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Site-selective direct arylation of unprotected adenine nucleosides mediated by palladium and copper: insights into the reaction mechanism

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Abstract

Reaction conditions facilitating the site-selective direct aryl functionalisation at the C-8 position of adenine nucleosides have been identified. Many different aromatic components may be effectively cross-coupled to provide a diverse array of arylated adenine nucleoside products without the need for ribose or adenine protecting groups. The optimal palladium catalyst loading lies between 0.5 and 5 mol %. Addition of excess mercury to the reaction had a negligible affect on catalysis, suggesting the involvement of a homogeneous catalytic species. A study by transmission electron microscopy (TEM) shows that metal containing nanoparticles, ca. 3 nm with good uniformity, are formed during the latter stages of the reaction. Stabilised PVP palladium colloids (PVP=*N*-polyvinylpyrrolidone) are catalytically active in the direct arylation process, releasing homogenous palladium into solution. The effect of various substituted 2-pyridine ligand additives has been investigated. A mechanism for the site-selective arylation of adenosine is proposed.

Keywords: Direct arylation; Purines; C–C Bond formation; Palladium; Copper(I) salts

1. Introduction

C-Modified nucleosides are widely used as pH sensors, fluorescent markers, therapeutic agents and supramolecular building blocks.[1] Studies that probe biomolecular structure and biochemical mechanisms[2] are of fundamental importance, driving the need for the development of efficient synthetic methods to access structurally diverse non-natural nucleosides, particularly purines.

There are several ways to functionalise purine compounds. Sonogashira, Suzuki and Stille cross-coupling (hereafter coupling) processes, catalysed by palladium(0),[3] are routinely used to access arylated purine nucleosides (Scheme 1).[4] Historically the protection of both the sugar hydroxyl groups and the reactive heteroaromatic substituents was required for successful couplings. However, recent studies have demonstrated that unprotected halogenated nucleosides may be effectively cross-coupled with various nucleophilic components.[5] Arguably more remarkable are the findings that Suzuki–Miyaura cross-couplings are possible on halogenated triphosphate purine bases,[6,7] this despite the thermal and base sensitivity of the phosphoester bonds in the triphosphate moiety.

Toxic reagents, e.g., organostannanes, limit the use of Stille couplings in industrial scale-up processes, and whilst organoboronic acids are versatile coupling components for Suzuki–Miyaura couplings, in some cases their stability (protodeborylation) can be problematic, particularly in certain heteroaromatic components. Furthermore, these reactions cannot generally be viewed as atom economic transformations. For example, only the phenyl group (77 mu) is transferred from

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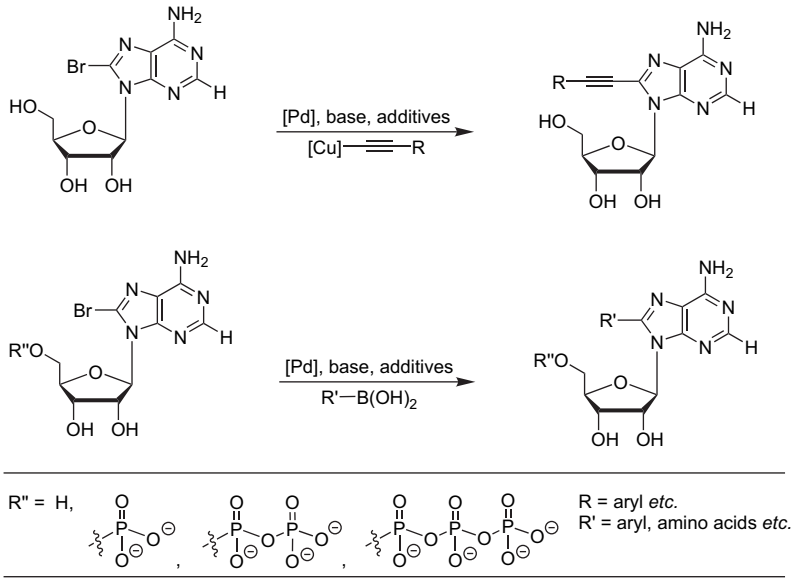


Scheme 1. Representative cross-couplings of unprotected purines with various nucleophilic components.

$PhSnBu_3$ and the rest is waste (290 mu), a problem derived from the need for prefunctionalisation in the 'nucleophilic' component. To combat these key issues, greener and more efficient methods for aryl functionalisation continue to be identified. Generally, protocols for direct arylation of organic compounds,[8] by C–H functionalisation, including the site-selective modification[9] of electron-rich heteroaromatics,[10] have reached a point where they may be applied to more challenging molecular architecture.[11]

With the primary aim of adding to the contemporary portfolio of modified molecular probes for practical use in bioapplications, we wished to investigate whether catalytic direct arylation methods can be employed for the synthesis of unprotected purine nucleosides. In unison with our studies, Hocek and co-workers recently disclosed that protected purines can be arylated at the 8-position using catalytic palladium in the presence of excess CuI in DMF at 160 °C for 60 h.[12] However, no sugar variants were given. Our studies on the site-selective direct arylation of purine nucleosides are reported in this paper.[13]

