Cross-coupling reactions of unprotected halopurine bases, nucleosides, nucleotides and nucleoside triphosphates with 4-boronophenylalanine in water. Synthesis of (purin-8-yl)- and (purin-6-yl)phenylalanines†

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An expeditious and highly efficient single-step methodology for the introduction of a phenylalanine moiety into position 8 and 6 of the purine scaffold was developed based on aqueous-phase Pd-catalysed Suzuki–Miyaura cross-coupling reactions of unprotected 4-boronophenylalanine with 8-bromo- or 6-chloropurines. The scope of the methodology was demonstrated by syntheses of unprotected (adenin-8-yl)phenylalanine base, nucleosides, nucleotides and nucleoside triphosphates as well as (purin-6-yl)phenylalanine base and nucleosides. All these products were obtained in high yields and in optically pure form.

Introduction

Modified nucleic acids attract growing interest due to potential applications ranging from therapeutics to catalysis or nanotechnology. To expand the scope of these applications, the introduction of a variety of functional groups to DNA (especially to the nucleobase) is desirable. Apart from classical oligonucleotide synthesis[1] using functionalised nucleoside phosphoramidites, nucleobase-functionalised DNA can be prepared by PCR using modified nucleoside triphosphates[2] (NTP). The latter approach using functionalised NTPs is particularly interesting due to its potential use in *in vitro* selection.[3] Bioconjugates of oligonucleotides and peptides or proteins are another important class of compounds.[4] Attachment of a peptide part to an oligonucleotide may facilitate transport through membranes,[5] increase stability to exonucleases,[6] and enhance the antisense effect.[7] These conjugates are usually constructed by postsynthetic ligation[8] or by stepwise synthesis of both parts on a solid support.[9]

Recently, we have, within the framework of our project on bioactive purines bearing functionalised C-substituents,[10] entered the field of C–C-linked conjugates of purines and amino acids. A new methodology for the synthesis of (purin-6-yl)alanines[11] and (purin-6-yl)phenylalanines[12] was developed based on the cross-coupling reactions of protected iodozinc alanines and 4-borono- or 4-(trimethylstannyl)phenylalanines, respectively, with 6-halopurines. Purine bases and nucleosides with the amino acid attached to position 8 are particularly attractive, since such conjugates should retain H-bonding ability to form duplexes (8-substituted adenosines are known[13] to favour the undesired *syn*-conformation but there are several examples[2c,14] of stable duplexes containing these compounds) and thus are potential building blocks for functionalised DNA or DNA–peptide conjugates. Very recently we have reported in a preliminary communication[15] on the synthesis of 4-(adenosin-8-yl)phenylalanines by the Suzuki–Miyaura cross-coupling of unprotected nucleosides in predominantly aqueous solvent. Here we give the full account of this methodology, which is further extended to the cross-coupling of the corresponding free bases and mono- and triphosphates as potential substrates for PCR, and to the cross-coupling of 9-unprotected purines and unprotected 6-halopurine nucleosides.

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Results and discussion

As we have already reported,[15] we first tried to apply reactions of protected 4-trimethylstannyl- and 4-boronophenylalanines in organic solvents (DMF or dioxane), successfully used in reactions of 6-halopurines,[12] to the analogous reactions of protected 8-bromoadenines. Surprisingly, though there are many examples of such cross-coupling reactions of 8-bromopurines with diverse organostannanes[16] or arylboronic acids,[17] these reactions with the protected phenylalanine-derived organometallics did not proceed.[15]

Aqueous-phase cross-coupling reactions using water-soluble phosphine ligands have attracted great attention in recent years and found a wide range of applications.[18] Shaughnessy *et al.*[19] have recently applied them to the reactions of unprotected 8-bromoadenosine with simple arylboronic acids. Therefore we decided to apply these conditions for the synthesis of 4-(adenosin-8-yl)phenylalanines. Fortunately, the reactions of unprotected (*S*)-4-boronophenylalanine **2** with 8-bromoadenine nucleosides **1a** and **1b** (Scheme 1) gave the desired 4-(adenin-8-yl)phenylalanine nucleosides[15] **3a** and **3b** in a single step and in very good yields (Table 1, entries 1–2). The reactions were carried out in a water–acetonitrile (2 : 1) solvent mixture at 90 °C in the presence of Na_2CO_3 as a base and a water-soluble catalytic system consisting of $Pd(OAc)_2/P(m\text{-}C_6H_4SO_3Na)_3$ (**L1**, ratio 1 : 2.5). The products were isolated from crude reaction mixtures by preparative reverse-phase HPLC on a C18 phase (this separation technique was used also for isolation of all other final products).

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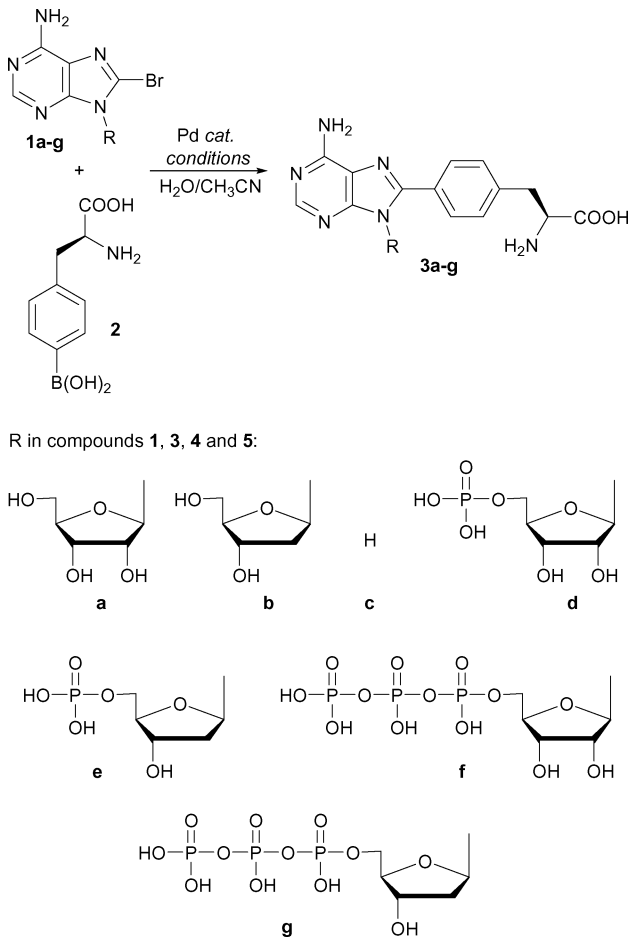
Table 1 Synthesis of (adenin-8-yl)phenylalanines

