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Palladium-catalyzed Suzuki reaction in aqueous solvents applied to unprotected nucleosides and nucleotides

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Abstract : Nucleoside analogues have attracted much attention due to their potential biological activities. Amongst all synthetic nucleosides, C5-modified pyrimidines and C2- or C8-modified purines have been particularly studied. A large variety of palladium cross-coupling reactions, with a preference for the Suzuki-Miyaura reaction, have been developed for preparing the desired nucleoside derivatives. Our objective is to focus this review on the Suzuki-Miyaura cross-coupling of nucleosides using methodologies compatible with green chemistry and sustainable development for one part and bioorthogonality for the other part which means aqueous medium and no protection/deprotection steps.

Keywords : nucleoside, nucleotide, Suzuki-Miyaura, water, green chemistry.

This work was dedicated to Professor Gordon Shaw 1922-1997

Gordon Shaw obtained a first class honours degree in chemistry in 1942 from Imperial College of Science and Technology and a PhD (supervised by Sir Ian Heilbron and A. H. Cook on the synthesis of penicillin and analogues) in 1945. Following a spell in the pharmaceutical industry he became Senior Lecturer in Organic Chemistry at the University of New South Wales between 1948 and 1959. He won a Nuffield Research Fellowship to work at the University of Cambridge with Lord Todd, the Nobel Prize Laureate, from 1955 and 1956. In 1960 took up the post of Reader in Organic Chemistry at the University of Bradford and in 1989 he became a Professor at the University of Bradford. He continued his teaching and research until his death on 25 June 1997.

He published work on the field of nucleosides and nucleotides but also focused on the origins of life on Earth largely through the study of the polymer sporopollenin which is the extremely stable polymer that coats pollen grains and is found in some of Earth's oldest sedimentary rocks book he wrote with J. Brooks entitled 'Origin and Development of Living Systems'. He showed that this sporopollenin could be adapted as solid phase support for such as peptide synthesis. Most of his nucleoside and nucleotide work was reported in his 67 Part series in the Journal of the Chemical Society on the 'synthesis of purines, pyrimidines and imidazoles including nucleosides'. His approach was notable by being the first to employ acyclic intermediate to obtain regiospecificity and in many cases stereoselectivity. His work shone much light on the de novo biosynthesis of purines and included such as the first synthesis of the naturally occurring cytokinin zeatin. In the latter part of his work he used an innovative route anthracyclinones and their via a modified Marschalk reaction using a carbohydrate as a chiral template. He published this work in a five Part series in the Journal of the Chemical Society.

Gordon Shaw will be well remembered by a wide circle of collaborators and friends for his modesty, humility and capacity for original thought.

1. INTRODUCTION

Natural nucleosides are of great biological importance in metabolic pathways and as building blocks of nucleic acids. Their common structural characteristic is the presence of two molecular moieties: D-ribo or D-2'-deoxyribopentofuranose as the glycone fragments and purine or pyrimidine as the aglycone moiety. These two moieties are covalently bonded at the anomeric site (C1') of the glycone to either the *N*1 of the pyrimidine (uracil, thymine, and cytosine) or *N*9 of the purine (adenine and guanine) in a β-D configuration to form,

correspondingly, the nucleosides thimidine (**1**), uridine (**2**), cytidine (**3**), adenosine (**4**) and guanosine (**5**) (Figure 1).

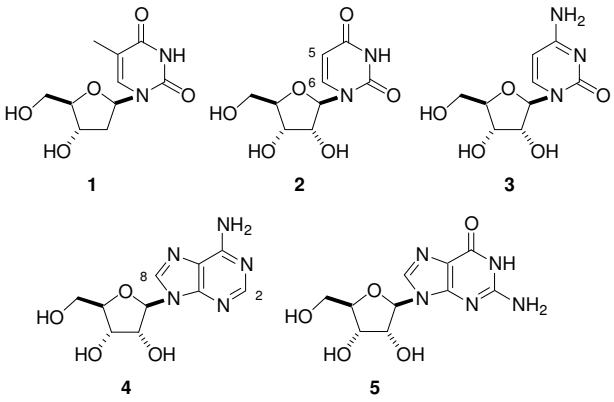
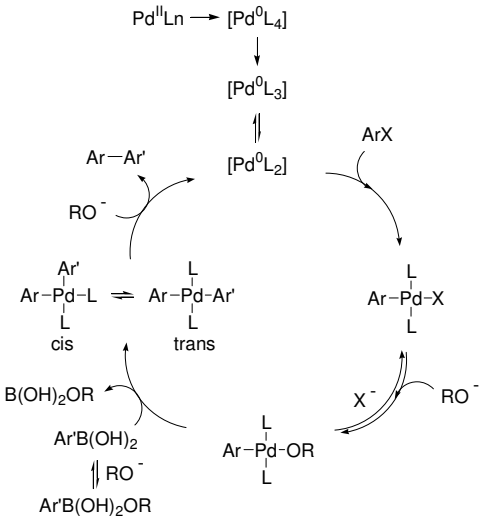


Figure 1. Nucleosides **1-5**.

Since the discovery that nucleoside analogues have shown high effectiveness as antiviral and antitumor agents,[1] the search for new agents with a higher therapeutic index have been developed. In this regard, many modifications of the glycone moiety and/or the nucleobase have been reported. A variety of functionalities[2] have been introduced into the ribose glycone moiety. Such have included simple substituents including halogeno, N_3, CF_3, CN, alkyl. Alkenyl, alkynyl, aryl, thio and seleno groups have been reported but have included more complicated modifications to form acyclic nucleosides, L-isomers, thio or amino analogues, *C*-nucleosides and nucleosides having restricted conformations[2k,3] such as bicyclonucleosides, cyclonucleosides and cyclic phosphoesters. Major modifications to the nucleobase have included the introduction of aryl, polyaryl, heteroaryl and heteropolyaryl groups *via* C-C bond coupling. These were synthesized for the study of biological environments such as protein-DNA complexes, DNA damage, mutation and cancers.[4] These new tools such as DNA and RNA structural probes are aimed at gaining a better understanding of various diseases and

establishing methods for diagnosis and high-throughput screening. Starting from the natural nucleosides **1-5**, the synthesis of the aryl nucleoside analogues, having a C-C bond coupling, permitted selective modification at the C-5 and C-6 positions of the pyrimidine moiety and the C-2 and C-8 positions of the purine ring system. Of the main strategies used for the preparation of aryl, polyaryl, heteroaryl and heteropolyaryl nucleoside analogues (C sp^2 – C sp^2 bond formation), the palladium-catalyzed Suzuki-Miyaura, Stille, Negishi and Hiyama reactions appear to the most prefered.[5] In general, the C-C cross coupling reactions have been effected in organic solvents using totally protected nucleosides.

The aims of green chemistry[6] are to: (i) develop less hazardous chemical syntheses; (ii) use safer solvents and auxiliaries; (iii) use renewable feedstocks; (iv) reduce intermediate (v) develop or discover better catalysts. Even if the Stille, Negishi and Hiyama reactions comply with some of the green chemistry principles, only the Suzuki-Miyaura reaction offers the most attractive potential for development. An important feature is that the Suzuki-Miyaura reaction can be carried out in green solvents, such as water, without the need for protection and deprotection steps. The general Suzuki-Miyaura catalytic cycle occurs by oxidative addition, transmetallation and reductive elimination.[7] After formation of the catalytic species Pd(0), *in situ* starting from palladium Pd(II) or from direct starting Pd(0) derivatives, the oxidative addition of the aryl halide ArX leads to the palladium complex [ArPdXLn]. The transmetallation step occurs by conversion of the palladium halide [ArPdXLn] in presence of base RO^- to a nucleophilic palladium alkoxy complex [ArPdORLn] that subsequently reacts with a neutral organoboron compound Ar□$B(OH)_2$ to afford the diaryl complex [ArPdAr□Ln] in a *cis-trans* equilibrium. Reductive elimination of the *cis* form gives the biaryl derivative Ar-Ar□ and Pd(0) (Scheme 1).[7e]



Scheme 1. Mechanism for the Suzuki-Miyaura reaction.

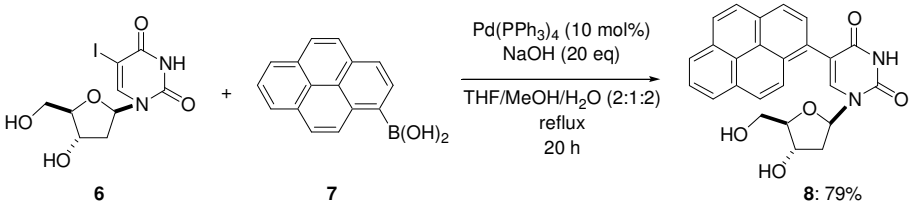
This review is concerned with green chemistry and sustainable development in the field of modified nucleoside analogues with particular focus on the Suzuki-Miyaura C-C cross-coupling reaction applied to unprotected nucleosides and nucleotides in aqueous media or water as the sole solvent. The particular C-C bond formations in this review are those in position 5 and 6 of the pyrimidine nucleoside analogues and in the position 8 of the purine nucleoside analogues. Examples of Suzuki-Miyaura coupling in position 6 of purine and using 7-deazapurine are also covered as well as postsynthetic arylation of DNA by Suzuki-Miyaura cross-coupling. For the sake of clarity, this review has been arranged to describe the different methodologies varying: (i) the nature of the solvent THF/MeOH/H_2O, DME/H_2O, DMF/H_2O, CH_3CN/H_2O, MeOH/H_2O, H_2O; (ii) the palladium source and nature in respect of Pd(II) and Pd(0); (iii) the nature of the base. One special chapter is reserved to the postsynthetic strategy.

2. SUZUKI-MIYAURA IN THF/MeOH/H_2O

The Suzuki-Miyaura cross-coupling reaction in THF/MeOH/H_2O was developed using both Pd(0) as the active catalyst and Pd(II) as a pre-catalyst when used in a large amount (10-11 mol%).

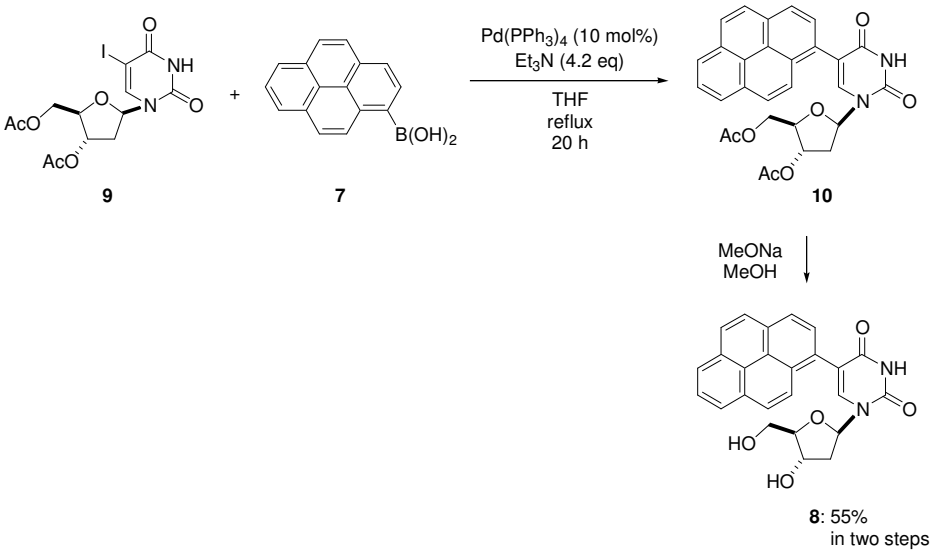
2.1. $Pd(PPh_3)_4$ as Pd(0) and NaOH

In 2002, Wagenknecht and co-workers reported the first direct synthesis of unprotected arylated pyrimidine derivatives using a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction.[8] Starting from the 5-iodo-2□-deoxyuridine (**6**), the modified nucleoside 5-(pyren-1-yl)-2□-deoxyuridine (**8**) was obtained in 70% yield using pyren-1-yl boronic acid (**7**) (1.0 eq), a large amount of $Pd(PPh_3)_4$ as the catalyst (10 mol%) in a mixture of THF/MeOH/H_2O (2:1:2) as the solvent (Scheme 2) for 20 hours under reflux. NaOH (20 eq) as a strong base was required to obtain the desired sterically hindered coupling product **8** in sufficient yield. The yield of nucleoside analogue **8** was increased slightly a few months later (79% *vs* 70% yield) by the authors using the same experimental conditions.[9]



Scheme 2. Synthesis of pyren-1-yl-modified nucleoside **8**.

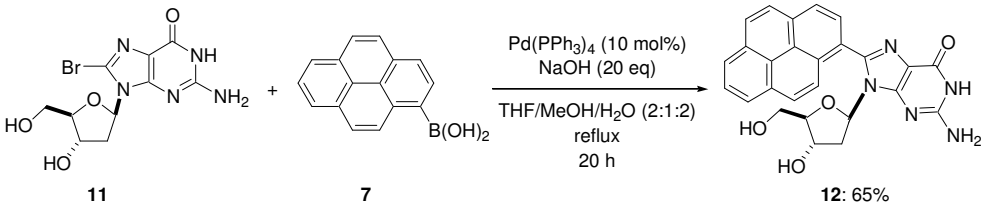
The authors showed that protection of the two hydroxyl groups of the 2′-deoxyribose moiety of compound **6** was not necessary. In order to validate their new pathway, Wagenknecht and co-workers prepared compound **8** starting from the 3′,5′-di-*O*-acetyl-2′-deoxy-5-iodouridine (**9**) and boronic acid **7** (1.0 eq). The use of the protected nucleoside analogue **9** induced modifications to the protocol. In this case, dry THF as solvent and Et_3N (4.2 eq) as base were used.[8] The cross-coupling furnished the pyrene analogue **10** and subsequent classical deprotection of the nucleoside analogue **10** afforded the target pyrene derivative **8** in 55% yield (two steps) (Scheme 3).



Scheme 3. Synthesis of pyren-1-yl-modified nucleoside **8** starting from the protected nucleoside analogue **9**.

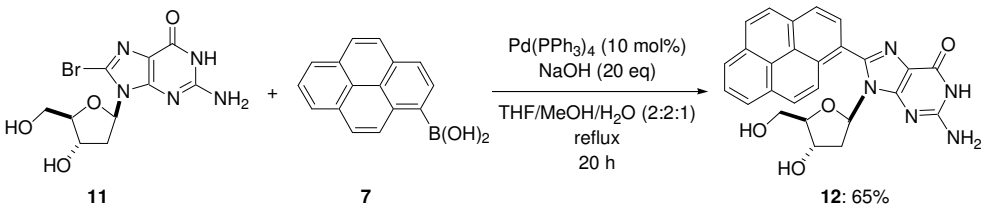
A second 8-(pyren-1-yl)-nucleoside (**12**) was prepared in a similar way (Scheme 4) starting from 8-bromo-2′-deoxyguanosine (**11**) having an unprotected hydroxyl group on the ribose moiety and an exocyclic amino group on the nucleobase and boronic acid **7** (1.0 eq). After

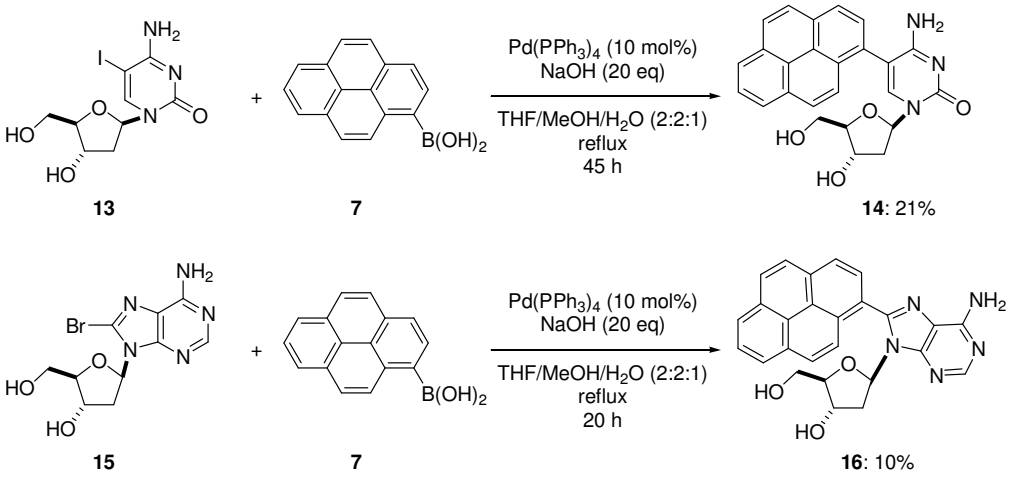
purification of the crude product, the pyrene-modified nucleoside **12** was obtained in 65% yield.[8]



Scheme 4. Synthesis of pyren-1-yl-modified nucleoside **12**.

Subsequently, Wagenknecht and co-workers applied their protocol to the preparation of two others pyrene-modified derivatives, **14** and **16**, starting from the corresponding 5-iodo and 8-bromo derivatives **13** and **15**, respectively. Each of the starting materials **13** and **15** had two hydroxyl groups and one exocyclic amino group (Scheme 5).[10] Starting from the nucleoside analogues **11**, **13** and **15**, the Suzuki-Miyaura cross-couplings were performed with an excess of boronic acid (1.2 eq) using the same previously described catalyst and base in THF/MeOH/H_2O (2:2:1), as in their earlier study. Even with a little excess of boronic acid **7** (1.2 eq *vs* 1.0 eq) and modulation of the water ratio (20% *vs* 40%), the guanosine analogue **12** was obtained in similar yield (Schemes 4 and 5). The target compounds **14** and **16** were prepared in 21% and 10% yields, respectively with a longer reaction time required for the cytosine analogue **14**.



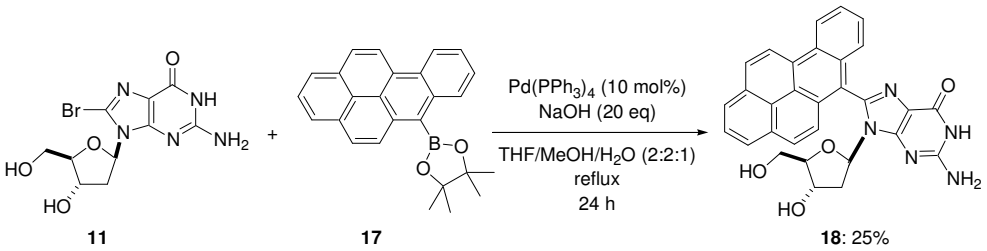


Scheme 5. Synthesis of pyren-1-yl-modified nucleoside analogues **12**, **14** and **16**.

Compared with preceding results, compounds **14** and **16** were obtained in lower yields. Since the authors have consistently used unprotected starting nucleosides, the difference in reactivity is likely to be attributed to the structural differences on the four nucleobases but more particularly to the exocyclic amino function present in the cytidine and adenosine scaffold. Furthermore, the exocyclic amino function could be involved in palladium-complex formation leading to side-products. Therefore to improve the yields of compound **14**, further attempts were performed such as: (i) changing the catalyst $Pd(PPh_3)_4$ to $PdCl_2(dppf)$; (ii) substituting the boronic acid by the propanediol ester derivative; (iii) extending the reaction time; however, these modifications were not successful. Finally, Wagenknecht and co-workers decided to protect their starting cytidine analogue and to proceed with the cross-coupling in dry THF as a solvent in the presence of Et_3N as a base using similar strategy outlined in Scheme 3. As expected, the yield of the cross-coupling adduct **14** was higher (49%). [10]

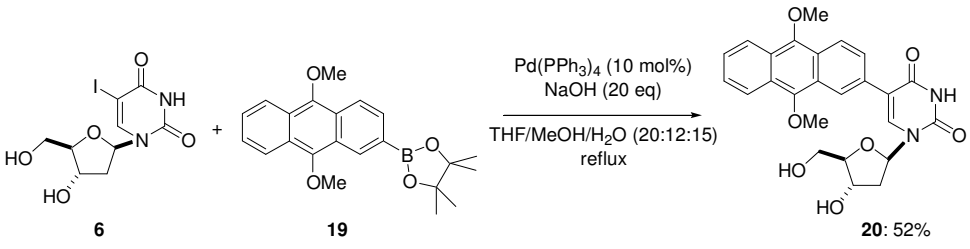
Two years later, the same team directed their efforts to synthesize chromophores-modified nucleosides, by applying the palladium Pd(0)-catalyzed Suzuki cross coupling reaction to the

8-bromo-2′-deoxyguanosine (**11**) employing an excess of the pinacol ester **17** of boronic acid (1.2 eq). After 24 hours of reflux, the target C-8 adduct **18** was obtained in 25% yield (Scheme 6).[11] It is noteworthy that the benzo[a]pyren-6-yl boronic acid was difficult to isolate and the synthesis of the corresponding pinacol ester **17** was the preferred product.



