

Control of solid-supported intra- vs. inter-strand Stille coupling reactions for synthesis of DNA-oligophenylene conjugates

Chu-Fan Yang, Thanuka Udumulla, Ruojie Sha, James W. Canary**

Department of Chemistry, New York University, New York, NY 10003

ABSTRACT: Programmed DNA structures and assemblies are readily accessible, but site-specific functionalization is critical to realize applications in various fields such as nanoelectronics, nanomaterials and biomedicine. Besides pre- and post-DNA synthesis conjugation strategies, on-solid support reactions offer advantages in certain circumstances. We describe on-solid support internucleotide coupling reactions, often considered undesirable, and a workaround strategy to overcome them. Palladium coupling reactions enabled on-solid support intra- and inter-strand coupling between single-stranded DNAs (ss-DNAs). Dilution with a capping agent suppressed inter-strand coupling, maximizing intra-strand coupling. Alternatively, inter-strand coupling actually proved advantageous to provide dimeric organic/DNA conjugates that could be conveniently separated from higher oligomers, and was more favorable with longer terphenyl coupling partners.

With a few simple tools, structural DNA nanotechnology allows the design and assembly of an unparalleled variety of programmed molecular structures and assemblies.¹⁻³ Covalent conjugation of organic molecules to DNA imparts new functions to DNA assemblies: DNA modified with functional groups create intricate three-dimensional DNA nanostructures.^{3, 4} Synthetic methodology towards functionalized DNA nanostructures should amplify the impact of this field.

Covalent DNA conjugates are formed using synthetic nucleoside analogue reagents in automated DNA synthesis (a “pre-strategy”), or by chemical reaction on natural or post-synthetic DNA molecules (“post-strategy”).⁵⁻¹⁰ The “pre-strategy” usually suffers from low yield of both multi-step synthesis and coupling into DNA sequences, while the “post-strategy” is often impeded by not only difficult purification, but also low coupling yield and incompatibility to reaction conditions.^{11, 12} Alternatively, “on solid support” palladium-catalyzed coupling reactions functionalize nucleotides and oligonucleotides *during* nucleoside oligomerization, while the incipient ssDNA molecule is still

attached to the solid support,¹¹⁻¹⁵ providing easier synthesis and purification, tolerance to harsh reaction conditions, as well as avoiding difficulties in cross-coupling of dsDNA.¹⁶⁻²³ (We note that some authors classify the on solid support strategy together with other post-synthetic methods.²⁴) Polymer templation by DNA sequences attracts our interest for control of dispersity and topology.^{25, 26} However, interstrand coupling may occur on solid support to produce mixtures with bifunctional reagents. Here, we explore inter- and intra-strand coupling, and find that we can control the outcome of the reaction to achieve the desired aim (Figure 1).

Previously, we synthesized several monodisperse organic oligomers on DNA. We combined pre- and post-strategies to prepare nylon nucleic acids.^{25, 27, 28} The same technology created a variety of templated linkages within and between DNA molecules.²⁹⁻³² When 2'-propargyl phosphoramidite reagents became commercially available, we constructed DNA-oligoaniline^{26, 33, 34} and DNA-oligophenylenevinylene^{26, 35} conjugates on the solid support with a synthetic step in

the middle of the automated DNA synthesis. We observed on-solid support inter-strand coupling of bifunctional

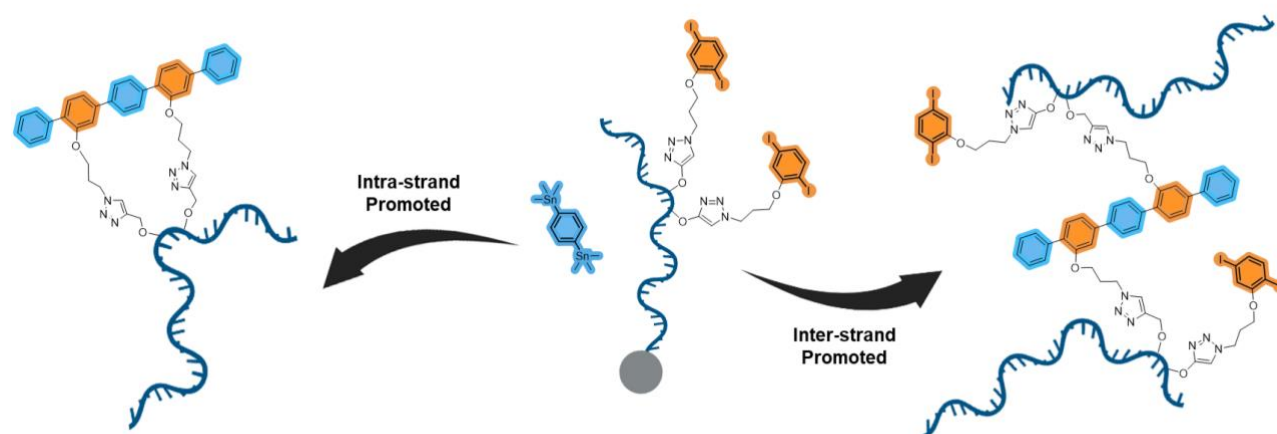


Figure 1. On-solid support inter- and intra-strand coupling reactions.