On consideration of the structures of the nucleosides a problem that emerges is the potential instability of the glycosyl bond at high temperatures, e.g., 160 °C (for adenosine the $t_{1/2}$>8000 h at 90–100 °C in water or formamide).[14] Site selectivity[9,15] further needs to be considered; C-arylation can potentially occur at C2 or C8 (Fig. 1). Whilst accurate experimental pK_a values for the C–H bonds in adenosine are not known, based on the theoretical pK_a values determined for

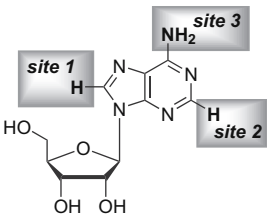


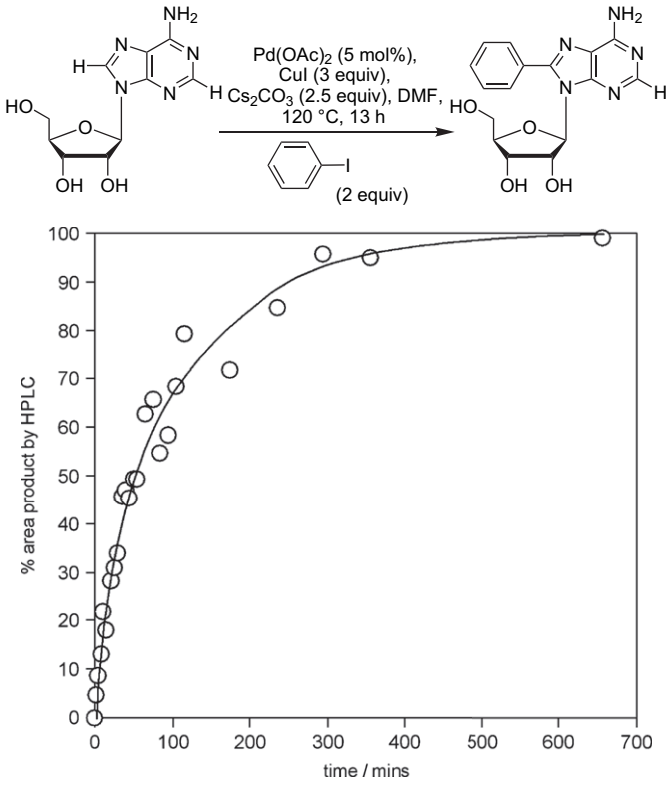
Figure 1. Potential sites of reaction for C–H and N–H bonds in adenosine.

9-methyl-9*H*-purine (in DMSO, H2=40.3; H8=29.3)[16] we predict that preferential C–H activation should occur at site 1. N-arylation is further possible—a recent report details that a Pd–Xantphos catalytic system can promote selective N-arylation of protected 2′-deoxyadenosines and 2′-deoxyguanosines with aryl bromides.[17]

Initially, reaction conditions reported in the literature for direct arylation of various heteroaromatic compounds were screened to assess whether reactions of adenosine with aryl iodides were possible. Using standard arylation conditions {$Pd(OAc)_2$, P(*t*-Bu)$_3$·HBF_4, PhCl or PhBr, K_3PO_4, DMA, 100 °C, 24 h}, or {$Pd(OAc)_2$, PhBr, NaOAc, 120 °C, 20 h} negligible direct arylation was seen. More success was had using the conditions described by Bellina and Rossi,[18] which are similar to those reported by Hocek and co-workers.[12] However, deglycosylation was found to be an issue at high temperatures over prolonged reaction times. On monitoring a reaction at 160 °C by HPLC it was revealed that direct arylation had occurred within minutes! On consumption and through extensive deglycosylation of adenosine, any remaining PhI rapidly homocoupled to give biphenyl. Deglycosylation of the cross-coupled product then occurred steadily over the course of several hours. Running the reaction at 120 °C improved the reaction efficacy considerably; the product profile is shown in Scheme 2. Note: homocoupling of adenosine was not observed under these conditions.[19]

Rapid colour changes are observed in reaction mixtures of adenosine and iodobenzene (Fig. 2). After 5 min of heating a yellow/orange colour was evident (plate A), which changed to a green/brown colour after 25 min (~30% conversion, plate B). After 1.5 h the formation of metal containing nanoparticles was observed in the reaction mixture (~65% conversion, plate C).

