMS showed compound 4 was consumed completely and desired mass was detected. Four batches were combined together, and the reaction mixture was added NH_4Cl (11g * 4) and then the mixture was filtered and concentrated. The residue was purified by column chromatography (SiO_2, Ethyl acetate: Methanol = 1: 0 to 10: 1) to give 3-((2R,3R,4R,5R)-4-hydroxy-5-(hydroxymethyl)-3-methoxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (5) (59 g, 89.4% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 11.33 - 11.02 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 6.09 (d, J = 3.0 Hz, 1H), 5.58 (d, J = 7.6 Hz, 1H), 4.88 (br d, J = 6.4 Hz, 1H), 4.61 (br s, 1H), 4.27 - 4.14 (m, 2H), 3.67-3.66 (m, 1H), 3.59 (br d, J = 11.8 Hz, 1H), 3.39 (br dd, J = 5.6, 11.3 Hz, 1H), 3.33 - 3.27 (m, 3H); LCMS: ($M+Na^+$): 281.0, purity: 100%.

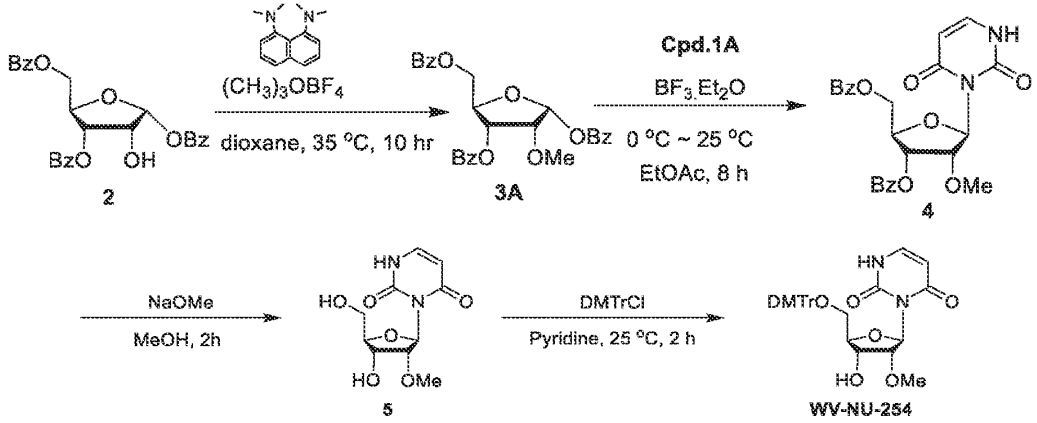
[00287] Step 5. For two batches: A mixture of compound 5 (29.5 g, 114.24 mmol), DMTCl (42.58 g, 125.66 mmol) in pyridine (500 mL) was stirred at 25 °C for 2 hr. TLC indicated compound 5 was consumed completely and new spots formed. Two batches were combined together, and the mixture was concentrated. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 1: 0 to 0: 1) to give 3-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-254) (85.38 g, 66.7% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 11.19 (br s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.4 Hz, 2H), 7.30 - 7.18 (m, 7H), 6.87-6.84 (m, 4H), 6.16 (d, J = 2.4 Hz, 1H), 5.61 (d, J = 7.6 Hz, 1H), 4.86 (d, J = 8.2 Hz, 1H), 4.31 - 4.23 (m, 1H), 4.09-4.07 (m, 1H), 3.86-3.85 (m, 1H), 3.74 (d, J = 1.0 Hz, 6H), 3.34 (s, 3H), 3.18 - 3.06 (m, 2H); LCMS: ($M-H^+$):559.2, purity: 92.92%.

[00288] Example 3. Additional preparations of nucleosides.

[00289] An additional preparation of 3-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxy-3-methoxytetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (WV-NU-254) is presented below as an example.



1 1A



[00290] Step 1. To a solution of compound 1 (95.03 g, 0.8478 mol) in HMDS (1901 mL) was added $(NH_4)_2SO_4$ (11.20 g, 0.0848 mol). The reaction mixture was stirred at 140 °C for 4 h. TLC indicated compound 1 was consumed completely and one new spot was formed. Cool the reaction mixture to room temperature. The reaction mixture was concentrated under reduced pressure to remove HMDS. Compound 1A (210.0 g, crude) was obtained as a colorless oil, which is directly used for next step.

