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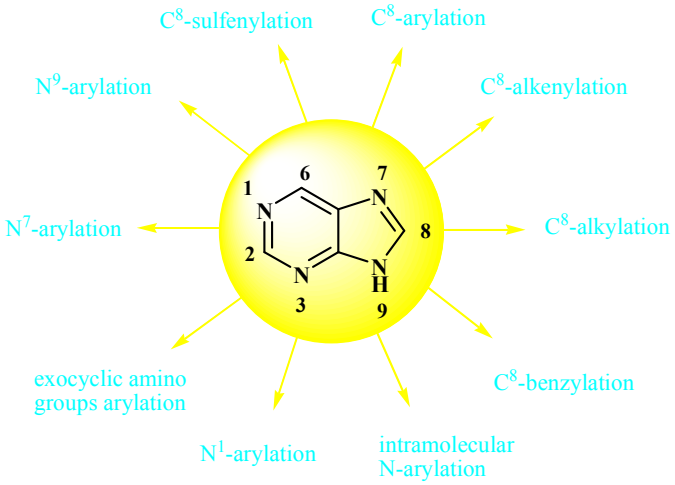

This review provides concise overview on the cross-coupling reactions on direct functionalization of purine bases in recent years.

New developments in direct functionalization of C–H and N-H bonds of purine bases *via* metal catalyzed cross-coupling reactions

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Abstract: Purine bases have attracted much attention due to their potential biological activities. Developing more efficient methods for the modification of purine bases with a substitution such as aryl or alkyl is particularly interesting. This review gives an overview of new developments in direct functionalization of C–H and N-H bonds of purine bases *via* metal catalyzed cross-coupling reactions in recent years.

Keywords: Purine, cross-coupling reactions, palladium, copper, Grignard reagents

1. Introduction

The fused imidazo [4,5-d]pyrimidine was named purine by Emil Fisher in 1884 who later achieved its synthesis in 1898. He showed that various substances, such as adenine, xanthine, caffeine, uric acid, and guanine all belonged to one homogeneous family and corresponded to different hydroxyl and amino derivatives of the same fundamental system.[1] Purines constitute a major class of naturally occurring compounds (Figure 1) and privileged medicinal scaffolds (Figure 2) that exhibit a broad range of biological and pharmaceutical properties, such as antimicrobial,[2] antibacterial,[3] antiviral,[4] antileishmanial,[5] antifungal,[6] antitumor,[7] anticonvulsant,[8] antidepressant,[9] anti-inflammatory,[10] antiparkinson[11] and antidiabetic[12] activities. In this regard, developing more efficient methods for the construction of compounds containing purine is a topic of immense importance.

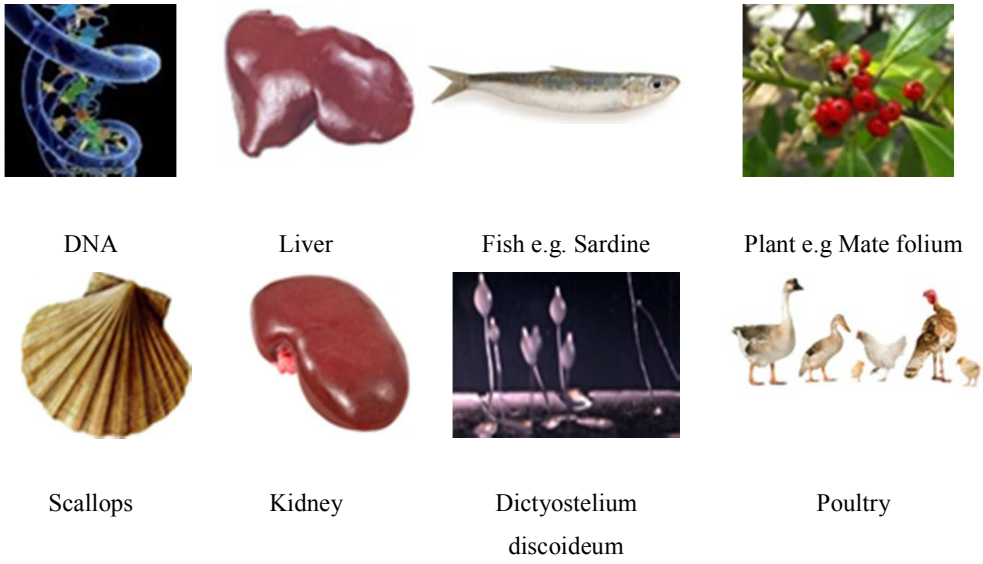


Figure 1. Some natural sources of purines.

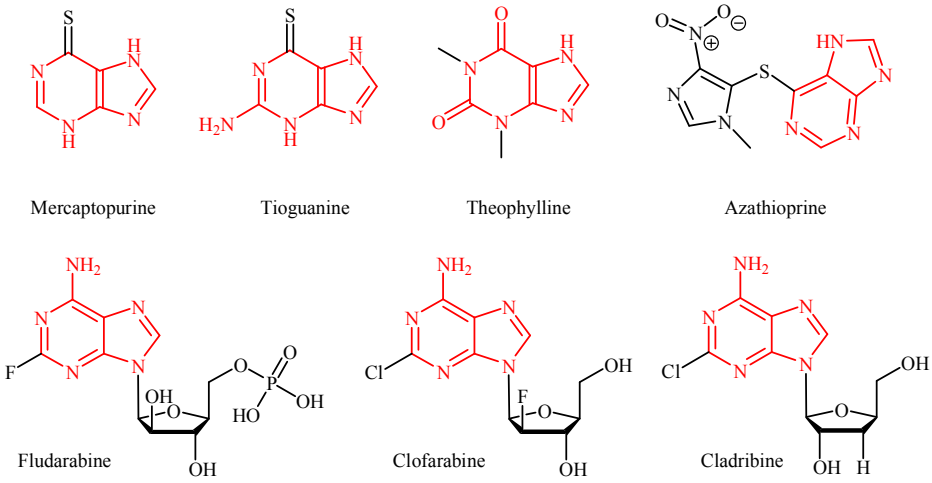
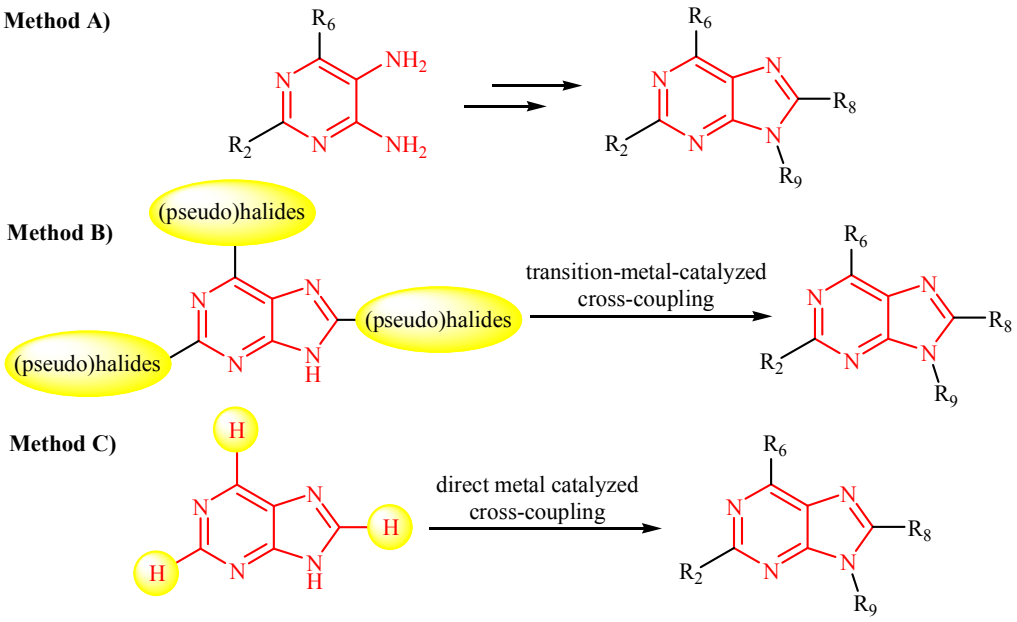


Figure 2. Some purine-containing bioactive compounds.

Three strategies have been utilized for the synthesis of functionalized purines in literature (Scheme 1): Heterocyclization[13] (method A) which the scope of it has been limited due to the harsh conditions, poor substituent tolerance, low chemical yields, and multistep synthesis. Metal-catalyzed cross-coupling reactions[14] (method B) is a powerful and flexible protocol for the synthesis of functionalized purines which is well highlighted in literature in recent years.[15] Direct metal-catalyzed C–H and N–H bond functionalization (method C) has emerged over the past 25 years as a powerful tool for the synthesis of organic molecules and pharmaceutical scaffolds that may complement or even replace traditional catalytic cross-coupling reactions. In these methods the inactive C-H bonds can be treated as a functional group, similar to the traditionally used C–(pseudo)halide bonds.[16] This synthetic methodology offers several advantages:

1- High atom economy
2- High functional group tolerance
3- Ease of handling
4- Shorter synthetic routes
5- Environmentally friendly processes (Green Chemistry)



Scheme 1. The methods for the synthesis of functionalized purines.

To the best of our knowledge, a comprehensive review has not appeared on direct functionalization of C–H and N–H bonds of purines *via* transition-metal-catalyzed cross-coupling reactions in literature in recent years. In this review, we have classified these reactions based on the type (e.g. arylation, alkylation, alkenylation) and the position of functionalization. The most detailed discussion

will be focused on the C^8-arylation of titled compounds. There are few protocols for functionalization of C^2-H and C^6-H bonds *via* direct metal catalyzed processes, and inevitably we have only discussed C^8-functionalization of the titled compounds. In the final section of this review, the new and regioselective methodologies for functionalization of N-H bonds of purines will be discussed. The main methods for direct functionalization of purines *via* metal catalyzed cross-coupling reactions are summarized in Figure 3.

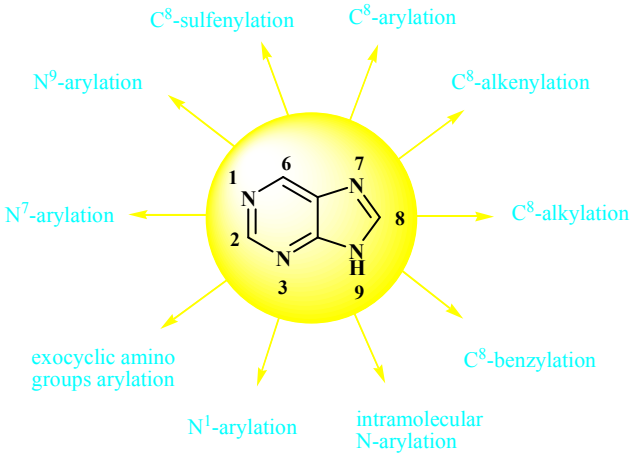
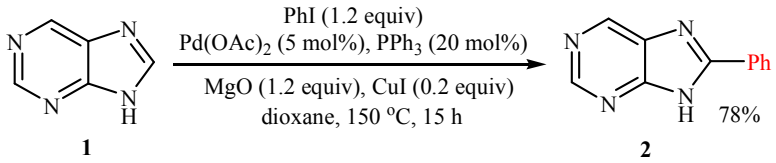


Figure 3. The main methods for direct functionalization of purines *via* metal catalyzed cross-coupling reactions.

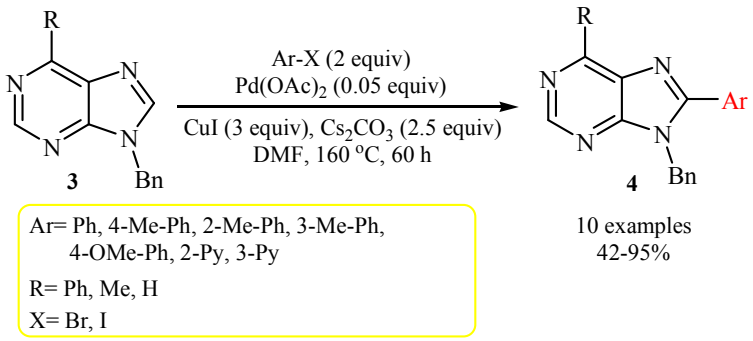
2- Direct C^8-H arylation

2-1-Intermolecular Pd-catalyzed direct C^8-H arylation

Almost all known direct C^8-H arylations of purines proceeded by using palladium as a catalyst. The first example has been accomplished for synthesis of phenyl purine via direct C^8-H activation employing $Pd(OAc)_2/PPh_3$ combination as catalytic system (Scheme 2).[17] Hocek and co-workers described C^8-H arylation of purines **3** using aryl iodides as an arylation agent in the presence of CuI and Cs_2CO_3 to form **4** (Scheme 3).[18,19] It is noted that aryl chlorides under similar conditions did not follow through C-H activation reactions.