The pH upon work-up should be ~6.5, which allows the product to be extracted with an ethyl acetate/isopropanol solvent mixture (9:1). Subjecting the crude product to



Scheme 2. Product evolution profile for direct arylation of adenosine with iodobenzene monitored by HPLC (open circles=8-phenyladenosine).

chromatography on silica gel gave the direct arylation product in 65% yield (Table 1, entry 1). A similar yield was obtained using *N*-methylpyrrolidone (NMP) as the solvent (63%). The reproducibility of these reactions is ±5%. In the presence of catalytic quantities of CuI negligible turnover was observed (entry 2). Omission of $Pd(OAc)_2$ from the reaction resulted in poor turnover (4%), significant decomposition and deglycosylation (entry 3). The Pd(0) source, $Pd_2(dba)_3$ (dba=*E*,*E*-dibenzylidene acetone) acted as a catalyst (29% yield, entry 4), but was not as effective as $Pd(OAc)_2$. The more activated $Pd_2(dm\text{-}dba)_3\cdot dm\text{-}dba$[20] complex gave an improved yield (59%, entry 5), showing that the dibenzylidene acetone ligand is non-innocent in this direct arylation reaction, in accord with other cross-coupling processes.[21] Finally, microwave heating is ineffective for direct arylation of adenosine due to significant decomposition (mainly deglycosylation).

Having identified the *key* reaction/work-up parameters a library of aryl halides were evaluated for direct arylation of adenosine (Table 2). A series of *para*-substituted aryl iodides

Table 1
Evaluation of different palladium sources for direct arylation of adenosine[a]

Entry	Pd source (5 mol %)/CuI (mol %)	Yield[b]/%
1	$Pd(OAc)_2$/Cu (300)	65[c,d]
2	$Pd(OAc)_2$/Cu (5)	<5
3	—/Cu (300)	4[e]
4	$Pd_2(dba\text{-}H)_3$[f]/Cu (300)	29
5	$Pd_2(dm\text{-}dba)_2\cdot dm\text{-}dba$[g]/Cu (300)	59

[a] Reaction conditions: as for Scheme 2, changing the Pd source.
[b] Yield obtained after chromatography on silica gel.
[c] A yield of 4% was obtained for the *N*-arylated product (8-phenyl-*N*6-phenyl-adenosine, see Fig. 3).
[d] Under identical conditions using NMP as the solvent a yield of 63% was obtained.
[e] Significant deglycosylation observed.
[f] dba-H=dibenzylidene acetone (1,5-bis-phenyl-penta-1*E*,4*E*-dien-3-one).
[g] dm-dba=1,5-bis-(3′,5′-dimethoxyphenyl)penta-1*E*,4*E*-dien-3-one.

afforded the 8-arylated purine products in good yields (entries 1–4). Remarkably, ionisable substituents, e.g., OH and NH_2 groups are also tolerated (entries 5 and 6, respectively). Substrates possessing electron-deficient *ortho*-substituents are not accepted for C-arylation (entries 7 and 10). Catellani and co-workers reported that the *ortho*-trifluoromethyl group can interact with Pd(II), reducing its subsequent reactivity, in norbornene-assisted arylation processes.[22] On switching this substituent to the *meta* position the coupled product was formed in good yield (entry 8). In the presence of a *meta*-nitro substituent, the cross-coupled product was obtained in modest yield (entry 11). The *p*-nitro substituent gave the best yield from the most strongly ‘electron-deficient substituent series’ (entry 12). Iodonapthalene couples in near quantitative yield (entry 13). Quite remarkably the chemoselectivity was reversed when an *ortho*-nitro substituent is present—N-arylation emerged as the exclusive reaction pathway (Fig. 3).

We have established that 1,4-diiodobenzene can also be used as an arylation substrate (Scheme 3). Despite using fewer equivalents of 1,4-diiodobenzene (0.5 rather than 2 equiv with respect to the adenosine), both 1,4-di-(8′-adenosinyl)benzene and 8-(*p*-iodophenyl)adenosine were formed in this reaction, albeit in low yield (non-optimised). These compounds could be useful in supramolecular assembly or ligand design.

2′-Deoxyadenosine can also be arylated under the standard conditions by slight modification to the reaction conditions; at 120 °C substantial deglycosylation was observed, giving 8-phenyladenine (Scheme 4), reflecting the lower stability of 2′-deoxyribose. However, arylation worked well at 80 °C giving the coupled product in 84% yield.

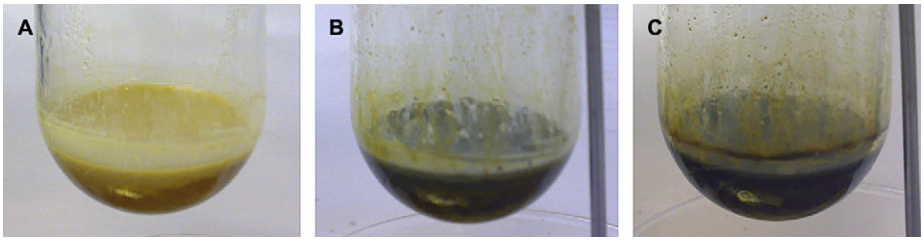
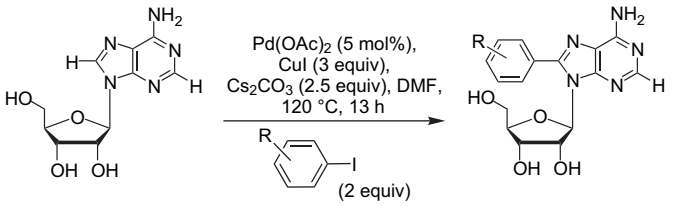


Figure 2. Colour changes during direct arylation of adenosine with iodobenzene (A: at 5 min; B: at 25 min; C: at 1.5 h).

