Synthesis of Organometallic Oligonucleotides through Oximation with Metalated Benzaldehydes
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ABSTRACT: A phthaloyl-protected aminooxymethyl-C-2′-deoxyribose building block has been prepared and incorporated in the middle of an oligodeoxyribonucleotide. Removal of the phthaloyl protection followed by on-support oximation with either mercurated or palladated benzaldehydes yielded oligonucleotides bearing the respective benzaldoxime metallacycles.

INTRODUCTION
Oligonucleotides functionalized with transition metal ions are studied intensively for potential applications in DNA nanotechnology1−4 as well as diagnostics and chemotherapy5−8. Such structures are typically obtained through coordination of the desired metal ion to a high-affinity ligand within the oligonucleotide. We, on the other hand, have recently become interested in an alternative approach in which the metal ion is held in place by an organometallic bond formed by postsynthetic metatation of an oligonucleotide, incorporating an appropriate “hot spot” in a solution.9 The main advantage of this strategy is that the organometallic complex resists dissociation even at extreme dilution, widening the scope of metal ions usable in intracellular applications from the kinetically inert Pt(II) and Ru(II) to more labile ones, such as Pd(II) and Hg(II). For example, the high thermodynamic stability of kinetically labile metal-mediated base pairs2,3 could be harnessed to promote hybridization of therapeutic oligonucleotides with their target sequences.10 A notable disadvantage is that the formation of carbon—metal bonds often requires conditions hardly compatible with the solubility or chemical stability of oligonucleotides. Even when the metatation is achieved under sufficiently mild conditions, the removal of excess free transition metal ions from the product mixture can present a problem.

Herein, we describe the synthesis of a modified oligonucleotide containing an aminooxymethyl-functionalized residue for the introduction of diverse organometallic complexes through oxime coupling on a solid support. A deoxyribose scaffold bearing the aminooxymethyl function on its β face was chosen so that the resulting benzaldoxime metallacycles would resemble natural nucleosides, allowing high-affinity metal-mediated base pairing with a complementary oligonucleotide. For the same reason, the sequences flanking the metallacyclic residue were the same as in our previous studies on metal-mediated base pairing.11,12 The method described effectively removes the limitations on the reaction conditions used in the preparation of the organometallic complex. Furthermore, the use of oximation for the introduction of conjugate groups to oligonucleotides is well established13 and should proceed predictably, exhibiting little dependence on the structure of the organometallic complex. Finally, any excess reagent is conveniently removed by washing the solid support with appropriate solvents. The utility of the method has been demonstrated with one arylmercury(II) compound and one arylpalladium(II) compound.

RESULTS AND DISCUSSION
Synthesis of the phthaloyl-protected aminoxy sugar 1 and the corresponding phosphoramidite building block 2 is described in Scheme 1. First, lactone 3 was transformed to the corresponding lactol 4 by treatment with DIBAL-H, as described previously.14 The reaction with vinyl magnesium bromide then provided compound 5 as a mixture of two
Scheme 1. Synthesis of Aminooxy Sugar 1 and the Corresponding Phosphoramidite Building Block 2

Reagents and conditions: (a) DIBAL-H, THF, −78 °C, 1 h; (b) C₃H₇MgBr, THF, 0 °C, 4 h; (c) MsCl, pyridine, CH₂Cl₂, −25 °C, 12 h; (d) (i) RuCl₃, NaIO₄, CeCl₃, MeCN, EtOAc, H₂O, 25 °C, 10 min; (ii) NaIO₄, THF, H₂O, Et₂O, 25 °C, 90 min; (e) NaBH₄, EtOH, Et₂O, 25 °C, 3 h; (f) MsCl, pyridine, CH₂Cl₂, 25 °C, 3 h; (g) Et,N-3HF, THF, 25 °C, 16 h; (h) HONPhth, DIPEA, DMF, 70 °C, 30 h; (i) DMTrCl, pyridine, 25 °C, 12 h; and (j) 2-cyanoethyl-N,N-disopropylchlorophosphoramidite, Et₃N, CH₂Cl₂, N₂ atmosphere, 25 °C, 2 h.

