The Suzuki–Miyaura Cross-Coupling Reactions of 2-, 6- or 8-Halopurines with Boronic Acids Leading to 2-, 6- or 8-Aryl- and -Alkenylpurine Derivatives

Martina Havelková,[a] Dalimil Dvořák,*[a] Michal Hocek*[b]

[a] Department of Organic Chemistry, Prague Institute of Chemical Technology, 16628 Prague 6, Czech Republic
   Fax +420(2)24354288; E-mail: dvorakd@vscht.cz
[b] Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 16610 Prague 6, Czech Republic
   Fax +420(2)3111271; E-mail: hocek@uochb.cas.cz

Abstract: The Suzuki–Miyaura cross-coupling reactions of 9-benzyl-6-chloropurine, 9- or 3-benzyl-8-bromoadenine and 2,6-dihalopurines with boronic acids gave the corresponding 6-, 8- or 2-aryl- or -alkenylpurines in good yields. Anhydrous conditions in toluene were superior for coupling of electron-rich boronic acids, while aqueous DME was used for electron-poor arylboronic acids as well as for alkenylboronic acids. A good regioselectivity was observed for the coupling of 2,6-dihalopurines: 9-benzyl-2,6-dichloropurine reacted with one equivalent of phenyl boronic acid to give 9-benzyl-2-chloro-6-phenylpurine, while an analogous reaction of 9-benzyl-6-chloro-2-iodopurine gave selectively 9-benzyl-6-chloro-2-phenylpurine.

**Key words:** purines, nucleobases, boronic acids, cross-coupling, palladium

Purines bearing carbon substituents in positions 2, 6 or 8 possess a broad spectrum of biological activity. Thus 6-methylpurine is highly cytotoxic,[1] while 2-alkynyladenosines are an important class of adenosine receptors agonists.[2] Recently, a cytokinin activity of 6-(arylalkynyl)-, 6-(arylalkenyl)- and 6-(arylalkyl)purines,[3] a cytostatic activity of 6-(trifluoromethyl)purine riboside[4] and of 6-arylpurine ribonucleosides,[5] a corticotropin-releasing hormone antagonist activity of some 2,8,9-trisubstituted-6-arylpurines[6] and an antimycobacterial activity of 9-benzyl-6-arylpurines[7] were also reported.

Cross-coupling reactions of halopurines with organometallics is an efficient approach for the preparation of purines bearing carbon substituents in the positions 2, 6 or 8. Diverse types of organometallics have been used and each type turned out to be superior for introduction of different types of C-substituents. Thus Ni-catalyzed coupling reactions of aryl- and alkylmagnesium halides with 6-halopurines were used for the preparation of 6-aryl- and 6-alkylpurines[8]. Pd-catalyzed cross-couplings of halopurines with organostannanes were used for the introduction of aryl, hetaryl, alkenyl or (less efficiently) alkyl groups[9–11] to positions 2, 6 and/or 8. Organozinc reagents, the most versatile organometallics, were successfully used for the attachment of alkyl, alkenyl, aryl or hetaryl groups[10–12] into position 6. Trialkylaluminums could be used for the

introduction of simple alkyl groups,[11,13] while cuprates are superior for *sec*- and *tert*-alkyl[14], alkynyl[15] and perfluoroalkyl[11,16] groups. Our recent alternative method[17] consisting in the use of the Suzuki–Miyaura cross-coupling reactions of 6-halopurines with boronic acids is applicable for the introduction of aryl and alkenyl groups and overcomes most of the drawback of the previous methods: many boronic acids are commercially available and inexpensive, they are non-toxic and they tolerate the presence of some unprotected functional groups. Since our preliminary communication,[17] this method has been successfully applied for the synthesis of 6-arylpurine bases and nucleosides[5] as well as acyclic nucleotide analogues[11] and a significant cytostatic activity[5] was found in some 6-arylpurine ribonucleosides. In this full paper we report in detail on the methodology of Suzuki–Miyaura cross-coupling reactions of 2, 6 and 8-halopurines with diverse types of aryl- and alkenylboronic acids as well as on regioselectivity of coupling with 2,6-dihalopurines.

In our preliminary communication[17] we reported on the cross-coupling reactions of 6-halopurines with boronic acids. Optimization of the procedure (catalytic systems, bases, solvents and conditions) revealed the following results: i) Pd(PPh$_3$)$_4$ turned out to be the superior catalyst [compared to other tested systems: Pd(dba)$_2$/P(*o*-tol)$_3$, Pd(dba)$_2$/AsPh$_3$, PdCl$_2$(PPh$_3$)$_2$]; ii) the use of potassium carbonate as base resulted in very efficient coupling [while other bases, i.e. Na$_2$CO$_3$, Cs$_2$CO$_3$, EtN(*i*-Pr)$_2$, NaOMe, did not give any reaction]; iii) the reactions are significantly affected by the choice of solvent: while the coupling of 7- or 9-benzyl-6-chloro- as well as of 9-benzyl-6-iodopurine with electron rich arylboronic acids proceeds smoothly under anhydrous conditions [Method A: 100 °C, Pd(PPh$_3$)$_4$ (2.5–5 mol%), K$_2$CO$_3$/toluene at 100 °C], electron deficient arylboronic acids and alkenylboronic acids required aqueous conditions in DME [Method B: 85 °C, Pd(PPh$_3$)$_4$ (2.5–5 mol%), K$_2$CO$_3$/DME–H$_2$O].

