Imine-palladacycles as phosphine-free precatalysts for low temperature Suzuki-Miyaura synthesis of nucleoside analogues in aqueous media

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Abstract

The synthesis and characterization of new water soluble dinuclear palladacycles of general formula [{Pd(R-C^N-SO_3Na)(μ-AcO)}$_2$] (R = -H (**1**); -OMe (**2**) or -Cl (**3**)) incorporating an orthometalated sodium 4-(N-benzylideneamino)benzenesulfonate) moiety is reported. These complexes have revealed as excellent phosphine-free catalysts for the synthesis of functionalized nucleoside analogues involving a low temperature Suzuki-Miyaura coupling of 5-iodo-2'-deoxyuridine with different aryl boronic acids in neat water. The potential of **1**-**3** as synthetic precursors was also tested, and bridging acetates were cleaved by reaction with neutral PPh_3, yielding the corresponding mononuclear derivatives [Pd(R-C^N-SO_3Na)(AcO)(PPh_3)] (R = H (**4**), MeO-(**5**) or Cl-(**6**)). Analytical and spectroscopic techniques confirmed the proposed formulae and reactivity reported for complexes **1**-**6**. Structural characterisation by X-ray diffraction of singles crystals grown from **4** and **6** samples produced unexpected but valuable crystallization-mediated compounds **4cm** and **6cm** that also supported the results presented here.

Introduction

It is being almost three decades since a natural and unstoppable approach between metal catalysis and the use of water as reaction solvent is taking place.[1] The development of hydrophilic ligands able to improve both solubility and stability of organometallic complexes has definitely set the pace of such approach.[1,2] To accomplish this the incorporation of hydrophilic anionic functionalities, like sulfonate or carboxylate, in common ligands has been a successful strategy.[3] Thus, sulfonated triphenylphosphine ligands focused the attention of the first studies[4] and, from the initial Casalnuovo´s work on the TPPMS/$Pd(OAc)_2$ system[5] to more recent examples,[6] still

have a prominent role in palladium-catalyzed reactions carried out in water.[7] In the case of palladacycles the inclusion of such functionalities has provided promising results.[7,8] Those and other different approaches to introduce water-solubility in palladacycles, like the significant results on oxime complexes with an hydroxy substituent[9] or initial work by Ryabov including a crown ether fragment,[10] have been recently reviewed by Shaughnessy.[11] Given the fact that the identity of the palladacycle precursor has being claimed to affect both the activity and lifetime of the catalysts,[8a] it is surprising that just one example of dinuclear acetate-bridged water soluble palladacycle has been described to date.[12] Most examples display the chloride bridged moiety, that in the case of Shaugnessy´s palladacycle [{Pd(C^N)(μ-Cl)}$_2$] (C^N = sodium 4-(N-benzylideneamino)benzenesulfonate) has generated a particularly labile complex.[8a] In previous studies we found that the availability of both halide and acetate-bridged dinuclear palladacycles, owing differentiated properties like solubility and robustness but also dissimilar reactivity, is a powerful synthetic tool in order to prepare new derivatives.[13] Clearly those different properties would also affect the catalytic performance of the complexes. Regarding mono- and dinuclear palladacycles catalysing Suzuki coupling, we also disclosed a non-spectator role for halide, acetate and pseudohalide imidate ligands.[14] In addition, mechanistic studies were developed with non-sulfonated N-phenylbenzaldimine palladacycles.[15] These results with analogous water-insoluble complexes encouraged us to explore the synthesis and catalytic properties of the bridging acetate complexes reported in this article. The usefulness of the new complexes as synthetic precursors has also been incipiently explored, with the report of three new mononuclear PPh_3 derivatives.

On the other hand, nucleosides are important molecules of biological relevance due to their occurrence as the building block of DNA (deoxyribose nucleic acid) and RNA

(ribose nucleic acid). Functionalization of nucleosides *via* a large number of catalytic processes including Suzuki-Miyaura cross-coupling, C─H bond functionalization, Sonogashira coupling and many others[16] has been carried out over the years. Application of the functionalized nucleosides has varied over time from biological to fluorescent probes[17] while more recently, antiviral or anticancer applications of nucleosides[18] have also grown.

Amongst the various catalytic processes employed in literature for the modification of nucleosides, the Suzuki-Miyaura cross-coupling is the one that has found most applications due to its simplicity and ease of implementation.[19] Regarding uridine, several research groups have been involved in the development of efficient protocols for the Suzuki-Miyaura modification of 5-iodo-2'-deoxyuridine with boronic acids.[20] Our research group has also been active in the development of efficient catalytic processes for the modification of nucleosides including Suzuki-Miyaura cross-coupling.[21]

Problems associated with these catalytic protocols include the use of phosphine ligands for the activation of palladium center that could eventually lead to the formation of a phosphine oxide byproduct. Relatively higher temperature of the catalytic system also is a hindrance for the further application to the modification of thermally labile nucleoside structural features as well as nucleotides. In literature, these issues have been addressed to a certain extent, although separately. Len and co-workers, recently reported the Suzuki-Miyaura cross-coupling of 6-iodouridine at ambient temperature in aqueous media.[22] Few other examples for the modification of 6-iodouridine at low temperature are also known,[23] however to the best of our knowledge there are no reports for the functionalization of 5-iodo-2'-deoxyuridine without any added phosphine/N-heterocyclic carbene ligand. We present here the application of the developed phosphine-free palladacyclic complexes in the first low-temperature Suzuki-Miyaura

coupling of 5-iodo-2'-deoxyuridine as well as 5-iodo-2'-deoxycytidine with different aryl boronic acids reported in literature, performed in water as the sole reaction solvent.

Results and discussion

Synthesis and characterisation

Ligands Synthesis. Three hydrophilic imine-based ligands **L1**, **L2, L3** were prepared by condensation of the sodium salt of sulfanilic acid with benzaldehyde, *p*-anisaldehyde or *p*-Cl-benzaldehyde respectively, adapting a reported procedure.[24] Synthetic details and characterization by analytical and spectroscopic techniques are collected in the Experimental Section.

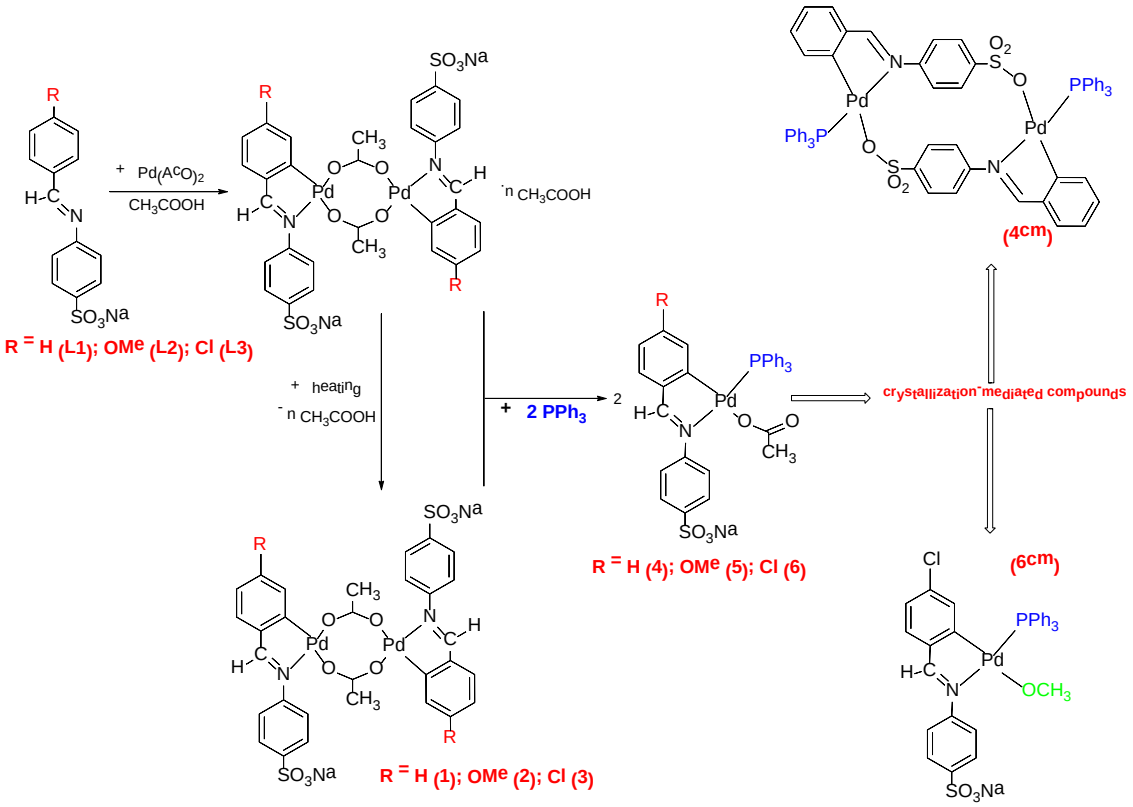
Dinuclear palladacycles. As displayed in Scheme 1, solvated orange acetato-bridged cyclometallated dimers containing **L1-L3** ligands [{Pd(R-C^N-SO_3Na)(μ-AcO)}$_2$]·nCH_3COOH were easily prepared following the classical method that involves reacting $Pd(AcO)_2$ with Schiff base ligands in boiling acetic acid. The infrared spectra of the new complexes showed iminic absorptions and a strong broad band of carbonyl stretching close to 1600 cm^{-1}, together with characteristic absorptions of *p*-substitution around 1045 and 840 cm^{-1} and those at *ca.* 1200 cm^{-1} featuring -SO_3 groups, that have been reported in analogous chloride-bridged complexes.[8b] In addition, a strong band around 1720 cm^{-1} was also observed in the spectra of the three complexes, pointing out the likely presence of solvated acetic acid molecules. This extent was supported by ^1H NMR spectroscopy as resonances of variable integral at *ca.* 1.90 ppm accompanied the expected signals of bridging CH_3COO- groups when spectra were recorded in D_2O or CD_3OD. This extra resonance was not observed when the spectra was taken in a 2:1 mixture D_2O:CD_3CN (solvents used in the preliminary catalytic experiments, as