Entry	Purine	Product	Catalyst[a]	Base	Temperature/°C [b]	Time	Yield (%)
1	**1a**	**3a**	$Pd(OAc)_2$/**L1** (1 : 2.5)	Na_2CO_3	90	2 h	71
2	**1b**	**3b**	$Pd(OAc)_2$/**L1** (1 : 2.5)	Na_2CO_3	90	2 h	75
3	**1a**	**3a**	$Pd(OAc)_2$/**L1** (1 : 2.5)	Na_2CO_3	150 (MW)	5 min	56
4	**1b**	**3b**	$Pd(OAc)_2$/**L1** (1 : 2.5)	Na_2CO_3	150 (MW)	5 min	52
5	**1a**	**3a**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	150 (MW)	5 min	76
6	**1b**	**3b**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	150 (MW)	5 min	68
7	**1c**	**3c**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	150 (MW)	5 min	84
8	**1d**	**3d**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	90	4 h	0
9	**1d**	**3d**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	150 (MW)	5 min	51
10	**1d**	**3d**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	125	1.5 h	72
11	**1e**	**3e**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	150 (MW)	5 min	<1
12	**1e**	**3e**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	125	20 min	71
13	**1f**	**3f**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	90	2 h	0
14	**1f**	**3f**	$Pd(OAc)_2$/**L1** (1 : 5)	Na_2CO_3	150 (MW)	5 min	<5
15	**1f**	**3f**	$Pd(OAc)_2$/**L1** (1 : 5)[c]	Cs_2CO_3	125	30 min	51
16	**1g**	**3g**	$Pd(OAc)_2$/**L1** (1 : 5)[c]	Cs_2CO_3	125	20 min	55

[a] 0.05 eq. of $Pd(OAc)_2$ with respect to 8-halopurine reagent was used. [b] (MW) means that the reaction was performed under microwave irradiation. [c] 0.1 eq. of of $Pd(OAc)_2$ with respect to 8-halopurine reagent was used.



Scheme 1 Synthesis of (adenin-8-yl)phenylalanines.

As an alternative, we also tried to carry out the reactions of **1a–b** under microwave irradiation for 5 min at 150 °C (Table 1, entries 3 and 4). The preparative yields were somewhat lower but the reaction time was substantially reduced. Additional studies of microwave-mediated reactions of **1a** and **1b** showed that yields can be further improved to *ca.* 70% by increasing the ratio of the ligand **L1** to $Pd(OAc)_2$ to 5 : 1 (Table 1, entries 5–6). These yields were already comparable to the classically heated reactions (entries 1 and 2). This ratio was further confirmed to be generally superior in all other studied reactions.

The success with nucleosides encouraged us to try an application of this method to the synthesis of purine base **3c**. It is noteworthy that 9-unsubstituted halopurine bases are generally known[17a,20] to be unreactive under classical Suzuki–Miyaura reaction conditions, and 9-(tetrahydropyran-2-yl)-protected halopurines are usually used as their synthetic equivalents. Fortunately, the reaction of free 8-bromoadenine (**1c**) with boronic acid **2** under the optimised microwave-mediated conditions gave (adenin-8-yl)phenylalanine **3c** in excellent yield of 84% (Table 1, entry 7). This is thus the first example of a successful cross-coupling reaction of a 9-unsubstituted 8-halopurine base. The extent of this reaction with other boronic acids and other halopurines is currently under study and will be published separately.

In order to extend the scope of this methodology to other biologically relevant derivatives, we have decided to apply it to the synthesis of important but rather labile purine nucleotides and nucleoside triphosphates. However, the reaction of boronophenylalanine **2** with 8-bromoAMP **1d** under conventional heating at 90 °C did not give any conversion to the desired product **3d** (Table 1, entry 8). Application of microwave irradiation at 150 °C was more successful, giving the product **3d** in 51% yield (entry 9). Finally, classical heating at the optimum temperature of 125 °C (high enough to promote the reaction but without significant decomposition), provided the nucleotide **3d** in very good yield of 72% (entry 10). In contrast to the reaction of ribonucleotide **1d**, complete decomposition of the nucleotides was observed in the case of microwave-mediated reaction of 2′-deoxyribonucleotide **1e** (entry 11). On the other hand, reaction of **1e** under classical heating at 125 °C proceeded smoothly with an even higher reaction rate than the reaction of ribonucleotide **1d**, to give the desired product in a high preparative yield of 71% (entry 12).

The most challenging substrates were the nucleoside triphosphates **1f** and **1g**. Nucleoside triphosphates are rather labile compounds, which are easily hydrolysed. Therefore, we tried to employ the mildest possible conditions. At first, we employed

Na_2CO_3 as base and heating at 90 °C for the reaction of the triphosphate **1f** with boronic acid **2**, but no desired product **3f** was formed (Table 1, entry 13). On the other hand, application of microwave irradiation (150 °C, 5 min) in this reaction resulted in a complex mixture of by-products, including monophosphates and diphosphates as the products of hydrolysis of **1f** and **3f** (by HPLC), with only traces of target triphosphate **3f** (<5%, entry 14). We therefore further optimised the reaction conditions in two ways: (i) by improving the catalytic system in order to increase the cross-coupling reaction rate and (ii) by decreasing the triphosphate hydrolysis rate.

