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Water-Soluble Pd-Imidate Complexes as Versatile Catalysts for the Modification of Unprotected Halonucleosides

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Dedicated to the memory of Professor Dr. Gregorio Sánchez.

Abstract: Modification of unprotected nucleosides has been attracting continuous interest, since these building blocks themselves and their phosphate-upgraded corresponding nucleotides have shown a plethora of uses in fields like biochemistry or pharmacy. Pd-catalyzed cross-coupling reactions, conducted in water or its mixtures with polar organic solvents, have frequently been the researchers' choice for the functionalization of the purine/pyrimidine base of the unprotected nucleosides. In this scenario, the availability of hydrophilic ligands and its water-soluble palladium complexes has markedly set the pace of the advances. The approach of our group to the synthesis of such complexes, Pd-imidates specifically, has faced critical stages, namely the jump to synthesize water soluble complexes from our experience working in conventional solvents, the preparation of phosphine free complexes and the overall goal of getting catalytic systems able to work close to room temperature. The continuous feedback with Kapdi's group, experienced in the chemistry of nucleosides, has produced over the last decade the interesting results in both fields presented here.

Keywords: Water-soluble palladium complexes, homogeneous catalysis, nucleosides, coupling reactions

1. Introduction

The last decades have witnessed an increasing interest, from both academia and industry, in the use of water-soluble catalysts whether in neat water or biphasic organic/aqueous systems.[1] As stated in the seminal review by Herrmann and Kohlpaintner[2] the main advantages that make them so attractive for commercial applications include a simple extractive work-up with easy separation of the catalyst in the aqueous phase from the water insoluble organic product, and its excellent long-term stability. The consequent reduction of costs and waste output, combined with their high activity and high selectivity, were the reasons that initially motivated this approach to environmentally respectful processes, and still operates today.[3]

The main challenges of improving the stability/solubility of the homogeneous catalysts in water can be addressed by including in its coordination sphere selected ligands containing hydrophilic substituents. Since this strategy has been preferably chosen, the commercial availability of such water-solubilizing ligands has conditioned the advances in this field.[1,4] Hydrophilic phosphines, nitrogen ligands and *N*-heterocyclic carbenes are the three main categories of hydrophilic ligands, as reported by Shaughnessy in his 2009 critical review.[4a] Among them, we focused our initial efforts in 1,3,5-Triaza-7-phosphaadamantane (PTA), which is a well-known caged phosphine ligand that displays both water solubility and σ-donation capability.[5] These singular properties have motivated a continuous interest ranging from its basic coordination chemistry[6] to the catalytic, anticancer or antibacterial activity

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of its metallic complexes.[7] Other general characteristics of caged phosphines, that PTA shares with the main exponents of this family of ligands[8] are the reduced freedom of phosphorus in the resulting three dimensional scaffold, the enhanced steric properties of the cage system that improve the control of selectivity in catalytic processes, and the easy tuning of electronic properties through functionalization. Overall, caged phosphines have played a relevant role in the development of efficient metal-catalyzed processes, although it is worth it to note that the very ground-breaking studies were however conducted around sulfonated triphenylphosphine ligands,[9] and that hydrophilic phosphorus ligands maintain continuous interest nowadays.[10] When it comes to palladium-catalyzed reactions in water, these ligands have also been playing a crucial role,[11] from pioneering use of the TPPMS/$Pd(OAc)_2$ system by Casalnuovo[12] for the cross-coupling of aryl halides to date.[13] It is worth it to mention that although Casalnuovo's coupling report included the use of both hydrophobic and hydrophilic substrates, like 5-IdU and 5-IdCMP, the incredible potential of related TPPTS/$Pd(OAc)_2$ as water-soluble catalyst system for nucleoside modification was not unveiled till 2003,[14] when Shaughnessy group developed a general methodology well beyond those initial more reactive substrates, nowadays successfully applied not only in the synthesis of functionalized unprotected purine and pyrimidine nucleosides, but also for nucleotides and oligonucleotides.[15]

In addition to the above mentioned sulfonate group, other ionic substituents like carboxylate or ammonium are often employed as water-solubilizing groups when attached to phosphines, nitrogen ligands or *N*-heterocyclic carbenes.[4a,16] It has been less common to use non-ionic hydrophilic substituents, like polyols, thioureas or phosphonate esters, attached at electrophilic or nucleophilic sites on prefunctionalized ligands.[4a,10] Regarding Pd-catalyzed cross-coupling reactions, hydrophilic N-donor ligands have received lesser attention than phosphines, probably due to its inferior electron donating properties and weak coordination to palladium that yields low stability complexes.[11] When compared to phosphine ligands, those alternative nitrogen-based provide lower cost and toxicity, and for these reasons there is a continued interest in its development. It is worth it to mention that the use of neutral hydrophilic N-donor ligands is still rare if we compare it with the main trend that prefer anionic/cationic solubilizing groups.[4a]

The above mentioned Pd catalyzed cross-coupling reactions are versatile methods that can usually be conducted under mild conditions, showing outstanding functional group tolerance. For this reason, they are very often the preferred choice when building new C–C bonds with heteroaromatic structures or substrates bearing sensitive functionalities. Among those, nucleosides can be particularly challenging due, for example, to their potential for oxidatively add to low valent Pd species in the case of electron-rich halogenated ones, or to deactivate the Pd catalysts through coordination.[15] Thus, it has been found that some ligands considered highly effective for typical aryl halides, like sterically demanding, electron-rich phosphines, do not provide similar results with nucleoside substrates.

The poor solubility of nucleosides, nucleotides and oligonucleotides in conventional organic solvents used for cross-couplings, such as toluene and THF, also represents a major challenge that traditionally has been confronted through protection of the sugar hydroxyl groups to increase the solubility in such solvents. For this particular problem, the use of water and a minimum content of water-soluble Pd catalysts would allow to overcome the protection strategies, not always available, with obvious benefits in terms of yields, atom/time economy and environmental benignity of the overall process.[17] As mentioned above, led by TPPTS/$Pd(OAc)_2$ and related systems like TXPTS, palladium-catalyzed cross-coupling reactions have lately tackled these challenging synthetic difficulties inherent to nucleoside transformations.[18] Of course these efforts have not only been driven for an academic/synthetic interest but for the ascertainment that small changes in the structure of nucleosides has an important effect on their potential bioactivity.[19] This applied side of modified nucleosides has been profusely investigated for decades in fields like the discovery and development of antivirals,[20] models to study the carcinogenesis and mutagenesis mechanisms,[21] antitumor drugs,[22] C-nucleosides[23] or fluorescent nucleosides[24] among other applications of aryl- or alkynyl-substituted nucleosides that have been thoroughly collected recently.[15,17] Thus the very practical output of having available a variety of synthetic approaches for accessing nucleoside-based antiviral or anti-

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cancer drugs is that nowadays there are more than 40 nucleoside analogs that have been approved as drugs, some of them widely recognized and close to us, like Zidovudine, Entecavir, Imuran or BVDU among others.[15,25] This plethora of interesting applications in such hot fields would explain the continuous development of catalytic protocols for the modification of nucleosides under Suzuki-Miyaura cross-coupling conditions.[26] Such protocols have been conveniently applied to the synthesis of modified nucleotides, able then to be enzymatically incorporated into oligonucleotides. Again the potential of the most used system, TPPTS combined with $Pd(OAc)_2$ or Na_2PdCl_4, was demonstrated,[27] also in the Sonogashira coupling of halonucleotides.[28] There are many recent examples of the Suzuki cross-coupling of halogenated nucleobases in nucleic acids[29a–c] and the cross-couplings of nucleoside triphosphates,[29d–e] while a complete picture with several specific examples of cross-coupling synthesis of modified nucleotides and oligonucleotides and its biological relevance can be found elsewhere.[15]

Over the past several years, a continued collaboration with Kapdi's research group has resulted in the development of efficient catalytic systems for the modification of nucleosides especially the 2′-deoxyuridine -based precursor, 5-iodo-2′-deoxyuridine.[30] Water solubility, absence of phosphine ligands in its composition and the search of 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, have been the required criteria for those systems, that will be reviewed in this account. The following lines present a personal perspective of the path travelled to reach those simple, yet sophisticated, water-soluble ligands and catalytic systems starting from our highly serendipitous and non-oriented research around Pd-imidate complexes.

