group operatively associates with said first tag via a first linkage ~~for which a polymerase has reduced ability to read or translocate through~~ wherein said first linkage comprises:

a) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

b) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

c) a cross-linking oligonucleotide.

In another aspect, there is provided a complex comprising: (i) a chemical entity comprising one or more scaffolds or one or more building blocks; (ii) *n* number of oligonucleotide tags having *n-1* linkages, wherein *n* is an integer between 1 and 10, and wherein each of said linkages is between two adjacent tags and each tag encodes the identity of at least one of said one or more scaffolds or building blocks; and (iii) a headpiece having a first functional group operatively associated with said chemical entity and a second functional group operatively associated with at least one of said *n* number of tags via a first linkage, wherein ~~a polymerase has reduced ability to read or translocate through~~ at least one of said first linkage and *n-1* linkages comprises:

a) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

b) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

c) a cross-linking oligonucleotide.

In some embodiments, *n* is between 1 and 2, 1 and 3, 1 and 4, 1 and 5, 1 and 6, 1 and 7, 1 and 8, 1 and 9, 1 and 10, 1 and 12, 1 and 15, 1 and 18, 1 and 20, 2 and 3, 2 and 4, 2 and 5, 2 and 6, 2 and 7, 2 and 8, 2 and 9, 2 and 10, 2 and 12, 2 and 15, 2 and 18, 2 and 20, 3 and 4, 3 and 5, 3 and 6, 3 and 7, 3 and 8, 3 and 9, 3 and 10, 3 and 12, 3 and 15, 3 and 18, 3 and 20, 4 and 5, 4 and 6, 4 and 7, 4 and 8, 4 and 9, 4 and 10, 4 and 12, 4 and 15, 4 and 18, or 4 and 20.

In some embodiments, the polymerase has reduced ability to read or translocate through at least about 10% (e.g., about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or even 100%, as compared to control) of the first linkage and *n-1* linkages. In particular embodiments, the polymerase has reduced ability to read or translocate through about 10% to about 100% of the first linkage and *n-1* linkages (e.g., 20% to 100%, 25% to 100%, 50% to 100%, 75% to 100%, 90% to 100%, 95% to 100%, 10% to 95%, 20% to 95%, 25% to 95%, 50% to 95%, 75% to 95%, 90% to 95%, 10% to 90%, 20% to 90%, 25% to 90%, 50% to 90%, or 75% to 90%, as compared to control (e.g., as compared to a control oligonucleotide lacking the linkage)).

In some embodiments, one or more tags include a 5'-connector at the 5'-terminus of the one or more tags and a 3'-connector at the 3'-terminus of the one or more tags. In particular embodiments, each 5'-connector and/or each 3'-connector includes the same sequence. In other embodiments, each 5'-connector and/or each 3'-connector include a different sequence.

In some embodiments, the first linkage and/or *n-1* linkages are at least about 3 angstroms in length (e.g., at least about 5, 8, 10, 15, 20, 30, 35, 40, 50, 60, 65 or 70 angstroms). In some embodiments, the first linkage and/or *n-1* linkages are less than about 30 angstroms in length (e.g., less than about 25, 20, 15, or 10 angstroms).

In some embodiments, a DNA polymerase and/or an RNA polymerase (e.g., as described herein) has reduced ability to read or translocate through the first linkage and/or *n-1* linkages.

In some embodiments, less than about 10% (e.g., about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%) of the first linkage and *n-1* linkages include an enzymatic linkage. In some embodiments, the first linkage and *n-1* linkages include between 0% to 90% enzymatic linkages (e.g., about 0% to 40%, 0% to 45%, 0% to 50%, 0% to 55%, 0% to 60%, 0% to 65%, 0% to 70%, 0% to 75%, 0% to 80%, 0% to 85%, 0% to 90%, 0% to 95%, 0% to 96%, 0% to 97%, 0% to 98%, 0% to 99%, 5% to 40%, 5% to 45%, 5% to 50%, 5% to 55%, 5% to 60%, 5% to 65%, 5% to 70%, 5% to 75%, 5% to 80%, 5% to 85%, 5% to 90%, 5% to 95%, 5% to 96%, 5% to 97%, 5% to 98%, 5% to 99%, 10% to 40%, 10% to 45%, 10% to 50%, 10% to 55%, 10% to 60%, 10% to 65%, 10% to 70%, 10% to 75%, 10% to 80%, 10% to 85%, 10% to 90%, 10% to 95%, 10% to 96%, 10% to 97%, 10% to 98%, 10% to 99%, 15% to 40%, 15% to 45%, 15% to 50%, 15% to 55%, 15% to 60%, 15% to 65%, 15% to 70%, 15% to 75%, 15% to 80%, 15% to 85%, 15% to 90%, 15% to 95%, 15% to 96%, 15% to 97%, 15% to 98%, 15% to 99%, 20% to 40%, 20% to 45%, 20% to 50%, 20% to 55%, 20% to 60%, 20% to

(b) binding said first functional group of said headpiece to a first component of said chemical entity, wherein said headpiece is directly connected to said first component or said headpiece is indirectly connected to said first component by a bifunctional spacer; and

(c) binding said second functional group of said headpiece to a first oligonucleotide tag via a first linkage to form a complex, wherein ~~a polymerase has reduced ability to read or translocate through said first linkage~~ said first linkage comprises:

i) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

ii) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

iii) a cross-linking oligonucleotide;

wherein said steps (b) and (c) can be performed in any order and wherein said first tag encodes for the binding reaction of said step (b), thereby providing a tagged library.