Scheme 2. Synthesis of the Organomercury and Organopalladium Oligonucleotides ON1-Hg and ON1-Pd

Reagents and conditions: (a) H₂NNH₂, AcOH, pyridine, 25 °C, 45 min; (b) 12, DMSO, 25 °C, 12 h; (c) 13, CH₂Cl₂, 25 °C, 12 h; and (d) MeNH₂, NH₃, H₂O, 65 °C, 10 min.
diastereomers ((SR)-S and (SS)-S). Chromatographic separation of the desired diastereomer (SS)-S followed by mesyl chloride-promoted ring closure afforded the β-vinyl C-glycoside 6. Synthesis of an analogous compound with tert-butylidylenedisilysilyl, rather than tert-butylidimethylsilyl, protection by the same pathway has been described in the literature.\(^{15}\) The desired β-stereochemistry was confirmed by a 1D NOESY experiment, where irradiation of the anomic proton (H1) at 4.58 ppm lead to a single positive NOE enhancement at 4.35 ppm, corresponding to H4 (Figure S1, spectra presented in the Supporting Information).

RuO\(_4\) (generated in situ from RuCl\(_3\))-catalyzed dihydroxylation of the vinyl group to a vicinal diol\(^ {16}\) followed by oxidative cleavage with NaIO\(_4\) gave the formyl glycoside anion. It is worth pointing out that attempts to introduce the phthaloyl-protected aminooxy sugar in the middle of the chain was ruled out by 31P NMR (spectrum presented in the Supporting Information).

**EXPERIMENTAL SECTION**

**General Information.** All experiments involving air- and/or moisture-sensitive compounds were performed using oven-dried glassware under an argon atmosphere. For the preparation of HPLC elution buffers, freshly distilled triethylamine was used. Other commercially available chemicals were used without further purification, unless otherwise stated. The solvents for organic synthesis were of reagent grade and were dried over 4 Å molecular sieves. All reactions were monitored by thin-layer chromatography (TLC), performed on Merck 60 (silica gel F254) plates. Chromatographic purification of products was accomplished using flash column chromatography on a silica gel (230–400 mesh) column. 1H, 13C, and 31P NMR spectra were recorded in deuterated solvents on Bruker Biospin 500 and 600 MHz NMR spectrometers. Chemical shifts (δ, ppm) are quoted relative to the residual solvent peak as an internal standard. Mass spectra were recorded on a Bruker microOTOF-Q ESI mass spectrometer.

**Oligonucleotide Synthesis.** The modified oligonucleotide scaffold was assembled on an Applied Biosystems Incoporated 3400 automated DNA/RNA synthesizer by a conventional phosphoramidite strategy. The exocyclic amino functions of adenine, cytosine, and guanine bases were protected by the standard acyl-protecting groups (benzoyl, acetyl, and isobutyryl, respectively). For the phthaloyl-protected aminooxy-C-deoxyriboside phosphoramidite building block 2, the coupling time was extended to 600 s.

Hg(II) ion and one Pd(II) ion, respectively. On the other hand, no exchangeable ligands of the metal centers could be detected. In ON1-Pd, the oxime nitrogen probably occupies one coordination site. While oxime coupling can yield both E and Z isomers of the C==N bond, ortho-palladated benzaldoximes have invariably been reported as palladacycles with the oxygen and the phenyl carbon trans to each other and the nitrogen coordinated to palladium.\(^{21–23}\) Hg(II) tends to form linear complexes, but weak N–Hg bonds in organomercury complexes similar to the one in ON1-Hg have nonetheless been proposed based on X-ray crystallographic evidence.\(^ {24}\)

Possible candidates for the remaining ligands (one in ON1-Hg and two in ON1-Pd) include methylamine and ammonia used for deprotection of the oligonucleotides as well as the HPLC buffer components triethylamine and acetate ion. With ON1-Pd, the presence of a triphenylphosphine ligand was ruled out by 31P NMR (spectrum presented in the Supporting Information).

