Synthesis of 2′-deoxyadenosine nucleosides bearing bipyridine-type ligands and their Ru-complexes in position 8 through cross-coupling reactions†‡

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The synthesis of the title 2′-deoxyadenosine derivatives bearing bipyridine, phenanthroline or terpyridine ligands and their corresponding Ru^{II}-complexes in position 8 linked *via* acetylene or phenylene tethers was accomplished through cross-coupling reactions. The Suzuki–Miyaura reactions of boronic acids or the Sonogashira reactions of terminal acetylene derivatives of oligopyridine ligands were performed either on protected 8-bromoadenosines in organic solvents or, more efficiently, directly on unprotected nucleosides in aqueous acetonitrile or DMF. Direct cross-coupling reactions of unprotected nucleosides with Ru^{II}-complexes or the oligopyridine-boronic acids or -acetylenes gave the Ru-labelled nucleosides in one step in fair to good yields. This method was also proven to be applicable for direct Ru-labelling of dATP. Terpyridine-containing 2′-deoxyadenosine exerted significant antiviral and cytostatic effects.

Introduction

Complexes of bidentate N-ligands[1] (in particular phenanthrolines and bipyridines) with transition metals (Ru, Rh, Ni, Cu, Co, Os *etc.*) possess unique electrochemical and photophysical properties. Some of the phenanthroline complexes, which are efficient DNA intercalators, have been extensively used as luminescent and electroactive DNA labels.[2] Attachment of probes based on metal complexes directly to the nucleobase *via* conjugate linkers should increase the efficiency of the charge transfer and thus enhance sensitivity.

There are many examples of such probes connected to pyrimidine nucleobases. 5-Ferrocenylethynylpyrimidine nucleosides were synthesized by Sonogashira coupling of 5-iodopyrimidines with ethynylferrocene and incorporated into DNA as electroactive redox markers.[3] Covalently bound conjugates of pyrimidine nucleotides and phenanthroline complexes of Ru and Os have been studied[4] as fluorescence probes for DNA hybridization and charge transfer through DNA. However, there are very few reports of probes conjugated to purines, presumably due to the greater difficulty in preparation and incorporation. Ferrocenylethynylpurines[5] have been prepared but the corresponding protected phosphoramidite of 8-(ferrocenylethynyl)-2′-deoxyadenosine was not efficiently incorporated into oligonucleotides[6] presumably due to oxidation of ferrocene followed by nucleophilic displacement.

Therefore our next probes of choice for labelling purines are complexes (Ru and Os) of bipyridine and phenanthroline. Very recently we have reported[7] on the synthesis and electrochemistry of model 9-benzyladenine derivatives bearing oligopyridine ligands or their Ru or Os complexes linked to position 8 *via* conjugate phenylene or acetylene tethers that are designed to transmit electronic changes on the nucleobase to the electroactive label. Here we report on the synthesis of the corresponding 2′-deoxyadenosine nucleoside analogs.

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Results and discussion

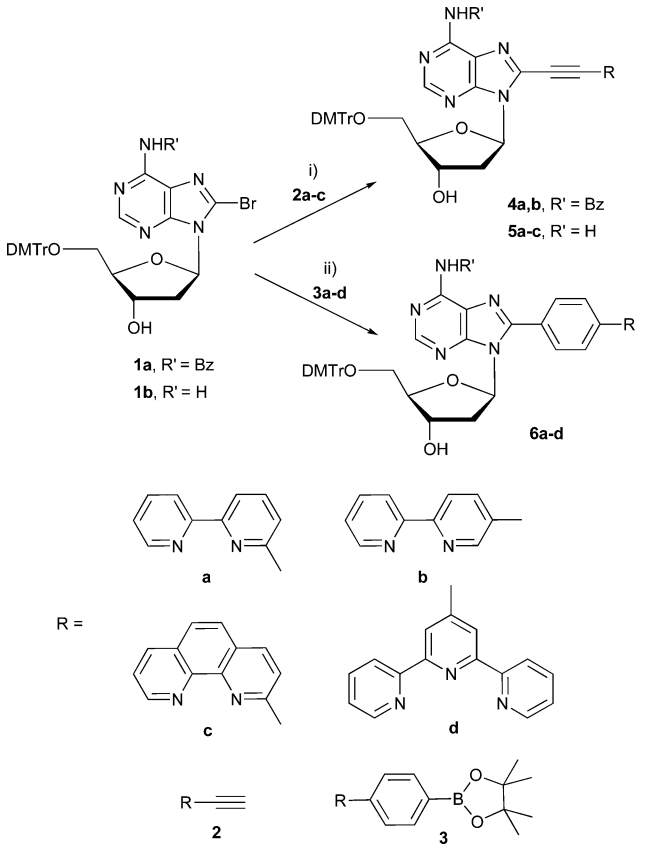
Synthesis of protected nucleosides

In order to prepare the title nucleosides bearing oligopyridine ligands as building blocks for oligonucleotide synthesis, we have studied cross-coupling reactions[8] of 5′-DMTr-N^6-benzoyl-8-bromo-2′-deoxyadenosine[9] **1a** as a fully protected intermediate, that can easily be converted to a phosphoramidite. The Sonogashira cross-coupling reaction is a frequently used method[10] for introducing alkynyl groups to position 8 of purine bases and nucleosides. Unfortunately our efforts to perform the cross-coupling reaction on 5′-DMTr-N^6-benzoyl protected 8-bromodeoxyadenosine **1a** with either 6-(ethynyl)-2,2′-bipyridine **2a** or 2-ethynyl-1,10-phenanthroline **2c**[11] under standard conditions were not successful (Scheme 1, Table 1). Most probably, the steric hindrance of the benzoyl group in combination with the relatively low thermal stability of the starting protected nucleoside led to decomposition of the starting material without formation of any cross-coupling product **4**. Therefore, we have performed cross-coupling reactions on N^6-unsubstituted 5′-DMTr-8-bromodeoxyadenosine **1b**. Reaction of **1b** with 6-(ethynyl)-2,2′-bipyridine **2a** and 5-(ethynyl)-2,2′-bipyridine **2b** in the presence of $PdCl_2$–dppf catalyst and CuI–Et_3N in dry DMF (Scheme 1, Table 1) afforded the desired bipyridine-linked nucleosides **5a**,**b** in good yields of 63 and 72%, respectively. Analogous reaction of **1b** with 2-ethynyl-1,10-phenanthroline **2c** afforded the phenanthroline-linked derivative **5c** in only a modest yield. The Suzuki–Miyaura cross-coupling reaction of boronates **3a–d**[7] with 5′-DMTr-8-bromo-2′-deoxyadenosine **1b** were performed in DMF using

Table 1 Synthesis of protected nucleosides

Entry	Starting nucleoside	Reagent	Product	Yield (%)
1	**1a**	**2a**	**4a**	0
2	**1a**	**2c**	**4c**	0
3	**1b**	**2a**	**5a**	63
4	**1b**	**2b**	**5b**	72
5	**1b**	**2c**	**5c**	32
6	**1b**	**3a**	**6a**	58
7	**1b**	**3b**	**6b**	49
8	**1b**	**3c**	**6c**	66
9	**1b**	**3d**	**6d**	59
10	**5a**	BzCl[a]	**4a**	76
11	**5b**	BzCl[a]	**4b**	58

[a] Benzoylation: 1. Pyridine, TMSCl (5 equiv.), 2. BzCl (5 equiv.), 3. EtOH, 1 M NH_4OH.



Scheme 1 *Reagents and conditions*: i) $PdCl_2$ (10 mol%), dppf (1 equiv. to Pd), CuI (10 mol%), Et_3N (10 equiv.), DMF, 80 °C; ii) $PdCl_2$ (5 mol%), dppf (1 equiv. to Pd), K_2CO_3 (4 equiv.), DMF, 90 °C.

$PdCl_2$–dppf catalyst and K_2CO_3 as a base. In all cases the reactions proceeded relatively well to give the desired conjugated nucleosides **6a–d** in moderate yields of 49–66% (Scheme 1, Table 1).

These results show that, in accord with the previous study on benzyladenine derivatives, the cross-coupling reactions of 8-bromoadenines with organometallics containing oligopyridine-type ligands are problematic due to strong complexation of the ligand to the catalyst. Nevertheless, this approach can still be used preparatively for the synthesis of the title modified nucleosides with moderate efficiency. The conjugates can be further benzoylated at the amino group in position 6 of adenine using a standard three-step, one-pot procedure (silylation at 2′-OH, benzoylation in position 6 and subsequent desilylation with 1 M solution of NH_4OH) to afford the fully protected nucleosides, as documented by the conversion of nucleosides **5a**,**b** to the fully protected conjugates **4a**,**b** (Scheme 1, Table 1).

