Review Article

Applications of Boronic Acids in Selective C-C and C-N Arylation of Purines

J. Jacob Strouse, Marjan Ješelnik, and Jeffrey B. Arterburn*

Department of Chemistry & Biochemistry MSC 3C, New Mexico State University, P.O. Box 30001, Las Cruces, NM 88003 U.S.A.
E-mail: jarterbu@nmsu.edu

Received 17-08-2005

Abstract

Substituted purine derivatives have broad biomedical value as therapeutics, and have attracted great interest as molecular tools and probes for investigating biological systems. The modification of purines with aryl or heteroaryl substituents dramatically alters conformational preferences, the steric profile, and hydrogen-bonding capacity. The development of new methods for metal-mediated coupling with aryl or heteroaryl halide substrates has greatly expanded the range of synthetically accessible arylpurine derivatives. Arylboronic acids have proven to be extremely effective reagents for the synthesis of arylpurine compounds. Arylboronic acids are stable, versatile, and readily available reagents for metal-mediated C-C and C-N coupling reactions. Coupling reactions resulting in C-C bond formation are catalyzed by palladium and nickel catalysts at positions C^2, C^6, and C^8. Copper mediated N-arylation occurs at positions N^1, $N^{2'}$, N^7, and N^9. These methods are also applicable using solid supported purine substrates. Successful coupling involves careful optimization of catalyst, ligand, base, solvent, and reaction temperature. These methods provide convenient access to structurally unique arylpurine derivatives with applications in drug discovery and chemical biology.

Key words: C-C coupling, C-N coupling, Aryl-Purine Derivatives

Contents

Introduction

Purines are one of the most important classes of heterocyclic compounds in biology, fulfilling functional roles as nucleic acids, coenzymes, and constituents in metabolic processes, energy storage, and cell signaling. A wide variety of substituted purine derivatives have been isolated from natural sources.[1] The purine ring system is susceptible to substitution through both nucleophilic S_NAr and alkylation with electrophilic reagents. The introduction of substituents can affect the sterics, hydrogen-bonding, and hydrophobicity that results in altered interactions with nucleic acids and proteins. It is well known that even minor structural modifications of nucleosides can greatly affect their biological activity and metabolism. Substituted purine derivatives have broad biomedical value as therapeutics, and have attracted great interest as molecular tools and probes for investigating biological systems.[2]

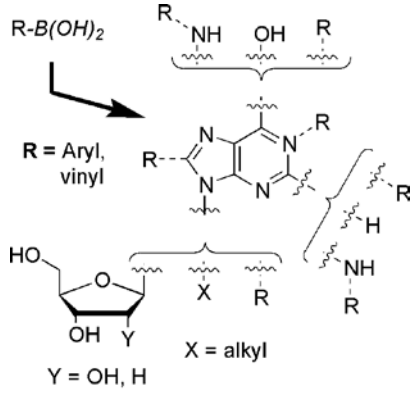
The modification of purines with aryl or heteroaryl substituents dramatically alters conformational preferences, the steric profile, and hydrogen-bonding capacity. The alkylation of purines with polycyclic aromatic hydrocarbons is related to the carcinogenic

and other genotoxic effects associated with these compounds.[3] Mutagenic intrastrand DNA cross-links are formed from dietary and environmental exposure to oxides of nitrogen.[4] Aryl purine derivatives exhibit biomedically relevant activity including antiviral, antibacterial, anticancer, and antihypertensive properties.

Aryl purine derivatives can be prepared by displacement of electrophilic halogenated purines with aryl nucleophiles, or through the reaction of nucleophilic purines with activated, electron deficient arylating agents. While direct substitution has been successful for the synthesis of many derivatives, the electronic requirements and forcing reaction conditions limit the scope of this approach. The development of new methods for metal-mediated coupling with aryl or heteroaryl halide substrates has greatly expanded the range of synthetically accessible aryl purine derivatives. These methods have been the subject of several recent reviews.[5] The inherent capacity of heteroatoms as ligands constitutes one of the greatest challenges to metal-mediated coupling reactions of heterocyclic compounds. The N^1, $N^{2'}$, N^3, $N^{6'}$, $O^{6'}$ and N^7-positions of purines are possible coordination sites with mono and bidentate binding modes. The application of metal-mediated arylation with purine substrates requires careful optimization of catalyst, ligand, base, solvent, and reaction temperature. Frequently, individualized experimental conditions are required for a specific reactive pair of purine substrate and arylating reagent.

Boronic acids exhibit desirable characteristics that are advantageous when compared to other organometallic and organometalloid reagents. Boronic acids can be synthesized from a variety of precursors and are typically stable and easily stored. A wide range of substituted aryl and heteroarylboronic acids are commercially available, including a variety of functional groups, different ring sizes and conjugated systems. This diversity in boronic acid substrates facilitates mechanistic investigations and is particularly valuable for structure activity relationships in medicinal chemistry. Boronic acids and boron-containing byproducts are typically non-toxic and easily removed from reaction mixtures, even on large scale. Arylboronic acids have proven to be extremely effective reagents for the synthesis of biaryl compounds using the palladium catalyzed Suzuki-Miyaura coupling reaction.[6] Suzuki reactions can be performed using a variety of organic solvents including aqueous systems. The success achieved in palladium-catalyzed cross coupling chemistry has been paralleled by new developments in the classical copper mediated Ullmann Reaction.[7] The Chan-Evans-Lam copper(II)-catalyzed C-N and C-O coupling procedure with boronic acids has been extended to amines, analines, amides, imides, ureas, carbamates, sulfonamides, and phenols.[8]

Recently, coupling procedures involving boronic acids have been extended to purine substrates. This review focuses on the metal-mediated C-C and C-N arylation of purine derivatives with arylboronic acids. This approach provides access to a wide variety of mono-, di-, and tri-substituted aryl and heteroarylpurines as summarized graphically in Scheme 1.