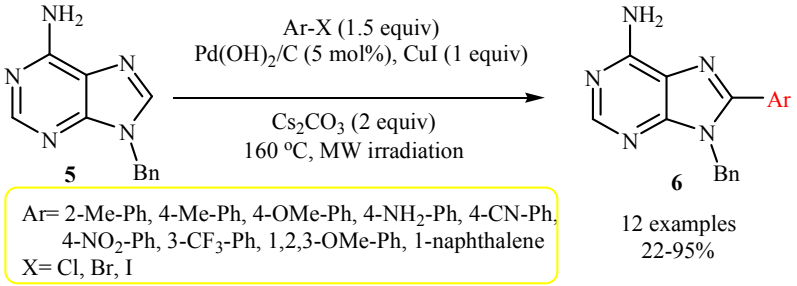
Scheme 2. The first example of intermolecular Pd-catalyzed direct C^8-H arylation of purines.



Scheme 3. C^8-H arylation of purines **3** using aryl iodides.

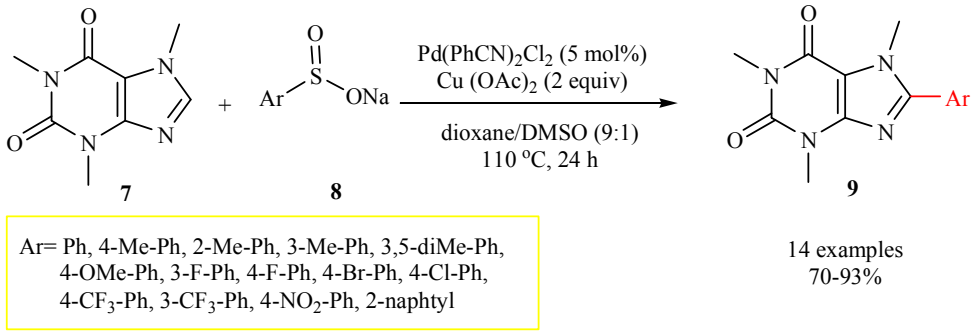
However, in 2007 Chiong and Daugulis, attempted a similar conversion involving aryl chlorides instead of aryl iodides.[20] The authors extended their methodology to the first successful direct C^8-H arylation of caffeine with aryl chlorides in *N*-methyl-2-pyrrolidone involved treating $Pd(OAc)_2/BuAd_2P$ as catalytic system with K_3PO_4 as base.

Free-(NH_2) adenines **5** were found to undergo efficient C^8-H arylation with various aryl halides in the presence of Pearlman's catalyst ($Pd(OH)_2/C$) (Scheme 4). The reaction was more efficient using microwave irradiation. This system shows relatively good reactivity for a range of aryl halides. Under these conditions the yields of C^8-H arylation using aryl chlorides were equally effective with as iodo and bromo reagents.[21] *Para* electron-rich aryl halides and 1-halonaphthalene worked well under these reaction conditions. *Meta*- and *para* electron-deficient aryl halides gave the coupling products in moderate to good yields. However, *ortho*-substituted and sterically hindered aryl halides were relatively incompatible in this system.



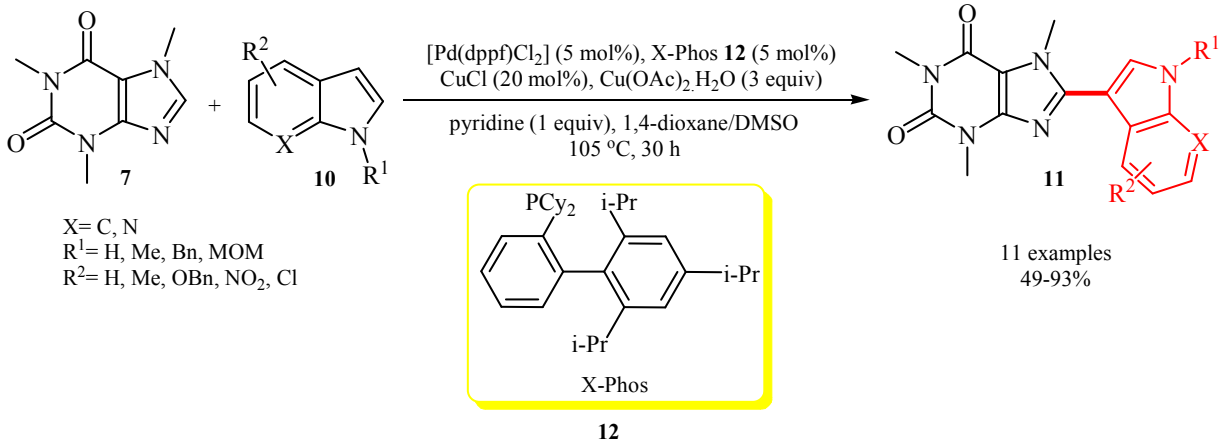
Scheme 4. C^8-H arylation of free-(NH_2) adenines **5.**

With the objective of designing a comprehensive protocol to direct C^8-arylation of purines, the scope of electrophilic partners were extended to aromatic sulfinic acid sodium salt.[22] So several palladium sources, oxidants, additives and solvents were tested, and the system $Pd(PhCN)_2Cl_2/Cu(OAc)_2$/dioxane/DMSO (9: 1) was found to be superior. It is worth noting that the electronic character of the substituents in sulfinic acid had remarkably little effect on the facility of reaction. Various substrates were examined involving electron donating and withdrawing groups in the *para, ortho*, and *meta* positions according to Scheme 5.

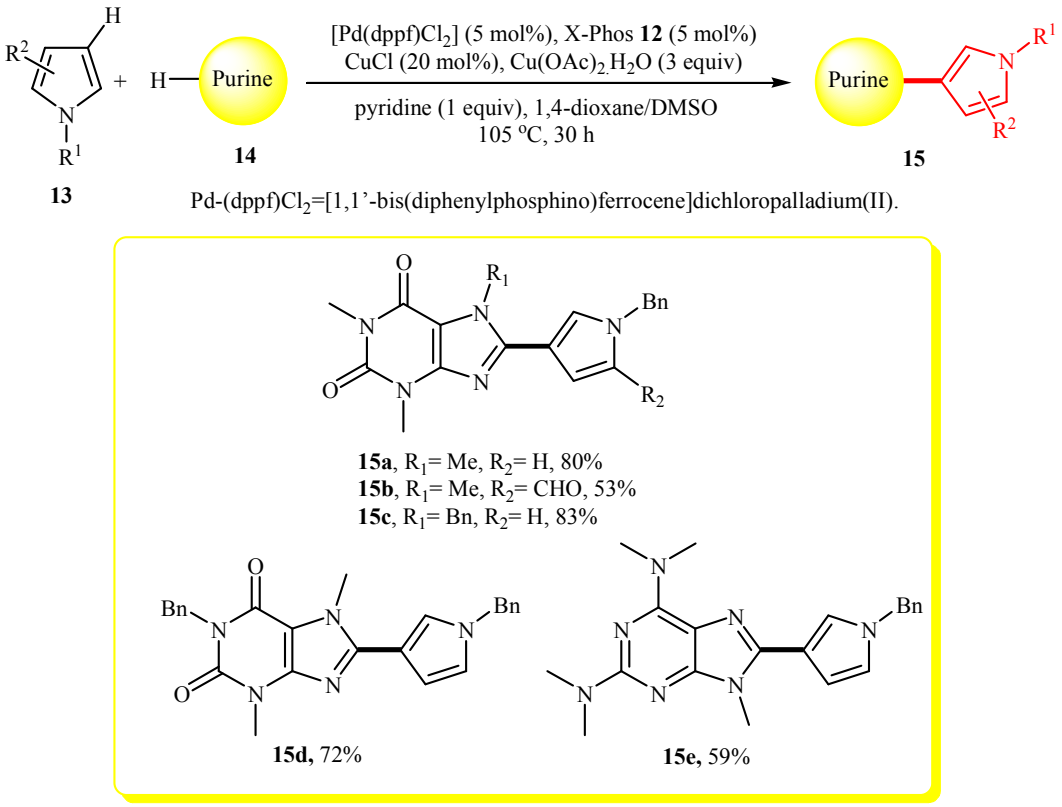


Scheme 5. Using aromatic sulfinic acid sodium salts as an electrophilic partners in direct C^8-H arylation of purines.

An interesting palladium-catalyzed selective dehydrogenative cross-coupling of purines with various heterocycles such as thiophenes and furans was reported by You *et al.*[23] The $Pd(OAc)_2$/ $Cu(OAc)_2.H_2O$/ Pyridine/ 1,4-dioxane system was found to be optimal for this reaction, while addition of 10 mol% CuCl as an activator gave excellent results. In 2011, this methodology was extended to regioselective C^3-heteroarylation of indoles (Scheme 6) and pyrroles (Scheme 7) with an array of purines.[24]



Scheme 6. Regioselective C^3-heteroarylation of indoles with purines.



Scheme 7. Regioselective C^3-heteroarylation of pyrroles with purines.

The direct C-H arylation of purine nucleosides was reported by Hocek's research team in 2007.[25] Adenosines **16** and 6-(4-methoxyphenyl)purine ribonucleoside **17** (Figure 4) were observed to undergo C^8-H arylation in the presence of alkyl halides with catalytic amounts of $Cu(OAc)_2$ and CuI.

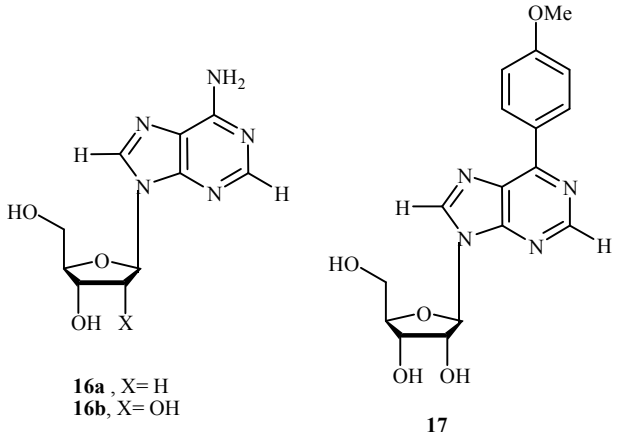
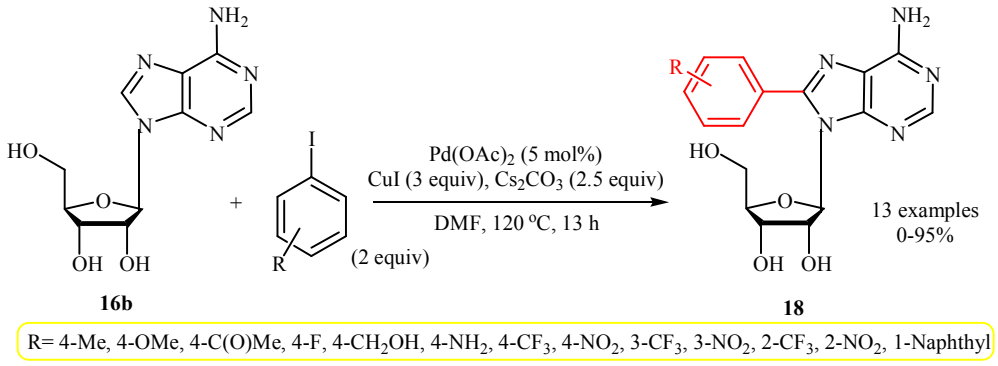


Figure 4. Structure of adenosines **16** and 6-(4-methoxyphenyl)purine ribonucleosides **17**

In an effort towards the development of an effective methodology for regioselective C^8-arylation of adenine, Fairlamb's group employed $Pd(OAc)_2/CuI/Cs_2CO_3/DMF$ combination as a relatively efficient system for regioselective C^8-arylation of unprotected adenine nucleosides using aryl iodides (Scheme 8).[26] High yield was obtained with iodonapthalene under these conditions, and *para*

electron-deficient aryl iodides gave the coupling products in moderate yields. A plausible catalytic cycle for the direct arylation of adenosine mediated by Pd/Cu in the presence of Cs_2CO_3 is outlined in Figure 5. CuI metalation of acidic C^8-H bond of adenosine followed by deprotonation at C^8, leads to *in situ* generation of an organocuprate, which participates in metal exchange with Pd(II) intermediate in the catalytic cycle.



