

### Synthesis of Nucleobase-Functionalized Morpholino-Modified Nucleoside Monomers Through Palladium-Catalyzed Cross-Coupling Reactions

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Morpholino-modified nucleoside analogues have widespread applications in developmental biology. To achieve nucleobase-functionalized forms of morpholino nucleosides, syntheses of 5-substituted cytidine, 8-substituted adenosine, and 8-substituted guanosine morpholino nucleoside monomers are described for the first time. The syntheses are based on the use of 5-iodocytidine, 8-bromoadenosine, and 8bromoguanosine morpholino nucleosides as the key starting materials. These iodo or bromo derivatives have also been synthesized for the first time. Palladium-mediated cross-coupling reactions (Sonogashira, Suzuki, and Heck) were then employed with the halo derivatives to accomplish the substitutions. Different reaction conditions for C, A, and G were standardized to achieve the conversions. The strategy was devised in such a way that the useful *N*-trityl protecting

### Introduction

Morpholino-modified (MO) antisense oligonucleotides (Figure 1, Gene Tools LLC<sup>[1]</sup>) are a special class of DNA analogues extensively used for evaluating the functions of specific genes.<sup>[2]</sup> These reagents can block RNA splicing or translation by targeting to the 5'-UTR region and have high resistance to cellular enzymatic degradation processes.[3,4] They have been employed to study a range of model organisms including sea urchins, zebrafish, frogs, mice, etc.<sup>[5]</sup> Morpholino-modified nucleotides contain regular DNA bases with the modification of the deoxyribose rings by morpholine rings, linked through phosphorodiamidate linkages (Figure 1). Modified oligonucleotides (DNA or siRNA)<sup>[6,7]</sup> containing single morpholino units (T- or Umorpholino) show better efficacy for gene silencing and better resistance towards nuclease activity.<sup>[8]</sup> Applications of MO oligomers are not limited only to antisense activity; these oligomers have also found growing applications in

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groups remain at the end. The catalyst combinations used for Sonogashira, Suzuki, and Heck reactions were Pd-(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>·CuI, Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub>, and Pd(OAc)<sub>2</sub>, respectively. Heck coupling between 5-iodocytidine monomer and methyl acrylate worked well, whereas with acrylonitrile the exocyclic amine of cytidine was found to form the aza-Michael adduct. In this context, treatment of iodocytidine with methyl acrylate under two different sets of conditions was found to produce either the Michael addition product or the Heck coupling product. Four of the functionalized morpholino monomers have been further confirmed by single-crystal X-ray structural analysis. All of these functionalized monomers were obtained in good to excellent overall yields.

nanotechnology<sup>[9]</sup> and in surface hybridization<sup>[10,11]</sup> as neutral DNA analogues. Synthesis and applications of MO triphosphates as chain-terminating reagents in DNA sequencing have been reported recently.<sup>[12,13]</sup> In spite of the potential wide application of morpholinos, nucleobase-functionalized forms of such compounds have yet to be explored; whereas modified oligonucleotides in general have shown significant antiviral<sup>[14]</sup> or anticancer<sup>[14b,15]</sup> activities and bioanalytical applications,<sup>[16]</sup> similar studies on modified morpholino analogues are not well documented. Ideal sites for the incorporation of any group in a nucleobase without



Figure 1. Structural differences between DNA and morpholinomodified oligonucleotides.

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disturbing Watson–Crick base pair formation are the C-5 position in a pyrimidine base and the C-8 position in a purine base. Palladium-catalyzed cross-coupling reactions remain the methods most widely used for introduction of various groups into these positions.<sup>[17]</sup>

Sonogashira, <sup>[18]</sup> Suzuki, <sup>[19]</sup> and Heck<sup>[20]</sup> coupling reactions have been used to prepare modified nucleosides. Many such C-modified nucleoside triphosphates can be enzymatically incorporated into oligonucleotides.<sup>[21]</sup> The presence of a triethylsilylethynyl group in a nucleobase is known to provide transient stability against endonucleases.<sup>[22]</sup> Incorporation of a propyne group in a nucleobase is known to provide better duplex stability in DNA.<sup>[23]</sup> Summerton et al. have reported the synthesis of regular morpholino monomers (A, G, C, and T) and oligomers, but no functionalized forms of these monomers were reported in their patent.<sup>[24]</sup> Recently, we have reported the synthesis of functionalized U-morpholino monomers.<sup>[25]</sup> Here we describe the synthesis of 5-substituted cytidine and 8-substituted adenosine and guanosine morpholino monomers from the corresponding halo derivatives by means of Sonogashira, Suzuki, and Heck coupling reactions. In order to synthesize the key starting materials we required regular morpholino monomers of cytidine, adenosine, and guanosine, which were synthesized by our established protocol.<sup>[26]</sup> Because there is no literature precedence for the synthesis of iodo-/bromo-substituted derivatives of regular morpholino monomers, we then standardized the conditions from the available procedures for the halogenation of nucleosides or ribonucleosides.

#### **Results and Discussion**

# Synthesis of the Morpholino-Modified 5-Iodocytidine Nucleoside

Our initial attempts to iodinate cytidine morpholino nucleoside **2** are described in Table 1.

Our previously established conditions for the iodination of uridine monomer<sup>[25]</sup> with ICl/K<sub>2</sub>CO<sub>3</sub> in MeOH (Table 1, Entry 1) failed miserably to give the desired product 3: we instead isolated the unreacted starting material 2 (20%) and an assortment of unidentified side products. When Ag<sub>2</sub>CO<sub>3</sub> was used as a base (Table 1, Entry 2) the iodo compound 3 was obtained in very poor yield along with the detritylated monomer, unreacted starting material, and several other unidentified side products. *N*-Iodosuccinimide-mediated iodination reactions in DMF under heating or micowave conditions<sup>[27]</sup> were also unsatisfactory in our case (Table 1, Entry 3). Interestingly, though, when the solvent was changed to MeOH, a 52% yield of 3 was obtained, but on a larger scale the yield dropped to 40% because of enhanced detritylation (Table 1, Entry 4).

Notably, in all these cases a certain percentage of the detritylated starting material 1 was isolated as a side product, and so we abandoned the use of the trityl protecting group on the morpholine component, instead deploying the acid-stable trifluoroacetyl derivative 4 (Scheme 1). This Table 1. Attempted iodination of cytidine morpholino monomer  $2^{[a]}$ 



[a] Unless otherwise specified, all reactions were carried out on 0.08 mmol scales. [b] Reaction was carried out under microwave irradiation (200 W) for 8 min. [c] Result on 0.7 mmol scale.

modification allowed us to employ widely used iodination conditions for cytidine<sup>[28]</sup> in acidic media. Accordingly, iodine/iodic acid treatment in  $CCl_4/AcOH$  (1:1) afforded the iodinated product **5** in 91% yield. After removal of the



Scheme 1. Synthesis of *N*-trityl-protected 5-iodocytidine morpholino monomer.



trifluoroacetate group and reprotection with a trityl group (because it is commonly used during oligomerization<sup>[24]</sup>), we isolated the product **3** in 81% overall yield from **1** (Scheme 1). We were also able to isolate a consistent yield of **3** on a larger scale (10 g).

The structure of the iodo derivative **6** was confirmed by X-ray crystal structure determination (Figure 2). In the solid-state structure of **6** we observed two interesting noncovalent interactions: halogen bond<sup>[29]</sup> and C–H/ $\pi$  interactions<sup>[30]</sup> (Figure S1 in the Supporting Information).



Figure 2. ORTEP view of 6 with 30% thermal ellipsoid probability. Hydrogen atoms are omitted for clarity.

#### Sonogashira Coupling of the Morpholino-Modified 5-Iodocytidine Nucleoside

With the iodo-substituted monomer 3 to hand, we attempted Sonogashira coupling with various acetylenes (Table 2). In a model reaction with phenylacetylene, the Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/CuI catalyst system in CH<sub>2</sub>Cl<sub>2</sub>/MeCN (2:1) at room temperature was found to effect clean conversion with excellent yield (Table 2, Entry 1). Use of other diversely substituted acetylene counterparts allowed us to achieve C-5-substituted cytidine morpholino monomers ornamented with diversified functionalities in good to excellent yields. Excesses (2.1-2.5 equiv.) of acetylenes were needed, due to the formation of homocoupled acetylene byproducts. Different aromatic (Table 2, Entries 1-3), aliphatic (Table 2, Entries 4–10), and heteroaromatic (Table 2, Entry 11) acetylenes responded smoothly. Dansyl-labeled morpholino monomer 7j might be useful as a fluorescent probe and was synthesized in 91% yield. An X-ray crystal structure of 7i is shown in Figure 3.

The absorption/emission spectra of 7j show an absorption maximum at 304 nm and an emission maximum at 512 nm, which corresponds to green fluorescence (Figure 4).

Ferrocene-containing cytidine morpholino monomer 7l was synthesized and its redox behavior in  $CH_2Cl_2$  in the potential range between 0 and +1.1 V was studied by cyclic voltammetry (TBAP, 0.1 M) with a platinum disc as working electrode. The potential is referenced to the saturated Ag/AgCl electrode. A reversible oxidative response appeared near 0.61 V (Figure 5). This higher value (relative to 0.43 in the case of ferrocene/ferrocenium) is attributed to the re-





[a] Reaction conditions: reactions were performed on 0.12–0.2 mmol scales. [b] Isolated yields. [c] Conversion of **3** when 2.5 equiv. of cyclohexylacetylene was used. [d]  $Pd(PPh_3)_2Cl_2$  (6 mol-%) and CuI (16 mol-%) were added. [e] DMF as solvent, Et<sub>3</sub>N (6 equiv.),  $Pd(PPh_3)_2Cl_2$  (6 mol-%), CuI (16 mol-%) were used. [f] Yield based on recovered starting material.



Figure 3. ORTEP view of **7j** with 30% thermal ellipsoid probability. Hydrogen atoms are omitted for clarity.



Figure 4. UV/Vis absorption spectra (dashed line) of **7j** ( $1.31 \times 10^{-4}$  M in CH<sub>2</sub>Cl<sub>2</sub>) and fluorescence emission spectra (solid line;  $\lambda_{ex} = 300$  nm) of **7j** ( $1.26 \times 10^{-4}$  M in CH<sub>2</sub>Cl<sub>2</sub>).

duced electron density on the cytidine-conjugated Cp ring. Such a donor–acceptor combination in a ferrocene/cytidine conjugate could be useful for exhibiting nonlinear optical properties or for redox-active oligonucleotide synthesis.<sup>[31]</sup> Two morpholino units were also successfully coupled with the bis(propargyl) ether of catechol to provide the bis-coupled product in 46% yield (Table 2, Entry 13).



Figure 5. Cyclic voltammogram of 71 in CH<sub>2</sub>Cl<sub>2</sub>.

#### Suzuki Coupling of the Morpholino-Modified 5-Iodocytidine Nucleoside

To optimize the Suzuki coupling reactions, several sets of conditions were screened for a representative reaction between iodocytidine morpholino monomer 3 and phenylboronic acid with variation of base, catalyst, solvent, and temperature. The results are summarized in Table 3.

Table 3. Standardization of Suzuki coupling conditions.[a]



[a] Unless otherwise specified, all reactions were carried out with **3** (0.06 mmol, 1 equiv.),  $PhB(OH)_2$  (0.12 mmol, 2 equiv.), base (3 equiv.), and catalyst (7 mol-%) in dry solvent (1–1.5 mL) under Ar. [b] PhB(OH)<sub>2</sub> (1.5 equiv.) was used.

Our initially attempted Suzuki reaction with Pd(PPh<sub>3</sub>)<sub>4</sub> in toluene<sup>[32]</sup> gave the desired coupling product 8a in only 12% yield, along with recovered starting material 3 and, as the major product, the deiodinated product 2 (Table 3, Entry 1). In DMF, none of the desired product was formed (Table 3, Entry 2). Nor did the presence of  $Cs_2CO_3$  as a base improve the yield of 8a (Table 3, Entry 3). The reaction was carried out by Taylor's procedure,<sup>[33]</sup> in the presence of Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> as a catalyst in THF/DMF (1:1) at 60 °C, to afford 8a as a major product in 60% yield (Table 3, Entry 4). In order to minimize the side reaction, the experiment was repeated in THF or DMF at room temperature: in THF the yield of 8a was reduced to 36% (Table 3, Entry 5), whereas in DMF no conversion was observed (Table 3, Entry 6). Notably, however, formation of 2 was not observed in THF at room temperature. We thus increased the temperature to 60 °C, and a pleasing 81%



We then applied the optimized conditions to several other boronic acids, as depicted in Table 4. Substituted arylboronic acids underwent high-yielding coupling to yield 5substituted cytidine monomers. A boronic ester also gave the coupling product in 79% yield (Entry 7, Table 4).

