Cross-Coupling Reactions of Halopurines with Aryl- and Alkyltrifluoroborates; The Scope and Limitations in the Synthesis of Modified Purines

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Abstract: The scope and limitations of the use of the palladium-catalyzed cross-coupling reactions of diverse alkyl- and aryltrifluoroborates with halopurines have been studied. While aryl- and hetaryltrifluoroborates reacted readily with both 6-chloropurines and 8-bromoadenines to give the corresponding 6- or 8-aryl derivatives in high yields, the alkyltrifluoroborates were much less reactive and, even after thorough optimization, only methyl- and cyclopropyltrifluoroborates gave moderate yields of the desired alkylated purines, while other alkyl-, dialkylaminomethyl- and ethoxycarbonylethyltrifluoroborates did not give any reaction.

Key words: purines, cross-coupling reactions, organotrifluoroborates, palladium, phosphine ligands

The 6- and 8-aryl-substituted purines represent an important class of biologically active compounds.[1] 6-Arylpurine nucleosides possess cytostatic[2] and anti-HCV[3] effects. 9-Alkyl-6-arylpurines exert antimycobacterial and antibacterial properties[4] and corticotropine releasing hormone antagonist[5] activity.[6] 8-Arylpurines[7] and some 2,6-diarylpurines[8] are antagonists of A_1 and A_2 adenosine receptors. Also 6-alkylpurines are of interest: 6-methylpurine is strongly cytotoxic[9] and 6-cyclopropylpurine ribonucleoside exerts[10] interesting cytostatic activity. From functionalized derivatives, 6-hydroxymethyl-,[11] 6-fluoromethyl-[12] and 6-dialkylaminomethylpurine[13] nucleosides are also promising cytostatics. While the 6-aryl- and 6-alkylpurines can be readily prepared by the classical cross-coupling reactions[14] of halopurines with arylboronic acids or with alkylzinc, magnesium or aluminum organometallics, the synthesis of the latter functionalized derivatives is more challenging and requires multistep functional group transformations[12,13] of 6-hydroxymethylpurines.

The Suzuki–Miyaura cross-coupling is one of the most important reactions in current organic chemistry and is also widely used in purine chemistry. Usual substrates for this reaction, boronic acids, are sometimes difficult to purify because of the lack of crystallization or the formation of trimeric cyclic anhydrides (boroxines) – leading to difficulties in determining the stoichiometry of the boronic acid added into the reaction. On the other hand, boronate esters as alternative substrates are often unstable and less reactive. Recently, a novel type of boron reagent, organotrifluoroborates, is applied in these cross-coupling reactions.[15] The organotrifluoroborates are easily crystallizable, air-stable[16] and their reactivity is similar to boronic acids. After the primary investigation of the cross-coupling of aryltrifluoroborates with aryl[17] and alkenyl halides,[18] it was also shown that various vinyl-[19] and alkyltrifluoroborates[20,21] are stable enough to be successfully used in the cross-coupling. Molander et al. broadened the application of alkyltrifluoroborates not only to unfunctionalized species,[22] but developed a convenient methodology for the preparation and application of alkyltrifluoroborates with diverse substituents in the α- or β-position. They reported a cross-coupling reaction of β-aminoethyltrifluoroborates with either electron-deficient or electron-rich aryl bromides,[23] explored the scope and limitations of this approach[24] and also investigated the utilization of stable *N,N*-dialkylaminomethyltrifluoroborates for the preparation of aromatic compounds with functionalized α-subtituents.[25] They also focused on the preparation and application of various alkoxymethyltrifluoroborates[26] and trifluoroboratohomoenolates.[27] Synthesis of a set of cycloalkyltrifluoroborates and cross-coupling of these species was reported recently, extending the examples of alkyltrifluoroborates with β-hydrogens on the alkyl chain.[28,29] Because of the superior reactivity and wide tolerance to the presence of the functional groups, the organotrifluoroborates seemed to be promising reagents for the direct introduction of unfunctionalized and functionalized C-substituents to purines and so far no use of these regents in purine chemistry has been reported. Here we report on the scope and limitations of the utilization of organotrifluoroborates in the synthesis of 6- and 8-substituted purines as an alternative synthetic methodology to the standard Suzuki–Miyaura reaction.

Firstly we have tried to optimize the catalytic system and reaction conditions on model reactions of 9-benzyl-6-chloropurine (**1**) with phenyl- (**2a**) and methyltrifluoroborates (**2k**) as examples of aryl and alkyl derivatives. Several sources of palladium in combination with several phosphine ligands successful in related cross-couplings of boronates or trifluoroborates[25b,27,28,30,31] (Figure 1) have been used in these experiments. Results of the reactions of 6-chloropurine **1** with potassium phenyltrifluoroborate (**2a**) are summarized in Table 1. Using conventional heating of the mixture in tetrahydrofuran–water (9:1) or toluene–water (3:1), $Pd_2(dba)_3$ with JohnPhos does not give

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any reaction, while $Pd(OAc)_2$ with PPh_3 gave a low yield of the desired 6-phenylpurine **3a** (entries 1 and 2). On the other hand, the reaction in the presence of $PdCl_2(dppf)$[22] gave **3a** in good yield (78%) and, quite surprisingly, simple $Pd(PPh_3)_4$ was the most efficient catalyst giving excellent 88% yield of **3a** (entries 3 and 4). We have also tested the possibility of increasing the rate of the cross-coupling reaction by microwave irradiation of the mixture, which is known to increase the rate of the Suzuki–Miyaura cross-coupling on purine systems.[32] The optimum conditions previously reported[32] for boronic acids using $Pd(OAc)_2$ with TPPTS in acetonitrile–water (1:2) were completely inactive in this reaction. However, the use of $PdCl_2(dppf)$ under microwave irradiation (5 min, 150 °C) was more efficient (63% yield), while the use of $Pd(PPh_3)_4$ gave quantitative conversion yielding 95% of the desired product **3a** (entries 7–9).

