Quadrol-Pd(II) complexes: phosphine-free precatalysts for the room-temperature Suzuki-Miyaura synthesis of nucleoside analogues in aqueous media

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Abstract

Commercially available Quadrol, *N*,*N*,*N*',*N*'-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN), has been used for the first time as N^N- donor neutral hydrophilic ligand in the synthesis and characterization of new water soluble palladium (II) complexes containing chloride, phthalimidate or saccharinate as co-ligands. [$PdCl_2$(THPEN)] (**1**) [Pd(phthal)$_2$(THPEN)] (**2**), [Pd(sacc)$_2$(THPEN)] (**3**) and the analogous complex with the closely related *N*,*N*,*N*',*N*'-tetrakis(2-hydroxyethyl)ethylenediamine (THEEN) [Pd(sacc)$_2$(THEEN)] (**4**) were efficiently prepared in a one-pot reaction from [$PdCl_2(CH_3CN)_2$] or Pd(OAc)$_2$. Structural characterization of **1** and **3** by single crystal X-ray diffraction produced the first structures reported to date of palladium complexes with Quadrol. The resultant palladium complexes are highly soluble in water and were found to be effective as phosphine-free catalysts for the synthesis of functionalized nucleoside analogues under room-temperature Suzuki-Miyaura cross-coupling conditions between 5-iodo-2'-deoxyuridine (& 5-iodo-2'-deoxycytidine) with different aryl boronic acids in neat water. This is the first report of the coupling process performed on nucleosides in water at room temperature.

Introduction

The use of water-soluble catalysts in biphasic organic/aqueous systems, and in less extent in neat water, has received during the last two decades increasing attention from industry and academia.[1] Along with producing environmentally respectful processes, it has additional practical advantages, like the simple extractive work-up that allows the separation of the catalyst in the aqueous phase from the water insoluble organic product.

The incorporation of ligands containing hydrophilic substituents, with a double function of improving the stability and solubility of the homogeneous catalysts in water, has been the main approach to keep these metallic complexes into the aqueous phase, and the commercial availability of such ligands has undoubtedly set the pace of the progress in the field of transition metal-catalyzed reactions in aqueous media.[1,2]

The three main categories of hydrophilic ligands are, as presented in the pivotal review by Shaughnessy,[2a] hydrophilic phosphines, nitrogen ligands and *N*-heterocyclic carbenes, ordered by chronological development and its relevance back then in 2009.

Indeed, sulfonated triphenylphosphine ligands focused the first general studies[3] and still today hydrophilic phosphorus ligands, of course including sterically demanding hydrophilic trialkyl and dialkylbiarylphosphines attract continuous interest.[4] Regarding Pd complexes, from Casalnuovo´s TPPMS/$Pd(OAc)_2$ seminal system[5] to more recent examples,[6] these ligands have also been playing a significant role in palladium-catalyzed reactions carried out in water.[7] Besides the ubiquitous sulfonate, other ionic substituents like carboxylate, phosphonate or ammonium are commonly uses as water-solubilizing groups attached to the three main categories of ligands above mentioned.[2a,8] Polyols and related non-ionic hydrophilic substituents have also been used. although to a lesser extent.[2a] Thus, recent advances in this field have employed neutral hydroxyalkyls, polyethylene glycols, thioureas or phosphonate esters, either attached at electrophilic or nucleophilic sites on prefunctionalized ligands.[4]

So far, when it comes to Pd-catalyzed cross-coupling reactions, hydrophilic nitrogen ligands have received lesser attention than phosphines. Bipyridine ligands that yield stable complexes, are much less electron donating than phosphines, and it is known that amines usually coordinate weakly to palladium producing complexes of low stability.[7] Even so, and since nitrogen-based ligands offer a lower cost and toxicity

alternative, there is a continued interest in its development, and again the use of neutral hydrophilic N-donor ligands is scarce when compared with the incorporation of those usual anionic/cationic solubilizing groups.[2a] Thus, just a few examples using ethylenediamine tetracetic acid (EDTA)[9] and *N*,*N*,*N*',*N*'-Tetra(2-hydroxyethyl)ethylene diamine (THEEN)[10] as ligands for palladium-catalyzed Suzuki coupling of aryl bromides in water have been reported to date. [$PdCl_2$(THEEN)] has also been used as water-soluble catalyst in Heck coupling reactions[11] but, to the best of our knowledge, there are no examples of Pd complexes with commercially available Quadrol, *N*,*N*,*N*',*N*'-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN), like the ones we present here as promising water-soluble catalysts.

Nevertheless, the coordination chemistry of THPEN has indeed been explored with other metal. Thus, complexes of copper(II) ion with neutral THPEN were first reported in 1957[12] and have been the object of subsequent studies since then,[13] due to their antimicrobial properties[14] and the wide use of Quadrol as a ligand in solutions of electroless copper plating.[15] The coordination modes of this tetrapodal ligand has been studied in several complexes with Na(I), Ca(II), Sr(II) and Ba(II) extensively characterized by X-ray diffraction and DFT,[16] and a few silver complexes,[17a] some with antimicrobial activity have been recently reported.[17b] The use of THPEN as ligand has also been scarcely explored with other metal ions like cobalt(II)[18, 19], zinc(II) and lead(II)[19] or titanium(IV).[20] It is noteworthy that, since Quadrol was claimed to display biological activity in the 80s as an immunostimulant implicated as a potentially useful agent in accelerated wound healing[21], it has been profusely used in the cosmetic industry under different names (Quadrol, NEUTROL®TE or Tetrahydroxypropyl Ethylenediamine (THPE)) in slimming products[22] or as anti-aging agent.[23]

Water-solubility of the catalyst is a key parameter when it comes to the modification of biologically relevant molecules like nucleosides or amino acids that form a part of biopolymers such as DNA (RNA) or proteins. Nucleosides in this regard are privileged scaffolds and the functionalization of the base is commonly undertaken for the improvement of their photophysical properties.[24] Modification of these nucleoside structural features is done effectively by the employment of several C─C bond formation technologies such as Suzuki-Miyaura cross-coupling, C─H bond functionalization, Heck coupling and others[24]. Diversely substituted nucleoside analogues can exhibit promising photophysical properties and have the potential to perform as useful biological to fluorescent probes[25]. Such methodologies have also found applications in transforming these simple building-blocks into potential antiviral, anticancer drug candidates and oligonucleotides.[26]

Suzuki-Miyaura cross-coupling, amongst other coupling processes, is a versatile reaction involving the coupling of substrates with boronic acids as readily available and easy to handle nucleophilic reagents. Excellent functional group tolerance and the ease of performing the reactions under mild conditions makes Suzuki-Miyaura reaction the preferred choice for the modification of substrates containing sensitive functionalities. It is also one of the reasons for the extensive application of these coupling reactions in the modification of nucleosides.[27] Indeed, the past decade has seen a substantial rise in the development of efficient catalytic protocols for the modification of nucleosides, especially the 2'-deoxyuridine -based precursor, 5-iodo-2'-deoxyuridine, under Suzuki-Miyaura cross-coupling conditions with a wide variety of arylboronic acids.[28] Over the past several years, our research groups have been involved in the development of efficient catalytic systems for the modification of heteroarene core structures including nucleosides.[29]

Most catalytic processes in the past have been plagued with the problem of employing complexes containing phosphine ligands that led to the formation of phosphine oxide byproduct. This could be detrimental for their employment in the modification of biologically relevant nucleosides and a phosphine-free catalytic variant would be helpful in solving this problem. We have recently reported a catalytic system that was able to address this issue by the introduction of a phosphine-free palladacycle that was able to catalyze Suzuki-Miyaura coupling in water as the sole reaction solvent at 60°C.[30] However, our interest of achieving an ambient temperature catalytic protocol for nucleosides with the aim of applying such conditions further for the late-stage modification of oligonucleotides, DNA or RNA remains unfulfilled.