explained later). The stability in both D_2O and D_2O:CD_3CN solutions of the complex containing **L1** was investigated as a model by ^1H NMR over time and temperature (80ºC). Variable extention of cis/trans isomerization was observed depending on the solvent, as reported for related complexes.[8a] The absence of imine hydrolysis suggests that the new complexes are stable in these solvents and at the higher temperature used in the catalytic experiments. Representative spectra of these experiments are presented as Supplementary Information. $^{13}C\{^1H\}$ NMR also confirmed the proposed formulae displaying the expected signals of iminic ligands and bridging acetate. Additional support for their dinuclearity also arose from the negative ESI mass spectrometry. The addition of an aqueous solution of ammonium formate/formic acid in the mobile phase produced significant fragmentation of **1-3** and a common fragmentation path, that included signals generated from acetate/formate substitution. The solubility of the new complexes in water lies in the range $S_{20\ ºC}$ = 10.5-20.6 mg/mL, and compares well with the scarce data reported for related complexes (see "Catalytic studies" section below and SI for experimental details).[3b]

Initial attempts to remove solvated molecules and yield unsolvated samples were performed by two hours heating at 125ºC, slightly above the boiling point of acetic acid (118ºC). A drastic colour change from orange to yellow was then observed, and both IR and ^1H NMR revealed partial or complete disappearance of acetic-related signals, depending on the particular complex. A thorough thermal study including TG, DTG, DSC and coupled TG/MS (see supplementary material), that clearly displayed acetic-mass loss (60 uma) associated to several thermal events, allowed an individual diagnosis to prepare the corresponding yellow complexes [{Pd(R-C^N-SO_3Na)(μ-AcO)}$_2$] (R = -H (**1**); -OMe (**2**) or -Cl (**3**)) free of solvated molecules by simple oven treatment. Before complex decomposition, that begins at *ca.* 240ºC and implies the loss

of bridging acetate, there are two other events that take place with acetic loss. That means different types of acetic acid with different degrees of interaction between the solvated molecules and the complexes. The colour change associated to the heating of the samples is an interesting field to explore beyond the scope of the present work. Noteworthy, the behaviour of dinuclear solvated/unsolvated complexes was indistinguishable both for synthetic and catalytic purposes.

Unfortunately, suitable crystals for an X-ray diffraction study could not be prepared, and powder difractograms obtained with synchrotron source were of poor quality, thus preventing structural characterization of the dinuclear complexes by this technique. It is worth it to mention that, to date, there are no reports of crystal structures containing sulfonated imine palladacycles[8a, 8b], being the first examples those crystallization-mediated compounds **4cm** and **6cm** described below.



Scheme 1. **Synthesis of the dinuclear complexes and its PPh_3 derivatives.**

Phosphine derivatives. As mentioned above, we were interested in the synthetic application of the new complexes, both as supporting characterization of parent dinuclear precursors and as a route of new water soluble derivatives. Thus, PPh_3 adducts **4-6** were synthesized in good yields by reaction of the dinuclear acetate complexes **1-3** with this phosphine ligand in methanol (Scheme 1). Both solvated and unsolvated precursors yielded identical PPh_3 derivatives, as confirmed by parallel experiments.

The IR spectra of the new phosphine complexes exhibit the expected bands for the imine-cyclometallated backbone, and those attributed to the incoming PPh_3 ligand. A strong carbonyl band around 1570 cm^{-1} supports the presence of a terminal acetate ligand. In the experimental section the ^{1}H and $^{31}P\{^{1}H\}$ NMR spectroscopic data of the mononuclear Pd complexes are also collected. Good solubility in CD_3OD provided well defined ^{1}H NMR spectra of the new complexes, that display an aromatic region with both phosphine and palladacyclic ligand. The iminic proton experience a noticeable coupling to phosphorus appearing as a low field doublet signal, thus reproducing a behavior previously found in related complexes.[15a] The characteristic singlet resonances observed in the $^{31}P\{^{1}H\}$ NMR spectra of the new derivatives, are also in the expected chemical shifts range. ESI-MS spectrometry, that showed a common fragmentation pattern for complexes **4-6**, also confirmed the proposed formulae. The solubility of these PPh_3 derivative in water is in the range $S_{20\ ^{\circ}C}$ = 2.7-6.2 mg/mL, and is lower than the obtained for parent dinuclear precursor. Suitable crystals were grown from **4** and **6** samples by slow evaporation of their methanol solutions, enabling a study by X-ray single crystal diffraction. Due to further transformations during the crystallization, none of the single crystals reproduced the expected structures proposed for **4** and **6** in Scheme 1, that anyway have been thoroughly characterized in the bulk as shown in the experimental section. Nevertheless, the structures crystallization-mediated obtained

4cm and **6cm** still support the results presented in our work. Regarding the crystal structure **4cm**, an unexpected neutral dimeric structure was observed in which both AcO-groups and two Na^+ cations accompanying sulfonate anions had been removed. Coordination to Pd is then completed by oxygen atoms from two $-SO_3$ groups, as displayed in Figure 1. This process turned out to be not so unusual, since a similar unexpected structure of palladacycle containing carboxylated Schiff bases has been reported by Granell and coworkers in the course of their studies towards water-soluble metallacycles.[25] This type of structure has also been described by Shaughnessy in related carboxylated palladacycles, [8a] although our report is the first one involving the more weakly coordinating sulfonate anion. The poor catalytic performance of PPh_3 derivatives when compared with parent phosphine-free precursors can be tentatively attributed to the formation of such neutral species, although more evidence should be obtained in future work. On the other hand, **6cm** presented a MeO- group bound to Pd instead of terminal AcO-, which probably interchanged with the solvent during the crystallization process in MeOH. (Figure 2; selected data of both crystal structures are collated in Table 1) ^{1}H-NMR of the bulk solid **6** reported in the experimental section displayed a methyl resonance from acetate group at 0.923 ppm, that disappeared in the ^{1}H-NMR taken from crystal **6cm**. Here, a singlet in the typical methoxo range (4.5 ppm) was observed instead.

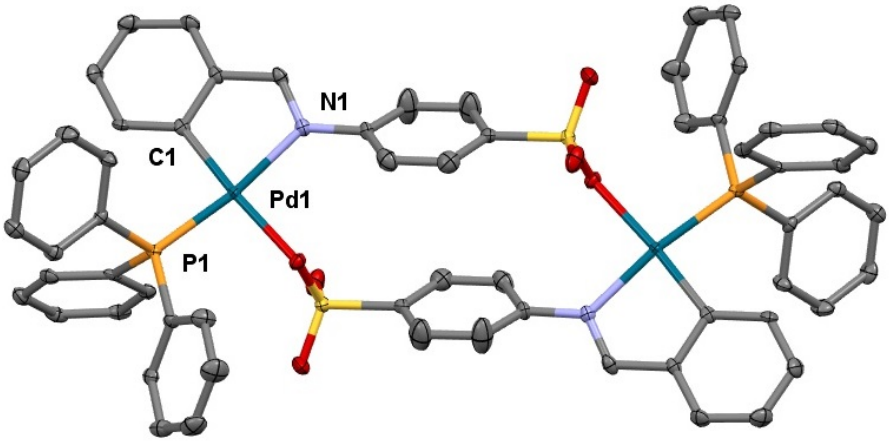


Figure 1. Thermal ellipsoid plot of the crystal structure of **4cm**, drawn at the 50% probability level. The hydrogen atoms have been omitted for clarity.

