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Water-Soluble Pd–Imidate Complexes: Broadly Applicable Catalysts for the Synthesis of Chemically Modified Nucleosides via Pd-Catalyzed Cross-Coupling

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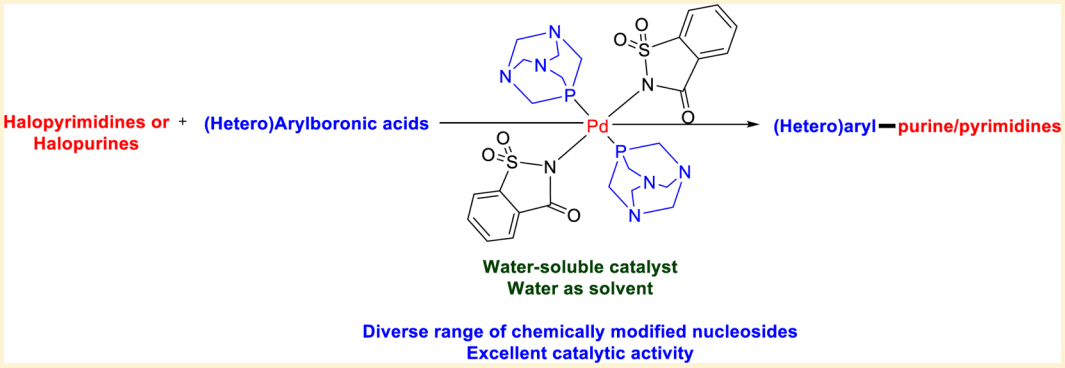
Supporting Information



ABSTRACT: A broadly applicable catalyst system consisting of water-soluble Pd–imidate complexes has been enployed for the Suzuki–Miyaura cross-coupling of four different nucleosides in water under mild conditions. The efficient nature of the catalyst system also allowed its application in developing a microwave-assisted protocol with the purpose of expediting the catalytic reaction. Preliminary mechanistic studies, assisted by catalyst poison tests and stoichiometric tests performed using an electrospray ionization spectrometer, revealed the possible presence of a homotopic catalyst system.

INTRODUCTION

Chemically modified nucleoside analogues are important structural motifs useful for a variety of applications.[1] Modified nucleosides, nucleotides, and oligonucleotides obtained via synthetic methods have in recent years acquired much attention in pharmaceutics,[2] cancer treatment,[3] and use as biological probes.[4] An overview of the pharmaceutical industry reveals an upward trend in the development of antiviral or anticancer drugs possessing nucleoside structural motifs.[2c]

Modification of nucleosides via functionalization of the purine or pyrimidine bases is an attractive synthetic strategy, which could be accomplished efficiently by metal-catalyzed cross-coupling reactions.[5] With regard to their success in functionalizing a variety of arenes and heteroarenes, metal-catalyzed cross-coupling reactions[6] have provided greener and cleaner alternatives to other synthetic procedures. Palladium-catalyzed coupling reactions[7] have played a major role in such modifications, with processes such as Suzuki–Miyaura,[8] Sonogashira,[9] Heck,[10] and Stille[11] at the forefront.

Palladium-catalyzed Suzuki–Miyaura[8] cross-coupling, among others, has allowed researchers to achieve both improved reactivity as well as better control over the reaction conditions leading to the development of more efficient catalytic systems for the modification of nucleosides.[12] Functionalization can be carried out by performing the cross-coupling reactions in aprotic polar solvents (DMF, NMP, etc.) or mixed-organic solvent systems. However, a synthetically more attractive alternative involves the use of water as the solvent.[13] This topic has been elegantly covered by Shaughnessy in a more recent review article.[5]

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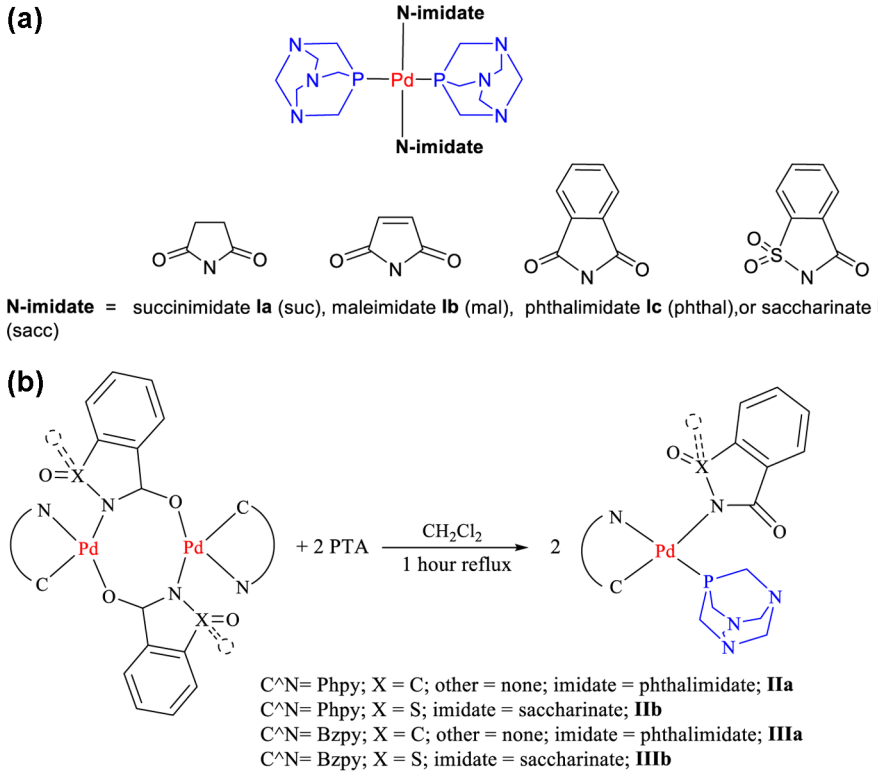
Scheme 1. Synthesis of Pd−Imidate Complexes



Literature reports on the use of water (either as the reaction solvent or in combination with other organic solvents) for the palladium-catalyzed Suzuki−Miyaura coupling of nucleosides have described hydrophilic catalytic systems.[12] Both Shaughnessy and Hocek have independently shown the successful application, furnishing a wide variety of modified nucleosides for purine as well as pyrimidine analogues.[14] Most protocols employ water in combination with organic solvents such as MeCN. Recently, we reported on the cross-coupling of nucleosides in water as the sole reaction solvent,[15] which was made possible by the utilization of water-soluble Pd−imidate complexes of the type [*trans*-[Pd(imidate)$_2$(PTA)$_2$] (1,3,5-triaza-7-phosphaadamantane). This report, however, only covered the Suzuki−Miyaura cross-coupling of 5-iodo-2′-deoxyuridine with different arylboronic acids.[15] In view of the encouraging results obtained with this combination of imidate/PTA ligands, we envisaged the potential utility of complexes [Pd(C^N)-(imidate)(PTA)] incorporating a palladacyclic backbone, since the analogous water-insoluble derivatives (bearing PR3 instead of PTA) have already displayed excellent Suzuki performance in our hands.[16] Related [Pd(C^N) (Cl) (PTA)] complexes, however have been reported to exhibit poor water solubility,[17,18] and with only one example in Sonogashira coupling[19] to date, there are no reported studies about such complexes carrying out Suzuki coupling in aqueous media.

Herein, we report a comprehensive study utilizing Pd−PTA−imidate complexes for palladium-catalyzed Suzuki−Miyaura cross-couplings in water for all four nucleosides with a wide variety of aryl and heteroarylboronic acids leading to an eclectic array of modified nucleosides of synthetic relevance. We have also been successful in developing an efficient coupling protocol for the synthesis of 5-styryl-2′-deoxyuridines via Suzuki−Miyaura cross-coupling of BVDU (brivudine). Finally, a microwave-assisted protocol for accelerating the cross-coupling reaction was devised based on the reactivity of the Pd−PTA−imidate complexes.

RESULT AND DISCUSSION

The facile synthesis of [*trans*-[Pd(imidate)$_2$(PTA)$_2$]] **Ia−d** (*N*-imidate = succinimidate **Ia** (suc), maleimidate **Ib** (mal), phthalimidate **Ic** (phthal), or saccharinate **Id** (sacc)) has been reported previously (Scheme 1a).[15] The four new water-soluble palladacyclic derivatives [Pd(C^N) (imidate) (PTA)] (**IIa,b−IIIa,b**) have been prepared by bridge-splitting reactions of the corresponding di-μ-imidate complexes with PTA as displayed in Scheme 1b.

Recently, we have been involved in the study of 2-phenylpyridine (**II**) and scarce 2-benzoylpyridine (**III**) backbones in cyclometalated compounds as convenient precursors for organometallic synthesis.[20] These complexes were fully characterized by spectroscopic methods. The outstanding features of the IR spectra are the characteristic strong carbonyl-imidato absorptions in the 1675−1609 cm^{-1} region, which together with weak or absent ν_{sim}(CO) bands beyond 1720 cm^{-1} indicate monodentate *N*-imidate coordination. The incoming PTA, which has infrared absorptions at 452 and 405 cm^{-1} when free, displays typical bands shifted downfield upon complexation.[21]

The singlet resonance in the range −47/−50 ppm displayed in **IIa,b−IIIa,b** ^{31}P{^{1}H} NMR spectra are in agreement with palladium compounds containing PTA acting as a P-donor ligand as previously reported.[22] The corresponding ^{1}H NMR spectra exhibit an overlapped aromatic region and two broad singlet resonances for NCH$_2$N and PCH$_2$N at the usual chemical shifts.[22d,23] Additional support for the proposed structure of the new complexes arises from mass spectrometry, which shows fragments for the *m*/*z* values corresponding to M$^+$ imidate and an abundance of the signals around the parent ions consistent with the natural isotopic abundances. The molecular

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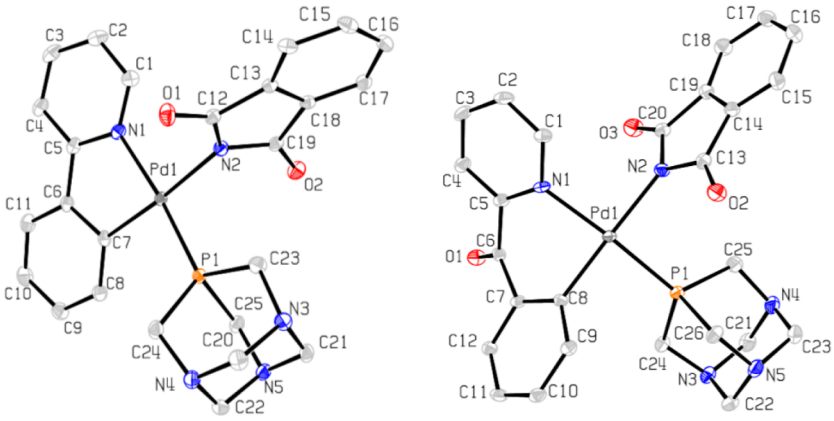

IIa **IIIa**

Figure 1. Single-crystal X-ray structure for **IIa** and **IIIa**. Ellipsoids are shown with 50% probability.

structures of **IIa** and **IIIa** were elucidated using single-crystal X-ray diffraction (Figure 1).[24] The coordination around the Pd atoms is approximately planar. Its deviation from the planar coordination geometry has been quantified by the measurement of improper torsion angles[25] $w1 = 3.59°$ and $w2 = 0.49°$ for Pd1 in **IIa** and $w1 = -7.49°$ and $w2 = -0.63°$ for **IIIa**. These values correspond to a moderate tetrahedral distortion from the ideal square planar geometry. The narrow NPdC angle in **IIa** (81.36(5)°) in the ortho-metalated moiety is similar to that found in complexes containing 2-phenylpyridine ligand.[26]

The N−Pd−C bond angle in **IIIa**, 88.76(10)°, is in the range of that found in the two previously reported structures 90.05(6)°, (87.4(3)°).[27] The conformation of the six-membered ring Pd(1)−C(8)−C(7)−C(6)−C(5)−N(1) is *screw-boat* deformed 18° ($E = 0.0031$; $B = 0.0622$; SB = 0.9346).[28] The structural analysis of complexes **IIa** and **IIIa** confirms the relative *cis* position of the phosphine ligand and the metalated carbon atom. This is the typical arrangement of the phosphine group in cyclopalladated complexes of the type [Pd(C^N)(phosphine)(L)] (X = anionic monodentate ligand) due to the so-called transphobia effect.[29] All of the six-membered rings in each TPA ligand exhibit a chair conformation deformed less than 10°.[30]

Besides these details, it is also important to note that the catalysts are easy to handle owing to their excellent air and moisture stability. This in turn has led to them exhibiting a very good shelf life of several months without any physical or chemical change. (The catalyst was kept on the shelf for several weeks, and any degradation that might occur was monitored by ^{1}H and ^{31}P NMR analysis. This was performed every week to check for possible phosphine oxide formation. However, even at the end of 8 weeks no visible degradation was observed, suggesting good air and moisture stability of the catalyst on storage.) Water solubility of the complexes was also found to be satisfactory with complex **1d** exhibiting a maximum solubility value of 0.1 g/mL.

Suzuki−Miyaura Cross-Coupling of Halo-2′-deoxynucleosides. *Catalyst Comparison Study for Suzuki−Miyaura Cross-Coupling of 5-Iodo-2′-deoxyuridine.* Our initial report on the Suzuki−Miyaura cross-coupling of 5-iodo-2′-deoxyuridine was focused on the arylation using substituted arylboronic acids, giving good to excellent yields of the cross-coupled products.[15] To evaluate the applicability of the newly synthesized Pd−imidate complexes, we set about investigating the Suzuki−Miyaura coupling of all four 2′-deoxynucleosides, namely uridine, cytidine, adenosine, and guanosine.