In summary, we have developed a method for the preparation of covalently metalated oligonucleotides through oxime coupling between aminooxy-functionalized oligonucleotides and organometallic benzaldehyde derivatives. The scope of the method has been demonstrated with Hg(II) and Pd(II) but, in all likelihood, can be expanded to other metals. The most important improvement compared to previously reported methods is that the metalation conditions are not limited by the solubility or chemical stability of oligonucleotides. The metal as well as the organic ligand can be easily varied without the need to synthesize new phosphoramidite building blocks. We therefore believe that our method will enable rapid synthesis of previously unattainable metalated oligonucleotides.
support-bound oligonucleotide was then treated with a mixture of H2NNH2·H2O, pyridine, and AcOH (1:32:8, v/v) for 45 min. The support was washed subsequently with pyridine, methanol, and acetonitrile and dried under vacuum. The support-bound oligonucleotide was placed in two microcentrifuge tubes (approximately 0.25 μmol each), and a solution of either acetato(2-formyl-6-hydroxyphenyl)-mercury19 (12, 10 μmol) in dry DMSO (100 μL) or bromo(2-formylphosphinyl)palladium20 (13, 10 μmol) in dry CH3Cl2 (200 μL) was added. Note that the organomercury compound 12 is potentially highly toxic and should be handled appropriately. The resulting mixtures were shaken for 12 h at 25 °C. The solutions were discarded, and the solid supports were washed with either DMSO or CH3Cl2, and then treated with a mixture of methylamine and 25% aqueous ammonia (1:1, v/v) for 25 min. The support was washed subsequently with pyridine, 25% aqueous ammonia (1:1, v/v) for 10 min at 65 °C. The support was washed with pyridine, and the solution was recovered and evaporated to dryness. The residue was purified by silica gel flash chromatography eluting with a mixture of hexane and EtOAc (24:1, v/v), yielding 343 mg (69%) of 6 as a colorless oil.1H NMR (500 MHz, CDCl3): δ = 5.84 (dd, J = 17.0, 10.0, 7.0 Hz, 1H), 5.30 (s, 1H), 5.12 (d, J = 10.5 Hz, 1H), 4.58 (m, 1H), 4.35 (d, J = 5.0 Hz, 1H), 3.87 (m, 1H), 3.68 (dd, J = 10.5, 4.0 Hz, 1H), 3.47 (dd, J = 10.5, 6.5 Hz, 1H), 1.92 (m, 1H), 1.74 (m, 1H), 0.92 (s, 18H), 0.10 (s, 6H), 0.08 (s, 6H).13C NMR (125 MHz, CDCl3): δ = 138.8, 116.0, 87.8, 79.6, 74.3, 63.9, 41.6, 25.0, 18.4, 18.0, −4.67, −4.69, −5.3, −5.4. HRMS (ESI+): m/z calcd for C19H40O3Si2K [M + K]+, 411.2148; found, 411.2146.