Synthesis of unprotected nucleosides

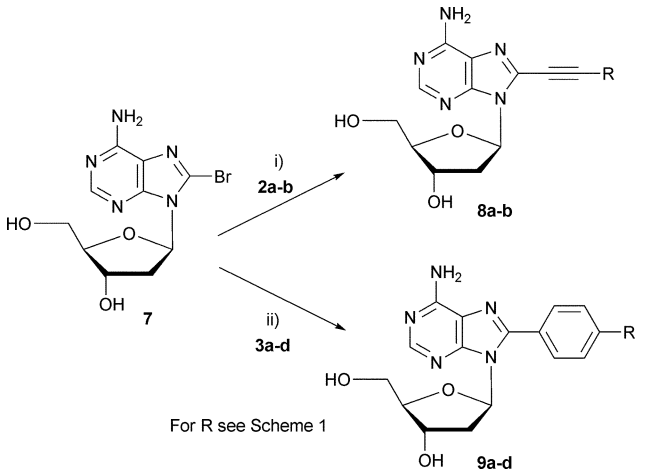
In order to prepare unprotected purine nucleosides bearing oligopyridine ligands in position 8, one can certainly consider deprotection of the above mentioned protected nucleosides **4–6**. However, due to quite moderate yields in their synthesis, we were interested in developing a direct protection-free approach. Recently, the aqueous-phase cross-coupling reactions[12] have been successfully used in the attachment of aryl groups (including hydrophilic amino acid residues) to unprotected nucleobases, nucleosides and nucleotides.[13,14] Due to the relatively mild conditions and tolerance to unprotected functional groups this could be the method of choice for further applications in direct labeling of nucleosides, nucleotides and oligonucleotides by diverse functional groups. Therefore, we have studied the application of these reactions to the attachment of oligopyridine ligands to nucleosides. First we attempted the Sonogashira cross-coupling reaction of 8-bromo-deoxyadenosine **7** with 6-(ethynyl)-2,2′-bipyridine **2a** and 5-(ethynyl)-2,2′-bipyridine **2b** using $Pd(OAc)_2$ and a water soluble ligand, $P(PhSO_3Na)_3$ (TPPTS), in the presence of CuI and $Et(iPr)_2N$ and a mixture of H_2O–CH_3CN. However, under these conditions, complex mixtures of the desired products with some inseparable byproducts were obtained. Fortunately, in DMF the reactions proceeded quite cleanly to give the desired products **8a** or **8b** in excellent yields of 96% and 90%, respectively (Scheme 2, Table 2). An application of the aqueous-phase conditions for the Suzuki–Miyaura cross-coupling reaction of boronates **3a–d** with 8-bromo-deoxyadenosine **7** was also successful. Using a mixture of H_2O–CH_3CN as solvent, in the presence of $Pd(OAc)_2$, TPPTS and Cs_2CO_3 as a base, afforded the products **9a–d** in excellent yields (Scheme 2, Table 2). The only exception was the bipyridin-4-yl derivative **9b** which was only obtained in a moderate yield of 38%. In this example even a prolonged reaction time, higher temperature, or higher excess of boronate did not improve the yield. In addition, the product could only have been isolated by preparative silica gel HPLC (in all other cases, standard column chromatography was sufficient). Despite this less convincing example, the catalytic system consisting of $Pd(OAc)_2$ and water soluble ligand TPPTS was shown to be applicable for direct protection-free cross-coupling modifications of unprotected nucleosides either in H_2O–CH_3CN or in anhydrous DMF.

Synthesis of the Ru^{II} complexes of nucleosides

The next goal of our study was to prepare the corresponding Ru^{II} complexes of the oligopyridine–nucleoside conjugates. An obvious approach was the complexation of the ligands **4–6** or **8–9** with $Ru(bpy)_2Cl_2$ in analogy to our previous study[7] on model compounds. However, quite harsh conditions (hardly compatible with rather labile nucleosides) were required[7] in the complexation and, moreover, the isolation of the resulting complexes was very problematic due to unwanted anion exchange. Therefore, we have tried to develop a direct functionalization of unprotected

Table 2 Synthesis of unprotected nucleosides

Entry	Reagent	Product	Yield (%)
1	**2a**	**8a**	96
2	**2b**	**8b**	90
3	**3a**	**9a**	93
4	**3b**	**9b**	38
5	**3c**	**9c**	95
6	**3d**	**9d**	95



Scheme 2 *Reagents and conditions*: i) $Pd(OAc)_2$ (10 mol%), TPPTS (2.5 equiv. to Pd), CuI (10 mol%), Et(*i*Pr)$_2$N (10 equiv.), DMF, 75 °C; ii) $Pd(OAc)_2$ (5 mol%), TPPTS (2.5 equiv. to Pd), Cs_2CO_3 (3 equiv.), H_2O–CH_3CN = 2 : 1, 80 °C.

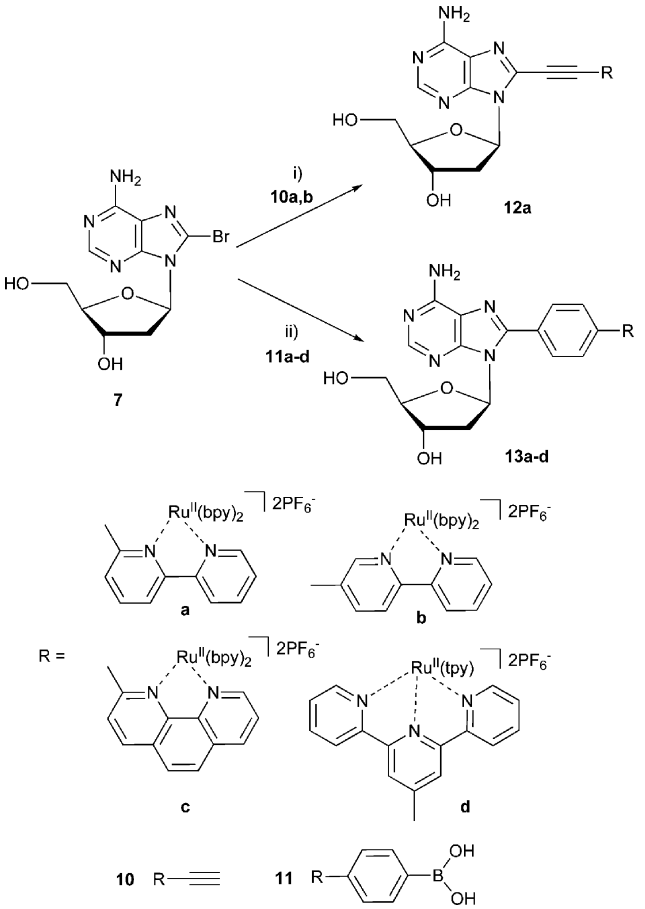
nucleosides by Ru^{II}-complexes through aqueous cross-coupling reactions.

The corresponding Ru^{II} building blocks, acetylenes **10a**, **b** and boronic acids **11a–d**, were reported earlier.[7] Here we have studied their cross-coupling reactions with 8-bromo-deoxyadenosine **7** (Scheme 3, Table 3) under analogous conditions to those mentioned before ($Pd(OAc)_2$–TPPTS, water–acetonitrile). The Sonogashira reactions of acetylenes **10a**,**b** with **7** did not proceed very well due to decomposition of the starting materials. In case of **10a**, the reaction was performed at 75 °C for 6.5 h to provide a complex mixture out of which the desired product **12a** was isolated in a low yield of 16%. The analogous coupling of acetylene **10b** completely failed and even after varying reaction time, temperature and catalyst loading, only complex mixtures that did not contain the desired product (as determined by MS analysis) were obtained.

On the other hand, the aqueous-phase Suzuki–Miyaura cross-couplings of **7** with Ru-containing boronic acids were successful. Reaction of boronates **11a–d** with 8-bromo-deoxyadenosine **7**

Table 3 Synthesis of Ru^{II} complexes of nucleosides

Entry	Reagent	Product	Yield (%)
1	**10a**	**12a**	16
2	**10b**	**12b**	0
3	**11a**	**13a**	55
4	**11b**	**13b**	86
5	**11c**	**13c**	80
6	**11d**	**13d**	52

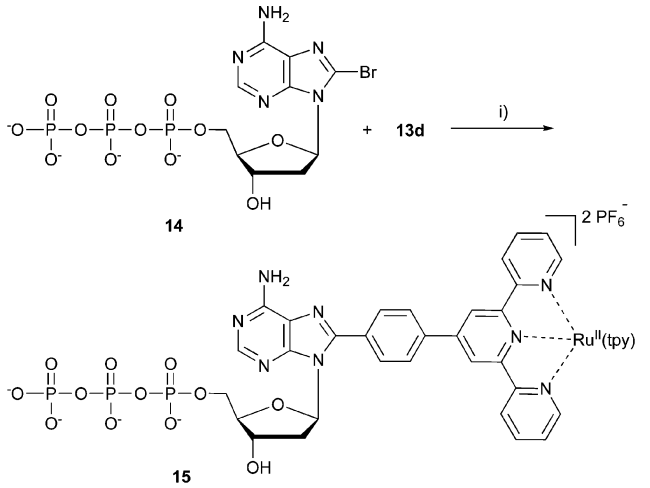


Scheme 3 Synthesis of the complexes. *Reagents and conditions*: i) $Pd(OAc)_2$ (5 mol%), TPPTS (2.5 equiv. to Pd), CuI (10 mol%), Et(*i*Pr)$_2$N (10 equiv.), H_2O–CH_3CN 2 : 1, 75 °C; ii) $Pd(OAc)_2$ (5 mol%), TPPTS (2.5 equiv. to Pd), Cs_2CO_3 (3 equiv.), H_2O–CH_3CN 2 : 1, 80–115 °C.

proceeded smoothly in the presence of Cs_2CO_3 to afford the desired complexes **13a–d** in good yields (52–86%). All the Ru^{II} complexes **13a–d** were isolated by silica gel column chromatography using a mixture of H_2O–CH_3CN–sat. KNO_3 as eluent. Final anion exchange was achieved by precipitation from water as PF_6^- salts using a saturated solution of NH_4PF_6. The aqueous-phase Suzuki–Myiaura cross-coupling reactions of boronic acids bearing Ru^{II}–oligopyridine complexes have been shown to be an efficient and practical methodology for direct labeling of nucleosides by Ru-complexes.