Scheme 8. Regioselective C^8-arylation of unprotected adenine **18** with aryl iodides.

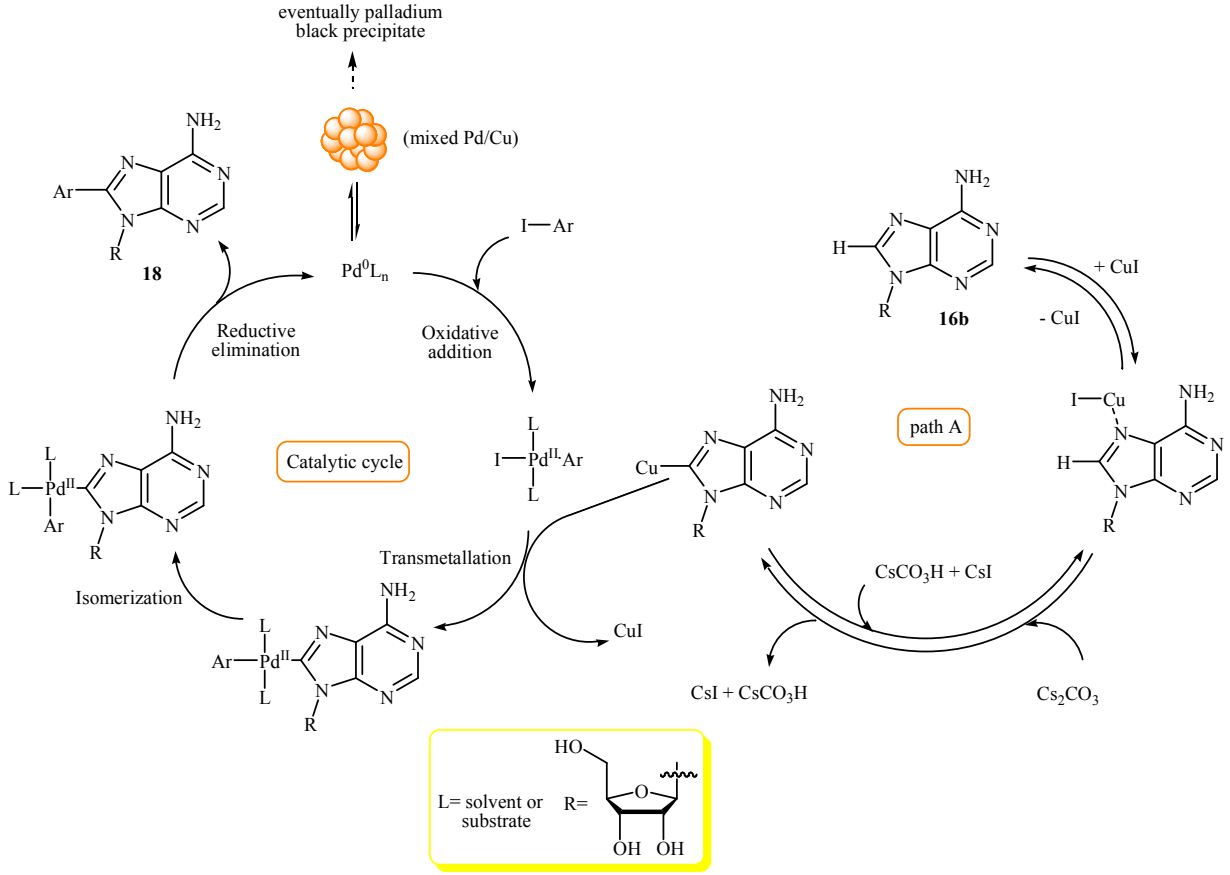
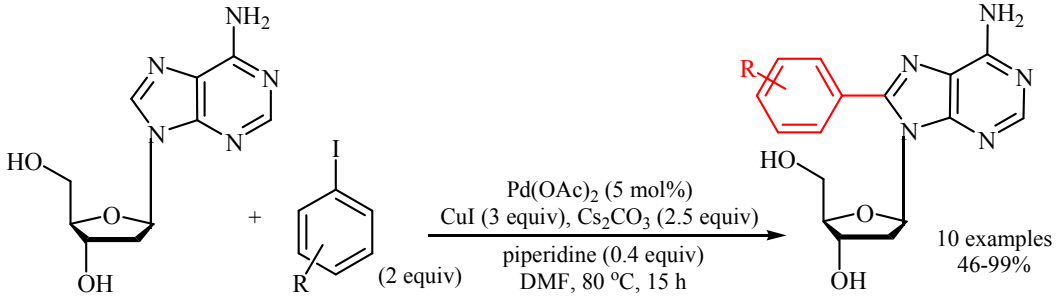


Figure 5. Proposed preliminary mechanism for C^8-arylation of adenines **16b** with aryl iodides.

To develop a practical method for the synthesis of C^8-arylated purine nucleosides, Fairlamb showed $Pd(OAc)_2$/CuI is an effective catalytic system for direct C^8-arylation of unprotected 2′-

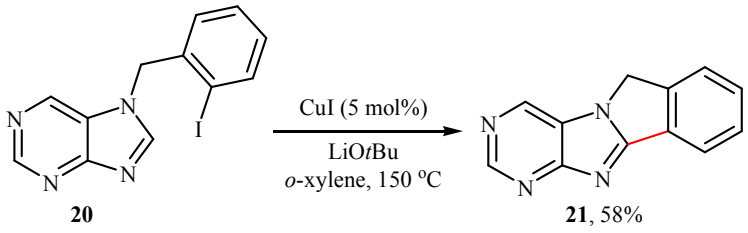
deoxyguanosine with aryl iodides at 80 °C (Scheme 9).[27] DMF and Cs_2CO_3 were the best solvent and base, respectively, and addition of secondary amines was found to be necessary for efficiency of the reaction.



Scheme 9. Direct C^8-arylation of unprotected 2′-deoxyguanosine **16a** with aryl iodides.

2-2-Intramolecular Pd-catalyzed direct C^8-H arylation

In 2009, Barbero and co-workers reported an example of intramolecular C-H arylations of purines. They showed that 9H-purine **20** underwent intramolecular direct C^8-H arylation in the presence of CuI as catalyst, LiO*t*Bu as base in *o*-xylene at 150 °C. The corresponding fused purine **21** was obtained in yield of 58% (Scheme 10).[28]



Scheme 10. An example of intramolecular C-H arylations of purines.

Comprehensive synthesis of fused purines **22** and **23** (Figure 6) *via* intramolecular direct arylation were reported by Hocek's group.[29] They examined three approaches relying on palladium catalyzed C-H arylation for synthesis of purino[8,9-f]phenanthridines **22** (Scheme 11).

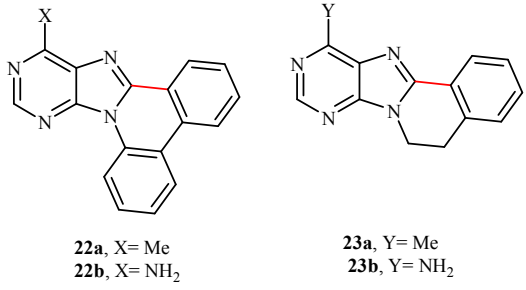
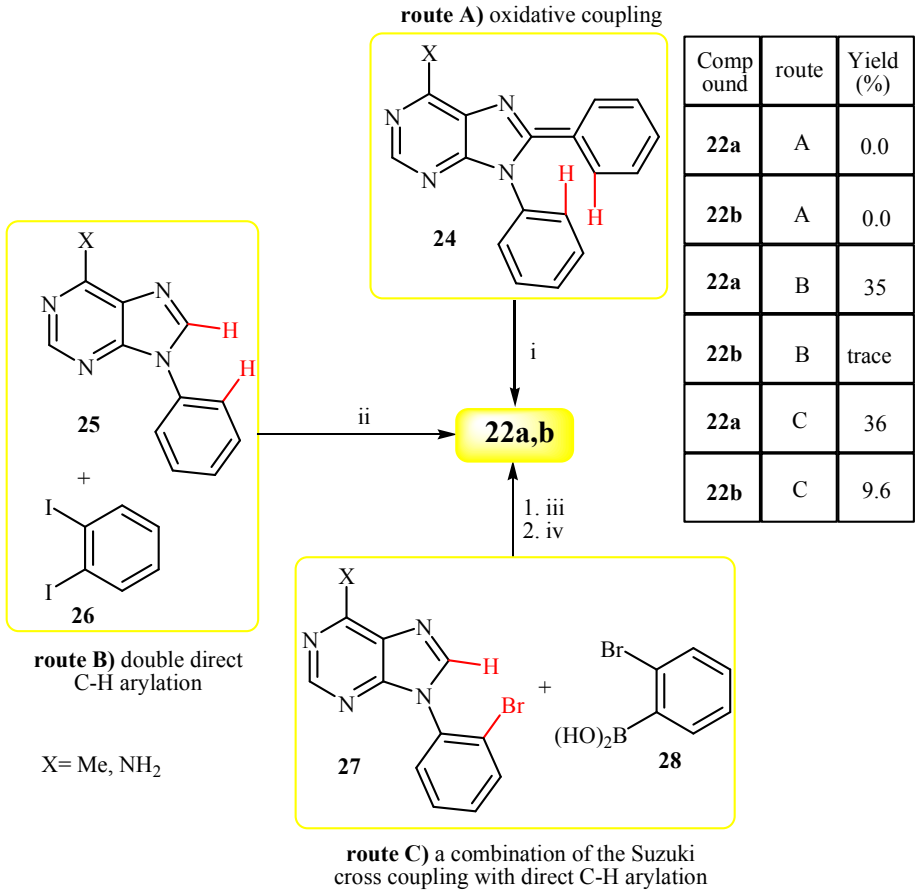


Figure 6. Chemical structure of purino[8,9-f]phenanthridines **22** and 5,6-dihydropurino[8,9-a]isoquinolines **23**.

8,9-diphenylpurines **24** underwent no reaction under oxidative coupling conditions.[30-34] Moreover, double C-H arylation of 9-phenylpurines **25** with 1,2-diiodobenzene **26** gave moderate yields of the desired products (~35%). The best result was obtained with consecutive Suzuki cross-coupling of 9-(2-bromophenyl)purines **27** with 2-bromophenylboronic acid **28** followed by intramolecular direct C-H arylation using $Pd(OAc)_2/PCy_3$-HBF_4 as catalytic system at 130 °C for 8-16 h. Analogously, 5,6-dihydropurino[8,9-a]isoquinolines **23** were prepared *via* direct intramolecular C^8-H arylation of **30**. Intermediates **30** were generated by alkylation of purines **29** with 2-chlorophenethyl bromide in the presence of K_2CO_3 with reasonable yields (Scheme 12).