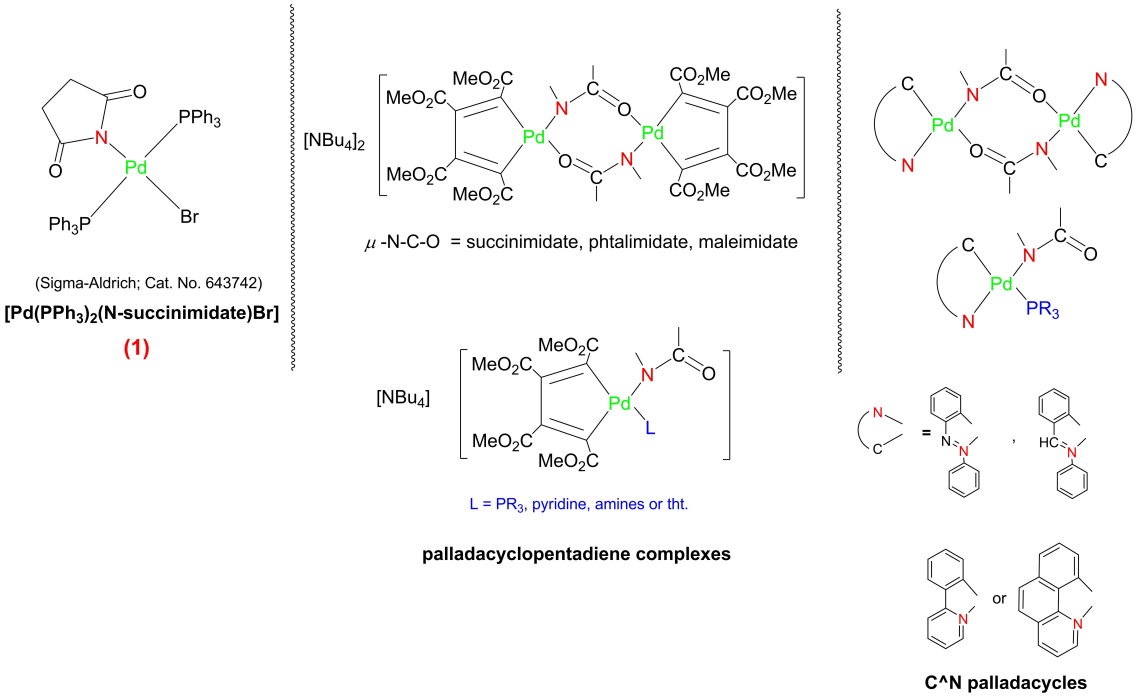
2. Background

It is approaching twenty years since the very first use of a Pd-imidate complex, namely $[Pd(PPh_3)_2$(N-succinimidate)Br] (**1**), as catalyst in cross-coupling reactions,[31] which meant the starting signal of our continued interest for halide/pseudohalide effects in catalysis and the beginning of a fruitful collaboration with Fairlamb's and Kapdi's groups. On the journey from that serendipitous finding that involved catalytic NBS (N-bromosuccinimide) accelerative effect for successful Stille cross coupling of oxazole bromide with trienyl organostannanes, to the wider use of (**1**) as precatalyst for Suzuki-Miyaura cross-couplings of benzylic halides with aryl- or heteroarylboronic acids,[32] this seminal complex was commercialized (Sigma–Aldrich; Cat. No. 643742). A few years before,[33] it was the unexpected obtention of a single crystal structure for the Pt-analogue of (**1**) what put us on the track of a new use of NBS as oxidative addition agent to low valent metallic centers, that nowadays is well recognized.[34] In the meanwhile we kept exploring different synthetic routes to next generation imidato Pd(II) precatalysts (see Scheme 1), that eventually brought us to specific water-soluble Pd-imidate complexes for the modification of unprotected nucleosides.

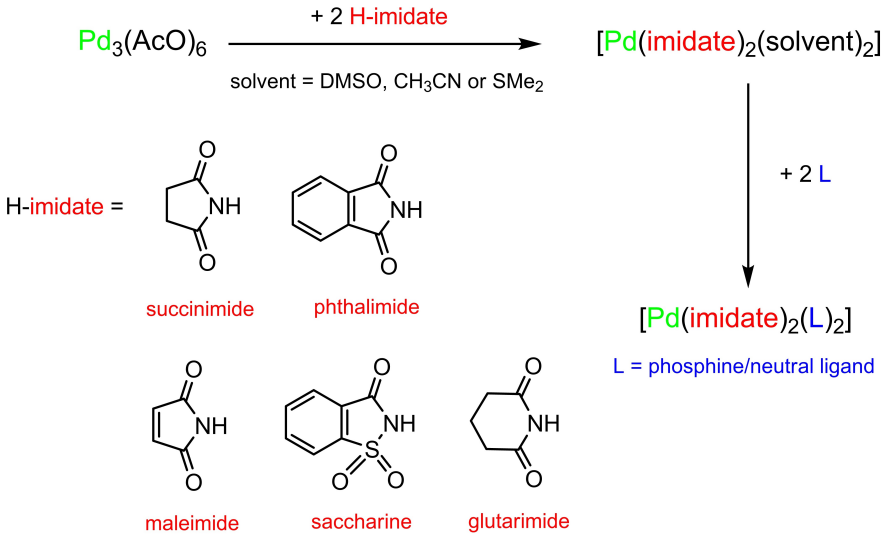
Indeed, once the potential of (**1**) as active catalyst was stated, we envisaged that other Pd (II) complexes possessing imidate ligands could also promote Stille coupling. The first extension of our library involved the use of the palladacyclopentadiene precursor $[NBu_4]_2[Pd_2\{C_4(COOMe)_4\}_2(\mu\text{-}OH)_2]$, basic enough to induce imide deprotonation when reacting with succinimide, maleimide and phthalimide, generating air-, light- and moisture-stable anionic palladacyclic structures containing bridging -NCO- anionic imidate ligands.[35] These new di-μ-imidate complexes in turn reacted easily with monodentate ligands, such as phosphines and pyridines, to yield mononuclear imidate palladacyclopentadiene derivatives (Scheme 1), which are also catalytically active in the Stille reaction. A comparison of their catalytic properties with (**1**) in the Stille reaction was reported, revealing an interesting dependence in both the yields and reaction times on the presence and type of imidate ligand bound to Pd, that with a blend σ-donating and π-accepting properties exerted a pronounced pseudohalide effect.[36]

Having incorporated the acid-base synthetic route towards imidate derivatives, it offered wider possibilities than the oxidative addition one, clearly in terms of Pd-sources and bare imides/related ligands available. Thus Scheme 1 also displays binuclear cyclometallated palladium complexes $[\{Pd(\mu\text{-}NCO)(CN)\}_2]$, again containing asymmetric imidato–NCO bridging units, and its corresponding mononuclear phosphine derivatives $[Pd(CN)(imidate)(PR_3)]$, that were prepared this way using either di-μOH/Acetate palladacyclic precursors.[37] A correlation of the main features in the new complexes was performed when assessing its catalytic activity in the Sonogashira and Suzuki–Miyaura cross-coupling reactions.[38] A subsequent expanded study with imine-based orthometallated ligands included 2,3-dibromomaleimide, glutarimide, 2-oxazolidone and δ-valerolactam in our list of imidate "pseudohalide" ligands and reported our mechanistic findings that pointed to a common catalyst species in these types of Suzuki cross-couplings.[39,40]

With the initial aim of expanding our Pd-sources, beyond the palladacyclic backbones explored for a decade, we disclosed a novel synthetic route towards complexes formulated as $[Pd(X)_2(solvent)_2]$.[41] It just involved an acid-base reaction in acetonitrile, dimethyl sulfoxide or dimethyl sulfide between $Pd_3(AcO)_6$ and the stoichiometric amount of protic imidate ligands, yielding the corresponding bis-imidate complexes (Scheme 2). Easy substitution of solvent in $[Pd(imidate)_2(solvent)_2]$ for neutral ligands, showed the synthetic



Scheme 1. Evolution of not-water-soluble imidate complexes synthesized in previous work.



Scheme 2. Synthesis of bis-imidate precursors anits derivatives with neutral ligands

potential of these mimics of classical precursors in coordination chemistry. However, with X being imidate instead of an halogen ligand one would expect, to the light of our previous experience, that the coordinative possibilities in [Pd(imidate)$_2$(solvent)$_2$] would be expanded/improved, and so would do its behaviour in fields like catalysis or self-assembly in which [PdCl$_2$(solvent)$_2$] complexes are usually involved. In this sense we introduced for the first time in our studies saccharine as "imidate" ligand, able to display a wider variety of coordination modes.

Surprisingly, although its coordination chemistry with alkaline, alkaline-earth and first row divalent metal ions was

well known[42] just a few examples of Pd-complexes had been described at that time.[43] As very initial results, we presented the application of novel Pd-saccharinate complexes in Suzuki–Miyaura cross-coupling of different aryl and benzyl bromides with aryl boronic acids.[41] Their excellent performance in comparison with related compounds,[44] and the confirmation of its singular properties coordinating palladium,[45] put saccharine at the forefront of our efforts developing new catalytic systems,[46] that eventually found application in the modification of nucleosides.

Particularly the complex $[Pd(PPh_3)_2(saccharinate)_2]$, that we had incipiently tested in benchmark reactions,[41] revealed as a general catalyst for Suzuki and Negishi cross-couplings and C–H bond functionalization of synthetically more relevant coumaryl and pyrone substrates.[47] This was our first attempt beyond aryl and benzyl halides as substrates. At this point, after a decade of fruitful collaboration gravitating back and forth from the more fundamental (synthetically oriented) to the more catalytically applied in a mutually beneficial manner, we realized that we were ready for the sought-after move to do some chemistry in water. Would a water-soluble analogue of $[Pd(PPh_3)_2(saccharinate)_2]$ produce equivalent satisfactory results catalyzing coupling reactions conducted in aqueous media of challenging, and now accessible, substrates?

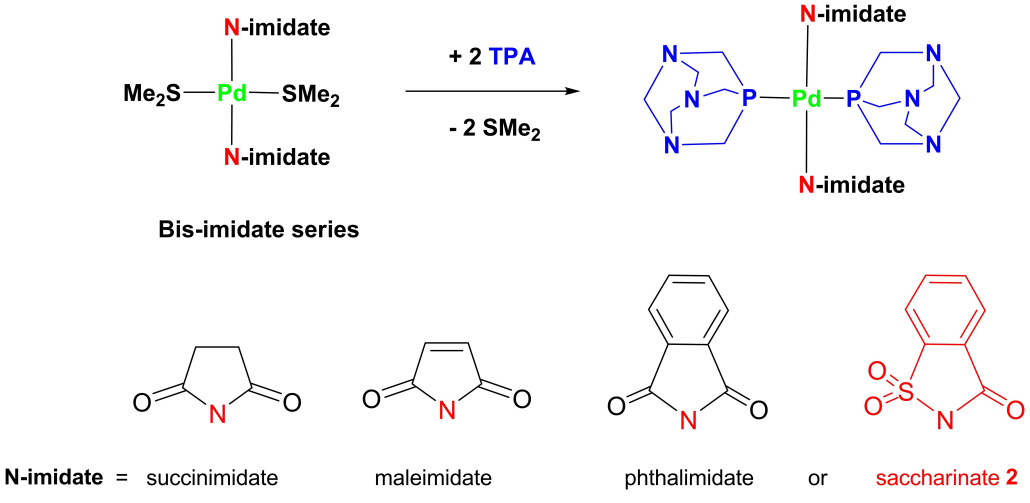
3. Palladium Complexes of PTA for Nucleoside Modifications