Synthesis of a Ru^{II} complex of dATP

The aqueous-phase Suzuki–Miyaura cross-coupling reactions in the presence of $Pd(OAc)_2$ and water soluble, TPPTS ligand, were previously used, with success, in the preparation of modified nucleoside mono- and tri- phosphates bearing amino acid residues.[13c,15] Here we have applied this reaction toward the synthesis of a model Ru^{II}–tpy derivative of dATP. The reaction of 8-bromo dATP **14** with the Ru^{II}–tpy boronic acid building block **13d** proceeded within 1 hour at 80 °C under the conditions mentioned before ($Pd(OAc)_2$–TPPTS, Cs_2CO_3, water–acetonitrile). The desired product **15** was isolated as a red powder by RP HPLC followed by freeze-drying in 39% yield (Scheme 4).



Scheme 4 Synthesis of a Ru^{II} complex of dATP. *Reagents and conditions*: i) $Pd(OAc)_2$ (5 mol%), TPPTS (5 equiv. to Pd), Cs_2CO_3 (3 equiv.), H_2O–CH_3CN 2 : 1, 80 °C, 1 h.

This shows that the aqueous-phase cross-coupling reactions are suitable for direct labelling of nucleoside triphosphates by Ru–oligopyridine complexes. As modified nucleoside triphosphates are substrates of DNA polymerases,[15,16] this approach could be used for simple and efficient construction of labelled DNA. Studies in this direction are now underway and will be published separately.

Structures of compounds

All compounds were fully characterized by analytical and spectroscopic methods including assignment of all NMR signals by H,H-COSY, H,C-HSQC and H,C-HMBC experiments. Nucleosides bearing Ru-complexes **12a** and **13a–c** were isolated as mixtures of two diastereoisomers due to the chirality of the substituted $Ru(bpy)_3$ moiety. This resulted in the splitting of most of the NMR signals in these compounds.

Compounds **9c** and **13c** gave monocrystals suitable for X-ray diffraction (Fig. 1). However, the crystals of **9c** diffracted rather poorly, which resulted in a low number of reflections. To obtain a reasonable number of reflections for the refinement it was necessary to include weak reflections (by reducing the cutoff threshold to $I > 1.8\sigma(I)$). This resulted in a slightly lower precision of structure determination. The crystals of diastereomeric Ru-complex **13c** were 1 : 1 mixture of diastereoisomers and the unit cell in crystal structure contained both of them (not shown).

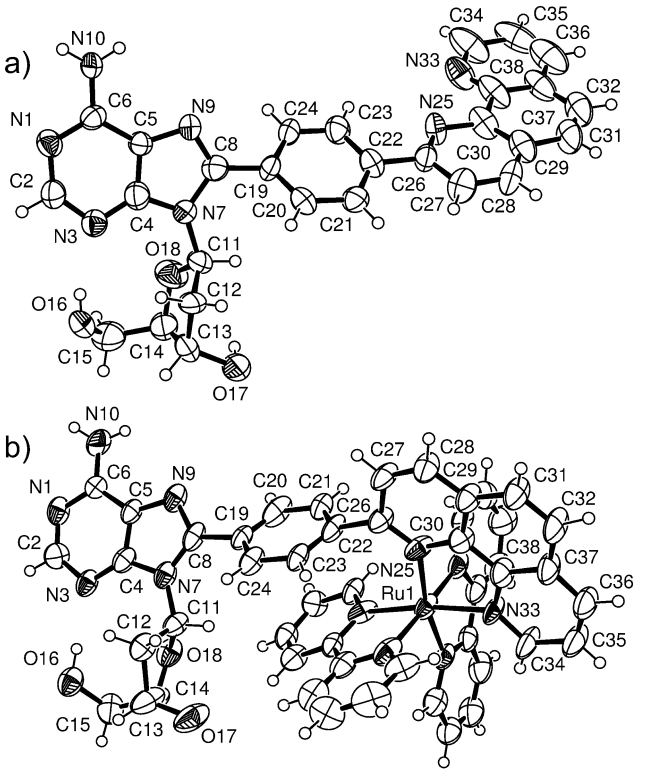


Fig. 1 ORTEP diagram of **9c** (a) and **13c** (b, only one diastereoisomer without counteranions is shown). Thermal ellipsoids drawn at the 50% probability level.

Biological activity

All the compounds were subjected to biological activity screening (Table 4). The cytostatic activity *in vitro* (inhibition of cell growth) was studied on the following cell cultures: (i) mouse leukemia L1210 cells (ATCC CCL 219); (ii) human promyelocytic leukemia HL60 cells (ATCC CCL 240); (iii) human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2) and (iv) human T lymphoblastoid

Table 4 Cytostatic and antiviral activity of nucleosides

	Cytostatic activity IC_{50}/μM[a]			HCV antiviral activity/μM	
Compd	HeLa S3	HL60	CCRF-CEM	EC_{50} replicon[b]	CC_{50} Huh7[c] (MT-4)[d]
8a	n.a.	n.a.	n.a.	5.9	15
8b	n.a.	n.a.	6.68 ± 0.70	6	15
9a	n.a.	n.a.	n.a.	19	28
9b	n.a.	n.a.	n.a.	> 100	>100
9c	n.a.	n.a.	n.a.	> 100	27
9d	3.9 ± 0.62	3.13 ± 0.2	0.85 ± 0.13	0.22	>100 (<0.2)
12a	n.a.	n.a.	n.a.	100	>100
13a	n.a.	n.a.	n.a.	> 100	>100
13b	n.a.	n.a.	n.a.	> 100	>100
13c	n.a.	n.a.	n.a.	100	>100
13d	n.a.	n.a.	n.a.	84	>100

[a] Concentration of a compound needed to reduce population growth by 50% *in vitro* (XTT test). [b] Antiviral activity in HCV-Con1 replicon ($N = 2$). [c] MTT measurement of cellular toxicity in Huh-7 cells harboring con-1 replicon ($N = 2$). [d] Cellular toxicity in MT-4 cells ($N = 2$).

CCRF-CEM cell line (ATCC CCL 119).[17] Terpyridine nucleoside **9d** showed a significant cytostatic effect in all the cell-lines studied, while bipyridine nucleoside **8b** was much less effective. All the other compounds, including the Ru complexes were entirely inactive. This is in contrast to the previously reported[7] related benzyladenine bipyridine conjugates and their Ru complexes, most of which showed cytostatic activities.

The title modified nucleosides were also tested up to 100 μM for antiviral activity in the HCV genotype 1b replicon.[18] Again, the terpyridine nucleoside **9d** showed very strong effects. Unfortunately, the compound is toxic to MT-4 cells at the same concentration. As the activity of the nucleoside **9d** is approximately the same as that observed for the 9-benzyl derivative,[7] it suggests that a non-nucleoside biochemical pathway must be involved. Three other bipyridine nucleosides showed anti-HCV effects in the low micromolar range but with low selectivity.

Conclusions

Two approaches toward the synthesis of adenine nucleosides bearing bipyridine-type ligands in position 8 were studied and compared. Cross-coupling reactions of bipiridine-linked boronic acids and acetylenes with unprotected 8-bromoadenosine in the presence of the $Pd(OAc)_2$–TPPTS catalytic system, in H_2O–acetonitrile or in DMF, were more efficient than classical cross-coupling reactions of protected nucleosides under standard conditions. The aqueous-phase cross-coupling reactions were also applicable for the direct attachment of Ru-complexes of bipyridine ligands through cross-coupling reactions of unprotected nucleoside with boronic acid or acetylene derivatives of Ru-complexes. A direct attachment of $Ru(tpy)_2$ complex to dATP was also achieved through this cross-coupling. Further studies will now focus on chemical and/or enzymatic incorporation of the nucleoside building blocks to oligonucleotides and nucleic acids.

Experimental section

All cross-coupling reactions were performed under argon atmosphere. Et_3N and $Et(iPr)_2N$ were degassed *in vacuo* and stored over molecular sieves under argon. Compounds **1a**,**b** [lit. 9], **2a**,**b**, **3a–d**, **10a**,**b**, **11a–d**, [lit. 7], were prepared according to the literature procedures. Typical experimental procedures and representative examples of characterization of compounds are given below. Complete detailed experimental part including characterization data for all compounds is in the Electronic Supplementary Information (ESI)†.