Compound	route	Yield (%)
22a	A	0.0
22b	A	0.0
22a	B	35
22b	B	trace
22a	C	36
22b	C	9.6

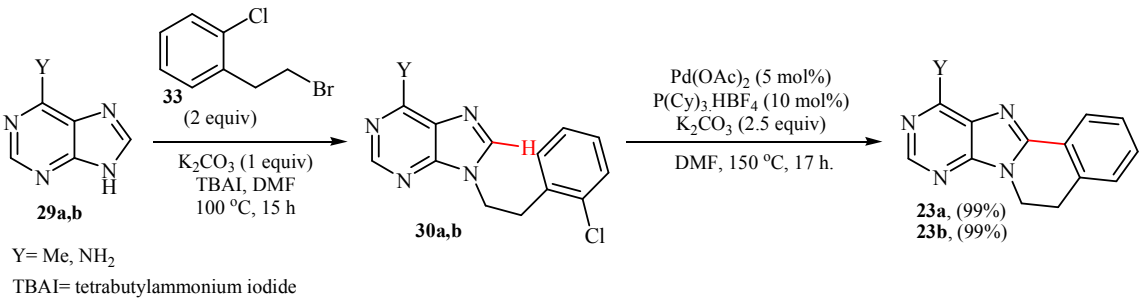
i) Several procedures [30-34]

ii) $Pd(OAc)_2$ (10 mol%), $P(Cy)_3.HBF_4$ (20 mol%), TBAB (1 equiv), KOAc (4 equiv), 140 °C, 25 h.

iii) $Pd(PPh_3)_4$ (4 mol%), Na_2CO_3 (4 equiv), Aliquat 100 (8 mol%), toluene/H_2O (2:1), 110 °C, 36 h

iv) $Pd(OAc)_2$ (5 mol%), $P(Cy)_3.HBF_4$ (10 mol%), K_2CO_3 (2.5 equiv), DMF, 150 °C, 20 h (30 h for 1b)

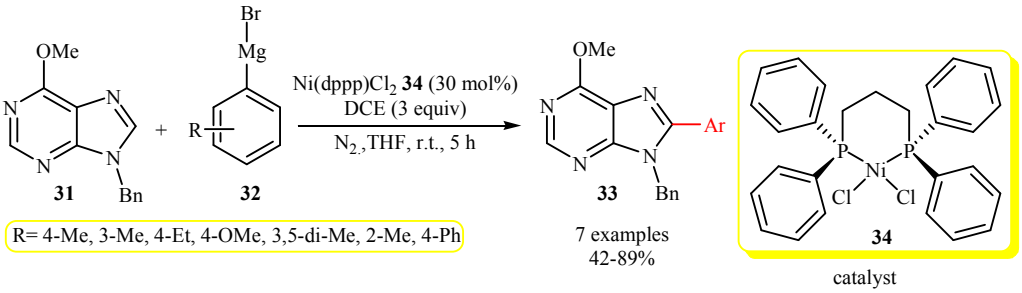
Scheme 11. Retrosynthetic analysis of construction of the purino[8,9-f]phenanthridine core.



Scheme 12. Synthesis of 5,6-dihydropurino[8,9-a]isoquinolines **23**.

2-3-Intermolecular Ni and Cu-catalyzed direct C^8-H arylation

In 2011, Qu and co-workers developed a novel protocol for nickel-catalyzed direct C^8-arylation of purines with Grignard reagent at room temperature (Scheme 13).[35] They tested several catalysts and oxidants, and the system Ni(dppp)Cl_2/1,2-dichloroethane was found to be superior. Under optimized conditions, the reaction tolerates electron-donating substituents at *meta* and *para* positions of aryl moiety and gave corresponding coupling products in good to high yields, but extension of the reaction to electron-withdrawing and *ortho*-substituents aryl rings was failed. However, this methodology for synthesis of C^8-arylated purines was problematic due to the requirement of a very high catalyst loading (30 mol%).



Scheme 13. Direct C–H arylation of 9-benzyl-6-methoxy-9H-purine **31** with various aryl Grignard reagents.

A plausible mechanism for Ni-catalyzed C^8–H arylation of purine **31** with Grignard reagents **32** in 1,2-dichloroethane is presented in Figure 7. Reaction of Ni(dppp)Cl_2 with 1,2-dichloroethane afforded $NiCl_2$ which used for metalation of purines to give intermediate B. Transmetallation between **32** and **B** followed by reductive elimination provided the desired products.

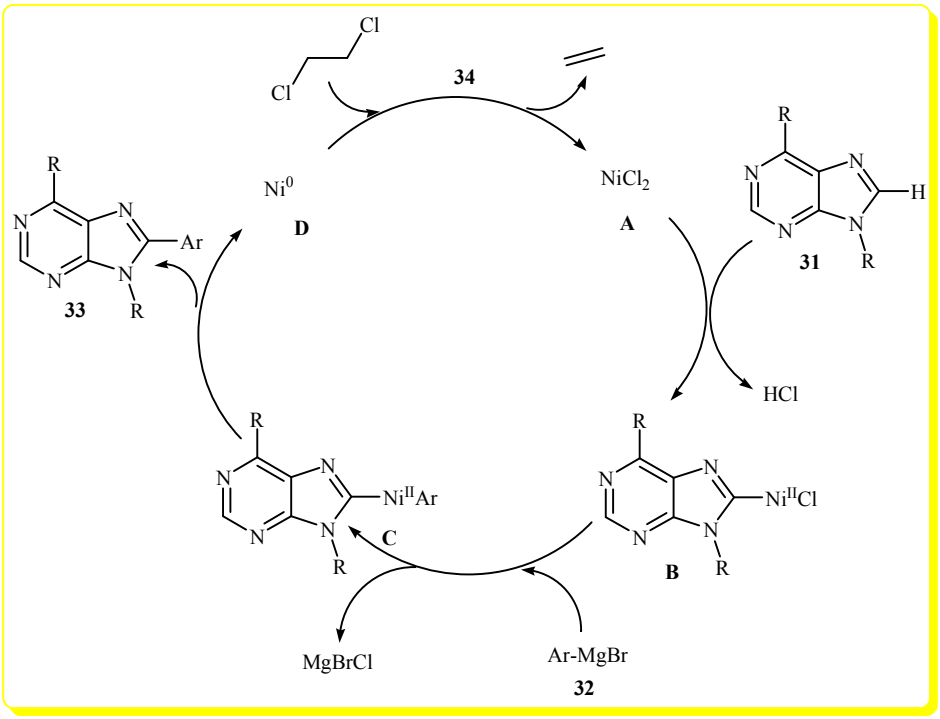
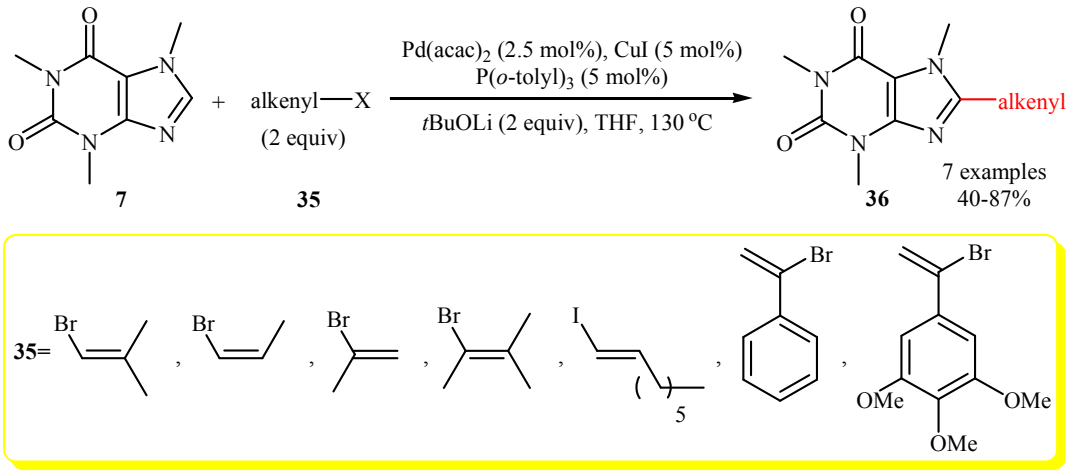


Figure 7. Proposed preliminary mechanism for intermolecular Ni -catalyzed direct C^8-H arylation of purines.

Hong *et al.* described the use of CuI as a catalyst for selective dehydrogenative cross-coupling reactions of a range of azoles with quinolones[36] in the presence of LiO*t*Bu in 1,4-dioxane at 110 ^oC, and only one C^8-heteroarylated purine was obtained in a yield of 79%.

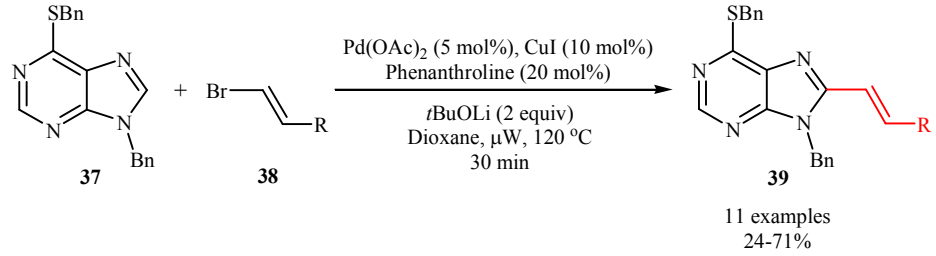
2-4-Direct C^8-alkenylation

Alami and co-workers recently reported one of the first palladium catalyzed direct C^8-alkenylation of purines with alkenyl halides. The reaction was undertaken at 130 ^oC using $Pd(acac)_2$/CuI/$P(o\text{-tolyl})_3$ as catalytic system and *t*-BuOLi as base in THF.[37] This method afforded the C^8-alkenylated caffeine **36** in moderate to good yields with various mono-, di- and tri-substituted alkenyl halides **35** (Scheme 14).

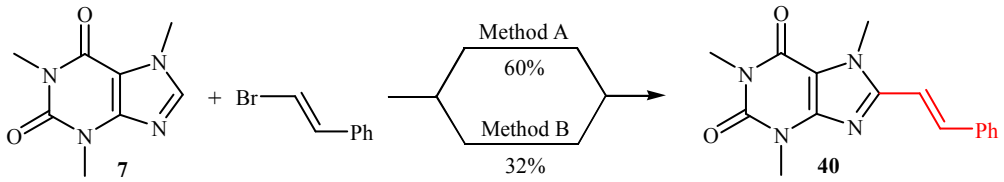


Scheme 14. The first example of palladium catalyzed direct C[8]-alkenylations of purines with alkenyl halides.

One year later, Piguel and co-workers investigated the effect of reaction parameters, such as different palladium catalyst, additives, solvents, and electronic effects of the coupling partners on the efficiency of the coupling reactions.[38] Considering the catalyst, ligand, base and temperature, the optimized conditions of the reaction involved using $Pd(OAc)_2$/CuI paired with phenantroline as a catalytic system, *t*-BuOLi as the base at 120 °C in dioxane under microwave irradiation for 30 min (Scheme 15). Although their optimized conditions allowed the reaction to be carried out at a relatively low temperature and short time comparing with those reported by Alami, an increased catalyst loading of up to 5 mol% was essentially required for effective coupling. It should be mentioned that in the only same example, Alami's method (A) gave higher yield than Piguel's method (B) (Scheme 16). Oxidation of sulfur atom of **39** with *m*-CPBA in dichloromethane afforded the corresponding sulfone, which underwent facile SNAr displacement with amines.

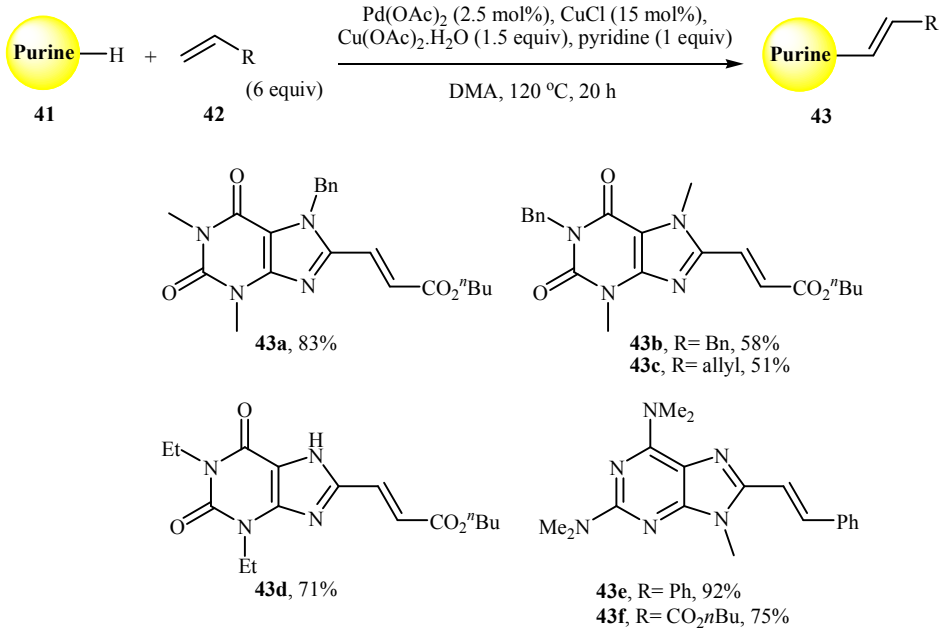


Scheme 15. Microwave-assisted direct alkenylation of purines with alkenyl bromides.