Scheme 6. Synthesis of modified nucleoside **18**.

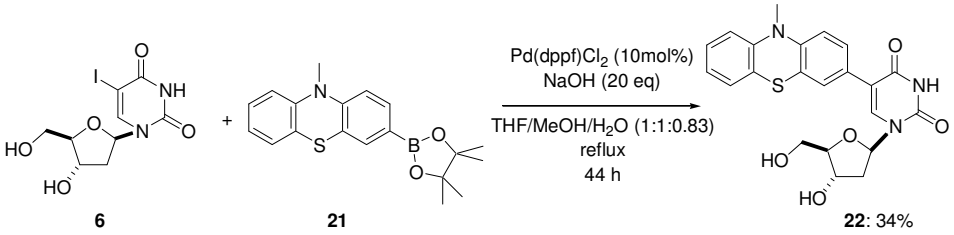
The synthesis of the anthraquinone-modified nucleoside **20** (Scheme 7) was described by Gothelf and co-workers in 2009 using the methodology developed by Wagenknecht.[12] Starting from the 5-iodo derivative **6** and the corresponding pinacolate **19**, the authors modified the solvent ratio THF/MeOH/H_2O (20:12:15) but used $Pd(PPh_3)_4$ (10 mol%) as catalyst in keeping with their previous work but employed NaOH (20 eq) as base. In their hands, the target nucleoside analogue **20** was obtained in 52% yield.



Scheme 7. Synthesis of anthraquinone-conjugated nucleoside analogue **20**.

2.2. $PdCl_2(dppf)$ as Pd(II) and NaOH

Wagenknecht and co-workers also reported the synthesis of the phenothiazine derivative of 2□-deoxyuridine **22**.[13] Starting from compound **6** and the corresponding pinacolate **21** (1.2 eq), they changed their source of palladium $Pd(PPh_3)_4$ for $PdCl_2(dppf)$ (Pd(II) *vs* Pd(0)) and modified the ratio of the solvent mixture (THF/MeOH/H_2O, 2:2:1 *vs* THF/MeOH/H_2O, 1:1:0.83). After 44 hours under reflux, compound **22** was obtained in 34% yield (Scheme 8).

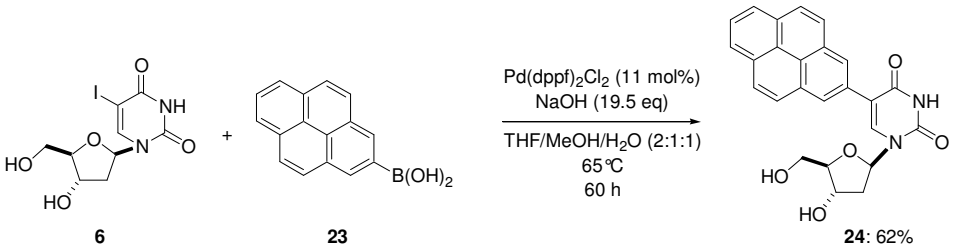


Scheme 8. Synthesis of phenothiazine-modified nucleoside **22**.

2.3. $PdCl_2(dppf)_2$ as Pd(II) and NaOH

In the continuity of their work on pyrene-modified nucleosides, Wagenknecht and co-workers described the synthesis of 5-(pyren-2-yl)-2□-deoxyuridine (**24**) in 2008 (Scheme 9).[14] In this case, the uridine moiety was linked to the 2-position of the pyrene chromophore instead of the 1-position as on previously described compounds. For this purpose, the main modifications were the palladium source $PdCl_2(dppf)_2$ (11 mol%) and the ratio of the solvent mixture (THF/MeOH/H_2O, 2:1:1 *vs* THF/MeOH/H_2O, 2:2:1). Starting from the uridine analogue **6** and the boronic acid **23**, the pyren-2-yl derivative **24** was prepared in 62% yield,

after 60 hours treatment at 65°C. Using this catalyst system, the yield of compound **24** was lower than that obtained for the preparation of the regioisomer **8** (79% *vs* 62%, Scheme 2).



Scheme 9. Synthesis of pyren-2-yl-modified nucleoside analogue **24**.

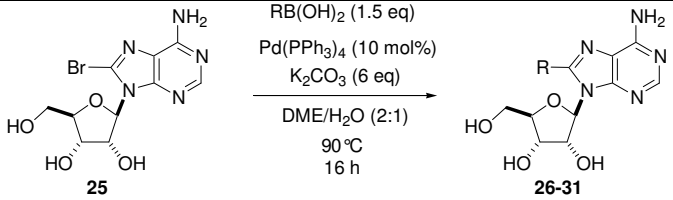
3. SUZUKI-MIYAURA IN DME/H_2O

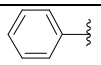
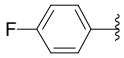
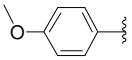
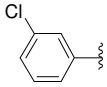
Only Pd(0) as catalyst in a large quantity (10 mol%) and Pd(II) as precatalyst (2.5 mol%) were used for the development of Suzuki-Miyaura cross-coupling reaction in DME/H_2O.

3.1. $Pd(PPh_3)_4$ as Pd(0) and K_2CO_3

In 2004, Yamamoto and co-workers described the Suzuki-Miyaura cross coupling reaction starting from 8-bromoadenosine (**25**) and phenyl boronic acid (1.5 eq) using $Pd(PPh_3)_4$ (10 mol%) as the catalyst and K_2CO_3 (6 eq) as the base in DME:H_2O (2:1) at 90°C for 16 hours (Table 1, entry 1).[15] The 8-phenyl derivative **26** was obtained in 81% yield (Table 1, entry 1).

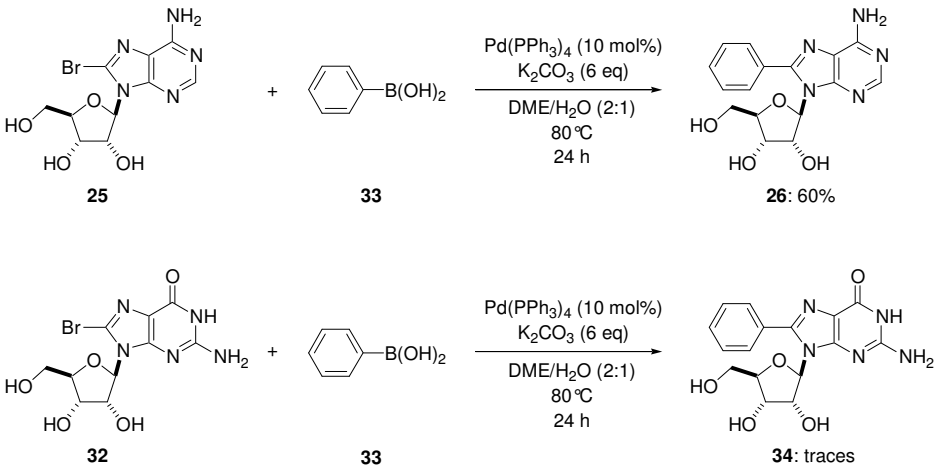
Table 1. Synthesis of 8-aryl and 8-heteroaryl adenosine nucleoside analogue **26**-**31**.



Entry	R	Product	Yield (%)
1		**26**	81
2		**27**	75
3		**28**	73
4		**29**	63
5		**30**	40
6		**31**	25

The methodology was applied to different boronic acids and the adducts **27-31** were obtained (Table 1**,** entries 2-6). One can note that the yields were dependent on the boronic acid used. In the case of *para* substituted phenyl boronic acids, the electron-rich substituents (fluorine and methoxy group) afforded the cross-coupling adducts **27** and **28** in 75% and 73% yields (Table 1, entries 2-3). In the case of the *meta* substituted phenyl boronic acid, the electron-deficient substituent (chloride atom) furnished the target compound **29** in lower yield (63%) (Table 1, entry 4). The heterocyclic boronic acids having thien-2-yl and furan-2-yl moieties gave the compounds **30** and **31** in 40% and 26% yields, respectively (Table 1, entries 5-6). In these cases, the lower yields might be explained by the presence of a heteroatom, steric hindrance and the lack of solubility in chloroform and methanol eluents used in the chromatography step.[15]

Two years later, Wagner and co-workers used a slightly different methodology to conduct the Suzuki-Miyaura cross couplings of 8-bromoadenosine (**25**) and 8-bromoguanosine (**32**) in the presence of phenylboronic acid (**33**) (1.5 eq).[16] In the cases where $Pd(PPh_3)_4$ (10 mol%) and K_2CO_3 (6 eq) were continued to be used by the authors, reactions were conducted at 80°C for 24 hours in DME:H_2O (2:1). Using these conditions, 8-phenyladenosine (**26**) was obtained in 60% yield but authors were unsuccessful in isolating 8-phenylguanosine (**34**). However, in the case of adenosine analogue, it could have been that the increase in temperature (90°C *vs* 80°C) contributed to an increase in the yield (81% *vs* 60% yield) (Table 1, entry 1 and Scheme 10).

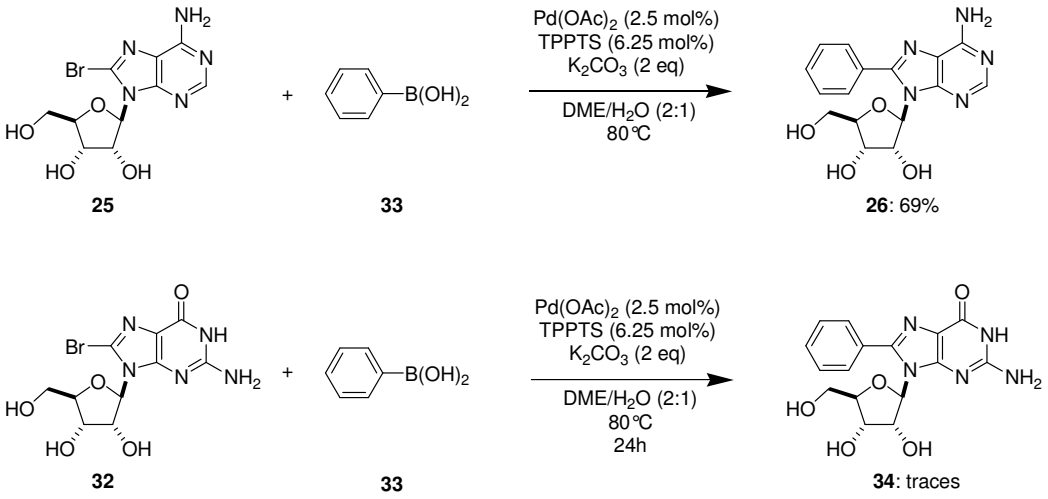


Scheme 10. Synthesis of 8-phenyladenosine and guanosine analogues **26** and **34**.

Ealick and co-workers used Yamamoto's procedure to obtain 8-phenyladenosine (**26**) starting from deprotected 8-bromoadenosine (**25**) in the course of their studies towards new inhibitors of human *S*-adenosylmethionine decarboxylase.[17] No yield was reported but this research group claimed that the use of the unprotected starting material was superior both in time and yield to that using a blocked nucleoside.

3.2. $Pd(OAc)_2$ as Pd(II), TPPTS and K_2CO_3

When Wagner and co-workers used the catalyst system $Pd(OAc)_2$ (2.5 mol%), TPPTS (6.25 mol%) and less amount of K_2CO_3 as base (2 eq) in a DME/H_2O (2:1) mixture at 80°C, the target compound **26** was obtained in 69% yield starting from the bromine derivative **25** (Scheme 11).[16] As described, when using $Pd(PPh_3)_4$ and the guanosine derivative **32** only traces of the coupling adduct could be detected.



Scheme 11. Synthesis of 8-phenyladenosine and guanosine analogues **26** and **34**.

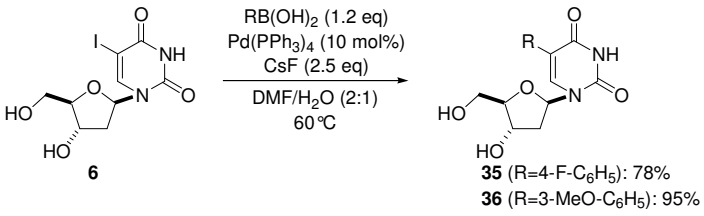
4 SUZUKI-MIYAURA IN DMF/H_2O

The Suzuki-Miyaura cross-coupling reaction in DMF/H_2O was described with Pd(0) as catalyst (10 mol%).

4.1. $Pd(PPh_3)_4$ as Pd(0) and CsF

In 2011, Herdewijn's group reported a study on the synthesis and evaluation of 5-substituted-2□-deoxyuridine monophosphate analogues against *Mycobacterium*

Tuberculosis.[18] In this work, the authors decided to use the unprotected 5-iodo-2□-deoxyuridine (**6**) as starting material and the chosen boronic acids. They conducted a systematic study and showed that the varying nature of the base (K_2CO_3, Na_2CO_3, NaOH, KF) in organic solvent/H_2O mixtures led predominantly to dehalogenation. Herdewijn and co-workers successfully achieved the cross-coupling by reacting 4-fluorophenyl boronic acid (1.2 eq) with CsF (2.5 eq) as base in a mixture of DMF/H_2O (2:1) as solvent and $Pd(PPh_3)_4$ (10mol%) as the catalyst at 60°C. Under these reaction conditions, only small amount of 2□-deoxyuridine were detected and the target nucleoside analogue **35** was obtained in 78% yield (Scheme 12). Application of this protocol afforded the 3-methoxy analogue **36** in 95% yield (Scheme 12).[18]



Scheme 12. Synthesis of 5-aryluridine analogues **35** and **36**.

Phosphorylation of compounds **35** and **36** afforded the desired 5-aryl-2□-deoxyuridine monophosphate analogues **37** and **38**, respectively (Figure 2). The 2-(4-fluorophenyl) analogue **37** exhibited good activity against a novel flavin dependent thymidylate synthase in *Mycobacterium Tuberculosis* (ThyX), whereas no activity could be detected against the classical mycobacterial thymidylate synthase (ThyA). On the other hand, the 5-(3-methoxyphenyl) analogue **38** showed no activity against both enzymes. This indicates that the

nature of the substitution pattern on the phenyl ring has a large influence on the biological activity.

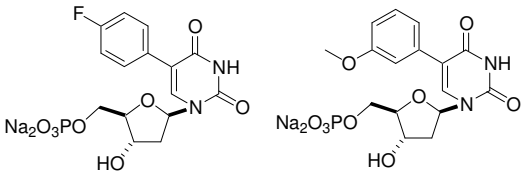


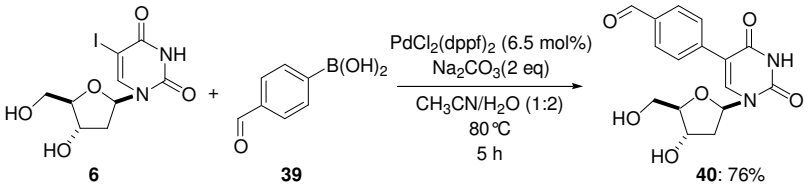
Figure 2. 5-Phenyluridine monophosphate analogues **37-38**.

5 SUZUKI-MIYAURA IN CH_3CN/H_2O

In contrast to the Suzuki-Miyaura cross-coupling reaction developed in aqueous solvents, Pd(0) and Pd(II) were used as catalyst and pre-catalyst respectively in different excess (1.8 - 10 mol%) in CH_3CN/H_2O.

5.1. $PdCl_2(dppf)_2$ as Pd(II) and Na_2CO_3

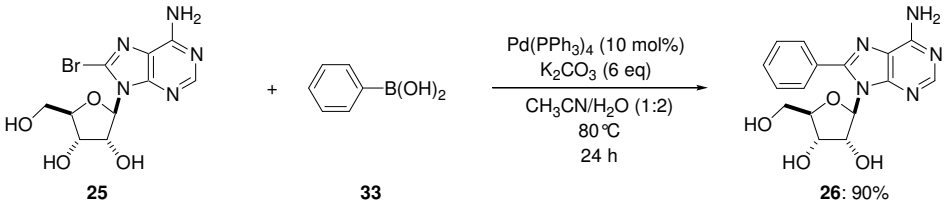
In 2008, Wagenknecht's group used $Pd(dppf)_2Cl_2$ as source of palladium for their Suzuki-Miyaura cross-coupling to furnish the nucleoside analogue **40** as a potential fluorescent probe for nucleic acids. Reacting 2□-deoxyuridine **6,** 4-formylphenylboronic acid (**39**) (1.2 eq), and Na_2CO_3 (2 eq) as base in presence of $Pd(dppf)_2Cl_2$ (6.5 mol%) as catalyst in a CH_3CN/H_2O (1:2) mixture for 5 hours at 80°C afforded the target aldehyde **40** in 76% yield (Scheme 13).[19] The presence of a formyl group, an electron-withdrawing function, in the *para* position of the phenyl core was influential in obtaining a good yield.



Scheme 13. Synthesis of 5-(4-formylphenyl)uridine analogue **40**.

5.2. $Pd(PPh_3)_4$ as Pd(0) and K_2CO_3

In 2006, Wagner and co-workers described the synthesis of the 8-phenyladenosine analogue **26** in 90% yield.[16] The reaction was undertake at 80°C, used the 8-bromo derivative **25**, boronic acid **33** (1.5 eq), a palladium catalyst based on a hydrophobic triphenylphosphine ligand (10 mol%) in presence of K_2CO_3 as base (6 eq) in a CH_3CN/H_2O (1:2) mixture as solvent and furnished the target nucleoside analogue **26** (Scheme 14). This method afforded the targeted compound **26** in a higher yield than that using DME/H_2O (Table 1, entry 1). With 8-bromoguanosine (**32**), no reaction was observed as previously described using DME/H_2O as solvent (Scheme 10).[16]



Scheme 14. Synthesis of 5-phenyladenosine analogue **26**.

5.3. $Pd(OAc)_2$ as Pd(II), TPPTS and Na_2CO_3

In 2003, Shaughnessy and co-workers reported the first methodology using commercially available, or easily prepared, water-soluble phosphine ligands and its application to the

Suzuki coupling of different halonucleoside analogues.[20] The methodology started from 8-bromo-2□-deoxyguanosine (**11**) and phenyl boronic acid (**33**). The ligands explored were water-soluble phophines such as TPPTS, t-Bu-Pip-phos and DCPES and hydrophobic phosphines such as tri-*ter*-butylphosphine (**41**) and tri-o-tolylphosphine (**42**) (Figure 3). Screening reactions were carried out in the presence of $Pd(OAc)_2$ (5 mol%), the ligand (5-12.5 mol%) and Na_2CO_3 (2 eq) in a CH_3CN/H_2O (1:2) mixture as solvent. Shaughnessy and co-workers found that the best catalytic system was TPPTS/$Pd(OAc)_2$. After optimization, the catalyst loading was lowered to 2.5-2.7 mol% without any change in reactivity.