General procedure for Sonogashira cross-coupling reactions (protected nucleosides)

DMF (1.5 ml) and Et_3N (0.35 ml, 2.5 mmol, 10 equiv.) were added to an argon-purged flask containing nucleoside **1b** (158 mg, 0.25 mmol), an alkyne **2a–c** (0.375 mmol, 1.5 equiv.), $PdCl_2$ (2.2 mg, 0.0125 mmol, 5 mol%), dppf (1,1′-bis-diphenylphosphino-ferrocene) (7 mg, 0.0125 mmol, 5 mol%) and CuI (4.8 mg, 0.025 mmol, 10 mol%). The reaction mixture was stirred at 80 °C until complete consumption of the starting material. The solvent was then evaporated *in vacuo*. The products were purified by silica gel column chromatography (pre-equilibrated with 1% Et_3N in hexanes) using AcOEt–hexanes (1:4 to 1:1) as eluent.

5′-*O*-DMTr-8-[(2″,2‴-bipyridin-6″-yl)ethynyl]-2′-deoxyadenosine (5a)

The product was isolated as white powder 115 mg (63%). Mp 134–138 °C. ^{1}H NMR (500 MHz, DMSO-d_6): 2.40 (ddd, 1H, J_{gem} = 13.4, $J_{2'b,1'}$ = 7.7, $J_{2'b,3'}$ = 5.3, H-2′b); 3.17 (dd, 1H, J_{gem} = 10.2, $J_{5'b,4'}$ = 3.8, H-5′b); 3.27 (dd, 1H, J_{gem} = 10.2, $J_{5'a,4'}$ = 6.9, H-5′a); 3.30 (ddd, 1H, J_{gem} = 13.4, $J_{2'a,3'}$ = 7.3, $J_{2'a,1'}$ = 5.8, H-2′a); 3.67 (s, 6H, OCH_3); 4.01 (ddd, 1H, $J_{4',5'}$ = 6.9, 3.8, $J_{4',3'}$ = 5.1, H-4′); 4.76 (dq, 1H, $J_{3',2'}$ = 7.3, 5.3, $J_{3',4'}$ = 5.1, $J_{3',OH}$ = 5.0, H-3′); 5.42 (d, 1H, $J_{OH,3'}$ = 5.0, OH-3′); 6.64 (dd, 1H, $J_{1',2'}$ = 7.7, 5.8, H-1′); 6.66 and 6.69 (2 × m, 2 × 2H, H-*m*-C_6H_4-DMTr); 7.06 (m, 4H, H-*o*-C_6H_4-DMTr); 7.10–7.16 (m, 3H, H-*m* + *p*-C_6H_5-DMTr); 7.23 (m, 2H, H-*o*-C_6H_5-DMTr); 7.51 (ddd, 1H, $J_{5''',4'''}$ = 7.5, $J_{5''',6'''}$ = 4.8, $J_{5''',3'''}$ = 1.2, H-5‴); 7.63 (bs, 2H, NH_2); 7.70 (dd, 1H, $J_{5,''4''}$ = 7.7, $J_{5,''3''}$ = 1.1, H-5″); 7.93 (td, 1H, $J_{4''',3'''}$ = 8.0, $J_{4''',5'''}$ = 7.5, $J_{4''',6'''}$ = 1.7, H-4‴); 8.06 (t, 1H, $J_{4,''3''}$ = 8.0, $J_{4,''5''}$ = 7.7, H-4″); 8.13 (s, 1H, H-2); 8.35 (dt, 1H, $J_{3''',4'''}$ = 8.0, $J_{3''',5'''}$ = 1.2, $J_{3''',6'''}$ = 0.9, H-3‴); 8.51 (dd, 1H, $J_{3,''4''}$ = 8.0, $J_{3,''5''}$ = 1.1, H-3″); 8.74 (ddd, 1H, $J_{6''',5'''}$ = 4.8, $J_{6''',4'''}$ = 1.7, $J_{6''',3'''}$ = 0.9, H-6‴); ^{13}C NMR (125.8 MHz, DMSO-d_6): 37.86 (CH_2 2′); 55.09 and 55.10 (OCH_3); 64.06 (CH_2-5′); 70.89 (CH-3′); 77.36 (pur-*C*≡C-); 84.02 (CH-1′); 85.35 (C-DMTr); 85.94 (CH-4′); 93.37 (bpy-*C*≡C-); 113.04 and 113.07 (CH-*m*-C_6H_4-DMTr); 119.57 (C-5); 120.98 (CH-3‴); 121.48 (CH-3″); 124.96 (CH-5‴); 126.57 and 127.73 (CH-C_6H_5-DMTr); 128.28 (CH-5″); 129.71 and 129.74 (CH-*o*-C_6H_4-DMTr); 132.16 (C-8); 135.64 and 135.82 (C-*i*-C_6H_4-DMTr); 137.72 (CH-4‴); 138.48 (CH-4″); 140.29 (C-6″); 145.10 (C-*i*-C_6H_5-DMTr); 149.07 (C-4); 149.61 (CH-6‴); 154.15 (CH-2); 154.27 (C-2‴); 156.27 (C-6 and C-2″); 158.01 and 158.04 (C-*p*-C_6H_4-DMTr); FAB MS: *m*/*z* (%) 303.3 (40) [DMTr], 754.2 (100) [M^+ + Na]; HRMS (FAB) calc. 732.2934 found. 732.2933.

N^6-Benzoyl-5′-*O*-DMTr-8-[(2″,2‴-bipyridin-6″-yl)ethynyl]-2′-deoxyadenosine (4a)

A solution of **5a** (0.5 g, 0.68 mmol) in dry pyridine (10 ml) was cooled to 0 °C. TMSCl (0.45 ml, 5 equiv.) was added and the mixture was stirred for 2 hours during which the temperature rises to room temperature. Then the reaction mixture was cooled to 0 °C and BzCl (0.4 ml, 5 equiv.) was added. The reaction mixture was stirred for 4 hours at room temperature and then MeOH (15 ml) was added. The solvents were evaporated under vacuum. The crude product was extracted in $CHCl_3$ and purified by silica gel column chromatography (pre-equilibrated with 1% Et_3N) using AcOEt and hexanes as eluent. The corresponding fractions were collected and the solvent was evaporated. The di-benzoylated intermediate (280 mg, 44%) was then dissolved in 25 ml of EtOH and 1 M NH_4OH (2 ml) was added and the mixture was stirred at rt until complete consumption of the starting material. The mono-benzoylated product **4a** was purified by silica gel column chromatography (pre-equilibrated with 1% Et_3N) using AcOEt–hexanes (1 : 6 to 1 : 1) as eluent (189 mg, 76% for second step, 33% overall from **5a**). **4a**: Mp 132–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.49 (overlapped with DMSO, H-2′b); 3.19 (dd, 1H, J_{gem} = 10.2, $J_{5'b,4'}$ = 3.7, H-5′b); 3.29–3.35 (m, 2H, H-2′a and H-5′a); 3.66

(s, 6H, OCH_3); 4.08 (ddd, 1H, $J_{4',5'} = 6.9, 3.7, J_{4',3'} = 5.0$, H-4′); 4.80 (bm, 1H, H-3′); 5.50 (bd, 1H, OH-3′); 6.67 and 6.70 (2 × m, 2 × 2H, H-*m*-C_6H_4-DMTr); 6.78 (dd, 1H, $J_{1',2'} = 7.5, 5.7$, H-1′); 7.05–7.16 (m, 7H, H-*o*-C_6H_4-DMTr and H-*m* + *p*-C_6H_5-DMTr); 7.24 (m, 2H, H-*o*-C_6H_5-DMTr); 7.51 (ddd, 1H, $J_{5''',4'''} = 7.5$, $J_{5''',6'''} = 4.7$, $J_{5''',3'''} = 1.2$, H-5‴); 7.58 (m, 2H, H-*m*-Bz); 7.67 (m, 1H, H-*p*-Bz); 7.78 (dd, 1H, $J_{5,''4''} = 7.7$, $J_{5,''3''} = 1.1$, H-5″); 7.91 (td, 1H, $J_{4''',3'''} = 8.0$, $J_{4''',5'''} = 7.5$, $J_{4''',6'''} = 1.8$, H-4‴); 8.05–8.10 (m, 3H, H-4″ and H-*o*-Bz); 8.37 (dt, 1H, $J_{3''',4'''} = 8.0$, $J_{3''',5'''} = 1.2$, $J_{3''',6'''} = 0.9$, H-3‴); 8.53 (dd, 1H, $J_{3,''4''} = 8.1$, $J_{3,''5''} = 1.1$, H-3″); 8.69 (s, 1H, H-2); 8.74 (ddd, 1H, $J_{6''',5'''} = 4.7$, $J_{6''',4'''} = 1.8$, $J_{6''',3'''} = 0.9$, H-6‴); ^{13}C NMR (100.6 MHz, DMSO-d_6): 38.00 (CH_2-2′); 55.09 (OCH_3); 64.12 (CH_2-5′); 70.92 (CH-3′); 77.59 (pur-*C*≡C-); 84.38 (CH-1′); 85.39 (C-DMTr); 86.15 (CH-4′); 94.78 (bpy-*C*≡C-); 113.06 (CH-*m*-C_6H_4-DMTr); 121.06 (CH-3‴); 121.87 (CH-3″); 125.00 (CH-5‴); 125.41 (C-5); 126.62 (CH-*p*-C_6H_5-DMTr); 127.73 (CH-*o* + *m*-C_6H_5-DMTr); 128.60 (CH-5″); 128.67 (CH-*m*-Bz); 128.82 (CH-*o*-Bz); 129.72 (CH-*o*-C_6H_4-DMTr); 132.80 (CH-*p*-Bz); 133.43 (C-*i*-Bz); 135.54 (C-8 and C-*i*-C_6H_4-DMTr); 135.81 (C-*i*-C_6H_4-DMTr); 137.72 (CH-4‴); 138.55 (CH-4″); 139.82 (C-6″); 145.04 (C-*i*-C_6H_5-DMTr); 149.60 (CH-6‴); 151.06 (C-6); 151.51 (C-4); 152.84 (CH-2); 154.17 (C-2‴); 156.39 (C-2″); 158.04 (C-*p*-C_6H_4-DMTr); 166.00 (CO); FAB MS: *m*/*z* (%) 303.1 (100) [DMTr], 418.2 (30) [M^+ − DMTrdRf], 858.4 (25) [M^+ + Na]; HR MS (FAB) calc. 836.3197 found. 836.3181.