At the outset of our studies, the reactivity of different Pd−imidate complexes was investigated by obtaining the HPLC profiles for the catalytic reaction of 5-iodo-2′-deoxyuridine with benzofuran-2-boronic acid in water (Figure 2: injecting small aliquots of reaction mixture at regular intervals). The analysis was carried out on a Waters HPLC system. The injections were carried out at intervals of 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 6.0 h to obtain sufficient data points. In comparison to the Pd−imidate complexes possessing the cyclopalladated backbones, namely **IIa-b** and **IIIa-b**, complexes of the formula $[Pd(imidate)_2(PTA)_2]$ (**Ia−d**) exhibited enhanced reactivity with the catalyst **Id** giving the best results in terms of the yield of the desired cross-coupled product (quantitative conversion after 4 h). Commonly used Pd precursors such as $[PdCl_2(PTA)_2]$, $[PdBr_2(PTA)_2]$, and $[PdCl_2(TPPTS)_2]$ gave poor yields of the product as was found for $Pd(OAc)_2$, further confirming the versatility and potency of the Pd−imidate complexes $[Pd(imidate)_2(PTA)_2]$ (**Ia−d**). The $Pd(OAc)_2$/TPPTS system gave the same results, which showed a conversion of 87% after 6.0 h.

Catalyst Concentration Study. With the active catalyst **Id** in hand, we further investigated the effect of catalyst loading on the reactivity toward the cross-coupling of 5-iodo-2′-deoxyuridine with benzofuran-2-boronic acid. It was found that the catalyst loading when reduced from 1.0 to 0.5 mol % had little effect on the catalytic activity of the catalyst **Id** (Figure 3). Complete conversion to the desired product was observed, albeit at longer reaction time (complete conversion after 12.0 h). Similar observations were made for 0.1 mol % catalyst loading, which resulted in quantitative yield of the cross-coupled product in 24 h. Any further reduction in the catalyst concentration brought about reduction in the yield, giving only 64% of the product in 24 h. To keep the catalytic system competitive, it was decided to perform all of the subsequent coupling reactions at 1.0 mol % catalyst loading, although as demonstrated, the catalyst can also perform efficiently at lower catalyst loading.

Substrate Scope for Suzuki−Miyaura Cross-Coupling of 5-Iodo-2′-deoxyuridine. Encouraged by these results we decided to employ the water-soluble Pd−imidate complex **Id** for catalyzing the Suzuki−Miyaura cross-coupling of different heteroarylboronic acids as well as bulkier and substituted arylboronic acids at 1.0 mol % catalyst loading in water (Scheme 2).

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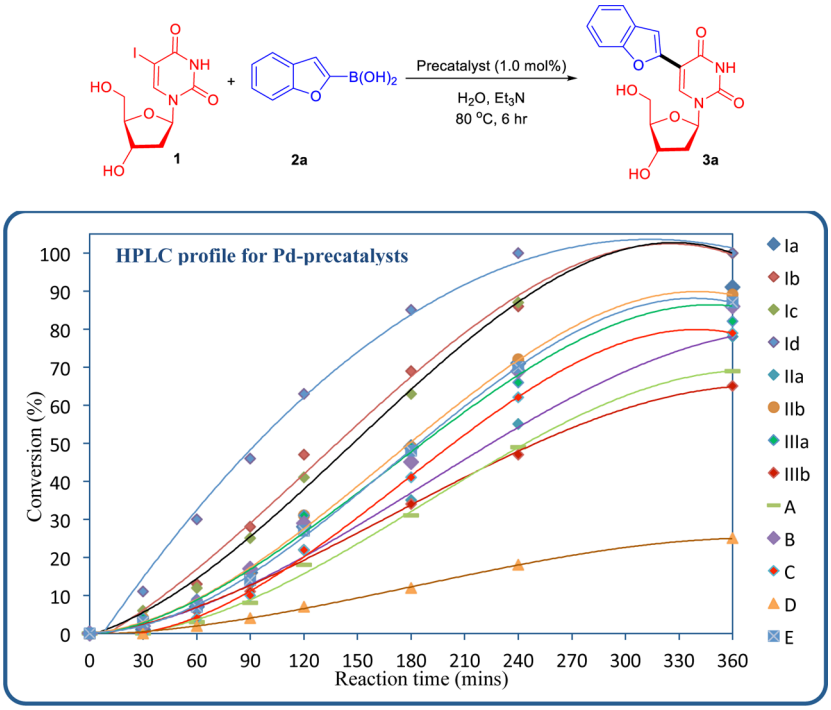

Figure 2. HPLC profiles for Pd(II) precatalysts. Catalysts employed **Ia-d**, **IIa-b**, **IIIa-b**, **A** = $[PdCl_2(PTA)_2]$, **B** = $[PdBr_2(PTA)_2]$, **C** = $[PdCl_2(TPPTS)_2]$, **D** = $Pd(OAc)_2$, **E** = $Pd(OAc)_2$ + TPPTS.

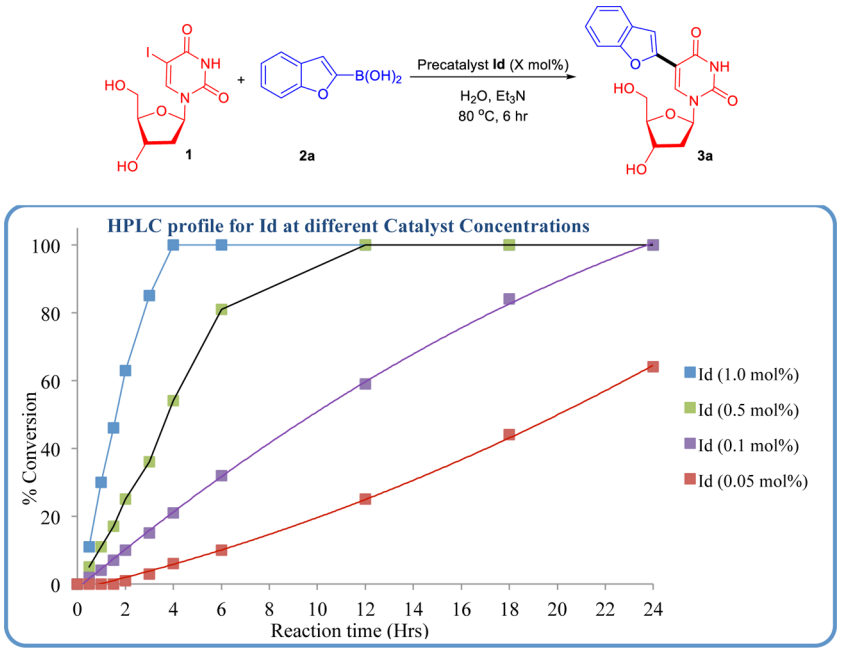

Figure 3. HPLC profiles for Pd(II) precatalyst **Id** at different catalyst concentrations.

The use of heteroarylboronic acids as coupling partners is important given the unique fluorescence properties of the amidites obtained from the respective cross-coupled products, especially the ones containing a 2-benzofuranyl (**3a**)[31a] or 2-furanyl (**3c**)[31b] moiety (exhibiting excellent photophysical properties leading to their use as effective DNA probes[32]). Another important example is that of (4-formylphenyl)boronic acid (**3l**), which has been used in the past as the starting material for preparing spin-labeled nucleosides[33a] (for EPR analysis of DNA structures), which furnished the product in very good yields compared to that reported in literature.[33a,b]

The reactivity of complex **Id** toward cross-coupling the heteroarylboronic acids was in general found to provide the cross-coupled products in good to excellent yields (48−92%).

Similarly, substituted and bulky arylboronic acids when employed as coupling partners also furnished the cross-coupled products in good yields. Pyrene and phenanthrene structural motifs with more steric bulk have in recent years found applications as fluorescent probes,[34] which could assist the development of novel fluorescent nucleoside[35] molecules. The respective precursors also gave decent yields of the cross-coupled products (**3g** and **3h**). Similarly, the introduction of a formyl

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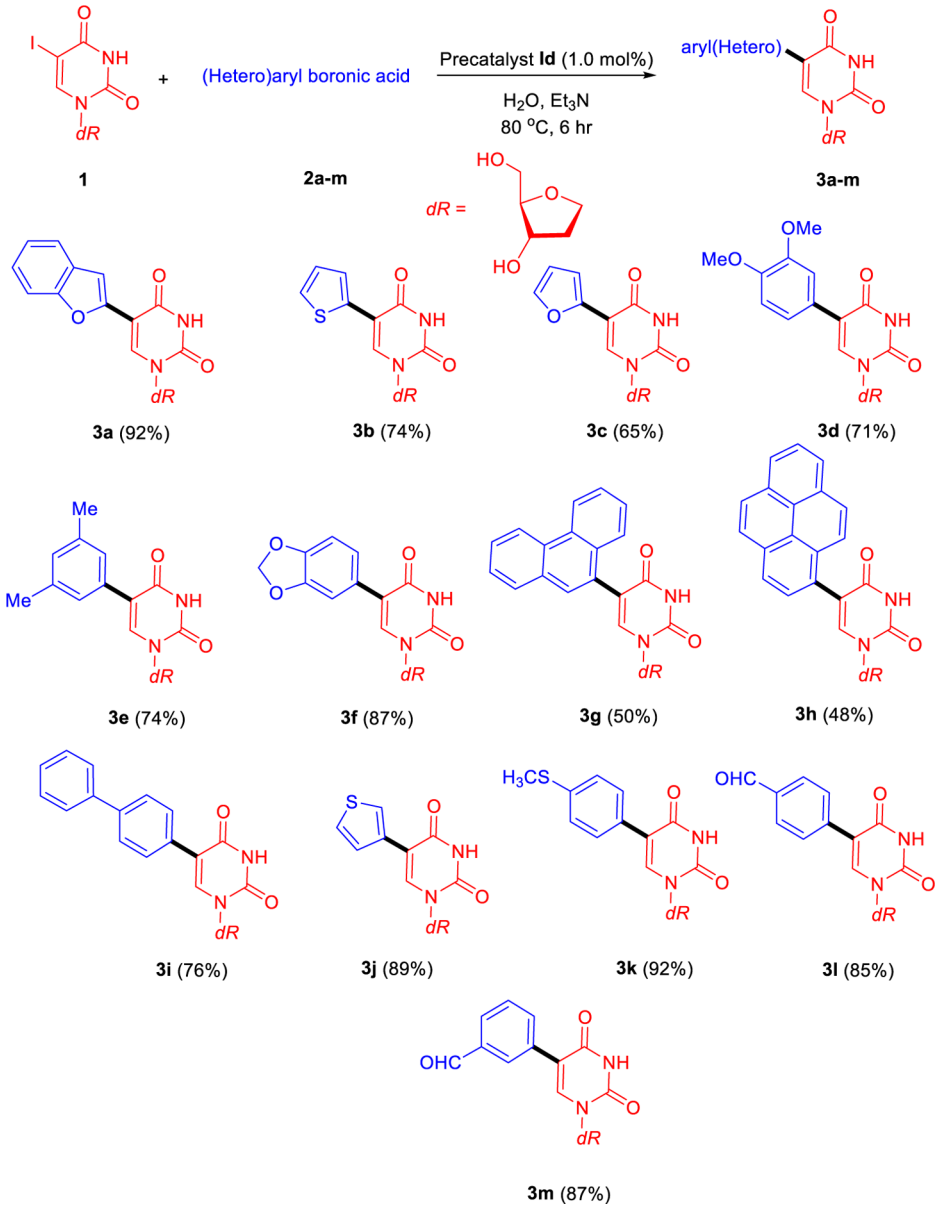
Scheme 2. Suzuki–Miyaura Cross-Coupling of 5-Iodo-2′-deoxyuridine



group via Suzuki–Miyaura cross-coupling of 5-IdU with (3-formylphenyl)- or (4-formylphenyl)boronic acid[36] was also achieved in good yields. These products have found extensive application in the development of spin-labeled nucleosides.[37]

Single-Crystal X-ray Analysis of Suzuki–Miyaura Cross-Coupling Products. All modified uridine nucleosides were characterized by general spectroscopic techniques. However, for some of the compounds it was also possible to obtain single crystals that were suitable for X-ray structural analysis. Good crystals for **3a**, **3f**, and **3i** were obtained from the H_2O/MeOH solvent system, and the following characteristics were observed (Figure 4).

Nucleoside **3a** crystallized in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit.[38] An extensive network of hydrogen bonds was present in the crystal lattice. Only oxygen atoms were found as acceptors, whereas the donors were carbon, nitrogen, and oxygen atoms. In this case, the aromatic systems are nearly coplanar with a torsion angle of only 8.2° indicating a joint π-system throughout most parts of the molecule. In the crystal lattice, $\pi-\pi$-interactions in the range of the typical value appear to be present between the *N*-heterocycle and the phenyl ring with distances between the atoms ranging from 3.37 to 3.94 Å; i.e., the two rings are not perfectly coplanar but the $\pi-\pi$-interactions still seem to be strong despite this.