Table 4. Suzuki coupling reactions between 5-iodocytidine morpholino monomer  ${\bf 3}$  and arylboronic acids.<sup>[a]</sup>



[a] Reaction conditions: reactions were performed on 0.12–0.15 mmol scales. [b] Isolated yields.

# Heck Coupling of the Morpholino-Modified 5-Iodocytidine Nucleoside

Heck coupling of **3** with methyl acrylate was performed. The best result was obtained when dioxane was used as a solvent (Table 5).

Table 5. Optimization of Heck coupling of 3 with methyl acrylate.

3 — Pd(C Pf	CO <sub>2</sub> Me (8 equiv.) Et <sub>3</sub> N (4 equiv.) DAc) <sub>2</sub> (10 mol-%) Ph <sub>3</sub> (20 mol-%) conditions	Ph Ph−Si <sup>-</sup> tBu		NH <sub>2</sub>	∠CO₂Me 3 + 2 vered)
Entry	Conditions		Isolated yield [%]		
	Solv. /Temp. / Tin	ne	9	3	2
1 THF / 60 °C / 30 h		0	48	40	
2 dioxane / 90 °C / 5 h			83	0	8
3 DMF / 90 °C / 10 h		62	0	19	

With acrylonitrile, no Heck coupling product was formed under these conditions, and mostly the starting material **3** was recovered. The combination of  $Pd(OAc)_2$  and  $KOAc/nBu_4NBr^{[34]}$  was then used with acrylonitrile, but surprisingly the Michael addition product **10** (Scheme 2)



Scheme 2. Unexpected Michael addition product formation with iodocytine monomer **3**.

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was isolated rather than the Heck coupling product. A similar result was obtained even in the absence of Pd(OAc)<sub>2</sub>. After TBDPS removal, the Michael addition product **10a** was also confirmed by X-ray crystal structure analysis (Figure 6). Use of methyl acrylate as the Michael acceptor under otherwise identical reaction conditions was also found to yield the corresponding adduct **11** (Scheme 2).

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Figure 6. ORTEP view of **10a** with 30% thermal ellipsoid probability. Hydrogen atoms are omitted for clarity.

# Synthesis of the Morpholino-Modified 8-Substituted Adenosine Nucleoside

To synthesize 8-substituted morpholino-modified adenosine nucleosides through Pd-catalyzed cross-coupling reactions, an 8-halo-substituted adenosine monomer was required. The bromo derivative was used as the starting material in preference to the iodo derivative because direct iodination of a purine nucleoside is not fruitful, due to the electrophilic character of the C-8 center.<sup>[35]</sup> The greater oxidation potential of bromine helps bromination at this position. The bromination was performed in Na<sub>2</sub>HPO<sub>4</sub> (10%) buffer<sup>[36]</sup> medium, to take care of the formed HBr, so that the trityl group would survive (Scheme 3).



Scheme 3. Synthesis of 8-bromoadenosine morpholino monomer.

The bromo compound 13 did not undergo Sonogashira coupling under the conditions previously applied for cytidine monomer 3 at room temperature. The conversion was achieved, however, by repeating the reaction in DMF at 90 °C; this was essential because the bromo compounds are less reactive than their iodo counterparts. After Sonogashira coupling with various alkynes, we isolated a number of 8-alkynylated adenosine morpholino monomers featuring diverse functionalities in good yields (Table 6).

Table 6. Sonogashira coupling of 8-bromoadenosine morpholino monomer  $13.^{\left[ a \right]}$ 



[a] Reaction conditions: reactions were performed on 0.12–0.15 mmol scales. [b] Isolated yields.

We also then prepared several aryl-substituted adenosine monomers (Table 7) through Suzuki reactions in the presence of the same catalyst/base combination as discussed above for cytidine monomers. The reactions gave incomplete conversion in THF at 60 °C even for longer reaction times, so this solvent was replaced by 1,4-dioxane to allow the reactions to be performed at 90 °C, providing complete conversions. Table 7. Suzuki coupling reactions between 13 and arylboronic  $\operatorname{acids}^{[a]}$ 



[a] Reaction conditions: reactions were performed on 0.12–0.15 mmol scales. [b] Isolated yields.

Under the optimized conditions for cytidine we failed to obtain the corresponding Heck coupling product for adenosine when methyl acrylate was used.

# Synthesis of the Morpholino-Modified 8-Substituted Guanosine Nucleoside

The bromination conditions used with adenosine morpholino 12 were not satisfactory in the case of guanosine morpholino monomer 16: we only isolated a 24% yield of the bromo-guanosine monomer 17 along with a large amount of the unreacted starting material (Table 8, Entry 1). Replacement of Na<sub>2</sub>HPO<sub>4</sub> with KOAc did not improve the yield (Table 8, Entry 2). To increase the solubility, the reaction was performed in MeCN in the presence of NBS, and a mixture of undesired products was isolated (Table 8, Entry 3).





Of these three sets of conditions,  $Br_2/Na_2HPO_4$  in dioxane/water was the best for G-monomer and also worked well for A-monomer **12**. Accordingly, to improve the solubility of the monomer, TBDPS was removed and the reaction was carried out in water/dioxane. To our delight, the bromo derivative was obtained in very good yield (Scheme 4).



Scheme 4. Synthesis of morpholino-modified 8-bromoguanosine monomer 19.

The bromo compound **19** was next used for Sonogashira and Suzuki couplings under the conditions already optimized for adenosine, and we isolated the desired products **20** and **21** (Scheme 5) in 88% and 62% yields, respectively. An X-ray crystal structure of **20** is shown in Figure 7.



Scheme 5. Sonogashira and Suzuki couplings of the morpholinomodified 8-bromoguanosine monomer **19**.



Figure 7. ORTEP view of **20** with 30% thermal ellipsoid probability. Hydrogen atoms are omitted for clarity.

### Conclusions

In summary, 5-substituted morpholino-modified cytidine monomers and 8-substituted adenosine and morpholinomodified guanosine monomers have been synthesized for the first time. Such functionalized monomers could be useful for the synthesis of functionalized MO oligomers and might also be potential nucleotide analogues for biomedical applications. In this context, we also have synthesized key compounds such as 5-iodocytidine and 8-bromoadenosine or -guanosine for the first time. We have also standardized two different sets of conditions to obtain either the Michael addition product or the Heck coupling product of cytidine monomer with methyl acrylate. Work directed towards the synthesis of functionalized oligomers is now underway and results will be reported in due course.

### **Experimental Section**

**General:** All reagents were purchased from commercial sources and used without further purification unless otherwise stated. Chromatographic purification of products was accomplished by flash col-

umn chromatography on silica gels (mesh 230-400) under nitrogen. Thin-layer chromatography (TLC) was carried out on sheets of silica gel 60 F254 on aluminum (layer thickness 0.25 mm). Visualization of the developed chromatogram was achieved with UV light and/or vanillin or ceric ammonium molybdate stains. All melting points were measured with a Gallenkamp melting point apparatus. Infrared spectra were recorded with a FTIR instrument; the frequencies are reported as wavenumbers (cm<sup>-1</sup>). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at 500 and 125 MHz, respectively. Chemical shifts are reported in parts per million (ppm) on the delta  $(\delta)$  scale. Coupling constants are reported wherever necessary in Hertz [Hz]. Data are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; m = multiplet; br. = broad; app = apparent; comp = complex. HRMS was performed with a QTOF I (quadrupole-hexapole-TOF) mass spectrometer. Solution electronic spectra were measured with a diode array spectrophotometer. Cyclic voltammetry was carried out in  $Bu_4NClO_4$  solution (0.1 M) with a three-electrode configuration (platinum disc working electrode, Pt counter electrode, Ag/AgCl reference electrode) and a PC-controlled electrochemistry system. The  $E_{1/2}$  value for the ferrocenium/ferrocene couple under our experimental condition was 0.43 V. Crystallographic data for 6, 7j, 10a, and 20 are provided in Table S1 in the Supporting Information. Single-crystal X-ray data were collected at 150 K with use of Mo- $K_{\alpha}$  ( $\lambda = 0.7107$  Å) radiation and a SMART APEX diffractometer and CCD area detector. Data collection and reduction and structure solution/refinement were carried out with the APEX II software package.<sup>[37]</sup> All the structures were solved by direct methods and refined in a routine manner. The non-hydrogen atoms were treated anisotropically. All hydrogen atoms except for those in amine groups were geometrically fixed. CCDC-903846 (for 6), -903847 (for 7j), -903848 (for 10a), and -903849 (for 20) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.

Morpholino-Modified 7'-O-TBDPS-N-(trifluoroacetyl)cytidine (4): Freshly distilled trifluoroacetic acid anhydride (2.5 mL, 17.7 mmol, diluted in ca. 12 mL CH<sub>2</sub>Cl<sub>2</sub>) was added dropwise, at ice/salt bath temperature and under Ar, to a stirred solution of 1 (8.22 g, 17.7 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (170 mL). The mixture was stirred for 45 min (monitored by TLC) without removal of the ice/salt bath. After completion of the reaction, the reaction mixture was taken up in CHCl<sub>3</sub> (200 mL), transferred to a separating funnel, and washed with water (250 mL) and brine (200 mL). The organic layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 5-7%) to give the product 4 as a colorless foamy solid (9.43 g, 95%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, mixture of rotamers):  $\delta = 8.84$  (br. s, 0.62 H), 8.45 (br. s, 0.38 H), 7.69-7.64 (comp, 4 H), 7.48-7.33 (comp, 7 H), 7.15 (br. s, 0.62 H), 6.89 (br. s, 0.38 H), 6.06 (d, J = 7.5 Hz, 0.62 H), 6.00 (d, J = 7.5 Hz, 0.38 H), 5.77 (dd, J = 9.5, 2.5 Hz, 1 H), 4.67 (d, J = 12.0 Hz, 0.62 H), 4.60 (d, J = 12.5 Hz, 0.38 H), 4.26 (d, J = 12.5 Hz, 0.38 H), 4.18 (d, J = 13.0 Hz, 0.62 H), 3.89–3.81 (comp, 2.38 H), 3.74–3.70 (m, 0.62 H), 3.14 (dd, J = 13.2, 10.8 Hz, 0.62 H), 3.02–2.94 (m, 0.76 H), 2.65 (app t, J = 11.2 Hz, 0.62 H), 1.09 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, mixture of rotamers):  $\delta$  = 166.4, 166.3, 156.0 (q,  ${}^{2}J_{C,F}$  = 36.5 Hz), 155.8 (q,  ${}^{2}J_{C,F}$  = 36.5 Hz), 155.21, 155.18, 139.4, 139.3, 135.54, 135.51, 135.47, 132.9, 132.8, 132.75, 132.6, 130.1, 130.0, 127.93, 127.9. 116.3 (q,  ${}^{1}J_{C,F}$  = 288.0 Hz), 116.2  $(q, {}^{1}J_{C,F} = 288.0 \text{ Hz}), 96.5, 96.1, 80.2, 79.7, 76.4, 76.3, 64.1, 63.6,$ 48.8, 47.5, 46.3, 44.2, 26.8, 26.7, 19.3, 19.2 ppm. IR (KBr):  $\tilde{v}$  = 3341, 2932, 2859, 1701, 1647, 1487, 1184, 1113 cm<sup>-1</sup>. HRMS



(ESI<sup>+</sup>): calcd. for  $C_{27}H_{31}N_4O_4F_3Si\ [M + Na]\ 583.1964;$  found 583.1960.

