ELSEVIER

Journal of Organometallic Chemistry 653 (2002) 234–251

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

Mini review

Palladium-catalyzed C–N and C–C cross-couplings as versatile, new avenues for modifications of purine 2′-deoxynucleosides☆

Mahesh K. Lakshman *

Department of Chemistry, City College of CUNY, 138th Street at Convent Avenue, New York, NY 10031-9198, USA

Received 22 August 2001; accepted 28 September 2001

Abstract

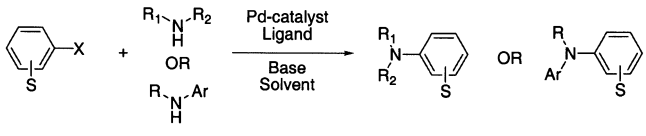
Methods involving palladium-catalysis can be efficiently applied to the relatively labile purine 2′-deoxynucleosidic systems. The net result is the remarkably ready access to new and unusual 2′-deoxyribonucleoside analogs bearing subsitutents on the purine moiety. C–N cross-coupling reactions are particularly attractive for the synthesis of N^6 and N^2 substituted 2′-deoxyadenosines and 2′-deoxyguanosines, respectively, as well as C-8 modified 2′-deoxyguanosines. C–C bond-formation on the other hand, provides access to nucleosides containing hydrophobic hydrocarbon entities. Although the common theme for C–N and C–C cross-coupling is catalysis by Pd, there are substantial differences between the two classes of reactions. Furthermore, there are pronounced differences in reactivity trends at the C-6 position compared to those at the C-2. Optimized reaction conditions for both varieties of transformations can be found whereby novel purine 2′-deoxynucleosides can be readily obtained. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: 2′-Deoxynucleosides; Palladium; C–N bond-formation; C–C bond-formation; Suzuki–Miyaura; Cross-coupling

1. Introduction

About 18 years ago the discovery of the Pd-catalyzed cross-coupling of stannyl amides with aryl bromides was described in the literature by Migita and coworkers [1]. Based upon this discovery, much interest has developed in the area of Pd-catalyzed C–N bond-forming reactions. In particular, methods for accomplishing 'tin-free' cross-coupling that circumvented the use of toxic and labile *N*-stannyl reagents prompted an evaluation of the direct cross-coupling of amines with suitable aromatic substrates. Much of the development in this area has stemmed from excellent studies by the research groups of Buchwald and Hartwig [2]. Results of studies by these groups as well as those by Yamamoto et al. [3] have led to the development of a generally applicable methodology for C–N bond-formation among small molecules. This is represented in Scheme 1. In this methodology, group X on the aryl moiety (Cl, Br, I, or a sulfonate) undergoes a Pd-mediated replacement with an amine, and a plethora of examples demonstrating the amination of all of these aryl derivatives can be found in the literature [4]. Pd-catalyzed C–C bond-formation is also a very important class of transformations, and methodologies such as the Stille [5], Negishi [6], Heck [7], Sonogashira [8] and Suzuki and Miyaura [9] cross-coupling reactions have gained immensely from the explosive growth in newer catalytic systems [10].

It was in mid 1998 that we became interested in evaluating whether the Pd-catalyzed C–N bond-formation developed by Buchwald and Hartwig, as well as C–



Scheme 1.

☆ *Palladium* —name derived from the planetoid Pallas. *Palladium* also appears in ancient mythology, where a statue of Pallas-Athene was supposedly hurled by Zeus from Olympus as a sign of good favor to the city of Troy. For as long as the *Palladium* remained in the city, the city would be safe. The *Palladium* was eventually stolen from the city by Diomedes and Odysseus.

* Tel.: +1-212-6507835; fax: +1-212-6506107.

E-mail address: lakshman@sci.ccny.cuny.edu (M.K. Lakshman).

0022-328X/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0022-328X(02)01267-6

C bond-forming Suzuki–Miyaura reactions would be applicable to 2′-deoxynucleosides. As can be anticipated, the biological properties of N^6-modified adenine and N^2-modified guanine derivatives are quite significant. For instance, several are known modulators of adenosine A_1 and A_2 receptors, many are cytokinines that stimulate plant cell growth and division, others possess inhibitory properties towards bacterial and mammalian DNA polymerases and they are known to inhibit normal as well as cancer cell growth [11–14]. In addition to the therapeutic potential of *N*-modified nucleosides, several mutagens and carcinogens are metabolically activated to electrophiles that subsequently alkylate adenine and guanine bases in DNA. The net result in this DNA alkylation is the formation of a C–N bond between purine and the electrophilic alkylating agent (see Fig. 1). Such reactions result in the alteration of the intracellular DNA that can ultimately be reflected in mutations and even oncogenesis.

On the basis of the foregoing reasons, as well as to understand the details of Pd-catalyzed cross-coupling reactions among 2′-deoxynucleosides, we initiated studies on C–N as well as C–C cross-coupling on these substrates. This report addresses the major developments in this area over the past 2 years arising from our own efforts as well as those from other laboratories. Among the many varieties of C–C bond-forming reactions, only the results on the Suzuki–Miyaura reactions of 2′-deoxynucleosides are presented herein, since this class of reactions on deoxynucleoside substrates is relatively new.

2. C–N bond-forming reactions among 2′-deoxynucleosides

2.1. Reactions at the C-6 position of purine 2′-deoxynucleosides

The most common method for accessing N^6-modified adenine nucleosides is by displacement reactions of a leaving group from an electrophilic nucleoside analog by an amine [15], and this approach has been effectively used to synthesize various classes of compounds. Typically, the electrophilic nucleosides are 6-halo-9[2-deoxy-β-D-*erythro*-pentofuranosyl]purines (halogen = Cl, Br, I). If exceptional reactivity is sought in the substitution reaction, then 6-fluoro-9[2-deoxy-β-D-*erythro*-pentofuranosyl]purine [16] is a substrate of choice, which upon reaction with amines furnishes the N^6-modified 2′-deoxyadenosine derivatives. We and others have previously utilized the high reactivity of the C-6 fluoro nucleoside for the synthesis of N^6-carcinogen modified 2′-deoxyadenosine derivatives [17,18]. Among these halo derivatives, the expected order of reactivity is $F \gg Cl > Br > I$. There are also instances where C-6 sulfonate, phenoxide or triazolyl moieties have been subjected to displacement reactions by amines [19–22].

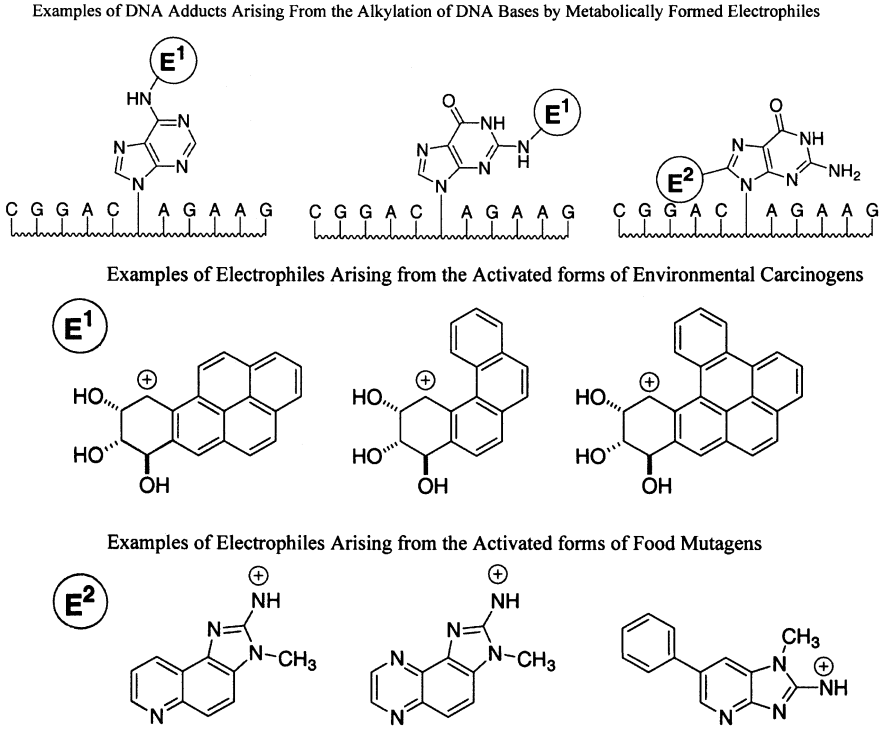


Fig. 1. Alkylation of DNA by electrophilic derivatives of mutagens and carcinogens.

We reasoned that Pd-mediated cross-coupling between a C-6 halonucleoside and arylamines would provide a novel entry to N^6-aryl 2′-deoxyadenosine derivatives, thus complementing displacement reactions. A factor that led us to evaluating the method using arylamines rather than alkylamines was because direct displacement of the halide from the C-6 position of 6-halo-9[2-deoxy-β-D-*erythro*-pentofuranosyl]purines by aliphatic amines is well known but is less common with aromatic amines. Another important consideration arose from a study by Wagaw and Buchwald [23]. In this report, 2- and 4-bromopyridines were efficiently aminated to provide 2- and 4-aminopyridine derivatives. The key appeared to be the use of bis-coordinating ligands that likely resisted ligand exchange by the pyridine. Inspection of the 6-bromo-9[2-deoxy-β-D-*erythro*-pentofuranosyl]purine structure clearly indicates structural analogies to both 2- and 4-bromopyridine (Fig. 2).

Despite the structural analogies, there are multiple coordinating atoms in the nucleoside moiety and it was initially unclear whether there would be ligand exchange problems between the nucleoside and the ligand–Pd complex. Although Pd-catalyzed reactions are quite known among purines and purine nucleosides, these have largely been C–C bond-forming reactions (for some examples, see Refs. [24–30]). Based on these considerations, we set upon the synthesis of 6-bromo-9[2-deoxy-β-D-*erythro*-pentofuranosyl]purine. However, for solubility reasons and to prevent undesired side reactions at the hydroxyl groups we chose to prepare the 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl) derivative **1**. The synthesis of **1** (Scheme 2) [31] largely parallels known methodology [32] and involves the diazotization-bromination of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine in $CHBr_3$ under irradiation by a 150 W tungsten lamp. The corresponding C-6 iodo analog **2** was also synthesized [15e] as a substrate for the cross-coupling based on the reported successful amination of iodoaromatics [4s,33].

