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SUSTAINABLE CHEMICAL PROCESSES

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Heck and Sonogashira couplings in aqueous media – application to unprotected nucleosides and nucleotides

Gwénaëlle Hervé[1] and Christophe Len[1,2*]

Abstract

Amongst all synthetic nucleosides having high potential biological activities, C5-modified pyrimidines and C7-deaza or C8-modified purines have been particularly studied. These main chemical modifications have been developed using palladium cross-coupling reactions. This review focus on both Heck and Sonogashira cross-coupling of nucleosides using different aspects of the twelve principles of green chemistry: use of aqueous medium and no protection/deprotection steps.

Keywords: Heck, Sonogashira, Green chemistry, Water

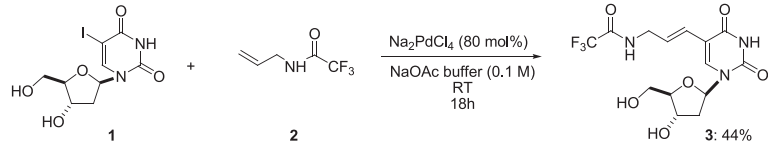
Nucleoside analogues having modifications of the glycone moiety [1-3] (eg AZT [4]) and/or the nucleobase [5-7] (eg BVDU [8,9]) are of great biological importance due to their high effectiveness as antiviral and antitumor agents. Among all the potent modifications, introduction of aryl, polyaryl, heteroaryl, heteropolyaryl, alkenyl and alkynyl groups on either the pyrimidine or the purine moiety *via* C-C cross-coupling was described for the study of biological environments such as DNA and RNA structural probes, protein–DNA complexes, DNA damage, mutation and cancers [10,11]. The most efficient C-C cross-coupling strategies are the palladium-catalyzed reactions such as (i) Suzuki–Miyaura, Stille, Negishi and Hiyama reactions for the formation of aromatic C sp^2 – C sp^2; (ii) Heck reaction for the formation of vinyl derivatives and (iii) Sonogashira reaction for the formation of acetylenyl derivatives. These cross-coupling reactions were realized most often in organic solvents with protected nucleoside analogues. In order to use safer solvents and auxiliaries, to limit the risks and hazards, different groups have reported recently those cross-couplings in greener solvents such as water without the need for protection and deprotection steps. Since recent developments and a complete review on Suzuki-Miyaura reaction applied to unprotected nucleosides were reported by our group [7,12-15], this paper will focused on the Heck reactions and Sonogashira reactions applied to unprotected nucleosides and nucleotides in aqueous media or water as sole solvent. For the sake of clarity, this review has been arranged to describe the Heck reaction and then the Sonogashira reaction. For each part, the different methodologies by varying the palladium source and nature with respect to Pd(0) and Pd(II), the nature of the base will be discussed.

Heck cross-coupling

Heck cross-coupling reaction in aqueous solution was developed using only Pd(II) as a pre-catalyst in water and in CH_3CN/H_2O.

The first Heck cross-coupling reaction starting from deprotected nucleoside was reported in 1998 by Barbas *et al.* [16]. Starting from 5-iodo-2'-deoxyuridine (1) and allyl amide 2 in presence of Na_2PdCl_4 (80 mol%) as palladium source in sodium acetate buffer (0.1 M, pH = 5.2) as solvent at room temperature for 18 hours, (*E*)-[3-(trifluoroacetamido)propenyl]-2'-deoxyuridine (3) was isolated in 44% yield (Scheme 1). Compound 3 is a precursor of functionalized dUTP derivatives that are substrates for thermostable DNA polymerases. Nucleoside analogue 3 was obtained a few years later in

* Correspondence: christophe.len@utc.fr
[1]Université de Technologie de Compiègne, Ecole Supérieure de Chimie Organique et Minérale, EA4297, Centre de recherche de Royallieu, BP20529, F-60205 Compiègne Cedex, France
[2]Department of Chemistry, University of Hull, England HU6 7RX, UK



Scheme 1 Synthesis of nucleoside analogue 3.

the same range of yields by Williams *et al.* using the same experimental conditions [17].

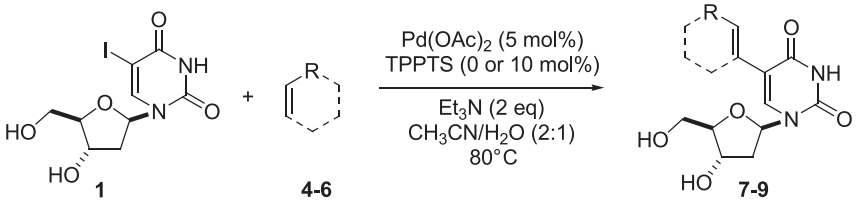
Pd(II)-catalyzed Heck cross-coupling in CH_3CN/H_2O

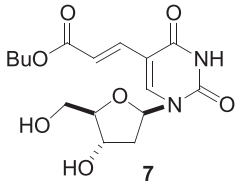
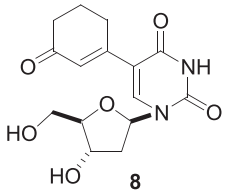
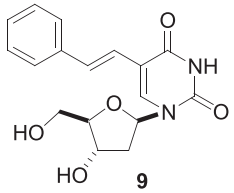
More than a decade later, Shaughnessy *et al.* reported the first aqueous-phase Heck coupling of 5-iodo-2'-deoxyuridine (1) under phosphine-free conditions [18]. After a classical optimization between iodo derivative 1 and butyl acrylate (4), best results were obtained using $Pd(OAc)_2$ (5 mol%) alone or in combination with water soluble TPPTS (10 mol%) in presence of Et_3N (2 eq) as base in CH_3CN/H_2O (2:1) as solvent at 80°C. Authors extended their optimized conditions to the coupling of cyclohexenone (5) and styrene (6) (Table 1).