Morpholino-Modified 7'-O-TBDPS-N-trifluoroacetyl-5-iodocytidine (5): Iodine (2.52 g, 9.93 mmol) was added to a stirred solution of 4 (9.25 g, 16.5 mmol) in CCl<sub>4</sub>/CH<sub>3</sub>COOH (1:1, 110 mL). After the system had been heated at 40 °C, iodic acid (2.62 g, 14.9 mmol) was added and the mixture was stirred at 40 °C for 55 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>/CHCl<sub>3</sub> (1:1, 300 mL). The organic phase was washed with aqueous NaHCO<sub>3</sub> (5%, 100 mL) and brine (100 mL). It was dried with Na<sub>2</sub>SO<sub>4</sub> and the solvents were evaporated. The solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 3-5%) to give the product 5 as a colorless foamy solid (10.31 g, 91%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, mixture of rotamers):  $\delta = 9.38$  (br. s, 0.53 H), 9.26 (br. s, 0.47 H), 7.80 (s, 0.53 H), 7.72 (s, 0.47 H), 7.69-7.63 (comp, 4 H), 7.47-7.38 (comp, 6 H), 5.86 (br. s, 0.53 H), 5.84 (br. s, 0.47 H), 5.76 (dd, J = 9.8, 2.8 Hz, 0.47 H), 5.70 (dd, J = 10.0, 2.5 Hz, 0.53 H), 4.76 (d, J = 13.0 Hz, 0.47 H), 4.57 (d, J = 13.5 Hz, 0.53 H), 4.34 (d, J =13.0 Hz, 0.53 H), 4.12 (d, J = 13.5 Hz, 0.47 H), 3.92–3.83 (comp, 2.53 H), 3.76 (dd, J = 10.8, 6.2 Hz, 0.47 H), 3.20 (dd, J = 13.5, 11.0 Hz, 0.47 H), 3.04–2.94 (m, 1.06 H), 2.63 (dd, J = 13.0, 10.5 Hz, 0.47 H), 1.10 (s, 4.77 H), 1.09 (s, 4.23 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, mixture of rotamers):  $\delta = 164.0$ , 163.8, 156.1  $(q, {}^{2}J_{C,F} = 37.7 \text{ Hz}), 153.6, 153.5, 145.8, 145.6, 135.5, 135.4, 132.8,$ 132.61, 132.59, 132.5, 130.1, 130.03, 129.99, 127.94, 127.88, 116.2 (q,  ${}^{1}J_{C,F}$  = 288.0 Hz), 116.1 (q,  ${}^{1}J_{C,F}$  = 288.0 Hz), 80.3, 79.8, 76.5, 76.4, 63.9, 63.6, 57.5, 48.8, 47.0, 46.2, 43.9, 26.8, 26.7, 19.3, 19.2 ppm. IR (neat): v = 3314, 2932, 2857, 1703, 1652, 1634, 1472, 1186, 1113 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{27}H_{30}N_4O_4F_3SiI$  [M + Na] 709.0931; found 709.0931.

**Morpholino-Modified** 7'-O-TBDPS-N-trityl-5-iodocytidine (3):  $K_2CO_3$  (3.9 g, 28.2 mmol) was added to a solution of 5 (9.82 g, 14.3 mmol) in MeOH (170 mL). The resulting mixture was stirred for 3 h at room temperature and then concentrated in vacuo, and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (280 mL). The organic phase was washed carefully with water (120 mL), in order to avoid the formation of emulsion, and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvents were evaporated. The gummy solid residue was azeo-tropically dried by evaporation of dry CH<sub>2</sub>Cl<sub>2</sub> or benzene in vacuo two to three times and finally dried under vacuum for a long time to afford white powder 6.

Triethylamine (3 mL, 21.5 mmol) and trityl chloride (4.38 g, 15.7 mmol) were added at 5 °C under Ar to a stirred suspension of the crude product 6 in dry CH<sub>2</sub>Cl<sub>2</sub> (220 mL). The resulting mixture was stirred overnight at room temperature. The reaction mixture was taken up in chloroform (150 mL), transferred to a separating funnel, and washed with water (250 mL) and brine (200 mL). The organic layer was dried with anhydrous Na2SO4, filtered, and concentrated in vacuo. The solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2-3%) to give the product 3 as a colorless foamy solid (10.8 g, 90%) together with recovered starting material 6 (338 mg, 4%, recovered in 15-20%) MeOH/CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.71 (br. s, 1 H), 7.60–7.28 (comp, 23 H), 7.20–7.17 (m, 3 H), 6.11 (dd, J = 9.2, 2.2 Hz, 1 H), 5.60 (br. s, 1 H), 4.27-4.24 (m, 1 H), 3.74 (dd, J = 10.5, 4.5 Hz, 1 H), 3.60 (dd, J = 10.2, 5.8 Hz, 1 H), 3.48 (d, J = 11.5 Hz, 1 H), 3.26 (d, J = 12.0 Hz, 1 H), 1.50 (app t, J = 11.0 Hz, 1 H), 1.19 (dd, J = 11.0, 9.5 Hz, 1 H), 0.98 (s, 9 H) ppm. <sup>13</sup>C NMR  $(125 \text{ MHz}, \text{ CDCl}_3): \delta = 163.7, 154.0, 146.7, 135.6, 133.3, 129.9,$ 129.8, 129.4, 127.9, 127.84, 127.81, 126.5, 81.9, 77.4, 76.9, 64.7, 56.2, 53.1, 50.0, 26.9, 19.3 ppm. IR (KBr):  $\tilde{v} = 3452$ , 3053, 2857,

1668, 1626, 1489, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{44}H_{45}N_4O_{3}SiI [M + Na] 855.2203$ ; found 855.2204.

General Procedure for Sonogashira Coupling of Morpholino-Modified 7'-O-TBDPS-N-trityl-5-iodocytidine (3): Compound 3 (167 mg, 0.2 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN (2:1, 3 mL) was placed in an oven-dried round-bottomed flask. The solution was purged with Ar for 5-10 min. Triethylamine (110 µL, 0.8 mmol), the terminal acetylene (amount according to Table 2), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (4 mg, 3 mol-%), and CuI (3 mg, 8 mol-%) were added under Ar to the stirred solution. The resulting mixture was then stirred for a further 1-65 h (depending on the acetylene, Table 2) at room temperature. The reaction mixture was extracted with CHCl<sub>3</sub> (60 mL), washed sequentially with water and brine, and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel with MeOH/CH2Cl2. Occasionally the isolated product required further purification by flash column chromatography on silica gel with EtOAc/petroleum ether to remove trace amounts of catalyst impurity to afford a colorless solid product.

Morpholino-Modified 7'-*O*-TBDPS-*N*-trityI-5-(phenylethynyl)cytidine (7a): A colorless foamy solid (yield 87%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1–2%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.79 (br. s, 1 H), 7.60–7.27 (comp, 28 H), 7.16 (m, 3 H), 6.16 (dd, *J* = 9.0, 2.0 Hz, 1 H), 5.93 (br. s, 1 H), 4.28–4.26 (m, 1 H), 3.73 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.59 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.49 (d, *J* = 11.0 Hz, 1 H), 3.25 (d, *J* = 12.0 Hz, 1 H), 1.48 (app t, *J* = 11.2 Hz, 1 H), 1.20 (app t, *J* = 10.0 Hz, 1 H), 0.96 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ = 164.5, 153.6, 143.8, 135.60, 135.56, 133.29, 133.26, 131.5, 129.85, 129.81, 129.3, 128.8, 128.5, 127.9, 127.8, 126.4, 122.3, 95.3, 91.2, 81.9, 80.1, 77.3, 76.9, 64.8, 53.1, 50.0, 26.8, 19.3 ppm. IR (KBr):  $\tilde{v}$ = 3458, 3387, 3055, 2930, 2245, 2207, 1667, 1645, 1493, 1115, 706 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>52</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>Si [M + Na] 829.3550; found 829.3550.

Morpholino-Modified 7'-*O*-TBDPS-*N*-trityI-5-(4-cyanophenylethynyl)cytidine (7b): A colorless foamy solid (yield 88%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1– 2%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.17 (br. s, 1 H), 7.69–7.26 (comp, 27 H), 7.16 (m, 3 H), 6.15 (dd, *J* = 9.2, 1.8 Hz, 1 H), 5.95 (br. s, 1 H), 4.30–4.28 (m, 1 H), 3.74 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.62 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.51 (d, *J* = 11.0 Hz, 1 H), 1.20 (app t, *J* = 10.2 Hz, 1 H), 0.96 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.3, 153.4, 144.8, 135.6, 135.5, 133.3, 133.2, 132.2, 131.8, 129.85, 129.8, 129.3, 127.9, 127.8, 127.1, 126.5, 118.4, 112.0, 93.6, 90.2, 84.7, 81.9, 77.3, 76.9, 64.7, 53.2, 50.0, 26.8, 19.3 ppm. IR (neat):  $\tilde{v}$  = 3428, 3331, 3069, 2930, 2228, 2214, 1654, 1503, 1116, 910, 737 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>53</sub>H<sub>49</sub>N<sub>5</sub>O<sub>3</sub>Si [M + Na] 854.3502; found 854.3503.

**Morpholino-Modified** 7'-O-TBDPS-N-trityl-5-(2-nitrophenylethynyl)cytidine (7c): A colorless foamy solid (yield 94%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1–2%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.14 (d, *J* = 8.0 Hz, 1 H), 7.66 (s, 1 H), 7.61–7.28 (comp, 25 H), 7.17 (m, 3 H), 6.57 (br. s, 1 H), 6.39 (br. s, 1 H), 6.21 (dd, *J* = 9.2, 1.2 Hz, 1 H), 4.30–4.28 (m, 1 H), 3.76 (dd, *J* = 10.8, 4.2 Hz, 1 H), 3.62 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.56 (d, *J* = 11.0 Hz, 1 H), 3.27 (d, *J* = 12.0 Hz, 1 H), 1.51 (app t, *J* = 11.0 Hz, 1 H), 1.20 (app t, *J* = 10.2 Hz, 1 H), 0.97 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.4, 153.3, 148.2, 145.2, 135.59, 135.56, 133.8, 133.5, 133.4, 133.3, 129.9, 129.8, 129.4, 128.7, 127.9, 127.8, 126.4, 125.3, 118.5, 92.1, 89.9, 89.3, 82.1, 77.4, 77.0, 64.8, 53.3, 50.0, 26.9, 19.3 ppm. IR (neat):  $\tilde{v}$  = 3443,

3069, 2930, 2205, 1667, 1649, 1607, 1524, 1503, 1120 cm  $^{-1}$  . HRMS (ESI+): calcd. for  $C_{52}H_{49}N_5O_5Si\ [M\ +\ Na]\ 874.3401;$  found 874.3402.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(cyclohexylethynyl)cytidine (7d): An off-white foamy solid (yield 68%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1-2%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.84 (br. s, 1 H), 7.59–7.27 (comp, 23 H), 7.17 (m, 3 H), 6.15 (dd, J = 9.0, 2.0 Hz, 1 H), 5.71 (br. s, 1 H), 4.26-4.24 (m, 1 H), 3.72 (dd, J = 10.5, 4.5 Hz, 1 H), 3.57 (dd, J = 10.8, 5.8 Hz, 1 H), 3.45 (d, J = 11.0 Hz, 1 H), 3.23 (d, J = 11.5 Hz, 1 H), 2.53–2.50 (m, 1 H), 1.83–1.81 (m, 2 H), 1.69– 1.65 (m, 2 H), 1.54-1.42 (comp, 4 H), 1.34-1.26 (comp, 3 H), 1.19 (app t, J = 10.0 Hz, 1 H), 0.96 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ ):  $\delta = 164.8, 153.7, 143.0, 135.6, 133.4, 129.84, 129.8, 129.4,$ 127.9, 127.83, 127.82, 126.4, 100.8, 91.7, 81.9, 77.3, 77.0, 71.2, 53.0, 50.0, 32.7, 30.0, 26.0, 25.8, 25.1, 19.3 ppm. IR (KBr):  $\tilde{v} = 3457$ , 3055, 2930, 2855, 2246, 1665, 1647, 1503, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>52</sub>H<sub>56</sub>N<sub>4</sub>O<sub>3</sub>Si [M + Na] 835.4019; found 835.4019.