The optimisation of the cross-coupling was performed on a stable, cheap and easily available 8-bromoadenosine, **1a**. We examined several Pd-based catalytic systems (Table 2, entries 1–8) in a water–acetonitrile (2 : 1) mixture, with Na_2CO_3 as base and with heating at 125 °C for 6 min. Entries 1 and 2 show the results of the originally used catalytic system, consisting of $Pd(OAc)_2/P(m\text{-}C_6H_4SO_3Na)_3$ (1 : 5). $Pd(OAc)_2$/**L1** premixed in reaction solvents and injected into the reaction mixture gave the product **3a** in 32% yield (entry 1), while a separate addition of solid $Pd(OAc)_2$ and **L1** into the reaction gave somewhat lower yield of 30% (entry 2). The direct use of Pd(**L1**)$_4$ prepared according to literature[21] gave the lowest yield of 23% (entry 3). The second catalytic system was based on a more sterically hindered phosphine ligand **L2** (Fig. 1), reported to be superior to **L1** in reactions of 8-bromo-2′-deoxyadenosine with several simple arylboronic acids.[19] In our case, it gave yields of *ca.* 11% only (entries 4 and 5). A catalytic system based on a water-soluble Buchwald-type ligand **L3** (Fig. 1), recently reported to be excellent for Suzuki–Miyaura couplings of low reactivity aryl chlorides and bromides,[22] failed completely in our model experiment, with only about 1% yield of **3f** (entry 6). Similarly unsuccessful were experiments catalysed by

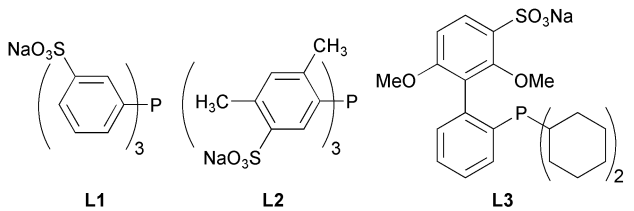


Fig. 1 Structures of water-soluble phosphine ligands **L1–L3**.

Table 2 Optimisation of reaction conditions of model cross-coupling experiments of 8-bromoadenosine **1a** with **2** to give product **3a**

Entry	Catalyst[a]	Base	Yield of **3a** (%)[b]
1	$Pd(OAc)_2$/**L1** (1 : 5)[c]	Na_2CO_3	32
2	$Pd(OAc)_2$/**L1** (1 : 5)[d]	Na_2CO_3	30
3	Pd(**L1**)$_4$	Na_2CO_3	23
4	$Pd(OAc)_2$/**L2** (1 : 5)	Na_2CO_3	11
5	$Pd(OAc)_2$/**L2** (1 : 2.5)	Na_2CO_3	12
6	$Pd(OAc)_2$/**L3** (1 : 2)	Na_2CO_3	1
7	$PdCl_4Na_2$/EDTA (1 : 1)	Na_2CO_3	<1
8	Pd/C	Na_2CO_3	0
9	$Pd(OAc)_2$/**L1** (1 : 5)	Cs_2CO_3	44

[a] 0.05 eq. of Pd catalyst with respect to 8-halopurine reagent was used. [b] Yields were determined by analytical HPLC after 6 min of heating at 125 °C. [c] A premixed solution of $Pd(OAc)_2$/**L1** was injected into the reaction. [d] Solid $Pd(OAc)_2$ and **L1** were added separately.

$PdCl_4Na_2$/EDTA[23] and Pd/C[24] (entries 7 and 8), other systems used for Suzuki couplings in aqueous media. Results of all these experiments showed that the originally used $Pd(OAc)_2$/**L1** catalytic system is probably the best one for our reaction. With no space for improvement of the catalyst, we examined the use of a stronger base Cs_2CO_3 instead of Na_2CO_3. It increased the efficiency of the reaction, giving the product **3a** in 44% yield (entry 9).

Additionally, the stability of model adenosine triphosphate (ATP) under heating (125 °C) in diverse water–organic solvent mixtures (H_2O and acetonitrile, acetone, DMF, EtOH, THF, or DMSO) with a variety of bases was studied by analytical HPLC (for details, see ESI†). There were no significant differences in the hydrolysis rates of ATP in diverse solvent mixtures. On the other hand, the stability of ATP rose dramatically with the strength of the base used, in the order $Li_2CO_3 < Na_2CO_3 \sim K_3PO_4 < Cs_2CO_3$. As the use of Cs_2CO_3 was superior in both tests, it was clearly the base of choice. Stronger bases were not tested due to the risk of racemisation of the amino acid moiety.[12]

Finally, the preparative reaction of triphosphate **1f** was carried out under the optimum conditions, employing Cs_2CO_3 base, 1.5 eq. of boronic acid **2**, 10% of $Pd(OAc)_2$, ligand **L1** and heating at 125 °C. Despite partial decomposition of the reaction mixture (again, products of hydrolysis of both starting and final compounds were observed) desired product **3f** was isolated from reaction after 30 min (the reaction was stopped before full conversion of **1f**) in good yield of 51% (Table 1, entry 15). Attempts to reach full conversion of starting **1f** by prolongation of reaction time resulted in lower yields caused by further decomposition of the final triphosphate. Analogous reaction of 2′-deoxyribonucleoside triphosphate **1g** under the same conditions gave 55% of product **3g** after 20 min of heating (Table 1, entry 16). In this case, full conversion of starting material was achieved after this time (again indicating a higher reaction rate). A small amount of diphosphate analogue of **3g** was observed as the only by-product.

To the best of our knowledge, the syntheses of compounds **3d–g** represent the first examples of cross-coupling reactions of purine nucleoside monophosphates and triphosphates (though one related example of the Suzuki reaction was recently described[25] for cyclic 8-bromoinosine 5′-diphosphate ribose). When applied to reactions of 2′-deoxyribonucleoside triphosphate **3g** with diverse boronic acids, this methodology should have great value for facile and efficient single-step syntheses of a variety of 8-C-modified-2′-deoxyATPs. Use of these as substrates of PCR reactions would lead to enzymatic synthesis of modified nucleic acids. This study is under way and will be published in due course.