Initial experimentation (Scheme 3) involved the cross-coupling of **1** with 4-toluidine as a representative amine that is neither significantly electron-rich nor -deficient [31]. $Pd_2(dba)_3$ and (±)-BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, (**L-1**) in Fig. 3] were chosen to

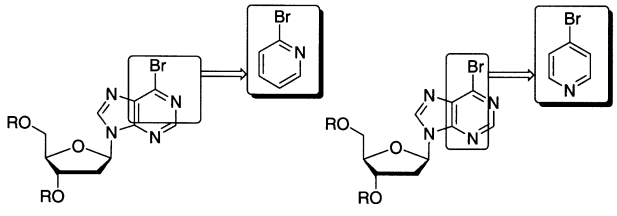
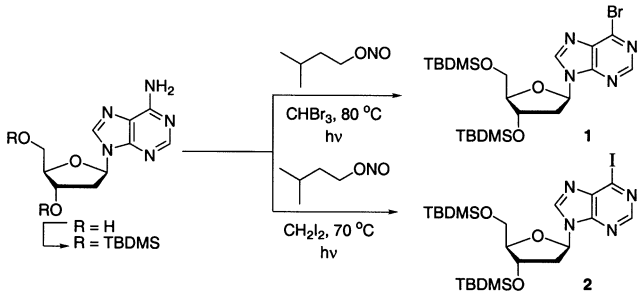


Fig. 2. Structural similarity of a 6-bromo-9[2-deoxy-β-D-*erythro*-pentofuranosyl]purine derivative to both 1- and 2-bromopyridine.



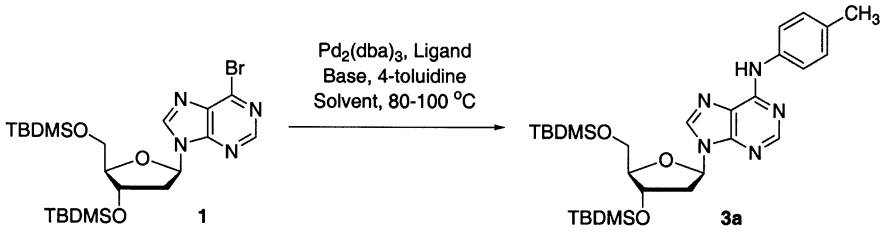
Scheme 2.

constitute the catalytic system. Upon conducting the reaction with *tert*-BuONa as base in toluene at 100 °C, degradation of **1** was predominant. Although not entirely unexpected, it is likely that the halonucleoside does not tolerate the strongly basic conditions. Replacement of *tert*-BuONa with the milder Cs_2CO_3 resulted in conversion to the N^6-(4-methylphenyl)-2′-deoxyadenosine analog **3a** in ca. 60% yield. At the time these results were obtained, Buchwald's group reported the synthesis and applications of 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl (**L-3** in Fig. 3) [34]. This ligand was shown to possess an exceptional effect on C–N bond-formation, and aryl chlorides were aminated at room temperature when catalytic systems derived from it were utilized.

On the basis of Buchwald's results, we performed the cross-coupling with the catalytic system composed of $Pd_2(dba)_3$/2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl (1 Pd:1.5 ligand), using K_3PO_4 as base in 1,2-dimethoxyethane (1,2-DME) at 80 °C. Under these conditions, product **3a** was obtained in 69% yield and was less colored than that obtained from the (±)-BINAP reaction. Subsequently, to assess the generality of the transformation, a variety of arylamines bearing electron-donating or -withdrawing groups on the aryl ring were tested. Table 1 shows the structures of the amines, the products obtained and the yields of these products.

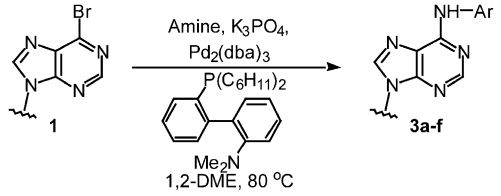
Compounds **3e** and **3f** are noteworthy as these are derived from arylamines that are health hazards. At the time our paper was in press in 1999, a report on the use of Pd-catalyzed cross-coupling for the synthesis of a 2′-deoxyguanosine–2′-deoxyguanosine cross-link was described by Harwood et al. This is discussed in more detail in Section 2.2.

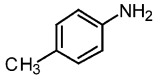
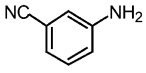
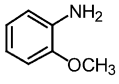
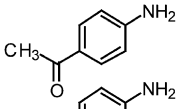
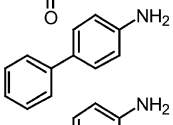
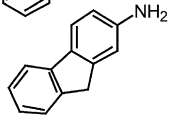
Johnson and coworkers have described a Pd-catalyzed cross-coupling methodology, where exact opposite coupling partners were utilized [35]. Namely, 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine was the arylamine component that was cross-coupled with *o*-nitroaryl bromides and *o*-nitroaryl triflates (see Scheme 4 for a general example). A similar strategy was adopted



Scheme 3.

Table 1
Reactions of various arylamines with 6-bromo-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine (**1**) [31]



Entry	Amine	Product	Yield (%)
1		**3a**	69
2		**3b**	61
3		**3c**	72
4		**3d**	52
5		**3e**	64
6		**3f**	68

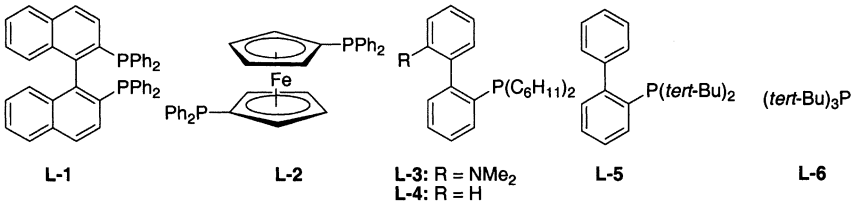
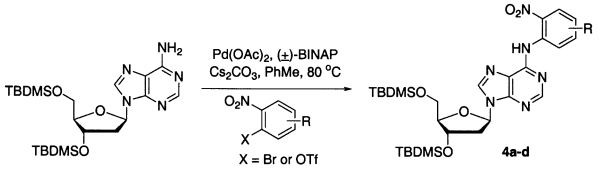


Fig. 3. Structures of ligands that are potentially useful for C–N and C–C cross-coupling reactions.

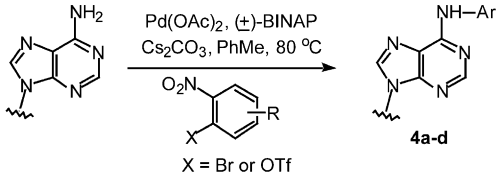
for the synthesis of N^2-aryl-2′-deoxyguanosines, and is discussed in Section 2.2.

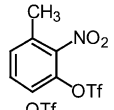
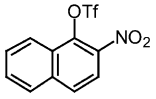
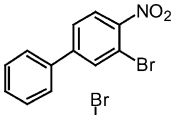
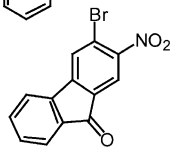
What is noteworthy in Johnson's study is the stoichiometry of the reactants. When equivalent amounts of the bromide or triflate and 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine were employed, product **4** underwent a second arylation to a small extent,



Scheme 4.

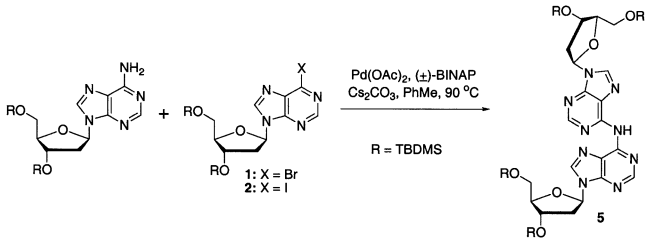
Table 2
Reactions of various *o*-nitroaryl bromides and triflates with 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine [35]



Entry	Arylbromide or Aryltriflate	Product	Yield (%)
1		**4a**	88
2		**4b**	85
3		**4c**	85
4		**4d**	84

resulting in the N^6,N^6-diarylnucleoside [35]. This problem was circumvented through the use of ca. 40% excess of the 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine. The arylbromides and triflates used in this study and the products as well as their yields are shown in Table 2.

Subsequently De Riccardis and Johnson, based on their earlier work [35], showed that a 2′-deoxyguanosine-2′-deoxyguanosine dimer (described in Section 2.2) and a 2′-deoxyadenosine–2′-deoxyadenosine dimer (**5**) could be synthesized by the cross-coupling strategy as shown in Scheme 5 [36]. Interesting to note, the use of **1** for the reaction afforded only a 21% yield of **5**. However, when the iodonucleoside **2** was utilized, a substantially better 51% yield of **5** was attained.



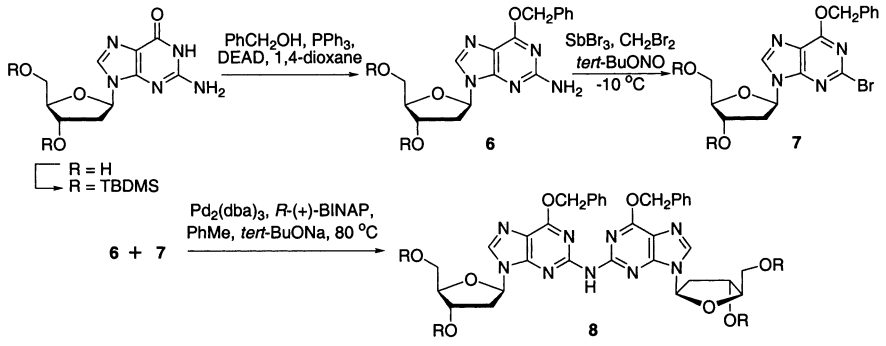
Scheme 5.

2.2. Reactions at the C-2 position of purine 2′-deoxynucleosides

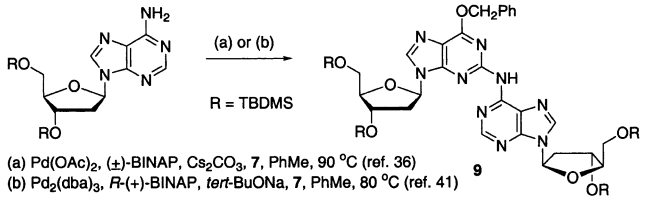
Similar to reactions at the C-6 position of purines, C–N bond-formations at the C-2 position are also conducted by displacement reactions. Halides [15a,15c,15d,37] and triflate [38] have been commonly employed leaving groups, whereas reactions with highly unreactive nucleophiles are conducted with the substantially more reactive 2-fluoro-2′-deoxyinosine derivatives [39].

Here again, the use of Pd-catalyzed cross-coupling for C–N reactions at C-2 is highly novel and would provide access to new classes of compounds. Such an approach was adopted by Harwood et al. and a single example of the synthesis of a 2′-deoxyguanosine-2′-deoxyguanosine dimer was initially disclosed [40]. Such dimers are thought to arise in DNA cross-linking induced by nitrous acid, and formation of such cross-links is believed to be related to the dietary uptake of nitrite [40].