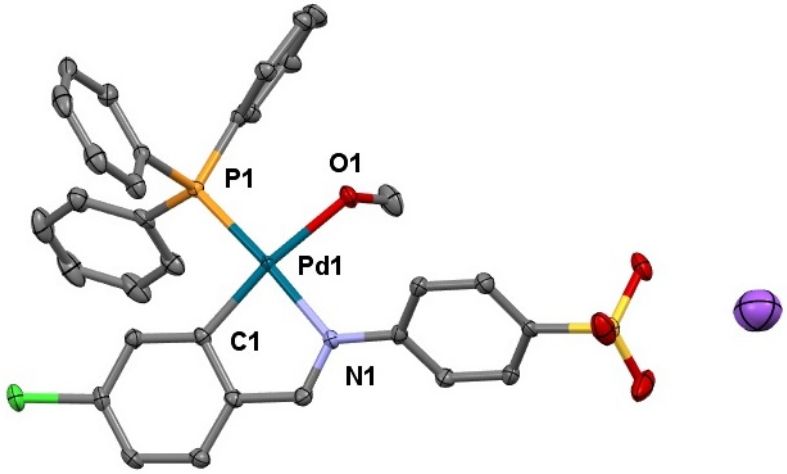


Figure 2. Thermal ellipsoid plot of crystal structure of **6cm**, drawn at the 50% probability level. The hydrogen atoms have been omitted for clarity.

Table 1. Selected Bond Distances and Angles for 4cm and 6cm

	4cm	**6cm**
Pd(1)-C(1)	1.999(9)	1.995(6)
Pd(1)-N(1)	2.122(7)	2.107(5)
Pd(1)-O(1)	2.155(6)	2.136(4)
Pd(1)-P(1)	2.247(2)	2.2585(16)
C(1)-Pd(1)-N(1)	81.3(4)	81.7(2)
C(1)-Pd(1)-O(1)	173.4(3)	171.2(2)
C(1)-Pd(1)-P(1)	92.6(3)	94.62(19)
N(1)-Pd(1)-O(1)	93.7(3)	90.94(19)
N(1)-Pd(1)-P(1)	171.4(2)	175.38(15)
O(1)-Pd(1)-P(1)	92.77(16)	92.48(13)

The deviation from the planar coordination has been quantified by measurement of the improper torsion angles.[26] The values in the crystal of **4cm**, dimeric with symmetry, are w_1 = -4.87º and w_2 = -2.56º while in the one from **6cm** the values found were w_1 = - 2.19º and w_2 = -3.50º. Thus, the ligand coordination around the Pd center is essentially planar in the two Pd complexes, with a slight tetrahedral distortion in the first one and square pyramidal in the second one. The Pd- Pd distance in **4cm** is 9.412 Å and the bite angle involving the C^N ligand is also close to 81º, similar to that found in analogous complexes.[15a]

Following the classification put forward by Dance and Scudder,[27] the conformation of the Pd-PPh_3 group can be described as a no *rotor* for both structures (T_1 = 5.44; T_2 = 41.26; T_3 = 56.35º and T_1 = - 76.11; T_2 = - 34.60; T_3 = - 16.90º respectively), based on the M-P-C_{ipso}-C torsion angle.

Catalytic studies

Phosphine-free Suzuki-Miyaura coupling of 5-iodo-2'-deoxyuridine with boronic acids at low temperature.

The synthesized palladium complexes were next to be employed as catalysts for Suzuki-Miyaura cross-coupling of nucleosides in neat water. To investigate the applicability of the complexes, it was necessary to first analyze the extent of water-solubility exhibited by them. The solubility of the complexes **1-6** in water was therefore determined and the results have been summarized below in Table 2.

Table 2: Water-solubility study for complexes 1-6.

Complex	Solubility in water at 298 K (mg/mL)[a]
1	10.47(0.05)
2	12.73(0.12)
3	20.57(0.05)
4	3.13(0.12)
5	2.73(0.17)
6	6.23(0.12)

[a]Mean value. Standard deviation (σ) in parenthesis, see SI for details.

Appreciable water-solubility could be observed for complexes **1-3** as the dimeric complexes with sulfonate groups have a higher affinity for water, while complexes **4-6** are less soluble, maybe due to the presence of hydrophobic aryl groups of the PPh_3 or the evolution to neutral species in solution. The stage, therefore, is set to test these complexes for Suzuki-Miyaura cross-coupling of nucleosides. Before we initiate these studies, it is important to understand the lacunae in literature for the modification of nucleosides that accordingly decided the applicability of the synthesized complexes.

a) Our research group has recently published a catalytic protocol involving Pd/PTABS system for carrying out nucleoside modification in neat water.[21b,c] However, despite the reactivity of the highly water-soluble system, reactions were performed at an elevated temperature of 80 ^{o}C. This would restrict the future application of the catalytic system to nucleosides with temperature-labile functional groups as well as the modification of nucleotides. The lability of the glycosidic bond also complicates the situation as lower temperatures favor better product formation.

b) Catalyst concentration has always been a cause of concern as high concentration employed in most literature protocols could be due to the possible coordination of the

heteroatom-rich backbone of the nucleosides. This was addressed to a certain extent by the Pd/PTABS system but any further reduction would be desirable.

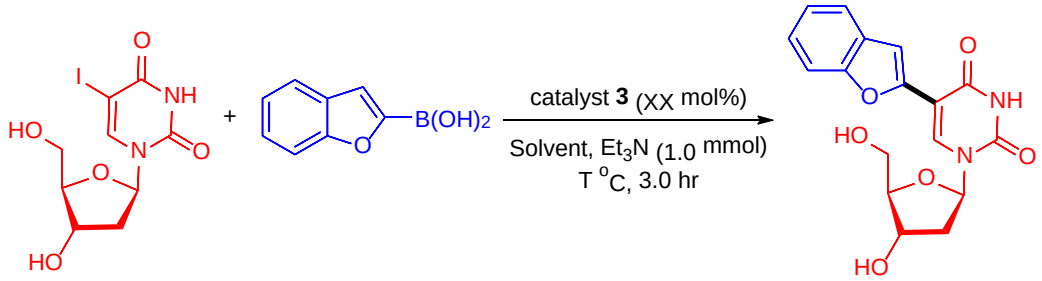
c) The requirement of an activating phosphine ligand for catalytic modification generates phosphine oxide as the by-product and in many processes would be an undesirable result. Difficulty in the removal of the generated by-product could also complicate the isolation process of the modified nucleosides. A phosphine-free catalytic system for promoting these transformations would be an attractive alternative to the existing options.

The synthesized and well-characterized phosphines-free palladacycles and their phosphines variants were next to be tested for the development of a low-temperature Suzuki-Miyaura protocol for 5-iodo-2'-deoxyuridine nucleoside.

Screening studies: We first investigated the coupling reaction of 5-iodo-2'-deoxyuridine with benzofuran-2-boronic acid using the various synthesized complexes.

Initial conditions for the screening of the complexes involved the reaction to be performed at 80 ^{o}C in H_2O:CH_3CN (2:1) (that is the most commonly used solvent system employed in catalytic Suzuki-Miyaura coupling of nucleosides) with triethylamine as the soluble base. All the six synthesized complexes were first employed to conduct the catalyst screening (at 1.0 mol% Pd concentration, Table 3).

Table 3: Catalyst screening studies[a,b]



7 (0.5 mmol) **8a** (0.75 mmol) **9a**

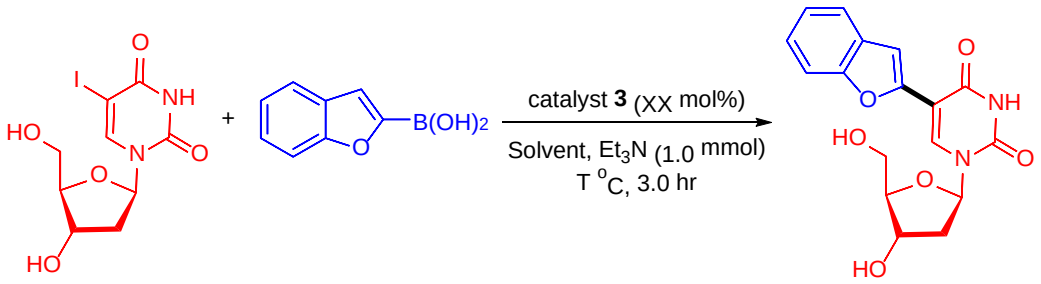
Catalyst[c]	Time	%Yield[b]
1	3.0 hrs	86
2	3.0 hrs	81
3	**3.0 hrs**	**90**
4	3.0 hrs	78
5	3.0 hrs	72
6	3.0 hrs	83