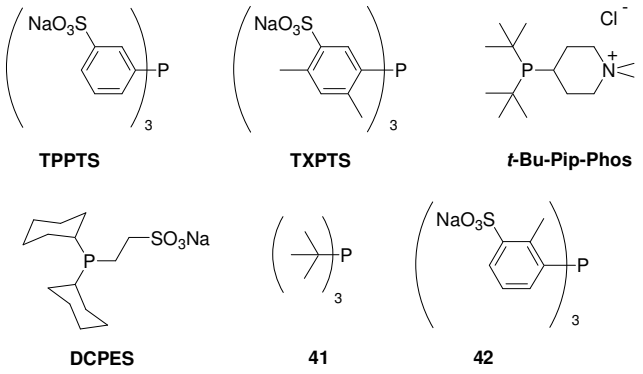
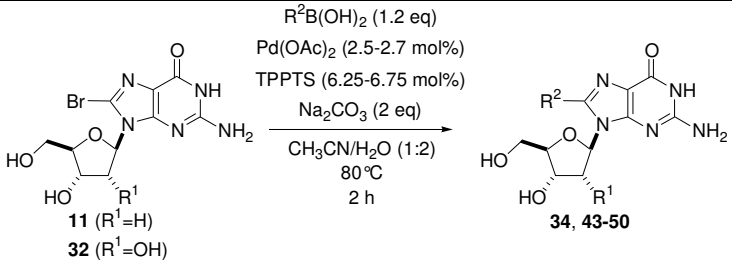


Figure 3. Phosphine derivatives TPPTS, TXPTS, t-Bu-Pip-Phos, DCPES, **41** and **42**.

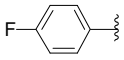
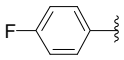
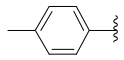
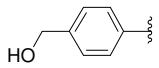
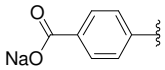
The reaction of compound **11** and boronic acid **33** in presence of $Pd(OAc)_2$ (2.5 mol%) and TPPTS (6.25 mol%) at 80°C over 2 hours resulted in a complete conversion of 8-bromo derivative **11** to the target nucleoside analogue **43** in 82% yield (Table 2, entry 2). The same authors extended their work, using the same reaction conditions, to a series of both arylboronic acids and halonucleoside analogues **6**, **11**, **15**, **25** and **32** to determine the scope and utility of the reaction (Tables 2-4). Targets were chosen both to probe the electronic effects of the boronic acid on the reaction and to provide nucleoside and 2□-deoxynucleoside adducts of interest **16**, **26**-**28**, **34**, **35**, **43**-**56** (Table 2-4).[20] For a given starting material, the nature of the substituent in position 4 of the arylboronic acid did not modulate the yield. It is

noteworthy that starting from the guanosine derivative, the 2□-deoxy derivatives **43**, **45** and **47** were always prepared in better yields (+20%) than the corresponding guanosine analogues **34**, **44** and **46** (Table 2, entries 1-6). The presence or not of an hydroxyl group in position 2□ of adenosine compounds had no such impact on the yield of the cross coupling adducts (Table 2). Other halonucleoside analogues **6**, **15** and **25** were explored (Tables 3 and 4) and the methodology was efficient for the tested starting materials even if the coupling of 8-bromoguanosine (**32**) furnished lower yield.

Table 2. Synthesis of 8-arylguanosine nucleoside analogues **34, 43-50.**



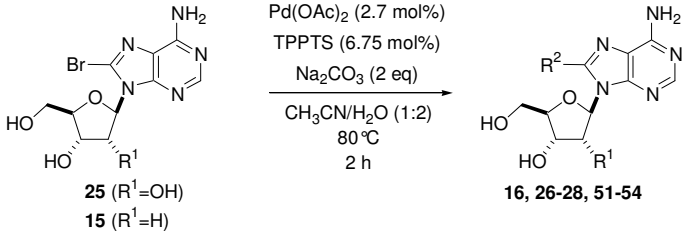
Entry	R^1	Starting material	R^2	Product	Yield (%)
1	OH	**32**		**34**	64[a]
2	H	**11**		**43**	82[b]
3	OH	**32**		**44**	65[a]
4	H	**11**		**45**	85[b]

5	OH	**32**		**46**	73[a]
6	H	**11**		**47**	82[b]
7	H	**11**		**48**	95[b]
8	H	**11**		**49**	73[b]
9	H	**11**		**50**	77[b]

[a] $Pd(OAc)_2$ (2.7 mol%) and TPPTS (6.75 mol%)

[b] $Pd(OAc)_2$ (2.5 mol%) and TPPTS (6.25 mol%)

Table 3. Synthesis of 8-aryladenosine nucleoside analogues **16, 26-28** and **51-54.**



Entry	R^1	Starting material	R^2	Product	Yield (%)
1	OH	**25**		**26**	88
2	H	**15**		**51**	87

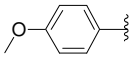
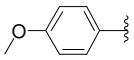
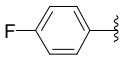
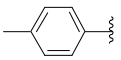
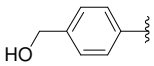
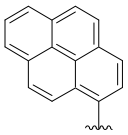
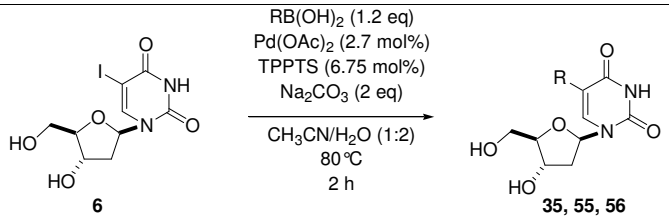
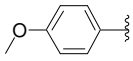
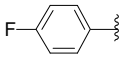
3	OH	**25**		**28**	85
4	H	**15**		**52**	77
5	OH	**25**		**27**	99
6	H	**15**		**53**	90
7	H	**15**		**54**	91
8	H	**15**		**16**	68

Table 4. Synthesis of 5-aryl-2'-deoxyuridine nucleoside analogues **35**, **55** and **56**.

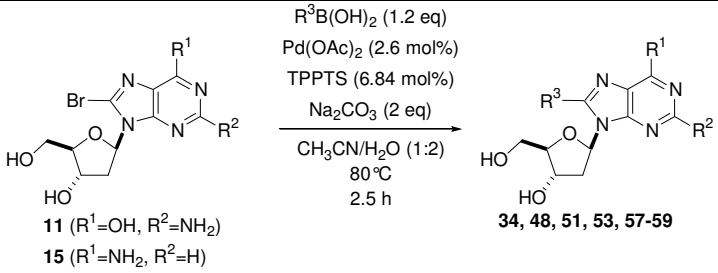


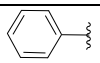
Entry	R	Product	Yield (%)
1		**55**	83
2		**56**	82

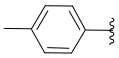
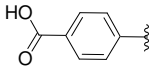
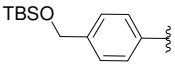
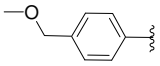
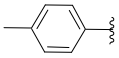
3		**35**	92

In 2008, Shaughnessy and co-workers reported the development of a general strategy for the synthesis of C8-arylpurine phosphoramidites.[21] C8-Arylation of both the 8-bromo-2□-deoxyguanosine (**11**) and the corresponding adenosine analogue **15** was the key-step of the process and was achieved using a Suzuki-Miyaura reaction. This cross-coupling reaction was conducted in a CH_3CN/H_2O (1:2) mixture containing Na_2CO_3 (2 eq) and $Pd(OAc)_2$ (2.6 mol%), at 80°C for 2.5 hours. The ligand TPPTS (6.84 mol%) was used as the catalyst in all cases. Reactions were readily followed by TLC and run until the C8-bromopurine starting material had been consumed (Table 5). The yields obtained using this method were similar to those obtained in 2003 by the same authors except for the tolyl derivative **53** (90% *vs* 80%) (Table 3, entry 6 and Table 5, entry 7).[21]

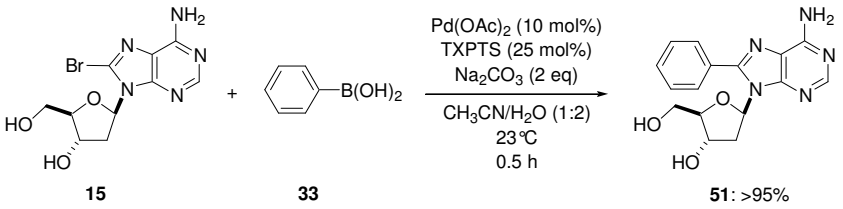
Table 5. Synthesis of 8-arylguanosine and 8-aryladenosine nucleoside analogues **34**, **48**, **51**, **53** and **57**-**59**.



Entry	R^1	R^2	Starting material	R^3	Product	Yield (%)
1	OH	NH_2	**11**		**43**	83

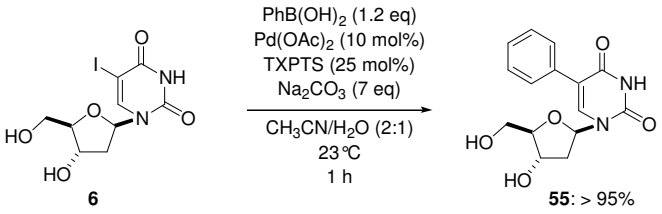
2	OH	NH_2	**11**		**48**	99
3	OH	NH_2	**11**		**57**	83
4	OH	NH_2	**11**		**58**	72
5	OH	NH_2	**11**		**59**	67
6	NH_2	H	**15**		**51**	85
7	NH_2	H	**15**		**53**	80

Shaughnessy and co-workers showed that the reactivity was dependant on the nature of the halonucleoside analogue.[20] After optimization by varying the nature of the solvent, the palladium source and the ligand, the authors found two new methods starting from 2□-deoxyadenosine derivative **15** and 2□-deoxyuridine (**6**), respectively. These new methodologies were followed by HPLC; only relative HPLC peaks areas were reported. The starting substrate **15** and the boronic acid **33** (1.2 eq) were reacted in presence of $Pd(OAc)_2$ (10 mol%), TXPTS (25 mol%) and Na_2CO_3 (2 eq) in CH_3CN/H_2O (1:2) at room temperature for 30 minutes. The target nucleoside analogue **51** was obtained in yield higher than 95% (Scheme 15). It was the first reporting of a room temperature reaction giving a cross-coupling adduct in good yield.



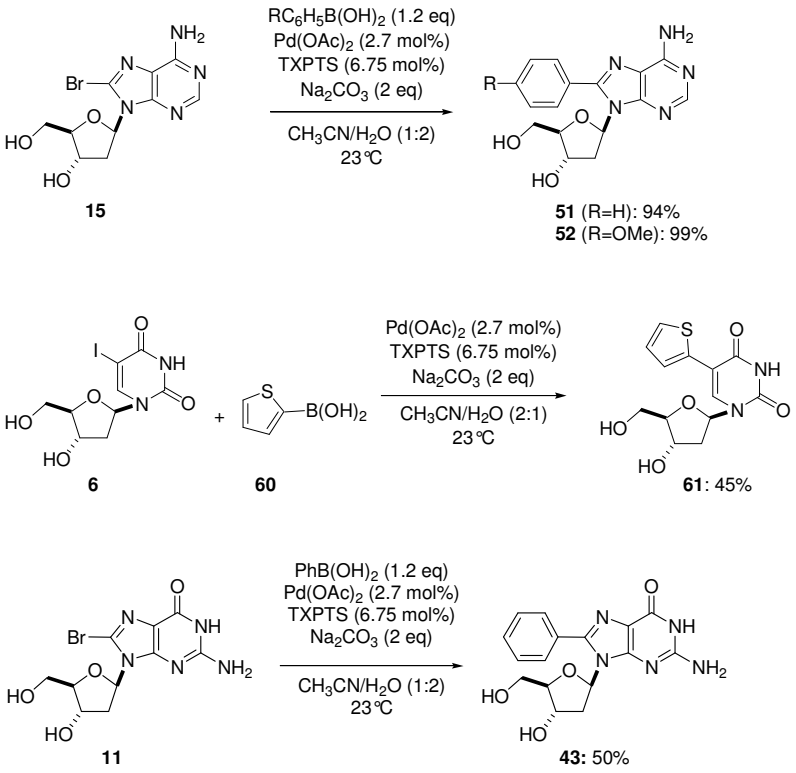
Scheme 15. Synthesis of 8-phenyl-2'-deoxyadenosine (**51**).

Starting from substrate **6**, a similar reaction over 1 hour at room temperature, but using a larger amount of Na_2CO_3 (7 eq), gave the uridine analogue **55** in a yield higher than 95%. (Scheme 16).



Scheme 16. Synthesis of 8-phenyl-2□-deoxyuridine (**55**).

With the aim to design a preparatory scale reaction, Shaughnessy and co-workers used the TXPTS/$Pd(OAc)_2$ (2.5:1) catalyst system with a lower amount of palladium (2.7 mol%). This protocol afforded the nucleoside analogues **51** and **52** in 94% and 99% yields, respectively (Scheme 17). Application to the uridine and guanosine derivatives **6** and **11** furnished the corresponding nucleoside analogues **61** and **43** in 45% and 50% yields. It is clear that at room temperature, the use of TXPTS improved the method for the adenosine derivatives **51** and **52** (for compound **51**: 94% *vs* 87%; for compound **52**: 99% *vs* 77%, Scheme 17 and Table 3) but not for the uridine and guanosine nucleoside analogues **61** and **43**.[20]



Scheme 17. Synthesis of 8-aryl nucleoside analogues **43**, **51**, **52** and **61**.

Shaughnessy and co-workers noted that there was an unexpected ligand dependence on catalytic activity starting from 8-bromo derivative **11**. In order to investigate this phenomenon, the authors carried out a series of reactivity and NMR spectroscopic studies, which showed that the guanine nucleoside **11** coordinated to Pd(II), thus inhibiting reduction to the Pd(0) active species.[22] The authors showed that this competitive coordination could be avoided by replacement of the acidic *N*-1 proton of the nucleoside (Figure 4).

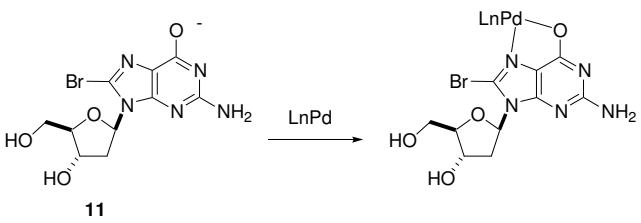
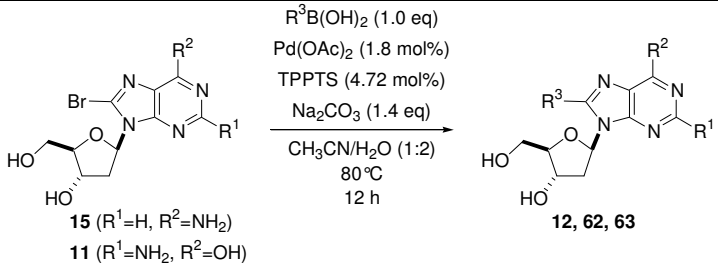


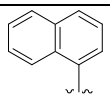
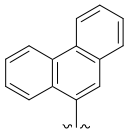
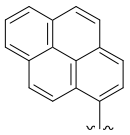
Figure 4. Palladium coordination to nucleoside analogue **11**.

The previously described Shaughnessy methodology [20] was used in 2008 by Blaauwen and co-workers.[23] After longer reaction time (3h *vs* 2h), they were able to isolate compound (**34**) in 75% yield instead of 64% yield.

In 2007, Harvey and co-workers tried to extend the work of Wagenknecht's and Shaughnessy to obtain new C^8-pyrenyl adducts starting from 8-halogenated purines.[24] For this purpose, they synthesized different boronic acids and engaged them in a Suzuki cross-coupling reaction with 8-bromo-2□-deoxyguanosine (**11**) and 8-bromo-2□-deoxyadenosine (**15**) (Table 6). Their catalytic system consisted of $Pd(OAc)_2$ (1.8 mol%) and TPPTS (4.72 mol%) maintaining the choice of CH_3CN/H_2O (1:2) in presence of the corresponding boronic acid (1.0 eq) and Na_2CO_3 (1.4 eq). Reactions were conducted in a sealed tube heated at 80°C overnight. In these conditions, the nucleoside analogues **12, 62** and **63** were obtained in yields higher than 58%. In spite of a range of polycyclic aromatic hydrocarbon boronic acids tested, only the three adducts **12, 62** and **63** were obtained. The other boronic acids failed to engage in coupling with both 8-halogenated purines **11** and **15**, and afforded instead the corresponding hydrogenated polycyclic aromatic molecules as the major product. The authors concluded that the failure of coupling to take place appeared to be the net consequence of steric retardation of the rate of coupling and acceleration of the rate of hydrolysis of the boronic acid group.[24]

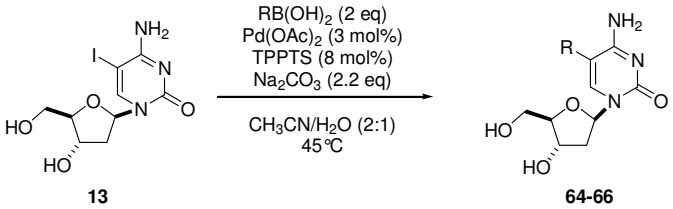
Table 6. Synthesis of 8-aryladenosine and guanosine nucleoside analogues **12, 62** and **63.**



Entry	R^1	R^2	Starting material	R^3	Product	Yield (%)
1	H	NH_2	**15**		**62**	58
2	H	NH_2	**15**		**63**	80
3	NH_2	OH	**11**		**12**	65

Still 2007, Sekine's group published an attempt to use 5-arylcytosine derivatives **64-66** as an artificial base pair to form a DNA triplex.[25] The very efficient synthesis of such derivatives was achieved by reacting a mixture of 5-iodo-deoxycytidine (**13**), the water-soluble phosphine ligand TPPTS (8 mol%), $Pd(OAc)_2$ (3 mol%), CH_3CN:H_2O (2:1) and Na_2CO_3 (2.2 eq) at 45°C (Table 7). It is important to note that on this occasion, H_2O was not the main solvent of the mixture but represented only 1/3.

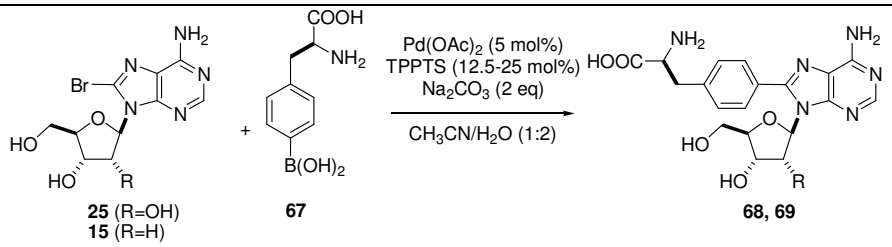
Table 7. Synthesis of 5-aryl cytosine nucleoside analogues **64**-**66.**



Entry	R	Product	Yield (%)
1		**64**	85
2		**65**	99
3		**66**	100

In 2006, Hocek and co-workers reported an application of Shaughnessy's conditions for the synthesis of 4-(adenosine-8-yl)alanine derivatives.[26] After screening different ligands, bases and solvent mixtures, the authors chose to use a large amount of catalyst $Pd(OAc)_2$ (5 mol%), TPPTS (12.5 mol%), boronic acid **67** (1.25 eq) and Na_2CO_3 (2 eq) in a mixture of CH_3CN/H_2O (1:2) for their coupling reactions as well as two ways of heating: conventional heating (90°C) and microwave irradiation assistance (150°C). The reactions of unprotected (*S*)-4-boronophenylalanine **67** with 8-bromoadenine nucleosides **15** and **25** gave the desired compounds **68** and **69**, respectively, in a single step (Table 8). Microwave irradiation assistance permitted reduction of the reaction time but the preparative yields were somewhat lower. Additional studies of microwave-mediated reactions showed that yields could be further improved (> 68%) (Table 8, entries 5 and 6) by increasing the ratio of ligand to $Pd(OAc)_2$ to 5:1 instead of 2.5:1.