PPh_3 and organophosphines in general are ubiquitous ligands in organometallic chemistry, and, as mentioned in the introduction, tertiary water-soluble phosphines also have a prominent role in the construction of hydrophilic transition metal complexes. Among them, the cage-like aliphatic monophosphine 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (PTA, or 1,3,5-triaza-7-phosphadamantane) and its derivatives as DAPTA are the subject of continuous and growing interest, well beyond the original application of PTA as ligand in coordination chemistry.[48]

Halide complexes formulated *cis*-$[Pd(PTA)_2X_2]$ and its derivatives have been crucial in the development of Pd–TPA chemistry,[6,49] and we decide to prepare the analogous containing pseudohalide imidate ligands, expecting from them an intense activity for cross-coupling reactions. The precursors *trans*-$[Pd(imidate)_2(SMe_2)_2]$ that allowed the synthesis of $[Pd(PPh_3)_2(saccharinate)_2]$ were useful here too, as displayed in Scheme 3 (Adapted from Ref. 30a with permission from the Royal Society of Chemistry), and the four new complexes *trans*-$[Pd(imidate)_2(TPA)_2]$ were fully characterized.[30a]

Their appreciable water-solubility (around 100 mg/mL) encouraged us to test them against several *in situ* and preformed catalyst systems in a Suzuki–Miyaura cross-coupling protocol for aryl bromides in water. The saccharinate precatalyst was particularly able to catalyse these reactions in very good yields when compared with the others. We also explored the possibility of extracting with ethyl acetate the aqueous solution containing the catalytically active species, recharging the reaction with fresh substrates and base, repeating this process for five consecutive runs without losing significant activity.

As mentioned in the introduction, modification of nucleosides using palladium-catalysed Suzuki–Miyaura coupling in aqueous media had scarcely been performed at the time we described this first series of water-soluble palladium



Scheme 3. Easy synthesis of water-soluble PTA imidate complexes. Adapted from Ref. 30a with permission from the Royal Society of Chemistry

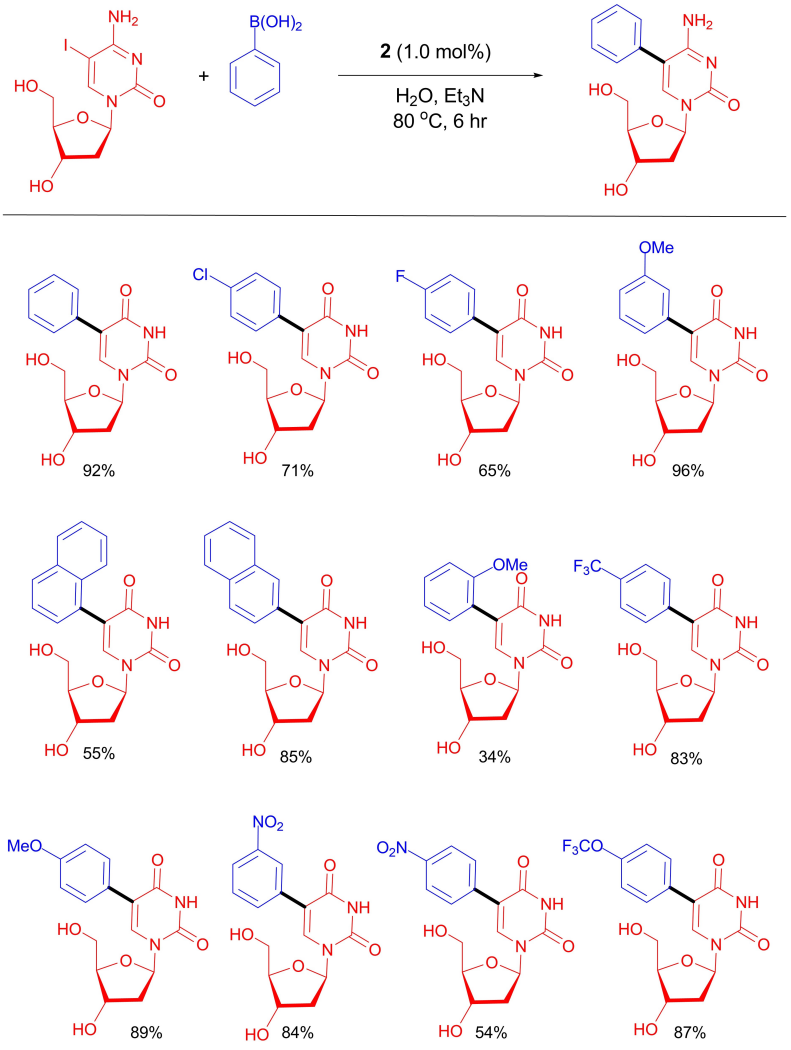
complexes.[50] This relatively unexplored field oriented our collaboration with Kapdi's group, trying to improve some pending aspects, like low yields or the need of using high temperatures and mixtures of solvents.

3.1. Suzuki-Miyaura Arylation of Purine/Pyrimidine Nucleosides at C-5/C-8 Positions with $[Pd(N\text{-}Imidate)_2(PTA)_2]$ as Catalysts

In fact the solvent issue was the first to be addressed, focusing our efforts in using water as the sole reaction solvent. A preliminary catalyst comparison study for the reaction of 5-Iodo-2′-deoxyuridine with benzofuran-2-boronic acid in water was made by obtaining the HPLC profiles, injecting small aliquots of reaction mixture at intervals ranging from 0.5 to 6.0 h. $[Pd(imidate)_2(PTA)_2]$ complexes exhibited enhanced reactivity with the saccharinate precatalyst being again particularly able to catalyse these reactions in very good yields when compared with the others (quantitative conversion after 4 h). Common Pd precursors such as $Pd(OAc)_2$, $[PdCl_2(PTA)_2]$, $[PdBr_2(PTA)_2]$, or $[PdCl_2(TPPTS)_2]$ gave poor yields of the product, while the $Pd(OAc)_2$/TPPTS system compared better, showing a conversion of 87 % after 6.0 h.

The scope of substrates initially explored using the saccharinate precatalyst, and the reaction conditions are displayed in Scheme 4. Catalyst loading could be reduced up to 0.1 mol% without any appreciable reduction in yields but increasing the reaction time.

Our next challenge was a comprehensive study utilizing PTA-imidate complexes for palladium-catalyzed Suzuki cou-



Scheme 4. Scope study for Suzuki–Miyaura arylation 5-iodo-2′-deoxyuridine in water. (a)Arylboronicacid (0.75 mmol), 5-iodo-20-deoxyuridine (0.5 mmol), catalyst (1.0 mol%), 3 mL H2O, Et3 N (1.0 mmol). (b) Yields are isolated yields. Adapted from Ref. 30a with permission from the Royal Society of Chemistry.

plings in water of all four halo-2'-deoxynucleosides, specifically, 5-iodo-2′-deoxyuridine, 5-iodocytidine, 8-bromo-2′-deoxyadenosine and 8-Bromo-2′-deoxyguanosine, with a wide variety of aryl and heteroarylboronic acids providing an array of substituted nucleosides of synthetic relevance in good to excellent yields.[30c] It should be pointed out that the catalytic reactions were performed with unprotected nucleosides.

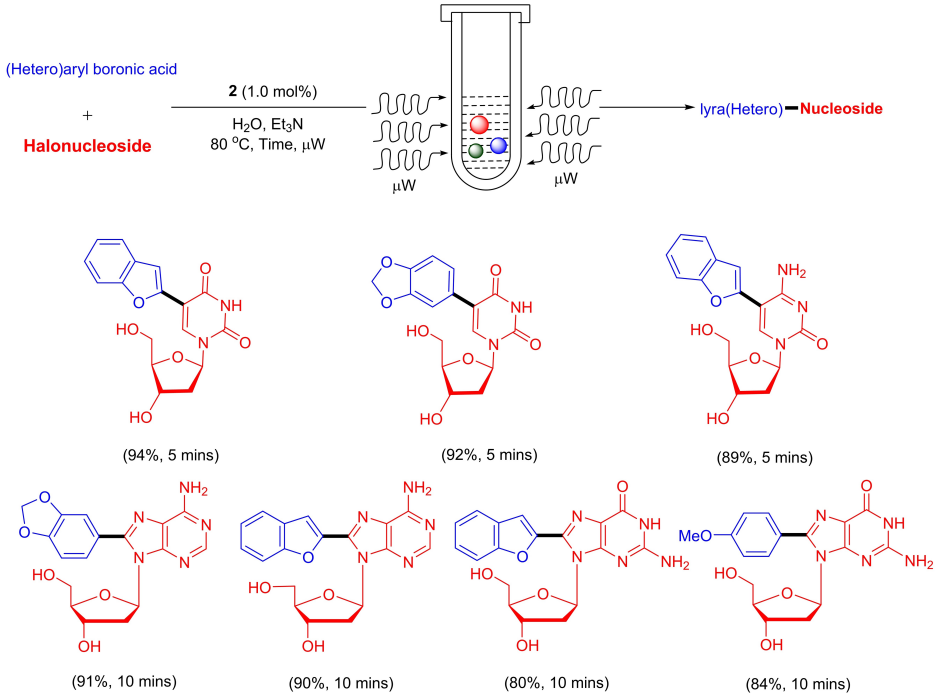
UV-vis absorption and emission analysis of the coupled products were conducted in order to produce a detailed catalogue of potential fluorescent nucleoside analogues. A noticeable improvement in fluorescence properties can be envisaged since most of the modified nucleosides displayed a bathocromic shift when compared to their corresponding naturally occurring nucleosides. Regarding emission, good results were obtained with all the purine analogues, but only with a few of the pyrimidine derivatives.