Scheme 1

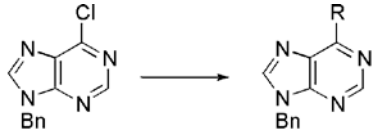
Biographical Sketches

J. Jacob Strouse *(left), born in Las Cruces, New Mexico (USA) in 1976, completed his undergraduate degrees in 2000 from New Mexico State University. He continued under the mentorship of Jeffrey B. Arterburn at New Mexico State University and is currently a senior chemistry Ph.D. candidate with focus on the copper mediated synthesis of arylnucleoside derivatives.* ***Marjan Ješelnik*** *(center), born in Ljubljana (Slovenia) in 1970, completed his Ph.D. in organic chemistry in 2000 at the University of Ljubjana. He conducted postdoctoral research in metal-mediated arylation of heterocycles under supervision of Prof. Jeffrey B. Arterburn.* ***Jeffrey B. Arterburn*** *(right), born in Denver, Colorado (USA) in 1962, completed his Ph.D. in organic chemistry in 1990 at the University of Arizona, Tucson under the direction of E.A. Mash. He conducted postdoctoral research in organometallic chemistry at the ETH Zurich with Prof. D. Seebach, and the University of Washington with Prof. J. M. Mayer. He has been a faculty member in the Department of Chemistry & Biochemistry at New Mexico State University since 1992, where he holds the rank of Professor, and serves as the Director of the New Mexico IDeA Network of Biomedical Research Program.*

Catalytic C-C Coupling

C^6-arylation

The first example of the Suzuki-Miyaura cross coupling reaction using halogenated purine derivatives was reported by Havelková in 1999.[9] Several different catalyst precursors, bases, solvents, and reaction conditions were evaluated for C^6-arylation of the 9-benzyl 6-chloropurine substrate. Two optimized procedures employing $Pd(PPh_3)_4$ as catalyst were developed; anhydrous conditions using K_2CO_3 and toluene, or aqueous K_2CO_3 and dimethoxyethane (DME). Both of these procedures were effective for C^6-arylation with phenylboronic acid, providing the 6-phenylpurine product in 95% yield (Scheme 2).



Anhydrous Conditions

2.5 mol% $Pd(PPh_3)_4$, K_2CO_3, MePh, 100°C

Aqueous Conditions

2.5 mol% $Pd(PPh_3)_4$, aq. K_2CO_3, DME, 85 °C

R	Anhyd.	Aq.
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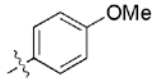
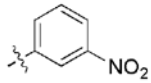
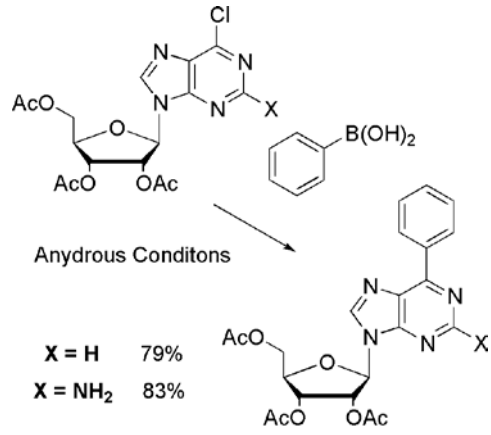
	62%	—
	19%	66%
	39%	82%

Scheme 2

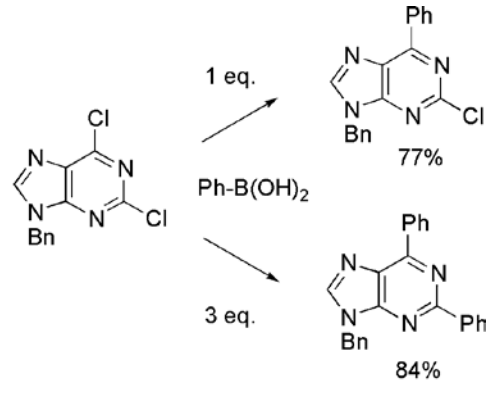
The more sterically hindered substrate 7-benzyl-6-chloropurine was converted to the 6-phenyl derivative in 70% yield under the anhydrous conditions. A trend based on the electron donating ability was observed within a series of substituted boronic acids. The anhydrous conditions were effective for arylboronic acids possessing electroneutral or electron rich groups, but reduced yields were observed when strong electron withdrawing substituents were present. Significantly improved yields were obtained for 3-nitrophenylboronic acid using the aqueous conditions. Other boronic acids such as 2-thienyl, styrenyl, and heptenyl also gave higher yields using the aqueous conditions. No coupling was observed using pentafluorophenylboronic acid under either of these reaction conditions. The coupling reaction also proceeded in aqueous DMF but at reduced rates. Butylboronic acid gave low yields of coupled product using the anhydrous conditions. These procedures have been applied in a series of related synthetic investigations.

The tri-O-acetyl protected ribonucleosides of 6-chloropurine and 2-amino-6-chloropurine were converted to the 6-phenyl derivatives in good yields using the anhydrous conditions (Scheme 3). The acetyl protecting groups were stable under these conditions, and no arylation of the N$^{2'}$-amine was observed.



Scheme 3

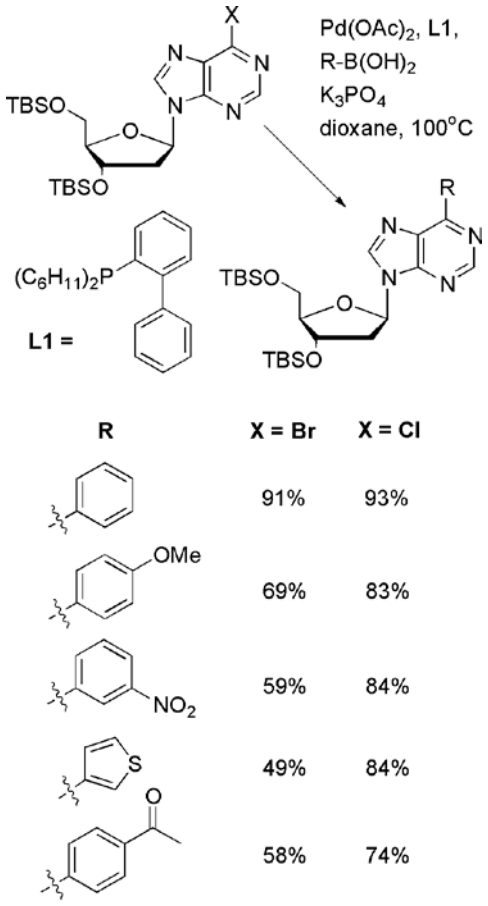
Selective arylation of 2,6-dichloropurines can be accomplished due to the greater reactivity of the 6-position. C^6-Arylation of 9-benzyl-2,6-dichloropurine with phenylboronic acid using the anhydrous conditions provided the 6-phenyl-2-chloropurine product in 77% yield. Arylation at both positions 6 and 2 occurred in the presence of excess boronic acid as shown in Scheme 4.[10] Catalytic palladium systems employing carbene ligands have also been used for selective 6-arylation of 2,6-dichloropurine.[11]