The second model reaction of **1** with methyltrifluoroborate **2k** showed completely different behavior (Table 2). Firstly, we tried the conditions most successful in the phenyltrifluoroborate **2a**. However, all attempts to perform the reaction with **2k** in presence of $Pd(PPh_3)_4$ or $PdCl_2(dppf)$ under both conventional heating or microwave totally failed. Also unsuccessful was the use of $Pd(OAc)_2$ with XPhos or the use of $Pd(PtBu_3)_2$ (entries 1–4). Therefore, we returned to the microwave irradiation[32] in acetonitrile–water using $Pd(OAc)_2$–TPPTS which at least gave traces of the desired product **3k**. Then we further optimized these conditions by increasing the amount of the catalyst, using different bases and comparing microwave irradiation with conventional heating (entries 6–12). Although complete consumption of the starting chloropurine **1** was observed in all cases, the isolated yields of **3k** varied only between 10–44%. The rest was a mixture of unidentified

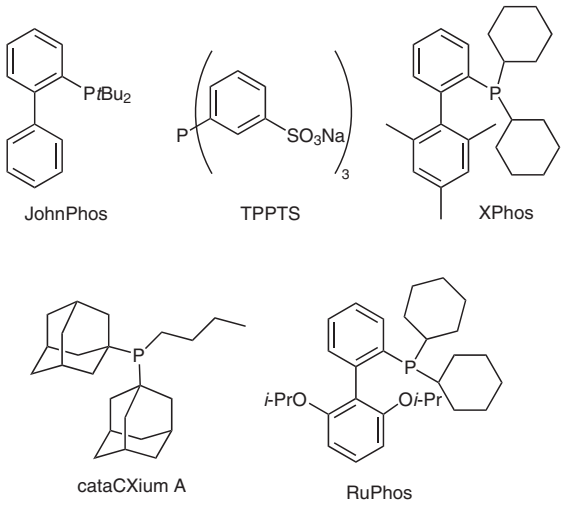
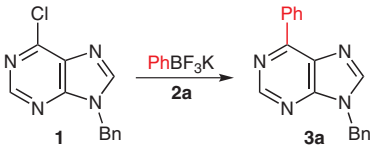


Figure 1 Ligands used during optimization

chromatographically immobile side-products (presumably products of degradation). It appears that the methyltrifluoroborate is much less reactive than the phenyl derivative and its use for modification of purines will be limited [the yield is much lower than the corresponding methylation by cross-couplings with trimethylaluminum or methylmagnesium chloride in the presence of $Fe(acac)_3$].[33]

The little success of the reaction with methyltrifluoroborates did not discourage us from also testing other alkyl- and dialkylaminomethyltrifluoroborates (Table 3). At first we tried cyclopropyl- and cyclopentyltrifluoroborates **2l** and **2o**. Standard procedure[25b,28] using $Pd(OAc)_2$ with XPhos did not work with cyclopropyltrifluoroborate **2l**, however, the use of cataCXium A ligand[28] in toluene–water was successful giving 6-cyclopropylpurine **3l** in

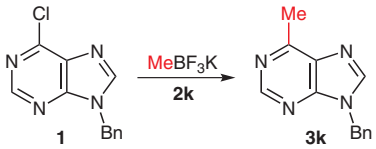
Table 1 Cross-Coupling of **1** with Phenyltrifluoroborate **2a**



Entry	Catalytic system	Pd (mol %)	Base (3 equiv)	Conditions	Solvent	Yield of **3a** (%)
1	$Pd_2(dba)_3$/JohnPhos	2[a]	K_2CO_3	80 °C, 18 h	THF–H_2O	0
2	$Pd(OAc)_2$/PPh_3	2	K_2CO_3	80 °C, 18 h	THF–H_2O	14
3	$PdCl_2(dppf)$	2	K_2CO_3	80 °C, 18 h	toluene–H_2O	78
4	$Pd(PPh_3)_4$	2	K_2CO_3	80 °C, 18 h	THF–H_2O	88
5	$Pd(PPh_3)_4$	1	K_2CO_3	80 °C, 18 h	THF–H_2O	39
6	$Pd(PPh_3)_4$	5	Na_2CO_3	80 °C, 18 h	THF–H_2O	73
7	$Pd(OAc)_2$/TPPTS	2	K_2CO_3	μW, 150 °C, 5 min	MeCN–H_2O	0
8	$PdCl_2(dppf)$	2	K_2CO_3	μW, 150 °C, 5 min	MeCN–H_2O	63
9	$Pd(PPh_3)_4$	2	K_2CO_3	μW, 150 °C, 5 min	MeCN–H_2O	95

[a] Mol% of $Pd_2(dba)_3$.

Table 2 Cross-Coupling of **1** with Methyltrifluoroborate **2k**



Entry	Catalytic system	Pd (mol%)	Base (3 equiv)	Conditions	Solvent	Yield of **3k** (%)
1	$Pd(PPh_3)_4$	2	K_2CO_3	80 °C, 18 h	THF–H_2O or MeCN–H_2O	0
2	$PdCl_2$(dppf)	2	Cs_2CO_3	80 °C, 18 h	THF–H_2O or MeCN–H_2O	0
3	$Pd(OAc)_2$/XPhos	5	Cs_2CO_3	80 °C, 18 h	THF–H_2O or MeCN–H_2O	0
4	$Pd(PtBu_3)_2$	5	K_2CO_3	80 °C, 18 h or μW, 150 °C, 5 min	THF–H_2O or MeCN–H_2O	0
5	$Pd(OAc)_2$/TPPTS	2	Cs_2CO_3	μW, 150 °C, 5 min	MeCN–H_2O	traces
6	$Pd(OAc)_2$/TPPTS	5	Cs_2CO_3	μW, 150 °C, 5 min	MeCN–H_2O	30
7	$Pd(OAc)_2$/TPPTS	10	Cs_2CO_3	μW, 150 °C, 5 min	MeCN–H_2O	44
8	$Pd(OAc)_2$/TPPTS	5	Cs_2CO_3	μW, 150 °C, 60 min	MeCN–H_2O	39
9	$Pd(OAc)_2$/TPPTS	5	Cs_2CO_3	80 °C, 30 min	MeCN–H_2O	10
10	$Pd(OAc)_2$/TPPTS	5	Cs_2CO_3	80 °C, 2 h	MeCN–H_2O	20
11	$Pd(OAc)_2$/TPPTS	5	K_2CO_3	μW, 150 °C, 5 min	MeCN–H_2O	18
12	$Pd(OAc)_2$/TPPTS	5	K_3PO_4	μW, 150 °C, 5 min	MeCN–H_2O	27

75% yield (entry 2). On the other hand, the reaction with cyclopentyltrifluoroborate **2o** was tested under diverse conditions[27–29] using JohnPhos,[30] cataCXinium A,[28] RuPhos,[27,29] TPPTS,[31,32] and $Pd(PPh_3)_4$[34] without any success (entries 3–8). The major advantage of the Molander protocol is the possibility using directly functionalized alkyltrifluoroborates in cross-coupling. Therefore, we further tested several attractive functionalized trifluoroborates: dimethylaminomethyl- (**2p**), (piperidin-1-yl)methyl-[25b] (**2q**), cyclohexylaminomethyl-[35] (**2r**) and 2-(ethoxycarbonyl)ethyl-[27] (**2s**) trifluoroborates. Different conditions from the literature and from our previous experience with phenyl- and methyltrifluoroborates both under conventional heating and under microwave have been tested with all these reagents but no cross-coupling reaction was observed in any case (entries 7–23). Only in the case of cyclohexylaminomethyltrifluoroborate (**2r**), almost quantitative conversion was observed to give 9-benzyl-6-(*N*-cyclohexyl-*N*-methyl)aminopurine (**3t**) as a product of N-arylation and deborylation of the reagent. Apparently, unlike in other aryl and hetaryl halides,[25b,27] the functionalized alkyltrifluoroborates are not suitable reagents for modification of halopurines.