Thus the reactions (Scheme 1) of 9-benzyl-6-chloropurine (**1a**) with phenylboronic acids bearing electron-donor, electroneutral and slightly electron-withdrawing substituents under anhydrous conditions (Method A) gave the corresponding 6-phenylpurines **2** in good yields (Table 1, entries 1,2,5,6,12), the reactions with electron-deficient phenylboronic acids, thienyl-, alkenyl- and alkylboronic acids gave only yields from moderate to very
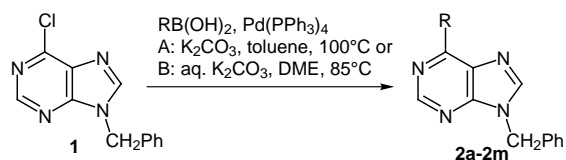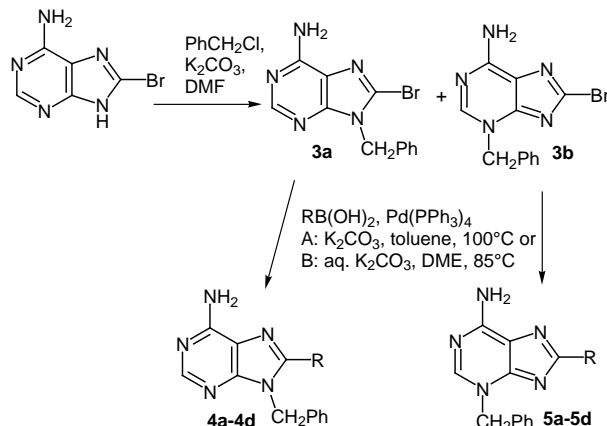
Scheme 1

low. On the other hand, when using aqueous conditions (Method B), the yields of the reactions with electron-deficient phenylboronic acids (nitro-, formyl- and acetylphenyl), thienyl-, alkenylboronic acids were substantially increased (Table 1, entries 3,4,7,8,10,11). The formyl derivative **2g** was accompanied by some difficult to isolate impurities, probably as a result of instability of formyl derivatives to aqueous base. Surprisingly, also 3-aminophenylboronic acid afforded better results using Method B (Table 1, entry 9). The use of aqueous conditions (Method B) seems to be more versatile for introduction of various types of substituents. On the other hand, the use of basic aqueous solutions of K_2CO_3 is often incompatible with reactive or labile functional and/or protective groups (e.g. acyl protection of nucleosides).

Table 1 Reaction of 9-Benzyl-6-chloropurine (**1a**) with $RB(OH)_2$ (1.2 equiv)

Entry	Product	R	Reaction Time (h)	Method[a]	Yield (%)
1	**2a**	C_6H_5	24	A	95
			7	B	95
2	**2b**	$4\text{-}FC_6H_4$	24	A	89
3	**2c**	$(E)\text{-}C_6H_5CH=CH$	24[b]	A	14
			7.5	B	76
4	**2d**	$3\text{-}NO_2C_6H_4$	48[b]	A	19
			7	B	66
5	**2e**	$3\text{-}MeOC_6H_4$	4	A	62
6	**2f**	$2\text{-}MeC_6H_4$	24	A	86
7	**2g**	$4\text{-}CHOC_6H_4$	23	B	61
8	**2h**	$4\text{-}CH_3COC_6H_4$	24	B	73
9	**2i**	$3\text{-}NH_2C_6H_4$	24[b]	B	78
10	**2j**	2-thienyl	24[b]	A	39
			7[b]	B	87
11	**2k**	$(E)\text{-}C_5H_{11}CH=CH$	24[b]	A	18
			8	B	98
12	**2l**	C_4H_9	24[b]	A	18
			24	B	0
13	**2m**	C_6F_5	24	A	0
			24	B	0

[a] Method A: 2.5 mol% $Pd(PPh_3)_4$, K_2CO_3, toluene, 100 °C; Method B: 2.5 mol% $Pd(PPh_3)_4$, 2 M aq K_2CO_3, DME, 85 °C.
[b] Unreacted **1a** remains in the reaction mixture.

Scheme 2

Furthermore, the methodology of the Suzuki–Miyaura cross-coupling reaction has been extended to the substitution at other positions of the purine ring. Thus 9-benzyl-(**3a**) and 3-benzyl-8-bromoadenine (**3b**), the model compounds for the study of reactivity of adenine derivatives were prepared by benzylation of 8-bromoadenine[18] with benzyl chloride in the presence of K_2CO_3 in DMF at 120 °C in 60:40 ratio (Scheme 2). The compounds were separated chromatographically and their structure was unambiguously identified on the basis ^{1}H NMR, ^{13}C NMR and HMBC. The reactivity of 9-benzyl-8-bromoadenine (**3a**) parallels that of 9-benzyl-6-chloropurine (**1a**). Phenylboronic acid coupled almost quantitatively to give the 8-phenyladenine **4a** no matter what method was used, while

Table 2 Reaction of 9-benzyl-8-bromoadenine (**3a**) and 3-benzyl-8-bromoadenine (**3b**) with $RB(OH)_2$ (1.2 equiv)