Table 8. Synthesis of 8-aryladenosine nucleoside analogues **68** and **69.**



Entry	R^1	Starting material	T (°C)	Time	Product	Yield (%)
1	OH	**25**	90	2 h	**68**	71
2	H	**15**	90	2 h	**69**	75
3	OH	**25**	150 (MW)	5 min	**68**	56
4	H	**15**	150 (MW)	5 min	**69**	52
5	OH	**25**	150 (MW)	5 min	**68**	76[a]
6	H	**15**	150 (MW)	5 min	**69**	68[a]

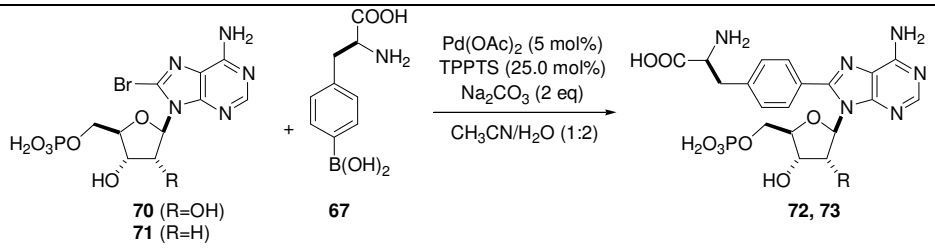
[a] $Pd(OAc)_2$ (5 mol%) and TPPTS (25.0 mol%)

In the study to obtain the monophosphate derivatives **72** and **73**, it was found that compound **72** could not be obtained by conventional heating at 90°C (Table 9, entry 1). However, application of microwave irradiation at 150°C was more successful and showed the possibility of cross-coupling (Table 9, entry 2).[26] Finally, classical heating at the optimum temperature of 125°C provided the desired nucleotide **72** in 72% yield (Table 9, entry 3). In contrast to the nucleoside analogue **70**, complete decomposition of the nucleotide

monophosphate **71** was observed in the case of microwave-mediated conditions to obtain **73** (Table 9, entry 4). In this case, the nucleotide analogue **73** was furnished under classical heating (125°C) in 71% yield (Table 9, entry 5). These results confirmed that, in the Suzuki-Miyaura conditions, the 2□-deoxy derivatives of adenosine were less stable than the corresponding adenosine analogue using alternative technologies such as microwave-mediation.

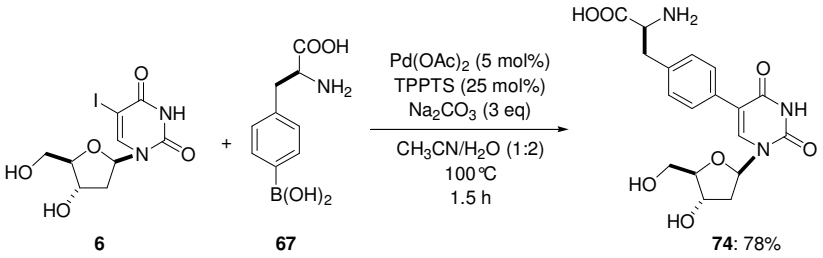
In contrast to the successful preparation of the monophosphate derivatives **72** and **73**, using conventional heating, complete decomposition of the nucleotide triphosphates was observed when using microwaves-mediated activation.

Table 9. Synthesis of 8-aryl adenosine nucleoside analogues **72** and **73.**



Entry	R^1	Starting material	T (°C)	Time	Product	Yield (%)
1	OH	**70**	90	4 h	**72**	0
2	OH	**70**	150 (MW)	5min	**72**	51
3	OH	**70**	125	1.5 h	**72**	72
4	H	**71**	150 (MW)	5 min	**73**	< 1
5	H	**71**	125	20 min	**73**	71

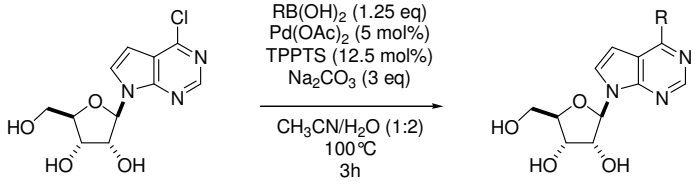
In continuity of their work on nucleosides and nucleotides chemistry, Hocek and co-workers reported new results on aqueous cross-coupling reactions of halogenated 2□-deoxynucleosides.[27] They applied the above optimized catalytic system, namely, $Pd(OAc)_2$ (5 mol%), TPPTS (25 mol%) in reaction with 5-iodo-2□-deoxyuridine (**6**) in presence of boronic acid **67** (1.3 eq) and a large excess of Na_2CO_3 (3 eq) as base. Reactions were run for 1.5 hour at 100°C to give compound **74** in 78% yield (Scheme 18).

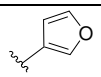
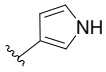
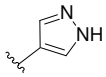


Scheme 18. Synthesis of 5-aryl uridine analogue **74**.

In the continuity of this work, Hocek's group reported, in 2010, a series of 6-hetearyl-7-deaazapurine riboside analogues **76-81**. Those compounds were prepared directly from the corresponding unprotected 6-chloro-7-deazapurine (**75**) and boronic acid (1.25 eq) using $Pd(OAc)_2$ (5 mol%), TPPTS (12.5 mol%) as the catalyst and Na_2CO_3 (3 eq) as the base at 100°C for 3 hours (Table 10).[28] In this work the concentration of ligand was lower (12.5 mol% *vs* 25 mol%) than for the synthesis of analogues **72-73** (Table 9).

Table 10. Synthesis of 6-hetearyl-7-deaazapurine nucleoside analogues **76-81**.

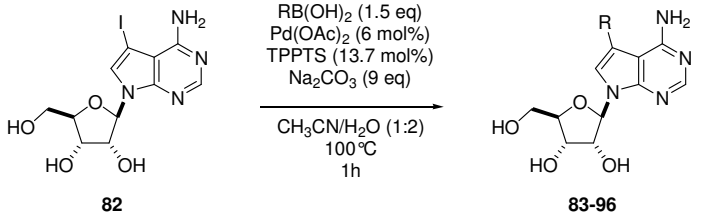


Entry	R	Product	Yield (%)
1		**76**	69
2		**77**	67
3		**78**	55
4		**79**	64
5		**80**	64
6		**81**	12

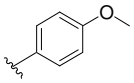
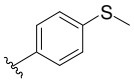
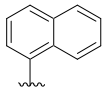
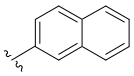
In the case of 3-pyrrolyl derivative, the boronic used was a *N*-protected triisopropylsilyl derivative (Table 10, entry 3). Authors reported that the protecting group was removed simultaneously to the Suzuki coupling due to the strongly basic conditions of the reaction. It has been noted that in case of *N*H containing boronic acid, a formation of *N*-arylated product was formed by coupling of the 5-membered heterocycle with chlorinated starting material.

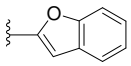
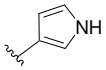
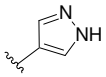
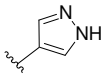
Application of previously described methodology[26] with a larger amount of catalyst and base allowed Hocek and co-workers to obtain, in 2011, fourteen 7-aryl- and 7-hetearayltubercidin derivatives **83-96**.[29] The desired products were prepared in a single step mostly in good yields (Table 11).

Table 11. Synthesis of 7-hetearyl-7-deaazapurine nucleoside analogues **83- 96**.



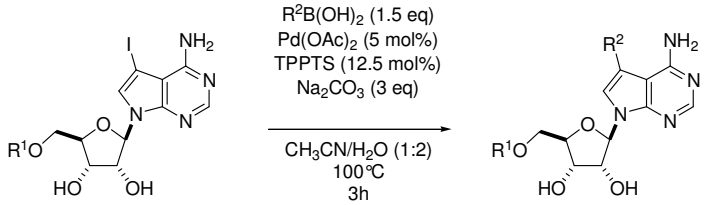
82 **83-96**

Entry	R	Product	Yield (%)
1		**83**	54
2		**84**	36
3		**85**	74
4		**86**	47
5		**87**	56
6		**88**	48
7		**89**	82
8		**90**	72
9		**91**	77

10		**92**	38
11		**93**	77
12		**94**	63
13		**95**	9
14		**96**	82

In addition to the compounds **83-96** (Table 11), authors prepared several nucleotides: 5-*O*-monophosphate and 5'-*O*-triphosphate derivatives respectively still by aqueous Suzuki-Miyaura reaction (Table 12).[29]

Table 12. Synthesis of 7-hetearyl-7-deazapurine nucleotide analogues **99-108**



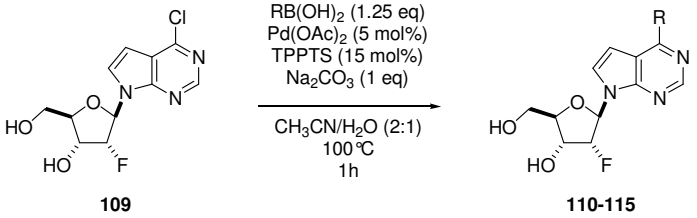
Entry	R^1	Starting material	R^2	Product	Yield (%)
1	PO_3H_2	**97**		**99**	46

2	$P_3O_9H_4$	**98**		**100**	94
2	PO_3H_2	**97**		**101**	27
3	$P_3O_9H_4$	**98**		**102**	34
4	PO_3H_2	**97**		**103**	53
5	$P_3O_9H_4$	**98**		**104**	51
6	PO_3H_2	**97**		**105**	37
7	$P_3O_9H_4$	**98**		**106**	45
8	PO_3H_2	**97**		**107**	67
9	$P_3O_9H_4$	**98**		**108**	47

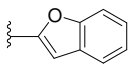
In their continuous research on synthesis and biological activity of modified purine nucleoside derivatives and analogues, Hocek and co-workers reported the obtention of 2'-deoxy-2'-fluororibonucleosides derived from 6-chloro-7-deazapurines.[30] This time, the cross-coupling reactions were done in a H_2O/CH_3CN (1:2) medium, still in presence of $Pd(OAc)_2$ (5 mol%), TPPTS (15 mol%) and a smaller amount of Na_2CO_3 (1 eq) at 100°C for 1 hour. Different

boronic acids were used and desired products **110-115** were isolated in moderate to good yields (Table 13).

Table 13. Synthesis of 6-(hete)aryl-7-deazapurine-2'-fluoro-2'-deoxyribonucleosides **110-115**.



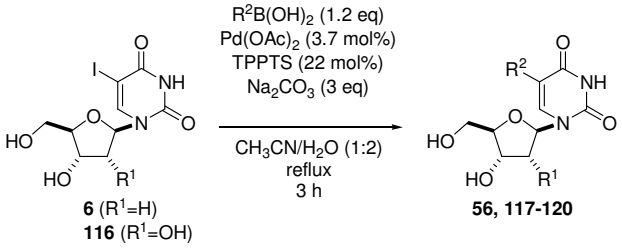
109 **110-115**

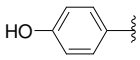
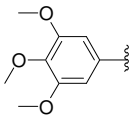
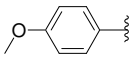
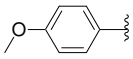
Entry	R	Product	Yield (%)
1		**110**	47
2		**111**	39
3		**112**	65
4		**113**	37
5		**114**	89
6		**115**	89

In 2012, application of Hocek's method was described by Fisher and co-workers as part of their work to produce fluorescence studies on modified nucleosides.[31] This team studied the

contribution of both the type and position of the aromatic substituents on the fluorescence of the resulting uridine derivatives. For this purpose, they synthesized and characterized different uridine and 2□-deoxyuridine analogues, which have an aromatic system directly linked to the C5 positions of the unprotected starting nucleoside (Table 14). Once again, the catalytic system was composed of $Pd(OAc)_2$ (3.7 mol%), TPPTS (22 mol%) and Na_2CO_3 (3 eq) as base in a mixture H_2O/CH_3CN (2:1). In this protocol the authors used a large excess of TPPTS as ligand.

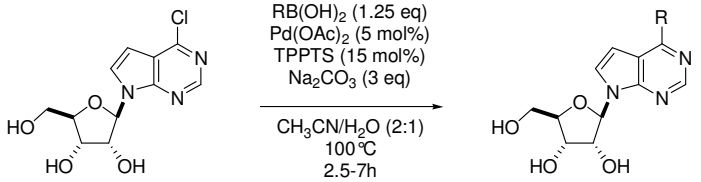
Table 14. Synthesis of 8-aryl adenosine nucleoside analogues **56** and **117-120.**



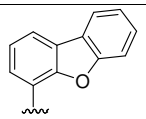
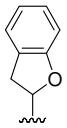
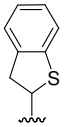
Entry	R^1	Starting material	R^2	Product	Yield (%)
1	OH	**116**		**117**	50
2	OH	**116**		**118**	64
3	OH	**116**		**119**	42
4	OH	**116**		**120**	13
5	H	**6**		**56**	50

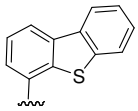
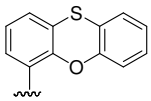
Recently, Hocek and co-workers reported the obtention of five 6-hetearyl-7-deazapurine ribonucleosides **121-125** starting from deprotected 6-chloro-7-deazapurine analogues using a direct aqueous Suzuki coupling in presence of $Pd(OAc)_2$ (5 mol%), TPPTS (15 mol%) and Na_2CO_3 (3 eq) for (Table 15).[32]

Table 15. Synthesis of 6-hetearyl-7-deazapurine ribonucleoside analogues **121-125.**



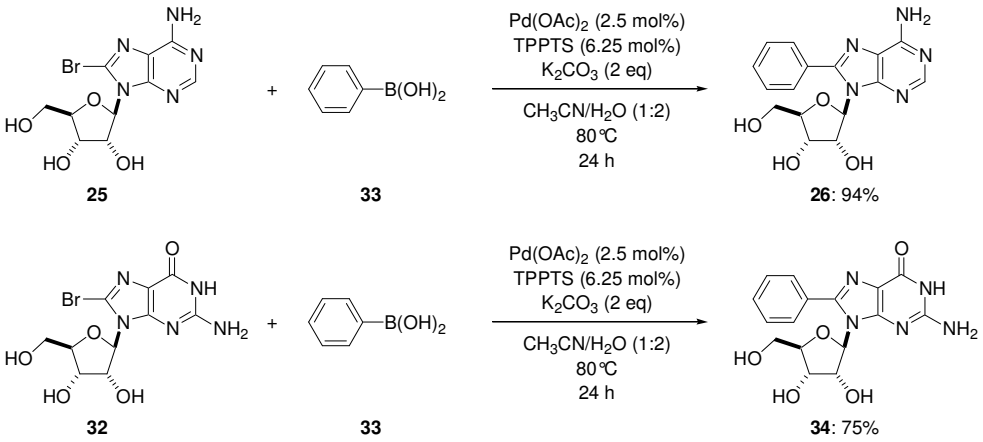
75 **121-125**

Entry	R	Product	Yield (%)
1		**121**	76
2		**122**	75
3		**123**	71

4		**124**	73
5		**125**	71

5.4. $Pd(OAc)_2$ as Pd(II), TPPTS and K_2CO_3

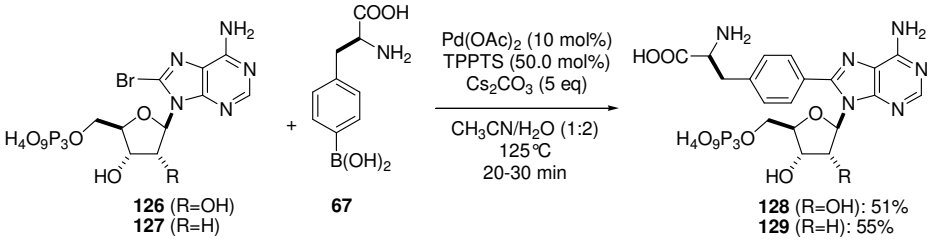
In 2006, Wagner and co-workers used part of the methodology described by Shaughnessy and co-worker[20] for the synthesis of 8-phenyladenosine analogue **26**.[16] They reacted the mixture of 8-bromo derivative **25**, boronic acid **33** (1.5 eq), $Pd(OAc)_2$ (2.5 mol%) and TPPTS (6.25 mol%) in presence of K_2CO_3 as base (2 eq) in CH_3CN/H_2O (1:2) to give the target nucleoside analogue **26** in 94 % yield (Scheme 19). Using a similar method but with K_2CO_3 as base instead of Na_2CO_3 permitted them to increase the yield of compound **26** (94% *vs* 88%, Table 3, entry 1). In contrast with the use of $Pd(PPh_3)_4$ catalyst, this method permitted 8-phenylguanosine (**34**) to be obtained in 75% yield. It is notable that none of reagents $Pd(PPh_3)_4$ or $Pd(OAc)_2$, TPPTS in a DME/H_2O mixture or $Pd(PPh_3)_4$ in CH_3CN/H_2O allowed the target guanosine derivative **34** to be obtained (Scheme 19).



Scheme 19. Synthesis of 8-phenyladenosine and 8-phenylguanosine analogues **26** and **34**.

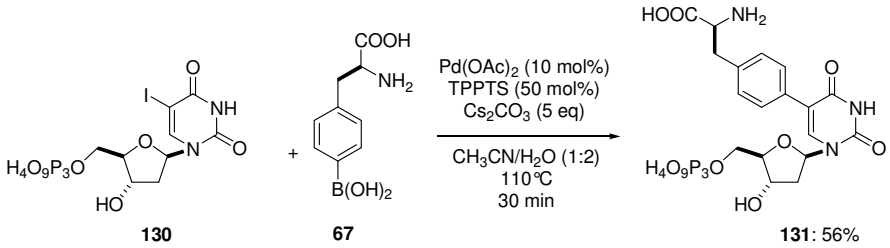
5.5. $Pd(OAc)_2$ as Pd(II), TPPTS and Cs_2CO_3

In order to prepare new nucleotide analogues having an amino acid moiety, different studies were reported by Hocek's group.[26] In 2003, the authors described an efficient methodology for cross-coupling reactions starting from nucleotide triphosphate analogues. As those particular nucleosides are known to be rather labile compounds, different mild methodologies such as lower heating or microwaves irradiation assistance, were tested but without any success since a complex mixture of by-products were obtained including hydrolysis products of starting nucleotide. The use of conventional base most often afforded the degradation of the triphosphate analogue. To limit this step, other bases were studied. Thus, the triphosphate derivatives **126** and **127**, boronic acid **67** (1.5 eq), $Pd(OAc)_2$ (10 mol%), TPPTS (50 mol%) as catalyst and Cs_2CO_3 (5 eq) as base in a mixture of CH_3CN/H_2O (1:2) at 125°C for 20-30 minutes furnished the target nucleotide analogues **128** and **129** in 51% and 55% yields, respectively (Scheme 20).



Scheme 20. Synthesis of (adenine-8-yl)phenylalanine analogues **128** and **129**.

Starting from the 5-iodo derivative **130** and modification of the above methodology allowed Hocek and co-workers to obtain the cytosine analogue **131**. The authors used the unchanged catalytic system but preferred to modulate the temperature (110°C *vs* 125°C). The mixture of 5-iodo derivative **130** and boronic acid **67** (2.0 eq) in presence of $Pd(OAc)_2$ (10 mol%), TPPTS (50 mol%) and Cs_2CO_3 (5 eq) in a CH_3CN/H_2O (1:2) afforded the amino acid derivative **131** in 56% yield (Scheme 21) in 30 minutes.[27]

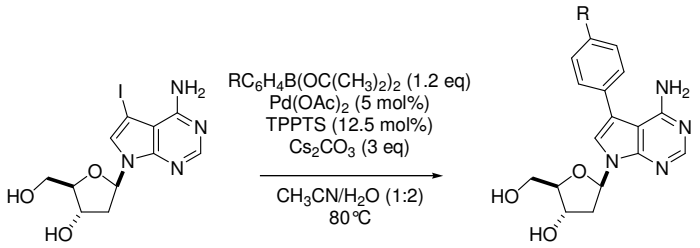


Scheme 21. Synthesis of (uridin-5-yl)phenylalanine analogue **131**.

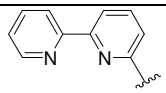
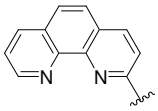
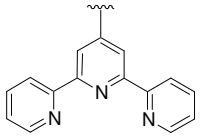
In 2008, Hocek and co-workers described the obtention of 7-deaza-2'-deoxyadenosine derivatives bearing bipyridine and phenanthroline ligands linked *via* acetylene or phenylene to position 7 of the nucleoside, as well as their Ru(II) complexes.[33] The aim of this work was to study the electrochemical and photophysical properties of the resulting labeled nucleosides. In order to attach the phenylene linker to position 7 of the 7-deaza-2'-deoxyadenosine, the

authors have used an aqueous-phase Suzuki-Miyaura cross-coupling reaction and the phenylene-bridged conjugates **133-135** were prepared in excellent yields. Starting from 7-iodo-7-deaza-2'-deoxyadenosine (**132**), pinacol boronate ester (1.2 eq), $Pd(OAc)_2$ (5 mol%) and TPPTS (12.5 mol%) in presence of Cs_2CO_3 (3 eq) in a CH_3CN/H_2O (1:2) mixture as solvent furnished the target compounds **133-135** in 78-96% yields (Table **16**).