Coupling of nucleoside analogue **1** with butyl acrylate (4) in the absence of ligand gave the target product 7 in 64% yield, while a higher yield (74%) was achieved when TPPTS (10 mol%) was used (Table 1, entries 1 and 2). Cyclohexenone (5) and styrene (6) were coupled with iodo derivative 1, under ligand free conditions, to afford 8 and 9 in 72% and 82% yields, respectively (Table 1, entries 3 and 5). These yields were similar to those achieved when TPPTS (10 mol%) was used (Table 1, entries 4 and 6). Aromatic styrene (6) gave higher yields than those obtained with alkenes 4 and 5. Based on these results, Heck couplings of 5-bromo-2'-deoxyuridine as pyrimidine analogue, 8-bromo-2'-deoxyguanosine and 8-bromo-2'-deoxyadenosine as purine analogues were explored but without success.

Recently, Hocek *et al.* described the preparation of target acrylated-modified nucleotide analogues for polymerase synthesis of acrylate-labeled DNA. In this light, a

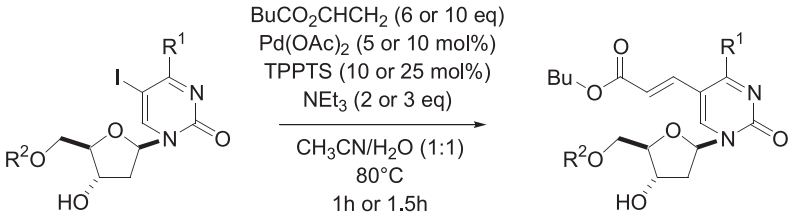
Table 1 Synthesis of 5-vinyl nucleoside analogues 7-9



Entry	Alkene	Ligand	Product	Yield (%)[a]
1	4	None		64
2		TPPTS		74
3	5	None		72
4		TPPTS		71
5	6	None		82
6		TPPTS		81

[a]Average isolated yields of two independent trials.

Table 2 Synthesis of butyl acrylate uridine and cytosine analogues 7, 15-19



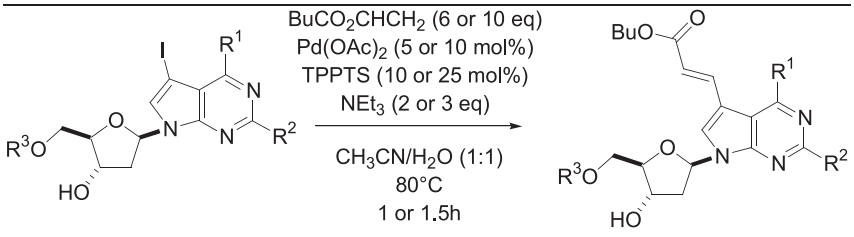
1 (R^1=OH, R^2 = H)
10 (R^1=OH, R^2 = PO_3H_2)
11 (R^1=OH, R^2 = $P_3O_9H_4$)
12 (R^1=NH_2, R^2 = H)
13 (R^1=NH_2, R^2 = PO_3H_2)
14 (R^1=NH_2, R^2 = $P_3O_9H_4$)

7, 15-19

Entry	R^1	R^2	Starting material	Product	Yield (%)
1	OH	H	1	7	98[a]
2	OH	PO_3H_2	10	15	35[b]
3	OH	$P_3O_9H_4$	11	16	4[b]
4	NH_2	H	12	17	16[a]
5	NH_2	PO_3H_2	13	18	-[b]
6	NH_2	$P_3O_9H_4$	14	19	-[b]

[a]$BuCO_2CHCH_2$ (6 eq), $Pd(OAc)_2$ (5 mol%), TPPTS (10 mol%), NEt_3 (2 eq), 1,5 h. [b]$BuCO_2CHCH_2$ (10 eq), $Pd(OAc)_2$ (10 mol%), TPPTS (25 mol%), NEt_3 (3 eq), 1 h.

Table 3 Synthesis of butyl acrylate 7-deaza purine analogues 26-31



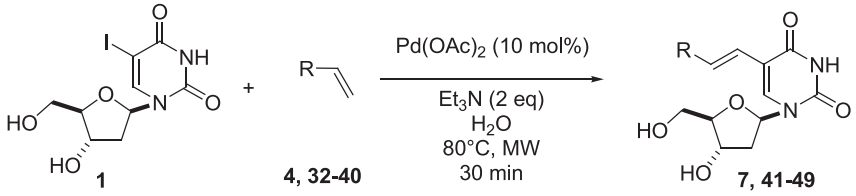
20 (R^1=NH_2, R^2 = H, R^3 = H)
21 (R^1=NH_2, R^2 = H, R^3 = PO_3H_2)
22 (R^1=NH_2, R^2 = H, R^3 = $P_3O_9H_4$)
23 (R^1=OH, R^2 = NH_2, R^3 = H)
24 (R^1=OH, R^2 = NH_2, R^3 = PO_3H_2)
25 (R^1=OH, R^2 = NH_2, R^3 = $P_3O_9H_4$)

26-31

Entry	R^1	R^2	R^3	Starting Material	Product	Yield (%)
1	NH_2	H	H	20	26	81[a]
2	NH_2	H	PO_3H_2	21	27	55[b]
3	NH_2	H	$P_3O_9H_4$	22	28	43[b]
4	OH	NH_2	H	23	29	84[a]
5	OH	NH_2	PO_3H_2	24	30	38[b]
6	OH	NH_2	$P_3O_9H_4$	25	31	44[b]

[a]$BuCO_2CHCH_2$ (6 eq), $Pd(OAc)_2$ (5 mol%), TPPTS (10 mol%), NEt_3 (2 eq), 1,5 h. [b]$BuCO_2CHCH_2$ (10 eq), $Pd(OAc)_2$ (10 mol%), TPPTS (25 mol%), NEt_3 (3 eq), 1 h.