Nucleoside **3f** crystallized in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.[39] The second isomer was generated by symmetry operation; hence, a racemic mixture had crystallized. Again, there are many hydrogen bonds in the crystal lattice with both inter- and intramolecular ones with oxygen atoms as the sole acceptors and carbon, nitrogen, and oxygen atom donors. The amine proton was located and refined freely. No coplanarity between aromatic rings, i.e., $\pi-\pi$ interactions, were found. In contrast to **3i** where three aromatic rings were present, such interaromatic interactions do not play a role in the crystal lattice of **3f**. The torsion angle between the two aromatic moieties in **3f** was 36.3°. Compound **3i** crystallizes in the orthorhombic space group $C222_1$ with one molecule in the asymmetric unit and two

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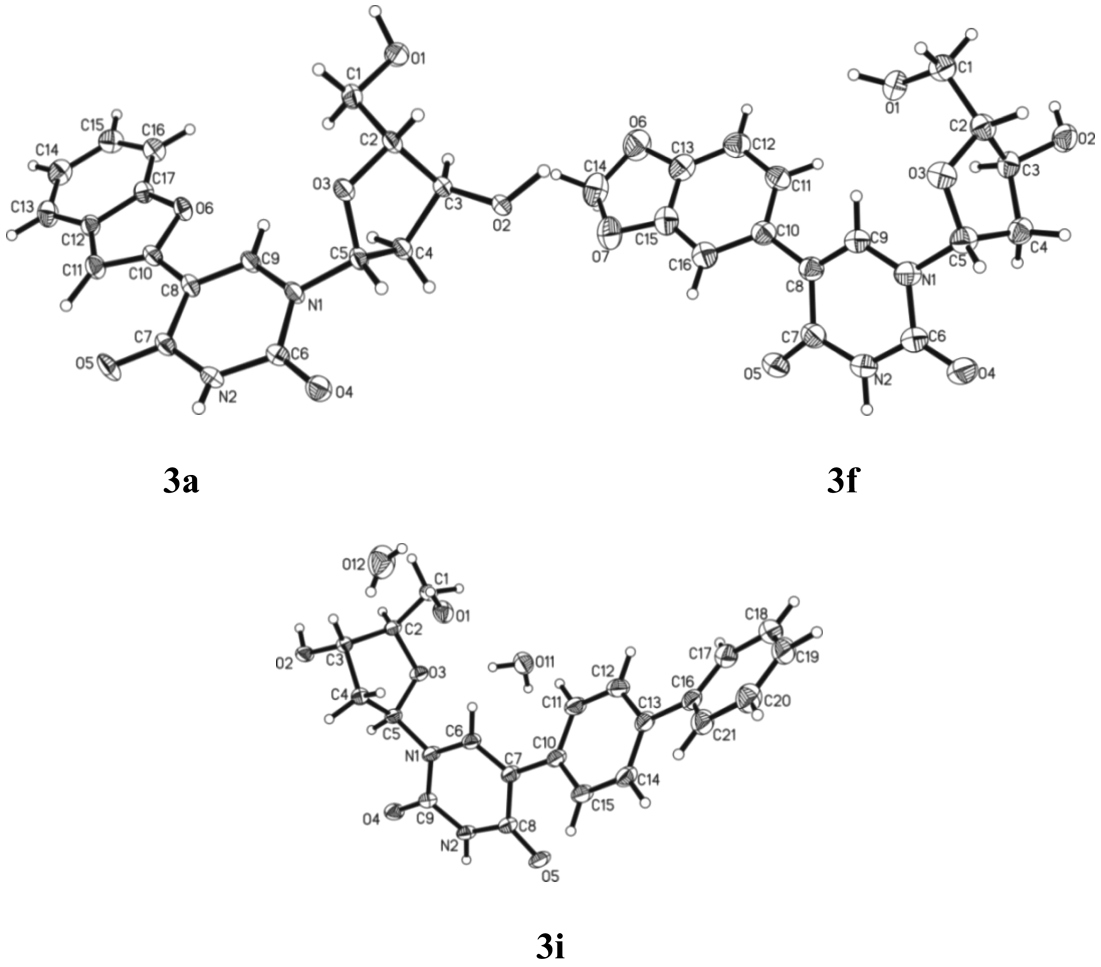

Figure 4. X-ray crystallographical representation of cross-coupled nucleosides. Ellipsoids are shown with 50% probability.

cocrystallized water molecules.[40] The torsion angle between the two phenyl rings was 31.1°, i.e., they are not coplanar. The torsion angle between the *N*-heterocycle and the directly attached phenyl ring was 37.2°.

The torsion angle to the outer phenyl ring was 68.0°. In the crystal lattice, the molecules pair up in opposite directions (the heterocycle faces the outermost phenyl ring of the second molecule) with all three aromatic rings of one molecule almost coplanar with those of the second molecule. There exists an extensive net of inter- and intramolecular hydrogen bonding in the crystal lattice stabilizing the structure. The nitrogen of the heterocycle was not protonated at the oxygen atom attached to the adjacent carbon; i.e., a different tautomer crystallized. The respective hydrogen atom was located and refined freely.

Suzuki–Miyaura Cross-Coupling of 5-Iodo-2′-deoxycytidine. Next, we turned our attention to the cytidine nucleoside which upon cross-coupling exhibits promising fluorescence properties.[41] The increased quantum yield upon C5-modification further warrants its use as a fluorescent probe.

Since 5-iodo-2′-deoxycytidine shows good solubility in water, catalytic cross-coupling was performed in water at 80 °C (Scheme 3). More promising results were observed in this case, and the reactivity of catalyst **Id** was found to be good, resulting in the synthesis of a series of 5-arylated 2′-deoxycytidines **5a–j**. The electronic effect on the arylboronic acid does not seem to play a significant role in the yield of the cross-coupling product. These results strengthen our claim for the catalyst **Id** to provide broad substrate scope and good yield (52–75%) of modified nucleosides.

Suzuki–Miyaura Cross-Coupling of 8-Bromo-2′-deoxypurines. In literature, few examples are reported for the application of a single catalytic system for the cross-coupling of pyrimidine as well as purine nucleosides. In 2003, Shaughnessy and co-workers reported the application of a Pd/TPPTS system for the cross-coupling of three different nucleosides.[14a] The catalytic concentration employed in such transformations, however, was higher (2.5 mol % Pd) than desired for scale-up of these synthetically useful molecules. Consequently, it was of interest to us to test the applicability of the catalyst in hand (**Id**) toward the coupling of purine nucleosides, namely 8-bromo-2′-deoxyadenosine (8-Br-dA) and 8-bromo-2′-deoxyguanosine (8-Br-dG). In order to address the issue of catalyst concentration, catalytic reactions with the purine nucleosides were performed at 1.0 mol % in water as solvent at 80 °C.

Initially, Suzuki–Miyaura cross-coupling of 8-Br-dA was carried out in water using trimethylamine as base (Scheme 4). After 12 h, the catalytic reaction showed complete conversion of the starting material after which the cross-coupled products were subjected to column chromatographic purification. Even in the case of purine nucleoside (adenosine in this case), the reactivity of **Id** was found to be satisfactory with good yields obtained for the cross-coupled products. As already observed in this study, the nature of boronic acid did not influence the catalytic activity, with both aryl- and heteroarylboronic acids exhibiting similar to identical reactivity.

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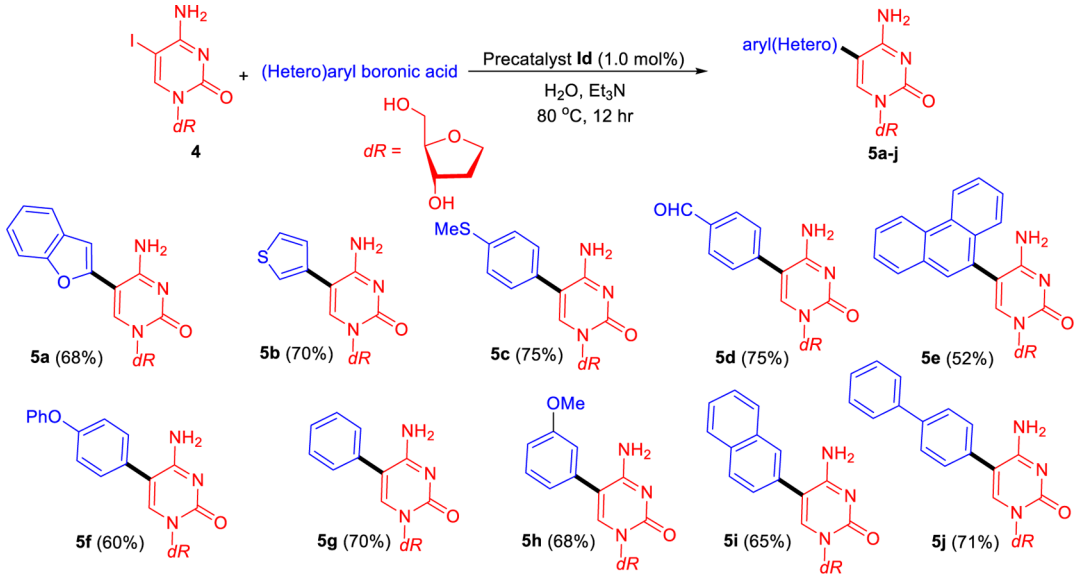
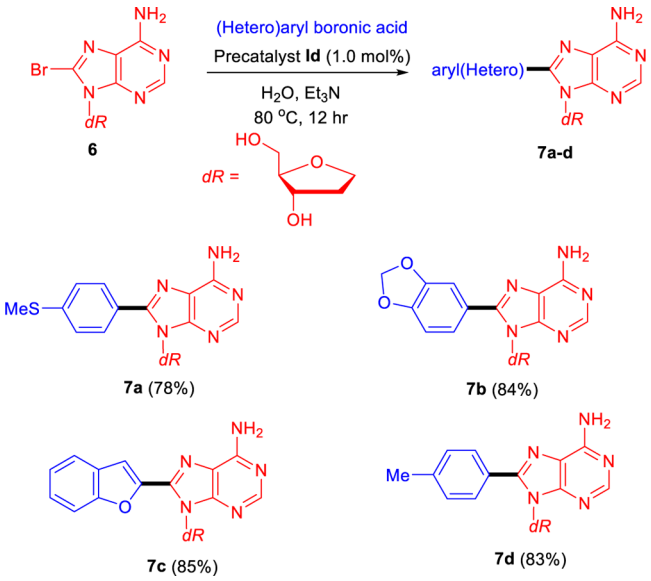
Scheme 3. Suzuki–Miyaura Cross-Coupling of 5-Iodocytidine with Heteroaryl and Bulky Boronic Acids



Scheme 4. Suzuki–Miyaura Cross-Coupling of 8-Bromo-2′-deoxyadenosine with Heteroaryl and Bulky Boronic Acids



We then turned our attention to assess the catalytic activity of **Id** for the Suzuki–Miyaura cross-coupling of 8-Br-dG with aryl- and heteroarylboronic acid (Scheme 5). In the literature, the reactivity of 8-Br-dG was found to be much lower compared to 5-iodo-2′-deoxyuridine and 8-Br-dA.[42] Therefore, developing an efficient cross-coupling protocol for 8-Br-dG[14a,43] has to be considered a major challenge, and preliminary results toward achieving this goal are presented below. To establish our new catalytic system to be a versatile contender, the following experiments were conducted next. The catalyst concentration was maintained at 5.0 mol % with the reaction performed in water as solvent at 80 °C.

The cross-coupling proceeded in good yields in most cases, irrespective of the arylboronic acids employed, although the isolation of the cross-coupled could not be achieved using column chromatographic techniques as extensive deglycosylation was observed. The products were therefore isolated by the precipitation method by adjustment of pH (see the Experimental Section for further details).

Suzuki–Miyaura Cross-Coupling of (E)-5-(2-Bromovinyl)-2′-deoxyuridine (BVDU). Since its discovery as a drug for the early treatment of herpes simplex virus type I (HSV-I), brivudine, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), has found commercial importance mainly in Europe.[44] Promising inhibitory activity against varicella zoster virus (VZV) is another reason for its commercial success.[45] Literature reports on the possible mode of action of BVDU suggest complete inhibition of the viral replication process by blockage of the DNA polymerases enzyme.[44,45] It is therefore of significant importance to develop more efficient and sustainable synthetic procedures for BVDU and its analogues. One of the routes for the synthesis of BVDU that has acquired more attention in recent years is via palladium-catalyzed Heck alkenylation of 5-iodo-2-deoxyuridine (itself identified as an effective HSV-1 inhibitor) followed by further transformations.[46]

A variety of catalytic systems[46a] have been analyzed in the past, and in this regard, we have recently reported a high-yielding protocol using the above-mentioned Pd–imidate complexes[46b] to furnish (*E*)-5-(2-bromovinyl)-2′-deoxyuridine in an overall yield of 72% over three steps (the Heck alkenylation step using Pd–imidate complex **Id** gave 90% product formation for the starting precursor for BVDU synthesis; see Scheme 6). With this methodology, we were also able to demonstrate the possibility of scale up to 10 mmol. Given the presence of a synthetically exploitable vinylic bromide functional group that could act as a potential handle for the modification of BVDU, we envisaged the employment of Suzuki–Miyaura cross-coupling using catalyst **Id** in water to prepare (*E*)-5-(2-arylvinyl)-2′-deoxyuridines (Scheme 7). In the literature, few of these compounds have been obtained by the employment of the Stille coupling reaction by De Clercq and co-workers with the compounds exhibiting good antiviral activity.[46c] It was therefore of interest to develop an efficient protocol to access such molecules under milder conditions. From the initial results, we conclude that using certain boronic acids that have exhibited good fluorescent properties in combination with nucleosides would be beneficial in our case, too. Accordingly, phenyl- and (2-benzofuryl)boronic acids were

