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ARTICLE TYPE

New water soluble Pd-Imidate complexes as highly efficient catalysts for the synthesis of C5-arylated pyrimidine nucleosides via Suzuki-Miyaura cross-coupling

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The direct reactions between the precursors *trans*-[Pd(Imidate)$_2$(SMe$_2$)$_2$] and 1,3,5-triaza-7-phosphaadamantane (PTA) yield new water-soluble palladium(II) complexes *trans*-[Pd(Imidate)$_2$(PTA)$_2$](Imidate = succinimidate (suc) **1**, maleimidate (mal) **2**, phthalimidate (phthal) **3** or saccharinate (sacc) **4**. The new complexes have revealed as excellent catalysts for environmentally friendly, efficient Suzuki-Miyaura cross-coupling of synthetically challenging substrates like the antiviral nucleoside analogue 5-iodo-2´-deoxyuridine in water as solvent.

1. Introduction

Suzuki-Miyaura cross-coupling of aryl halides with aryl boronic acids is one of the most important and industrially viable reactions developed during the past century. This becomes evident from the large amount of research devoted to it, which has allowed the coupling of challenging substrates and produced relevant building blocks in natural product synthesis or pharmaceutical targets, among other fields.[1] It was definitely recognized when the shared 2010 Nobel Prize in Chemistry was awarded to Suzuki for his contribution to the field of C–C bond formation using palladium catalysis.[2] However, a major drawback from an environmental and economic perspective is the use of toxic organic solvents in most of the aforementioned catalytic transformations. Thus, Suzuki coupling has been fully involved in the recent increasing interest of using water as a solvent for many homogeneously catalyzed reactions.[3] Since Casalnuovo and Calabrese initial report in 1990,[4] several strategies to perform Suzuki cross-coupling reactions in water have been developed. The use of water-soluble palladium catalysts is one of those strategies that has attracted more attention,[5,6] as might lead to an easy catalyst recovery by separating the water phase and the organic coupled products.[6h,7]

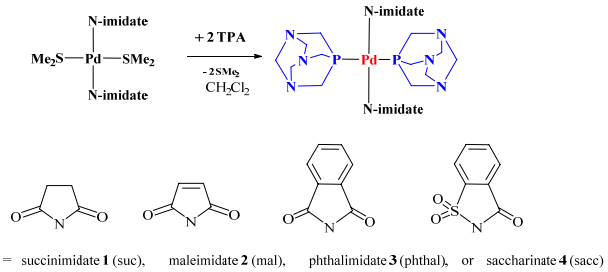
The use of water-soluble ligands to enhance the solubility in water of transition metal complexes has been a common approach to this field. Among them, conveniently substituted monodentated aryl phosphines or cage-like phosphines (as phosphine, 1,3,5-triaza-7-phosphaadamantane: PTA that enables the synthesis of water-soluble complexes without introducing a charged species) have received continuous attention.[8] In fact, the coordination chemistry of PTA has been mostly developed at the same time as the interest for environmentally friendly catalysts. Halide complexes of the general formula cis-[PdX2(PTA)2] (X = Cl, Br, I) have played a relevant role in the early development of Pd-TPA chemistry,[8a,9,10] and either themselves or used as precursors of new derivatives still keep their relevance in this field.[8b,11-13] However to date there are no reports on related complexes containing imidate ligands, a variety of pseudohalides showing mixed σ-donating and π-accepting properties[14] that in the course of our collaboration with Fairlamb and co-workers have shown incredible potential for cross-coupling reactions.[15]

Our most recent contribution to this field has focused on the use of *trans*-[Pd(PPh$_3$)$_2$(Saccharinate)$_2$] as a general catalyst for Suzuki-Miyaura, Negishi cross-coupling and C-H bond functionalization of challenging substrates.[16] The outstanding performance of this complex encouraged us to synthesize the water-soluble analogues of the type *trans*-[Pd(Imidate)$_2$(PTA)$_2$] reported here, that would allow us to explore the above mentioned reactions in water. For this purpose we had available the precursors *trans*-[Pd(Imidate)$_2$(SMe$_2$)$_2$][15i] that provided a straightforward route to the desired complexes. We present here, together with the synthesis and characterization of the new [Pd(Imidate)$_2$(PTA)$_2$] complexes, a study of their ability/recyclability to perform Suzuki-Miyaura cross-coupling reactions of (hetero)aryl halides as well as 5-iodo-2´-deoxyuridine with differently substituted aryl boronic acids in water, under milder conditions than previously reported.

