Palladium-Assisted Routes to Nucleosides

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I. Introduction

Study of the biological activity of nucleosides and their phosphorylated derivatives has been a funda-

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Luigi A. Agrofoglio, born in Antibes, France (1965), received his B.S. (1987) and Ph.D. (1993) degrees in chemistry from the University of Nice Sophia-Antipolis (France), working with Professor R. Condom and Professor R. Guedj on the synthesis of carbocyclic analogues of nucleosides. Dr. Agrofoglio has held postdoctoral appointments at the University of Alabama at Birmingham (U.S.A.), working with Professor J.-P. Sommadossi, as well as at the University of Georgia at Athens (U.S.A.) with Professor C. K. Chu. He joined the Institute of Organic and Analytical Chemistry (ICOA), a CNRS research laboratory associated with the University of Orléans (France), as Assistant Professor in 1995; he assumed his current position as Associate Professor at the same institution in 1999. At present, he is the leader of the "Synthesis and Bioanalysis of Inhibitors of Viral Enzymes" group in the same institution. His current research focuses on organic reactions applied to the antiviral chemistry (HIV, HBV, HCV, HCMV) of new nucleosides as well as the development of new bioanalysis for intracellular quantification of HIV drugs. He is also involved in several projects in connection with pharmaceutical companies.

Isabelle Gillaizeau, born in Nantes, France (1970), obtained her Ph.D. in 1997 from the University of René Descartes (Paris VI, France) under the direction of Professor H.-P. Husson and Dr. J. Royer, for the asymmetric synthesis of azabicyclo[*n*.2.1]alkanes according to the CN(*R*,*S*) method. She conducted postdoctoral studies first at the University College of London (1998) with Professor W. B. Motherwell, and then at Ecole Polytechnique (1999) in Palaiseau (Paris) with Professor S. Z. Zard and at the University of Nantes (France) (1999–2000) with Dr. F. Odobel. In September 2000, she was appointed Assistant Professor in the group of Dr. L. A. Agrofoglio at the Institute of Organic and Analytical Chemistry (Orléans, France), where she works in the field of heterocyclic and nucleoside chemistry.

mental and fruitful field of research since the 1940s and 1950s.[1] It was then that the role of nucleic acids in cells was established, ultimately resulting in the identification of the double-helix structure of DNA and the explanation of the genetic code. As the metabolic processes by which these materials were processed in vivo became understood, so the investigation of close analogues of the components of nucleic acids grew, with the expectation that they might interfere in some way with the natural pathways and perhaps have utility as drugs. Early work focused on traditional nucleoside analogues in which either a modified base was linked to one or other of the naturally occurring sugars, or the sugar itself was altered. Some of the compounds resulting from this work were, indeed, shown to possess antimetabolic properties, but it became apparent that their usefulness was severely limited by instability, poor selectivity, and consequent toxicity. Since the discovery of the first successful antiviral drug, acyclovir (**1**),[2] in 1974, interest has diversified toward compounds in which the heterocycle and sugar components of the nucleoside have departed significantly from the natural form. Some of the compounds made exemplify structures containing unusual substituents, such as ribavirin (**2**), AZT (**3**), ddC (**4**), BVDU (**5**), and showdomycin (**6**) (Figure 1), and these novel types of nucleoside have been variously found to have anticancer, antiviral, and antibacterial activity.

Yoshio Saito, born in Niigita, Japan (1973), received his Ph.D. degree (2001) in organic and bio-organic chemistry from the Keio University (Japan), working with Professor K. Umezawa. Dr. Saito held a two-year postdoctoral fellowship in the group of Dr. L. A. Agrofoglio at the Institute of Organic and Analytical Chemistry (Orléans, France), for a project concerning the synthesis and quantitation of anti-HIV nucleosides and their phosphorylated metabolites. In September 2002, he moved back to the Keio University (Japan) as a postdoctoral fellow, working with Professor I. Saito on oligonucleotides.

The intense search for clinically useful nucleoside derivatives has resulted in a wealth of new approaches for their synthesis. One of the more useful approaches has involved the use of palladium-catalyzed addition and substitution reactions, a field

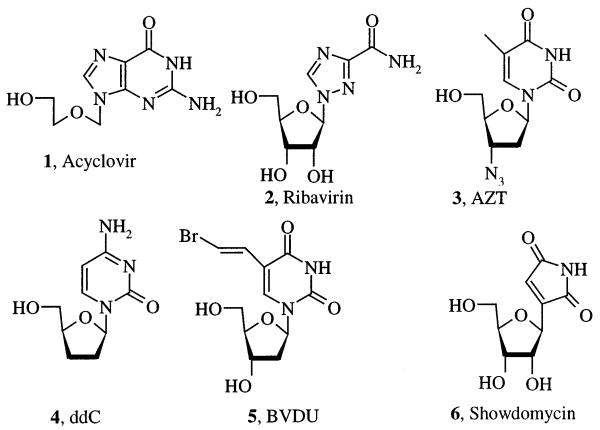


Figure 1. Structural diversity of antiviral nucleosides.

that has developed rapidly in recent years. Although the Heck reaction was discovered in the late 1960s, and initially received much attention as a new method for C−C bond formation, it was not until the 1980s that its full potential began to be realized. The Heck reaction[3] consists of the coupling of an aryl iodide or arylmercury halide with an activated olefin in the presence of an organopalladium complex, and it was first utilized for the synthesis of nucleoside analogues by Bergstrom et al., who published a series of papers in which coupling reactions of nucleosides with allylic halides,[4] olefinic compounds,[5] and allylic chlorides, alcohols, and acetates[6] were described. Since then, the Heck reaction has been widely used for the synthesis of nucleoside analogues, including those functionalized at the 5-position of the pyrimidine ring or at the C-2 or C-8 position of the purine ring; for example, 5-acetoxymercury nucleosides in the presence of Li_2PdCl_4 were used for the synthesis of C-5-biotinylated nucleosides and for 5-vinylic carbocyclic analogues.[7] More recently, in 1996,[8a] zincated nucleic acid base derivatives were described which undergo efficient palladium-catalyzed cross-coupling reactions (the so-called Negishi reaction).[8b] Palladium-catalyzed cross-couplings have been found to occur with a variety of organometallic and related reagents including organostannanes (Stille), organozinc (Negishi), organosilicon (Hiyama), and organoboron reagents (Suzuki). In the 1990s, the Heck reaction was used for the stereospecific synthesis of *C*-nucleosides. In particular, furan derivatives and 2,4-(*R*,*R*′)-5-iodopyrimidine undergo palladium-mediated coupling by two different, complementary procedures to form enantiomeric pairs of (2′,3′-dideoxy-2′,3′-didehydrofuranosyl)pyrimidine *C*-nucleosides.[9] These reactions, catalyzed by palladium(0) species, were found to be both regio- and stereospecific. More recently, the palladium(0)-catalyzed allylation of nucleophiles, the so-called Tsuji−Trost reaction,[10] has been found to be a powerful and versatile procedure, which has gained high recognition due to its broad scope and straightforward experimental conditions. In the case of carbanucleosides, or carbocyclic analogues of nucleosides, in which the oxygen of the sugar moiety has been replaced by a methylene group, a wide variety of starting materials has been used for the allylation of purines and pyrimidines under Pd(0) catalysis. Trost et al. reported in 1988 the first example of direct substitution of a heterocyclic base on a carbocycle through a palladium-catalyzed substitution, in which a racemic synthesis of aristeromycin was achieved.[11] In the case of sugar derivatives, less information is available, but another application of a Pd-catalyzed reaction that might be used in nucleoside chemistry is the cyclization of the γ-oxoallenes 4,5-hexadienal and 3-*tert*-butyldimethylsilyloxy-4,5-hexadienal, which undergo palladium(II)-mediated acetalization−cyclization−methoxycarbonylation[12] in the presence of acid and water scavengers. This transformation could be used as the means for synthesizing nucleoside analogues having a branched, extended, and difunctionalized 5′-side chain. Yet another, as described by Tsuji and Yamakawa,[13] is an interesting radical and palladium-catalyzed deoxygenation of the allylic alcohol system in the sugar moiety of carbocyclic nucleosides. Some of the most common palladium-assisted modifications on nucleosides are summarized in Figure 2.

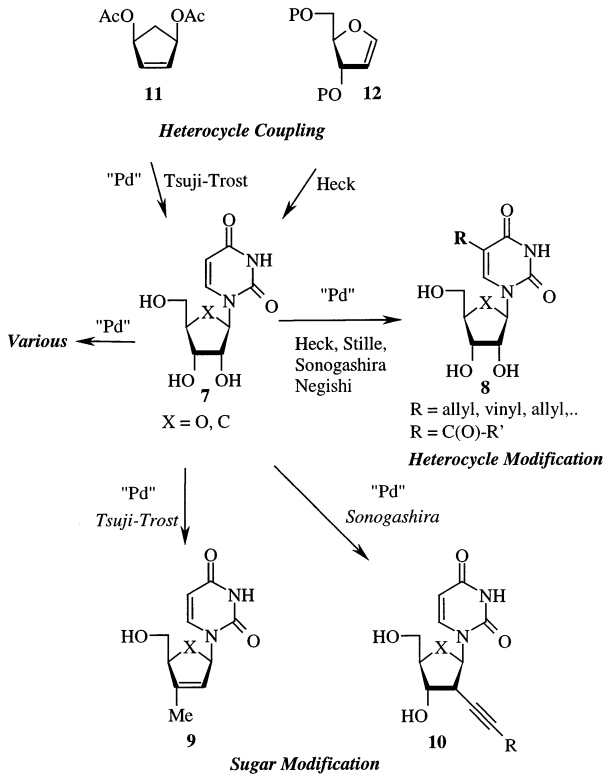


Figure 2. Main palladium-assisted modifications on nucleosides.

Experience has shown that the essential structural features of nucleosides, which must be retained if biological activity is being sought, are the ability of the base to engage in base pairing with its complementary partner in DNA and the presence of a 5′-hydroxyl group (or equivalent), which is capable of phosphorylation. It is clear, therefore, that there is more scope for variation in the sugar moiety, and it is this which has been most exploited in the search for novel compounds. Finally, our objective in this review is to draw together all of this material in a form which is easily consulted and at the same time guides the reader into the primary literature on the subject. The coverage is primarily from the point of view of the organic and medicinal chemist. It is our intention to describe in detail those strategies that have been employed to make nucleosides, including those with unusual substituents and substructures, focusing especially on the use of palladium cross-coupling reactions and other palladium-assisted routes. Modifications of the heterocyclic base alone, and applications to peptide nucleic acids and to oligonucleotides, are not within the scope of this review. The literature has been surveyed through June 2002. Applications of metal−complex catalysts in nucleoside synthesis have previously been partially reviewed.[14]

II. Palladium Compounds, Complexes, and Ligands

A. Palladium Compounds and Complexes

Organic synthesis generally makes use of palladium compounds in either the Pd(0) or Pd(II) oxidation state. Palladium(II) salts may be used either as stoichiometric reagents or as catalysts, while palladium(0) complexes are used only as catalysts.

1. Palladium(II) Compounds

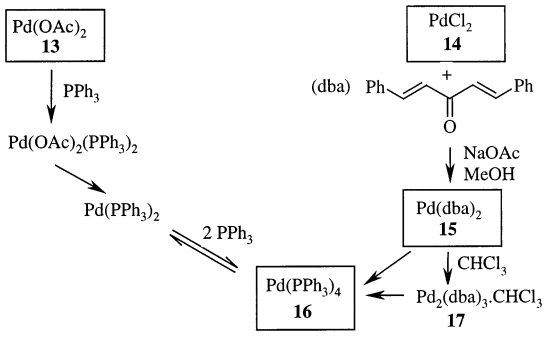
Palladium(II) compounds such as $Pd(OAc)_2$ (**13**) and $PdCl_2$ (**14**) are commercially available and widely used. Palladium(II) chloride is stable and exists in an oligomeric form, $[PdCl_2]_n$, which has low solubility in water and organic solvents. However, this oligomeric structure can be broken in the presence of ligands to form $PdCl_2L_2$ complexes that are soluble in organic solvents. For example, treatment of $[PdCl_2]_n$ with triphenylphosphine gives the soluble yellow complex, $PdCl_2(PPh_3)_2$, that can also be used as a precursor of Pd(0) complexes if excess phosphine is present (see below). Complexes with organic nitriles such as $PdCl_2(RCN)_2$ (R = Me, Ph) are also commonly used in palladium(II)-catalyzed reactions.

$Pd(OAc)_2$ is easily reduced to Pd(0) complexes in situ in the presence of phosphine ligands with reducing agents, such as metal hydrides ($NaBH_4$, $LiAlH_4$), alkenes, alcohols, and tertiary amines, to form $Pd(0)(R_3P)_n$. The phosphine itself may act as the reducing agent. For example, when $Pd(OAc)_2$ is treated with the appropriate quantity of PPh_3, Pd(0) species and phosphine oxide are formed.

2. Palladium(0) Complexes

Two Pd(0) complexes are commercially available (Scheme 1).

Scheme 1



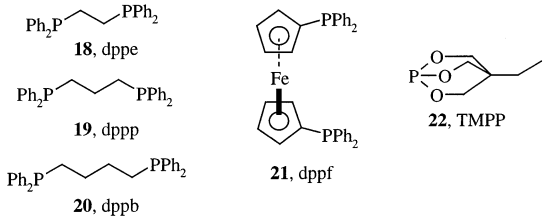
(a) Tetrakis(triphenylphosphine)palladium(0) ($Pd(Ph_3P)_4$, **16**) is light-sensitive, unstable in air, yellowish-green, and a coordinately saturated Pd(0) complex. Sometimes $Pd(Ph_3P)_4$ is less reactive as a catalyst because it has too many ligands to allow the coordination of some reactants. In fact, when the palladium bears bulky phosphine ligands, such as PPh_3, the energy necessary for the formation of the transition state increases due to steric congestion around the central, reactive palladium atom.

(b) Tris(dibenzylideneacetone)dipalladium ($Pd_2dba_3 \cdot CHCl_3$, **17**; dba = dibenzylideneacetone) is also commercially available. The palladium atom is coordinated to the olefinic bonds of dba and may be converted into PdL_n (where L is usually a phosphine ligand) by a ligand-exchange reaction in solution. Pd_2dba_3 is obtained by recrystallization from $CHCl_3$, is stable in air, and even without the phosphine ligands has catalytic properties similar to those of $Pd(Ph_3P)_4$.

B. Ligands

1. Achiral Ligands

Phosphines have been widely used as ligands in palladium catalysis.[15] The most commonly used ligand is PPh_3, but an $AsPh_3$ or tri-2-furylphosphine ($(2\text{-furyl})_3P$) ligand has been shown to increase the rate of the transmetalation step, for instance, in a Sonogashira-type reaction. $P(o\text{-tol})_3$ is also a suitable ligand for cross-coupling reactions. Chelating bidentate phosphine ligands such as dppe (**18**), dppp (**19**), and dppb (**20**) (Figure 3) also play important



dppe = 1,2-bis(diphenylphosphino-ethane),
dppb = 1,4-bis(diphenylphosphino-butane),
dppf = 1,1'-bis(diphenylphosphinoferrocene),
dppp = 1,3-bis(diphenylphosphino-propane)
TMPP = trimethylolpropane phosphite

Figure 3. Bidentate achiral ligands.

roles in some reactions. The type of diphosphine used may have widely variable effects on the reactions in which they are used, although these effects are not yet fully understood.[16,17] One of the steric parameters for diphosphines is the "bite angle" induced by the ligand,[18] which can have significant influence, for example, upon the regioselectivity of substitution in purines. The use of a bidentate phosphine ligand in conjunction with Pd_2dba_3 markedly increases the N-9/N-7 isomer ratio for allylation.[19] The bidentate phosphine, dppf (**21**), shows its own characteristic activity. This ligand was designed partly with the aim of reducing steric congestion in the transition state and partly because phosphites are known to be good π-acceptor ligands.[20] Thus, triisopropyl phosphite ($Pd[(i\text{-}C_3H_7O)_3P]_4$) can be prepared from $Pd_2dba_3 \cdot CHCl_3$ and 4 equiv of $(i\text{-}C_3H_7O)_3P$ in tetrahydrofuran (THF). Other phosphates, such as $P(OMe)_3$ and $P(OPh)_3$, have also been used. The cyclic phosphite, TMPP (**22**), which has a small cone angle and small steric hindrance, shows high catalytic activity in some reactions.

2. Chiral Ligands

Chiral phosphines are ligands that are pre-eminent in asymmetric catalysis, and among them, the most frequently employed are those possessing the bi-

naphthyl scaffold.[21,22] Despite the great success that the BINAP-type ligands **23** have enjoyed over the years, less satisfactory or even poor results have been reported for their application in palladium(0)-catalyzed allylic substitutions, especially desymmetrization of meso-compounds.[10,23,24] Recently, the bidentate phosphine ligands **24**, derived from C_2-symmetric diamines, were shown by Trost and Van Vranken[10a] to be very efficient in a number of examples, due to their unique, dome-type architecture, which controls the stereochemistry of the reaction primarily by steric effects (Figure 4).

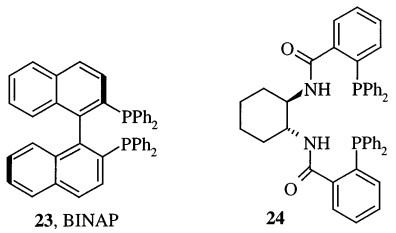


Figure 4. Bidentate chiral ligands.

III. Survey of the Principal Palladium Cross-Coupling Reactions

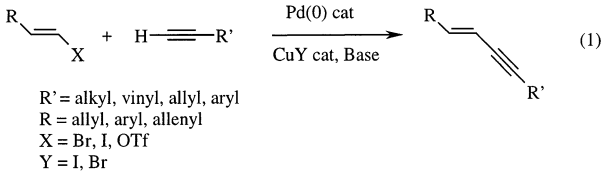
The potential of nucleoside analogues as therapeutic agents has provided much of the impetus for developing new approaches to their synthesis. Transition metal-catalyzed carbon−carbon bond formation is an important tool for organic chemists and a challenging area of research. Palladium catalysts with tailored phosphine ligands have been applied successfully to many instances of cross-coupling reactions. The following are the most common ones found in the chemistry of nucleosides (Table 1).

Table 1. Different Transformations of Organopalladated Derivatives Found in Nucleoside Chemistry

Reaction	*Trans*formation	Reaction's Name
RPdX + ⟶ R PdX	Insertion (carbopalladation)	Heck
RPdX + CO ⟶ O, R, PdX	Insertion	carbonylation
RPdX + RM ⟶ R-R'	*Trans*metallation and cross-coupling	M = Sn Stille M = B Suzuki M = Zn Neghishi M = Si Hiyama
RPdX + H—≡—R' (CuI) ⟶ R—≡—R'	*Trans*metallation Cu -> Pd	Sonogashira
X (Pd(0)) ⟶ PdX, Nu- ⟶ Nu	π-allyl complexes	Tsuji-Trost

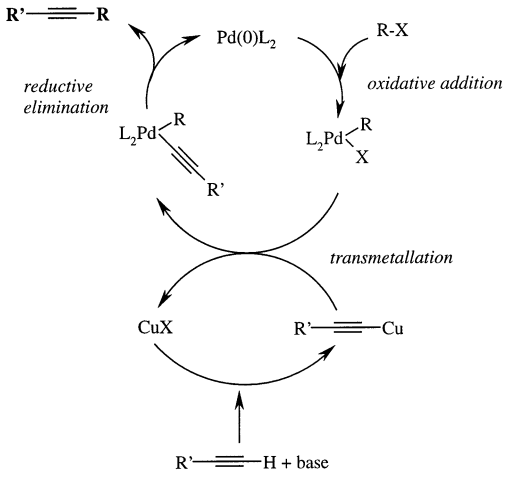
A. Sonogashira Reaction

Direct introduction of sp^2 carbon into alkynes, otherwise quite a tricky procedure, can be done easily using Pd catalysts. Terminal alkynes undergo Pd-catalyzed reactions, in the presence of CuI as a cocatalyst, with organic halides or vinyl triflate, whereby substitution of the alkynic hydrogen forms disubstituted alkynes. This reaction is known as the Sonogashira coupling (eq 1).[25,26]



Two methods of coupling are known: the direct coupling of terminal alkynes and the coupling of metal acetylides. The direct coupling reaction is catalyzed by palladium phosphine catalyst in the presence of amines.[27] The addition of CuI (3−5% mol) as a cocatalyst gives better results, because CuI activates alkynes by forming a copper acetylide, which is more reactive and undergoes transmetalation with $RPd(0)L_2$ to form the alkynyl−Pd−R species. Reductive elimination is the final step (Scheme 2).[28]

Scheme 2

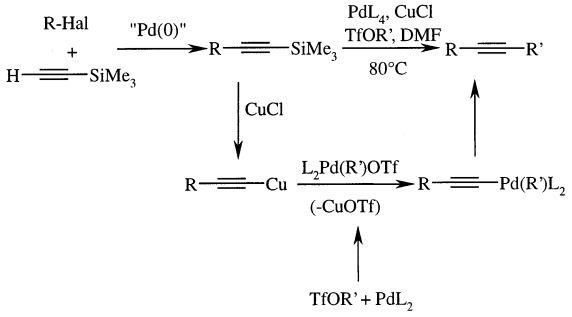


Coupling without CuI gives arylalkynes or enynes in high yields when the reaction is carried out in piperidine or pyrrolidine, but generally poor results are obtained when Et_3N, Pr_2NH, Et_2NH, or morpholine is used.[29] Solvent also has been reported to be an important determinant for successful coupling of terminal alkynes with iodonucleosides.[30] A potential problem with the palladium-catalyzed coupling of an alkyne with an organic electrophile is the production of the homocoupled alkyne in preference to the cross-coupled product. A significant amount of homocoupled alkyne has been reported when the oxidative addition of the aryl halide species is slow (such as when the electrophile is an aryl bromide or electron-rich aryl iodide).[31] The use of the catalytic system $Pd_2dba_3/AsPh_3$ has been reported to increase the rate of the transmetalation step.[32] Finally, a mole ratio of 2:1 copper to palladium has been shown to offer the best coupling conditions for alkynes, as the production of side products is minimized. The general procedure for the Sonogashira reaction involves $PdCl_2(PPh_3)_2$, CuI, base, and THF at 25 °C. Numer-

ous applications of the Sonogashira cross-coupling have been reported.

The synthesis of disubstituted alkynes is generally achieved from a trimethylsilylacetylene and is known as the "sila-Sonogashira−Hagihara" reaction (Scheme 3).

Scheme 3



B. Stille Reaction

The Stille coupling, or Migita−Kosugi−Stille coupling,[33,34] involves organotin compounds (organostannanes). Aryl-, alkenyl-, and alkylstannanes are used for coupling with aryl and alkenyl halides, pseudo-halides, and arenediazonium salts (eq 2).

$$R_3Sn{-}R' + R''{-}X \xrightarrow{\text{Pd(0) cat.}} R'{-}R'' + R_3Sn{-}X \quad (2)$$

R′ = alkyl, vinyl, allyl, aryl

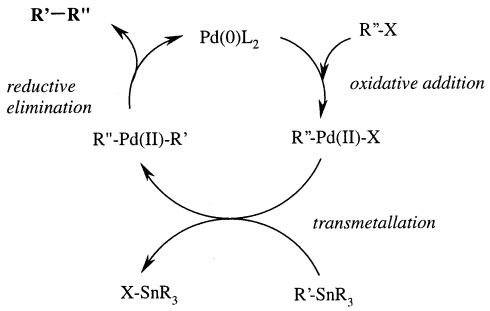
R″ = vinyl, acyl, aryl, allyl

R = alkyl, aryl

X = Br, I, OTf, Cl, ...

The leaving group X is generally either halide or triflate. Aryl bromides are generally preferred to aryl iodides for Pd-catalyzed allylation with allyltributyltin.[35] Reactions involving a vinyl triflate and various organotins were studied in detail by Scott and Stille,[36] who found that the reactions often require addition of an inorganic salt, usually lithium chloride, though its purpose has not been fully rationalized.[37] Generally, only one of the four groups of the organostannanes enters into the coupling reaction. It has been reported that a single alkyl group has the lowest transfer rate; thus, unsymmetrical organotin reagents containing three simple alkyl groups (Me, Bu) are chosen, and the fourth group (alkynyl, alkenyl, aryl, allyl, ...) is then the preferred one to be transferred (Scheme 4).

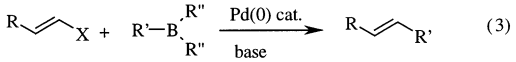
Scheme 4



Catalysts used in the Stille reaction are tetrakis(triphenylphosphine)palladium ($(PPh_3)_4Pd$) as palladium(0) catalyst and benzyl bis(triphenylphosphine)-chloropalladium ($BnPdCl(PPh_3)_2$) as palladium(II) catalyst. Usually, PPh_3 is used as a ligand, but the use of other ligands, for example, tri-2-furylphosphine and triphenylarsine, has been reported to increase the rate of the organostannane reaction.[32a] Other catalysts prepared in situ from $LiPdCl_3$, RX, and $R'SnMe_3$ are active in promoting cross-coupling at room temperature.[38] If neither of the two above catalysts works, then $PdCl_2(PPh_3)_2$, $PdCl_2(PhCN)_2$, $PdCl_2(MeCN)_2$, $Pd(dba)_2$, or Pd_2dba_3 could offer an alternative. Polar solvents are normally used, such as *N*-methylpyrrolidinone (NMP), *N*,*N*-dimethylformamide (DMF), and dimethylsulfoxide (DMSO), and reflux temperatures are preferred. The addition of CuI as a cocatalyst has been reported to favor transmetalation, which is the rate-limiting step, and is recommended in case of bulky organotin derivatives. One of the advantages of the Stille reaction is the great versatility of functional groups tolerated, as well as the stability and accessibility of the required organotin derivatives.

C. Suzuki–Miyaura Reaction

The Suzuki−Miyaura reaction[39,40,41] consists of the coupling of organoboron compounds with aryl, alkenyl, and alkynyl halides (eq 3). This catalyzed

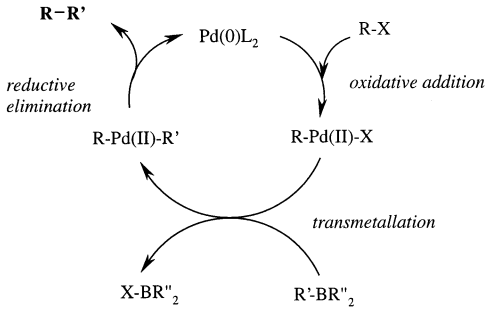


(3)

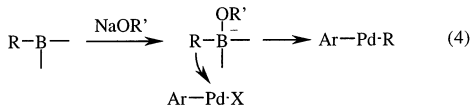
R = vinyl, aryl
R' = vinyl, aryl, alkyl
R" = OH, OR, alkyl
X = I, OTf, Br, Cl

reaction (Scheme 5) has numerous synthetic applications in medicinal chemistry, as boron derivatives are

Scheme 5



nontoxic, easily prepared, and stable. The reaction proceeds via transmetalation in the necessary presence of a base, as described in eq 4. The base activates the B−C bond by attack at the boron atom, rendering the carbon center more nucleophilic.