molecules²⁶ by polyacrylamide gel electrophoresis. We previously used a desymmetrization strategy to avoid inter-strand coupling.³⁴ A recent publication did not report inter-strand coupling in a similar scenario.³⁶

In this paper, we fabricate DNA-polyparaphenylene ladder oligomers (DNA-PPPs). Known for remarkable stiffness and strength, PPPs could provide strong reinforcement to DNA nanostructures similar to DNA-silica hybrid materials.³⁷ An important material in organic electronics, PPP's bipolar doping capability, stability, and other properties lead to its application in batteries and other applications.³⁸⁻⁴⁰ PPP is difficult to synthesize by direct polymerization routes due to insolubility of even short oligomers.⁴¹

We envisaged a sequence of automatic DNA synthesis, conjugation with exogenous reagents, and palladium-catalyzed coupling in solid phase to access DNA-PPP conjugates. We prepared solid supported propargyl-modified single-strand DNAs (ss-DNAs) with commercially available solid supports and nucleoside phosphoramidites. A multistep synthetic sequence gave building blocks with azide groups (Figure S1), which were subsequently subjected to copper-catalyzed azide-alkyne cycloaddition

(CuAAC reaction, known as 'click reaction')⁴²⁻⁴⁴ with previously prepared propargyl-modified ss-DNAs. MALDI-TOF characterization confirmed the complete conversion by click reaction and formation of DNA iodides on two different solid supports (Table S1).

We chose to perform aryl-aryl coupling reactions⁴⁵ on-solid support to leverage the benefits of solid-phase chemistry.^{46, 47} Different named reactions (Suzuki, Stille, etc.) describe reaction conditions used in Pd coupling reactions. We initially worked with organoboron reagents (Suzuki) but found the required base reagents to be incompatible with basic-cleavable CPG solid support with the standard long chain alkylamino (lcaa) linker. Suzuki conditions worked better with basic-uncleavable oligo affinity support polystyrene (OAS PS) solid support, but ultimately the organotin reagents (Stille) allowed better optimization.

We examined a DNA sequence containing a phenyl monoiodide moiety reacting with phenyltrialkyltin (Table S2). We probed solid phase coupling reaction conditions with phenyltrialkyltin, catalyzed by Pd₂dba₃ and AsPh₃ in DMF. MALDI-TOF analysis indicated a failed coupling reaction with commonly used phenyltributyltin coupling

partner. By contrast, phenyltrimethyltin gave complete conversion, consistent with the superiority of trimethyltin over its tributyl analogue in transmetalation, typically the rate-determining step in the Stille coupling reaction.⁴⁸⁻⁵⁰ Besides trimethyltin species, the soluble copper(I) complex $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ also accelerated the on-solid support Stille reactions.⁵⁰⁻⁵² With successful coupling between monoiodide building blocks and phenyltrimethyltin, we turned our attention to the coupling reaction involving 1,4-bis(trimethylstannyl)benzene (C_1), which is expected to provide both intra- and inter-strand coupling products (Figure 1). The anticipated pentaphenyl species (intra-strand product, “monomer”) was observed clearly as a significant product (Figure S15) in MALDI-TOF analysis, accompanied by a minor bis(terphenyl) by-product.

PAGE (polyacrylamide gel electrophoresis) was used to further analyze the reaction mixture to investigate high mass species that are difficult to observe for MALDI-TOF. PAGE indicated that for reactions involving doubly and triply modified DNA strands producing bands with lower mobilities, corresponding to high-mass species (inter-strand products).

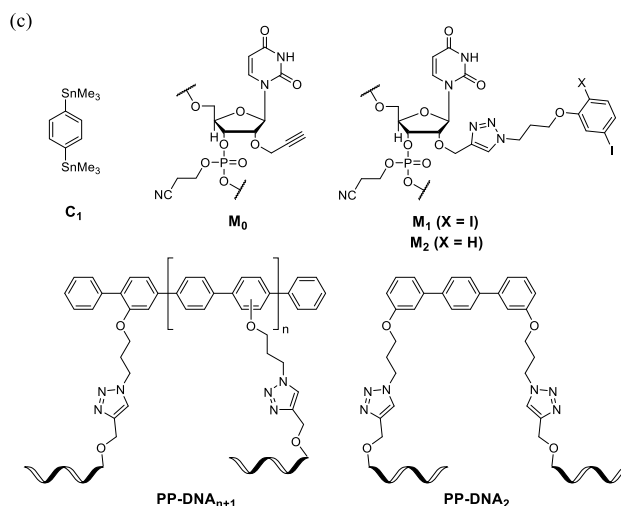
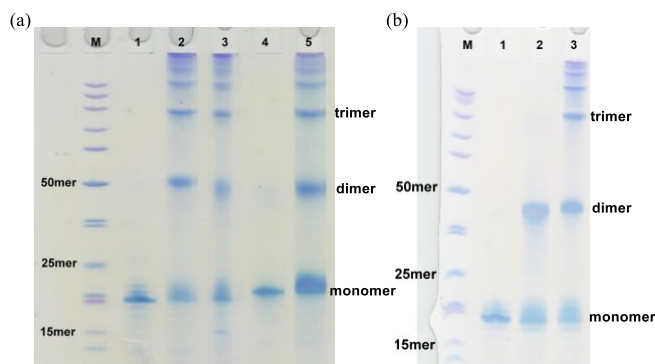