General procedure for Suzuki–Miyaura cross-coupling reactions (protected nucleosides)

DMF (2 ml) was added to an argon-purged flask containing nucleoside **1b** (158 mg, 0.25 mmol), a boronate **3a–d** (0.3 mmol, 1.2 equiv.), $PdCl_2$ (4.4 mg, 0.025 mmol, 10 mol%), dppf (1,1′-bis-diphenylphosphino-ferrocene) (14 mg, 0.025 mmol, 10 mol%) and K_2CO_3 (138 mg, 1 mmol, 4 equiv.). The reaction mixture was then stirred at 90 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. The products were purified by silica gel column chromatography (preequilibrated with 1% Et_3N in hexanes) using AcOEt–hexanes (1:4 to 1:1) as eluent.

5′-*O*-DMTr-8-[(2″,2‴-bipyridin-6‴-yl)phenyl]-2′-deoxyadenosine (6a)

The product was isolated as white powder 114 mg (58%). Mp 139–146 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 2.20 (ddd, 1H, $J_{gem} = 13.0$, $J_{2'b,1'} = 7.5$, $J_{2'b,3'} = 4.7$, H-2′b); 3.23 (dd, 1H, $J_{gem} = 10.1$, $J_{5'b,4'} = 6.0$, H-5′b); 3.27 (dd, 1H, $J_{gem} = 10.1$, $J_{5'a,4'} = 4.8$, H-5′a); 3.50 (ddd, 1H, $J_{gem} = 13.0$, $J_{2'a,3'} = 6.3$, $J_{2'a,1'} = 6.3$, H-2′a); 3.71 (s, 6H, OCH_3); 4.02 (dt, 1H, $J_{4',5'} = 6.0, 4.8$, $J_{4',3'} = 4.8$, H-4′); 4.70 (dq, 1H, $J_{3',2'} = 6.3, 4.7$, $J_{3',4'} = 4.8$, $J_{3',OH} = 4.7$, H-3′); 5.31 (d, 1H, $J_{OH,3'} = 4.7$, OH-3′); 6.26 (dd, 1H, $J_{1',2'} = 7.5, 6.3$, H-1′); 6.77 and 6.80 (2 × m, 2 × 2H, H-*m*-C_6H_4-DMTr); 7.16 (m, 1H, H-*p*-C_6H_5-DMTr); 7.19–7.24 (m, 6H, H-*o*-C_6H_4-DMTr and H-*m*-C_6H_5-DMTr); 7.36 (m, 4H, H-*o*-C_6H_5-DMTr and NH_2); 7.51 (ddd, 1H, $J_{5''',4'''} = 7.5$, $J_{5''',6'''} = 4.8$, $J_{5''',3'''} = 1.2$, H-5‴); 7.99 (m, 2H, H-*o*-phenylene); 8.00 (s, 1H, H-2); 8.03 (td, 1H, $J_{4''',3'''} = 8.0$, $J_{4''',5'''} = 7.5$, $J_{4''',6'''} = 1.8$, H-4‴); 8.11 (t, 1H, $J_{4,''5''} = 7.9$, $J_{4,''3''} = 7.7$, H-4″); 8.18 (dd, 1H, $J_{5,''4''} = 7.9$, $J_{5,''3''} = 1.1$, H-5″); 8.42 (dd, 1H, $J_{3,''4''} = 7.7$, $J_{3,''5''} = 1.1$, H-3″); 8.48 (m, 2H, H-*m*-phenylene); 8.65 (dt, 1H, $J_{3''',4'''} = 8.0$, $J_{3''',5'''} = 1.2$, $J_{3''',6'''} = 1.0$, H-3‴); 8.74 (ddd, 1H, $J_{6''',5'''} = 4.8$, $J_{6''',4'''} = 1.8$, $J_{6''',3'''} = 1.0$, H-6‴); ^{13}C NMR (125.8 MHz, DMSO-d_6): 36.42 (CH_2-2′); 55.15 and 55.17 (OCH_3); 63.90 (CH_2-5′); 71.24 (CH-3′); 84.91 (CH-1′); 85.41 (C-DMTr); 86.02 (CH-4′); 113.14 and 113.19 (CH-*m*-C_6H_4-DMTr); 119.34 (C-5); 119.83 (CH-3″); 120.99 and 121.02 (CH-3‴ and CH-5″); 124.62 (CH-5‴); 126.68 (CH-*p*-C_6H_6-DMTr); 127.05 (CH-*m*-phenylene); 127.82 and 127.86 (CH-*o* + *m*-C_6H_5-DMTr); 129.81 and 129.91 (CH-*o*-C_6H_4-DMTr); 130.19 (CH-*o*-phenylene); 130.78 (C-*i*-phenylene); 135.90 and 135.93 (C-*i*-C_6H_4-DMTr); 137.63 (CH-4‴); 138.85 (CH-4″); 139.86 (C-*p*-phenylene); 145.25 (C-*i*-C_6H_5-DMTr); 149.53 (CH-6‴); 150.41 (C-4); 150.60 (C-8); 152.36 (CH-2); 154.67 (C-6″); 155.36 and 155.37 (C-2″ and C-2‴); 156.21 (C-6); 158.11 and 158.16 (C-*p*-C_6H_4-DMTr); FAB MS: *m*/*z* (%) 303.1 (100) [DMTr], 366.2 (40) [M^+ − DMTrdRf], 784.3 [M^+], 806.4 (35) [M^+ + Na]; HRMS (TOF ES MS+) calc. 784.3247 found. 784.3262.

General procedure for Sonogashira cross-coupling reactions (unprotected nucleosides)

DMF (1 ml) and Et(*i*Pr)$_2$N (0.22 ml, 1.25 mmol, 10 equiv.) were added to an argon-purged flask containing nucleoside **7** (41 mg, 0.125 mmol), alkyne **2a**,**b** (0.188 mmol, 1.5 equiv.) and CuI (2.4 mg, 0.0125 mmol, 10 mol%). In a separate flask, $Pd(OAc)_2$ (1.4 mg, 0.00625 mmol, 5 mol%) and $P(PhSO_3Na)_3$ (8.9 mg, 0.0156 mmol, 2.5 equiv. to Pd) were combined, evacuated and purged with argon followed by addition of DMF (0.5 ml). This solution of catalyst was added through a syringe to the reaction mixture which was then stirred at 75 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. The products were purified by silica gel column chromatography using MeOH–$CHCl_3$ (1% to 20%) as eluent.

8-[(2″,2‴-Bipyridin-6″-yl)ethynyl]-2′-deoxyadenosine (8a)