Scheme 4

The versatility of the anhydrous conditions was demonstrated through coupling a variety of *p*-substituted arylboronic acids (-SCH_3, -$N(CH_3)_2$, CF_3, O-THP).[12] Several 9-substituted 6-chloropurine nucleoside substrates, including tetrahydropyran-2-yl, toluoyl-protected 2'-deoxyribose, acetyl-protected 5'-deoxyribose, acyclic analogs and indan derivatives have also been coupled using the anhydrous conditions.[13] The cross-coupling of benzene-1,4-diboronic acid with 9-benzyl-6-chloropurine was used to prepare the novel C^6-phenyl-linked dimer.[14] The aqueous conditions have also been found to be superior for arylboronic acids possessing substituents such as 4-formyl, 4-acyl, and 3-amino.[10]

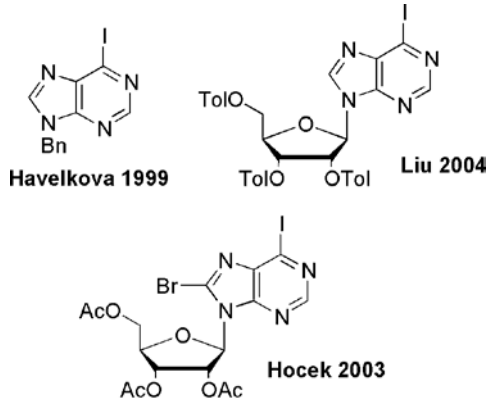
Lakshman evaluated a variety of different catalysts, ligands, bases, and solvents, in order to develop reaction conditions suitable for the arylation of labile 2'-deoxyribonucleosides.[15] The optimized conditions for *t*-butyl-dimethylsilyl (TBS)-protected 6-bromo-2'-deoxyadenosine combined catalytic $Pd(OAc)_2$, the 2-(dicyclohexylphosphino)biphenyl ligand L1, and K_3PO_4 in 1,4-dioxane at elevated temperatures (Scheme 5).



Scheme 5

Reaction times were significantly shorter using these conditions than the anhydrous conditions involving $Pd(PPh_3)_4$/anhydrous K_2CO_3 (1h vs. 8h respectively) and product yields were comparable. The bis-cyclohexyl ligand was much more effective than the closely related *t*-butyl analog. This investigation directly compared the reactivity of 6-Cl and 6-bromopurine substrates. A similar electronic preference to that previously observed using the anhydrous conditions for electroneutral and electron rich arylboronic acids was reflected in the product yields obtained from the 6-bromopurine substrate. Interestingly, the 6-chloropurine substrate gave good product yields using both electron rich and electron poor arylboronic acids. The catalytic procedure for the 6-chloro substrate was modified slightly by pre-mixing the Pd/ligand, however, no advantage for pre-mixing was observed for the 6-bromopurine. Chlorination of guanosine provides a convenient method for preparation of the 2-amino-6-chloropurine ribonucleoside, however, the analogous conversion of the labile 2'-deoxyguanosine analog proceeds in low yields.

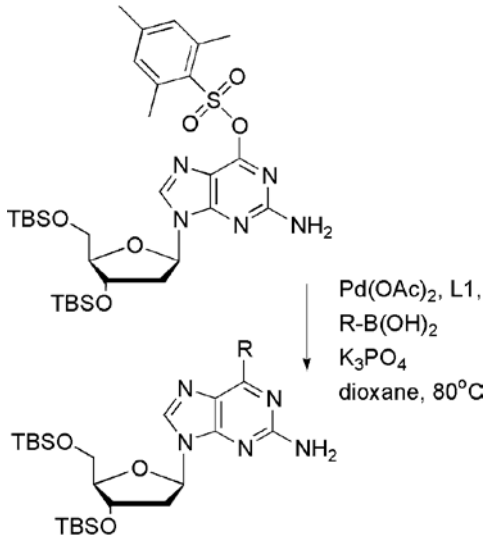
Aryl iodides are typically much more reactive than bromides and chlorides in palladium catalyzed reactions. A series of iodopurine substrates have been investigated (Scheme 6). The reaction of the 9-benzyl-6-iodopurine with phenylboronic acid proceeded rapidly under the anhydrous conditions, but the resulting reaction mixture was not as clean as that obtained from the 6-chloro substrate.[9] Liu et al. recently reported the facile conversion of toluoyl-protected 6-chloro ribonucleosides to the 6-iodopurine derivatives using a low temperature S_NAr reaction.[16] The 6-iodopurine gave better yields of 6-*p*-methoxyphenyl product than the corresponding chloro-derivative under the anhydrous conditions. Selective C^6-arylation was observed using the acetyl protected 8-bromo-6-iodopurine ribonucleoside under anhydrous conditions.[17] Subsequent nucleophilic displacement of the 8-bromo group in the coupled product was facile.

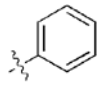
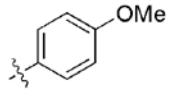
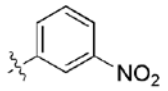
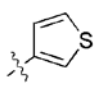
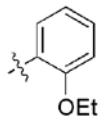


Scheme 6

The reaction of arylsulfonyl chlorides with TBS-protected 2-deoxyguanosine provides convenient

access to O^6-arylsulfonate derivatives. Lakshman has investigated the cross coupling chemistry of these substrates with boronic acids as shown in Scheme 7. The optimized reaction conditions developed previously for the 6-halopurine derivatives also proved to be successful with O^6-arylsulfonate substrates. Both electron rich and electron deficient arylboronic acids coupled effectively under these conditions. These reactions proceeded rapidly and were typically complete in 30 minutes. The reaction stoichiometry was modified for difficult boronic acids such as 3-thiophene- and 2-ethoxyphenylboronic acid, where a three-fold excess resulted in accelerated reactions and improved yields.[18] Further investigations have revealed relatively minor affects due to variation in the O^6-arylsulfonate substituent, and demonstrated that catalytic systems employing $Pd(PPh_3)_4$ are also effective with these substrates.[19]

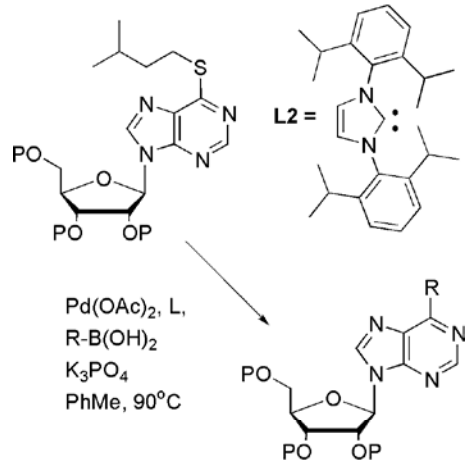


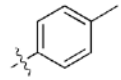
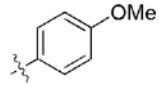
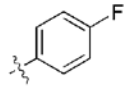
R	Time	Yield
	0.5 h	76%
	0.5 h	73%
	0.5 h	82%
	0.5 h	78%[a]
	5.0 h	65%[a]