Table 4 Synthesis of various 5-acrylate-2′-deoxuridine analogues 7, 41-49



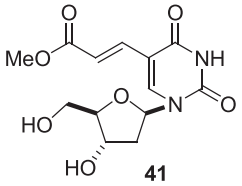
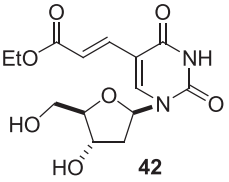
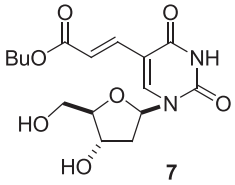
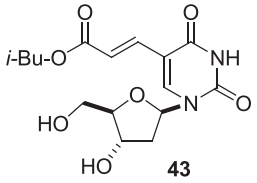
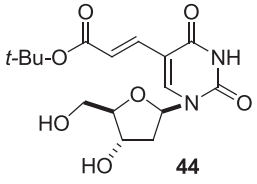
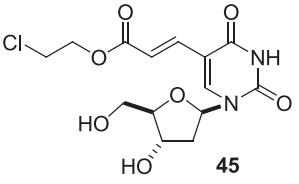
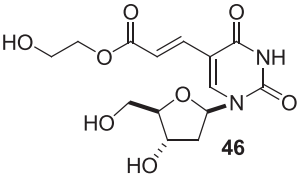
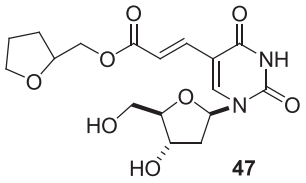
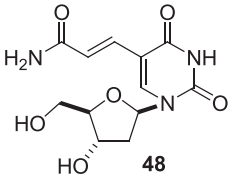
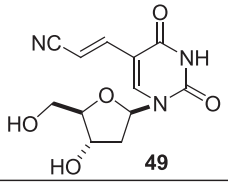
Entry	Acrylate	Product	Yield (%)
1	32	 **41**	90
2	33	 **42**	90
3	4	 **7**	45
4	34	 **43**	45
5	35	 **44**	45
6	36	 **45**	40
7	37	 **46**	45

Table 4 Synthesis of various 5-acrylate-2′-deoxuridine analogues 7, 41-49 *(Continued)*

8	38	 **47**	35
9	39	 **48**	60
10	40	 **49**	51

methodology for direct attachment of butyl acrylate (4) to various deoxyribonucleosides and their corresponding 5′-*O*-monophosphate (dNMPs) and 5′-*O*-triphosphate (dNTPs) derivatives was reported using the same catalytic promoter ($Pd(OAc)_2$ and TPPTS), in presence of NEt_3 as base in CH_3CN/H_2O (1:1) mixture as solvent [19]. In order to minimize hydrolysis of the phosphate group, higher amounts of acrylate 4 (10 eq *vs* 6 eq), catalyst (10 mol% *vs* 5 mol%) and base (3 eq *vs* 2 eq) were used for the couplings of dNMPs and dNTPs compared to the couplings of the corresponding nucleosides but the reaction times were shorter. Heck couplings on nucleoside analogue 1 proceeded with good isolated yield (98%) of modified nucleoside 7 (Table 2, entry 1). Both increase of amount of acrylate 4 (6 eq *vs* 4 eq) and CH_3CN permitted to obtained compound 7 in better yield than that reported previously [18]. Modified aqueous conditions were tested with halogenated monophosphate 10 and triphosphate 11 and furnished the corresponding acrylated derivatives 15 and 16 in 35% and 4% yields, respectively (Table 2, entries 2 and 3). Application of the method to cytosine derivatives 12–14, having an amino group in position 4, gave yields inferior to 16% (Table 2, entries 4–6). Starting from the 7-deazapurines 20 and 23 led to cross-coupled products 26 and 29 in 81% and 84% yields, respectively (Table 3, entries 1 and 4). Nucleotide derivatives 21, 22, 24 and 25 gave the corresponding acrylate analogues 27, 28, 30 and 31 in 55%, 43%, 38% and 44% yields, respectively (Table 3, entries 2, 3, 5 and 6). In these conditions pyrimidine nucleotide derivatives gave poor yields or no target compounds probably due to substantial hydrolysis of the starting materials (Table 2, entries 2, 3, 5 and 6).

Pd(II)-catalyzed Heck cross-coupling in H_2O

In 2014, for the first time, Len *et al.* reported a palladium catalyzed Heck cross-coupling reaction between 5-iodo-2′-deoxyuridine and various acrylate derivatives using ligand-free conditions and assisted-microwaves in pure water [20]. Those new conditions allowed a totally aqueous access to antiviral BVDU. Heck cross-coupling of 5-iodo-2′-deoxyuridine (**1**) with various acrylate derivatives was carried out using $Pd(OAc)_2$ (10 mol%) alone in presence of Et_3N (2 eq) as base in H_2O as solvent at 80°C.

The reported method was very efficient with the shortest acrylate chains since it permit to furnish compounds 41 and 42 in 90% yields (Table 4, entries 1 and 2). Compounds 7 and 43 in 45% yield even if the starting esters presented lipophilic properties (Table 4, entries 3 and 5). Shaugnessy and Hocek reported independently the obtention of 7 using aqueous conditions (H_2O/CH_3CN) [17, 18]. Isobutylacrylate has never been used in Heck cross-coupling reaction on nucleosides. It showed the same low solubility as butyl- and *t*-butylacrylate in water and original product 43 was isolated in 45% yields (Table 2, entry 4). Because the introduction of a heteroatom on the carbonated chain of the acrylate might allow access to more evolved compounds, authors undertook to examine the behavior of 2-chloro-, 2-hydroxylethylacrylate 36 and 37 and its corresponding cyclic ether in our totally aqueous Heck conditions. The presence of the chlorine or of the oxygen atoms did not seem to change the lipophilic properties of the reactant. Consequently compounds 45, 46 and 47 were isolated in the same range of yields (Table 4, entries 6–8). In order to modulate the structure, substitution

of the ester by amido and cyano groups was studied. Application of the methodology allowed to isolate compounds 48 and 49 in respectively 60% and 51% yields (Table 4, entries 9 and 10). Authors were able to obtain BVDU in sole water in three successive steps: free-ligand microwaves-assisted Heck cross-coupling of 1 with methylacrylate (32); hydrolysis and Hunsdiecker reaction. Finally, BVDU was obtained with a better total yield compared with the literature (56% *vs* 31% [9]).