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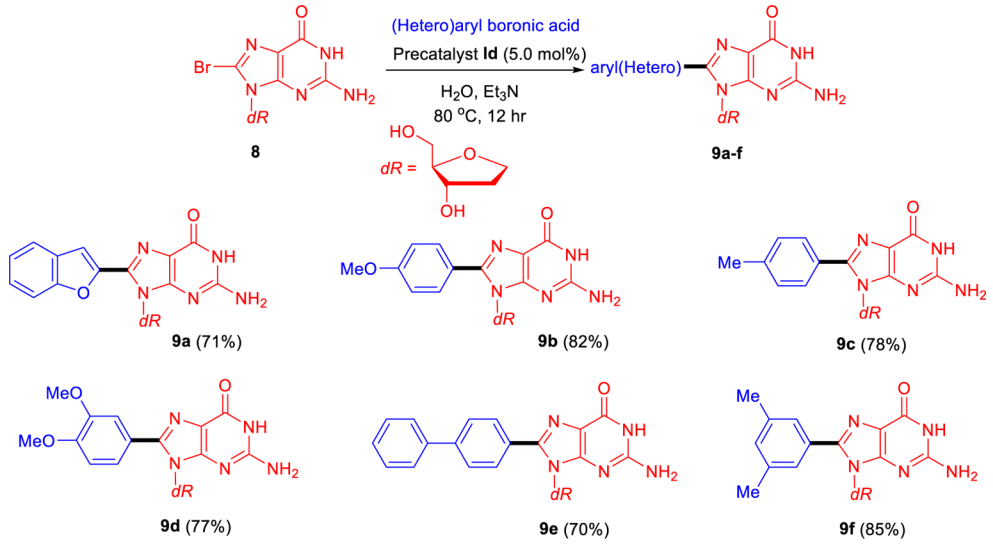
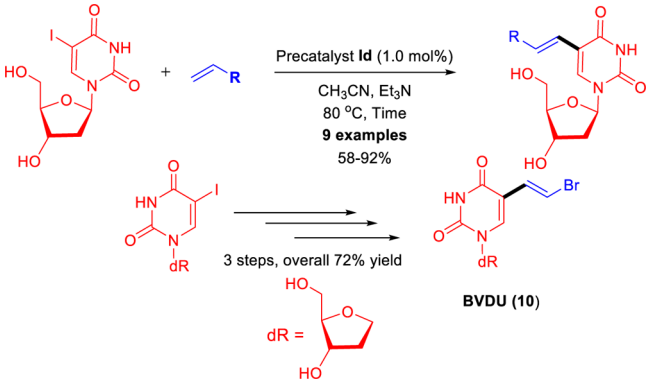
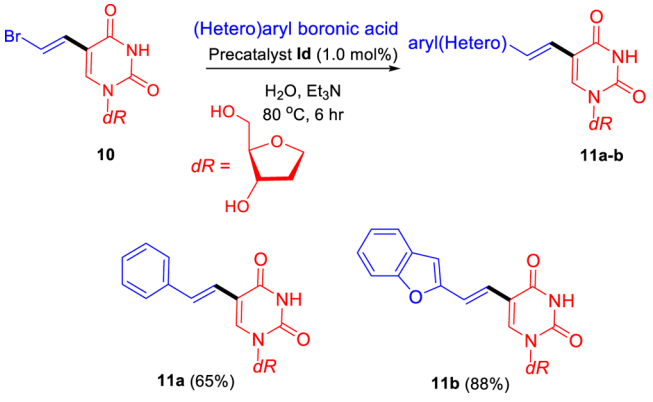
Scheme 5. Suzuki–Miyaura Cross-Coupling of 8-Bromo-2′-deoxyguanosine with Aryl and Heteroaryl Boronic Acids



Scheme 6. Heck Alkenylation of Nucleosides Using Pd–Imidate Complexes



Scheme 7. Suzuki–Miyaura Modification of HSV-1 Inhibitor BVDU



employed as precursors, resulting in good to excellent yields (65–88%) of the respective cross-coupled products.

Microwave-Assisted Protocol for Suzuki–Miyaura Arylation of Nucleosides. Microwave-assisted synthesis has in recent years attracted a lot of interest due to the possibility of drastically reducing the reaction time required for the synthetic reactions in comparison to conventional methods.[47] The application of microwave heating to palladium-catalyzed processes[48] has had a similar impact with catalytic reactions proceeding toward completion within minutes as opposed to several hours using traditional heating and, therefore, has been recognized as alternative technology for a sustainable development that is compatible with green chemistry principles.[49] Rapid heating of the reaction mass also has shown certain visible effects in terms of rate enhancement and improvement in the efficiency of the catalytic systems (with respect to the selective formation of the product over other side products).[48c]

Although microwave-assisted coupling processes are well-known, their application to the modification of nucleosides (via cross-coupling reactions) has been explored more recently. Len and co-workers have elegantly reviewed this area highlighting the problems and possible future.[46a,50] Keeping this in mind, we investigated the possibility of developing a microwave-assisted protocol for the Suzuki–Miyaura cross-coupling of the different nucleosides discussed previously. The reactions were performed on a CEM Discover Microwave on a 0.25 mmol scale for the different halonucleosides in water as the reaction solvent using 1.0 mol % of precatalyst **Id** at 80 °C (Scheme 8).

Because of the rapid heating technology of microwave radiations, the time required for synthesis of the desired products could be reduced drastically from several hours to a matter of few minutes. Pyrimidine nucleosides, namely uridine and cytidine, underwent facile formation of the desired cross-coupled product in good to excellent yield (88–94%) within 5 min under microwave conditions. The reactivity compared to the conventional procedure was found to be similar (although at a much faster rate), but an appreciable increase in product formation could be observed in the case of cytidine. Similarly, for purine nucleosides (adenosine and guanosine) the reactivity was found to be better than that observed in the coupling reaction under conventional heating, albeit at longer reaction time compared to their pyrimidine analogues.

Mechanistic Studies. Having developed a broadly applicable catalytic system for accessing a variety of modified nucleosides, our next step was to investigate the mechanism operating in the Suzuki–Miyaura coupling of these substrates. Initially, we performed the catalyst poison experiments for differentiating homotopic or heterotopic catalysts (Scheme 9).

The mercury-drop test[51] was first introduced by Whitesides to identify homotopic components in a catalytic reaction.

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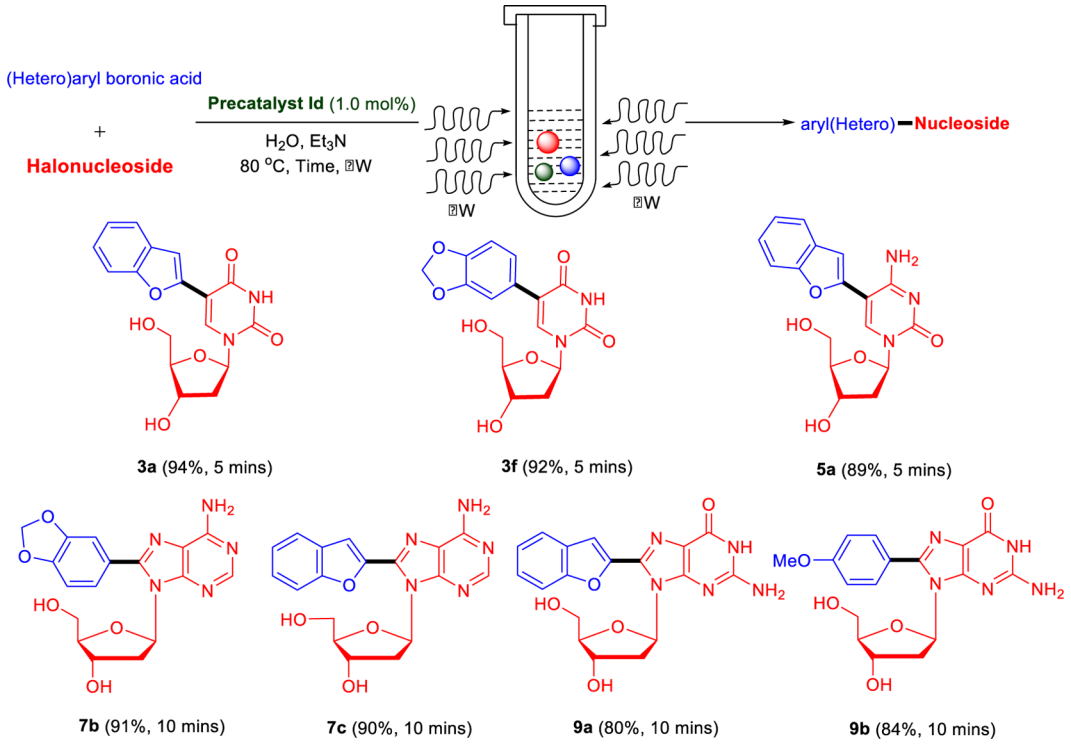
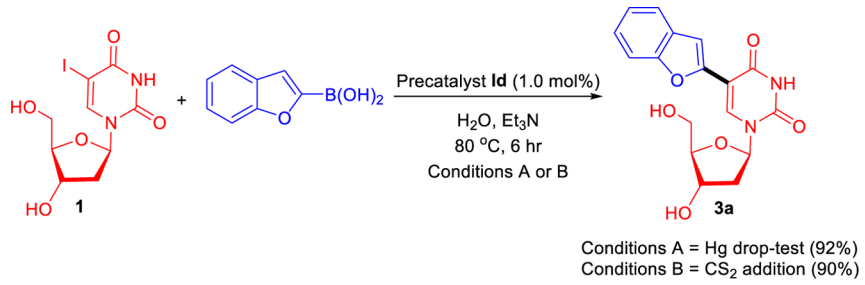
Scheme 8. Microwave-Assisted Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling of Purine and Pyrimidine Nucleosides



Scheme 9. Mercury-Drop Test and CS_2 Addition Test Confirmation of Homogeneity of Catalyst



Addition of a mercury drop is generally found to suppress colloidal or nanoparticular catalysts by covering the catalyst surface. No change in the catalytic activity could imply the presence of a homotopic catalytic system involving the presence of active molecular catalysts. For testing the nature of the catalytic system operating in our case, we performed the mercury-drop test on the Suzuki–Miyaura cross-coupling of 5-iodo-2′-deoxyuridine with benzofuran-2-boronic acid in water using catalyst **Id**. It was found that the cross-coupling reaction proceeded smoothly and no reduction in catalytic activity was observed, strongly suggesting the presence of a homotopic catalyst (presence of an active molecular catalyst rather than nanoparticular or colloidal catalyst). This assumption was further supported by the CS_2 addition[51b−d] test that gave results identical to those of the mercury-drop test.

With this understanding, we further investigated the mechanistic pathway followed by the Pd–imidate catalyst **Id** in the Suzuki–Miyaura cross-coupling of nucleosides. Electroionization mass spectrometry (ESI-MS),[52] is a versatile and relatively mild analytical technique for the careful analysis of catalytic reactions.[53] Analysis by ESI-MS has in most cases produced startling results based on the well-separated signals of different components of the catalytic reactions allowing the precise prediction of catalytic intermediates operating in such reactions.

Given the possibility of homotopic catalyst acting in these cross-coupling reactions, we investigated the reaction between precatalyst **Id** with halonucleoside by ESI-MS analysis in order to trap intermediates that could ascertain such assumption. A stoichiometric reaction of 8-bromo-2′-deoxyadenosine with precatalyst **Id** in DMF at 80 °C was followed by ESI-MS (Scheme 10). After 1 h of reaction, an aliquot was injected into the electrospray ionization spectrometer to give the mass spectral data that have been tentatively interpreted below.

From the spectral analysis, it was possible to identify several catalytic species that formed under the conditions. Species **A** was identified as the main catalytically active species $Pd^{(0)}L_2$ formed by the dissociation of the two saccharinate groups obtained at m/z = 421.0624 ($M^+ + H^+$). Besides other intermediate species (**C** and **B**), we were also able to identify the oxidative addition product **D** formed by the direct reaction of the catalytic species **A** and 8-bromo-2′-deoxyadenosine at m/z = 791.9393. The greater reactivity of this species which is evident from the HPLC profiles represented in Figure 3 also gives rise to the catalytic species **E** possibly through double addition of 8-bromo-2′-deoxyadenosine to species **A**. All these