[a]Yields with extra eq. R-B(OH)$_2$

Scheme 7

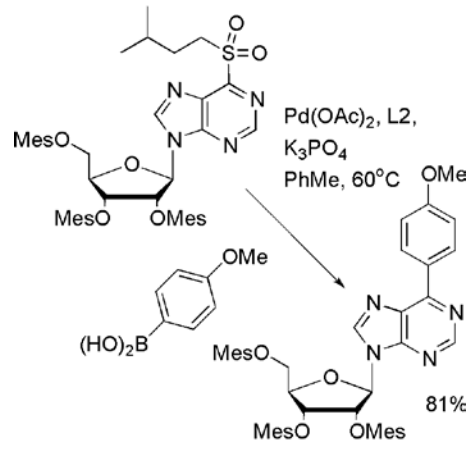
Liu et al. developed a catalytic system for the coupling of 6-alkylsulfanyl and 6-alkylsulfonylpurine ribonucleosides with arylboronic acids using $Pd(OAc)_2$ and the carbene ligand 1,3-bis(2,6-diisopropylphenyl) imidazolin-2-ylidene L2. The sulfanyl couplings were conducted at 90 °C and were effective using a variety of phenylboronic acids (Scheme 8).



R	P	Yield
	Tol	69%
	Ac	78%
	Tol	71%

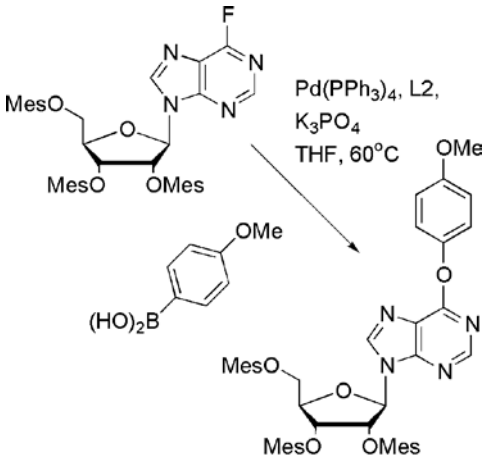
Scheme 8

The 6-sulfonylpurine derivative was prepared by oxidation of the sulfanyl compound with Oxone®. The coupling of the sulfone derivative with 4-methoxyphenylboronic acid occurred efficiently at lower temperatures 60 °C (Scheme 9).[20]



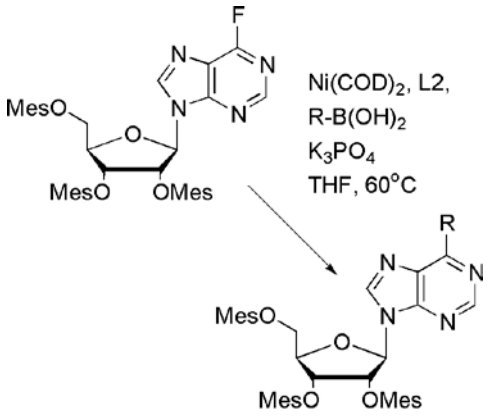
Scheme 9

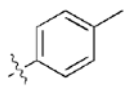
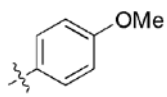
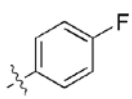
Reported attempts to couple 6-fluoropurine derivatives with boronic acids using $Pd(PPh_3)_4$ were unsuccessful and resulted in the formation of O^6–phenyl derivatives as shown in Scheme 10.[20] This product could potentially result from S_NAr substitution involving the phenol produced by degradation of the boronic acid.



Scheme 10

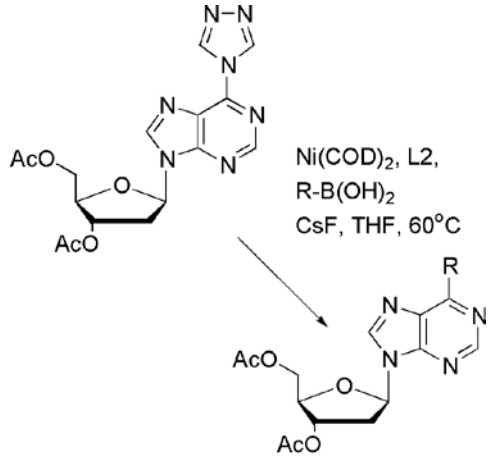
Cross-coupling of 6-fluoropurine nucleoside substrates with arylboronic acids was accomplished in high yield using a nickel catalyst and carbene ligand L2 as shown in Scheme 11. Both protected ribose and 2'-deoxyribose derivatives were successfully coupled under these conditions.

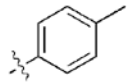
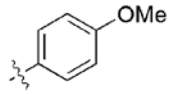
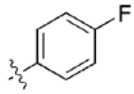


R	Yield
	82%
	84%
	73%

Scheme 11

Liu et al. have described nickel-carbene catalyzed cross coupling reactions of 6-azol-purine nucleoside substrates (Scheme 12). Derivatives such as the 6-(imidazol-1-yl)purine and 6-(1,2,4-triazol-4-yl)purine are readily prepared from the corresponding nucleosides. Cesium fluoride was the most effective base for coupling the triazole derivatives, while potassium phosphate was effective for the imidazole substrates. Small amounts of O^6–phenyl byproducts were observed under these conditions.[21]