Entry	Starting Compound	Product	R	Method[a]	Yield (%)
1	**3a**	**4a**	C_6H_5	A	96
				B	96
2	**3a**	**4b**	$4\text{-}FC_6H_4$	A	63
				B	94
3	**3a**	**4c**	$(E)\text{-}C_6H_5CH=CH$	A	44
				B	68
4	**3a**	**4d**	$3\text{-}NO_2C_6H_4$	A	36
				B	76
5	**3b**	**5a**	C_6H_5	A	92
				B	66
6	**3b**	**5b**	$4\text{-}FC_6H_4$	A	98
				B	75
7	**3b**	**5c**	$(E)\text{-}C_6H_5CH=CH$	A	41
				B	77
8	**3b**	**5d**	$3\text{-}NO_2C_6H_4$	A	95
				B	89

[a] Method A: 2.5 mol% $Pd(PPh_3)_4$, K_2CO_3, toluene–DMF 8:2, 100 °C, 24 h; Method B: 2.5 mol% $Pd(PPh_3)_4$, 2 M aq K_2CO_3, DME, 85 °C, 24 h.

styrylboronic and an electron-poor 3-nitrophenylboronic acids afforded better yields of the corresponding 8-substituted adenines **4c** and **4d** when aqueous conditions (Method B) were used (Scheme 2, Table 2, entries 1,3,4). Somewhat surprisingly also 4-fluorophenylboronic acid gave better results using aqueous conditions (Table 2, entry 2). 3-Benzyl-8-bromoadenine (**3b**) reacted smoothly with phenyl- and 4-fluorophenylboronic acids, giving the corresponding 3-benzyl-8-phenyladenines **5a** and **5b** in somewhat better yields under anhydrous conditions. Also with styrylboronic acid the starting purine derivative **3b** was consumed in less than 24 hours. The yield of **5c** was in this case better with aqueous procedure (Table 2, entry 7). 3-Nitrophenylboronic acid reacted with 3-benzyl-8-bromoadenine (**3b**) sluggishly under both aqueous and anhydrous conditions. In both cases however, high yields of **5d** were achieved after prolonged reaction time (Table 2, entry 8).

The Stille cross-coupling reactions of 9-benzyl-2,6-dihalopurines with organostannanes have been reported[9i] to proceed with a good regioselectivity: the reaction with one equivalent of organostannane gave the substitution in the position 6, while the use of 6-chloro-2-iodopurine resulted in the preferential substitution in the position 2. Therefore we have studied the Suzuki–Miyaura coupling reactions of 2,6-dihalopurines with phenylboronic acid and the results were analogous. The reaction of 9-benzyl-2,6-dichloropurine (**6**) with one equivalent of phenylboronic acid under anhydrous conditions afforded smoothly and selectively 9-benzyl-2-chloro-6-phenylpurine (**7**) in 77% yield, while with excess (3 equiv) of the phenylboronic acid both chlorine atoms were substituted to give 9-benzyl-2,6-diphenylpurine (**8**) in 84% yield (Scheme 3). On the other hand, the reaction of 9-benzyl-6-chloro-2-iodopurine (**9**) with one equivalent of the phenylboronic acid under anhydrous conditions afforded selectively 9-benzyl-6-chloro-2-phenylpurine (**10**) in 81% yield, while the reaction with an excess of phenylboronic acid gave the 2,6-diphenylpurine **8** in 88% yield (Scheme 3). Although the reactivity of the iodine atom in the position 2 is apparently higher that that of chlorine, the reactions of the 6-chloro-2-iodopurine derivative **9** were substantially slower (prolonged reaction times were required for completion of the conversion) than the reactions of the 2,6-dichloroderivative **6** which is probably due to the fact that the leaving iodide anion is more strongly complexed to palladium thus slowing down the transmetallation with boric acid.

In conclusion, we proved, that the Suzuki–Miyaura cross-coupling reactions of halopurines with boronic acids is a versatile, efficient and non-toxic alternative method for an introduction of an aryl, hetaryl or alkenyl substituent into positions 2, 6 or 8 of various purine derivatives. The excellent regioselectivity of the coupling reactions of 2,6-dihalopurines allows, together with the previously known[9i] regioselective Stille couplings, a selective and efficient synthesis of 6-substituted 2-chloropurines or 2-substituted 6-chloropurines that could be used for further substitution
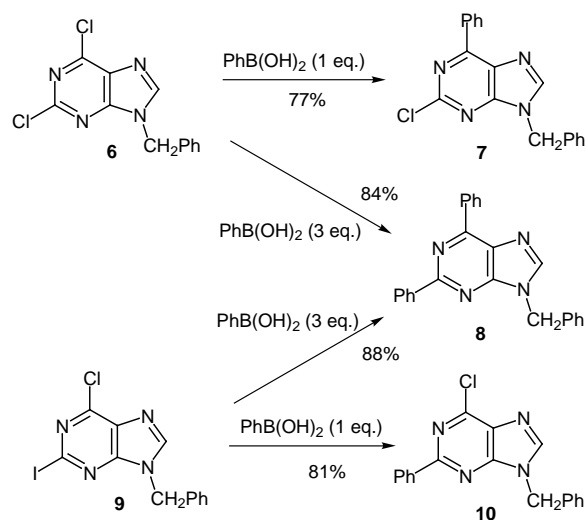
Scheme 3

or coupling reactions. This opens up an avenue to the synthesis of a variety (a library) of potentially biologically active purine derivatives bearing two different substituents in positions 2 and 6. This study is now under way.