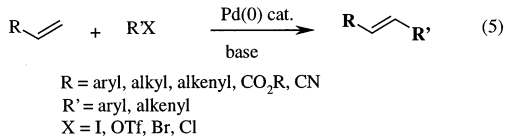
(4)

The formation of Ar−Pd−OR′ (in which OR′ = base) facilitates the transmetalation with organo-

boranes.[41b,42] The rate-limiting step of the overall process depends on the nature of the X group and is transmetalation when X = I but tends toward oxidative addition when X = Br. A standard procedure involves $Pd(PPh_3)_4$, Na_2CO_3 (KOH, NaOH, Tl_2CO_3), and DMF (DME, THF, acetone, or benzene) at 60−80 °C for 12 h.

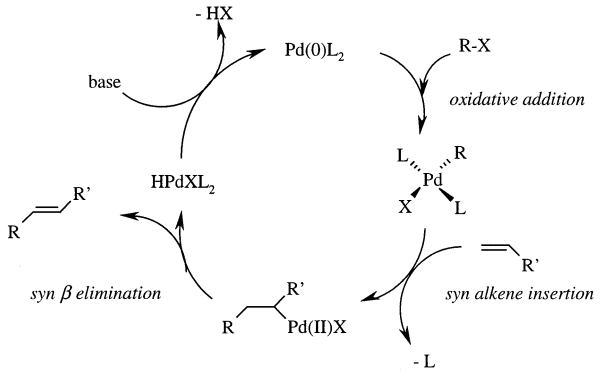
D. Heck Reaction

The Heck reaction,[3a,b] discovered at the same time by the group of Mizoroki et al.[43] and Julia and Duteil,[44] consists of the coupling of an aryl or vinyl halide with an olefin, according to eq 5. Many detailed reviews of the reaction are available.[16,17,45]

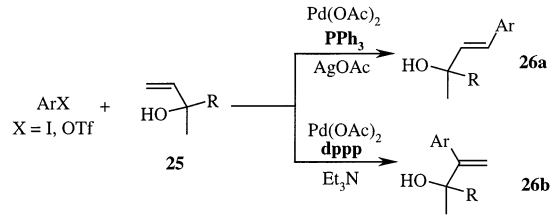


The mechanism[46] of the Heck reaction can be described as shown in Scheme 6. The general procedure involves up to 1 mol % of catalyst, 2 equiv of triarylphosphine (to stabilize the arylpalladated intermediates, and a base (Et_3N, $NaHCO_3$) to trap the released HX and regenerate the catalyst. The rate-limiting step is the oxidative addition of RX that depends on the nature of X (ArI > ArOTf > ArBr ≫ArCl). The temperature range is 70−120 °C, and the most common medium for the reaction is one of the aprotic polar solvents, such as hexamethylphosphoric triamide (HMPA), DMF, CH_3CN, and NMP. The Heck reaction is also reported to be highly regioselective, as shown in Scheme 7.[46b] Depending upon which ligand is used, β-regioisomers **26a** or α-regioisomers **26b** may be selectively formed.

Scheme 6



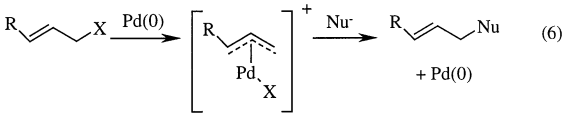
Scheme 7



E. Tsuji–Trost Reaction for Allylic Alkylation

1. Regio- and Stereoselectivity of the Reaction

The palladium(0)-catalyzed allylation of nucleophiles is a powerful method which has gained recognition due to its regio- and stereoselectivity and broad scope.[23a,47] The area is developing rapidly and has been widely used in nucleoside chemistry, both for the introduction of the heterocycle into the sugar moiety and for the introduction of the 5′-hydroxyl precursor group of the sugar itself. The catalytic cycle requires the initial formation of a cationic η^3-allylpalladium(II) complex, which can be attacked by nucleophiles (soft and hard) at its less hindered site. Allylic esters and carbonates have been employed mainly as substrates for the catalytic reaction, but many other types of allylic compound (embracing carbamate, oxirane, phenyl ether, alcohol, chloride, nitro, sulfone, phosphate, amine, ammonium salt, vinylcyclopropane) are known to react with Pd(0) and to form the cationic η^3-allylpalladium(II) complex (eq 6). The oxidative addition of allylic acetates to Pd(0)

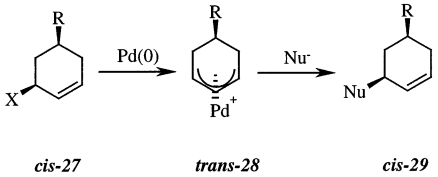


X = OAc, OCO_2R, OCONHR, OPh, OH
X = $OP(O)(OR)_2$, Cl, NO_2, SO_2R, NR_2
X = oxirane, cyclopropane

is reversible and must be carried out in the presence of base, but neutral conditions are required for allylic carbonates, carbamates,[48] aryl ethers,[49] and vinyl epoxides.[50]

The stereochemistry of the Pd-catalyzed allylation of nucleophiles has been widely studied[51] and seems to depend on the nucleophile used.[52] The first step is the formation of the cationic η^3-allylpalladium(II) complex, which occurs with inversion of configuration (from *cis*-**27** to *trans*-**28**). Many common soft nucleophiles (e.g., malonates, β-ketoesters, amines) then attack the cationic palladium intermediate with a second inversion of configuration, affording the final compound (from *trans*-**28** to *cis*-**29**) with overall retention of configuration (Scheme 8).

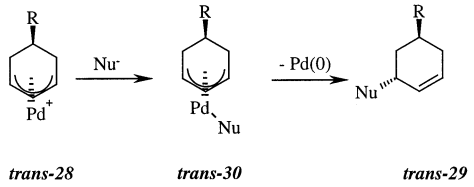
Scheme 8



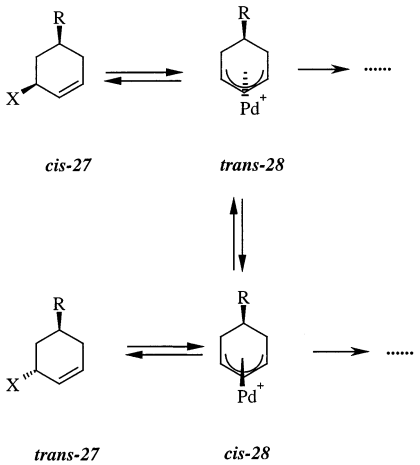
In the case of hard nucleophiles (such as organometallic derivatives of Mg, Al, Zr, Sn, and B), a transmetalation step (from *trans*-**28** to *trans*-**30**) occurs, followed by intramolecular delivery or reductive elimination with retention of configuration (from *trans*-**30** to *trans*-**29**) (Scheme 9).

Variation of the experimental conditions may lead to the formation of other isomers, arising from

Scheme 9



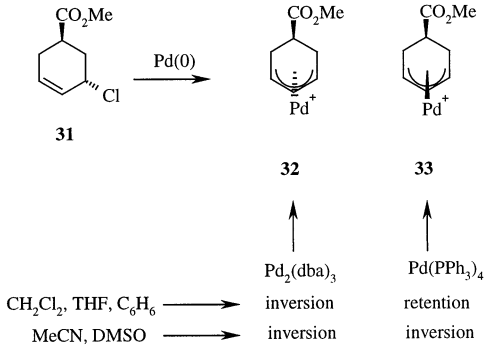
Scheme 10



isomerization of either the starting material or the cationic intermediate (Scheme 10).

The important factors influencing the stereochemistry of the reaction are the nature of the stabilizing phosphine (bidentate phosphines give overall retention of stereochemistry), the nature of the leaving group (e.g., replacement of acetoxy by trifluoroacetoxy reduced the preponderance of the S_N2 mechanism), the nature of the nucleophile (active nucleophiles are too short-lived to allow equilibration of starting and cationic species), and the nature of the solvent (Scheme 11).

Scheme 11



Recently, Hoke *et* al.[53] reported a comparison of the regioselectivity of Pd-catalyzed malonate additions and arylations to cycloalkenyl esters and found that the cyclopentenyl substrates displayed lower regioselectivity than the cyclohexyl counterparts, due to the altered planarity of the ring system.

2. Enantioselective Allylic Alkylation

The achievement of asymmetric transition metal-catalyzed allylic alkylation is a challenge for organic chemists. Important developments were recently reviewed by Trost and Van Vranken.[10a,54] Access to both the *l*- and *d*-enantiomeric series of nucleosides and their analogues is being increasingly demonstrated. In developing their own strategy, incorporating asymmetric palladium complexes, for the synthesis of nucleosides, Trost and Kallander[55] focused on the ability of the methods used to generate either enantiomer equally well, according to the reagent used. Of the various scenarios for asymmetric induction in allylic alkylation, differentiating between prochiral leaving groups, as formulated in Figure 5, represents a generally useful strategy. The ligand stereochemistry correlates with the product stereochemistry.

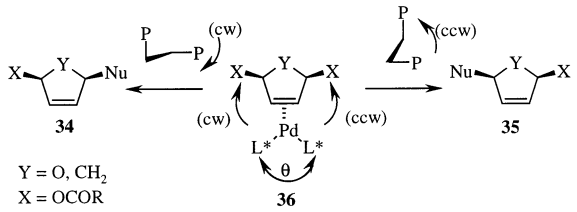


Figure 5. Diastereoselectivity of metal-catalyzed allylic alkylation.

Based on the orientation, in a Newman-type model, of the two phosphines, the ligands can be arranged in a clockwise (cw) manner (e.g., **37**−**39**, Figure 6) and in a counterclockwise manner (ccw) (e.g., **40**−**43**).[56] The clockwise arrangement of the ligands induces ionization of the prochiral leaving group by a clockwise rotation of the palladium in **36**, and vice versa for the counterclockwise ligands. The chiral space enveloping the allyl substrate is related to the P−Pd−P angle θ. Increasing this angle will push the chiral environment of the ligands creating the chiral space upward, thereby better embracing the π-allyl moiety. The geometric constraints of large chelating rings may increase this angle.[24a,57] Diamides were also particularly desirable as ligands, because the amide linkage makes them more rigid than esters.

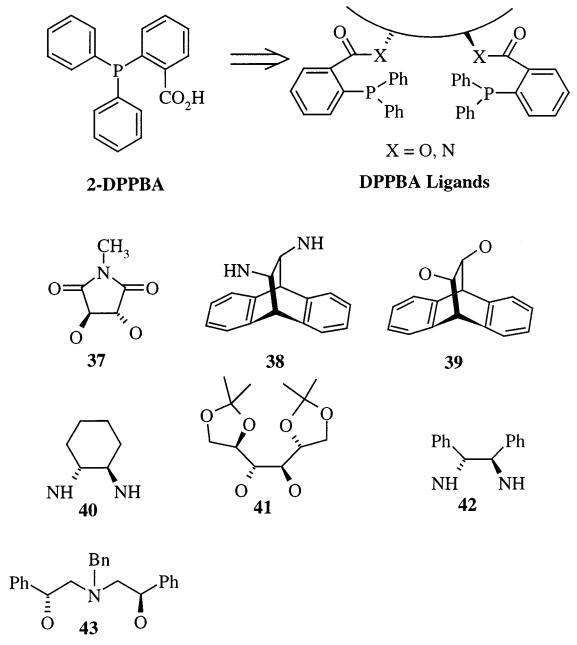
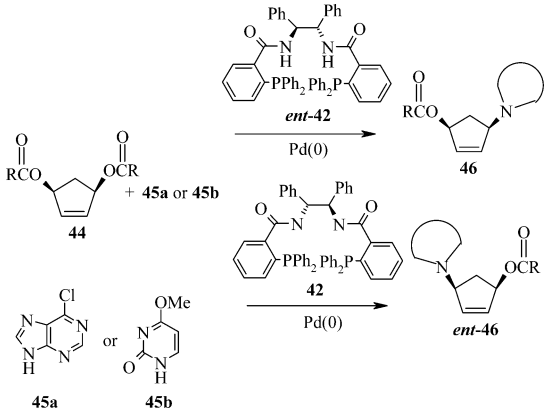


Figure 6. Some C_2-symmetrical ligands.

Numerous new chiral ligands continue to be reported, almost on a daily basis.[58]

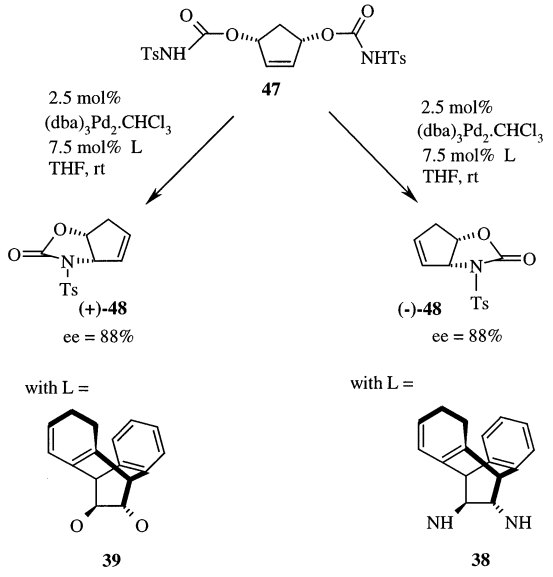
By choosing appropriate nucleophiles, nucleosides may be readily accessed. For example, by using purine or pyrimidine bases, both D- and L-nucleosides were prepared.[59] Starting from *cis*-2,5-diacyloxy-2,5-dihydrofuran (**44**), available in one step by oxidation of furan[60] and by choice of ligand, substitution of either prochiral leaving group leads to either enantiomeric series **46** or *ent*-**46** (Scheme 12).

Scheme 12



Another example of a desymmetrization with chiral ligands is reported through an internal substitution of **47**, yielding optically pure carbamate derivatives **48** (Scheme 13).

Scheme 13

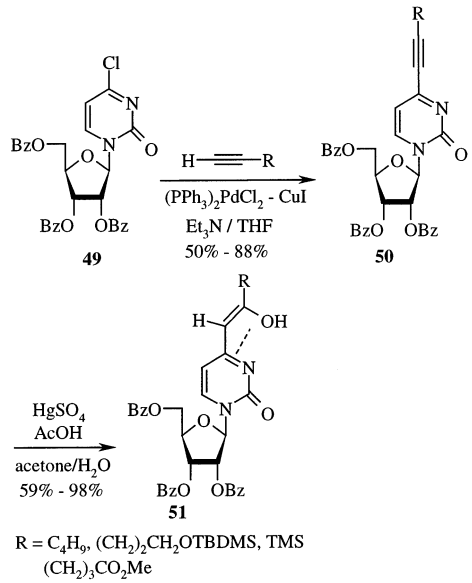


IV. Palladium Cross-Coupling to Pyrimidine Nucleosides

A. Palladium-Catalyzed Sonogashira Reaction To Give C-4-Substituted Pyrimidines

Several C-4-substituted pyrimidines with alkyl tethers have been designed for incorporation into antisense oligonucleotides while maintaining groups that would support Watson−Crick hybridization. Thus, some 4-(2-oxoalkylidene)-2(1*H*)-pyrimidinone ribonucleosides (**51**) have been reached by coupling the 4-chloro derivative **49** with several terminal alkynes under Sonogashira conditions to produce C-4 alkynyl derivatives **50** (Scheme 14).[61] After protection

Scheme 14



of the sugar hydroxyls, the cross-coupling reaction occurred with $PdCl_2(PPh_3)_2$−CuI in Et_3N/THF as solvent. Previous work in this area was limited to that described by Vorbrüggen, who developed a sulfur-extrusion method for the introduction of a phenacyl group at the C-4 position of uridine.[62] Further modification on the alkyne gave, for instance, by hydration using mercuric sulfate−acetic acid, the 4-(2-oxoalkenyl)-4(1*H*)-pyrimidinone analogues **51**.

B. Palladium-Catalyzed Substitution To Give C-5-Substituted Pyrimidines

Many nucleoside analogues substituted at the 5-position of the heterocycle, especially those in the 2′-deoxyuridine series, are known to have potent biological properties and have been investigated as antiviral and anticancer agents (e.g., BVDU (**5**), IDU (**52**), FIAU (**53**), etc.) (Figure 7). The 5-(2-substituted vinyl)-2′-deoxyuridines have emerged as potent and selective inhibitors of herpes viruses (HSV-1 and HSV-2).[63]

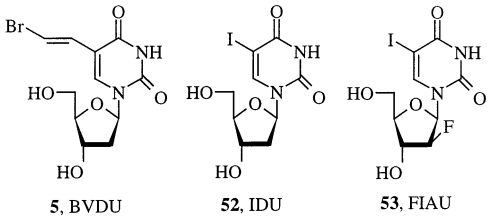


Figure 7. Some C-5-substituted anti-HSV nucleosides.

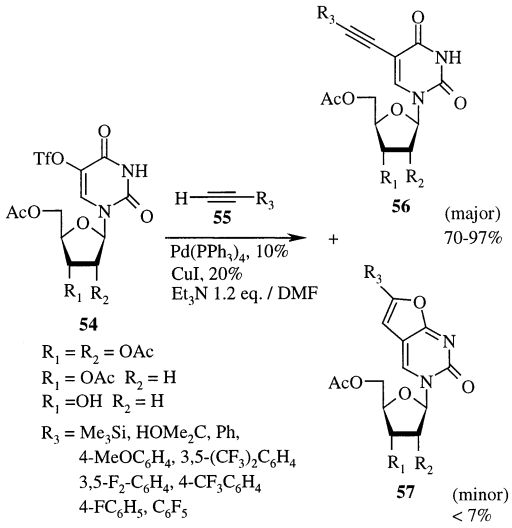
5-Alkynyl-2′-deoxyuridines has been also evaluated as potential antiviral agents.[64] The structure−activity relationship (SAR) studies seem to indicate that the type of C-5 substituents likely to confer activity

are those which are electron-withdrawing and conjugated to the heterocycle.[65]

1. By Sonogashira Reaction

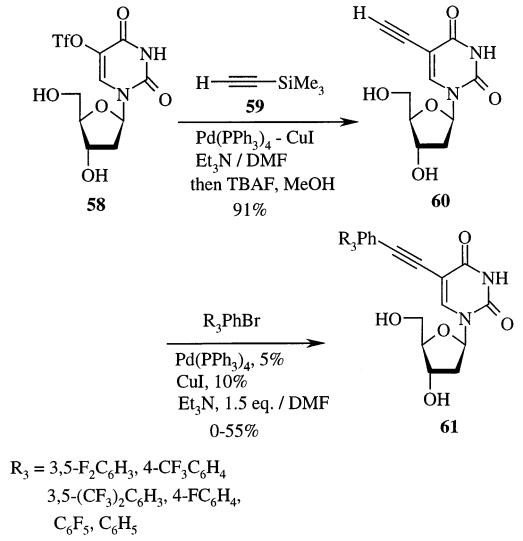
Various C-5 alkynyl derivatives **56** were obtained in high yields (70−97%) by cross-coupling of the acetylated uridine triflate **54** with several terminal alkynes **55** (Scheme 15).[66a] In most cases, it has been

Scheme 15



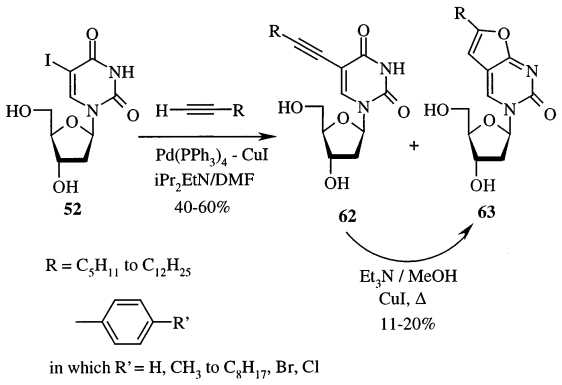
observed that slight elevation of the reaction temperature led to an increase in the rate of coupling. In all cases, furanopyrimidine derivative byproducts **57** have been either isolated with a <7% yield or just detected by thin-layer chromatography; nevertheless, using DMF as solvent reduced the amount of the cyclic byproduct. This base-catalyzed cyclization was previously reported by Bleackley et al.[66b] to occur by base treatment of (*E*)-5-(2-bromovinyl)uracil (**5**). Considerable amounts of this cyclized byproduct were isolated when longer reaction times were employed or when an electron-withdrawing group was present. Performing the reaction in the presence of CuI was also reported to increase the conversion rate to byproducts. Apart from this, homocoupling competes with cross-coupling, depending upon the steric hindrance around the catalyst. Optimal conditions have been found to be 2.0−2.5 equiv of terminal alkyne, 10% $Pd(PPh_3)_4$, 20% CuI, and 1.2 equiv Et_3N in DMF. An alternative would be to prepare the 5-terminal alkyne and then couple this to another aryl bromide through a second Sonogashira coupling. Thus, addition of trimethylsilylacetylene (**59**) to unprotected 2′-deoxyuridine-C-5-triflate (**58**) in the presence of $Pd(PPh_3)_4$, CuI, and Et_3N in DMF afforded, after deprotection of the silyl group, the C-5-ethynyl-2′-deoxyuridine **60** (Scheme 16).[66a] Subsequent palladium cross-coupling with aryl bromide derivatives gave the corresponding 5-arylalkyne-nucleoside analogues **61**, though in low yields (0−55%). The poor yields may result from competitive decomposition of the 5-ethynyl-2′-deoxyuridine under the reaction conditions of the coupling, or from the use of the unprotected sugar and the bromide as the aryl reagent.

Scheme 16



Recently, McGuigan et al.[67] reported that the analogous furanopyridine byproduct formed during the preparation of the parent 5-alkynyl-2′-deoxyuridine displayed important potency and exclusive selectivity against Varicella zoster virus (VZV). Meanwhile imidazo[1,2-*c*]pyrimidin-5(6*H*)-one-heterosubstituted nucleoside analogues were discovered by Mansour et al.[68] to have anti-hepatitis B virus (HBV) activity. The chemistry used was the Pd-catalyzed coupling of arylacetylenes or terminal alkynes with 5-iodonucleosides (Scheme 17).[66a,b] Starting with

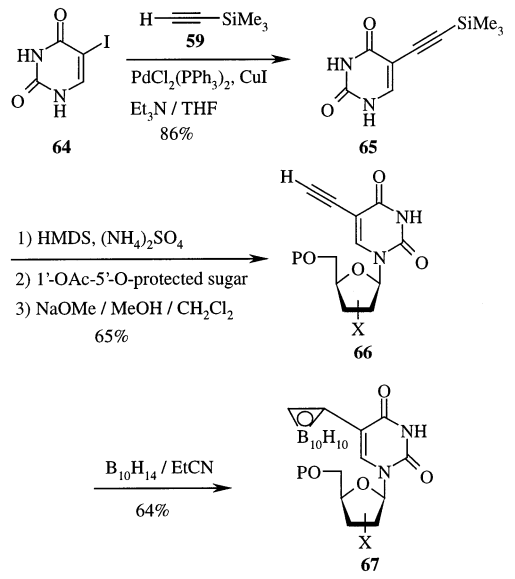
Scheme 17



unprotected IDU (**52**), several C-5-alkynylnucleosides **62** were obtained in moderate yield. As reported by Robins and Barr,[69] treatment of **62** with CuI in triethylamine/methanol at reflux gave the furanopyridine analogues **63**. Similar cyclization was noted in Stephens−Castro couplings of *o*-iodoanilines with copper(I) acetylides[70] and by Bleackley et al.[66b]

Boronic acids and their esters (boronates) are valuable intermediates, useful in synthetic applications such as Suzuki−Miyaura couplings and Matteson asymmetric homologations. In addition, boronated analogues of biomolecules are of interest for their possible use in boron neutron capture therapy (BNCT), as inhibitors of serine proteases, and as chemosensors during recognition events. Imamura and Yamamoto reported the Sonogashira cross-coupling reaction of 5-iodouracil (**64**) with tri-

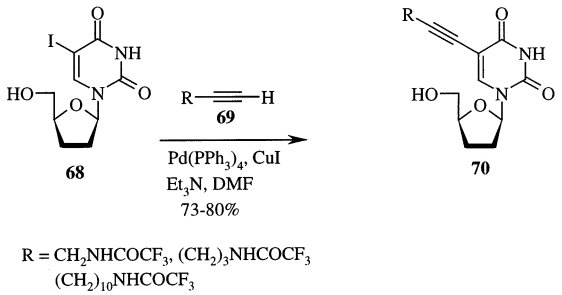
Scheme 18



methylsilylacetylene (**59**) as a precursor of carboranyluridines **67** (Scheme 18).[71] These products are under investigation for the BNCT of cancer,[72] for which a key requirement is the selective delivery of an adequate concentration of boron-10 to the tumor. Thus, 5-(trimethylsilylacetylenyl)uracil (**65**) was condensed with several protected modified sugars under Vorbrüggen conditions; treatment of the resulting compounds **66** with $B_{10}H_{12}(EtCN)_2$ gave the desired carboranyluridines **67**.

The C-5 alkynyl group has been also extensively employed as a linker arm for the attachment of fluorescent labels on chain-terminating 2′,3′-dideoxynucleotides in DNA sequencing techniques.[73] Derivatives of the (alkyn-1-yl)nucleosides bearing 3-(acylamino)propynes have anticancer and antiviral activities and have been synthesized by this reaction. Here, too, the use of DMF as the solvent is important for achieving efficient conversion. It was reported that attempted coupling reactions of 5-iodo-2′,3′-dideoxyuridine (**68**) with *N*-alkynyltrifluroacetamide derivatives **69**, using bis(triphenylphosphine)palladium(II) chloride and CuI in Et_3N, failed in part due to nucleoside insolubility. Successful couplings were achieved by changing $(Ph_3)_2PdCl_2$ to $(Ph_3P)_4Pd$, whence no secondary cyclized products were observed; thus, the 3-(acylamino)propynes nucleoside analogue **70** was isolated (Scheme 19).[74]

Scheme 19



Finally, this reaction has been applied to the synthesis of 5-substituted analogues of the anti-

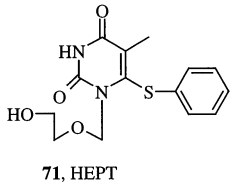
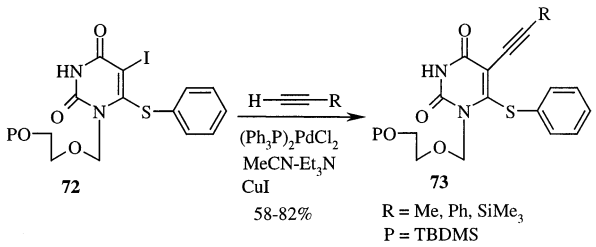


Figure 8. Chemical structure of anti-HIV HEPT.