3,5-Di-O-(tert-butyldimethylsilyl)-C-ethenyl-2-deoxy-β-ribofuranose (6). To a solution of (SS)-5 (1.10 g, 2.82 mmol) in CH3Cl2 (15 mL) was added 3.4 mL of dry pyridine. The solution was cooled to −25 °C, and a solution of MsCl (502 μL, 6.49 mmol) in CH3Cl2 (3.0 mL) was added gradually over 30 min with stirring. After standing overnight at −25 °C, the reaction mixture was quenched by addition of 5.0 mL of saturated aqueous NH4Cl. The aqueous phase was extracted with diethyl ether (2 × 20 mL), and the combined organic extracts were dried over anhydrous Na2SO4 and evaporated to dryness. The residue was purified by silica gel flash column chromatography eluting with a mixture of hexane and EtOAc (24:1, v/v), yielding 343 mg (69%) of 6 as a colorless oil.1H NMR (500 MHz, CDCl3): δ = 5.84 (dd, J = 17.0, 10.0, 7.0 Hz, 1H), 5.30 (s, 1H), 5.12 (d, J = 10.5 Hz, 1H), 4.58 (m, 1H), 4.35 (d, J = 5.0 Hz, 1H), 3.87 (m, 1H), 3.68 (dd, J = 10.5, 4.0 Hz, 1H), 3.47 (dd, J = 10.5, 6.5 Hz, 1H), 1.92 (m, 1H), 1.74 (m, 1H), 0.92 (s, 18H), 0.10 (s, 6H), 0.08 (s, 6H).13C NMR (125 MHz, CDCl3): δ = 138.8, 116.0, 87.8, 79.6, 74.3, 63.9, 41.6, 25.0, 18.4, 18.0, −4.67, −4.69, −5.3, −5.4. HRMS (ESI+): m/z calcd for C19H40O3Si2K [M + K]+, 411.2148; found, 411.2146.
mmol) was dissolved in a mixture of EtOH and H₂O (2/1, v/v, 25.0 mL), and the resulting solution was cooled to 0 °C. NaN₃H (142.1 mg, 3.760 mmol) was added, and the resulting mixture was stirred for 3 h at 25 °C. The reaction mixture was then poured into brine (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and evaporated to dryness. The residue was purified by silica gel flash column chromatography eluting with a mixture of hexane and EtOAc (17:3, v/v), yielding 311 mg (88%) of an orange gum. ¹H NMR (500 MHz, CDCl₃): δ = 4.43 (dd, J = 6.0, 4.0 Hz, 1H), 4.39 (dd, J = 10.0, 7.0, 3.0 Hz, 1H), 3.85−3.81 (m, 2H), 3.73−3.67 (m, 2H), 3.46 (dd, J = 12.0, 8.5, 3.0 Hz, 1H), 2.47 (dd, J = 8.5, 3.0 Hz, 1H), 2.11 (m, 1H), 1.87 (m, 1H), 0.93 (s, 9H), 0.91 (s, 9H), 0.10−0.09 (m, 12H). ¹³C NMR (125 MHz, CDCl₃): δ = 78.0, 77.8, 73.1, 64.9, 63.3, 36.9, 25.9, 25.8, 18.4, 18.0, −4.6, −4.8, −5.48, −5.51. HRMS (ESI⁺): m/z calcd for C₁₁H₁₉O₄NNa [M + Na]⁺, 316.0792; found, 316.0792.

5-O-(4,4′-Dimethoxytrityl)-C-phthalamidoxy(methyl-2-deoxy-β-α-ribofuranose (11)). Compound 1 (69.0 mg, 0.235 mmol) was coevaporated from dry pyridine (2 × 10 mL), and the residue was dissolved in dry pyridine (5 mL). DMTrCl (88.0 mg, 0.260 mmol) was added, and the resulting mixture was stirred at room temperature for 12 h, after which it was concentrated under reduced pressure. The residue was diluted with CH₂Cl₂ (20 mL), washed with saturated aqueous NaHCO₃ (20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was evaporated to dryness, and the residue was purified by silica gel flash chromatography eluting with a mixture of hexane, EtOAc, and Et₃N (38:7:5, v/v) to yield 84.2 mg (60%) of 11 as a white foam. ¹H NMR (500 MHz, CDCl₃): δ = 7.83−7.80 (m, 2H), 7.75−7.72 (m, 2H), 7.42−7.40 (m, 2H), 7.32−7.28 (m, 6H), 7.21 (m, 1H), 6.88−6.84 (m, 4H), 4.61 (m, 1H), 4.35 (m, 1H), 4.33−4.28 (m, 2H), 3.95 (m, 1H), 3.81 (s, 6H), 3.21 (dd, J = 9.5, 4.5 Hz, 1H), 3.13 (dd, J = 10.0, 5.5 Hz, 1H), 2.11−2.07 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ = 163.3, 158.5, 144.8, 136.0, 134.4, 131.0, 130.0, 129.0, 128.1, 127.8, 126.8, 123.5, 113.1, 86.2, 79.9, 76.0, 74.1, 64.5, 55.2, 37.4. HRMS (ESI⁺): m/z calcd for C₃₂H₂₄O₁₀N₃Na [M + Na]⁺, 618.2098; found, 618.2096.