Table 2
Direct arylation of adenosines with aryl halides



Entry	R	Yield[a]/%
1	4-Me	85
2	4-MeO	70
3	4-C(O)Me	48
4	4-F	44
5	4-CH_2OH	53
6	4-NH_2	42
7	2-CF_3	0
8	3-CF_3	66
9	4-CF_3	75
10	2-NO_2	0 (51)[b]
11	3-NO_2	34
12	4-NO_2	43
13	1-Napthyl	>95

[a] Yield obtained after chromatography on silica gel.
[b] The number in brackets refers to selective *N*6-mono-arylation.

their impact on the benchmark reaction (Scheme 2) with a view to gaining additional insight into the reaction mechanism.

2.1. On the involvement of amine

Most of the direct arylation reactions produced a strong amine odour, most likely due to degradation of DMF to give Me_2NH (and CO↑). To test the importance of the degradation process a standard reaction was performed in the presence of 2.5 equiv of Et_2NH. In this case the additive slowed down the catalytic turnover (38% yield). By contrast the reaction does proceed in the presence of 2.5 equiv of Et_2NH in the absence of Cs_2CO_3, albeit slowly and in low yield (18%).

2.2. On the involvement of carbon monoxide

To establish whether trace quantities of CO vide supra could be influencing these reactions, CO was generated in situ by employing $Co_2(CO)_8$, a reagent, which rapidly decomposes under thermal heating in polar solvents such as DMF and DMSO. Thus $Co_2(CO)_8$ (10 mol %) was added to the benchmark reaction at t=0. Upon heating rapid CO evolution was evident; after

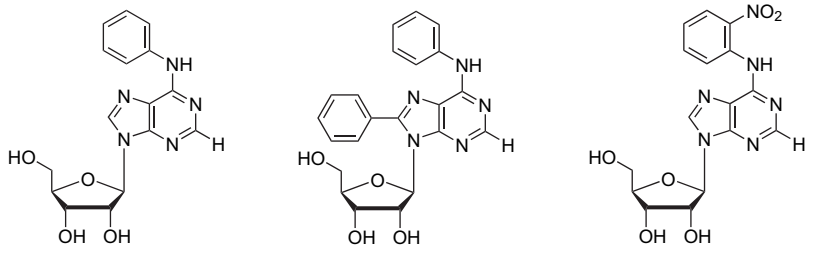
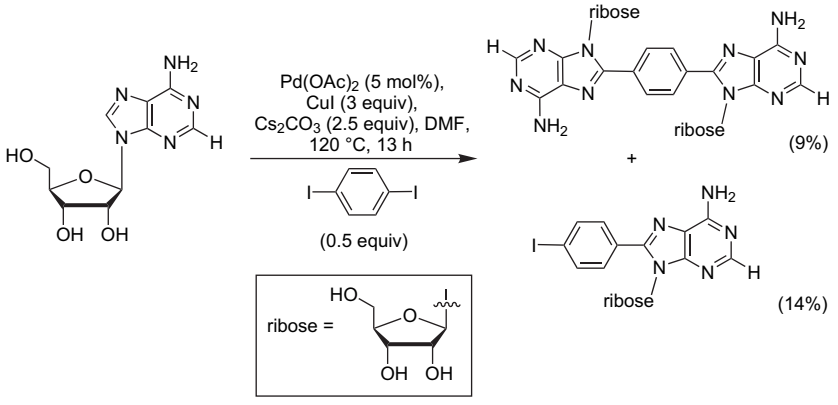


Figure 3. N-arylation products of adenosine.

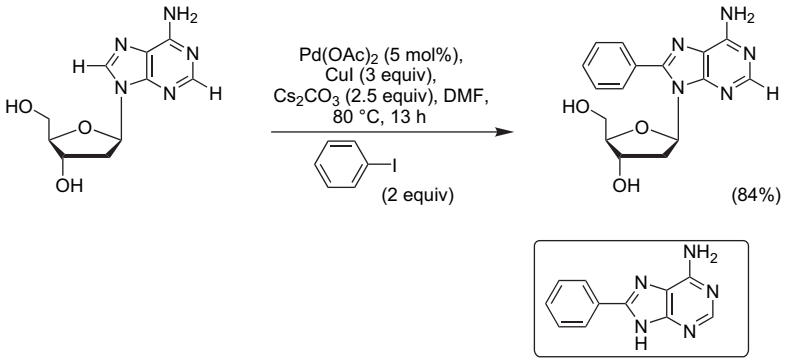


Scheme 3. Reaction of adenosine with 1,4-diiodobenzene.

2. Mechanistic studies

Having developed a generic set of conditions for the direct arylation of adenosine and 2′-deoxyadenosine we felt that some of the observations made in the study warranted further investigation. Several parameters have been probed to assess

ca. 5 min a palladium black precipitate was produced. This ‘palladium black’ was catalytically inactive, inferred by the finding that negligible direct arylation was seen over a period of 13 h; adenosine degradation accounts for the majority of the consumed material. Furthermore, a trace quantity of the N-arylation product was obtained in 3% yield (see Fig. 3).