Figure 2. 20% denaturing polyacrylamide gel electrophoresis (PAGE). (a) Lane M: standard DNA size markers. Lane 1: S_1 : 5'-TTT $\text{M}_1\text{M}_1\text{T}$ TTT TTT TTT TTT-3'. Lane 2: Coupling product (PP-DNA_{n+1}) of S_1 . Lane 3: Coupling product (PP-DNA_{n+1}) of S_2 : 5'-TTT M_1TT M_1TT TTT TTT TTT-3'. Lane 4: S_3 : 5'-TTT M_1TT TTT TTT TTT TTT-3'. Lane 5: Coupling product (PP-DNA_{n+1}) of S_3 . (b) Lane M: Standard DNA size markers. Lane 1: S_4 : 5'-TTT M_0TT TTT TTT TTT TTT-3'. Lane 2: Coupling product (PP-DNA_2) of S_5 : 5'-TTT M_2TT TTT TTT TTT TTT-3'. Lane 3: Coupling product (PP-DNA_2) of S_6 : 5'-TTT M_1TT TTT TTT TTT TTT-3'. (c) Coupling partner C_1 . Modified uridines: M_0 , M_1 and M_2 . Structures of inter-strand products PP-DNA_{n+1} and PP-DNA_2 .

These bands were consistent with the generation of oligomers via on-solid support, intermolecular coupling (Figure 2a). The coupling reaction between monoiodide moieties and bis(trimethylstannyl) reagent theoretically yields monomer and dimer products, which aligned with the results observed in the PAGE analysis (Figure 2b, Lane 2). Introducing diiodide building blocks allowed for the formation of oligomers through continuous intermolecular coupling, as demonstrated in Lane 3 (Figure 2b).

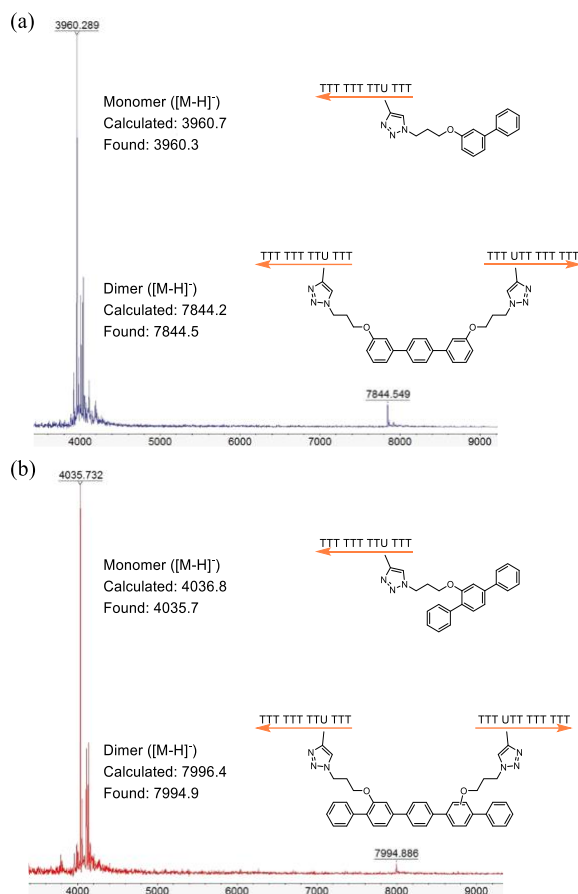


Figure 3. (a) DNA strand: 5'-TTT M₂TT TTT TTT-3'. (b) DNA strand: 5'-TTT M₁TT TTT TTT-3'. Coupling partner C₁.

Our attempts to identify those oligomers by mass spectrometry failed, consistent with our inability to observe high mass DNA conjugates by MALDI-TOF. As an alternative, we confirmed the structures of the oligomers by characterizing the coupling reactions of short T12 strands using 1,4-bis(trimethylstannyl)benzene as the coupling partner. Major peaks corresponding to monomers were found at 3960 Da and 4035 Da, respectively (Figure 3). Weaker but distinct signals representing dimers were detected at 7845 Da for the monoiodide strand and 7995 Da for the diiodide species. The pentaphenyl product may be formed by a variety of sequences of reactions as illustrated in Figure S16. Two proximal aryl iodides may be bridged by a phenyl bis(trimethyltin) reagent. The remaining aryl iodides may react with excess phenyl bis(trimethyltin) reagent to produce pentamer terminated by trimethyltin

substituents. Protodestannylation under the reaction conditions provides the observed product. Three regioisomers of products are likely to be formed, although we did not attempt to separate them.