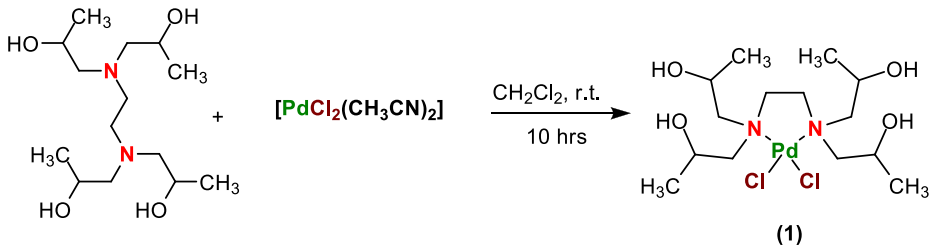
Room temperature Suzuki-Miyaura cross-coupling[31] of 6-iodouridine has been described under aqueous conditions,[32,33] however the functionalization of the 5-iodo-2'-deoxyuridine or 5-iodo-2'-deoxycytidine at ambient temperature is still elusive. We therefore present herein the first report of water-soluble *N*,*N*,*N*',*N*'-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN) palladium(II) complexes, their X-ray characterization and the application of the developed phosphine-free complexes in the first room-temperature Suzuki-Miyaura coupling, in water as the sole reaction solvent, of 5-iodo-2'-deoxyuridine and 5-iodo-2'-deoxycytidine with a variety of aryl boronic acids.

Results and discussion

Synthesis and characterization

[$PdCl_2$(THPEN)] (**1**) was obtained by the dropwise addition of an equimolar dichloromethane solution of *N*,*N*,*N*',*N*'-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN) to a stirred solution of the labile precursor [$PdCl_2(MeCN)_2$] in the same

solvent (Scheme 1). Synthetic details and characterization by analytical and spectroscopic techniques of new complexes **1-4** are collected in the Experimental Section.



Scheme 1. Synthesis of [$PdCl_2$(THPEN)] (**1**).

The IR spectra of **1** displayed the expected -OH bands for the incoming THPEN ligand above 3000 cm^{-1}, while the disappearance of acetonitrile signals in both IR (around 2300 cm^{-1}) and NMR provided quick evidence of reaction completion. Here a crowded aliphatic region with satisfactory integration was observed above the clearly identified CH_3- broad signal. A general splitting and downfield shift of resonances if compared with the free THPEN spectrum is observed, as previously reported for the related complex with THEEN.[10] ESI-MS spectrometry analysis (+ve mode) showed the expected fragmentation pattern with the loss of one or two chlorides, supporting the proposed formulae that was also confirmed by the single crystal X-ray diffraction structure of **1** (Figure 1). This study constitutes the first report of a Pd complex with *N*,*N*,*N*',*N*'-tetrakis(2-hydroxypropyl)ethylenediamine, as searched in the webCSD, the on line portal to the Cambridge Structural Database.

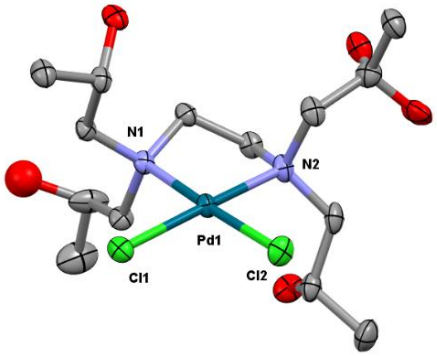


Figure 1. Thermal ellipsoid plot of the crystal structure of **1**, drawn at the 50% probability level. The hydrogen atoms have been omitted for clarity.

Suitable crystals were obtained by slow evaporation of a methanol solution. Crystal structure contains two diastereomers: SRSR (45%) and SSSR (55%); the two positions for O4 in the refinement accounts for them. Regarding the crystal packing, two molecules related by a center of symmetry are connected by two hydrogen bonds (O•••O distance 2.611(14) Å). This "pair" is part of a 3D network linked by O-H•••O and O-H•••Cl contacts, each molecule is surrounded by four closest as it is shown in Figure 2.

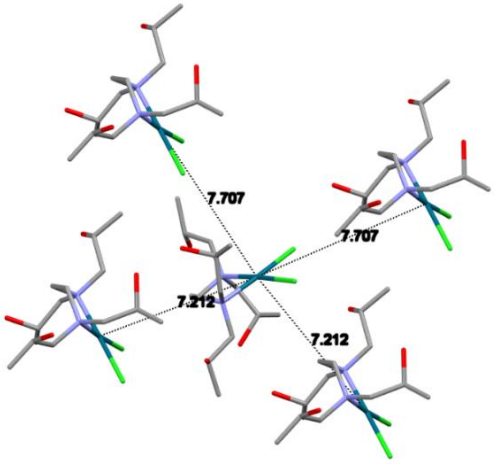


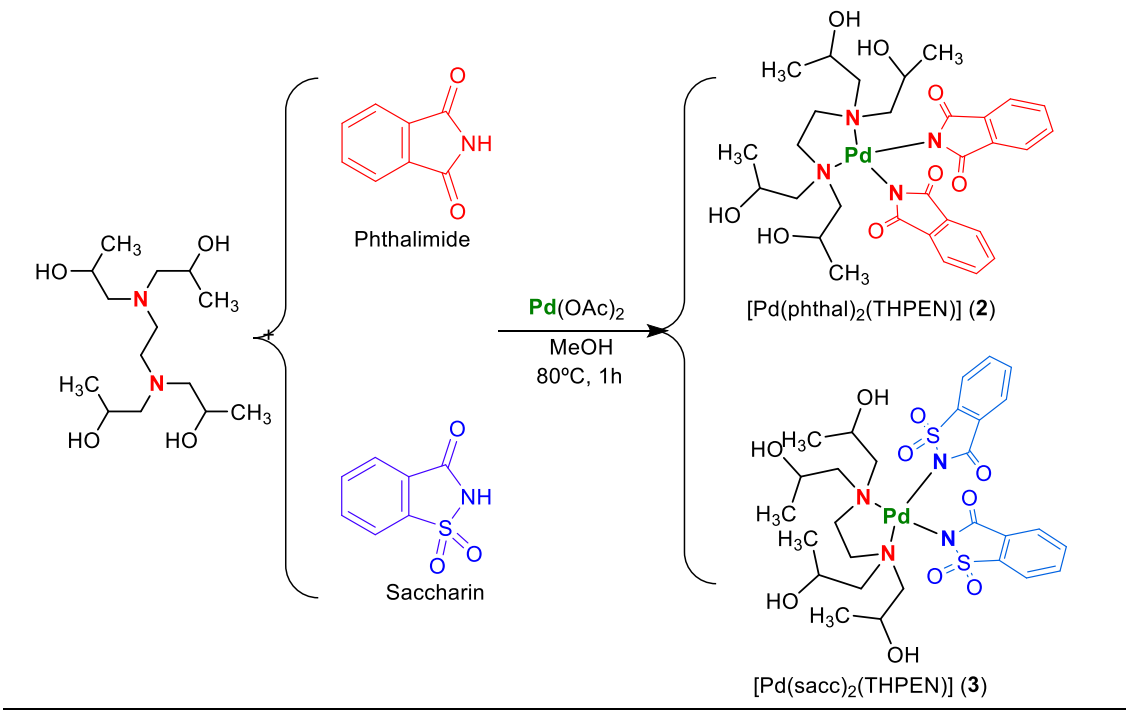
Figure 2. Crystal packing in **1.** Pd···Pd distances are 7.212(1) and 7.707 (1) Å.

The deviation from the planar coordination has been quantified by measurement of the improper torsion angles,[34] (w_1 = 2.1(1)º and w_2 = 0.0(1)º). Thus, the ligand coordination around the Pd center is essentially planar with a slight tetrahedral distortion. Pd-N and Pd-Cl distances, as well as the small N(1)-Pd(1)-N(2) bite angle are very similar to those reported for the related THEEN complex[10], and are collected in Table 1.