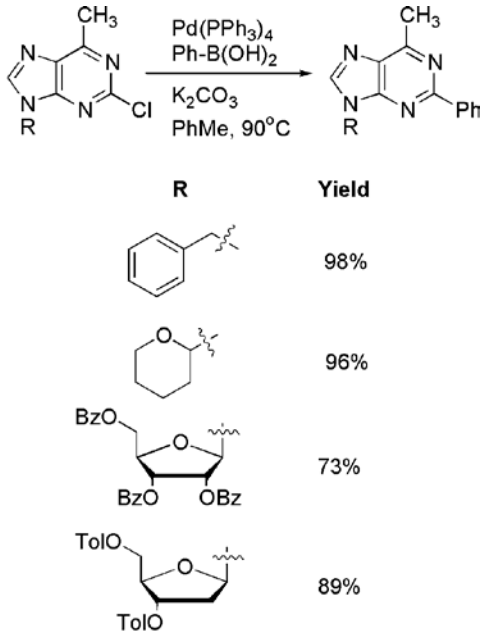
R	Yield
	78%
	85%
	75%

Scheme 12

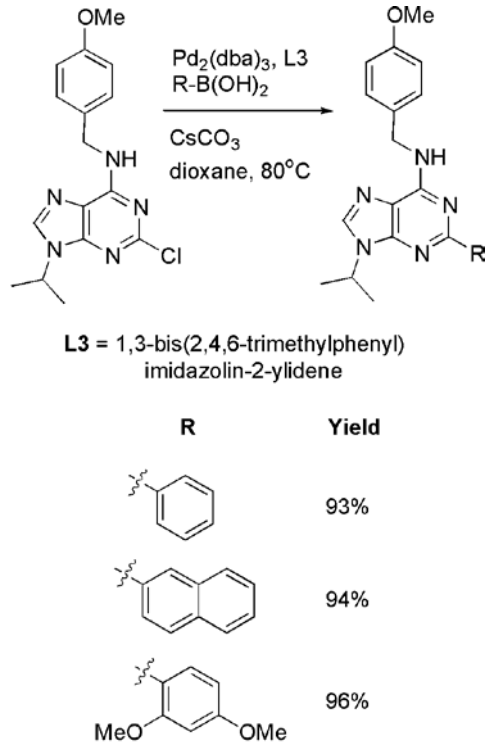
C^2-arylation

A variety of N^9-substituted (benzyl, tetrahydropyranyl, tribenzyl-ribose, ditolyl-2'-deoxy-ribose) 2-chloro-6-methylpurine derivatives have been shown to react efficiently at C^2 under the anhydrous conditions (Scheme 13).[22]

Ding et al. showed the 6,9-disubstituted 2-chloropurine substrate coupled in high yield with tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) and the carbene ligand 1,3-bis(2,4,6-trimethylphenyl)imida zolin-2-ylidene L3. The choice of base was significant and Cs_2CO_3 provided the best results. Lower yields were obtained using *ortho*-substituted or electron deficient arylboronic acids (Scheme 14).[11] The anhydrous conditions ($Pd(PPh_3)_4$, K_2CO_3) are also effective with this substrate.[23]



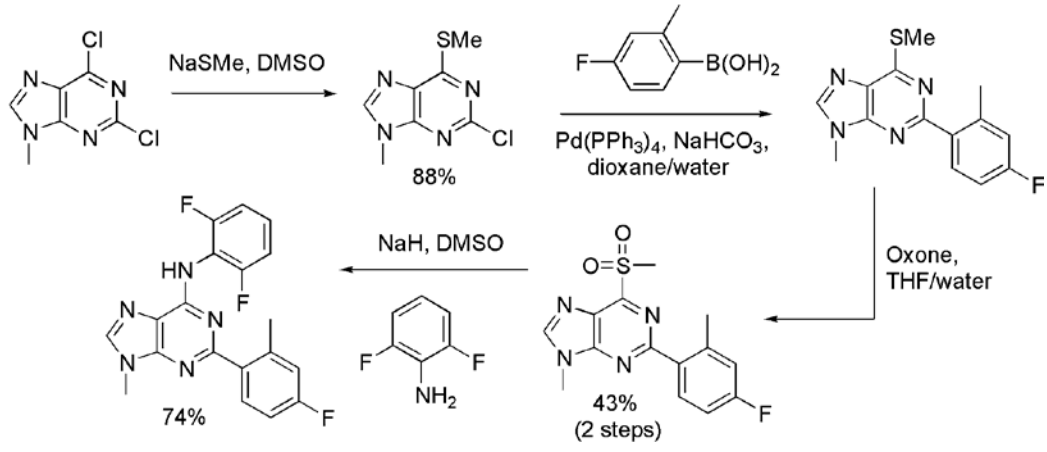
Scheme 13



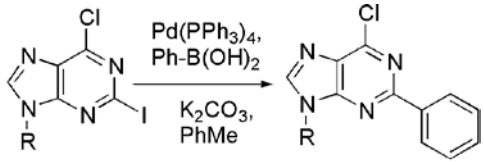
Scheme 14

Wan et al. synthesized a novel set of trisubstituted C^2-arylpurine derivatives utilizing the differential reactivity of halogens at C^2 and C^6 as illustrated in Scheme 15. Selective S_NAr substitution with sodium methylsulfide occurred at the more reactive 6-position of 2,6-dichloro-9-methylpurine. Cross-coupling of the resulting 2-chloropurine substrate with aqueous $NaHCO_3$, dioxane conditions afforded the C^2-aryl product. Subsequent oxidation of the 6-sulfanyl group with Oxone® gave the sulfonyl compound in 43% over two steps. The activated 6-sulfonyl derivative then undergoes substitution at C^6 with 2,6-difluoroaniline in high yield.[24]

Selective C^2-arylation has been accomplished using 6-chloro-2-iodopurine substrates as shown in Scheme 16. Using 1 eq. $PhB(OH)_2$ under anhydrous conditions with 9-benzyl 6-chloro-2-iodopurine gave the 2-phenyl product in excellent yield.[10] The reaction was noted to be slower than the C^6-arylation of 9-benzyl-2,6-dichloropurine. These same conditions were used for the acetyl-protected ribonucleoside derivative.[25] Diarylation occurs in the presence of excess boronic acid. Selective nucleophilic displacement occurs at the more reactive C^6 position of 6-chloro-2-iodopurine derivatives, and the resulting 2-iodopurine substrates have been shown to undergo efficient cross coupling at C^2.[24]



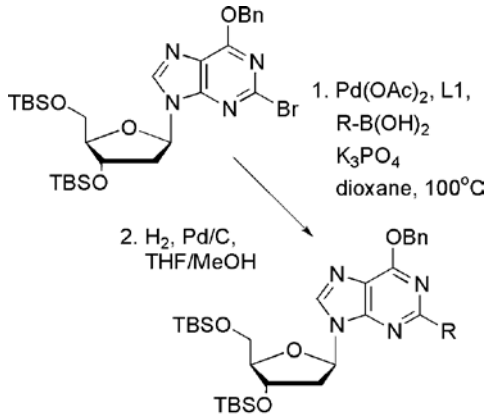
Scheme 15



R	Yield
Bn	81%
triacetylribose	76%

Scheme 16

Lakshman et al. investigated cross-coupling reactions with the protected O^6-benzyl-2-bromopurine substrate derived from 2'-deoxyguanosine as shown in Scheme 17. The catalyst and reaction conditions previously optimized for C^6-arylation were also effective for C^2-arylation. The efficient two-step process for synthesizing 2-aryl-2'-deoxyinosine derivatives was completed by subsequent deprotection.[15]