The product was isolated as white powder 51 mg (96%). Mp 210–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 2.32 (ddd, 1H, $J_{gem} = 13.4$, $J_{2'b,1'} = 6.6$, $J_{2'b,3'} = 2.8$, H-2′b); 3.19 (ddd, 1H, $J_{gem} = 13.4$, $J_{2'a,1'} = 7.9$, $J_{2'a,3'} = 6.3$, H-2′a); 3.56 (ddd, 1H, $J_{gem} = 11.8$, $J_{5'b,OH} = 7.5$, $J_{5'b,4'} = 5.2$, 1H, H-5′b); 3.72 (dt, 1H, $J_{gem} = 11.8$, $J_{5'a,OH} = J_{5'a,4'} = 4.6$, H-5′a); 3.94 (ddd, 1H, $J_{4',5'} = 5.2, 4.6$, $J_{4',3'} = 2.9$, 1H, H-4′); 4.56 (dddd, 1H, $J_{3',2'} = 6.3, 2.8$, $J_{3',OH} = 4.2$, $J_{3',4'} = 2.0$, H-3′); 5.26 (dd, $J_{OH,5'} = 7.5, 4.6$, 1H, OH-5′); 5.39 (d, $J_{OH,3'} = 4.2$, OH-3′); 6.59 (dd, $J_{1',2'} = 7.9, 6.6$, 1H, H-1′); 7.52 (ddd, $J_{5''',4'''} = 7.5$, $J_{5'''6'''} = 4.8$, $J_{5'''3'''} = 1.2$, 1H, H-5‴); 7.71 (bs, 2H, NH_2); 7.87 (dd, $J_{5'',4''} = 7.7$, $J_{5'',3''} = 1.0$, 1H, H-5″); 7.99 (ddd, $J_{4'''3'''} = 8.0$, $J_{4'''5'''} = 7.5$, $J_{4'''6'''} = 1.8$, 1H, H-4‴); 8.11 (dd, $J_{4'',3''} = 8.1$, $J_{4'',5''} = 7.7$, 1H, H-4″); 8.21 (s, 1H, H-2); 8.43 (ddd, $J_{3'''4'''} = 8.0$, $J_{3'''5'''} = 1.2$, $J_{3'''6'''} = 0.9$, 1H, H-3‴); 8.51 (dd, $J_{3'',4''} = 8.1$, $J_{3'',5''} = 1.0$, 1H, H-3″); 8.73 (ddd, $J_{6'''5'''} = 4.8$, $J_{6'''4'''} = 1.8$, $J_{6'''3'''} = 0.9$, 1H, H-6‴). ^{13}C NMR (100.6 MHz, DMSO-d_6): 38.07 (CH_2-2′); 62.39 (CH_2-5′); 71.41 (CH-3′); 77.69 (pur-*C*≡C-); 85.10 (CH-1′); 88.53 (CH-4′); 93.51 (bpy-*C*≡C-); 119.92 (C-5); 121.05 (CH-3‴); 121.70 (CH-3″); 124.98 (CH-5‴); 128.47 (CH-5″); 132.23 (C-8); 137.76 (CH-4‴); 138.64 (CH-4″); 140.23 (C-6″); 148.90 (C-4); 149.62 (CH-6‴); 153.99 (C-2‴); 154.28 (CH-2); 156.41 (C-6); 156.42 (C-2″); ESI MS: *m*/*z* (%) 452.1 (100) [M^+ + Na], 314.3 (10) [M^+ − dRf], $C_{22}H_{19}N_7O_3 \cdot \frac{1}{2}H_2O$ (429.43) calcd. C 60.27, H 4.60, N 22.36; found

C 60.13, H 4.33, N 22.21; IR (KBr): 3414, 3186, 2229, 1652, 1572, 1427, 1336, 1102, 779.

General procedure for Suzuki–Miyaura cross-coupling reactions (unprotected nucleosides)

A mixture of H_2O–CH_3CN = 2 : 1 (1 ml) was added to an argon-purged flask containing nucleoside **7** (83 mg, 0.25 mmol), a boronate **3a–d** (0.3 mmol, 1.2 equiv.) and Cs_2CO_3 (247 mg, 0.75 mmol, 3 equiv.). H_2O–CH_3CN = 2 : 1 (1 ml) was added to the argon purged reaction mixture. In a separate flask, $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 5 mol%) and $P(PhSO_3Na)_3$ (17.5 mg, 0.0313 mmol, l2.5 equiv. to Pd) were combined, evacuated and purged with argon followed by addition of H_2O–CH_3CN = 2 : 1 (0.5 ml). The mixture of catalyst was then injected to the reaction mixture and the reaction mixture was stirred at 80 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. Products **9a**,**c**,**d** were purified by silica gel column chromatography using MeOH–$CHCl_3$ (1% to 20%) as eluent. Product **9b** was purified by HPLC on silica gel (25 × 250 mm column) using a linear gradient of MeOH in $CHCl_3$ (1% to 20%).

8-[(2,″2‴-Bipyridin-6″-yl)phenyl]-2′-deoxyadenosine (9a)

The product was isolated as white powder 112 mg (93%). Mp 166–168 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 2.20 (ddd, 1H, J_{gem} = 13.2, $J_{2'b,1'}$ = 6.2, $J_{2'b,3'}$ = 2.4, H-2′b); 3.36 (ddd, 1H, J_{gem} = 13.2, $J_{2'a,1'}$ = 8.5, $J_{2'a,3'}$ = 5.6, H-2′a); 3.56 (ddd, 1H, J_{gem} = 11.9, $J_{5'b,OH}$ = 8.2, $J_{5'b,4'}$ = 4.5, H-5′b); 3.73 (dt, 1H, J_{gem} = 11.9, $J_{5'a,OH}$ = $J_{5'a,4'}$ = 4.2, H-5′a); 3.90 (ddd, 1H, $J_{4',5'}$ = 4.5, 4.2, $J_{4',3'}$ = 2.2, H-4′); 4.49 (dddd, 1H, $J_{3',2'}$ = 5.6, 2.4, $J_{3',OH}$ = 4.1, $J_{3',4'}$ = 2.2, H-3′); 5.26 (d, 1H, $J_{OH,3'}$ = 4.1, OH-3′); 5.54 (dd, 1H, $J_{OH,5'}$ = 8.2, 4.2, OH-5′); 6.25 (dd, 1H, $J_{1',2'}$ = 8.5, 6.2, H-1′); 7.51 (ddd, 1H, $J_{5'''4'''}$ = 7.5, $J_{5'''6'''}$ = 4.7, $J_{5'''3'''}$ = 1.2, H-5‴); 7.51 (bs, 2H, NH_2); 7.91 (m, 2H, H-*o*-phenylene); 8.02 (ddd, 1H, $J_{4'''3'''}$ = 8.0, $J_{4'''5'''}$ = 7.5, $J_{4'''6'''}$ = 1.8, H-4‴); 8.10 (dd, 1H, $J_{4'',5''}$ = 8.0, $J_{4'',3''}$ = 7.8, H-4″); 8.17 (s, 1H, H-2); 8.18 (dd, 1H, $J_{5'',4''}$ = 8.0, $J_{5'',3''}$ = 1.1, H-5″); 8.41 (dd, 1H, $J_{3'',4''}$ = 7.8, $J_{3'',5''}$ = 1.1, H-3″); 8.49 (m, 2H, H-*m*-phenylene); 8.65 (ddd, 1H, $J_{3'''4'''}$ = 8.0, $J_{3'''5'''}$ = 1.2, $J_{3'''6'''}$ = 0.9, H-3‴); 8.73 (ddd, 1H, $J_{6'''5'''}$ = 4.7, $J_{6'''4'''}$ = 1.8, $J_{6'''3'''}$ = 0.9, H-6‴); ^{13}C NMR (100.6 MHz, DMSO-d_6): 37.65 (CH_2-2′); 62.69 (CH_2-5′); 71.83 (CH-3′); 86.12 (CH-1′); 88.76 (CH-4′); 119.61 (C-5) 120.06 (CH-3″); 121.17 and 121.21 (CH-3‴ and CH-5″); 124.79 (CH-5‴); 127.30 (CH-*m*-phenylene); 130.33 (CH-*o*-phenylene); 130.52 (C-*i*-phenylene); 137.83 (CH-4‴); 139.05 (CH-4″); 140.19 (C-*p*-phenylene); 149.67, 150.35 and 150.54 (C-4, C-8 and CH-6‴); 152.44 (CH-2); 154.78 (CH-6″); 155.48 and 155.53 (C-2″ and C-2‴); 156.51 (C-6); ESI MS: *m*/*z* (%) 366.4 (100) [M$^+$ − dRf], 504.2 (60) [M$^+$ + Na]; $C_{26}H_{23}N_7O_3\cdot\frac{1}{2}H_2O$ (481.51) calcd. C 63.66, H 4.93, N 19.99; found C 63.57, H 4.78, N 19.72; IR (KBr): 3400, 3187, 2297, 1639, 1582, 1430, 1091, 781.

General procedure for Sonogashira cross-coupling reactions (Ru^{II} complexes)

A mixture of H_2O–CH_3CN = 2 : 1 (1 ml) was added to an argon-purged flask containing nucleoside **7** (53 mg, 0.16 mmol), alkyne **10a**,**b** (0.24 mmol, 1.5 equiv.), CuI (3 mg, 0.016 mmol, 10 mol%) and Et(*i*Pr)$_2$N (0.28 ml, 1.6 mmol, 10 equiv.). In a separate flask, $Pd(OAc)_2$ (1.8 mg, 0.008 mmol, 5 mol%) and $P(PhSO_3Na)_3$ (11 mg, 0.02 mmol, 2.5 equiv. to Pd) were combined, evacuated and purged with argon followed by an addition of H_2O–CH_3CN = 2 : 1 (0.5 ml). This catalyst solution was then injected into the reaction mixture which was further stirred at 75 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. The product was purified by silica gel column chromatography using a mixture of CH_3CN–H_2O–sat. KNO_3 = 10 : 1 : 0.1 as eluent. The products were isolated as PF_6^- salt by precipitation from water solution by addition of sat. NH_4PF_6.