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Varian Gemini 300 (^{1}H, 300.07 MHz; ^{13}C, 75.46 MHz), a Bruker AMX3 400 (^{1}H, 400.13 MHz and ^{13}C, 100.62 MHz) or a Bruker DRX 500 Avance (^{1}H, 500.13 MHz and ^{13}C, 125.77 MHz) spectrometer at 298 K. Unambiguous assignment of the NMR signals is based on ^{13}C{^{1}H}, ^{13}C APT, COSY and ^{13}C HMBC spectra. IR spectra were recorded on Nicolet 750 FT-IR. Mass spectra were measured on ZAB-SEQ (VG Analytical) The solvents were dried and degassed by standard procedures, silica gel (ICN SiliTech, 32-63) was used for column chromatography. 9-Benzyl-6-chloropurine[10b] (**1**), 9-benzyl-2,6-dichloropurine[9i] (**6**) and 9-benzyl-6-chloro-2-iodopurine[9i] (**9**) were prepared by the reported procedures.

Coupling of 9-Benzyl-6-chloropurine (1) with Boronic Acids; General Procedure
Method A: Toluene (5 mL) was added through a septum to an argon purged flask containing a 9-benzyl-6-chloropurine (**1**; 0.122 g, 0.5 mmol), boronic acid (0.75 mmol), anhyd K_2CO_3 (0.086 g, 0.625 mmol), Pd(PPh$_3$)$_4$ (0.014 g, 0.012 mmol) and the mixture was stirred under argon at 100 °C until the reaction was completed (TLC). The reaction mixture was cooled to r.t. and filtered through Celite. The solvent was evaporated and the residue chromatographed on silica gel (CHCl$_3$–MeOH, 98:2). The crude product was purified by crystallization from CH$_2$Cl$_2$–heptane.

Method B: The reaction under aqueous conditions was analogous, except for the higher amount of K_2CO_3 (0.187 g, 1.35 mmol) together with H$_2$O (0.7 mL) in DME (5 mL) was used. The reaction mixture was then stirred under argon at 85 °C. The workup was the same as above.

9-Benzyl-6-phenylpurine (2a)
Both Methods A and B afforded 95% yield; mp 124–126 °C (Lit.[10b] mp 124–125 °C).

9-Benzyl-6-(4-fluorophenyl)purine (2b)
Yield: 89% (Method A), mp 127–129 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.48 (s, 2 H, CH$_2$), 7.24 (m, 2 H, ArH), 7.35 (m, 5 H, C$_6$H$_5$), 8.09 (s, 1 H, H-8 Pu), 8.86 (m, 2 H, ArH), 9.03 (s, 1 H, H-2 Pu).

IR (CHCl$_3$): ν = 2998, 1603, 1585, 1572, 1513, 1450, 1328 cm^{-1}.

MS-EI: *m/z* (%) = 304 (M$^+$, 100).

HRMS (EI): *m/z* Calcd for C$_{18}$H$_{13}$FN$_4$ 304.1124. Found: 304.1119.

Anal. Calcd for C$_{18}$H$_{13}$FN$_4$ (304.3): C, 71.04; H, 4.31; N, 18.41; F, 6.24. Found: C, 70.71; H, 4.75; N, 18.09; F, 6.33.

9-Benzyl-6-[(*E*)-styryl]purine (2c)
Yield: 14% (Method A), 82% (Method B); mp 127–129 °C (Lit.^{10b} mp 132–134 °C).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.46 (s, 2 H, CH$_2$), 7.37 (m, 8 H, C$_6$H$_5$), 7.73 (m, 3 H, C$_6$H$_5$ + C*H*=CH), 8.05 (s, 1 H, H-8 Pu), 8.42 (d, *J* = 15.9 Hz, 2 H, CH=C*H*), 8.94 (s, 1 H, H-2 Pu).

9-Benzyl-6-(3-nitrophenyl)purine (2d)
Yield: 66% (Method B), 19% (Method A); mp 187–188 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.51 (s, 2 H, CH$_2$), 7.36 (m, 5 H, C$_6$H$_5$), 7.73 (t, *J* = 8 Hz, 1 H, ArH), 8.16 (s, 1 H, H-8 Pu), 8.35 (m, 1 H, ArH), 9.10 (s, 1 H, H-2 Pu), 9.21 (m, 1 H, ArH), 9.75 (t, *J* = 2 Hz, 1 H, ArH).

IR (CHCl$_3$): ν = 3030, 3002, 1583, 1533, 1351 cm^{-1}.

MS-EI: *m/z* (%) = 331 (M$^+$, 15), 227 (100).

Anal. Calcd for C$_{18}$H$_{13}$N$_5$O$_2$ (331.3): C, 65.25; H, 3.95; N, 21.44. Found: C, 65.25; H, 4.12; N, 21.17.

9-Benzyl-6-(3-methoxyphenyl)purine (2e)
Yield: 66% (Method A); mp 111–114 °C (Lit.^{10b} mp 114–116 °C).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.93 (s, 3 H, CH$_3$), 5.49 (s, 2 H, CH$_2$), 7.08 (m, 1 H, ArH), 7.35 (m, 5 H, C$_6$H$_5$), 7.47 (t, *J* = 8 Hz, 1 H, ArH), 8.09 (s, 1 H, H-8 Pu), 8.36 (m, 1 H, ArH), 8.45 (m, 1 H, ArH), 9.06 (s, 1 H, H-2 Pu).

9-Benzyl-6-(2-methylphenyl)purine (2f)
Yield: 89% (Method A); oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.44 (s, 3 H, CH$_3$), 5.49 (s, 2 H, CH$_2$), 7.35 (m, 8 H, C$_6$H$_5$ + ArH), 7.70 (m, 1 H, ArH), 8.06 (s, 1 H, H-8 Pu), 9.08 (s, 1 H, H-2 Pu).

