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A REVIEW: SYNTHESIS OF ARYL *C*-GLYCOSIDES VIA THE HECK COUPLING REACTION

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□ *In this article, we focus on the synthesis of aryl C-glycosides via Heck coupling. It is organized based on the type of structures used in the assembly of the C-glycosides (also called C-nucleosides) with the following subsections: pyrimidine C-nucleosides, purine C-nucleosides, and monocyclic, bicyclic, and tetracyclic C-nucleosides. The reagents and conditions used for conducting the Heck coupling reactions are discussed. The subsequent conversion of the Heck products to the corresponding target molecules and the application of the target molecules are also described.*

INTRODUCTION

It has been over 3 decades since Pitha et al.[1] reported the synthesis of the first molecule that might be called an oligonucleotide analog, in 1970. It is difficult to remember that at that time, RNA sequencing was difficult, and no practical DNA sequencing technology of any type was available. As a consequence, this early oligonucleotide analog was built by simply polymerizing an acrylic derivative of thymine. With no defined sequence, the analog was not a starting point for research.

Times have changed greatly. Today, 12 independently replicating nucleobases are available as independently replicatable entities. Oligonucleotides containing nonstandard nucleobases are commercial products made on the millimole scale. Over 400,000 people have their health care improved using diagnostics tools that incorporate portions of an artificially expanded genetic alphabet.[2,3]

The utility of oligonucleotides containing nonstandard nucleobases and other base-modified oligonucleotide analogs has driven the need to synthesize these. In part, the target structures are constrained by our increasingly detailed understanding of the roles of various parts of the nucleic acid molecule.[4] For example, the repeating charge delivered by the phosphate

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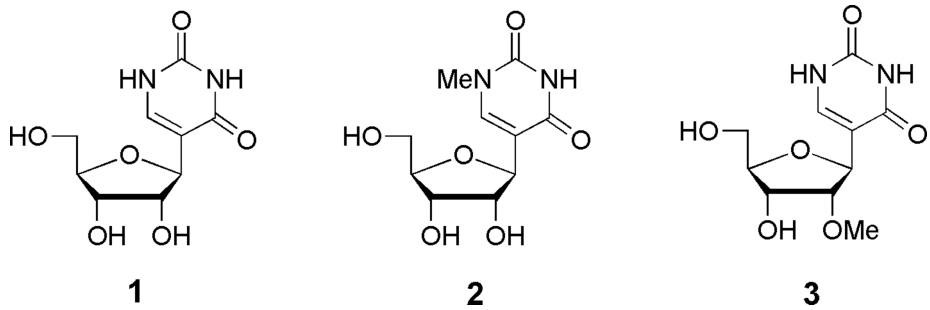


FIGURE 1 Naturally occurring *C*-nucleosides.

linkers is now believed to be an intrinsic component of rule-based molecular recognition in nucleic acids.[5,6] Further, as a surprise emerging from groups attempting to form a synthetic biology from backbone nucleic acids, ribose is not replaced easily without lowering the affinity of nucleic acids for their complement.[7,8] Even DNA, where a single OH group is replaced by –H in the backbone carbohydrate, binds quite weakly to its complement unless salt is present in the buffer.

These considerations have focused design of nucleic acid analogs on ribose-like backbones with aromatic rings as the aglycone. This ring may be an unfunctionalized aromatic system,[9] a heterocycle,[10] or a heterocycle functionalized with hydrogen bonding groups,[11] depending on its intended use.

The demonstrated utility of these nucleic acid analogs in research and diagnostics[12] creates the need to prepare nucleoside analogs that, in the parlance of natural product chemistry, are "*C*-glycosides." These are compounds that join a ribose or 2'-deoxyribose unit to the aglycone.

C-GLYCOSIDES

C-glycosides also are known as *C*-nucleosides and generally are defined as compounds that contain a heterocyclic aglycone and a carbohydrate moiety that are joined together by a carbon–nitrogen bond. *C*-nucleosides, however, have the sugar and heterocyclic aglycon connected by a C–C rather than a C–N bond.

The first reported *C*-nucleoside, pseudouridine **1** (Figure 1), was isolated from transfer RNA in 1957.[13] 1-Methylpseudouridine **2**, 2'-*O*-methylpseudouridine **3** (Figure 1) and several other *C*-nucleosides later were found to occur naturally.[13]

Most naturally occurring *C*-nucleosides are antibiotics and many also exhibit anticancer and/or antiviral activity.[13–17] *C*-nucleosides also are suitable candidates for use as building blocks of oligonucleotides for the

construction of triplex DNA in gene therapy.[14,15] A characteristic of *C*-nucleosides is that the C–C bond is resistant to hydrolytic and enzymatic cleavage.[14] Pioneering work in employing Heck-type coupling reactions to form C–C bonds between the anomeric carbon atom of sugar derivatives and heterocycles was carried out by Daves et al.[18–20] Heck reaction conditions can be regioselective and stereoselective in the formation of a C–C bond.[21,22] A suitable protecting group at the 3'-hydroxy function of the sugar moiety controls the anomeric configuration of the *C*–nucleoside in the Heck reaction. It causes glycosidic bond formation to occur on the least sterically hindered face of the glycal ring during the attack by organopalladium reagents and results in the formation of the β-anomer.[19] Many *C*-nucleosides are found in nature and long have been the target of natural product synthetic organic chemists.

There are 2 major approaches to the synthesis of *C*-nucleosides in the literature.[23,24] In one approach a preformed aglycone is coupled to a sugar derivative. In the other a functional group is introduced at the anomeric position of the sugar derivative and is followed by construction of a heterocyclic base.

The first review of the Heck-type coupling was published by Hacksell and Daves in 1985,[25] with an update in 1990.[26] A review covering recent developments in *C*-glycoside synthesis was covered by Postema in 1992.[27] An important review by Jaramillo and Knapp covering the synthesis of *C*-arylglycosides was done in 1994.[28] In 1998, Du and Linhardt covered advances in stereoselective *C*-glycoside synthesis.[29] Since then 2 other reviews,[30] in 2005, have covered the field of which the most recent was by Lee and He.[31] The key reviews are by Du and Linhardt[29] and by Lee and He.[31]

New methods for the synthesis of *C*-glycosides involve the Friedel Crafts reaction,[32] attack of nucleophilic species on an electrophilic ribose derivative[33] and lewis acid catalyzed processes.[34] Some synthetic routes involve the synthesis of a ring after the formation of a *C*-glycoside.[35] Nonnucleosidic *C*-glycosides also have been synthesized.[36,37] Thiol-carrying aryl *C*-glycosides have also been prepared by non-Heck methods.[38]

The synthesis of unsaturated glycals, precursors for the reactions discussed here, recently was reviewed.[39,40] The Pederson laboratory recently has reported a new version of their classical synthesis of the glycal intermediate.[41] Other improved syntheses of the glycal also have been reported.[42]

Non-Heck methods recently reported involve boronates[43] and radical reactions.[44] *C*-glycosides also are used to study issues in physical organic chemistry such as the anomeric effect.[45]

In this review we will focus specifically on the Heck coupling approach and *C*-glycosides will be referred to as *C*-nucleosides hereafter.