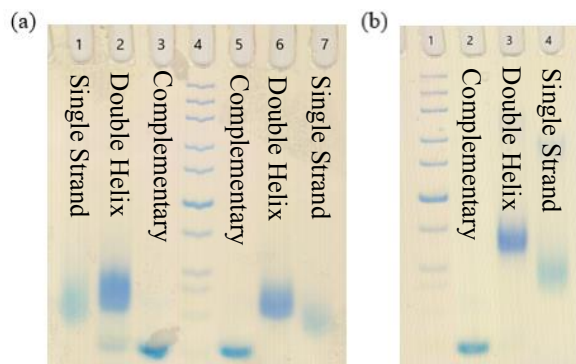


Figure 4: 10% non-denaturing PAGE. (a) Lane 1: HB-S₂ monomer. Lane 2: Duplex of HB-S₂ monomer with its complement. Lane 3: Complementary strand. Lane 4: Standard marker. Lane 5: Complementary strand. Lane 6: Duplex of HB-S₁ monomer with its complement. Lane 7: HB-S₁ monomer. (b) Lane 1: Standard marker. Lane 2: Complementary strand. Lane 3: Duplex of HB-S₂ dimer with its complement. Lane 4: HB-S₂ dimer. ss-DNA strands: HB-S₁: 5'-M₁TG CAG TCT TTT TT-3', HB-S₂: 5'-M₁TM₁ GCA GTC TTT TTT-3', Complementary strand: 5'-AAA AAA GAC TGC AAA-3'

Coupling reactions on singly or doubly modified heterobase strands, consisting of all four ATCG nucleotides was also investigated and observed to undergo inter-strand coupling successfully (Figure S17). As shown in Figure 4a, monomers of both heterobase (HB) strands HB-S₁ and HB-S₂ annealed with complementary strands to form duplexes, indicated by their slower mobility. The high conversion was confirmed by disappearance of both the monomer bands and the complementary bands. The same scenario was observed for dimers (Figure 4b), indicating that heterobase strands remain viable for hybridization after coupling reactions.

To obtain intra-strand coupling, we devised a strategy to "dilute" the DNA strands on solid support by capping them with phosphoramidite without 5'-hydroxy groups and reduce the statistical proximity of the aryl iodides. Figure 5a shows the design by diluting solid supported oligodeoxynucleotides (ODNs) with a biotin additive end-cap. During automated DNA synthesis, a mixture of 90% 5'-

biotin and 10% thymidine was used instead of 100% thymidine. This approach aimed to generate a majority of terminated single-stranded DNA ODNs, which lack any reactive sites for the Stille reaction.

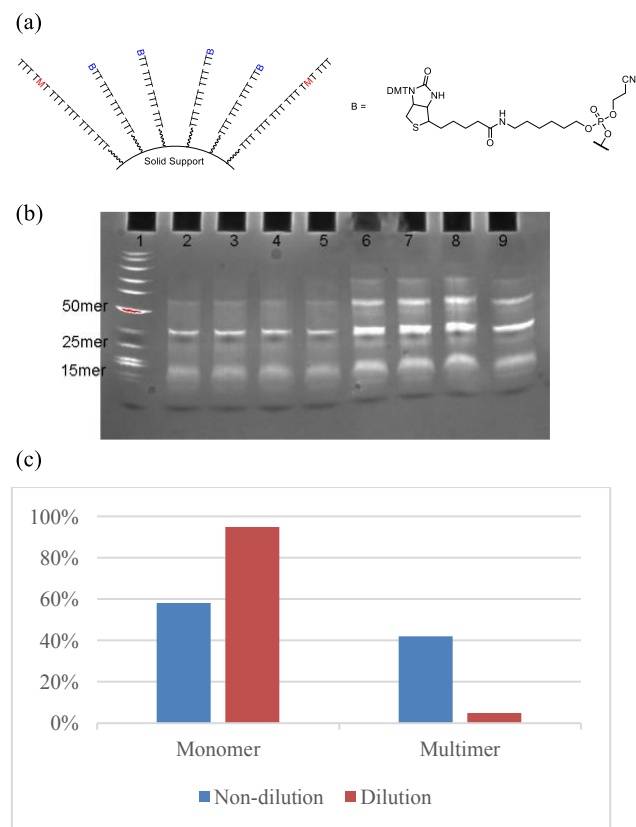


Figure 5: (a) Dilution of ss-DNA on solid support. (b) 20% denaturing PAGE: Lane 1: Standard markers. Lane 2 to 5: Coupling products of S₇ and C₁. Lane 6 to 9: Coupling products of S₈ and C₁. (c) After gel purification, OD₂₆₀ measurement gave relative yields of monomer vs. the sum of multimers: with 100% T, the ratio of monomer : dimer : trimer = 58% : 30% : 12%; with 90% 5'-biotin and 10% T: the ratio of multimers < 5%. ss-DNA strands: S₇: 5'-TTT M₁TM₁ TTT XTT TTT TTT-3'; S₈: 5'-TTT M₁TM₁ TTT TTT TTT TTT-3'; X: amidites mixtures (90% 5'-biotin and 10% T).