IR (CHCl$_3$): ν = 2996, 1587, 1503, 1455, 1404, 1330 cm^{-1}.

MS-EI: *m/z* (%) = 300 (M$^+$, 28), 209 (100).

HRMS (EI): *m/z* Calcd for C$_{19}$H$_{16}$N$_4$ 300.1374. Found: 300.1367.

Anal. Calcd for C$_{19}$H$_{16}$N$_4$ (300.4): C, 75.98; H, 5.37; N, 18.65. Found: C, 75.50; H, 5.48; N, 18.35.

9-Benzyl-6-(4-formylphenyl)purine (2g)
Yield: 61% (Method B), mp 161–164 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.51 (s, 2 H, CH$_2$), 7.37 (m, 5 H, C$_6$H$_5$), 8.06 (d, *J* = 8.2 Hz, 2 H, ArH), 8.16 (s, 1 H, H-8 Pu), 8.99 (s, *J* = 8.2 Hz, 2 H, ArH), 9.11 (s, 1 H, H-2 Pu), 10.13 (s, 1 H, CHO).

IR (CHCl$_3$): ν = 3024, 1706, 1583, 1561, 1328 cm^{-1}.

MS (EI): *m/z* (%) = 314 (M$^+$, 100).

HRMS (EI): *m/z* Calcd for C$_{19}$H$_{14}$N$_4$O 314.1167 Found: 314.1161.

9-Benzyl-6-(4-acetylphenyl)purine (2h)
Yield: 73% (Method B), mp 137–139 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.67 (s, 3 H, CH$_3$), 5.51 (s, 2 H, CH$_2$), 7.35 (m, 5 H, C$_6$H$_5$), 8.13 (d, *J* = 8.8 Hz, 2 H, ArH), 8.15 (s, 1 H, H-8 Pu), 8.91 (d, *J* = 8.8 Hz, 2 H, ArH), 9.10 (s, 1 H, H-2 Pu).

IR (CHCl$_3$): ν = 3025, 3010, 1664, 1582, 1557, 1327, 1267 cm^{-1}.

MS-EI: *m/z* (%) = 328 (M$^+$, 69), 91 (100).

HRMS (EI): *m/z* Calcd for C$_{20}$H$_{16}$N$_4$O 328.1324. Found: 328.1327.

Anal. Calcd for C$_{20}$H$_{16}$N$_4$O (328.4): C, 73.15; H, 4.91; N, 17.06. Found: C, 73.15; H, 5.23; N, 17.00.

9-Benzyl-6-(3-aminophenyl)purine (2i)
Yield: 78% (Method B), mp 148–150 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.86 (s, 2 H, NH$_2$), 5.48 (s, 2 H, CH$_2$), 6.85 (dd, *J* = 2.5, 7.9 Hz, 1 H, ArH), 7.35 (m, 6 H, C$_6$H$_5$ + ArH), 8.09 (s, 1 H, H-8 Pu), 8.10 (m, 1 H, ArH), 8.22 (d, *J* = 7.7 Hz, 1 H, ArH), 9.04 (s, 1 H, H-2 Pu).

IR (CHCl$_3$): ν = 2997, 2927, 1621, 1582, 1571, 1327 cm^{-1}.

MS (EI): *m/z* (%) = 301 (M$^+$, 17), 91 (100).

Anal. Calcd for C$_{18}$H$_{15}$N$_5$ (301.4): C, 71.74; H, 5.02; N, 23.24. Found: C, 72.04; H, 5.50; N, 23.39.

9-Benzyl-6-(2-thienyl)purine (2j)
Yield: 39% (Method A), 87% (Method B); mp 198–200 °C (Lit.^{10b} mp 198–200 °C).

9-Benzyl-6-((*E*)-hepten-1-yl)purine (2k)
Yield: 18% (Method A), 98% (Method B), mp 40–42 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.89 (m, 3 H, CH$_3$), 1.36 (m, 4 H, CH$_2$), 1.57 (m, 2 H, CH$_2$), 2.39 (dq, *J* = 7.1, 1.6 Hz, 2 H, CH$_2$), 7.01 (dt, *J* = 15.9, 1.6 Hz, Pu-C*H*=CH), 7.23–7.40 (m, 5 H, C$_6$H$_5$), 7.63 (dt, *J* = 15.9, 7.1 Hz, Pu-CH=C*H*), 8.00 (s, 1 H, H-8 Pu), 8.89 (s, 1 H, H-2 Pu).

IR (CHCl$_3$): ν = 2961, 2932, 1651, 1587, 1327 cm^{-1}.

MS-EI: *m/z* (%) = 306 (M$^+$, 49), 91 (100).

HRMS (EI): *m/z* Calcd for C$_{19}$H$_{22}$N$_4$ 306.1896. Found: 306.1844.

9-Benzyl-6-butylpurine (2l)^{10b}
Yield: 18% (Method A), oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.95 (t, *J* = 7.1 Hz, 3 H, CH$_3$), 1.45 (m, 2 H, CH$_2$), 1.88 (m, 2 H, CH$_2$), 3.20 (t, *J* = 7.7 Hz, Pu-CH$_2$), 5.43 (s, 2 H, CH$_2$), 7.33 (m, 5 H, C$_6$H$_5$), 7.99 (s, 1 H, H-8 Pu), (s, 1 H, H-2 Pu).