Table 16. Synthesis of 7-aryl-7-deaza-2'-deoxyadenosine **133-135.**



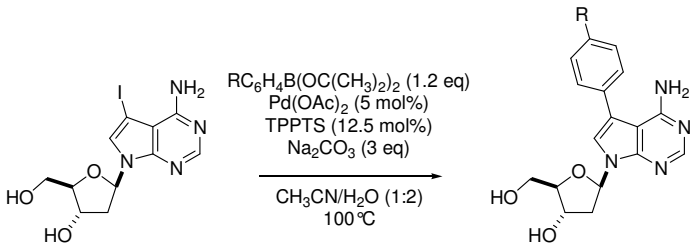
132 **133-135**

Entry	R	Product	Yield (%)
1		**133**	95
2		**134**	96
3		**135**	78

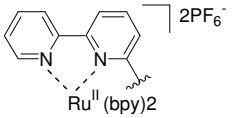
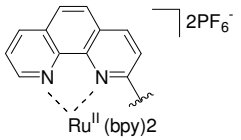
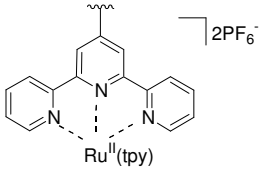
Using exactly the same methodology, the authors have also obtained three corresponding Ru(II) complexes **136-138** of the 7-deazapurine nucleoside in good yields (Table 17). Authors

prepared themselves the boronate-Ru(II) building blocks necessary to the Suzuki-Miyaura cross couplings.

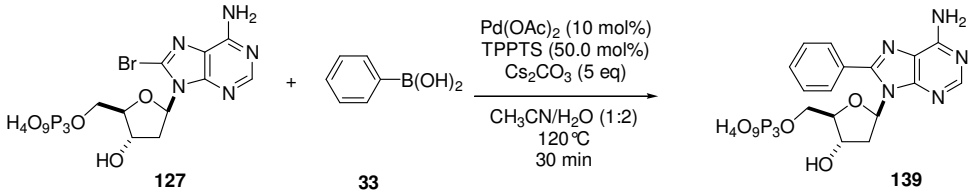
Table 17. Synthesis of Ru(II) complexes of 7-aryl-7-deaza-2'-deoxyadenosine **136**-**138**.



132 **136-138**

Entry	R	Product	Yield (%)
1		**136**	95
2		**137**	73
3		**138**	76

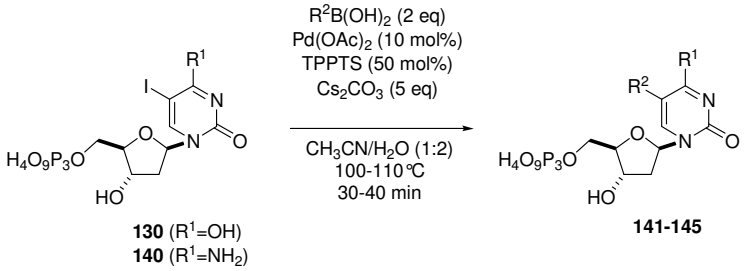
Still in 2008, Hocek's group reported the synthesis of 8-phenyl-dATP **139** and its use as subtrate for DNA polymerases.[34] The Suzuki-Miyaura cross-coupling reaction of 8-Br-dATP **127** with phenylboronic acid **33** (2 eq) was performed in presence of $Pd(OAc)_2$ (10 mol%), TPPTS (50 mol%) in a CH_3CN-H_2O (1:2) mixture for 30 minutes at 120°C (Scheme 22).

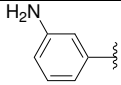


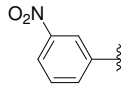
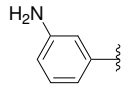
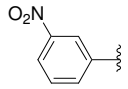
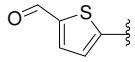
Scheme 22. Synthesis of 8-phenyl-dATP **139**.

The coupling of more conventional aromatic boronic acids was described by the Hocek group using a similar method.[35, 36] By application of the first methodology, starting from 5-iodo nucleotide derivatives **130** and **140**, Hocek and co-workers obtained the uridine and cytosine analogues **141-145**. The reactions were performed, at 110°C for 30 minutes, using a mixture of **130** or **140** and boronic acid (2 eq) in presence of $Pd(OAc)_2$ (10 mol%), TPPTS (50 mol%) and Cs_2CO_3 (5 eq) in a CH_3CN/H_2O (1:2). The large amount of palladium resulted in furnishing the target uridine analogues **141** and **142** and the cytosine derivatives **143-145** in 26-65% yields (Table 18).

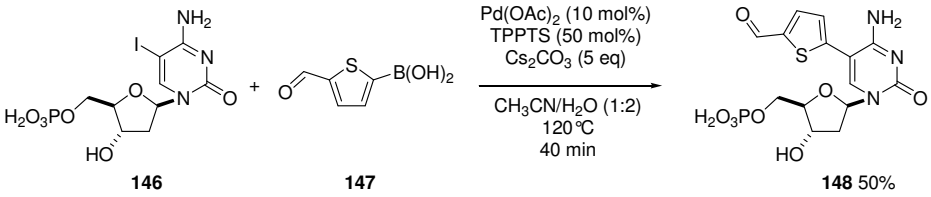
Table 18. Synthesis of 8-aryl adenosine nucleoside analogues **141-145.**



Entry	R^1	Starting material	R^2	Product	Yield (%)
1	OH	**130**		**141**	43

2	OH	**130**		**142**	26
3	NH_2	**140**		**143**	43
4	NH_2	**140**		**144**	26
5	NH_2	**140**		**145**	65

Application of this cross-coupling protocol in the reactions of the iodinated nucleotide monophosphate **146** and 5-formylthiophene boronic acid (**147**) gave the corresponding triphosphate **148** in 50% yield (Scheme 23).[36]

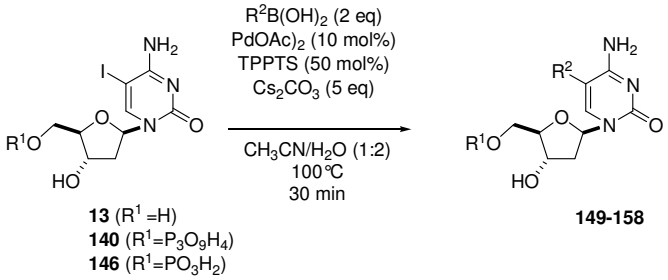


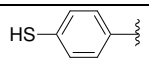
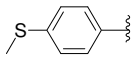
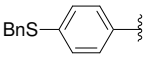
Scheme 23. Synthesis of 5-aryl cytosine monophosphate analogue **148**.

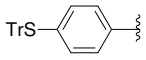
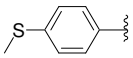
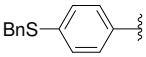
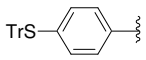
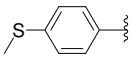
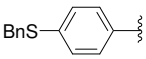
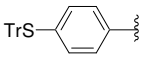
Recently, Hocek and co-workers targeted nucleoside derivatives functionalized with alkylsulfanylphenyl groups at the 5-position of the pyrimidine.[37] Their project started with a model study of cross-couplings of different halogenated nucleosides with alkylsulfanylphenylboronic acid. Because the free-sulfanyl phenylboronic acid was presumed to be potentially unreactive due to Pd-catalyst poisoning, they selected stable methylsulfanyl derivatives, as well as more labile benzyl- and tritylsulfanyl derivatives with potentially cleavable protecting groups at the sulfur atom. The iodinated nucleosides **13**, **140** and **146**

were selected and the previously described conditions ($Pd(OAc)_2$ (10 mol%), TPPTS (50 mol%), Cs_2CO_3 (5 eq) in CH_3CN/H_2O (1:2)) were applied. All the reactions were performed at 100°C for 30 minutes. Final nucleoside analogue products **150-154** were obtained in 78-82% yields (Table 19, entries 2-6). The corresponding nucleotide analogues **155**-**158** were prepared in lower yields with the worst one possessing the trityl protecting group (Table 19, entries 7 and 10). As expected by the authors, reactions involving free-sulfanyl phenylboronic acid gave no positive result, which supported the anticipated Pd-catalyst poisoning (Table 19, entry 1). In all cases, the desired triphosphates were isolated by semi-preparative HPLC and were accompanied by substantial amounts (15-25%) of the corresponding diphosphates resulting from hydrolysis.[37]

Table 19. Synthesis of 5-aryl cytosine analogues **149**-**158.**



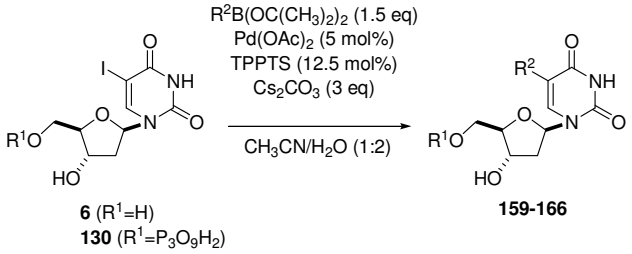
Entry	R^1	Starting material	R^2	Product	Yield (%)
1	H	**13**		**149**	0
2	H	**13**		**150**	82
3	H	**13**		**151**	79

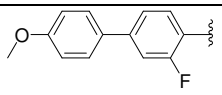
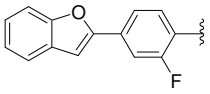
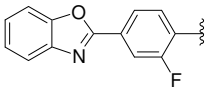
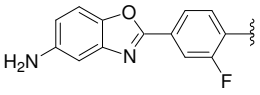
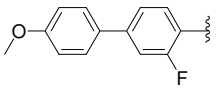
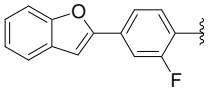
4	H	**13**		**152**	78
5	PO_3H_2	**146**		**153**	78
6	PO_3H_2	**146**		**154**	96
7	PO_3H_2	**146**		**155**	14
8	$P_3O_9H_4$	**140**		**156**	50
9	$P_3O_9H_4$	**140**		**157**	34
10	$P_3O_9H_4$	**140**		**158**	10

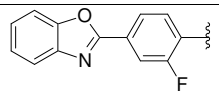
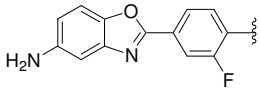
In 2012, Hocek's group reported four new fluorinated biaryl fluorescent labels and their attachment to nucleosides and nucleosides triphosphate by aqueous cross-coupling reactions of biarylboronates.[38] For this purpose, four different types of biaryl groups were designed in which the following were attached directly at the 5-position of pyrimidines: 4-methoxybiphenyl (BIF); 2-phenylbenzofuryl (BFU); 2-phenylbenzoxazole (BOX); 2-phenyl-5-aminobenzoxazole (ABOX). The frequently described cross-coupling protocol involving pinacol ester boronate acid (1.5 eq), $Pd(OAc)_2$ (5 mol%), TPPTS (12.5 mol%), Cs_2CO_3 (3 eq) and CH_3CN/H_2O (1:2) was used for the two reactions conducted at 80°C for 2 hours starting from iodinated nucleoside **6**; 90°C for 45 minutes starting from iodinated nucleotides triphosphates **130** (Table 20). The desired biaryl-substituted nucleosides **159-162** were obtained in good to moderate yields (59-71%). Analogously, the halogenated nucleotide

triphosphate **130** reacted with the four boronates to give directly the biaryl compounds **163-166** in somewhat lower yields (17-25%), due to the hydrolysis of the triphosphates during the coupling reaction.

Table 20. Synthesis of 5-biaryl uridine analogues **159-166.**



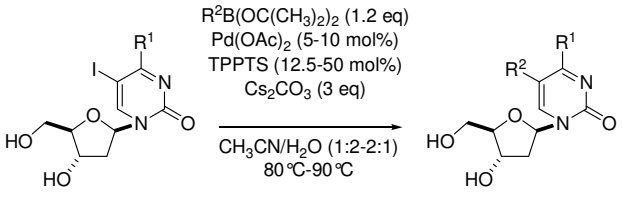
Entry	R^1	Starting material	R^2	Product	Yield (%)
1	H	**6**		**159**	65[a]
2	H	**6**		**160**	59[a]
3	H	**6**		**161**	71[a]
4	H	**6**		**162**	61[a]
5	$P_3O_9H_4$	**130**		**163**	21[b]
6	$P_3O_9H_4$	**130**		**164**	17[b]

7	$P_3O_9H_4$	**130**		**165**	20[b]
8	$P_3O_9H_4$	**130**		**166**	25[b]

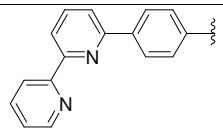
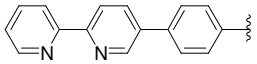
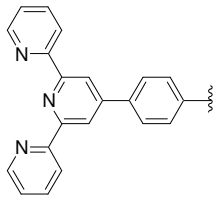
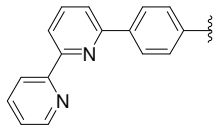
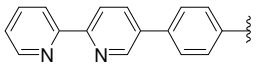
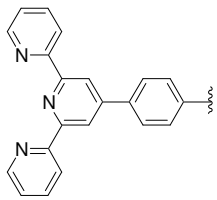
[a] 80°C, 2 hours; [b] 90°C, 45 minutes

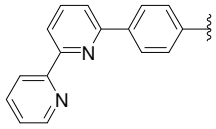
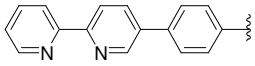
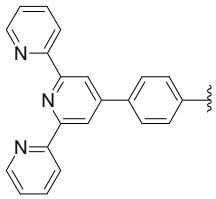
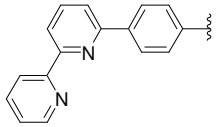
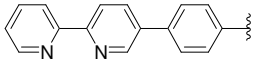
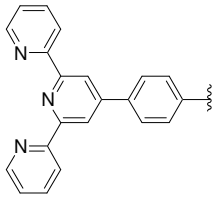
In 2009, the same laboratory reported the synthesis of 2□-deoxyuridine and 2□-deoxycytidine nucleoside analogues **167-172** bearing bipyridine (bpy) or terpyridine (tpy) ligands linked *via* phenylene linkers.[39] In a first time, the Suzuki-Miyaura couplings were achieved using 4-(pinacolboronato)phenyl derivatives (1.2 eq) in presence of Cs_2CO_3 (3eq), $Pd(OAc)_2$ (5 mol%) and TPPTS (12.5 mol%) in a mixture of CH_3CN/H_2O (1:2) at 80°C (Table 21, entries 1-3 and 7-9). Under these conditions, the yields of the target compounds **167** and **170** were acceptable, respectively 60% and 65% but using the other boronate esters the coupling adducts were not obtained in satisfactory yields. In a second phase of the study, variations in the source of palladium, the nature of ligand revealed that best results were obtained when $Pd(OAc)_2$ was present in 10 mol% in association with TPPTS (50 mol%) in a mixture of CH_3CN/H_2O (2:1) at 90°C. All the target nucleoside analogues **167-172** were obtained in better yields (35-75% *vs* 7-65%) (Table 21, entries 4-6 and 10-12). In the work of Sekine and co-workers published in 2007,[25] water was not the main solvent.

Table 21. Synthesis of 5-aryl uridine and cytosine analogues **167**-**172.**



6 (R^1=OH)
13 (R^1=NH_2)

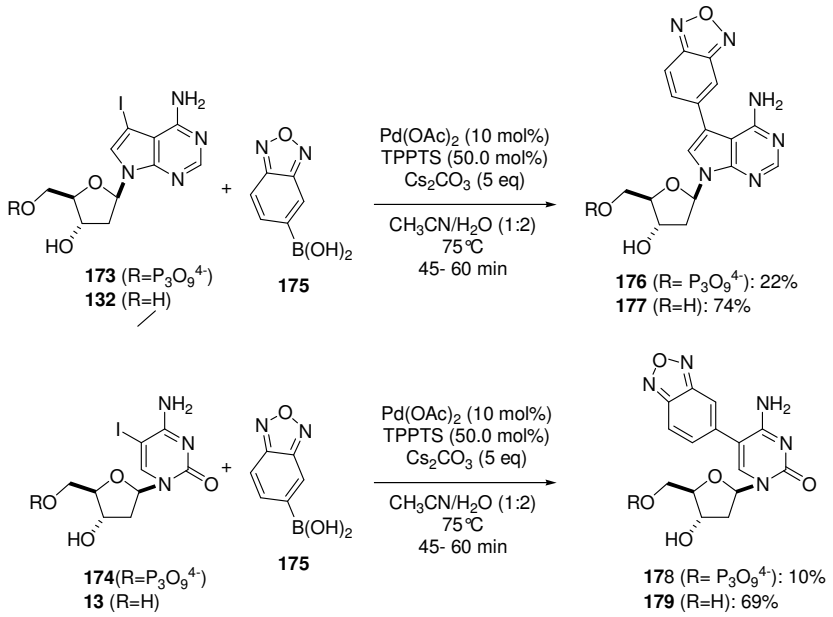
Entry	R^1	Starting material	R^2	Product	Yield (%)
1	OH	**6**		**167**	60[a]
2	OH	**6**		**168**	7[a]
3	OH	**6**		**169**	24[a]
4	OH	**6**		**167**	75[b]
5	OH	**6**		**168**	35[b]
6	OH	**6**		**169**	70[b]

7	NH_2	**13**		**170**	65[a]
8	NH_2	**13**		**171**	12[a]
9	NH_2	**13**		**172**	28[a]
10	NH_2	**13**		**170**	75[b]
11	NH_2	**13**		**171**	55[b]
12	NH_2	**13**		**172**	70[b]

[a] $Pd(OAc)_2$ (5 mol%), TPPTS (12.5 mol%), CH_3CN-H_2O (1:2), 80°C; [b] $Pd(OAc)_2$ (10 mol%), TPPTS (50 mol%), CH_3CN-H_2O (2:1), 90°C

In 2013, Hocek and co-workers used their previously described methodology[33] in order to obtain four benzofurazane labeled derivatives of 5-iodo-2'-deoxycytidine (**13**) and 7-deaza-7-iodo-2'deoxyadenosine (**132**) and their respective triphosphate forms **173** and **174**.[40] The Suzuki-Miyaura coupling was done in presence of benzo[*c*][1,2,5]oxadiazole-5-boronic acid (**175**) (1.2 eq) in presence of a large excess of catalyst and base at 75° C for 45 minutes to 1

hour. The resulting compounds **176-179** were isolated in good to moderate yields (Scheme 24).



Scheme 24. Synthesis of benzofurazane nucleosides **175**-**178**

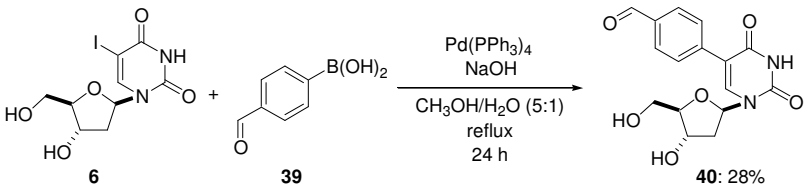
6 SUZUKI-MIYAURA IN CH_3OH/H_2O

The Suzuki-Miyaura cross-coupling reaction in a mixture of CH_3OH-H_2O was studied only using Pd(0).

6.1. $Pd(PPh_3)_4$ as Pd(0) and NaOH

In 2004, Saito and co-workers conducted a Suzuki-Miyaura cross coupling of 5-iodo-2□-deoxyuridine (**6**) with 4-formylboronic acid (**39**) in MeOH/H_2O (5:1) as solvent mixture.[41] If it were that the authors used $Pd(PPh_3)_4$ and NaOH as palladium source and base respectively they gave no indication about the amounts employed. However, it was claimed that the

desired cross-coupling product **40** was obtained in 28% after refluxing for 24 hours (Scheme 25). The target compound **40** was also obtained by Wagenknecht in 2008 in 76% yield.[19] Due to the lack of information in the work of Saito, it is difficult to compare the results.