[00291] Step 2. To a solution of compound 2 (300 g, 0.649 mol) in dioxane (6.0 Lit) was added N1,N1,N8,N8-tetramethylnaphthalene-1,8-diamine (417.0 g, 1.946 mol), and trimethyloxonium tetrafluoroborate (286.6 g, 1.938 mol), then the reaction mixture was stirred at 35 °C for 10 h. TLC showed compound 1C was consumed completely and new spots were formed (TLC – 20% Ethyl acetate: hexane). After completion of reaction, RM was evaporated to dryness. The residue was purified by column chromatography (SiO2, hexane: Ethyl acetate =1: 0 to 8:2). Compound 3A (216.0 g, 70% yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.12 - 8.00 (m, 6H), 7.73 - 7.65 (m, 3H), 7.58 - 7.46 (m, 6H), 6.70 (d, J = 4.2 Hz, 1H), 5.74-5.72 (m, 1H), 4.86- 4.85 (m, 1H), 4.56 (d, J = 4.4 Hz, 2H), 4.40-4.37 (m, 1H), 3.39 (s, 3H); LCMS: ($M+Na^+$): 499.

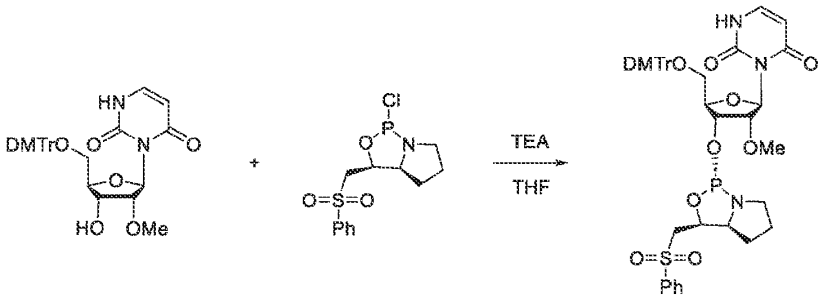
[00292] Step 3. To a solution of compound 3A (231.0 g, 0.484805 mol) in EtOAc (3.60 Lit) at -20 °C and then Compound 1A (186.5 g, 0.7272 mol) and BF_3.Et2O (894.5 g, 777.8 mL, 6.302 mol) was added to reaction mixture under N_2. The mixture was stirred at 0 °C to room temperature for 8 h. TLC showed compound 3A was consumed completely and new spots were formed (TLC: 30% ethyl acetate: hexane). The reaction mixture was adjusted to pH = 7 by sat. $NaHCO_3$ at 0 °C, and then extracted with EtOAc (1200 mL * 3). The residue was purified by column chromatography (SiO_2, hexane: Ethyl acetate = 1:0 to 0:1). Compound 3C (152 g, 67% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 11.41 - 11.19 (m, 1H), 8.03 - 7.93 (m, 4H), 7.71 - 7.60 (m, 2H), 7.56 - 7.43 (m, 5H), 6.31 (d, J = 2.4 Hz, 1H), 5.72 (t, J = 7.2 Hz, 1H), 5.64 (d, J = 7.6 Hz, 1H), 4.66 - 4.53 (m, 2H), 4.53 - 4.43 (m, 2H), 3.24 (s, 3H); LCMS: ($M+Na^+$): 489.2.

[00293] Step 4. To a solution of compound 4 (300.0 g, 0.6431 mol) in MeOH (4.86 Lit) was added NaOMe (104.25 g, 1.929467 mol) at room temperature and stir for 2 h. TLC showed compound 4 was consumed completely and new spots were formed (TLC - 5% MeOH:DCM). The reaction mixture was added NH_4Cl (104.0 g) and then the mixture was filtered and concentrated. The residue was purified by column chromatography (SiO_2, Ethyl acetate: Methanol = 1: 0 to 10: 1). Compound 5 (150.0 g, 90% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d6) δ = 11.33 - 11.02 (m, 1H), 7.46 (d, J = 7.6 Hz, 1H), 6.09 (d, J = 3.0 Hz, 1H), 5.58 (d, J = 7.6 Hz, 1H), 4.88 (br d, J = 6.4 Hz, 1H), 4.61 (br s, 1H), 4.27 - 4.14 (m, 2H), 3.67-3.66 (m, 1H), 3.59 (br d, J = 11.8 Hz, 1H), 3.39 (br dd, J = 5.6, 11.3 Hz, 1H), 3.33 - 3.27 (m, 3H); LCMS: ($M+Na^+$): 281.0.