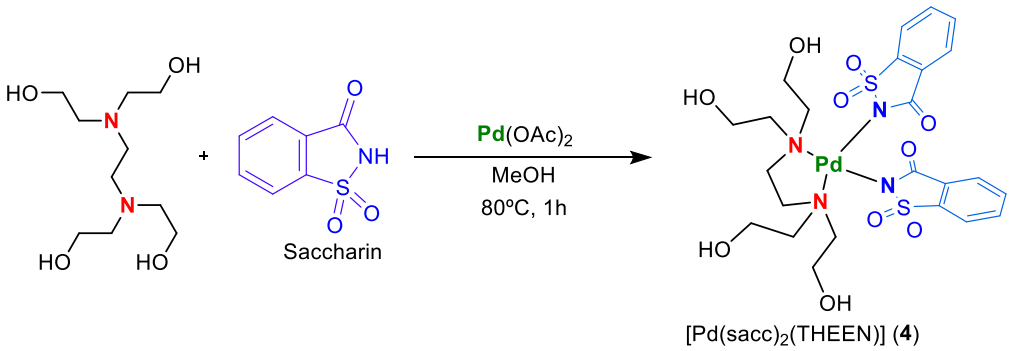
Table 1. Selected Bond Distances and Angles for 1 and 3

Complex 1		**Complex 3**	
Pd(1)-Cl(1)	2.296(2)	Pd(1)-N(1)	2.065(3)
Pd(1)-Cl(2)	2.322(2)	Pd(1)-N(2)	2.069(3)
Pd(1)-N(1)	2.096(5)	Pd(1)-N(3)	2.083(3)
Pd(1)-N(2)	2.107(5)	Pd(1)-N(4)	2.081(3)
N(1)-Pd(1)-N(2)	85.5(2)	N(1)-Pd(1)-N(2)	88.8(1)
N(1)-Pd(1)-Cl(1)	92.4(1)	N(1)-Pd(1)-N(4)	175.6(1)
N(2)-Pd(1)-Cl(1)	176.5(1)	N(2)-Pd(1)-N(4)	92.9(1)
N(1)-Pd(1)-Cl(2)	177.0(1)	N(1)-Pd(1)-N(3)	91.8(3)
N(2)-Pd(1)-Cl(2)	91.5(1)	N(2)-Pd(1)-N(3)	177.7(1)
Cl(1)-Pd(1)-Cl(2)	90.6(1)	N(4)-Pd(1)-N(3)	86.7(1)

A novel one-pot synthetic route starting from $Pd(OAc)_2$, allowed the preparation of THPEN/imidate complexes **2** and **3** as displayed in Scheme 2. Saccharinate complex **4** with THEEN instead was prepared in a similar way (Scheme 3). Again, IR spectroscopy offered a quick monitoring of the reaction by checking carbonyl and hydroxyl regions, and ESI-MS showed the same pattern found for complex **1**, with M^+- imidate fragments instead. Regarding ^{1}H-NMR, the usual aliphatic-quadrol region is accompanied by new resonances around 7.5 ppm that support the presence of the incoming saccharinate/phathalimidate ligands.



Scheme 2. One pot synthesis of (**2**) and (**3**) in methanol.



Scheme 3: One-pot synthesis of complex **4**.

Slow diffusion from an acetone/n-heptane mixture produced single crystals of **3** that were subjected to an X-ray study (Figure 3). The molecule in the crystal structure is the SRRR diastereomer. As the space group is centrosymmetric, crystal also contains the enantiomer RSSS. A tetrahedral distortion from the planar coordination is observed (w_1 = - 1.54 (9)º and w_2 = - 3.02(9)º). Relevant bond distances and angles are collected in Table 1.

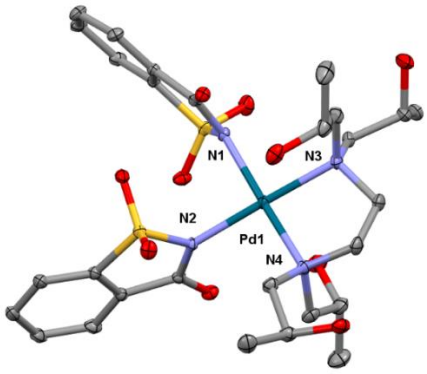


Figure 3. Thermal ellipsoid plot of the crystal structure of **3**, drawn at the 50% probability level. The hydrogen atoms have been omitted for clarity.

Saccharinate ligands show an *anti*-configuration. C=O groups show short non-covalent intramolecular contacts with two OH groups (O•••O distances: 2.721(4) Å and 2.770(5) Å). In saccharinate complexes, it has been reported that C=O group produces shorter supramolecular interactions than SO_2,[35] the deprotonated nitrogen (N-) and carbonyl group have been reported[36] as the groups able to make the strongest synthons.

The remaining two OH groups in Quadrol ligand link by hydrogen bonds with two different complex molecules (distance O•••O = 2.701(4) Å): the result is a polymeric chain (see Figure 4).

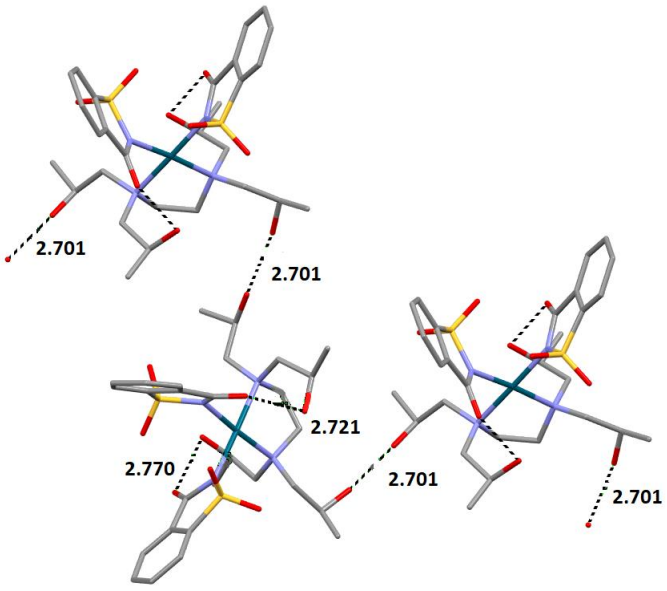


Figure 4. Crystal packing in **3.**

In [$PdCl_2$(THPEN)] (**1**), the four OH groups are oriented outside from the coordination plane (see figure 5), while saccharinate ligand has a stronger capability to organize the supramolecular structure than chloride.

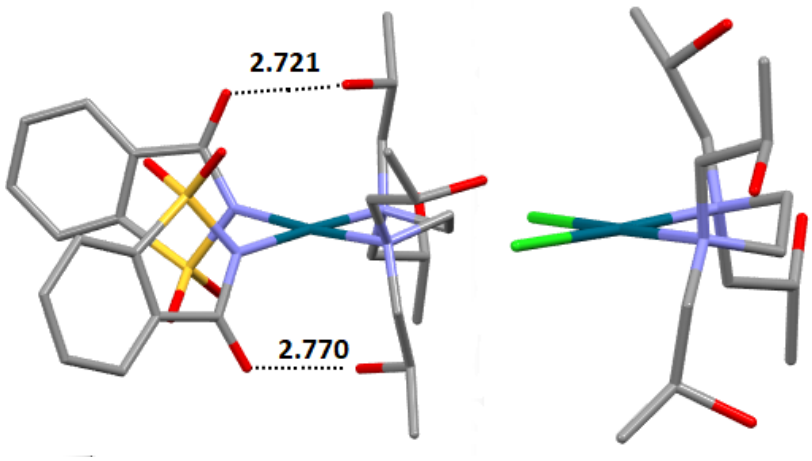
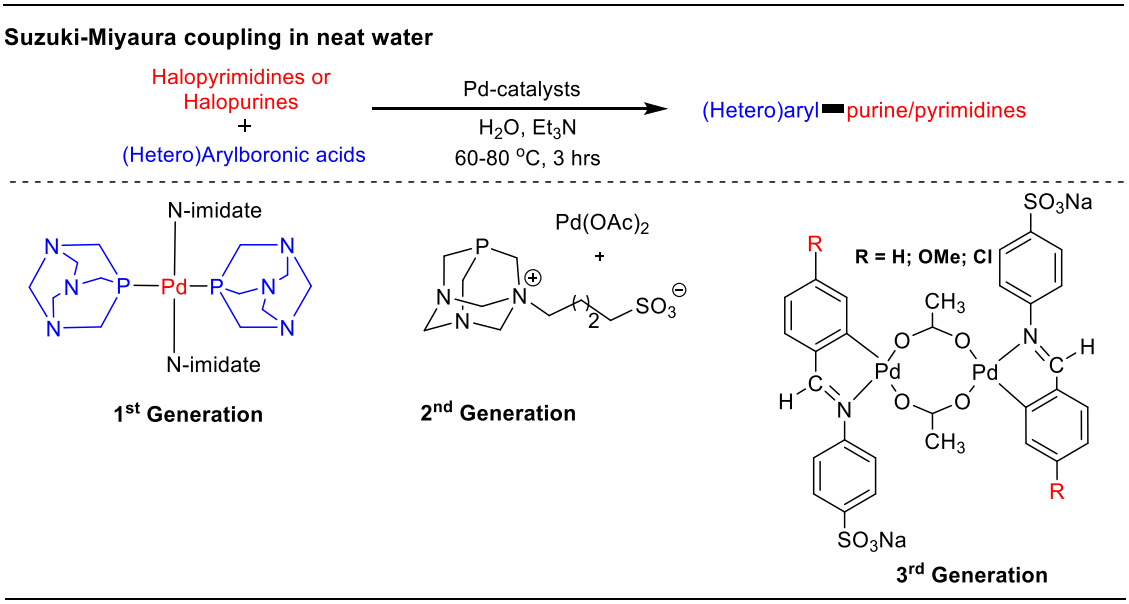


Figure 5. Supramolecular relative orienting ability of saccharinate (left) and chloride ligands.