3-O-[(2-Cyanooxy)(N,N-diisopropylamino)-phosphonyl]-5-O-(4,4′-dimethoxytrityl)-C-phthalamidoxy(methyl-2-deoxy-β-α-ribofuranose (2)). To a stirred solution of compound 11 (108.0 mg, 0.181 mmol) in dry CH₂Cl₂ (1.5 mL) were added Et₃N (152 μL, 1.09 mmol) and 2-cyanoethyl-N,N-diisopropylchlorophosphoramidite (49 μL, 0.22 mmol). The reaction mixture was stirred at 25 °C under a N₂ atmosphere for 2 h, after which it was diluted with CH₂Cl₂ (20 mL) and washed with saturated aqueous NaHCO₃ (20 mL). The organic phase was dried over anhydrous Na₂SO₄ and evaporated to dryness. The residue was purified by silica gel flash column chromatography eluting with a mixture of hexane, EtOAc, and Et₃N (57:38:5, v/v) to yield 108.4 mg (75% as a mixture of Rₐ and Sₐ diastereomers) of 2 as a white foam. ¹H NMR (500 MHz, CDCl₃, a mixture of Rₐ and Sₐ diastereomers): δ = 7.84−7.81 (m, 2H), 7.74−7.71 (m, 2H), 7.43−7.41 (m, 2H), 7.33−7.27 (m, 6H), 7.22−7.18 (m, 1H), 6.85−6.82 (m, 4H), 4.62 (m, 1H), 4.44 (m, 1H), 4.37−4.35 (m, 2H), 4.13 (m, 1H), 3.81−3.80 (m, 6H), 3.69 (m, 1H), 3.63−3.54 (m, 2H), 3.19 (m, 1H), 3.10 (m, 1H), 2.64 (d, J = 6.5 Hz, 1H), 2.45 (t, J = 6.5 Hz, 1H), 2.14−2.03 (m, 2H), 1.20−1.16 (m, 10H), 1.08−1.07 (m, 3H). ¹³C NMR (125 MHz, CDCl₃, a mixture of Rₐ and Sₐ diastereomers): δ = 163.31, 163.29, 158.4, 144.9, 136.1, 136.04, 136.03, 134.4, 131.03, 131.0, 131.0, 129.0, 128.3, 128.2, 127.77, 127.76, 126.69, 126.66, 123.5, 117.6, 117.5, 113.9, 113.08, 86.19, 86.16, 86.0, 79.96, 79.86, 76.4, 76.3, 75.4, 75.2, 75.0, 74.9, 64.1, 64.0, 58.81, 58.39, 58.3, 58.2, 55.22, 55.2, 43.3, 43.22, 43.19, 43.1, 37.09, 37.06, 36.93, 36.89, 24.65, 24.63, 24.59, 24.57, 24.50, 24.45, 24.41, 20.4, 20.3, 20.2, 20.1. 31P (162 MHz, CDCl₃, an internal standard of Rₚ and Sₚ diastereomers): δ = 148.1, 147.8. HRMS (ESI⁺): m/z calcd for C₃₂H₂₄O₁₀PNa [M + Na]⁺, 818.3177; found, 818.3175.
ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b02804.

NMR spectra of small molecules and HPLC traces and mass spectra of oligonucleotides (PDF)

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S.K.M. carried out all of the experimental work and wrote the first draft of the manuscript. T.A.L. wrote the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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