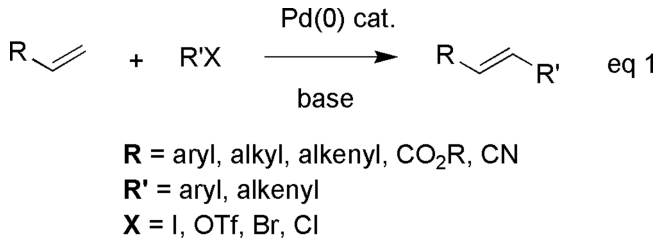


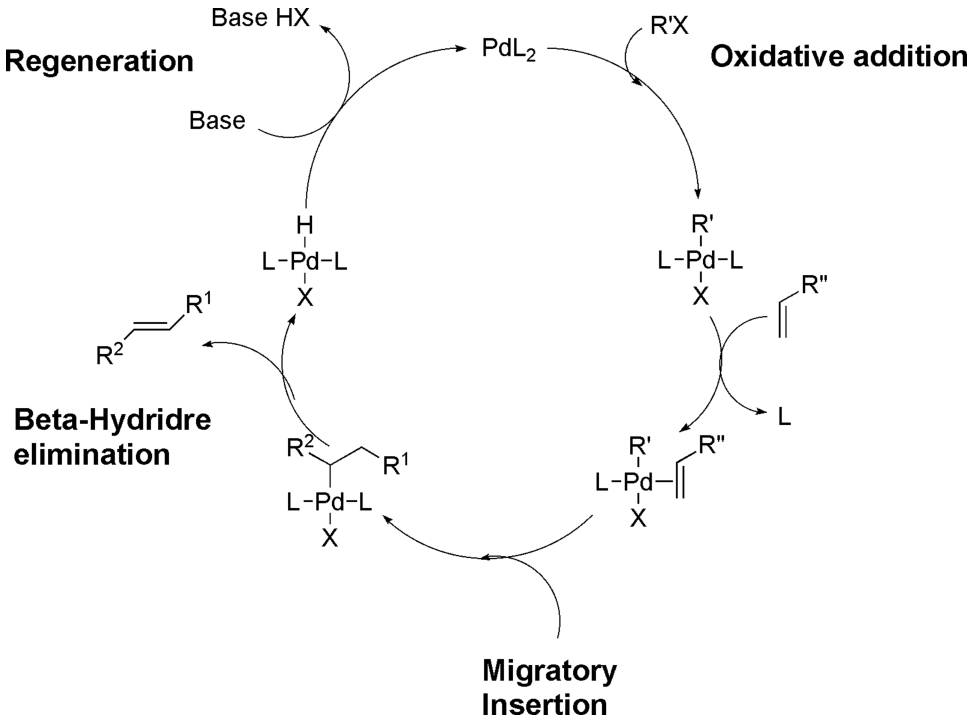
FIGURE 2 The Heck coupling reaction.

The Heck Coupling Reaction

This reaction was first reported By Heck in 1968 and later became known as the Heck reaction,[46,47] which involves coupling of an aryl or vinyl halide with an olefin as depicted in Figure 2 (eq. 1).

The proposed mechanism[48] for the Heck reaction is shown in Scheme 1.

The general procedure involves up to 1 mole% of catalyst, 2 equivalents of triarylphosphine (for stabilizing the arylpalladated intermediates), and a base (Et_3N, $NaHCO_3$) to trap the released HX and regenerate the catalyst. The rate-limiting step is the oxidative addition of RX that depends on the



SCHEME 1 Mechanism of the heck coupling reaction.

nature of X (ArI > ArOTf > ArBr, ArCl). A temperature range of 70°C to120°C is used for conducting the reaction. Aprotic polar solvents such as hexamethylphosphorictriamide (HMPA), *N*,*N*-dimethylformamide (DMF), acetonitrile (MeCN), and *N*-methyl-2-pyrrolidone (NMP) commonly are used. The Heck reaction also is reported to be highly regioselective, as shown in Scheme 1.[49]

PYRIMIDINE *C*-NUCLEOSIDES

Synthetic Targets

Several *C*-nucleosides that bear a pyrimidine, pyrazine, or pyridine ring as nucleobase have been synthesized and are depicted in Table 1 (entries 1–11).

Potential HIV Reverse Transcriptase Inhibitors

The synthesis of 2'-deoxypseudouridine was achieved by coupling of 5-iodouracil with a ribofuranoid glycal (designed for stereospecific formation of β C-glycosyl bonds) using palladium acetate ($Pd(OAc)_2$) and triphenylarsine ($ArPh_3$) (Table 1, entry 1).[50] The Heck product, which was not isolated from the reaction, was desilylated with a fluoride ion and the resulting 2'-deoxy-3'-keto *C*-nucleoside was stereoselectively reduced with sodium triacetoxyborohydride to afford 2'-deoxypseudouridine. It is interesting to note that in this Heck coupling reaction the iodopyrimidine is *unprotected*.

A new strategy for synthesizing enantio- and diastereoisomers of *C*-nucleosides was reported by Zhang et al. (Table 1, entries 2 and 3).[51] This strategy involves a 2-step syntheses of 2',3'-deoxy *C*-nuceosides whereby a D-series *C*-nucleoside is prepared from an L-series glycal (and vice versa).

Coupling of 2,4-dimethoxy-5-iodopyrimidine (a protected heterocycle) with each of the enantiomeric 2,3-dideoxy furanoid glycols, using $Pd(OAc)_2$ and $AsPh_3$, affords enantiomeric pairs of 2',3'-dideoxy pyrimidine *C*-nucleosides (Table 1, entries 2 and 3). The enantiomeric 2,3-dideoxy furanoid glycals were obtained from the conversion of (S) and (R)-γ-(hydroxymethyl-γ-butyrolactones derived from D- and L- glutamic acids. The Heck products have been reduced with Pd-C to afford a D-and L-series of α- and β-*C*-nucleosides, potential HIV reverse transcriptase inhibitors.[51]

Triple Helix-Forming Molecules

A pyrimidine analogue (Table 1, entry 4) was designed to interact with a dC-dG base pair target by oligonucleotide directed triple helix formation.[52] This analogue was obtained by coupling an *unprotected* iodinated pyrimidine heterocycle with a ribofuranoid glycal

TABLE 1 Synthesized *C*-nucleosides bearing a pyrimidine, pyrazine, or pyridine ring as nucleobase