[a]Unless stated otherwise: 0.5 mmol of **7**, 0.75 mmol of **8a**, 1.0 mmol of Et_3N, CH_3CN:H_2O (3.0 mL); [b]isolated yields; [c] catalysts **1-3** (0.5 mol%) or catalysts **4-6** (1.0 mol%)

It was observed that the phosphines-free palladacyclic complex **3** performed better than other catalysts including the phosphine-based analogs possibly due to the generation of the catalytic active species at a faster rate than others. The presence of chloro group in the catalyst structural backbone could provide enhanced stability to the catalytically active Pd species thus formed. Better solubilization of complex **3** as evident from the solubility studies also could be an important factor in providing better yields. A series of screening parameters such as solvent, temperature, base, and catalyst concentration were also investigated (Table 4). Initially, CH_3CN:H_2O at 80 and 40 ^oC performed better (Entries 1 & 2, Table 4) compared to the use of CH_3N or H_2O (Entries 3 & 4, Table 4). However, an increase in temperature from 40 ^oC to 60 ^oC using H_2O as the

sole reaction solvent provided a competitive yield of the coupled product (Entry 5, Table 4). An increase in temperature for H_2O as the reaction solvent to 80 ^oC failed to provide any further improvement in yield (Entry 6, Table 4). It was therefore decided to continue the screening study in H_2O at 60 ^oC.

Table 4: Screening of complex 3 for Suzuki-Miyaura coupling in neat water.[a,b]



7 (0.5 mmol) **8a** (0.75 mmol) **9a**

Sr. No	5- IDU (eq)	Boronic acid (eq)	Catalyst (mol %)	Base (eq)	Solvent (ml)	Temp. (°C)	Yields (%)
1	1.0	1.5	0.5	NEt_3 (2.0 eq)	$CH_3CN:H_2O$	80	90
2	1.0	1.5	0.5	NEt_3 (2.0 eq)	$CH_3CN:H_2O$	40	90
3	1.0	1.5	0.5	NEt_3 (2.0 eq)	CH_3CN	40	52
4	1.0	1.5	0.5	NEt_3 (2.0 eq)	H_2O	40	55
5	**1.0**	**1.5**	**0.5**	**NEt_3 (2.0 eq)**	**H_2O**	**60**	**89**
6	1.0	1.5	0.5	NEt_3 (2.0 eq)	H_2O	80	87
7	1.0	1.5	0.5	K_3PO_4 (2.0 eq)	H_2O	60	80
8	1.0	1.5	0.5	K_2CO_3 (2.0 eq)	H_2O	60	84
9	1.0	1.5	0.5	Cs_2CO_3 (2.0 eq)	H_2O	60	71
10	1.0	1.5	0.5	DBU(2.0 eq)	H_2O	60	65
11	1.0	1.5	0.1	NEt_3 (2.0 eq)	H_2O	60	71
12	1.0	1.5	0.01	NEt_3 (2.0 eq)	H_2O	60	NR

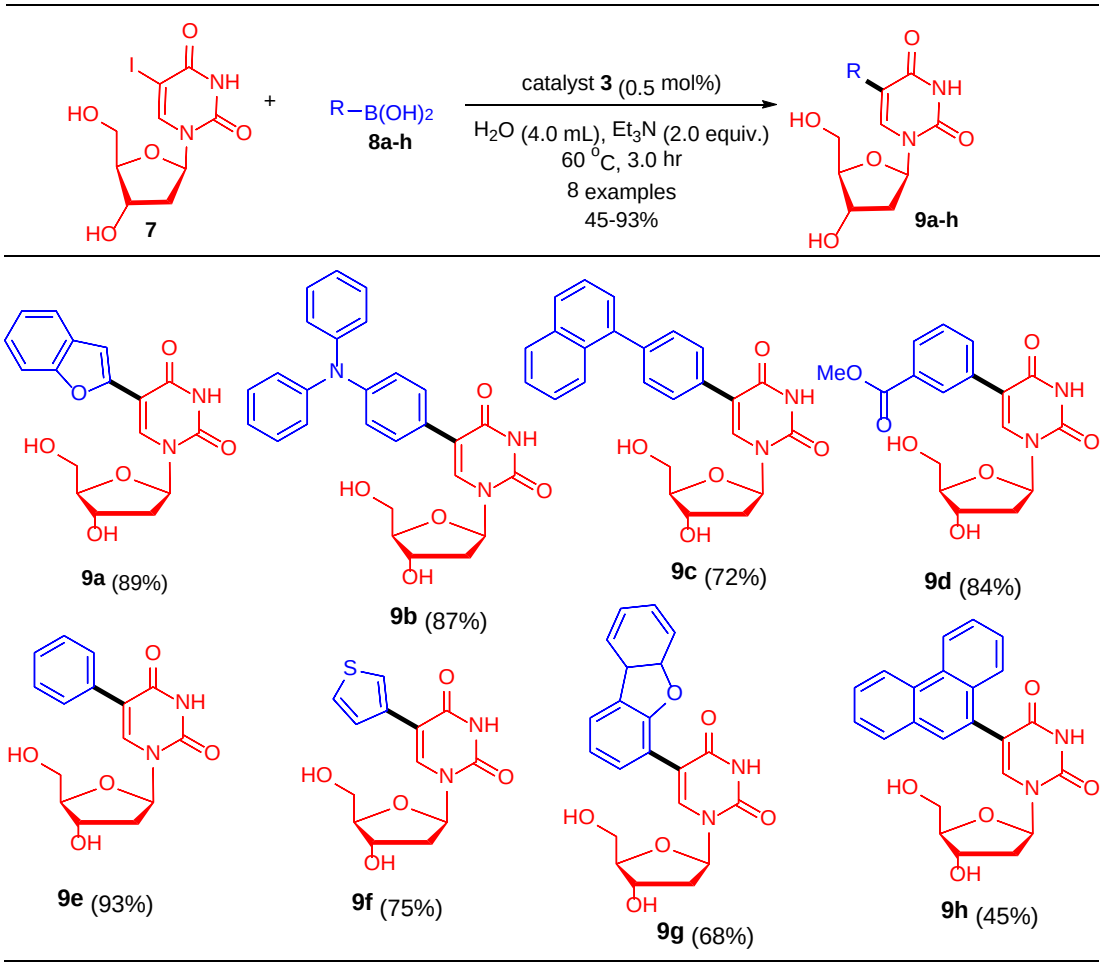
[a]Unless stated otherwise: 0.5 mmol of **7**, 0.75 mmol of **8a**, 1.0 mmol of Et_3N, H_2O (4.0 mL); [b]isolated yields

The base study was next to be conducted with Et_3N replaced by K_3PO_4, K_2CO_3, Cs_2CO_3, and DBU (Entries 7-10, Table 4). In all the cases, reactivity was found to be lower than that obtained for Et_3N. Finally, catalyst loading experiments were also

performed but the best result still was obtained with 0.5 mol% catalyst concentration of complex **3**. It is to be noted that 0.1 mol% of catalyst loading could also be possible at a comprised reactivity in cases where metal concentration needs to be restricted.

With this catalytic system in hand, the substrate scope for the modification of nucleoside was next undertaken. 5-Iodo-2'-deoxyuridine was subjected to Suzuki-Miyaura cross-coupling conditions using complex **3** (0.5 mol%) in H_2O as the reaction solvent at 60 ^oC with differently substituted arylboronic acids. Activating aryl and heteroaryl boronic acids provided good to excellent yields of the desired cross-coupled products. However, reduced yields were observed for bulky arylboronic acids such as tripehylamine, phenylnaphthyl, and phenanthrene, as displayed in Scheme 2.