Scheme 4. Arylation of 2′-deoxyadenosine.

2.3. On the involvement of heterogeneous and/or radical species

It has been noted that all the reactions from this study produced black heterogeneous mixtures after 13 h. Fagnou and Campeau reported similar observations in palladium-catalysed direct arylation reactions.[11b] Generally, it is well established that addition of Hg(0) poisons metal(0) heterogeneous catalysts,[23] through amalgamation of the metal catalyst or through surface adsorption. This is perhaps the most popular test for the homogeneous versus heterogeneous catalysis question.[24] The suppression of catalysis by a large excess of Hg(0), in a well-stirred solution, is seen as evidence for a heterogeneous catalyst. Where catalysis continues it is inferred that the reaction is homogeneous. It should be noted that the Hg(0) poison test is not a universal test for all metal catalysts; some caution is necessary as Hg(0) can react with certain mononuclear transition metal complexes.[25] General rules for the use of this test, and other means for addressing the homogeneous versus heterogeneous question in transition metal catalysed processes, have been clearly defined by Finke and co-workers.[26] The Hg(0) poison test has also been used to test for heterogeneous behaviour in related C–H activation processes mediated by $Pd(OAc)_2$, where no catalyst inhibition was observed.[27] Hg(0) (ca. 325 equiv) was added to the benchmark reaction after 25 min at 120 °C (~30% conversion to product by HPLC). Further conversion to product was recorded up to 45 min (~65–70%), thus Hg(0) does not quench the reaction {note: a deleterious secondary reaction of either Hg(0) or Hg(II) with 8-phenyladenosine was noticeable after 45 min (deglycosylation)}. The fact that the reaction continues in the presence of Hg(0) points to homogeneous species playing a key role in the reaction.

It is worthy of note that galvinoxyl radical,[28] a common test for the participation of radical mechanisms where addition of an exogenous radical is assumed to slow or stop a radical-mediated reaction, had no affect on the global efficacy of the benchmark reaction giving 8-phenyladenosine in 65% yield.

2.4. Effect of Pd loading

Sames and Lane reported that the arylation reactions of *N*-substituted indoles were accompanied by significant homocoupling of iodobenzene at higher Pd loadings.[29] For the direct arylation reactions described herein (at 120 °C), this was not an issue. Furthermore, on lowering the $Pd(OAc)_2$ loading to 0.5 mol %, a 51% yield of the arylated product was obtained. Lowering the loading further by an order of magnitude {0.05 mol % $Pd(OAc)_2$)} gave only a 9% yield.

2.5. Study by transmission electron microscopy (TEM) and X-ray photoelectron spectroscopy (XPS)

TEM has been widely used to characterise metal containing nanoparticles in a variety of different reactions.[30] Two 1 ml samples were removed from the benchmark reaction after 1.5 h for analysis by TEM. The first sample was concentrated under high vacuum at 40 °C to remove the DMF. The crude black solid was resuspended in ethanol and subjected to analysis by TEM. One concern was that in removing the DMF (a potential metal colloid stabiliser) we would be artificially favouring the formation of aggregated metal species. Thus to the second sample we added *N*-polyvinylpyrrolidone (PVP) (M_w=29,000; 20 monomer equivalents with respect to Pd) to stabilise any metal nanoparticles that were formed. A comparison of the TEM micrographs for each sample revealed similar sized metal containing nanoparticles (Fig. 4).

The nanoparticles contained within the unstabilised reaction sample were analysed further by X-ray photoelectron spectroscopy (XPS) to identify whether both Cu and Pd are present and to determine their oxidation states. Figure 5 shows the Pd 3d and Cu 2p regions, which revealed the presence of both Pd(0) and Pd(II) species with characteristic $3d_{5/2}$ binding energies of 335.9 and 337.8 eV, respectively, and a significant amount of Cu(I) with a $2p_{3/2}$ binding energy of 932.7 eV. Quantification of the Cu 2p and Pd 3d regions revealed that the Cu/Pd atomic ratio is ~19:1 (theoretical ratio=60:1). XPS is a surface technique, thus this difference can be explained by the presence of larger particles containing bulk Cu(I). The presence of mixed Pd–Cu species cannot be confirmed from XPS alone; however, the high Pd content might be attributed to Pd segregation to form a capped Pd–Cu particle. The presence of other higher oxidation state Cu species, such as those derived from Cu(II), can be ruled out due to the absence of any characteristic Cu 2p satellite peaks approximately 8 eV above the main photoelectron peak.[31]