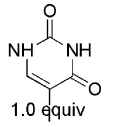
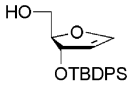
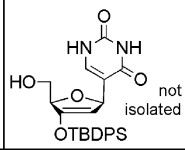
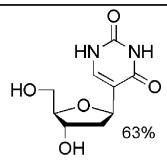
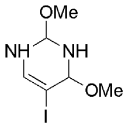
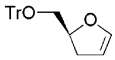
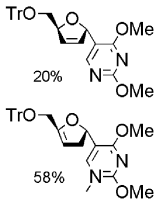
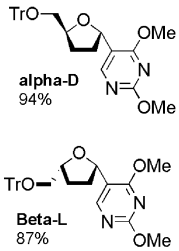
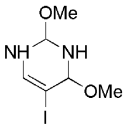
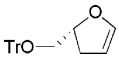
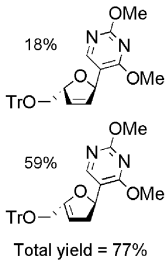
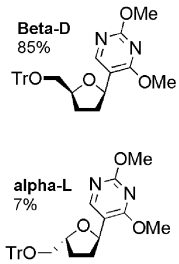
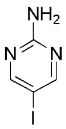
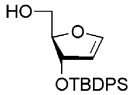
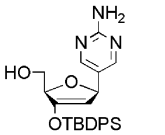
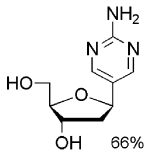
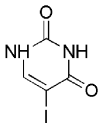
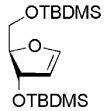
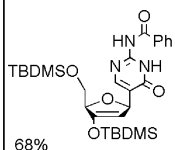
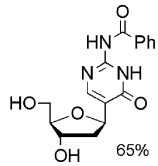
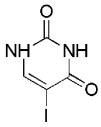
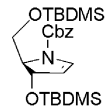
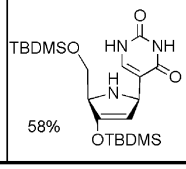
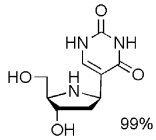
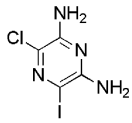
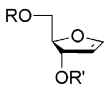
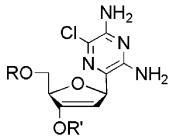
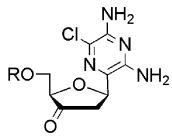
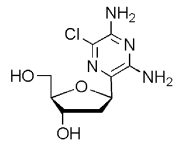
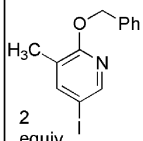
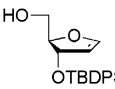
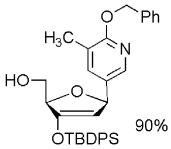
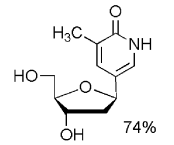
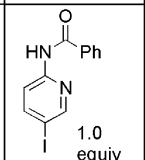
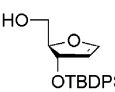
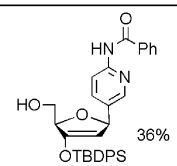
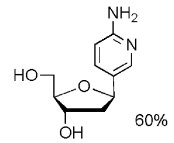
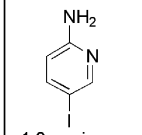
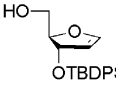
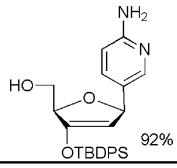
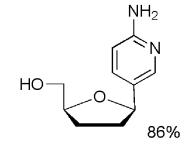
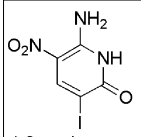
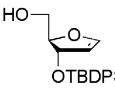
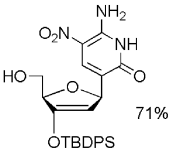
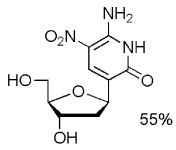
	Aglycon	Glycal	Pd source Ligand Base	Solvent Time Temp	Heck product	Target	Ref
1	 1.0 equiv		$Pd(OAc)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 1.5 equiv	DMF 15 h 60 °C	 not isolated	 63%	50
2	 1.0 equiv	 D	$Pd(OAc)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 2 equiv	MeCN 10 h 75 °C	 20% 58% Total yield = 78%	 alpha-D 94% Beta-L 87%	51
3	 1.0 equiv	 L	$Pd(OAc)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 2 equiv	MeCN 10 h 75 °C	 18% 59% Total yield = 77%	 Beta-D 85% alpha-L 7%	51
4	 1.0 equiv		$Pd(dba)_2$ 0.05 equiv $P(C_6F_5)_3$ 0.1 equiv $i\text{-}Pr_2EtN$ 4.5 equiv	MeCN 66 h 95 °C	 "crude" yield = 92%	 66%	52
5	 2.4 equiv	 1.0 equiv	$Pd(OAc)_2$ 0.21 equiv $AsPh_3$ 0.38 equiv $i\text{-}Pr_2EtNH$ 3.3 equiv	DMF 22 h 80 °C	 68%	 65%	53
6	 2.5 equiv	 1.0 equiv	$Pd(OAc)_2$ 0.16 equiv $AsPh_3$ 0.3 equiv Bu_3N 1.6 equiv	DMF 20 h 65 °C	 58%	 99%	56

TABLE 1 Synthesized *C*-nucleosides bearing a pyrimidine, pyrazine, or pyridine ring as nucleobase *(Continued)*

7	 1.0 equiv	 **R**, **R'** = TBDMS **R**, **R'** = TBDPS **R** = TBDPS, **R'** = TMS	$Pd(OAc)_2$ $AsPh_3$ Et_3N	MeCN 50 °C	 **R** = **R'** = TBDMS **R** = **R'** TBDPS 33% **R** = TBDPS, **R'** = TMS  **R** = TBDMS 73% **R** = TBDPS 44%		**57**
8	 2 equiv	 1 equiv	$Pd(dba)_2$ 0.1 equiv bppp 0.1 equiv Bu_3N 3.0 equiv	MeCN 8 h 80 °C	 90%	 74%	**58**
9	 1.0 equiv		$Pd(dba)_2$ 0.10 equiv $P(C_6F_5)_3$ 0.20 equiv Bu_3N 3.0 equiv	MeCN - 80 °C	 36%	 60%	**58**
10	 1.0 equiv	 1.0 equiv	$Pd(OAc)_2$ 0.05 equiv PPh_3 0.10 equiv i-Pr_2EtN 2 equiv	MeCN - 80 °C	 92%	 86%	**60**
11	 1.0 equiv		$Pd(OAc)_2$ 0.10 equiv $AsPh_3$ 0.02 equiv Et_3N 1.4 equiv	DMF 6 days 60 °C	 71%	 55%	**61**

using bis(dibenzylideneacetone)palladium [$Pd(dba)_2$] and tris(pentafluorophenyl)phosphine [$P(C_6F_5)_3$] as ligand. The crude Heck product was sufficiently pure and used directly in the desilylation step. The resulting ketone, after reduction, afforded the desired β *C*-nucleoside (pK_a = 3.3). This nucleoside was converted to the phosphoramidite, which was incorporated into an oligonucleotide. A study conducted on it's interaction with a dC-dG base pair found that it is more effective than dC (pK_a = 4.3) in targeting dC-dG base pairs.

2′-Deoxypseudoisocytidine

Watanabe and coworkers were the first to synthesize pseudoisocytidine and its 2'-deoxy derivative for potential use as a therapeutic agent with anti-leukemic properties.[53,54] Mayer and Leumann reported a novel and improved synthesis of 2'-deoxypseudoisocytidine (Table 1, entry 5).[55] In this improved synthesis, a *N*-benzoylated pseudoisocytidine was coupled with a furanoid glycal having silyl protecting groups at both the 3- and 5-positions. The *N*-benzoylated base was found to have poor solubility and, as a result, it was *O*-silylated with *N*,O-bis(trimethylsilyl)acetamide to improve solubility. The coupling reaction, in the presence of $Pd(OAc)_2$ and $AsPh_3$, afforded the Heck product in good yield (68%). The desilylation reaction was conducted with HF-pyridine in THF followed by a diastereoselective reduction of the ketone at -15°C. The resulting β-*C*-nucleoside was subsequently converted to a phosphoramidite.

Pyrrolidine C-*Nucleosides*

A novel route to the synthesis of pyrrolidine *C*-nucleosides via Heck coupling was reported by Haberli and Leumann (Table 1, entry 6).[56] Coupling of the *unprotected* iodouracil to a Cbz protected-enamine (prepared from commercially available *trans*-3-hydroxy-L-proline) in the presence of $Pd(OAc)_2$ and $AsPh_3$ afforded the Heck product in moderate yield (58%). Coupling reactions in which PPh_3, diethyl 4-(2,2′-bipyrid-4-yl)-phenylphosphonote (bppp), and $P(C_6F_5)_3$ were used as ligands were unsuccessful. Desilylation of the Heck product followed by stereoselective reduction of the ketone afforded the desired *C*-nucleoside. This *C*-nucleoside, as well as its *N*-methyl derivative, was converted to the corresponding phosphoramidite building blocks for DNA synthesis.