The optical purity of products **3a–c** prepared under both standard heating and microwave irradiation was examined by derivatisation with Marfey's reagent.[26] No racemisation of the amino acid moiety was observed in these reactions (all products had optical purity >98% ee/de; optical purity of the commercial starting boronic acid **2** was determined to be 99% ee). To prove that no racemisation takes place when stronger Cs_2CO_3 was used in reaction, the compound **3a** was prepared under the conditions of entries 15 and 16 (using Cs_2CO_3 base and heating at 125 °C for 30 min). This sample of **3a** had optical purity 98% ee, indicating that no racemisation took place even with Cs_2CO_3.

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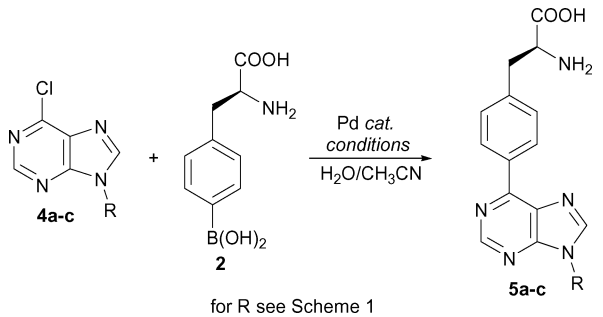
With this efficient and straightforward methodology in hand, we decided to come back to (purin-6-yl)phenylalanines, originally prepared[12] by a multistep sequence consisting of the protection of nucleosides and amino acids, cross-coupling reactions and deprotections. The aqueous methodology would be a much shorter and more efficient alternative for their synthesis. Therefore, the scope of the methodology was further examined on the cross-coupling reactions of 6-chloropurine derivatives **4a–c** with boronic acid **2** (Scheme 2).



Scheme 2 Synthesis of (purin-6-yl)phenylalanines.

Reactions of 6-chloropurine nucleosides **4a–b** with boronic acid **2** were carried out using $Pd(OAc)_2$/**L1** and Na_2CO_3 under conventional heating at 90 °C. Complete conversion was observed after 1.5 h and products **5a** and **5b** were isolated in good yields of 65% and 63% (Table 3, entries 1 and 3). Reaction of **4a** repeated under microwave irradiation gave even better yield of 84% of **5a** in less than 1 minute (entry 2). Free 6-halopurine bases are known[20] to be unreactive in Suzuki coupling reactions in organic solvents with $Pd(PPh_3)_4$ catalyst. However, with our catalytic system and aqueous solvent system, free purine base **4c** underwent reaction with **2** under heating at 90 °C, reaching full conversion within 9 h and giving the product **5c** in 67% preparative yield (entry 4). Furthermore, both reaction rate and product yield were enhanced significantly by the use of microwave irradiation (yield 90% in 5 min, entry 5). The optical purity of all prepared (purin-6-yl)phenylalanines (**5a–c**) was >98% ee/de, according to the assay with Marfey's reagent.

Conclusions

The Shaughnessy method[19] for Suzuki–Miyaura cross-coupling reactions in aqueous media was further optimised and applied to the synthesis of novel purine–amino acid conjugates. An efficient single-step synthesis of optically pure (adenin-8-yl)phenylalanines and (purin-6-yl)phenylalanines was elaborated using both classical heating and microwave irradiations. Classical heating was more efficient for the synthesis of 8-substituted nucleosides and more labile nucleotides and NTPs, while microwave irradiation was more efficient for purine bases and 6-substituted nucleosides. The wide tolerance of this methodology towards a variety of functionalities and applicability to extremely labile systems was demonstrated particularly clearly by the very first examples of couplings of free purine bases and nucleoside monophosphates and triphosphates. In particular, the application of the methodology to the reaction of 8-bromo-2′-deoxyATP is of great value for the synthesis of novel 8-C-modified purine NTPs, which are potential substrates in PCR reactions.

Experimental

General

NMR spectra were measured on Bruker AMX-3 400 (400 MHz for ^{1}H and 100.6 MHz for ^{13}C nuclei) and Bruker DRX 500 (500 MHz for ^{1}H and 125.8 MHz for ^{13}C) spectrometers in D_2O (referenced to dioxane as internal standard, δ_H = 3.75 ppm, δ_C = 67.19 ppm) or in DMSO-d_6 (referenced to the residual solvent signal). Chemical shifts (δ) are given in ppm, and coupling constants (J) in Hz. Complete assignment of all NMR signals was performed using a combination of H,H-COSY, H,C-HSQC and H,C-HMBC experiments. Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using FAB (ionisation by Xe, accelerating voltage 8 kV, glycerol + thioglycerol matrix) or LCQ classic (Thermo-Finnigan) spectrometer using ES−. Optical rotations were measured at 25 °C on a Autopol IV (Rudolph Research Analytical) polarimeter, and $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}. H_2O–acetonitrile was degassed *in vacuo* and stored under argon. Preparative HPLC separations were performed on a column packed with 10 µm C18 reversed phase (Phenomenex, Luna C18(2)). Microwave-mediated reactions were performed in an Initiator (Biotage, Inc.) microwave reactor, operated in a temperature-priority mode (*i.e.* the microwave source performance changes automatically to maintain the set temperature over the course of the reaction). For the synthesis and availability of starting materials, see ESI†.