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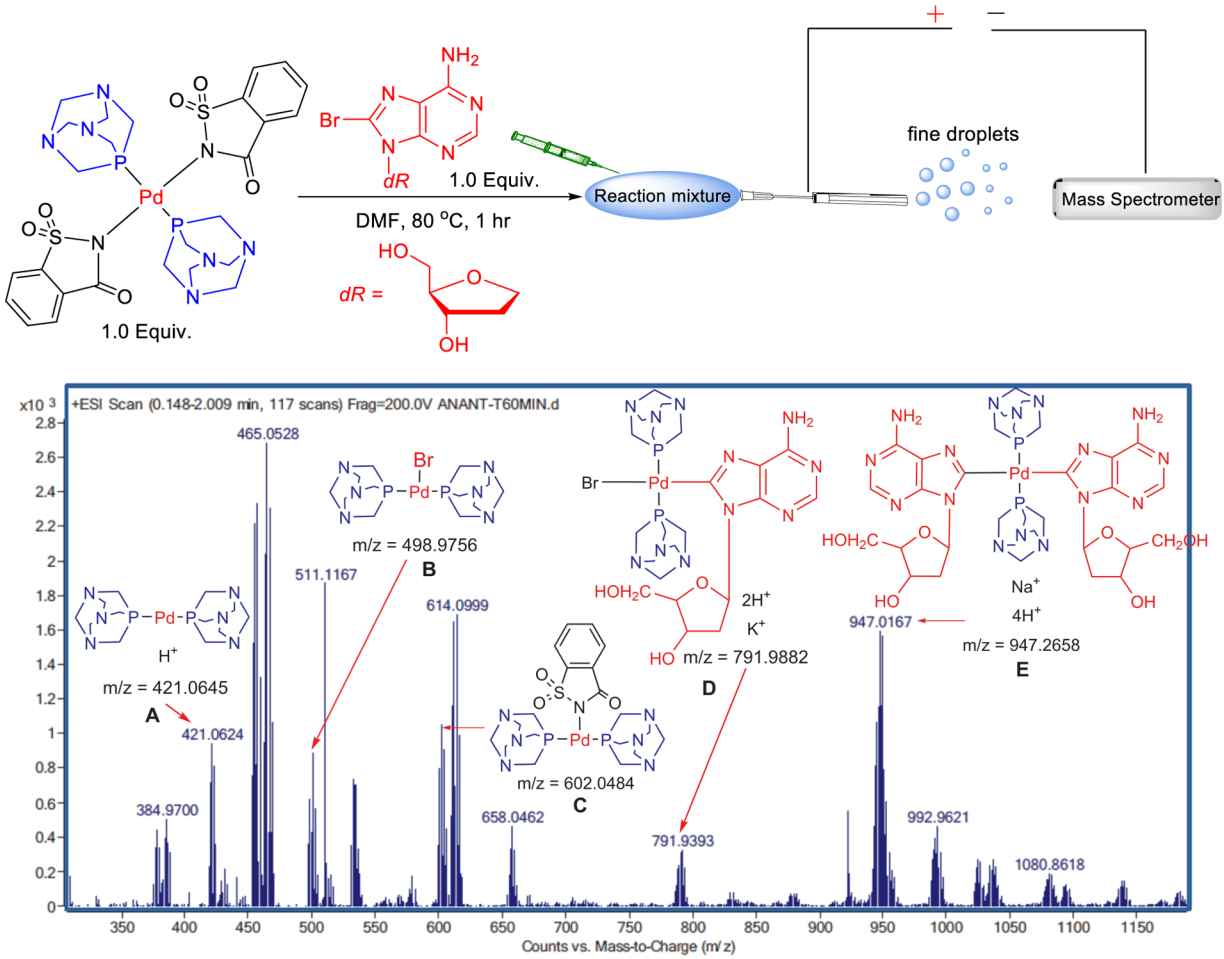
Scheme 10. ESI-MS Analysis of Stoichiometric Reaction between Id and 8-Bromo-2-deoxyadenosine



results strongly point toward the involvement of a homotopic catalyst and we can safely infer the absence of nanoparticular or heterogeneous pathway.

UV−vis Spectroscopic Data for Modified Nucleosides. Finally, we conducted UV absorption and emission analysis of the modified nucleosides to identify the potential fluorescent nucleosides. UV−vis absorptions were performed on a Shimadzu UV−vis spectrophotometer at concentrations of 30 μM (30×10^{-6} M). In most cases, the modified nucleosides showed absorbance at longer wavelengths than the naturally occurring nucleosides, thus suggesting a definite improvement in fluorescence properties. These results have been summarized below in Table 1.

The emission wavelengths were also obtained for the nucleosides at 6 μM concentration (6×10^{-6} M); however, apart from all the purine analogues, which showed very good emission wavelengths, only a few of the pyrimidines showed promising emissions. BVDU analogues exhibiting extended conjugation compared to the other cross-coupled products showed better absorption and emission, with **11a** and **11b** showing the best results. These results give us the choice to identify potentially useful nucleoside analogues for further applications.

CONCLUSION

A robust and a generally applicable catalytic system consisting of water-soluble Pd catalyst has been successfully employed toward the arylation of four different nucleosides under Suzuki−Miyaura cross-coupling conditions in water as the reaction solvent. The cross-coupled products have in most cases been obtained in good to excellent yields. This unique reactivity of the catalytic system also allowed the development of a microwave-assisted process, bringing about drastic reduction in the reaction time and also providing excellent yields of the coupled products. Mechanistic studies have also been performed with the poison tests showing the presence of a homotopic catalyst system, which was also confirmed by the ESI-MS based stoichiometric studies. Finally, UV−vis absorption and emission analysis of the coupled products have been carried out to provide a detailed summary of potential fluorescent nucleoside analogues for possible further applications.

EXPERIMENTAL SECTION

General Remarks. C, H, and N analyses were carried out locally. NMR data (^{1}H or ^{31}P) were recorded locally on 400 and 500 spectrometers. HPLC−MS analyses were performed locally. The ionization mechanism used was electrospray in positive and negative ion full-scan mode using acetonitrile as solvent and nitrogen gas for desolvation. Imides and other commercially available chemicals were purchased locally and were used without further purification. All of the solvents were dried by standard methods before use. HPLC analysis was performed locally. UV absorptions study was performed locally. Emission wavelengths were measured with 300 W xenon lamp. Microwave-assisted synthesis of modified nucleosides was carried out on CEM Discover Microwave reactor. ^{13}C NMR analysis could not be performed on the metal complexes mentioned here due to the infeasibility of such measurements. All other characterizations details

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Table 1. UV−vis Absorption and Emission Wavelengths for Nucleosides

sr. no.	compd	Λ_{abs} (nm)	Λ_{emm} (nm)	sr. no.	compd	Λ_{abs} (nm)	Λ_{emm} (nm)
		Uridine Analogues				Cytidine Analogues	
1	**3a**	246, 323	437	1	**5a**	322, 271, 261	421
2	**3b**	317, 261		2	**5b**	297	425
3	**3c**	314, 246		3	**5c**	268	
4	**3d**	299, 249	442	4	**5d**	296	
5	**3e**	286		5	**5e**	298, 254	
6	**3f**	302	427	6	**5f**	290	
7	**3g**	254		7	**5g**	282, 242	
8	**3h**	343, 277, 242	429	8	**5h**	283	
9	**3i**	295, 225		9	**5i**	279, 228	
10	**3j**	296, 277		10	**5j**	269	
11	**3k**	296, 262	431				
12	**3l**	307					
13	**3m**	285, 240					
		Guanosine Analogues				Adenosine Analogues	
1	**9a**	320	406	1	**7a**	280	367
2	**9b**	282	383	2	**7b**	298	365
3	**9c**	298	390	3	**7c**	324, 255	382
4	**9d**	284	382	4	**7d**	301, 227	371
5	**9e**	309	**431**				
6	**9f**	308	389				
			BVDU Analogues				
1	**11a**	314	**438**				
2	**11b**	341	**425**				

Table 2. Basic Crystallographic Data and Structure Refinement Parameters for Compounds IIa, IIIa, 3a, 3f, and 3i

parameters	IIa	IIIa	3a	3f	3i
empirical formula	$C_{25}H_{24}N_5O_2PPd$	$C_{26}H_{24}N_5O_3PPd$	$C_{17}H_{16}N_2O_6$	$C_{16}H_{16}N_2O_7$	$C_{21}H_{24}N_2O_7$
CCDC no.	1415033	1415034	1411201	1411202	1411203
formula weight	563.86	591.87	344.32	348.31	416.42
cryst syst	monoclinic	orthorhombic	monoclinic	orthorhombic	orthorhombic
space group	$P2_1/a$	$P2_1/ca$	$P2_1$	$P2_12_12_1$	$C222_1$
a (Å)	14.8466(6)	9.3167(6)	10.590(2)	6.3928(13)	8.503(2)
b (Å)	9.9164(4)	12.8999(8)	6.6123(13)	14.653(3)	19.136(4)
c (Å)	15.3707(6)	20.3246(14)	10.786(2)	16.301(3)	24.138(5)
α (deg)	90	90	90	90	90
β (deg)	94.9730(10)	90	95.25(3)	90	90
γ (deg)	90	90	90	90	90
V (Å^3)	2254.43(16)	2442.7(3)	752.1(3)	1527.0(5)	3927.6(15)
Z	4	4	2	4	8
T (K)	100	100	170	170	170
μ (mm^{-1})	0.929	0.865	0.117	0.121	0.107
D_{calcd} (g/cm^3)	1.661	1.609	1.520	1.515	1.408
F (000)	1144	1200	360	728	1760
unique reflections	6920	7472	3791	4110	5300
measured	72321	45038	8969	15534	20628
reflections	0.0370	0.0575	0.1256	0.0826	0.1049
R_{int}	0.910	0.995	1.328	1.140	1.001
GOF on F^2	0.0217	0.0338	0.0683	0.0437	0.0458
$R_1[I > 2\sigma(I)]$[a]	0.0531	0.0734	0.1973	0.1114	0.1119
$R_w[I > 2\sigma(I)]$[b]	0.596/−0.498	0.599/ −0.361	0.567/ −0.593	0.325/ −0.242	0.323/−0.326

[a] $R_1 = \Sigma F_o - F_c/\Sigma F_o$. [b] $R_w = [\Sigma\{w(F_o^2 - F_c^2)^2\}/\Sigma\{w(F_o^2)^2\}]^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (xP)^2]$, where $P = (F_o^2 + 2F_c^2)/3$.

have been provided to conclusively ascertain the structure of all the complexes (see the Supporting Information for ^{1}H and ^{13}C NMR for all compounds and crystallographic data for **IIa**, **IIIa**, **3a**, **3f**, and **3i**).

Single-Crystal X-ray Diffraction. Suitable single crystals of **3a**, **3f**, **3j**, **IIa**, and **IIIa** were mounted on a thin glass fiber coated with paraffin oil. X-ray single-crystal structural data were collected at low temperature (170 k) equipped with a normal-focus, 2.4 kW, sealed-tube X-ray source with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The program X Area was used for integration of diffraction profiles; numerical absorption correction was made with the programs X-shape

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and X-red32. The structures were solved by SIR92[54] and refined by full-matrix least-squares methods using SHELXL-2013.[55] The non-hydrogen atoms were refined anisotropically. Unless otherwise stated, the hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to $1.5U_{eq}$ of their pivot atoms for terminal sp^3 carbon atoms and 1.2 times for all other carbon atoms. In **3a** with the exception of the methylene protons on C1 and the four aromatic protons of the phenyl moiety, all hydrogen atoms were located. The hydrogen atoms on nitrogen and the second methylene carbon were refined freely. For **3f**, one alcoholic proton and the amine protons were located and refined freely. The second alcoholic proton was calculated using the riding model. For **3j**, the two water molecules are refined with hydrogen atoms, which were located but had to be restrained with respect to the overall geometry. The proton on N2 was located and refined freely. All other hydrogen atoms were refined with a constraint on the displacement parameter but freely with respect to position.

All calculations were carried out using SHELXL-2013[53] and the WinGX GUI, Ver2013.2.[56] Crystallographic data are summarized in Table 2.

Synthesis. *Preparation of Complexes [trans-[Pd(Imidate)$_2$(PTA)$_2$] (Imidate = Succinimidate (suc) **Ia**, Maleimidate (mal) **Ib**, Phthalimidate (phthal) **Ic**, or Saccharinate (sacc) **Id**.*[15] The complexes were obtained as described previously by treating the appropriate precursor [Pd(Imidate)$_2$(SMe$_2$)$_2$] with neutral monodentated PTA (molar ratio 1:2) in dichloromethane, according to the following general method. To a dichloromethane (15 mL) solution of [Pd(Imidate)$_2$(SMe$_2$)$_2$] (0.100g) was added a stoichiometric amount of PTA (0.0736 g for **a**; 0.0743 g for **b**; 0.0601 g for **c**; 0.0528 g for **d**). The solution was refluxed for 1 h and then concentrated to one-third of the initial volume. The addition of diethyl ether caused the precipitation of the title complexes, which were isolated by filtration, washed with diethyl ether, and air dried. (We have observed that residual trace amounts of dimethyl sulfide in precatalyst inhibit the coupling reaction lowering the yield of desired product. Therefore, it is highly recommended that the user should ensure that dimethyl sulfide is completely washed away during synthesis of the precatalyst. This can be easily confirmed by ^{1}H NMR of the precatalyst.)

*Preparation of New PTA Derivatives [Pd(C^N)(Imidate)(PTA)] (C^N = 2-Phenylpiridine; Imidate = Phthalimidate **IIa** or Saccharinate **IIb**; C^N = 2-Benzoylpyridine; Imidate = Phthalimidate **IIIa** or Saccharinate **IIIb**).* To a 0.2 g solution of the corresponding precursor [Pd(C^N)(μ-imidate)]$_2$ in 30 mL of dichloromethane were added the corresponding stoichiometric amounts (1:2) of PTA. After 1 h of stirring at reflux temperature, the solution was concentrated under reduced pressure until it was approximately one-fifth the initial volume. Slow addition of diethyl ether caused the formation of the white complexes, which were filtered off, washed with diethyl ether, and air dried.

*[Pd(Phpy)(Phthalimidate)(PTA)] (**IIa**).* Yield: 0.35 g, 79%. IR (KBr, cm^{-1}): ν(Phpy) 1603vs, 1580s, 752s; ν(Phthal) 1650vs; ν(PTA) 483s, 393s. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.12 (d, J = 5.4 Hz), 7.79−7.72 (m, 4H), 7.61−7.57 (m, 3H), 7.36 (s, 1H), 7.24−7.17 (m, 2H), 7.10 (s, 1H), 4.54 (s, 6H); 4.37 (s, 6 H). ^{31}P{^{1}H} NMR (200 MHz; CDCl$_3$, 298 K): δ −47.1 ppm. HPLC−MS (positive mode) m/z: 417.05 (M$^+$ − Phthal). Anal. Calcd for $C_{25}H_{24}N_5O_2PPd$: C, 53.25; H, 4.29; N, 12.42. Found: C, 53.15; H, 4.36; N, 12.49.