A Pyrazine C-*Nucleoside*

Chen et al. reported a synthesis of a novel pyrazine *C*-nucleoside via a Heck coupling reaction (Table 1, entry 7).[57] In this reaction, a glycal that had silyl protecting groups in both the 3- and 5-positions was coupled with an *unprotected* iodinated pyrazine heterocycle in the presence of $Pd(OAc)_2$ and $AsPh_3$. The *unprotected* primary amines of the heterocycle *did not inactivate* the catalyst and the chloro functionality *did not react with* the glycal during the coupling reaction. The Heck product having TBDMS groups in the 3'- and 5'-positions of the sugar was unstable and could not be isolated. The Heck product having a TBDPS group in the 5'-position and a TMS group at the 3'-position of the sugar was not observed. In all these coupling reactions the β-anomer was reported to be the major product, the α-anomer being formed in a trace amount. The glycal having the di-TBDMS protecting groups was the best candidate for the cross-coupling reaction due to its stability. Desilylation of the Heck product was achieved by reacting with

fluoride ion and reduction with sodium triacetoxyborohydride to afford the β-*C*-pyrazine nucleoside, the yield of which was not reported.

Deletion Modified analogues of dT and dC

The 2 β-C-pyridine nucleosides (Table 1, entries 8 and 9) were synthesized as deletion modified analogues of dT and dC, respectively.[58] Both of these structures lack the carbonyl group at the 6-position of the aglycon. The dT analogue is a derivative of 2-pyridone and prefers the carbonyl tautomer,[59] while the dC analogue prefers the amino[59] rather than the imino tautomeric form. The same tautomeric character and hydrogen bonding patterns observed for the native dT and dC nucleosides are expected for the analogues.

Following the approach for the synthesis of pseudouridine from 5-iodouracil,[50] 5-iodo-3-methyl-2-pyridone (unprotected pyridone) was directly coupled with the glycal in an attempt to produce the dT (Table 1, entry 8), but this approach failed. This failure may be attributed to the coordination of the aglycon to palladium as a result of deprotonation of the amide functionality under the basic conditions used for this reaction. Only moderate yields for the coupling reaction were obtained when the protected aglycon, 2-(benzyloxy)-3-methyl-5-iodopyridine, was coupled to the glycal employing ($P(C_6F_5)_3$), $AsPh_3$ or 1, 1'-bis(diphenylphosphino)ferrocene (dppf) as ligands. The employment of a chelating ligand, bppp, afforded the Heck product in 90% yield. Desilylation followed by reduction afforded the 2'-deoxyribose sugar. The dT was obtained after removing the benzyloxy-protecting group by catalytic hydrogenation.

For the synthesis of the dC (Table 1, entry 9), direct coupling of the unprotected iodopyridine with glycal using and $Pd(dba)_2$ failed. This most likely is due to coordination of the aglycon primary and aromatic amine functionalities to palladium. When bppp was employed as a ligand multiple products were obtained that could not be satisfactorily identified. The iodopyridine was therefore protected with a benzoyl group and subsequent coupling with glycal afforded the Heck product in low yield (36%) using $Pd(dba)_2$ and ($P(C_6F_5)_3$). After desilylation of the Heck product followed by reduction and then debenzoylation, the dC was obtained in good yield (60%).

An HIV Reverse Transcriptase Chain Terminator

The β-C-pyridine nucleoside (Table 1, entry 10) has been synthesized as a HIV reverse transcriptase chain terminator.[60] The mode of action of a chain terminator involves in vivo conversion to the corresponding 5′-triphosphate which enables it to function as a substrate for retroviral reverse transcriptases. The absence of a 3'-hydroxyl results in chain termination after incorporationand DNA synthesis of the viral cDNA ceases.

The synthesis of the β-C-pyridine nucleoside involved coupling the *unprotected* iodopyridine with glycal using $Pd(dba)_2$ and triphenylphosphine (PPh_3) and afforded the Heck product in high yield (92%). After desilylation the resulting ketone was reacted with hydrazide generating a hydrazone. Reduction of the hydrazone with sodium triacetoxyborohydride afforded the 2',3'-dideoxy *C*-nucleoside.

This nucleoside was converted to the corresponding triphosphate and studies were conducted to determine whether it is a good substrate for incorporation by deoxycytidine kinase. Results from initial experiments indicate that this nucleoside is a poor substrate for this enzyme. In order to determine the toxicity of this nucleoside, incorporation studies were conducted with human polymerases. The low binding activity observed for these enzymes could result in reduced toxicity effects for this class of derivatives.

A Nonepimerizing Nucleoside

The *C*-nucleoside synthesized by Hutter and Benner is part of a research program that aims to expand the genetic alphabet (Table1, entry 11).[61] *C*-nucleosides are prone to epimerization when an electron-donating group is present in a suitable position on the heterocycle. Epimerization has been reported for pseudouridine[62,63] and other *C*-nucleosides.[64–66] In order to reduce or inhibit epimerization, the heterocycle may be functionalized with an electron-withdrawing group. In this case, the nucleoside in entry 11 was functionalized with a nitro group in the 5-position of the pyridine ring.

Direct coupling of the *unprotected* iodopyridine with glycal using $Pd(OAc)_2$ and $AsPh_3$ afforded the Heck product in good yield (71%). The iodopyridine was prepared from 2,6-dichloro-3-nitropyridine in 2 steps, first aminolysis and second hydrolysis with sodium hydroxide. Subsequent desilylation of the Heck product followed by reduction afforded the desired nucleoside.

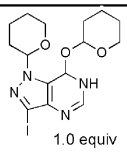
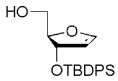
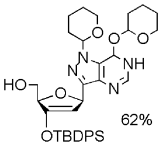
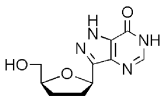
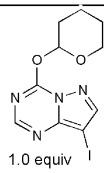
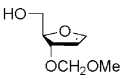
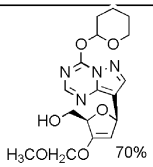
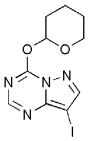
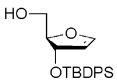
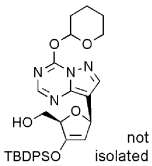
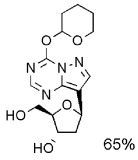
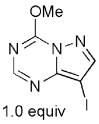
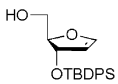
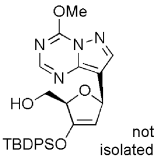
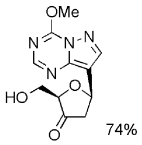
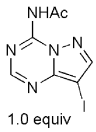
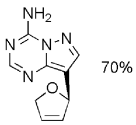
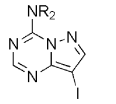
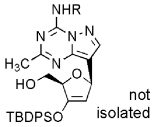
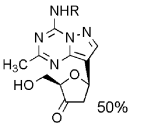
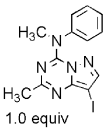
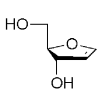
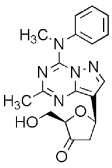
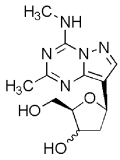
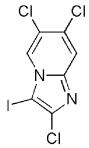
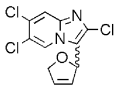
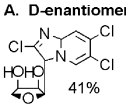
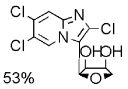
From an epimerization study it was found that the nitro group at the C-5 position of pyridine does in fact reduce the rate of epimerization in the *C*-nucleoside.

PURINE *C*-NUCLEOSIDES

Synthetic Targets

The Heck coupling reaction also has been used in the synthesis of purine *C*-nucleosides which are depicted in Table 2 (entries 1–8).