HIV-1 agent 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymidine (HEPT, **71**) (Figure 8).[75] C-5 substitution on protected 5-iodo-HEPT (**72**) occurred with various alkynes (propyne, phenylacetylene, (trimethylsilyl)acetylene)[76] in MeCN−Et_3N at 60 °C, in the presence of $PdCl_2(PPh_3)_2$−CuI, and the C-5 alkynyl derivatives **73** were obtained in moderate yield (Scheme 20).[76a]

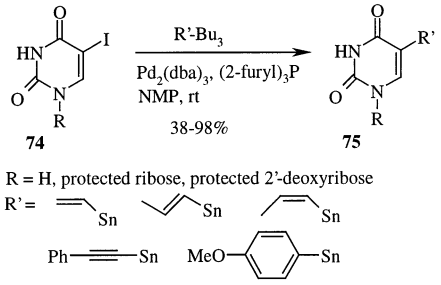
Scheme 20



2. By Stille Reaction

Farina and Hauck used the reaction of heteroaryl iodides **74** with various unsaturated stannanes for the synthesis of 5-substituted uracil and uridine derivatives (Scheme 21).[77] The interesting feature of

Scheme 21



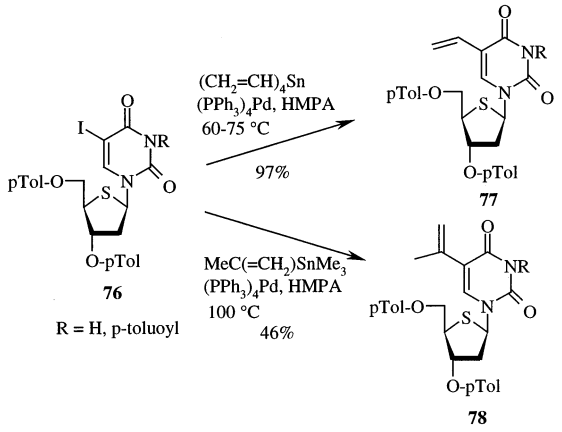
this reaction is its dependence upon the type and amount of palladium catalyst used. With only 2 mol % of $(MeCN)_2PdCl_2$ as catalyst, there was rapid decomposition and a very low yield of cross-coupling product (14%). $Pd(Ph_3)_4$ gave 50% conversion under similar conditions, while the catalyst obtained from Pd_2dba_3 and tri(2-furyl)phosphine led to 89% conversion at room temperature. Thus, 5-(1-alkenyl)-, 5-(2-phenyl-ethynyl)-, and 5-(4-methoxyphenyl)uracils (38−92% yield) and uridines **75** (76−98% yield) were obtained. The reaction tolerated different blocking groups on the sugar moiety, as well as working with the unprotected sugar.

Herdewijn et al.[78] used a similar reaction to synthesize some 5-substituted 2′-deoxyuridines, using symmetric tetraorganotin compounds[79] R_4Sn (in which R = Me, vinyl, phenyl). Nevertheless, their method has the disadvantage that HMPA is necessary as a solvent when the usual catalyst, $Pd(PPh_3)_4$, is used.

Whereas the vinylation occurs easily (80%), the reaction was unsuccessful using tetraethyltin. This is due to β-elimination competing with the reductive elimination of the intermediate $R^1PdL_2R^2$ complex.

Another application of the procedure for the vinylation of heterocycles was described by Rahim et al. for the synthesis of the antiherpetic agent 2′-deoxy-4′-thiopyrimidine (Scheme 22).[80] In several instances,

Scheme 22



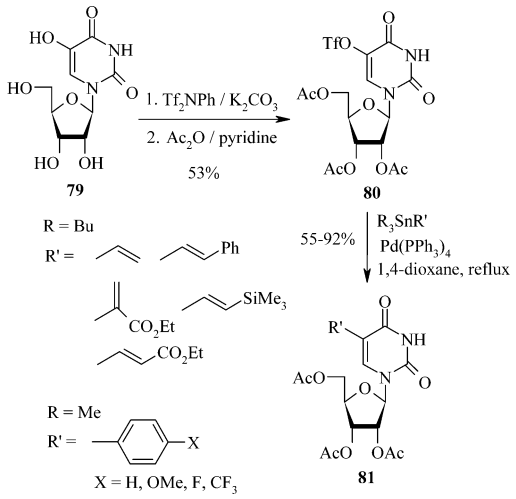
the replacement of the 4′-oxygen by sulfur produced 4′-thioribonucleosides with biological and especially anticancer activity.[81] Starting from a protected 5-iodo-2′-deoxythiouridine (**76**), the cross-coupling with tetravinyltin or isopropenyltrimethyltin in the presence of $Pd(PPh_3)_4$ in HMPA at 60−100 °C gave the C-5 vinyl (**77**) and C-5 propen-2-yl (**78**) thionucleoside derivatives in 97% and 46% yield, respectively.

It is interesting to note that, for the synthesis of the 5-vinyl derivative **77**, the N-3 position had to be protected by acylation (R = *p*-toluoyl) to avoid complex mixtures, while the synthesis of the 5-isopropenyl derivative **78** could be performed without N-3 protection (R = H). Nevertheless, the major byproduct isolated by cross-coupling between the 5-iodouracil analogue **76** and isopropenyltrimethyltin[82] was found to be the 4′-thiothymidine, presumably due to methyl abstraction at the high temperatures used in the coupling reaction. Other workers reported the palladium-catalyzed coupling of C-5 iodouracils and uridines with vinyl halides.[83] Vinyl triflates were also shown to be useful as the organic substrate, as exemplified by the reaction of unprotected 5-hydroxyuridine (**79**) with *N*-phenyltriflimide, followed by a peracetylation to afford the peracetylated 5-trifluoromethanesulfonyluridine (**80**) (Scheme 23).[84] The uridine triflate was found to couple with a variety of aryl- and vinylstannanes to produce nucleosides **81**.

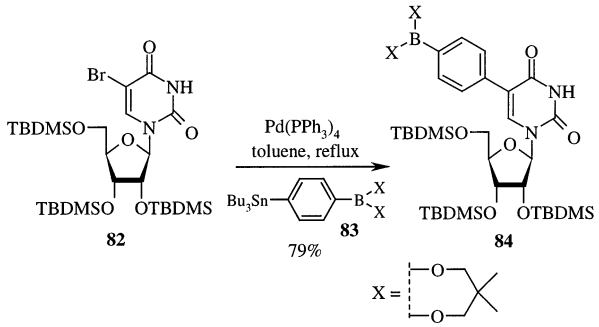
Yamamoto et al. reported an interesting variation in which the halogenated nucleoside **82** reacts with aryltin compounds having a boronic moiety **83**, to give the boron-10-containing nucleoside **84** in 79% yield (eq 7 and Scheme 24).[85] This reaction proceeded

$$R{-}X + R'_3Sn{-}Ar{-}B(OR'')_2 \xrightarrow{Pd(cat.)} R{-}Ar{-}B(OR'')_2 \quad (7)$$

Scheme 23



Scheme 24



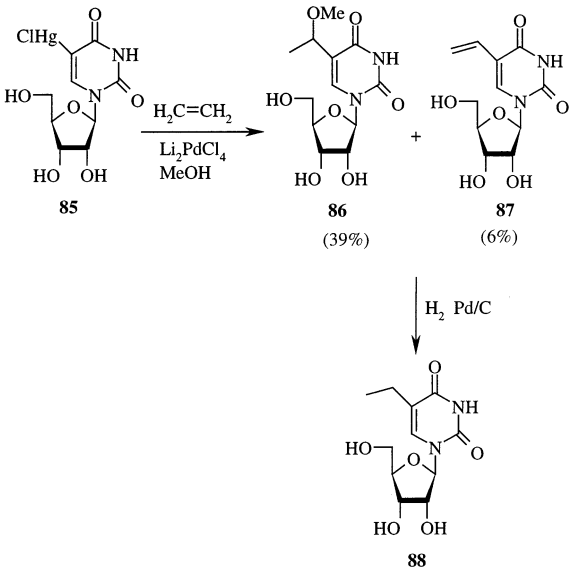
chemoselectively at the C−Sn bond rather than at the C−B bond in the absence of a base, despite the fact that both C−B (Suzuki−Miyaura reaction) and C−Sn (Stille reaction) bonds can undergo Pd-catalyzed cross-coupling reaction with the aryl or vinyl halide. The variable factors operating in the reaction were thoroughly investigated; it was found that the boronic acid of the boronic aryltin reagent must be protected (**83**) in order to avoid any activation of the C−B bond with the palladium catalyst. $Pd(Ph_3)_4$ gave better results than either $PdCl_2(PBu_3)_2$ or $PdCl_2(COD)$, and the use of a less polar solvent and a higher reaction temperature, such as refluxing toluene, was necessary to achieve the most efficient coupling. The influence of the protecting group of the sugar moiety was also examined. The bulky *tert*-butyldimethylsilyl group in **82** was preferred over the acetonide or methoxymethyl group or even unprotected sugar, as it must prevent coordination of the Pd catalyst to the oxygen atoms of the sugar moiety. The boron-10-containing nucleoside **84**, produced in the reaction after deprotection, can be used for neutron capture therapy.[72b,86]

3. By Heck Reaction

Bergstrom comprehensively reviewed C-5-substituted pyrimidine nucleosides in 1982.[14d] In the early applications of Heck chemistry to nucleoside synthesis, the organopalladium intermediates were generated in situ from aryl iodides and arylmercurials and reacted with olefins. The reaction was carried out

with a solubilized form of palladium(II) in the form of $LiPdCl_3$ in acetonitrile or Li_2PdCl_4 in methanol. Since aryl bromides and iodides are more readily available and less toxic than the mercurials, the direct oxidative addition of Pd(0) to the aryl halide at >80 °C has more recently been preferred. Nevertheless, the synthesis of C-5-substituted pyrimidine nucleosides via the palladium cross-coupling procedure has been most frequently accomplished from the 5-mercuri-derivatives. Bergstrom et al. reported the first coupling reaction between an olefin and a nucleoside (Scheme 19).[4,5,87a] Corresponding methodology has been utilized by several groups to prepare C-5 pyrimidine thioether nucleosides,[87b] to prepare biotin-labeled DNA probes,[87c] to link iron−EDTA to an oligonucleotide,[87d] to construct oligomers with tris(2,2′-bipyridine)ruthenium(II),[87e] to prepare nucleoside−peptide conjugates,[87f] and to synthesize oligodeoxyribonucleotide methyl thioether probes.[87g] In a typical example, cross-coupling of unprotected 5-chloromercuriuridine (**85**) with ethylene and Li_2PdCl_4 in MeOH produced the 5-(1-methoxyethyl)-uridine (**86**), along with the 5-vinyl analogue, **87**. After removal of **86** by crystallization, **87** was hydrogenated to the 5-ethylnucleoside, **88** (Scheme 25). This method provided a clean route to 5-ethyl derivatives.

Scheme 25



On the basis of the structure of the alkene, the pattern of product formation may be regarded as belonging to four categories (Scheme 26):[14d]

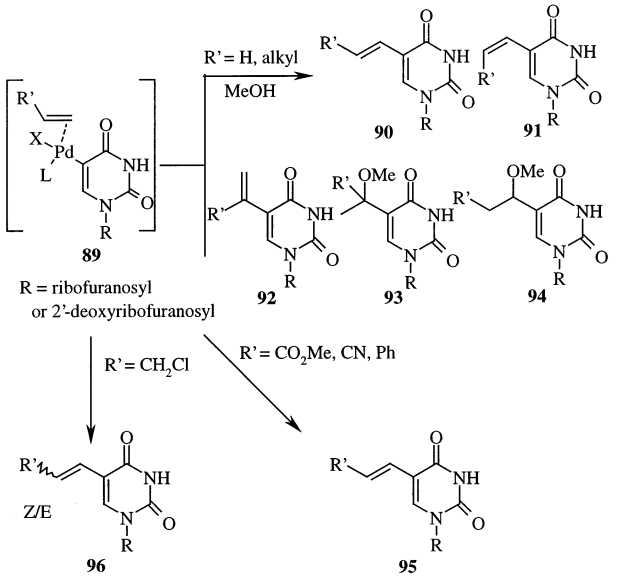
(1) terminal alkenes couple at both vinyl carbons, to give alkenyl (**90**−**92**) and methoxyalkyl side chains (**93**, **94**);

(2) conjugated olefins couple regioselectively at the terminal alkenyl carbon, to give trans olefins **95**;

(3) allylic chlorides couple at the terminal alkenyl carbon and eliminate $PdCl_2$, to give a mixture of (*E*)- and (*Z*)-5-alkenylpyrimidine nucleosides, **96**; and

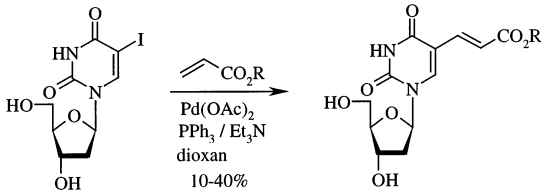
(4) olefins with functional groups that complex with or react with Pd behave unreliably and may give rise to unpredictable products.

Scheme 26



Whale et al. reported the reaction of 5-iodouridine (**52**) with esters of acrylic acid in the palladium-catalyzed Heck reaction to generate a series of esters of the acid (*E*)-5-(2-carboxyvinyl)uridine (**97a**−**r**) (Scheme 27)[88] in poor to moderate yield. An alternative method was esterification through the acid chloride of the (*E*)-5-(2-carboxyvinyl)uridine, generated in situ.

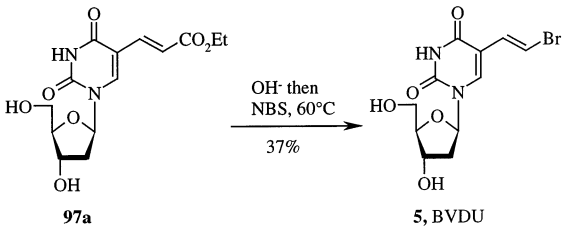
Scheme 27



R = a. ethyl, b. *n*-propyl, c. *iso*-propyl, d. *n*-butyl, e. *t*butyl, f. *n*-pentyl, g. *n*-octyl, h. benzyl, i. methoxyethyl, j. 2-ethoxyethyl, k. 2-butoxyethyl, l. 2-hydroxyethyl, m. 4-hydroxybutyl, n. 2-cyanoethyl, o. 2-chloroethyl, p. 2-bromoethyl, q. trifluoroethyl, r. tetrahydrofuryl

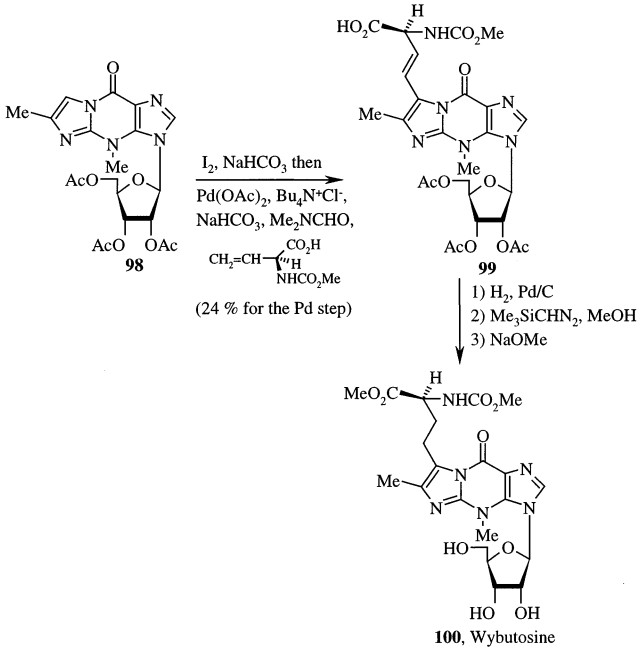
Basic hydrolysis, followed by radical decarboxylation−bromination (Hunsdiecker reaction) of **97a** at 60 °C with *N*-bromosuccinimide, generated (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**5**), one of the most potent antiherpetic agents yet discovered (Scheme 28).

Scheme 28



Itaya et al. reported an interesting route to wybutosine (**100**), the first tricyclic fluorescent nucleoside isolated from phenylalanine-transfer ribonucleic acids.[89b,c] For its synthesis, nucleoside **98**[89d] was submitted first to iodination and then to the Heck reaction with an optically active derivative of L-vinylglycine (Scheme 29).[89a] The Heck reaction was

Scheme 29



conducted in the presence of $Pd(OAc)_2$, $NaHCO_3$, and $Bu_4N^+Cl^-$ in Me_2NCHO at 45 °C. The resulting compound, **99**, was transformed in three steps (catalytic hydrogenation, methylation, and deacylation) to wybutosine (**100**).

4. By Hiyama Reaction

Matsuhashi et al. described a palladium-catalyzed cross-coupling reaction of organofluorosilanes with organic electrophiles, mediated by fluoride ion (the Hiyama reaction).[90] It occurs through transmetalation, followed by a cross-coupling reaction, as shown in eq 8 and Scheme 30).[91] This method provides a

$$R{-}X + R'{-}SiR''_3 \xrightarrow[F^-]{Pd(cat.)} R{-}R' \qquad (8)$$

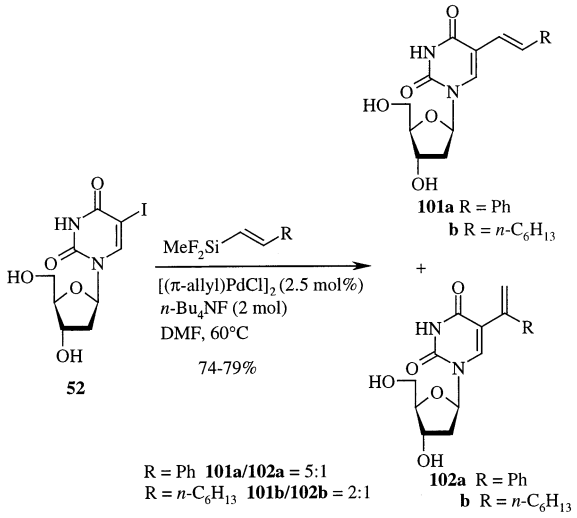
convenient synthesis of 5-substituted uracil derivatives and 5-substituted 2′-deoxyuridines. Starting from **52**, palladium-catalyzed cross-coupling reaction of organofluorosilane with 5-iodouracil afforded derivatives **101a**,**b** and **102a**,**b**. It is worth noting that nonprotected 5-iodo-2′-deoxyuridines also react with alkenyl(difluoro)methylsilane in good yield.

More recently, Hanamoto et al.[90d] applied the cross-coupling reaction of an aryl iodide with (α-fluorovinyl)diphenylmethylsilane, catalyzed by the triple combination of CsF (2.3 equiv), Pd(0) (5 mol %), and CuI (5 mol %) in DMI at room temperature.

C. Palladium-Catalyzed Substitution To Give C-6-Substituted Pyrimidines

In contrast to the extensive studies which have been done on 5-substituted uracils and their nucleo-

Scheme 30

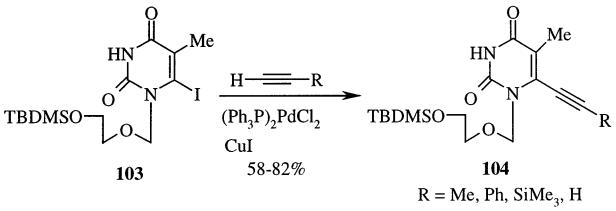


sides, there has been less emphasis on the development of novel 6-substituted analogues, even though orotic acid (6-carboxyuracil) plays an important role in pyrimidine biosynthesis. Only a limited number of 6-substituted uracils have been synthesized.[92] Recently, however, interest[93] in the above-mentioned HEPT analogues **71** as anti-HIV agents has led to some novel modifications at the C-6 position of pyrimidines. Other studies have been motivated by interest in the conformation of the glycosidic bond (for instance, as applied to the selectivity of adenosine receptors).[94]

1. By Sonogashira Reaction

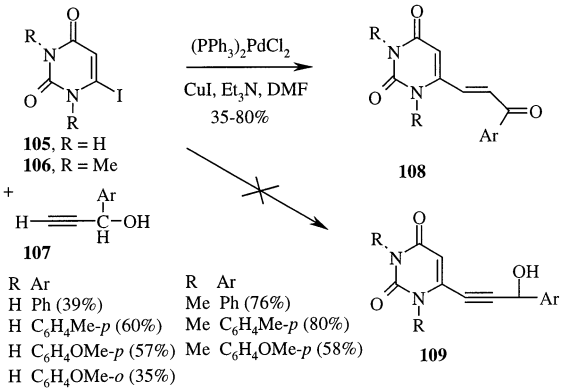
Realization of the aforementioned palladium-catalyzed cross-coupling reaction was carried out by treatment of the 6-iodo derivative **103** with an alkyne, such as propyne, phenylacetylene, or (trimethylsilyl)acetylene, in $MeCN{-}Et_3N$ in the presence of bis(triphenylphosphine)palladium(II). C-6 alkynyl HEPT analogues **104** were obtained (Scheme 31).[76a]

Scheme 31



Novel 6-substituted uracils were obtained by treatment of a mixture of 6-iodouracil (**105**) or an N^1,N^3-dimethyl-6-iodouracil analogue (**106**) and an acetylenic carbinol (**107**) in DMF in the presence of $(PPh_3)_2PdCl_2$ (6.8 mol %), CuI (12.5 mol %), and Et_3N (Scheme 32).[95] The desired 6-(2-acylvinyl)uracils **108** were obtained, rather than 6-[(3-aryl-3-hydroxy)-propyn-1-yl]uracils **109**, which might have been expected. The mechanism involves a syn-elimination of the Pd,[96] leading to an allenol that rearranges to the obtained acyl vinyl ketone.

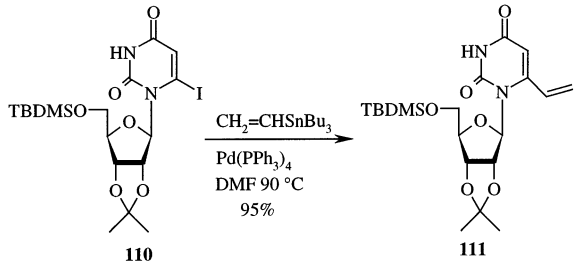
Scheme 32



2. By Stille Reaction

Manfredini et al. reported a short synthesis of protected C-6-vinyluridine (**111**) by a $(PPh_3)_4Pd$-catalyzed cross-coupling reaction of the 6-iodo nucleoside **110** with tributylvinylstannane in DMF (Scheme 33),[97] in almost quantitative yield. The introduction

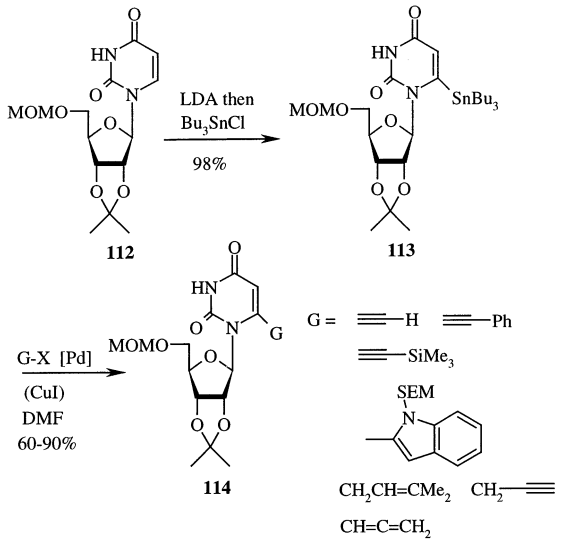
Scheme 33



of a vinyl group at C-6 of uridine resulted in nucleoside derivatives that demonstrated cytostatic activity against several tumor cell lines.

An interesting reaction, reported by Palmisano and Santagostino, consisted of the quantitative incorporation of trialkyltin into nucleosides by treatment of the protected uridine **112** with LDA and Bu_3SnCl (Scheme 34).[98] The intermediate **113**, which was reportedly stable at 0 °C for prolonged periods,

Scheme 34



could be employed in a Stille reaction with a variety of aryl, vinyl (C-sp^2), alkynyl (C-sp), and alkyl (C-sp^3) halides. The use of CuI as cocatalyst increased the efficiency of the reaction; for instance, in the presence of Pd catalyst alone (Pd_2dba_3, TFP, NMP), the model reaction of 6-tributylstannyluridine (**113**) with iodobenzene gave the 6-phenyl analogue **114** in 35% yield, whereas in the presence of 5 mol % Pd_2dba_3 and 20 mol % CuI (Pd:ligand:CuI = 1:2:2), the yield increased to 72%. Yet further improvement, to 88%, could be achieved by the use of $Pd(PPh_3)_4$ (10 mol %) in the presence of CuI. The same 6-tributylstannyluridine **113** has been successfully used for the $Pd(PPh_3)_4$-catalyzed cross-coupling reaction with various 1-haloalkynes (e.g., PhC≡CI, TMSC≡CI, $HC{\equiv}CCH_2Br$) in DMF in 60−90% yield.

V. Palladium-Mediated Substituted Purine Nucleosides

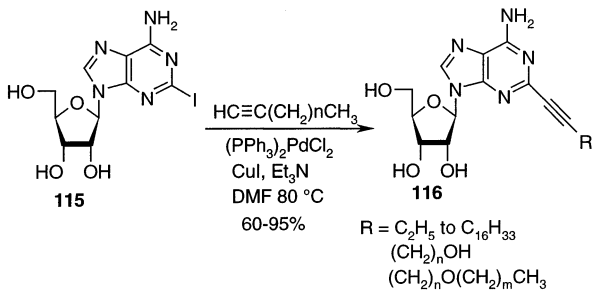
A. Palladium-Catalyzed Substitution To Give C-2-Substituted Purines

The synthesis of modified analogues of adenosine has been of considerable interest due to the potential use of these compounds as agonists for A_1 and A_2 adenosine receptors.[99] SAR studies of the binding characteristics of the A2 receptor indicate a preference for C-2 substitution, particularly by alkynyl substituents. Purine nucleosides and related systems are otherwise of great interest because of their established activity as antiviral agents[100] and their potential as inhibitors of key enzymes in purine metabolism.[101]

1. By Sonogashira Reaction

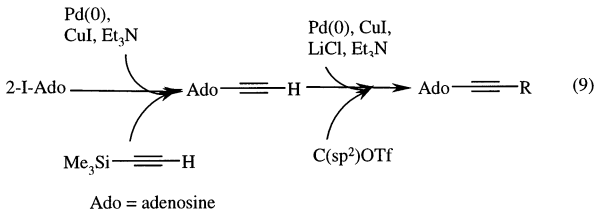
The method of choice for use with purines appears to be the Pd-catalyzed cross-coupling reaction of 2-iodoadenosine (**115**) with various terminal alkynes under Sonogashira conditions, yielding the desired 2-alkynyladenosines **116** (Scheme 35).[102] Satisfactory

Scheme 35



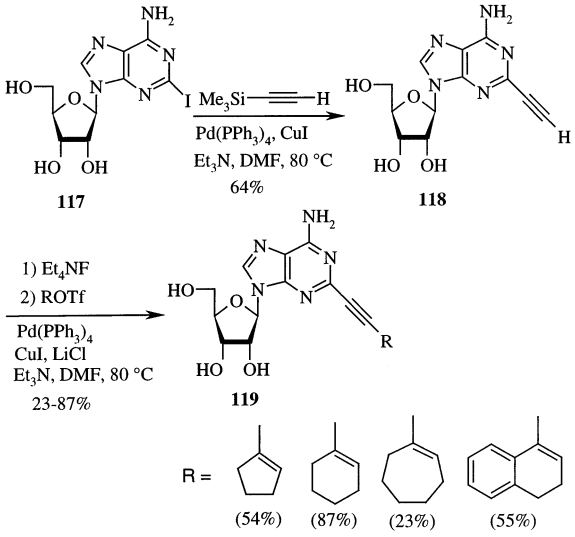
to high isolated yields are generally obtained. Similar reactions with 6-chloro- or 8-bromopurine derivatives gave the 6-alkynyl- or 8-alkynyladenosines, respectively.