Room temperature Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxyuridine

The modification of 5-iodo-2'-deoxyuridine is of special interest to biochemists and chemical biologists as the introduction of functionalities on the C5 position of the pyrimidine ring could help enhance the photophysical properties of the resultant molecules. Our research groups have been lately exploring the development of an efficient catalytic system that would enable the functionalization of 5-iodo-2'-deoxyuridine, as well as other nucleosides, to be performed in water as the sole reaction solvent at room temperature.[29,30] Our recent report on phosphine-free palladacyclic complexes gave us the opportunity to perform the catalytic reactions at 60ºC (Scheme 4).[30] However, any further lowering in the reaction temperature led to a drastic reduction in the catalytic activity.



Scheme 4: Catalytic systems developed by our research groups.

Achieving a room temperature catalytic protocol for the modification of nucleosides in water as the reaction solvent has been a long-standing desire of our research groups. Catalytic reactions performed under these conditions would further enable the late-stage modification of temperature sensitive oligonucleotides, DNA or RNA. With this thought in mind, it was decided to first investigate the water-solubility of the synthesized palladium complexes. Table 2 provides the water-solubility data for the palladium complexes **1-4** performed in triplicate (mean value as well as standard deviation provided).

Table 2: Water-solubility studies for complexes **1-4**

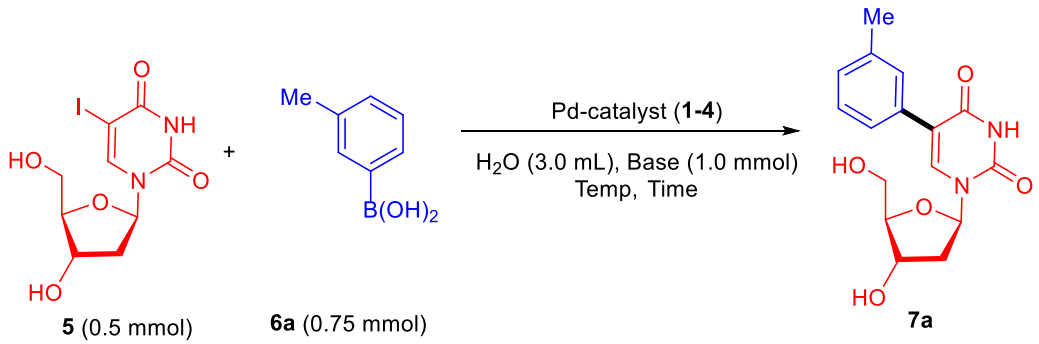
Complexes 1-4	**Experiment 1**	**Experiment 2**	**Experiment 3**	**Solubility in H_2O at 298K (mg/mL)[a]**
1	10.5	10.4	10.4	10.43(0.05)
2	24.2	24.3	24.3	24.26(0.05)
3	36.5	36.6	36.6	36.56(0.05)
4	31.3	31.4	31.4	31.36(0.05)

[a]Mean value. Standard deviations (σ) are given in parentheses.

Water-solubility studies revealed an interesting trend with the pseudohalide, saccharinate coordinated palladium complexes (**3** & **4**) showing better solubility at room temperature as compared to their phthalimide counterpart (**2**) or to the chloro coordinated complex (**1**). This could be attributed to the better H-bonding capacity of the saccharinate substructure that when bound to the palladium centre would help enhance the water-solubility of the resultant complex. These were encouraging results given our interest in performing the catalytic reactions in water as the sole reaction solvent. Next, we turned our attention to test the synthesised complexes for the Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxyuridine with 3-methylphenyl boronic acid in water as the reaction solvent, initiating the screening studies with the intent of developing a room temperature catalytic protocol.

Optimization studies: Our previous attempts to achieve so had failed with the earlier catalytic systems. Previous experience suggested that the catalytic reactions proceeded efficiently at a temperature range of 60-80^{o}C. It was, therefore, decided to initiate the optimization studies at 80^{o}C for a reaction of 5-iodo-2'-deoxyuridine with 3-methylphenyl boronic acid in water as the solvent with Et_3N (2.0 Equiv.) as the base. Palladium complexes (0.5 mol%) were tested in those conditions (Table 3, Entries 1-4) with the complex **3** providing better conversion and yield of the desired cross-coupled product within 3 hrs (84%, Table 3, Entry 3). Reactions performed with complex **3** at lower temperature of 60^{o}C (3 hrs) & 40^{o}C (24 hrs) did not alter the reaction outcome (Table 3, Entries 5 & 6, respectively). Encouraged by these results, it was decided to perform the catalytic cross-coupling at room temperature (30^{o}C). Although the reaction proceeded smoothly to give 94% of product formation (quantitative conversion), the time taken (54 hrs) suggested a slower reaction rate, which certainly could be altered by changing the parameters of the reaction (Table 3, Entry 7).

Table 3: Optimization studies for the Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxyuridine with 3-methylphenyl boronic acid.



Sr No	Catalyst (mol%)	Time (hr)	Temperature (ºC)	Base (Equiv.)	%Yield
1)	**1** (0.5)	3	80	Et_3N (2.0)	80
2)	**2** (0.5)	3	80	Et_3N (2.0)	78
3)	**3** (0.5)	3	80	Et_3N (2.0)	**84**
4)	**4** (0.5)	3	80	Et_3N (2.0)	77
5)	**3** (0.5)	8	60	Et_3N (2.0)	84
6)	**3** (0.5)	24	40	Et_3N (2.0)	84
7)	**3** (0.5)	54	30 (rt)	Et_3N (2.0)	94
8)	**3** (1.0)	24	30 (rt)	Et_3N (2.0)	**87**
9)	**3** (1.0)	24	30 (rt)	K_2CO_3 (2.0)	40
10)	**3** (1.0)	24	30 (rt)	DBU (2.0)	14
11)	**3** (1.0)	24	30 (rt)	Cs_2CO_3(2.0)	48
12)	**3** (1.0)	24	30 (rt)	Et_3N (1.0)	**88**
13)	**1 (1.0)**	24	30 (rt)	Et_3N (1.0)	**77**
14)	**2** (1.0)	24	30 (rt)	Et_3N (1.0)	80
15)	**4** (1.0)	24	30 (rt)	Et_3N (1.0)	79
16)	**1st** Generation	24	30 (rt)	Et_3N (1.0)	No reaction
17)	**2nd** Generation ($Pd(OAc)_2$/PT ABS)	24	30 (rt)	Et_3N (1.0)	50
18)	**3rd** Generation	24	30 (rt)	Et_3N (1.0)	No reaction
19)	**3** (1.0)	24	30 (rt)	Et_3N (3.0)	82
20)	**3** (1.0)	24	30 (rt)	Et_3N (4.0)	84
21)	**3** (0.5)	24	30 (rt)	Et_3N (1.0)	54
22)	**3** (0.1)	24	30 (rt)	Et_3N (1.0)	15
23)	**3** (0.02)	24	30 (rt)	Et_3N (1.0)	NR