Scheme 2: Substrate scope for phosphines-free Suzuki-Miyaura cross-coupling of 5-Iodo-2'-deoxyuridine.[a,b]

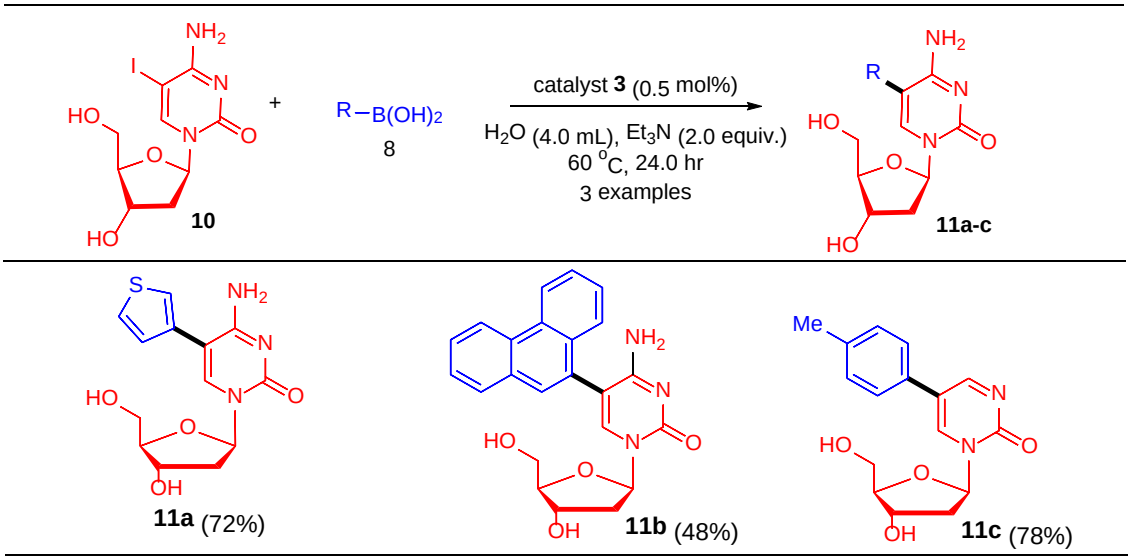


[a]Unless stated otherwise: 0.5 mmol of **7**, 0.75 mmol of **8a-h**, 1.0 mmol of Et_3N, H_2O (4.0 mL), complex 3 (0.5 mol%); [b]isolated yields.

Phosphine-free Suzuki-Miyaura coupling of 5-iodo-2'-deoxycytidine with boronic acids at low temperature

Successful cross-coupling of 5-iodo-2'-deoxyuridine with arylboronic acids allowed further exploration of the scope to incorporate 5-iodo-2'-deoxycytidine as a coupling partner in water as the solvent. Complex **3** furnished good yield of the cross-coupled 5-arylated 2'-deoxycytidine derivatives (two examples provided, Scheme 3) at 0.5 mol% catalyst loading in water as the sole reaction solvent.

Scheme 3: Substrate scope for phosphines-free Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxycytidine in water.[a,b]



[a]Unless stated otherwise: 0.5 mmol of **10**, 0.75 mmol of **8**, 1.0 mmol of Et_3N, H_2O (4.0 mL), complex 3 (0.5 mol%); [b]isolated yields.

Mechanistic studies of the Suzuki-Miyaura coupling of iodo nucleosides in water using complex 3.

At the start of the reaction, a yellow clear solution was observed, and as it progressed the reaction changed color to a dark solution, while on completion of the reaction black

particulate matter was found to be settled at the bottom of the reaction vessel. These observations point towards the possible involvement of a colloidal or nanoparticular catalytic species as the complex **3** as well as the related complex could easily dissociate to provide such an outcome. To investigate such a possibility, it was decided to subject the catalytic reaction to catalyst poisoning experiments and deduce the mechanistic pathway followed.

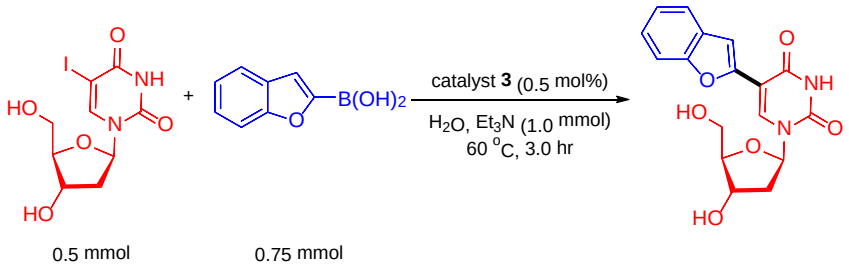
Whiteside's in the early 80's had put forth the simple and commonly applicable catalyst poisoning procedure known as mercury (Hg) drop experiment.[28] The addition of a drop of Hg at the start of the catalytic reaction would engulf any colloid/nanoparticles present in the catalytic solution amalgamating the palladium species. As a result, complete inhibition of the catalyst reactivity was observed in our case, as the catalytic active species was not available for promoting the cross-coupling process. Although it is a positive result pointing out a nanoparticular catalytic pathway, it is only the starting point and further experiments are needed to ascertain these observations.

Next, the carbon disulfide test involving the excess addition of carbon disulfide (CS_2) was undertaken. Sulfides are effective poisons for a variety of metal catalysts due to the strong and preferential binding to the metal center compared to other ligands.[29] The catalytic activity of the complex **3** was therefore found to be completely arrested again, supporting the involvement of a colloidal/nanoparticular pathway. On the other hand, the addition of tetra-n-butylammonium bromide (TBAB) is commonly employed in ligand-free catalytic reactions, as TBAB is an excellent stabilizer of the nanoparticles. An enhancement in catalytic reactivity, as it happened in our case, would also suggest the presence of naked Pd nanoparticles that could be effectively stabilized by TBAB. (Scheme 4a).[30]

All the above tests were directly related to the possible presence of nanoparticles in the solution, and typically occur by coordination/interaction to the nanoparticular surface. On the other hand, the Crabtree test[31] involves the employment of a bulky metal-coordinating ligand dibenzo[a,e]cyclooctatetraene (DCT) that is capable of displacing the accompanying ligands leading to the formation of a strong and preferential Pd-DCT complex (Scheme 4b). This acts as a specific sterically demanding poison for homogeneous catalytic species bringing about a reduction in catalytic activity, while heterogeneous or nanoparticular systems are not affected by the DCT coordination. In our case, it was observed that the reactivity of the catalytic system remained intact as no reduction in catalytic activity was observed, providing additional support of a nanoparticular pathway operating in our system.

Noteworthy, it has been reported[8b] for closely related phosphine-free Shaughnessy-type Pd complexes with five-membered rings that the catalytic process for the Suzuki couplings proceeds on Pd(0) nanoparticles (as proved by TEM analysis and experiments with stabilizes for nanoparticles TBAB and PVP). On the other hand Shaughnessy suggested that, in the presence of the phosphine ligand t-Bu-Amphos, the chloride-bridged analogue of **1** would form (t-Bu-Amphos)$_2$Pd(0) as homogeneous catalytically active species, [8a] although the displaced palladacycle ligand still had an effect in the activity and lifetime of these species.

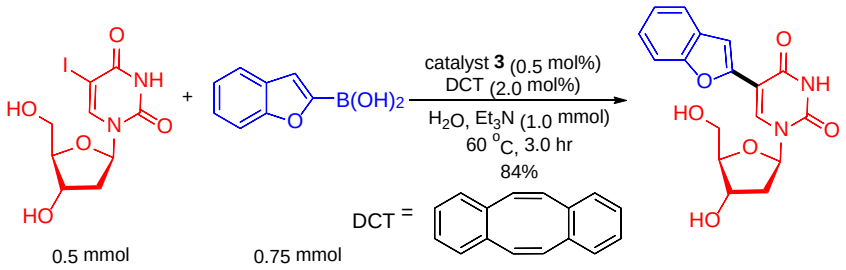
Scheme 4: **Poisoning tests and Crabtree tests to disclose the mechanistic pathway**



Complex	Additive	%Yield

3	Mercury drop (Hg)	0
3	Carbon disulphide (CS_2)	0
3	Tetra-*n*-butylammonium bromide (TBAB)	92

Crabtree test:



Conclusion

Water soluble dinuclear palladacycles that contain the orthometalated backbone sodium 4-(N-benzylideneamino)benzenesulfonate) and bridging acetate groups can be prepared by the straightforward classical route from palladium acetate. Their potential as synthetic precursors was demonstrated by bridging cleavage with neutral PPh_3. Besides, dinuclear complexes have revealed as excellent phosphine-free catalysts for the synthesis of functionalized nucleoside analogues involving a low temperature Suzuki-Miyaura coupling of 5-iodo-2'-deoxyuridine with different aryl boronic acids in neat water. Specifically, catalyst **3** has provided the following advantages in comparison to literature reports: phosphine-free complexes provide an excellent alternative to the phosphine-based catalytic systems; catalyst concentration is lower than most examples reported till date; catalytic reactions were achieved at a lower temperature than reported in literature either for phosphine-based or phosphine-free systems; with water as the sole reaction solvent, very few protocols provide a combination of catalyst properties as

exhibited by the synthesized complexes. Several catalyst poisoning experiments and a Crabtree test were conducted to get insight into the mechanism of the catalytic reaction, pointing out the likely nanoparticular nature of the pathway operating in our system. This would be in accordance with previously reported results for analogous phosphine-free dinuclear palladacycles claimed to act as a source of highly active palladium nanoparticles.

Experimental Section.