In order to further explore the scope and limitations of this reaction for other types of trifluoroborates, we have chosen a set of diverse aryl-, hetaryl- and the mentioned alkyltrifluoroborates **2a**–**m** and used the optimized conditions for the preparation of desired 6-substituted purines starting from 6-chloropurine **1** (Table 4).

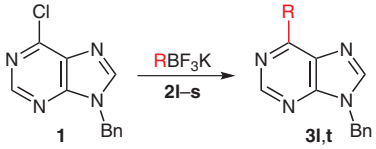
Electron-rich aryltrifluoroborates **2b** and **2c** reacted readily to give the desired compounds in quantitative yields, even when sterically hindered trifluoroborate **2c** was used (entries 2 and 3). When electron-deficient arylborates **2d**,**f** were used, the conversions were not complete, but still we have obtained the desired substituted purines **3d**,**f** in good yields. In the case of hetaryltrifluoroborates, thiophenylborates **2h**,**i** reacted almost quantitatively, while in the reaction with 2-furyltrifluoroborate (**2g**) the conversion was only around 50% under standard conditions. However, when using a double portion of catalyst we have obtained the desired product **3g** in excellent yield (entry 7). We have also tried the conditions developed for aromatic trifluoroborates for vinyl- and allylborates (**2j**,**m**). While the vinylborate **2j** reacted readily and gave the corresponding product **3j** in excellent yield, in the reaction of allylborate **2m** isomerization occurred on the allyl system and we produced 6-(2-methylvinyl)purine **3n** in a moderate yield of 23% (entries 10 and 13).

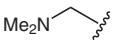
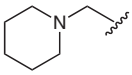
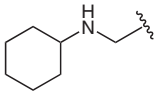
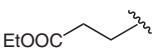
To explore the applicability of this procedure for functionalization of the purine ring in position 8 and to test the tolerance to free amino group, we have studied the reactions of 8-bromoadenine **4** with trifluoroborates **2a**–**l** (Table 5). In aryltrifluoroborates, we have observed the same reactivity of electron-rich trifluoroborates **2a**–**c**,**e** and increased reactivity of 3-carboxyphenyltrifluoroborate **2f** leading to the desired derivatives **5a**–**c**,**e**,**f** in excellent yields. Only in the case of 3-nitrophenyltrifluoroborate **2d** did we need to double the amount of the catalyst in order to complete the conversion and get good yields of **5d** (en-

tries 1–6). For the preparation of the furyl derivative **5g**, we again had to use a larger amount of $Pd(PPh_3)_4$ (4 mol%) to reach complete conversion and to get good yield of **5g** (73%). On the other hand, 3-thiophenetrifluoroborate **2h** gave corresponding substituted adenine **5h** in excellent yield even in the presence of 2 mol% of catalyst, while in the case of 5-methyl-2-thiophenetrifluoroborate **2i**, the lower yield was caused by incomplete conversion of starting material (entries 7–9). Position 8 on the purine moiety showed low reactivity in the cross-couplings with vinyl- and alkyltrifluoroborates **2j–l**. Vinyl- and methyltrifluoroborate were completely unreactive (only the starting material was recovered from the reaction mixture), while potassium cyclopropyltrifluoroborate (**2l**) reacted with 8-bromoadenine **4** under catalysis with $Pd(OAc)_2$ and cataCXium A giving 8-cyclopropyladenine **5l** in a moderate yield of 48%.

In conclusion, aryltrifluoroborates were found to be excellent reagents for the cross-coupling reactions with 6- or 8-halopurines under Pd catalysis. These cross-couplings are fully comparable to the classical Suzuki–Miyaura cross-coupling reactions of halopurines with arylboronic acids. However, similar to the low reactivity of alkylboronic acids, alkyltrifluoroborates were found to be of very poor reactivity in cross-couplings with halopurines and only in the case of methyl- and cyclopropylborates, reasonable reactivity was observed to give the methyl- or cyclopropylpurines in moderate yields. Functionalized alkyltrifluoroborates (substituted aminomethyl- and (ethoxycarbonylethyl)trifluoroborates) were totally unreactive in these reactions and thus cannot be used for direct functionalization of purines. We have no explanation for the lack of reactivity of these reagents in purines because other cross-couplings usually proceed in halopurines better than in more electron-rich aryl halides.

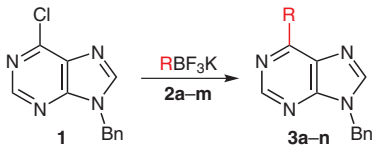
Table 3 Attempts to Carry Out the Cross-Coupling of **1** with Unfunctionalised and Functionalised Alkylborates **2l–s**

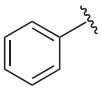
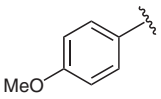
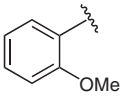
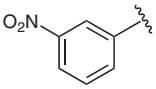
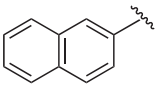
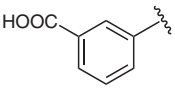
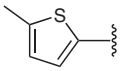
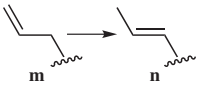


Entry	Borate	R	Catalyst	Base	Solvent	Method[a]	Yield (%)
1	**2l**		$Pd(OAc)_2$/XPhos	K_2CO_3	THF–H_2O	C	0
2			$Pd(OAc)_2$/cataCXium A	Cs_2CO_3	toluene–H_2O	C	75
3	**2o**		$Pd(OAc)_2$/TPPTS	Cs_2CO_3	MeCN–H_2O	A	0
4			$Pd(PPh_3)_4$	K_2CO_3 or Cs_2CO_3	MeCN–H_2O, DMF–H_2O or toluene–H_2O	A	0
5			$Pd(OAc)_2$/RuPhos	K_3PO_4 or K_2CO_3	toluene–H_2O	A or B	0
6			$Pd_2(dba)_3$/JohnPhos	K_2CO_3	toluene–H_2O, THF–H_2O or MeCN–H_2O	A	0[b]
7			$Pd_2(dba)_3$/TPPTS	K_2CO_3 or Cs_2CO_3	MeCN–H_2O	A	0
8			$Pd(OAc)_2$/cataCXium A	Cs_2CO_3	toluene–H_2O	C	0
9	**2p**		$Pd(OAc)_2$/TPPTS	Cs_2CO_3	MeCN–H_2O	A	dec.
10			$Pd(PPh_3)_4$	K_2CO_3	MeCN–H_2O	A	dec.
11			$Pd(OAc)_2$/RuPhos	K_3PO_4	MeCN–H_2O	A	dec.
12			$Pd(OAc)_2$/cataCXium A	Cs_2CO_3	toluene–H_2O	C	dec.
13	**2q**		$Pd(OAc)_2$/TPPTS	K_2CO_3	toluene–H_2O	C	0
14			$Pd(OAc)_2$/cataCXium A	Cs_2CO_3	toluene–H_2O	C	dec.
15	**2r**		$Pd(OAc)_2$/TPPTS	Cs_2CO_3	MeCN–H_2O	A	0 (70)[c]
16			$Pd(OAc)_2$/XPhos	Cs_2CO_3	MeCN–H_2O	A	0 (85)[c]
17			$Pd(PPh_3)_4$	K_2CO_3	MeCN–H_2O	A	0 (93)[c]
18	**2s**		$Pd(OAc)_2$/TPPTS	Cs_2CO_3	MeCN–H_2O	A	dec.
19			$Pd(PPh_3)_4$	K_2CO_3	MeCN–H_2O	A	0
20			$Pd(OAc)_2$/RuPhos	K_3PO_4	toluene–H_2O	A	0
21			$Pd(OAc)_2$/TPPTS	K_2CO_3	toluene–H_2O, MeCN–H_2O, dioxane–H_2O or DMF–H_2O	C	0
22			$Pd(PPh_3)_4$	K_2CO_3		C	0
23			$Pd(OAc)_2$/cataCXium A	Cs_2CO_3	THF–H_2O, dioxane–H_2O or DMF–H_2O toluene–H_2O	C	0