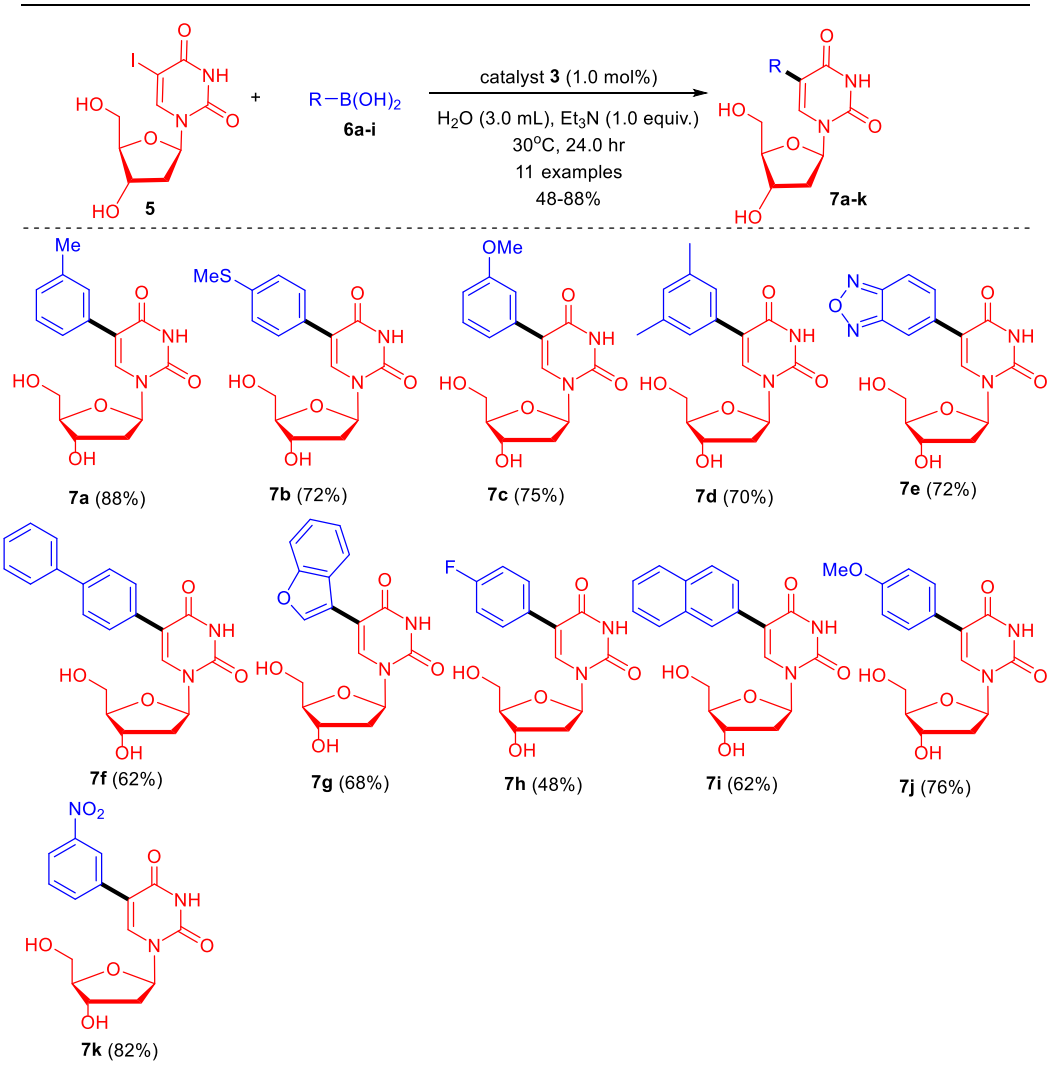
Catalyst concentration can play an important role towards improving the conversion rate and keeping this in mind, the concentration of complex **3** was increased to 1.0 mol%. As predicted, the reaction proceeded smoothly at ambient temperature in 24 hrs providing 87% product formation (Table 3, Entry 8). To further enhance the product yield, Et_3N was replaced by K_2CO_3, DBU and Cs_2CO_3 to check the effect of base (Tables 3, Entries 9-11). Rather than observing any improvement in the yield, the product formation in all the cases was found to be lower confirming Et_3N as the best base for the above transformation. All the reactions performed were having base in an excess amount (2.0 Equiv.) and, therefore, the next reaction was tried by adding the base (Et_3N) in an equimolar amount (1.0 Equiv.). With no appreciable reduction in the product yield observed for the given transformation, it was decided to continue the further processes with 1.0 Equiv. Et_3N (Table 3, Entry 12). Similar experiments when performed on the complexes 1, 2 & 4 under the developed conditions (30 ^oC, 24 hr) provided slightly lower yields of the coupled product (Table 3, Entry 13-15). Previously reported catalytic systems from our group such as the 1st, 2nd and 3rd generation depicted in Scheme 4 were also tested with only the 2nd generation comprising of $Pd(OAc)_2$ as the Pd precursor and PTABS (KapdiPhos) as the ligand providing 50% isolated yield of the desired product Table 3, Entry 16-18).

Increase in the amount of base to 3.0 and subsequently 4.0 Equiv. resulted into no further improvement in yield (Table 3, Entries 19 & 20). Finally, catalyst loading experiments performed on the coupling reaction confirmed 1.0 mol% as the optimum concentration for obtaining very good yield of the coupled product (Table 3, Entries 21-23).

Optimization studies have revealed that the Quadrol-based palladium complex **3** is a highly active catalyst promoting the Suzuki-Miyaura cross-coupling of uridine

nucleoside at room temperature (30°C) in water as the sole reaction solvent. This is the first such report in literature and it paves the way for further exploration of substrate scope and provides us with a unique opportunity to pursue our ambition of performing late-stage modification of temperature sensitive oligonucleotides, DNA or RNA (not part of the current manuscript). The substrate scope of the developed catalytic reaction was further explored with several substituted arylboronic acids.

Scheme 5: Substrate scope for phosphine-free Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxyuridine with different arylboronic acids at room temperature.[a,b]

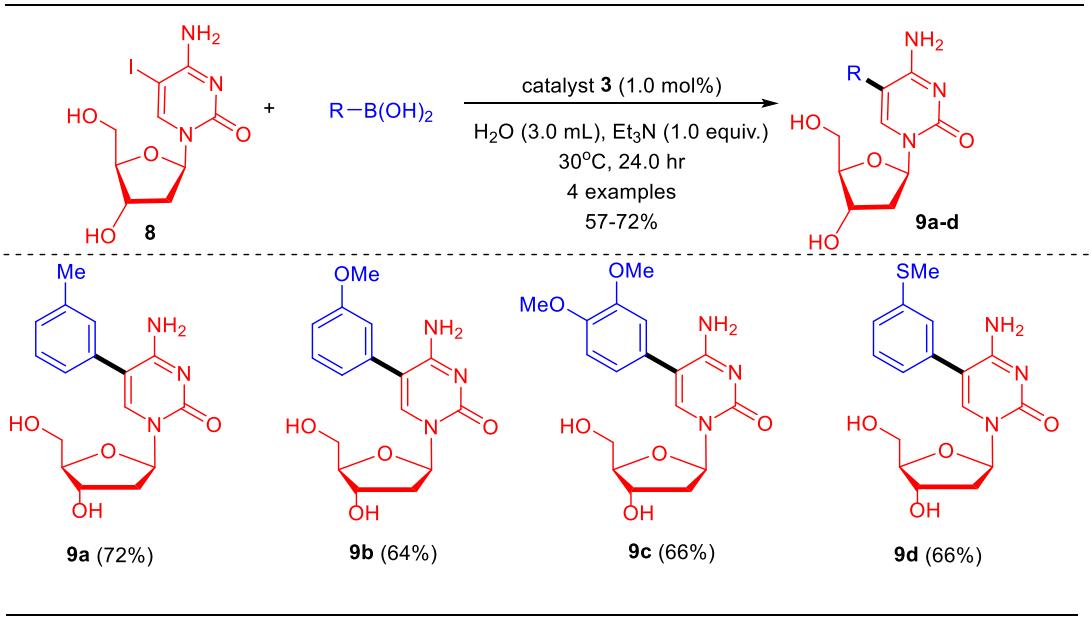


[a]Unless stated otherwise: 0.5 mmol of **5**, 0.75 mmol of **6a-i**, 1.0 mmol of Et_3N, H_2O (3.0 mL), complex **3** (1.0 mol%) at 30°C; [b]isolated yields.

Electron-donating substituents (4-SMe, 3-OMe, 3,5-$(Me)_2$) on the arylboronic acids when reacted with 5-iodo-2'-deoxyuridine proceeded in good yields of the cross-coupled product (Scheme 5, **7b-d**). A strongly electron-donating substituent, benzoxadiazole when employed as the nucleophilic partner, resulted into the formation of good yield of the desired product that was observed to be fluorescent in nature (Scheme 5, **7e**). We intend to develop several more such analogs and study their photophysical properties. This will be reported at a later stage. 4-Biphenylboronic acid and 3-benzofuranyl boronic acid were next to be coupled with 5-iodo-2'-deoxyuridine (Scheme 5, **7f, g**). In both the cases, decent yields were obtained. Introduction of an electron-withdrawing 4-fluoro substituent brought about reduction in the coupled product yield (Scheme 5, **7h**). Other substrates such as 2-napthyl, 4-methoxy and 3-nitro were also tried and provided good yields (Scheme 5, **7i-k**).