General Procedures. All catalytic reactions were conducted under an inert atmosphere of N_2 on a Schlenk line. Melting points were recorded on an electrothermal IA9000 Digital Melting Point Apparatus and are uncorrected. TLC analysis was performed on Merck 5554 aluminium backed silica gel plates and compounds visualized by ultraviolet light (254 nm), phosphomolybdic acid solution (5% in EtOH), or 1% ninhydrin in EtOH. ^{1}H NMR spectra of organic compounds were recorded at 270 MHz using a JEOL EX270 spectrometer or at 400 MHz using a JEOL ECX400 spectrometer; $^{13}C\{^{1}H\}$ NMR spectra at 67.9 or 100.5 MHz. Chemical shifts are reported in parts per million downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz).

C, H, and N analyses were carried out with a Leco CNHS-932 instrument. IR spectra were recorded on a Perkin-Elmer spectrophotometer 16F PC FT-IR, using Nujol mulls between polyethylene sheets. NMR spectroscopic data of complexes (^{1}H and $^{31}P\{^{1}H\}$) were recorded on Bruker Avance 200, 300 and 400 spectrometers. ESI-MS analyses were performed on an Agilent 6220 Accurate Mass TOF LC/MS. The ionization mechanism used was electrospray in positive and negative ion full scan mode using acetonitrile as solvent and nitrogen gas for desolvation. Specific conditions were 350ºC

of source temperature using ESI (electro-spray), 40psi nebulizer pressure and nitrogen gas for drying at 11 L/min. Scan source parameters: Fragmentor (175 V), skimmer (65V) and Vcap (3500V). Mobile phase: H_20/MeOH 25/75 with 5mM $HC00NH_4$ and 0.1% HCOOH. Flow rate: 0.4ml/min. TG and DTG curves were recorded on a Mettler TG-50 thermobalance using an atmosphere of pure nitrogen (50 cm^3 min^{-1}; heating rate 5 ºC min^{-1}). DSC curves were recorded on a DSC822e Mettler Toledo instrument.

Materials and methods. The 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 of the ligands: sodium salts of *N*-(R)benzylidene *para*-aminobenzenesulfonate (R = H, (L1); R = OMe, (L2); R = Cl, (L3)).

Sulfanilic acid (2.50 g, 14.4 mmol) was suspended in 40 mL of hot methanol and deprotonated by adding a previously prepared 10 mL solution of NaOH (0,57 g, 14.4 mmol, 1 equiv.). After 15 minutes stirring, the stoichiometric amount of the corresponding aldehyde was added to the clear solution and a white suspension was immediately formed. The mixture was the further stirred for 30 min. at room temperature and then concentrated and filtered. The crystalline white product was washed with methanol and acetone and dried under vacuum.

Sodium salt of *N*-benzylidene *para*-aminobenzenesulfonate (L1) (2.85 g, 70%). Anal. Found: C, 55.3; H, 3.9; N, 4.0; S, 11.5. Calc. for $C_{13}H_{10}NNaO_3S$: C, 55.1; H, 3.6; N, 4.9; S, 11.3. %. IR(cm^{-1}): 1625m, 1581m, 1473s, 1378m, 1242m, 1185m (SO_3), 1141m (SO_3), 1059m (SO_3), 849m, 736s, 723s, 641m, 574m, 565m. ^{1}H NMR. (400

MHz, $(CD_3)_2SO$) δ(ppm): 8.62 (s, 1H, N=CH), 7.94 (m, 2H, Ho-ald), 7.67 (d, 2H, Hm-sulf, *J*= 8.4 Hz), 7.51 (m, 3H, Hm, p-ald), 7.22 (d, 2H, Ho-sulf, *J*= 8.4 Hz). $^{13}C\{^1H\}$ NMR. (400 MHz, $(CD_3)_2SO$) δ(ppm): 161.0 (N=CH), 151.4, 146.0, 136.0, 131.6, 128.9, 128.7, 126.6, 120.2.

Sodium salt of *N*-(4-methoxi)benzylidene *para*-aminobenzenesulfonate (L2) (2.19 g, 51%). Anal. Found: C, 53.9; H, 4.0; N, 4.7; S, 10.3. Calc. for $C_{14}H_{12}NNaO_4S$: C, 53.7; H, 3.9; N, 4.5; S, 10.2. %. IR(cm^{-1}): 1610m, 1575m, 1477s, 1381s, 1309m, 1239m, 1189 m (SO_3), 1166m, 1138m (SO_3), 1055m, 1030m (SO_3), 853m, 736s, 628m, 581m. ^1H NMR. (400 MHz, $(CD_3)_2SO$) δ(ppm): 8.53 (s, 1H, N=CH), 7,88 (d, 2H, Ho-ald, *J*= 8.8 Hz), 7.61(d, 2H, Hm-sulf, *J*= 8.4 Hz), 7.16 (d, 2H, Ho-sulf, *J*= 8.4 Hz), 7.06 (d, 2H, Hm-ald, *J*= 8.8 Hz), 3.84 (m, 3H, OCH_3). $^{13}C\{^1H\}$ NMR (400 MHz, $(CD_3)_2SO$) δ(ppm): 161.9 (N=CH), 159.9, 153.6, 133.3, 130.3, 128.6, 127.6, 113.4, 113.1, 54.3.

Sodium salt of *N*-(4 chloro)benzylidene *para*-aminobenzenesulfonate (L3) (2.96 g, 65%). Anal. Found: C, 49.3; H, 3.0; N, 4.6; S, 10.3. Calc. for $C_{13}H_9ClNNaO_3S$: C, 49.1; H, 2.9; N, 4.4; S, 10.1. %. IR(cm^{-1}): 1625m, 1584m, 1375s, 1220m, 1185m (SO_3), 1128m (SO_3), 1100m, 1040m (SO_3), 1011m, 888m, 843m, 737s, 688m, 577m, 561m. ^1H NMR. (400 MHz, $(CD_3)_2SO$) δ(ppm): 8.64 (s, 1H, N=CH), 7.95 (d, 2H, Ho-ald, *J*= 8.8 Hz), 7.63 (d, 2H, Hm-sulf, *J*= 8.4 Hz), 7.58 (d, 2H, Hm-ald, *J*= 8.8 Hz), 7.21 (d, 2H, Ho-sulf, *J*= 8.4 Hz). $^{13}C\{^1H\}$ NMR (400 MHz, $(CD_3)_2SO$) δ(ppm): 159.8 (N=CH), 151.0, 146.2, 136.1, 134.8, 130.4, 129.0, 126.6, 120.3.

Synthesis of precursors $[Pd(\mu\text{-}AcO)(R\text{-}C\hat{}N\text{-}SO_3Na)]_2$ (R = H (1); OMe (2); Cl (3)).

Palladium acetate (500 mg (2.22 mmol) was suspended in hot glacial acetic acid (60 mL) and the stoichiometric amount of the corresponding Schiff base was added in one portion with stirring. The dark orange suspension formed was kept for 3 hours at reflux temperature and then cooled in the fridge for 1 hour. The orange·nCH_3COOH-solvated product was then isolated by filtration, washed with diethyl ether and acetone and air dried. It was then placed on a watch glass and left overnight in the air oven (150 **1**, 125 **2** and 180ºC **3**), yielding the desired desolvated yellow products.

[Pd(μ-AcO)(H-C^N-SO_3Na)]$_2$ (**1)** (0.98 g, 95%). Anal. Found: C, 40.6; H, 2.9; N, 3.1; S, 7.1. Calc. for $C_{30}H_{24}N_2Na_2O_{10}Pd_2S_2$: C, 40.2; H, 2.7; N, 3.0; S, 7.0. %. IR(cm^{-1}): 1586s, 1568vs, 1549s, 1197s (SO_3), 1137m (SO_3), 1045m (SO_3), 843s, 652s, 589m. ESI-MS (negative mode): calc. for $C_{14}H_{10}NO_5SPd$ [PdL1(formate)]-Na m/z 409.9320 (found 409.9319); calc. for $C_{27}H_{19}N_2O_8S_2Pd_2$ [Pd_2L1_2(formate)]-2Na m/z 776.8667 (found 776.8667). ^{1}H NMR. (400 MHz, CD_3OD) δ(ppm): 7.96 (s, 1H; N=CH), 7.56 (d, 2H, Hm-sulf; *J*= 8.4 Hz), 7.34 (d, 1H; Ho-ald, *J*=6.8 Hz), 7.07 (m, 1H; Hp-ald), 6.93 (m, 1H; Hm, ald), 6.80 (d, 2H; Ho-sulf, *J*= 8.4 Hz), 6.40 (d, 1H; Hm-ald, *J*= 8.0 Hz), 1.81 (s, 3H; AcO). ^{13}C{^{1}H} NMR. (300 MHz, CD_3OD) δ(ppm): 181.8 (C=O, AcO), 176.7 (N=CH), 155.9, 150.3, 147.3, 145.1, 133.0, 132.4, 129.9, 127.2, 125.7, 124.0, 24.2 (CH_3, AcO). $\overline{S}_{H2O,20\,°C}$ = 10.47 mg/mL.