Scheme 16. Compare the efficiency of Alami's and Piguel's methods for direct C[8]-alkenylations of caffeine.

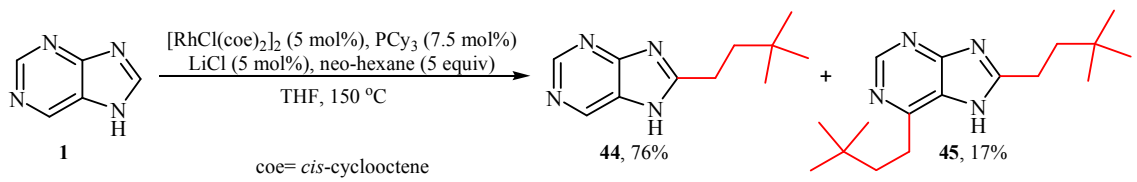
Interestingly, a recent work by You and co-workers disclosed that inactivated alkenes were also efficient coupling partners for direct alkenylation of purines.[39] They established the dehydrogenative Heck coupling of *N*-heteroarenes involving purines **41** with alkenes **42** in the presence of o $Pd(OAc)_2$ /CuCl/$Cu(OAc)_2.H_2O$ afforded the corresponding π-extended alkenylated products **43** in good to high yields (Scheme 17).



Scheme 17. Direct C^8-alkenylation of purines with inactivated alkenes.

2-5-Direct alkylation and benzylation

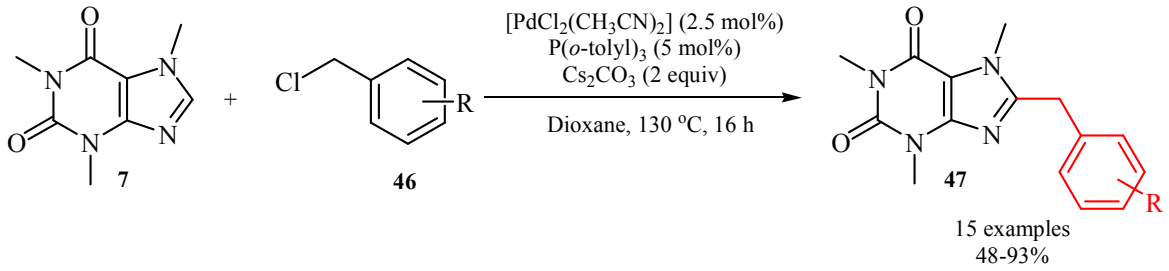
A preliminary example of intermolecular direct alkylation of purines with inactive alkenes has been reported by Bergman *et al.*, requiring elevated temperature (150 °C), 5 mol% of $[RhCl(coe)_2]_2$ as a catalyst in the presence of LiCl. The low yields of C^6/C^8 alkylated byproduct (17%) were also observed (Scheme 18).[40] Following this work, the same group in 2004, has investigated the alkylation of caffeine with 4-methylpent-1-ene under the aforementioned rhodium catalyst, but the low yield of desired product was observed (15 %).[41]



Scheme 18. Intermolecular direct alkylation of purines with inactive alkenes.

Seven years later, a more robust and versatile method for benzylation of xanthines was contributed by Alami's team. They have exemplified the benzylation of C-8 position of xanthine with a variety of

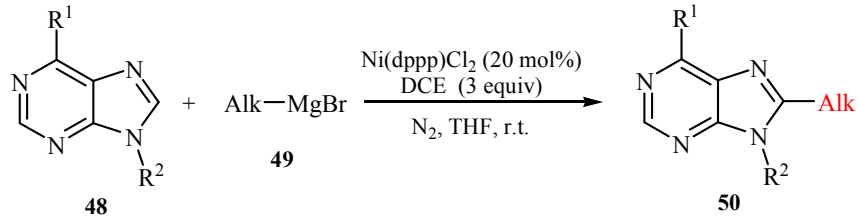
benzyl chlorides in the presence of a combination of 2.5 mol% of $[PdCl_2(CH_3CN)_2]$ and 5 mol% of P(*o*-tolyl)$_3$ as catalytic system (Scheme 19).[42] Generally, both electron-donating and electron-withdrawing groups in the phenyl ring periphery of either coupling partner were well tolerated. In addition, *ortho*-substituted as well as bicyclic derivatives were also viable substrates. However, 3-fluorobenzyl chloride was failed to react condition and the starting material was recovered unchanged. Notably, the reaction conditions were compatible with functional groups such as halogens, esters, and sulfanes which are useful for further synthetic transformations.

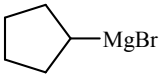


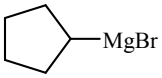
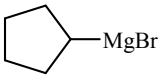
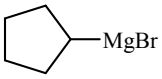
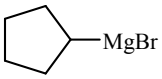
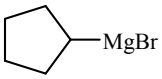
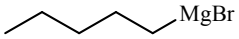
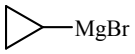
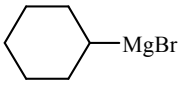
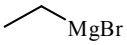
Scheme 19. Palladium-catalyzed direct benzylation of caffeine **7** with benzyl chlorides **46**.

A fascinating opportunity for synthesis of C^8-alkylated purines with relatively good yields has been observed by using different primary and secondary Grignard reagents as an efficient coupling reagent using 20 mol% of Ni(dppp)Cl$_2$ at room temperature (Table 1).[43] Possible mechanism for formation of C^8-alkylated purines with Grignard reagents is the same as shown in Figure 7.

Table 1. Direct C–H alkylation of various purines **48** with Grignard reagents **49**.

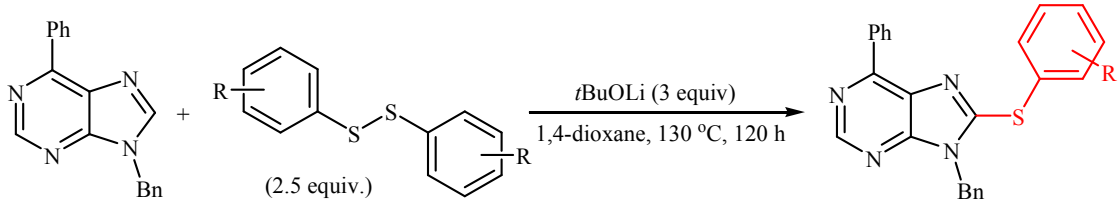


Entry	R^1	R^2	Alk-MgBr	Product	Yield (%)
1	OMe	Bn		**50a**	81

2	OMe	Me		**50b**	87
3	OMe	Et		**50c**	91
4	OMe	Cyclo-pentyl		**50d**	75
5	Cl	Bn		**50e**	77
6	4-Ethyl-phenyl	Bn		**50f**	89
7	OMe	Bn		**50g**	76
8	OMe	Bn		**50h**	72
9	OMe	Bn		**50i**	94
10	4-Ethyl-phenyl	Bn		**50j**	53

2-6-Direct C^8–H sulfenylation

Hocek and co-workers recently applied aryldisulfidesin as the coupling reagent in direct oxidative C–S bond formation at the C^8-position of purines, providing a novel entry to arylsulfanyl derivatives of purine (Scheme 20).[44] Purine **51** underwent sulfenylation with 1,2-diphenyldisulfane **52a** and 1,2-bis(4-methoxyphenyl)disulfane **52b** in the presence of *t*-BuOLi which gave corresponding C^8-arylsulfenylation purines **53a-b** in 60% and 56% yield, respectively. While the reaction with electron-poor 1,2-bis(4-nitrophenyl)disulfane **52c** did not work. It should be mentioned that, the resulting 8-arylsulfanylpurines **53** undergo Liebeskind–Srogl coupling[45] with arylstannanes or boronic acids in moderate to high yields (Scheme 21). To the best of our awareness, this is the only example of direct C^8–H sulfenylation of purines reported so far.

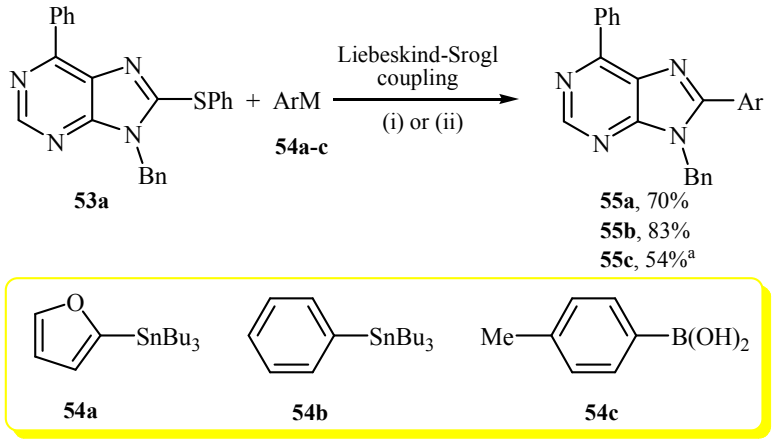


51

52a, R=H
52b, R=4-OMe
52c, R=4-NO_2

53a, 60%
53b, 56%
53c, 0.0%

Scheme 20. Direct C–S bond formation at the C^8-position of purines.



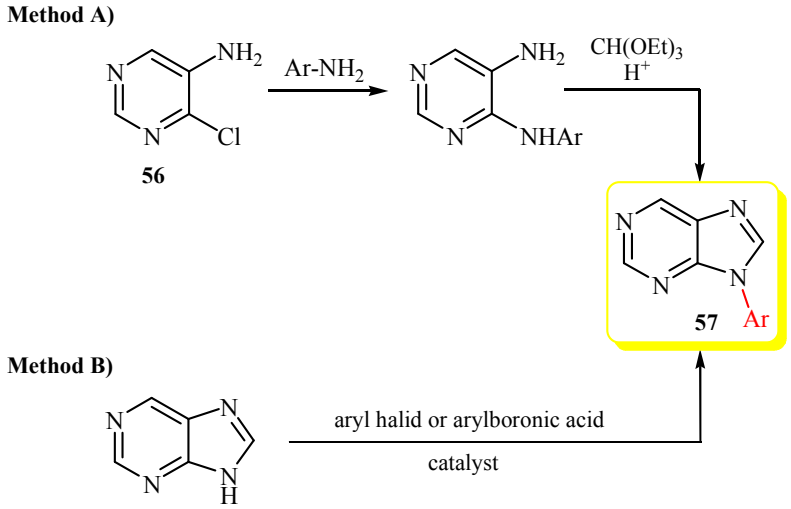
(i) $ArSnBu_3$ (1.2 equiv), $Pd(PPh_3)_4$ (5% mol), CuMeSal (2.2 equiv), 50 °C, THF, 17h.
(ii) $ArB(OH)_2$, $Pd(dba)_3$ (4 mol%), $(2\text{-furyl})_3P$ (16 mol%), CuTc (1.3 equiv), 50 °C, THF, 18h.

Scheme 21. Liebeskind–Srogl coupling of 8-arylsulfanylpurines.