By utilizing enol triflates in Pd-catalyzed reactions,[103] a number of C-2-modified adenosine analogues have been easily reached (eq 9).



The second palladium cross-coupling reaction occurs with an organic triflate and the 2-ethynylpurine nucleoside. The addition of LiCl was necessary in the case of the vinylpalladium chloride complex to ensure efficient transmetalation.[33a] Starting from unprotected 2-iodoadenosine (**117**), several 2-(2-substituted ethynyl)purine nucleosides **119** were synthesized (Scheme 36)[104] in moderate to good yields.

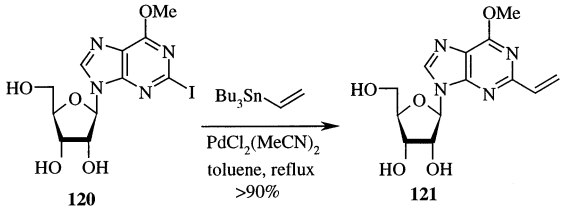
Scheme 36



2. By Stille Reaction

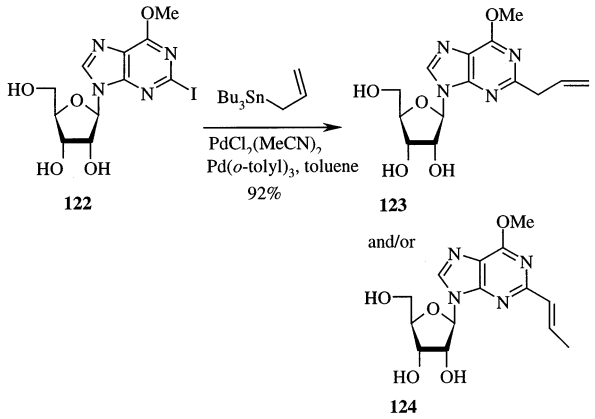
Nair et al.[105] explored the cross-coupling reactions between 2-iodopurine-6-methoxypurine nucleoside (**120**) and vinyltin for the synthesis of the functionalized purine nucleoside **121** (Scheme 37).[105c] The

Scheme 37



reaction was used to synthesize new 2-unsaturated nucleosides, such as 2-allyl-6-methoxypurine (**123**) and the rearranged product, (*E*)-2-(1-propenyl)-6-methoxypurine (**124**), from unprotected 6-methoxy-2-iodoinosine **122** (Scheme 38).[105d] The synthesis of 2-allyl derivatives was effected with allyltributyltin and $PdCl_2(CH_3CN)_2$ in the presence of tri-*o*-tolylphosphine in toluene. It appears that temperature and reaction time are important factors to be taken into account in controlling these Pd cross-coupling

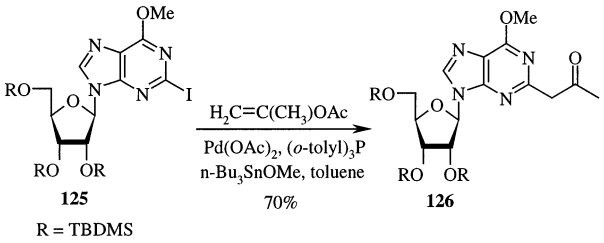
Scheme 38



reactions. Between 90 and 95 °C, formation of the allyl product **123** predominates, whereas raising the temperature to 105 °C gave, with high selectivity, the vinyl compound **124**.

The reaction with enolacetates has considerable potential for the production of 2-acetonyl derivatives **126**, starting from silylated 2-iodo-6-methoxypurine **125** (Scheme 39).[105a] The tributyltin enolate of ace-

Scheme 39



tone, required for the cross-coupling step, is generated in situ from isopropenyl acetate and tributyltin methoxide. Other enol acetates may be employed under similar conditions to generate the 2-keto products.

The synthesis of 2′-vinyl-2′-deoxyadenosine and 2-(1-propen-3-yl)-2′-deoxyadenosine from 2-iodo-2′-deoxyadenosine using vinyl tri-*n*-butylstannane/$PdCl_2(CH_3CN)_2$ and allyl tri-*n*-butylstannane/$Pd(PPh_3)_4$ was reported by Van Aerschot et al.[106] The temperature must be carefully controlled to avoid isomerization of the 1-propen-3-yl group to the 1-propen-1-yl group. Finally, the synthesis of the C-2 aryl derivative containing a boronic moiety, **127**, has been realized according to the above-described method (Figure 9).[85]

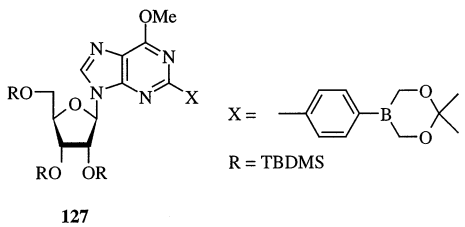


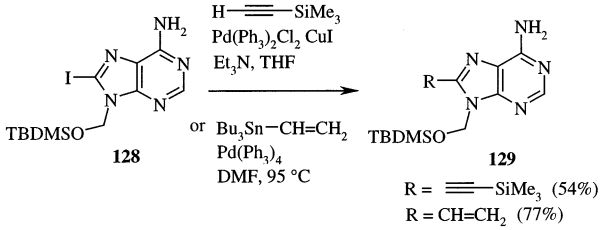
Figure 9. Chemical structure of C-2 aryl containing a boronic moiety.

B. Palladium-Catalyzed Substitution To Give C-6- or C-8-Substituted Purines

1. C-6- and C-8-Substituted Compounds via the Sonogashira Reaction

Not very much is known yet about the biological effect of systematic substitution of the purine nucleosides at the C-2, C-6, and C-8 positions with C-linked substituents. The anti-HSV agent acyclovir (**1**) has served, however, as a model for the synthesis of a number of C-8 alkynyl-, alkenyl-, and alkyl-2′-deoxyadenosine derivatives.[107] Interestingly, several of them have higher selectivity in vitro as antiviral agents than the parent molecule. Following from these observations, several adenine analogues **129**, linked at C-8 to a flexible ω-hydroxyalk-1-ynyl (alk-1-enyl or alkyl) group, were developed from the 8-iodoadenosine analogue **128**, making use of Stille or Sonogashira reactions (Scheme 40).[108]

Scheme 40

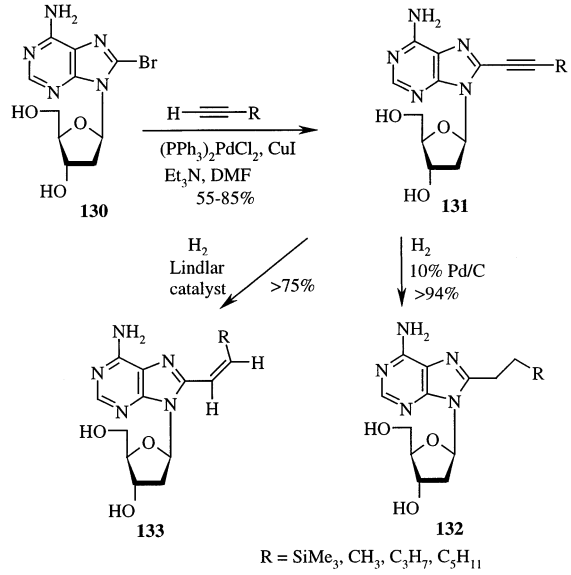


Generally, there are two main routes to substituted adenines. One is by Pd-catalyzed coupling of the 8-halogenated (especially the 8-bromo-) adenosine with a Grignard reagent;[109] another is by the condensation of protected 8-lithio-6-chloropurineribofuranoside with alkyl halogenides.[110] Alternatively, multistep methods have to be used.[111] As a rule, Pd-catalyzed chemistry has been preferred, because the multistep procedures have generally poor yields and are not very suitable for the economical preparation of C-8 alkylpurines. Thus, treatment of the unprotected C-8-brominated 2′-deoxyadenosine **130** with several terminal alkynes in DMF in the presence of 0.1 equiv of $PdCl_2(PPh_3)_2$, 0.2 equiv of CuI, and 2.0 equiv of Et_3N afforded the desired 8-(1-alkynyl-1-yl)-2′-deoxyadenosine **131** in 55−85% overall yields (Scheme 41).[112] Total or partial hydrogenation of the alkynyl derivatives gave the alkyl (**132**) or the cis-olefin analogue (**133**), respectively. This approach was also used to make 6- and 8-alkynylated ribonucleoside purines.[113]

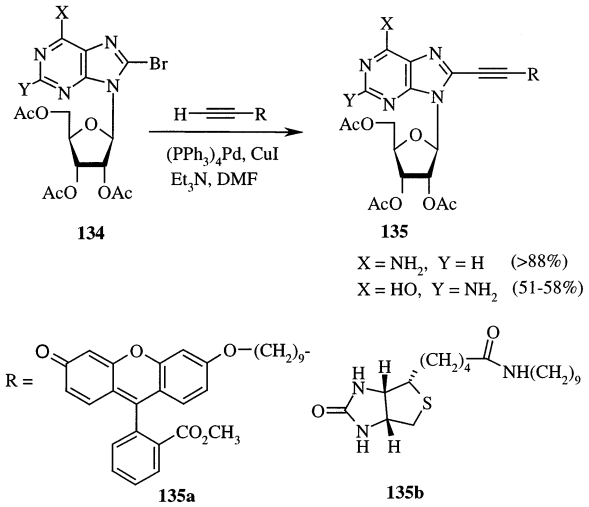
A useful application of C-8- or C-6-substituted purines is to attach a series of fluorescent (acridonyl, pyrenyl, dansyl, fluoresceinyl (**135a**), ...) or enzymatically active (biotinyl, **135b**) labels containing a terminal alkyne (Scheme 42).[114] Such compounds are widely used as labels in DNA sequencing. Steroidal substituents have also been attached by a similar procedure.

Recently, Volpini et al. reported the synthesis (Scheme 43)[115] of some 8-alkynyladenosines with the objective of evaluating their activity at adenosine receptors. It was hoped that such compounds might demonstrate selectivity at these receptors and provide a possible lead to new types of drugs.[116] The synthesis of 8-substituted adenosines **137** was carried out from 8-bromoadenosine (**136**), through cross-coupling reaction with several alkynyl compounds in DMF/Et_3N in the presence of $(PPh_3)_2PdCl_2$ and CuI. These nucleosides behave as selective ligands for adenosine A3 receptors.

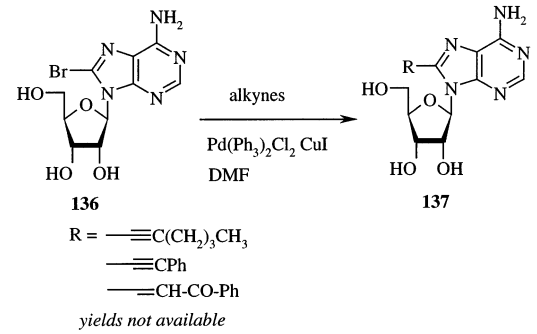
Scheme 41



Scheme 42



Scheme 43

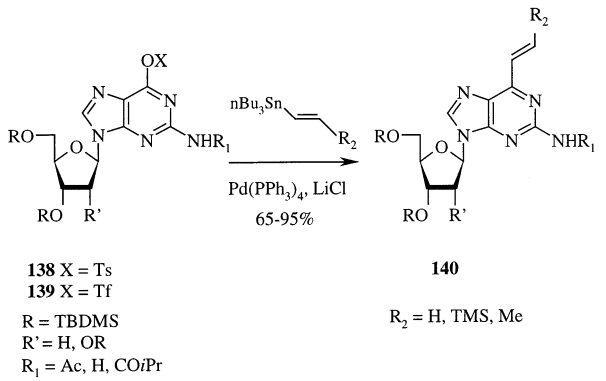


2. C-6-Substituted Compounds via the Stille Reaction

Methods for the preparation of 6-alkyl-substituted purine nucleosides are rather limited, usually being

confined either to a fusion reaction between the appropriate 6-alkylpurine and the peracetylated carbohydrate[117] or to reaction of 6-methylsulfonylpurine with carbon nucleophiles.[118] Van Aerschot et al.[106] reported a straightforward procedure for the synthesis of 6-alkylated purines (6-methyl, 6-ethyl, 6-vinyl) based on Pd chemistry using tetraalkyltin reagents. Other 6-substituted compounds have been intended as potential cross-linking agents between adjacent chains in sense−antisense complexes.[119] For instance, Nagatsugi et al. prepared the 6-vinylated (and 6-(2-substituted vinyl)) 2-aminopurine nucleosides **140**, in satisfactory to high yield, by a Pd(0)-catalyzed cross-coupling reaction using guanosine 6-*O*-tosylate **138** (or the *O*-triflate **139**) and vinyltributylstannane or its derivatives (Scheme 44).[120] It should be noted

Scheme 44



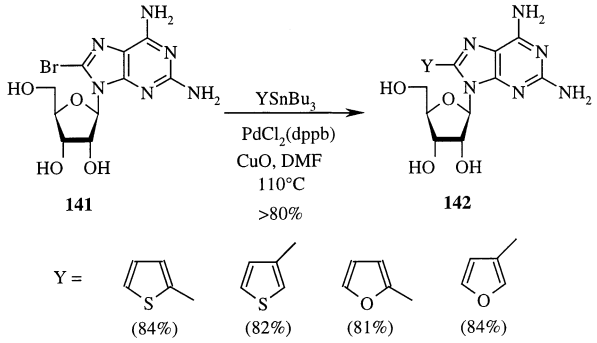
that 6-*O*-tosylates appear to be superior substrates to the unstable triflates in this particular cross-coupling reaction. Moreover, this reaction, which was conducted either at 100 °C in dioxane or at 60 °C in toluene, took place only with $Pd(Ph_3)_4$, and not with $PdCl_2(PPh_3)_2$.

Langli et al.[121] reported the regioselective Stille cross-coupling reactions of 9-benzyl-2,6-dihalopurines with organostannanes. Substitution occurred at the 6-position when 1 equiv of organostannane was used and at the 2-position when 6-chloro-2-iodopurine was employed as the starting material. Finally, it is worth mentioning the binuclear purinylpalladium complex **I** that is involved in the coupling of 9-benzyl-6-chloro-9*H*-purine with $RSnBu_3$.[122]

3. C-8-Substituted Compounds via the Stille Reaction

Modifications (such as alkylation) at the 8-position of purine nucleosides are of particular interest because it confers the capacity to change the syn/anti conformation of the nucleosides in which they are contained. Ozola et al. described several 8-(2- and 3-thienyl)- and 8-(2- and 3-furyl)-2,6-diaminopurine derivatives (**142**), the synthesis of which was accomplished through a Stille cross-coupling reaction between 2- and 3-tributylstannylthiophene or 2- and 3-tributylstannylfuran and the 8-bromopurine analogue **141** (Scheme 45).[123] The use of DMF[124] at 110 °C, and dichloro(diphenylphosphinepropane)-palladium(II) ($PdCl_2$(dppb)) with cupric oxide as cocatalyst,[125] was necessary to obtain optimal yields (80%).

Scheme 45



Nucleosides **143** and **144** were obtained from palladium-catalyzed C-8 allylation, vinylation, and alkylation under Stille coupling conditions with symmetrical (R_4Sn) or unsymmetrical stannanes ($YSnR_3$, where Y = allyl, vinyl) (Figure 10).[126]

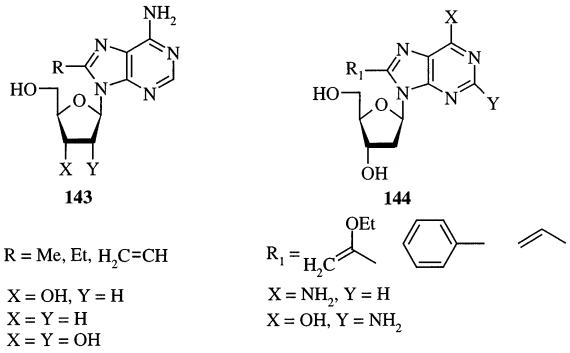
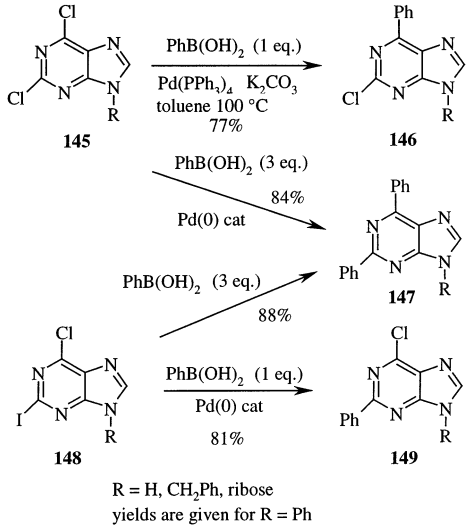


Figure 10. Some C-8-substituted purines, obtained by the Stille cross-coupling reaction.

4. C-6- and C-8-Substituted Compounds via the Suzuki–Miyaura Reaction

The application of the Suzuki−Miyaura cross-coupling reaction for the modification of purine nucleosides has just recently received some attention.[127] The Pd-catalyzed reaction of 2,6- and 2,8-halopurine derivatives with diverse types of aryl- and alkenylboronic acids was reported (Scheme 46).[127a] Optimization of the procedure showed that $Pd(PPh_3)_4$

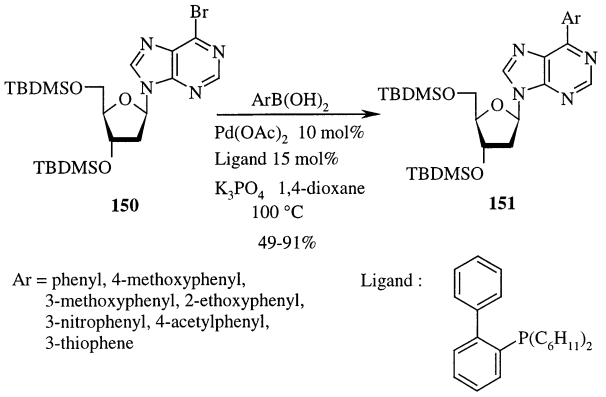
Scheme 46



is a superior catalyst as compared to $Pd(dba)_2/P(o\text{-}tol)_3$, $Pd(dba)_2/AsPh_3$, or $PdCl_2(PPh_3)_2$. Furthermore, potassium carbonate turned out to be superior to other bases; Na_2CO_3, Cs_2CO_3, $EtN(iPr)_2$, and NaOMe did not give any reaction at all. Where there were electron-rich substituents on the arylboronic acid (e.g., methoxyphenyl, 4-fluorophenyl, etc.), anhydrous conditions were preferred, but where the substituents were electron-deficient (e.g., nitro-, formyl-, acetylphenyl-) thienyl- and alkenylboronic acids, aqueous conditions in DME were preferred. Starting from 2,6-dichloropurine compounds **145**, the reaction was applied either to the synthesis of 6-arylpurine heterocycles, nucleosides **146**,[127b−d] and the disubstituted derivative **147** or to acyclonucleosides.[128] Good regioselectivity has been observed for the Suzuki−Miyaura cross-coupling of 2,6-dihalopurines. The C-6-substituted compound **146** was formed first when 1 equiv of organoboronic acid was used, and the C-2 analogue **149** was preferred when 6-chloro-2-iodopurine (**148**) was used as starting material.

The introduction of an aryl group into the C-6 position of purines has received somewhat more attention. From the extensive studies of Lakshman et al., several lessons can be drawn (Scheme 47).[129]

Scheme 47



C−C bond formation at the C-6 position is relatively independent of the ligand used; thus, both mono- and bis-coordinating ligands provide complete reaction with good to high yields. Reactions at the C-2 position are also easy to achieve. Both 6-chloro- or 6-bromonucleosides can be used for the C−C alkylation. Moreover, protection of the hydroxyl groups of ribose moiety is preferred, even if it is not normally necessary under the Suzuki−Miyaura conditions. Thus, 6-bromo(or 6-chloro)3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**150**) was treated at 100 °C with several arylboronic acids in anhydrous 1,4-dioxane, in the presence of 10 mol % $Pd(OAc)_2$ and 15 mol % phosphine ligand, to afford the desired C-6 aryl 2′-deoxynucleosides **151**.

It should be noted that, when the arylboronic acid contains a functional group, such as 2-ethoxyphenyl, which can coordinate to the Pd atom (Figure 11) or an electron-deficient group, the yield and reaction time are significantly reduced. Given the overall superiority and generality of the $Pd(OAc)_2$/phosphine ligand/K_3PO_4 system for C−C bond formation at C-6, this is the method by which most of the C-2 aryl 2′-deoxynucleosides have been obtained.

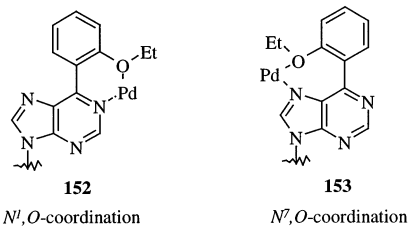
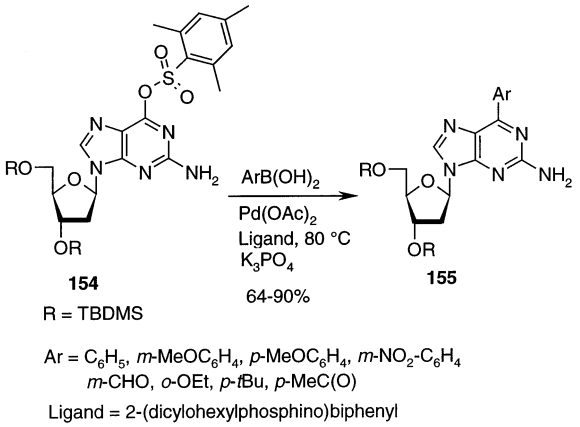


Figure 11. Two possible structures of a coordinated Pd aryl derivative.

The procedure was also applied to cross-coupling of O^6-arylsulfonate 2′-deoxyguanosines with arylboronic acids (Scheme 48),[130] in a fashion similar to

Scheme 48



the use of O^6-sulfonate (triflate and tosylate) derivatives of guanosine and 2′-deoxyguanosine for cross-coupling with vinylstannanes under Stille conditions.[120] Several arylboronic acids were condensed with 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-O^6-(2-mesitylenesulfonyl)-2′-deoxyguanosine (**154**) in the presence of the above-mentioned catalytic system ($Pd(OAc)_2$, 2-(dicyclohexylphosphino)biphenyl, and K_3PO_4), affording the desired 6-arylpurine 2′-deoxynucleosides (**155**) in moderate to good yield. Provided that the temperature was 80 °C, the reaction proceeded rapidly and was complete in 0.5 h.

More recently, Amann and Wagenknecht described the modified nucleosides, 5-pyrenyl-2′-deoxyuridine (**156**) (Figure 12),[131] synthesized in 65% yield via the

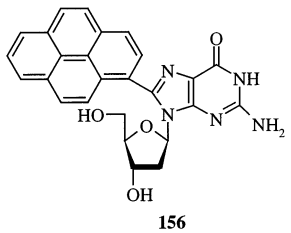


Figure 12. C-8 pyrene-modified nucleosides.

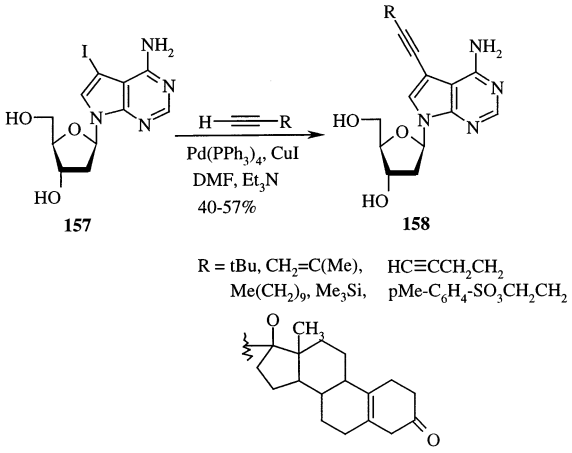
palladium-catalyzed Suzuki−Miyaura cross-coupling reaction of pyren-1-ylboronic acid with 8-bromo-2′-deoxyguanosine. The nucleosides so obtained were intended to serve as models for the spectroscopic investigation of reductive electron transfer through DNA.[132] Such charge migration processes might assist in explaining how DNA is damaged by poly-

nuclear hydrocarbons, leading to mutations and cancer.

C. Palladium-Catalyzed Sonogashira Substitution at C-7 of 7-Deazapurine

C-7 substitution of 7-deazapurines has been exploited in the development of antisense oligonucleotides and anticancer agents, and in incorporating nonradioactive fluorescent labels into DNA. For instance, based on the strong fluorescence of 7-deaza-2′-deoxy-7-(hex-1-ynyl)adenosine,[133] a series of 7-alkynyl-7-deaza-2′-deoxyadenosines **158** were synthesized by Seela et al. through a cross-coupling reaction of 7-deaza-2′-deoxy-7-iodoadenosine (**157**) with various alkynes (Scheme 49).[134] The critical

Scheme 49



point in the design of fluorescence-tagged substrates for DNA polymerases[135] is that the group that covalently links the nucleoside to the fluorescent moiety must not interfere either with the enzymatic processing of the molecule, nor with base-pairing within the DNA molecule itself.

The same team used similar methodology for the synthesis of 8-aza-7-deazapurine nucleosides **159**.[136] Other "linkers" **160**, having a similar function, were described by Hobbs[74] (Figure 13).

The ratio of the Pd(0) to copper(I) is important for this reaction to proceed with maximum efficiency. For instance, when the alkynylamine is unprotected, a

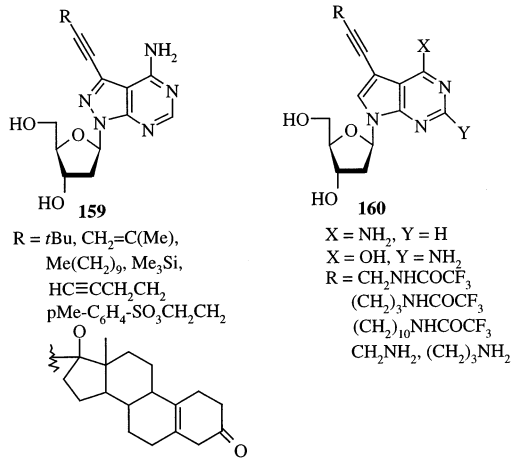


Figure 13. Linkers for fluorescence-tagged nucleosides.

5:1 Pd:Cu ratio is preferable to the usual 2:1 ratio. It has been speculated that the reason for this is that copper(I) removes two ligands from $(PPh_3)_4Pd$, so that when a large excess of unprotected alkynylamine is present, more copper(I) is necessary to avoid competition between these ligands. Another application of potential biological interest among C-7-substituted 7-deazapurine nucleosides is the synthesis of analogues of the naturally occurring antibiotic nucleosides,[137] tubercidin (**161**), toyocamycin (**162**), and sangivamycin (**163**). 7-Deazaguanines and especially the pyrrolo[2,3-*d*]pyrimidine-based compounds, cadeguomycin (**164**) and echiguanine A (**165**) or B (**166**), represent a class of agents with broad biological activity (Figure 14).