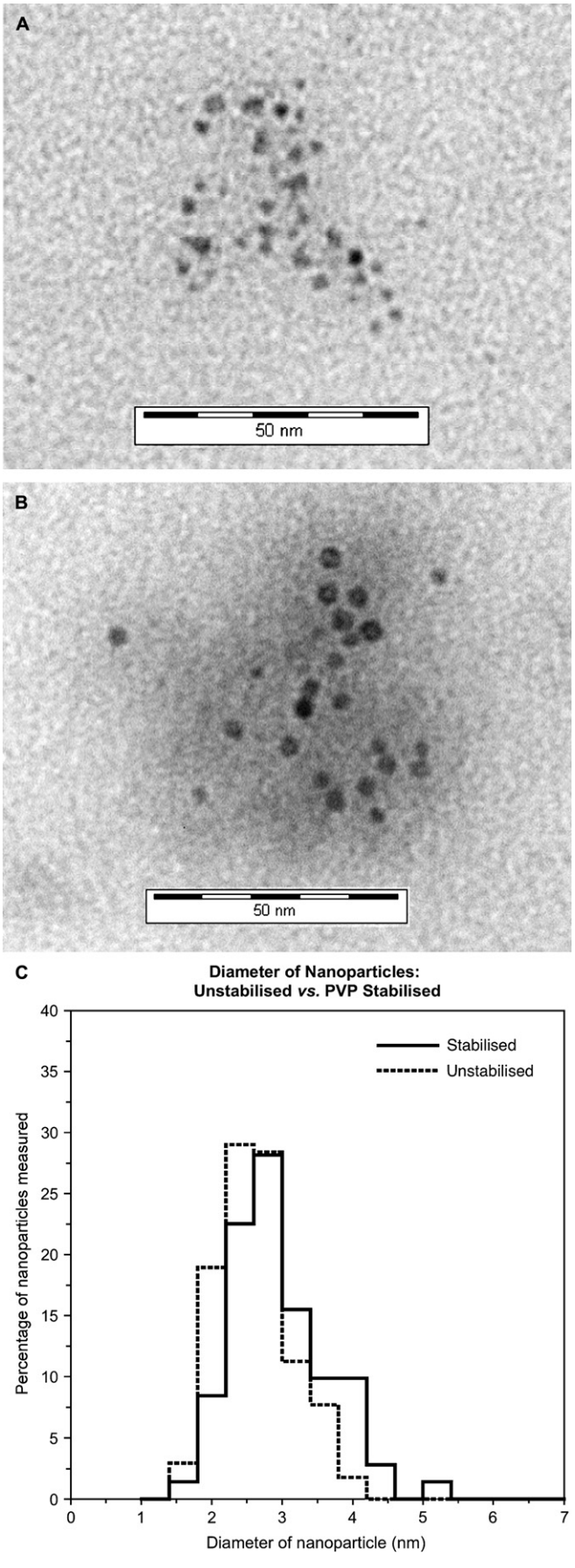


Figure 4. A: TEM micrograph of unstabilised metal containing nanoparticles. B: PVP stabilised metal containing nanoparticles. C: Percentage distribution of metal containing nanoparticles (by ImageJ; shown using KaleidaGraph).

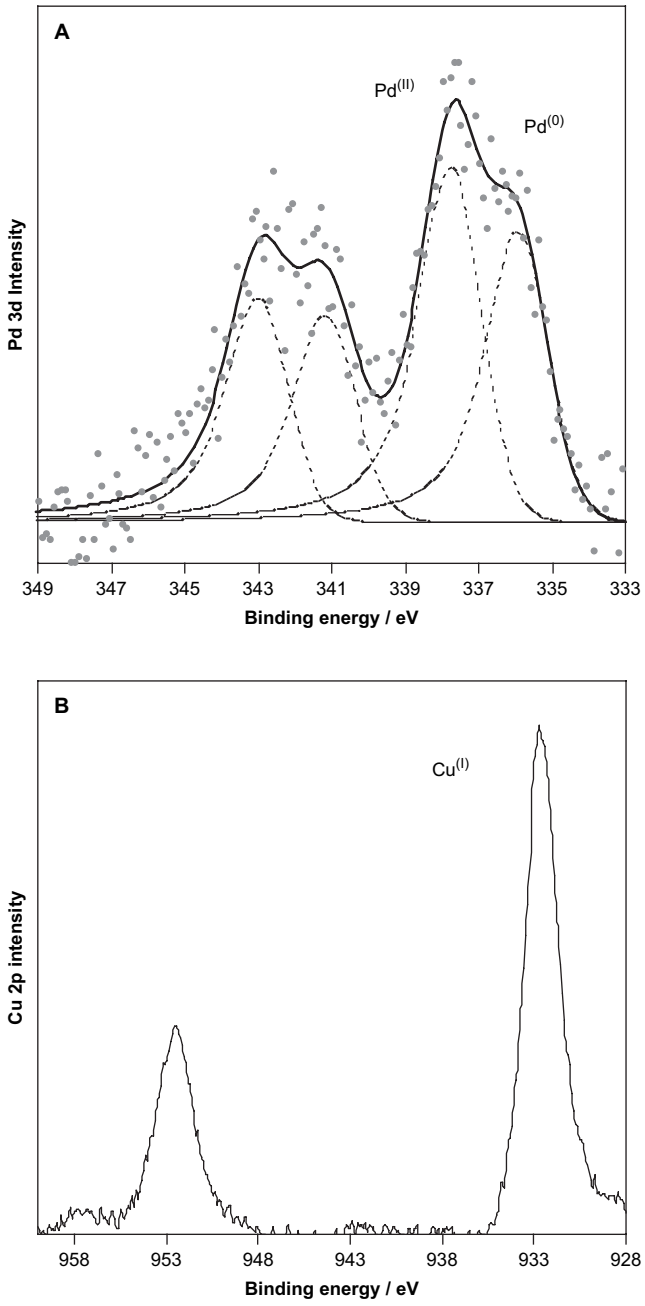
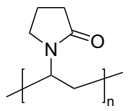


Figure 5. A: Pd 3d spectrum of post-reaction sample. B: Cu 2p spectrum of post-reaction sample.