Benzylation of 8-Bromoadenine
A mixture of 8-bromoadenine (0.905 g, 4.23 mmol), K$_2$CO$_3$ (2.10 g, 14.8 mmol) and benzyl chloride (0.8 mL, 6.6 mmol) in DMF (40 mL) was heated to 120 °C for 9 h under argon. ^{1}H NMR spectrum of the crude reaction mixture showed formation of **3a** and **3b** in approximately 6:4 ratio. DMF was then evaporated in vacuum and the residue chromatographed on silica gel (CHCl$_3$–MeOH, 97:3) to give 0.410 g of 9-benzyl-8-bromoadenine (**3a**) (more mobile) and 0.193 g of 3-benzyl-8-bromoadenine (**3b**) (less mobile). Analytically pure compounds were obtained by crystallization from EtOH.

9-Benzyl-8-bromoadenine (3a)
Yield: 32%, mp 226–227 °C.

^{1}H NMR (500 MHz, DMSO-*d$_6$*): δ = 5.35 (s, 2 H, CH$_2$), 7.22 (d, 2 H, *J* = 7.1 Hz, C$_6$H$_5$), 7.29 (m, 1 H, C$_6$H$_5$), 7.34 (m, 2 H, C$_6$H$_5$), 7.45 (br s, 2 H, NH$_2$), 8.16 (s, 1 H, H-2 Pu).

^{13}C NMR (APT): δ = 46.6 (CH$_2$), 119.0 (C-5), 126.5 (C-8), 127.1 (CH-Ph), 127.8 (CH-Ph), 128.7 (CH-Ph), 136.0 (C-Ph), 151.0 (C-4), 153.1 (C-2), 154.8 (C-6).

MS (EI): *m/z* (%) = 305 (M$^+$, 17), 91 (100).

IR (KBr): ν = 3354, 3139, 1659, 1607, 1579, 1318, 1302 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}BrN_5$ (304.1): C, 47.39; H, 3.31; N, 23.03. Found: C, 47.57; H, 3.62; N, 22.87.

3-Benzyl-8-bromoadenine (3b)
Yield: 15%; mp 239–240.5 °C (Lit.[19] mp 206 °C).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.47 (s, 2 H, CH$_2$), 7.35 (m, 5 H, C$_6$H$_5$), 8.09 (br s, 1 H, NH$_2$), 8.26 (br s, 1 H, NH$_2$), 8.55 (s, 1 H, H-2 Pu).

^{13}C NMR (APT): δ = 52.0 (CH$_2$), 121.5 (C-5), 127.8 (CH-Ph), 128.1 (CH-Ph), 128.7 (CH-Ph), 135.8 (C-Ph), 139.3 (C-8), 144.0 (C-2), 149.8 (C-4), 153.6 (C-6).

MS (EI): m/z (%) = 305 (M$^+$, 16), 91 (100).

IR (KBr): ν = 3442, 3088, 1665, 1620, 1455, 1432, 1242, 1219 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}BrN_5$ (304.1): C, 47.39; H, 3.31; N, 23.03. Found: C, 47.40; H, 3.37; N, 23.05.

Coupling of 9-Benzyl-8-bromoadenine (3a) and 3-Benzyl-8-bromoadenine (3b) with Boronic acids; General Procedure
Method A: Toluene (5 mL) was added through a septum to an argon purged flask containing a benzyl-8-bromoadenine (**3a** or **3b**) (0.076 g, 0.25 mmol), boronic acid (0.375 mmol), anhyd K$_2$CO$_3$ (0.043 g, 0.312 mmol), Pd(PPh$_3$)$_4$ (0.007 g, 0.006 mmol) and the mixture was stirred under argon at 100 °C until the reaction was completed (TLC). The mixture was cooled to r.t. and filtered through Celite. The solvent evaporated and chromatographed on silica gel [light petroleum (bp 40–60 °C)–Et$_2$O–acetone–MeOH, 50:30:17:3]. The crude product was purified by crystallization from EtOAc–EtOH (5:1).

Method B: The reaction under aqueous conditions was analogous, except that a higher amount of K$_2$CO$_3$ (0.093 g, 0.675 mmol) together with H$_2$O (0.34 mL) and DME (2 mL) were used. The reaction mixture was then stirred under argon at 85 °C. The workup was the same as above.

9-Benzyl-8-phenyladenine (4a)
Yield: 96% (both Methods A and B); mp 102–104 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.49 (s, 2 H, CH$_2$), 6.97 (m, 2 H, ArH), 7.25 (m, 3 H, ArH), 7.39 (br s, 2 H, NH$_2$), 7.50 (m, 3 H, ArH), 7.67 (m, 2 H, ArH), 8.18 (s, 1 H, H-2 Pu).

MS (EI): m/z (%) = 301 (M$^+$, 39), 91 (100).

HRMS (EI): m/z Calcd for $C_{18}H_{15}N_5$ 301.1327. Found: 301.1307.

IR (KBr): ν = 3318, 3140, 1656, 1597, 1475, 1372, 1331, 1298 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}N_5\cdot0.5H_2O$ (310.4): C, 69.66; H, 5.20; N, 22.38. Found: C, 69.43; H, 5.43; N, 22.38.