In another embodiment, the disclosure features a method of tagging a first library including an encoded chemical entity, the method including: (a) providing a headpiece having a first functional group and a second functional group (e.g., where the headpiece optionally encodes information); (b) binding the first functional group of the headpiece to a first component of the chemical entity, where the headpiece is directly connected to the first component or the headpiece is indirectly connected to the first component by a bifunctional spacer; and (c) binding the second functional group of the headpiece to a first oligonucleotide tag via a first linkage to form a complex, where a polymerase has reduced ability to read or translocate through the first linkage; where the steps (b) and (c) can be

performed in any order and where the first tag encodes for the binding reaction of the step (b), thereby providing a tagged library.

In one aspect, there is provided a method of tagging a first library comprising an encoded chemical entity, said method comprising:

(a) providing a headpiece having a first functional group and a second functional group;

(b) binding said first functional group of said headpiece to a first component of said chemical entity, wherein said headpiece is directly connected to said first component or said headpiece is indirectly connected to said first component by a bifunctional spacer;

(c) binding said second functional group of said headpiece to a first oligonucleotide tag via a first linkage;

(d) binding n_c number of additional components of said chemical entity, wherein n_c is an integer between 1 and 10; and

(e) binding n_t number of additional oligonucleotide tags having n_t linkages to form a complex, wherein n_t is an integer between 1 and 10 and wherein each of said linkages is between two adjacent tags and each tag encodes the identity of at least one of said components;

wherein ~~a polymerase has reduced ability to read or translocate through~~ at least one of said first linkage and n_t linkages comprises:

i) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

ii) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

iii) a cross-linking oligonucleotide; and

wherein said steps (b) and (c) can be performed in any order and wherein said first tag encodes for the binding reaction of said step (b); wherein said steps (d) and (e) can be performed in any order and wherein each additional tag encodes for the binding reaction of each additional component of said step (d), thereby providing a tagged library.

In yet another embodiment, the disclosure features a method of tagging a first library including an encoded chemical entity, the method including: (a) providing a headpiece having a first functional group and a second functional group (e.g., where the headpiece optionally encodes information); (b) binding the first functional group of the headpiece to a first component of the chemical entity, where the headpiece is directly connected to the first component or the headpiece is indirectly connected to the first component by a bifunctional spacer; (c) binding the second functional group of the headpiece to a first oligonucleotide tag via a first linkage; (d) binding n_c number of additional components of the chemical entity, where n_c is an integer between 1 and 10; and (e) binding n_t number of additional oligonucleotide tags having n_t linkages to form a complex, where n_t is an integer between 1 and 10, where each of the linkages is between two adjacent tags and where each tag encodes the identity of at least one of the components; where a polymerase has reduced ability to read or translocate through at least one of the first linkage and n_t linkages; and where the steps (b) and (c) can be performed in any order and where the first tag encodes for the binding reaction of the step (b); where the steps (d) and (e) can be performed in any order and where each additional tag encodes for the binding reaction of each additional component of the step (d), thereby providing a tagged library.

In some embodiments, n_c and n_t are each independently an integer between 1 and 2, 1 and 3, 1 and 4, 1 and 5, 1 and 6, 1 and 7, 1 and 8, 1 and 9, 1 and 10, 1 and 12, 1 and 15, 1 and 18, 1 and 20, 2 and 3, 2 and 4, 2 and 5, 2 and 6, 2 and 7, 2 and 8, 2 and 9, 2 and 10, 2 and 12, 2 and 15, 2 and 18, 2 and 20, 3 and 4, 3 and 5, 3 and 6, 3 and 7,

In yet another aspect, there is provided a method of screening a plurality of chemical entities, said method comprising: (a) contacting a target with a complex described herein and/or a library described herein; and (b) selecting one or more complexes having a predetermined characteristic for said target, as compared to a control, thereby screening the chemical entity.

In some embodiments, the predetermined characteristic includes increased binding for the target (e.g., a biological target, as described herein), as compared to a control.

In some embodiments, prior to step (a) one or more operations are performed selected from the list consisting of: annealing one or more relay primers with said complex, wherein said one or more relay primers span said first linkage and/or *n-1* linkages; extending said relay primers using a polymerase to produce oligonucleotide fragments; and ligating said oligonucleotide fragments to produce a template.