2.6. Benchmark test using PVP stabilised palladium colloids

Palladium colloids stabilised by PVP were synthesised according to the method described by El-Sayed and Narayanan.[32] A characterised Pd–PVP colloid (average particle size=2 nm) was tested as a substitute for $Pd(OAc)_2$. The amount of Pd–PVP colloid added corresponds to 0.5 mol % Pd. Remarkably, Pd–PVP was an efficient mediator of the reaction producing the direct arylation product in 51% yield

(after 13 h). It is interesting to note that a larger Pd–PVP colloid (average particle size=3.4 nm) performed less well in the reaction (18% yield after 13 h), indicating that there is a particle size dependence on catalytic activity. Further studies are in progress to elucidate the origin of this phenomenon.



PVP (M_W = 29,000)

2.7. Additive effects: substituted pyridines

The addition of sub-stoichiometric amounts of electron-deficient pyridines has been shown to be beneficial for certain direct arylation processes.[33] It can be postulated that this additive stabilises catalytically active Pd(0) species[34] and may also increase the reactivity (electrophilicity) of Pd(II) species.[33a] We have investigated a range of substituted pyridines to assess their effect on the reaction of adenosine and iodobenzene under the optimised reaction conditions (Table 3). Addition of 3-nitropyridine to the generic reaction gave the arylated product in >95% yield (entry 1). The other pyridines lowered the yield of the *C*-arylated product as compared to the benchmark reaction (entries 2–5); the electron-releasing substituents on the pyridine appeared to reduce the global efficacy of the reaction (entries 4 and 5). More critical was the observation that despite the effectiveness of 3-nitropyridine as an additive in the benchmark reaction other aryl halide reactions did not benefit from its addition. For example, 4-acetylphenyl iodide and 3-trifluoromethylphenyl iodide reacted with adenosine in yields of 23 and 47%, respectively, which are markedly lower than the yields observed in the absence of this additive {compare entries 3 and 8 (Table 1)}. The beneficial effect of the 3-nitropyridine on direct arylation appears to be substrate dependent.

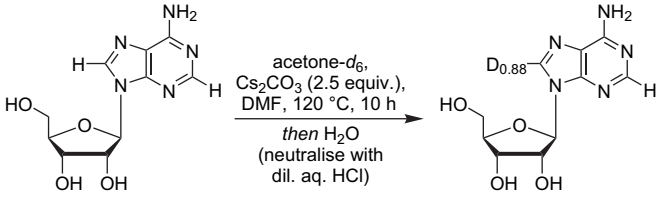
2.8. Deprotonation of adenosine at C8

Deprotonation at C8 of adenosine occurs under 'arylation conditions' in the absence of metal. This was confirmed by a control experiment using acetone-d_6 as a source of deuterium in the presence of Cs_2CO_3 in DMF at 120 °C for 10 h (Scheme 5). A near complete exchange occurred at C8 within 10 h at this temperature and there was no evidence for deuterium incorporation at C2.

Table 3
Effect of substituted pyridines on the direct arylation of adenosine with iodobenzene[a]

Entry	Additive (40 mol %)	Yield[b]/%
1	3-Nitropyridine	95
2	3-Methoxypyridine	44
3	Pyridine	50
4	4-Dimethylaminopyridine	42
5	4-Methoxypyridine	30
6	Nitrobenzene	48

[a] Reaction conditions as for Scheme 2.
[b] Yield obtained after chromatography on silica gel.



Scheme 5. Deprotonation at the C8 position of adenosine.

3. Mechanistic discussion

Adenosine, as a substrate, is a complicated ligand with several possible coordination modes to palladium.[35] Monomers such as **I** are known (Fig. 6), as are dimeric and higher order complexes, where *N*7 is the dominant ligating atom. Similar copper complexes can also be formed (e.g., **II**).