*[Pd(Phpy)(Saccharinate)(PTA)] (**IIb**).* 0.24 g, 88%. IR (KBr, cm^{-1}): ν(Phpy) 1603vs, 1592s, 752 vs; ν(Sacc) 1659vs, 1243s; ν(PTA) 486s, 393s. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.51 (d, J = 5.2 Hz, 1H), 7.96−7.85 (m, 2H), 7.74−7.69 (m, 4H), 7.59 (m, 1H), 7.34 (s, 1H), 7.21 (s, 2H), 7.16 (m, 1H), 4.53 (s, 6H); 4.38 (s, 6 H). ^{31}P{^{1}H} NMR (200 MHz; CDCl$_3$, 298 K): δ −49.5 ppm. HPLC−MS (positive mode) m/z: 417.05 (M$^+$ − Sacc). Anal. Calcd For $C_{24}H_{24}N_5O_3PPdS$: C, 48.05; H, 4.03; N, 11.67; S, 5.34. Found: C, 48.20; H, 4.17; N, 11.83; S, 5.54.

*[Pd(Bzpy)(Phthalimidate)(PTA)] (**IIIa**).* 0.23 g, 86%. IR (KBr, cm^{-1}): ν(Bzpy) 1594vs, 1570s, 754s. ν(Phthal) 1643vs; ν(PTA) 483s, 393s. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.49 (d, J = 5.4 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.95 (s, 1H), 7.71−7.53 (m, 6H), 7.31−7.16 (m, 3H), 4.39 (s, 6H), 4.10 (s, 6 H). ^{31}P{^{1}H} NMR (200 MHz; CDCl$_3$, 298 K): δ −48.5 ppm. HPLC−MS (positive mode) m/z: 445.04 (M$^+$ − Phthal). Anal. Calcd for $C_{26}H_{24}N_5O_3PPd$: C, 52.76; H, 4.09; N, 11.83. Found: C, 52.90; H, 4.12; N, 11.99.

*[Pd(Bzpy)(Saccharinate)(PTA)] (**IIIb**).* 0.22 g, 84%. IR (KBr, cm^{-1}): ν(Bzpy) 1594vs, 1567s, 767s. ν(Sacc) 1676vs, 1254s; ν(PTA) 483s, 392s. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.80 (s br, 1H), 8.21 (d, J = 7.2 Hz, 1H), 7.95 (m, 1H), 7.83−7.63 (m, 5H), 7.55−7.21 (m, 4H), 4.39 (s, 6H), 4.17 (s, 6 H). ^{31}P{^{1}H} NMR (200 MHz; CDCl$_3$, 298 K): δ −48.9 ppm. HPLC−MS (positive mode) m/z: 445.04 (M$^+$ − Phthal). Anal. Calcd for $C_{25}H_{24}N_5O_4PPdS$: C, 47.82; H, 3.85; N, 11.15; S, 5.11. Found: C, 48.01; H, 4.02; N, 11.31; S, 5.23.

General Procedure for Suzuki−Miyaura Cross-Coupling of 5-Iodo-2′-deoxyuridine with Arylboronic Acids. A solution of precatalyst **Id** (0.005 mmol, 1.0 mol %) in degassed H_2O (1.0 mL) was stirred for 5 min at ambient temperature under N_2. Then, 5-iodo-2′-deoxyuridine (177 mg, 0.5 mmol) was added and the solution stirred for 5 min at 80 °C. Thereafter, phenylboronic acid (91 mg, 0.75 mmol) was added along with Et_3N (1.0 mmol) and degassed water (2.0 mL). The resulting solution was then stirred at 80 °C for 6.0 h. After the completion of the reaction, the solvent was removed in vacuo and the resultant residue obtained was purified using column chromatography in the CH_2Cl_2/MeOH solvent system (96:4) to afford the desired product as a white solid. (Note: For furan-2-boronic acid, thiophene-3- and thiophene-2-boronic acid are added in 3.0 equiv of the iodopyrimidine.)

*5-(2-Benzofuranyl)-2′-deoxyuridine (**3a**).*[31a] 0.158 g, 92%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.72 (s, 1H), 8.70 (s, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.20 (t, J = 6.3 Hz, 1H), 5.27 (d, J = 3.6 Hz, 1H), 5.19 (t, J = 4.0 Hz, 1H), 4.30 (d, J = 2.8 Hz, 1H), 3.85 (d, J = 2.2 Hz, 1H), 3.74−3.55 (m, 2H), 2.20−2.18 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 160.7, 153.3, 149.7, 149.4, 137.5, 129.2, 124.6, 123.4, 121.4, 111.1, 105.0, 104.2, 88.0, 85.4, 70.4, 61.2, 40.8. ESI-MS (m/z) = 345 (M$^+$ + H$^+$).

*5-(Thiophene-2-yl)-2′-deoxyuridine (**3b**).*[14a] 0.115 g, 74%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.31 (s, 2H), 7.86 (d, J = 8.1 Hz, 2H), 7.63 (dt, J = 28.9, 4.8 Hz, 1H), 6.15 (t,J = 6.7 Hz, 2H), 5.64 (d, J = 8.0 Hz, 2H), 5.26 (d, J = 3.9 Hz, 2H), 5.03 (t, J = 4.8 Hz, 2H), 4.23 (s, 2H), 3.80−3.75 (m, 3H), 3.60−3.49 (m, 4H), 2.06 (dd, J = 15.6, 9.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.5, 149.5, 135.8, 134.1, 126.5, 125.8, 122.6, 108.4, 87.7, 84.8, 70.0, 60.8, 45.4. ESI-MS (m/z) = 310 (M$^+$ + H$^+$).

*5-(Furan-2-yl)-2′-deoxyuridine (**3c**).*[31b] 0.092 g, 65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.64 (s, 1H), 8.34 (s, 1H), 7.62 (s, 1H), 6.86 (d, J = 2.7 Hz, 1H), 6.52 (s, 1H), 6.22 (t, J = 6.6 Hz, 1H), 5.28 (d, J = 4.0 Hz, 1H), 5.09 (t, J = 4.4 Hz, 1H), 4.28 (s, 1H), 3.84 (d, J = 2.5 Hz, 1H), 3.65−3.55 (m, 2H), 2.22−2.11 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 160.3, 149.5, 141.7, 134.8, 111.6, 107.9, 105.7, 100.2, 87.6, 84.8, 70.4, 61.1, 45.8. ESI-MS (m/z) = 295 (M$^+$ + H$^+$).

*5-(3,4-Dimethoxyphenyl)-2′-deoxyuridine (**3d**).* 0.129 g, 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.43 (s, 1H), 8.12 (s, 1H), 7.14−7.05 (m, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.20 (t, J = 6.6 Hz, 1H), 5.19 (d, 2H), 4.27 (d, J = 2.6 Hz, 1H), 3.78 (d, J = 3.0 Hz, 1H), 3.72 (s, 6H), 3.63−3.51 (m, 2H), 2.26−2.07 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.5, 150.2, 148.7, 148.5, 137.5, 126.1, 120.7, 113.7, 112.0, 111.9, 87.9, 84.9, 70.7, 61.4, 55.9, 55.8, 41.4. ESI-MS (m/z) = 365 (M$^+$ + H$^+$). Anal. Calcd for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 56.18; H, 5.62; N, 7.77.

*5-(3,5-Dimethylphenyl)-2′-deoxyuridine (**3e**).* 0.123 g, 74%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.42 (s, 1H), 8.10 (s, 1H), 7.10 (s, 2H), 6.89 (s, 1H), 6.19 (t, J = 6.6 Hz, 1H), 5.23 (d, J = 4.3 Hz, 1H), 5.07 (t, J = 4.8 Hz, 1H), 4.29−4.22 (m, 1H), 3.77 (dd, J = 6.1, 3.0 Hz, 1H), 3.62−3.51 (m, 2H), 2.25−2.08 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.5, 150.3, 138.2, 137.3, 133.4, 129.0, 126.1, 114.0, 87.8, 84.8, 70.5, 61.2, 40.4, 21.4. ESI-MS (m/z) = 333 (M$^+$ + H$^+$). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.33; H, 6.11; N, 8.30.

*5-(3,4-Methylenedioxyphenyl)-2′-deoxyuridine (**3f**).* 0.151 g, 87%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.48 (s, 1H), 8.09 (s, 1H), 7.09 (s, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 6.22 (t, J = 6.6 Hz, 1H), 6.02 (s, 2H), 5.25 (d, J = 4.1 Hz, 1H), 5.11 (t, J = 4.7 Hz,

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1H), 4.28 (s, 1H), 3.80 (d, J = 2.9 Hz, 1H), 3.65−3.53 (m, 2H), 2.18 (tdd, J = 13.3, 11.2, 4.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.5, 150.2, 147.3, 146.8, 137.7, 127.3, 121.8, 113.6, 108.8, 108.4, 101.3, 87.8, 84.8, 70.6, 61.4, 40.3. ESI-MS (m/z) = 349 ($M^+ + H^+$). Anal. Calcd for $C_{16}H_{16}N_2O_7$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.02; H, 4.54; N, 7.96.

5-(Phenanthren-9-yl)-2′-deoxyuridine (**3g**). 0.101 g, 50%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.61 (s, 1H), 8.87 (t, J = 8.1 Hz, 2H), 8.15 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.1 Hz, 1H), 7.77−7.64 (m, 4 H), 7.61 (t, J = 7.5 Hz, 1H), 6.30 (t, J = 6.6 Hz, 1H), 5.29 (d, J = 11.9 Hz, 1H), 4.87 (s, 1H), 4.24 (s, 1H), 4.12 (dd, 1H), 3.77 (d, J = 9.5 Hz, 2H), 2.28−2.16 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.5, 150.4, 139.3, 130.9, 129.7, 128.5, 127.1, 126.6, 122.9, 122.6, 113.7, 87.2, 84.3, 70.1, 60.8, 45.5. ESI-MS (m/z) = 405 ($M^+ + H^+$). Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.18; H, 4.89; N, 6.82.

5-(Pyrene-1-yl)-2′-deoxyuridine (**3h**).[35] 0.103 g, 48%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.66 (s, 1H), 8.32 (t, J = 6.8 Hz, 3H), 8.21 (d, J = 5.6 Hz, 3H), 8.17 (d, J = 9.3 Hz, 1H), 8.09 (t, J = 7.6 Hz, 2H), 7.95 (d, J = 7.8 Hz, 1H), 6.33 (t, J = 6.7 Hz, 1H), 5.26 (d, J = 4.2 Hz, 1H), 4.81 (s, 1H), 4.25 (s, 1H), 3.80 (d, J = 3.0 Hz, 1H), 3.52−3.40 (m, 2H), 2.39−2.13 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.7, 150.6, 140.2, 130.6, 130.5, 128.9, 128.8, 127.3, 127.3, 126.4, 125.4, 125.2, 124.7, 123.9, 87.5, 84.6, 70.4, 61.0, 45.7. ESI-MS (m/z) = 429 ($M^+ + H^+$).

5-([1,1′-Biphenyl]-4-yl) 2′-deoxyuridine (**3i**). 0.145 g, 76%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H), 8.28 (s, 1H), 7.67 (s, 6H), 7.48 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 6.26 (t, J = 6.5 Hz, 1H), 5.28 (d, J = 4.2 Hz, 1H), 5.16 (t, J = 4.7 Hz, 1H), 4.31 (s, 1H), 3.84 (d, J = 2.8 Hz, 1H), 3.74−3.53 (m, 2H), 2.34−2.12 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.3, 150.0, 139.8, 139.0, 138.1, 132.5, 129.1, 128.5, 126.5, 113.1, 87.6, 84.6, 70.3, 61.0, 45.8. ESI-MS (m/z) = 381 ($M^+ + H^+$). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.36; H, 5.43; N, 7.45.

5-(Thiophene-3-yl)- 2′-deoxyuridine (**3j**).[12e] 0.138 g, 89%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (s, 1H), 8.47 (s, 1H), 7.97 (s, 1H), 7.58−7.39 (m, 2H), 6.24 (t, J = 6.0 Hz, 1H), 5.35−5.27 (m, 2H), 4.32 (s, 1H), 3.84 (s, 1H), 3.66 (d, J = 8.5 Hz, 2H), 2.23 (ddd, J = 15.6, 10.7, 5.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.1, 149.7, 137.1, 133.2, 126.0, 125.7, 121.8, 109.2, 87.6, 84.8, 70.1, 60.9, 45.4. ESI-MS (m/z) = 311 ($M^+ + H^+$).

5-(4-(Methylthio)phenyl)-2′-deoxyuridine (**3k**). 0.161 g, 92%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.17 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 6.18 (t, J = 6.6 Hz, 1H), 5.27 (s, 1H), 5.12 (s, 1H), 4.25 (s, 1H), 3.78 (dd, J = 5.8, 2.7 Hz, 1H), 3.61−3.51 (m, 2H), 2.44 (s, 3H), 2.24−2.08 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.2, 149.9, 137.7, 137.1, 129.8, 128.3, 125.7, 112.9, 87.5, 70.2, 60.9, 45.7, 40.0. ESI-MS (m/z) = 351 ($M^+ + H^+$). Anal. Calcd for $C_{16}H_{18}N_2O_5S$: C, 54.85; H, 5.18; N, 8.00. Found: C, 54.71; H, 5.06; N, 7.92.

5-(4-Formylphenyl)-2′-deoxyuridine (**3l**).[12e] 0.141 g, 85%. ^{1}H NMR (400 MHz, DMSO): δ 11.57 (s, 1H), 9.95 (s, 1H), 8.40 (s, 1H), 7.90−7.69 (m, 4H), 6.17 (s, 1H), 5.20 (d, J = 4.1 Hz, 2H), 4.26 (s, 1H), 3.78 (s, 1H), 3.66−3.52 (m, 2H), 2.26−2.10 (m, 2H). ^{13}C NMR (101 MHz, DMSO): δ 193.0, 162.2, 150.1, 140.0, 139.9, 135.0, 129.7, 128.5, 112.4, 87.9, 85.1, 70.3, 61.1, 46.0. ESI-MS (m/z) = 333 ($M^+ + H^+$).