TABLE 2 Synthesized *C*-nucleosides bearing a purine-like nucleobase

	Aglycon	Glycal	Pd source Ligand Base	Solvent Time Temp	Heck product	Target	Ref
1	 1.0 equiv	 15 equiv	$Pd(dba)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 15 equiv	MeCN 20 h 80 °C	 62%	 52%	**50**
2	 1.0 equiv	 1.3 equiv	$Pd(dba)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 1.5 equiv	MeCN 18 h 60 °C	 70%	Heck product	**72**
3	 1.0 equiv	 1.3 equiv	$Pd(dba)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 1.5 equiv	MeCN 8 h 70 °C	 not isolated	 65%	**72**
4	 1.0 equiv	 1.3 equiv	$Pd(dba)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 1.5 equiv	MeCN 8 h 70 °C	 not isolated	 74%	**72**
5	 1.0 equiv	 20 equiv	$Pd(OAc)_2$ 0.1 equiv PPh_3 0.2 equiv Bu_3N 1 equiv TBAC 1 equiv	MeCN 12 h 80 °C	 70%	Heck product	**72**
6	 **R** = $COCH_2C(Me)_2$ 1.0 equiv	 1.3 equiv	$Pd(dba)_2$ (0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 1.5 equiv	MeCN 24 h 70 °C	 not isolated **R** = $COCH_2C(CH_3)_2$	 50% **R** = $COCH_2C(CH_3)_2$	**72**
7	 1.0 equiv	 1.0 equiv	$Pd(dba)_2$ (0.08 equiv) $AsPh_3$ (0.16 equiv.) Bu_3N (1.17 equiv	MeCN 18 h 60 °C	 75%	 92%	**73**
8	 1.3 equiv	 5 equiv	$Pd(dba)_2$ (0.08 equiv) $AsPh_3$ (0.16 equiv.) Bu_3N (1.17 equiv	DMF - 45 °C	Beta-anomer only  98%	**A. D-enantiomer**  41%  53% **B. L-enantiomer**	**74**

HIV Reverse Transcriptase Inhibitors

As part of an intensive effort to find a cure for the acquired immunodeficiency syndrome (AIDS), the *C*-purine nucleoside (Table 2, entry 1) was synthesized as a potential inhibitor of HIV reverse transcriptase.[50] This nucleoside is also an analog of Formycin B,[50] which exhibits important and interesting biological properties.[67–71] Attempts to couple the *unprotected* brominated aglycon as well as the TBDPS-protected iodo aglycone with glycal failed. Coupling of a bis(tetrahydropyranyl)–protected aglycone with glycal afforded the Heck product in good yield (62%), but as a mixture of diastereoisomers. Fluoride ion was used for desilylation and the tetrahydropyran groups were removed with *p*-toluenesulfonic acid at 40°C in a mixture of water and methanol to afford α- and β-anomers of the keto nucleoside. Reduction of the β-anomer afforded 2'-deoxyformycin B which was used to produce the 2',3'-dideoxynucleoside in 5 steps.[50]

Adenosine Related* C*-Nucleosides

Several *C*-nucleosides of the pyrazolo[1,5-a]-1,3,5-triazine aglycon system have been synthesized and are depicted in Table 2 (entries 2–6).[72] The *C*-nucleoside in entry 6 was prepared as a *C*-nucleoside analogue of adenosine.

The tetrahydropyranylated aglycon was coupled to the protected glycal using $Pd(dba)_2$ and $AsPh_3$ to afford the Heck product in good yield (70%) as well as 15% of deiodinated aglycone (Table 2, entry 2). For the corresponding reaction in the pyrazolo[4,3-d]pyrimidine series dimerization occurred.[50]

Similarly, the tetrahydropyranylated aglycon also was coupled with a TBDPS protected glycal to afford the Heck product as an intermediate (Table 2, entry 3). After in situ desilylation of the intermediate the resulting 3'-hydroxy ketone was reduced with sodium triacetoxyborohydride to stereoselectively afford the diol as diastereoisomers (65%).

A methyl protected aglycon was also successfully coupled with a TBDPS protected glycal (Table 2, entry 4) and the resulting Heck product was desilylated in situ to afford the 3'-hydroxy ketone (74%).

Coupling of a furanoid glycal to an acetyl-protected aglycon at 80–100°C afforded the *unprotected* Heck product in 70% yield (Table 2, entry 5). It may be concluded that the acetyl group is labile under the conditions used for this coupling reaction. An attempt to couple the TBDPS glycal (Table 2, entry 4) under the same conditions failed to afford the Heck product. Failure was attributed to the lability of the acetyl group and aglycone nitrogens coordinating to palladium thereby inactivating the catalyst.

As a result, the bulky biscarbamate aglycone (Table 2, entry 6) was prepared to prevent coordination of the aglycone nitrogens to palladium. Coupling with the TBDPS protected glycal was, in this case, successful.

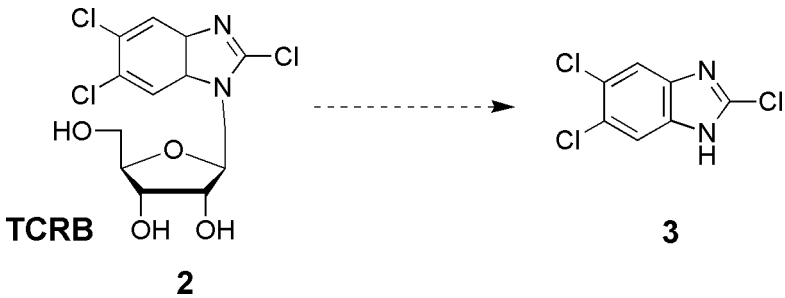


FIGURE 3 A $P2Y_1$ receptor antagonist.

The Heck product was desilylated in situ with fluoride ion to afford the 3'-hydroxy ketone nucleoside in moderate yield (50%). This nucleoside also lost an acyl group from the amino aglycone under the reaction conditions used and is similar to that observed for entry 5.

A $P2Y_1$ Receptor Antagonist

The *C*-nucleoside depicted in Table 3, entry 7 was synthesized as a $P2Y_1$ receptor antagonist (an anti-aggregating agent).[73] This nucleoside is an isostere of the *N*-nucleoside shown in Figure 3 which has shown very brief activity as an anti-aggregating agent.

The rationale behind the synthesis of the *C*-nucleosides in Table 2, entry 7 is that replacing the glycosidic-nitrogen linkage with a carbon-carbon linkage might increase metabolic stability toward nucleosidase enzymes that cleave the glycosidic bond.

For the synthesis, the *unprotected* glycal was coupled with the iodinated heterocycle using $Pd(OAc)_2$ and $AsPh_3$ and afforded the Heck product as the β-anomer in good yield (75%) as well as deiodinated aglycone (15%). Stereoselective reduction of the β-anomer with sodium triacetoxyborohydride followed by displacement of the *N*-methyl-*N*-phenylamino group with methylamine, afforded diol **A**. Reduction, however, with K-selectride on the less sterically hindered face, followed by displacement of the *N*-methyl-*N*-phenylamino group with methylamine, afforded diol **B**.

The 3',5'-bisphosphate derivative of diol **A** inhibits ADP-induced human platelet aggregation and shape change. Significant efficacies 30 minutes after injection in rat is an indication of a strong $P2Y_1$-receptor antagonist activity combined with a prolonged duration of action in vivo.