In another aspect, there is provided a method of determining the nucleotide sequence of a complex described herein, said method comprising: (a) annealing one or more relay primers with said complex, wherein said one or more relay primers span said first linkage and/or *n-1* linkages; (b) extending said relay primers using a polymerase to produce oligonucleotide fragments; (c) ligating said oligonucleotide fragments to produce a template; (d) ~~optionally~~ amplifying said template by polymerase chain reaction to produce an amplified mix; and (e) sequencing said ~~optionally~~ amplified mix to determine the sequence of said complex.

In some embodiments, the complex includes a 5'-connector at the 5'-terminus of one or more tags and a 3'-connector at the 3'-terminus of one or more tags, and where each of the one or more relay primers hybridizes to adjacent 5'- and 3'-connectors. In particular embodiments, each 5'-connector includes the same sequence, and/or each 3'-connector includes the same sequence. In some embodiments, the sequence of at least one of the 5'-connector is complementary to the sequence of the adjacent 3'-connector (e.g., to form a duplex between the 5'- and 3'-connectors under hybridization conditions) or identical or sufficiently similar to allow for hybridization to a complementary oligonucleotide. In further embodiments, the method includes hybridizing the 5'-connecter to the adjacent 3'-connector. In some embodiments, each relay primer for a specific junction (e.g., thereby forming a three-helix junction) between the 5'- and 3'-connectors includes the same sequence.

In one aspect, there is provided a method of determining the nucleotide sequence of a complex described herein, said method comprising:

(a) providing said complex comprising the chemical linkage, wherein said chemical linkage is a cross-linking oligonucleotide that spans the junction between two adjacent tags and that operatively associates with said two adjacent tags via one or more reversible co-reactive groups;

(b) releasing said cross-linking oligonucleotide to produce a template;

(c) ~~optionally~~ amplifying said template by polymerase chain reaction to produce an amplified mix; and

(d) sequencing said ~~optionally~~ amplified mix to determine the sequence of said complex.

In another embodiment, the disclosure features a method of determining the nucleotide sequence of any complex described herein, the method including: (a) providing the complex including the chemical linkage, where the chemical linkage is a cross-linking oligonucleotide that spans the junction between two adjacent tags and that

Claims

1. A complex comprising:

(i) a chemical entity comprising one or more scaffolds or one or more building blocks;

(ii) a first oligonucleotide tag encoding the identity of at least one of said one or more scaffolds or building blocks; and

(iii) a headpiece having a first functional group and a second functional group, wherein said first functional group operatively associates with said chemical entity and said second functional group operatively associates with said first tag via a first linkage wherein said first linkage comprises:

a) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

b) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

c) a cross-linking oligonucleotide.

2. A complex comprising:

(i) a chemical entity comprising one or more scaffolds or one or more building blocks;

(ii) *n* number of oligonucleotide tags having *n-1* linkages, wherein *n* is an integer between 1 and 10, and wherein each of said linkages is between two adjacent tags and each tag encodes the identity of at least one of said one or more scaffolds or building blocks; and

(iii) a headpiece having a first functional group operatively associated with said chemical entity and a second functional group operatively associated with at least one of said *n* number of tags via a first linkage,

wherein at least one of said first linkage and *n-1* linkages comprises:

a) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an

optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

b) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

c) a cross-linking oligonucleotide.

3. The complex of claim 2, wherein said polymerase has reduced ability to read or translocate through at least about 10% of said first linkage and *n-1* linkages.

4. The complex of any one of claims 1 to 3, wherein one or more tags comprise a 5'-connector at the 5'-terminus of said one or more tags and a 3'-connector at the 3'-terminus of said one or more tags.

5. The complex of claim 4, wherein each 5'-connector comprises the same sequence.

6. The complex of claim 4 or 5, wherein each 3'-connector comprises the same sequence.

7. The complex of claim 4, wherein each 5'-connector and/or each 3'-connector comprise a different sequence.

8. The complex of any one of claims 1 to 7, wherein said first linkage and/or *n-1* linkages are at least about 3 angstroms in length.

9. The complex of any one of claims 1 to 8, wherein said first linkage and/or *n-1* linkages are less than about 30 angstroms in length.

10. The complex of any one of claims 1 to 9, wherein a DNA polymerase and/or an RNA polymerase has reduced ability to read or translocate through said first linkage and/or *n-1* linkages.

11. The complex of any one of claims 1 to 10, wherein less than about 50% of said first linkage and *n-1* linkages comprise an enzymatic linkage.

12. The complex of any one of claims 1 to 11, wherein said first linkage and/or *n-1* linkages comprise a chemical linkage.

13. The complex of any one of claims 1 to 12, wherein at least one photo-reactive group, or intercalating moiety is present in a 5'-connector at or in proximity to the 5'-terminus of said tag and/or in a 3'-connector at or in proximity to the 3'-terminus of said tag.

14. The complex of claim 13, wherein the sequence of at least one of said 5'-connector is complementary to the sequence of the adjacent 3'-connector or is identical or is sufficiently similar to allow for hybridization to the same complementary oligonucleotide on either side of the junction in separate hybridization events.