[00294] Step 5. A mixture of compound 5 (132.0 g, 0.5112 mol), DMTrCl (190.3 g, 0.5623 mol) in Pyridine (2244 mL) was stirred at room temperature. TLC indicated compound 5 was consumed completely and new spots were formed (TLC – 5% MeOH:DCM). The reaction mixture was concentrated to dryness. The residue was purified by column chromatography (SiO_2, Hexane : Ethyl acetate = 1: 0 to 0: 1). Compound WV-NU-254 (180.0 g, 63% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO-d6) δ = 11.19 (br s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 7.4 Hz, 2H), 7.30 - 7.18 (m, 7H), 6.87-6.84 (m, 4H), 6.16 (d, J = 2.4 Hz, 1H), 5.61 (d, J = 7.6 Hz, 1H), 4.86 (d, J = 8.2 Hz, 1H), 4.31 - 4.23 (m, 1H), 4.09-4.07 (m, 1H), 3.86-3.85 (m, 1H), 3.74 (d, J = 1.0 Hz, 6H), 3.34 (s, 3H), 3.18 - 3.06 (m, 2H); LCMS: ($M-H^+$): 559.2, purity: 98.5%.

[00295] Example 4. Preparation of phosphoramidites.

[00296] Various compounds of the present disclosure, e.g., compounds of formula P-5 or salts thereof, are useful for, e.g., manufacturing oligonucleotides. For example, compounds of formula P-5 or salts thereof can be utilized for manufacturing phosphoramidites that are useful for manufacturing oligonucleotides. A preparation of Synthesis of 3-((2R,3R,4R,5R)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-3-methoxy-4-(((1S,3S,3aS)-3-((phenylsulfonyl)methyl)tetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaphosphol-1-yl)oxy)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione is presented as an example.



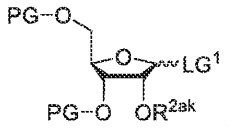
[00297] To a solution of dry 3-[(2R,3S,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-

hydroxy-3-methoxy-tetrahydrofuran-2-yl]-1H-pyrimidine-2,4-dione (30.0 g, 53.5 mmol) in THF (180 mL) was added triethylamine (22.4 mL, 161 mmol). The reaction flask was set in an ice/water bath. (3S,3aS)-3-(benzenesulfonylmethyl)-1-chloro-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,3,2]oxazaphosphole (0.806*M* in THF, 106 mL, 85.6 mmol) was added fast dropwise. The ice/water bath was removed. The resulting slurry was stirred at rt for 1 hr. TLC showed starting material was faint. LCMS showed the reaction conversion rate was 96.3%. The reaction mixture was stirred for another 2 hr. The reaction mixture was then filtered through celite, and the filtrate was concentrated. The resulting crude product was purified by normal phase column chromatography applying 40-100% EtOAc in hexanes (each mobile phase contained 1% triethylamine) as the gradient to afford the title compound as a white foam (37.6 g, 83.2% yield). ^{1}H NMR (600 MHz, Acetonitrile-d3) δ 8.75 (bs, 1H), 7.90 – 7.86 (m, 2H), 7.66 (ddt, J = 8.7, 7.1, 1.2 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.46 – 7.43 (m, 2H), 7.34 – 7.29 (m, 4H), 7.29 – 7.24 (m, 2H), 7.26 (d, J = 7.7 Hz, 1H), 7.22 – 7.18 (m, 1H), 6.85 – 6.81 (m, 4H), 6.20 (d, J = 2.5 Hz, 1H), 5.61 (d, J = 7.7 Hz, 1H), 4.99 – 4.93 (m, 1H), 4.75 (ddd, J = 10.1, 7.9, 6.1 Hz, 1H), 4.14 (dd, J = 6.1, 2.5 Hz, 1H), 3.93 – 3.88 (m, 1H), 3.75 (s, 6H), 3.55 (dq, J = 9.3, 5.8 Hz, 1H), 3.48 – 3.44 (m, 2H), 3.34 (s, 3H), 3.29 – 3.22 (m, 2H), 3.08 (dd, J = 10.4, 6.9 Hz, 1H), 2.70 – 2.62 (m, 1H), 1.76 (dtq, J = 12.3, 8.1, 3.6 Hz, 1H), 1.71 – 1.61 (m, 1H), 1.54 (dddd, J = 10.3, 6.9, 5.7, 3.3 Hz, 1H), 1.15 – 1.05 (m, 1H); ^{31}P NMR (243 MHz, Acetonitrile-d3) δ 146.50; MS (ESI), 842.71 $[M - H]^-$.