Sonogashira cross-coupling

Sonogashira cross-coupling reaction in aqueous solution was developed using both Pd(0) as catalyst in water or in CH_3CN/H_2O and Pd(II) as a pre-catalyst only in CH_3CN/H_2O.

Pd(0)-catalyzed Sonogashira cross-coupling in CH_3CN/H_2O

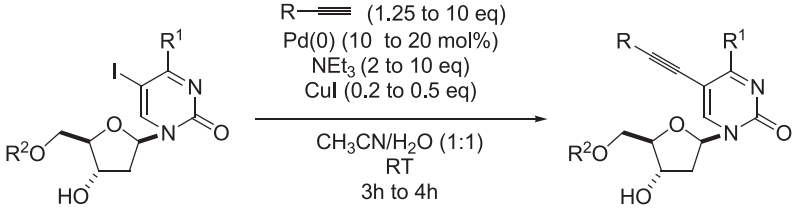
In 1990, Casalnuovo *et al*. undertook the Sonogashira coupling of unprotected nucleosides and nucleotides with acetylene derivatives [21]. Reactions were conducted in a mixture of CH_3CN/H_2O (various proportion) as solvent using a self-made water-soluble Pd(0) complex (10 to 20 mol%): $Pd(PPh_2(m\text{-}C_6H_4SO_3M))_3$ ($M = Na^+$, K^+) (10 to 20 mol%) in presence of CuI (0.2 eq to 0.5 eq) and NEt_3 (2 eq to 10 eq).

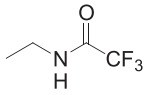
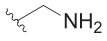
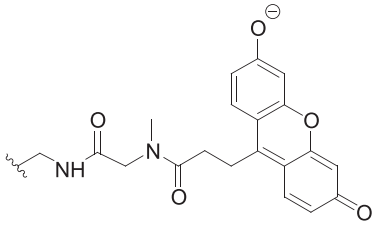
5-Iodo-2'-deoxyuridine (1) was coupled to propargyltrifluoroacetamide as precursor of the propargyl amine in 95% yield (Table 5, entry 1). Starting from cytosine analogues 13 and 14, application of the method with variation of the concentration of reagents permitted to isolate the nucleotide analogues 51 and 52 in good to moderate yields (Table 5, entries 2 and 3). Authors demonstrated the versatility of their methodology as they obtained an alternative route to T-505 (52), part of a family of chain-terminating nucleotide reagents used in automated DNA sequencing and labeling (Table 5, entry 3). Increasing the amount of water (CH_3CN/H_2O 04:96 *vs* CH_3CN/H_2O 1:1) led to lower yield (52% *vs* 73%).

Pd(0)-catalyzed Sonogashira cross-coupling in H_2O

In 2003, Burgess *et al*. successfully synthesized fluoresceinated thymidine triphosphate for polymerase mediated incorporation. Starting from the only water soluble triphosphate derivatives 11 and 53, Sonogashira coupling in presence of dye fragments furnished the target compounds 54–59 [22]. Compounds 54 and 55 were obtained in presence of $[Pd(P(C_6H_4SO_3Na)_3)_4]$

Table 5 Synthesis of 5-alkynyl pyrimidine analogues 50-52



Entry	R^1	R^2	Starting Material	R	Product	Yield (%)
1	OH	H	1		50	95[a]
2	NH_2	PO_3H_2	13		51	73[b]
3	NH_2	$P_3O_9H_4$	14		52	50[c]

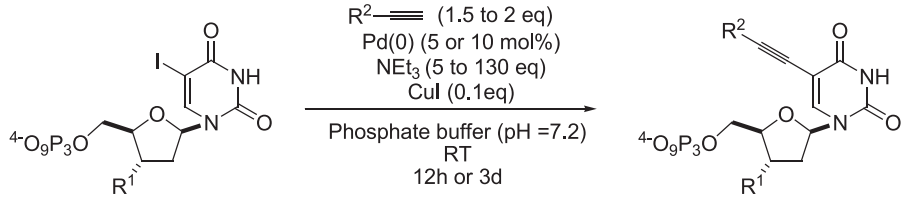
[a]Pd(0) (10 mol%), (R— 3 eq), NEt_3 (2 eq), CuI (0.2 eq), CH_3CN/H_2O (1:1), 4 h. [b]Pd(0) (20 mol%), (R— 10 eq), NEt_3 (10 eq), CuI (0.3 eq), CH_3CN/H_2O (1:1), 3 h. [c]Pd(0) (20 mol%), R— (1.25 eq), NEt_3 (10 eq), CuI (0.3 eq), CH_3CN/H_2O (1:1), 3 h.

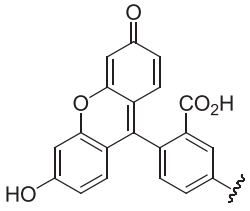
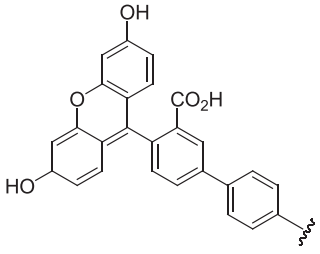
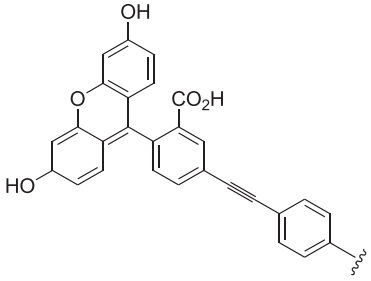
(5 mol%) as catalyst [23] at room temperature in 17% and 41% yields, respectively (Table 6, entries 1 and 2). By using another source of $[Pd(PPh_2(3\text{-}(NaO_3SC_6H_4))_4]$ (10 mol%) [21], the authors reported the preparation of nucleotide analogues 56–59 in 17-42% yields (Table 6, entries 3–6). Starting from compound 11, a shorter reaction time was necessary compared with that starting from 2',3-dideoxy derivative 53. Although the authors did not explain the kinetic difference, it might be possible that the presence of an additional hydroxyl group induced higher solubility of 11 in water compared to the analog 53. Both methods furnished the target compounds 54–59 as triethylammonium salts after purification.