BVDU analogues were the ones that displayed the best absorption and emission behaviour. Indeed, the further functionalization of BVDU following Suzuki–Miyaura cross-coupling described below, provided excellent yields of fluorescent nucleoside analogs never reported before.[30c]

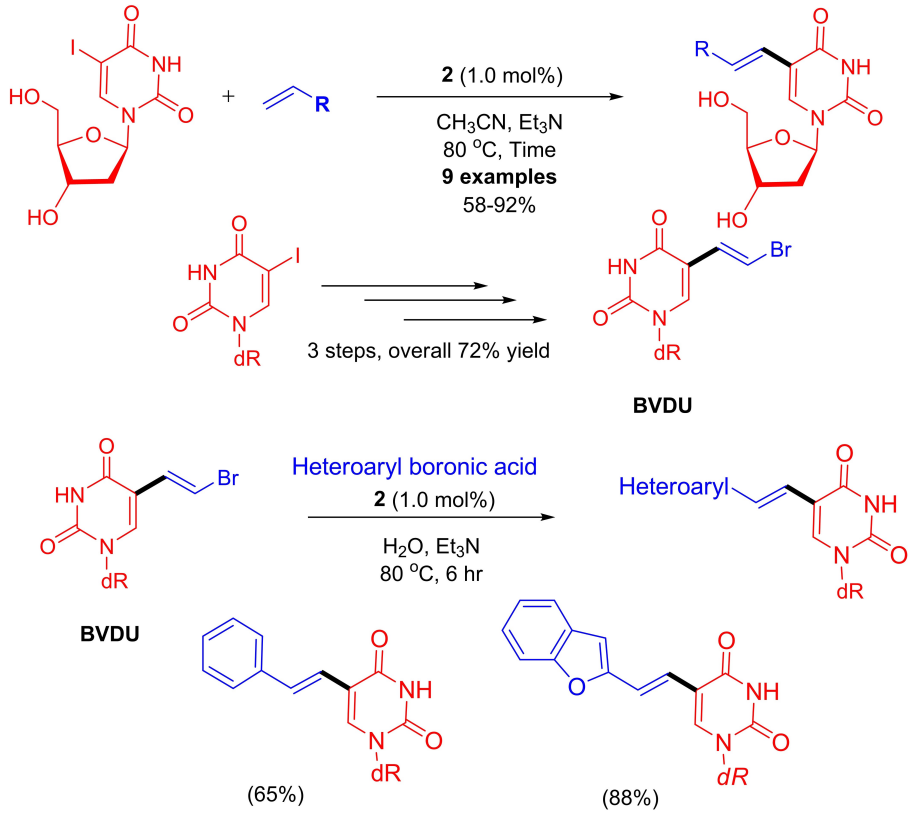
Despite the success achieved with the coupling reactions, the catalyst system failed to provide recyclability which could be attributed to a relatively low water solubility as one possible reason.

Catalyst poison experiments, namely the Mercury-Drop and the CS_2 addition tests were conducted to differentiate a homotopic or heterotopic behaviour of the catalysts. Both pointed out the homogeneity of the catalysts employed, extent confirmed with additional mechanistic studies performed with ^{31}P-NMR spectroscopic and electro-spray ionization mass spectrometric techniques, that also suggested the presence of a homogeneous catalytic pathway. Thus, a stoichiometric reaction of 8-bromo-2′-deoxyadenosine in DMF at 80 °C with the precatalyst 2 was followed by ESI-MS, allowing to identify several catalytic species that formed under the conditions. The suggested main catalytically active species $Pd(0)L_2$ was among them, and also some oxidative addition products. The reduction from hours to minutes in the reaction time was achieved by means of a microwave-assisted process, which still provided excellent yields of the coupled products as displayed in Scheme 5 Reprinted (adapted) with permission from 30c V. Gayakhe, A. V. Ardhapure, A. R. Kapdi, Y. S. Sanghvi, J. L. Serrano, *J. Org. Chem.* **2016**, *81*, 2713–2729. Copyright {2016} American Chemical Society.

We also reported there a coupling protocol for the synthesis of 5-styryl-2′-deoxyuridines *via* Suzuki-Miyaura cross-coupling of BVDU (brivudine), making use of its synthetically exploitable vinylic bromide functional group (See Scheme 6). At that time just a few of these derivatives exhibiting good antiviral activity had been reported, mostly



Scheme 5. Microwave-assisted process for Suzuki-Miyaura arylation 5-iodo-2′-deoxyuridine in water. Reprinted (adapted) with permission from 30c V. Gayakhe, A. V. Ardhapure, A. R. Kapdi, Y. S. Sanghvi, J. L. Serrano, *J. Org. Chem.* **2016**, *81*, 2713–2729. Copyright {2016} American Chemical Society.



Scheme 6. Heck alkenylation of Pyrimidine Nucleosides, scale-up synthesis of BVDU and its further modification via Suzuki coupling with [Pd(N-saccharinate)$_2$(PTA)$_2$] (**2**) Reprinted (adapted) with permission from 30c V. Gayakhe, A. V. Ardhapure, A. R. Kapdi, Y. S. Sanghvi, J. L. Serrano, *J. Org. Chem.* **2016**, *81*, 2713–2729. Copyright {2016} American Chemical Society).

prepared by means of the Stille coupling reaction.[51] Our last advance in this field was the conversion of the cross-coupled product obtained from Suzuki-Miyaura cross-coupling of 5-iodo-2-deoxyuridine with phenyl-boronic acid, into its phosphoramidite via a two-steps procedure.[30d]

3.2. C-5 Heck Alkenylation of Pyrimidine Nucleosides by Employing [Pd(N-Imidate)$_2$(PTA)$_2$]

The BVDU modification via Suzuki coupling presented above was in fact an extension of our work using [Pd(N-imidate)$_2$(PTA)$_2$] complexes as catalysts in the Heck alkenylation of nucleosides(Scheme 6 Reprinted (adapted) with permission from 30c V. Gayakhe, A. V. Ardhapure, A. R. Kapdi, Y. S. Sanghvi, J. L. Serrano, *J. Org. Chem.* **2016**, *81*, 2713–2729. Copyright {2016} American Chemical Society).[52] This Pd-catalyzed reaction was indeed used in one of the first examples of nucleoside modification, accomplished by Bergstrom in 1976.[53] Since then, Heck alkenylation reactions have been profusely applied in the synthesis of fluorescent nucleosides, incorporating structural features with extensive conjugation.[54]

Improving the reaction efficiency, in terms of lowering the catalyst concentration while getting higher product yields, was the main challenges associated with the Heck alkenylation of nucleosides[55] that we faced in out attempt to extend the scope of our saccharinate complex [Pd(N-saccharinate)$_2$(PTA)$_2$] (**2**). This precatalyst, based on its superior activity compared to the others, was employed to catalyze the alkenylation of both unprotected 5-iodo-2'-deoxyuridine and 5-iodo-2'-deoxycytidine with a variety of activated alkenes in acetonitrile. We obtained excellent yields with just 1.0 mol% of catalyst amount required (Scheme 6). The obtention of a precursor of BVDU in 92% yield following this protocol, encouraged us to achieve its scale-up synthesis in a three-step process with overall 72% yield, that improved the analogous examples reported to date.[56]

In order to enhance the water solubility of the complexes, and trying to promote both recyclability as well as a wider use in other catalytic reactions like the Sonogashira coupling, Kapdi and coworkers developed the zwitter-ionic derivative of

PTA, PTABS (KapdiPhos). The synthesis of this modified caged phosphine ligands, obtained by the reaction of PTA with sultones, and its use in palladium-catalyzed selective functionalization of nucleosides and heteroarenes, have been recently reviewed.[57]

4. Phosphine-Free Palladacycles for Low-Temperature Suzuki-Miyaura Synthesis of Nucleoside Analogues in Aqueous Media

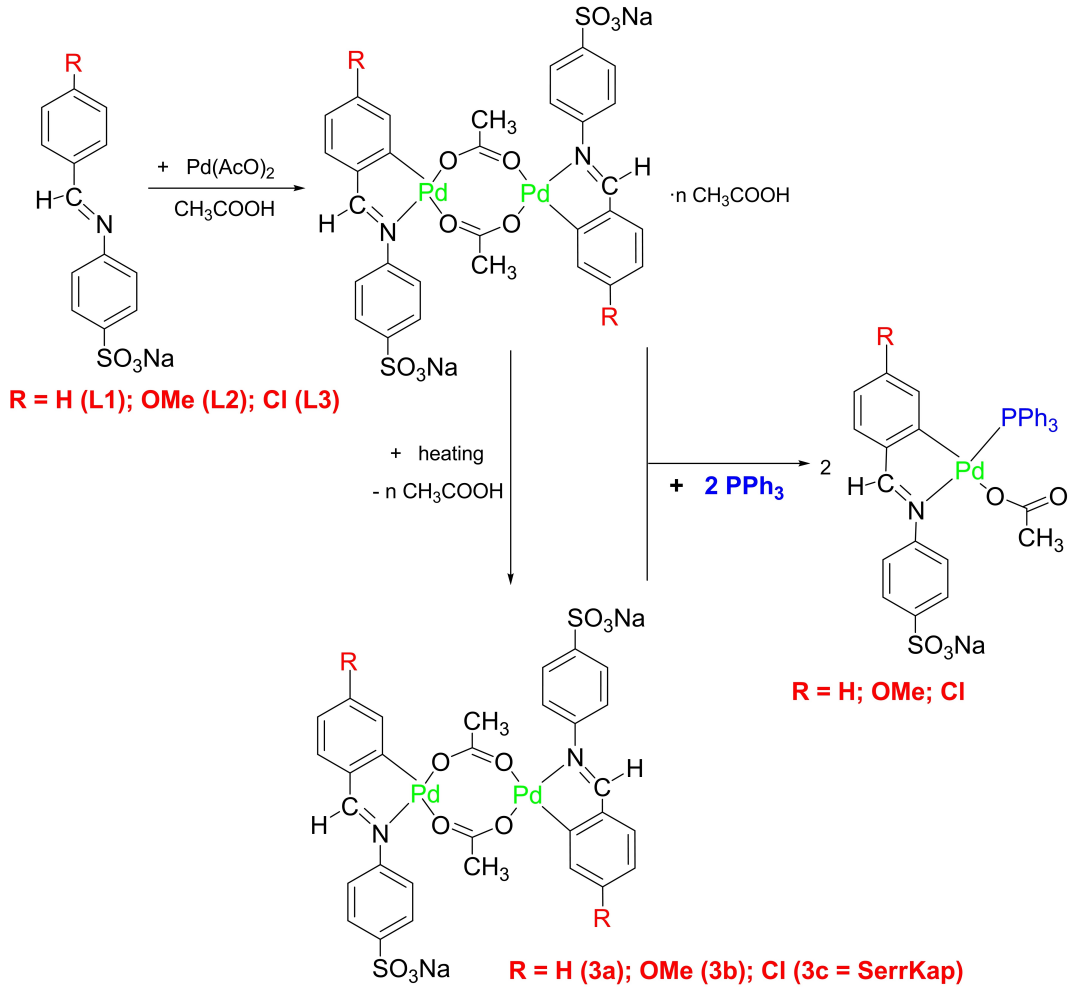
As happened with PTABS, the ionic character in the ligands usually reflects in more solubility of its corresponding complexes. We mentioned in the introduction that the attachment of water-solubilizing groups, like carboxylate or sulfonate, to phosphines or nitrogen ligands is a common strategy in this sense, that has also worked well regarding palladacycles.[58] Shaughnessy has recently reviewed the available approaches to introduce water solubility in this particular class of ligands,[59] exploring himself a range of hydrophilic amine- and imine-based palladacycle precursor ligands and its corresponding chloride-bridged complexes like [{Pd(CN)(μ-Cl)}$_2$], with CN = sodium 4-(N-benzylideneamino)benzenesulfonate. Since the identity of the palladacycle precursor has affected the activity and lifetime of the catalysts,[58a] we focused our attention in the synthesis of analogous acetate-bridged water-soluble complexes as just one example had been described at that time.[60] In our hands the availability of both halide- and acetate-bridged dinuclear palladacycles, previously also revealed as a powerful synthetic tool.[61] As mentioned in the introduction, we had some experience with conventional mono- and dinuclear palladacycles catalyzing Sonogashira and Suzuki coupling,[35–40] so we planned next to explore the synthesis and catalytic properties of the water-soluble bridging acetate palladacycles with imine-based ligands analogous to the chloride ones reported by Shaughnessy, applying them in the modification of nucleosides.[62] Scheme 7 shows the easy preparation of solvated orange acetato-bridged cyclometalated dimers [{Pd-(R–CN-SO_3Na)(μ-AcO)}$_2$]·nCH_3COOH containing L1–L3 ligands, and a test of their synthetic application towards new water-soluble derivatives containing PPh_3.