[00298] The foregoing written specification is sufficient to enable one skilled in the art to practice technologies of the present disclosure. The present disclosure is not to be limited in scope by examples provided. Examples are intended as illustrations of one or more aspects of technologies of the present disclosure and other functionally equivalent embodiments are within the scope of the technologies of the present disclosure or claims. Various modifications of the disclosure in addition to those shown and described herein may become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages and objects of the disclosure are not necessarily encompassed by each embodiment of the disclosure.

CLAIMS

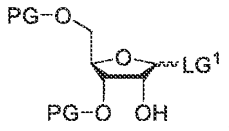
1. A method for preparing a compound of formula P-2:



P-2

or a salt thereof,

comprising reacting a compound of formula P-1:



P-1

or a salt thereof with an alkylating agent, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

LG^1 is a leaving group, or is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$, wherein each R^{LG} is independently R;

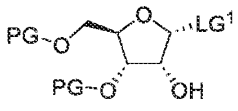
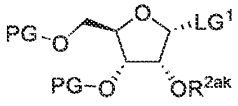
each PG is independently a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R';

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:

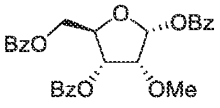
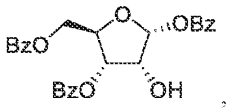
two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

2. The method of claim 1, wherein the compound of formula P-1 is  , and the compound of formula P-2 is  .

3. The method of any one of claims 1-2, wherein the alkylating agent is $(R^{2ak})_3OY$, wherein Y is a counter ion.

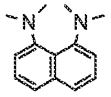
4. The method of any one of claims 1-3, wherein R^{2ak} is methyl.

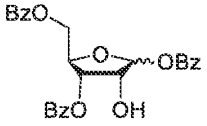
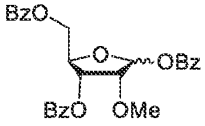
5. The method of any one of claims 1-4, wherein Y is BF_4.

6. The method of claim 1, wherein the compound of formula P-2 is  , the compound of P-1 is  , and the alkylating agent is $(CH_3)_3OBF_4$.

7. The method of any one of claims 1-2, wherein the alkylating agent is a methylating agent, preferably wherein the methylating agent is selected from CH_3I, dimethyl sulfate, dimethyl carbonate, $N(CH_3)_4X$, CH_3OTf, diazomethane, methyl fluorosulfonate, and $(CH_3)_3OY$, wherein X and Y are each independently a counterion.

8. The method of any one of claims 1-7, wherein the reacting is carried out in the presence of a base.

9. The method of any one of claims 1-7, wherein the reacting is carried out in the presence of  .

10. The method of any one of claims 1-3, 5, and 7-10, wherein the compound of formula P-1 is  , and the compound of formula P-2 is  .

11. The method of any one of claims 1-10, wherein LG^1 is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$.

12. The method of any one of claims 1-10, wherein LG^1 is halogen.

13. The method of any one of claims 1-10, wherein LG^1 is $-OR^{LG}$.

14. The method of any one of claims 1-10, wherein LG^1 is $-OC(O)R^{LG}$.

15. The method of any one of claims 1-10, wherein LG^1 is $-OC(O)R^{LG}$ and R^{LG} is optionally substituted C_{6-14} aryl.

16. The method of any one of claims 1-10, wherein LG^1 is $-OC(O)Ph$.

17. The method of any one of claims 1-16, wherein each PG is independently a protecting group;

18. The method of any one of claims 1-16, wherein each occurrence of PG is $-C(O)Ph$.

19. The method of any one of claims 1-18, wherein the reacting is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%.

20. The method of claim 19, wherein the solvent compound has a polarity index lower than dimethylformamide (about 6.4).

21. The method of claim 19, wherein the solvent compound is C_{1-3} alkane substituted with halogen.

22. The method of claim 19, wherein the solvent compound is C_{1-3} alkane substituted with two or more $-Cl$.

23. The method of claim 19, wherein the solvent compound has the structure of R^a-O-R^b, wherein R^a and R^b are each independently selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic, or R^a and R^b are taken together with the oxygen atom to which they are attached to form a 3-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