Synthesis of compounds 3a–e: General procedure

Water–acetonitrile (2 : 1, 1.2 ml) was added through a septum to an argon-purged vial containing 8-bromoadenine **1** (0.1 mmol), boronic acid **2** (26 mg, 0.125 mmol), $Pd(OAc)_2$ (1.12 mg, 0.005 mmol), $P(m\text{-}C_6H_4SO_3Na)_3$ (14.2 mg, 0.025 mmol), and Na_2CO_3 (32 mg, 0.3 mmol). The mixture was stirred under heating or under microwave irradiation (for temperature and reaction time see Table 1). Products were isolated from the crude reaction

Table 3 Synthesis of (purin-6-yl)phenylalanines

Entry	Purine	Product	Conditions[a]	Yield (%)
1	**4a**	**5a**	$Pd(OAc)_2$/**L1**, Na_2CO_3, 90 °C, 80 min	65
2	**4a**	**5a**	$Pd(OAc)_2$/**L1**, Na_2CO_3, 150 °C MW, 1 min	84
3	**4b**	**5b**	$Pd(OAc)_2$/**L1**, Na_2CO_3, 90 °C, 90 min	63
4	**4c**	**5c**	$Pd(OAc)_2$/**L1**, Na_2CO_3, 90 °C, 9 h	67
5	**4c**	**5c**	$Pd(OAc)_2$/**L1**, Na_2CO_3, 150 °C MW, 5 min	90

[a] The ratio of $Pd(OAc)_2$/**L1** was 1 : 2.5 in all cases and was not further optimised.

mixture by HPLC on a C18 column: (i) compounds **3a–c** with a linear gradient of 0.3% AcOH in H_2O to 0.3% AcOH in MeOH as eluent; (ii) compounds **3d–e** with a linear gradient of 0.1 M TEAB (triethylammonium bicarbonate) in H_2O to 0.1 M TEAB in H_2O–MeOH (1 : 1) as eluent. Several co-distillations with water (to remove remaining TEAB or AcOH) followed by freeze-drying from water gave the products as white solids.

(*S*)-2-Amino-3-{4-[6-amino-9-(β-D-ribofuranosyl)purin-8-yl]-phenyl}propanoic acid (3a). Prepared from **1a** (35 mg, 0.1 mmol); isolated as **3a**·$2H_2O$. For reaction conditions and yields, see Table 1. MS (FAB): 432 (28, M + 1); 299 (100, M − Rf + 2). HRMS (FAB): for $C_{19}H_{23}N_6O_6$ calculated 431.1679, found 431.1701. ^{1}H NMR (400 MHz, D_2O, ref$_{dioxane}$ = 3.75 ppm): 3.20 (dd, 1H, J_{gem} = 14.4, $J_{bCH_2,CH}$ = 7.5, bCH_2); 3.32 (dd, 1H, J_{gem} = 14.4, $J_{aCH_2,CH}$ = 5.3, aCH_2); 3.82 (dd, 1H, J_{gem} = 12.9, $J_{5'b,4'}$ = 3.0, H-5′b); 3.88 (dd, 1H, J_{gem} = 12.9, $J_{5'a,4'}$ = 2.4, H-5′a); 4.04 (dd, 1H, J_{CH,bCH_2} = 7.5, J_{CH,aCH_2} = 5.3, CH); 4.20 (q, 1H, $J_{4',5'b}$ = 3.0, $J_{4',5'a}$ = 2.4, $J_{4',3'}$ = 2.3, H-4′); 4.40 (dd, 1H, $J_{3',2'}$ = 5.5, $J_{3',4'}$ = 2.3, H-3′); 5.07 (dd, 1H, $J_{2',1'}$ = 7.2, $J_{2',3'}$ = 5.5, H-2′); 5.92 (d, 1H, $J_{1'2'}$ = 7.2, H-1′); 7.42 (m, 2H, H-*m*-phenylene); 7.63 (m, 2H, H-*o*-phenylene); 8.19 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, D_2O, ref$_{dioxane}$ = 67.19 ppm): 36.87 (CH_2); 56.38 (CH); 62.77 (CH_2-5′); 71.56 (CH-3′); 72.71 (CH-2′); 87.08 (CH-4′); 89.88 (CH-1′); 119.29 (C-5); 127.29 (C-*i*-phenylene); 130.54 and 130.77 (CH-phenylene); 138.96 (C-*p*-phenylene); 149.78 (C-4); 151.04 (CH-2); 153.46 (C-8); 154.83 (C-6); 174.15 (CO). IR (KBr): 3335, 3191, 1641, 1484, 1397, 1336, 1085, 1034, 799. $[\alpha]_D^{20} = -41.0$ (c = 3.50, DMSO).

(*S*)-2-Amino-3-{4-[6-amino-9-(2-deoxy-β-D-erythropentofuranosyl)-purin-8-yl]phenyl}propanoic acid (3b). Prepared from **1b** (33 mg, 0.1 mmol); isolated as **3b**·$2H_2O$. For reaction conditions and yields, see Table 1. MS (FAB): 415 (70, M + 1); 299 (100, M − Rf + 2). HRMS (FAB): for $C_{19}H_{23}N_6O_5$ calculated 415.1730, found 415.1716. ^{1}H NMR (400 MHz, D_2O, ref$_{dioxane}$ = 3.75 ppm): 2.29 (ddd, 1H, J_{gem} = 14.0, $J_{2'b,1'}$ = 6.2, $J_{2'b,3'}$ = 2.2, H-2′b); 3.01 (ddd, 1H, J_{gem} = 14.0, $J_{2'a,1'}$ = 8.9, $J_{2'a,3'}$ = 6.2, H-2′b); 3.22 (dd, 1H, J_{gem} = 14.4, $J_{bCH_2,CH}$ = 7.5, bCH_2); 3.32 (dd, 1H, J_{gem} = 14.4, $J_{aCH_2,CH}$ = 5.4, aCH_2); 3.81 (dd, 1H, J_{gem} = 12.6, $J_{5'b,4'}$ = 3.5, H-5′b); 3.87 (dd, 1H, J_{gem} = 12.6, $J_{5'a,4'}$ = 2.7, H-5′a); 4.05 (dd, 1H, J_{CH,bCH_2} = 7.5, J_{CH,aCH_2} = 5.4, CH); 4.10 (q, 1H, $J_{4',5'}$ = 3.5, 2.7, $J_{4',3'}$ = 2.2, H-4′); 4.63 (dt, 1H, $J_{3',2'}$ = 6.2, 2.2, $J_{3',4'}$ = 2.2, H-3′); 6.29 (dd, 1H, $J_{1'2'}$ = 8.9, 6.2, H-1′); 7.44 (m, 2H, H-*m*-phenylene); 7.55 (m, 2H, H-*o*-phenylene); 8.17 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, D_2O, ref$_{dioxane}$ = 67.19 ppm): 36.87 (CH_2); 38.82 (CH_2-2′); 56.37 (CH); 62.95 (CH_2-5′); 72.52 (CH-3′); 87.13 (CH-1′); 88.53 (CH-4′); 119.36 (C-5); 127.57 (C-*i*-phenylene); 130.48 and 130.58 (CH-phenylene); 138.95 (C-*p*-phenylene); 149.73 (C-4); 150.76 (CH-2); 152.91 (C-8); 154.79 (C-6); 174.17 (CO). IR (KBr): 3354, 3205, 1642, 1526, 1483, 1406, 1337, 1091, 1055, 1032, 798. $[\alpha]_D^{20} = -35.0$ (c = 4.15, DMSO).