The development of the room temperature protocol could certainly prove to be useful for other nucleosides and with this in mind, we envisaged the possibility of employing 5-iodo-2'-deoxycytidine as the electrophilic coupling partner against several arylboronic acids using 1.0 mol% of complex **3** in water (Scheme 6). Starting with the coupling of 3-methylphenyl boronic acid with 5-iodo-2'-deoxycytidine, it was observed that compared to its uridine counterpart, cytidine is less reactive. Even after 24 hrs, the reaction did not proceed to completion giving decent yield of the coupled product (Scheme 6, **9a**). Electron-donating 3-methoxyphenyl boronic acid & 3,4-dimethoxyphenyl boronic acid (Scheme 6, **9b-c**) furnished decent yields of the coupled product suggesting the C—I oxidative addition as the possible challenge in the case of 5-iodo-2'-deoxycytidine and it was further confirmed by the employment of 3-SMephenyl boronic acid (Scheme 6, **9d**).

Scheme 6: Substrate scope for phosphine-free Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxycytidine with different arylboronic acids at room temperature.[a,b]



[a]Unless stated otherwise: 0.5 mmol of **8**, 0.75 mmol of **arylboronic acid**, 1.0 mmol of Et_3N, H_2O (3.0 mL), complex **3** (1.0 mol%) at 30°C; [b]isolated yields.

Mechanistic understanding of the catalytic system

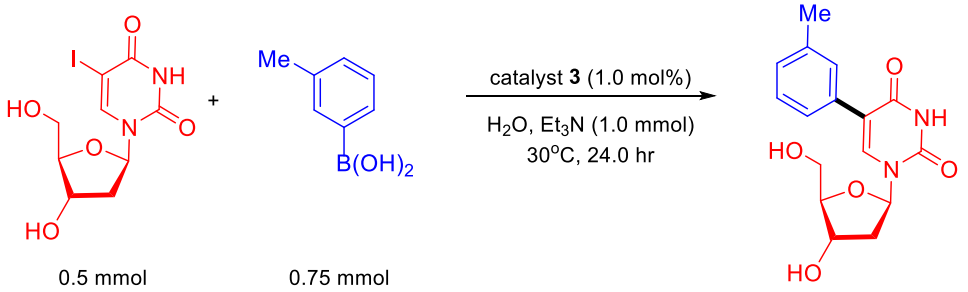
Room temperature cross-coupling of unprotected uridine and cytidine nucleosides with different arylboronic acids in water using the phosphine-free palladium-Quadrol complex **3** is a major advantage in nucleoside transformations. Despite lacking any activating ligand, the ability of complex **3** to efficiently catalyze the above transformations is certainly very intriguing and further investigation of the pathway followed for catalysis was, therefore, undertaken. Initial observations of the catalytic solution suggested the possible presence of Pd colloids or nanoparticles rather than a homogeneous catalyst (black particles formation). To evaluate such a possibility, catalyst poison tests were performed on the catalytic system. First reported by Whitesides, Hg-drop has been one of the preliminary tests to indicate the presence of colloids or nanoparticles as it proceeds through the formation of an amalgam of Hg with the metallic colloids or nanoparticles.[37] Homotopic catalysts are well-defined with

ligands coordinated to the metal center and, therefore, are less likely to form such an amalgam with Hg. The formation of Hg amalgam should deactivate or mask the active catalytic sites on the nanoparticles or colloids and would lead to a complete shutdown of the catalytic reaction. Nevertheless, as the validity of this test has recently been questioned,[38] definitive conclusions should not be extracted from its results, and the performance of complementary experiments is highly recommended. In the case of complex **3**, complete deactivation was observed suggesting the presence of a colloidal or nanoparticular pathway (Scheme 7, Entry 1).

The above observation was further supported by the carbon disulfide (CS_2) test with the sulfur-based compound acting as a poison for colloids or nanoparticles.[39] No conversion was observed in this reaction (Scheme 7, Entry 2), while the addition of tetra-n-butyl ammonium bromide (TBAB)[40] provided additional proof (Scheme 7, Entry 3).

We also performed the Hg-drop test and CS_2 addition test by first continuing the reaction for 6 hrs and then adding the poisons to check if the catalytic reaction gets arrested after their addition. On the completion of 6 hrs and on subjecting the reaction mixture to LCMS analysis, reactions have proceeded to 28% & 24% product formation, respectively (Scheme 7, Entries 4 & 5). On completion of 24 hrs, LCMS analysis did not show any further improvement in the conversion. It is thus inferred that the addition of Hg-drop or CS_2 results into complete retardation of the catalytic reaction further suggesting the loss of activity of the catalyst in a heterogeneous/colloidal form that is engulfed by the added poisons.

Scheme 7: Poison tests for studying the likely nanoparticular or colloidal catalyst[a]



Entry	Complex	Additive	%Conversion[b]
1	Complex 3	Mercury drop (Hg)	0
2	Complex 3	Carbon disulphide (CS_2)	0
3	Complex 3	Tetra-*n*-butylammonium bromide (TBAB)	NR
4[c]	Complex 3	Mercury drop (Hg)	28
5[c]	Complex 3	Carbon disulphide (CS_2)	24

[a]Unless stated, reactions were performed by adding the poisons at the start of the catalytic reaction carried out using 0.5 mmol of 5-iodo-2-deoxyuridine and 1.0 mol% of Complex 3. [b]%Conversion was found out by subjecting the reaction mixture to LCMS analysis. [c]Addition of Hg-drop or CS_2 was done after 6 hrs of reaction (LCMS analysis done just before the addition of poisons) and then on the completion of 24 hrs LCMS was again done to determine the %conversion.

Next, it was decided to identify substrate combination with the Pd-Quadrol catalyst (**3**) leading to the formation of the Pd colloids or nanoparticles.[30] Combination of complex **3** & 5-iodo-2'-deoxyuridine (**5**) in an equimolar ratio in water (without the added base) as the solvent at room temperature (30°C) gave a yellow-colored solution even after 24 hrs (Table 4, Reaction **01**). The replacement of 5-iodo-2'-deoxyuridine (**5**) with a combination of 3-methylphenylboronic acid (**6a**) and Et_3N in water at room temperature led to the formation of a black mass (Table 4, Reaction **02**), while replacing 5-iodo-2'-deoxyuridine (**5**) with only boronic acid (**6a**) (with no added Et_3N) in water brought

about a drastic colour change from yellow to black within the first 15 minutes of the reaction and resulted into the formation of black particles suggesting the possible formation of the colloidal or nanoparticular Pd species (Table 4, Reaction **03**).

Table 4: Experiments for ascertaining substrate combination for active palladium colloid formation. Attached figure represents the reactions.

Reaction No	Complex 3	5	Boronic acid (6a)	Et_3N	H_2O	Observation
01	√	√	X	X	√	No change
02	√	X	√	√	√	**Black particles**
03	√	X	√	X	√	**Black particles**
04	√	√	X	√	√	No change

However, no change was observed when 5-iodo-2'-deoxyuridine (**5**) was reacted with complex **3** in the presence of Et_3N in water (Table 4, Reaction **04**). On closer inspection of the reaction mass (TLC and GCMS analysis) in both cases, quantitative formation of biphenyl (3,3'-dimethylbiphenyl as the homo-coupled product starting from 3-methylphenyl boronic acid) was observed. As expected, the arylboronic acid reagent is the reducing agent responsible for the formation of palladium(0) species in the reaction mixture, through an oxidative homocoupling pathway.

In literature, there have been several reports suggesting homogeneous catalytic systems as reservoirs of active Pd(0) either in the form of nanoparticles or colloids.[41] Several research groups have provided evidence for the presence of such colloids/nanoparticles by the Transmission Electron Microscope analysis of the catalytic solutions.[42-46] Recently, our research group has also been interested in investigating this pathway and have been the first to isolate such colloids as well as thoroughly characterizing them using TEM, XRD, XPS and EXAFS.[30,47] In these and preceding studies, we have shown

the active role of substrate (such as arylboronic acids) in the degradation of the homogeneous catalysts into catalytically active palladium colloids.