2. Results and discussion

2.1. Synthesis and characterization

The new complexes of general formula trans-[Pd(Imidate)$_2$(PTA)$_2$] (Imidate = succinimidate (suc) **1**, maleimidate (mal) **2**, phthalimidate (phthal) **3** or saccharinate (sacc) **4** are obtained in high yields when PTA displaces the labile thioether ligands in the precursors trans-[Pd(SMe$_2$)$_2$(Imidate)$_2$].[15i,16] The insolubility in water of such precursors prevented its use in this step, although the use of the volatile SMe$_2$ has been claimed to result in cleaner products if compared with alternative routes.[11] The structures of the ligands employed, labelled with their abbreviations are shown in Scheme 1.



N-imidate = succinimidate **1** (suc), maleimidate **2** (mal), phthalimidate **3** (phthal), or saccharinate **4** (sacc)

Scheme 1: Synthetic route for novel $[Pd(Imidate)_2(PTA)_2]$ complexes.

The new complexes have been fully characterized by analytical and spectroscopic techniques, (Experimental Section) including a single crystal X-ray diffraction study of **4** that confirms the trans- geometry around the palladium centre. The corresponding ORTEP drawing is shown in Figure 1 with the relevant bond lengths and angles. The structure around the palladium atom may be described as nearly planar, and other outstanding molecular features are the *syn-* configuration of saccharinate ligands and the *anti-* configuration of TPA ligands.

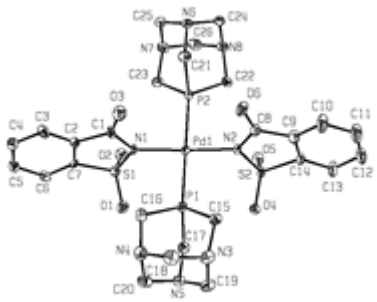


Figure 1. ORTEP diagram of complex **4** with the atom numbering scheme; thermal ellipsoids are drawn at the 50% probability level. H_2O found in the unit cell is not shown. Selected bond lengths (Å) and angles (º): Pd-N1: 2.027 Å, Pd-N2: 2.048 Å, Pd-P1: 2.320 Å, Pd-P2: 2.290 Å. Square planar coordination: N1-Pd-N2: 177.35º, P1-Pd-P2: 175.08º, N1-Pd-P1: 90.90º, N1-Pd-P2: 88.33º, N2-Pd-P1: 90.15º, N2-Pd-P2: 90.42º.

This configuration favours the most relevant supramolecular interaction: C=O•••H hydrogen bonds between both carbonyl groups from one complex and hydrogen atoms in a saccharinate ligand on the next molecule defining a R22 (11) ring (Figure 2).

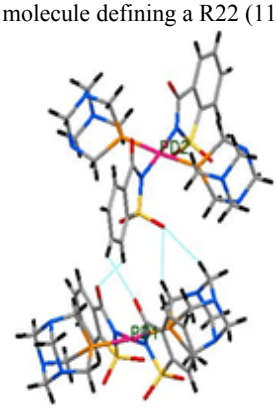


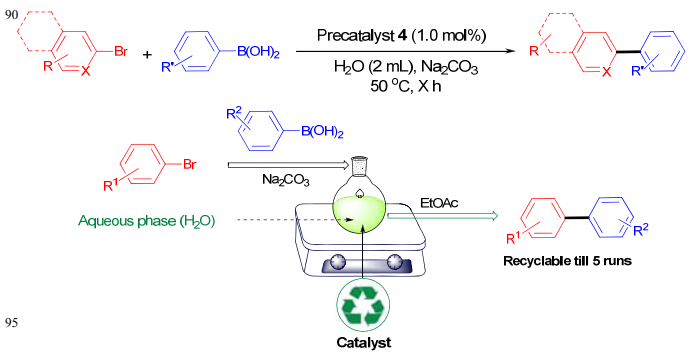
Figure 2. Crystal packing in **4**.

IR spectra displays characteristic strong carbonyl-imidato absorptions ν_{asim}(C=O) in the 1675-1609 cm^{-1} region, together with weak bands at 1711-1724 cm^{-1}attributed to ν_{sim}(C=O). The incoming ligand PTA, that uncoordinated has infrared absorptions at 452 and 405 cm^{-1}, displays typical bands that appear shifted downfield upon complexation.[17] Good solubility of the new complexes in common solvents allowed its ^{1}H- and ^{31}P{^{1}H}-NMR characterization. (see Experimental Section) The latter singlet resonances of the complexes are shifted to a higher field than those of the chloride derivatives and closer to previously reported thiolato Pd-PTA complexes.[8, 13] Additional support for the proposed formula of the new complexes arises from mass spectrometry, which shows fragments for the m/z values corresponding to M^+ and abundance of the signals around the parent ions consistent with the natural isotopic abundances.