[a] Method A: μW, 150 °C, 5 min; Method B: heating, 18 h, 125 °C; Method C: heating, 24 h, 80 °C.
[b] Decomposition in MeCN–H_2O.
[c] Yield of 9-benzyl-6-(*N*-cyclohexyl-*N*-methyl)amino-9*H*-purine (**3t**).

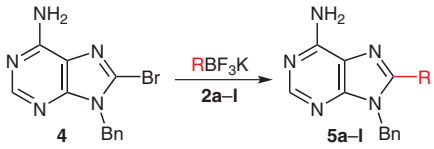
Table 4 Cross-Coupling of **1** with Trifluoroborates **2a–m**

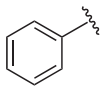
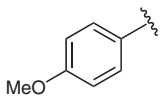
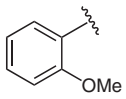
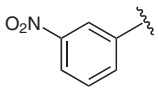
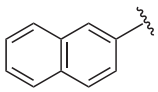
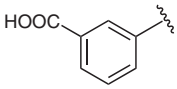
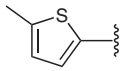


Entry	Borate	R	Method[a]	Product (Yield, %)
1	**2a**		A	**3a** (95)
2	**2b**		A	**3b** (95)
3	**2c**		A	**3c** (94)
4	**2d**		A	**3d** (79)
5	**2e**		A	**3e** (94)
6	**2f**		A	**3f** (71)
7	**2g**		A	**3g** (52, 95[b])
8	**2h**		A	**3h** (90)
9	**2i**		A	**3i** (91)
10	**2j**		A	**3j** (97)
11	**2k**		B	**3k** (44)
12	**2l**		C	**3l** (75)
13	**2m**		A	**3n** (23)[c]

[a] Method A: 2 mol% $Pd(PPh_3)_4$, K_2CO_3, μW, 150 °C, 5 min, MeCN–H_2O; Method B: 10 mol% $Pd(OAc)_2$/TPPTS, Cs_2CO_3, μW, 150 °C, 5 min, MeCN–H_2O; Method C: 3 mol% $Pd(OAc)_2$/cataCXium A, Cs_2CO_3, toluene–H_2O, 100 °C, 24 h.
[b] 4 mol% of catalyst was used.
[c] 9-Benzyl-6-[(*E*)-2-methylvinyl]-9*H*-purine (**3n**).

Table 5 Cross-Coupling of **4** with Trifluoroborates **2a–l**



Entry	Borate	R	Method[a]	Product (Yield, %)
1	**2a**		A	**5a** (96)
2	**2b**		A	**5b** (97)
3	**2c**		A	**5c** (96)
4	**2d**		A	**5d** (53, 90[b])
5	**2e**		A	**5e** (97)
6	**2f**		A	**5f** (99)
7	**2g**		A	**5g** (51, 73[b])
8	**2h**		A	**5h** (96)
9	**2i**		A	**5i** (76)
10	**2j**		A	**5j** (0)
11	**2k**		B	**5k** (0)
12	**2l**		C	**5l** (48)

[a] MethodA: 2 mol% $Pd(PPh_3)_4$, K_2CO_3, μW, 150 °C, 5 min, MeCN–H_2O; Method B: 10 mol% $Pd(OAc)_2$/TPPTS, Cs_2CO_3, μW, 150 °C, 5 min, MeCN–H_2O; Method C: 3 mol% $Pd(OAc)_2$/cataCXium A, Cs_2CO_3, toluene–H_2O, 100 °C, 24 h.
[b] 4 mol% of catalyst was used.

All chemicals were commercially available and used without further purification. JohnPhos and cataCXium A were purchased from Aldrich; TPPTS, XPhos and RuPhos from STREM Chemicals, Inc. Trifluoroborates **2a–m**,**o** were purchased from Aldrich, **2p**,**q**,**s** from Frontiers Scientific and trifluoroborate **2r** was prepared according to a previously published procedure.[35] NMR spectra were measured on a Bruker Avance 400 (400 MHz for ^1H and 100.6 MHz for ^{13}C nuclei) and a Bruker Avance 500 (500 MHz for ^1H and 125.8 MHz for ^{13}C) in $CDCl_3$ and DMSO-d_6 (referenced to the residual solvent signal). MS were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionization by Xe, accelerating voltage 8 kV, glycerol+thioglycerol matrix). The H_2O–MeCN mixture was degassed in vacuo and stored under argon. Microwave-mediated reactions were performed in a microwave reactor (Initiator, Biotage, Inc.), operated in mode with priority of temperature (microwave source performance changes automatically to maintain the set temperature in the course of the reaction).

Cross-Coupling Reactions: General Procedure

A mixture of H_2O–MeCN (2:1; 2 mL) was added through a septum to an argon-purged vial containing 6-chloropurine **1** (122 mg, 0.5

mmol), trifluoroborate (0.6 mmol), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) and K_2CO_3 (207 mg, 3 mmol). The mixture was stirred under microwave irradiation heating at 150 °C for 5 min. The mixture was filtered through Celite, evaporated to dryness and product was obtained by silica gel column chromatography (EtOAc–hexanes). Pure product was obtained by crystallization from CH_2Cl_2–heptane.

9-Benzyl-6-phenyl-9*H*-purine (3a)
Prepared from potassium phenyltrifluoroborate (**2a**; 55 mg) as white crystals, yield 95%.

^{1}H NMR spectra were in accord with previously published data.[36]

9-Benzyl-6-(4-methoxyphenyl)-9*H*-purine (3b)
Prepared from potassium 4-methoxyphenyltrifluoroborate (**2b**; 128 mg) as yellowish crystals, yield 95%.