We hypothesized that the remaining normal ODNs, not terminated by biotin, would have greater distances between them compared to a typical solid support sample. We conducted polyacrylamide gel electrophoresis (PAGE) analysis of the coupling reactions using these biotin-diluted ODNs. Various diluted ODNs were examined, and the results (Figure 5b) showed minimal material in the high mass range and only a few dimers compared to the reactions using normal single-stranded DNA strands. The gel

purification and following OD₂₆₀ measurement suggested that with the non-diluted solid support, more than 40% of the products were obtained as the dimer and trimer (higher-mass oligomers are excluded here), and less than 60% of the starting strands were involved in the intra-strand coupling. By contrast, with a diluted strand, more than 95% was detected as the monomer that resulted from the intra-strand coupling.

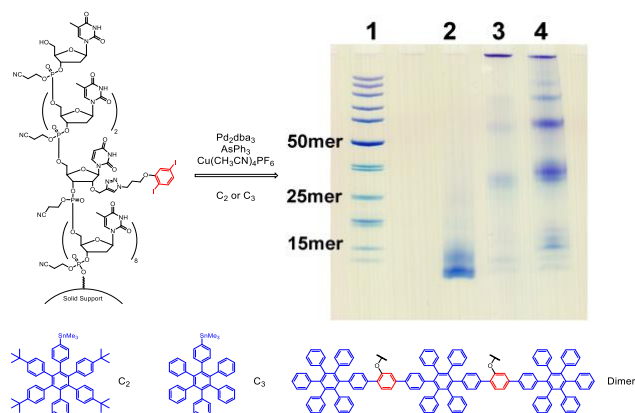


Figure 6: 20% denaturing PAGE: Lane 1: Standard markers. Lane 2: Starting materials. Lane 3: Coupling products with C₂. Lane 4: Coupling products with C₃.

This outcome provided further confirmation that: 1) inter-strand coupling indeed occurs in the on-solid support coupling reactions as the major conversion route, and 2) by increasing the distances between ODNs that possess reactive sites using the biotin dilution strategy, inter-strand coupling was significantly suppressed.

These results hinted that longer coupling partners may favor inter-strand coupling over intra-strand coupling. Instead of suppressing inter-strand couplings, we could promote inter-strand crosslinking between ss-DNAs and fabricate novel materials conjugated to multiple ssDNA. To enable these inter-strand couplings, a new series of hexaarylbis(trimethylstannyl)benzenes were synthesized as coupling partners for Stille reactions. Precise mass determination using MALDI-TOF analysis for these high-mass species, particularly those with large aromatic moieties, proved challenging. However, PAGE analysis

displayed characteristic bands indicating the formation of oligomers (Figure 6). The butylated bis(trimethylstannyl) coupling partner notably gave faint bands for oligomers, apparently with most of the material concentrated in the well. In contrast, the coupling partner lacking t-butyl groups exhibited a well-dispersed lane on the gel, showing intense bands corresponding to dimers and trimers. One possibility is that the hydrophobic nature of the tert-butyl modifications significantly reduces the solubility of DNA-polyaromatic conjugates in the aqueous solution. Moreover, the faint band for the monomer product in Lane 4 clearly indicated a suppression of the intra-strand coupling while inter-strand coupling dominated, which agreed with our hypothesis.

In summary, our strategy differentiates intra- and inter-strand DNA crosslinking on solid support. We optimized solid phase Stille coupling of aryl iodides and bis(trimethylstannyl) coupling partners, using various ss-DNA containing all the canonical bases. The efficiency of our coupling reactions may be attributed to harsher reaction conditions and less hinderance of ssDNA compared to dsDNA coupling.^{16, 17} Diluting the solid supported ODNs with capping reagents and reducing the proximity of reactive ssDNA maximized the yield of intra-strand coupling. Conversely, the use of large stannyl coupling partners promoted inter-strand coupling. Intra- vs. inter-strand coupling products were easily characterized and purified by PAGE. The inter-strand coupling reactions with large coupling partners creates possibilities for more intricate crosslinks and fabrication of prototype PPP hybrid materials. Inter-strand crosslinked DNA, which prevents DNA separation during transcription and replication, is useful in its own right.⁵³ Pristine DNA-PPP ladder products were freely soluble in water and owed to the high compression strength of PPP (207 MPa),³⁸ there's potential applications in DNA origami to improve the structural integrity of DNA nano-constructs. Further, using DNA self-assembly, the DNA-PPP would allow directional orientation

of monodisperse PPP⁵⁴ - a long-standing challenge - to provide a pathway to produce better performing PPP based electronics (FET, Blue-OLED, sensors).^{55, 56} These achievements in intra- and inter-strand couplings present a convenient and controllable approach for DNA functionalization and the fabrication of PPP materials within DNA scaffolds.