(*S*)-2-Amino-3-[4-(6-amino-9*H*-purin-8-yl)phenyl]propanoic acid (3c). Prepared from **1c** (22 mg, 0.1 mmol) by microwave-mediated reaction (150 °C, 5 min), to give 25 mg (84%) of **3c**. MS (FAB): 299 (100, M + 1); 279 (16); 253 (22). HRMS (FAB): for $C_{14}H_{15}N_6O_2$ calculated 299.1256, found 299.1265. ^{1}H NMR (500 MHz, D_2O + NaOD, ref$_{dioxane}$ = 3.75 ppm): 2.89 (dd, 1H, J_{gem} = 13.5, J_{vic} = 7.5, bCH_2); 3.05 (dd, 1H, J_{gem} = 13.5, J_{vic} = 5.6, aCH_2); 3.55 (dd, 1H, J_{vic} = 7.5, 5.6, CH); 7.38 (m, 2H, H-*m*-phenylene); 8.08 (m, 2H, H-*o*-phenylene); 8.11 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, D_2O + NaOD, ref$_{dioxane}$ = 69.3 ppm): 43.43 (CH_2); 60.14 (CH); 124.47 (C-5); 129.36 (CH-*o*-phenylene); 132.53 (CH-*m*-phenylene); 134.79 (C-*i*-phenylene); 142.19 (C-*p*-phenylene); 152.53 (CH-2); 156.30 (C-4); 163.57 (C-6); 164.39 (C-8); 185.10 (CO). IR (KBr): 3322, 3187, 2870, 1637, 1620, 1599, 1490, 1406, 1331, 796, 628. $[\alpha]_D^{20} = -10.2$ (c = 2.76, DMSO).

(*S*)-2-Amino-3-{4-[6-amino-9-(β-D-ribofuranosyl)purin-8-yl]-phenyl}propanoic acid 5′-*O*-phosphate (3d). Prepared from **1d**·$2H_2O$ (46 mg, 0.1 mmol); isolated as **3f**·Et_3N·$4H_2O$. For reaction conditions and yields, see Table 1. MS (FAB): 511 (78, M + 1); 317 (100); 299 (80, M − $PO(OH)_2$Rf + 2). HRMS (FAB): for $C_{19}H_{24}N_6O_9P_1$ calculated 511.1342, found 511.1340. ^{1}H NMR (500 MHz, D_2O, ref$_{dioxane}$ = 3.75 ppm): 1.26 (t, 9H, J_{vic} = 7.4, CH_3-Et_3N); 3.17 (dd, 1H, J_{gem} = 14.5, J_{vic} = 7.5, bCH_2); 3.19 (q, 6H, J_{vic} = 7.4, CH_2-Et_3N); 3.28 (dd, 1H, J_{gem} = 14.4, J_{vic} = 5.3, aCH_2); 4.04 (dd, 1H, J_{vic} = 7.4, 5.3, CH); 4.13–4.23 (m, 3H, H-4′ and H-5′); 4.47 (dd, 1H, $J_{3',2'}$ = 6.1, $J_{3',4'}$ = 4.4, H-3′); 5.20 (t, 1H, $J_{2',3'}$ = 6.1, $J_{2',1'}$ = 6.0, H-2′); 5.85 (d, 1H, $J_{1'2'}$ = 6.0, H-1′); 7.38 (m, 2H, H-*m*-phenylene); 7.60 (m, 2H, H-*o*-phenylene); 8.20 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, D_2O, ref$_{dioxane}$ = 69.3 ppm): 10.95, CH_3-Et_3N); 38.89 (CH_2); 49.38 CH_2-Et_3N); 58.36 (CH); 67.24 (d, $J_{C,P}$ = 5, CH_2-5′); 72.25 (CH-3′); 73.00 (CH-2′); 85.82 (d, $J_{C,P}$ = 8, CH-4′); 91.63 (CH-1′); 120.95 (C-5); 129.49 (C-*i*-phenylene); 132.49 and 132.65 (CH-*o*,*m*-phenylene); 140.78 (C-*p*-phenylene); 152.58 (C-4); 154.52 (CH-2); 155.28 (C-8); 157.18 (C-6); 176.36 (CO). ^{31}P (^{1}H dec.) NMR (162 MHz, D_2O, ref$_{H_3PO_4}$ = 0 ppm): 1.18. IR (KBr): 3413, 3182, 2927, 2680, 1637, 1478, 1396, 1333, 1060, 1045, 910, 519. $[\alpha]_D^{20} = -28.5$ (c = 2.68, H_2O). Anal. calculated for **3d**·Et_3N·$4H_2O$, $C_{25}H_{46}N_7O_{13}P$ (683.6): C 43.92%, H 6.78%, N 14.34%; found: C 43.57%, H 6.47%, N 14.06%.