3-Functionalization of N-H bonds

3-1- N^9-H arylation

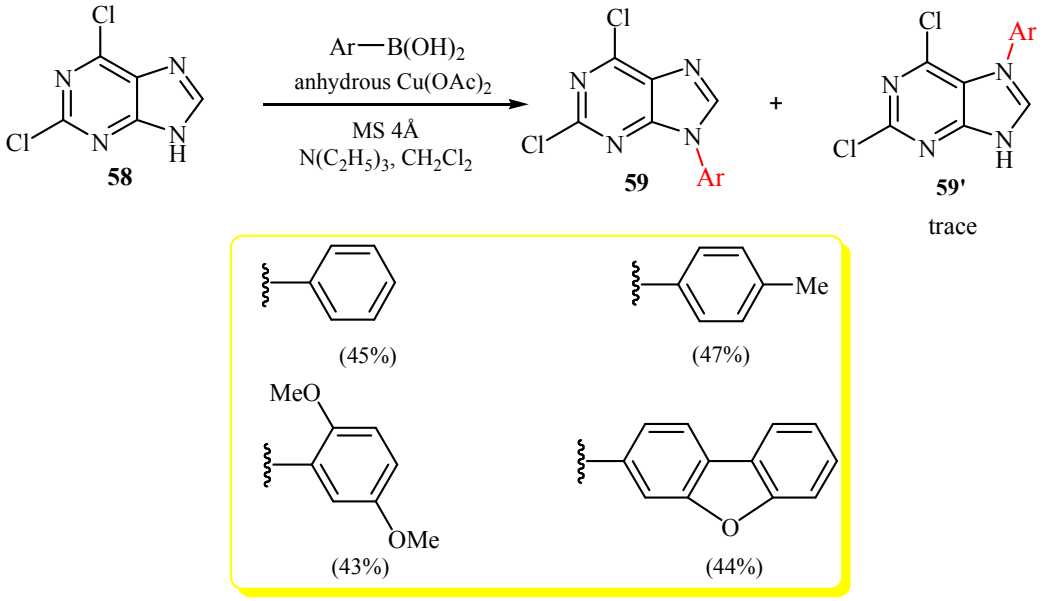
There are two general routes for generation of N^9-arylpurines **57** (Scheme 22). Traditionally, N^9-arylpurines are prepared from the reaction of arylamine with chloropyrimidines **56** followed by ring closer (method A).[46] An efficient and new method for the one-step synthesis of N^9-arylpurines involves N^9-arylation of purine *via* a C–N cross-coupling reaction (method B). The method A was not an efficient access because many tedious steps are required.[47-49]



Scheme 22. The general methods for generation of N^9-arylpurines.

N^9-arylation of purines has been reported by Lam and Chan, by using arylboronic acids as electrophilic partners.[50] The use of $Cu(OAc)_2/N(C_2H_5)_3$ or $Cu(OAc)_2$/pyridine system was found to be optimal for the Lam-Chan reaction conditions.[51-54] This method is compatible with a very large range of *meta*- and *para*-substituted arylboronic acids, but it could not be extended to *ortho*-

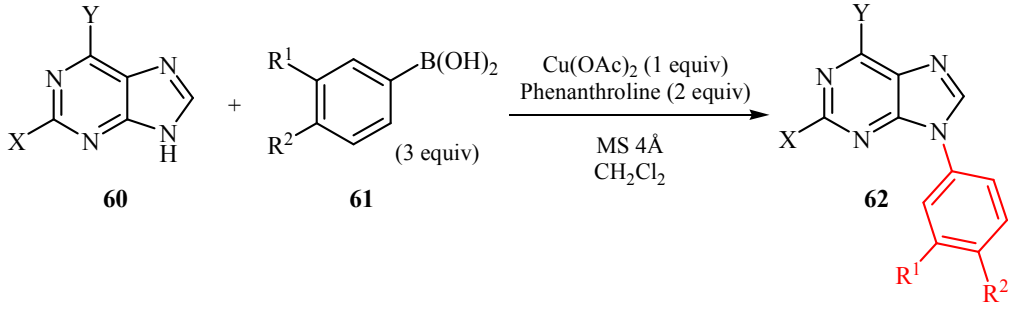
substituted arylboronic acids[52]. It should be mentioned that during N^9-arylation of purines with the Lam-Chan reaction, low yields (10%<) of N^7-regioisomer **59′** were also observed (Scheme 23).[55]



Scheme 23. N^9-arylation of purine **58** *via* the Lam and Chan's method.

A completely regioselective N^9-arylation of purines **60** has been developed in the presence of $Cu(OAc)_2$, molecular sieves and phenanthroline (Table 2).[48] It is noteworthy that this method doesn't work well for adenine, due to its low solubility.

Table 2. Cu-mediated reaction between purines **60** and arylboronic acids **61.**

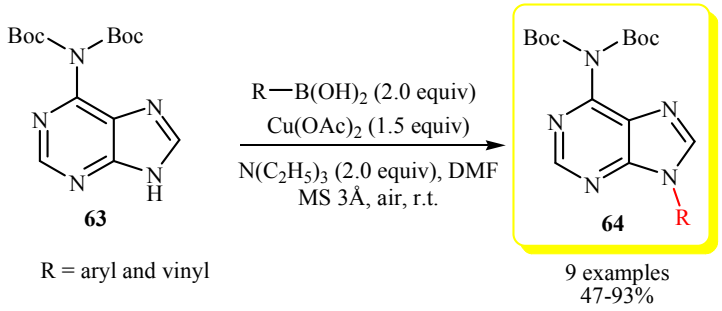


Entry	X	Y	R^1	R^2	Yield (%)
1	H	Cl	H	H	71
2	H	Cl	H	CH_3	68
3	H	Cl	H	OCH_3	52
4	H	Cl	H	Cl	41
5	H	Cl	Cl	H	73

6	Cl	Cl	H	H	52
7	Cl	Cl	H	CH_3	48
8	NH_2	Cl	H	H	42
9	H	NH_2	H	H	N.R
10	H	SCH_3	H	H	76
11	H	SH/SPh	H	H	81
12	H	2-Thienyl	H	H	68

Adenine can be efficiently arylated at the N^9 position with arylboronic acids at room temperature in a CH_3OH/H_2O (4:1) mixture as solvent.[49] This method is compatible with a very large range of substrates, and gave corresponding coupling products in moderate to high yields.

A versatile process for N^9-arylation of amino-protected adenine derivatives **63** with arylboronic acids was described by Gothelf *et al*.[56] They showed that the bis-Boc-adenine can be efficiently reacted with electron-rich, electron-poor and sterically hindered arylboronic acids at room temperature (Scheme 24).

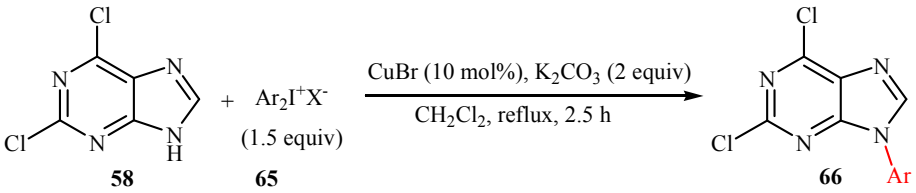


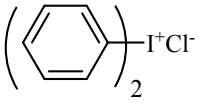
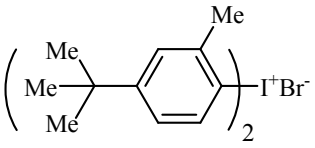
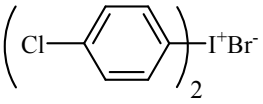
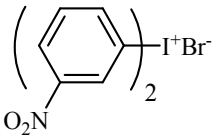
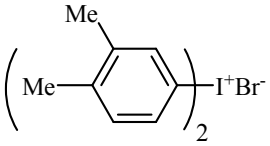
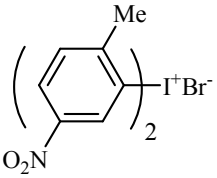
Scheme 24. N-arylation of bis-Boc-adenine **63**.

The reported methods for N^9-arylation of purines with arylboronic acids are associated with some drawbacks such as: 1) tedious separation of products from the arylboronic acid anhydrides, 2) low reaction yields with electron-deficient arylboronic acids and 3) in the most cases, long reaction time is required.

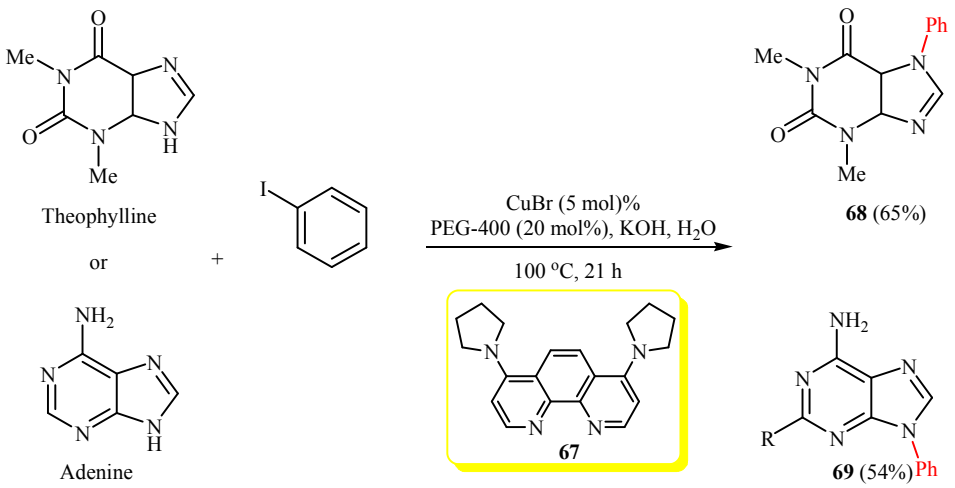
In 2011, Guo and co-workers reported an efficient and elegant protocol for regioselective N^9-arylation of purines by using diaryliodonium salts **65** in the presence of $CuBr/K_2CO_3/CH_2Cl_2$ system.[47] This method has several advantages such as good to excellent yields and broad substrate scope. It is worth to note that due to the poor solubility, $(3\text{-}NO_2C_6H_4)_2I^+Br^-$ underwent no reaction (Table 2, entry 5), and $(3\text{-}NO_2\text{-}6\text{-}MeC_6H_3)_2I^+Br^-$ gave a low yield (20%) (Table 3, entry 6).

Table 3. N^9- arylation of purine **58** with $Ar_2I^+Cl^-$



Entry	$Ar_2I^+X^-$	Yield (%)	Entry	$Ar_2I^+X^-$	Yield (%)
1		>99	4		>99
2		99	5		0
3		96	6		20

Recently, a new and beautiful method was reported for selective aromatic N-arylation of amino-containing purines with aryl halides in water.[57] The CuBr/DPPhen **67**/KOH combination was found to be optimal for this reaction. Theophylline and adenine underwent coupling reaction with iodo- and bromobenzene in moderate to good yields (Scheme 25).

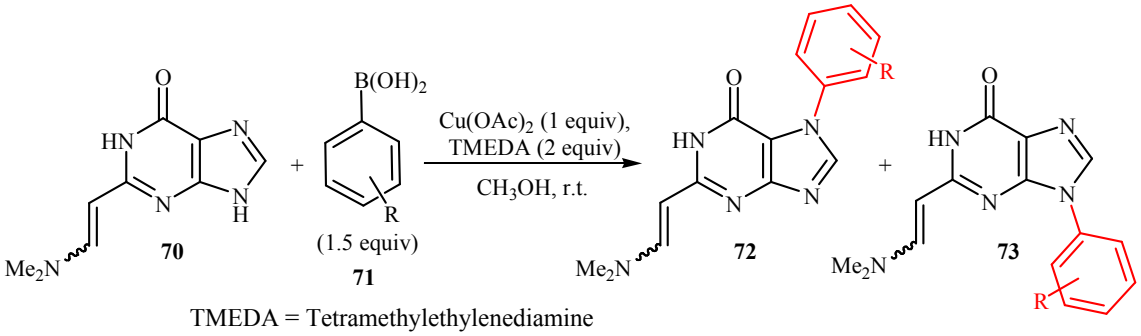


Scheme 25. Cu-mediated synthesis of N^9-phenylated theophylline **68** and adenine **69** with phenyl iodide.

3-2- N^7-H arylation

Dvořák and co-workers utilized the copper(II) catalyzed a cross-coupling reaction for the synthesis of N^7-arylated guanine **72** and adenine derivatives.[58] The amino-protected guanine **70** was found to undergo N^7/N^9 arylation with moderate to high selectivity (2:1 to 6:1) by using $Cu(OAc)_2/CH_3OH$/TMEDA system. The regioselectivity for this coupling reaction was highly affected by substitution on arylboronic acids (Table 4).

Table 4. *N*-arylation of N^2-(dimethylamino)methyleneguanine.