Morpholino-Modified 7'-O-TBDPS-*N*-trityl- 5-(1-octanyl)cytidine (7e): An off-white foamy solid (yield 67%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1–2%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.33 (br. s, 1 H), 7.59–7.27 (comp, 23 H), 7.16 (m, 3 H), 6.14 (d, *J* = 8.5 Hz, 1 H), 5.76 (br. s, 1 H), 4.26–4.24 (m, 1 H), 3.71 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.56 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.44 (d, *J* = 11.0 Hz, 1 H), 3.24 (d, *J* = 11.5 Hz, 1 H), 2.34 (t, *J* = 7.2 Hz, 2 H), 1.53–1.16 (comp, 9 H), 1.44 (app t, *J* = 11.0 Hz, 1 H), 0.95 (s, 9 H), 0.87 (t, *J* = 6.8 Hz, 3 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.9, 153.7, 143.0, 135.6, 133.3, 129.82, 129.77, 129.4, 127.9, 127.8, 126.4, 96.7, 91.7, 81.8, 77.2, 76.9, 71.4, 64.7, 53.0, 50.0, 31.4, 28.8, 28.7, 26.8, 22.6, 19.6, 19.3, 14.1 ppm. IR (neat):  $\tilde{v}$  = 3458, 3317, 3057, 2930, 2857, 2242, 1667, 1651, 1505, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>52</sub>H<sub>58</sub>N<sub>4</sub>O<sub>3</sub>Si [M + Na] 837.4176; found 837.4175.

Morpholino-Modified 7'-*O*-TBDPS-*N*-trityl-5-(trimethylsilylethynyl)cytidine (7f): A colorless foamy solid (yield 89%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1–2%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.41 (br. s, 1 H), 7.59–7.27 (comp, 23 H), 7.16 (m, 3 H), 6.13 (dd, *J* = 9.2, 1.8 Hz, 1 H), 5.78 (br. s, 1 H), 4.26–4.24 (m, 1 H), 3.71 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.58 (dd, *J* = 10.8, 5.2 Hz, 1 H), 3.46 (d, *J* = 11.0 Hz, 1 H), 3.23 (d, *J* = 11.5 Hz, 1 H), 1.48 (app t, *J* = 11.0 Hz, 1 H), 1.17 (dd, *J* = 11.0, 9.5 Hz, 1 H), 0.96 (s, 9 H), 0.20 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.6, 153.5, 144.4, 135.6, 133.34, 133.27, 129.9, 129.8, 129.3, 127.9, 127.84, 127.81, 126.5, 101.3, 95.8, 91.1, 82.0, 77.4, 77.0, 64.7, 53.1, 50.0, 26.9, 19.3, 0.0 ppm. IR (neat):  $\tilde{v}$ = 3460, 2959, 2857, 2153, 1667, 1505, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>49</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>Si<sub>2</sub> [M + Na] 825.3632; found 825.3631.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(1-hydroxyprop-2ynyl)cytidine (7g): A colorless solid (yield 70%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 3–4%). <sup>1</sup>H NMR (500 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 7.82 (br. s, 1 H), 7.55–7.31 (comp, 23 H), 7.21 (m, 3 H), 5.88 (br. s, 1 H), 6.04 (d, *J* = 9.0 Hz, 1 H), 5.15 (t, *J* = 5.5 Hz, 1 H), 4.32–4.30 (m, 1 H), 4.22 (d, *J* = 6.0 Hz, 2 H), 3.73 (dd, *J* = 10.2, 4.2 Hz, 1 H), 3.62 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.23 (d, *J* = 10.5 Hz, 1 H), 3.17 (d, *J* = 11.5 Hz, 1 H), 1.44 (app t, *J* = 11.0 Hz, 1 H), 1.18 (app t, *J* = 10.2 Hz, 1 H), 0.90 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 164.8, 153.2, 144.0, 135.62, 135.56, 133.37, 133.35, 130.5, 129.5, 128.4, 126.9, 95.8, 90.3, 81.4, 76.9, 76.6, 76.0, 64.9, 53.0, 50.3, 50.0, 27.2, 19.4 ppm. IR (KBr):  $\tilde{v}$  = 3391, 3347, 3055, 2857, 2226, 1645, 1505, 1116, 706 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{47}H_{48}N_4O_4Si$  [M + Na] 783.3342; found 783.3343.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(1-hydroxybut-3ynyl)cytidine (7h): A colorless solid (yield 86%) was isolated by flash column chromatography on silica gel (MeOH/CH2Cl2 3-3.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.36 (br. s, 1 H), 7.59– 7.26 (comp, 23 H), 7.15 (m, 3 H), 6.33 (br. s, 1 H), 6.11 (d, J =9.0 Hz, 1 H), 4.27–4.25 (m, 1 H), 3.77–3.68 (m, 3 H), 3.56 (dd, J = 10.5, 6.0 Hz, 1 H), 3.43 (d, J = 11.0 Hz, 1 H), 3.26 (d, J =11.5 Hz, 1 H), 2.60 (t, J = 6.0 Hz, 2 H), 2.46 (t, J = 6.2 Hz, 1 H), 1.43 (app t, J = 11.0 Hz, 1 H), 1.16 (app t, J = 10.2 Hz, 1 H), 0.97 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 165.0, 153.9, 142.8, 135.60, 135.58, 133.33, 133.26, 129.9, 129.8, 129.3, 127.9, 127.8, 126.5, 94.2, 91.8, 81.8, 77.3, 75.0, 72.9, 66.7, 60.7, 53.0, 50.1, 26.9, 23.8, 23.6, 19.3 ppm. IR (KBr):  $\tilde{v}$  = 3335, 2928, 2857, 2232, 1647, 1505, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>48</sub>H<sub>50</sub>N<sub>4</sub>O<sub>4</sub>Si [M + Na] 797.3499; found 797.3499.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(N-trifluoroacetyl-1aminoprop-2-ynyl)cytidine (7i): An off-white foamy solid (yield 88%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2–3%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.04 (br. s, 1 H), 7.58–7.23 (comp, 24 H), 7.15–7.12 (m, 3 H), 6.06 (dd, J = 9.0, 1.5 Hz, 1 H), 5.97 (br. s, 1 H), 4.25-4.20 (m, 2 H), 4.05 (dd, J = 17.8, 4.2 Hz, 1 H), 3.72 (dd, J = 10.8, 4.8 Hz, 1 H), 3.53 (dd, J = 10.5, 6.0 Hz, 1 H), 3.43 (d, J = 11.0 Hz, 1 H), 3.28 (d, J =11.5 Hz, 1 H), 1.41 (app t, J = 11.2 Hz, 1 H), 1.13 (app t, J =10.2 Hz, 1 H), 0.96 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ = 164.6, 157.3 (q,  ${}^{2}J_{C,F}$  = 37.7 Hz), 153.9, 144.5, 135.6, 135.56, 133.3, 133.2, 129.9, 129.8, 129.3, 127.9, 127.86, 126.6, 115.8 (q,  ${}^{1}J_{C,F}$  = 286.8 Hz), 90.2, 89.9, 82.1, 77.5, 76.9, 75.2, 64.6, 53.2, 50.2, 30.3, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} = 3187, 3057, 2859, 2236, 1719,$ 1651, 1505, 1163 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>49</sub>H<sub>48</sub>N<sub>5</sub>O<sub>4</sub>F<sub>3</sub>Si [M + Na] 878.3325; found 878.3326.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(N-dansyl-1-aminoprop-2-ynyl)cytidine (7j): The reaction was carried out in the dark. A pale greenish-yellow crystalline solid (yield 91%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2–3%), m.p. 209–210 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.39 (d, J = 8.5 Hz, 1 H), 8.29-8.25 (m, 2 H), 7.57-7.01 (comp, 30 H), 6.27 (br. s, 1 H), 6.08 (dd, J = 9.0, 1.5 Hz, 1 H), 5.96 (br. s, 1 H), 4.26–4.24 (m, 1 H), 3.88 (br. s, 2 H), 3.70 (dd, J = 10.2, 4.2 Hz, 1 H), 3.53(dd, J = 10.5, 6.0 Hz, 1 H), 3.46 (d, J = 11.0 Hz, 1 H), 3.25 (d, J)= 12.0 Hz, 1 H), 2.63 (s, 6 H), 1.45 (app t, J = 11.0 Hz, 1 H), 1.21 (app t, J = 10.2 Hz, 1 H), 0.94 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ ):  $\delta = 164.1, 153.4, 151.9, 143.6, 135.63, 135.58, 134.8, 133.4,$ 133.3, 130.7, 130.2, 130.1, 129.9, 129.8, 129.4, 128.7, 128.0, 127.84, 127.82, 126.5, 123.3, 118.9, 115.3, 90.5, 89.9, 81.8, 77.4, 76.9, 74.8, 64.6, 53.1, 50.2, 45.3, 33.4, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} = 3399$ , 3341, 3055, 2928, 2855, 2230, 1668, 1641, 1595, 1501, 1323, 1144, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>59</sub>H<sub>60</sub>N<sub>6</sub>O<sub>5</sub>SiS [M + Na] 1015.4013; found 1015.4012.

**Morpholino-Modified** 7'-*O*-**TBDPS-***N*-**trityl-5-(2-pyridylethynyl)cytidine (7k):** An off-white foamy solid (yield 90%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2.5– 3.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.59 (br. s, 1 H), 8.54 (d, *J* = 4.0 Hz, 1 H), 7.62–7.16 (comp, 29 H), 6.17 (dd, *J* = 8.8, 1.8 Hz, 1 H), 6.17 (br. s, overlapped, 1 H), 4.29–4.27 (m, 1 H), 3.75 (dd, *J* = 10.8, 4.8 Hz, 1 H), 3.57 (dd, *J* = 10.8, 6.2 Hz, 1 H), 3.48 (d, *J* = 11.5 Hz, 1 H), 3.29 (d, *J* = 11.5 Hz, 1 H), 1.42 (app t, *J* = 11.0 Hz, 1 H), 1.19 (dd, *J* = 10.8, 9.8 Hz, 1 H), 0.97 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.2, 153.3, 150.0, 145.1, 142.5, 136.2, 135.46, 135.43, 133.18, 133.15, 129.8, 129.7, 129.2, 127.8, 127.71,



127.69, 126.6, 126.4, 123.0, 94.4, 90.0, 81.7, 80.4, 77.2, 76.8, 64.6, 53.1, 50.1, 26.8, 19.2 ppm. IR (KBr):  $\tilde{\nu}$  = 3458, 3331, 3055, 2930, 2214, 1667, 1645, 1495, 1113, 708 cm^{-1}. HRMS (ESI<sup>+</sup>): calcd. for  $C_{51}H_{49}N_5O_3Si\ [M$  + Na] 830.3502; found 830.3503.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(ferrocenylethynyl)cytidine (71): The general procedure with slight modifications (described in Table 2, Entry 12) was employed. An off-white solid (yield 84%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2–3%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.29 (br. s, 1 H), 7.60–7.28 (comp, 23 H), 7.16 (br. s, 3 H), 6.17 (d, J =9.0 Hz, 1 H), 5.82 (br. s, 1 H), 4.42 (s, 2 H), 4.28–4.24 (m, 1 H), 4.24 (s, 2 H), 4.18 (s, 5 H), 3.73 (dd, J = 10.5, 4.0 Hz, 1 H), 3.59 (dd, J = 10.0, 5.5 Hz, 1 H), 3.48 (d, J = 11.0 Hz, 1 H), 3.25 (d, J)= 11.5 Hz, 1 H), 1.48 (app t, J = 11.0 Hz, 1 H), 1.22 (app t, J =10.2 Hz, 1 H), 0.97 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.5, 153.6, 142.9, 135.6, 133.3, 133.28, 129.9, 129.8, 129.4, 127.9, 127.85, 127.82, 126.5, 94.8, 91.9, 81.9, 77.4, 77.0, 76.3, 71.4, 70.1, 69.2, 64.8, 64.1, 53.1, 50.0, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} = 3455$ , 3057, 2930, 2210, 1685, 1647, 1501, 1107, 754 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>56</sub>H<sub>54</sub>N<sub>4</sub>O<sub>3</sub>SiFe [M + Na] 937.3212; found 937.3214.