(*S*)-2-Amino-3-{4-[6-amino-9-(2′-deoxy-β-D-erythropentofuranosyl)-purin-8-yl]phenyl}propanoic acid 5′-*O*-phosphate (3e). Prepared from **1e**·Et_3N·$2H_2O$ (55 mg, 0.1 mmol); isolated as **3e**·Et_3N·$2H_2O$. For the reaction conditions and yields, see Table 1. MS (FAB): 596.6 (38, M + Et_3N + 1); 495 (76, M + 1); 299 (100, M − $PO(OH)_2$dRf + 2). HRMS (FAB): for $C_{19}H_{24}N_6O_8P_1$ calculated 495.1393, found 495.1383. ^{1}H NMR (400 MHz, D_2O, ref$_{dioxane}$ = 3.75 ppm): 1.27 (t, 9H, J_{vic} = 7.3, CH_3-Et_3N); 2.23 (ddd, 1H, J_{gem} = 14.0, $J_{2'b,1'}$ = 7.2, $J_{2'b,3'}$ = 3.8, H-2′b); 3.19 (q, 6H, J_{vic} = 7.4, CH_2-Et_3N); 3.20 (dd, 1H, J_{gem} = 14.7, J_{vic} = 7.6, bCH_2); 3.23 (dt, 1H, J_{gem} = 14.0, $J_{2'a,1'}$ = $J_{2'a,3'}$ = 7.4, H-2′a); 3.32 (dd, 1H, J_{gem} = 14.7, J_{vic} = 5.3, aCH_2); 4.05 (dd, 1H, J_{vic} = 7.6, 5.3, CH); 4.07–4.17 (m, 3H, H-4′ and H-5′); 4.64 (dt, 1H, $J_{3',2'}$ = 7.4, 3.8, $J_{3',4'}$ = 3.8, H-3′); 6.30 (t, 1H, $J_{1'2'}$ = 7.6, 7.4, H-1′); 7.44 (m, 2H, H-*m*-phenylene); 7.65 (m, 2H, H-*o*-phenylene); 8.23 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, D_2O, ref$_{dioxane}$ = 69.3 ppm): 10.95 (CH_3-Et_3N); 38.48 (CH_2-2′); 38.87 (CH_2); 49.37 (CH_2-Et_3N); 58.37 (CH); 67.31 (d, $J_{C,P}$ = 5, CH_2-5′); 73.68 (CH-3′); 87.42 (CH-1′); 87.79 (d, $J_{C,P}$ = 8, CH-4′); 121.17 (C-5); 130.05 (C-*i*-phenylene); 132.55 (CH-*o*,*m*-phenylene); 140.60 (C-*p*-phenylene); 152.56 (C-4); 154.59 (CH-2); 154.99 (C-8); 157.43 (C-6); 176.35 (CO). ^{31}P (^{1}H dec.) NMR (162 MHz, D_2O, ref$_{H_3PO_4}$ = 0 ppm): 0.89. IR (KBr): 3421, 3179, 2683, 2488, 1637, 1577, 1478, 1397, 1334, 1179, 1052, 921, 618, 522. $[\alpha]_D^{20} = -34.6$ (c = 1.49, H_2O). Anal. calculated for **3e**·Et_3N·$2H_2O$, $C_{25}H_{42}N_7O_{10}P$ (631.6): C 47.54%, H 6.70%, N 15.52%; found: C 47.06%, H 6.57%, N 15.16%.

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Synthesis of triphosphates 3f–g: General procedure

Water–acetonitrile (2 : 1, 0.8 ml) was added through a septum to an argon-purged vial containing 8-bromoadenosine triphosphate **1** (0.1 mmol), boronic acid **2** (31 mg, 0.15 mmol) and Cs_2CO_3 (163 mg, 0.5 mmol). When the solid had dissolved, a solution of $Pd(OAc)_2$ (2.25 mg, 0.01 mmol) and $P(m\text{-}C_6H_4SO_3Na)_3$ (28.4 mg, 0.05 mmol) in water–acetonitrile (2 : 1, 0.4 ml) was added, and the mixture stirred with heating at 125 °C.

(*S*)-2-Amino-3-{4-[6-amino-9-(β-D-ribofuranosyl)purin-8-yl]-phenyl}propanoic acid 5′-*O*-triphosphate (3f). Prepared from **1f**·$3Et_3N{\cdot}2H_2O$ (93 mg, 0.1 mmol). The reaction was heated at 125 °C for 30 min. The product was isolated from the crude reaction mixture by HPLC on a C18 column with a linear gradient of 0.1 M TEAB in H_2O to 0.1 M TEAB in H_2O–MeOH (1 : 1). Several co-distillations with water followed by freeze-drying from water gave the product, **3f**·$3Et_3N{\cdot}2H_2O$, in 51% yield as white solid. MS (ES^-): 669 (100, M − 1); 589 (60, M − $PO(OH)_2$); 297 (18, M − $P_3O_9H_4$Rf). HRMS (ES^-) for $C_{19}H_{24}N_6O_{15}P_3$: calculated 669.0513, found 669.0489. ^{1}H NMR (400 MHz, D_2O, $ref_{dioxane}$ = 3.75 ppm): 1.26 (t, 27H, J_{vic} = 7.3, CH_3-Et_3N); 3.17 (q, 18H, J_{vic} = 7.3, CH_2-Et_3N); 3.21 (dd, 1H, J_{gem} = 14.3, J_{vic} = 7.7, bCH_2); 3.37 (dd, 1H, J_{gem} = 14.3, J_{vic} = 4.9, aCH_2); 4.07 (dd, 1H, J_{vic} = 7.7, 4.9, CH); 4.21–4.35 (m, 3H, H-4′ and H-5′); 4.49 (dd, 1H, $J_{3',2'}$ = 6.2, $J_{3',4'}$ = 4.1, H-3′); 5.19 (t, 1H, $J_{2',1'} = J_{2',3'}$ = 6.2, H-2′); 5.93 (d, 1H, $J_{1'2'}$ = 6.2, H-1′); 7.49 (m, 2H, H-*m*-phenylene); 7.70 (m, 2H, H-*o*-phenylene); 8.31 (s, 1H, H-2). ^{13}C NMR (100.6 MHz, D_2O, $ref_{dioxane}$ = 69.3 ppm): 10.95 (CH_3-Et_3N); 38.92 (CH_2); 49.37 (CH_2-Et_3N); 58.38 (CH); 67.95 (d, $J_{C,P}$ = 5, CH_2-5′); 72.09 (CH-3′); 73.12 (CH-2′); 85.81 (d, $J_{C,P}$ = 9, CH-4′); 91.49 (CH-1′); 121.09 (C-5); 129.76 (C-*i*-phenylene); 132.77 (CH-*o*,*m*-phenylene); 141.11 (C-*p*-phenylene); 152.90 (C-4); 153.99 (CH-2); 155.77 (C-8); 156.90 (C-6); 176.41 (CO). ^{31}P (^{1}H dec.) NMR (162 MHz, D_2O, $ref_{H_3PO_4}$ = 0 ppm): −23.15 (t, J = 19.6, 18.4, P_β); −11.32 (d, J = 19.6, P_α); −10.77 (t, J = 18.4, P_γ). IR (KBr): 3428, 2679, 2492, 1637, 1478, 1397, 1332, 1237, 1062, 1033, 946, 899, 618. $[\alpha]_D^{20}$ = −17.5 (c = 2.57, H_2O).