15. The complex of claim 1, wherein said chemical linkage comprises said cross-linking oligonucleotide, wherein the sequence of at least five nucleotides at the 5'-terminus of said cross-linking oligonucleotide is complementary to the sequence of at least five nucleotides at the 3'-terminus of one or more tags, and wherein the sequence of at least five nucleotides at the 3'-terminus of said cross-linking oligonucleotide is complementary to the sequence of at least five nucleotides at the 5'-terminus of one or more tags.

16. The complex of claim 15, wherein said 3'-terminus of one or more tags comprises a 3'-connector.

17. The complex of claim 15 or 16, wherein said 5'-terminus of one or more tags comprises a 5'-connector.

18. The complex of any one of claims 15 to 17, wherein said 5'-terminus and/or 3'-terminus of said cross-linking oligonucleotide comprise a reversible co-reactive group.

19. The complex of claim 16 or 17, wherein said 3'-connector and/or 5'-connector comprise a reversible co-reactive group.

20. The complex of claims 18 or 19, wherein said reversible co-reactive group is a cyanovinylcarbazole group, a cyanovinyl group, an acrylamide group, a thiol group, or a vinyl sulfone group,

21. The complex of any one of claims 1 to 20, wherein said chemical entity is operatively associated to said headpiece via a bifunctional spacer.

22. The complex of any one of claims 1 to 21, wherein said chemical entity is covalently attached to said headpiece.

23. The complex of any one of claims 1 to 22, wherein said headpiece comprises an oligonucleotide selected from the group consisting of a double-stranded oligonucleotide, a single-stranded oligonucleotide, or a hairpin oligonucleotide.

24. The complex of claim 23, wherein said headpiece comprises a primer-binding region.

25. The complex of any one of claims 1 to 24, further comprising one or more first library-identifying tag(s), use tag(s), and/or origin tag(s).

26. The complex of any one of claims 1 to 25, wherein said complex comprises between 2 to 20 tags.

27. The complex of any one of claims 1 to 26, wherein each of said tags comprises from 5 to 75 nucleotides.

28. The complex of any one of claims 1 to 27, wherein each of said tags within an individual tag set comprises about the same mass.

29. The complex of any one of claims 1 to 28, wherein said complex comprises RNA, DNA, modified DNA, and/or modified RNA.

30. The complex of claim 29, wherein said modified DNA or modified RNA is PNA, LNA, GNA, TNA, or a mixture thereof within the same oligonucleotide.

31. The complex of any one of claims 1 to 30, further comprising a tailpiece.

32. A library comprising one or more complexes of any one of claims 1 to 31.

33. The library of claims 1 to 32, wherein said library comprises a plurality of headpieces.

34. The library of claim 33, wherein each headpiece of said plurality of headpieces comprises an identical sequence region and a different encoding region.

35. The library of claim 34, wherein said identical sequence region is a primer-binding region.

36. The library of claim 34 or 35, wherein said different encoding region is a first tag that encodes for use of the library, origin of the library, identity of the library, history of the library, a linkage, a spacer, or addition of a first component; or an oligonucleotide sequence that facilitates hybridization, amplification, cloning, or sequencing technologies.

37. The library of any one of claims 32 to 36, comprising between about 10^2 to 10^{20} complexes.

38. The library of any one of claims 32 to 37, wherein each complex is different.

39. A method of tagging a first library comprising an encoded chemical entity, said method comprising:

(a) providing a headpiece having a first functional group and a second functional group;

(b) binding said first functional group of said headpiece to a first component of said chemical entity, wherein said headpiece is directly connected to said first component or said headpiece is indirectly connected to said first component by a bifunctional spacer; and

(c) binding said second functional group of said headpiece to a first oligonucleotide tag via a first linkage to form a complex, wherein said first linkage comprises:

i) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an

optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

ii) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

iii) a cross-linking oligonucleotide;

wherein said steps (b) and (c) can be performed in any order and wherein said first tag encodes for the binding reaction of said step (b), thereby providing a tagged library.

40. A method of tagging a first library comprising an encoded chemical entity, said method comprising:

(a) providing a headpiece having a first functional group and a second functional group;

(b) binding said first functional group of said headpiece to a first component of said chemical entity, wherein said headpiece is directly connected to said first component or said headpiece is indirectly connected to said first component by a bifunctional spacer;

(c) binding said second functional group of said headpiece to a first oligonucleotide tag via a first linkage;

(d) binding n_c number of additional components of said chemical entity, wherein n_c is an integer between 1 and 10; and

(e) binding n_t number of additional oligonucleotide tags having n_t linkages to form a complex, wherein n_t is an integer between 1 and 10 and wherein each of said linkages is between two adjacent tags and each tag encodes the identity of at least one of said components;

wherein at least one of said first linkage and n_t linkages comprises:

i) a photo-reactive group comprising an intercalating moiety, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group;

ii) an intercalating moiety selected from an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide; or

iii) a cross-linking oligonucleotide; and

wherein said steps (b) and (c) can be performed in any order and wherein said first tag encodes for the binding reaction of said step (b); wherein said steps (d) and (e) can be performed in any order and wherein each additional tag encodes for the binding reaction of each additional component of said step (d), thereby providing a tagged library.