Pd(II)-catalyzed Sonogashira cross-coupling in CH_3CN/H_2O

In order to prepare unprotected purine nucleosides bearing oligopyridine ligands, Hocek *et al*. attempted Sonogashira cross-coupling reaction of 8-bromo-2'-deoxyadenosine (60) and 7-deaaza-2'-deoxyadenosine (20) with 2,2'-bipyridine derivatives [24,25]. For this purpose, authors used $Pd(OAc)_2$ as catalyst (5 mol%), a water soluble ligand (TPPTS, 12.5 mol%), in presence of CuI (0.1 eq) and $Et(iPr)_2N$ (10 eq) as base in a mixture of CH_3CN/H_2O (1:2) as solvent at 75°C. However, under those conditions, complex mixtures were obtained. In this regard, the next goal of these authors was to prepare the corresponding Ru^{II} complexes of

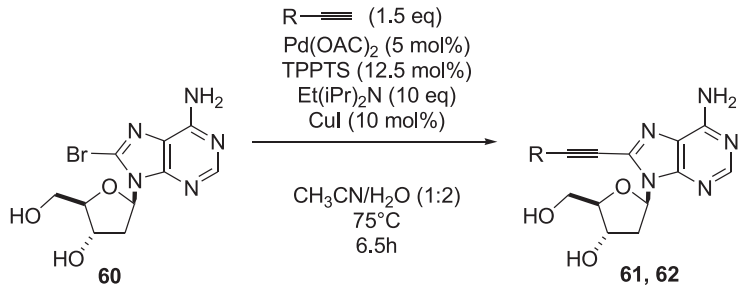
Table 6 Synthesis of 5-alkynyl pyrimidine analogues 54-59

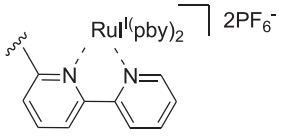
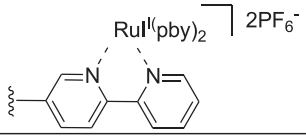


Entry	R^1	Starting Material	R^2	Product	Yield (%)
1	OH	11		54	17[a]
2	H	53		55	41[b]
3	OH	11		56	17[c]
4	H	53		57	42[d]
5	OH	11		58	42[e]
6	H	53		59	26[f]

[a]$[Pd(P(C_6H_4SO_3Na)_3)_4]$ (5 mol%), R^2—≡ (2 eq), NEt_3 (35.9 eq), CuI (0.2 eq), 24 h. [b]$[Pd(P(C_6H_4SO_3Na)_3)_4]$ (5 mol%), R^2—≡ (2 eq), NEt_3 (35.9 eq), CuI (0.2 eq), 17 h. [c]$[Pd(PPh_2(3\text{-}(NaO_3SC_6H_4))_4]$ (10 mol%), R^2—≡ (1.5 eq), NEt_3 (5 eq), CuI (0.1 eq), 3d. [d]$[Pd(PPh_2(3\text{-}(NaO_3SC_6H_4))_4]$ (10 mol%), R^2—≡ (1.5 eq), NEt_3 (130 eq), CuI (0.1 eq), 12 h. [e]$[Pd(PPh_2(3\text{-}(NaO_3SC_6H_4))_4]$ (10 mol%), R^2—≡ (1.8 eq), NEt_3 (130 eq), CuI (0.1 eq), 3d. [f]$[Pd(PPh_2(3\text{-}(NaO_3SC_6H_4))_4]$ (10 mol%), R^2—≡ (1.5 eq), NEt_3 (5 eq), CuI (0.1 eq), 12 h.

Table 7 Synthesis of Ru(II) complexes 61 and 62

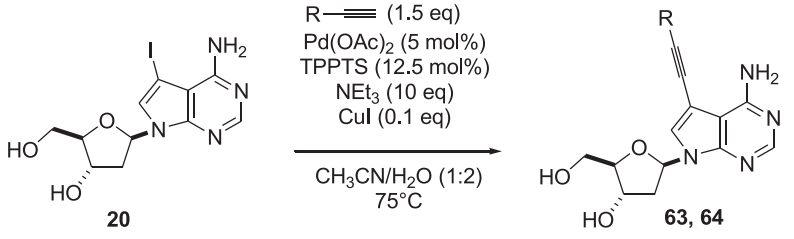


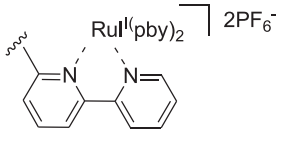
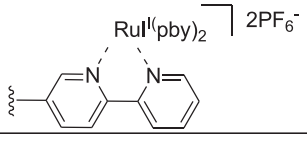
Entry	R	Product	Yield (%)
1		61	16
2		62	0