9-Benzyl-8-(4-fluorophenyl)adenine (4b)
Yield: 63% (Method A), 94% (Method B); mp 164–165 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.49 (s, 2 H, CH$_2$), 6.97 (m, 2 H, C$_6$H$_5$), 7.25 (m, 3 H, C$_6$H$_5$), 7.34 (m, 2 H, ArH), 7.39 (br s, 2 H, NH$_2$), 7.72 (m, 2 H, ArH), 8.19 (s, 1 H, H-2 Pu).

IR (KBr): ν = 3421, 3326, 3153, 1659, 1607, 1575, 1476, 1454, 1374, 1333, 1302, 1293 cm^{-1}.

MS (EI) m/z (%) = 319 (M$^+$, 61), 91 (100).

HRMS (EI): m/z Calcd 319.1233, found 319.1193.

Anal. Calcd for $C_{18}H_{14}N_5F\cdot H_2O$ (337.4): C, 64.09; H, 4.78; N, 20.76. Found: C, 64.57; H, 4.71; N, 20.91.

9-Benzyl-8-[(E)-styryl]adenine (4c)
Yield: 44% (Method A), 68% (Method B); mp 216–218 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.62 (s, 2 H, CH$_2$), 7.20–7.42 (m, 8 H, ArH), 7.48 (d, J = 15.9 Hz, 1 H, CH=CH), 7.70 (d, J = 7.1 Hz, ArH), 7.72 (d, J = 15.9 Hz, 1 H, CH=CH), 8.15 (s, 1 H, H-2 Pu).

IR (KBr): ν = 3474, 3058, 1634, 1599, 1465, 1380, 1361 cm^{-1}.

MS (EI): m/z (%) = 327 (M$^+$, 64), 91 (100).

HRMS (EI): m/z Calcd 327.1483, found 327.1482.

Anal. Calcd for $C_{20}H_{17}N_5$ (327.4): C, 73.37; H, 5.23; N, 21.39. Found: C, 73.35; H, 5.22; N, 21.27.

9-Benzyl-8-(3-nitrophenyl)adenine (4d)
Yield: 36% (Method A), 76% (Method B); mp 178–179 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.58 (s, 2 H, CH$_2$), 7.04 (m, 2 H, C$_6$H$_5$), 7.27 (m, 3 H, C$_6$H$_5$), 7.52 (br s, 2 H, NH$_2$), 7.78 (m, 1 H, ArH), 8.14 (m, 1 H, ArH), 8.23 (s, 1 H, H-2 Pu), 8.33 (m, 1 H, ArH), 8.49 (m, 1 H, ArH).

MS (EI): m/z (%) = 346 (M$^+$, 43), 91 (100).

IR (KBr): ν = 3140, 1641, 1601, 1535, 1352, 1300 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}N_6O_2$ (346.3): C, 62.42; H, 4.07; N, 24.26. Found: C, 62.44; H, 4.06; N, 24.19.

3-Benzyl-8-phenyladenine (5a)
Yield: 92% (Method A), 66% (Method B), mp 254–256 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.57 (s, 2 H, CH$_2$), 7.25–7.48 (m, 6 H, ArH), 7.53 (d, J = 7.2 Hz, 2 H, ArH), 7.90 (s, 2 H, NH$_2$), 8.23 (d, J = 7.2 Hz, 2 H, ArH), 8.52 (s, 1 H, H-2 Pu).

IR (KBr): ν = 3437, 3133, 1662, 1620, 1599, 1439, 1259 cm^{-1}.

MS (EI): m/z (%) = 301 (M$^+$, 93), 91 (100).

Anal. Calcd for $C_{18}H_{15}N_5$ (301.3): C, 71.74; H, 5.02; N, 23.24. Found: C, 71.47; H, 5.46; N, 22.92.

3-Benzyl-8-(4-fluorophenyl)adenine (5b)
Yield: 98% (Method A), 75% (Method B); mp 236–238 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.59 (s, 2 H, CH$_2$), 7.31–7.39 (m, 5 H, C$_6$H$_5$), 7.52 (d, J = 7.2 Hz, 2 H, ArH), 7.94 (br s, 2 H, NH$_2$), 8.24 (dd, J = 5.5, 8.8 Hz, 2 H, ArH), 8.54 (s, 1 H, H-2 Pu).

IR (KBr): ν = 3307, 3162, 1648, 1623, 1523, 1449, 1217 cm^{-1}.

MS (EI): m/z (%) = 319 (M$^+$, 36), 91 (100).

HRMS (EI): m/z Calcd 319.1233, found 319.1218.

Anal. Calcd for $C_{18}H_{14}N_5F\cdot H_2O$ (337.4): C, 64.09; H, 4.78; N, 20.76. Found: C, 63.83; H, 4.81; N, 20.27.

3-Benzyl-8-[(E)-styryl]adenine (5c)
Yield: 41% (Method A), 77% (Method B); mp 264–266 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.55 (s, 2 H, CH$_2$), 7.15–7.65 (m, 12 H, C$_6$H$_5$ + CH=CH), 7.93 (s, 2 H, NH$_2$), 8.49 (s, 1 H, H-2 Pu).

IR (KBr): ν = 3251, 3059, 1678, 1621, 1445, 1312, 1229 cm^{-1}.

MS (EI): m/z (%) = 327 (M$^+$, 45), 91 (100).

HRMS (EI): m/z Calcd 327.1483, found 327.1494.