Herpes Inhibitors

A nucleoside that has exhibited potent and highly selective activity against the human cytomegalovirus (HCMV) with low toxicity at concentrations inhibiting viral growth is 2,5,6-trichloro-1-(β-D-ribofuranosyl-benzimidazole (TCRB **2**, Figure 3).[74] From pharmacokinetic studies in

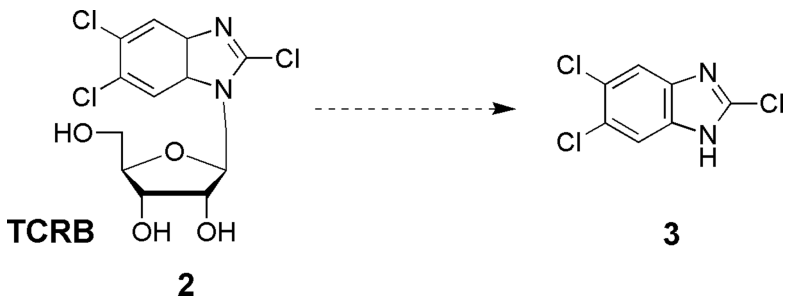


FIGURE 4 Depurination of a *N*-nucleoside herpes inhibitor.

rats and monkeys it was found that TCRB disappears rapidly from the bloodstream following either oral or intravenous dosage. In contrast, the concentration of the heterocycle **3** increased, an indication that the glycosidic bond had been cleaved. As a result of the metabolic instability of the benzimidazole nucleoside, syntheses of the structurally related imidazo-[1,2-a]pyridine *C*-nucleosides were attempted (Table 2, entry 8).[74]

Coupling of the iodinated heterocycle to 2,3-dihydrofuran was done in the presence of $AsPh_3$, $Pd(OAc)_2$ and *silver salts*. The Heck product, 2',3'-dideoxy-2',3'-didehydro, was obtained in quantitative yield (98%). The desired *C*-nucleosides were obtained after dihydroxylation, acetonide protection (acetone and 2,2-dimethoxypropane) and subsequent deprotection (trifluoroacetic acid).

Nucleosides **A** and **B** were screened against 2 selected herpes viruses (HMCV and HSV-1) but only nucleoside **A**, the D-enantiomer, exhibited biological activity against these viruses.

MONOCYCLIC, BICYCLIC, and TETRACYCLIC *C*-NUCLEOSIDES

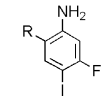
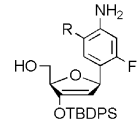
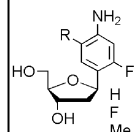
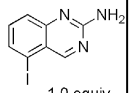
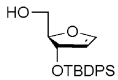
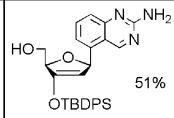
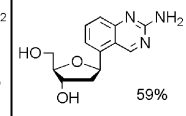
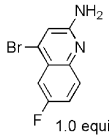
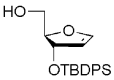
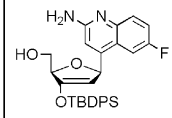
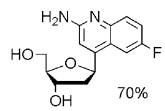
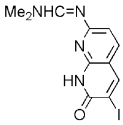
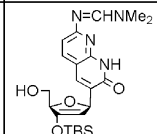
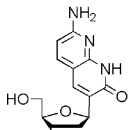
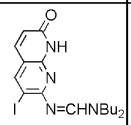
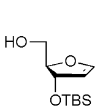
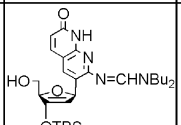
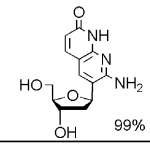
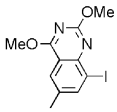
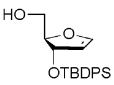
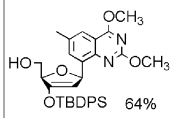
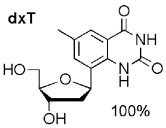
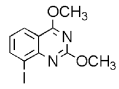
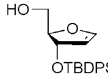
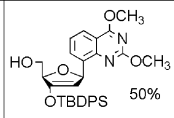
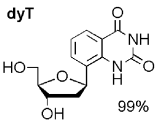
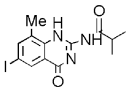
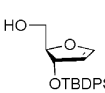
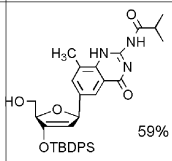
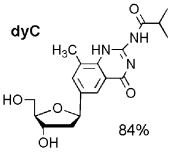
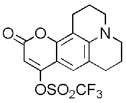
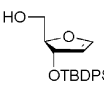
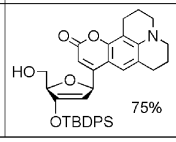
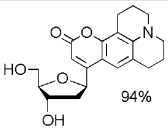
Synthetic Targets

Table 3 summarizes *C*-nucleosides containing cyclic or bicyclic aglycon units that are not classed as purines or pyrimidines.

Cytosine Replacement 2'-Deoxycytidine Mimics

Important biological activities sometimes are observed when a modification in the nucleoside structure is made. Incorporation of such modified structures into nucleic acids by normal enzymatic processes can result in a change in structure and/or function of these bioplolymers. The *C*-nucleosides in Table 3, entry 1 have been prepared as 2'-deoxycytidine mimics.[75] Coupling of *p*-iodoanilines with a *protected* glycal using $Pd(OAc)_2$ and $AsPh_3$ afforded the Heck products that were found to be unstable under the weakly basic reaction conditions. As a result, fluoride ion was added to the reaction mixture to achieve complete desilylation. Reduction of the

TABLE 3 Synthesized *C*-nucleosides bearing either a cyclic or a bicyclic aromatic ring as base

Entry	Aglycon	Glycal	Pd source Ligand Base	Solvent Time Temp	Heck product	Target	Ref
1	 **R** = H, F, Me 1.0 equiv	1.0 equiv	$Pd(OAc)_2$ 0.15 equiv $AsPh_3$ 0.45 equiv Et_3N 2.15 equiv	MeCN 22 h 60 °C	 not isolated	 H 75% F 73% Me 52%	**75**
2	 1.0 equiv	 1.4 equiv	$Pd(dba)_2$ (0.3 equiv $(t\text{-}Bu)_3P$ 0.75 equiv Et_3N 20 equiv	THF overnight reflux	 51%	 59%	**76** **77**
3	 1.0 equiv	 1.2 equiv	$Pd_2(dba)_3$ 0.2 equiv $(t\text{-}Bu)_3P$ 0.6 equiv Dicyclohexyl methylamine 1.3 equiv	Dioxane 20 h reflux	 not isolated	 70%	**78**
4			$Pd(OAc)_2$ $AsPh_3$ Bu_3N	DMF 16 h 60 °C	 not isolated	 85%	**82**
5			$Pd(OAc)_2$ $AsPh_3$ Bu_3N	DMF 16 h 60 °C		 99%	**82**
6	 1.0 equiv	 1.0 equiv	$Pd(OAc)_2$ 0.2 equiv $AsPh_3$ 0.4 equiv $n\text{-}Bu_3N$ 1.6 equiv	DMF 36 h 75 °C	 64%	**dxT**  100%	**83** **84**
7	 1.3 equiv	 1.0 equiv	$Pd(OAc)_2$ 0.05 equiv. Ph_3P 0.1 equiv $n\text{-}Bu_3N$ 1.4 equiv	MeCN 24 h 85 °C	 50%	**dyT**  99%	**85**
8	 1.0 equiv	 1.2 equiv	$Pd(dba)_2$ 0.1 equiv $AsPh_3$ 0.2 equiv Bu_3N 1.3 equiv	MeCN 22 h 85 °C	 59%	**dyC**  84%	**85**
9	 1.0 equiv	 1.3 equiv	$Pd(OAc)_2$, 0.4 equiv bppp 0.05 equiv $NaHCO_3$ 3.0 equiv	MeCN 3 h 24 °C	 75%	 94%	**92**

hydroxy ketone derivatives afforded the deoxycytidine *C*-nucleoside mimics in moderate to good yields (52–75%).

The *C*-nucleoside having **R** = H as well as its hydroxy-keto precursor showed no inhibition of proliferation of cancer cells and no protection of human T-lymphocytes against HIV (HIV-1 and HIV-2). The lack of activity of this unnatural deoxycytidine mimic was attributed to the nucleoside's inability to undergo phosphorylation by host cell- and virus-induced kinases.