^{1}H NMR spectra were in accord with previously published data.[37]

9-Benzyl-6-(2-methoxyphenyl)-9*H*-purine (3c)
Prepared from potassium 2-methoxyphenyltrifluoroborate (**2c**; 128 mg) as white crystals, yield 94%. ^{1}H NMR spectra were in accord with previously published data.[38]

9-Benzyl-6-(3-nitrophenyl)-9*H*-purine (3d)
Prepared from potassium 3-nitrophenyltrifluoroborate (**2d**; 137 mg) as yellowish crystals, yield 95%. ^{1}H NMR spectra were in accord with previously published data.[38]

9-Benzyl-6-(2-naphthyl)-9*H*-purine (3e)
Prepared from potassium 2-naphthyltrifluoroborate (**2e**; 140 mg) as white crystals, yield 94%.

IR (CCl_4): 3062, 1581, 1570, 1449, 1325, 1193 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.50 (s, 2 H, CH_2Ph), 7.32–7.40 (m, 5 H, H-*o,m,p*-Ph), 7.53 (ddd, $J_{7,8}$ = 8.2 Hz, $J_{7,6}$ = 6.8 Hz, $J_{7,5}$ = 1.4 Hz, 1 H, H-7-naphth), 7.56 (ddd, $J_{6,5}$ = 8.2 Hz, $J_{6,7}$ = 6.8 Hz, $J_{6,8}$ = 1.4 Hz, 1 H, H-6-naphth), 7.90 (ddt, $J_{5,6}$ = 8.2 Hz, $J_{5,7}$ = 1.4 Hz, $J_{5,1}$ = $J_{5,4}$ = 0.7 Hz, 1 H, H-5-naphth), 8.01 (dq, $J_{4,3}$ = 8.6 Hz, $J_{5,1}$ = $J_{4,5}$ = $J_{4,8}$ = 0.7 Hz, 1 H, H-4-naphth), 8.06 (ddt, $J_{8,7}$ = 8.2 Hz, $J_{8,6}$ = 1.4 Hz, $J_{8,1}$ = $J_{8,4}$ = 0.7 Hz, 1 H, H-8-naphth), 8.14 (s, 1 H, H-8), 8.88 (dd, $J_{3,4}$ = 8.6 Hz, $J_{3,1}$ = 1.7 Hz, 1 H, H-3-naphth), 9.11 (s, 1 H, H-2), 9.42 (dq, 1 H, $J_{1,3}$ = 1.7 Hz, $J_{1,4}$ = $J_{1,5}$ = $J_{1,8}$ = 0.7 Hz, H-1-naphth).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 47.28 (CH_2Ph), 125.96 (CH-3-naphth), 126.26 (CH-7-naphth), 127.47 (CH-6-naphth), 127.69 (CH-5-naphth), 127.80 (CH-*o*-Ph), 128.26 (CH-4-naphth), 128.58 (CH-*p*-Ph), 129.16 (CH-*m*-Ph), 129.47 (CH-8-naphth), 130.82 (CH-1-naphth), 131.15 (C-5), 133.05 (C-8a-naphth), 133.22 (C-2-naphth), 134.65 (C-4a-naphth), 135.17 (C-*ipso*-Ph), 144.15 (CH-8), 152.58 (C-4), 152.61 (CH-2), 154.77 (C-6).

ESI-MS: *m*/*z* (%) = 337 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{17}N_4$: 337.1448; found: 337.1445.

Anal. Calcd for $C_{22}H_{16}N_4 \cdot 1/6\ H_2O$ (339.4): C, 77.86; H, 4.85; N, 16.51. Found: C, 77.81; H, 4.77; N, 16.50.

9-Benzyl-6-(3-carboxyphenyl)-9*H*-purine (3f)
Prepared from potassium 3-carboxyphenyltrifluoroborate (**2f**; 137 mg) as white crystals, yield 71%. Mp 233–235 °C (CH_2Cl_2–heptane).

IR (KBr): 3075, 2537, 1687, 1567, 1433, 1325, 1296 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.58 (s, 2 H, CH_2Ph), 7.30 (m, 1 H, H-*p*-Ph), 7.36 (m, 2 H, H-*m*-Ph), 7.39 (m, 2 H, H-*o*-Ph), 7.74 (dd, $J_{5',6'}$ = 7.9 Hz, $J_{5',4'}$ = 7.7 Hz, 1H, H-5′), 8.13 (ddd, $J_{4',5'}$ = 7.7 Hz, $J_{4',2'}$ = 1.7 Hz, $J_{4',6'}$ = 1.4 Hz, 1 H, H-4′), 8.89 (s, 1 H, H-8), 9.04 (s, 1 H, H-2), 9.06 (ddd, $J_{6',5'}$ = 7.9 Hz, $J_{6',2'}$ = 1.7 Hz, $J_{6',4'}$ = 1.4 Hz, 1 H, H-6′), 9.47 (t, $J_{2',4'}$ = $J_{2',6'}$ = 1.7 Hz, 1 H, H-2′), 13.20 (br s, 1 H, COOH).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 46.78 (CH_2Ph), 127.88 (CH-*o*-Ph), 128.19 (CH-*p*-Ph), 129.03 (CH-*m*-Ph), 129.38 (CH-5′), 130.53 (CH-2′), 130.64 (C-5), 131.57 (C-3′), 131.90 (CH-4′), 133.60 (CH-6′), 135.92 (C-1′), 136.69 (C-*ipso*-Ph), 147.20 (CH-8), 151.84 (C-6), 152.74 (CH-2), 152.74 (C-4), 167.32 (COOH).

ESI-MS: *m*/*z* (%) = 331 (50) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{15}N_4O_2$: 331.1190; found: 331.1183.

Anal. Calcd for $C_{19}H_{14}N_4O_2 \cdot 1/3\ H_2O$ (336.3): C, 67.85; H, 4.40; N, 16.66. Found: C, 67.67; H, 4.31; N, 16.37.

9-Benzyl-6-(furan-2-yl)-9*H*-purine (3g)
Prepared from potassium 2-furantrifluoroborate (**2g**; 104 mg) as yellowish crystals, yield 52%. Using 4 mol% of $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) the yield increased to 95%.

^{1}H NMR spectra were in accord with previously published data.[39]

9-Benzyl-6-(thiophen-3-yl)-9*H*-purine (3h)
Prepared from potassium 5-methyl-2-thiophenetrifluoroborate (**2h**; 114 mg) as yellowish crystals, yield 91%.

^{1}H NMR spectra were in accord with previously published data.[38]

9-Benzyl-6-(5-methylthiophen-2-yl)-9*H*-purine (3i)
Prepared from potassium 3-thiophenetrifluoroborate (**2i**; 122 mg) as yellowish crystals, yield 90%.

Mp 167–169 °C (CH_2Cl_2–heptane).