(*S*)-2-Amino-3-{4-[6-amino-9-(2′-deoxy-β-D-erythropentofuranosyl)-purin-8-yl]phenyl}propanoic acid 5′-*O*-triphosphate (3g). Prepared from **1g**·$3Et_3N{\cdot}2H_2O$ (91 mg, 0.1 mmol). The reaction was heated at 125 °C for 20 min. The product was isolated from the crude reaction mixture by HPLC on a C18 column with 0.1 M TEAB in H_2O–MeOH (5 : 1) as eluent. Several co-distillations with water followed by freeze-drying from water gave the product, **3g**·$3Et_3N{\cdot}2H_2O$, in 55% yield as a white solid. MS (ES^-): 653 (100, M − 1); 573 (51, M − $PO(OH)_2$); 297 (23, M − $P_3O_9H_4$dRf). HRMS (ES^-) for $C_{19}H_{24}N_6O_{14}P_3$: calculated 653.0563, found 653.0544. ^{1}H NMR (400 MHz, D_2O, $ref_{dioxane}$ = 3.75 ppm): 1.26 (t, 27H, J_{vic} = 7.3, CH_3-Et_3N); 2.24 (ddd, 1H, J_{gem} = 13.9, $J_{2'b,1'}$ = 7.2, $J_{2'b,3'}$ = 4.3, H-2′b); 3.18 (q, 18H, J_{vic} = 7.3, CH_2-Et_3N); 3.20–3.27 (m, 2H, H-2′a and bCH_2); 3.39 (dd, 1H, J_{gem} = 14.4, J_{vic} = 5.0, aCH_2); 4.07 (dd, 1H, J_{vic} = 7.8, 5.0, CH); 4.14–4.32 (m, 3H, H-4′ and H-5′); 4.64 (dt, 1H, $J_{3',2'}$ = 8.0, 4.3, $J_{3',4'}$ = 4.0, H-3′); 6.37 (t, 1H, $J_{1'2'}$ = 7.8, 7.2, H-1′); 7.52 (m, 2H, H-*m*-phenylene); 7.72 (m, 2H, H-*o*-phenylene); 8.29 (s, 1H, H-2). ^{13}C NMR (125.8 MHz, D_2O, $ref_{dioxane}$ = 69.3 ppm): 10.95 (CH_3-Et_3N); 38.54 (CH_2-2′); 38.94 (CH_2); 49.38 (CH_2-Et_3N); 58.43 (CH); 68.07 (d, $J_{C,P}$ = 5, CH_2-5′); 73.29 (CH-3′); 87.15 (CH-1′); 87.49 (d, $J_{C,P}$ = 8, CH-4′); 121.25 (C-5); 130.46 (C-*i*-phenylene); 132.66 and 132.89 (CH-*o*,*m*-phenylene); 140.95 (C-*p*-phenylene); 152.95 (C-4); 155.03 (CH-2); 155.34 (C-8); 157.77 (C-6); 176.46 (CO). ^{31}P (^{1}H dec.) NMR (162 MHz, D_2O, $ref_{H_3PO_4}$ = 0 ppm): −22.46 (b, P_β); −11.07 (d, J = 18.4, P_α); −9.60 (b, P_γ). IR (KBr): 3429, 3189, 2679, 2490, 1638, 1478, 1398, 1333, 1235, 1056, 945, 897, 839, 618. $[\alpha]_D^{20}$ = −16.5 (c = 2.23, H_2O).

Synthesis of compounds 5a–d: General procedure

Water–acetonitrile (2 : 1, 1.2 ml) was added through a septum to an argon-purged vial containing 6-chloropurine **4** (0.1 mmol), boronic acid **2** (26 mg, 0.125 mmol), $Pd(OAc)_2$ (1.12 mg, 0.005 mmol), $P(m\text{-}C_6H_4SO_3Na)_3$ (7.1 mg, 0.0125 mmol), and Na_2CO_3 (32 mg, 0.3 mmol). The mixture was stirred under heating or under microwave irradiation (for temperatures and reaction time see Table 3). After neutralisation to pH 7 by aq. HCl, the products were isolated from crude reaction mixture by HPLC on a C18 column with a linear gradient of 0.3% AcOH in H_2O to 0.3% AcOH in MeOH. Several co-distillations with water followed by freeze-drying from water gave the products as white solids. For the yields, see Table 3. All analytical and spectral data of compounds **5a–c** were in accord with authentic samples and previously published data.[12]

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