Triple Helix-Forming Molecules

Intense interest in molecules that can bind sequence specifically via a triple helix motif to mixed purine/pyrimidine sequences in Watson-Crick DNA has prompted the design of the 2-aminoquinazoline and 2-amino-6-fluoroquinazoline *C*-nucleosides (entries 2 and 3, respectively).[76–78]

The synthesis of the 2-aminoquinazoline nucleoside involved coupling of an *unprotected* 2-amino-4-bromo-quinoline to a *protected* ribofuranoid glycal using tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) and tris(tertiarybutyl)amine ($(t\text{-Bu})_3P$)) to afford the Heck product in good yield (51%). Desilylation afforded the 3-keto derivative that was stereoselectively reduced to afford the desired *C*-nucleoside (Table 3, entry 2).[76,77]

In a similar manner, the *unprotected* 2-amino-4-bromo-6-fluoroquinazoline (Table 3, entry 3) also was coupled to a *protected* ribofuranoid glycal using $Pd(dba)_2$ and tris(tertiarybutyl)amine $(t\text{-Bu})_3P$.[78] A mixture of the Heck product and a quinoline-quinoline dimer were obtained. Desilylation afforded the 3-keto derivative in low yield (33%) and stereoselective reduction afforded the desired *C*-nucleoside (Table 3, entry 3).[78]

Each of these *C*-nucleosides were converted to phosphoramidites and incorporated into oligomers. By UV-visible melting experiments it was shown that they form sequence specific intramolecular triplets with A:T base pairs, presumably via Hoogsteen base pairing in the major groove.

Size Expanded Systems

The synthesis of size expanded bases and nucleotides have been inspired by Leonard's early work in which a fused benzo-analogue (Figure 5) of an adenine ribonucleotide was used as a tool in studies of ATP-dependent enzymes.[79–81] Size expanded bases and nucleotides may be useful in biophysical studies of DNA and proteins that react with it. The *C*-nucleosides depicted in Table 3 (entries 4–8) are examples of size expanded nucleosides. The nucleosides in entries 4 and 5 have been designed to form 4 hydrogen bonds[82] with its complement unlike those in entries 6–8 that only can form 3. The nucleosides in entries 6 and 7 have been synthesized as thymidine (dxT[83,84] and dyT,[85] respectively) while that in entry 8 is an of cytidine (dyC[85]).

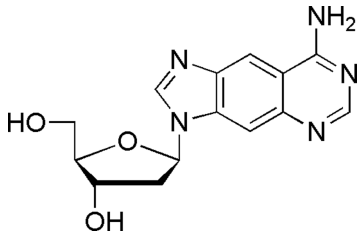


FIGURE 5 A fused benzo-analogue of an adenine ribonucleotide.

(i) *Four hydrogen bond base pair motifs.* The nucleoside in Table 3, entry 4 was prepared by coupling the *protected* 6-iodo-1,8-naphthyridine to a silyl-protected glycal using $Pd(OAc)_2$ and $AsPh_3$ to afford the Heck product which was not isolated. After desilylation, reduction followed by base hydrolysis afforded the free *C*-nucleoside.[82] In the same manner, the 1,8-naphthyridine based *C*-nucleoside in entry 5 also was obtained.[82] These nucleosides were converted to their corresponding phosphoramidites for incorporation into oligonucleotides to investigate their base pairing properties.

The oligonucleotides containing these 1,8-naphthyridine nucleosides were found to form extremely stable duplexes by their base pairing motifs. The specificity of these motifs would make these nucleosides versatile in stabilizing and regulating a variety of DNA structures.

(ii) *Thymidine.* For the dxT[83,84] (Table 3, entry 6) coupling of a dimethyl-*protected* iodoquinazoline to a silyl-*protected* glycal in the presence of $Pd(OAc)_2$ and $AsPh_3$ afforded the Heck product in good yield (64%). An attempt to couple the *unprotected* iodoquinazoline with silyl-protected glycal failed. This may be due to coordination of the *unprotected* iodoquinazoline to palladium as a result of deprotonation of the amide functionality under basic conditions. The dimethyl-protected nucleoside is obtained after desilylation followed by reduction. Acetylation (Ac_2O) followed by acid hydrolysis (AcOH) and then base hydrolysis (ammonia) yielded the dxT.[83,84]

This displayed fluorescence and was incorporated into oligonucleotides as a protected phosphoramidite derivative. It is a key component in a 4-base genetic system designed to form helical paired structures having a diameter greater than that of natural DNA.[83,84]

The synthesis of the dyT[85] (Table 3, entry 7) also has been achieved by coupling a dimethyl-*protected* iodoquinazoline to a silyl-*protected* glycal in the presence of $Pd(OAc)_2$ and PPh_3 and afforded the Heck product in good yield (50%). Desilylation followed by reduction yielded the dimethyl-protected nucleoside. This was then acetylated (Ac_2O) and after acid hydrolysis (AcOH) followed by base hydrolysis (ammonia), the dyT analogue was obtained.[85]

(iii) *A cytidine.* For the dyC[85] (Table 3, entry 8), an isobutyramide-protected quinazoline was coupled to a silyl-protected glycal using the same coupling conditions as those used for dyT. The Heck product was obtained in good yield (59%) and after desilylation, reduction yielded the dyC.

The dyT and dyC nucleosides also display fluorescence and readily were incorporated into oligonucleotides, each as a protected phosphoramidite derivative. These. i) stack more favorably than their natural counterparts; ii) form equally stable base-pairs with their natural partners and; iii) also are selective for their Watson-Crick complementary partners.

A Photophysical Probe

By studying the local dynamics of the DNA double helix, information about the flexibility and structure of oligonucleotides relevant to its function can be obtained.[86–88] Many features observed for both DNA and RNA are sequence-dependent and the time-dependent description of oligonucleotide conformation is of significance in this regard.[89,90] Studies on the dynamic properties of the interior of the DNA duplex, by measuring Stokes shifts of intercalated dyes, was reported by Murphy and Berg.[91] The availability of a larger variety of suitable photophysical probes would certainly increase studies in this area. A large Stokes shift, characteristic of the coumarin nucleus, makes it ideal for studies in solvation dynamics. As a result, the coumarin *C*-nucleoside depicted in entry 9 was synthesized as a photophysical probe designed for use in studies of ultrafast DNA dynamics.[92]

Initial experiments to couple the iodocoumarin to the silyl-*protected* glycal in the presence of Pd failed under a variety of conditions. As a result: i) the *more reactive* triflate derivative of the coumarin was prepared; ii) the *chelating* phosphine 1,3-(diphenylphosphino)propane (dppp) was introduced and; iii) the *bulky* t-$BuPh_2Si$ group was replaced with the *less bulky* t-$BuMe_2Si$ group in the glycal. Coupling of the triflate-coumarin to the silyl-*protected* glycal afforded the Heck product in low yield. The sequential addition of aliquots of $Pd(OAc)_2$ to the reaction, as it progressed, improved the yield to 79%. Subsequent addition of fluoride ion produced the hydroxy-ketone which was stereoselectively reduced to the desired C-glycoside.[92]

HECK COUPLING OF *C*-NUCLEOSIDES

From the data in Table 1 (entry 7) and Table 3 (entry 3) it is evident that coupling is favored at the iodo moiety in the presence of either chloro or fluoro moieties since in both entries the anticipated Heck products were observed.

The excellent yield (90%) observed for the Heck product in Table 1, entry 8 is attributed to the utilization of the bidentate ligand bppp. The bidentate ligand, bppp, has been reported to be, in some cases, much more effective in the Heck reaction than monodentate ligands such as PPh_3.[93]

A rather low yield (36%) for the Heck product was reported for the *C*-nucleoside in Table 1, entry 9 when the reaction was conducted in MeCN. A change of solvent to DMF, use of 0.2 equivalents of $Pd(dba)_2$ (instead of 0.05 equivalents), 1.5 equivalents of glycal (instead of 1.2 equivalents) may afford a higher yield.