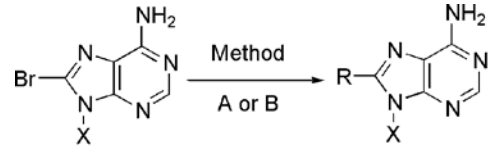


R	Yield (2 step)
	73%
OMe	58%
O	56%

Scheme 17

C^8-arylation

Cross-coupling with 6-amino-8-bromopurine substrates has been investigated as shown in Scheme 18. The $Pd(PPh_3)_4$ catalyzed coupling reactions of 9-benzyl protected 6-amino-8-bromopurine with phenylboronic acid were successful using both anhydrous conditions and the aqueous K_2CO_3 system. The aqueous conditions were more effective with electron deficient boronic acids.[10] This approach was also used to prepare C^8-phenyl-2'3'-dideoxyadenosine in good yield.[26] The unprotected ribonucleoside 8-bromoadenosine was arylated in good yield using a series of boronic acids under these conditions.[27] Aqueous conditions using water-soluble sulfonated phosphine ligands have also been investigated for the coupling of 8-bromoadenosine. Catalytic palladium acetate, tris(3-sulfonatophenyl)phosphine, Na_2CO_3, and H_2O-CH_3CN at 80 °C afforded C^8-aryl products in good yields.[28] The 2'-deoxyribose derivative was also arylated effectively under these conditions. The reaction could be performed at room temperature using the more sterically hindered *o,p*-dimethyl substituted (3-sulfonatophenyl)phosphine ligand. This method has been used to prepare 8-aryl-2'-deoxyguanosine derivatives.[29]



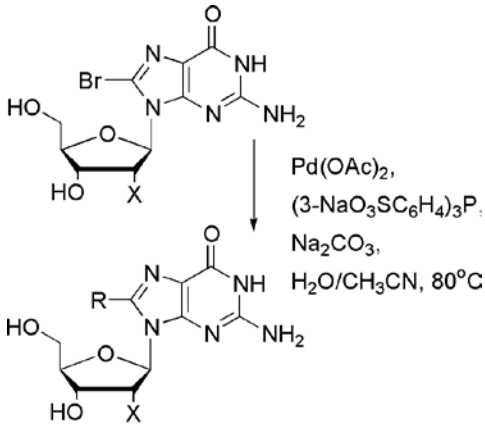
R	X = Bn	X = ribose	
	A	A	B
	96%	81%	88%
OMe	—	73%	85%
F	94%	75%	99%
NO_2	76%	—	—

A = $Pd(PPh_3)_4$, aq. K_2CO_3, DME, 85°C
B = $Pd(OAc)_2$, $(3\text{-}NaO_3SC_6H_4)3P$,
Na_2CO_3, H_2O/CH3CN, 80°C

Scheme 18

The aqueous conditions using catalytic palladium acetate and water-soluble sulfonated phosphine ligands were also used for cross coupling 8-bromoguanosine derivatives (Scheme 19).[28] While 2'-deoxyribonucleosides are typically more labile than the ribose analogues, higher yields were obtained using the 2-deoxyribose substrates under these conditions. The unprotected substrates 8-bromo-2'-deoxyguanosine and 8-bromo-2'-deoxyadenosine have also been coupled

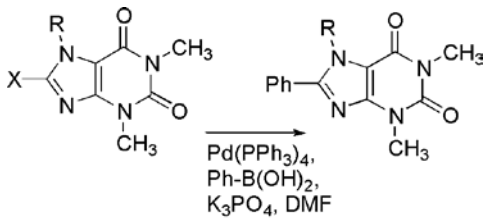
with 1-pyrenylboronic acid using $Pd(PPh_3)_4$, 20 eq. NaOH, THF/MeOH/H_2O in 65% and 10% yields respectively.[30]



R	X = OH	X = H
	64%	82%
OMe	65%	85%
F	73%	82%

Scheme 19

8-Haloxanthine substrates derived from caffeine and theophylline have been used in cross-coupling reactions using $Pd(PPh_3)_4$ and K_3PO_4 in DMF as shown in Scheme 20. The 8-bromo- and 8-chloro-derivatives were compared directly. Higher yields were obtained from the bromides in all cases investigated. The N-methyl and N-benzyl derivatives coupled in higher yields than the N-H substrates.[31]

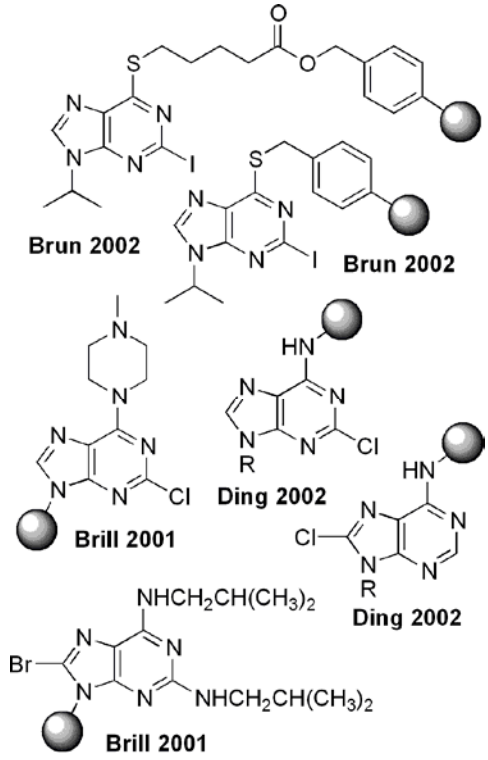


R	X = Cl	X = Br
H	6%	19%
Me	49%	63%
Bn	38%	48%

Scheme 20

Solid supported purine substrates

The discovery of new biologically active compounds and molecular tools can be accelerated through the use of combinatorial techniques. Solid supported substrates and reagents are useful for the synthesis of diverse libraries of compounds. Solid phase chemistry provides advantages including acceleration of bimolecular reactions using excess reagents, and relative ease of work up and purification. The selection of solid support and linkage to the substrate are important factors due to the swelling characteristics of polymers, steric effects, and chemical and thermal stability. Cross coupling reactions using a variety of solid-supported halopurine substrates have been reported for the synthesis of multi-substituted purines (Scheme 21).[32]



Scheme 21

Brun et al. investigated the coupling of Merrifield resin C^6-sulfide linked 2-iodopurine substrates with arylboronic acids using $Pd(PPh_3)_4$ and diisopropyl ethylamine in dimethylformamide.[33] The substrate consisting of the purine directly linked to the Merrifield-SH resin afforded relatively low product yields. Extending the purine-resin distance through a 5-thiovaleric acid linkage improved coupling efficiency. The S-linkage was subsequently activated for nucleophilic substitution by oxidation to the alkylsulfonate.