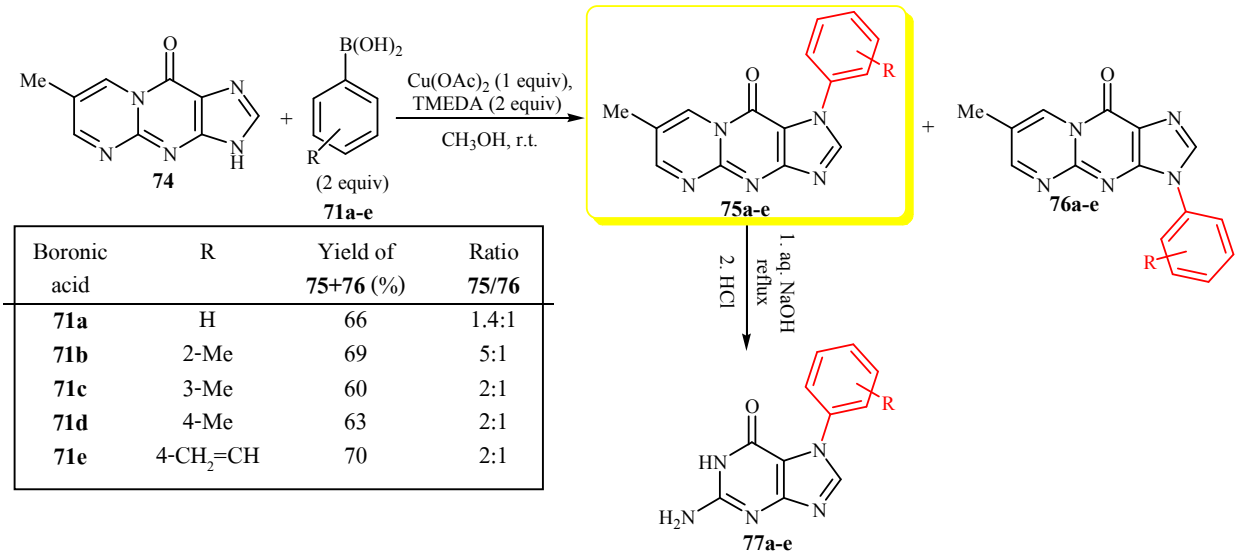


TMEDA = Tetramethylethylenediamine

Boronic acid	R	Yield of **72**+**73** (%)	Ratio **72**/**73**
71a	H	62	6:1
71b	2-Me	58	9:1
71c	3-Me	63	4:1
71d	4-Me	69	3:1

71e	4-CH_2=CH	52	2:1

A reported route for the synthesis of N^7-arylated adenines **77** involves the copper-mediated arylation of 7-methylpyrimido[1,2-a]purin-10(3H)-one **74** with arylboronic acids **71** by using $Cu(OAc)_2$/TMEDA system followed by hydrolysis of generated 1-aryl-7 methylpyrimido[1,2-a]purin-10(3H)-ones **75** (Scheme 26).[58]

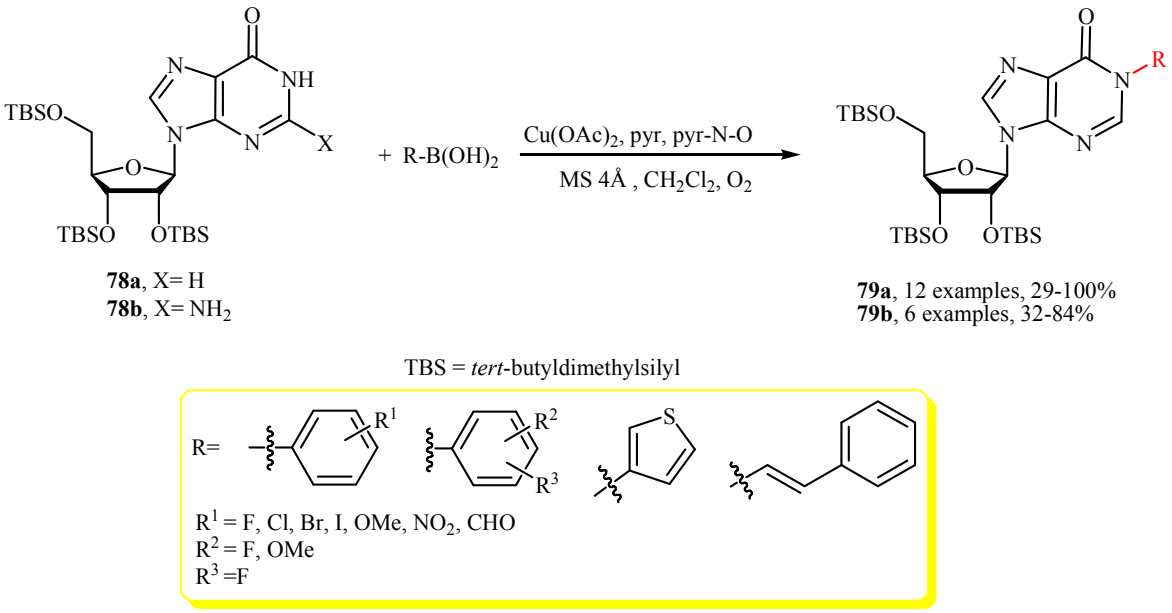


Boronic acid	R	Yield of **75+76** (%)	Ratio **75/76**
71a	H	66	1.4:1
71b	2-Me	69	5:1
71c	3-Me	60	2:1
71d	4-Me	63	2:1
71e	4-CH_2=CH	70	2:1

Scheme 26. Cu-mediated synthesis of N^7-arylated adenines **77a-e** from 7-methylpyrimido[1,2-a]purin-10(3H)-one **74**.

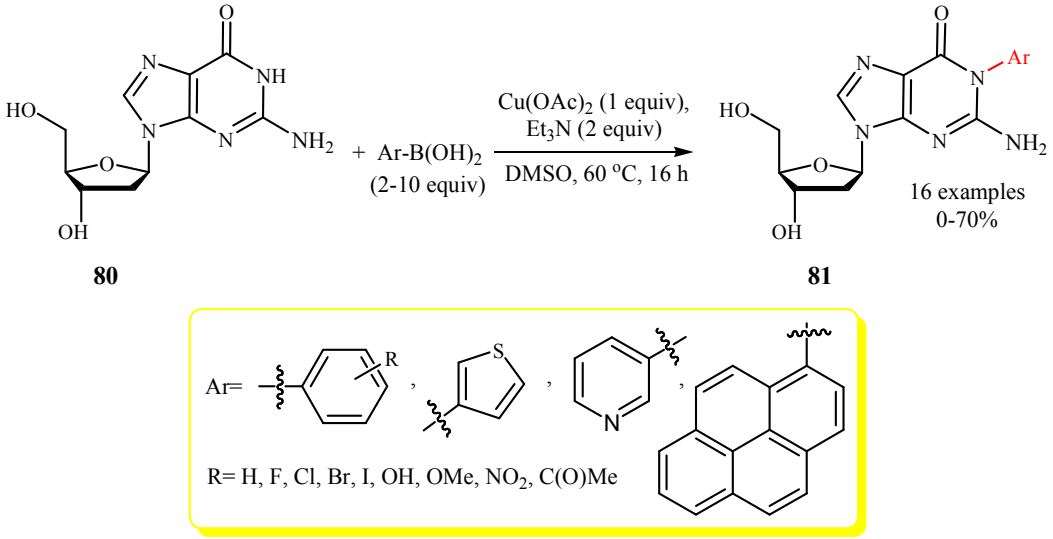
3-3- N^1-H arylation

Arterburn and co-workers investigated N^1-arylation of inosine **78a** and guanosin **78b** with arylboronic acids in 2005 (Scheme 27).[59] Both electron-donating and electron-withdrawing substituents at the *meta*- and *para*-position of arylboronic acids underwent the coupling in moderate to excellent yields, but it could not be extended to *ortho*-substituted aryl moiety. The presence of pyridine-N-oxide (pyr-N-O) as a co-oxidant or oxygen is vital for this reaction. In the absence of co-oxidant or oxygen, low reaction yields and long reaction time were observed.



Scheme 27. N^1-arylation of inosine **78a** and guanosin **78b** with arylboronic acids.

A method for the synthesis of N^1-arylated 2′-deoxyribonucleosides **81** have been reported by Harvey *et al.* (Scheme 28).[60] Copper (II)-catalyzed cross-coupling reaction of unprotected 2′-deoxyribonucleosides **80** with arylboronic acids in DMSO, affording N^1-arylated 2′-deoxyribonucleosides in a vast range of yields (in the presence and the absence of ligand 0-92% and < 10-95%, respectively).

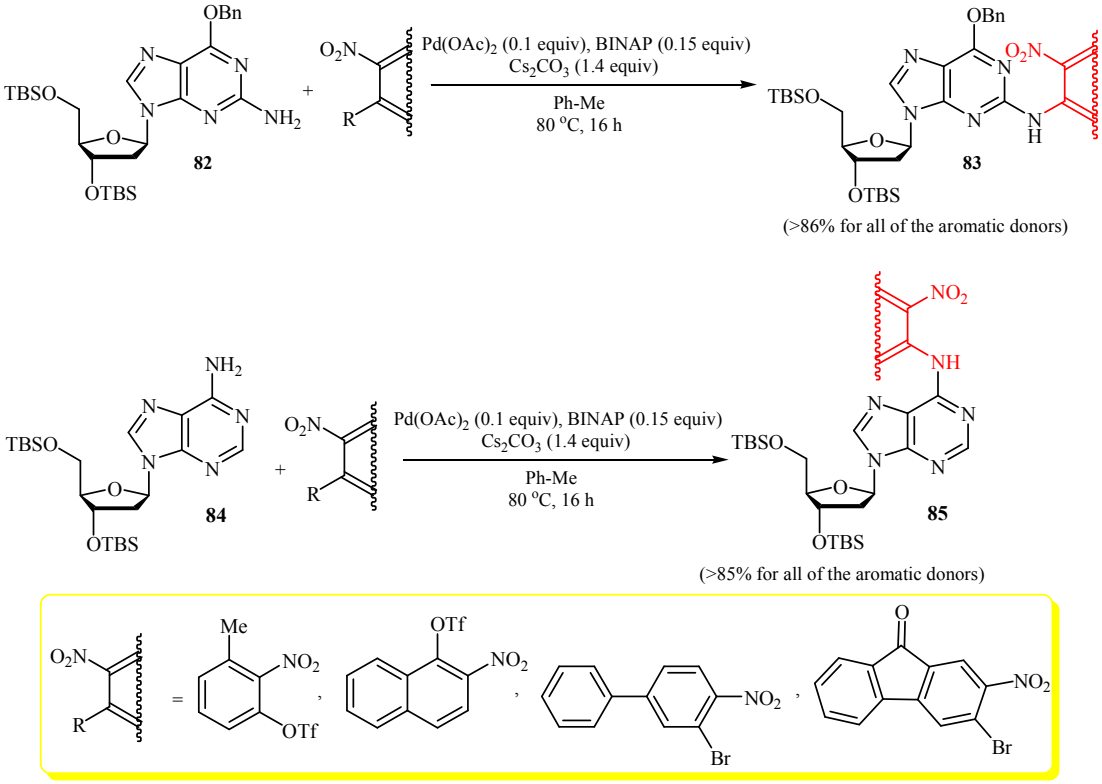


Scheme 28. Synthesis of N^1-aryl- 2′-deoxyribonucleosides **81** from **80** *via* cross-coupling reaction.

3-4- Exocyclic amino group arylation

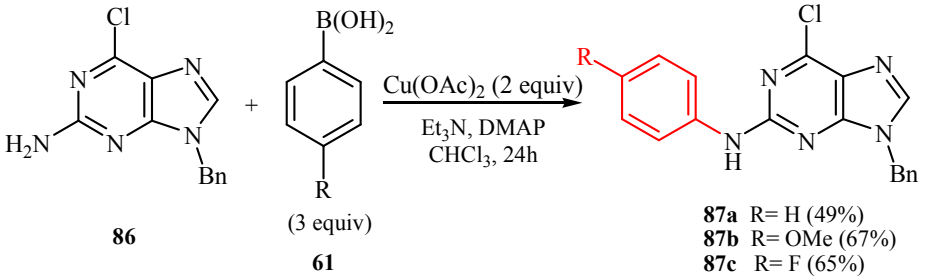
Protected derivative of 2′-deoxyguanosine (dG) **82** or 2′-deoxyadenosine (dA) **84** underwent Buchwald-Hartwing reaction in excellent yields with *ortho*-nitroaryl bromide or triflate, in the

presence of catalytic amounts of palladium(II) acetate and racemic 2, 2′-bis(diphenylphosphino)-1, 1′-binaphthyl (BINAP) (Scheme 29).[61]



Scheme 29. Buchwald-Hartwing reaction of **82** and **84** with *ortho*-nitroaryl bromides and triflates.