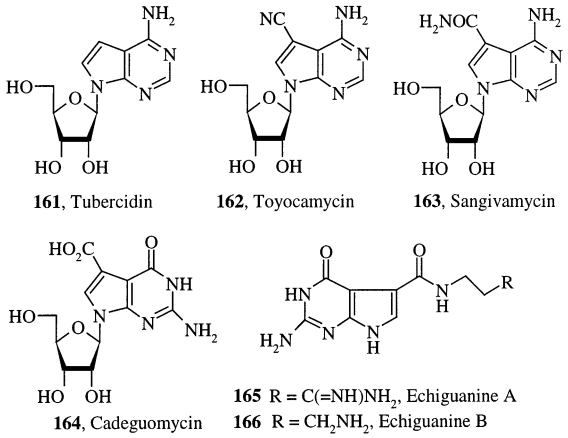


Figure 14. C-7-substituted purine antibiotics nucleosides.

Several 7-substituted 7-deazapurine analogues of tubercidin (**167**)[137a] and 2′-deoxytubercidin (**168**)[138] (Figure 15), were synthesized by alkynylation under Sonogashira conditions. Some of them exhibited anticancer activities as well as properties against regulatory subunits of protein kinase A (PKA).[139]

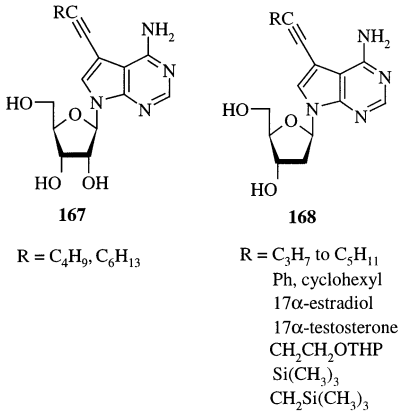
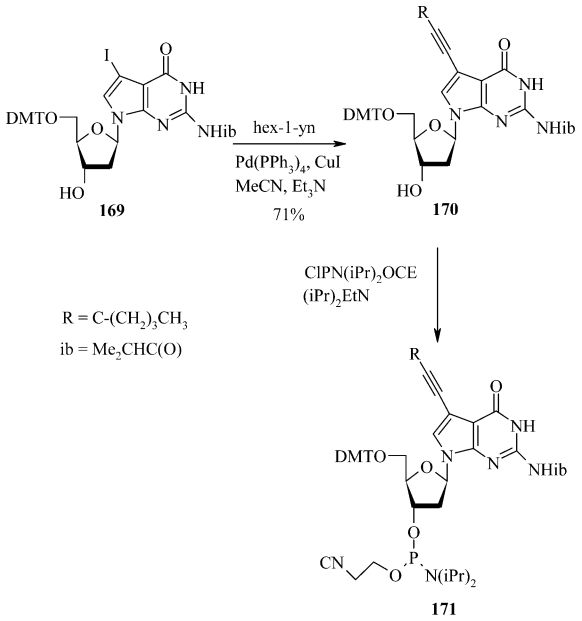


Figure 15. C-7 alkynyl tubercidin analogues.

Finally, a series of 7-alkynylated 7-deazaadenines, 7-alkynylated 7-deazaadenines, and 7-substituted 8-aza-7-deaza-2′-deoxyguanosines were designed and incorporated by Seela et al.[140] into antisense oligonucleotides. For instance, the protected 7-deaza-2′-deoxy-7-iodoguanosine (**169**) was used as a starting material for the synthesis of 7-deaza-2′-deoxy-7-(hex-1-ynyl)guanosine (**170**), employing the palladium-catalyzed cross-coupling reaction (Scheme 50).[140a]

Scheme 50



Phosphitylation of **170** with 2-cyanoethyl diisopropylphosphoramido-chloridite in the presence of $(i\text{Pr})_2\text{EtN}$ furnished the phosphoramidite **171** monomer, which was used in the solid-phase oligodeoxynucleoside synthesis.

D. Palladium-Catalyzed Synthesis of Substituted Imidazole or Pyrazole Nucleosides

Nucleoside analogues with a five-membered heterocycle such as ribavirin (**2**), which was developed commercially, thiazofurin (**173**), and bredinin (**178**) are structurally related to 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICAR, **172**) and are known to have antiviral and anticancer properties (Figure 16).[141] Such properties have provided the motivation

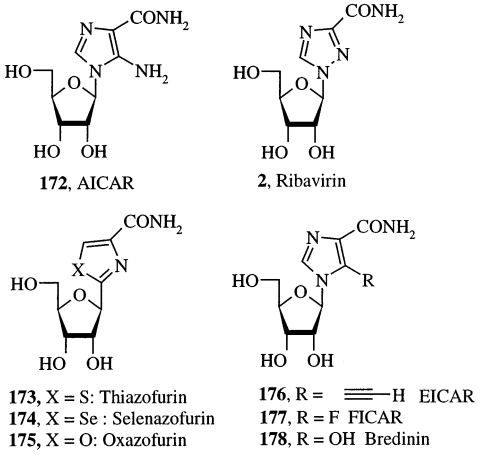
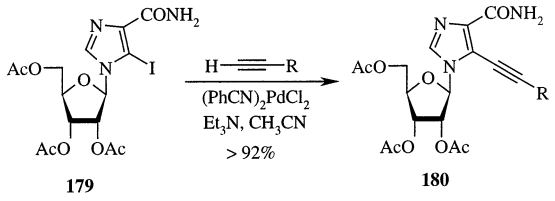


Figure 16. AICAR derivatives.

for carrying out further synthetic studies on this system. Several derivatives **180**, which are structurally similar to AICAR, have been obtained in high yield, using organopalladium chemistry, starting from the protected 4-carboxamide-5-iodoimidazole-1-β-D-ribose (**179**) (Scheme 51).[142a]

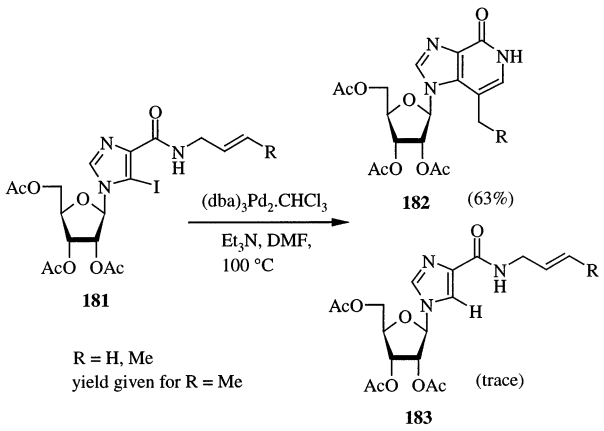
Scheme 51



R = $SiMe_3$, H, CH_2OH, CH_2CH_2OH, Pr, Ph
$C(CH)_3OH$, cyclohexyl, CH_2-cyclopentyl, CH_2CH_2Ph

When the coupling was performed with propargyl alcohol, the most effective catalytic system appeared to be bis(benzonitrile)palladium dichloride in acetonitrile. The use of other Pd catalysts, such as $(PPh_3)_2PdCl_2$ and $Pd(OAc)_2$, in DMF gave reduced yields. In this reaction, the addition of a catalytic amount of cuprous iodide according to standard Sonogashira conditions lowered the yield from 94% to 19%. Aoyagi et al. reported a compound in which the alkyl group at the 3-position of 3-deazainosine is locked into the anti conformation. Conditions for the synthesis were the same as those for a normal Heck reaction using a palladium catalyst (Scheme 52).[143] The cyclization

Scheme 52

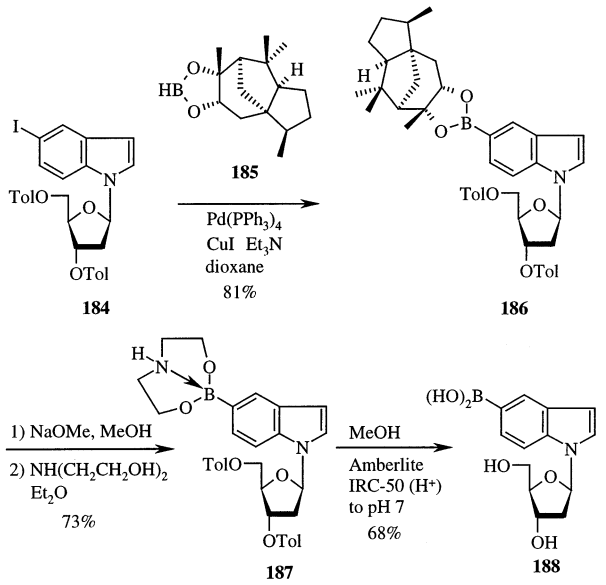


of the 5-iodoimidazole derivative **181** with a variety of Pd catalysts ($(dba)_3Pd_2{\cdot}CHCl_3$, $Pd(Ph_3P)_4$, $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, etc.) and in several solvents (DMF, CH_3CN, or dioxane) was examined. The best system proved to be $(dba)_3Pd_2{\cdot}CHCl_3$ in DMF, furnishing the desired cyclized nucleosides **182** with traces of the reduced byproduct **183** (when R = H). Yields are lower where R = Me.

E. Palladium-Catalyzed Synthesis of Boronated Indolonucleosides

Song et al. reported the preparation of a boronated nucleoside indole analogue (Scheme 53).[144] Cedrarediolborane (**185**) was cross-coupled with iodoindole (**184**) using catalytic amounts of $Pd(PPh_3)_4$ and CuI. The boronate **186**, thus readily formed, was converted to the free boronic acid by transesterification with diethanolamine to **187**, followed by acidic treatment to give **188**. This nucleoside analogue, whose nucleobase is expected to take part in hydrophobic and stacking interactions with neighboring residues, may be useful as well for the introduction of substitu-

Scheme 53



ents at C-5 on the indole ring through subsequent Suzuki−Miyaura couplings. The incorporation of the boron atom may again give rise to possible applications in BNCT.

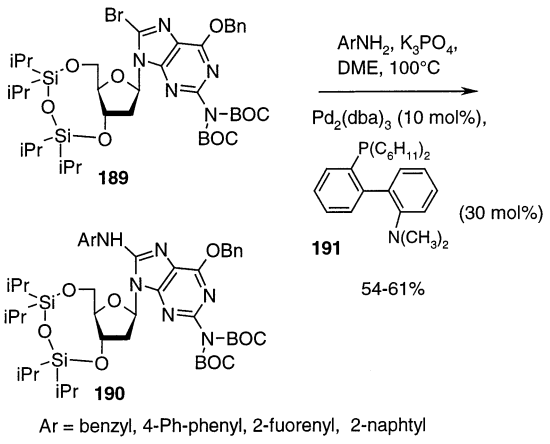
F. Palladium-Catalyzed C–N Bond Formation

One of the most recent illustrations of Pd-catalyzed modification of nucleosides is the C−N cross-coupling reaction. The compounds resulting from these reactions were first conceived as having potential as antitumor agents, since it is theorized that covalent alterations of DNA induced by electrophiles might be one explanation for the onset of chemical carcinogenesis. If these covalent modifications are not repaired, they compromise the fidelity of DNA replication, leading to mutations and possibly cancer. Poly- and monocyclic aromatic amines belong to the class of chemical carcinogens that, after metabolic activation, form covalently bonded adducts with DNA.[145] These mutagenic heterocyclic amines undergo metabolism to *N*-hydroxyl compounds that are then converted to nitrenium ions through the intermediary of *N*-hydroxyesters. Such electrophilic intermediates react with DNA bases and produce covalent adducts. The usual site of reaction is at the C-8 position of 2′-deoxyguanosine, but N-2 and N-6 adducts of guanosine and adenosine have also been isolated. Nucleosides modified in this way are difficult to study because they cannot be prepared in high yield by traditional methods. Apart from this, they are also needed as building blocks for synthetic oligonucleotides[129] and in the study of DNA recognition[146] and repair mechanisms.[147] Although Pd-catalyzed reactions are already well known among purines and purine nucleosides, these have largely been confined to C−C bond-forming reactions, but now palladium catalysis has begun to emerge as a versatile technique for C−N bond formation as well through cross-coupling reactions of aryl halides with amines.[148−150]

1. C–N Cross-Coupling at the C-8 Position

Wang and Rizzo utilized Pd-catalyzed cross-coupling for the synthesis of the 2-amino-3-methyl-

Scheme 54

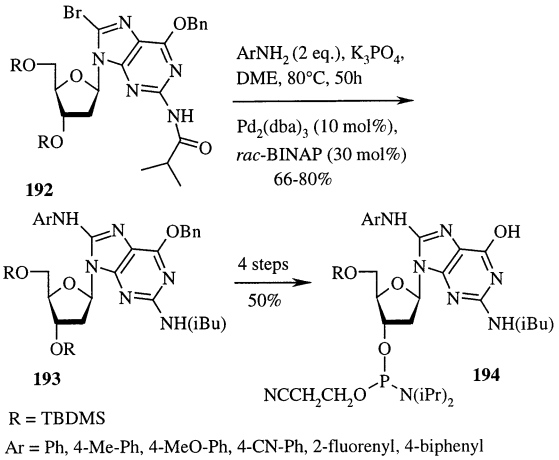


imidazo[4,5-*f*]quinoline (IQ)−2′-deoxy guanosine adduct at the C-8 position (Scheme 54).[151] From initial studies, it became apparent that the O-6 position and the exocyclic 2-amino group of the guanine moiety as well as the hydroxy groups of the 2′-deoxyribose should be blocked during the cross-coupling reaction. The bis-*N*-BOC derivative **189** appeared to be suitable for this purpose.

Optimal efficiency in the cross-coupling with mutagenic alkyl- or arylamines was obtained by using 10 mol % $Pd_2(dba)_3$, 30 mol % 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl (**191**), K_3PO_4 (a mild base compared to LiHMDS or sodium *tert*-butoxide), and 1,2-DME. The desired compounds **190** were isolated. Buchwald's group also reported the synthesis and application of the electron-rich ligand **191**, which is thought to accelerate the initial oxidative-addition step.[152] Comparable yields were obtained by using (±)-BINAP as the catalyst.

Meier and Gräsl reported as well a similar route to C-8 arylamine−dG adducts **193**, starting from the C-8-brominated precursor **192** and using palladium-catalyzed C−N bond formation in very good yield (Scheme 55).[153] These adducts were then converted

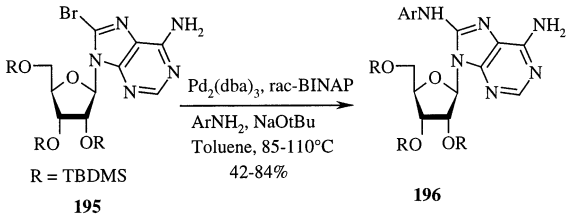
Scheme 55



into potential monomeric phosphoramidite building blocks **194** in yields high enough to satisfy the conditions for automated DNA−oligonucleotide synthesis.

C-8 guanine adducts, usually formed as the major products in vivo, have dominated carcinogenesis studies. The alternative C-8 adenine adducts, hitherto regarded as of minor importance, have been less studied, and their role, if any, is not well understood. Schoffers et al. achieved the synthesis of C-8 adenosine arylamine adducts by employing palladium-catalyzed *N*-arylation methods with good yield (Scheme 56).[154] Starting from **195**, the reactions

Scheme 56



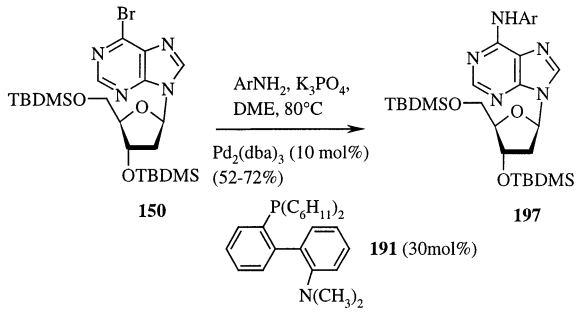
proceeded with 1.25 mol % $Pd_2(dba)_3$, 3.75 mol % racemic BINAP, and 1.4 equiv of NaO*t*Bu in anhydrous toluene at 80 °C for 6 h, affording the corresponding C-8 adduct in 84% isolated yield. Reactions of polycyclic arylamines were more capricious and slower (8−24 h), and they required more catalyst (30 mol % $Pd_2(dba)_3$, 50 mol % BINAP). Shorter reaction times (6 h) and comparable yields were observed when $Pd(OAc)_2$ was employed premixed with the ligand. It is noteworthy that no additional N-6 protection was necessary in this procedure.

A palladium-catalyzed carboxamidation at the 8-position of 8-bromoadenosine and 8-bromoguanosine was achieved by Tu et al.[155] which allowed several primary, secondary, heterocyclic, and aromatic amine and amino acids to be incorporated into purine nucleosides.

2. C–N Cross-Coupling at the C-6 Position

The most common method for accessing N-6-modified adenine nucleosides involves displacement reactions of a leaving group from an electrophilic nucleoside analogue by an amine,[156] and this approach has been effectively used to synthesize various classes of compounds. Recently, Lakshman et al. reported the synthesis of N^6-aryl 2′-deoxyadenosine derivatives **197** through Pd catalysis, which provides a novel entry to this type of compound (Scheme 57).[157] This also represents the first facile and general approach for introduction of aryl groups at the

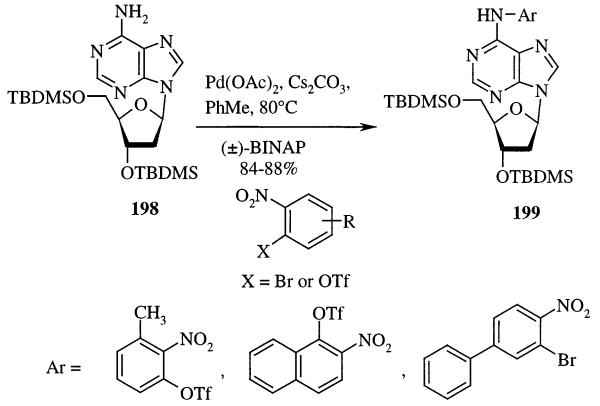
Scheme 57



exocyclic amine functionalities of nucleosides. The key appears to be the use of bis-coordinating ligands that are likely to resist ligand exchange by the pyridine and generally produce faster reactions.[129,158] The best results were obtained with 6-bromo-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-erythropentafuranosyl]purine (**150**), which is apparently the substrate of choice for Pd-mediated arylaminations, comparing favorably with the corresponding C-6 chloro or C-6 fluoro analogues, which do not react. It was found that the combination of $Pd_2(dba)_3$ (10 mol %), ligand **191** (30 mol %), and K_3PO_4 (1.5 equiv) in 1,2-DME at 80 °C proved to be best for effecting arylamination of **150**. In every case, the amination was complete within 3.5−4 h, regardless of the substituent on the arylamine.

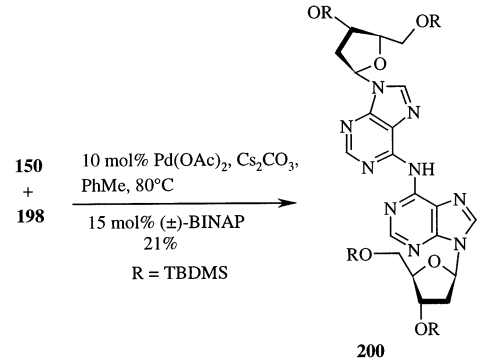
De Riccardis et al. described a Pd-catalyzed cross-coupling reaction where the exact opposite coupling partners were utilized (Scheme 58).[159] In this case,

Scheme 58



3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (**198**) was the arylamine component that was cross-coupled with *o*-nitroaryl bromides and *o*-nitroaryl triflates to give **199**. Apart from this, it was shown that a 2′-deoxyguanosine-2′- deoxyguanosine dimer **200** could be synthesized by a similar cross-coupling strategy (Scheme 59).[160] The yield of coupling was improved by using the 6-iodo instead of the 6-bromo compound **150**.

Scheme 59

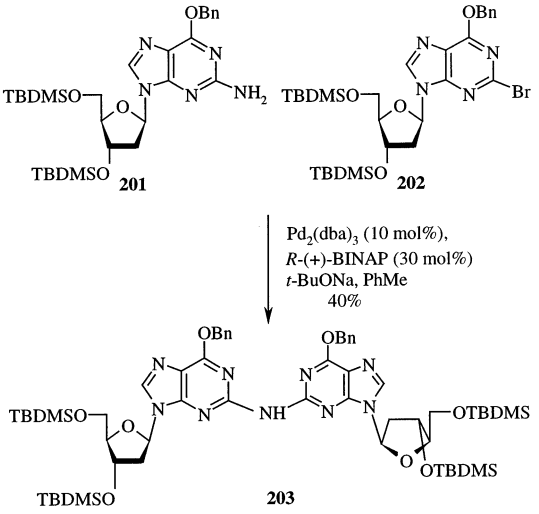


3. C–N Cross-Coupling at the C-2 Position

As in the case of reactions at the C-6 position of purines, C−N bond formations at the C-2 positions can also be effected by using Pd-catalyzed cross-

coupling methods. There is again good potential for gaining access to new classes of compounds. Harwood et al. described the synthesis of a 2′-deoxyguanosine-2′-deoxyguanosine dimer in which the guanines share a common N-2 atom (Scheme 60).[161] Such dimers

Scheme 60



represent synthetic examples of those thought to arise in DNA cross links induced by nitrous acid. In contrast to the C-6 halogenation of 2′-deoxyadenosine, which requires only protection of the sugar hydroxyls, the synthesis of C-2 halonucleosides requires additional protection of the O-6 moiety. So, Pd-catalyzed reaction of **201** and **202** provided dimer **203** in 40% yield. A similar approach was described by De Riccardis and Johnson.[160]

VI. Palladium-Mediated Allylic Alkylation to Nucleoside Analogues

The chemistry of natural nucleosides and their analogues has been widely studied, because of their potential as antiviral, antifungal, and anticancer agents. However, these close analogues of natural nucleosides are often also substrates for nucleoside phosphorylases, enzymes that cleave the *N*-glycosidic bond between the heterocycle moiety and the sugar, and when this happens biological activity may be rapidly reduced.[162] To avoid this problem and to investigate the potential for improved antiviral activity of nucleosides, a great number of modifications have been carried out on both the sugar and the heterocycle. The notional replacement of the oxygen of the furan ring by a methylene group gives rise to a corresponding series of carbocyclic analogues of nucleosides.[1b,c,j,163] Many such analogues have been synthesized, and several have been shown to exhibit biological activity as well as resistance to the above-mentioned degradation by phosphorylases. As expected, the carbocyclic analogues of BVDU (**5**) and IDU (**52**), namely C-BVDU (**204**) and C-IDU (**205**) respectively, are not substrates for phosphorylases,[164] but they maintain in vitro activity against HSV-1.[165] During the most recent period, research on the chemistry of the carbocyclic nucleoside analogues has been directed toward the development of agents with

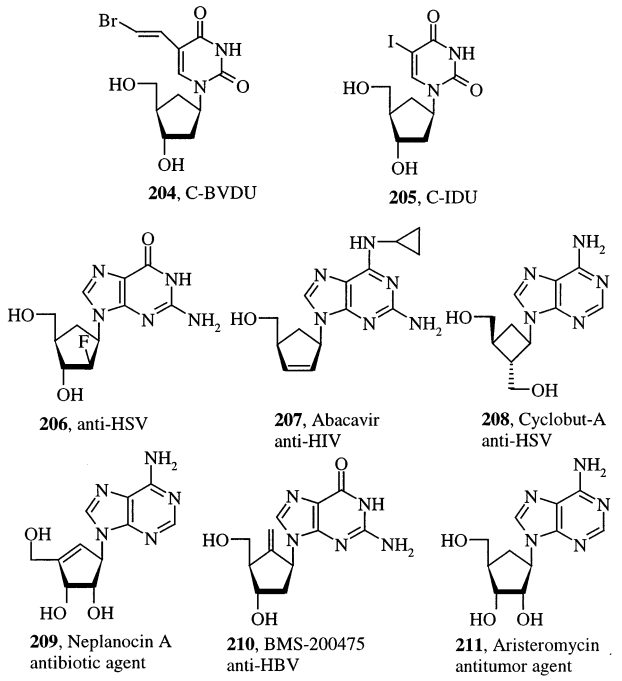


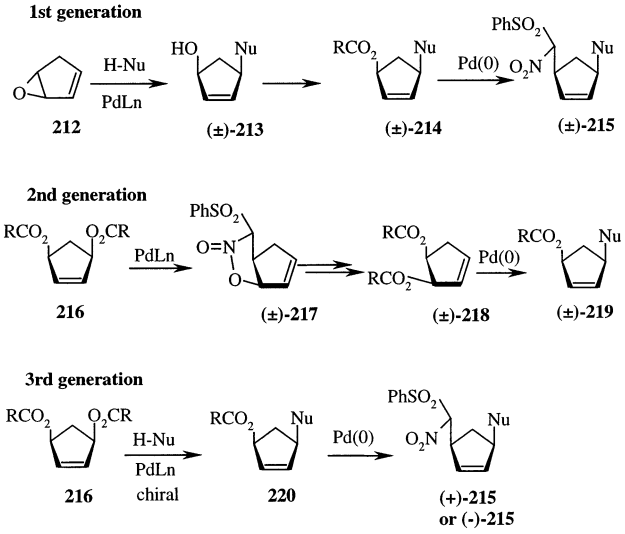
Figure 17. Some important antiviral carbocyclic analogues of nucleosides.

activities against HIV, HSV types 1 and 2, VZV, HCMV, and EBV (Figure 17).

The pharmaceutical importance of carbocyclic nucleoside analogues has thus been amply demonstrated and has prompted research into new methods for the synthesis of these compounds.One of the methods that has been pursued is the palladium(0)-catalyzed allylic substitution pioneered by Tsuji and Trost.[10a,b]

The Tsuji−Trost Pd(0)-catalyzed alkylations on an activated cyclopentene skeleton, to introduce the nucleobase and the hydroxymethyl side chain, have been widely applied (Scheme 61). In the first genera-

Scheme 61



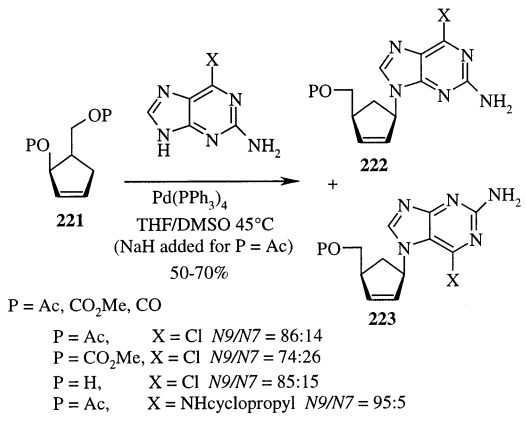
tion of methods, the heterocycle was introduced by ring opening of the cyclopentadiene monoepoxide **212**. Subsequently, a second generation of methods, making use of the Pd(0)-catalyzed alkylation of **216** with

the anion of phenylsulfonyl(nitro)methane, was developed. Both approaches yielded the racemic carbanucleosides (±)-**215** and (±)-**219**. Finally, a third approach, utilizing the above-mentioned Tsuji−Trost reaction and some chiral modular ligands, was developed for enantioselective synthesis of carbanucleosides (+)-**215** or (−)-**215** as single enantiomers (Scheme 61). Acetate and carbonate derivatives were found to be most useful for the palladium-catalyzed substitution at the allylic position with nucleoside bases. A basic catalyst, such as NaH, LiH and *n*-BuLi, Cs_2CO_3, or even Et_3Al, was necessary when the acetate derivatives were used.[166] Long reaction times in polar and high-boiling solvents are usually necessary because of the poor solubility of the salts of the heterocycles in the reaction media. However, methyl carbonate derivatives can be condensed under Pd(0) catalysis with nucleobases under neutral reaction conditions.