The IR spectra of dinuclear palladacycles displayed an intense band around 1720 cm^{-1} indicative of free or solvated acetic acid molecules, supported by ^{1}H-NMR spectroscopy. Heating the solid samples above the boiling point of acetic acid produced a colour change from orange to yellow, and the loss of solvated molecules could be followed by those spectroscopic techniques.

4.1. Phosphine-Free Suzuki-Miyaura Coupling of 5-Iodo-2′-deoxyuridine and 5-Iodo- 2′-deoxycytidine with Boronic Acids at Low Temperature

With this new phosphine-free catalytic system in hands, we faced one of the recurrent problems associated with the usual protocols for the modification of nucleosides by Suzuki-Miyaura coupling: the use of phosphine ligands for the activation of the palladium center that could eventually lead to the formation of a phosphine oxide byproduct. The use of relatively high temperatures required by reported protocols also hampers their applications to modify nucleotides or thermally labile nucleoside structural features. Relevant examples of low temperature modification of 6-iodouridine in aqueous media had been reported,[63] but none had combined this feature avoiding at the same time the use of any added phosphine/N-heterocyclic carbene ligand and conducting the Suzuki coupling in water as the sole reaction solvent. Since the catalyst concentration required with our new system is lower than for most examples reported to date, we found it quite unique in terms of the combination of catalyst properties exhibited.

As initial screening studies we investigated the coupling reaction of 5-iodo-2′-deoxyuridine with benzofuran-2-boronic acid. Phosphine-free complexes overall produced higher yields than mononuclear PPh_3 derivatives, probably due to the lower water solubility of the latter (S_{20} °C = 2.7–6.2 mg/mL). The obtention of two unexpected crystal structures for them pointed out to the formation of neutral intermediates as tentative explanation for this behaviour.[62] Adjustment of relevant parameters such as solvent, temperature, base, and catalyst concentration were conducted with complex **3c (SerrKap)** that incorporated a chloride substituent in the benzylideneaniline ligand, since it was the one showing a better performance. The substrate scope for the modification of 5-Iodo-2′-deoxyuridine was next undertaken by Suzuki-Miyaura cross coupling with differently substituted arylboronic acids, using 0.5 mol% of this complex in water at 60 °C as the sole reaction solvent, using Et_3N as base outperforming K_3PO_4, K_2CO_3, Cs_2CO_3, and DBU. Activated aryl/heteroaryl boronic acids produced very good yields of the desired cross-coupled products, while lower yields were observed for bulky arylboronic acids such as triphenylamine, phenylnaphthyl, and phenanthrene, (Scheme 8). An accurate comparison with the published phosphine-free system $Pd(AcO)_2$/ADHP (ADHP = 2- aminopyrimidine-4,6-diolate) cannot be done, since the reported results for Suzuki coupling of aryl- and alkenylboronic acids with 5-IdU are conducted in different condition like a 3:1 H_2O/CH_3CN mixture, 5 mol% and 50 °C,[64] but in similar reaction time **SerrKap** produced a higher yield (93% vs 80%) of the phenylboronic derivative.



Scheme 7. Synthesis of the dinuclear palladacyclic complexes and its PPh_3 derivatives. Reprinted (adapted) with permission from [62] J. L, Serrano, L. García, J. Pérez, P. Lozano, J. Correia, S. Kori, A. R. Kapdi, Y. S. Sanghvi, Organometallics 2020, 39, 4479–4490. Copyright {2020} American Chemical Society.

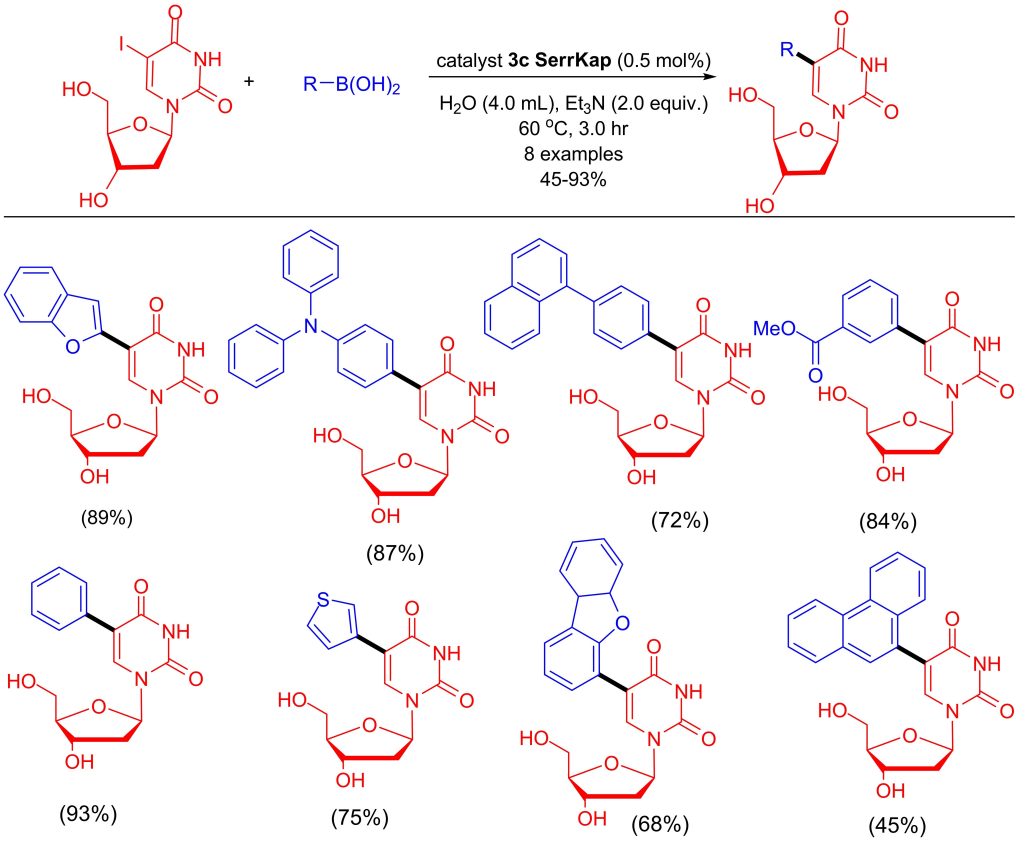
We also studied the cross-coupling of 5-iodo-2′-deoxycytidine with arylboronic acids in neat water as solvent, obtaining three examples of the cross-coupled 5-arylated 2′-deoxycytidine derivatives in good yields (Scheme 9).

Since a noticeable change in the aspect of the reaction was observed from the clear yellow solution at the start of the reaction to a dark color at the end, when a black particulate matter appeared at the bottom of the reaction vessel, we explored the involvement of colloidal or nanoparticular catalytic species. A Crabtree test and different catalyst poisoning experiments were conducted to get deeper knowledge about the mechanism of the reactions, pointing out a likely nanoparticular nature of the operating pathway, in accordance with previously reported results for analogous phosphine-free dinuclear palladacycles.