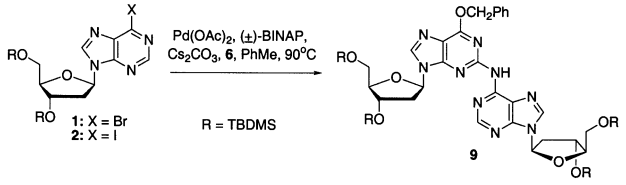
In contrast to the C-6 halogenation of 2′-deoxyadenosine, which requires only hydroxyl protection on the saccharide moiety [31,32], the synthesis of C-2 halonucleosides from 2′-deoxyguanosine requires protection of the O^6-moiety, in addition to hydroxyl protection. Harwood et al. chose 2-bromo-O^6-benzyl-3′,5′-bis-*O*-



Scheme 6.



Scheme 7.



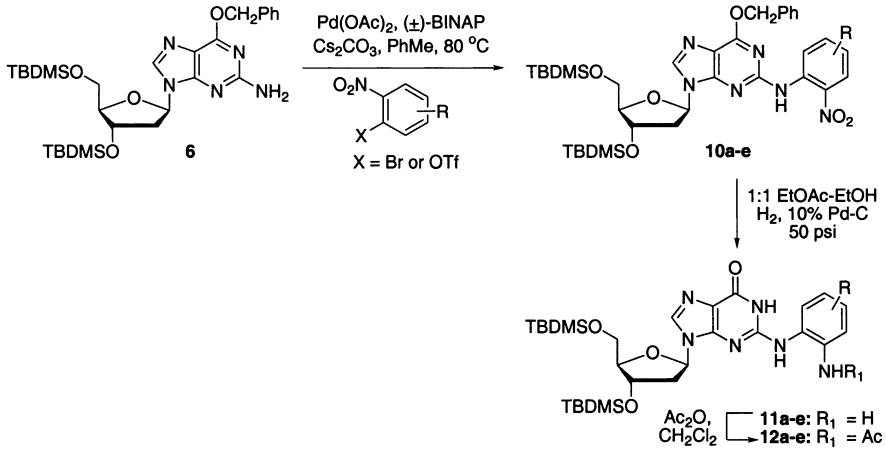
Scheme 8.

(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**7**) as the precursor, which was synthesized according to Scheme 6. The cross-coupling of **6** with **7** (Scheme 6) was conducted with $Pd_2(dba)_3$, *R*-(+)-BINAP and *tert*-BuONa, in toluene to provide compound **8** in 40% yield [40].

De Riccardis and Johnson used a similar approach for the synthesis of **8** [36]. However, their catalytic system comprised $Pd(OAc)_2$, (±)-BINAP and Cs_2CO_3 in toluene as solvent, at 90 °C. Under these conditions, **8** was obtained in an excellent 90% yield [36]. Along similar lines, Harwood et al., and De Riccardis and Johnson have synthesized a 2′-deoxyadenosine–2′-deoxyguanosine dimer as shown in Scheme 7 [36,41].

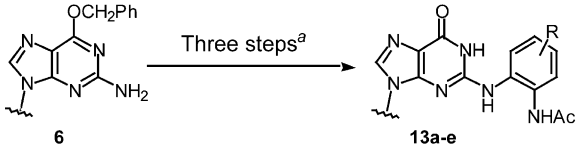
Interestingly, in this case, the conditions utilized by Harwood et al. afforded **9** in 47% yield [41], whereas the use of Cs_2CO_3 in place of *tert*-BuONa yielded **9** in only 24% [36]. With a view to improving the yield of **9**, the amino and halonucleoside precursors were interchanged as shown in Scheme 8. Cross-coupling of bromonucleoside **1** with **6** provided a 60% yield of **9**, on the other hand, use of the iodonucleoside **2** afforded only a 45% yield of this product [36]. In the latter case a minor product (17%), assigned a trimeric structure, is formed via a second arylation of **9** [36]. Finally, in each of these cases, various stages of dimer deprotection can be obtained by routine desilylation and/or catalytic hydrogenolyis of the O^6-benzyl group [36,41].

Although these procedures provide specifically the dimeric nucleosides produced from DNA cross-linking, more general procedures have also been developed for the synthesis of other N^2-modified 2′-deoxyguanosine nucleoside analogs by the Pd-mediated cross-coupling strategy [35,41,42]. Johnson and coworkers, initially using the approach described for N^6 modification in

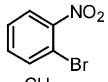
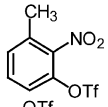
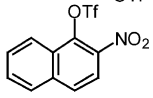
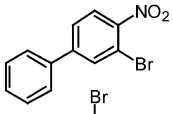
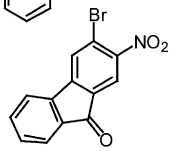


Scheme 9.

Table 3
Reactions of various *o*-nitroaryl bromides and triflates with O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (**6**) [35]



6 **13a-e**

Entry	Arylbromide or Aryltriflate	Product	Yield (%)
1		**13a**	87
2		**13b**	84
3		**13c**	70
4		**13d**	85
5		**13e**	73[b]

[a]Step 1: $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, PhMe, 80 °C. Step 2: 10% Pd–C, 1:1 EtOAc–EtOH, 50 psi, then CH_2Cl_2, Ac_2O. Step 3: THF, $Bu_4N^+F^-$. [b]The carbonyl group underwent reduction to a methylene in step 2.

Section 2.1, have cross-coupled **6** with arylbromides and aryltriflates (Scheme 9). However, the hydrogenolytic removal of the O^6-benzyl group in **10a–e** was accompanied by reduction of the nitro group to yield **11a–e** (in the case of **10e → 11e** the carbonyl group also underwent reduction) [35].

The resulting *o*-phenylenediamino compounds **11a–e** were prone to air-oxidation and were, therefore, isolated as the *N*-acetyl derivatives **12a–e** [35]. Table 3 shows the *o*-nitroaryl bromides or the *o*-nitroaryl triflates used in the Johnson study, as well as the yields of the final N^2-aryl-2′-deoxyguanosine derivatives (**13a–e**) obtained after removal of the silyl protecting groups.

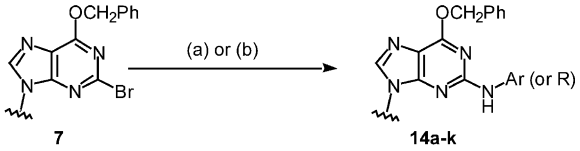
Harwood et al. and Bonala et al. have also reported a general methodology for the C–N bond-formation at C-2 [41,42], using an approach that is similar to that used for the N^6 modification (discussed in Section 2.1). Five arylamines and two alkylamines were cross-coupled with 2-bromo-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**7**) in the first report [41] while four alkylamines and one arylamine were utilized in the second [42]. Table 4 lists the amines used in these reports as well as the yields of the products in each case.

A point that is important to note is the following. Whereas a direct displacement of the C-2 halogen is possible with aliphatic amines, this has been shown not to be the case by conducting the cross-coupling without the Pd catalyst [41]. Harwood and coworkers have also investigated the coupling of **6** with bromoaromatics [41] along similar lines to what was reported by Johnson and coworkers with *o*-nitroaryl bromides and triflates [35]. The arylbromides tested in this approach as well as the product yields are shown in Table 5.

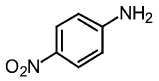
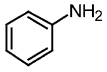
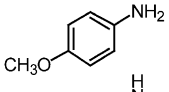
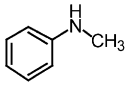
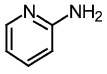
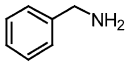
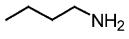
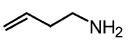
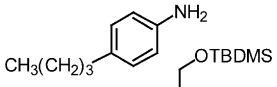
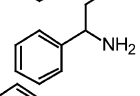
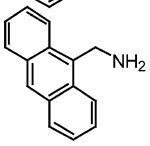
We have very recently conducted additional studies with a view to understanding the dependence of the C–N bond-formation on the catalytic systems used [43]. For this purpose, we have investigated the cross-coupling at the C-6 position between **1** and 4-toluidine with several ligands for Pd that were not available at the time of our initial work. These ligands are shown in Fig. 3.

The results of these studies suggest some interesting trends. Bis-coordinating ligands **L-1**, **L-2** and **L-3** appear to be generally better compared to the mono-coordinating **L-4** and **L-5**. With **L-4** the cross-coupling was complete in 19 h, but only a low yield of the product was obtained. On the other hand, use of **L-5** resulted in incomplete reaction after 20 h. Among the bis-coordinating ligands, **L-3** produced the best result. The base used, in conjunction with the ligand and solvent also

Table 4
Reactions of various aryl and alkylamines with 2-bromo-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine **7** [41,42]



7 **14a-k**

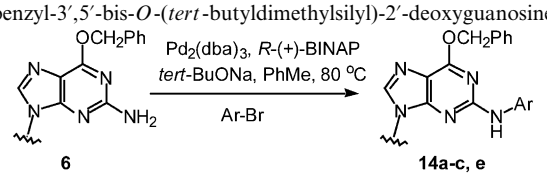
Entry	Amine	Product	Yield (%)
1		**14a**[(a)]	58 [41]
2		**14b**[(a)]	82 [41]
3		**14c**[(a)]	73 [41]
4		**14d**[(a)]	45 [41]
5		**14e**[(a)]	51 [41]
6		**14f**[(a),(b)]	58 [41], 88 [42]
7		**14g**[(a)]	49 [41]
8		**14h**[(b)]	90 [42]
9		**14i**[(b)]	93 [42]
10		**14j**[(b)]	94 [42]
11		**14k**[(b)]	40 [42]

Conditions: (a) $Pd_2(dba)_3$, *R*-(+)-BINAP, *tert*-BuONa, PhMe, 80 °C. (b) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, PhMe, 80 °C.

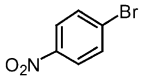
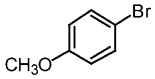
apparently contribute to the result. For instance, use of Cs_2CO_3 in PhMe with either **L-1** or **L-2** resulted in ca. 60% yield of product, whereas the use of K_3PO_4 and 1,2-DME with these ligands gave only ca. 30% product yield. The combination of 10 mol% $Pd_2(dba)_3$, 30 mol% **L-3**, and K_3PO_4 in 1,2-DME produced the best result in our hands for arylamination at the C-6 position [43]. In the reaction of **1** with 4-toluidine, no product was observed in the absence of Pd [31].