ASSOCIATED CONTENT

Supporting Information. Synthetic protocols, additional mass spectra, and other characterization data are included as supporting information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*James W. Canary, Department of Chemistry, New York University, New York, NY 10003

*Ruojie Sha, Department of Chemistry, New York University, New York, NY 10003

ACKNOWLEDGMENT

We acknowledge support of grant N000141912596 from the Office of Naval Research.

REFERENCES

- Seeman, N. C., *Structural DNA Nanotechnology*. Cambridge University Press: UK, 2015.
- Seeman, N. C.; Sleiman, H. F., DNA nanotechnology. *Nature Reviews Materials* **2017**, *3* (1), 17068.
- Zhan, P.; Peil, A.; Jiang, Q.; Wang, D.; Mousavi, S.; Xiong, Q.; Shen, Q.; Shang, Y.; Ding, B.; Lin, C.; Ke, Y.; Liu, N., Recent Advances in DNA Origami-Engineered Nanomaterials and Applications. *Chemical Reviews* **2023**, *123* (7), 3976–4050.
- Madsen, M.; Gothelf, K. V., Chemistries for DNA Nanotechnology. *Chemical Reviews* **2019**, *119* (10), 6384–6458.
- Herdewijn, P., *Oligonucleotide synthesis : methods and applications*. Humana Press: Totowa, N.J., 2005; p xvi, 435 p.
- Weisbrod, S. H.; Marx, A., Novel strategies for the site-specific covalent labelling of nucleic acids. *Chemical Communications* **2008**, (44), 5675-5685.
- Bartosik, K.; Debiec, K.; Czarnecka, A.; Sochacka, E.; Leszczynska, G., Synthesis of Nucleobase-Modified RNA Oligonucleotides by Post-Synthetic Approach. *Molecules* **2020**, *25* (15), 3344.
- Glazier, D. A.; Liao, J.; Roberts, B. L.; Li, X.; Yang, K.; Stevens, C. M.; Tang, W., Chemical Synthesis and Biological Application of Modified Oligonucleotides. *Bioconjugate Chemistry* **2020**, *31* (5), 1213-1233.
- Mckenzie, L. K.; El-Khoury, R.; Thorpe, J. D.; Damha, M. J.; Hollenstein, M., Recent progress in non-native nucleic acid modifications. *Chemical Society Reviews* **2021**, *50* (8), 5126-5164.