IR ($CHCl_3$): 2996, 1582, 1471, 1403, 1329, 1227 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, Me), 5.43 (s, 2 H, CH_2-9), 6.90 (d, *J* = 3.6 Hz, 1 H, H-4′), 7.25–7.39 (m, 5 H, Ph), 8.02 (s, 1 H, H-8), 8.45 (d, *J* = 3.6 Hz, 1 H, H-3′), 8.87 (s, 1 H, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.77 (CH_3), 47.18 (CH_2Ph), 127.36 (CH-4′), 127.74 (CH-*o*-Ph), 128.50 (CH-*p*-Ph), 129.08 (CH-*m*-Ph), 133.12 (CH-3′), 135.20 (C-*ipso*-Ph), 137.42 (C-2′), 143.71 (CH-8), 146.35 (C-5′), 150.30 (C-5), 151.81 (C-4), 152.62 (CH-2), 153.61 (C-6).

ESI-MS: *m*/*z* (%) = 307 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{15}N_4S$: 307.1012; found: 307.1009.

Anal. Calcd for $C_{17}H_{14}N_4S$ (306.4): C, 66.64; H, 4.69; N, 18.29; Found: C, 66.37; H, 4.69; N, 18.13.

9-Benzyl-6-vinyl-9*H*-purine (3j)
Prepared from potassium vinyltrifluoroborate (**2j**; 80 mg) as a white solid, yield 97%.

^{1}H NMR spectra were in accord with previously published data.[37]

9-Benzyl-6-methyl-9*H*-purine (3k)
A mixture of H_2O–MeCN (2:1; 2 mL) was added through a septum to an argon-purged vial containing 6-chloropurine **1** (122 mg, 0.5 mmol), potassium methyltrifluoroborate (**2k**, 73 mg, 0.6 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), TPPTS (71 mg, 0.125 mmol) and Cs_2CO_3 (488 mg, 1.5 mmol). The mixture was stirred under microwave irradiation heating at 150 °C for 5 min. The mixture was filtered through Celite, evaporated to dryness and product was obtained by silica gel column chromatography (EtOAc–hexanes). Pure product was obtained by crystallization from CH_2Cl_2–heptane to obtain 25 mg (44% yield) of **3k** as white crystals.

^{1}H NMR spectra were in accord with previously published data.[37]

9-Benzyl-6-cyclopropyl-9*H*-purine (3l)

A mixture of toluene–H_2O (10:1; 2 mL) was added through a septum to an argon-purged vial containing 6-chloropurine **1** (122 mg, 0.5 mmol), potassium cyclopropyltrifluoroborate (**2l**, 85 mg, 0.6 mmol), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol), cataCXium A (8 mg, 0.022 mmol) and Cs_2CO_3 (488 mg, 1.5 mmol). The mixture was stirred at 100 °C for 24 h. The reaction was quenched with H_2O and extracted with $CHCl_3$ (3 × 20 mL), collected organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was chromatographed on a silica gel column (EtOAc–hexane). Pure product was obtained by crystallization from CH_2Cl_2–heptane to obtain 94 mg (75% yield) of **3l** as yellowish crystals.

^{1}H NMR spectra were in accord with previously published data.[10]

9-Benzyl-6-(2-methylvinyl)-9*H*-purine (3n)

Prepared from potassium allyltrifluoroborate (**2m**; 89 mg) as yellowish crystals, yield 23%.

^{1}H NMR spectra were in accord with previously published data.[40]

Cross-Coupling Reactions of Adenines; General Procedure

A mixture of H_2O–MeCN (2:1; 2 mL) was added through a septum to an argon-purged vial containing 8-bromoadenine **4** (152 mg, 0.5 mmol), trifluoroborate (0.6 mmol), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) and K_2CO_3 (207 mg, 3 mmol). The mixture was stirred under microwave irradiation heating at 150 °C for 5 min. The mixture was filtered through Celite, evaporated to dryness and product was obtained by silica gel column chromatography (EtOAc–hexanes). Pure product was obtained by crystallization from CH_2Cl_2–heptane.

9-Benzyl-8-phenyladenine (5a)

Prepared from potassium phenyltrifluoroborate (**2a**; 55 mg) as white crystals, yield 96%.

^{1}H NMR spectra were in accord with previously published data.[41]

9-Benzyl-8-(4-methoxyphenyl)adenine (5b)

Prepared from potassium 4-methoxyphenyltrifluoroborate (**2b**; 128 mg) as white crystals, yield 97%. Mp 152–154 °C (CH_2Cl_2–heptane).

IR (CCl_4): 3419, 1630, 1480, 1353, 1254, 1177 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.80 (s, 3 H, CH_3O), 5.48 (s, 2 H, CH_2Ph), 6.99 (m, 2 H, H-*o*-Ph), 7.04 (m, 2 H, H-*m*-C_6H_4OMe), 7.22 (m, 1 H, H-*p*-Ph), 7.27 (m, 2 H, H-*m*-Ph), 7.35 (br s, 2 H, NH_2), 7.62 (m, 2 H, H-*o*-C_6H_4OMe), 8.15 (s, 1 H, H-2).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 46.31 (CH_2Ph), 55.51 (CH_3O), 114.38 (CH-*m*-C_6H_4OMe), 118.64 (C-5), 122.24 (C-*i*-C_6H_4OMe), 126.41 (CH-*o*-Ph), 127.62 (CH-*p*-Ph), 128.93 (CH-*m*-Ph), 130.43 (CH-*o*-C_6H_4OMe), 137.31 (C-*ipso*-Ph), 149.99 (C-8), 151.56 (C-4), 152.75 (CH-2), 155.86 (C-6), 160.58 (C-*p*-C_6H_4OMe).

ESI-MS: *m*/*z* (%) = 332 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}N_5O$: 332.1506; found: 332.1504.

Anal. Calcd for $C_{19}H_{17}N_5O·1/2\ H_2O$ (340.4): C, 67.04; H, 5.33; N, 20.58. Found: C, 66.60; H, 5.17; N, 20.23%.

9-Benzyl-8-(2-methoxyphenyl)adenine (5c)

Prepared from potassium 2-methoxyphenyltrifluoroborate (**2c**; 128 mg) as brownish crystals, yield 96%.

IR (CCl_4): 3420, 2927, 1742, 1631, 1466, 1293 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.68 (s, 3 H, CH_3O), 5.19 (s, 2 H, CH_2Ph), 6.86 (m, 2 H, H-*o*-Ph), 7.03 (td, $J_{5',4'} = J_{5',6'} = 7.5$ Hz, $J_{5',3'} = 1.0$ Hz, 1 H, H-5′), 7.13–7.20 (m, 4 H, H-3′ and H-*m*,*p*-Ph), 7.26 (br s, 2 H, NH_2), 7.31 (dd, $J_{6',5'} = 7.5$ Hz, $J_{6',4'} = 1.8$ Hz, 1 H, H-6′), 7.52 (ddd, $J_{4',3'} = 8.4$ Hz, $J_{4',5'} = 7.5$ Hz, $J_{4',6'} = 1.8$ Hz, 1 H, H-4′), 8.17 (s, 1 H, H-2).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 46.04 (CH_2Ph), 55.54 (CH_3O), 111.73 (CH-3′), 118.73 (C-5), 119.17 (C-1′), 120.07 (CH-5′), 127.01 (CH-*o*-Ph), 127.44 (CH-*p*-Ph), 128.48 (CH-*m*-Ph), 131.94 (CH-6′), 132.07 (CH-4′), 137.00 (C-*ipso*-Ph), 148.25 (C-8), 150.78 (C-4), 152.74 (CH-2), 155.87 (C-6), 157.32 (C-2′).