4.2. Phosphine-Free Catalysts for the Direct Functionalization of 5'-O-DMT-5-iodo-2′-deoxyuridine via Suzuki-Miyaura Cross-Coupling and Heck Alkenylation

An important goal in the chemistry of functionalized nucleosides implies them being further transformed into phosphoramidites and oligonucleotides to demonstrate their applicability into the field of fluorescent sensors. A key steps for the incorporation of such nucleoside analogues is the protection of the position 5'-OH of the sugar with the protecting group 4,4'-dimethoxytrityl (DMT), followed by 3'-O-phosphoramidite synthesis. DMT-protection is critical and involves the use of the 4,4'-dimethoxytrityl group, that is acid- sensitive, and relatively high temperature, which makes the overall process synthetically challenging.[65]

To overcome the poor yields intrinsic to the DMT-protection route, we envisaged the usefulness of the direct



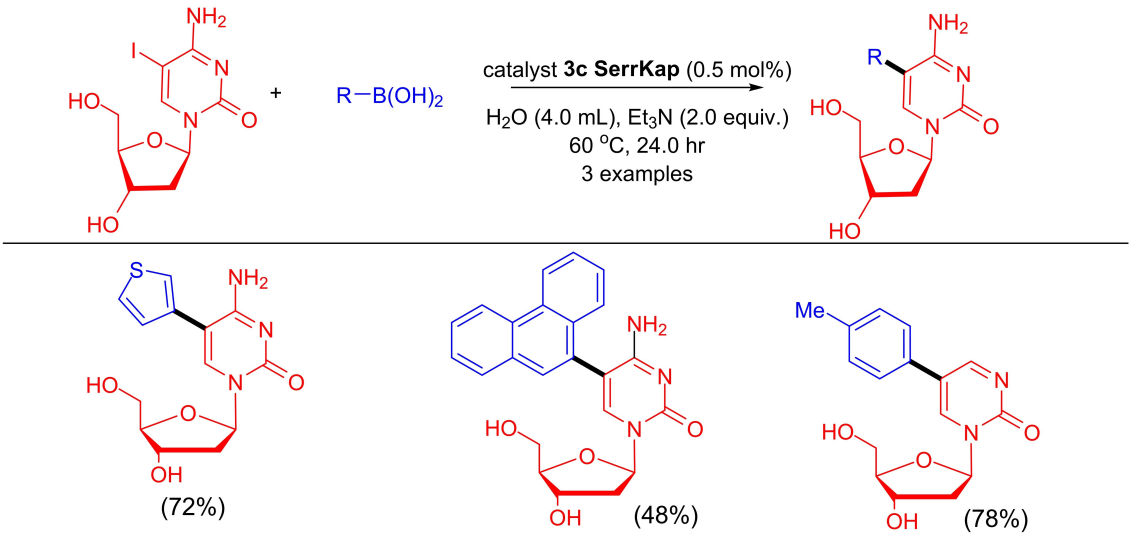
Scheme 8. Substrate scope for phosphines-free Suzuki-Miyaura cross-coupling of 5-iodo-2′-deoxyuridine in water.[a,b] [a]Unless stated otherwise: 0.5 mmol of 5-iodo-2′-deoxyuridine, 0.75 mmol of boronic acids, 1.0 mmol of Et_3N, H_2O (4.0 mL), complex 3 (0.5 mol%); [b]isolated yields "Reprinted (adapted) with permission from [62] J. L, Serrano, L. García, J. Pérez, P. Lozano, J. Correia, S. Kori, A. R. Kapdi, Y. S. Sanghvi, Organometallics 2020, 39, 4479–4490. Copyright {2020} American Chemical Society.

functionalization of 5'-O-DMT-5-iodo-2′-deoxyuridine as a late-stage strategy involving Suzuki-Miyaura cross-coupling and Heck alkenylation. **SerrKap** palladacycle (**3c**), which had worked efficiently for the unprotected version of the nucleosides, was successfully tested in both reactions.[66] Thus Suzuki-Miyaura cross-coupling of 5'-O-DMT-5-iodo-2'-deoxyuridine was catalyzed by **3c** with several aryl and heteroarylboronic acids, as displayed in Scheme 10. Although the reaction was initially tried in water, the scarce solubility of the starting DMT-protected 5-iodo-2'-deoxyuridine in it prompted us to use DMF as a solvent instead, obtaining the corresponding C5 substituted 2'-deoxyuridines in good yields.

Scheme 11 displays the Heck alkenylation of 5'-O-DMT-5-iodo-2'-deoxyuridine with 5 different alkenes that was catalyzed by SerrKap palladacycle **3c**, in DMF as a solvent at 80 °C. Substituted styrene and other alkenes were the coupling partners tested, providing the coupled products in good yields, although lower if compared with the ones obtained in the Suzuki-Miyaura cross-coupling discussed above.

5. Phosphine-Free Quadrol Palladium Complexes for the Room-Temperature Suzuki-Miyaura Synthesis of Nucleoside Analogues in Aqueous Media

As mentioned in the introduction, regarding Pd-catalyzed cross-coupling reactions in aqueous media, hydrophilic nitrogen ligands have received lesser attention than phosphines, and among the first ones, the use of neutral hydrophilic N-donor ligands is still rare if compared with the most extended incorporation of the usual anionic/cationic solubilizing groups. To the best of our knowledge, only some examples that used ethylenediamine tetracetic acid (EDTA) and *N*,*N*,*N*′,*N*′-Tetra(2-hydroxyethyl)ethylene diamine (THEEN) as ligands in Suzuki- Miyaura coupling of aryl bromides in water have been reported.[67] In this section is described our pioneer report of Quadrol, *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN) used as a neutral NN- donor ligand leading to the synthesis and characterization of new water-soluble palladium (II) complexes. The



Scheme 9. 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. "Reprinted (adapted) with permission from [62] J. L, Serrano, L. García, J. Pérez, P. Lozano, J. Correia, S. Kori, A. R. Kapdi, Y. S. Sanghvi, Organometallics 2020, 39, 4479–4490. Copyright {2020} American Chemical Society."

application of such Quadrol complexes as catalysts for Suzuki-Miyaura cross-coupling of 5-iodo-2′-deoxyuridine and 5-iodo-2′-deoxycytidine with different arylboronic acids made us able to perform the catalytic reaction working at room temperature in water as the sole reaction solvent.[68]

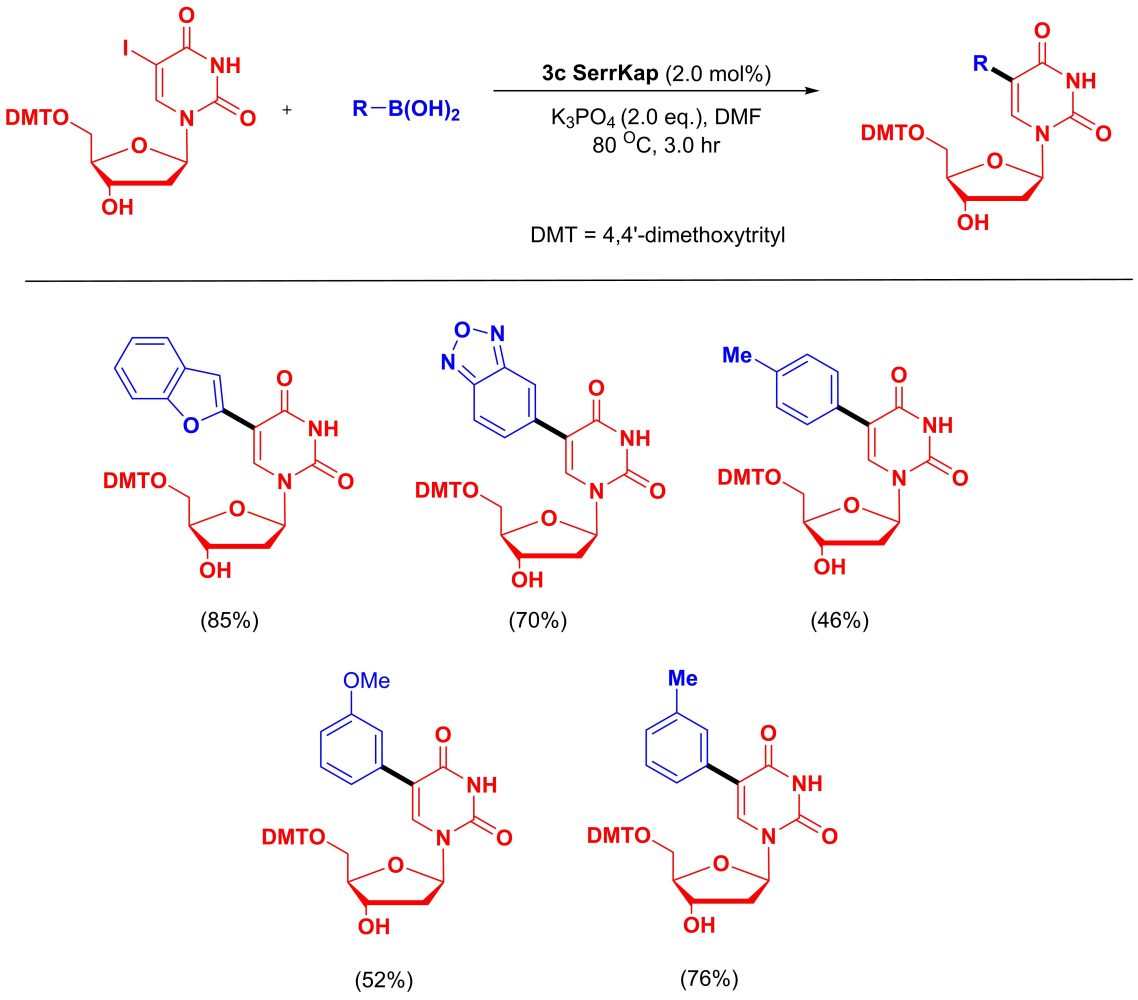
Although we synthesized its first Pd complexes, the coordination chemistry of THPEN has been previously explored with other metals. Of particular interest are Cu(II) complexes[69] with neutral THPEN due to their antimicrobial properties.[70] We approached the synthesis of the Quadrol complexes from two routes and precursors: $[PdCl_2(THPEN)]$ (**4**) was obtained by adding a dichloromethane solution of *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxypropyl)ethylenediamine (THPEN) to a stirred solution of $[PdCl_2(MeCN)_2]$ in the same solvent, while a one-pot synthetic route from $Pd(OAc)_2$ allowed the preparation of THPEN/imidate complexes. Saccharinate complex **7** with THEEN instead was also prepared in a similar way (all shown in Scheme 12). A detailed experimental characterization of the new derivatives, including the two first crystal structures reported to date of Pd-Quadrol complexes can be found in the original article.[68]

Although our previous work on phosphine-free palladacyclic complexes allowed us to perform the catalytic reactions of nucleoside modification at 60 °C, any further temperature lowering led to a reduction in the catalytic activity. As mentioned, a room temperature catalytic protocol for such modification in water was one major target of our research groups. Catalytic reactions conducted under these conditions would be expected to further enable the late-stage modification of temperature sensitive oligonucleotides, DNA or RNA.