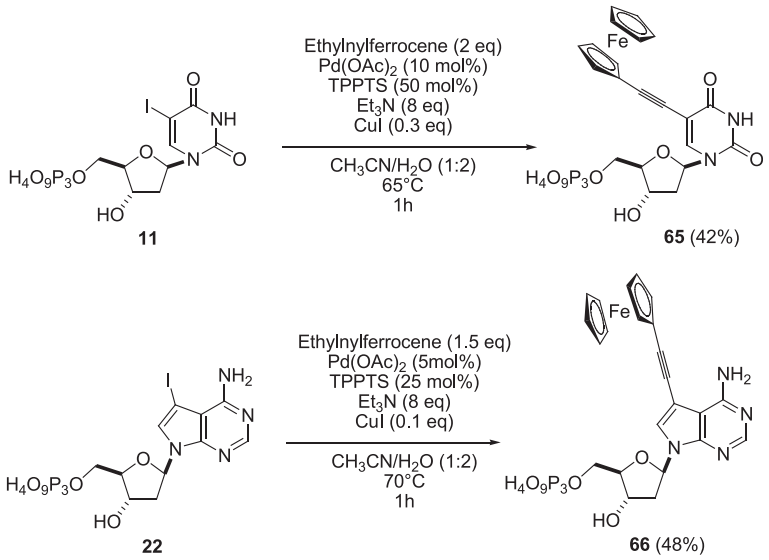
the oligopyridine-nucleoside conjugates. The Sonogashira reactions of acetylenes Ru^{II} building blocks were reacted with 8-bromo analogue 60 using the just above described methodology. The cross-coupling did not proceed very well due to the decomposition of the starting materials (Table 7) and only one compound, 61, was obtained in 16% yield (Table 7, entry 1). Starting from the 7-deaaza purine 20, modification of this method: NEt_3, (10 eq) instead of $EtN(iPr)_2$ (10 eq) permitted the synthesis of the target nucleoside analogues 63 and 64 bearing bipyridine ligands and their Ru(II)-complexes in position 7 in moderate yields (Table 8). Authors noticed that in both cases some byproducts were formed, probably due to the decomposition of the starting materials as already observed starting from compound 60.

In 2007, *Hocek et al.* synthesized modified 2'-deoxyadenosine-5'-triphosphate and 2'-deoxyuridine-5'-triphosphate derivatives bearing ferrocene labels linked *via* a conjugate acetylene spacer [26]. Authors used a single-step Sonogashira aqueous-phase cross-coupling reaction starting from deprotected triphosphated deoxynucleosides 11 and 22.

Table 8 Synthesis of Ru(II) complexes 63 and 64



Entry	R	Product	Yield (%)
1		63	47
2		64	59



Scheme 2 Synthesis of ferrocene analogue 65 and 66.

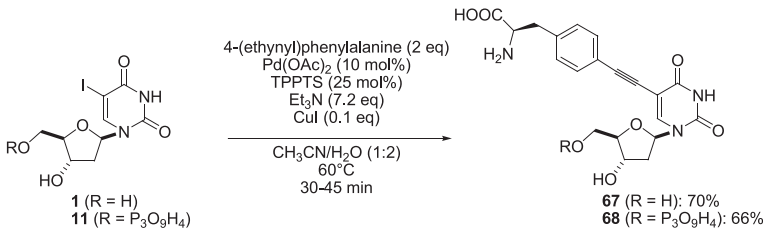
Reactions were performed in presence of $Pd(OAc)_2$ (5 or 10 mol%), TPPTS (25 or 50 mol%), CuI (10 or 30 mol%), Et_3N (8 eq) in a mixture CH_3CN/H_2O (1:2) as solvent. Variations of the amounts of reagents were not discussed by the authors. The cross-coupled products 65 and 66 were obtained in the same range of yields (42% and 48%) (Scheme 2).

In 2007, Hocek *et al*. used an aqueous Sonogashira reaction in order to couple different halonucleosides and their corresponding triphosphate with 4-(ethynyl)phenylalanine as amino acid moiety [27]. Thus, the nucleoside analogues 1 and 11 in presence of water-soluble catalytic system ($Pd(OAc)_2$/TPPTS, 10 mol%/25 mol%), triethylamine (7.2 eq) as base and CuI (0.1 eq) as additive in a mixture of CH_3CN/H_2O (1:2) furnished the target nucleoside analogues 67 and 68 in 70% and 66% yields, respectively (Scheme 3).

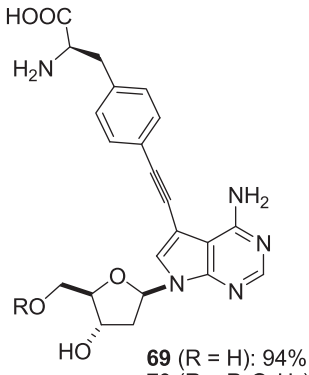
Using very similar methodology, the authors also obtained the four phenylalanine derivatives 69–72 in good yields (61-74%) (Figure 1).

After few modifications, the same group reported the synthesis of nucleoside and nucleotide conjugates of bile acids 73–87 using $Pd(OAc)_2$ (5 mol%), TPPTS (25 mol%), CuI (0.1 eq), $EtN(iPr)_2$ (10 eq) in a mixture of CH_3CN/H_2O (1:2) at 65-75°C for 0.25-1 hour (Figure 2) [28].

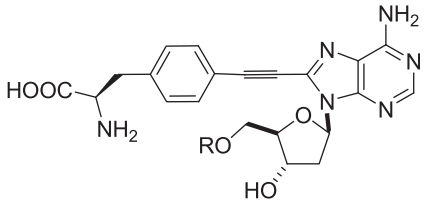
In 2010, Shaughnessy *et al*. published their work on Sonogashira coupling of unprotected halonucleosides in aqueous solvent using water-soluble palladium catalysts [29]. First, a series of water-soluble phosphoranes (TPPTS, TXPTS, DCPES, *t*Bu-Amphos) were screened for their ability to provide active palladium catalysts in a model Sonogashira coupling of unprotected 5-iodo-2'-deoxyuridine (1) and phenylacetylene. Authors showed the superior performance of TXPTS and concluded that increased steric demand of TXPTS (cone angle 206°) compared to TPPTS (165°) may account for the increased catalyst activity by promoting formation of low LPd^0 active species. Compound 1 was then coupled with various alkynes using $Pd(OAc)_2$ (10 mol%), TXPTS (30 mol%), CuI (0.1 eq) and triethylamine (1 eq) at 65°C for 30 minutes in a mixture of



Scheme 3 Synthesis of phenylalanine analogues 67 and 68.