3-Benzyl-8-(3-nitrophenyl)adenine (5d)
Yield: 95% (Method A), 89% (Method B); mp 263–264 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.59 (s, 2 H, CH$_2$), 7.28–7.40 (m, 3 H, C$_6$H$_5$), 7.52 (d, J = 7.4 Hz, 2 H, C$_6$H$_5$), 7.73 (t, J = 7.8 Hz, 1 H, ArH), 8.18 (br s, 2 H, NH$_2$), 8.18 (d, J = 8 Hz, 1 H, ArH), 8.58 (s, 1 H, ArH), 8.60 (d, J = 7.7 Hz, 1 H, ArH), 9.00 (s, 1 H, H-2 Pu).

IR (KBr): ν = 3436, 3154, 1659, 1610, 1532, 1350 cm^{-1}.

MS (EI): m/z (%) = 346 (M$^+$, 35%), 91 (100).

Anal. Calcd for $C_{18}H_{14}N_6O_2$ (346.3): C, 62.42; H, 4.07; N, 24.26. Found: C, 62.19; H, 4.31; N, 23.96.

Cross-Coupling Reactions of 2,6-Dihalopurines with Phenylboronic Acid; General Procedure

Toluene (5 mL) was added through a septum to an argon purged flask containing a 2,6-dichloropurine (**6**; 138 mg, 0.5 mmol) or 2-iodo-6-chloropurine (**9**; 0.186 g, 0.5 mmol), phenylboronic acid (0.065 g, 0.54 mmol or 0.183 g, 1.5 mmol), K_2CO_3 (0.100 g, 0.72 mmol) and Pd(PPh$_3$)$_4$ (0.03 g, 0.026 mmol) and the mixture was stirred at 100 °C for 8–20 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was chromatographed on a silica gel column [50 g, light petroleum (bp 40–60 °C)–EtOAc, 2:1 to 1:1]. The crude products were crystallized from CH_2Cl_2–heptane.

9-Benzyl-2-chloro-6-phenylpurine (7)

Prepared from **6** with 1 equivalent of PhB(OH)$_2$ (reaction time 8 h) in 77% yield. Colorless needles; mp 143–146 °C (Lit.[9i] mp 150–151 °C).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 5.44 (s, 2 H, CH_2Ph), 7.32–7.40 (m, 5 H, C$_6$H$_5$), 7.54–7.57 (m, 3 H, C$_6$H$_5$), 8.04 (s, 1 H, H-8 Pu), 8.78–8.81 (m, 2 H, C$_6$H$_5$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 47.4 (CH$_2$), 128.0, 128.7, 128.7, 129.2, 130.0 and 131.7 (CH-Ph), ca 130 (very weak, C-5), 134.5 and 134.7 (C-Ph), 144.6 (C-8), 154.2, 154.4 and 156.7 (C-2, C-4 and C-6).

FAB-MS: m/z (%) = 321 (46) [M + H], 91 (100).

Anal. Calcd for $C_{18}H_{13}ClN_4$ (320.8): C, 67.40; H, 4.08; N, 17.47. Found: C, 67.10; H, 4.13; N, 17.21.

9-Benzyl-6-chloro-2-phenylpurine (10)

Prepared from **9** with 1 equivalent of PhB(OH)$_2$ (reaction time 20 h) in 81% yield. Colorless needles; mp 143–144 °C (Lit.[9i] mp 158–160 °C).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 5.48 (s, 2 H, CH_2Ph), 7.37 (br s, 5 H, C$_6$H$_5$), 7.48–7.51 (m, 3 H, C$_6$H$_5$), 8.03 (s, 1 H, H-8 Pu), 8.52–8.54 (m, 2 H, C$_6$H$_5$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 47.8 (CH$_2$), 128.1, 128.5, 128.6, 128.8, 129.22 and 131.8 (CH-Ph), 129.9 (C-5), 134.9 and 136.6 (C-Ph), 144.8 (C-8), 151.0, 152.6 and 159.4 (C-2, C-4 and C-6).

FAB-MS: m/z (%) = 321 (35) [M + H], 91 (100).

Anal. Calcd for $C_{18}H_{13}ClN_4$ (320.8): C, 67.40; H, 4.08; N, 17.47. Found: C, 67.08; H, 4.16; N, 17.68.

9-Benzyl-2,6-diphenylpurine (8)

Prepared from **6** (reaction time 8 h) or from **9** (reaction time 20 h) with 3 equivalents of PhB(OH)$_2$ in 84% (from **6**) or 88% (from **9**) yields; colorless needles; mp 166–168 °C.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 5.51 (s, 2 H, CH_2Ph), 7.32–7.40 (m, 5 H, C$_6$H$_5$), 7.46–7.60 (m, 6 H, ArH), 8.05 (s, 1 H, H-8), 8.70 (d, 2 H, J = 7.3, H$_o$-C$_6$H$_5$), 8.94 (d, 2 H, J = 7.3, H$_o$-C$_6$H$_5$).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 47.2 (CH$_2$), 128.0, 128.3, 128.4, 128.5, 128.6 and 129.1 (CH-Ph), 129.6 (C-5), 129.6, 130.1 and 130.8 (CH-Ph), 135.6, 136.2 and 138.4 (C-Ph), 144.1 (C-8), 153.5, 154.3 and 158.7 (C-2, C-4 and C-6).

FAB-MS: m/z (%) = 363 (100) [M + H].

Anal. Calcd for $C_{24}H_{18}N_4$ (362.4): C, 79.54; H, 5.01; N, 15.46. Found: C, 79.21; H, 5.04; N, 15.26.

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