5-(3-Formylphenyl)-2′-deoxyuridine (**3m**). 0.145 g, 87%. ^{1}H NMR (400 MHz, DMSO): δ 11.63 (s, 1H), 10.03 (s, 1H), 8.38 (s, 1H), 8.13 (s, 1H), 7.86 (dd, J = 15.2, 7.7 Hz, 2H), 7.61 (t, J = 7.7 Hz, 1H), 6.23 (t, J = 6.5 Hz, 1H), 5.33−5.26 (m, 1H), 5.18 (s, 1H), 4.31 (s, 1H), 3.83 (d, J = 3.1 Hz, 1H), 3.62 (q, J = 11.8 Hz, 2H), 2.35−2.13 (m, 2H). ^{13}C NMR (101 MHz, DMSO): δ 193.4, 162.2, 150.0, 139.0, 136.2, 134.3, 133.8, 129.4, 129.2, 127.9, 112.2, 87.6, 84.7, 70.0, 60.8, 45.4. ESI-MS (m/z) = 333 ($M^+ + H^+$). Anal. Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.71; H, 4.92; N, 8.33.

General Procedure for Suzuki−Miyaura Cross-Coupling of 5-Iodo-2′-deoxycytidine with Arylboronic Acids. A solution of precatalyst **Id** (0.005 mmol, 1.0 mol %) in degassed H_2O (2.0 mL) was stirred for 5 min at ambient temperature under N_2. Then 5-iodo-2′-deoxycytidine (177 mg, 0.5 mmol) was added and the solution stirred for 5 min at 80 °C. Thereafter, phenylboronic acid (91 mg, 0.75 mmol) was added along with Et_3N (1.0 mmol) and degassed water (1.0 mL). The resulting solution was then stirred at 80 °C for 12.0 h. After completion of the reaction, the solvent was removed in vacuo and the resultant residue obtained was purified using column chromatography in CH_2Cl_2/MeOH solvent system (96:4) to afford the desired product as a white solid. (Note: For furan-2-boronic acid, thiophene-3- and thiophene-2-boronic acid are added in 3.0 equiv of the iodopyrimidine.)

5-(2-Benzofuranyl)-2′-deoxycytidine (**5a**). 0.116 g, 68%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 7.71 (s, 1H), 7.56 (t, J = 7.1 Hz, 2H), 7.24 (dtd, J = 18.5, 7.3, 1.2 Hz, 2H), 6.99 (s, 1H), 6.93 (s, 1H), 6.15 (t, J = 6.3 Hz, 1H), 5.22 (d, J = 4.2 Hz, 1H), 5.12 (t, J = 4.7 Hz, 1H), 4.23 (s, 1H), 3.80 (d, J = 3.4 Hz, 1H), 3.69−3.53 (m, 2H), 2.26−2.02 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.0, 154.5, 153.6, 150.5, 142.6, 129.0, 124.8, 123.7, 121.3, 111.9, 103.7, 98.1, 88.1, 86.2, 70.2, 61.1, 45.9. ESI-MS (m/z) = 344 ($M^+ + H^+$). Anal. Calcd for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24. Found: C, 59.41; H, 5.05; N, 12.34.

5-(Thiophene-3-yl)-2′-deoxycytidine (**5b**).[57a] 0.108 g, 70%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98 (s, 1H), 7.62 (dd, J = 29.1, 24.8 Hz, 3H), 7.16 (d, J = 4.7 Hz, 1H), 6.47 (s, 1H), 6.20 (t, J = 6.4 Hz, 1H), 5.23 (d, J = 3.6 Hz, 1H), 5.05 (s, 1H), 4.23 (s, 1H), 3.79 (d, J = 2.9 Hz, 1H), 3.57 (dd, J = 24.1, 11.5 Hz, 2H), 2.20−2.03 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.3, 154.2, 140.1, 133.8, 128.0, 127.1, 123.3, 103.0, 87.3, 85.2, 70.1, 61.0, 45.4. ESI-MS (m/z) = 310 ($M^+ + H^+$).

5-(4-(Methylthio)phenyl)-2′-deoxycytidine (**5c**).[57a] 0.131 g, 75%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (s, 1H), 7.29 (q, J = 8.5 Hz, 4H), 6.39 (s, 1H), 6.21 (t, J = 6.5 Hz, 1H), 5.23 (d, J = 3.7 Hz, 1H), 5.00 (s, 1H), 4.23 (s, 1H), 3.78 (d, J = 3.3 Hz, 1H), 3.59−3.49 (m, 2H), 3.35 (s, 3H), 2.17−2.04 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.9, 155.0, 140.4, 138.0, 130.8, 129.8, 126.8, 107.6, 87.7, 85.5, 70.5, 61.4, 52.4, 45.6. ESI-MS (m/z) = 350 ($M^+ + H^+$).

5-(4-Formylphenyl)-2′-deoxycytidine (**5d**). 0.124 g, 75%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.00 (s, 1H), 8.00 (s, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.46 (s, 1H), 6.59 (s, 1H), 6.15 (t, J = 6.4 Hz, 1H), 5.21 (d, J = 4.3 Hz, 1H), 5.00 (t, J = 4.9 Hz, 1H), 4.19 (dt, J = 8.0, 3.9 Hz, 1H), 3.75 (dd, J = 6.5, 3.1 Hz, 1H), 3.52 (tdd, J = 11.8, 8.4, 4.2 Hz, 2H), 2.18−2.01 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 193.1, 163.2, 154.6, 141.4, 140.7, 135.4, 130.5, 129.7, 107.0, 87.7, 85.6, 70.3, 61.2, 41.1. ESI-MS (m/z) = 332 ($M^+ + H^+$). Anal. Calcd for $C_{16}H_{19}N_3O_4S$: C, 55.00; H, 5.48; N, 12.03. Found: C, 54.89; H, 5.34; N, 11.87.

5-(Phenanthren-9-yl)-2′-deoxycytidine (**5e**). 0.105 g, 52%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.85 (dd, J = 14.4, 8.2 Hz, 2H), 7.99 (t, J = 7.4 Hz, 1H), 7.92 (s, 1H), 7.76 (d, J = 4.7 Hz, 1H), 7.73−7.51 (m, 5H), 7.25 (s, 1H), 6.24 (dt, J = 10.1, 6.8 Hz, 1H), 6.14 (s, 1H), 5.18 (dd, J = 9.7, 4.2 Hz, 1H), 4.75 (dt, J = 14.0, 5.0 Hz, 1H), 4.20−4.09 (m, 1H), 3.76−3.68 (m, 1H), 3.48−3.37 (m, 2H), 2.19−1.98 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 164.6, 155.3, 141.1, 131.7, 131.6, 131.4, 130.8, 130.6, 130.6, 130.1, 129.2, 129.2, 127.6, 127.4, 127.3, 127.2, 126.2, 106.3, 87.6, 85.4, 70.7, 61.4, 52.4. ESI-MS (m/z) = 392 ($M^+ + H^+$). Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42. Found: C, 68.33; H, 5.17; N, 10.31.

5-(4-Phenoxyphenyl)-2′-deoxycytidine (**5f**). 0.118 g, 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (s, 1H), 7.51−7.00 (m, 10H), 6.50 (s, 1H), 6.21 (t, J = 6.1 Hz, 1H), 5.22 (d, J = 1.2 Hz, 1H), 5.06−4.91 (m, 1H), 4.22 (s, 1H), 3.78 (d, J = 0.4 Hz, 1H), 3.52 (d, J = 9.1 Hz, 2H), 2.21−2.00 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.1, 156.2, 156.0, 154.0, 139.8, 130.5, 129.9, 123.5, 118.6, 106.9, 87.0, 84.8, 69.8, 60.7, 45.1. ESI-MS (m/z) = 396 ($M^+ + H^+$). Anal. Calcd for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.65; H, 5.47; N, 10.51.

5-Phenyl-2′-deoxycytidine (**5g**).[57b] 0.106 g, 70%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (s, 1H), 7.42−7.33 (m, 6H),6.44 (s, 1H), 6.20 (t, J = 6.2 Hz, 1H), 5.21−5.19 (m, 1H), 4.96 (s, 1H), 4.22 (s, 1H),3.77 (s, 1H),3.54−3.51 (m, 2H), 2.13−2.05 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.1, 154.3, 140.2, 133.7, 129.0,

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128.8, 127.6, 107.7, 87.3, 85.1, 70.1, 61.0, 40.5. ESI-MS (m/z) = 304 ($M^+ + H^+$).

*5-(3-Methoxyphenyl)-2′-deoxycytidine (**5h**).* 0.113 g, 68%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (s, 1H), 7.36 (dd, J = 23.4, 15.5 Hz, 2H), 6.95−6.84 (m, 3H), 6.46 (s, 1H), 6.21 (t, J = 6.5 Hz, 1H), 5.21 (d, J = 4.0 Hz, 1H), 4.98 (t, J = 4.8 Hz, 1H), 4.22 (d, J = 3.4 Hz, 1H), 3.78 (s, 4H), 3.61−3.48 (m, 2H), 2.20−2.05 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.2, 159.7, 154.4, 140.3, 135.2, 130.1, 121.0, 114.1, 113.6, 107.7, 87.3, 85.2, 70.2, 61.0, 55.0, 45.6. ESI-MS (m/z) = 334 ($M^+ + H^+$). Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.54; H, 5.66; N, 12.48.

*5-(2-Naphthyl)-2′-deoxycytidine (**5i**).* 0.114 g, 65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04−7.88 (m, 5H), 7.62−7.42 (m, 4H), 6.61 (s, 1H), 6.24 (t, J = 6.4 Hz, 1H), 5.22 (d, J = 3.5 Hz, 1H), 4.97 (s, 1H), 4.24 (s, 1H), 3.79 (d, J = 3.2 Hz, 1H), 3.54 (dd, J = 24.5, 11.6 Hz, 2H), 2.26−2.05 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.8, 154.9, 140.8, 133.5, 132.6, 131.8, 128.8, 128.5, 128.0, 127.8, 127.4, 126.7, 126.6, 108.0, 87.6, 85.5, 70.5, 61.3, 41.0. ESI-MS (m/z) = 354 ($M^+ + H^+$). Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.45; H, 5.31; N, 11.74.

*5-(4-Biphenyl)-2′-deoxycytidine (**5j**).* 0.134 g, 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (s, 1 H), 7.68−7.76 (m, 5 H), 7.49 (t, J = 7.63 Hz, 2 H), 7.44 (d, J = 7.94 Hz, 2 H), 7.36−7.41 (m, 1 H), 6.23 (t, J = 6.41 Hz, 1 H), 5.23 (d, J = 4.27 Hz, 1 H, 5.00 (t, J = 5.19 Hz, 1 H), 4.20−4.27 (m, 1 H), 3.75−3.81 (m, 1 H), 3.49−3.62 (m, 2 H), 2.05−2.21 (m, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 163.7, 154.8, 140.5, 140.0, 139.6, 133.5, 129.7, 129.4, 128.0, 127.6, 126.9, 107.7, 87.6, 85.5, 70.6, 61.4, 41.0. ESI-MS (m/z) = 380 ($M^+ + H^+$). Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.53; H, 5.68; N, 11.12.

General Procedure for Suzuki−Miyaura Cross-Coupling of 8-BrdA with Arylboronic Acids. A solution of precatalyst **Id** (0.005 mmol, 1.0 mol %) in degassed H_2O (1.0 mL) was stirred for 5 min at ambient temperature under N_2. Then, 8-bromo-2′- deoxyadenosine (173 mg, 0.5 mmol) was added and the solution stirred for 5 min at 80 °C. Thereafter, phenylboronic acid (91 mg, 0.75 mmol) was added along with Et_3N (1.0 mmol) and degassed water (2.0 mL). The resulting solution was then stirred at 80 °C for 6.0 h. After completion of the reaction, the solvent was removed in vacuo and the resultant residue obtained was purified using column chromatography in a CH_2Cl_2/MeOH solvent system (96:4) to afford the desired product as a white solid. (Note: For furan-2-boronic acid, thiophene-3- and thiophene-2-boronic acid are added in 3.0 equiv of the iodopurine.)

*8-(4-(Methylthio)phenyl)-2′-deoxyadenosine (**7a**).* 0.145 g, 78%. ^{1}H NMR (500 MHz, DMSO): δ 8.13 (s, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.40 (t, J = 12.1 Hz, 4H), 6.13 (dd, J = 8.3, 6.4 Hz, 1H), 5.60 (dd, J = 8.4, 3.7 Hz, 1H), 5.24 (d, J = 3.9 Hz, 1H), 4.45 (s, 1H), 3.87 (s, 1H), 3.72−3.48 (m, 2H), 2.40 (s, 3H), 2.13 (dd, J = 12.7, 6.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO): δ 156.5, 152.2, 151.0, 150.2, 140.3, 129.7, 127.1, 119.5, 88.8, 86.1, 71.9, 62.7, 37.6, 21.4, ESI-MS (m/z) = 374 ($M^+ + H^+$). Anal. Calcd for $C_{17}H_{19}N_5O_3S$: C, 54.68; H, 5.13; N, 18.75. Found: C, 54.55; H, 5.02; N, 18.62.