Scheme 25. Synthesis of 5-(4-formylphenyl)uridine analogue **40**.

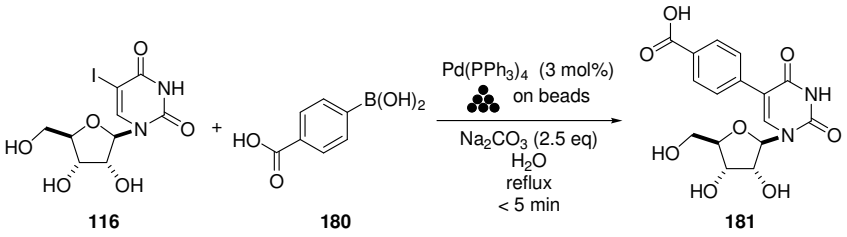
7 SUZUKI-MIYAURA IN H_2O

Surprisingly, only a few publications report the palladium-catalyzed cross-coupling syntheses of modified nucleosides using Pd(0) or Pd(II) and water as the sole solvent. In the case of Pd(II), recent reports describe a ligand-free Suzuki-Miyaura reaction for the first time in nucleoside chemistry.

7.1. $Pd(PPh_3)_4$ as Pd(0) and Na_2CO_3

The first reported use of water as the sole solvent for a Suzuki cross-coupling reaction was in 2003 by Williams and co-workers. They studied this reaction involving 5-iodouridine (**75**), boronic acid **180,** $Pd(PPh_3)_4$ (3 mol%) and reverse phase glass beads (Scheme 26).[42] The authors described the reaction as fast with a full conversion of the starting material **75** being completed within 4 hours. The cross-coupling product **181** and self-coupling product were obtained in a ratio of roughly 7:3. Further purification of the target carboxy derivative **181** was not mentioned in the report. Relatively low levels of palladium loading were used and authors described briefly an investigation into the recycling of the reverse phase glass-beads

but not for the nucleoside case. It is noteworthy that palladium leaching of 0.40% was detected.

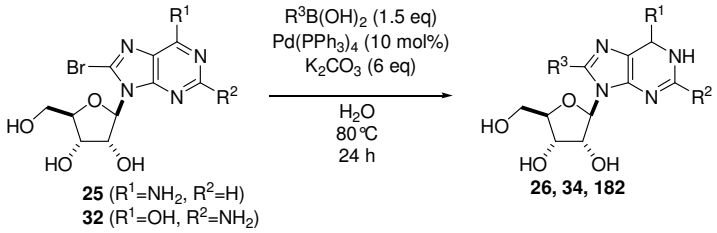


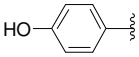
Scheme 26. Synthesis of 5-(4-formylphenyl)uridine analogue **181**.

7.2. $Pd(PPh_3)_4$ as Pd(0) and K_2CO_3

Wagner and co-workers reported the Suzuki-Miyaura coupling of unprotected compounds **25** and **32** carried out with the traditional catalyst $Pd(PPh_3)_4$ in water.[16] Starting from adenosine derivative **25**, addition of phenylboronic acid (**33**) (1.5 eq), $Pd(PPh_3)_4$ (10 mol%) and a large excess of K_2CO_3 (6 eq) in neat water at 80°C for one day furnished the target derivative **26** in 75% (Table 22, entry 1). Application of the methodology to the 8-bromoguanosine (**32**) did not give a cross-coupling product (Table 22, entry 2). However, the use of 4-hydroxyphenylboronic acid gave the adduct **182** albeit in low yield (Table 22, entry 3).

Table 22. Synthesis of 8-aryl nucleoside analogues **26, 34** and **182**.

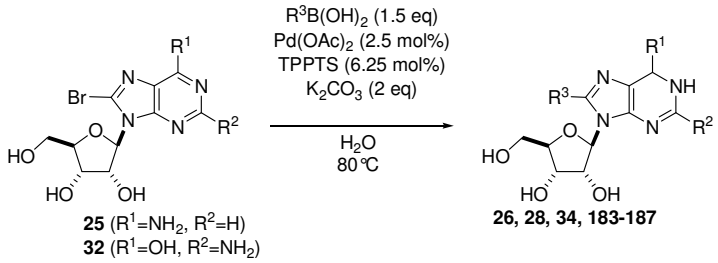


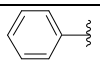
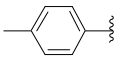
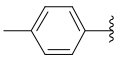
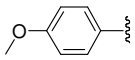
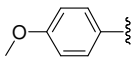
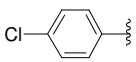
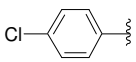
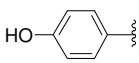
Entry	R^1	R^2	Starting material	R^3	Product	Yield (%)
1	NH_2	H	**25**		**26**	75
2	OH	NH_2	**32**		**34**	0
3	NH_2	H	**25**		**182**	26

7.3. $Pd(OAc)_2$ as Pd(II), TPPTS and K_2CO_3

In the same paper, Wagner and co-workers described the use of $Pd(OAc)_2$ with TPPTS as catalytic system (Table 23).[16] At 80°C, a mixture of 8-bromo nucleoside derivative **25** and boronic acid **33** (1.5 eq) in presence of $Pd(OAc)_2$ (2.5 mol%), TPPTS (6.25 mol%) and K_2CO_3 (2 eq) in water furnished the phenyl analogue **26** in 75% yield (Table 23, entry 1) as described by the authors with the $Pd(PPh_3)_4$ (Table 22, entry 1). In contrast to the former method, the guanosine derivative **34** was prepared in 61% yield (Table 23, entry 2). By varying the boronic acid, the aryl nucleoside analogues **26**, **28**, **34**, **44** and **183-187** were obtained successfully (Table 23). It is noteworthy that the cross-coupling was not achieved using 4-hydroxyphenylboronic acid (Table 23, entry 9). The authors noted that most of the 8-arylguanosine derivatives prepared by this method were obtained as black powders that required further purification by either recrystallization or column chromatography.

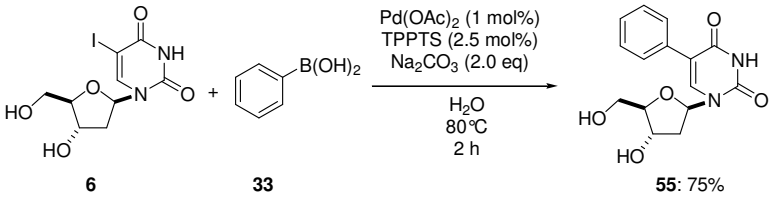
Table 23. Synthesis of 8-aryl nucleoside analogues **26, 28, 34**, **44** and **183**-**187**.



Entry	R^1	R^2	Starting material	R^3	Product	Yield (%)
1	NH_2	H	**25**		**26**	75
2	OH	NH_2	**32**		**34**	61
3	NH_2	H	**25**		**183**	70
4	OH	NH_2	**32**		**184**	83
5	NH_2	H	**25**		**28**	79
6	OH	NH_2	**32**		**44**	87
7	NH_2	H	**25**		**185**	96
8	OH	NH_2	**32**		**186**	84
9	NH_2	H	**25**		**187**	0

7.4. $Pd(OAc)_2$ as Pd(II), TPPTS and Na_2CO_3

Recently, Len's group described the use of the same catalytic system described by Wagner's team[16] except for the choice of base.[43] Reaction of the uridine analogue **6**, with boronic acid **33** (1.3 eq) in presence of a much smaller amount of palladium $Pd(OAc)_2$ (1.0 mol%), TPPTS (2.5 mol%) and Na_2CO_3 in water at 80°C for 4 hours furnished the corresponding adduct **55** in 75% yield (Scheme 27).

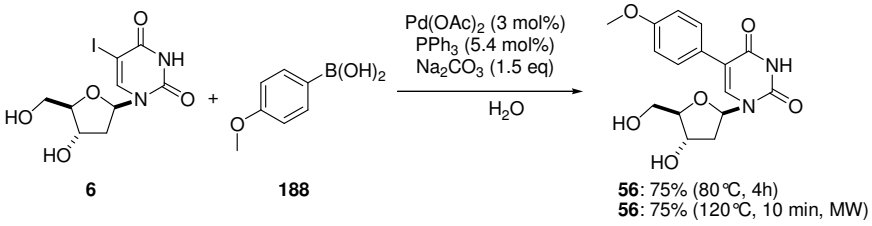


Scheme 27. Synthesis of 5-phenyluridine analogue **55**.

7.5. $Pd(OAc)_2$ as Pd(II), PPh_3 and Na_2CO_3

Agrofoglio and co-workers investigated the development of a Suzuki-Miyaura reaction involving 2□-deoxyuridine in a completely aqueous medium using a readily available and inexpensive catalyst/ligand system.[44] The conditions of this model reaction were optimized using the unprotected 5-iodo-2□-deoxyuridine (**6**) and 4-methoxyphenylboronic acid (**188**). After varying the nature of the ligand (eg. PPh_3, TXTPS, CataXcium F Sulf or tris[bis(*N*-2-hydroxyethyl)aminomethyl]phosphine)) and the amount of either the ligand or the solvent, the best method found was the coupling of compound **6** with the boronic acid (1.5 eq) in presence of Na_2CO_3 (1.5 eq), $Pd(OAc)_2$ (3 mol%) and PPh_3 (5.4 mol%) in neat water at 80°C for 4 hours. The authors decided then to use, under such optimised conditions, microwave irradiation assistance at 120°C, which permitted a significant reduction in the reaction time

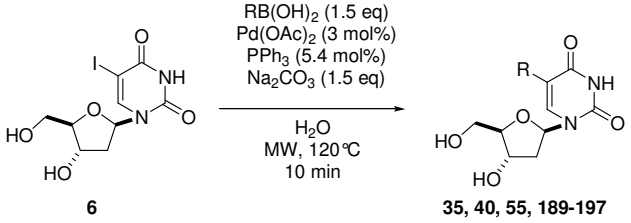
with the same yield (4 hours *vs* 10 minutes) and the furnishing of the desired adduct **56** in 75% yield (Scheme 28).



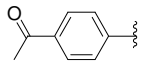
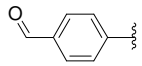
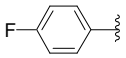
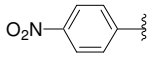
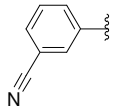
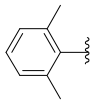
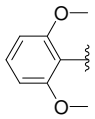
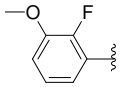
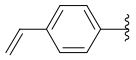
Scheme 28. Synthesis of 5-(4-methoxyphenyl)uridine analogue **56**.

Application of the optimized method to different arylboronic acids afforded the cross-coupled products **35**, **40**, **55** and **189-197** in good yield with substrates that contained either electron-donating or withdrawing groups in the *para* and *meta* positions of the aromatic core. Thus, 5-iodo-2□-deoxyuridine (**6**) was coupled with a variety of heteroarylboronic acids including thiophene-3-, furan-2-, furan-3-boronic acids (Table 24, entries 11-13).

Table 24. Synthesis of 5-aryl uridine analogues **35, 40, 55** and **189**-**197**.



Entry	R	Product	Yield (%)
1		**55**	70

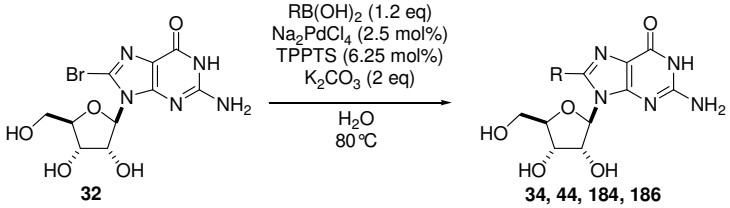
2		**189**	72
3		**40**	79
4		**35**	74
5		**190**	68
6		**191**	70
7		**192**	-
8		**193**	-
9		**194**	53[a]
10		**195**	30
11		**196**	67
12		**61**	81
13		**197**	44

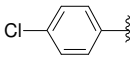
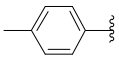
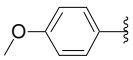
[a] $RB(OH)_2$ (3 eq)

7.6. Na_2PdCl_4 as Pd(II) and K_2CO_3

Wagner and co-workers reported a challenging Suzuki-Miyaura coupling of unprotected 8-bromo-5'-mono- and triphosphates guanosine.[45] In the same paper, the authors initially chose a model reaction starting from 8-bromoguanosine (**32**) to identify the optimum conditions in neat water.[45] Several catalytic systems were tested including $Pd(OAc)_2$, $Pd(NO_3)_2$, Na_2PdCl_4 and $PdCl_2$ as source of palladium and TPPTS along with the Buchwald ligand and EDTA as source of ligand. Out of the catalytic systems screened, only those with a phosphine ligand were found to be active. The role of Pd source was highlighted by the finding that replacement of $Pd(OAc)_2$ with a water-soluble Pd source resulted in a cleaner product. The best results, with regard to yield and reaction times, were achieved with catalytic systems combining either $Pd(NO_3)_2$ or Na_2PdCl_4 with the water-soluble phosphine ligand TPPTS. Because of the lower cost and higher stability of Na_2PdCl_4 (compared to $Pd(NO_3)_2$, the catalytic system Na_2PdCl_4 (2.5 mol%) and TPPTS (6.25 mol%) was chosen for the reaction in presence of K_2CO_3 (2 eq) in neat water at 80°C (Table 25). Using this method, the nucleoside analogues **34**, **44**, **184** and **186** were obtained in yields higher than 70%. It is noteworthy that Shaughnessy and co-workers obtained similar results (determination by HPLC analysis) starting from 8-bromo-2□-deoxyadenosine (**15**) to furnish the corresponding 8-phenyl derivative **51** using different sources of palladium and TPPTS or TXPTS as ligand.[20]

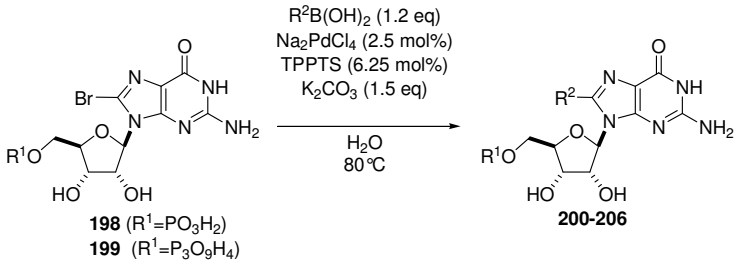
Table 25. Synthesis of 8-arylguanosine analogues **34, 44, 184** and **186**.

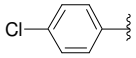
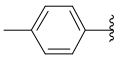
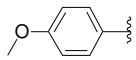
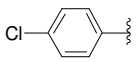
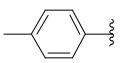


Entry	R	Product	Time (min)	Yield (%)
1		**34**	20	77
2		**186**	30	84
3		**184**	20	70
4		**44**	30	84

The authors next applied their optimized cross-coupling conditions with a lower excess of base (K_2CO_3 1.5 eq) to the reaction of the mono- and triphosphate guanosine derivatives **198** and **199**.[45] All of the 8-aryl monophosphate derivatives **200-203** were obtained in good to excellent yields, and most reactions were completed within 2 hours at 80°C. (Table 26, entries 1-4). The cross-coupling reactions of the nucleotides triphosphates **204-206** proceeded smoothly, in short reaction times and good yields (Table 26, entries 5-7).

Table 26. Synthesis of 8-arylguanosine analogues **200**-**206**.

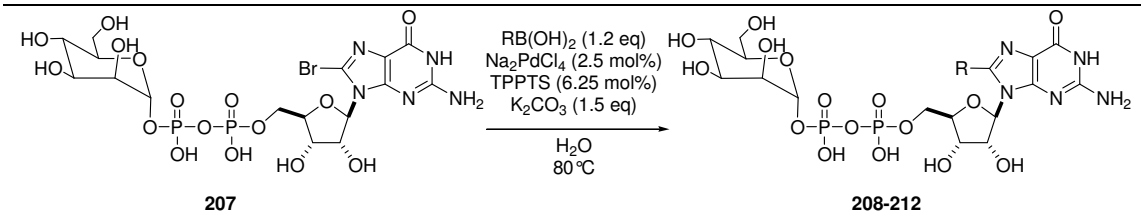


Entry	R^1	Starting material	R^2	Product	Time (min)	Yield (%)
1	PO_3H_2	**198**		**200**	15	63
2	PO_3H_2	**198**		**201**	80	92
3	PO_3H_2	**198**		**202**	60	90
4	PO_3H_2	**198**		**203**	360	71
5	$P_3O_9H_4$	**199**		**204**	60	85
6	$P_3O_9H_4$	**199**		**205**	60	56
7	$P_3O_9H_4$	**199**		**206**	120	65

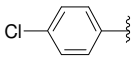
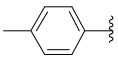
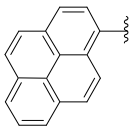
In 2008, the same team extended their methodology to the preparation of 8-aryl-5□-diphosphateguanosine-mannose **208-212** starting from the bromo derivative **207** (Table 27).[46]

This synthesis is the first example, to date of the cross-coupling of a sugar-nucleotide in aqueous media.

Table 27. Synthesis of 8-arylguanosine analogues **208**-**212**.



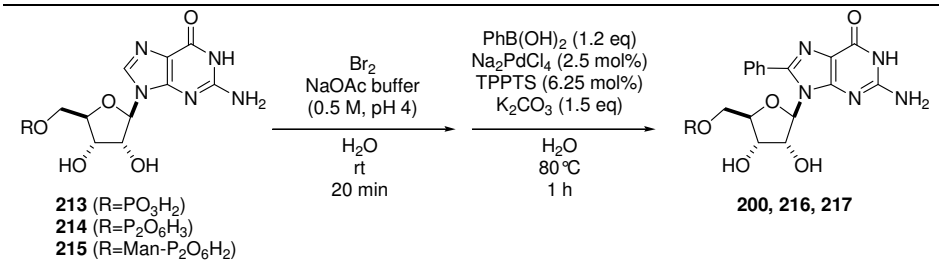
207 **208-212**

Entry	R^2	Product	Yield (%)
1		**208**	48
2		**209**	82
3		**210**	82
4		**211**	57
5		**212**	73

To minimize the number of lengthy purification steps in the sequence, the one pot-two steps procedure (bromination and cross-coupling) starting from the guanosine derivatives **213-215** was studied. The corresponding monophosphate, diphosphate and the sugar-

nucleotide furnished the target 8-phenyl derivatives **200**, **216** and **217** in 75%, 50% and 44% yield (two steps) respectively (Table 28). [46]

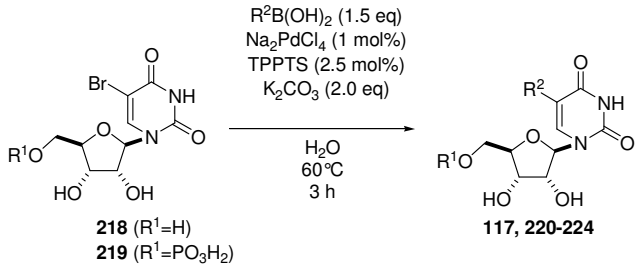
Table 28. Synthesis of 8-arylguanosine analogues **200**, **216** and **217**.