2.2 Suzuki-Miyaura cross-coupling

At the outset of these studies, we tested several *in-situ* and preformed catalyst systems to optimise of an efficient Suzuki-Miyaura cross-coupling protocol for aryl bromides in water (Scheme 2). It is worth mentioning that the precatalysts were able to catalyse these transformations under mild conditions in water. The water solubility of the palladium catalyst offers an important advantage for catalyst recycling[18], combined with the separation of the products either by filtration or extraction with minimal amounts of organic solvents. In order to explore the possibility of reusing the aqueous solution containing the catalytically active species catalytic reactions between different aryl bromides and aryl boronic acids was performed using precatalysts **4** (See supporting information).

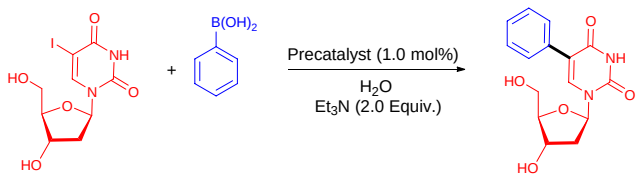
The product obtained was isolated by extracting the aqueous layer with ethyl acetate and then recharging the reaction vessel containing the aqueous phase with fresh substrates and base. Remarkably this catalytic solution was found to be active for five consecutive runs without significant loss in activity. The EtOAc layer on extraction of products after 1st, 4th and 5th recycle was analysed by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) for any leaching of the palladium complex. No leaching of palladium complex was observed (organic layer analysis after 1st, 4th and 5th recycle) even though there is drastic reduction in catalytic activity. This could be attributed to the possible "salting out effect" of carbonate salts[19] which reduces the water solubility of organic solutes also making the aqueous phase more viscous and less manageable for further use.



Scheme 2: Suzuki-Miyaura cross-coupling of aryl halides using $[Pd(Imidate)_2(PTA)_2]$ complexes.

Nucleosides and their modification via metal-mediated cross-coupling processes have attracted considerable attention during the last decades due to their biological properties. Palladium complexes have shown excellent reactivity towards the modification of nucleosides containing purines or pyrimidine series.[20] Arylation of 5-halo-2´-deoxyuridine has been demonstrated consistently using palladium-catalysed Suzuki-Miyaura or Stille cross-coupling reactions by several research groups. However, most of these reactions have been performed in organic solvents making the synthetic procedures environmentally less attractive.[21]

Table 1: Suzuki-Miyaura arylation of 5-iodo-2´-deoxyuridine[a,b]



No.	Complex	Temp. (^{0}C)	Reaction time (hrs)	%Yield
1.	$Pd(OAc)_2$	r.t.	48	29
2.	$Pd(OAc)_2$/TPA	r.t.	48	40
3.	**1**	r.t.	48	66
4.	**2**	r.t.	48	68
5.	**3**	r.t.	48	75
6.	**4**	r.t.	48	72
7.	$[PdCl_2(TPA)_2]$	r.t.	48	35
8.	$[PdBr_2(TPA)_2]$	r.t.	48	48
9.	$[PdI_2(TPA)_2]$	r.t.	48	21
10.	**3**	60	8	78
11	**3**	80	6	92
12	**3**	100	4	82
13.	**3**	80	15	72[c]
14.	**3**	80	24	69[d]
15.	**3**	80	48	51[e]
16.	**3**	80	48	39[f]