Sonogashira Bis-Coupled Product 7m of 3 with the Bis(propargyl) Ether of Catechol: The general procedure with slight modifications (described in Table 2, Entry 13) was employed. An off-white solid (yield 46%, based on recovered 3) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2-3%). <sup>1</sup>H NMR  $(500 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 7.58-7.16$  (comp, 55 H), 6.58 (dd, J = 8.5, 1.5 Hz, 2 H), 6.53 (br. s, 1 H), 6.14 (d, J = 8.5 Hz, 2 H), 5.61 (br. s, 2 H), 4.79 (br. s, 4 H), 4.27–4.25 (m, 2 H), 3.72 (dd, J = 10.5, 4.5 Hz, 2 H), 3.56 (dd, J = 10.8, 5.8 Hz, 2 H), 3.46 (d, J = 11.0 Hz, 2 H), 3.25 (d, J = 11.5 Hz, 2 H), 1.43 (app t, J = 12.0 Hz, 2 H), 1.14 (app t, J = 10.2 Hz, 2 H), 0.96 (s, 18 H) ppm. <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ ):  $\delta = 164.4, 158.9, 153.4, 145.0, 135.63, 135.61, 133.4, 133.3, 155.61, 135$ 130.4, 129.9, 129.8, 129.4, 128.0, 127.8, 126.5, 107.9, 103.1, 90.2, 89.7, 81.9, 78.7, 77.4, 77.0, 64.7, 56.7, 53.2, 50.1, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} = 3312$ , 3056, 2928, 2228, 1647, 1593, 1489, 1146, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{99}^{13}CH_{98}N_8O_8Si_2$  [M + Na] 1618.6977; found 1618.6974.

General Procedure for Suzuki Coupling of Morpholino-Modified 7'-O-TBDPS-N-trityl-5-iodocytidine (3):  $K_3PO_4$  (3 m in H<sub>2</sub>O, 150 µL, 0.45 mmol), the arylboronic acid/ester (0.3 mmol), and Pd(dppf)-Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (9 mg, 0.011 mmol) were added under Ar to a stirred solution of 3 (125 mg, 0.15 mmol) in dry THF (2.5 mL). The resulting mixture was heated at 60 °C for 6–12 h (depending on the boronic acid, Table 4). The reaction mixture was concentrated in vacuo and the residue was dissolved in CHCl<sub>3</sub> (50 mL). The organic phase was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel with MeOH/CH<sub>2</sub>Cl<sub>2</sub>. Occasionally the isolated product needed further purification by flash column chromatography on silica gel with EtOAc/petroleum ether to remove trace catalyst impurity to afford a colorless solid product.

**Morpholino-Modified** 7'-*O*-**TBDPS-***N***-trityl-5-(phenyl)cytidine (8a):** A colorless foamy solid (yield 81%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2–2.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 8.17$  (br. s, 1 H), 7.54–7.13 (comp, 31 H), 6.20 (dd, J = 9.0, 1.5 Hz, 1 H), 5.26 (br. s, 1 H), 4.26–4.24 (m, 1 H), 3.68 (dd, J = 10.5, 4.5 Hz, 1 H), 3.52 (dd, J = 10.5, 6.0 Hz, 1 H), 3.48 (d, J = 11.0 Hz, 1 H), 3.24 (d, J = 11.5 Hz, 1 H), 1.42 (app t, J = 11.2 Hz, 1 H), 1.24 (app t, J = 10.2 Hz, 1 H), 0.90 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 164.2, 154.7, 139.4, 135.6, 135.56, 133.3, 133.2, 129.8, 129.7, 129.4, 129.36 (over-$ 

lapped), 129.2, 128.5, 127.9, 127.7, 126.4, 108.6, 81.6, 77.2, 77.0, 64.7, 53.0, 50.2, 26.8, 19.3 ppm. IR (neat):  $\tilde{v} = 3320$ , 3068, 2930, 1640, 1620, 1479, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>50</sub>H<sub>50</sub>N<sub>4</sub>O<sub>3</sub>Si [M + Na] 805.3550; found 805.3550.

7'-O-TBDPS-N-trityl-5-(4-methylphenyl)-Morpholino-Modified cytidine (8b): An off-white foamy solid (yield 75%) was isolated by flash column chromatography on silica gel (MeOH/CH2Cl2 1.5-2.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.76 (br. s, 1 H), 7.58– 7.04 (comp, 30 H), 6.21 (dd, J = 9.0, 2.0 Hz, 1 H), 5.24 (br. s, 1 H), 4.26-4.24 (m, 1 H), 3.68 (dd, J = 11.0, 4.5 Hz, 1 H), 3.51 (dd, J = 10.5, 6.0 Hz, 1 H), 3.47 (d, J = 11.5 Hz, 1 H), 3.24 (d, J =11.5 Hz, 1 H), 2.34 (s, 3 H), 1.40 (app t, J = 11.0 Hz, 1 H), 1.24 (app t, J = 10.5 Hz, 1 H), 0.91 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ ):  $\delta = 164.2, 154.8, 139.3, 138.4, 135.6, 135.57, 133.38,$ 133.35, 130.2, 130.1, 129.8, 129.7, 129.4, 129.1, 127.9, 127.77, 127.75, 126.4, 108.4, 81.6, 77.2, 77.0, 64.7, 53.0, 50.2, 26.8, 21.3, 19.3 ppm. IR (neat):  $\tilde{v} = 3292$ , 3055, 2928, 1660, 1649, 1487, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{51}H_{52}N_4O_3Si$  [M + Na] 819.3706; found 819.3707.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(4-methoxylphenyl)cytidine (8c): An off-white foamy solid (yield 78%) was isolated by flash column chromatography on silica gel (MeOH/CH2Cl2 1.5-2.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.28 (br. s, 1 H), 7.54 (d, J = 7.0 Hz, 2 H), 7.50–7.06 (comp, 26 H), 6.87 (d, J = 8.5 Hz, 2 H), 6.20 (dd, J = 9.0, 2.0 Hz, 1 H), 5.26 (br. s, 1 H), 4.26–4.24 (m, 1 H), 3.79 (s, 3 H), 3.69 (dd, J = 10.5, 4.5 Hz, 1 H), 3.52 (dd, J =10.5, 6.0 Hz, 1 H), 3.46 (d, J = 11.0 Hz, 1 H), 3.24 (d, J = 12.0 Hz, 1 H), 1.41 (app t, J = 11.0 Hz, 1 H), 1.24 (app t, J = 10.5 Hz, 1 H), 0.91 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.5, 159.8, 154.8, 139.0, 135.57, 135.54, 133.34, 133.31, 130.5, 129.8, 129.7, 129.4, 127.9, 127.7, 126.4, 125.3, 114.8, 108.2, 81.6, 77.1, 76.9, 64.7, 55.5, 52.9, 50.2, 26.8, 19.3 ppm. IR (neat):  $\tilde{v} = 3470$ , 3316, 3071, 2930, 1661, 1651, 1645, 1512, 1487, 1246, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>51</sub>H<sub>52</sub>N<sub>4</sub>O<sub>4</sub>Si [M + Na] 835.3656; found 835.3570.

7'-O-TBDPS-N-trityl-5-(4-fluorophenyl)-Morpholino-Modified cytidine (8d): An off-white foamy solid (yield 80%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1.5-2.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.73 (br. s, 1 H), 7.54– 7.00 (comp, 30 H), 6.17 (d, J = 9.0 Hz, 1 H), 5.30 (br. s, 1 H), 4.26-4.24 (m, 1 H), 3.69 (dd, J = 10.2, 4.2 Hz, 1 H), 3.54 (dd, J = 10.0, 6.0 Hz, 1 H), 3.46 (d, J = 11.0 Hz, 1 H), 3.24 (d, J = 11.5 Hz, 1 H), 1.44 (app t, J = 11.0 Hz, 1 H), 1.22 (app t, J = 10.2 Hz, 1 H), 0.90 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 164.3, 162.7  $({}^{1}J_{C,F} = 247.8 \text{ Hz}), 154.7, 139.4, 135.57, 135.52, 133.4, 133.3, 131.2$  $({}^{3}J_{C,F} = 8.8 \text{ Hz})$ , 129.8, 129.7, 129.4, 129.1  $({}^{4}J_{C,F} = 2.3 \text{ Hz})$ , 127.9, 127.74, 127.72, 126.4, 116.4 ( ${}^{2}J_{C,F}$  = 21.4 Hz), 107.6, 81.6, 77.1, 77.0, 64.7, 52.9, 50.1, 26.8, 19.3 ppm. IR (neat):  $\tilde{v} = 3315$ , 3069, 2930, 2857, 1657, 1649, 1489, 1107 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>50</sub>H<sub>49</sub>N<sub>4</sub>O<sub>3</sub>FSi [M + Na] 823.3456; found 823.3456.

**Morpholino-Modified** 7'-*O*-**TBDPS**-*N*-**trityl-5**-(**4**-**trifluoromethoxyphenyl)cytidine (8e):** An off-white foamy solid (yield 81%) was isolated by flash column chromatography on silica gel (MeOH/ CH<sub>2</sub>Cl<sub>2</sub> 1.5–2.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.82 (br. s, 1 H), 7.54–7.12 (comp, 30 H), 6.17 (d, *J* = 10.0 Hz, 1 H), 5.33 (br. s, 1 H), 4.26–4.24 (m, 1 H), 3.69 (dd, *J* = 10.5, 4.0 Hz, 1 H), 3.55 (dd, *J* = 10.4, 5.8 Hz, 1 H), 3.47 (d, *J* = 11.0 Hz, 1 H), 3.24 (d, *J* = 11.5 Hz, 1 H), 1.46 (app t, *J* = 11.0 Hz, 1 H), 1.22 (app t, *J* = 10.0 Hz, 1 H), 0.90 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ = 164.0, 154.6, 149.2, 139.7, 135.56, 135.5, 133.33, 133.26, 131.9, 130.9, 129.8, 129.7, 129.4, 127.9, 127.74, 127.72, 126.4, 121.9, 120.5 (q, <sup>1</sup>*J*<sub>C,F</sub> = 286.3 Hz), 107.3, 81.7, 77.2, 77.0, 64.7, 53.0, 50.1, 26.8,

19.3 ppm. IR (neat):  $\tilde{v}$  = 3296, 3067, 2930, 1647, 1489, 1256 cm $^{-1}.$  HRMS (ESI+): calcd. for  $C_{51}H_{49}N_4O_4F_3Si$  [M + Na] 889.3373; found 889.3374.

Morpholino-Modified 7'-O-TBDPS-N-trityl-5-(1-naphthyl)cytidine (8f): An off-white foamy solid (yield 87%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1.5-2.5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, mixture of rotamers):  $\delta$  = 8.46 (br. s, 1 H), 7.89-7.85 (m, 2 H), 7.55-7.06 (comp, 31 H), 6.23-6.18 (m, 1 H), 4.82 (br. m, 1 H), 4.24-4.22 (m, 1 H), 3.68-3.60 (m, 1 H), 3.50-3.41 (m, 2 H), 3.21 (d, J = 12.0 Hz, 1 H), 1.36 (app t, J = 11.2 Hz, 1 H), 1.26–1.23 (m, 1 H), 0.86 and 0.84 (2×s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, mixture of rotamers):  $\delta$  = 164.7, 154.9, 140.5, 140.3, 135.6, 135.5, 135.4, 134.0, 133.3, 133.2, 132.2, 129.8, 129.7, 129.64, 129.57, 129.5, 129.4, 129.0, 128.9, 128.7, 128.6, 127.8, 127.7, 127.64, 127.57, 127.2, 126.9, 126.6, 126.5, 126.4, 125.8, 125.6, 125.3, 125.1, 106.4, 106.3, 81.7, 81.5, 77.2, 77.0, 76.9, 64.6, 53.1, 53.0, 50.1, 26.8, 19.2 ppm. IR (neat):  $\tilde{v} = 3466$ , 3057, 2930, 1670, 1650, 1495, 1109 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>54</sub>H<sub>52</sub>N<sub>4</sub>O<sub>3</sub>Si [M + Na] 855.3706; found 855.3707.