41. The method of claim 40, wherein said polymerase has reduced ability to read or translocate through at least about 10% of said first linkage and n_t linkages.

42. The method of any one of claims 39 to 41, wherein said first component and/or additional components comprise a scaffold or a building block.

43. The method of any one of claims 39 to 42, wherein step (b) comprises binding said headpiece indirectly to said first component via a bifunctional spacer.

44. The method of any one of claims 39 to 43, further comprising binding a use tag and/or an origin tag to said complex.

45. The method of any one of claims 39 to 44, further comprising binding a first library-identifying tag to said complex.

46. The method of claim 45, further comprising providing a second library and combining said first library with said second library.

47. The method of any one of claims 39 to 46, further comprising binding a tailpiece to said complex.

48. The method of any one of claims 39 to 47, further comprising performing split-and-pool synthesis in one or more steps, separating one or more complexes, and/or purifying one or more complexes.

49. The method of any one of claims 39 to 47, further comprising a complex of any one of claims 1 to 31 and/or a library of any one of claims 42 to 38.

50. A method of screening a plurality of chemical entities, said method comprising:

(a) contacting a target with a complex of any one of claims 1 to 31 and/or a library of any one of claims 32 to 38; and

(b) selecting one or more complexes having a predetermined characteristic for said target, as compared to a control, thereby screening said chemical entity.

51. The method of claim 50, where said predetermined characteristic comprises increased binding for said target, as compared to a control.

52. The method of claims 50 or 51, wherein, prior to step (a), one or more operations are performed, said operations being selected from the list consisting of: annealing one or more relay primers with said complex, wherein said one or more relay primers span said first linkage and/or *n-1* linkages; extending said relay primers using a polymerase to produce oligonucleotide fragments; and ligating said oligonucleotide fragments to produce a template.

53. A method of determining the nucleotide sequence of a complex of any one of claims 1 to 31, said method comprising:

(a) annealing one or more relay primers with said complex, wherein said one or more relay primers span said first linkage and/or *n-1* linkages;

(b) extending said relay primers using a polymerase to produce oligonucleotide fragments;

(c) ligating said oligonucleotide fragments to produce a template;

(d) amplifying said template by polymerase chain reaction to produce an amplified mix; and

(e) sequencing said amplified mix to determine the sequence of said complex.

54. The method of claim 53, wherein said complex comprises a 5'-connector at the 5'-terminus of one or more tags and a 3'-connector at the 3'-terminus of one or more tags, and wherein each of said one or more relay primers hybridizes to adjacent 5'- and 3'-connectors.

55. The method of claim 54, wherein each 5'-connector comprises the same sequence.

56. The method of claim 55, wherein each 3'-connector comprises the same sequence.

57. The method of any one of claims 54 to 56, wherein the sequence of at least one of said 5'-connector is complementary to the sequence of the adjacent 3'-connector or is identical

or is sufficiently similar to allow hybridization to the same complementary oligonucleotide on either side of the junction in separate hybridization events.

58. The method of claim 57, further comprising hybridizing said 5'-connecter to said adjacent 3'-connector.

59. The method of any one of claims 54 to 58, wherein each relay primer for a specific junction between the 5'- and 3'-connectors comprises the same sequence.

60. A method of determining the nucleotide sequence of a complex of any one of claims 1 to 31, said method comprising:

(a) providing said complex comprising the chemical linkage, wherein said chemical linkage is a cross-linking oligonucleotide that spans the junction between two adjacent tags and that operatively associates with said two adjacent tags via one or more reversible co-reactive groups;

(b) releasing said cross-linking oligonucleotide to produce a template;

(c) amplifying said template by polymerase chain reaction to produce an amplified mix; and

(d) sequencing said amplified mix to determine the sequence of said complex.

61. The method of claim 60, wherein a portion of said cross-linking oligonucleotide hybridizes to the termini of two adjacent tags, thereby producing a nick or a gap between said two adjacent tags.

62. The method of claim 61, further comprising ligating said tags using a chemical process or an enzymatic process prior to step (b).

63. The method of claim 62, wherein said chemical process or enzymatic process comprises 5'-phosphorylation.

64. The method of any one of claims 53 to 63, further comprising repairing said template prior to said optional amplifying step or said sequencing step.

65. The method of claim 64, wherein said repairing step comprises modifying at least one of said first linkage and/or *n-1* linkages to be a repaired linkage capable of being read or translocated through by a polymerase.

66. The method of claim 65, wherein said polymerase can read or translocate through at least 90% of said repaired linkages.

67. The method of any one of claims 64 to 66, wherein said repairing step comprises providing said template with a repair enzyme.