24. The method of claim 23, wherein each R^a and R^b is independently C_{1-6} alkyl.

25. The method of claim 23, wherein R^a and R^b are taken together with the oxygen atom to which they are attached to form a 4-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

26. The method of claim 19, wherein the solvent compound is R^a–C(O)–OR^b, wherein R^a and R^b are each independently selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic, or R^a and R^b are taken together with the oxygen atom to which they are attached to form a 3-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

27. The method of claim 19, wherein the solvent compound is EtOAc.

28. The method of claim 19, wherein the solvent compound is 1,4-dioxane.

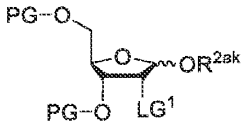
29. The method of claim any one of claims 19-28, wherein the percentage is v%.

30. The method of claim any one of claims 19-29, wherein the percentage is about or at least about 95% v%.

31. The method of any one of claims 1-18, wherein the reacting is carried out in EtOAc.

32. The method of any one of claims 1-18, wherein the reacting is carried out in 1,4-dioxane.

33. The method of any one of claims 1-32, wherein the method produces a compound of formula P-2':



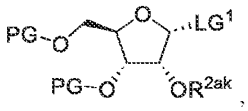
P-2'

or a salt thereof.

34. The method of any one of claims 1-33, wherein the method produces a compound of formula P-2 or a salt thereof over a compound of formula P-2' or a salt thereof.

35. The method of claim 34, wherein the ratio of a compound of formula P-2 or a salt thereof over a compound of formula P-2' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

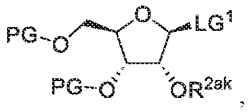
36. The method of any one of claims 1-35, wherein the method produces a compound of formula P-2A:



P-2A

or a salt thereof.

37. The method of any one of claims 1-36, wherein the method produces a compound of formula P-2B:



P-2B

or a salt thereof.

38. The method of any one of claims 1-37, wherein the method selectively produces a compound of formula P-2A or a salt thereof over a compound of formula P-2B or a salt thereof.

39. The method of claim 38, wherein the ratio of a compound of formula P-2A or a salt thereof over a compound of formula P-2B or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

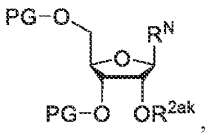
40. The method of any one of claims 1-39, wherein the reacting is performed at about 20-50 °C.

41. The method of any one of claims 1-39, wherein the reacting is performed at about 35 °C.

42. The method of any one of claims 1-41, wherein the concentration of the compound of formula P-1 or a salt thereof is about 1-2000 mg/mL.

43. The method of any one of claims 1-42, wherein the concentration of the compound of formula P-1 or a salt thereof is about 1-3000 mmol.

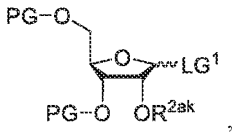
44. A method for preparing a compound of formula P-3:



P-3

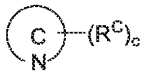
or a salt thereof,

comprising reacting a compound of formula P-2:



P-2

or a salt thereof with a compound of formula P-A:

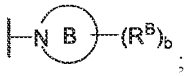


P-A

or a salt thereof, wherein:

each PG is independently a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

each of Ring B and Ring C is independently an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each of R^B and R^C is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each of b and c is independently 0-5;

LG^1 is a leaving group;

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

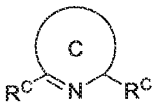
each R is independently $-H$, or an optionally substituted group selected from C_{1-10} aliphatic, C_{1-10}

heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; or

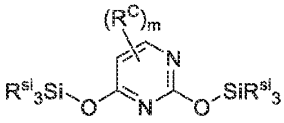
each R is independently −H, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 1-10 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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

45. The method of claim 44, wherein the compound of formula P-A has a structure of  or a salt thereof.

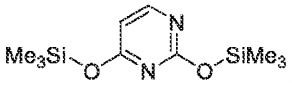
46. The method of any one of claims 44-45, wherein the compound of formula P-A is an optionally substituted or protected nucleobase selected from A, T, C, G, U and tautomers thereof.

47. The method of any one of claims 44-45, wherein the compound of formula P-A has a structure of  or a salt thereof, wherein m is 0-2.

48. The method of any one of claims 44-47, wherein each R^C is independently R, −OR, $-OSi(R^{si})_3$, halogen, −CN, $-NO_2$, $-N(R')_2$, −C(O)R, −C(O)OR, or $-S(O)_2R$.