10. Štambaský, J.; Hocek, M.; Kočovský, P., C-Nucleosides: Synthetic Strategies and Biological Applications. *Chemical Reviews* **2009**, *109* (12), 6729-6764.
11. Khan, S. I.; Grinstaff, M. W., Palladium(0)-Catalyzed Modification of Oligonucleotides during Automated Solid-Phase Synthesis. *Journal of the American Chemical Society* **1999**, *121* (19), 4704-4705.
12. Ejlersen, M.; Lou, C.; Sanghvi, Y. S.; Tor, Y.; Wengel, J., Modification of oligodeoxynucleotides by on-column Suzuki cross-coupling reactions. *Chemical Communications* **2018**, *54*, 8003-8006.
13. Wicke, L.; Engels, J. W., Postsynthetic on Column RNA Labeling via Stille Coupling. *Bioconjugate Chemistry* **2012**, *23* (3), 627-642.
14. Kapdi, A. R.; Maiti, D.; Sanghvi, Y. S., *Palladium-catalyzed modification of nucleosides, nucleotides and oligonucleotides*. Elsevier: 2018.
15. Okamura, H.; Trinh, G. H.; Dong, Z.; Fan, W.; Nagatsugi, F., Synthesis of 6-Alkynylated Purine-Containing DNA via On-Column Sonogashira Coupling and Investigation of Their Base-Pairing Properties. *Molecules* **2023**, *28* (4), 1766.
16. Šýkorová, V.; Tichý, M.; Hocek, M., Polymerase Synthesis of DNA Containing Iodinated Pyrimidine or 7-Deazapurine Nucleobases and Their Post-synthetic Modifications through the Suzuki-Miyaura Cross-Coupling Reactions. *ChemBioChem* **2022**, *23*, e2021006.
17. Walunj, M. B.; Srivatsan, S. G., Nucleic Acid Conformation Influences Postsynthetic Suzuki-Miyaura Labeling of Oligonucleotides. *Bioconjugate Chemistry* **2020**, *31* (11), 2513-2521.
18. Teo, Y. N.; Kool, E. T., DNA-Multichromophore Systems. *Chemical Reviews* **2012**, *112* (7), 4221-4245.
19. Badi, N.; Lutz, J.-F., Sequence control in polymer synthesis. *Chemical Society Reviews* **2009**, *38*, 3383-3390.
20. Chen, W.; Schuster, G. B., Precise Sequence Control in Linear and Cyclic Copolymers of 2,5-Bis(2-thienyl)pyrrole and Aniline by DNA-Programmed Assembly. *Journal of American Chemical Society* **2013**, *135* (11), 4438-4449.
21. Nezakati, T.; Seifalian, A.; Tan, A.; Seifalian, A. M., Conductive Polymers: Opportunities and Challenges in Biomedical Applications. *Chemical Reviews* **2018**, *118* (14), 6766-6843.
22. Datta, B.; Schuster, G. B.; McCook, A.; Harvey, S. C.; Zakrzewski, K., DNA-Directed Assembly of Polyanilines: Modified Cytosine Nucleotides Transfer Sequence Programmability to a Conjoined Polymer. *Journal of American Chemical Society* **2006**, *128* (45), 14428-14429.
23. Xu, X.; Winterwerber, P.; Ng, D.; Wu, Y., DNA-Programmed Chemical Synthesis of Polymers and Inorganic Nanomaterials. *Topics in Current Chemistry* **2020**, *378*, 31.
24. Bartosik, K.; Debiec, K.; Czarnecka, A.; Sochacka, E.; Leszczynska, G., Synthesis of Nucleobase-Modified RNA Oligonucleotides by Post-Synthetic Approach. *Molecules* **2020**, *25* (15), 3342.
25. Liu, Y.; Wang, R.; Ding, L.; Sha, R.; Lukeman, P. S.; Canary, J. W.; Seeman, N. C., Thermodynamic Analysis of Nylon Nucleic Acids. *ChemBioChem* **2008**, *9* (10), 1641-1648.
26. Wang, X.; Li, C.; Niu, D.; Sha, R.; Seeman, N. C.; Canary, J. W., Construction of a DNA Origami Based Molecular Electro-optical Modulator. *Nano Letters* **2018**, *18* (3), 2112-2115.
27. Liu, Y.; Wang, R.; Ding, L.; Sha, R.; Seeman, N. C.; Canary, J. W., Templated synthesis of nylon nucleic acids and characterization by nuclease digestion. *Chemical Science* **2012**, *3* (6), 1930.
28. Zhu, L.; Lukeman, P. S.; Canary, J. W.; Seeman, N. C., Nylon/DNA: Single-Stranded DNA with a Covalently Stitched Nylon Lining. *Journal of the American Chemical Society* **2003**, *125* (34), 10178-10179.
29. Li, D.; Wang, X.; Shi, F.; Sha, R.; Seeman, N. C.; Canary, J. W., Templated DNA ligation with thiol chemistry. *Org. Biomol. Chem.* **2014**, *12* (44), 8823-8827.
30. Liu, Y.; Kuzuya, A.; Sha, R.; Guillaume, J.; Wang, R.; Canary, J. W.; Seeman, N. C., Coupling Across a DNA Helical Turn Yields a Hybrid DNA/Organic Catenane Doubly Tailed with Functional Termini. *Journal of the American Chemical Society* **2008**, *130* (33), 10882-10883.
31. Liu, Y.; Sha, R.; Wang, R.; Ding, L.; Canary, J. W.; Seeman, N. C., 2',2'-Ligation demonstrates the thermal dependence of DNA-directed positional control. *Tetrahedron* **2008**, *64* (36), 8417-8422.
32. Ye, M.; Guillaume, J.; Liu, Y.; Sha, R.; Wang, R.; Seeman, N. C.; Canary, J. W., Site-specific inter-strand cross-links of DNA duplexes. *Chemical Science* **2013**, *4* (3), 1319.
33. Wang, X.; Sha, R.; Knowlton, W. B.; Seeman, N. C.; Canary, J. W.; Yurke, B., Exciton Delocalization in a DNA-Templated Organic Semiconductor Dimer Assembly. *ACS Nano* **2022**, *16* (1), 1301-1307.
34. Wang, X.; Sha, R.; Kristiansen, M.; Hernandez, C.; Hao, Y.; Mao, C.; Canary, J. W.; Seeman, N. C., An Organic Semiconductor Organized into 3D DNA Arrays by "Bottom-up" Rational Design. *Angewandte Chemie International Edition* **2017**, *56* (23), 6445-6448.
35. Wang, X.; Deshmukh, R.; Sha, R.; Birktoft, J. J.; Menon, V.; Seeman, N. C.; Canary, J. W., Orienting an Organic Semiconductor into DNA 3D Arrays by Covalent Bonds. *Angewandte Chemie* **2022**, *134* (5).
36. Orsborne, S. R. E.; Gorman, J.; Weiss, L. R.; Sridhar, A.; Panjwani, N. A.; Divitini, G.; Budden, P.; Palecek, D.; Ryan, S. T. J.; Rao, A.; Collepardo-Guevara, R.; El-Sagheer, A. H.; Brown, T.; Behrends, J.; Friend, R. H.; Auras, F., Photogeneration of Spin Quintet Triplet-Triplet Excitations in DNA-Assembled Pentacene Stacks. *Journal of the American Chemical Society* **2023**, *145* (9), 5431-5438.
37. Liu, X.; Zhang, F.; Jing, X.; Pan, M.; Liu, P.; Li, W.; Zhu, B.; Li, J.; Chen, H.; Wang, L.; Lin, J.; Liu, Y.; Zhao, D.; Yan, H.; Fan, C., Complex silica composite nanomaterials templated with DNA origami. *Nature* **2018**, *559* (7715), 593-598.
38. Friedrich, K.; Sue, H. J.; Liu, P.; Almajid, A. A., Scratch resistance of high performance polymers. *Tribology International* **2011**, *44* (9), 1032-1046.
39. Kong, W.; Ge, X.; Yang, M.; Zhang, Q.; Lu, J.; Wen, H.; Wen, H.; Kong, D.; Zhang, M.; Zhu, X.; Feng, Y., Poly-p-phenylene as a novel pseudocapacitive anode or cathode material for hybrid capacitive deionization. *Desalination* **2023**, *553*.
40. Li, T.; Hu, H.; Cai, T.; Liu, X.; Zhang, Y.; Zhao, L.; Xing, W.; Yan, Z., Ultrafast and Long-Cycle Stable Aluminum Polyphenylene Batteries. *ACS Applied Materials & Interfaces* **2022**, *14* (27), 30927-30936.
41. Abdulkarim, A.; Hinkel, F.; Jansch, D.; Freudenberg, J.; Golling, F. E.; Müllen, K., A New Solution to an Old Problem: Synthesis of Unsubstituted Poly(*para*-phenylene). *Journal of the American Chemical Society* **2016**, *138* (50), 16208-16211.
42. Kolb, H. C.; Finn, M. G. K.; Sharpless, K. B., Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angewandte Chemie International Edition* **2001**, *40* (11), 2004-2021.
43. Huisgen, R., 1,3-Dipolar Cycloadditions. Past and Future. *Angewandte Chemie International Edition in English* **1963**, *2* (10), 565-598.
44. Tornøe, C. W.; Christensen, C.; Meldal, M., Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *The Journal of Organic Chemistry* **2002**, *67* (9), 3057-3064.
45. Stille, J. K., The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles [New Synthetic Methods(58)]. *Angewandte Chemie International Edition in English* **1986**, *25* (6), 508-524.
46. Guillier, F.; Orain, D.; Bradley, M., Linkers and Cleavage Strategies in Solid-Phase Organic Synthesis and Combinatorial Chemistry. *Chemical Reviews* **2000**, *100* (6), 2091-2157.
47. Merrifield, B., Solid Phase Synthesis. *Science* **1986**, *232* (4748), 341-347.
48. Farina, V.; Krishnan, B., Large rate accelerations in the stille reaction with tri-2-furylphosphine and triphenylarsine as palladium ligands: mechanistic and synthetic implications. *Journal of the American Chemical Society* **1991**, *113* (25), 9585-9595.
49. Trost, B. M.; King, S. A.; Schmidt, T., Palladium-catalyzed trimethylenemethane reaction to form methylenetetrahydrofurans.