We have also evaluated C–N bond-formation at the C-2 position between **7** and 4-toluidine using ligands **L-3** and **L-4** [43]. This was largely because positive results with (±)- and *R*-(+)-BINAP (**L-1**) were already reported [36,41,42]. Comparisons of reactions involving **L-3** and **L-4**, therefore, allow for an understanding of the influence of mono- versus bis-coordination on the cross-coupling reaction at C-2. Results obtained provide an interesting contrast to the C–N bond-formation at the C-6 position. With both **L-3** and **L-4** rapid reactions were observed (within 3 h) and comparable product yields were obtained (75% with **L-3** and 65% with **L-4**). This indicates that whereas C–N bond-formation at the C-6 position is largely facilitated by bis-coordinating ligands, reactions at the C-2 are not as dependent on this factor. It is possible to postulate reasonable explanations for this. One of these is the ability for the products in these cross-coupling reactions to coordinate to Pd. Pd is a Class B or 'soft metal' that has been known to

Table 5
Reactions of various aryl bromides with O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (**6**) [41]



6 **14a-c, e**

Entry	Arylbromide	Product	Yield (%)
1		**14a**	77
2		**14b**	57
3		**14c**	0
4		**14e**	55

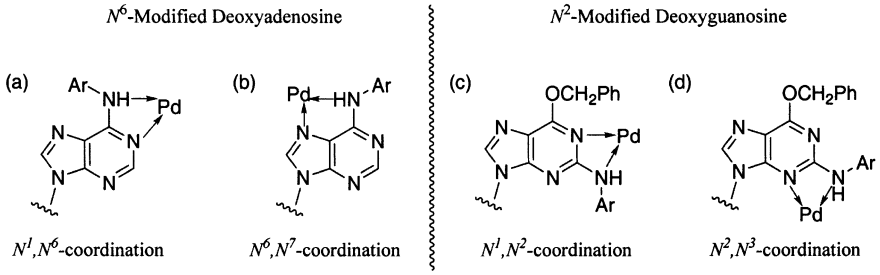


Fig. 4. Four possible structures of *N*-aryl-2′-deoxynucleoside analogs coordinated to Pd.

coordinate to N^1 and N^7 of nucleobases [44–46]. Possible Pd–nucleoside complexes that can be formed in these reactions are shown in Fig. 4.

Among these, structure (b) is the most favorable based on a preferred site of coordination (N^7) as well as size of the palladacycle formed (five-membered) involving the newly introduced *N*. Thus, formation of such a species in the cross-coupling reaction could potentially contribute to degradation of the catalytic system or cause product degradation, resulting in lowered yields. Bis-coordinating ligands that are better able to sequester the Pd are, therefore, more likely to be effective in C–N bond-formation at the C-6 position. Such an effect is perhaps attenuated in the reactions at the C-2, with both the mono- and bis-coordinating ligands being effective [43].

Some other reactivity trends are also apparent from the studies described so far [31,35,41]. Use of haloaromatics or aryltriflates for cross-coupling with protected nucleosides has utility only when the aryl moieties are highly electron-deficient [35,41]. On the other hand, when halonucleosides are cross-coupled with arylamines, highest yields are obtained with electron-rich arylamines [31,41]. Finally, although cross-coupling reactions using *tert*-BuONa as base are successful at the C-2 position, this base is apparently detrimental to the C-6 halo nucleosides.

2.3. Reactions at the C-8 position of 2′-deoxyguanosine

The cooking of meat is thought to be the source of several food mutagens that are produced by the pyrolysis of amino acids. These mutagenic heterocyclic amines undergo metabolism to *N*-hydroxy compounds that are then converted to nitrenium ions through the intermediacy of *N*-hydroxyesters. Such electrophilic intermediates react with DNA bases and produce covalent lesions, with a preponderance of reactions occurring at the C-8 position of 2′-deoxyguanosine (Fig. 1). Recently, Wang and Rizzo have utilized Pd-catalyzed cross-coupling for the synthesis of the 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ)-2′-deoxy-

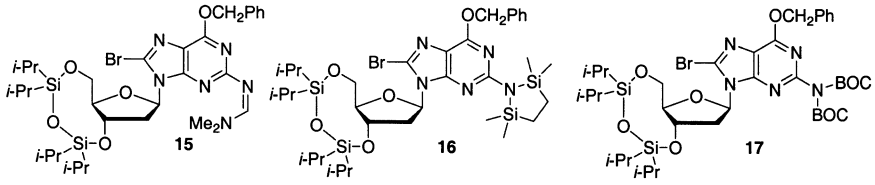


Fig. 5. Three O^6-benzyl 8-bromo 2′-deoxyguanosine derivatives that are useful for C–N cross-coupling at the C-8 position.

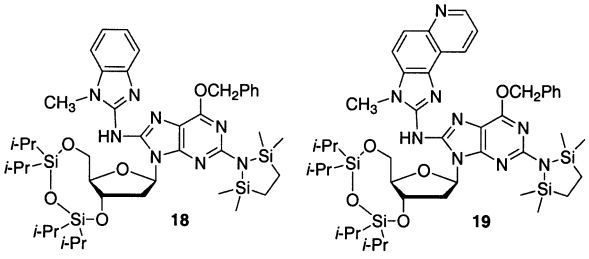


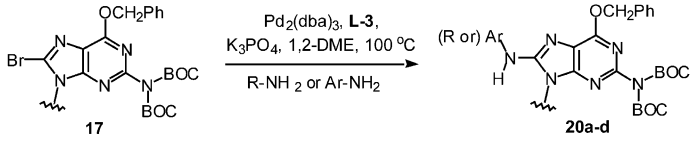
Fig. 6. Structures of 2′-deoxyguanosine derivatives containing a benzimidazole and IQ adduct at the C-8 position.

guanosine adduct at the C-8 position [47]. Their methodology hinged on the utility of the three protected 2′-deoxyguanosine derivatives shown in Fig. 5.

Among the three, **15** proved to be incompatible, since the formamidine protection at N^2 underwent transfer, under the reaction conditions, to the model amine that was initially used in the study [47]. On the other hand, **16** proved to be more useful and its cross-coupling (using 10 mol% $Pd_2(dba)_3$, 30 mol% BINAP, LiHMDS, PhMe, 100 °C) with both a model aminobenzimidazole as well as with IQ proceeded smoothly and in good yields to afford the products **18** and **19** shown in Fig. 6 [47].

Interestingly, use of *tert*-BuONa, or the milder Cs_2CO_3 and K_3PO_4 in the cross-coupling reactions gave poorer yields. Desilylation of **19** followed by removal of the O^6-benzyl group provided the C-8 IQ-2′-deoxyguanosine adduct [47]. Attempts were also made to evaluate the generality of the cross-coupling with simpler amines. However, **16** proved to be a poor substrate in these reactions. On the other hand, the bis *N*-BOC derivative **17** was a much better reagent, but it suffered from sensitivity to bases such as *tert*-BuONa and LiHMDS [47]. Compound **17** could be cross-coupled with simple amines (three aryl and one alkyl) using conditions similar to what we had reported [31] [10 mol% $Pd_2(dba)_3$, 30 mol% 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl (**L-3**), K_3PO_4, 1,2-DME]. Table 6 shows the amines used as well as the yields of the C-8 aminated products obtained through this method [47].

Table 6
Reactions of alkyl and aryl amines with 8-bromo-*N*,*N*-bis-BOC-O^6-benzyl-2′-deoxyguanosine derivative (**17**) [47]



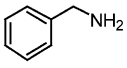
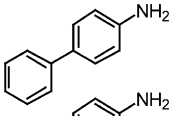
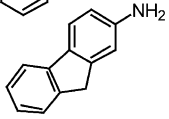
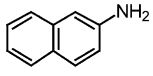
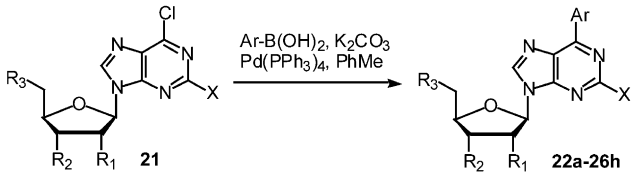
Entry	Amine	Product	Yield (%)
1		**20a**	56
2		**20b**	54
3		**20c**	61
4		**20d**	56

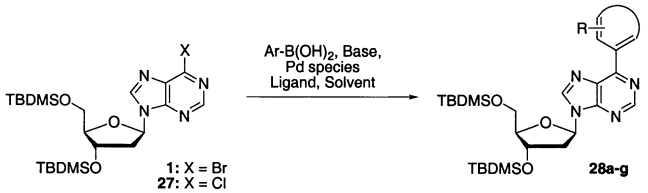
Table 7
Suzuki–Miyura C–C bond-forming reactions at the C-6 position on five different nucleosidic substrates [53,57,58]



Entry	Ar-B(OH)$_2$	X, R$_1$, R$_2$, R$_3$	Product	Yield (%)
1	Phenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22a**	79 [57]
2	4-Fluorophenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22b**	87 [57]
3	2,4-Difluorophenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22c**	65 [57]
4	3,4-Difluorophenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22d**	81 [57]
5	2-Tolyl-B(OH)$_2$	H, OAc, OAc, OAc	**22e**	89 [57]
6	4-Tolyl-B(OH)$_2$	H, OAc, OAc, OAc	**22f**	79 [57]
7	4-Methoxyphenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22g**	84 [57]
8	3-Methoxyphenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22i**	74 [57]
9	4-Ethoxyphenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22j**	80 [57]
10	4-Chlorophenyl-B(OH)$_2$	H, OAc, OAc, OAc	**22k**	65 [57]
11	Phenyl-B(OH)$_2$	NH$_2$, OAc, OAc, OAc	**23a**	83 [57]
12	4-Fluorophenyl-B(OH)$_2$	NH$_2$, OAc, OAc, OAc	**23b**	80 [57]
13	2,4-Difluorophenyl-B(OH)$_2$	NH$_2$, OAc, OAc, OAc	**23c**	75 [57]
14	3,4-Difluorophenyl-B(OH)$_2$	NH$_2$, OAc, OAc, OAc	**23d**	81 [57]
15	Phenyl-B(OH)$_2$	H, H, OTol, OTol	**24a**	94 [58]
16	4-Fluorophenyl-B(OH)$_2$	H, H, OTol, OTol	**24b**	95 [58]
17	4-Methoxyphenyl-B(OH)$_2$	H, H, OTol, OTol	**24c**	97 [58]
18	Phenyl-B(OH)$_2$	H, OAc, OAc, H	**25a**	96 [58]
19	4-Fluorophenyl-B(OH)$_2$	H, OAc, OAc, H	**25b**	89 [58]
20	4-Methoxyphenyl-B(OH)$_2$	H, OAc, OAc, H	**25c**	96 [58]
21	4-(Methylsulfanyl)phenyl-B(OH)$_2$	H, OAc, OAc, OAc	**26a**	68 [53]
22	4-(Dimethylamino)phenyl-B(OH)$_2$	H, OAc, OAc, OAc	**26b**	82 [53]
23	4-(Trifluoromethyl)phenyl-B(OH)$_2$	H, OAc, OAc, OAc	**26c**	55 [53]
24	4-(2-Tetrahydropyranyloxy)phenyl-B(OH)$_2$	H, OAc, OAc, OAc	**26d**	83 [53]
25	3,4-Dimethoxyphenyl-B(OH)$_2$	H, OAc, OAc, OAc	**26e**	74 [53]
26	3,4-(Methylenedioxy)phenyl-B(OH)$_2$	H, OAc, OAc, OAc	**26f**	72 [53]
27	1-Naphthyl-B(OH)$_2$	H, OAc, OAc, OAc	**26g**	76 [53]
28	2-Naphthyl-B(OH)$_2$	H, OAc, OAc, OAc	**26h**	72 [53]