49. The method of any one of claims 44-47, wherein each R^C is −H.

50. The method of any one of claims 44-49, wherein each R^{si} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl.

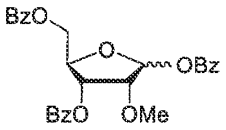
51. The method of any one of claims 44-49, wherein the compound of formula P-A has a structure of  or a salt thereof.

52. The method of any one of claims 44-51, wherein LG^1 is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$.

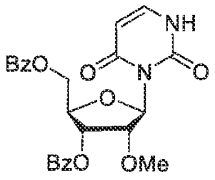
53. The method of any one of claims 44-51, wherein LG^1 is $-OC(O)R^{LG}$.

54. The method of any one of claims 44-51, wherein LG^1 is $-OC(O)Ph$.

55. The method of any one of claims 44-51, wherein the compound of formula P-2 is



56. The method of any one of claims 44-55, the compound of formula P-3 is



57. The method of any one of claims 44-56, wherein the method is reacting out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%.

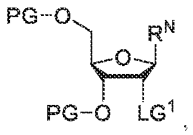
58. The method of any one of claims 44-57, wherein the solvent compound is $R^a-C(O)-OR^b$, wherein R^a and R^b are each independently selected from C_{1-6} aliphatic and C_{3-10} cycloaliphatic, or R^a and R^b are taken together with the oxygen atom to which they are attached to form a 3-10 membered ring having 0-2 additional heteroatoms independently selected from oxygen and nitrogen.

59. The method of claim 58, wherein the solvent compound is EtOAc.

60. The method of any one of claims 44-59, wherein the percentage is v%.

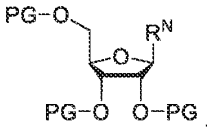
61. The method of claim any one of claims 44-60, wherein the reacting is carried out in EtOAc.

62. The method of any one of claims 44-61, wherein the method produces a compound of formula P-3':



P-3'

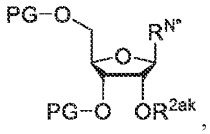
or a salt thereof, preferably wherein the compound of formula P-3' is a compound having the structure of



63. The method of any one of claims 44-62, wherein the method selectively produces a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof.

64. The method of claim 63, wherein the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

65. The method of any one of claims 44-64, wherein the method produces a compound of formula P-3":



P-3"

or a salt thereof, wherein $R^{N"}$ is R^N but is different from R^N in a compound of formula P-3 or a salt thereof.

66. The method of any one of claims 44-65, wherein the method selectively produces a compound of formula P-3 or a salt thereof over a compound of formula P-3" or a salt thereof.

67. The method of claim 66, wherein the ratio of a compound of formula P-3 or a salt thereof over a compound of formula P-3' or a salt thereof is about or at least about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, 40, 50 or 100.

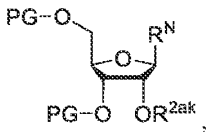
68. The method of claim any one of claims 44-67, wherein the reaction is performed in the presence of a Lewis acid.

69. The method of claim any one of claims 44-67, wherein the reaction is performed in the presence of $BF_3 \cdot Et_2O$.

70. The method of any one of claims 1-43, further comprises a method of one of claims 44-69.

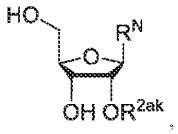
71. A method, comprising:

converting a compound of formula P-3:



P-3

or a salt thereof, into a compound of formula P-4:

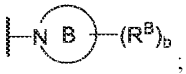


P-4

or a salt thereof, wherein:

each PG is independently a protecting group, or is independently R^p, $-C(O)R^r$, $-Si(R^p)_3$, wherein each R^p is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

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_{1-10} aliphatic, C_{1-10} heteroaliphatic having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, C_{6-14} aryl, a 5-14 membered heteroaryl ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, and a 3-15 membered heterocyclic ring having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur; or

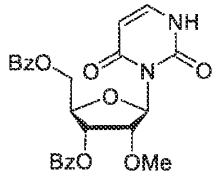
each R is independently $-H$, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

72. The method of claim 71, wherein each occurrence of PG is $-C(O)Ph$.

73. The method of any one of claims 71-72, wherein the converting is carried out in the presence of a base.



74. The method of any one of claims 71-73, the compound of formula P-3 is .

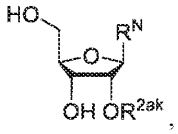
75. The method of any one of claims 71-74, wherein the converting is carried out in a solvent system comprising a solvent compound, wherein the percentage of the compound in the solvent system is about or at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, 99% or 100% v% or wt%.