Complex 12a

The product was isolated as orange powder 29 mg (16%). Mp > 300 °C. Mixture of two diastereoisomers 5 : 2. NMR spectra of the major isomer: ^{1}H NMR (600 MHz, acetone-d_6): 2.25 (ddd, 1H, J_{gem} = 13.3, $J_{2'b,1'}$ = 6.0, $J_{2'b,3'}$ = 1.6, H-2′b); 3.08 (ddd, 1H, J_{gem} = 13.3, $J_{2'a,1'}$ = 8.7, $J_{2'a,3'}$ = 5.6, H-2′a); 3.60 (bdd, 1H, J_{gem} = 12.5, $J_{5'b,4'}$ = 2.5, H-5′b); 3.73 (dd, 1H, J_{gem} = 12.5, $J_{5'a,4}$ = 2.5, H-5′a); 3.94 (td, 1H, $J_{4',5'}$ = 2.5, $J_{4',3'}$ = 1.5, H-4′); 4.48 (bs, 1H, OH-3′); 4.67 (bd, 1H, $J_{3',2'a}$ = 5.6, H-3′); 5.53 (bs, 1H, OH-5′); 6.24 (dd, 1H, $J_{1',2'}$ = 8.7, 6.0, H-1′); 6.89 (ddd, 1H, $J_{5,4}$ = 7.6, $J_{5,6}$ = 5.6, $J_{5,3}$ = 1.3, H-5-bpy); 6.99 (bs, 2H, NH_2); 7.50 (ddd, 1H, $J_{5,4}$ = 7.6, $J_{5,6}$ = 5.6, $J_{5,3}$ = 1.3, H-5-bpy); 7.55 (ddd, 1H, $J_{4,3}$ = 8.3, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.5, H-4-bpy); 7.58, 7.59, 7.77 (3 × ddd, 3 × 1H, $J_{5,4}$ = 7.6, $J_{5,6}$ = 5.6, $J_{5,3}$ = 1.3, H-5‴ and H-5-bpy); 7.89, 7.91, 7.92, 7.93 (4 × ddd, 4 × 1H, $J_{6,5}$ = 5.6, $J_{6,4}$ = 1.5, $J_{6,3}$ = 0.7, H-6‴ and H-6-bpy); 8.06 (dd, 1H, $J_{5'',4''}$ = 7.8, $J_{5'',3''}$ = 1.3, H-5″); 8.19 (ddd, 1H, $J_{4,3}$ = 8.3, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.5, H-4-bpy); 8.20 (s, 1H, H-2); 8.24, 8.25 (2 × ddd, 2 × 1H, $J_{4,3}$ = 8.3, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.5, H-4-bpy); 8.31 (ddd, 1H, $J_{4'''3'''}$ = 8.3, $J_{4'''5'''}$ = 7.6, $J_{4'''6'''}$ = 1.5, H-4‴); 8.33 (dd, 1H, $J_{4'',3''}$ = 8.3, $J_{4'',5''}$ = 7.8, H-4″); 8.58 (ddd, 1H, $J_{3,4}$ = 8.3, $J_{3,5}$ = 1.3, $J_{3,6}$ = 0.7, H-3-bpy); 8.66 (ddd, 1H, $J_{6,5}$ = 5.6, $J_{6,4}$ = 1.5, $J_{6,3}$ = 0.7, H-6-bpy); 8.80, 8.83, 8.85 (3 × ddd, 3 × 1H, $J_{3,4}$ = 8.3, $J_{3,5}$ = 1.3, $J_{3,6}$ = 0.7, H-3-bpy); 8.91 (ddd, 1H, $J_{3'''4'''}$ = 8.3, $J_{3'''5'''}$ = 1.3, $J_{3'''6'''}$ = 0.7, H-3‴); 8.94 (dd, 1H, $J_{3'',4''}$ = 8.3, $J_{3'',5''}$ = 1.3, H-3″). ^{13}C NMR (151 MHz, acetone-d_6): 40.03 (CH_2-2′); 63.81 (CH_2-5′); 73.15 (CH-3′); 86.53 (pur-*C*≡C-); 87.82 (CH-1′); 90.16 (bpy-*C*≡C-); 90.73 (CH-4′); 121.09 (C-5); 124.89, 125.21, 125.55, 125.63, 125.71 (CH-3″, CH-3-bpy); 126.30 (CH-3‴); 128.40, 128.60, 128.77, 129.02, 129.38 (CH-5‴ CH-5-bpy); 132.52 (C-8); 135.86 (CH-5″); 137.85 (CH-4-bpy); 139.07, 139.18, 139.21, 139.28, 139.40 (CH-4″,4‴ CH-4-bpy); 147.29 (C-6″); 149.31 (C-4); 152.12, 152.47, 152.57, 152.77, 154.05 (CH-6‴ CH-6-bpy); 154.69 (CH-2); 157.71, 157.75, 157.98, 158.01, 158.11, 158.68 (C-6, C-2‴ C-2-bpy); 159.75 (C-2″). ESI MS: *m*/*z* (%) 988.0 (100) [M$^+$ − PF_6^-], 842.2 (15) [M$^+$ − 2PF_6^-], 726.1 (25) [M$^+$ − dRf, − 2PF_6^-], $C_{42}H_{35}F_{12}N_{11}O_3P_2Ru\cdot H_2O$ (1132.8) calcd. C 43.83, H 3.24, N 13.39; found C 43.63, H 3.21, N 12.89.

General procedure for Suzuki–Miyaura cross-coupling reactions (Ru^{II} complexes)

A mixture of H_2O–CH_3CN = 2 : 1 (1 ml) was added to an argon-purged flask containing nucleoside 7 (53 mg, 0.16 mmol), a boronate **11a–d** (0.192 mmol, 1.2 equiv.) and Cs_2CO_3 (158 mg, 0.48 mmol, 3 equiv.). In a separate flask, $Pd(OAc)_2$ (1.8 mg, 0.008 mmol, 5 mol%) and $P(PhSO_3Na)_3$ (11 mg, 0.02 mmol, 2.5 equiv. to Pd) were combined evacuated and purged with argon

followed by an addition of H_2O–CH_3CN = 2 : 1 (0.5 ml). The solution of catalyst was injected to the reaction mixture which was then stirred at 80 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. The products **13a–d** were purified by silica gel column chromatography using a mixture of CH_3CN–H_2O–sat. KNO_3 = 10 : 1 : 0.1 as eluent. The products were isolated as PF_6^- salt by precipitation from water solution by addition of sat. NH_4PF_6.