Ding et al. attached 2,6-dichloropurine to PAL-amine resin via S_NAr amine substitution at C^6. The resulting 6-amino-linked 2-chloropurine derivative was

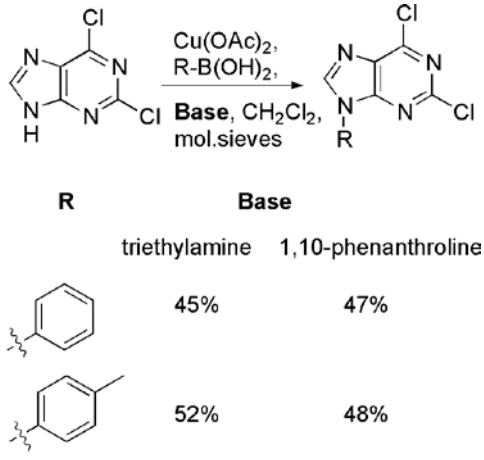
then modified at N^9 via Mitsunobu alkylation. The cross-coupling reaction at C^2 was highly efficient using the Pd(0)/carbene catalyst with over 95% conversion. The same approach was utilized for 6,8-dichloropurine and afforded the final C^8-aryl products in good yields.[34]

Brill et al. attached 2,6-dichloropurine to Rink-resin via N^9-alkylation followed by amine substitution at the more reactive C^6 position. The 6-amino-2-chloropurine derivative was coupled using $Pd_2(dba)_3$, $P(^tBu)_3$, K_3PO_4, N-methylpyrollidinone at 100 °C for 48 h. Both 3,5-bis(trifluoromethyl)phenylboronic acid and 1-naphthylboronic acid gave C^2-aryl products in high yield.[35] The related N^9-linked 2,6-diamino-8-bromopurine was a poor substrate that underwent sluggish C-C coupling and produced significant amounts of dehalogenated substrate.[36]

Copper Mediated C-N Coupling

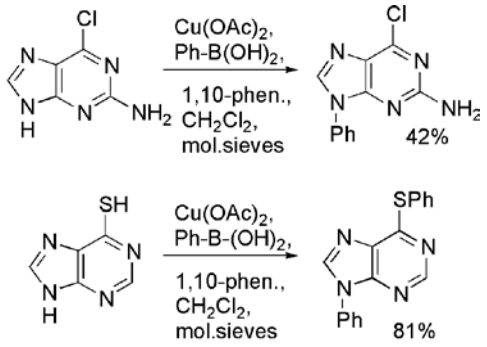
N^9-arylation

The N^9-arylation of purines occurs using the standard Chan-Evans-Lam reaction conditions of $Cu(OAc)_2$, triethylamine, and boronic acid.[8] The coupling of 2,6-dichloropurine exhibited greater than 90% regioselectivity for N^9-arylation. Low yields of the N^7-regioisomer were observed.[23] The modified Cu(II) phenanthroline conditions gave similar yields of N^9-aryl products, and regioisomeric N^7-products were not detected (Scheme 22).[37]



Scheme 22

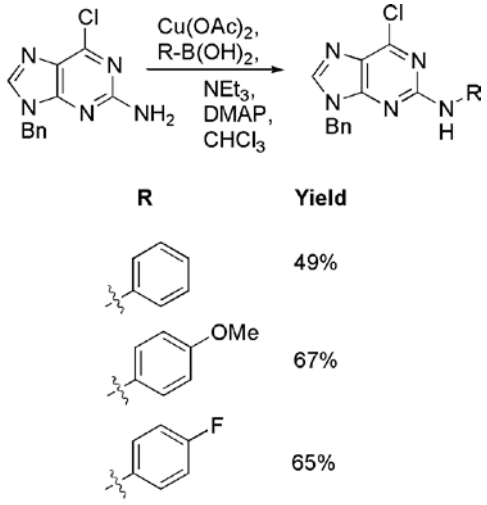
Selective N^9-arylation takes place in the presence of the 2-amino group in 6-chloroguanine with the Cu(II)/phenanthroline system as shown in Scheme 23. No reaction was observed for adenine under these conditions, a result attributed to the low solubility of this substrate. Interestingly, 6-mercaptopurine was arylated at both the N^9 and the C^6-thiol to provide the 6,9-disubstituted purine product in high yield.[37]



Scheme 23

$N^{2'}$-arylation

The N^9-benzyl-protected 6-chloro guanine derivative was found to undergo efficient $N^{2'}$-arylation using copper(II) triethylamine/DMAP conditions as shown in Scheme 24.[38] To the best of our awareness this is the only example of copper mediated exocyclic purine N'-arylation reported so far.

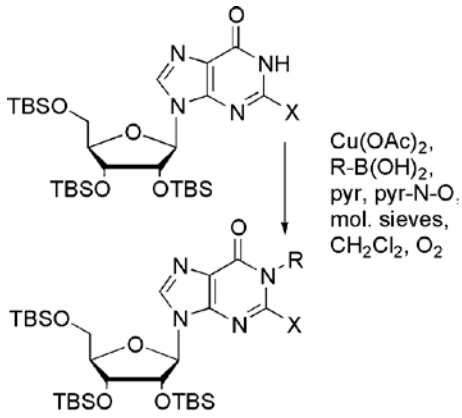


Scheme 24

N^1-arylation

We recently reported a general procedure for N^1-arylation of inosine and guanosine that employs copper catalyzed coupling with boronic acids (Scheme 25).[39] This approach provides efficient access to novel N^1-aryl derivatives and accommodates diverse functionality in the aryl substrate. The optimized conditions for cross-coupling include $Cu(OAc)_2$, pyridine, and pyridine-N-oxide as co-oxidant in dichloromethane at ambient temperature under an atmosphere of oxygen. The addition of co-oxidant and added oxygen

increased product yields and reduced reaction times. No O^6-arylation was observed with either substrate. No $N^{2'}$-arylation was observed with the guanosine substrates. Isolated product yields were generally lower for the guanosine substrates compared to the inosine counterparts. Improved yields in these cases were achieved by increasing the amount of $Cu(OAc)_2$. Both electron rich and electron poor arylboronic acids were coupled efficiently. Reduced product yields were obtained with sterically hindered *ortho*-substituted boronic acids.