3. C–C bond-forming Suzuki–Miyaura reactions among 2′-deoxynucleosides

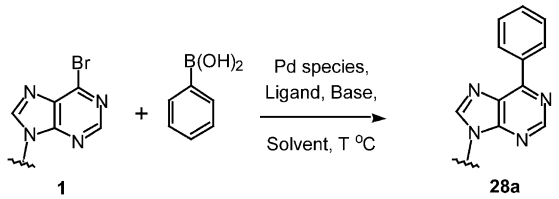
In contrast to Pd-catalyzed C–N cross-coupling reactions, metal-catalyzed C–C bond-formations are more common among nucleobases and nucleosides. Examples of such methods include the following: (a) Pd-catalyzed cross-coupling of Grignard reagents with halonucleosides or reactions of a halonucleobase with organocuprates [24,48]; (b) Pd-mediated reactions of halonucleosides with trialkylaluminum reagents [25,49]; (c) Cu-mediated alkylation with perfluoroalkylsilyl reagents [50]; (d) Pd-catalyzed cross-coupling of organostannanes with halopurines and halonucleosides [26–28,49,51–55]; (e) Negishi-type Pd-mediated cross-coupling of organozinc compounds with halopurines or halonucleosides [49,52,53]; and (f) Negishi-type Pd-mediated cross-coupling of zincated nucleoside derivatives with organic halides [29,30].



Scheme 10.

Surprisingly, to our knowledge, the first reports on the Suzuki–Miyaura cross-coupling methodology [9] for C–C bond-formation among nucleobases and nucleosides appeared only in 1999 [56]. Thus, we had also become interested in this procedure for 2′-deoxyribonucleoside modification, and this review now focuses on the recent developments in this area.

Table 8
Optimization of catalytic systems for the Suzuki–Miyura reactions of 6-bromo-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine (**1**) with phenylboronic acid [a]



Entry	Pd species/ligand/base	Solvent (Temp. °C)	Time, yield (%)/result
1	$Pd(OAc)_2$/**L-1**/K_3PO_4	1,4-dioxane, (100)	12 h, 40
2	$Pd(OAc)_2$/**L-2**/K_3PO_4	1,4-dioxane, (100)	1.75 h, 73
3	$Pd(OAc)_2$/**L-3**/K_3PO_4	1,4-dioxane, (100)	6 h, 67
4	$Pd(OAc)_2$/**L-4**/K_3PO_4	1,4-dioxane, (100)	1 h, 91
5	$Pd(OAc)_2$/**L-5**/K_3PO_4	1,4-dioxane, (100)	Rxn. ~50% complete in 48 h [b]
6	$Pd(OAc)_2$/**L-6**/K_3PO_4	1,4-dioxane, (100)	Rxn. ~50% complete in 48 h [b]
7	$Pd(OAc)_2$/**L-3**/K_3PO_4	1,2-DME, (80)	Very slow reaction [c]
8	$Pd_2(dba)_3$/**L-2**/K_3PO_4	1,4-dioxane, (100)	0.5 h, 80
9	$Pd(PPh)_3/K_2CO_3$	toluene, (100)	8 h, 87 [d]

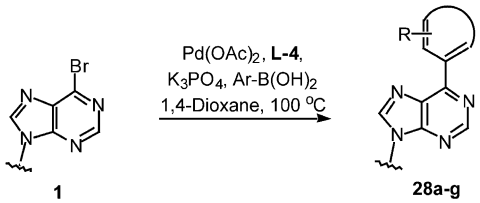
[a] 10 mol % $Pd(OAc)_2$, 15 mol% **L**, two molar equivalents K_3PO_4, 1.5 molar equivalent $PhB(OH)_2$.
[b] Product was not isolated.
[c] Product formation seemed to cease after 12 h and degradation was observed after ca. 36 h.
[d] 25 mol% $Pd(PPh_3)_4$, 1.25 molar equivalent powdered anhydrous K_2CO_3, 1.5 molar equivalent $PhB(OH)_2$.

3.1. Reactions at the C-6 position of purine 2′-deoxynucleosides

The first report on Suzuki–Miyaura cross-coupling reactions focussed largely on the modification of nucleobases and two ribonucleosides [56]. The extensive investigation that was performed with 6-chloro-9-benzylpurine evaluated the efficiency of the cross-coupling of electron-rich, -deficient, vinyl, alkyl and heterocyclic boronic acids using $Pd(PPh_3)_4$ as the catalyst [56]. Two different solvent-base combinations were used; one was PhMe with anhydrous K_2CO_3 and the other was 1,2-DME and aqueous K_2CO_3 [56]. In every case where 1,2-DME–aqueous K_2CO_3 was used, the reactions were significantly faster compared to the reactions utilizing PhMe–anhydrous K_2CO_3. Two notable examples are as follows. With 3-nitrophenylboronic acid, the Suzuki–Miyaura cross-coupling reaction in PhMe with anhydrous K_2CO_3 was incomplete after 48 h at 100 °C (19% yield of the cross-coupled product), whereas in 1,2-DME with aqueous K_2CO_3 complete reaction occurred in 7 h at 85 °C (66% yield of the product) [56]. The reaction involving 2-thiopheneboronic acid was incomplete after 24 h with PhMe–anhydrous K_2CO_3 (39% product yield), while a better yield was obtained with 1,2-DME–aqueous K_2CO_3 (82%) in 7 h even though the reaction remained incomplete [56]. Reaction with butylboronic acid and pentafluorophenylboronic acid yielded very little or no product [56]. Thus, the method appeared to be ideally suited for reactions with arylboronic acids that were electron-rich or neutral but had only limited applicability for alkyl and electron-deficient arylboronic acids.

This method has gained utility for the synthesis of C-6 arylated acyclic nucleoside analogs [49], for ribonucleosides [53,56–58] and for 5′-deoxynucleoside derivatives [58]. Although 2′-deoxyribonucleosides have been tested under the Suzuki–Miyaura reaction conditions these are limited to three examples [58]. Furthermore, cross-

Table 9
Suzuki–Miyura cross-coupling reactions of 6-bromo-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine (**1**) with various arylboronic acids [43]



Entry	Ar-$B(OH)_2$	Time (h)	Product, yield (%)
1	Phenylboronic acid	1	**28a**, 91
2	4-Methoxyphenylboronic acid	1.5	**28b**, 69
3	3-Methoxyphenylboronic acid	1	**28c**, 73
4	2-Ethoxyphenylboronic acid	19.5	**28d**, 62
5	3-Nitrophenylboronic acid	1.5	**28e**, 59
6	4-Acetylphenylboronic acid	8.5	**28f**, 49
7	3-Thiopheneboronic acid	6	**28g**, 58

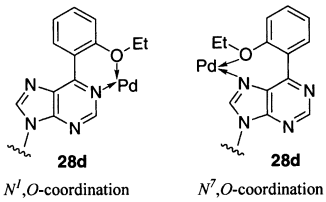
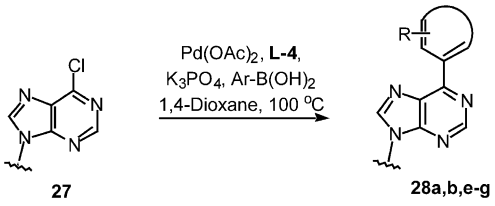


Fig. 7. Two possible structures of a C-6 (*o*-ethoxyaryl)-nucleoside with coordinated Pd.

Table 10
Suzuki–Miyura cross-coupling reactions of 6-chloro-9[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranosyl]purine (**27**) with various arylboronic acids [43]



Entry	Ar-B(OH)$_2$	Time (h)	Product, yield (%)
1	Phenylboronic acid	1.5	**28a**, 93
2	4-Methoxyphenylboronic acid	1.5	**28b**, 83
3	3-Nitrophenylboronic acid	1.5	**28e**, 84
4	4-Acetylphenylboronic acid	1.5	**28f**, 84
5	3-Thiopheneboronic acid	8	**28g**, 74

coupling reactions with nucleosides requires the protection of the carbohydrate hydroxyls for enhancing the solubility of these substrates in the reaction media. For this purpose, acyl groups have been used, but this precluded the use of 1,2-DME–aqueous K_2CO_3. Thus, the anhydrous conditions (PhMe–anhydrous K_2CO_3) have been utilized [53,56–58]. Table 7 summarizes some of the Suzuki–Miyaura reactions on various nucleoside substrates as well as the cross-coupling yields.

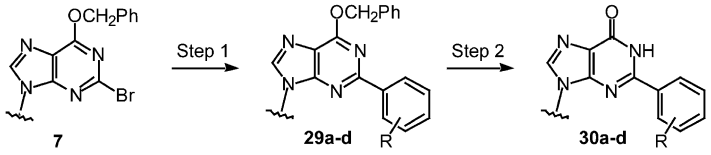
Recently, we have also investigated the Suzuki–Miyaura cross-coupling reaction at the C-6 position of 2′-deoxyribonucleosides [43]. In this study we have evaluated the following in detail. (a) Utility of different catalytic systems; (b) the efficiency of cross-couplings involving bromonucleoside **1** and chloronucleoside **27**; (c) C–C bond-formation in comparison to C–N bond-formation; and (d) Suzuki–Miyaura cross-coupling at the C-2 position as a way to generate 2-aryl 2′-deoxyinosine derivatives (which is described in more detail in Section 3.2). Chloronucleoside **27** required for this work was readily synthesized through known procedures [16,59]. Scheme 10 shows the methodology we have studied utilizing the Suzuki–Miyaura cross-coupling [43]. A point worthy of mention is that we chose *tert*-butyldimethylsilyl protecting groups for the deoxyribose moiety largely based on their robustness under the Pd-catalysis conditions we anticipated utilizing. We believe, however, that other groups including acyl functionalities would be well tolerated under the reaction conditions.