An overview of the optimization studies that were conducted with 1–4 for the Suzuki-Miyaura cross-coupling of 5-iodo-2′-deoxyuridine with 3-methylphenyl boronic acid is collected in Table 1. $[Pd(sacc)_2(THPEN)]$ soon revealed as the best option working at 80 °C with 0.5 mol% concentration. The temperature could be lowered to 30 °C employing longer reaction times, that were then reduced using double load of catalysts. Again the base Et_3N revealed as the best one, even used in an equimolar amount. Previously reported catalytic systems from our groups were also tested, and only the combination of $Pd(OAc)_2$ and PTABS (KapdiPhos) as ligand produced 50% isolated yield in the benchmark reaction. The conditions were not improved increasing the amount of base or reducing the catalyst loading.

Similar room-temperature results were reported with the classical sulfonated-phosphine systems in water/acetonitrile, with complete conversion of 8-bromo-deoxyadenosine to 8-PhdA in only 30 minutes using Pd/TXPTS and 24 h with the TPPTS analogue (74%).[14] Other authors reported good results working with this systems in neat water, although varying other conditions as catalyst loading.[26c,63a]

The main output of those optimization studies is that the Quadrol-based palladium complex **5** is a highly active catalyst free of phosphine that promotes the Suzuki-Miyaura cross-coupling of uridine nucleosides in neat water working at as low temperature as 30 °C. It is indeed the first report of this characteristics that can be found in literature, and definitively



Scheme 10. Palladium-catalyzed Suzuki-Miyaura coupling of DMT-protected 5-iodo-2'-deoxyuridine.

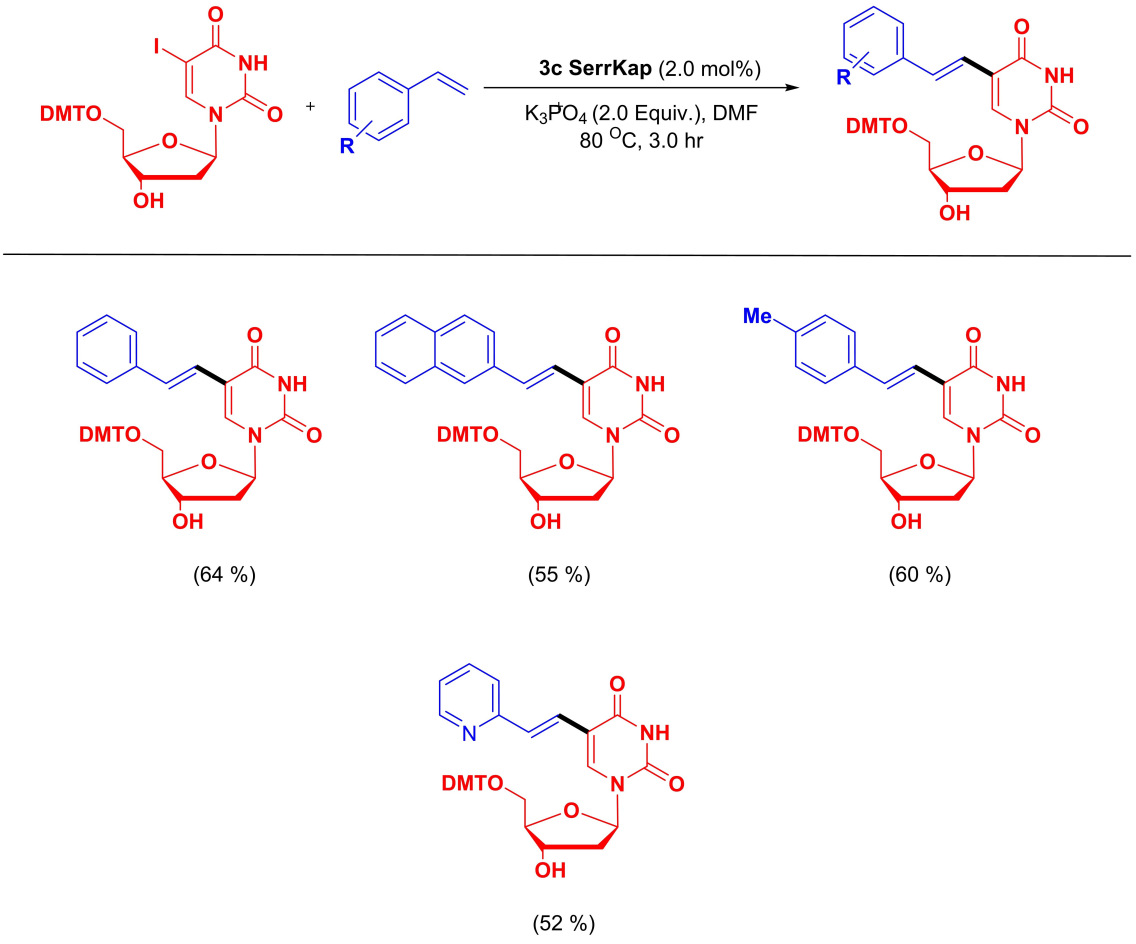
opens us future perspectives regarding substrate scope, even the most ambitious late-stage modification of temperature sensitive oligonucleotides, DNA or RNA.

The substrate scope of the developed catalytic reaction was further explored with several substituted arylboronic acids, and is shown below in Scheme 13.

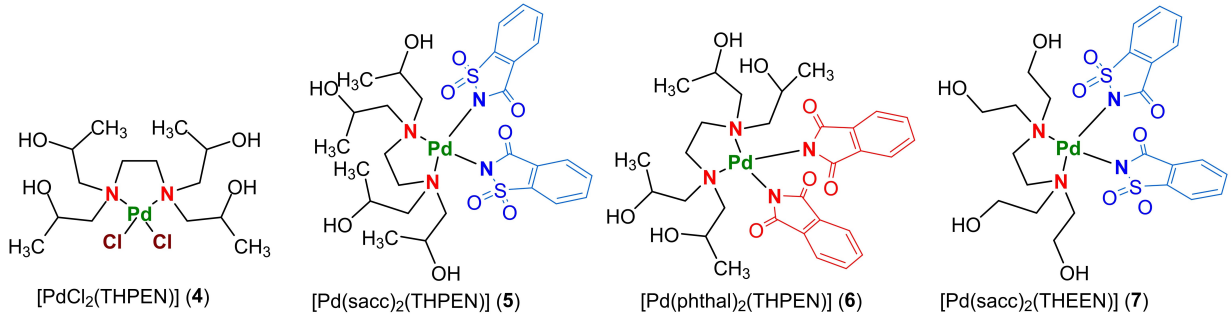
As can be seen in Scheme 13, the incorporation of classical electron-donating substituents on the arylboronic acids, like 4-SMe, 3-OMe or 3,5-$(Me)_2$, allow them to react with 5-iodo-2′-deoxyuridine to produce the desired cross-coupled products in good yields. When a strongly electron-donating substituent as benzoxadiazole was incorporated in the boronic acid used as the nucleophilic partner, a good yield of the desired product (fluorescent in nature) was also obtained. Decent yields can be reported when 4-biphenylboronic acid and 3-benzofuranyl boronic acid were coupled with 5-iodo-2′-deoxyuridine, while the introduction of an electron-withdrawing 4-fluoro substituent reflected in the reduction of the coupled product yield.

As we did with the TPA complex **1** and palladacyle **3**, we included here the extension of the room temperature protocol for other nucleosides, thus employing 5-iodo-2′-deoxycytidine as the electrophilic coupling partner. Several arylboronic acids were tested using 1.0 mol% of complex **5** in water, as displayed in Scheme 14. It was concluded, in comparison with its uridine analogue, that cytidine is less reactive. Even after 24 hours the reaction with 3-Methyl boronic acid did not proceed to completion giving however decent yield of the coupled product.

Mechanistic studies were conducted to investigate the nature of the catalytic species. They involved poison tests and indicated the presence of colloids/nanoparticles, differing from the results reported for Pd complexes with related ligands as TMEDA or N,N,N′,N′-tetrakis(2-



Scheme 11. Palladium-catalyzed Heck coupling of DMT-protected 5-iodo-2'-deoxypyrimidines.



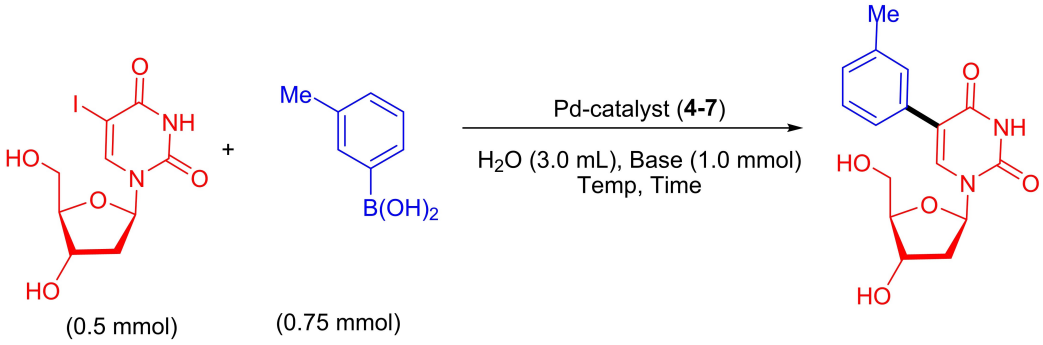
Scheme 12. New palladium complexes with neutral hydrophilic nitrogen ligands.

hydroxyethyl)ethylenediamine, that were not active at room temperature and specifically described the absence of Pd-black, thus emphasizing the novelty of the Quadrol catalytic system (**5**).