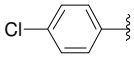
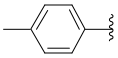
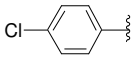
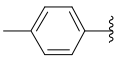


Entry	R	Starting material	Product	Yield (%)
1	PO_3H_2	**213**	**200**	75
2	$P_2O_6H_3$	**214**	**216**	50
3	Man-$(PO_3)_2^{--}$	**215**	**217**	44

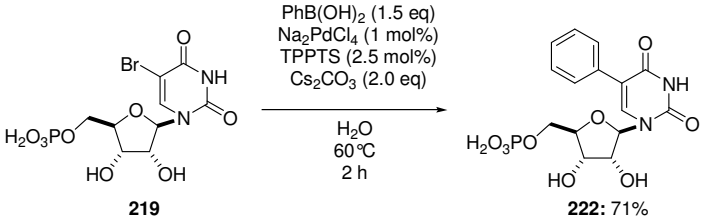
Wagner and co-workers in 2008, reported the first successful Suzuki-Miyaura reaction of an unprotected 5-halo-5□-mono and diphosphate uridine-sugar.[47] The authors found an optimized catalytic system for the coupling of 5-bromouridine (**218**) and 5-bromouridine monophosphate (**219**) in neat water involved treating Na_2PdCl_4 (1mol%), TPPTS (2.5 mol%) and K_2CO_3 (2eq) as base at 60°C for 3 hours. Six adducts **117** and **220-224** were obtained using this methodology (Table 29). It was the first time that a bromo derivative was used as the starting material in the case of pyrimidine analogues.

Table 29. Synthesis of 8-arylguanosine analogues **117** and **220**-**224**.



Entry	R^1	Starting material	R^2	Product	Yield (%)
1	H	**218**		**117**	45
2	H	**218**		**220**	43
3	H	**218**		**221**	46
4	PO_3H_2	**219**		**222**	57
5	PO_3H_2	**219**		**223**	26
6	PO_3H_2	**219**		**224**	27

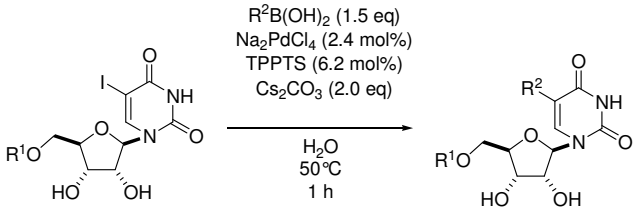
The authors advised that neither an increase in the amount of base (K_2CO_3) nor use of a stronger base (NaOH) improved cross-coupling efficiency. However, replacement of K_2CO_3 (2eq) with Cs_2CO_3 (2eq) for 2 hours resulted in a substantially higher yield of the nucleotide **222** (71% *vs* 57%) (Scheme 29).



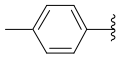
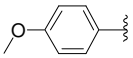
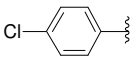
Scheme 29. Synthesis of monophosphate 5-(phenyl)uridine analogue **222**.

It is of note that the aforementioned optimized Suzuki-Miyaura conditions were unsuccessfully applied to 5-bromouridine diphosphate.[47] The authors attempted a similar conversion involving the iodinated derivatives **225** and **226** instead of the brominated analogues since the iodides are generally more reactive in cross-coupling reactions than the corresponding bromide analogues. In this case, six different adducts **117**, **221** and **227-230** were prepared by addition of boronic acid (1.5 eq) in presence of Cs_2CO_3 (2.0 eq) as base, Na_2PdCl_4 (2.4 mol%) and TPPTS (6.21 mol%) in neat water at 50°C for 1 hour (Table 30). Using this method, compounds **117** and **221** were obtained in better yields than those previously mentioned here (for **117** 71% *vs* 45%; for **221** 66% *vs* 46%).

Table 30. Synthesis of 8-arylguanosine nucleoside analogues **117, 221** and **227**-**230**.



Entry	R^1	Starting material	R^2	Product	Yield (%)
1	PO_3H_2	**225**		**117**	71

2	PO_3H_2	**225**		**221**	66
3	Glu-($P_2O_6H_2$)	**226**		**227**	64
4	Glu-($P_2O_6H_2$)	**226**		**228**	58
5	Glu-($P_2O_6H_2$)	**226**		**229**	57
6	Glu-($P_2O_6H_2$)	**226**		**230**	40

To investigate the possibility that the 5-brominated derivative **231** may, in solution, adopt a conformation, which restricts access of the palladium-ligand catalytic complex, the authors carried out a comparative conformational analysis of both sugar-nucleotides **226** and **231** (Figure 5). It appears that the iodinated derivative **226** adopts a *syn* conformation in which the 5-iodo substituent is pointing away from the glucose diphosphate group, and the 5 position is more easily accessible by the Pd catalyst. The brominated derivative **231** was found to prefer the *anti* conformation where the 5-bromo substituent is facing towards the bulky glucose diphosphate moiety. Therefore, authors concluded that the superior cross-coupling reactivity of the iodinated substrate may be attributed, as least in part, to the capacity of the bulky iodo-substituent to induce a conformation, which is favorable for the insertion of the reactive Pd species during the oxidative addition step.[47]

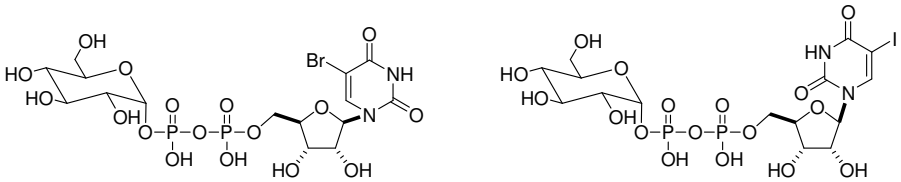
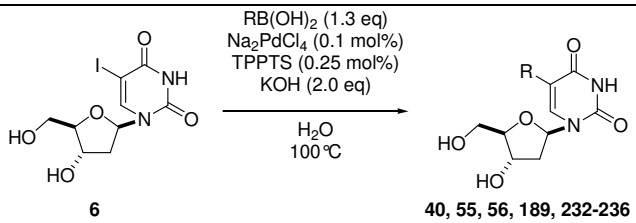


Figure 5. *Anti* and *syn* conformation of nucleotides **231** and **226**.

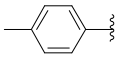
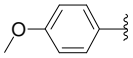
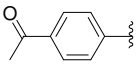
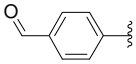
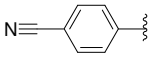
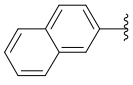
7.7. Na_2PdCl_4 as Pd(II) and KOH

In an attempt to expand on the sustainable aspect of the Suzuki-Miyaura reaction, our group recently reported the development of three successful water-based methods starting from the commercially available unprotected 5-iodo-2□-deoxyuridine (**6**).[43,48-50] Using a very low loading of catalyst (Na_2PdCl_4 0.1 mol% and TPPTS 0.25 mol%) in presence of KOH (2 eq) as base, various 5-aryl-2□-deoxyuridine analogues **40**, **55**, **56**, **189** and **232-236** were obtained in good to very good yields (Table 31).[43] Substituent effects in the arylboronic acids did not appear to be significant, with the exception of compound **233**, which has a nitrile substituent in the *para* position (Table 31, entry 6). No hydrolysis was detected under our aqueous basic conditions used for the synthesis of nucleoside analogue **233**; hence, the reaction was stopped after no more conversion was detected. All the aryl boronic acids with diverse electron-donating and electron-withdrawing substituents delivered the cross-coupled products in good yields (Table 31). The sterically demanding 2-methyl- and 2-methoxyphenyl boronic acids (Table 31, entries 7 and 8) proved to be difficult substrates for the Suzuki–Miyaura reaction. However, after extending reaction times, the target nucleoside analogues **234** and **235** were isolated in high (94%) and modest (36%) yield, respectively. A good conversion using 2-naphthylboronic acid furnished the nucleoside analogue **236** in 77% yields after five hours (Table 31, entry 9).

Table 31. Synthesis of 5-aryl uridine analogues **40**, **55**, **56, 189** and **232**-**236**.

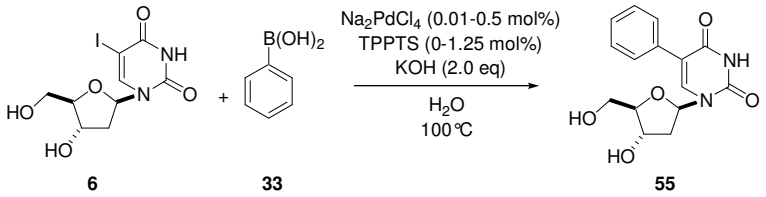


6 **40, 55, 56, 189, 232-236**

Entry	Time (h)	R	Product	Yield (%)
1	0.5		**55**	85
2	1		**232**	78
3	6		**56**	66
4	1		**189**	70
5	4		**40**	84
6	0.5		**233**	26
7	24		**234**	94
8	24		**235**	36
9	5		**236**	77

With the objective of designing a "greener" protocol, attention was drawn to improving atom economy and reducing the number of derivatives. Our group reported an efficient extension of the previous work to establish whether the presence of the ligand may or not influence cross-coupling efficiency.[48] For this purpose, 5-iodo-2□-deoxyuridine (**6**) and phenyl boronic acid (**33**) were engaged in Suzuki-Miyaura cross-coupling reactions with low amounts of palladium (0.5-0.01 mol%), either in the presence or absence of TPPTS (2.5 eq to Pd) at 100°C in neat water (Table 32). Our results showed clearly that the presence of TPPTS in the mixture was not necessary at 100°C. Whatever the amount of palladium (0.5-0.01 mol%) employed, the absence of TPPTS had no inhibitory effect on the reaction course. In our hands, no significant differences in reaction time and/or yields were observed between 0.5 mol%, 0.1 mol% and 0.05 mol% of Pd(II). Indeed using such catalytic conditions (Table 32, entries 1-6), the desired cross-coupling product **55** was obtained in very good yields (79-86%) within a maximum of 30 minutes. One can also see that by dramatically decreasing the amount of palladium there is an expected increasing of the reaction time. However, even after 24 hours 5-phenyl-2□-deoxyuridine (**55**) was obtained in moderate yields even with only 0.01 mol% of $Pd(OAc)_2$ used (Table 32, entries 9 and 10).

Table 32. Synthesis of 5-phenyl uridine analogue **55**.

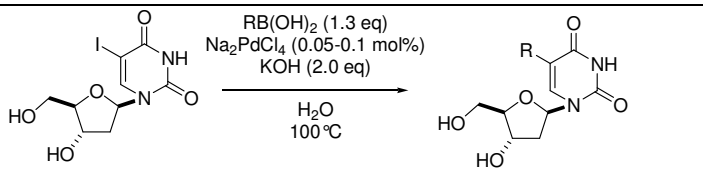


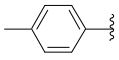
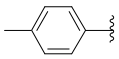
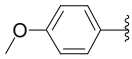
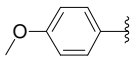
Entry	Na_2PdCl_4 (mol%)	TPPTS (mol%)	Time (h)	Yield (%)
1	0.5	1.25	0.25	79
2	0.5	0	0.08	82
3	0.1	0.25	0.25	80
4	0.1	0	0.25	80
5	0.05	0.125	0.50	84
6	0.05	0	0.50	86
7	0.02	0.05	4	73
8	0.02	0	4	72
9	0.01	0.025	24	60
10	0.01	0	24	58

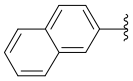
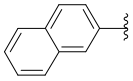
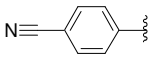
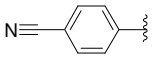
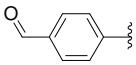
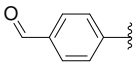
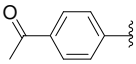
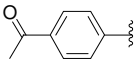
These encouraging experiments (Table 32, entries 4 and 6) led us to define two ligand-free methods to: (i) establish a different optimized reaction; (ii) produce a consistent library of nucleoside analogues. For this purpose different arylboronic acids were engaged in the cross-

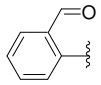
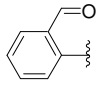
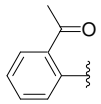
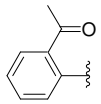
coupling reactions. Various substrates were examined with electron-donating and withdrawing groups in the *para* or *ortho* positions accordingly. Also different means heating were studied: classical and microwave irradiation assisted.[49]

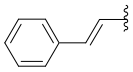
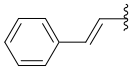
Table 33. Synthesis of 5-aryl uridine analogues **40**, **55**, **56**, **189**, **197** and **232**-**240**.



Entry	Na_2PdCl_4 (mol%)	Time (h)	R	Product	Yield (%)
1	0.1	0.08[b] (0.25)[c]		**55**	85[b] (80)[c]
2	0.05	0.25[b] (0.50)[c]		**55**	82[b] (86)[c]
3	0.1	0.08[b] (0.50)[c]		**232**	79[b] (79)[c]
4	0.05	0.50[b] (2.00)[c]		**232**	79[b] (80)[c]
5	0.1	1.00[b] (7.00)[c]		**56**	84[b] (64)[c]
6	0.05	1.00[b] (24.00)[c]		**56**	67[b] (57)[c]

7	0.1	0.50[b] (2.00)[c]		**236**	84[b] (80)[c]
8	0.05	1.00[b,d] (24.00)[c]		**236**	36[b] (70)[c]
9	0.1	0.25[b] (1.00)[c]		**233**	33[b] (39)[c]
10	0.05	0.50[b] (5.00)[c]		**233**	10[b] (13)[c]
11	0.1	0.50[b] (6.00)[c]		**40**	66[b] (17)[c]
12	0.05	1.00[b,d] (5.00)[c]		**40**	56[b] (13)[c]
13	0.1	0.25[b] (0.50)[c]		**189**	78[b] (69)[c]
14	0.05	0.50[b] (24.00)[c]		**189**	57[b] (49)[c]
15	0.1	1.00[b,d] (24.00)[c]		**234**	30[b] (22)[c]
16	0.05	1.00[b,d] (24.00)[c]		**234**	21[b] (19)[c]

17	0.1	1.00[b,d] (24.00)[c]		**235**	45[b] (23)[c]
18	0.05	1.00[b,d] (24.00)[c]		**235**	23[b] (18)[c]
19	0.1	1.00[b,d] (24.00)[c]		**237**	0[b] (0)[c]
20	0.05	1.00[b,d] (24.00)[c]		**237**	0[b] (0)[c]
21	0.1	1.00[b] (24.00)[c]		**238**	23[b] (0)[c]
22	0.05	1.00[b,d] (24.00)[c]		**238**	0[b] (0)[c]
23	0.1	1.00[b,d] (6.00)[c]		**239**	40[b] (32)[c]
24	0.05	1.00[b,d] (24.00)[c]		**239**	45[b] (0)[c]
25	0.1	1.00[b,d] (24.00)[c]		**197**	75[b] (0)[c]
26	0.05	1.00[b,d] (24.00)[c]		**197**	18[b] (0)[c]

27	0.1	0.50[b] (2.00)[c]		**240**	85[b] (58)[c]
28	0.05	1.00[b] (4.00)[c]		**240**	66[b] (33)[c]

[a] Isolated yields. [b] under MW irradiation. [c] under conventional heating. [d] reaction did not reach completion.

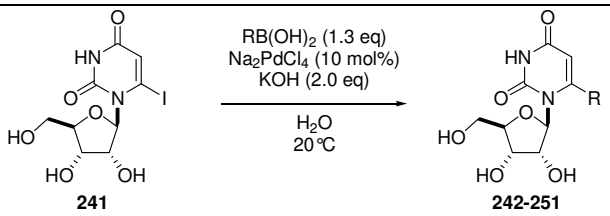
The reaction times and yields in presence of Na_2PdCl_4 (0.1 mol%) were always shorter and higher respectively than those observed in the presence of a lower loading of Na_2PdCl_4 (0.05 mol%) under thermal as well as microwave irradiation conditions.[49] In addition, the cross-coupling reactions were more efficient when the microwave irradiation was employed. Aryl boronic acids with an electron-donating substituent in the *para* position gave the cross-coupling products **56** and **232** in good yields (Table 33, entries 3-6) either with 0.1 mol% or 0.05 mol% Na_2PdCl_4. Comparing with compound **55**, the presence of methyl group in *para* position of the aromatic ring does not change significantly the reaction result since compound **232** was isolated in the same range of yields and times (Table 33, entries 1-4). On the contrary, when a heteroatom was directly bound to the aryl boronic acid in *para* position, an extended time reaction was needed to reach completion (Table 33, entries 5 and 6). Due to a lower nucleophilicity of aryl boronic acids with electron-withdrawing groups particularly with a nitrile and formaldehyde groups reactions were less efficient (Table 33, entries 9-12). The sterically demanding 2-methyl- and 2-methoxyphenyl boronic acids proved to be difficult substrates for Suzuki-Miyaura cross-coupling of nucleosides even using "standard" conditions. It is of note that both methods proved successful albeit in giving modest yields (Table 33, entries 15-18). However, whatever the atom that was directly attached to the aromatic

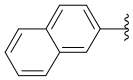
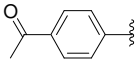
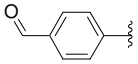
moeity of the boronic (methyl and methoxy groups) acid no difference was observed in reaction time. It is proposed that steric restrictions may take over from electronic effects in such cases. In the cases of boronic acids which involved both steric effect and electron-withdrawing substituents such as 2-acetylphenylboronic acid and 2-formylphenylboronic acid, as might be expected no cross-coupling reaction was observed when using conventional heating and only in one case a product was observed when microwave irradiations (Table 33, entries 19-22) was applied. To expand on the array of substrates for study, 5-iodo-2'-deoxyuridine (**6**) was coupled with a variety of heteroarylboronic acids (Table 33, entries 23-26) and with the (*E*) styrylboronic acid (Table 33, entries 27, 28). It was found that thiophen-2-boronic acid was the only heteroarylboronic acid reactive enough to give the desired cross-coupling product **239** albeit in modest yield using either conventional heating or microwave irradiation (Table 33, entries 23-24). Also furan-2-yl boronic acid was only sufficiently reactive when the alternative technology was used (Table 33, entries 25-26). Interestingly, compound **240**, was obtained using our methodolgy *via* the Suzuki-Miyaura reaction under heating with either conditions (Table 33, entries 27-28). To the best of our knowledge, this is the first time in nucleoside chemistry that the Suzuki-Miyaura reaction has been shown to be successful in respect of the use of green and economic conditions.

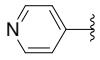
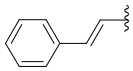
In 2013, Len's group described the first synthesis of the 6-aryl nucleoside analogues **242-251** using Suzuki-Miyaura cross-coupling reaction in water without the use of a ligand.[50] After a systematic variation of different parameters, the optimized method found was that described above which involved an enhancement of the amount of palladium Na_2PdCl_4 (10 mol%) in water without ligand. Due to the instability of the starting material **241** having an iodine atom in position 6, the cross-coupling was developed futher to enable it to be conducted effectively at room temperature. Thus, a series of aryl boronic acids with

different electronic and steric factors were succesfully screened leading to the target compounds **242**, **243**, **245-247** and **251** (Table 34).

Table 34. Synthesis of 6-aryl uridine analogues **242**-**251**.