A. Regioselectivity of the Allylation of a Nucleobase

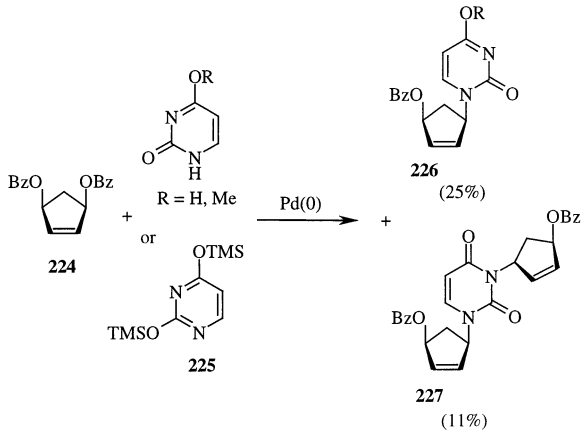
With ready access to an allylic acetate, carbonate, or cyclic carbonate, the Pd-catalyzed coupling with a purine base can, in principle, lead to a mixture of N-7 and N-9 isomers. This problem, which is classic in Vorbrüggen coupling of purines with sugars,[167] has been recognized only recently in Pd(0)-catalyzed couplings. Gundersen et al.[168a,b] reported that the coupling of purines with allylic esters and carbonates led to a mixture of regioisomers, of which the ratio could be modified by substitution at the 6-position of the purine. The best compromise was obtained with a 6-chloropurine analogue or a 6-aminocyclopropylpurine derivative (Scheme 62).[168a]

Scheme 62



It is known that several factors influence the regioselectivity of purine alkylations, including the size and nature of the ligand ($P(OMe)_3$, $P(OiPr)_3$, $P(OPh)_3$, BINAP, dppe, PPh_3, TMPP). When the bidentate phosphine ligand dppe was used in conjunction with Pd_2dba_3, a dramatic increase in the N-9/N-7 isomer ratio (up to 35:1) occurred. The corresponding problem, which might be encountered when using a pyrimidine base under either Vorbrüggen or Mitsunobu conditions, has not been fully assessed. The only reported byproduct formed from the condensation of **224** with pyrimidine **225** is the bis-alkylated product **227**. It is interesting to note that addition of tetra-*n*-butylammonium chloride to the reaction mixture suppresses the formation of this secondary product in favor of **226** (Scheme 63).[168c]

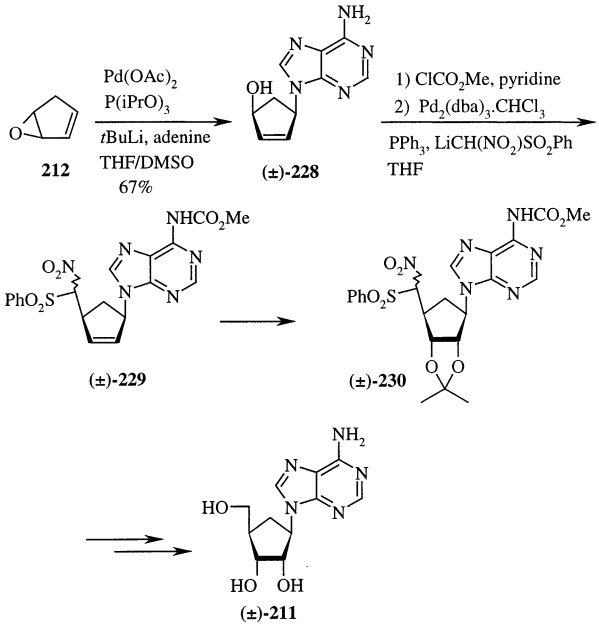
Scheme 63



B. From Cyclopentadiene Epoxide

Trost et al.[11] were the first to report the use of a Pd(0)-catalyzed cross-coupling reaction between a heterocycle and the cyclopentadiene monoepoxide (**212**) as part of the synthesis of racemic aristeromycin (**211**) (Scheme 64). Cyclopentadiene monoepoxide was already known to capture weakly acidic nucleophiles in a cis-1,4 fashion upon exposure to Pd(0) catalysts.[50b,169] Thus, the reaction of cyclopentadiene monoepoxide (**212**) with $Pd(OAc)_2$ and adenine gave the cyclopentenol **228** in 67% yield. The optimal conditions were 0.6 mol % of $Pd(OAc)_2$ with 6 mol % of $P(iPrO)_3$ and 1.2 mol % of *t*BuLi in a THF/DMSO mixture. The allylic carbonate, generated by treatment of **228** with $ClCO_2Me$, was subjected to a second palladium cross-coupling reaction with a phenylsulfonylnitromethane anion (5% Pd(0), 50% PPh_3 in THF) to afford **229**, containing a group from

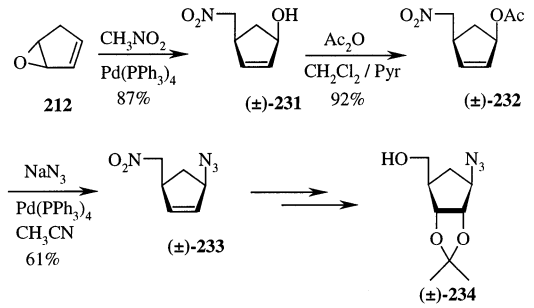
Scheme 64



which the 5′-hydroxymethyl group could be elaborated. After hydroxylation and protection of the formed diol **230**, conversion of the nitrosulfone to its nitronate and subsequent ozonolysis produced the ester, which was then converted to (±)-aristeromycin (**211**).

Following the same approach, Deardorff et al. reported the synthesis of (±)-aristeromycin (**211**) by introduction via cyclopentenyl(π-allyl)palladium complexes, first of a nitromethyl group **231**, and then an azido group **233**, in satisfactory overall yield (Scheme 65).[170] Nitromethane was used as the solvent with 1

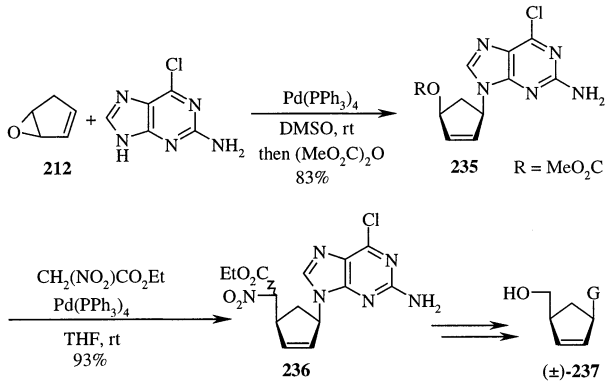
Scheme 65



mol % $Pd(Ph_3)_4$, thus avoiding the formation of any bis-alkylated derivative. By a two-step oxidation−reduction, the nitromethyl moiety was transformed into the corresponding 5′-hydroxymethyl function **(**±)-**234**; meanwhile, the azido group serves as a precursor of the heterocycle.

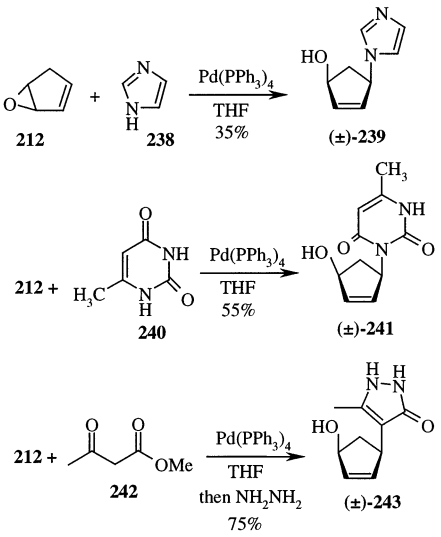
Using a similar route that involved the sequential Pd-catalyzed introduction of the heterocycle followed by another Pd(0)-catalyzed addition of a sulfonylnitronate, Peel et al.[171,172] reported the synthesis of (±)-carbovir (**(**±)-**237**) (Scheme 66). The regio-

Scheme 66



selectivity of the coupling step, with regard to the preference for either N-9 or N-7 substitution, had not been clearly assessed at that time. After activation of the resulting allylic alcohol as the carbonate **235**, the nitroacetic acid ethyl ester was introduced under palladium catalysis. **236**, the precursor of (±)-carbovir, was isolated in quantitative yield. This synthesis has also been applied to optically pure cyclopentene allylic acetate, which is available by an enzymatic desymmetrization of 2-cyclopentene-1,4-diacetate.

Scheme 67



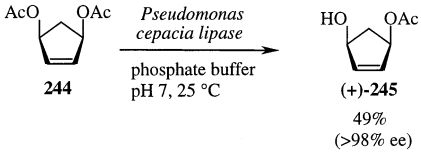
Palladium(0)-catalyzed allylation of various groups, such as imidazoles and 6-methyluracil, with cyclopentadiene monoepoxide was reported (Scheme 67).[173] Thus, the reaction of **212** with imidazole (**238**) in the presence of a catalytic amount of $Pd(PPh_3)_4$ in THF afforded *cis*-1-(4-hydroxy-2-cyclopentenyl)imidazole (**239**). A byproduct resulted from dimerization of the cyclopentadiene epoxide. Although uracil and 5-methyluracil reacted under Pd(0) catalysis to give the N-1-substituted product, 6-methyluracil (**240**) reacted at N-3 to form **241**, seemingly due to steric hindrance. Finally, when cyclopentadiene epoxide was treated first with methyl acetoacetate (**242**) under Pd(0) catalysis, and then with hydrazine hydrate, a mixture of *cis*-4-(4-hydroxy-2-cyclopentenyl)-3-methyl-5-pyrazolone ((±)-**243**) was isolated. It has been concluded that reactions with **212** should be performed at low temperature and at fairly high concentration to avoid any isomerization. Other carbocyclic *C*-nucleosides,[137] such as (±)-**243**, containing pyrimidine-2,4,6-triamine or pyrimidine-2(1*H*)-thione, were reported by Hildbrand et al.,[174] who made use of a stereoselective Pd(0)-catalyzed allylic substitution as the key step.

Cyclopentadiene monoepoxide has also been reacted under Pd(0) catalysis with many noncyclic nucleophiles, such as carboxylates or phenoxides,[175] active methylene compounds,[50b,176] and nitromethane.[170]

C. From Enzymatically Resolved *cis*-4-Acetoxy-2-cyclopenten-1-ol

Treatment of the diacetate of *cis*-3,5-cyclopentenediol ((±)-**244)** with *Pseudomonas cepacia* lipase (PCL) yielded the (+)-(1*R*,4*S*)-4-hydroxyl-2-cyclopentyl-1-acetate ((+)-**245**), a useful chiral intermediate for the

Scheme 68



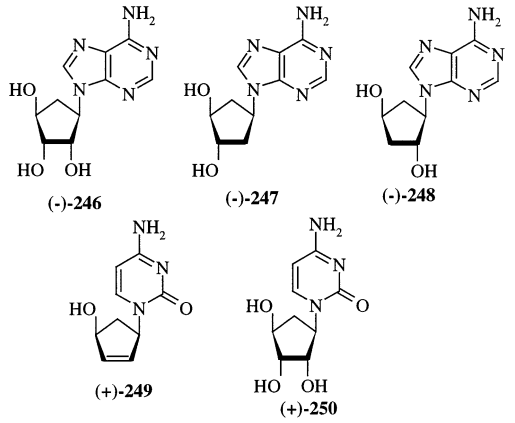
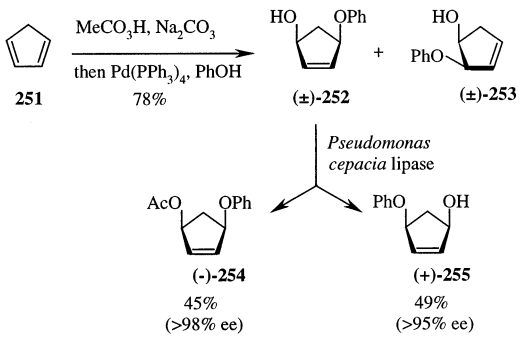


Figure 18. Some 5′-norcarbocylic nucleosides.

synthesis of carbocyclic nucleoside analogues (Scheme 68). This monoacetate was employed for the synthesis of various optically pure 5′-norcarbocylic nucleosides, **246**−**250** (Figure 18).[177] Following the palladium-promoted coupling of the allylic acetate with either a purine or a pyrimidine base, and subsequent modification of the double bond, the various optically pure 5′-norcarbocyclic nucleosides shown were obtained.

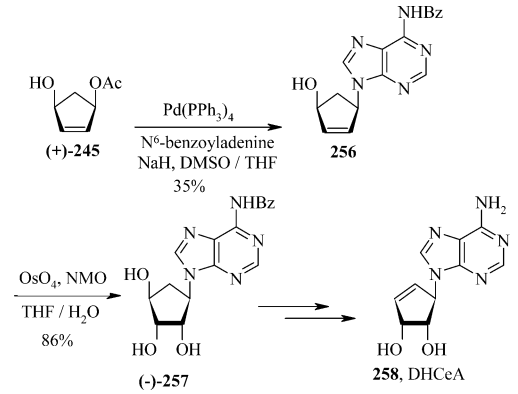
Cyclopentadiene (**251**) was converted with peracetic acid to the monoepoxide **212**, which was treated in situ with phenol under Pd(0) catalysis to afford *cis*-4-phenoxycylopent-2-enol ((±)-**252**) and, as a byproduct, *cis*-2-phenoxycyclopent-2-enol ((±)-**253**) (Scheme 69). Treatment of the racemic alcohol with PCL yielded, after separation, the optically pure acetate (−)-**254** and the allylic alcohol counterpart (+)-**255**.[178]

Scheme 69



Pd(0)-catalyzed coupling of various heterocycles with these enantiomerically pure allylic acetates afforded exclusively the cis-oriented products. Kitade et al. reported the synthesis (Scheme 70)[179] of optically pure (2′-hydroxy-3′-oxocyclopentan-1′-yl)-9*H*-adenine, possessing inhibitory activity against the enzyme *S*-adenosyl-L-homocysteine hydrolase (SAH), a target enzyme for antiviral and anticancer chemotherapy.[180] *S*-Adenosyl-L-homocysteine is formed from *S*-adenosyl-L-methionine (SAM) by the action of a methyl transferase and is then hydrolyzed by SAH to adenosine and homocysteine. Inhibition of SAH would, in principle, produce an accumulation of SAH, which is a potent feedback inhibitor of SAM-dependent biological methylation. Several inhibitors of SAH hydrolase have shown not only an antiviral effect but

Scheme 70



also antiparasitic,[181] antiarthritic, and immunosuppressive effects.[182]

Thus, treatment of the single enantiomer, (+)-*cis*-4-acetoxy-2-cyclopent-1-ol ((+)-**245**), with N^6-benzoyladenine under Pd(0) catalysis afforded **256**, which was oxidized by osmium tetroxide to N^6-benzoyl-5′-noraristeromycin (**257**). Subsequent diol protection, mesylation, elimination, and deprotection afforded the 9-[2′,3′-dihydroxy-4′-cyclopenten-1′-yl]-9*H*-adenine, DHCeA (**258**), a well-known antiviral agent.[183]

In the search for new medicinal agents derived from nucleosides, Seley et al.[184] obtained, using the same procedure as described above, two L-like carbocyclic nucleosides with promising activity (Figure 18). (+)-5′-Noraristeromycin ((+)-**246**) possesses anti-HBV activity,[185] while (−)-5′-noraristeromycin ((−)-**246**) has shown antiviral activity against cytomegalovirus, vaccinia virus, and measles. Activity against Epstein−Barr virus has been shown for the carbocyclic 5′-norguanosine (**259**).[186] (+)-7-Deaza-5′-noraristeromycin (**260**) is reported to be a candidate for treating trypanosome infections (Figure 19).[187]

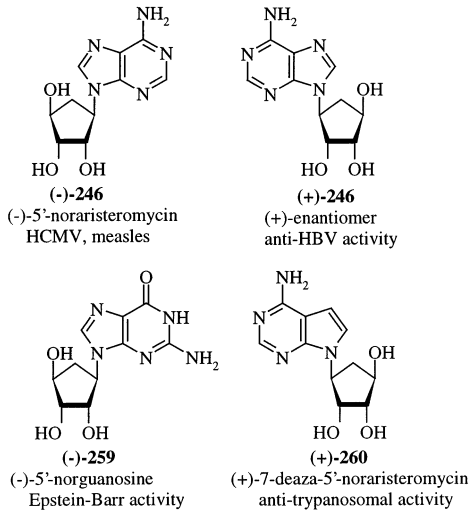
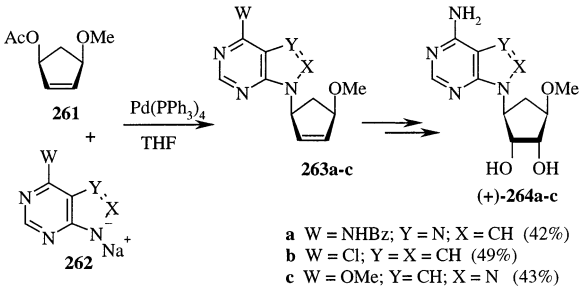


Figure 19. Structures of antiviral D- and L-5′-norcarbocyclic nucleosides.

To explore the SAR of the two L-5′-norcarbocyclic nucleosides, 4′-OMe derivatives were obtained by a similar approach: the key step was the introduction of the salt of the heterocycle **262**, to give **261** under

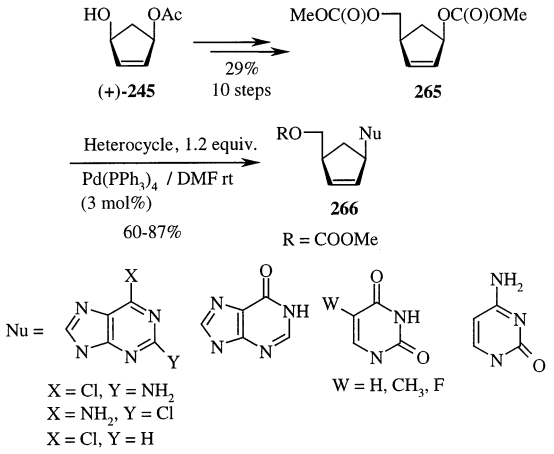
Scheme 71



Pd(0) catalysis (Scheme 71).[184] Ammonolyzis and glycosylation of the 4′-OMe analogues **263a**−**c** afforded the desired adenine **264a**, 7,8-dideazaadenine (**264b**), and 8-aza-7-deazaadenine (**264c**), respectively.

Finally, the (+)- and (−)-enantiomers of carbovir were obtained in a 12-step procedure, starting with the optically pure (+)-4-acetoxycyclopent-2-en-1-ol ((+)-**245**), via the allylic carbonate **265**. The latter was condensed under Pd(0) catalysis ($Pd(PPh_3)_4$, 3 mol %; heterocycle, 1.2 equiv) to afford the corresponding carbovirs **266**, with yields in the range 60−87% (Scheme 72).[188] When the methyl carbonate **265** was reacted with 2-amino-6-chloropurine in the presence of Pd(0), ∼20% of the N-7 isomer was isolated.

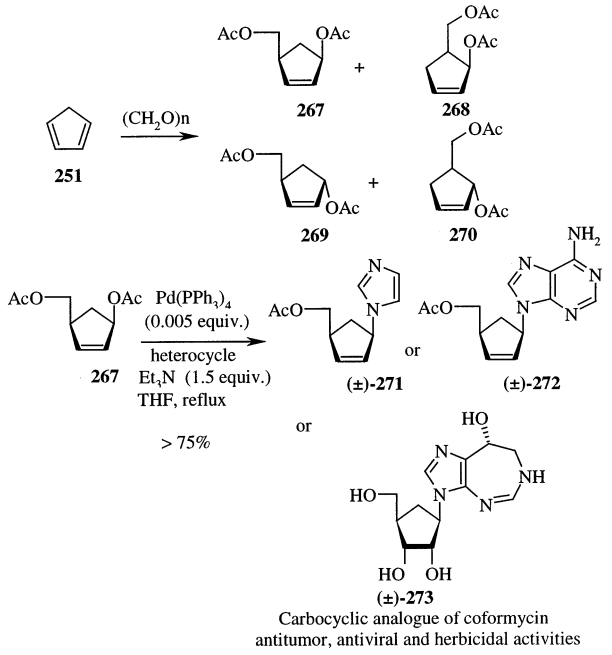
Scheme 72



D. Via a Modified Prins Reaction

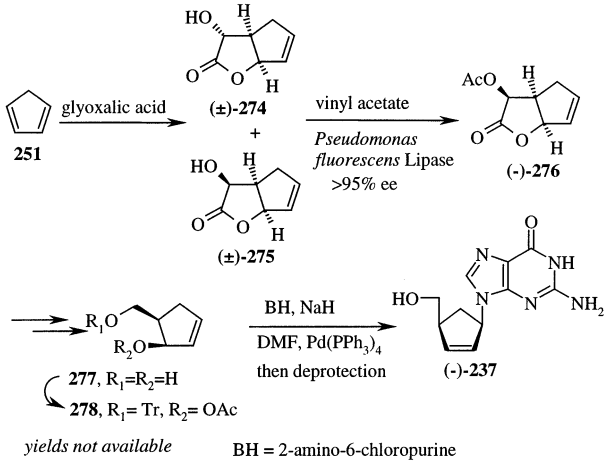
Saville-Stones et al. prepared cyclopentenyl allylic acetates by modification of the Prins reaction between cyclopentadiene and paraformaldehyde (Scheme 73).[189] The ratio of the diacetates **267**−**270** obtained after acylation of the Prins products is in favor of the *cis*-1,4-diacetates **267** and **269**, provided that the reaction is conducted under mild conditions (1 mol of cyclopentadiene, 3 mol of paraformaldehyde, and 0.4 mmol of tosic acid in AcOH, 10 °C, 23 h). A Pd(0)-catalyzed coupling between these allylic acetates and a suitable heterocycle provided carbocyclic 2′,3′-didehydro-2′,3′-dideoxynucleosides. In a simple model, the imidazole ring (±)-**271** was first introduced in 51% yield under Pd(0) catalysis ($Pd(PPh_3)_4$, Et_3N, THF, reflux). Then, extending the methodology from imidazole to adenine, it was found best to first form the sodium salt of the heterocycle and to then add the allylic acetate and palladium catalyst. The compound so obtained, (±)-**272**, was converted into (±)-aristeromycin triacetate by cis-hydroxylation followed by acylation. Following the same approach, the carbocyclic analogue of coformycin (±)-**273**, a naturally occurring nucleoside with anticancer, antiviral, and herbicidal properties, was synthesized, but the low yield (17%) seems to be due to the greater instability of the condensed diazepinone.[190]

Scheme 73



Prins reaction between cyclopentadiene (**251**) and glyoxalic acid afforded racemic lactones **274** and **275**,[191] which were separated and resolved enzymatically to (−)-**276** and used in enantioselective syntheses of carbovir ((−)-**237**) and aristeromycin (**211**). A three-step sequence involving reduction of the lactone, oxidative cleavage of the triol, and subsequent reduction afforded the optically pure diol **277**, which was duly converted to the tritylated allylic acetate **278** (Scheme 74).[191a] 2-Amino-6-chloropurine was

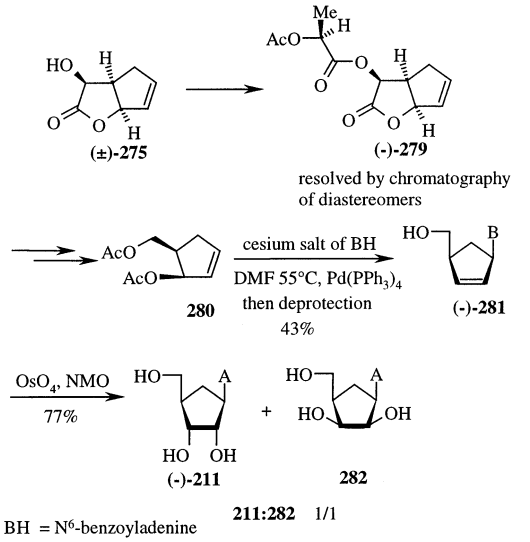
Scheme 74



then condensed with $Pd(PPh_3)_4$ in the presence of NaH to afford, after functionalization of the heterocycle and deprotection, the desired (−)-carbovir (**237**).

An elegant asymmetric aldol/ring-closing metathesis was developed by Crimmins et al.[192] that gives access to the optically pure 5-hydroxymethyl-2-cyclopent-1-ol (**277**), onto which the heterocycle has been condensed by Pd(0) catalysis (Pd_2dba_3, THF/DMSO, 45 °C, >65%). Burlina et al. resolved the lactone (±)-**275** by conversion of the secondary alcohol to its 2-acetoxypropionate (±)-**279** and subsequent chromatographic separation.[193] In a manner similar to that described above, the optically active lactone (−)-**279** was converted to the carbocyclic nucleoside (−)-**281** by exposure of the allylic acetate **280** to $Pd(PPh_3)_4$ and N^6-benzoyladenine (Scheme 75).[194] The introduction of the two hydroxyl groups

Scheme 75



into the cyclopentene system, to reach (−)-aristeromycin ((−)-**211**) and its isomer **282**, has been accomplished by osmylation, but with poor stereoselectivity. This contrasts with the high stereoselectivity for the addition of OsO_4 to 5′-noraristeromycin previously reported.

E. To 4′- or 5′-Amino Derivatives

The synthesis of carbocyclic analogues of nikkomycins or polyoxins **283**, a class of nucleosides in which the 5′-position is substituted by an amino acid, was accomplished from the resolved lactone by Aggarwal et al. (Figure 20).[195] The natural compounds exhibit selective activity against certain pathogenic fungi.[196]

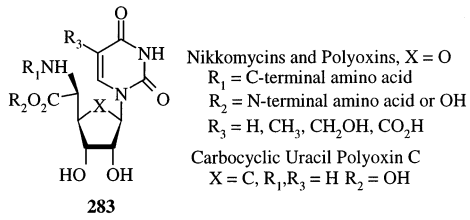
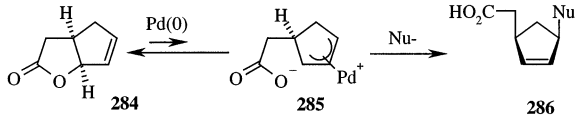


Figure 20. Chemical structures of nikkomycins and polyoxins.