As an initial step, we decided to investigate the cross-coupling of **1** with phenylboronic acid. Of the two Pd species, $Pd(OAc)_2$ and $Pd_2(dba)_3$, we preferred the former based on a recent report that suggested its superiority over the latter [60], as well as the beneficial influence of the acetate counter ion in Pd-mediated cross-coupling reactions [61]. The availability of a variety of ligands (shown in Fig. 3) led us to consider optimization of the catalytic system and conditions for the cross-coupling. Table 8 shows the results of these initial experiments.

Clear from Table 8 is the fact that a variety of catalytic systems are effective for the Suzuki–Miyaura cross-coupling of **1** with phenylboronic acid with yields ranging from 67–91%. However, the ligands that bore bulky *tert*-butyl groups on the phosphorus (**L-5** and **L-6**) were relatively ineffective. The $Pd(PPh)_3$–anhydrous K_2CO_3 system used in the literature [53,56–58] also provided a respectable yield, although the reaction time was somewhat longer (comparable to what has been reported in the literature). The optimal catalytic system, $Pd(OAc)_2$/**L-4**/K_3PO_4 in 1,4-dioxane at 100 °C, provided a fast reaction in good yield [43]. The next stage involved the exploration of the scope of the reaction. For this, several arylboronic acids were selected with varying functionalities, and Table 9 is a compilation of the results obtained in this exercise.

Whereas six of the seven boronic acids coupled rather effectively when 1.5 molar equivalents of each were used, 2-ethoxyphenylboronic acid presented an unusual case. Under the optimized conditions which involved 10 mol% $Pd(OAc)_2$, 15 mol% **L-4**, two molar equivalents of K_3PO_4 and 1.5 molar equivalents of the arylboronic acid, only a 31% yield of **28d** was obtained (reaction incomplete after 67 h at 100 °C). Utilizing **L-3** in place of **L-4** under otherwise identical conditions also resulted in an incomplete reaction. Increasing the catalyst concentration (30 mol% $Pd(OAc)_2$ and 45 mol% **L-4**) led to complete reaction within 20 h albeit in only 13% yield. On the other hand, increasing the molar equivalence of 2-ethoxyphenylboronic acid from 1.5 to 3 led to complete reaction within 20 h with a 62% isolated yield of **28d**. Although it is difficult at this stage to predict the reasons for this behavior, it is possible that proximity of the oxygen on the aryl moiety to the purine nitrogens could lead to complexation of Pd with **28d**. This in turn could be a contributing factor leading to destruction of the catalytic system or degradation of the product. Such a rationale is somewhat similar to that presented in Section 2.2 for the ligand-dependence observed in C–N bond-formation at the C-6 position. Support for such a

Table 11
Two-step synthesis of 2-aryl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine derivatives from 2-bromo-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (**7**) [43]



Entry	Ar-B(OH)$_2$	Step 1	Step 1	Step 2
		Time (h)	Product, yield (%)	Product, yield (%)
1	Phenylboronic acid	1	**29a**, 87	**30a**, 84
2	4-Methoxyphenylboronic acid	6	**29b**, 67	**30b**, 86
3	3-Methoxyphenylboronic acid	4	**29c**, 78	**30c**, 93
4	4-Acetylphenylboronic acid	1.25	**29d**, 80	**30d**, 70

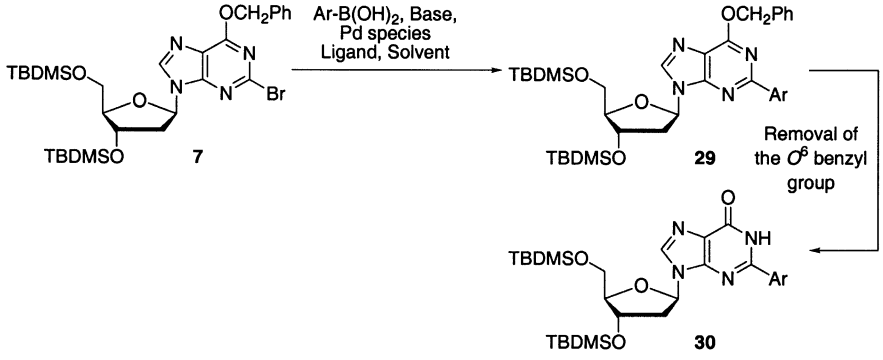
Step 1: (cross-coupling): 10 mol% Pd(OAc)$_2$, 15 mol% **L-4**, two molar equivalents K_3PO_4, 1,4-dioxane, 100 °C. Step 2: (catalytic reduction): 5% Pd–C, 1:1 THF–MeOH, 1 atm H_2, room temperature.

complexation can also be obtained from the fact that 2-tolylboronic acid has been shown to couple rather efficiently at the C-6 position of purines and nucleosides [56,57]. Fig. 7 shows potential bis coordination of Pd with the oxygen on the aryl moiety and the ring N^1 or N^7. It is, therefore, conceivable that 2-alkoxyarylboronic acids may require an altered stoichiometry where larger excesses of the arylboronic acid are required for efficient coupling.

Once the chemistry with the bromonucleoside **1** was established, it was interesting to compare the reactivity trends of **1** and the C-6 chloro analog **27**. Whereas C-6 chloro nucleosides have been arylated through the Suzuki–Miyaura cross-coupling [53,56–58] as well as by a Ni-catalyzed reaction [62], comparison of the reactivities of the two halo nucleosides had not been undertaken. Again initial experiments involved the reaction of **27** with phenylboronic acid under the conditions that had been optimized for reactions with **1**. However, considering the likely lower reactivity of **27** compared to **1**, the catalytic system was preformed [Pd(OAc)$_2$ and **L-4** were premixed in 1,4-dioxane for a few minutes, after which the remaining components were added]. Under these conditions, the cross-coupling of **27** with phenylboronic acid was complete within 1.5 h and produced **28a** in 93% yield [43]. In order to test whether preforming the catalytic system influenced the rapidity or yield of cross-couplings involving **1**, a single cross-coupling of **1** and 3-nitrophenylboronic acid was conducted using the preformed catalyst. The reaction time and product yield of this reaction were comparable to those observed without premixing, indicating that there may be no particular advantage to preforming the catalyst when **1** is utilized in the Suzuki–Miyaura cross-coupling reactions.

Since electronically neutral and rich arylboronic acids had already been shown to produce good product yields [53,56–58], our focus was mainly on the reportedly problematic cross-coupling of electron-deficient arylboronic acids with **27**. Table 10 shows the results of the Suzuki–Miyaura cross-coupling reactions involving chloronucleoside **27**.

These comparisons indicate some interesting and significant results. Whereas, both the bromo and chloronucleosides undergo Suzuki–Miyaura cross-coupling reactions, the chloro nucleoside appears to be a



Scheme 11.

much better coupling partner, leading to good product yields even with the highly electron-deficient arylboronic acids. The yields in the cross-couplings with the chloronucleoside **27** also seem relatively insensitive to the substituents on the arylboronic acid. On the other hand, in reactions involving the bromonucleoside **1**, arylboronic acids that bear electron-withdrawing groups return lower yields. Our results with **27** are in contrast to other studies on C-6 chloronucleosides, where inefficient coupling of electron-deficient arylboronic acids has been reported [57]. Although this may well be a function of the catalytic systems employed, all of the reported studies clearly indicate that halo nucleosides can be cross-coupled with a large variety of arylboronic acids ranging from highly electron deficient to highly electron rich.

3.2. Reactions at the C-2 position of purine 2′-deoxynucleosides

Pd-catalyzed C–C bond-formation via Heck and Stille types of reactions using an O^6 protected C-2 iodoinosine has been reported as a method for generating C-2 C-linked ribonucleosides [63,64]. However, the Suzuki–Miyaura cross-coupling had not found applicability for the synthesis of 2-aryl-2′-deoxyinosine analogs until recently [43]. The ready availability of the 2-bromo-O^6-benzyl-2′-deoxyinosine derivative **7** led us to rationalize its applicability for this purpose; application of the Suzuki–Miyaura cross-coupling followed by removal of the O^6-benzyl group should result in the desired 2′-deoxyinosine analogs (Scheme 11).

As a test, the cross-coupling of **7** with phenylboronic acid was performed using $Pd(OAc)_2$/**L-4**/K_3PO_4 in 1,4-dioxane at 100 °C. The reaction, which was complete within 1 h, provided the O^6-benzyl-2-phenyl-2′-deoxyinosine derivative **29a** in 87% yield. A second catalytic system that was investigated [$Pd(OAc)_2$/**L-1**/Cs_2CO_3], afforded **29a** in 84% yield, but the reaction time was longer. Thus, all subsequent experimentation was performed with the first catalytic system. Cross-coupling of **7** with arylboronic acids containing various substituents was tested in order to ascertain the scope of the reaction. However, there was a single limitation; arylboronic acids were chosen wherein the substituents would not pose problems in the catalytic hydrogenolysis step that was necessary for removal of the O^6 protecting group. In each case the cross-coupling step (step 1) proceeded smoothly and in good yield, and the catalytic hydrogenolysis (step 2) was relatively trivial. Table 11 summarizes the results of the two-step transformation leading to the 2-aryl-2′-deoxyinosine derivatives [43].

The trend that is apparent in Table 11 seems to indicate that very facile C–C bond-formation at the C-2 position occurs with the electron-deficient arylboronic acid (entry 4) whereas an electron-rich arylboronic acid shows slower reaction (entry 2). A somewhat similar situation exists in the C–N bond-formation shown in Table 5, where highly electron-deficient arylbromides are aminated readily whereas electron-rich ones are unreactive. However, it is very clear that C–C bond-formation can be accomplished in a facile manner at both the C-6 and the C-2 positions of purine 2′-deoxynucleosides via the Suzuki–Miyaura cross-coupling methodology.

4. Conclusions

From this review it is evident that advances in the development of newer Pd catalysts allow for the facile C–N bond-formation at the C-6, C-2 and C-8 positions leading to new structural paradigms among 2′-deoxynucleosides. Similarly, the Suzuki–Miyaura cross-coupling methodology enables the development of hydrophobic nucleosides bearing aryl moieties at the C-6 and C-2 positions. Several such modified nucleosides can be evaluated for biological activity, potentially leading to new pharmaceutical products, while several others can be chemically incorporated into DNA. Biochemical, biological, and structural explorations on these modified DNA will most likely provide some fascinating insights into the influence of DNA perturbation on the ensuing enzymatic response. Remarkably, from a chemical standpoint, despite the multiple coordination sites in nucleosides that are known to sequester metals such as Pd and Pt, Pd-catalyzed transformations can be readily accomplished on these substrates. Methods described in this review add to the growing number of achievable transformations on nucleosides and nicely complement the known chemistry of these compounds such as the S_NAr displacement. Due to the tremendous potential offered by metal catalyzed reactions in providing access to unusual molecules, applications of such methodology to nucleic acid chemistry will most likely leave an enduring impact in this field. In our own laboratories we continue to test the limits of metal-catalyzed methods in providing easy entries to molecules that can lead to a greater understanding of biological and biochemical processes.