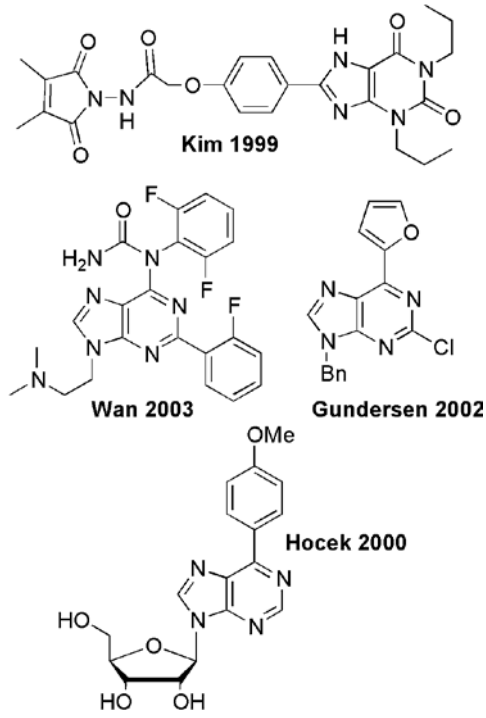
R	X = H	X = NH_2
OMe	86%	61%[a]
NO_2	97%	51%[a]
F	100%	89%[a]
Cl	97%	53%
Br	78%	56%
I	93%	43%

[a]Yields with 1.1 eq. $Cu(OAc)_2$

Scheme 25

Bioactive Aryl-Purine Derivatives

While a comprehensive review of the biological activity of purine derivatives is beyond the scope of this review, it is clear that arylpurines constitute a diverse class of compounds with important biological activity. 9-arylpurines have been identified as agonists or antagonists for adenosine receptors, corticotropin-releasing hormone receptors, and enzymes such as xanthine oxidase, phosphatidylinositol 4-kinase, adenosine deaminase, and guanosine deaminase. Other examples include antitumor activity, antimicrobial activity, and plant growth stimulating effects. The following section highlights some selected examples of arylated purine compounds with medicinally relevant biological activity (Scheme 26).



Scheme 26

The protein kinase family offers great challenge and opportunity for drug discovery targeting diseases such as cancer, autoimmune diseases, inflammation, allergic reactions, neurological disorders, and hormone-related diseases. Kinases regulate many different signal transduction pathways, cell differentiation, and cell proliferation processes. All of the identified kinases bind the cofactor adenosine triphosphate in a similar way; however structural diversity exists between members of the kinase family in regions unoccupied by ATP. Phenylation of purine substrates provides novel structures to probe this diversity and enhance selective interactions with hydrophobic regions.[40]

The C^8-arylpurine derivative developed by Kim et al. binds human A_{2B} receptor with K_i = 19 nM and exhibits selectivity factors of 160/100/35 for human A_1/A_{2A} and A_3 receptors respectively.[41]

Wan et al. have designed a novel series of 2,6,9-trisubstituted purine derivatives as inhibitors of p38α MAP kinase. Direct evidence for the selective

interaction of the C^2-fluorophenyl group with a hydrophobic pocket in p38α kinase was obtained by X-ray crystallography.[24]

Hocek et al. have identified 6-phenylpurine ribonucleosides that inhibit cell growth in vitro against mouse leukemia L1210 cells, human cervix carcinoma HeLa S3 cells, and human T-lymphoblastoid CCRF-CEM cells. The related 2-amino-6-aryl derivatives and aglycosides were inactive.[42] 9-benzyl-2-chloro-6-(2-furyl)purine exhibited antibacterial activity against *Mycobacterium tuberculosis* H_{37}-Rv and was active against several drug-resistant strains.[43]

Conclusions and Perspectives

The metal-mediated C-C and C-N coupling reaction of purines with boronic acids has been shown to be a powerful synthetic method for introducing aryl or heteroaryl substituents. Several different palladium catalyst-ligand combinations have been used for C-C coupling at the C^6 position. This reactivity has been demonstrated using fluoro-, chloro-, bromo-, iodo-, sulfanyl, sulfonyl, sulfonyloxy- and azole-substrates. The ease of obtaining the activated purine substrates is an important factor when selecting appropriate coupling conditions, particularly for nucleoside derivatives. Important advances in the general applicability of this methodology have been made, however, careful optimization of catalyst, ligand, base, solvent, and reaction temperature is frequently necessary. Palladium catalysts have also enabled C-C coupling at positions C^2, and C^8. Copper mediated N-arylation occurs at positions N^1, $N^{2'}$, N^7, and N^9. Examples of combinatorial approaches employing coupling reactions with solid supported purine substrates have also been reported. These methods provide convenient access to structurally unique arylpurine derivatives with applications in drug discovery and chemical biology. Continuing advances in this field can be expected to result through improved mechanistic understanding and the development of new catalysts and ligands.

Acknowledgements

The authors research program was supported by R21 AI053304 from NIAID. J.J.S. was supported by NIH/RISE GM61222.

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Povzetek

Substituirani derivati purina imajo velik biomedicinski pomen kot terapevtiki in so pritegnili veliko pozornost kot molekulska orodja in testne spojine za raziskave bioloških sistemov. Modifikacije purinov z arilnimi ali heteroarilnimi substituenti dramatično spremenijo konformacijske preference in sposobnost tvorbe vodikovih vezi. Razvoj novih metod za spajanje purinov z aril ali heteroaril halogenidi s pomočjo kovinskih katalizatorjev je zelo povečal možnosti sinteze arilpurinskih derivatov. Arilboronske kisline so se izkazale kot zelo učinkoviti reagenti za sintezo arilpurinskih spojin, s tvorbo bodisi C–C ali C–N vezi. Paladij in nikelj katalizirata nastanek vezi C–C na položajih C^2, C^6 ali C^8, baker pa nastanek vezi C–N na položajih N^1, N^2, N^7 in N^9. Metoda je uporabna tudi za purine, vezane na trdne nosilce. Za uspešnost reakcije je bistvena optimizacija katalizatorja, liganda, baze, topila in temperature reakcije. Te reakcije predstavljajo pripravno metodo za sintezo arilpurinskih derivatov za biološke in medicinske študije.