68. The method of claim 67, wherein said repair enzyme is a photolyase, a glycosylase, an endonuclease, a Flap endonuclease, an apurinic/apyrimidinic (AP) endonuclease, a poly ADP ribose polymerase, or a methyltransferase.

Claims

1. A complex comprising:

(i) a chemical entity comprising one or more scaffolds or one or more building blocks;

(ii) a first oligonucleotide tag encoding the identity of at least one of said one or more scaffolds or building blocks; and

(iii) a headpiece having a first functional group and a second functional group, wherein said first functional group operatively associates with said chemical entity and said second functional group operatively associates with said first tag via a first linkage for which a polymerase has reduced ability to read or translocate through.

2. A complex comprising:

(i) a chemical entity comprising one or more scaffolds or one or more building blocks;

(ii) *n* number of oligonucleotide tags having *n-1* linkages, wherein *n* is an integer between 1 and 10, and wherein each of said linkages is between two adjacent tags and each tag encodes the identity of at least one of said one or more scaffolds or building blocks; and

(iii) a headpiece having a first functional group operatively associated with said chemical entity and a second functional group operatively associated with at least one of said *n* number of tags via a first linkage,

wherein a polymerase has reduced ability to read or translocate through at least one of said first linkage and *n-1* linkages.

3. The complex of claim 2, wherein said polymerase has reduced ability to read or translocate through at least about 10% of said first linkage and *n-1* linkages.

4. The complex of any one of claims 1 to 3, wherein one or more tags comprise a 5'-connector at the 5'-terminus of said one or more tags and a 3'-connector at the 3'-terminus of said one or more tags.

5. The complex of claim 4, wherein each 5'-connector comprises the same sequence.

6. The complex of claim 4 or 5, wherein each 3'-connector comprises the same sequence.

7. The complex of claim 4, wherein each 5'-connector and/or each 3'-connector comprise a different sequence.

8. The complex of any one of claims 1 to 7, wherein said first linkage and/or *n-1* linkages are at least about 3 angstroms in length.

9. The complex of any one of claims 1 to 8, wherein said first linkage and/or *n-1* linkages are less than about 30 angstroms in length.

10. The complex of any one of claims 1 to 9, wherein a DNA polymerase and/or an RNA polymerase has reduced ability to read or translocate through said first linkage and/or *n-1* linkages.

11. The complex of any one of claims 1 to 10, wherein less than about 50% of said first linkage and *n-1* linkages comprise an enzymatic linkage.

12. The complex of any one of claims 1 to 11, wherein said first linkage and/or *n-1* linkages comprise a chemical linkage.

13. The complex of claim 12, wherein said chemical linkage comprises a chemical-reactive group, a photo-reactive group, an intercalating moiety, or a cross-linking oligonucleotide.

14. The complex of claim 13, wherein at least one chemical-reactive group, photo-reactive group, or intercalating moiety is present in a 5'-connector at or in proximity to the 5'-terminus of said tag and/or in a 3'-connector at or in proximity to the 3'-terminus of said tag.

15. The complex of claim 14, wherein the sequence of at least one of said 5'-connector is complementary to the sequence of the adjacent 3'-connector or is identical or is sufficiently similar to allow for hybridization to the same complementary oligonucleotide on either side of the junction in separate hybridization events.

16. The complex of any one of claims 13 to 15, wherein said chemical-reactive group is selected from a pair of an optionally substituted alkynyl group and an optionally substituted azido group; a pair of an optionally substituted diene having a 4 π-electron system and an optionally substituted dienophile or an optionally substituted heterodienophile having a 2 π-electron system; a pair of a nucleophile and a strained heterocyclyl electrophile; a pair of an optionally substituted amino group and an aldehyde or a ketone group; a pair of an optionally substituted amino group and a carboxylic acid group; a pair of an optionally substituted hydrazine and an aldehyde or a ketone group; a pair of an optionally substituted hydroxylamine and an aldehyde or a ketone group; a pair of a nucleophile and an optionally substituted alkyl halide; a platinum complex; an alkylating agent; or a furan-modified nucleotide.

17. The complex of any one of claims 13 to 15, wherein said photo-reactive group comprises an intercalating moiety, a psoralen derivative, an optionally substituted cyanovinylcarbazole group, an optionally substituted vinylcarbazole group, an optionally substituted cyanovinyl group, an optionally substituted acrylamide group, an optionally substituted diazirine group, an optionally substituted benzophenone, an optionally substituted 5-(carboxy)vinyl-uridine group, or an optionally substituted azide group.

18. The complex of any one of claims 13 to 15, wherein said intercalating moiety is a psoralen derivative, an alkaloid derivative, an ethidium cation, an acridine derivative, an anthracycline derivative, or thalidomide.

19. The complex of claim 18, wherein said psoralen derivative is psoralen, 8-methoxypsoralen, or 4-hydroxymethyl-4,5,8-trimethyl-psoralen.