Aldehyde and ketone substrates and the tin effect. *Journal of the American Chemical Society* **1989**, *111* (15), 5902-5915.

50. Mee, S. P. H.; Lee, V.; Baldwin, J. E., Significant Enhancement of the Stille Reaction with a New Combination of Reagents—Copper(I) Iodide with Cesium Fluoride. *Chemistry - A European Journal* **2005**, *11* (11), 3294-3308.

51. Casado, A. L.; Espinet, P., Quantitative Evaluation of the Factors Contributing to the “Copper Effect” in the Stille Reaction. *Organometallics* **2003**, *22* (6), 1305-1309.

52. Wang, M.; Lin, Z., Stille Cross-Coupling Reactions of Alkenylstannanes with Alkenyl Iodides Mediated by Copper(I) Thiophene-2-carboxylate: A Density Functional Study. *Organometallics* **2010**, *29* (14), 3077-3084.

53. Deans, A. J.; West, S. C., DNA interstrand crosslink repair and cancer. *Nature Reviews Cancer* **2011**, *11* (7), 467-480.

54. Strunk, K.-P.; Abdulkarim, A.; Beck, S.; Marszalek, T.; Bernhardt, J.; Koser, S.; Pisula, W.; Jänsch, D.; Freudenberg, J.; Pucci, A.; Bunz, U. H. F.; Melzer, C.; Müllen, K., Pristine Poly(*para*-phenylene): Relating Semiconducting Behavior to Kinetics of Precursor Conversion. *ACS Applied Materials & Interfaces* **2019**, *11* (21), 19481-19488.

55. Grem, G.; Leditzky, G.; Ullrich, B.; Leising, G., Realization of a blue-light-emitting device using poly(*p*-phenylene). *Advanced Materials* **1992**, *4* (1), 36-37.

56. Kleybolte, M. E.; Vagin, S. I.; Rieger, B., A Polymer Lost in the Shuffle: The Perspective of Poly(*para*)phenylenes. *Macromolecular Chemistry and Physics* **2023**, *224* (3), 2200441.