[Pd(μ-AcO)(MeO-C^N-SO_3Na)]$_2$ (2) (0.86 g, 86%). Anal. Found: C, 40.6; H, 3.1; N, 3.0; S, 6.9. Calc. for $C_{32}H_{28}N_2Na_2O_{12}Pd_2S_2$: C, 40.2; H, 2.9; N, 2.9; S, 6.7. %IR(cm^{-1}): 1587m, 1562s, 1542m, 1273m, 1200s (SO_3), 1133m (SO_3), 1045m (SO_3), 847m, 808m, 640s, 593m. ESI-MS (negative mode): calc. for $C_{15}H_{12}NO_6PdS$ [PdL2(formate)]-Na m/z 439.9426 (found 439.9426), calc. for $C_{29}H_{23}N_2O_{10}Pd_2S_2$ [Pd_2L2_2(formate)]-2Na

m/z 836.8879 (found 836.8877). ^{1}H NMR. (300 MHz, CD_3OD) δ(ppm):7.73 (s, 1H; N=CH), 7.58 (d, 2H; Hm-sulf, *J* = 8.4 Hz), 7.28 (d, 1H; Ho-ald, *J* = 8.4 Hz), 6.71 (d, 2H; Ho-sulf, *J* = 8.4 Hz), 6.61 (d, 1H; Hm-ald, *J* = 8.4 Hz), 5.89 (s, 1H; Hm-ald), 3.55 (s, 3H; OCH_3), 1.80 (s, 3H; AcO). $^{13}C\{^{1}H\}$ NMR (300 MHz, CD_3OD) δ(ppm): 181.7 (C=O, AcO), 175.0 (N=CH), 162.3, 159.3, 150.2, 144.9, 139.9, 131.4, 126.9, 123.9, 117.2, 112.5, 56.0 (OCH_3), 24.2 (CH_3, AcO). $\bar{S}_{H2O,20\,°C}$ = 12.73 mg/mL.

[Pd(μ-AcO)(Cl-C^N-SO_3Na)]$_2$ (3) (1.06 g, 97%). Anal. Found: C, 37.6; H, 2.6; N, 3.2; S, 6.9. Calc. for $C_{30}H_{22}Cl_2N_2Na_2O_{10}Pd_2S_2$: C, 37.3; H, 2.3; N, 2.9; S, 6.6%. IR(cm^{-1}): 1582m, 1557s, 1536m, 1201s (SO_3), 1137s (SO_3), 1093m, 1049m (SO_3), 840m, 814m, 751m, 664m, 623s 589m. ESI-MS (negative mode): calc. for $C_{14}H_9ClNO_5SPd$ [PdL3(formate)]-Na m/z 445.8921 (found 445.8931);. calc. for $C_{27}H_{17}Cl_2N_2O_8S_2Pd_2$ [Pd_2L3_2(formate)]-Na m/z 844.7875 (found 844.7870). ^{1}H NMR. (300 MHz, CD_3OD) δ(ppm): 7.92 (s, 1H; N=CH), 7.78 (d, 2H; Hm-sulf, *J* = 8.4 Hz), 7.28 (d, 1H; Ho-ald, *J* = 8.1 Hz), 7.13 (d, 1H; Hm-ald, *J* = 8.1 Hz), 6.90 (d, 2H; Ho-sulf, *J* = 8.4 Hz), 6.48 (s, 1H; Hm-ald), 1.69 (s, 3H; AcO). $^{13}C\{^{1}H\}$ NMR .(300 MHz, CD_3OD) δ(ppm): 182.6 (C=O), 176.0 (N=CH), 157.3, 149.5, 145.9, 137.5, 132.9, 130.9, 128.3, 127.5, 126.1, 124.1, 24.1 (CH_3, AcO). $\bar{S}_{H2O,20\,°C}$ = 20.57 mg/mL.

Preparation of complexes [Pd(*R-C^N-SO_3Na*)(AcO)(PPh_3)] [R = H (4), MeO- (5) or Cl-(6)].

The new complexes were obtained by treating 0.07 g of the appropriated precursor [Pd(μ-AcO)(R-C^N-SO_3Na)]$_2$ (R = -H (**1**); -OMe (**2**) or -Cl (**3**)) dissolved in MeOH (10 mL)with the stoichiometric amount of triphenylphosphine (molar ratio 1:2) previously dissolved in 5 mL MeOH. The resulting solution was stirred for 30 min, then filtered through a short celite column and concentrated until *ca.* one fifth of the initial volume. Slow addition of diethyl ether completed the precipitation of the title complexes, which were filtered off, washed with ether and air-dried.

[Pd(C^N-SO_3Na)(AcO)(PPh_3)] (4) (0.055 g, 50%). Anal. Found: C, 56.0; H, 4.0; N, 2.1;S, 4.6.Calc. for $C_{33}H_{27}NNaO_5PPdS$: C, 55.8; H, 3.8; N, 2.0; S, 4.5%. IR (cm^{-1}):ν(C=O) 1585s br, 1197s (SO_3), 1129s (SO_3), 1038m (SO_3); ν(PPh_3) 537, 518. ESI-MS (positive mode): calc. for $C_{31}H_{25}NO_3PPdS$ [PdL_1PPh_3 +1] - Na m/z 628.0338 (found 628.0323). ^{1}H NMR. (300 MHz, CD_3OD) δ(ppm): 8.34 (d, 1H, N=CH, *J*=6.9Hz), 7.72 (d, 2H, Hm-sulf, *J*= 8,4 Hz), 7.65 (m, 6H, 5H, PPh_3 + 1H, Ho-ald), 7.52 (m, 1H, Hp-ald), 7.39 (m, 5H, 4H, PPh_3 + 1H, Ho-ald), 7.29 (m, 8H, 6H, PPh_3 + 2H, Ho-sulf), 6.86 (m, 1H, Hm-ald), 0.99·s, 3H, AcO).^{31}P NMR{^{1}H} (300 MHz, CD_3OD) δ(ppm):42.40. $\bar{S}_{H2O,20\,°C}$ = 3.13 mg/mL.

[Pd(MeO-C^N-SO_3Na)(AcO)(PPh_3)] (**5**) (0.084 g, 77%). Anal. Found: C, 55.5; H, 4.1; N, 2.0;S, 4.4.Calc. for $C_{34}H_{29}NNaO_6PPdS$: C, 55.2; H, 3.9; N, 1.9;S, 4.3%. IR (cm^{-1}):ν(C=O) 1582s br, 1199s (SO_3), 1100s (SO_3), 1030m (SO_3); ν(PPh_3) 528, 512. ESI-MS (positive mode): calc. for $C_{32}H_{27}NO_4PPdS$ [PdL_2PPh_3 +1] - Na m/z 658.0445 (found 658.0446). ^{1}H NMR. (300 MHz, CD_3OD) δ(ppm): 8.09 (d, 1H, N=CH, *J*=6.0Hz), 7.66 (m, 6H, 4H PPh_3 + 2H Hm-sulf), 7.40 (m, 3H, PPh_3), 7.30 (m, 7H, 6H,

PPh_3 + 1H, Ho-ald), 7.10 (dd, 2H, Ho-sulf, *J1*=2.0 Hz *J2*=2.0 Hz), 6.34 (dd, 1H, Hm-ald; *J1*=2,4 Hz, *J2*=2,4 Hz), 5.88 (dd, br; 1H, Hm-ald; *J1*=2,4 Hz *J2*=2,4 Hz), 3.63 (s, 3H, OCH_3), 0.88 (s, 3H, AcO).^{31}PNMR{^{1}H} (300 MHz, CD_3OD) δ(ppm):42.09. $\bar{S}_{H2O,20\,°C}$ = 2.73 mg/mL.

[Pd(Cl-C^N-SO_3Na)(AcO)(PPh_3)] (**6)** (0.069 g, 63%). Anal. Found: C, 53.5; H, 3.6; N, 2.0; S, 4.5.Calc. for $C_{33}H_{26}ClNNaO_5PPdS$: C, 53.2; H, 3.5; N, 1.9; S, 4.3%. IR (cm^{-1}):ν(C=O) 1572s br, 1540m, 1194s (SO_3), 1127m (SO_3), 1037m (SO_3); ν(PPh_3) 543, 509. ESI-MS (positive mode): calc. for $C_{31}H_{24}ClNO_3PPdS$ [PdL_3PPh_3 +1] - Na m/z 663.9937 (found 663.9927). ^{1}H NMR. (300 MHz, CD_3OD) δ(ppm): 8.37 (d, 1H, N=CH, *J*=6.1Hz), 7.67 (m, 8H, 6H PPh_3 + 2H Hm-sulf), 7.36 (m, 12H, 9H, PPh_3 + 1H, Ho-ald + 2H, Ho-sulf), 6.88 (dd, 1H, Hm-ald, *J1*= 2,1 Hz *J2*=1,8 Hz), 6.29 (dd, 1H, Ho-ald, *J1*= 1,8 Hz *J2*=1,8 Hz), 0.87 (s, 3H, CH_3). ^{31}P{^{1}H}NMR (300 MHz, CD_3OD) δ(ppm): 40.07. $\bar{S}_{H2O,20\,°C}$ = 6.23 mg/mL.