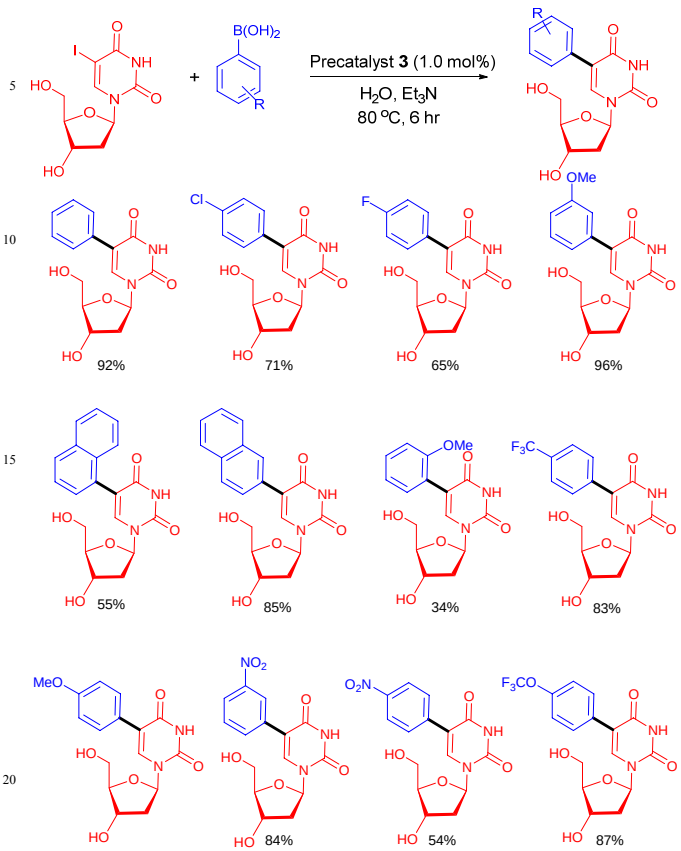
[a]Arylboronic acid (0.75mmol), **5-iodo-2´-deoxyuridine** (0.5mmol), **Catalyst** (1.0 mol%), 2 mL H_2O, Et_3N(1.0mmol). [b]Yields are isolatedyields.[c]Instead of 1.0 mol% of catalyst, 0.5 mol% wasemployed. [d]Instead of 1.0 mol% of catalyst, 0.1 mol% wasemployed. [e]Instead of 1.0 mol% of catalyst, 0.05 mol% wasemployed. [f]Instead of 1.0 mol% of catalyst, 0.01 mol% wasemployed.

Although some examples with water as the reaction solvent for palladium-catalysed cross-coupling of 5-halo-2´-deoxyuridine have been reported in literature, most of them however suffer from less than satisfactory yields of the desired products, and in certain cases higher reaction temperatures render the conditions synthetically less feasible.[22]

Encouraged by the results mentioned above we decided to employ the water soluble catalysts **1-4** towards developing an efficient and environmentally feasible Suzuki-Miyaura protocol for the synthesis of 5-arylated deoxyuridine analogs. It was observed (Table 1) that complex **3** furnished the 5-arylated nucleoside more efficiently than rest of the complexes in the presence of triethylamine as the base. The halide-containing counterparts (entries 7-9, Table 1) of palladium complexes **1-4** as well as the *in situ* generated catalytic systems (entries 1 and 2, Table 1) gave poor results towards the cross-coupling of 5-iodo-2-deoxyuridine and aryl boronic acids. This result confirms the ability of the water soluble palladium complexes to form the product under mild conditions, although the reaction requires longer time for completion. At elevated temperatures the 5-arylated product could be obtained in competitive reaction times with the best result obtained at 80 ^{o}C. Catalyst loading experiments have also been performed on the catalytic system with the catalyst **3** exhibiting good activity even at 0.1 mol%, although longer reaction times were required. At 0.05 mol% the reactivity reduced drastically, with similar trend observed at 0.01 mol% too. The isolation of the arylated nucleosides were done by column chromatography using CH_2Cl_2:MeOH system. However, given the toxic and the non-environmentally benign nature of CH_2Cl_2, we decided to try other greener alternatives for the chromatographic purification of nucleosides.[23,24] Although, solvents such as Methyl *tert*-butylether (MTBE), 2-methyl tetrahydrofuran (2-MeTHF) and ethyl acetate were employed as the possible replacements, a poorer separation coefficient (based on the Rf values in different solvents systems) suggest that CH_2Cl_2:MeOH system is best suited for the purification of these reactions.

With the best conditions in hand we then explored the scope for the Suzuki-Miyaura cross-coupling of 5-iodo-2´-deoxyuridine in water as solvent (Table 4). Electronic effects of the substituents on the aromatic ring played a crucial role in deciding the reactivity of the catalytic system with the more electron-rich coupling aryl boronic acids outperforming their electron-poor counterparts. Synthetically challenging nucleophilic coupling partners such as naphthalene boronic acids furnished the 5-arylated nucleoside product in good yields, however 2-methoxyphenyl boronic acid failed to give the desired product in good yield probably due to steric factors. Several other aryl boronic acids containing electron-withdrawing groups also gave good yields of the 5-arylated 2-deoxyuridine product.