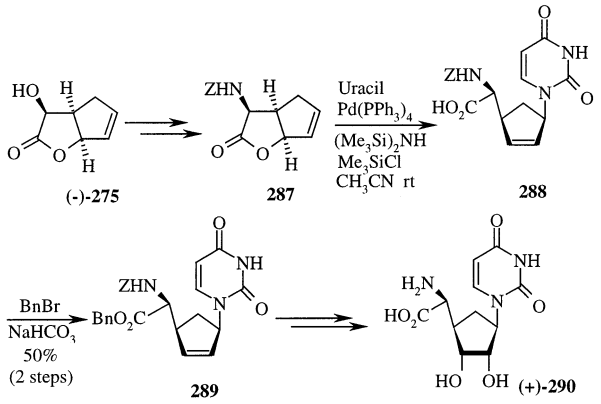
Initial attempts at opening the lactone **284** by using Pd(0) with either the uracil anion or NaN_3 failed, mainly due to competition from the internal carboxylate **285** during the substitution step (Scheme 76).[195]

Scheme 76



On the other hand, when the secondary alcohol of the lactone (−)-**275** was converted to the protected amine derivative **287**, the Pd(0) cross-coupling reaction was successful (Scheme 77).[195] To favor the

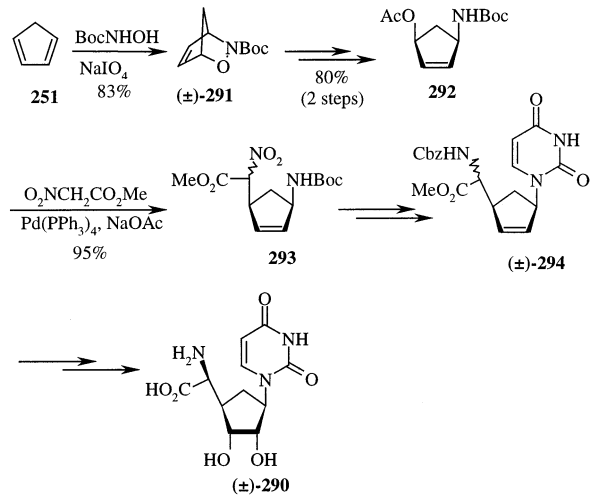
Scheme 77



formation of the active π-allyl palladium species rather than the closed lactone, the carboxylate, which is released during the Pd(0)-catalyzed reaction of **287** with the heterocycle to **288**, was trapped with TMSCl, without which no coupling occurred. Nonregioselective dihydroxylation was achieved using NMO with catalytic OsO_4; final hydrogenolysis of the benzyl protecting groups gave the desired carbocyclic analogues of nikkomycin ((+)-**290**).

(±)-Carbocyclic polyoxin C (**290**) has also been prepared from cyclopentadiene (**251**). The key steps were the use of acylnitroso hetero Diels−Alder reactions[197,198] to give **291**, followed by a Pd(0)-catalyzed alkylation reaction, affording **293** (Scheme 78).[199] Thus, hetero Diels−Alder reaction of cyclopentadiene

Scheme 78



with hydroxamic acid produced the bicyclic compound (±)-**291**. Allylic acetate **292** was obtained by reductive cleavage of the N−O bond using $Mo(CO)_6$ and $NaBH_4$, followed by acylation of the resulting allylic alcohol, which was subjected to Pd(0)-catalyzed nucleophilic substitution with methyl nitroacetate to give **293**. Here, nitroacetate was utilized as a synthon for an amino ester group. A five-step sequence, comprising reduction and protection of the nitro group, removal of the Boc protecting group, and incorporation of the heterocycle through an acyl isocyanate and subsequent cyclization, afforded the desired carbocyclic nucleoside (±)-**294**. Dihydroxylation with OsO_4/NMO and removal of all protecting groups provided the desired (±)-carbocyclic polyoxin C ((±)-**290**).

4′-Amino-substituted carbocyclic nucleosides **295**−**297** have been prepared as potential inhibitors of the enzyme adenosine kinase (Figure 21). It has been

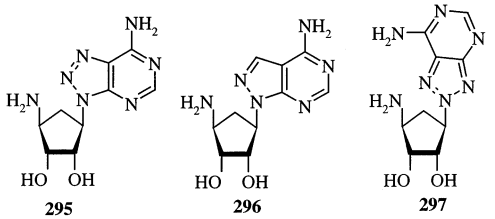
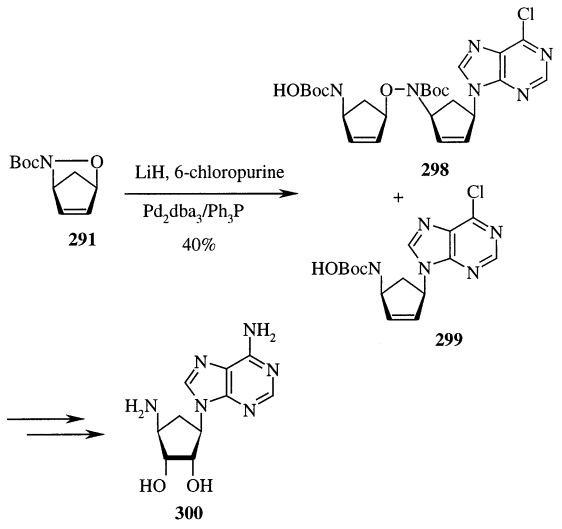


Figure 21. 4′-Amino-substituted carbocyclic nucleosides, inhibitors of adenosine kinase.

proposed that such compounds might represent a novel therapeutic approach to the treatment of neurodegenerative disorders such as epilepsy, stroke, and head injury as well as cardiac ischemia.[200]

The synthetic route to carbocyclic 4′-aminoadenosine (**300**) involved the Pd(0) catalysis reaction between the 6-chloropurine sodium salt and the heterobicycle **291**, obtained from a hetero-Diels−Alder reaction of cyclopentadiene on protected hydroxycarbamate (Scheme 79).[201]

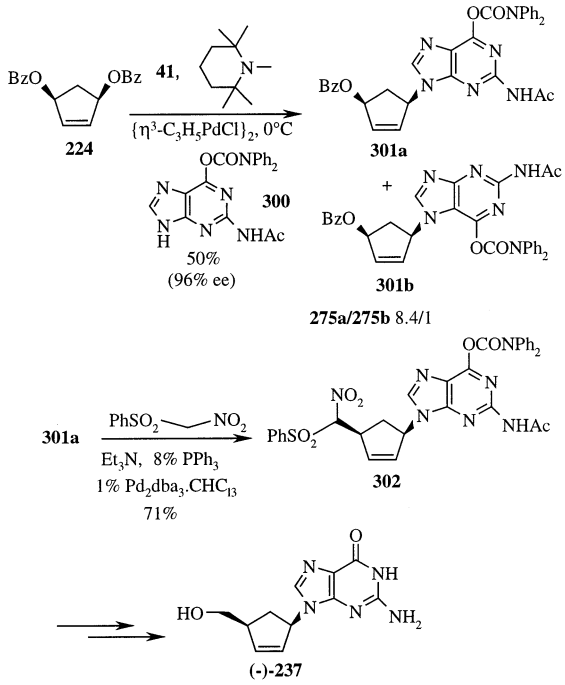
Scheme 79



F. Via Dissymmetrization with Chiral Ligands

Palladium (0)-catalyzed allylic substitution, as pioneered by Tsuji and Trost,[10a,b] is one of the most important methods for the substitution of allylic

Scheme 80

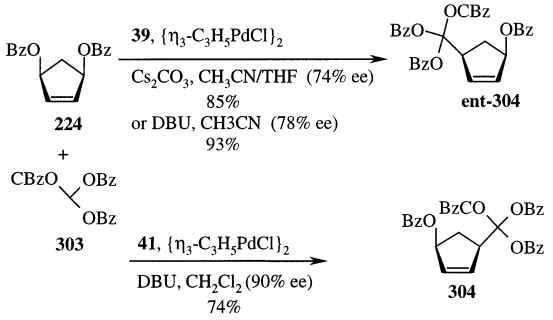


systems. On the basis of successes in dissymmetrization of carbocyles, Trost et al.[56a,59,202,203] also described an asymmetric synthesis of carbanucleosides (Scheme 80).[204] Starting from the dibenzoate **224**, a four-step synthesis of (−)-carbovir ((−)-**237**) was reported.[203] With the guanine, the products of alkylation at both N-9 (**301a**) and N-7 (**301b**) were observed, the proportion of each presumably depending on substituent electronic effects. The choice of base used played a significant role in this conversion: tertiary amine bases were superior to inorganic bases. In the series triethylamine, dicyclohexylamine, diisopropylethylamine, and 1,2,2,6,6-pentamethylpiperidine (pempidine), the yield of the alkylation product increased from 32 to 73%. To overcome the lack of stereoselectivity when 2-amino-6-chloropurine was used, substituting the C-6 position with an amido group, thereby reducing the electron-donating ability of the parent 2-amino group, blocked the N-7 position. In fact, upon reaction of diester **224** at 0 °C with the nucleophile **300** in the presence of pempidine as base, the η^3-allylpalladium complex and chiral ligand **41** led to the desired alkylated products **301a** and **301b** in a combined yield of 70% (**301a**:**301b** 8.4:1 and 96% ee). Since the product of monoalkylation is still an allylic ester, Pd(0)-catalyzed substitution can be performed a second time to introduce the one carbon unit regio- and diastereoselectively. In the event, treatment of **301a** with phenylsulfonylnitromethane in the presence of the palladium complex and triphenylphosphine gave **302**, which in two steps, after chemoselective oxidative cleavage and reduction, led to the desired (−)-carbovir (**237**).

Using the same approach, the enantio- and diastereocontrolled syntheses of (−)-carbovir, (−)-aristeromycin, (−)-neplanocin A, and its 2,3-di-epi isomer were performed.[205] This strategy is also applicable to *C*-nucleosides, which expands the scope significantly. Trost and Kallander reported a short and

versatile synthesis of (−)-showdomycin (**6**), predicated on the highly selective palladium-catalyzed desymmetrization of the dibenzoate **224**, which was reacted with nucleophile **303**, Pd(0) catalyst, and a chiral ligand **39** or **41** (Scheme 81).[55] By using **39** as

Scheme 81



the ligand and cesium carbonate as the base, a high yield (85%) of product *ent*-**304** (74% ee) was obtained. The enantioselectivity improved to 78% (93% yield) upon switching the base to DBU, with similar results being obtained in both acetonitrile and methylene chloride as solvents. On the other hand, by utilizing ligand **41**, which is believed to create a tighter pocket, the ee increased to 90% using DBU in methylene chloride to give **304**. In addition, either enantiomer of the product can be accessed, based on the choice of ligand stereochemistry. It appears that the palladium-catalyzed allylic alkylation offers an improvement in enantioselectivity over an alternative enzymatic strategy previously published for the synthesis of the antibiotic D-showdomycin.[206]

G. Miscellaneous Applications of Pd−Allylic Alkylation

(a) The Pd(0)-catalyzed allylic alkylation has been used to reach the six-membered ring compounds (±)-**305**−(±)-**308**,[54,207] as well as acyclonucleosides such as famciclovir (**309**),[19] an important antiherpetic nucleoside analogue (Figure 22).[208]

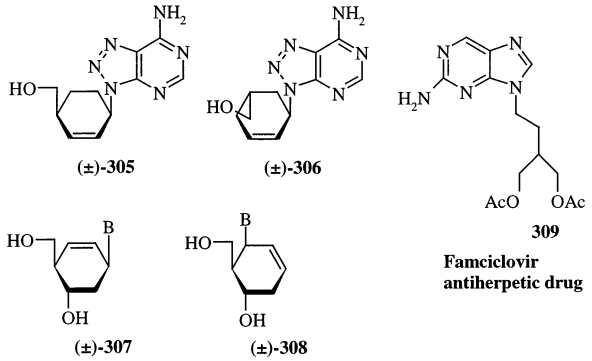
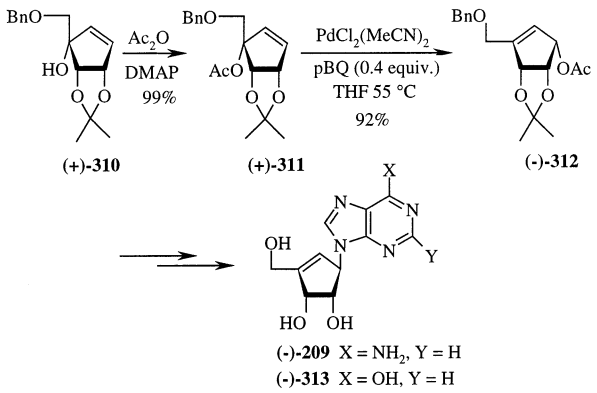


Figure 22. Various nucleosides obtained by Pd-allylic alkylation.

(b) Another interesting application of the Tsuji−Trost reaction is the allylic rearrangement of the hydroxy group from the enantiopure (+)-**310** to (−)-**312**. The method was successfully applied to the synthesis of (−)-neplanocin A[183b,209a] (**209**) and its analogue **313** (X = OH, Y = H) (Scheme 82)[209a] and

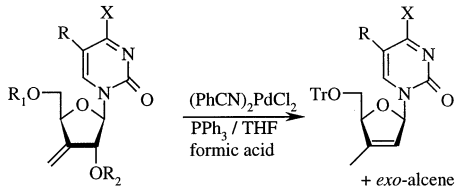
Scheme 82



to the enantioselective synthesis of 4′-α-substituted carbocyclic nucleosides.[209b] The same procedure was also reported Johnson and Penning.[210]

(c) Few applications of the Tsuji−Trost reaction have been reported affecting the sugar of a nucleoside. For instance, smooth deoxygenation of an allylic acetate (or allylic carbonate or allylic thionocarbonate) by formic acid in the presence of palladium catalyst, such as $(PhCN)_2PdCl_2$ in the presence of PPh_3 or Bu_3P, was first reported by Tsuji et al.[13,211] This method was applied to the synthesis of various 3′-branched-2′,3′-unsaturated pyrimidine nucleosides **315**, starting from allylic carbonate or acetate **314** (Scheme 83).[212a] Matsuda et al. also used this ap-

Scheme 83



proach[212] for the synthesis of antineoplastic nucleoside analogues of the so-called DMDC (2′-deoxy-2′-methylidenecytidine, **316**) or DMDT (**317**) (Figure 23).[212b]

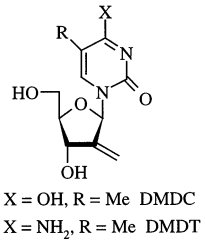
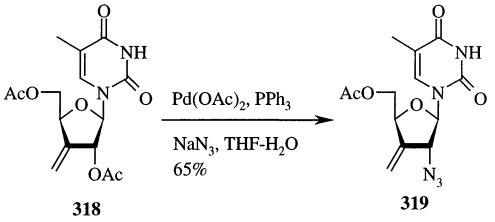


Figure 23. Antineoplastic nucleoside analogues.

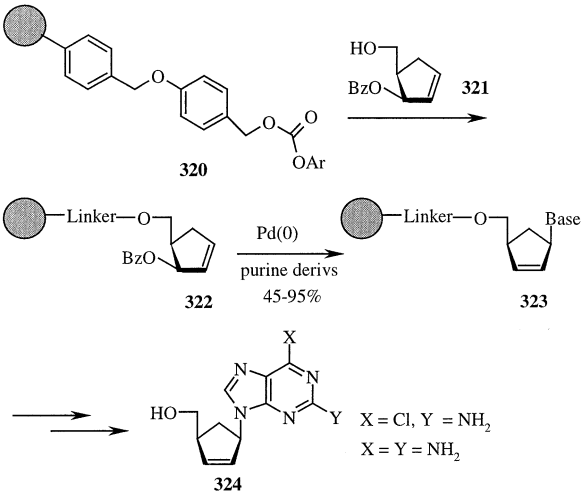
Another application is the Pd-catalyzed C-2′ azidation reported by Czernecki and Ezzitouni (Scheme 84).[213] This reaction occurs at the acetoxy-bearing carbon of **318** with retention of configuration via a (π-allyl)palladium complex. Optimal conditions were achieved by using $Pd(OAc)_2$ (1 equiv), PPh_3 (1 equiv), and NaN_3 in a solution of THF and H_2O; **319** was isolated in 65% yield.

Scheme 84



(d) Finally, very recently, Crimmins et al. reported the first solid-phase synthesis of carbocyclic nucleoside analogues of carbovir (Scheme 85).[214] Allylic

Scheme 85



benzoate **321** was loaded onto *p*-nitrophenyl Wang carbonate resin **320**, and the chloropurine was then introduced under Pd(0) catalysis; several parameters have been explored, embracing variation of the palladium catalyst ($Pd(PPh_3)_4$, $Pd_2(dba)_3$), the ligand (PPh_3, $P(OiPr)_3$), and the base ($EtNiPr_2$, Et_3N, pempidine). The solid-phase coupling reaction required a larger amount of catalyst than was required in the liquid phase and a bulkier amine for the highest conversion. Optimal conditions for the coupling utilized 10 mol % of $Pd_2(dba)_3$, 0.4 equiv of PPh_3, 6.0 equiv of pempidine, and 1.5 equiv of 2,6-dichloropurine in 1:1 THF:DMSO at 45 °C. After cleavage of the product **323** from the resin, the desired carbovir analogues **324** were obtained.

(e) Recently, two synthetic routes to novel 4′-α- or 3′-*C*-hydroxymethyl-branched carbocyclic nucleosides **325** and **326** (Figure 24) were described, based on a

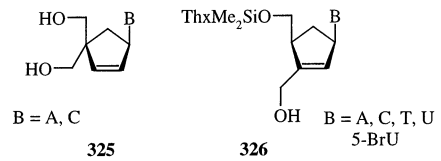
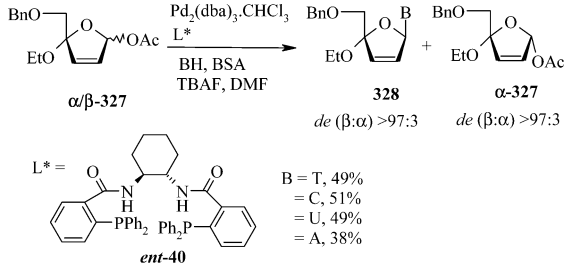


Figure 24. 4′- or 3′-*C*-hydroxymethyl branched carbocyclic nucleosides.

full linear synthesis of the cyclopentenyl moiety. Synthesis of **325** was performed through a Johnson ortho ester Claisen rearrangement, ring-closing metathesis, and Pd(0)-catalyzed allylic alkylation.[215] Meanwhile, the synthesis of the key intermediate for **326** was achieved by a cobalt-mediated Pauson−Khand reaction. In both cases, the introduction of the nucleobase was achieved with regio- and diastereoselectivity through a palladium-catalyzed allylic substitution [46−74% yield; nucleobase-H, NaH (or Cs_2CO_3), DMSO, 80 °C, $Pd(PPh_3)_4$ (5 mol %), PPh_3 (11 mol %) or $Pd_2(dba)_3{\cdot}CHCl_3$, $P(OiPr)_3$].

(f) Very recently, Hegedus et al. isolated new 4′-ethoxy-2′,3′-didehydro-2′,3′-dideoxynucleosides **328** by using a palladium-catalyzed kinetic discrimination between the corresponding lactol acetates α,*β*-**327** (Scheme 86).[216] Under asymmetric allylic amination conditions, using the *trans*-1,2-cyclohexanediamine-based ligand *ent*-**40**, the desired unsaturated nucleosides were obtained in high yields and <97:3 diastereoselectivity.

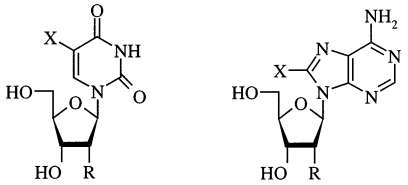
Scheme 86



VII. Miscellaneous Studies

A. Cross-Coupling in the Presence of Trialkylaluminum

Introduction of carbon chains onto the ring carbon atoms of the naturally occurring purine or pyrimidine nucleosides has been widely studied with the objective of discovering new biologically active compounds. Hirota et al. found that trialkylaluminum derivatives smoothly couple with halogenouridines[217] or halogenopurines[218] by palladium-catalyzed cross-coupling (Figure 25 and Table 2). After treatment with hexa-



	X	R
328a	Br	OH
b	Br	H
329a	Me	OH
b	Me	H
330a	H	OH
b	H	H
331a	I	OH
331b	I	H
332	Et	OH

	X	R
333	Br	OH
334	Br	H
335a	Me	OH
b	Et	OH
c	Pr	OH
d	*i*-Bu	OH
336a	Me	H
b	Et	H

Figure 25. Structure of halogenopurine or pyrimidine and resulting Pd(0) cross-coupling reaction.

methyldisilazane, 5-bromouridine (**328a**) was refluxed for 2.5 h in the presence of trimethylaluminum (2 equiv) and $(Ph_3P)_4Pd$ (0.05 equiv) in anhydrous tetrahydrofuran under argon, to afford the expected cross-coupling product, which was in turn smoothly deprotected to give 5-methyluridine (**329a**) in 71%

Table 2. Cross-Coupling of 5-Halogenouridine Derivatives 328 and 331 with Alkylaluminums

starting material	aluminum reagent	reaction time (h)	products (yield, %)	
328a[a]	$AlMe_3$	2.5	**329a** (71)	**330a** (21)
328a	$AlMe_3$	10	**329a** (86)	**330a** (7)
328b	$AlMe_3$	12	**329b** (81)	**330b** (0)
328a	$AlEt_3$	24	**332** (3)	**330a** (82)
331a	$AlMe_3$	4	**329a** (87)	**330a** (0)
331b	$AlMe_3$	24	**329b** (83)[b]	**330b** (0)

[a] $(PPh_3)_4Pd$ was used as a catalyst. [b] A mixture of α- and β-anomeric isomers was formed in the ratio of 9:11.

Table 3. Formation of Alkylated Purine Nucleosides

products	aluminum reagent	reaction time (h)	yield (%)[a]
335a	$AlMe_3$	2	95
335a	$AlEt_3$	8	42 (31)
335c	$AlPr_3$	24	53 (34)
335d	$Al(i\text{-}Bu)_3$	72	13 (59)
336a	$AlMe_3$	8	84
336b	$AlEt_3$	12	62 (21)

[a] Values in parenthese are yields of the debrominated products.

yield, together with a debrominated product (**330a**) in 21% yield. When a mixture of palladium chloride and triphenylphosphine (1:2) was used as catalyst, the yield of coupling product **329a** was improved from 71% to 86% and the formation of the debrominated product **330a** was reduced to 7%. Under similar conditions, starting from iodo compounds **331a**,**b**, thymidine derivatives **329a**,**b** were obtained in 83−87% yield. In the reaction of **328a** with triethylaluminum, the debromination occurs preferentially, and the yield of 5-ethyluridine (**332**) was extremely low.

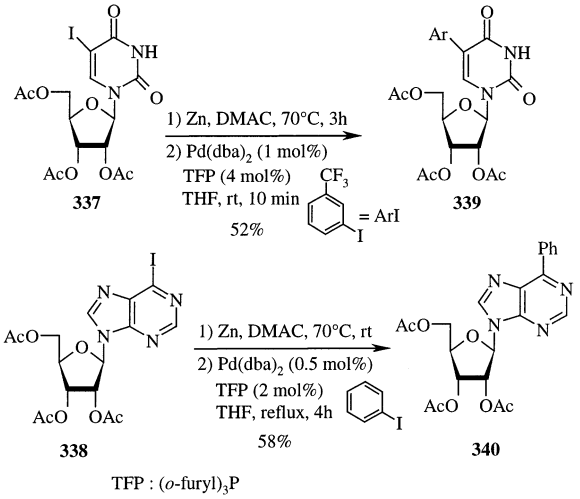
The same coupling reaction may be applied to introduce an alkyl group into various purine nucleosides (Table 3) and may thus provide further *C*-alkylated nucleoside analogues for biological studies.

B. Cross-Coupling with an Organozinc Nucleoside

Metalated nucleosides fulfilling the role of the nucleophile in cross-coupling reactions have been rarely used due to the difficulties of preparing reactive organometallics derived from these sensitive and complex organic molecules. Organozinc reagents, however, offer promise, as they are generally prepared under mild conditions and tolerate a broad range of organic functionalities. Stevenson et al. reported the preparation and Pd(0) cross-coupling reactions of several new zinc organometallics derived from nucleosides such as uridine and purine riboside (Scheme 87).[8a] Thus, treatment of the 5-iodouridine derivative **337** or the 6-iodopurine derivative **338** with zinc dust in *N*,*N*-dimethylacetamide at 70 °C or room temperature produces the expected zinc reagent in 80% yield. Palladium-catalyzed cross-coupling reaction with an iodoaryl compound furnishes the arylated nucleosides **339** and **340**, respectively, in 52 and 58% yield.

Another application of this process, the Negishi reaction, was the synthesis, in moderate yield, of

Scheme 87

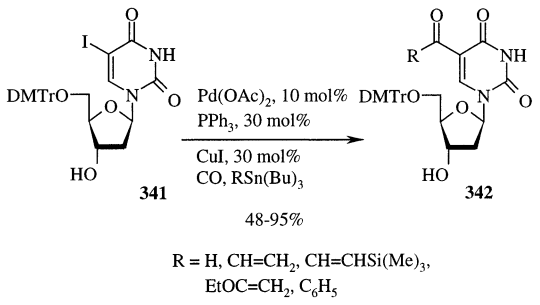


2-carbamoylmethyl-6-β-D-ribofuranosylpyridine with the aid of $Pd(Ph_3)_4$ and the Reformatsky reagent ($BrZnCH_2CO_2Et$).[219a] The reaction of new zincated nucleic acids/bases and nucleosides, obtained directly from an iodinated heterocycle, with various electrophiles under Pd(0) catalysis gave a broad range of polyfunctional nitrogen-containing heterocycles.[219b]

C. Palladium-Catalyzed CO Insertion

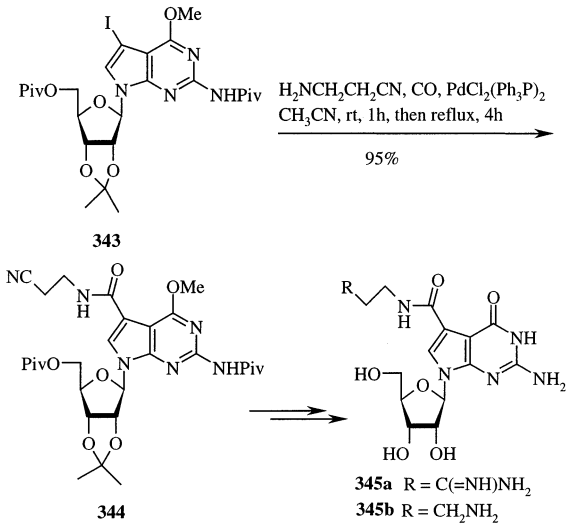
The use of palladium catalysis to introduce carbonyl substitutents at the 5-position of pyrimidine nucleosides gave rise to some new carbonyl-substituted 2′-deoxyuridine derivatives. Using Stille conditions in the presence of a palladium catalyst formed in situ from palladium(II) acetate and 3 equivs of triphenylphosphine and copper(I) iodide in THF, Crouch and Eaton prepared compound **342** in good yield. The reaction was conducted in an atmosphere of carbon monoxide (Scheme 88).[220]

Scheme 88



In addition to this, Sampei et al. reported the synthesis of ribofuranosyl echiguanines A (**345a**) and B (**345b**) (Scheme 89),[221] which were tested as potent inhibitors of phosphatidylinositol-4 kinase derived from the A431 cell membrane.[222] A palladium-catalyzed carbonylation reaction between protected 7-iodo-7-deazapurine (**343**) and cyanoethylamine was used as the key step for the synthesis of **344**, the precursor of **345a**,**b**. The coupling reaction proceeded very efficiently (95% yield) under carbon monoxide at atmospheric pressure using bis(triphenylphosphine)palladium (II) chloride as the catalyst.