Heck Coupling of Morpholino-Modified 7'-O-TBDPS-N-trityl-5iodocytidine (3) with Methyl Acrylate to Afford Compound 9: Methyl acrylate (110  $\mu$ L, 1.2 mmol), triethylamine (84  $\mu$ L, 0.6 mmol), Pd(OAc)<sub>2</sub> (3.3 mg, 0.015 mmol), and PPh<sub>3</sub> (8 mg, 0.03 mmol) were added under Ar to a stirred solution of 3 (125 mg, 0.15 mmol) in dry dioxane (2.5 mL). The resulting mixture was stirred and heated at 90 °C for 5 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in CHCl<sub>3</sub> (50 mL). The organic phase was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2-3%) to give the product 9 as a colorless foamy solid (98 mg, 83%). <sup>1</sup>H NMR  $(500 \text{ MHz}, \text{CDCl}_3)$ :  $\delta = 8.92$  (br. s, 1 H), 7.58–7.13 (comp, 28 H), 6.17 (dd, J = 9.5, 2.0 Hz, 1 H), 5.81 (d, J = 15.5 Hz, 1 H), 4.27– 4.25 (m, 1 H), 3.75 (dd, J = 10.5, 4.5 Hz, 1 H), 3.61 (s, 3 H) 3.59 (dd, J = 10.8, 6.2 Hz, 1 H), 3.46 (d, J = 11.5 Hz, 1 H), 3.28 (d, J = 12.0 Hz, 1 H), 1.43 (app t, J = 11.0 Hz, 1 H), 1.13 (app t, J =10.2 Hz, 1 H), 0.96 (s, 9 H) ppm.  $^{13}\mathrm{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ = 166.7, 163.6, 154.1, 141.4, 136.2, 135.58, 135.55, 133.3, 133.2, 129.9, 129.8, 129.3, 127.9, 127.8, 126.4, 116.8, 102.6, 81.9, 77.4, 76.9, 64.7, 53.2, 51.8, 50.2, 26.8, 19.3 ppm. IR (neat):  $\tilde{v} = 3300$ , 3052, 2930, 1717, 1645, 1622, 1489, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{48}H_{50}N_4O_5Si [M + Na] 813.3448$ ; found 813.3449.

Aza-Michael Addition Product 10a: Acrylonitrile (160 µL, 2.4 mmol), KOAc (74 mg, 0.75 mmol), and *n*Bu<sub>4</sub>NBr (106 mg, 0.33 mmol) were added under Ar to a stirred solution of 3 (250 mg, 0.3 mmol) in dry DMF (2.5 mL). The resulting mixture was stirred and heated at 80 °C for 3 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc (75 mL). The organic phase was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1-2%) to give the product 10 as a colorless foamy solid (250 mg, 94%). <sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta = 7.58-7.27$  (comp, 23 H), 7.19-7.16 (m, 3 H), 6.12 (dd, J = 9.2, 1.8 Hz, 1 H), 5.83 (t, J = 6.0 Hz, 1 H), 4.27–4.25 (m, 1 H), 3.75-3.66 (m, 3 H), 3.59 (dd, J = 10.8, 5.8 Hz, 1 H), 3.52 (d, J = 11.0 Hz, 1 H), 3.24 (d, J = 12.0 Hz, 1 H), 2.74 (t, J = 6.2 Hz, 2 H), 1.49 (app t, J = 11.0 Hz, 1 H), 1.17 (dd, J = 11.0, 9.5 Hz, 1 H), 0.96 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 160.8, 153.8, 146.4, 135.6, 133.3, 129.9, 129.8, 129.3, 127.9, 127.85, 127.82, 126.5, 118.1, 82.2, 77.5, 76.9, 64.6, 56.8, 53.1, 50.0, 38.0, 26.9, 19.3,

17.8 ppm. IR (neat):  $\tilde{v} = 3335$ , 3071, 2930, 2247, 1659, 1651, 1611, 1549, 1493, 1105 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{47}H_{48}N_5O_3SiI$  [M + Na] 908.2469; found 908.2469.

nBu<sub>4</sub>NF (0.4 mL, 0.4 mmol, 1 M in THF) was added dropwise under Ar to a stirred solution of 10 (220 mg, 0.25 mmol) in dry THF. The mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in CHCl<sub>3</sub> (60 mL). The organic layer was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 3-4%) to give the product 10a as a colorless solid (105 mg, 90%). <sup>1</sup>H NMR (500 MHz,  $[D_6]DMSO$ ):  $\delta = 7.80$  (s, 1 H), 7.42–7.30 (comp, 12 H), 7.19 (br. s, 3 H), 5.99 (d, J = 9.0 Hz, 1 H), 5.74 (s, 1 H), 4.73 (t, J = 6.0 Hz, 1 H), 4.17–3.15 (m, 1 H), 3.56–3.46 (m, 2 H), 3.40 (t, J = 5.0 Hz, 2 H), 3.24 (d, J = 11.0 Hz, 1 H), 3.01 (d, J = 12.0 Hz, 1 H), 2.77 (t, J = 6.8 Hz, 2 H), 1.42 (app t, J = 11.0 Hz, 1 H), 1.21 (app t, J = 10.0 Hz, 1 H) ppm. <sup>13</sup>C NMR (125 MHz, [D<sub>6</sub>]DMSO):  $\delta = 161.7, 153.3, 146.8, 129.5, 128.4, 126.9, 119.6, 81.7, 77.5, 76.9,$ 62.6, 58.4, 52.8, 49.7, 37.8, 17.2 ppm. IR (KBr):  $\tilde{v} = 3389$ , 3055, 2821, 2249, 1651, 1609, 1545, 1491 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{31}H_{30}N_5O_3I [M + Na] 670.1291$ ; found 670.1292.

Aza-Michael Addition Product 11: Methyl acrylate (130 µL, 1.44 mmol), KOAc (44 mg, 0.45 mmol), and *n*Bu<sub>4</sub>NBr (64 mg, 0.2 mmol) were added under Ar to a stirred solution of 3 (150 mg, 0.18 mmol) in dry DMF (1.5 mL). The resulting mixture was stirred and heated at 80 °C for 5 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc (50 mL). The organic phase was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 1-2%) to give the product 11 as a colorless foamy solid (152 mg, 92%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.58–7.27 (comp, 23 H), 7.18–7.15 (m, 3 H), 6.15-6.14 (m, 2 H), 4.27-4.23 (m, 1 H), 3.75-3.70 (m, 3 H), 3.69 (s, 3 H), 3.58 (dd, J = 10.5, 6.0 Hz, 1 H), 3.50 (d, J = 11.5 Hz, 1 H), 3.24 (d, J = 12.0 Hz, 1 H), 2.61 (t, J = 5.8 Hz, 2 H), 1.47 (app t, J = 11.0 Hz, 1 H), 1.17 (app t, J = 10.0 Hz, 1 H), 0.96 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 173.1, 160.4, 154.1, 145.7, 135.6, 133.3, 129.81, 129.77, 129.3, 127.9, 127.8, 126.4, 82.0, 77.3, 76.9, 64.6, 57.7, 53.0, 51.9, 50.0, 37.1, 33.2, 26.8, 19.3 ppm. IR (KBr):  $\tilde{v} = 3401, 2951, 1732, 1667, 1613, 1545, 1493, 1105 \text{ cm}^{-1}$ . HRMS (ESI<sup>+</sup>): calcd. for  $C_{48}H_{51}N_4O_5SiI$  [M + Na] 941.2571; found 941.2571.

Morpholino-Modified 7'-O-TBDPS-N-trityl-8-bromoadenosine (13): Bromine (0.42 mL) was added to an aqueous Na<sub>2</sub>HPO<sub>4</sub> solution (10% w/v, 50 mL) and the mixture was stirred vigorously for 15 min until most of the bromine had dissolved. The decanted bromine solution (30 mL) was then added dropwise to a stirred solution of 12 (1.4 g, 1.9 mmol) in dioxane (40 mL) at 15 °C. The resulting mixture was then stirred overnight at room temperature. The mixture was cooled again (ice bath), and aqueous Na<sub>2</sub>SO<sub>3</sub> (25 mL, 1.5 M) was added dropwise. The reaction mixture was extracted with EtOAc ( $2 \times 100 \text{ mL}$ ). The combined organic layers were washed with brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel (acetone/  $CH_2Cl_2$  5–7%) to give the product 13 as a colorless foamy solid (908 mg, conv. 59%; yield 71%, based on recovered starting material) together with unreacted 12 (236 mg). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.21 (s, 1 H), 7.56–7.25 (comp, 22 H), 7.20–7.17 (m, 3 H), 6.32 (dd, J = 10.2, 2.2 Hz, 1 H), 5.62 (br. s, 2 H), 4.31–4.28



(m, 1 H), 3.75 (dd, J = 10.8, 4.8 Hz, 1 H), 3.58 (dd, J = 10.5, 6.0 Hz, 1 H), 3.29 (d, J = 12.0 Hz, 1 H), 3.16 (d, J = 11.5 Hz, 1 H), 2.81 (app t, J = 10.8 Hz, 1 H), 1.62 (app t, J = 11.2 Hz, 1 H), 0.95 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 154.4$ , 153.0, 151.3, 135.61, 135.59, 133.4, 133.3, 129.74, 129.68, 129.3, 127.9, 127.7, 127.66, 126.5, 125.6, 119.8, 82.2, 77.6, 77.1, 64.6, 49.9, 26.9, 19.3 ppm. IR (KBr):  $\tilde{v} = 3391$ , 3320, 2930, 2857, 1634, 1597, 1449, 1113, 710 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>45</sub>H<sub>45</sub>N<sub>6</sub>O<sub>2</sub>SiBr [M + Na] 831.2454; found 831.2426.

General Procedure for Sonogashira Coupling of Morpholino-Modified 7'-O-TBDPS-N-trity1-8-bromoadenosine (13): Compound 13 (121 mg, 0.15 mmol) in dry DMF (1.6 mL) was placed in an ovendried round-bottomed flask. The solution was purged with Ar for 5–10 min. Triethylamine ( $84 \mu$ L, 0.6 mmol), the terminal acetylene (amount according to Table 6), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (3.2 mg, 3 mol-%), and CuI (2.3 mg, 8 mol-%), were added under Ar to this stirred solution. The resulting mixture was heated at 90 °C for 3.5–16 h (depending on the alkyne, Table 6). The reaction mixture was concentrated in vacuo and the residue was dissolved in CHCl<sub>3</sub> (60 mL). The organic layer was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel in acetone/CH<sub>2</sub>Cl<sub>2</sub> or MeOH/CH<sub>2</sub>Cl<sub>2</sub>.

**Morpholino-Modified** 7'-*O*-**TBDPS-***N*-**trityl-8-(phenylethynyl)adenosine (14a):** An off-white foamy solid (yield 78%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 5–6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.35 (s, 1 H), 7.54–7.07 (comp, 30 H), 6.49 (dd, *J* = 10.5, 2.5 Hz, 1 H), 6.01 (br. s, 2 H), 4.40–4.38 (m, 1 H), 3.78 (dd, *J* = 10.0, 10 Hz, 1 H), 3.51 (dd, *J* = 10.2, 7.2 Hz, 1 H), 3.42 (d, *J* = 12.0 Hz, 1 H), 3.24 (d, *J* = 11.5 Hz, 1 H), 2.76 (app t, *J* = 10.8 Hz, 1 H), 1.56 (app t, *J* = 11.0 Hz, 1 H), 0.93 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.2, 153.9, 149.7, 135.6, 133.6, 133.5, 133.3, 132.0, 129.8, 129.7, 129.4, 128.5, 127.9, 127.7, 126.5, 120.8, 119.3, 95.1, 80.6, 79.3, 77.4, 77.1, 64.8, 50.8, 50.6, 26.9, 19.3 ppm. IR (neat):  $\tilde{v}$  = 3314, 3165, 2928, 2857, 2222, 1649, 1597, 1329, 1111 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>53</sub>H<sub>50</sub>N<sub>6</sub>O<sub>2</sub>Si [M + Na] 853.3662; found 853.3663.

**Morpholino-Modified** 7'-*O*-**TBDPS-***N***-trityI-8-(4-cyanophenylethynyl)adenosine (14b):** An off-white foamy solid (yield 74%) was isolated by flash column chromatography on silica gel (acetone/ CH<sub>2</sub>Cl<sub>2</sub> 5–6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.42 (s, 1 H), 7.56–7.10 (comp, 27 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 6.53 (dd, *J* = 10.0, 2.5 Hz, 1 H), 5.93 (br. s, 2 H), 4.44–4.40 (m, 1 H), 3.78 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.51 (dd, *J* = 10.5, 6.5 Hz, 1 H), 3.45 (d, *J* = 11.5 Hz, 1 H), 3.30 (d, *J* = 11.0 Hz, 1 H), 2.67 (app t, *J* = 10.8 Hz, 1 H), 1.54 (app t, *J* = 11.0 Hz, 1 H), 0.93 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.3, 154.5, 149.7, 135.6, 135.3, 133.4, 133.2, 132.4, 132.2, 132.1, 129.8, 129.4, 127.9, 127.8, 126.6, 125.5, 119.4, 118.2, 112.9, 92.4, 83.3, 80.3, 77.4, 77.1, 64.9, 51.1, 50.5, 26.9, 19.3 ppm. IR (neat):  $\tilde{v}$  = 3314, 3161, 2928, 2857, 2228, 1653, 1603, 1489, 1109 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>54</sub>H<sub>49</sub>N<sub>7</sub>O<sub>2</sub>Si [M + Na] 878.3615; found 878.3616.