Complex 13a

The product was isolated as orange powder 104 mg (55%). Mp 243 – 251 °C. Mixture of diastereoisomers 1 : 1. ^{1}H NMR (600 MHz, acetone-d_6): 2.33, 2.47 (2 × dd, 2 × 1H, J_{gem} = 13.3, $J_{2'b,1'}$ = 5.4, H-2′b); 3.30, 3.38 (2 × ddd, 2 × 1H, J_{gem} = 13.3, $J_{2'a,1'}$ = 10.1, $J_{2'a,3'}$ = 4.9, H-2′a); 3.69 (bm, 2H, H-5′b); 3.82, 3.85 (2 × dd, 2 × 1H, J_{gem} = 12.3, $J_{5'a,4}$ = 2.3, H-5′a); 4.20, 4.28 (2 × t, 2 × 1H, $J_{4',5'}$ = 2.3, H-4′); 4.70, 4.77 (2 × d, 2 × 1H, $J_{3',2'a}$ = 4.9, H-3′); 4.79, 5.10 (2 × bs, 2 × 1H, OH-3′); 6.03 (bs, 1H, OH-5′); 6.22, 6.26 (2 × dd, 2 × 1H, $J_{1',2'}$ = 10.1, 5.4, H-1′); 6.31, 6.35 (2 × dd, 2 × 1H, J = 8.0, 1.8, H-*m*-phenylene); 6.38 (bs, 1H, OH-5′); 6.98 (bs, 4H, NH_2); 7.05, 7.13 (2 × ddd, 2 × 1H, $J_{5,4}$ = 7.6, $J_{5,6}$ = 5.6, $J_{5,3}$ = 1.3, H-5-bpy); 7.16, 7.20 (2 × dd, 2 × 1H, J = 8.0, 1.8, H-*o*-phenylene); 7.40–7.46 (m, 4H, 2 × H-5-bpy, H-*o*-phenylene); 7.46, 7.51 (2 × ddd, 2 × 1H, $J_{6,5}$ = 5.6, $J_{6,4}$ = 1.5, $J_{6,3}$ = 0.7, H-6-bpy); 7.53, 7.54 (2 × ddd, 2 × 1H, $J_{5'''4'''}$ = 7.6, $J_{5'''6'''}$ = 5.6, $J_{5'''3'''}$ = 1.3, H-5‴); 7.59, 7.62 (2 × dd, 2 × 1H, $J_{5'',4''}$ = 7.7, $J_{5'',3''}$ = 1.4, H-5″); 7.64, 7.66 (2 × ddd, 2 × 1H, $J_{5,4}$ = 7.6, $J_{5,6}$ = 5.6, $J_{5,3}$ = 1.3, H-5-bpy); 7.69–7.75 (m, 6H, 2 × H-6‴ 2 × H-5-bpy, 2 × H-*m*-phenylene); 7.79, 7.81, 8.08, 8.09 (4 × ddd, 4 × 1H, $J_{4,3}$ = 8.2, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.5, H-4-bpy); 8.19 (s, 2H, H-2); 8.20–8.25 (m, 6H, 2 × H-4,6-bpy, 2 × H-4‴); 8.25, 8.29 (2 × ddd, 2 × 1H, $J_{6,5}$ = 5.6, $J_{6,4}$ = 1.5, $J_{6,3}$ = 0.7, H-6-bpy); 8.30, 8.32 (2 × ddd, 2 × 1H, $J_{4,3}$ = 8.2, $J_{4,5}$ = 7.6, $J_{4,6}$ = 1.5, H-4-bpy); 8.37 (dd, 2H, $J_{4'',3''}$ = 8.3, $J_{4'',5''}$ = 7.7, H-4″); 8.37, 8.39, 8.64, 8.71, 8.72, 8.81, 8.85 (7 × ddd, 8H, $J_{3,4}$ = 8.3, $J_{3,5}$ = 1.3, $J_{3,6}$ = 0.7, H-3-bpy); 8.90, 8.91 (2 × ddd, 2 × 1H, $J_{3'''4'''}$ = 8.3, $J_{3'''5'''}$ = 1.3, $J_{3'''6'''}$ = 0.7, H-3‴); 8.96, 8.97 (2 × dd, 2 × 1H, $J_{3'',4''}$ = 8.3, $J_{3'',5''}$ = 1.4, H-3″). ^{13}C NMR (151 MHz, acetone-d_6): 39.22, 39.90 (CH_2-2′); 64.09, 64.12 (CH_2-5′); 73.68, 73.89 (CH-3′); 87.79, 87.94 (CH-1′); 90.73, 90.87 (CH-4′); 120.94 (C-5); 124.21, 124.41 (CH-3-bpy); 124.62, 124.72 (CH-3″); 125.07, 125.24, 125.26, 125.55, 125.58, 125.89 (CH-3‴ CH-3-bpy); 127.54, 127.68, 128.12, 128.16 (CH-5-bpy); 128.31, 128.35, 128.62 (CH-5-bpy, CH-5‴ CH-*m*-phenylene); 128.99, 129.05, 129.07 (CH-5-bpy); 129.54, 129.59, 130.08, 130.18 (CH-*o*-phenylene); 130.85, 130.89, 130.96 (CH-*o*-phenylene, CH-5″); 131.04, 131.05 (C-*i*-phenylene); 137.49, 137.57 (CH-4-bpy); 138.93, 138.96, 139.02, 139.07, 139.08, 139.14 (CH-4‴ CH-4-bpy); 139.30 (CH-4″); 141.05, 141.08 (C-*p*-phenylene); 150.57 (C-8); 150.89, 150.99 (C-4); 151.78, 151.81, 152.48, 152.51, 152.83, 153.06, 153.09, 153.42, 153.48 (CH-6‴ CH-6-bpy); 157.43, 157.45, 157.46, 157.99, 158.12, 158.15, 158.73, 158.77, 158.81, 158.90, 158.92 (C-6, C-2‴ C-2-bpy); 166.73, 166.78 (C-2″). ESI MS: *m*/*z* (%) 1040.2 (100) [$M^+ - PF_6^-$], 894.2 (15) [$M^+ - 2PF_6^-$], 777.3 (5) [M^+ − dRf, $-2PF_6^-$], $C_{46}H_{39}F_{12}N_{11}O_3P_2Ru{\cdot}H_2O$ (1184.9) calcd. C 45.93, H 3.44, N 12.81; found C 45.98, H 3.44, N 12.67.

Complex 15

A mixture of H_2O–CH_3CN = 2 : 1 (1 ml) was added to an argon-purged flask containing 8-bromo-dATP **14** (used as 3 × Et_3N salt and dihydrate) (40 mg, 0.044 mmol), boronate **13d** (86 mg, 0.088 mmol, 2 equiv.), and Cs_2CO_3 (43 mg, 0.13 mmol, 3 equiv.). In a separate flask, $Pd(OAc)_2$ (0.5 mg, 0.0022 mmol, 5 mol%) and $P(PhSO_3Na)_3$ (6.1 mg, 0.011 mmol, 5 equiv. to Pd) were combined, evacuated and purged with argon followed by an addition of H_2O–CH_3CN = 2 : 1 (0.5 ml). The solution of catalyst was injected into the reaction mixture which was then stirred at 80 °C for 1 hour. The solvent was evaporated *in vacuo*. The product **15** was purified by RP HPLC using a linear gradient of 0.1 M TEAB (triethylammonium bicarbonate) in H_2O to 0.1 M TEAB in H_2O–MeOH (1 : 1) as eluent. The product was isolated after lyophilization as a red powder 30 mg (39%) (isolated as 2 × Et_3N salt). ^{1}H NMR (500 MHz, D_2O): 1.25 (t, 18H, J_{vic} = 7.3, CH_3CH_2N); 2.30 (bm, 1H, H-2′b); 3.15 (q, 12H, J_{vic} = 7.3, CH_3CH_2N); 3.30 (bm, 1H, H-2′a); 4.34–4.43 (m, 2H, H-4′ and H-5′b); 4.48 (bm, 1H, H-5′a); 4.82 (bm, 1H, H-3′); 6.25 (bt, 1H, $J_{1',2'}$ = 6.5, H-1′); 6.89 (bm, 2H, H-5‴); 7.21 (bt, 2H, $J_{5',4'}$ = 7.5, $J_{5',6'}$ = 5.4, H-5′-tpy); 7.38 (bd, 2H, $J_{6'''5'''}$ = 5.4, H-6‴); 7.44 (bd, 2H, $J_{6',5'}$ = 5.4, H-6′-tpy); 7.61 (bs, 1H, H-2); 7.73 (bt, 2H, $J_{4'''3'''}$ = 8.2, $J_{4'''5'''}$ = 7.5, H-4‴); 7.81 (bm, 2H, H-*o*-phenylene); 7.93 (bm, 2H, H-*m*-phenylene); 8.04 (bt, 2H, $J_{4',3'}$ = 8.2, $J_{4',5'}$ = 7.5, H-4′-tpy); 8.37 (t, 1H, $J_{4,3\&5}$ = 8.4, H-4-tpy); 8.45 (bd, 2H, $J_{3'''4'''}$ = 8.2, H-3‴); 8.62 (bd, 2H, $J_{3',4'}$ = 8.2, H-3′-tpy); 8.72 (bs, 2H, H-3,″5″); 8.75 (d, 2H, $J_{3\&5,4}$ = 8.4, H-3,5-tpy); ^{31}P NMR (162 MHz, D_2O): −22.30 (t, J = 21, 20, P_β); −11.06 (d, J = 20, P_α); −6.30 (d, J = 21, P_γ); ESI MS: *m*/*z* (%) = 1132.0 (100) [$M^+ - 2PF_6^-$].

X-Ray diffraction

X-Ray crystallographic analysis of single crystals of **9c** (yellowish, 0.17 × 0.19 × 0.63 mm) and **13c** (red, 0.18 × 0.28 × 0.71 mm) was performed with an Xcalibur X-ray diffractometer with Cu-Kα (λ = 1.54184 Å), data collected at 150 K. Both structures were solved by direct methods with SIR92[19] and refined by full-matrix least-squares methods based on F with CRYSTALS.[20]

Crystal data for 9c. $C_{28}H_{23}N_7O_3$, $C_{28}H_{22}N_7O_3$, triclinic, space group $P1$, a = 10.790(4), b = 10.800(3), c = 13.163(4) Å, α = 96.79(3), β = 106.00(3), γ = 105.90(3)°, V = 1386.6(9) Å^3, Z = 1, M = 1010.06, 5801 reflections measured, 5801 independent reflections. Final R = 0.0576, wR = 0.0920 for 2973 reflections with $I > 1.8\sigma(I)$ and 685 parameters. Hydrogen atoms were located in a difference map, but those attached to carbon atoms were repositioned geometrically and then refined with riding constraints. Hydrogen atom on O55 has not been found. All non-hydrogen atoms were refined anisotropically. The methanol solvent molecules were not modelled and the disordered density was taken into account using the SQUEEZE/PLATON procedure.[21]

Crystal data for 13c. $C_{48}H_{38}N_{11}O_3Ru$, $C_{48}H_{37}N_{11}O_3Ru$, 4(F_6P), triclinic, space group $P1$, a = 13.291(5), b = 13.669(5), c = 16.242(5) Å, α = 89.02(3), β = 71.32(3), γ = 89.82(4)°, V = 2794.9(18) Å^3, Z = 1, M = 2414.80, 21182 reflections measured, 21182 independent reflections. Final R = 0.0585, wR = 0.0778 for 14870 reflections with $I > 2\sigma(I)$ and 1358 parameters. Hydrogen atoms were located in a difference map, but those attached to carbon atoms were repositioned geometrically and then refined with riding constraints. Hydrogen atoms on oxygen atoms have not been found except the one attached to O16. Six fluorine atoms on one of the hexafluorophosphate anions had to be

refined isotropically due to unresolved disorder. All other atoms were refined anisotropically in both cases. The methanol solvent molecules were not modelled and the disordered density was taken into account using the SQUEEZE/PLATON procedure.[21]

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