5. Note added in proof

The following developments have been reported since submission of this manuscript.

1) Schoffers et al. have reported Pd-mediated C–N bond-formation at the C-8 position of adenosine by cross-coupling 8-bromo-2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)adenosine with aromatic amines using $Pd_2(dba)_3$/(±)-BINAP/*tert*-BuONa, in toluene at

80 °C. (E. Schoffers, P.D. Olsen, J.C. Means, Org. Lett. 3 (2001) 4221–4223.)

2) Hocek and coworkers have reported Suzuki–Miyaura cross-coupling at the C-8 position of 3- and 9-benzyladenine. In addition, they have reported that 9-benzyl-2,6-dichloropurine undergoes selective C–C bond-formation at the C-6 position with 1 molar equivalent of phenylboronic acid. Use of 3 molar equivalents results in the 2,6-diphenyl product. Selectivity can be reversed by using 9-benzyl-6-chloro-2-iodopurine: use of one molar equivalent of phenylboronic acid affords selectively the 2-phenyl derivative while use of three molar equivalents of this boronic acid provides the 2,6-diphenyl product. (M. Havelková, D. Dvořák, M. Hocek, Synthesis (2001) 1704–1710.)
3) Veliź and Beal have reported that 6-bromonucleosides (ribo and 2′-deoxyribo) with acetyl protecting groups on the carbohydrate undergo a displacement of halide with 6 molar equivalents of p-toluidine, o-anisidine or imidazole in polar solvents such as DMF, MeOH or EtOH at 65 °C. They also report that the 6-chloro analog does not react under these conditions. This is contrary to the anticipated trend for aromatic substitution. Interestingly, in solvents such as CH_3CN and 1,2-DME, no direct displacement was observed. On the other hand, Pd-catalyzed arylamination reactions proceed in 1,2-DME. These authors also report that *tert*-butyldimethylsilyl protection in place of acetyl may be detrimental to direct displacement. (E.A. Veliź, P.A. Beal, J. Org. Chem. 66 (2001) 8592–8598.)
4) More recently, O^6-arylsulfonate derivatives of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine have been shown to be very effective coupling partners in Suzuki–Miyaura cross-coupling reactions. These are some of the fastest reactions of this type among nucleosides. (M.K. Lakshman, P.F. Thomson, M.A. Nuqui, J.H. Hilmer, N. Sevova, B. Boggess, Org. Lett. 4 (2002) in press.)

Acknowledgements

Financial support for this work by the NSF EPSCoR program (OSR 9452892), the NSF-REU program (CHE 9619804), a PSC-CUNY 32 award (63349 00 32), the Howard Hughes Undergraduate Apprenticeship program and the NIH (1 R15 CA94224-01) are all gratefully acknowledged. The author expresses gratitude to his dedicated coworkers John Hilmer, John Keeler, Felix Ngassa, Jocelyn Martin, Kyle Arneson, Paul Thomson, Padmaja Gunda, and Mark Nuqui for their significant contributions to these studies, as well as to Dr L. Russon (University of Oklahoma), Dr B. Boggess and N. Sevova (University of Notre Dame) for many mass spectral analyses.

References

[1] M. Kosugi, M. Kameyama, T. Migita, Chem. Lett. (1983) 927–928.
[2] For review articles in this area please see: (a) J.F. Hartwig, Synlett (1997) 329–340;
(b) J.F. Hartwig, Angew. Chem. Int. Ed. 37 (1998) 2046–2067;
(c) J.P. Wolfe, S. Wagaw, J.-F. Marcoux, S.L. Buchwald, Acc. Chem. Res. 31 (1998) 805–818;
(d) J.F. Hartwig, Acc. Chem. Res. 31 (1998) 852–860;
(e) B.H. Yang, S.L. Buchwald, J. Organomet. Chem. 576 (1999) 125–146.
[3] T. Yamamoto, M. Nishiyama, Y. Koie, Tetrahedron Lett. 39 (1998) 2367–2370.
[4] For some examples on the use of Pd-catalysis for amination reactions please see: (a) J. Louie, J.F. Hartwig, Tetrahedron Lett. 36 (1995) 3609–3612;
(b) J.P. Wolfe, S. Wagaw, S.L. Buchwald, J. Am. Chem. Soc. 118 (1996) 7215–7216;
(c) M.S. Driver, J.F. Hartwig, J. Am. Chem. Soc. 118 (1996) 7217–7218;
(d) J.P. Wolfe, S.L. Buchwald, Tetrahedron Lett. 38 (1997) 6359–6362;
(e) J. Åhman, S.L. Buchwald, Tetrahedron Lett. 38 (1997) 6363–6366;
(f) J.P. Sadighi, M.C. Harris, S.L. Buchwald, Tetrahedron Lett. 39 (1998) 5327–5330;
(g) B.C. Hamann, J.F. Hartwig, J. Am. Chem. Soc. 120 (1998) 7369–7370;
(h) G. Mann, J.F. Hartwig, M.S. Driver, C. Fernández-Rivas, J. Am. Chem. Soc. 120 (1998) 827–828;
(i) J.P. Wolfe, S.L. Buchwald, Angew. Chem. Int. Ed. 38 (1999) 2413–2416;
(j) J.F. Hartwig, M. Kawatsura, S.I. Hauck, K.H. Shaughnessy, L.M. Alcazar-Roman, J. Org. Chem. 64 (1999) 5575–5580;
(k) R.A. Singer, S.L. Buchwald, Tetrahedron Lett. 40 (1999) 1095–1098;
(l) X. Bei, A.S. Guram, H.W. Turner, W.H. Weinberg, Tetrahedron Lett. 40 (1999) 1237–1240;
(m) B. Witulski, Synlett (1999) 1223–1226;
(n) I. Cabanal-Duvillard, P. Mangeney, Tetrahedron Lett. 40 (1999) 3877–3880;
(o) Z. Wang, R.T. Skerlj, G.J. Bridger, Tetrahedron Lett. 40 (1999) 3543–3546;
(p) I.P. Beletskaya, A.G. Bessmertnykh, R. Guilard, Synlett (1999) 1459–1461;
(q) J.P. Wolfe, H. Tomori, J.P. Sadighi, J. Yin, S.L. Buchwald, J. Org. Chem. 65 (2000) 1158–1174;
(r) J. Košmrlj, B.U.W. Maes, G.L.F. Lemière, A. Haemers, Synlett (2000) 1581–1584;
(s) M.H. Ali, S.L. Buchwald, J. Org. Chem. 66 (2001) 2560–2565.
[5] (a) J.K. Stille, Angew. Chem. Int. Ed. Engl. 25 (1986) 508–524;
(b) T.N. Mitchell, in: F. Diederich, P.J. Stang (Eds.), Metal-Catalyzed Cross-Coupling Reactions (Chapter 4), Wiley-VCH, New York, 1998, pp. 167–202.
[6] (a) E.-i. Negishi, F. Liu, in: F. Diederich, P.J. Stang (Eds.), Metal-Catalyzed Cross-Coupling Reactions (Chapter 1), Wiley-VCH, New York, 1998, pp. 1–47;
(b) W.A. Herrmann, V.P.W. Böhm, C.-P. Reisinger, J. Organomet. Chem. 576 (1999) 23–41 (and references therein).
[7] (a) R.F. Heck, in: B.M. Trost (Ed.), Comprehensive Organic Synthesis, vol. 4 (Chapter 4.3), Pergamon Press, New York, 1991,