76. The method of claim any one of claims 71-73, wherein the converting is carried out in MeOH.

77. The method of any one of claims 1-70, further comprises a method of one of claims 71-76.

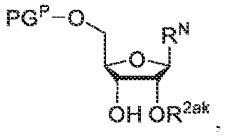
78. A method, comprising:

reacting a compound of formula P-4:



P-4

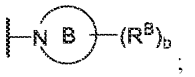
or a salt thereof, with a protecting agent to provide a compound of formula P-5:



P-5

or a salt thereof, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is  ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom, 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, –OR, $-OSi(R^{si})_3$, halogen, –CN, $-NO_2$, $-N(R')_2$, –C(O)R, –C(O)OR, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

PG^P is a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

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

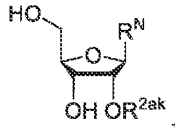
each R is independently $-H$, or an optionally substituted group selected from C_{1-30} aliphatic, C_{1-30} heteroaliphatic having 1-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon, C_{6-30} aryl, C_{6-30} arylaliphatic, C_{6-30} arylheteroaliphatic having 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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon; or

a method, comprising:

reacting a compound of formula P-4:



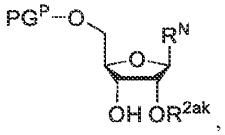
P-4

or a salt thereof, with a compound of formula P-B:

$PG\text{-}LG^2$,

P-B

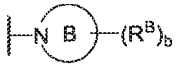
or a salt thereof, to provide a compound of formula P-5:



P-5

or a salt thereof, wherein:

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

Ring B is an optionally substituted 3-14 membered ring having, in addition to the nitrogen atom,

0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur;

each R^B is independently a protecting group, R, –OR, $-OSi(R^{si})_3$, halogen, –CN, $-NO_2$, $-N(R')_2$, –C(O)R, –C(O)OR, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

LG^2 is a leaving group, or is halogen, $-R^{LG}$, $-OR^{LG}$, $-C(O)R^{LG}$, $-OC(O)R^{LG}$, $-C(O)OR^{LG}$, $-C(O)N(R^{LG})_2$, $-OC(O)N(R^{LG})_2$, $-S(O)R^{LG}$, $-OS(O)R^{LG}$, $-S(O)_2R^{LG}$, or $-OS(O)_2R^{LG}$, wherein each R^{LG} is independently R;

PG^P is a protecting group, or is independently R^P, $-C(O)R^P$, $-Si(R^P)_3$, wherein each R^P is independently R';

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:

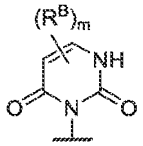
two or more R groups are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

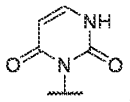
79. The method of claim 78, wherein the reacting is performed in the presence of a base.

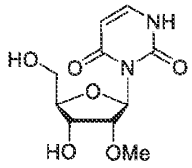
80. The method of any one of claims 78-79, wherein LG^2 is halogen.

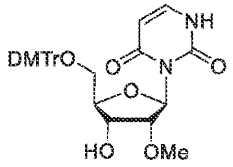
81. The method of any one of claims 78-80, wherein PG^P is –DMTr.

82. The method of any one of claims 44-81, wherein R^{2ak} is methyl.

83. The method of any one of claims 44-82, wherein R^N is an optionally substituted or protected nucleobase selected from A, T, C, G, U and tautomers thereof, or wherein R^N is , wherein m is 0-2.

84. The method of any one of claims 44-82, wherein R^N is .

85. The method of any one of claims 71-82, wherein the compound of formula P-4 is .

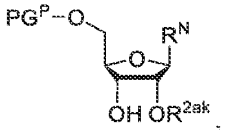
86. The method of any one of claims 78-85, wherein the compound of formula P-5 is .