20. The complex of claim 13, wherein said chemical linkage comprises said cross-linking oligonucleotide, wherein the sequence of at least five nucleotides at the 5'-terminus of said cross-linking oligonucleotide is complementary to the sequence of at least five nucleotides at the 3'-terminus of one or more tags, and wherein the sequence of at least five nucleotides at the 3'-terminus of said cross-linking oligonucleotide is complementary to the sequence of at least five nucleotides at the 5'-terminus of one or more tags.

21. The complex of claim 20, wherein said 3'-terminus of one or more tags comprises a 3'-connector.

22. The complex of claim 20 or 21, wherein said 5'-terminus of one or more tags comprises a 5'-connector.

23. The complex of any one of claims 20 to 22, wherein said 5'-terminus and/or 3'-terminus of said cross-linking oligonucleotide comprise a reversible co-reactive group.

24. The complex of claim 21 or 22, wherein said 3'-connector and/or 5'-connector comprise a reversible co-reactive group.

25. The complex of claim 23 or 24, wherein said reversible co-reactive group is a cyanovinylcarbazole group, a cyanovinyl group, an acrylamide group, a thiol group, or a vinyl sulfone group.

26. The complex of any one of claims 1 to 25, wherein said chemical entity is operatively associated to said headpiece via a bifunctional spacer.

27. The complex of any one of claims 1 to 26, wherein said chemical entity is covalently attached to said headpiece.

28. The complex of any one of claims 1 to 27, wherein said headpiece comprises an oligonucleotide selected from the group consisting of a double-stranded oligonucleotide, a single-stranded oligonucleotide, or a hairpin oligonucleotide.

29. The complex of claim 28, wherein said headpiece comprises a primer-binding region.

30. The complex of any one of claims 1 to 29, further comprising one or more first library-identifying tag(s), use tag(s), and/or origin tag(s).

31. The complex of any one of claims 1 to 30, wherein said complex comprises between 2 to 20 tags.

32. The complex of any one of claims 1 to 31, wherein each of said tags comprises from 5 to 75 nucleotides.

33. The complex of any one of claims 1 to 32, wherein each of said tags within an individual tag set comprises about the same mass.

34. The complex of any one of claims 1 to 33, wherein said complex comprises RNA, DNA, modified DNA, and/or modified RNA.

35. The complex of claim 34, wherein said modified DNA or modified RNA is PNA, LNA, GNA, TNA, or a mixture thereof within the same oligonucleotide.

36. The complex of any one of claims 1 to 35, further comprising a tailpiece.

37. A library comprising one or more complexes of any one of claims 1 to 36.

38. The library of claim 37, wherein said library comprises a plurality of headpieces.

39. The library of claim 38, wherein each headpiece of said plurality of headpieces comprises an identical sequence region and a different encoding region.

40. The library of claim 39, wherein said identical sequence region is a primer-binding region.

41. The library of claim 39 or 40, wherein said different encoding region is a first tag that encodes for use of the library, origin of the library, identity of the library, history of the library, a linkage, a spacer, or addition of a first component; or an oligonucleotide sequence that facilitates hybridization, amplification, cloning, or sequencing technologies.

42. The library of any one of claims 37 to 41, comprising between about 10^2 to 10^{20} complexes.

43. The library of any one of claims 37 to 42, wherein each complex is different.

44. A method of tagging a first library comprising an encoded chemical entity, said method comprising:

(a) providing a headpiece having a first functional group and a second functional group;

(b) binding said first functional group of said headpiece to a first component of said chemical entity, wherein said headpiece is directly connected to said first component or said headpiece is indirectly connected to said first component by a bifunctional spacer; and

(c) binding said second functional group of said headpiece to a first oligonucleotide tag via a first linkage to form a complex, wherein a polymerase has reduced ability to read or translocate through said first linkage;

wherein said steps (b) and (c) can be performed in any order and wherein said first tag encodes for the binding reaction of said step (b), thereby providing a tagged library.

45. A method of tagging a first library comprising an encoded chemical entity, said method comprising:

(a) providing a headpiece having a first functional group and a second functional group;

(b) binding said first functional group of said headpiece to a first component of said chemical entity, wherein said headpiece is directly connected to said first component or said headpiece is indirectly connected to said first component by a bifunctional spacer;

(c) binding said second functional group of said headpiece to a first oligonucleotide tag via a first linkage;

(d) binding n_c number of additional components of said chemical entity, wherein n_c is an integer between 1 and 10; and

(e) binding n_t number of additional oligonucleotide tags having n_t linkages to form a complex, wherein n_t is an integer between 1 and 10 and wherein each of said linkages is between two adjacent tags and each tag encodes the identity of at least one of said components;

wherein a polymerase has reduced ability to read or translocate through at least one of said first linkage and n_t linkages; and

wherein said steps (b) and (c) can be performed in any order and wherein said first tag encodes for the binding reaction of said step (b); wherein said steps (d) and (e) can be performed in any order and wherein each additional tag encodes for the binding reaction of each additional component of said step (d), thereby providing a tagged library.

46. The method of claim 45, wherein said polymerase has reduced ability to read or translocate through at least about 10% of said first linkage and n_t linkages.