6. Summary and Outlook

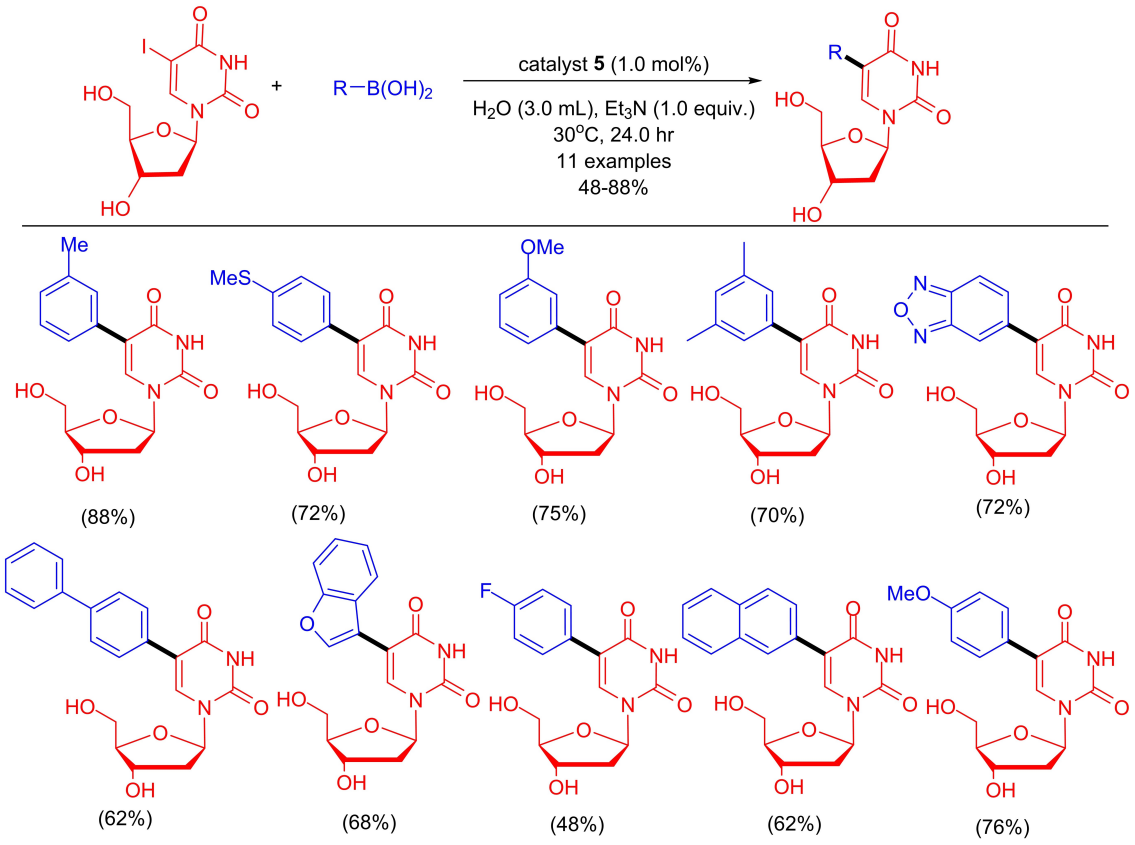
As presented above, we started our approach to Pd-complexes as versatile catalysts for the modification of unprotected halonucleosides back then in 1998 from a mere academic interest in the synthesis of new imidate-complexes. This

Table 1. Optimization studies for the Suzuki-Miyaura cross-coupling of 5-iodo-2′-deoxyuridine with 3-methylphenyl boronic acid. Adapted from Ref. 68 with permission from the Royal Society of Chemistry.



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

interest arose from the serendipitous obtention of a single crystal that raised from an odd experiment, and was fuelled equally by the unfinished urgent curiosity of young researchers and the *laissez-faire* and wise advice of senior supervisors. The combination with valuable international collaborations made possible the commercialization of **[Pd(PPh$_3$)$_2$(N-succinimidate)Br] (1)** five years later as catalysts in cross-coupling reactions, thus confirming the validity of all the ingredients in this old formula to get substantial advance in any field. After several years expanding our library of Pd-imidate complexes and gaining experience about its catalytic applications in cross-coupling reactions conducted in conventional solvents, we jumped into the development of several water-soluble catalytic systems that allowed the cross-coupling modification of nucleosides to be performed efficiently in aqueous media. Starting with the series **[Pd(imidate)$_2$(PTA)$_2$] (2) (H_2O/80 °C,** solvent and temperature are highlighted to compare relative merits of catalysts**)** that allowed the Suzuki-Miyaura cross-coupling of **all four nucleosides**, we disclosed the outstanding performance of the saccharinate complex. The reaction time could be reduced to minutes by means of a microwave-assisted process that kept the good yields of the conventional reaction. The saccharinate complex performed equally well in the C-5 Heck alkenylation of pyrimidine nucleosides, and following the optimized protocol we developed a scale-up synthesis of BVDU in a three-step process with overall 72% yield. Main limitations of this system are the lack of recyclability and the limited scope. We moved then to



Scheme 13. 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-iodo-2′-deoxyuridine, 0.75 mmol of boronic acids, 1.0 mmol of Et_3N, H_2O (3.0 mL), complex **5** (1.0 mol%) at 30 °C; [b]isolated yields. Adapted from Ref. 68 with permission from the Royal Society of Chemistry.

water-soluble dinuclear palladacycles that contain the orthometalated backbone sodium 4-(N-benzylideneamino)-benzenesulfonate and bridging acetate groups. **SerrKap palladacycle (3c) (H_2O/60 °C)** in low concentration acted as a phosphine-free catalyst for the synthesis of functionalized nucleoside analogues involving a low-temperature Suzuki-Miyaura coupling of 5-iodo-2′-deoxyuridine with different arylboronic acids in neat water. As our most recent result, we have presented here the direct functionalization of protected 5'-O-DMT-5-iodo-2′-deoxyuridine as a late-stage strategy using SerrKap palladacycle (3) in both Suzuki-Miyaura cross-coupling and Heck alkenylation. Finally, our results working with cheap and commercially available Quadrol (THPEN) as a neutral hydrophilic N N-donor ligand in the synthesis of new palladium(II) complexes have been presented here. **[Pd-(sacc)$_2$(THPEN)] (5) (H_2O/30 °C)** is another example of water-soluble phosphine-free catalyst promoting the 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. **3c** and **5** have not been extended to the less-reactive 8-halopurine nucleosides.

To reduce the reaction times and specially to make the scale-up obtention of modified nucleosides attainable, the development of a column-free flow catalytic protocol would be highly desirable (these systems require isolation by column chromatography) and is one of our future perspectives in this field. The application of water-soluble catalytic systems in the synthesis of modified oligo- molecules was the final goal we had in mind, and it is a challenge we are currently facing in collaboration with Ramón Eritja's Nucleic Acids group at the IQAQ-CSIC.

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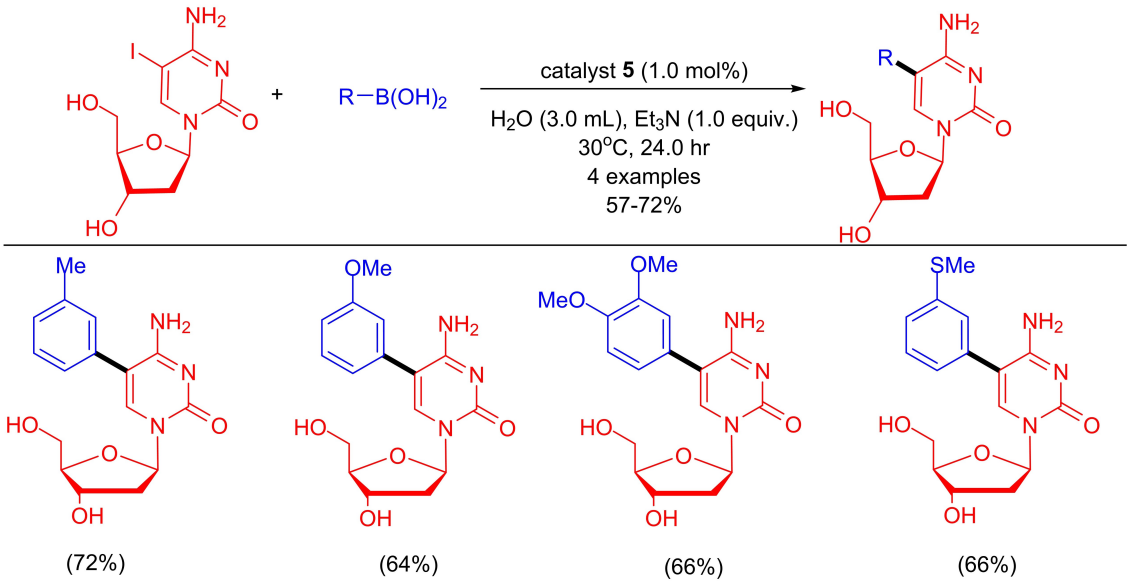

Scheme 14. Substrate scope for phosphine-free Suzuki-Miyaura cross-coupling of 5-iodo-2′-deoxycytidine with different arylboronic acids at room temperature.[a,b] [a]Unless stated otherwise: 0.5 mmol of 5-iodo-2′-deoxycytidine, 0.75 mmol of arylboronic acid, 1.0 mmol of Et_3N, H_2O (3.0 mL), complex **5** (1.0 mol%) at 30 °C; [b]isolated yields. Adapted from Ref. 68 with permission from the Royal Society of Chemistry.

the colleagues and supervisors from Universidad de Murcia, University of Sussex, Inorganic Chemistry Laboratory-University of Oxford, University of York, and Institute of Chemical Technology-Mumbai for his contribution to this work and his wise and continuous advice and support.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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