Morpholino-Modified 7'-O-TBDPS-N-trityl-8-(triethylsilylethynyl)adenosine (14c): An off-white foamy solid (yield 67%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 4– 5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.26 (s, 1 H), 7.56–6.16 (comp, 25 H), 6.44 (dd, *J* = 10.0, 2.0 Hz, 1 H), 5.92 (br. s, 2 H), 4.36–4.34 (m, 1 H), 3.80 (dd, *J* = 10.2, 4.8 Hz, 1 H), 3.53 (dd, *J* = 10.0, 8.0 Hz, 1 H), 3.41 (d, *J* = 11.5 Hz, 1 H), 3.18 (d, *J* = 11.0 Hz, 1 H), 2.75 (app t, *J* = 10.8 Hz, 1 H), 1.56 (app t, *J* = 11.0 Hz, 1 H), 1.00 (t, *J* = 7.8 Hz, 9 H), 0.96 (s, 9 H), 0.61 (q, *J* = 8.0 Hz, 6 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.3, 154.0, 149.5, 135.59, 135.56, 133.6, 133.5, 133.3, 129.74, 129.7, 129.4, 127.9, 127.73, 127.7, 126.5, 119.2, 100.8, 94.4, 81.9, 77.8, 76.9, 64.6, 50.6, 50.5, 26.9, 19.3, 7.6, 4.1 ppm. IR (neat):  $\tilde{v} = 3315, 3183, 2957, 2874, 2166, 1643, 1113 \text{ cm}^{-1}$ . HRMS (ESI<sup>+</sup>): calcd. for  $C_{53}H_{60}N_6O_2Si_2$  [M + Na] 891.4214; found 891.4214.

**Morpholino-Modified** 7'-*O*-**TBDPS**-*N*-**trityl-8**-(1-hydroxyprop-2ynyl)adenosine (14d): A colorless solid (yield 62%) was isolated by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 3–4%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.32 (s, 1 H), 7.56–7.18 (comp, 25 H), 6.40 (dd, *J* = 10.5, 2.5 Hz, 1 H), 6.39 (br. s, 2 H), 4.35–4.31 (m, 1 H), 4.03 (s, 2 H), 3.76 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.53 (dd, *J* = 10.5, 6.5 Hz, 1 H), 3.37 (d, *J* = 11.5 Hz, 1 H), 3.19 (d, *J* = 11.5 Hz, 1 H), 2.71 (app t, *J* = 10.8 Hz, 1 H), 1.52 (app t, *J* = 11.0 Hz, 1 H), 0.94 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ = 155.2, 154.0, 149.5, 135.63, 135.62, 133.4, 133.3, 132.9, 129.8, 129.7, 129.4, 127.9, 127.8, 127.7, 126.5, 118.6, 96.0, 80.3, 77.2, 77.1, 75.1, 64.7, 50.4, 50.3, 50.2, 26.9, 19.3 ppm. IR (neat):  $\tilde{v}$  = 3327, 3181, 2930, 2857, 2231, 1649, 1111 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>48</sub>H<sub>48</sub>N<sub>6</sub>O<sub>3</sub>Si [M + Na] 807.3455; found 807.3454.

7'-O-TBDPS-N-trityl Morpholino-Modified 8-(Hex-1-ynyl)adenosine (14e): An off-white foamy solid (yield 68%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 4-5%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.30 (s, 1 H), 7.56–7.26 (comp, 22 H), 7.19–7.16 (m, 3 H), 6.40 (dd, J = 10.0, 2.5 Hz, 1 H), 5.89 (br. s, 2 H), 4.36-4.34 (m, 1 H), 3.78 (dd, J = 10.5, 4.5 Hz, 1 H), 3.50 (dd, J = 10.0, 7.0 Hz, 1 H), 3.40 (d, J = 11.5 Hz, 1 H), 3.16(d, J = 11.0 Hz, 1 H), 2.75 (app t, J = 10.8 Hz, 1 H), 2.10–2.05 (m, 2 H), 1.51 (app t, J = 11.0 Hz, 1 H), 1.34–1.26 (comp, 4 H), 0.95 (s, 9 H), 0.85–0.82 (m, 3 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ = 155.0, 153.6, 149.6, 135.6, 134.2, 133.5, 133.3, 129.8, 129.7, 129.4, 127.9, 127.74, 127.71, 126.5, 118.9, 97.9, 80.6, 77.3, 77.0, 71.1, 64.7, 50.3, 29.8, 26.9, 22.1, 19.3, 18.9, 13.6 ppm. IR (neat):  $\tilde{v} = 3314$ , 3165, 2930, 2859, 2239, 1647, 1597, 1449, 1113 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{51}H_{54}N_6O_2Si$  [M + Na] 833.3975; found 833.3976.

Morpholino-Modified 7'-O-TBDPS-N-trityl-8-(N-trifluoroacetyl-1aminoprop-2-ynyl)adenosine (14f): An off-white foamy solid (yield 63%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 5–7%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.35 (s, 1 H), 7.56-7.26 (comp, 22 H), 7.18 (m, 3 H), 6.72 (s, 1 H), 6.52 (dd, J = 10.0, 2.0 Hz, 1 H), 5.64 (br. s, 2 H), 4.30-4.28 (m, 1 H),4.20 (br. s, 2 H), 3.72 (m, 2 H), 3.30 (d, J = 11.5 Hz, 1 H), 3.25 (d, J = 12.0 Hz, 1 H), 1.81 (app t, J = 11.0 Hz, 1 H), 1.70 (app t, J = 12.0 Hz, 1 H), 1.70 (app t, J = 12.0 Hz, 1 H), 1.81 (app t, J =11.2 Hz, 1 H), 0.94 (s, 9 H) ppm.  $^{13}\mathrm{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$ = 154.9, 153.1, 150.6, 150.22 (q,  ${}^{2}J_{C,F}$  = 44.0 Hz), 150.2, 146.0, 135.6, 135.5, 133.3, 133.0, 130.0, 129.9, 129.3, 128.0, 127.9, 127.8, 126.7, 125.9, 118.5, 116.5 (q,  ${}^{1}J_{C,F}$  = 271.6 Hz), 81.2, 77.6, 77.1, 64.7, 52.4, 49.9, 26.8, 26.6, 19.3 ppm. IR (neat):  $\tilde{v} = 3314$ , 3161, 2930, 2857, 2242, 1717, 1647, 1207, 1153, 1111 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>50</sub>H<sub>48</sub>N<sub>7</sub>O<sub>3</sub>F<sub>3</sub>Si [M + Na] 902.3438; found 902.3438.

**Morpholino-Modified** 7'-O-TBDPS-N-trityI-8-(2-pyridylethynyl)adenosine (14g): An off-white foamy solid (yield 65%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 6– 7%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.63 (d, *J* = 4.5 Hz, 1 H), 8.36 (s, 1 H), 7.56–7.06 (comp, 27 H), 6.97 (d, *J* = 7.5 Hz, 1 H), 6.53 (br. s, 2 H), 6.50 (dd, *J* = 9.8, 2.2 Hz, 1 H), 4.41–4.39 (m, 1 H), 3.83 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.60 (dd, *J* = 10.0, 7.0 Hz, 1 H), 3.42 (d, *J* = 12.0 Hz, 1 H), 3.26 (d, *J* = 11.5 Hz, 1 H), 2.76 (app t, *J* = 10.8 Hz, 1 H), 1.63 (app t, *J* = 11.0 Hz, 1 H), 0.94 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.6, 154.4, 150.5, 149.6, 141.4, 136.1, 135.6, 133.6, 133.3, 132.6, 129.7, 129.6, 129.4,

127.9, 127.73, 127.69, 127.4, 126.4, 123.9, 119.6, 93.7, 80.7, 78.6. 77.3, 77.1, 64.8, 50.9, 50.4, 26.9, 19.3 ppm. IR (neat):  $\tilde{v}$  = 3316, 3175, 2930, 2857, 2228, 1651, 1595, 1574, 1427, 1113 cm^{-1}. HRMS (ESI+): calcd. for  $C_{52}H_{49}N_7O_2Si$  [M + Na] 854.3615; found 854.3615.

General Procedure for Suzuki Coupling of Morpholino-Modified 7'-O-TBDPS-N-trityl-8-bromoadenosine (13):  $K_3PO_4$  (3 M in H<sub>2</sub>O, 150 µL, 0.45 mmol), the arylboronic acid (0.33 mmol), and Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (9 mg, 0.011 mmol) were added under Ar to a stirred solution of 13 (121 mg, 0.15 mmol) in dry dioxane (2.5 mL). The resulting mixture was heated at 90 °C for 11–14 h (depending on the boronic acid, Table 7). The reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc (60 mL). The organic phase was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel in acetone/CH<sub>2</sub>Cl<sub>2</sub> to give a colorless foamy solid product.

Morpholino-Modified 7'-O-TBDPS-N-trityl-8-(phenyl)adenosine (15a): An off-white foamy solid (yield 72%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 5-6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.26 (s, 1 H), 7.63 (d, J = 7.5 Hz, 2 H), 7.57 (d, J = 7.0 Hz, 2 H), 7.52 (d, J = 7.0 Hz, 2 H), 7.44–7.19 (comp, 21 H), 7.15–7.12 (m, 3 H), 6.21 (dd, J = 10.0, 1.5 Hz, 1 H), 5.91 (br. s, 2 H), 4.27–4.25 (m, 1 H), 3.78 (dd, J = 10.5, 5.0 Hz, 1 H), 3.56 (dd, J = 10.5, 6.5 Hz, 1 H), 3.22 (d, J = 12.0 Hz, 1 H), 2.97 (d, J = 11.0 Hz, 1 H), 2.58 (app t, J = 10.8 Hz, 1 H), 1.40 (app t, J = 11.0 Hz, 1 H), 0.97 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ ):  $\delta = 155.3, 152.8, 151.8, 151.4, 135.6, 133.4, 133.3, 130.44,$ 130.37, 129.9, 129.8, 129.7, 129.3, 128.5, 127.8, 127.7, 126.4, 119.2, 81.6, 77.3, 77.0, 64.8, 49.8, 49.7, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} =$ 3314, 3171, 2930, 2857, 1647, 1472, 1111 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>51</sub>H<sub>50</sub>N<sub>6</sub>O<sub>2</sub>Si [M + Na] 829.3662; found 829.3663.

Morpholino-Modified 7'-O-TBDPS-N-trityl-8-(4-methoxyphenyl)adenosine (15b): An off-white foamy solid (yield 76%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 5-6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.28 (s, 1 H), 7.59 (d, J = 9.0 Hz, 2 H), 7.58 (d, J = 8.5 Hz, 2 H), 7.54 (d, J = 7.5 Hz, 2 H), 7.40–7.18 (comp, 18 H), 7.14–7.11 (comp, 3 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.24 (d, J = 10.0 Hz, 1 H), 5.88 (br. s, 2 H), 4.30–4.28 (m, 1 H), 3.86 (s, 3 H), 3.80 (dd, J = 10.2, 5.2 Hz, 1 H), 3.61 (dd, J =10.5, 6.5 Hz, 1 H), 3.21 (d, J = 11.5 Hz, 1 H), 2.91 (d, J = 11.0 Hz, 1 H), 2.53 (app t, J = 11.0 Hz, 1 H), 1.43 (app t, J = 11.0 Hz, 1 H), 0.98 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 161.2, 155.1, 152.5, 151.8, 151.4, 135.64, 135.61, 133.4, 133.3, 131.4, 129.8, 129.7, 129.3, 127.8, 127.7, 126.4, 122.6, 119.0, 113.9, 81.2, 77.4, 77.0, 64.8, 55.4, 49.7, 49.3, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} =$ 3318, 3167, 2930, 2857, 1643, 1605, 1487, 1254, 1113 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>52</sub>H<sub>52</sub>N<sub>6</sub>O<sub>3</sub>Si [M + Na] 859.3768; found 859.3768.