To obtain further evidence for the nanoparticular/colloidal pathway, the catalytic reaction between 5-iodo-2'-deoxyuridine with 3-methylphenyl boronic in water at room temperature (30^{o}C) was carried out and, in order to trap the formed Pd colloids/nanoparticles, poly(ethylene)glycol (PEG)[48] was added at the start of the reaction. PEG offers to stabilize the formed colloids/nanoparticles as they become better dispersed and, therefore, are easier to analyze using TEM. At the end of the reaction, water was removed *in vacuo* and the resultant brown colored PEG solution was subjected to TEM analysis (Figure 6). Colloidal palladium particles (~10 nm in size) were observed to be dispersed into the reaction solution and EDS studies performed on the sample also revealed the presence of palladium colloids although in relatively low concentration as the major mass consisted of carbon (Figure 7). Further studies will be needed to ascertain the morphology as well as the size of the colloids and will be reported in due course.

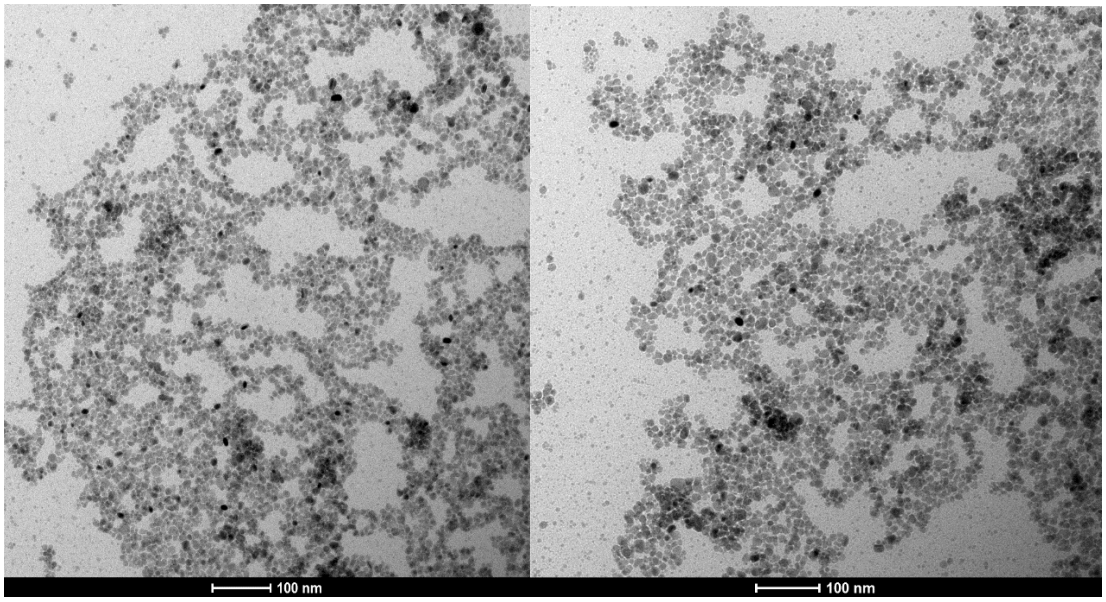


Figure 6: HRTEM images of PEG-stabilized palladium colloids in the catalytic reaction mixture.

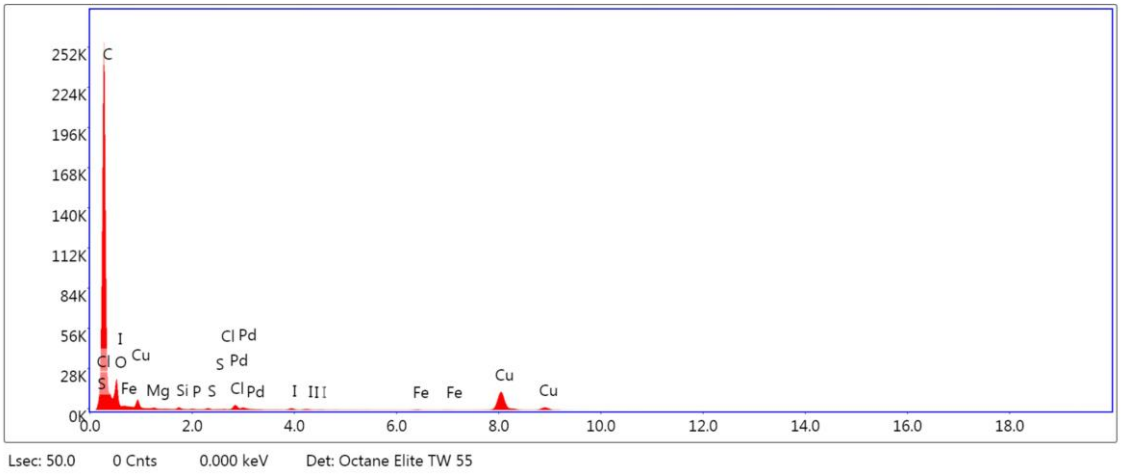


Figure 7: EDS of the catalytic reaction mixture (with PEG).

All the above results provide a first insight into the mode of action of the Pd-Quadrol complex **3** in catalyzing the Suzuki-Miyaura cross-coupling reaction, which would need further studies to elucidate the role of the Quadrol ligand, never used before coordinating a Pd-centre. A subtle blend of steric and σ-donor-only properties, together with the availability of the four branched -OH groups, should be the basis of both the improved catalytic performance at room temperature and the differentiated behaviour of **3** when compared to the only two references of Suzuki coupling with Pd complexes incorporating related ligands as TMEDA[49] and N,N,N',N'-tetrakis(2-hydroxyethyl)ethylenediamine,[10] that specifically described the absence of Pd-black and a negative Hg-test.

Conclusions

We have presented here the first report of Quadrol, *N*,*N*,*N*',*N*'-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN), as a neutral N^N- donor ligand leading to the synthesis and characterization of new palladium (II) complexes, thus expanding the traditional uses in cosmetics or electroless copper plating of this cheap and commercially available molecule. To the best of our knowledge, the single crystal X-ray structures of **1** & **3** are the first in the Cambridge Structural Database that contain THPEN coordinating a palladium centre. Depending on the nature of co-ligands, an interesting and differentiated supramolecular organization has been found. Hydrophilic nature of THPEN and related THEEN ligands enhances the water-solubility of the resultant complexes and makes them ideal candidates for exploring their application for catalyzing reactions in water. It was indeed beneficial for exploring their application as catalysts to promote Suzuki-Miyaura cross-coupling of 5-iodo-2'-deoxyuridine and 5-iodo-2'-deoxycytidine with different arylboronic acids in water as the sole reaction solvent at room temperature. This is the first report for the coupling of nucleosides at ambient temperature in water and exhibits a large substrate scope. Mechanistic studies involving poison tests to investigate the nature of the catalytic species revealed the presence of colloids/nanoparticles. This result differs from those reported for Pd complexes incorporating related ligands as TMEDA or N,N,N',N'-tetrakis(2-hydroxyethyl)ethylenediamine,[10] that specifically described the absence of Pd-black and can not work at room temperature, thus emphasizing the novelty of the catalytic system here reported.

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 aluminum 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 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 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.

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 [$PdCl_2$(THPEN)] (**1**). A solution of N,N,N',N'-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN) (293 mg, 1.0 mmol) in dichloromethane (10 mL) was added dropwise to a mixture of [$PdCl_2(MeCN)_2$] (260 mg, 1.0 mmol) in dichloromethane (10 mL). The reaction mixture was vigorously stirred at room temperature for 10 hours. An orange solid precipitated. The solvent was removed by filtration and the resulting solid was washed with diethyl ether to give complex (**1**) (422 mg, 90%) as a pale orange solid which was dried under vacuum. Anal. calc. for $C_{14}H_{32}Cl_2N_2O_4Pd$: C, 35.8; H, 6.9; N, 6.0. Found: C, 35.9; H, 7.1; N, 6.1 (%). IR (cm^{-1}): ν (THPEN) 3408s (br). ESI-MS (positive mode) m/z: calc. for $[C_{14}H_{32}ClN_2O_4Pd]^+$ 435.1083 $[M–Cl]^+$, found 435.1077; calc. for $[C_{14}H_{31}N_2O_4Pd]^+$ $[M–2Cl-H]^+$ 397.1325, found 397.1285.^{1}H NMR (400 MHz, DMSO-d_6) δ ($SiMe_4$) (ppm): 5.61-4.73 (m, br, 8H; 4H -CH- + 4H -OH), 4.25-2.22 (m, 12H, br, -CH_2-), 1.15 (m, 12H, CH_3).