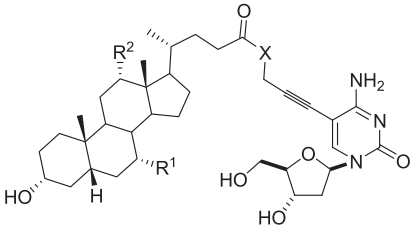


69 (R = H): 94%
70 (R = $P_3O_9H_4$): 67%

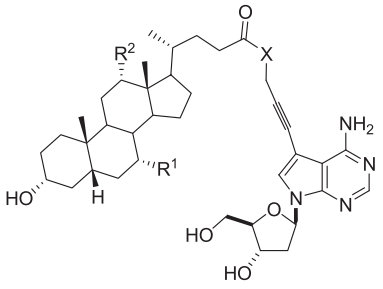


71 (R = H): 61%
72 (R = $P_3O_9H_4$): 61%

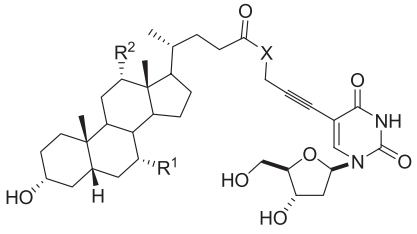
Figure 1 Synthesis of phenylalanine analogues 69–72.



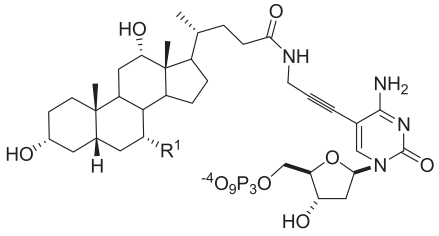
73 (X = O, R^1 = OH, R^2 = OH): 69%
74 (X = O, R^1 = H, R^2 = OH): 35%
75 (X = O, R^1 = OH, R^2 = H): 45%
76 (X = NH, R^1 = OH, R^2 = OH): 69%
77 (X = NH, R^1 = H, R^2 = OH): 65%



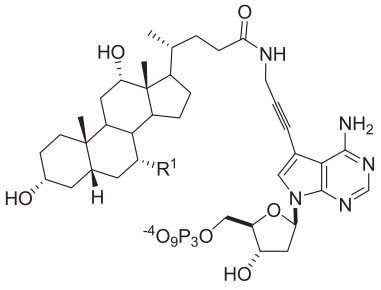
78 (X = O, R^1 = OH, R^2 = OH): 39%
79(X = O, R^1 = H, R^2 = OH): 88%
80 (X = O, R^1 = OH, R^2 = H): 90%
81 (X = NH, R^1 = OH, R^2 = OH): 66%
82 (X = NH, R^1 = H, R^2 = OH): 61%



83 (X = NH, R^1 = H, R^2 = OH): 58%



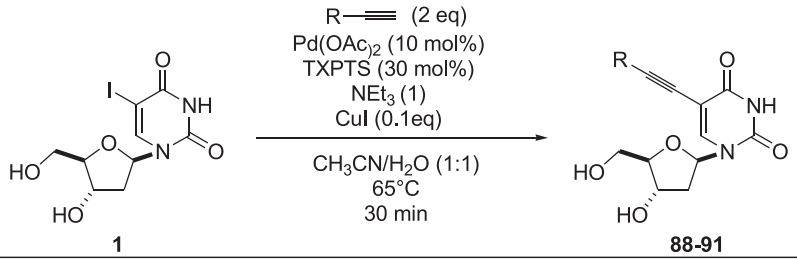
84 (R^1 = OH): 44%
85 (R^1 = H): 57%



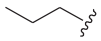
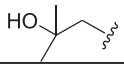
86 (R^1 = OH): 32%
87 (R^1 = H): 53%

Figure 2 Synthesis of alkynyl analogues 73–87.

Table 9 Synthesis of 5-alkynyl nucleoside analogues 88-91

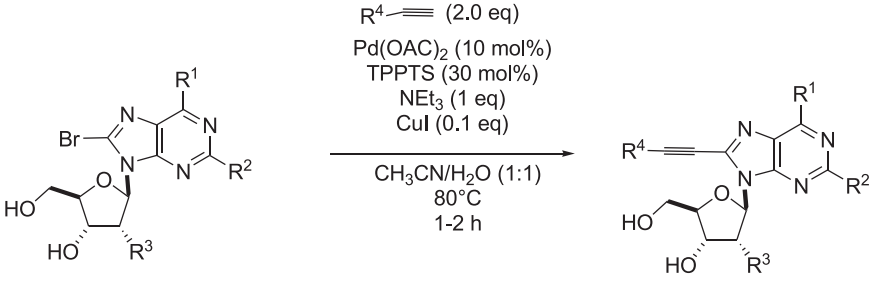


1 **88-91**

Entry	R	Product	Yield (%)[a]
1		88	71
2		89	42
3		90	55
4		91	84

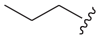
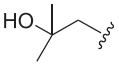
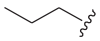
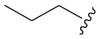
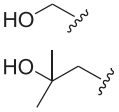
[a]Average isolated yield from two or more trials.

Table 10 Synthesis of 5-alkynyl nucleoside analogues 94-103



60 ($R^1 = NH_2$, $R^2 = H$, $R^3 = H$)
92 ($R^1 = NH_2$, $R^2 = H$, $R^3 = OH$)
93 ($R^1 = OH$, $R^2 = NH_2$, $R^3 = OH$)

94-103

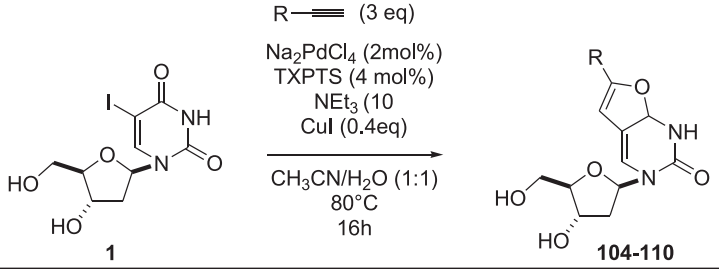
Entry	R^1	R^2	R^3	Starting material	R^4	Product	Yield (%)
1	NH_2	H	H	60		94	88
2	NH_2	H	H	60		95	89
3	NH_2	H	H	60		96	98
4	NH_2	H	H	60		97	98
5	NH_2	H	OH	92		98	53
6	NH_2	H	OH	92		99	74
7	OH	H	H	93		100	86
8	OH	H	H	93		101	85
9	OH	H	H	93		102	85
10	OH	H	H	93		103	84