87. The method of any one of claims 78-86, wherein the compound of formula P-B is DMTr-Cl.

88. The method of any one of claims 1-77, further comprises a method of one of claims 78-87.

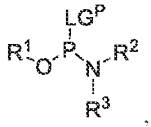
89. The method of any one of the preceding claims, comprising:

reacting a compound having the structure of formula P-5:



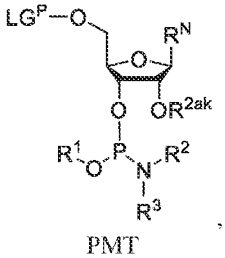
P-5

or a salt thereof with a compound having the structure of formula AX:



AX

or a salt thereof, to provide a compound of formula PMT:

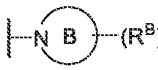


PMT

or a salt thereof, wherein:

PG^P is a protecting group, or is independently R^p, $-C(O)R^p$, $-Si(R^p)_3$, wherein each R^p is independently R';

R^{2ak} is optionally substituted C_{1-6} aliphatic;

R^N is ;

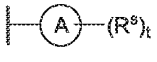
each Ring B is independently an optionally substituted ring selected from a 3-14 membered heterocyclyl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom, and a 5-14 membered heteroaryl ring having 0-6 heteroatoms independently selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom;

each R^B is independently a protecting group, R, $-OR$, $-OSi(R^{si})_3$, halogen, $-CN$, $-NO_2$, $-N(R')_2$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

each R^{si} is independently R; and

each b is independently 0-5;

LG^P is $-Cl$, $-Br$, or $-I$;

each of R^1, R^2, and R^3 is independently R', or two or three of R^1, R^2, and R^3 are taken together with their intervening atoms to form ;

Ring A is an optionally substituted 3-20 membered ring having, in addition to the intervening atoms, 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

t is 0-5;

each R^s is independently $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-N_3$, $-NO$, $-NO_2$, $-L^s-R^{s11}$, $-L^s-OR^{s11}$, $-L^s-SR^{s11}$, $-L^s-S(O)_2R^{s11}$, $-L^s-N(R^{s11})_2$, $-O-L^s-OR^{s11}$, $-O-L^s-SR^{s11}$, $-O-L^s-N(R^{s11})_2$, $-C(R^{s11})_3$ or $-L^s-Si(R^{s11})_3$;

each R^{s11} is independently R';

each L^s is independently L;

each L is independently a covalent bond, or a bivalent, optionally substituted group selected from C_{1-10} aliphatic and C_{1-10} heteroaliphatic group having 1-5 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur, wherein one or more methylene units of L are optionally and independently replaced by $-Cy-$, $-O-$, $-S-$, $-N(R')-$, $-C(O)-$, $-C(S)-$, $-C(NR')-$, $-C(O)N(R')-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2N(R')-$, $-SC(O)-$, or $-C(O)O-$;

$-Cy-$ is an optionally substituted bivalent 3-20 membered ring having 0-10 heteroatoms independently selected from silicon, nitrogen, oxygen, phosphorus and sulfur;

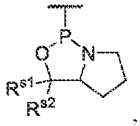
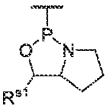
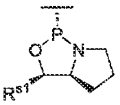
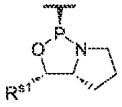
each R' is independently $-R$, $-C(O)R$, $-C(O)OR$, or $-S(O)_2R$;

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 are optionally and independently taken together with their intervening atom(s) to form an optionally substituted, 3-30 membered ring having 0-10 heteroatoms independently selected from oxygen, nitrogen, sulfur, phosphorus and silicon.

90. The method of claim 89, wherein $-P(OR^1)N(R^2)(R^3)$ is $-P(OCH_2CH_2CN)N[CH(CH_3)_2]_2$.

91. The method of claim 89, wherein $-P(OR^1)N(R^2)(R^3)$ is , , , or , wherein each R^{s1} and R^{s2} is independently R^s.

92. The method of claim 91, wherein each R^{s11} is independently an optionally substituted group selected from C_{1-6} aliphatic and phenyl.

93. The method of claim 92, wherein R^{s1} is $-CH_2-SiMePh_2$.

94. The method of claim 91, wherein R^{s1} is $-CH_2-S(O)_2R^{s11}$, wherein R^{s11} is independently R but is not –H.

95. The method of claim 94, wherein R^{s11} is optionally substituted phenyl or C_{1-6} aliphatic.

96. The method of claim 94, wherein R^{s11} is phenyl.

97. The method of claim 94, wherein R^{s11} is t-butyl.

98. The method of any one of claim 1-97, wherein the method is carried out at a scale of about 10, 20, 30, 40, 50, 100, 150, 200, 500, 1000 or more mmol of the product.

99. A method of any one of Embodiments 1-328.