Data related to nucleosides:

General procedure for Suzuki-Miyauracross-coupling of 5-iodo-2´-deoxyuridine with arylboronic acids: A solution of precatalyst **3** (0.5 mol%) in degassed H_2O (4 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 60 ºC. Thereafter, 2-benzofuranyl boronic acid (120 mg, 0.75 mmol) was added along with Et_3N (1.0 mmol). The resulting solution was then stirred at 60 °C for 3.0 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 in 89% yield (153 mg).

General procedure for Suzuki-Miyaura cross-coupling of 5-iodo-2´-deoxycytidine with arylboronic acids: A solution of precatalyst **3** (0.5 mol%) in degassed H_2O (4.0 mL) was stirred for 5 min at ambient temperature under N_2. Then, 5-iodo-2´-deoxycytidine (176 mg, 0.5 mmol) was added and the solution stirred for 5 min at 60 ^oC. Thereafter, 3-thiopheneboronic acid (0.75 mmol) was added along with Et_3N (1.0 mmol). The resulting solution was then stirred at 60 °C for 24.0 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 (95:5) to afford the desired product as a white solid in 72% yield (110 mg).

General procedure for Mercury (Hg) poisoning study

A solution of precatalyst **3** (0.5 mol%) in degassed H_2O (4.0 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 60 ^oC. Thereafter, 2-benzofuranylboronic acid (0.75 mmol) was added along with Et_3N (1.0 mmol). Mercury (Hg) (0.15 mmol, 30 mg) was then added (at the start of the reaction) and the reaction was stirred at 60 ^oC for 3 h. On completion of the stipulated time, TLC analysis of the reaction mixture revealed no progress in the reaction, thus suggesting complete inhibition of the catalytic reaction.

General procedure for carbon disulphide poisoning study

A solution of precatalyst **3** (0.5 mol%) in degassed H_2O (4.0 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 60 ^{o}C. Thereafter, 2-benzofuranylboronic acid (0.75 mmol) was added along with Et_3N (1.0 mmol). Carbon disulfide (CS_2) (0.25 mL, 5 mmol) was then added (**at the start of the reaction**) and the reaction was stirred at 60 ^{o}C for 3 h. On completion of the stipulated time, TLC analysis of the reaction mixture revealed no progress in the reaction, thus suggesting complete inhibition of the catalytic reaction.

General procedure for tetra-n-butylammonium bromide (TBAB) study

A solution of precatalyst **3** (0.5 mol%) in degassed H_2O (4.0 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 60 ^{o}C. Thereafter, 2-benzofuranylboronic acid (0.75 mmol) was added along with Et_3N (1.0 mmol). TBAB (0.161 g, 0.5 mmol, 1.0 equiv.) was then added to the reaction mixture and the resulting solution was then stirred at 60 °C for 3.0 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.

Crabtree Test:

A solution of precatalyst **3** (0.5 mol%) in degassed H_2O (4.0 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 60 ^{o}C. Thereafter, 2-benzofuranylboronic acid (0.75 mmol) was added along with Et_3N (1.0 mmol). After 15 min, DCT (0.002 g, 1 x 10^{-2} mmol) was then added to the reaction mixture and the resulting solution was then stirred at 60 °C for 3.0 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.

X-ray Data Collection, Structure Solution, and Refinement for 4cm and 6cm.

X-ray data were collected with a Bruker D8 QUEST. Data were collected at 100(2) and 133(2) K for **4cm** and **6cm** respectively, using Mo Kα radiation (Kα = 0.71073 Å). The strategy for the data collection was evaluated using the APEX2 (Bruker, 2013) software. The data were collected by the standard "omega scan techniques" and were scaled and reduced using SAINT (Bruker, 2013) software. The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares with SHELXL-97, refining on F2 (Table 5).[32]

CCDC 1973979 for **4cm** and 1973980 for **6cm** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Table 5. X-ray Data Collection Parameters for 4cm and 6cm

	4cm	**6cm**
formula	$C_{31}H_{24}NO_3PPdS$	$C_{32}H_{26}NO_4ClPPdSNa\cdot 2H_2O$
fw	627.94	752.44
cryst color, habit	colourless, block	coolourless, prism
cryst size (mm)	0.18 x 0.18 x 0.18	0.16 x 0.14 x 0.09
cryst syst	monoclinic	Triclinic
space group	P21/c (#14)	P-1 (#2)
a (Å)	9.7232(8)	9.2792(5)
b (Å)	28.575(2)	10.9951(7)
c (Å)	10.8223(9)	18.4733(11)
α (º)	90	77.442(2)
β (º)	112.621(3)	75.440(2)

γ (°)	90	88.903(2)
V (Å^3)	2775.5(4)	1779.32(18)
Z value	4	2
D_{calcd} (g/cm^3)	1.503	1.404
F_{000}	1272	764
no. of reflns measd	73077	122745
no. of observations	2256	6418
no. of variables	347	413
R1	0.0515	0.0691
wR2	0.1552	0.2086
goodness of fit	1.056	1.107

Supporting Information.

The NMR characterization of the catalysis products and figures giving spectra for those organic compounds **9a-h** and **11a-c** detailed in Schemes 2 and 3. Representative NMR stability studies and characterization of reported complexes by ESI-MS and thermogravimetric curves of solvated samples of **1-3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes.

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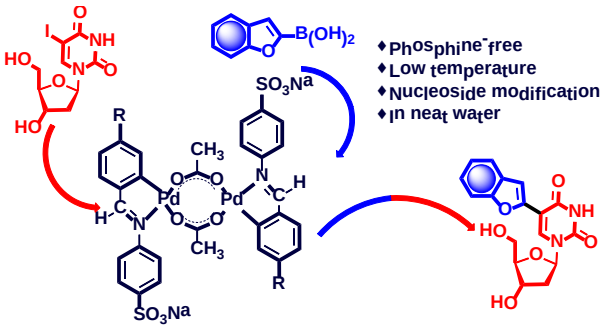

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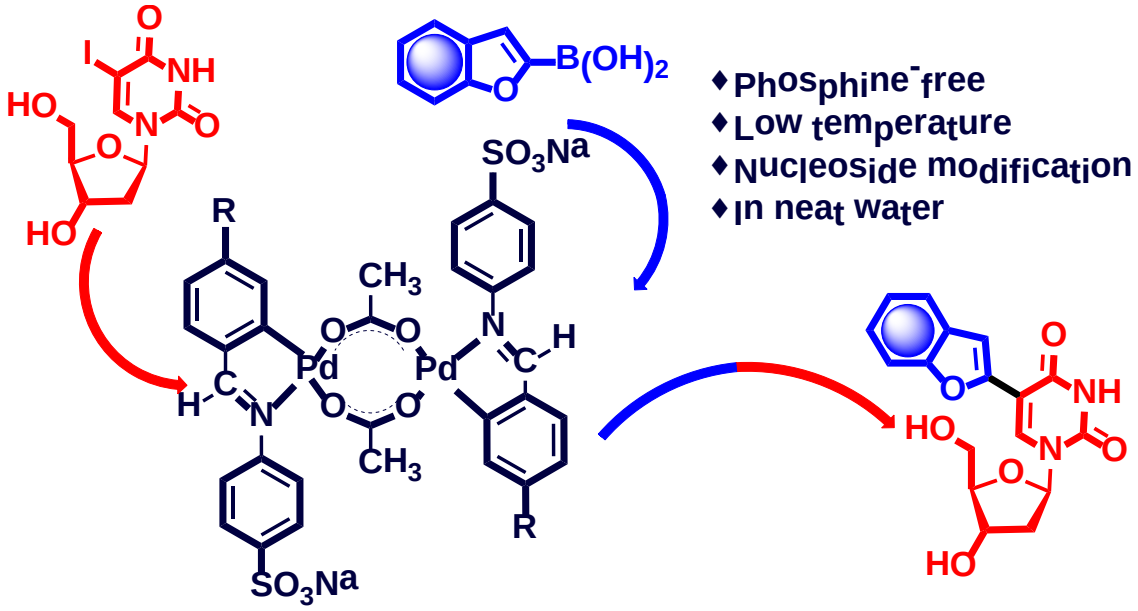

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