ESI-MS: *m*/*z* (%) = 332 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}N_5O$: 332.1506; found; 332.1506.

Anal. Calcd for $C_{19}H_{17}N_5O·1/3\ H_2O$ (337.4): C, 67.64; H, 5.28; N, 20.76. Found: C, 67.68; H, 5.14; N, 20.76.

9-Benzyl-8-(3-nitrophenyl)adenine (5d)

Prepared from potassium 3-nitrophenyltrifluoroborate (**2d**; 137 mg) as yellowish crystals, yield 53%. Using 4 mol% of $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) the yield increased to 90%.

^{1}H NMR spectra were in accord with previously published data.[41]

9-Benzyl-8-(2-naphthyl)adenine (5e)

Prepared from potassium 2-naphthyltrifluoroborate (**2f**; 140 mg) as a white solid, yield 97%.

Mp 188–191 °C (CH_2Cl_2–heptane).

IR ($CHCl_3$): 3412, 2984, 1636, 1588, 1466, 1329 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.61 (s, 2 H, CH_2Ph), 7.02 (m, 2 H, H-*o*-Ph), 7.20 (m, 1 H, H-*p*-Ph), 7.25 (m, 2 H, H-*m*-Ph), 7.41 (br s, 2 H, NH_2), 7.58 (ddd, $J_{7,8} = 8.6$ Hz, $J_{7,6} = 6.9$ Hz, $J_{7,5} = 1.7$ Hz, 1 H, H-7-naphth), 7.60 (ddd, $J_{6,5} = 8.6$ Hz, $J_{6,7} = 6.9$ Hz, $J_{6,8} = 1.7$ Hz, 1 H, H-6-naphth), 7.84 (dd, $J_{3,4} = 8.5$ Hz, $J_{3,1} = 1.8$ Hz, 1 H, H-3-naphth), 7.89 (dd, $J_{8,7} = 8.6$ Hz, $J_{8,6} = 1.7$ Hz, 1 H, H-8-naphth), 7.98 (dd, $J_{5,6} = 8.6$ Hz, $J_{5,7} = 1.7$ Hz, 1 H, H-5-naphth), 8.02 (d, $J_{4,3} = 8.5$ Hz, 1 H, H-4-naphth), 8.22 (s, 1 H, H-2), 8.23 (d, 1 H, $J_{1,3} = 1.8$ Hz, H-1-naphth).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 46.50 (CH_2Ph), 118.89 (C-5), 126.05 (CH-3-naphth), 126.60 (CH-*o*-Ph), 127.16 (CH-7-naphth), 127.40 (C-2-naphth), 127.62 (CH-6-naphth), 127.70 (CH-*p*-Ph), 127.92 (CH-5-naphth), 128.53 (CH-4-naphth), 128.56 (CH-8-naphth), 128.59 (CH-1-naphth), 128.92 (CH-*m*-Ph), 132.57 (C-8a-naphth), 133.30 (C-4a-naphth), 137.31 (C-*ipso*-Ph), 149.93 (C-8), 151.79 (C-4), 153.12 (CH-2), 156.10 (C-6).

ESI-MS: *m*/*z* (%) = 352 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}N_5$; 352.1557; found: 352.1553.

Anal. Calcd for $C_{22}H_{17}N_5·1/2\ H_2O$ (357.4): C, 73.31; H, 5.03; N, 19.43. Found: C, 73.46; H, 4.83; N, 19.32.

9-Benzyl-6-(3-carboxyphenyl)adenine (5f)

Prepared from potassium 3-carboxyphenyltrifluoroborate (**2f**; 137 mg) as a white solid, yield 99%.

Mp > 260 °C (CH_2Cl_2–heptane).

IR (KBr): 3318, 3180, 1638, 1567, 1399, 1331, 1298 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.52 (s, 2 H, CH_2Ph), 6.94 (m, 2 H, H-*o*-Ph), 7.17 (m, 1 H, H-*p*-Ph), 7.21 (m, 2 H, H-*m*-Ph), 7.40 (t, $J_{5',4'} = J_{5',6'} = 7.6$ Hz, 1 H, H-5′), 7.41 (br s, 2 H, NH_2), 7.62 (ddd, $J_{6',5'} = 7.6$ Hz, $J_{6',2'} = 1.7$ Hz, $J_{6',4'} = 1.4$ Hz, 1 H, H-6′), 8.05 (ddd, $J_{4',5'} = 7.6$ Hz, $J_{4',2'} = 1.7$ Hz, $J_{4',6'} = 1.4$ Hz, 1 H, H-4′), 8.17 (s, 1 H, H-2), 8.42 (t, $J_{2',4'} = J_{2',6'} = 1.7$ Hz, 1 H, H-2′).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 46.40 (CH_2Ph), 118.82 (C-5), 126.65 (CH-*o*-Ph), 127.70 (CH-*p*-Ph), 128.09 (CH-5′), 128.92 (CH-*m*-Ph), 129.30 (C-3′), 129.82 (CH-6′), 130.48 (CH-2′), 130.91 (CH-4′), 137.15 (C-*ipso*-Ph), 138.91 (C-1′), 150.23 (C-8), 151.57 (C-4), 153.01 (CH-2), 156.08 (C-6), 171.04 (COOH).

ESI-MS: *m*/*z* (%) = 346 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{16}N_5O_2$: 346.1299; found: 346.1295.

9-Benzyl-8-(furan-2-yl)adenine (5g)

Prepared from potassium 2-furantrifluoroborate (**2g**; 104 mg) as white crystals, yield 51%. Using 4 mol% of $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) the yield increased to 73%.

Mp 153–157 °C (CH_2Cl_2–heptane).

IR ($CHCl_3$): 3525, 3412, 2989, 2360, 1636, 1581, 1468, 1331, 1295 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 5.66 (s, 2 H, CH_2Ph), 6.68 (dd, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 1.8 Hz, 1 H, H-4-furyl), 7.01 (dd, $J_{3,4}$ = 3.5 Hz, $J_{3,5}$ = 0.8 Hz, 1 H, H-4-furyl), 7.12 (m, 2 H, H-*o*-Ph), 7.23 (m, 1 H, H-*p*-Ph), 7.29 (m, 2 H, H-*m*-Ph), 7.46 (br s, 2 H, NH_2), 7.92 (dd, 1 H, $J_{5,4}$ = 1.8 Hz, $J_{5,3}$ = 0.8 Hz, H-5-furyl), 8.19 (s, 1 H, H-2).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 46.24 (CH_2Ph), 112.41 and 112.42 (CH-3,4-furyl), 118.72 (C-5), 126.70 (CH-*o*-Ph), 127.71 (CH-*p*-Ph), 128.92 (CH-*m*-Ph), 137.21 (C-*ipso*-Ph), 140.81 (C-8), 144.44 (C-2-furyl), 145.17 (CH-5-furyl), 151.14 (C-4), 153.27 (CH-2), 156.01 (C-6).