pp. 833–863;
(b) S. Bräse, A. de Meijere, in: F. Diederich, P.J. Stang (Eds.), Metal-Catalyzed Cross-Coupling Reactions (Chapter 3), Wiley-VCH, New York, 1998, pp. 99–166.
[8] (a) K. Sonogashira, in: F. Diederich, P.J. Stang (Eds.), Metal-Catalyzed Cross-Coupling Reactions (Chapter 5), Wiley-VCH, New York, 1998, pp. 203–229;
(b) K. Sonogashira, Y. Tohda, N. Hagihara, Tetrahedron Lett. (1975) 4467–4470.
[9] (a) N. Miyaura, A. Suzuki, Chem. Rev. 95 (1995) 2457–2483;
(b) A. Suzuki, J. Organomet. Chem. 576 (1999) 147–168;
(c) A. Suzuki, in: F. Diederich, P.J. Stang (Eds.), Metal-Catalyzed Cross-Coupling Reactions (Chapter 2), Wiley-VCH, New York, 1998, pp. 49–97;
(d) For a general review, please see: S.P. Stanforth, Tetrahedron 54 (1998) 263–303.
[10] For some examples on newer developments in the Stille, Negishi, Sonogashira and Suzuki–Miyaura reactions, please see: (a) A.F. Littke, G.C. Fu, Angew. Chem. Int. Ed. 38 (1999) 2411–2413;
(b) C. Dai, G.C. Fu, J. Am. Chem. Soc. 123 (2001) 2719–2724;
(c) A.F. Littke, G.C. Fu, J. Org. Chem. 64 (1999) 10–11;
(d) K.H. Shaughnessy, P. Kim, J.F. Hartwig, J. Am. Chem. Soc. 121 (1999) 2123–2132;
(e) J.P. Stambuli, S.R. Stauffer, K.H. Shaughnessy, J.F. Hartwig, J. Am. Chem. Soc. 123 (2001) 2677–2678;
(f) T. Hundertmark, A.F. Littke, S.L. Buchwald, G.C. Fu, Org. Lett. 2 (2000) 1729–1731;
(g) D.A. Albisson, R.B. Bedford, S.E. Lawrence, P.N. Scully, J. Chem. Soc. Chem. Commun. (1998) 2095–2096;
(h) J.P. Wolfe, R.A. Singer, B.H. Yang, S.L. Buchwald, J. Am. Chem. Soc. 121 (1999) 9550–9561;
(i) C. Zhang, J. Huang, M.L. Trudell, S.P. Nolan, J. Org. Chem. 64 (1999) 3804–3805;
(j) X. Bei, T. Crevier, A.S. Guram, B. Jandeleit, T.S. Powers, H.W. Turner, T. Uno, W.H. Weinberg, Tetrahedron Lett. 40 (1999) 3855–3858;
(k) X. Bei, H.W. Turner, W.H. Weinberg, A.S. Guram, J.L. Peterson, J. Org. Chem. 64 (1999) 6769–6803;
(l) P. Kočovský, Š. Vyskočil, I. Císařová, J. Sejbal, I. Tišlerová, M. Smrčina, G.-C. Lloyd-Jones, S.C. Stephen, C.P. Butts, M. Murray, V. Langer, J. Am. Chem. Soc. 121 (1999) 7714–7715;
(m) A.F. Littke, C. Dai, G.C. Fu, J. Am. Chem. Soc. 122 (2000) 4020–4028;
(n) M.G. Andreu, A. Zapf, M. Beller, J. Chem. Soc. Chem. Commun. (2000) 2475–2476;
(o) C. Zhang, M.L. Trudell, Tetrahedron Lett. 41 (2000) 595–598;
(p) R.B. Bedford, S.L. Welch, J. Chem. Soc. Chem. Commun. (2001) 129–130;
(q) M. Feuerstein, D. Laurenti, C. Bougeant, H. Doucet, M. Santelli, J. Chem. Soc. Chem. Commun. (2001) 325–326;
(r) W.A. Herrmann, V.P.W. Böhm, C.W.K. Gstöttmayr, M. Grosche, C.-P. Reisinger, T. Weskamp, J. Organomet. Chem. 617–618 (2001) 616–628.
[11] (a) J.W. Daly, J. Med. Chem. 25 (1982) 197–207;
(b) K.A. Jacobson, P.J.M. van Galen, M. Williams, J. Med. Chem. 35 (1992) 407–422.
[12] (a) C.O. Miller, Ann. Rev. Plant Physiol. 12 (1961) 395–408;
(b) T.R. Henderson, C.R. Frihart, N.J. Leonard, R.Y. Schmitz, F. Skoog, Phytochemistry 14 (1975) 1687–1690;
(c) A. Bråthe, L.-L. Gundersen, F. Rise, A.B. Eriksen, A.V. Vollsnes, L.N. Wang, Tetrahedron 55 (1999) 211–228.
[13] (a) J.A. Montgomery, K. Hewson, J. Med. Chem. 11 (1968) 48–52;
(b) H.P. Schnebli, D.L. Hill, L.L. Bennett, Jr., J. Biol. Chem. 242 (1967) 1997–2004.
[14] G.E. Wright, L.W. Dudycz, J. Med. Chem. 27 (1984) 175–181.
[15] For some other examples on the displacement of halides from the C-6 position, please see: (a) P.C. Srivastava, R.K. Robins, R.B. Meyer, Jr., In: L.B. Townsend (Ed.), Chemistry of Nucleosides and Nucleotides, Chapter 2, Plenum Press, New York, 1988, pp. 113–280.
(b) M.J. Robins, B. Uznański, Can. J. Chem. 59 (1981) 2601–2607;
(c) B.K. Trivedi, Nucleosides Nucleotides 7 (1988) 393–402;
(d) B.K. Trivedi, R.F. Bruns, J. Med. Chem. 32 (1989) 1667–1673;
(e) R. Cosstick, M.E. Douglas, J. Chem. Soc. Perkin Trans. 1 (1991) 1035–1040;
(f) E.M. van der Wenden, J.K. von Frijtag Drabbe Künzel, R.A.A. Mathôt, M. Danhof, A.P. IJzerman, W. Soudijn, J. Med. Chem. 38 (1995) 4000–4006.
[16] M.J. Robins, G.L. Basom, Can. J. Chem. 51 (1973) 3161–3169.
[17] See for examples: (a) M. Lakshman, R.E. Lehr, Tetrahedron Lett. 31 (1990) 1547–1550;
(b) S. Chaturvedi, M.K. Lakshman, Carcinogenesis 17 (1996) 2747–2752 (and references therein).
[18] (a) S.J. Kim, C.M. Harris, K.-Y. Jung, M. Koreeda, T.M. Harris, Tetrahedron Lett. 32 (1991) 6073–6076;
(b) S.J. Kim, H.K. Jajoo, H.-Y. Kim, L. Zhou, P. Horton, C.M. Harris, T.M. Harris, Bioorg. Med. Chem. 3 (1995) 811–822.
[19] A.E. Ferentz, G.L. Verdine, Nucleosides Nucleotides 11 (1992) 1749–1763.
[20] M.K. Lakshman, F.N. Ngassa, J.C. Keeler, Y.Q.V. Dinh, J.H. Hilmer, L.M. Russon, Org. Lett. 2 (2000) 927–930.
[21] H. Gao, R. Fathi, B.L. Gaffney, B. Goswami, P.-P. Kung, Y. Rhee, R. Jin, R.A. Jones, J. Org. Chem. 57 (1992) 6954–6959.
[22] V. Samano, R.W. Miles, M.J. Robins, J. Am. Chem. Soc. 116 (1994) 9331–9332.
[23] S. Wagaw, S.L. Buchwald, J. Org. Chem. 61 (1996) 7240–7241.
[24] N. Công-Danh, J.-P. Beaucourt, L. Pichat, Tetrahedron Lett. (1979) 3159–3162.
[25] K. Hirota, Y. Kitade, Y. Kanbe, Y. Maki, J. Org. Chem. 57 (1992) 5268–5270.
[26] A.A. Van Aerschot, P. Mamos, N.J. Weyns, S. Ikeda, E. De Clercq, P.A. Herdewijn, J. Med. Chem. 36 (1993) 2938–2942.
[27] L.-L. Gundersen, Tetrahedron Lett. 35 (1994) 3155–3158.
[28] L.-L. Gundersen, A.K. Bakkestuen, A.J. Aasen, H. Øverås, F. Rise, Tetrahedron 50 (1994) 9743–9756.
[29] T.M. Stevenson, A.S.B. Prasad, J.R. Citineni, P. Knochel, Tetrahedron Lett. 37 (1996) 8375–8378.
[30] A.S.B. Prasad, T.M. Stevenson, J.R. Citineni, V. Nyzam, P. Knochel, Tetrahedron 53 (1997) 7237–7254.
[31] M.K. Lakshman, J.C. Keeler, J.H. Hilmer, J.Q. Martin, J. Am. Chem. Soc. 121 (1999) 6090–6091.
[32] V. Nair, S.G. Richardson, J. Org. Chem. 45 (1980) 3969–3974.
[33] J.P. Wolfe, S.L. Buchwald, J. Org. Chem. 62 (1997) 6066–6068.
[34] D.W. Old, J.P. Wolfe, S.L. Buchwald, J. Am. Chem. Soc. 120 (1998) 9722–9723.
[35] F. De Riccardis, R.R. Bonala, F. Johnson, J. Am. Chem. Soc. 121 (1999) 10453–10460.
[36] F. De Riccardis, F. Johnson, Org. Lett. 2 (2000) 293–295.
[37] J.F. Gerster, R.K. Robins, J. Am. Chem. Soc. 87 (1965) 3752–3759.
[38] (a) T. Steinbrecher, C. Wameling, F. Oesch, A. Seidel, Angew. Chem. 105 (1993) 408–410;
(b) T. Steinbrecher, C. Wameling, F. Oesch, A. Seidel, Angew. Chem. Int. Ed. Engl. 32 (1993) 404–406;
(c) C. Edwards, G. Boche, T. Steinbrecher, S. Scheer, J. Chem. Soc. Perkin Trans. 1 (1997) 1887–1893;
(d) M.D. Cooper, R.P. Hodge, P.J. Tamura, A.S. Wilkinson, C.M. Harris, T.M. Harris, Tetrahedron Lett. 41 (2000) 3555–3558.

[39] B. Zajc, M.K. Lakshman, J.M. Sayer, D.M. Jerina, Tetrahedron Lett. 33 (1992) 3409–3412.
[40] E.A. Harwood, S.T. Sigurdsson, N.B.F. Edfeldt, B.R. Reid, P.B. Hopkins, J. Am. Chem. Soc. 121 (1999) 5081–5082.
[41] E.A. Harwood, P.B. Hopkins, S.T. Sigurdsson, J. Org. Chem. 65 (2000) 2959–2964.
[42] R.R. Bonala, I.G. Shishkina, F. Johnson, Tetrahedron Lett. 41 (2000) 7281–7284.
[43] M.K. Lakshman, J.H. Hilmer, J.Q. Martin, J.C. Keeler, Y.Q.V. Dinh, F.N. Ngassa, L.M. Russon, J. Am. Chem. Soc. 123 (2001) 7779–7787.
[44] S.A. Kazakov, in: S.M. Hecht (Ed.), Bioorganic Chemistry: Nucleic Acids (Chapter 9), Oxford University Press, New York, 1996, pp. 244–287.
[45] Although N^3 could also potentially be a coordinating center, steric hindrance by the sugar is thought to render this an unfavorable site [44].
[46] R.B. Martin, in: A. Sigel, H. Sigel (Eds.), Metal Ions in Biological Systems, vol. 32 (Chapter 3), Marcel Dekker, Inc, New York, 1996, pp. 61–89.
[47] Z. Wang, C.J. Rizzo, Org. Lett. 3 (2001) 565–568.
[48] H. Dvořáková, D. Dvořák, A. Holý, Tetrahedron Lett. 37 (1996) 1285–1288.
[49] M. Česnek, M. Hocek, A. Holý, Collect. Czech. Chem. Commun. 65 (2000) 1357–1373.
[50] M. Hocek, A. Holý, Collect. Czech. Chem. Commun. 64 (1999) 229–241.
[51] M. Hocek, M. Masojídková, A. Holý, Tetrahedron 53 (1997) 2291–2302.
[52] M. Hocek, M. Masojídková, A. Holý, Collect. Czech. Chem. Commun. 62 (1997) 136–146.
[53] M. Hocek, A. Holý, I. Votruba, H. Dvořáková, Collect. Czech. Chem. Commun. 66 (2001) 483–499.
[54] J.L. Sessler, B. Wang, A. Harriman, J. Am. Chem. Soc. 115 (1993) 10418–10419.
[55] R.M. Moriarty, W.R. Epa, A.K. Awasthi, Tetrahedron Lett. 31 (1990) 5877–5880.
[56] M. Havelková, M. Hocek, M. Česnek, D. Dvořák, Synlett (1999) 1145–1147.
[57] M. Hocek, A. Holý, I. Votruba, H. Dvořková, J. Med. Chem. 43 (2000) 1817–1825.
[58] M. Hocek, A. Holý, I. Votruba, H. Dvořáková, Collect. Czech. Chem. Commun. 65 (2000) 1683–1697.
[59] H. Maruenda, A. Chenna, L.-K. Liem, B. Singer, J. Org. Chem. 63 (1998) 4385–4389.
[60] J.P. Wolfe, S.L. Buchwald, J. Org. Chem. 65 (2000) 1144–1157.
[61] C. Amatore, A. Jutand, Acc. Chem. Res. 33 (2000) 314–321.
[62] D.E. Bergstrom, P.A. Reddy, Tetrahedron Lett. 23 (1982) 4191–4194.
[63] V. Nair, G.A. Turner, S.D. Chamberlain, J. Am. Chem. Soc. 109 (1987) 7223–7224.
[64] V. Nair, G.A. Turner, G.S. Buenger, S.D. Chamberlain, J. Org. Chem. 53 (1988) 3051–3057.