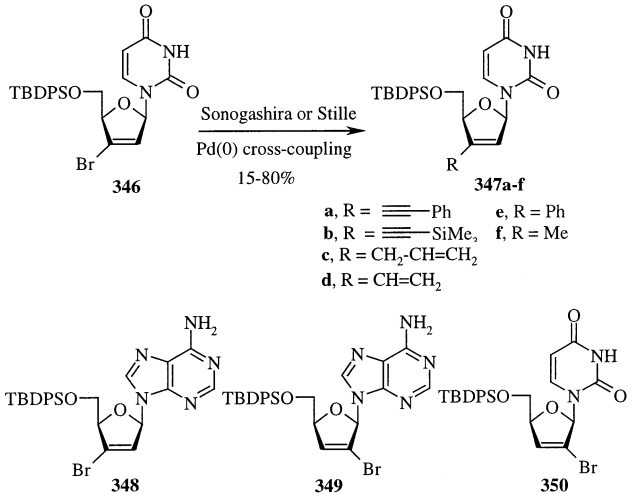
Scheme 89



D. Palladium-Catalyzed Cross-Coupling on the Sugar Moiety

Although the palladium-catalyzed cross-coupling reaction is frequently employed for C−C bond formation, its application in the field of nucleosides has usually been limited to reactions of the base moiety. Haraguchi et al.[223] described examples of its application to the sugar moiety of nucleosides (Scheme 90).[223a] In particular, palladium-catalyzed cross-

Scheme 90

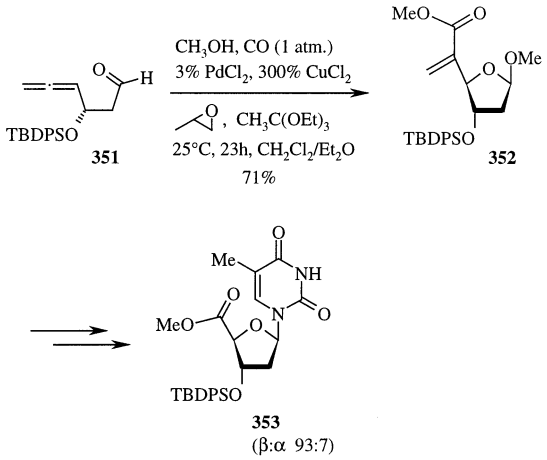


coupling of the bromovinyluracil nucleoside **346** under Sonogashira conditions afforded the corresponding alkynes **347a**,**b** in good yields (60−80%). The reaction was carried out in DMF and Et_3N at 80−100 °C for 1−5 h in the presence of 10 mol % of $(Ph_3P)_2PdCl_2$ or $(Ph_3P)_4Pd$ as catalyst. Introduction of an allyl or a vinyl group **347c**,**d** was achieved under relatively mild Stille conditions in the presence of the corresponding organotin reagent ($Bu_3SnCH{=}CH_2$ or $Bu_3SnCH_2CH{=}CH_2$) in DMF or benzene at 70 or 100 °C by using a palladium catalyst such as $(Ph_3P)_2PdCl_2$ or $(Ph_3P)_4Pd$. Transfer of the phenyl or methyl ligand **347e**,**f** required heating in the presence of the corresponding tin reagent in dioxane at 100 °C for 1−2 days, giving the 3′- or 2′-substituted products. The same reaction was carried out for the isomers **348**−**350**; it should be noted that none of the 3′-*C*-substituted adenine derivative was observed when **348** was reacted with Ph_4Sn or Me_4Sn.

E. Palladium-Mediated Cyclization of a γ-Oxoallene

Based on the discovery that γ-oxoallenes such as 4,5-hexadienal will undergo palladium(II)-mediated acetalization−cyclization−methoxycarbonylation in the presence of acid and water scavengers,[224] Walkup and Mosher[12] described the synthesis of nucleoside analogues having a branched, extended, and difunctionalized 5′ side chain (Scheme 91).[12] Such nucleo-

Scheme 91



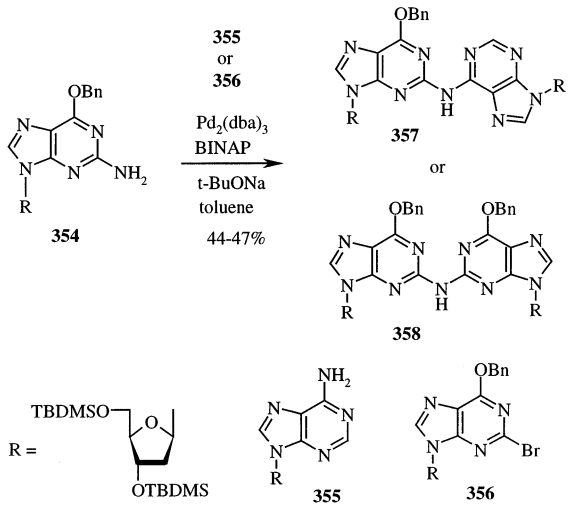
side analogues might be useful for the preparation of oligonucleotide analogues bearing "reporter" groups (for probing the structure and dynamics of DNA interactions) at selected locations via attachment of such groups to the branching group on the side chain.[225] A one-pot acetalization−cyclization−methoxycarbonylation procedure, mediated by palladium(II), cleanly converted **351** to the furanoside **352** as a single diastereomer in 71% yield. The stereoselectivity of this cyclization has been attributed to a combination of steric effects exerted by the bulky trialkylsilyl group and stereoelectronic constraints in the transition state of the cyclization step.[226] Reduction of the side-chain ester group of **352**, followed by acetylation, yielded the extended side chain deoxyribofuranoside, which was then subjected to a Vorbrüggen coupling using persilylated thymine, to yield the protected thymidine analogue **353** in excellent yield as a mixture of α and β anomers.

F. To N-2-Substituted 2′-Deoxyguanosines

Treatment of DNA with nitrous acid results in the formation of DNA−DNA cross links. Two types of cross-link lesions have so far been identified, and their structures have been assigned on the basis of spectroscopic data. The major lesion is proposed to consist of two deoxyguanosine nucleosides sharing a common N-2 atom, while the minor lesion is proposed to consist of a common nitrogen atom linking C-2 of a deoxyguanosine nucleoside to C-6 of deoxyadeno-

sine. Harwood et al.[227] reported the chemical synthesis of these two nucleoside analogues **357** and **358** by utilizing a palladium-catalyzed coupling reaction (Scheme 92).

Scheme 92



G. Palladium-Mediated Glycal–Aglycon Coupling: Synthesis of *C*-Nucleosides

Since the isolation[228] and structural elucidation of the naturally occurring *C*-nucleoside antibiotic formycin A, several reports have appeared in the literature describing its diverse biological properties.[137,229] Formycin A (**359**), a cytotoxic isostere of adenosine, is readily deaminated by the catabolic enzyme adenosine deaminase (ADA) to the less active inosine analogue formycin B (**360**) (Figure 26).[230]

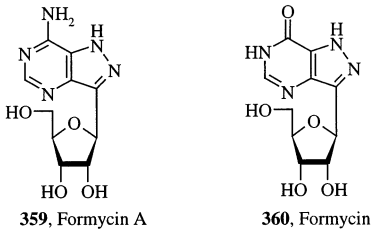


Figure 26. Examples of antiviral *C*-nucleosides.

However, interest in the potential of formycin A as an anticancer agent has been rekindled because, in combination with an ADA inhibitor, formycin A is effective in prolonging the life of mice infected with L1210 leukaemia.[231] Moderate antiviral activity with formycin A was also observed in cell culture. Due to its *C*-glycosidic linkage, formycin A is stable to the action of purine nucleoside phosphorylase, and this resistance to glycosidic cleavage provides a distinct potential advantage of this group of nucleosides as therapeutic agents.

All reported syntheses of *C*-nucleosides of the formycin series which involve formation of the *C*-glycosyl linkage have been accomplished by construction of the pyrazolo[4,3-*d*]pyrimidine aglycon ring system onto a C-1 carbon-substituted ribofuranosyl moiety.[232] However, Zhang et al.[9,233] were the first to report the synthesis of 2′-deoxyformycin B (**364a**) and 2′,3′-dideoxyformycin B (**364b**) by using the palladium-mediated regio- and stereospecific *C*-glycosyl bond-forming reaction (Scheme 93). The furanoid glycals **362**, with bulky protecting groups at the 3-position, have been used for stereospecific formation of the β-C-glycosyl bond with the iodinated heterocycle **361**. As shown in Table 4, introducing triphenylphosphine as a ligand and raising the reaction temperature to 80 °C led to *C*-glycosyl formation (5%), yielding the *C*-nucleoside together with large quantities of deiodinated aglycon and aglycon dimer (entry 2). The use of triphenylphosphine was more effective (entry 3), and the use of acetonitrile rather than DMF as reaction solvent further increased the yield of **363** (entry 4). A Pd(0) catalyst rather than Pd(II) (entries 5 and 6) increased *C*-glycosyl bond formation further. The best result was obtained with the use of a Pd(0) catalyst with triphenylphosphine as ligand in acetonitrile (entry 7), resulting in regio- and stereospecific formation of *C*-nucleoside **363** in 62% isolated yield.

Scheme 93

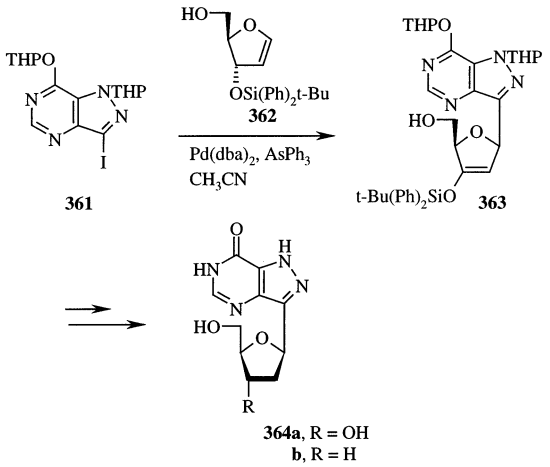


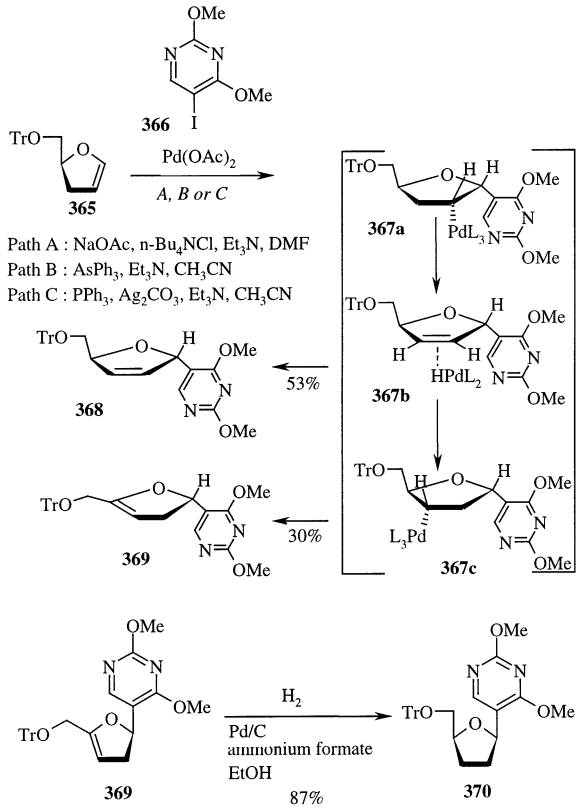
Table 4. Palladium-Mediated Glycal–Aglycon Coupling Reaction

entry	Pd source (0.1 equiv)	ligand (amount, equiv)	solvent	temp (°C)	yield (%)
1	$Pd(OAc)_2$	n-Bu_4NCl (0.5)	DMF	25	nr[a]
2	$Pd(OAc)_2$	PPh_3 (0.2)	DMF	80	5
3	$Pd(OAc)_2$	$AsPh_3$ (0.2)	DMF	80	19
4	$Pd(OAc)_2$	$AsPh_3$ (0.2)	CH_3CN	80	28
5	$Pd(dba)_2$	$AsPh_3$ (0.2)	DMF	80	39
6	$Pd(dba)_2$	$AsPh_3$ (0.2)	NMP[b]	80	36
7	$Pd(dba)_2$	PPh_3 (0.2)	CH_3CN	80	62

[a] No reaction. [b] *N*-Methylpyrrolidone.

Syntheses of enantio- and diastereoisomers of 2,4-dimethoxy-5-(2,3-dideoxy-5-*O*-tritylribofuranosyl)pyrimidine were been reported by the same group (Scheme 94).[9] The palladium-mediated coupling reaction yields two isomeric products, **368** and **369**, because the intermediate π-complex **367b**, formed by *syn*-β-hydridopalladium elimination from the σ-organopalladium adduct **367a**, proceeds in two ways. Not only can **367b** dissociate to the 2′,3′-unsaturated *C*-glycoside **368**, but also PdH can add to the double bond, to form a new σ-adduct **367c** and thereby effect double-bond migration to form the thermodynamically more stable 3′,4′-unsaturated *C*-glycoside **369**, which possesses a newly formed asymmetric center

Scheme 94

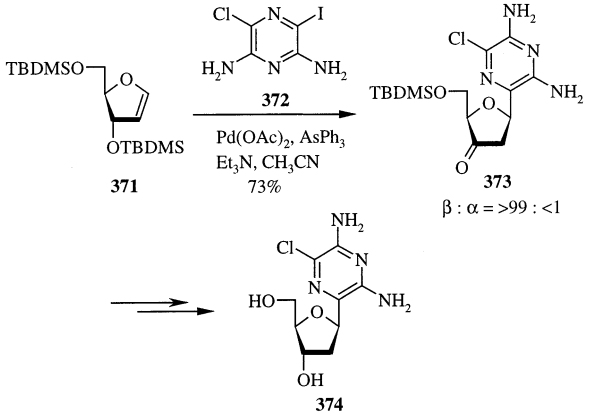


at C-1′ but has lost the original asymmetric center at C-4′. Carrying out the palladium-mediated coupling reaction in the presence of tetra-*n*-butylammonium chloride and in the absence of triphenylphosphine (path A) facilitates dissociation of the π-complex **367b** and slightly favors formation of the 2′,3′-unsaturated *C*-nucleoside **368**. When tetra-*n*-butylammonium chloride was omitted from the reaction mixture and supporting triphenylarsine ligands for palladium were provided (path B), π-complexation was stabilized, and carbohydrate double-bond migration was favored. Use of a silver salt (path C) completely suppressed double-bond migration. Hydrogenation of the 3′,4′-unsaturated *C*-nucleoside **369** occurred selectively from the less hindered face of the furanoid ring, yielding the cis-substituted product **370**.

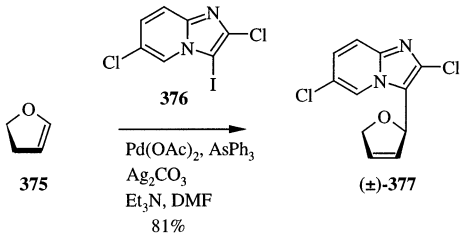
Townsend et al.[234] reported an efficient synthesis of the novel pyrazine *C*-nucleosides **374** via a stereospecific Pd(0)-mediated cross-coupling reaction of ribofuranoid glycal **371** with the heterocycle **372** (Scheme 95).[234a] In previous studies, ribofuranoid glycals, with a bulky protecting group only at the 3-position, have generally been used to optimize the cross-coupling reaction to give the β-product, but it has now been found that ribofuranoid glycals with both the 3- and 5- positions protected gave almost exclusively β-products.

The same workers also reported the first synthesis of a *C*-nucleoside derivative **377**, containing a sugar moiety attached to the C-3 position of an imidazo-[1,2-*a*]pyridine heterocycle via a palladium-catalyzed coupling reaction of the heterocycle **376** with the 2,3-dihydrofuran (**375**) (Scheme 96).[234b]

Scheme 95



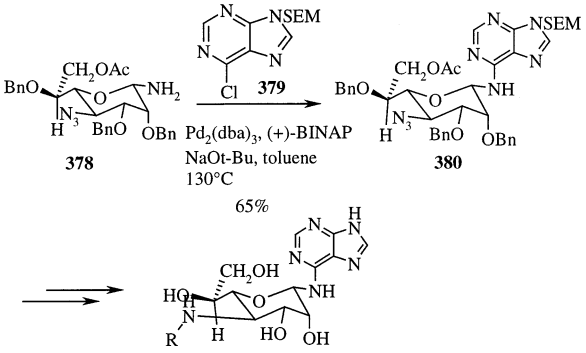
Scheme 96



H. Palladium-Catalyzed Coupling of Glycosylamine with 6-Halopurine Derivatives

Chida et al. reported the preparation of spicamycin amino nucleoside (SAN, **381**), which is a useful precursor for the synthesis of spicamycin (**382**) and its analogues. The key step in their synthesis consisted of a Pd-catalyzed coupling between the protected glycosylamine **378** and the 6-chloro-9-SEM purine **379** (Scheme 97).[235] This straightforward

Scheme 97

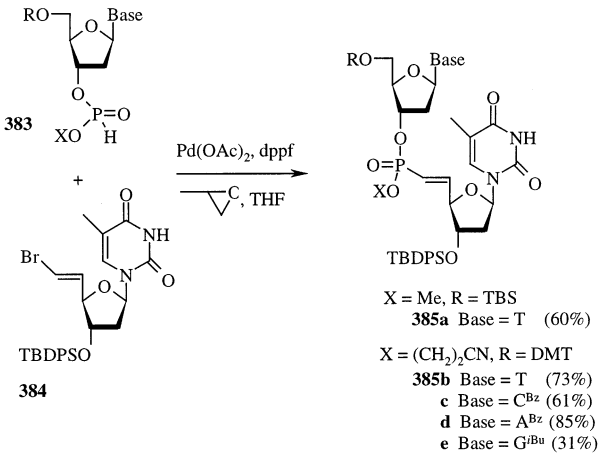


methodology, first reported by Wolfe and Buchwald,[236] Louie et al.,[237] and Reddy and Tanaka,[238] provided 6-(β-D-mannopyranosylamino)purine via a one-step reaction in good yield. The reaction of the amine **378**, which was prepared from *myo*-inositol, with **379** in the presence of $Pd_2(dba)_3$ (10 mol %), (*R*)-(+)-BINAP (20 mol %), and NaO*t*-Bu (150 mol %) in toluene at 130 °C, gave the desired coupling product **380**, which is a precursor of SAN **381**, in 65% yield.

I. Palladium-Catalyzed Coupling Reaction of *H*-Phosphonate with Bromoalkene

Recently, Abbas et al. reported a method for the synthesis of modified T*T and d(A)*T dimers which contain hydrolytically stable vinylphosphonate internucleotide linkages **385** (Scheme 98).[239] The key step

Scheme 98

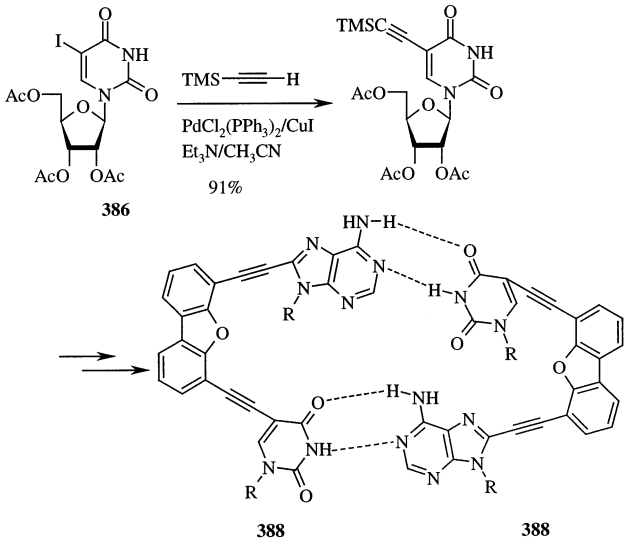


in this synthesis utilizes a Pd(0)-catalyzed coupling reaction between the thymidine-derived 1-bromo-1-alkene **384** and the nucleotide-derived *H*-phosphonates **383**. Coupling of each of the *H*-phosphonates (**383**, 1.4 equiv) with the thymidine-derived vinyl bromide (**384**) was accomplished by using 0.2 equiv of $Pd(OAc)_2$, 0.4 equiv of dppf, and 10 equiv of propylene oxideas an HBr scavenger, in THF, and provided the corresponding vinylphosphonate-linked dimers (T*T, **385a** and **385b**; d(C)*T, **385c**; d(A)*T, **385d**; and d(G)*T, **385e**) in modest to good yields. A range of functional groups, including the base-labile cyanoethyl group, was tolerated under these conditions. Abbas et al. also demonstrated that the T*T dimer synthesized using this methodology can be successfully used in the automated synthesis of oligonucleic acids.

J. Synthesis of Artificial Dinucleotide Duplexes

DNA provides a model for the way in which complementary functionality may be used to induce spontaneous assembly in complex supramolecules. In recent years, many self-complementary structures capable of undergoing assembly have been designed. However, this process has remained unpopular, which could be due to the facts that (1) the binding affinities associated with adenosine−thymidine (or uridine) "dimerization" are too low ($K_a \approx 10^2$ M^{-1} in $CDCl_3$) and (2) cytidine and guanosine, which do have high affinities for complementary association ($K_a \approx 10^4$ M^{-1} in $CHCl_3$), are highly insoluble in organic media and thus are difficult to work with. Indeed, Sessler and Wang[240] reported that self-assembly of DNA-like artificial dinucleotide duplex structures could be achieved by increasing the rigidity and solubility of their components (Scheme 99).[241] The monomer in this system contains an acetylene linker, which can be introduced by Pd cross-coupling chemistry. Four successive palladium-mediated couplings

Scheme 99



were needed to assemble the basic skeleton of the monomer **388**.

More recently, Hocek and Votruba achieved the synthesis of bis(purin-6-yl)acetylenes **390**, -diacetylenes **(391)** and the related compounds **392** and **393** (Figure 27).[242] This was achieved by Sonogashira cross-coupling and homocoupling reactions of 6-ethynylpurines and 6-iodopurines.

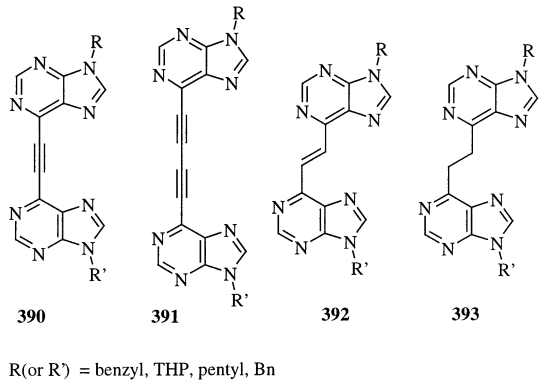
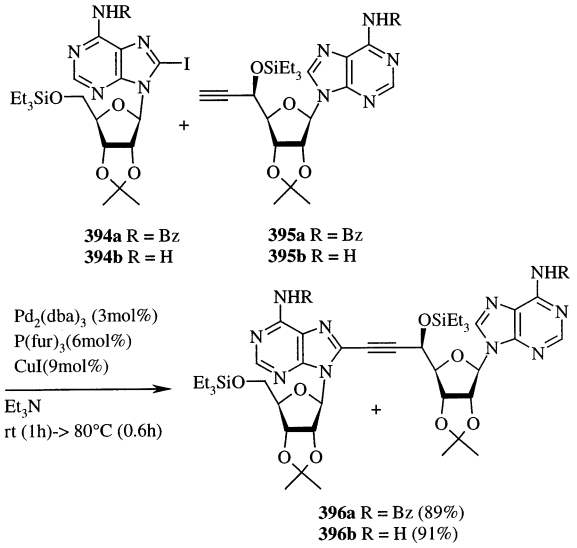


Figure 27. Covalent analogues of DNA base pairs.

K. Precursors of Oligonucleotides with a Nucleobase-Including Backbone

The synthesis of acetyleno-linked adenosine dimers and tetramers of oligonucleotide analogues in which the 3′,5′-phosphodiester moiety between adenosine units is replaced by an 8,5′-acetylene link (Scheme 100)[243] has been reported. These compounds may form stable complexes with uridine oligonucleotides and their 6,5′-acetyleno-linked analogues. The synthesis of dimers **396** was achieved by a Sonogashira reaction in which cross-coupling of a C-8-halogenated monomer **394** with a C-5′-ethynylated nucleoside **395** occurs.[244] The optimized catalytic system consists of $Pd_2(dba)_3$, Et_3N, and 6 mol % of tris(furan-2-yl)-phosphine, which accelerates the cross-coupling about 3-fold. The amine group on **395b** is reported to be more reactive than its *N*-benzoylated analogue **395a**. The NH_2 group in **395b** is too far from the alkynyl group for its increased reactivity to be due to a

Scheme 100



394a R = Bz
394b R = H

395a R = Bz
395b R = H

396a R = Bz (89%)
396b R = H (91%)

through-bond interaction; however, the difference between the amine and benzamide can be explained by the presence of a more strongly basic adenyl residue in **395b**. The regioselectivity of the coordination of the intermediate at the N-3 position may be due to oxidative addition of the catalytically active [PdL_2] species to the iodoadenosine in such as manner as to promote its interaction with the alkynyl moiety. Tetramers have been obtained using the same strategy.

VIII. Concluding Remarks

Over the past several years, explosive new developments have occurred in both palladium and nucleoside chemistry. As described in this review, palladium cross-coupling reactions have found many potential applications in the syntheses of nucleoside analogues used in antiviral or anticancer chemotherapy. While traditional approaches to producing these and other nucleoside derivatives have continued to be explored, attention has increasingly been focused on the development of more efficient and versatile routes. The wide varieties of palladium-assisted routes described in this review are a direct result of this effort. The predominant type of palladium cross-coupling reaction that occurs with nucleosides is palladium-mediated allylic alkylation, leading to carbanucleosides. Regioselective and enantioselective allylic alkylations are a new development and are of great interest because of their flexibility and because they may provide a practical route to various, potentially valuable nucleoside derivatives. The development of solid-phase palladium-catalyzed reactions, as well as the discovery of new applications of the C−N bond formation, will be of great value in exploring new families of nucleosides. Thus, in the future, the widespread use of nucleosides in chemotherapy, along with the power and increasing importance of stereo- or regioselective palladium-catalyzed cross-coupling reactions, seems certain to ensure continued interest in palladium-assisted route to nucleosides.[245]

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