Preparation of [[Pd(phthal)$_2$(THPEN)] (**2**). In a similar way, a solution of THPEN (130 mg, 1 eq) in methanol (10 mL) was added dropwise to a solution of $Pd(OAc)_2$ (100 mg, 1 eq) and phthaleimide (131 mg, 2 eq) in methanol (10 mL). The mixture was stirred at 80 °C for 1 hour. A yellow solution was formed which was evaporated to dryness. Few drops of acetonitrile were added to the crude reaction until complete solution. The solution was stirred in an ice bath and diethyl ether was added with a Pasteur pipette until the precipitation of a solid was observed. The solid was obtained by filtration, which was taken to dryness under high vacuum to provide complex (**2**) (205

mg, 66%) as a light yellow solid. Anal. calc. for $C_{30}H_{40}N_4O_8Pd$: C, 52.1; H, 5.8; N, 8.1. Found: C, 52.3; H, 6.0; N, 8.1 (%). IR (cm^{-1}): ν (THPEN) 3384s (br); ν (phthal) 1732s, 1662vs. ESI-MS (positive mode) m/z: calc. for $[C_{14}H_{32}N_2O_4Pd]^+$ 544.1639 $[M–phthal]^+$, found 544.1632; calc. for $[C_{14}H_{32}N_2O_4Pd]^+$ $[M–2phthal-H]^+$ 397.1325, found 397.1273. ^1H NMR (400 MHz, D_2O) δ ($SiMe_4$) (ppm): 7.45 (m, 8H, phthal), 5.74-4.12 (m, br, 8H; 4H -CH- + 4H -OH), 3.69-2.17 (m, 12H, br, -CH_2-), 1.01 (m, 12H, CH_3).

Preparation of [[Pd(sacc)$_2$(THPEN)] (**3**).To a stirred solution of $Pd(OAc)_2$ (100 mg, 1 eq) in methanol (10 mL), 163 mg of saccharin (2 eq) and the stochiometric amount of a methanolic solution of THPEN were added. The mixture was stirred at 80 °C for 1 hour. The yellow solution was evaporated to dryness and few drops of acetonitrile were added to dissolve the crude reaction. The solution was stirred in an ice bath and diethyl ether was added with a Pasteur pipette until the precipitation of a solid was observed. The solid was obtained by filtration, which was dried under high vacuum to provide complex (**3**) (290 mg, 85%) as a light yellow solid. Anal. calc. for $C_{28}H_{40}N_4O_{10}PdS_2$: C, 44.1; H, 5.3; N, 7.3. Found: C, 44.3; H, 5.6; N, 7.4 (%). IR (cm^{-1}): ν (THPEN) 3375s (br); ν (sacc) 1677vs, 1593s. ESI-MS (positive mode) m/z: calc. for $[C_{21}H_{36}N_3O_7PdS]^+$ 580.1309 $[M–sacc]^+$, found 580.1332; calc. for $[C_{14}H_{32}N_2O_4Pd]^+$ $[M–2sacc-H]^+$ 397.1325, found 397.1274. ^1H NMR (400 MHz, D_2O) δ ($SiMe_4$) (ppm): 7.71 (m, 8H, sacc), 5.00-4.30 (m, br, 8H; 4H -CH- + 4H -OH), 3.87-2.82 (m, 12H, br, -CH_2-), 1.16 (m, 12H, CH_3).

Preparation of [[Pd(sacc)$_2$(THEEN)] (**4**).To a stirred solution of $Pd(OAc)_2$ (100 mg, 1 eq) in methanol (10 mL), 163 mg of saccharin (2 eq) and the stochiometric amount of a methanolic solution of THEEN were added. The mixture was stirred at 80 °C for 1 hour.

The yellow solution was evaporated to dryness and few drops of acetonitrile were added to dissolve the crude reaction. The solution was stirred in an ice bath and diethyl ether was added with a Pasteur pipette until the precipitation of a solid was observed. The solid was obtained by filtration, which was dried under vacuum to provide complex (**4**) (290 mg, 85%) as a light yellow solid. Anal. calc. for $C_{24}H_{32}N_4O_{10}PdS_2$: C, 40.8; H, 4.6; N, 7.9. Found: C, 41.0; H, 4.7; N, 7.9 (%). IR (cm^{-1}): ν (THEEN) 3319m (br); ν (sacc) 1670vs, 1591s. ESI-MS (positive mode) m/z: calc. for $[C_{17}H_{28}N_3O_7PdS]^+$ 524.0683 [M–sacc]$^+$, found 524.0686; calc. for $[C_{10}H_{23}N_2O_4Pd]^+$ [M–2sacc-H]$^+$ 341.0697, found 341.0692. ^{1}H NMR (400 MHz, D_2O) δ ($SiMe_4$) (ppm): 7.63 (m, 8H, sacc), 4.67-2.77 (m, 20H, br, -CH_2-).

Data related to nucleosides:

General procedure for Suzuki-Miyaura cross-coupling of 5-iodo-2´-deoxyuridine with arylboronic acids (A)*:* A solution of precatalyst **3** (0.5 mol%) in degassed H_2O (3 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 30 ^{o}C. Thereafter, 3-methylphenyl boronic acid (102 mg, 0.75 mmol) was added along with Et_3N (1.0 mmol). The resulting solution was then stirred at 30 °C for 24 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 88% yield (139 mg).

General procedure for Suzuki-Miyaura cross-coupling of 5-iodo-2´-deoxyuridine with aryl boronic acids (B):

A solution of catalyst (0.005 mmol, 1.0 mol%) in degassed H2O (1.0 mL) was stirred for 5 min at ambient temperature under N2. Then, 5-iodo-2´-deoxyuridine (177 mg, 0.5 mmol) was added and the solution stirred for 5 min at RT. Thereafter, 3-methyl phenyl boronic acid (95 mg, 0.7 mmol) was added along with Et3N (70ul, 0.5 mmol) and degassed water (2.0 mL). The resulting solution was then stirred at RT for 6.0 h. After the completion of reaction, crude product was isolated by solvent extraction using (20 ml X 2) dichloromethane. dichloromethane layer was washed with 10 ml water. Dichloromethane layer was dried using sodium sulphate. the solvent was removed under vacuo and the resultant residue obtained was purified using column chromatography in CH2Cl2: MeOH solvent system (96:4) to afford the desired product as a white solid.

Isolated yield – (130mg) 82 %

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 (3.0 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 30 ^oC. Thereafter, 3-methylphenyl boronic acid (102 mg, 0.75 mmol) was added along with Et_3N (1.0 mmol). The resulting solution was then stirred at 30 °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 (114 mg).

X-ray Data Collection, Structure Solution, and Refinement for 1 and 3.

X-ray data were collected with a Bruker D8 QUEST. Data were collected at 100(2) K, 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 using version 2018/3 of **ShelXL,** refining on F2 (Table 5).[50] CCDC 2117261 for **1** and 2117260 for **3** 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 1 and 3

	1	**3**
formula	$C_{14}H_{32}Cl_2N_2O_4Pd$	$C_{28}H_{40}N_4O_{10}PdS_2 \cdot C_3H_6O \cdot H_2O$
Fw	469.71	839.25
cryst color, habit	yellow, lath	yellow, prism
cryst size (mm)	0.18 x 0.06 x 0.05	0.12 x 0.18 x 0.19
cryst syst	monoclinic	orthorhombic
space group	P21/c (#14)	Pcab (#61)
a (Å)	9.0082(5)	14.7548(7)
b (Å)	11.6508(8)	14.9919(8)
c (Å)	18.8174(12)	33.9400(17)
α (º)	90	90
β (º)	90.478(3)	90
γ (º)	90	90
V (Å^3)	1974.9(2)	7507.6(7)
Z value	4	8
D_{calcd} (g/cm^3)	1.580	1.485
F_{000}	968	3488
no. of reflns measd	37191	158800
no. of observations	4040	11463
no. of variables	255	474
R1	0.0569	0.0590
wR2	0.1391	0.1407
goodness of fit	1.079	1.210

Supporting Information.

Electronic supplementary information (ESI) available: Detailed experimental section, IR, HR-MS and ^{1}H NMR spectra. Data related to nucleosides: NMR and references.

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Conflict of interest

There are no conflicts to declare.

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