**Morpholino-Modified** 7'-*O*-**TBDPS**-*N*-**trityl-8**-(**4**-**trifluoromethoxyphenyl)adenosine (15c):** An off-white foamy solid (yield 77%) was isolated by flash column chromatography on silica gel (acetone/ CH<sub>2</sub>Cl<sub>2</sub> 5–6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.35 (s, 1 H), 7.67 (d, *J* = 8.5 Hz, 2 H), 7.58 (d, *J* = 7.0 Hz, 2 H), 7.53 (d, *J* = 7.5 Hz, 2 H), 7.41–7.14 (comp, 21 H), 7.04 (d, *J* = 8.5 Hz, 2 H), 6.33 (dd, *J* = 10.8, 2.2 Hz, 1 H), 5.93 (br. s, 2 H), 4.33–4.29 (m, 1 H), 3.79 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.58 (dd, *J* = 10.2, 6.2 Hz, 1 H), 3.22 (d, *J* = 12.0 Hz, 1 H), 2.92 (d, *J* = 12.0 Hz, 1 H), 2.29 (app t, *J* = 11.0 Hz, 1 H), 1.35 (app t, *J* = 11.2 Hz, 1 H), 0.98 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.4, 153.0, 151.5, 150.6, 150.4, 135.64, 135.62, 133.3, 133.2, 131.8, 129.9, 129.86, 129.3, 129.2, 127.85, 127.8, 126.5, 120.5 (q,  ${}^{1}J_{C,F}$  = 258.4 Hz), 120.3, 119.1, 80.9, 77.4, 77.0, 64.8, 49.7, 26.9, 19.3 ppm. IR (neat):  $\tilde{v}$  = 3318, 3169, 2930, 2857, 1645, 1599, 1258, 1113 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>52</sub>H<sub>49</sub>N<sub>6</sub>O<sub>3</sub>F<sub>3</sub>Si [M + Na] 913.3485; found 913.3486.

Morpholino-Modified 7'-O-TBDPS-N-trityl-8-(4-fluorophenyl)adenosine (15d): An off-white foamy solid (yield 79%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 5-6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.38 (s, 1 H), 7.60–7.14 (comp, 27 H), 6.88 (app t, J = 8.5 Hz, 2 H), 6.30 (dd, J = 10.2, 2.2 Hz, 1 H), 6.07 (br. s, 2 H), 4.32–4.28 (m, 1 H), 3.79 (dd, J =10.5, 4.5 Hz, 1 H), 3.57 (dd, J = 10.8, 6.2 Hz, 1 H), 3.22 (d, J =11.5 Hz, 1 H), 2.89 (d, J = 11.5 Hz, 1 H), 2.25 (app t, J = 11.0 Hz, 1 H), 1.36 (app t, J = 11.0 Hz, 1 H), 0.97 (s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 163.9 (<sup>1</sup> $J_{C,F}$  = 251.5 Hz), 155.1, 152.6, 151.3, 150.9, 135.6, 133.3, 133.2, 132.1 ( ${}^{3}J_{C,F} = 7.5 \text{ Hz}$ ), 129.9, 129.8, 129.2, 127.9, 127.8, 126.6 ( ${}^{4}J_{C,F} = 3.4 \text{ Hz}$ ), 126.4, 118.9, 115.6 ( ${}^{2}J_{C,F}$  = 21.4 Hz), 80.9, 77.3, 77.0, 64.7, 49.7, 49.5, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} = 3440, 3019, 2931, 1636, 1215, 758 \text{ cm}^{-1}$ . HRMS (ESI<sup>+</sup>): calcd. for  $C_{51}H_{49}N_6O_2FSi$  [M + Na] 847.3568; found 847.3566.

**7'-O-TBDPS-N-trityl Morpholino-Modified 8-(1-Naphthyl)adenosine (15e):** An off-white foamy solid (yield 84%) was isolated by flash column chromatography on silica gel (acetone/CH<sub>2</sub>Cl<sub>2</sub> 5–6%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, mixture of rotamers):  $\delta = 8.31$  (s, 1 H), 7.90–7.87 (m, 2 H), 7.52–7.10 (comp, 30 H), 6.02 (br. s, 1 H), 5.84 (br. s, 2 H), 4.00 (br. s, 1 H), 3.58 (br. s, 1 H), 3.19 (br. s, 1 H), 3.10 (d, J = 11.5 Hz, 1 H), 2.96 (d, J = 10.5 Hz, 1 H), 2.14 (br. s, 1 H), 1.06 (app t, J = 11.8 Hz, 1 H), 0.91(s, 9 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta = 155.3$ , 153.0, 151.0, 150.0, 135.6, 133.45, 133.0, 132.5, 130.7, 129.8, 129.7, 129.4, 129.2, 128.4, 127.7, 127.2, 126.5, 126.3, 125.5, 124.5, 119.3, 81.5, 77.0, 76.8, 64.4, 50.1, 50.0, 26.9, 19.3 ppm. IR (neat):  $\tilde{v} = 3312$ , 3167, 2928, 2856, 1645, 1113 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>55</sub>H<sub>52</sub>N<sub>6</sub>O<sub>2</sub>Si [M + Na] 879.3819; found 879.3768.

Morpholino-Modified N<sup>2</sup>-Isobutyryl-N-trityl-8-bromoguanosine (19): Bromine (0.21 mL) was added to an aqueous Na<sub>2</sub>HPO<sub>4</sub> solution (10% w/v, 25 mL) and the mixture was stirred vigorously for 15 min until most of the bromine had dissolved. The decanted bromine solution (10 mL) was then added dropwise at 15 °C to a stirred solution of 18 (410 mg, 0.71 mmol) in dioxane (13 mL). The reaction mixture was then stirred for 6 h at room temperature and became colorless. The reaction mixture was extracted with CHCl<sub>3</sub>  $(2 \times 60 \text{ mL})$ . The combined organic layers were washed with brine and dried with anhydrous Na2SO4. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2-3%) to give the product 19 as a colorless solid (331 mg, conv. 71%, yield 82% based on recovered starting material) together with unreacted 18 (58 mg), m.p. 188–190 °C (dec.). <sup>1</sup>H NMR (500 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 12.12 (br. s, 1 H), 11.62 (br. s, 1 H), 7.44–7.32 (comp, 12 H), 7.20 (br. s, 3 H), 6.26 (d, J = 10.0 Hz, 1 H), 4.83 (t, J = 5.2 Hz, 1 H), 4.17 (br. s, 1 H), 3.46–3.44 (m, 1 H), 3.31 (dd, *J* = 11.0, 5.5 Hz, 1 H), 3.16 (d, J = 11.5 Hz, 1 H), 3.10 (d, J = 11.0 Hz, 1 H), 2.84 (sept, J = 6.8 Hz, 1 H), 2.44 (app t, J = 10.5 Hz, 1 H), 1.42 (app t, J = 11.0 Hz, 1 H), 1.14 (d, J = 6.5 Hz, 6 H) ppm. <sup>13</sup>C NMR  $(125 \text{ MHz}, [D_6]\text{DMSO}): \delta = 180.2, 153.5, 149.6, 148.3, 128.8,$ 127.9, 126.4, 121.1, 120.3, 81.2, 77.5, 76.4, 61.8, 49.7, 49.4, 34.7, 18.83, 18.77 ppm. IR (neat):  $\tilde{v} = 3376$ , 3160, 2930, 1639, 1607, 1559, 1449 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for  $C_{33}H_{33}N_6O_4Br^{81}$  [M + Na] 681.1624; found 681.1631.

Morpholino-Modified N<sup>2</sup>-Isobutyryl-N-trityl-8-(phenylethynyl)guanosine (20): Compound 19 (105 mg, 0.16 mmol) in dry DMF (1.7 mL) was placed in an oven-dried round-bottomed flask. The solution was purged with Ar for 5–10 min. Triethylamine (90  $\mu$ L, 0.64 mmol), phenylacetylene (44  $\mu$ L, 0.4 mmol), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (4.5 mg, 4 mol-%), and CuI (2.4 mg, 8 mol-%) were added under Ar to this stirred solution. The resulting mixture was heated at 90 °C overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in CHCl<sub>3</sub> (60 mL). The organic layers were washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel (MeOH/CH<sub>2</sub>Cl<sub>2</sub> 2–3%; note:  $R_f$  of **20** is the same as that of the staring material 19 but product 20 is short-wavelength UV active) to give the product 20 as a colorless solid (96 mg, 88%). <sup>1</sup>H NMR (500 MHz,  $[D_6]DMSO$ ):  $\delta = 12.16$  (s, 1 H), 11.80 (s, 1 H), 7.49–7.25 (comp, 15 H), 7.10–7.08 (m, 5 H), 6.26 (d, J = 10.0 Hz, 1 H), 4.82 (t, J = 5.5 Hz, 1 H), 4.18–4.16 (m, 1 H), 3.41–3.38 (m, 1 H), 3.24-3.13 (m, 3 H), 2.85 (sept, J = 6.8 Hz, 1 H), 2.57 (app t, J = 10.8 Hz, 1 H), 1.48 (app t, J = 11.2 Hz, 1 H), 1.15 (d, J =6.5 Hz, 6 H) ppm. <sup>13</sup>C NMR (125 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 180.8, 154.6, 149.6, 148.6, 131.7, 130.6, 130.3, 129.2, 128.3, 126.9, 120.6, 120.3, 93.5, 80.2, 80.1, 77.6, 76.9, 62.5, 50.7, 50.2, 35.3, 19.4, 19.3 ppm. IR (KBr):  $\tilde{v} = 3434$ , 3061, 2997, 2876, 2218, 1713, 1682, 1599, 1543, 1190 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>41</sub>H<sub>38</sub>N<sub>6</sub>O<sub>4</sub> [M + Na] 701.2852; found 701.2850.

Morpholino-Modified N<sup>2</sup>-Isobutyryl-N-trityl-8-phenylguanosine (21):  $K_3PO_4$  (3 M in H<sub>2</sub>O, 160 µL, 0.48 mmol), phenylboronic acid (43 mg, 0.35 mmol), and Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (9 mg, 7 mol-%) were added under Ar to a stirred solution of 19 (105 mg, 0.16 mmol) in dry dioxane (2.5 mL). The resulting mixture was heated at 90 °C for 14 h and then concentrated in vacuo, and the residue was dissolved in CHCl<sub>3</sub> (60 mL). The organic phase was washed with water and brine and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography on silica gel  $(MeOH/CH_2Cl_2 2-3\%)$  to give the product 21 as a colorless solid (65 mg, 62%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 11.87 (s, 1 H), 9.14 (s, 1 H), 7.61-7.59 (m, 2 H), 7.55-7.42 (comp, 9 H), 7.26-7.23 (m, 6 H), 7.18-7.15 (m, 3 H), 5.95 (dd, J = 10.2, 2.8 Hz, 1 H), 4.12–4.09 (m, 1 H), 3.94 (br. s, 1 H), 3.59 (br. s, 2 H), 3.09 (d, J = 11.0 Hz, 1 H), 2.98 (d, J = 12.0 Hz, 1 H), 2.64 (app t, J = 10.8 Hz, 1 H), 2.58 (sept, J = 7.0 Hz, 1 H), 1.68 (app t, J = 11.2 Hz, 1 H), 1.22 (d, J = 7.0 Hz, 3 H), 1.18 (d, J = 6.5 Hz, 3 H) ppm. <sup>13</sup>C NMR  $(125 \text{ MHz}, \text{ CDCl}_3): \delta = 178.8, 155.5, 149.4, 149.2, 146.8, 130.3,$ 129.7, 129.6, 129.4, 128.7, 127.9, 126.6, 121.2, 82.2, 77.0, 76.7, 63.3, 49.7, 48.4, 36.3, 19.2, 18.7 ppm. IR (KBr):  $\tilde{v} = 3426$ , 3196, 2972, 1684, 1607, 1557, 700 cm<sup>-1</sup>. HRMS (ESI<sup>+</sup>): calcd. for C<sub>39</sub>H<sub>38</sub>N<sub>6</sub>O<sub>4</sub> [M + Na] 677.2852; found 677.2852.

**Supporting Information** (see footnote on the first page of this article): <sup>1</sup>H and <sup>13</sup>C NMR spectra of all new compounds and crystallographic data for **6**, **7j**, **10a**, and **20**.

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