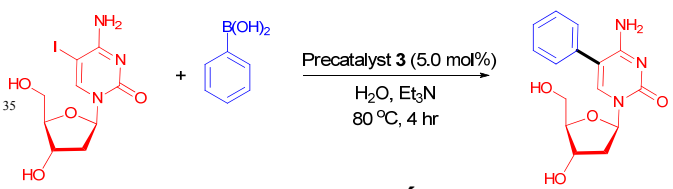
Scheme 3: Scope study for Suzuki-Miyaura arylation of 5-iodo-2´-deoxyuridine[a,b]



[a]arylboronicacid (0.75mmol), **5-iodo-2´-deoxyuridine** (0.5mmol), **Catalyst** (1.0 mol%), 2 mL H_2O, Et_3N(1.0mmol). [b]Yields are isolatedyields.

Furthermore, to extend the scope of the developed protocol we employed another synthetically important nucleoside, 5-iodo-2´-deoxycytidine towards cross-coupling with phenyl boronic acid (Scheme 4). The solubility of this compound in water is lower than that of the uridine analogue, and therefore the reactivity towards cross-coupling with phenyl boronic acid was found to be comparatively lower.

Scheme 4: Scope study for Suzuki-Miyaura arylation of 5-iodo-2´-deoxycytidine[a,b]



[a]phemylboronicacid (0.75mmol), **5-iodo-2´-deoxycytidine** (0.5mmol), **Catalyst** (1.0 mol%), 2 mL H_2O, Et_3N (1.0mmol). [b]Yields are isolatedyields.

3. Conclusions

The synthesis and characterization of new water soluble palladium complexes **1-4** has been achieved. The precatalysts have shown to efficiently catalyse Suzuki-Miyaura cross-coupling of synthetically challenging substrates like the antiviral nucleoside analogue 5-iodo-2´-deoxyuridine and its cytidine analogue in water as solvent under milder conditions and better yields that previously reported. Catalyst loading could be reduced up to 0.1 mol% without any appreciable reduction in yields (although reaction time increase drastically).

4. Experimental Section

General remarks: C, H and N analyses were carried out with a Carlo Erba instrument. IR spectra were recorded on a Perkin-Elmer spectrophotometer 16F PC FT-IR, using Nujol mulls between polyethylene sheets. NMR data (^1H or ^{31}P)were recorded on BrukerAvance 300 or 400 spectrometers. HPCL-MS analyses were performed on an Agilent VL mass spectrometer. The ionization mechanism used was electrospray in positive and negative ion full scan mode using acetonitrile as solvent and nitrogen gas for desolvation. ICP-MS analysis was performed on Thermo Fisher Scientific, Germany (Model Element XR).
Imides and other commercially available chemicals were purchased from Aldrich Chemical Co. and were used without further purification, and all the solvents were dried by standard methods before use.

Synthesis

Preparation of complexes [trans-[Pd(Imidate)$_2$(PTA)$_2$] (Imidate = succinimidate (suc) 1, maleimidate (mal) 2, phthalimidate (phthal) 3 or saccharinate (sacc) 4.

The complexes were obtained by treating the appropriated 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 (10 mL) solution of [Pd(Imidate)$_2$(SMe$_2$)$_2$] (0.100g) was added the stoichiometric amount of PTA (0.0736 g for **1**; 0.0743 g for **2**; 0.0601 g for **3**; 0.0528 g for **4**). The solution was refluxed for 1 h, and then concentrated until 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.

[Pd(succ)$_2$(PTA)$_2$] **1**. Yield 0.129g, 90%. Anal. calc. for $C_{20}H_{32}N_8O_4P_2Pd$; C, 38.9; H, 5.2; N, 18.2. Found: C, 39.2; H, 5.3; N, 18.3 %. IR (Nujol) $\bar{\nu}$ = 1711w, 1635vs, 1346s, 1234s, 1116s, 1102s, 974s, 943s, 669s, 526m, 452m, 390m cm^{-1}. HPLC-MS (positive mode)m/z: 616 M^+, 518 M^+ -succ, 361 M^+ -succ -PTA .^1H NMR (300MHz; $CDCl_3$, 298K, δ): 4.42 (s, 12H, PTA); 4.14 (s, 12H, PTA); 2.71 (s, 8H, succ) ppm. ^{31}P NMR (300MHz; $CDCl_3$, 298K, δ): -51.4 ppm.