*8-(3,4-(Methylenedioxy)phenyl)-2′-deoxyadenosine (**7b**).* 0.156 g, 84%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (s, 1H), 7.52−6.99 (m, 5H), 6.15 (s, 3H), 5.54 (s, 1H), 5.26 (s, 1H), 4.46 (s, 1H), 3.87 (s, 1H), 3.73−3.45 (m, 2H), 2.15 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 156.6, 152.4, 150.8, 150.5, 149.4, 148.1, 124.5, 123.7, 119.6, 110.0, 109.2, 102.3, 88.9, 86.2, 72.0, 62.8, 45.9. ESI-MS (m/z) = 372 ($M^+ + H^+$). Anal. Calcd for $C_{17}H_{17}N_5O_5$: C, 54.98; H, 4.61; N, 18.86. Found: C, 54.88; H, 4.54; N, 18.77.

*8-(2-Benzofuranyl)-2′-deoxyadenosine (**7c**).* 0.155 g, 85%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 1H), 7.89−7.33 (m, 7H), 6.63 (t, J = 6.8 Hz, 1H), 5.37 (t, J = 22.3 Hz, 2H), 4.56 (s, 1H), 4.01−3.88 (m, 1H), 3.78−3.48 (m, 2H), 2.34−2.23 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.2, 154.3, 152.6, 149.8, 144.9, 140.7, 127.2, 126.1, 123.6, 122.0, 119.4, 111.3, 109.4, 88.1, 85.3, 71.0, 61.9, 45.1. ESI-MS (m/z) = 368 ($M^+ + H^+$). Anal. Calcd for $C_{18}H_{17}N_5O_4$: C, 58.85; H, 4.66; N, 19.06. Found: C, 58.73; H, 4.71; N, 18.96.

*8-(4-Methylphenyl)-2′-deoxyadenosine (**7d**).* 0.142 g, 83%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.2 Hz, 4H), 6.15 (t, J = 7.3 Hz, 1H), 5.56 (s, 1H), 5.30 (d, J = 18.0 Hz, 1H), 4.47 (s, 1H), 3.88 (s, 1H), 3.74−3.49 (m, 2H), 2.56 (s, 3H), 2.14 (dd, J = 12.2, 5.7 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.9, 151.7, 150.1, 149.7, 141.1, 129.6, 125.4, 125.2, 119.0, 88.1, 85.4, 71.2, 62.0, 45.0, 36.8. ESI-MS (m/z) = 374 ($M^+ + H^+$). Anal. Calcd for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.52. Found: C, 59.68; H, 5.46; N, 20.44.

General Procedure for Suzuki−Miyaura Cross-Coupling of 8-BrdG with Arylboronic Acids. A solution of precatalyst **Id** (0.005 mmol, 1.0 mol %) in degassed H_2O (1.0 mL) was stirred for 5 min at ambient temperature under N_2. Then, 8-bromo-2′- deoxyguanosine (173 mg, 0.5 mmol) was added and the solution stirred for 5 min at 80 °C. Thereafter, boronic acid (0.75 mmol) was added along with Et_3N (1.0 mmol) and degassed water (2.0 mL). The resulting solution was then stirred at 80 °C for 12 h. After completion of the reaction, the reaction mass was diluted with ca. 10 mL of water and the pH adjusted to 7−8 with use of 10% aqueous HCl to give a precipitate. Precipitated solid was then filtered and washed with ethyl acetate and dried well in vacuo to afford the product as a white solid. (Note: For furan-2-boronic acid, thiophene-3- and thiophene-2-boronic acid are added in 3.0 equiv of the iodopurine.)

*8-(2-Benzofuranyl)-2′-deoxyguanosine (**9a**).*[57c] 0.136 g, 71%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.97 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.66 (dd, J = 8.3, 0.6 Hz, 1H), 7.45−7.37 (m, 2H), 7.34−7.28 (m, 1H), 6.60 (s, 2H), 6.46 (t, J = 7.2 Hz, 1H), 5.21 (d, J = 3.2 Hz, 1H), 4.99−4.91 (m, 1H), 4.46−4.36 (m, 1H), 3.81 (dd, J = 8.7, 5.1 Hz, 1H), 3.68−3.60 (m, 1H), 3.50 (dt, J = 11.0, 5.4 Hz, 1H), 2.13 (ddd, J = 13.0, 6.8, 3.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 157.0, 154.6, 153.9, 152.4, 146.3, 137.8, 128.0, 126.1, 124.1, 122.3, 118.2, 111.8, 108.4, 88.3, 84.8, 71.4, 62.4, 37.6. ESI-MS (m/z) = 384 ($M^+ + H^+$).

*8-(4-Methoxyphenyl)-2′-deoxyguanosine (**9b**).*[14a] 0.153 g, 82%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.74 (s, 1 H), 7.57−7.60 (m, 2 H), 7.08−7.11 (m, 2 H), 6.38 (br. s., 2 H), 6.05 (dd, J = 7.94, 6.71 Hz, 1 H), 4.96−5.01 (m, 1 H) 5.16 (s, 1 H), 4.29−4.39 (m, 1 H), 3.83 (s, 3 H), 3.78 (dt, J = 5.04, 2.67 Hz, 1 H), 3.60−3.69 (m, 1 H), 3.54 (dt, J = 12.06, 5.87 Hz, 1 H), 2.44 Hz, 1 H) 2.00 (ddd, J = 13.12, 6.41,2.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 160.3, 158.8, 153.0, 152.0, 147.3, 130.7, 122.7, 117.0, 114.2, 100.2, 87.9, 84.7, 71.2, 62.1, 55.3, 36.4. ESI-MS (m/z) = 374 ($M^+ + H^+$).

*8-(4-Methylphenyl)-2′-deoxyguanosine (**9c**).*[57d] 0.139 g, 78%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.75 (s, 1H), 7.52 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H), 6.39 (s, 2H), 6.04 (t, J = 7.0 Hz, 1H), 5.14 (d, J = 3.1 Hz, 1H), 4.99 (d, J = 4.6 Hz, 1H), 4.32 (s, 1H), 3.77 (s, 1H), 3.57 (ddd, J = 21.6, 11.2, 5.8 Hz, 2H), 2.37 (s, 3H), 1.99 (dd, J = 11.5, 5.6 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.0, 153.2, 152.3, 150.2, 149.0, 147.6, 122.9, 122.0, 117.3, 112.9, 111.9, 88.2, 79.6, 71.7, 62.6, 56.0, 36.8. ESI-MS (m/z) = 358 ($M^+ + H^+$).

*8-(3,4-Dimethoxyphenyl)-2′-deoxyguanosine (**9d**).* (0.155 g, 77%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.71 (s, 1H), 7.18 (d, J = 12.0 Hz, 2H), 7.10 (d, J = 8.2 Hz, 1H), 6.36 (s, 2H), 6.07 (t, J = 7.3 Hz, 1H), 5.14 (d, J = 4.0 Hz, 1H), 4.98 (t, J = 5.9 Hz, 1H), 4.33 (s, 1H), 3.81 (d, J = 8.2 Hz, 6H), 3.78 (d, J = 5.0 Hz, 1H), 3.56 (ddd, J = 23.6, 11.6, 6.0 Hz, 2H), 2.00 (dd, J = 11.4, 6.0 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 157.0, 153.3, 152.3, 147.6, 139.5, 129.6, 129.4, 127.8, 117.5, 88.2, 85.0, 79.6, 71.6, 62.5, 36.9, 21.3. ESI-MS (m/z) = 404 ($M^+ + H^+$). Anal. Calcd for $C_{18}H_{21}N_5O_6$: C, 53.59; H, 5.26; N, 17.36. Found: C, 53.45; H, 5.29; N, 17.31.

*8-(4-Biphenyl)-2′-deoxyguanosine (**9e**).* 0.147 g, 70%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.79 (s, 1H), 8.15−7.92 (m, 4H), 7.78 (d, J = 8.3 Hz, 2H), 7.67−7.52 (m, 3H), 6.45 (s, 2H), 6.18 (t, J = 7.3 Hz, 1H), 5.13 (d, J = 4.2 Hz, 1H), 5.02 (t, J = 5.6 Hz, 1H), 4.31 (s, 1H), 3.80 (d, J = 2.7 Hz, 1H), 3.72−3.53 (m, 2H), 2.06 (dd, J = 13.1, 6.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 157.0, 153.5, 152.5, 150.2, 147.4, 133.3, 132.8, 129.0, 128.5, 128.2, 128.1, 127.5, 127.2, 126.7, 117.6, 88.1, 84.9, 71.4, 62.4, 37.0. ESI-MS (m/z) = 420 ($M^+ + H^+$). Anal. Calcd for $C_{22}H_{21}N_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 63.09; H, 5.16; N, 16.79.

*8-(3,5-Dimethylphenyl)-2′-deoxyguanosine (**9f**).* 0.158 g, 85%. ^{1}H NMR (400 MHz, DMSO): δ 10.74 (s, 1H), 7.23 (s, 2H), 7.14 (s, 1H),

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6.39 (s, 2H), 6.08 (t, J = 7.4 Hz, 1H), 5.14 (d, J = 4.2 Hz, 1H), 4.99 (t, J = 5.7 Hz, 1H), 4.30 (d, J = 2.5 Hz, 1H), 3.77 (d, J = 2.8 Hz, 1H), 3.69−3.48 (m, 2H), 2.34 (s, 6H), 2.07−1.95 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 157.0, 153.3, 152.3, 147.6, 138.1, 131.2, 130.7, 127.2, 117.4, 88.2, 84.8, 71.5, 62.53, 37.1, 21.3. ESI-MS (m/z) = 372 ($M^+ + H^+$). Anal. Calcd for $C_{18}H_{21}N_5O_4$: C, 58.21; H, 5.70; N, 18.86. Found: C, 58.09; H, 5.81; N, 18.77.

General Procedure for Suzuki−Miyaura Cross-Coupling of BVDU with Arylboronic Acids. A solution of precatalyst **Id** (0.005 mmol, 1.0 mol %) in degassed H_2O (1.0 mL) was stirred for 5 min at ambient temperature under N_2. Then, BVDU (0.5 mmol) was added and the solution stirred for 5 min at 80 °C. Thereafter, phenylboronic acid (91 mg, 0.75 mmol) was added along with Et_3N (1.0 mmol) and degassed water (2.0 mL). The resulting solution was then stirred at 80 °C for 6.0 h. After completion of the reaction, the solvent was removed in vacuo, and the resultant residue obtained was purified using column chromatography in CH_2Cl_2/MeOH solvent system (96:4) to afford the desired product as a white solid.

*5-((E)-2-Phenylethenyl)-2′-deoxyuridine (**11a**).* 0.107 g, 65%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.19 (s, 1H), 7.45−7.28 (m, 5H), 7.19 (t, J = 7.2 Hz, 1H), 6.85 (d, J = 16.4 Hz, 1H), 6.15 (t, J = 6.5 Hz, 1H), 5.25 (d, J = 4.3 Hz, 1H), 5.17 (t, J = 4.9 Hz, 1H), 4.29−4.22 (m, 1H), 3.80−3.75 (m, 1H), 3.68−3.55 (m, 2H), 2.14 (dd, J = 11.7, 5.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.5, 160.2, 149.8, 138.5, 137.8, 129.1, 128.0, 127.7, 126.4, 121.6, 111.1, 87.8, 84.8, 70.3, 61.4, 40.3. ESI-MS (m/z) = 371 ($M^+ + H^+$). Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.50; H, 4.81; N, 7.47.

*5-((E)-2-Benzofuranylethenyl)-2′-deoxyuridine (**11b**).* 0.162 g, 88%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.56 (s, 1H), 8.24 (s, 1H), 7.59−7.46 (m, 3H), 7.21 (dtd, J = 25.9, 7.4, 1.1 Hz, 2H), 6.96 (d, J = 16.1 Hz, 1H), 6.85 (s, 1H), 6.15 (t, J = 6.6 Hz, 1H), 5.27 (d, J = 4.2 Hz, 1H), 5.19 (t, J = 5.2 Hz, 1H), 4.28−4.23 (m, 1H), 3.78 (dd, J = 7.0, 3.6 Hz, 1H), 3.68−3.55 (m, 2H), 2.21−2.08 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 162.4, 155.5, 154.5, 149.7, 140.1, 129.3, 125.0, 123.5, 121.3, 116.2, 111.0, 110.3, 105.2, 87.9, 84.8, 70.4, 61.4, 46.1. ESI-MS (m/z) = 331 ($M^+ + H^+$). Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.87; H, 5.59; N, 8.51.

General Procedure for Microwave-Assisted Suzuki−Miyaura Cross-Coupling of 5-Iodo-2′-deoxyuridine with Arylboronic Acids. 5-Iodo-2-deoxyuridine (88.5 mg, 0.25 mmol, 1 equiv) with Et_3N (50.6 mg, 0.5 mmol, 2 equiv) and the boronic acid (0.37 mmol, 1.5 equiv) were placed in a 10 mL vial. A nitrogen-flushed solution of precatalyst **Id** (0.0025 mmol, 1.0 mol %) was added in degassed water (2 mL). The mixture was stirred under microwave irradiation with heating (CEM Discover microwave) at 80 °C for the indicated times. After completion of the reaction, the solvent was removed in vacuo and the resultant residue obtained was purified using column chromatography in a CH_2Cl_2/MeOH solvent system (96:4) to afford the desired product as a white solid. Compounds **3a**, **3f**, **5a**, **7b**, **7c**, **9a**, and **9b** have been characterized in the previous schemes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02475.

Crystallographic data for **3a** (CIF)
Crystallographic data for **3f** (CIF)
Crystallographic data for **3i** (CIF)
Crystallographic data for **IIa** and **IIIa** (CIF)
^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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