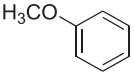
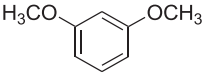
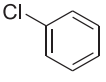
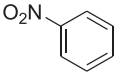
CH_3CN/H_2O (1:1) to furnish the corresponding alkynes 88–91 in 42-84% yields (Table 9). Authors noted that optimal yields were obtained when alkyne was added in three portions during the course of the reaction which limited the alkyne homocoupling.

In contrast to the high yield achieved with phenylacetylene (Table 8, entry 1), reactions of compound 1 with simple alkyl-substituted alkynes gave lower yields (42% and 55% *vs* 71%) of isolated products 89 and 90 (Table 9, entries 2 and 3). The more hindered alkyne permitted to isolate the desired cross-coupled compound 91 in 84% yield (Table 9, entry 4). In cases of the unhindered alkyne, authors noted the competitive formation of a well-known cyclized byproduct. Starting from purine analogues 60, 92 and 93, the authors used modified method (80°C *vs* 65°C) to afford the corresponding alkynyl nucleoside analogues 94–103. The alkylynation conditions were further optimized for the couplings of 8-bromopurines [29]. Thus, 8-bromo-2'-deoxyadenosine (60) and 8-bromo-2'-adenosine (92) were engaged with the previously described alkynes using, once again, $Pd(OAc)_2$ (10 mol%), TXPTS (30 mol%), CuI (0.1 eq) and NEt_3 (1 eq) in a mixture of CH_3CN/H_2O (1:1). This time, reactions were performed at 80°C for 1–2 hours to ensure a complete conversion of starting material (Table 9). Sonogashira couplings of 8-bromo-2'-deoxyadenosine (60) worked very well with both the phenylacetylene and the alkyl-substituted alkynes. Excellent yields of product were obtained with no formation of side-products (Table 10, entries 1–4). As usual the guanosine analogue 93 gave good but lower yields (Table 10, entries 7–10) and the nucleoside analogues having an hydroxyl group in the position 2' gave lower yields (Table 10, entries 5–6).

Two years later, Agrofoglio *et al.* developed a one-pot Sonogashira protocol to obtain substituted furopyrimidine nucleosides in aqueous conditions [30]. The conditions of the rection were optimized starting from 5-iodo-2'-deoxyuridine (1) and phenylacetylene. The desired furopyrimidine 104 was isolated in 47% yield following those conditions: Na_2PdCl_4 (2 mol%), TXPTS (4 mol%), CuI (0.4 eq), NEt_3 (10 eq) in a mixture CH_3CN/H_2O (1:1) as solvent. Then, the optimized conditions were applied to the coupling of various aromatic alkynes 104–110 (Table 11).

Table 11 Synthesis of furopyrimidine nucleoside analogues 104-110



Entry	R	Product	Yield (%)
1		104	47
2		105	33
3		106	45
4		107	57
5		108	53
6		109	-
7		110	-

The expected bicyclic products 104–110 were isolated in moderate to good yields (33-57%) with alkynes substituted with electron-rich aryl core (Table 11, entries 2–4). Concerning alkynes substituted with electron-poor aryl moiety, only one product was obtained (Table 11, entry 5). The bicyclic scaffold has already been observed before, but only as a by-product [29].

Conclusions

The principal objective of this review was to describe the Heck and Sonogashira couplings of nucleosides in accordance with the 12 principles of green chemistry. To date, the majority of the works involved the synthesis (i) of alkenes in 5-position of pyrimidines and 7-position of 7-deazapurines and (ii) of alkynes in position 5 of pyrimidines, in position 7 of 7- deazapurines and in position 8 position of purines. The usual starting materials used were 5-iodo, 7- and 8-bromo analogues. The review encompasses variations of the starting materials, alkene and alkyne, nature of the solvent, palladium source and ligand at either room temperature or higher temperature.

Concerning the Heck cross-couplings, only palladium Pd(II) such as Na_2PdCl_4 (80 mol%) and $Pd(OAc)_2$ (5–10 mol%) was used. Most of the reactions were realized in presence of TPPTS as ligand in a mixture of CH_3CN/H_2O and in sole water. Using these procedures, the yields were low to good (4-98%). It is noteworthy that recent results of Len's group starting from 5-iodo-2'-deoxyuridine furnished, in pure water, in presence of $Pd(OAc)_2$ (10 mol%) and NEt_3 without any ligand at 80°C under microwave irradiation the heterocyclic targets in 35-90% yields.

Concerning the Sonogashira cross-couplings, the reported procedures were similar (alkyne, NEt_3, CuI) excepted for the nature of the palladium (Pd(0) and Pd(II)) and the nature of the solvent (CH_3CN/H_2O and sole water). Pd(0) was used in aqueous media or in pure water while Pd(II) was used only in a mixture of CH_3CN/H_2O. The yields of the target nucleoside analogues were comprised between 16-98%. It is noteworthy that nucleotide analogues having either mono- and triphosphate as starting material afforded the corresponding cross-coupling adducts in presence of Pd(0) in water or in presence of Pd(II) in CH_3CN/H_2O.

In the future, the Heck and Sonogashira cross-coupling reactions of nucleoside analogues, in ligand-free conditions, as reported by Len with recycling of the catalytic system will open a new avenue for the green chemistry applied to heterocyclic chemistry.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

GH searched the current literature and drafted the manuscript. CL drafted the introduction and conclusion. Both authors contributed equally to the readings and corrections. Both authors read and approved the final manuscript.

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