[Pd(mal)$_2$(PTA)$_2$] **2**. Yield 0.130g, 90%. Anal. calc. for $C_{20}H_{28}N_8O_4P_2Pd$; C, 39.2; H, 4.6; N, 18.3. Found: C, 39.3; H, 4.7; N, 18.4 %. IR (Nujol) $\bar{\nu}$ = 1711w, 1635vs,1340s, 1186s, 1097s, 1012s, 970s, 942s, 694s, 526m, 455m, 392m cm^{-1}. HPLC-MS (positive mode)m/z: 612 M^+, 358 M^+ -mal -PTA .^1H NMR (300MHz; $CDCl_3$, 298K, δ): 6.68 (s, 4H, mal); 4.42 (s, 12H, PTA); 4.14 (s, 12H, PTA) ppm. ^{31}P NMR (300MHz; $CDCl_3$, 298K, δ): -49.5 ppm.

$[Pd(phthal)_2(PTA)_2]$ **3**. Yield 0.117g, 86%. Anal. calc. for $C_{28}H_{32}N_8O_4P_2Pd$; C, 47.2; H, 4.5; N, 15.7. Found: C, 47.5; H, 4.6; N, 15.9 %. IR (Nujol) $\bar{\nu}$ = 1724w, 1663vs,1305s, 1183s, 1099s, 1013s, 971s, 943s, 681s, 457m, 392m cm^{-1}. HPLC-MS (positive mode)m/z: 712 M^+, 556 M^+ -phthal, 409 M^+ -phthal -PTA .^{1}H NMR (300MHz; $CDCl_3$, 298K, δ): 7.74 (m, 4H, phthal); 7.61 (m, 4H, phthal); 4.38 (s, 12H, PTA); 4.17 (s, 12H, PTA) ppm. ^{31}P NMR (300MHz; $CDCl_3$, 298K, δ): -49.7 ppm.

$[Pd(sacc)_2(PTA)_2]$ **4**. Yield 0.125g, 95%. Anal. calc. for $C_{26}H_{32}N_8O_6P_2PdS_2$; C, 39.8; H, 4.1; N, 14.3. Found: C, 39.9; H, 4.3; N, 14.3 %. IR (Nujol) $\bar{\nu}$ = 1700w, 1675vs, 1593s, 1305s, 1252s, 1169s, 1014s, 972s, 942s, 679s, 526m, 456m, 392m cm^{-1}. HPLC-MS (positive mode)m/z: 784 M^+, 602 M^+ -sacc.^{1}H NMR (300MHz; $CDCl_3$, 298K, δ): 7.91 (m, 4H, sacc); 4.77 (m, 4H, sacc); 4.29-4.47 (m, 12H, PTA); 4.14 (s, 12H, PTA) ppm. ^{31}P NMR (300MHz; $CDCl_3$, 298K, δ): -41.8 ppm.

General procedure for Suzuki-Miyaura cross-coupling of 5-iodo-2´-deoxyuridine or 5-iodo-2´-deoxycytidinewith aryl boronic acids:

A solution of precatalyst**3** (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 ºC. Thereafter, phenyl boronic acid (90 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 reaction the solvent was removed under 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. (Characterization of cross-coupled products is collected as Electronic Supplementary information).

Crystal structure determination of 4.

Data collection for **4** were obtained at 100(2) K on a Bruker Smart CCD diffractometer with a nominal crystal to detector distance of 4.5 cm. Diffraction data were collected based on a ω scan run. A total of 2524 frames were collected at 0.3º intervals and 10 s per frame. The diffraction frames were integrated using the SAINT package[25] and corrected for absorption with SADABS[26]. The structures were solved by direct methods[27] and refined by full-matrix least-squares techniques using anisotropic thermal parameters for non-H atoms (Table 2). The structural data have been deposited with the Cambridge Crystallographic Data Center (CCDC 970233).

Table 2.Crystal data and structure refinement for complex 4

Formula	$C_{26}H_{32}N_8O_6P_2PdS_2{\cdot}1.5H_2O$
M	812.08
Crystal system	Hexagonal
Space group	$P6_4$
Z	6
a /Å	21.390(15)
c /Å	12.812(13)
V /Å^3	5077(6)
T / K	100
λ / Å	0.71073
μ / mm^{-1}	0.823
Reflections collected	73467
Independent reflections	9152
Goodness-of-fit on F^2	0.890
Final *R* indices [I>2σ(I)][a,b]	0.0460
R indices (all data)[a,b]	0.0617
Max /min Δρ[e· Å^{-3}]	1.407/-0.739

5. Acknowledgements

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6. Notes and references

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