47. The method of any one of claims 44 to 46, wherein said first component and/or additional components comprise a scaffold or a building block.

48. The method of any one of claims 44 to 47, wherein step (b) comprises binding said headpiece indirectly to said first component via a bifunctional spacer.

49. The method of any one of claims 44 to 48, further comprising binding a use tag and/or an origin tag to said complex.

50. The method of any one of claims 44 to 49, further comprising binding a first library-identifying tag to said complex.

51. The method of claim 50, further comprising providing a second library and combining said first library with said second library.

52. The method of any one of claims 44 to 51, further comprising binding a tailpiece to said complex.

53. The method of any one of claims 44 to 52, wherein said binding step comprises a chemical-reactive group, a photo-reactive group, an intercalating moiety, or a cross-linking oligonucleotide.

54. The method of any one of claims 44 to 53, further comprising performing split-and-pool synthesis in one or more steps, separating one or more complexes, and/or purifying one or more complexes.

55. The method of any one of claims 44 to 53, further comprising a complex of any one of claims 1 to 36 and/or a library of any one of claims 37 to 43.

56. A method of screening a plurality of chemical entities, said method comprising:

(a) contacting a target with a complex of any one of claims 1 to 36 and/or a library of any one of claims 37 to 43; and

(b) selecting one or more complexes having a predetermined characteristic for said target, as compared to a control, thereby screening said chemical entity.

57. The method of claim 56, where said predetermined characteristic comprises increased binding for said target, as compared to a control.

58. The method of claims 56 or 57, wherein, prior to step (a), one or more operations are performed, said operations being selected from the list consisting of: annealing one or more relay primers with said complex, wherein said one or more relay primers span said first linkage and/or *n-1* linkages; extending said relay primers using a polymerase to produce oligonucleotide fragments; and ligating said oligonucleotide fragments to produce a template.

59. A method of determining the nucleotide sequence of a complex of any one of claims 1 to 36, said method comprising:

(a) annealing one or more relay primers with said complex, wherein said one or more relay primers span said first linkage and/or *n-1* linkages;

(b) extending said relay primers using a polymerase to produce oligonucleotide fragments;

(c) ligating said oligonucleotide fragments to produce a template;

(d) optionally amplifying said template by polymerase chain reaction to produce an amplified mix; and

(e) sequencing said optionally amplified mix to determine the sequence of said complex.

60. The method of claim 59, wherein said complex comprises a 5'-connector at the 5'-terminus of one or more tags and a 3'-connector at the 3'-terminus of one or more tags, and wherein each of said one or more relay primers hybridizes to adjacent 5'- and 3'-connectors.

61. The method of claim 60, wherein each 5'-connector comprises the same sequence.

62. The method of claim 61, wherein each 3'-connector comprises the same sequence.

63. The method of any one of claims 60 to 62, wherein the sequence of at least one of said 5'-connector is complementary to the sequence of the adjacent 3'-connector or is identical or is sufficiently similar to

allow hybridization to the same complementary oligonucleotide on either side of the junction in separate hybridization events.

64. The method of claim 63, further comprising hybridizing said 5'-connecter to said adjacent 3'-connector.

65. The method of any one of claims 60 to 64, wherein each relay primer for a specific junction between the 5'- and 3'-connectors comprises the same sequence.

66. A method of determining the nucleotide sequence of a complex of any one of claims 1 to 36, said method comprising:

(a) providing said complex comprising the chemical linkage, wherein said chemical linkage is a cross-linking oligonucleotide that spans the junction between two adjacent tags and that operatively associates with said two adjacent tags via one or more reversible co-reactive groups;

(b) releasing said cross-linking oligonucleotide to produce a template;

(c) optionally amplifying said template by polymerase chain reaction to produce an amplified mix; and

(d) sequencing said optionally amplified mix to determine the sequence of said complex.

67. The method of claim 66, wherein a portion of said cross-linking oligonucleotide hybridizes to the termini of two adjacent tags, thereby producing a nick or a gap between said two adjacent tags.

68. The method of claim 67, further comprising ligating said tags using a chemical process or an enzymatic process prior to step (b).

69. The method of claim 68, wherein said chemical process or enzymatic process comprises 5'-phosphorylation.

70. The method of any one of claims 59 to 69, further comprising repairing said template prior to said optional amplifying step or said sequencing step.

71. The method of claim 70, wherein said repairing step comprises modifying at least one of said first linkage and/or *n-1* linkages to be a repaired linkage capable of being read or translocated through by a polymerase.

72. The method of claim 71, wherein said polymerase can read or translocate through at least 90% of said repaired linkages.

73. The method of any one of claims 70 to 72, wherein said repairing step comprises providing said template with a repair enzyme.

74. The method of claim 73, wherein said repair enzyme is a photolyase, a glycosylase, an endonuclease, a Flap endonuclease, an apurinic/apyrimidinic (AP) endonuclease, a poly ADP ribose polymerase, or a methyltransferase.