ESI-MS: *m*/*z* (%) = 292 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}N_5O$: 292.1193; found: 292.1194.

Anal. Calcd for $C_{16}H_{13}N_5O{\cdot}3/4\ H_2O$ (304.8): C, 63.04; H, 4.79; N, 22.98. Found: C, 63.05; H, 4.71; N, 22.82.

9-Benzyl-8-(thiophen-3-yl)adenine (5h)

Prepared from potassium 3-thiophenetrifluoroborate (**2h**; 114 mg) as brown crystals, yield 96%.

Mp 164–168 °C (CH_2Cl_2–heptane).

IR (KBr): 3317, 3115, 1665, 1601, 1453, 1301 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 5.60 (s, 2 H, CH_2Ph), 7.01 (m, 2 H, H-*o*-Ph), 7.23 (m, 1 H, H-*p*-Ph), 7.28 (m, 2 H, H-*m*-Ph), 7.37 (br s, 2 H, NH_2), 7.52 (dd, $J_{4,5}$ = 5.1 Hz, $J_{4,2}$ = 1.3 Hz, 1 H, H-4-thienyl), 7.69 (dd, $J_{5,4}$ = 5.1 Hz, $J_{5,2}$ = 2.9 Hz, 1 H, H-5-thienyl), 7.92 (dd, $J_{2,5}$ = 2.9 Hz, $J_{2,4}$ = 1.3 Hz, 1 H, H-2-thienyl), 8.17 (s, 1 H, H-2).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 46.03 (CH_2Ph), 118.49 (C-5), 126.44 (CH-*o*-Ph), 126.82 (CH-2-thienyl), 127.56 (CH-5-thienyl), 127.73 (CH-*p*-Ph), 128.04 (CH-4-thienyl), 129.04 (CH-*m*-Ph), 130.72 (C-3-thienyl), 137.09 (C-*ipso*-Ph), 145.84 (C-8), 151.44 (C-4), 153.04 (CH-2), 155.94 (C-6).

ESI-MS: : *m*/*z* (%) = 308 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}N_5S$: 308.0964; found: 308.0963.

Anal. Calcd for $C_{16}H_{13}N_5S{\cdot}4/5\ H_2O$ (321.8): C, 59.72; H, 4.57; N, 21.76. Found: C, 59.46; H, 4.56; N, 21.46.

9-Benzyl-8-(5-methylthiophen-2-yl)adenine (5i)

Prepared from potassium 5-methyl-2-thiophenetrifluoroborate (**2i**; 122 mg) as a yellowish powder, yield 76%.

Mp 208–213 °C (CH_2Cl_2–heptane).

IR ($CHCl_3$): 3413, 2988, 1632, 1590, 1464, 1294 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.45 (d, $J_{CH3,4}$ = 1.1 Hz, 3 H, CH_3), 5.63 (s, 2 H, CH_2Ph), 6.83 (dq, $J_{4,3}$ = 3.7 Hz, $J_{4,CH3}$ = 1.1 Hz, 1 H,H-4), 7.05 (m, 2 H, H-*o*-Ph), 7.23 (d, $J_{3,4}$ = 3.7 Hz, 1 H, H-3), 7.25 (m, 1 H, H-*p*-Ph), 7.31 (m, 2 H, H-*m*-Ph), 7.37 (br s, 2 H, NH_2), 8.15 (s, 1 H, H-2).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 15.17 (CH_3), 46.07 (CH_2Ph), 118.55 (C-5), 126.22 (CH-*o*-Ph), 127.07 (CH-4-thienyl), 127.71 (CH-3-thienyl), 128.01 (CH-*p*-Ph), 129.09 (CH-*m*-Ph), 129.62 (C-2-thienyl), 136.87 (C-*ipso*-Ph), 143.26 (C-5-thienyl), 144.37 (C-8), 151.76 (C-4), 153.04 (CH-2), 155.66 (C-6).

ESI-MS: *m*/*z* (%) = 322 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{16}N_5S$: 322.1121; found: 322.1121.

Anal. Calcd for $C_{17}H_{15}N_5S$ (321.4): C, 63.53; H, 4.70; N, 21.79. Found: C, 63.25; H, 4.75; N, 21.79.

9-Benzyl-8-cyclopropyladenine (5l)

A mixture of toluene–H_2O (10:1; 2 mL) was added through a septum to an argon-purged vial containing 8-bromoadenine **4** (152 mg, 0.5 mmol), potassium cyclopropyltrifluoroborate (**2l**, 85 mg, 0.6 mmol), $Pd(OAc)_2$ (3.3 mg, 0.015 mmol), cataCXium A (8 mg, 0.022 mmol) and Cs_2CO_3 (488 mg, 1.5 mmol). The mixture was stirred at 100 °C for 24 h. The reaction was quenched with H_2O and extracted with $CHCl_3$ (3 × 20 mL), collected organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was chromatographed on a silica gel column (EtOAc–MeOH). Pure product was obtained by crystallization from CH_2Cl_2–heptane to obtain 64 mg (48% yield) of **3l** as yellowish crystals.

IR (*i*-PrOH): 1652 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 0.94–1.00 (m, 4 H, H-2,3-*c*-Pr), 2.16 (m, 1 H, H-1-*c*-Pr), 5.47 (s, 2 H, CH_2Ph), 6.99 (br s, 2 H, NH_2), 7.23 (m, 2 H, H-*o*-Ph), 7.27 (m, 1 H, H-*p*-Ph), 7.33 (m, 2 H, H-*m*-Ph), 8.10 (s, 1 H, H-2).

^{13}C NMR (125.7 MHz, DMSO-d_6): δ = 7.81 (CH-1-*c*-Pr), 8.39 (CH_2-2,3-*c*-Pr), 44.91 (CH_2Ph), 117.60 (C-5), 127.22 (CH-*o*-Ph), 127.72 (CH-*p*-Ph), 128.86 (CH-*m*-Ph), 137.28 (C-*ipso*-Ph), 150.97 (C-4), 151.92 (CH-2), 153.57 (C-8), 155.10 (C-6).

ESI-MS: *m*/*z* (%) = 266 (100) [M + 1].

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}N_5$: 266.1400; found: 266.1401.

Anal. Calcd for $C_{15}H_{15}N_5$ (271.3): C, 66.40; H, 5.82; N, 25.81. Found: C, 66.30; H, 5.62; N, 25.63.

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