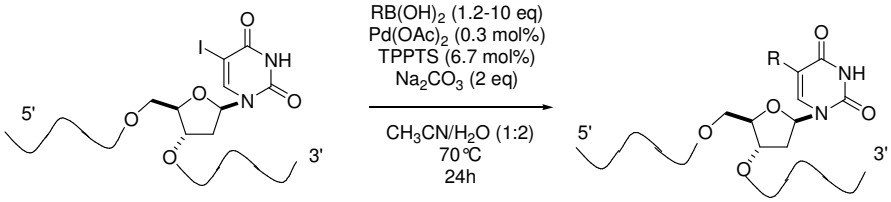
Entry	Time (h)	R	Product	Yield (%)
1	0.5		**242**	81
2	1.0		**243**	71
3	24		**244**	0
4	1.5		**245**	84
5	1.5		**246**	61
6	1.5		**247**	80
7	24		**248**	0
8	4		**249**	0

9	24		**250**	0
10	2		**251**	72

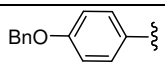
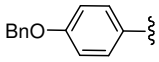
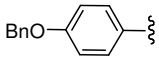
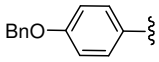
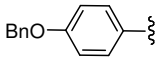
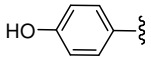
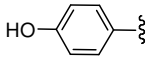
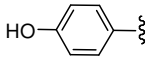
8. POST-SYNTHETIC MODIFICATION OF OLIGODEOXYNUCLEOTIDES (ODNs)

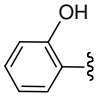
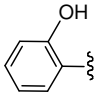
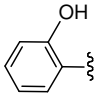
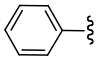
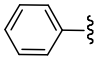
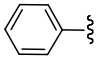
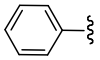
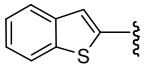
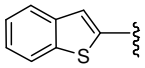
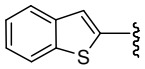
Multiples methods for the incorporation of modified building blocks with desired properties in oligodeoxynucleotides (ODNs) have been developed.[51-52] Each of those methods presents its advantages but also its difficulties and/or drawbacks. An alternative to those methods may consist in the post-synthetic modification of oligodeoxynucleotides. Concerning such Suzuki-Miyaura reactions, the first results were published by Manderville and co-workers in 2011.[53] The Suzuki-Miyaura cross-coupling reaction allowed this team to synthesize a number of C8-Ar-G-modified oligonucleotides (dimmers, trimers, decamers and a 15-mer) using a range of arylboronic acids. In order to optimize the Pd-postsynthetic reaction, shortest DNA substrates (0.1 μmol) having bromide group were utilized first and reacted with boronic acid (1.2 eq-10.0 eq) in the presence of $Pd(OAc)_2$ (0.3 mol%), TPPTS (6.7 mol%) and Na_2CO_3 (2 eq) in H_2O/CH_3CN (2:1) mixture as solvent at 70°C for 24 hours (Table 35). The corresponding oligomers were obtained in a large range of yield (15%-97%) that was not dependant of the nature of the oligomers. It is notable that the protection of the 4-hydroxy derivatives (Table 35, entries 1-4) did not permit to increase the yield of the coupling compared with the use of the free hydroxyl derivatives (Table 35, entries 6-8).

Table 35. Postsynthetic DNA synthesis of C8-Ar-G-modified oligonucletotides **252- 269**.



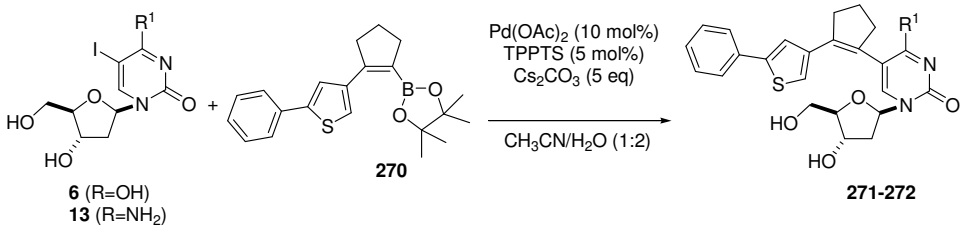
ODN**1** : 5'-**BrG**C
ODN**2** : 5'-C**BrG**C
ODN**3** : 5'-CCAT**BrG**CTACC
ODN**4** : 5'-GGTAG**BrG**ATGG
ODN**5** : 5'-CCCGGTAG**BrG**ATGGCC

Entry	Oligo	R	Product	Yield(%)
1	ODN1		**252**	60[a]
2	ODN2		**253**	41[a]
3	ODN3		**254**	15[a]
4	ODN3		**255**	45[b]
5	ODN4		**256**	71[b]
6	ODN2		**257**	60[b]
7	ODN3		**258**	79[b]
8	ODN4		**259**	77[b]

9	ODN2		**260**	39[b]
10	ODN3		**261**	83[b]
11	ODN4		**262**	87[b]
12	ODN2		**263**	49[b]
13	ODN3		**264**	55[b]
14	ODN4		**265**	97[b]
15	ODN5		**266**	83[b]
16	ODN2		**267**	47[b]
17	ODN3		**268**	78[b]
18	ODN4		**269**	39[b]

(a) 1.2 equivalents of boronic were used. (b) 10 equivalents of boronic acid were used.

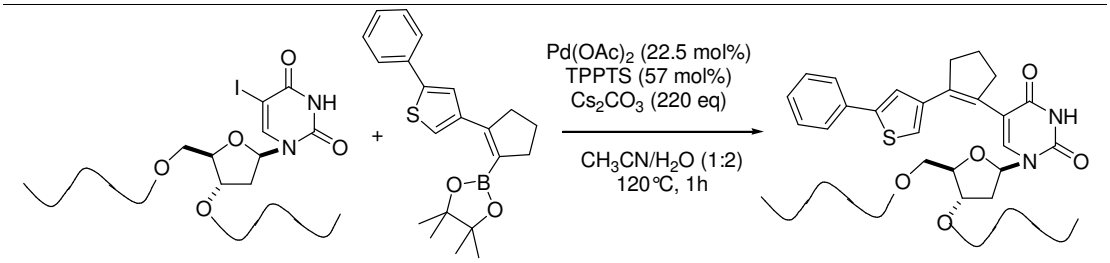
Very recently Jäschke and co-workers reported the obtention of a nucleoside-based diarylethene photoswitches starting from 5-iodo-2'-deoxyuridine (**6**) and 5-iodo-2'-deoxycytidine (**13**) as well as the obtention of nine photoswitch-modified oligonucleotides.[54] Reaction of compound **6** and compound **13** with 2-[2-methyl-5-phenylthien-3-yl]cyclopent-1-ene boronic acid pinacol ester (**270**), under Suzuki-Miyaura cross coupling conditions previously described[27] gave the corresponding products in yields of 44-61% (Scheme 30).



Scheme 30. Synthesis of nucleoside-base diarylethene photoswitches **271-272**.

Following this work, authors reported Suzuki-Miyaura cross-couplings of iodinated oligonucleotide and sterically demanding boronic acid.[54] First, authors tested the conditions elaborated by Manderville and co-workers.[53] However no detectable amounts of product were obtained. Therefore, they opted for the conditions developed for sensitive nucleosides triphosphate.[35-38] Nine different modified nucleotides bearing one or two photoswitchable groups were then isolated 16-35% yield (Table 36) starting from halogenated nucleotide (100 μmol), boronic acid pinacol ester (200 eq), Cs_2CO_3 (220 eq) , $Pd(OAc)_2$ (22.5 mol%) and TPPTS (57 mol%) at 120°C for 1 h. Authors reported the presence of dehalogenated starting material beside the cross-coupled compounds **273-281**.

Table 36. Synthesis of modified ODNs **273**-**281**.



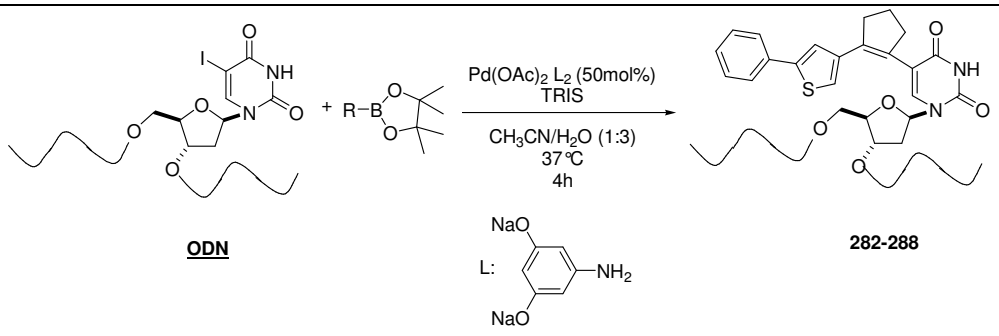
270 273-281

Entry	Oligo	Substrate	Product	Yield(%)
1	15mer-dU^{PS}1	5'-AGCAACA**IU**CGATCGG-3'	**273**	25
2	15mer-dC^{PS}1	5'-AGCAACA**IC**CGATCGG-3'	**274**	22
3	15mer-dU^{PS}2	5'-**IU**GCAACATCGATCGG-3'	**275**	26
4	15mer-dC^{PS}2	5'-**IC**GCAACATCGATCGG-3'	**276**	34
5	15mer-dU^{PS}3	5'-AGCAACATCGATCG**IU**-3'	**277**	25
6	15mer-dC^{PS}3	5'-AGCAACATCGATCG**IC**-3'	**278**	35
7	19mer-dU^{PS}1	5'-TCTAATACGACTCAC**IU**ATA-3'	**279**	20
8	19mer-dU^{PS}2	5'-TCTAATACGACTCACTA**IU**A-3'	**280**	19
9	19mer-dU^{PS}3	5'-TCTAATACGACTCAC**IU**A**IU**A-3'	**281**	16

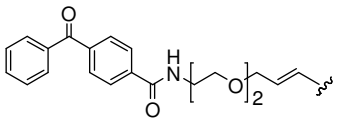
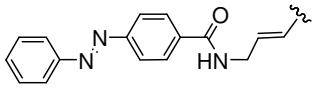
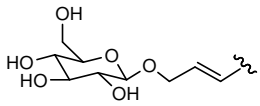
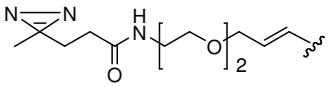
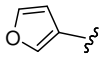
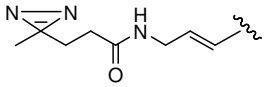
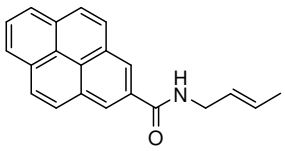
Authors noticed that a cross-coupling done at terminal positions (3' or 5') were generally more efficient than an internal one.

Still in 2013, Davis and coworkers reported the generation of functional probes by DNA modification under mild conditions by Suzuki-Miyaura cross-coupling.[55] For this purpose, authors started from commercially halogenated ODNs (100 μm) and used several pinacol boronic esters, a catalytic system composed by $Pd(OAc)_2$ and 2-aminopyrimidine-4,6-diol, at biological temperature (37°C) in a mixture of H_2O/CH_3CN (3:1) as solvent. Several biologically compatible buffer systems were tested (Na_2PO_4, NH_4OAc and TRIS) as well as a range of basic pH values (8 and 8.5). Authors found that tris(hydroxymethyl)aminomethane (TRIS) buffer at pH 8.5 provided the most robust cross-coupling conditions, meaning full conversion of the starting material with non noticeable side products, excepts traces of deiodinated ODN. Further optimization led the authors to obtain a complete conversion in 4 hours at 37°C using boronic ester (100 eq) and 50 mol% of [Pd]. Using this optimized conditions, authors isolated several modified ODNs **282-288** containing representative functionalities among which diazirine, benzophenone or azobenzene (Table 37).

Table 37. Synthesis of modified ODNs **282-288**.



Entry	Oligo	R	Product	Yield (%)

1	3'-AT[-IdU]GC-5'		**282**	86
2	3'-AT[-IdU]GC-5'		**283**	71
3	3'-AT[-IdU]GC-5'		**284**	88
4	3'-AT[-IdU]GC-5'		**285**	93
5	3'-AT[-IdU]GC-5'		**286**	78
6	3'-AT[-IdU]GC-5'		**287**	90
7	3'-AT[-IdU]GC-5'		**288**	61

Authors pointed out that the amount of [Pd] could be reduced to 10 mol% over longer reaction times. The reaction could also be done at room temperature but with a longer full conversion time of starting material (16 hours). Authors tried their reaction condition on another ODN which did not contain 5-iodo-2'-deoxyuridine residue in order to ruling out nonspecific reaction of other bases and then confirmed site selectivity.

9. CONCLUSION

A focus of this review has been observance of the twelve principles of green chemistry, in respect of the Suzuki-Miyaura cross-coupling reaction applied to the synthesis of nucleoside and nucleotide analogues having biological activities. To date, the majority of work has been directed towards 8-arylpurine (adenosin-9-yl and guanosin-9-yl) and 5-arylpyrimidine (uracil-1-yl and cytosin-1-yl) analogues having D-ribose and 2□-deoxy-D-ribose moiety. The normal starting materials used have been 8-bromo, 5-iodo analogues and in some cases it has been the 5-bromo derivatives.[46] Although most examples in this field have been aryl adducts, some heterocyclic examples have also received attention. The appropriated boronic acids have been of common use but esters have found applications applied for different cross-couplings.[11-13,38-39] The review encompasses variations of the starting materials, boronic acids, nature of the solvent, palladium source, ligand, base and reaction temperature (often higher than 80°C).

The use of THF/MeOH/H_2O (mainly 2:1:2 and 2:2:1)[8-14] afforded different 8-aryl-2□-deoxyadenosine, 8-aryl-2□-deoxyguanosine, 5-aryl-2□-deoxyuridine and 5-aryl-2□-deoxycytidine analogues using either Pd(0) (10 mol%) such as $Pd(PPh_3)_4$[8-10] or Pd(II) (10 mol%) such as $PdCl_2(dppf)$[13] and $PdCl_2(dppf)_2$[14] in presence of NaOH (20 eq) as base. This solvent mixture was used for the coupling of different boronic acids having 3-5 aromatic cores, with or without heteroatoms. Using these procedures, the yields were low to good (10-79%) and starting materials having an exocyclic amino group gave low yields (10-65%).

In DME/H_2O (2:1),[15-17] the cross coupling was effected starting from adenosine and guanosine derivatives, which are more polar than the corresponding 2□-deoxy analogues. Of the two nucleoside derivatives, only the adenosine afforded the target aryl adducts in

moderate to good yield (60-81%). In this solvent mixture, introduction of furan and thiophene cores furnished lower yields (25% and 40%, respectively). $Pd(PPh_3)_4$ (10 mol%)[15-17] and $Pd(OAc)_2$ (2.5 mol%) with TPPTS (6.25 mol%)[16] were used in this reaction media.

The use of DMF/H_2O (2:1)[18] and $Pd(PPh_3)_4$ (10 mol%) were reported only in one study which described the synthesis of the adducts of 2□-deoxyuridine.[18]

The CH_3CN/H_2O mixture (1:2)[16,19-39] was the most reported solvent for the cross coupling Suzuki-Miyaura reaction. In this media, $Pd(OAc)_2$ and TPPTS with Na_2CO_3, K_2CO_3 or Cs_2CO_3 were the reagents most studied. Starting materials such as 2□-deoxyadenosine, adenosine, 2□-deoxyguanosine, guanosine, 2□-deoxyuridine, 7-deazapurine and uridine in presence of $Pd(OAc)_2$/TPPTS (1:2.5) as catalytic system were transformed into the corresponding target compounds in good to excellent yield (> 50% yield); however, depending on the steric hindrances, electronic effects and presence or not of heteroatom, the yields could be lower. The amount of catalyst was often higher than 2.5 mol% with a maximum of 10 mol%. Using Na_2CO_3, the couple $Pd(OAc)_2$/TPPTS (1:2.5) in CH_3CN/H_2O enabled different non-canonical adducts such as aniline amino acid derivatives to be obtained.[26,27] In this media, the difference between Na_2CO_3 and K_2CO_3 was not significant. The use of Cs_2CO_3 as base led to successful cross coupling reactions with yields (7-82%) depending on the nature of the boronic acid.[38-39] Starting from 2□-deoxycytidine in presence of $Pd(OAc)_2$ (3 mol%) and TPPTS (8 mol%), a lower temperature (43°C) was enough to afford the desired amine derivative in good yield (85-100%).[25] It is significant that even with the use of room temperature, cross coupling reactions are still successful. Shaughnessy and co-workers reported the use of TXPTS ($Pd(OAc)_2$ (2.5:1) with 2.7 mol% of metal at 23°C to furnish the target nucleoside analogues in 45-99% yields.[20] As usually cited in this review, the lower yields (45 and 50%) were obtained starting from 2□-deoxyguanosine or thiophen-2-ylboronic acid. Two publications described the C-C bond formation using either $PdCl_2(dppf)_2$

(6.5 mol%)[19] or $Pd(PPh_3)_4$ (10 mol%)[16] respectively, starting from 2□-deoxyuridine and adenosine derivatives. Starting from the nucleotide analogues having 1-3 phosphorus atoms, the CH_3CN/H_2O mixture (1:2) with $Pd(OAc)_2$/TPPTS (1:2.5) in presence of Cs_2CO_3 was found to be the preferred protocol[26-38] even if Na_2CO_3 could afford the cross coupling conversion.[26] Microwave-assisted organic synthesis was applied to the cross-coupling Suzuki-Miyaura reaction starting from adenosine derivative and the corresponding nucleotide using $Pd(OAc)_2$ (5 mol%) and TPPTS (12.5-25 mol%) and Na_2CO_3 as base. Of course, reduction of the time of reaction was observed but the yields were lower than those obtained with classical thermal reaction.[26] There is one report of the mixture $MeOH/H_2O$ (5:1) as media for the Suzuki-Miyaura reaction but the yield was low (28%) for the preparation of the 5-formyl-2□-deoxyuridine.[41]

Recently, water as sole solvent was studied for the Suzuki-Miyaura cross coupling for the preparation of 2□-deoxyuridine, uridine, adenosine, guanosine and diphosphatenucleoside-hexose.[16,21,41-50] Suzuki-Miyaura cross coupling using $Pd(PPh_3)_4$ (3 mol%) and reverse phase glass beads was reported for the formation of uridine analogues in 28%.[42] This process was not fully reported in the literature. The use of $Pd(PPh_3)_4$ (10 mol%) in presence of K_2CO_3 permitted the synthesis of 8-aryladenosine derivative in medium to high yield (26-75%) but did not furnish the corresponding guanosine derivative.[16] $Pd(OAc)_2$ coupled with TPPTS[16,43] or PPh_3[44] was studied as a catalytic system. Using K_2CO_3 as base, the couple $Pd(OAc)_2$ (2.5 mol%) and TPPTS (6.25 mol%) gave the target adenosine and guanosine derivatives in yields often higher than 70%.[16] Microwave-assisted technology using PPh_3 instead of TPPTS was described to afford the 5-aryl-2□-deoxyuridine in yields regularly higher than 70%.[44] The latest metal to be studied was Na_2PdCl_4 with or without TPPTS as ligand in presence of K_2CO_3 or KOH as base.[43-50] Using Na_2PdCl_4 (2.5 mol%), TPPTS (6.25 mol%) and K_2CO_3, the cross coupling reaction afforded 8-arylguanosine derivatives in yields higher than 70%.[45]

The use of a similar protocol was described to furnish the corresponding mono-, di- and triphosphates frequently in good yields (> 50%). To the best of our knowledge, only one report has described of a one pot - two step procedure for the preparation of 8-phenyl guanosine derivatives in good yield (44-75%, over two steps). This protocol successively included activation and cross coupling reaction.[45-46]

In water, starting from nucleotide, it was not necessary to introduce Cs_2CO_3 for the preparation of the adduct.[45-47] The use of KOH instead of K_2CO_3 was described by our group.[43,48-50] Amongst the different methodologies described, the most significant development of this work has been the low loading of palladium (0.05-0.1 mol%) and the absence of ligand. Starting from 2□-deoxyuridine, the yields of the target 5-aryl nucleoside analogues were at least equal to those already reported in the literature. Microwave-assisted organic synthesis and conventional heating were compared leading to similar yields whatever the method applied. Typically, the reaction time was faster using the alternative microwave activation. A Suzuki-Miyaura cross coupling reaction was studied for the first time starting from 6-iodouridine in sole water.[50] In this case, our group described a novel ligand-free protocol using a more conventional amount of Na_2PdCl_4 (10 mol%) at room temperature.

In contrast to the published works described in this review, the recent results of Len's group[48-50] have revealed that Suzuki-Miyaura cross coupling reaction applied to 5-iodo-2□-deoxyuridine are feasible: (i) in refluxing pure water; (ii) with low loading of palladium (iii) without any ligand. Furthermore, when the starting materials are thermally unstable, room temperature and larger amount of palladium can be used.[50]

Finally, some very recent papers reported a postsynthetic strategy permitting to arylate DNA on a specific halogenated nucleoside by Suzuki-Miyaura cross coupling reactions [53-55]

Palladium-catalyzed reactions allow access to a wide range of fine chemicals or active pharmaceutical compounds. Nevertheless, they can present a problem in that palladium can often be retained in the isolated product.[56]

In the future, the Suzuki-Miyaura cross coupling reaction of canonical or non-canonical nucleoside analogues without a ligand in a green solvent at room temperature with recycling of the catalytic system will represent an interesting challenge for synthetic organic chemists and to offer a wider scope of materials biological investigations.

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