The result of the Heck coupling reaction for Table 2, entry 7 is rather extraordinary considering that both faces on the glycal are open to attack by the iodinated heterocycle and therefore both α- and β-anomers are expected. The excellent yield observed for the Heck product in Table 2, entry 8 most likely is due to the large excess of glycal (5 equivalents) employed in the reaction.

The sequential addition of aliquots of $Pd(OAc)_2$ to the coupling reaction mixture (Table 3, entry 9) is rather uncommon. In this case the possibility exists that the catalyst may very well have become poisoned as a result of impurities present in the substrates, reagents or solvent. Alternatively, the $Pd(OAc)_2$ used in this reaction may have decomposed, hence, the need for the sequential addition of aliquots of palladium.

Several other observations have been made for the Heck coupling reactions in Tables 1–3 and are discussed below:

i) Palladium and ligand combinations: The combination of $Pd(OAc)_2$-$AsPh_3$ is the most common for coupling the aglycons to the glycal. The less common combinations of $Pd(dba)_2$-bppp, $Pd(dba)_2$-$(C_6F_5)_3P$ (Table 1, entries 8 and 9, respectively), $Pd(dba)_2$-$(t\text{-}Bu)_3P$ (Table 3, entries 2 and 3) and $Pd(OAc)_2$-bppp (Table 3, entry 9) also were successfully employed.
ii) The salt: Only in Table 2, entry 8, has a salt, Ag_2CO_3, been used in the coupling reaction. It is uncertain whether its presence may have contributed to the excellent yield (98%) obtained for this coupling reaction since the yield of the reaction in its absence was not reported.
iii) The solvent, base, and temperature: The solvents DMF and MeCN are most commonly used, except for Table 3 where THF (entry 2) and dioxane (entry 3) were used. A variety of organic bases such as tributylamine (Bu_3N), triethylamine (Et_3N), and diisopropylethylamine ($i\text{-}Pr_2EtN$) were employed. Dicyclohexylmethylamine (Table 3, entry 3) and sodium bicarbonate ($NaHCO_3$, Table 3, entry 9) are not commonly used. Temperatures for conducting these reactions range from 45°C to 85°C. One exception is Table 3 (entry 9) where the

reaction was conducted at 24°C. The choice of solvent and temperature is, however, dependent upon the solubility of the aglycone.

iv) The glycal: The furanoid glycal can be protected with a silyl group at the 3-position alone (Table 1, entry 1) or at both the 3- and 5-positions (Table 1, entries 5–7); Table 2, entry 1, and Table 3, entry 1). Since both of these glycals are stereoselective, the β-anomer is obtained as the major Heck product in the coupling reaction. When the 3-deoxy furanoid glycals are employed, the Heck product is obtained as diastereomers (Table 1, entries 2 and 3). The unprotected glycal (Table 2, entry 7) and the 3,5-dideoxy furanoid glycal (Table 2, entry 8) also were successfully employed in these reactions.

v) The aglycone: From the data, it is apparent that protection of aglycone carbonyls (Table 1, entries 1 and 6) and exocyclic amines (Table 1, entries 4, 7, 10, and 11 and Table 3, entries 7 and 8) capable of inactivating the catalyst is not necessary. In other aglycones (Table 1, entries 2, 3, 5, 8, and 9; Table 2, entry 1, and Table 3, entries 4–8), these functionalities had to be protected prior to coupling.

Protection of aglycon carbonyls was achieved by methylation (Table 1, entries 2 and 3; Table 2, entry 4; and Table 3, entries 6 and 7), benzylation (Table 1, entry 8) and by tetrahydropyranylation (Table 2, entries 1–3) of the carbonyl oxygen. Demethylation (Table 3, entries 6 and 7) of the nucleoside was accomplished by reacting with acetic acid and sodium iodide at 60°C and debenzylation (Table 1, entry 8) by catalytic hydrogenation (10% Pd-C). Removal of the tetrahydropyranyl groups were achieved by reacting with pyridinium *p*-toluenesulfonate in methanol and water at 50°C (Table 2, entry 1).

Protection of exocyclic amines (primary amines) were accomplished through acylation (Table 1, entries 5 and 9; and Table 2, entry 5) by reacting with isobutyloxycarbonyl chloride (Table 2, entry 6), dimethylformamide dimethylacetal (Table 3, entry 4), and dibutylformamide dimethylacetal (Table 3, entry 5).

vi) Palladium source and ligand stoichiometry: The stoichiometry of the reactants is crucial when conducting the Heck coupling reaction. From the data in Tables 1–3, it can be seen that generally, 0.1 equivalents of the palladium source and 0.2 equivalents of the ligand was used for generating the catalyst in situ particularly when the ligand employed was $AsPh_3$, $P(C_6F_5)_3$, and PPh_3. In some cases (Table 1, entries 4 and 10, Table 2, entry 7) less than 0.1 equivalents of the palladium source and less than 0.2 equivalents of the ligand was used. In other cases (Table 1, entries 5 and 6; Table 2, entry 8; and Table 3, entries 1–3) more than 0.1 equivalents of the palladium source and more than 0.2 equivalents of the ligand have been used. The ratio of the palladium source to ligand is 1:2 for these reactions. For entry 9 (Table 3), 0.4 equivalents of $Pd(OAc)_2$ was used and only 0.05 equivalents

of the bidentate ligand, bppp, in a ratio of 8:1 of palladium source to ligand.

vii) Aglycone and glycal stoichiometry: When looking at the stoichiometry of the aglycon and the glycal for these reactions, the glycal was often used in excess, 1.0–1.5 equivalents often are used. There are, however, reactions where larger quantities of the glycal was used such as in entry 9 (Table 3) (3.0 equivalents), entry 8 (Table 2) (5.0 equivalents), entry 1 (Table 2) (15.0 equivalents), and entry 5 (Table 2) (20.0 equivalents). In some reactions, such as entries 5, 6, and 8 (Table 1) and Entry 7 (Table 3), the aglycone was used in excess.

SUMMARY

From the data in Tables 1–3 it is evident that the palladium-ligand combination of $Pd(OAc)_2$-$AsPh_3$ is generally a good combination for coupling the glycal to a variety of aglycons. When Heck coupling using this combination is unsuccessful other palladium-ligand combinations have to be explored.

When a chloro or a fluoro moiety is present on the aglycone having an iodo moiety, Heck coupling is favored at the iodo moiety.

The use of a bidentate ligand, such as bppp, can accelerate the Heck coupling reaction and result in a higher yield of the product.

It is possible, using the appropriate ligand, to obtain the β–anomer as the sole product even when unprotected glycal is employed in the reaction. In some reactions the aglycon does not require a protecting group while in other reactions, it does. It is, however, not apparent when examining a structure whether the Heck coupling will be successful with or without a protecting group. Heck couplings that were successful without protectings groups have had electron-withdrawing groups other than the iodo moiety on the aglycon.

CONCLUSION

It is not possible from the inspection of Tables 1–3 to infer general rules that might predict when a Heck coupling will be successful with a particular structure or not. It is also not possible to predict whether a Heck coupling will be successful or not with an unprotected aglycon having carbonyl and amine (exocyclic or aromatic) functionalities. Some regularities are observed, but these have exceptions. For example, Heck couplings have not proven particularly successful when the heterocycle bears an unprotected primary amine adjacent to the site of coupling. An example of particular interest is the attempt in our laboratory to couple the 2,4-diamino-5-iodo-pyrmidine heterocycle.

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