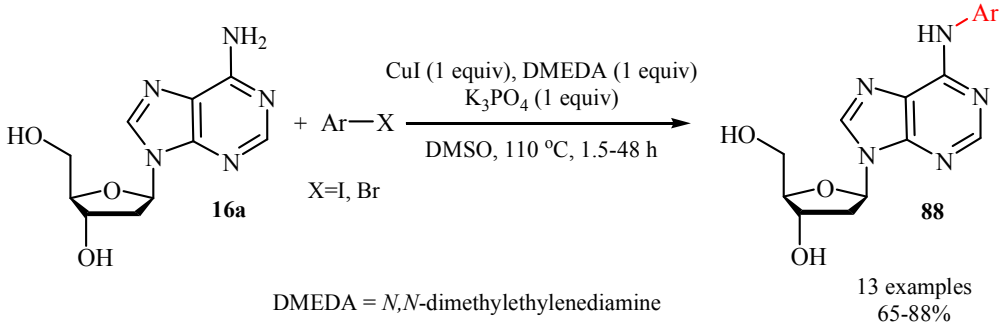
The selective *N*-arylation of aminopurines with arylboronic acids has been developed in 2004.[62] Treatment of the N^9-benzyl-protected 6-chloro guanine **86** with arylboronic acids in the presence of $Cu(OAc)_2/NEt_3$/DMAP system was shown to be an effective reaction for exocyclic amino group arylation of purines (Scheme 30).



Scheme 30. Synthesis of exocyclic amino group alkylated **87**.

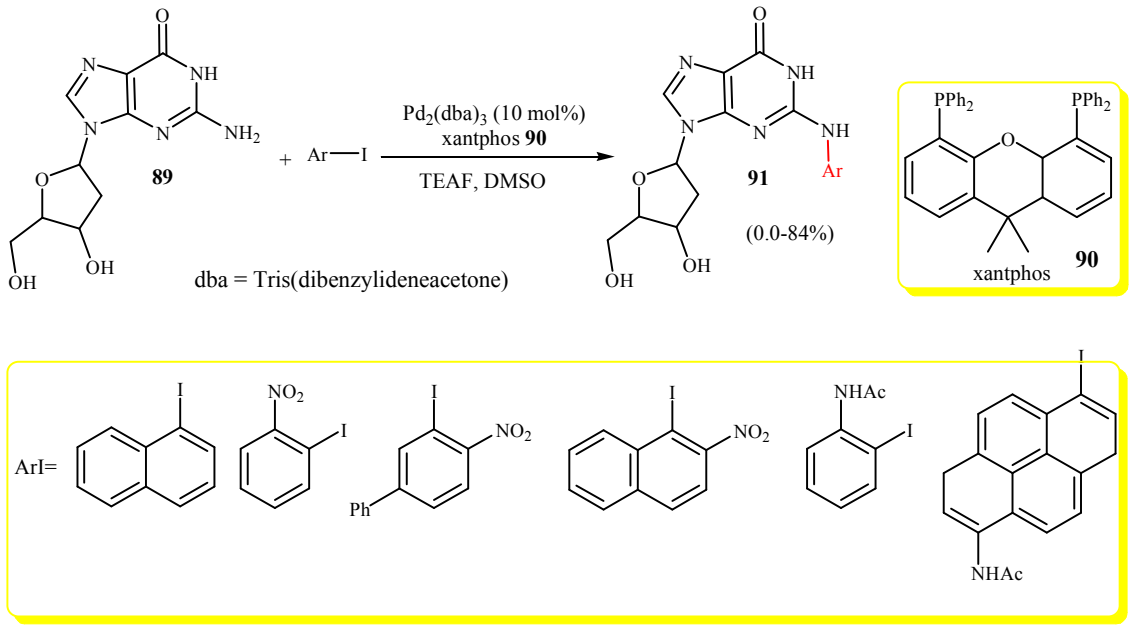
2′-Deoxyadenosine **16a** was found to undergo efficient N^6-arylation *via* copper-catalyzed direct coupling reaction with aryl halides as shown in Scheme 31. It is interesting to note that the electronic character of the substituents in the aryl halides had little effect on the facility of reaction. It should be

mentioned that aryl chlorides failed to enter into the coupling reaction but aryl bromides reacted smoothly to give the desired products with reasonable yields. The reaction rate of the aryl bromides was increased by addition of sodium iodide.[63]



Scheme 31. Selective coupling reaction at exocyclic amino group of 2′-deoxyadenosine **16a** with aryl halides.

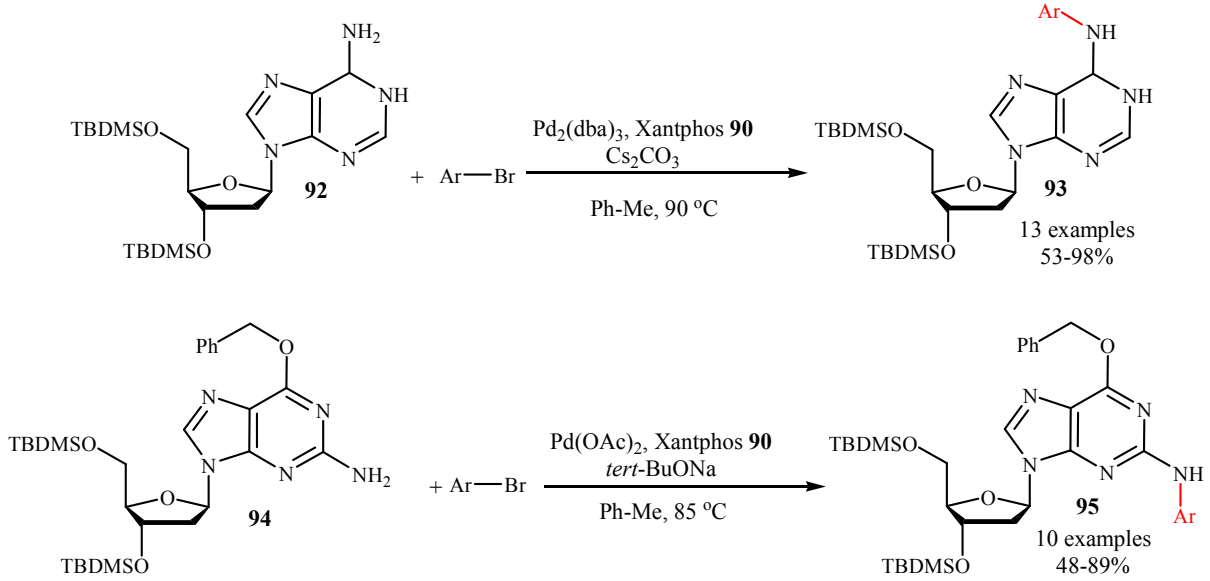
A different method for exocyclic *N*-arylation of aminopurines has been developed by using aryl iodide reagents in the presence of $Pd_2(dba)_3$ and xantphos **90**. This study was mainly focused on arylation of 2′-deoxyguanosine **89** with *ortho*-iodonitrobenzenes (Scheme 32), some cases of other aryl donors such as 3-iodopyren and purines was also disclosed.[64]



Scheme 32. Pd-catalyzed arylamination with DG and selected iodoarenes.

A very similar approach for arylation of the exocyclic amino group of nucleosides **92** and **94** was reported by Ngassa and co-workers (Scheme 33).[65] $Pd_2(dba)_3$/xantphos/Cs_2CO_3/$PhCH_3$ system was found to be optimal for arylation of 2′-deoxyadenosine analogue **92**. The optimized conditions for 2′-deoxyguanosine analogue **94** is $Pd(OAc)_2$/xantphos/tert-BuONa/$PhCH_3$. The reactions work well

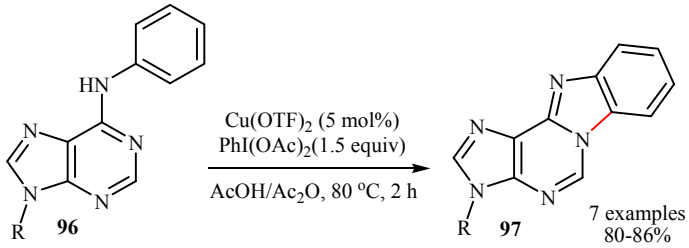
with electron-rich, electron-poor, naphthalene systems, and sterically hindered aryl bromides. The authors demonstrated that Pd catalyst with xanthos **90** as the supporting ligand is superior to BINAP-based ones.



Scheme 33. Arylation of the exocyclic amino group of nucleosides **92** and **94** with aryl bromides.

3-5- Intramolecular N-arylation

The 6-anilinopurine derivatives **96** was found to undergo efficient direct C-H activation/intramolecular amination by using $Cu(OTf)_2$ (5 mol %) and $PhI(OAc)_2$ as oxidant (1.5 equiv) in a mixture of $AcOH/Ac_2O$ as shown in Scheme 34. Depending on the electronic and steric effects of substituents on the aniline ring, substrates with electron-withdrawing groups gave higher yields than those with electron-donating groups, and *para*-substituted aniline ring were more reactive than *ortho*-substituted. A plausible catalytic cycle is depicted in Figure 8.[66] Combination of $Cu(OTf)_2$ with purines **96**, followed by an electrophilic substitution reaction resulted metallated purines **B**. Reductive elimination afforded the desired products **97**.



R= alkyl, allyl, benzyl, *etc.*

Scheme 34. Cu-mediated direct C-H activation/intramolecular amination of **96**.

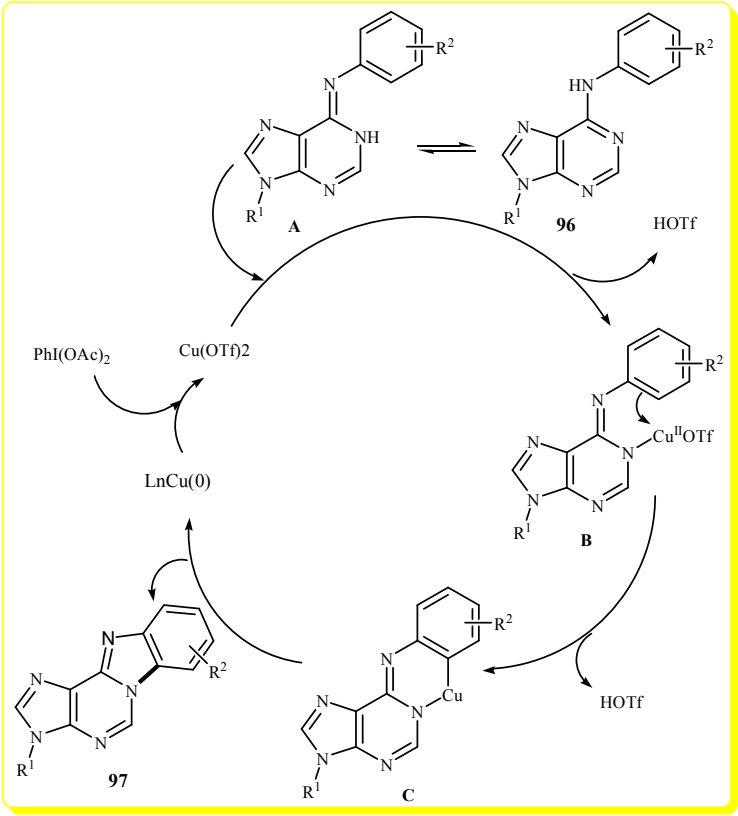


Figure 8. Plausible catalytic cycle for direct C-H activation/intramolecular amination.

4. Summary and outlook

In conclusion, this review provides concise overview on the cross-coupling reactions on direct functionalization of purine bases. In these transformations the inactive C-H bonds can be treated as a functional group, similar to the traditionally used C–(pseudo)halide bonds. This research area has still further possibilities for growth and we believed that the highly versatile and extremely effective and novel procedures for the synthesis of functionalized purine bases will be attainable in the near future.

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