In terms of the reaction mechanism an electrophilic substitution, via intermediate **III**, can be proposed, in accord with the proposals made by Miura (in the arylation of thiazoles and imidazoles),[36] Gevorgyan (in the arylation of indolizines),[37] and Daugulis (for arylations of caffeine and other electron-rich heterocycles).[10] However, counting against this is the susceptibility of intermediate **III** towards deglycosylation. Amine coordination[38] (from the adenine ring system) to Cu(I) aids *activation* of the C–H bond (as in structure **II**). The stoichiometric requirement for Cu(I) is key to the direct arylation of adenosine, which mirrors the observations made by Bellina, Rossi and co-workers[18] for the direct arylation of imidazoles. These researchers proposed that the imidazole exists in equilibrium with the corresponding organocuprate derivative (not directly observed). The in situ generation of such species is supported by literature precedent,[39] which shows that Cu(I) salts can metallate acidic C–H bonds, specifically the C-2 position of imidazoles, which are expected to possess similar acidity to the C-8 position in adenosine. Whilst CuI would be expected to act as a co-catalyst in this reaction it is likely that higher concentrations are necessary to increase the concentration of the

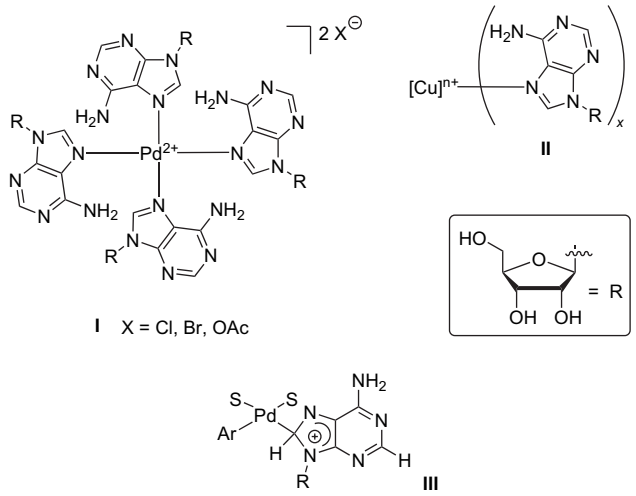


Figure 6. Possible intermediates in the direct arylation of purines.

organocuprate in solution. From our study it is pertinent to point out that the XPS data indicates the presence of Cu(I) species only.

The negative Hg(0) poison test strongly supports the involvement of homogeneous catalytic species in the direct arylations of adenosine. However, metal containing nanoparticles are formed under the reaction conditions. In classical cross-coupling reactions an inverse correlation, e.g., higher turnover frequencies at lower palladium catalyst loadings {for $Pd(OAc)_2$ and various palladacycles in Heck, Sonogashira and Suzuki cross-couplings}, has been used as circumstantial evidence implicating palladium clusters/nanoparticles in catalytic turnover.[40] Moreover at lower 'global' palladium concentrations there is a higher concentration of mononuclear species capable of promoting the 'homogenous' cross-coupling reaction. Whilst the palladium/substrate ratio is important, the observations made in our study indicate that relatively high palladium loadings are necessary for optimum conversions. In a Heck reaction[41] of bromobenzene and *n*-butyl acrylate {mediated by $Pd(OAc)_2$ in NMP at 135 °C} negligible catalytic turnover was observed at a concentration of palladium similar to that used in the direct arylations of adenosine. Oxidative addition is proposed to be rate limiting in the case of bromobenzene, leading to aggregation of Pd(0), a particular problem at >1 mol % $Pd(OAc)_2$ catalyst loadings. In the case of iodobenzene, oxidative addition is fast and gives a higher concentration of 'Ph–Pd–I'. Moreover, adenosine is capable of stabilising such a complex (via *N*7 coordination to Pd), as is the solvent DMF (and a pyridine additive). Such N-coordination will increase arylation efficacy; the Ullmann-type homocoupling of iodobenzene, formed via halide bridged Pd(II) dimers/disproportionation[42] or via '$Ar_2L_2PdX^-$' species,[43] would be slowed down in that case.

The beneficial effect of in situ generated Me_2NH {formed by degradation of DMF, also producing CO(g)} remains unclear at this stage. Sames and co-workers[44] reported that addition of $(^iPr)_2NH$ dramatically improved the yields obtained in the Pd-catalysed C2-arylation of indoles by increasing the rate of oxidative addition of the aryl halide to Pd(0). A higher concentration of the 'Ph–Pd–X' species also led to increased amounts of biphenyl (for PhBr). It remains a possibility that a sub-stoichiometric amount of Me_2NH could assist the direct arylations of adenosine. Addition of 10 mol % $Co_2(CO)_8$ to the benchmark reaction led to rapid CO evolution and rapid palladium black formation, which was catalytically inactive (for C-arylation). CO is an excellent π-acceptor ligand, which will reduce the reactivity of Pd(0) species. The study on PVP–Pd stabilised colloids revealed that such species are catalytically active under the benchmark conditions. These heterogenised sources release catalytically active Pd(0) into solution (either monomeric or small clusters) allowing the homogeneous reaction to take place.[45] In the direct arylations mediated by $Pd(OAc)_2$, the TEM micrographs reveal that metal containing nanoparticles are formed, which are ca. 3–4 nm (after 1.5 h; ~65% conversion); a key question remaining unanswered is what is their role in the reaction?

The deprotonation experiment, performed in the absence of metal, indicates that H/D exchange takes place under arylation conditions. Based on the assumption that ring-opening[46] of the purine heterocycle is unlikely, we propose that Cu(I) is able to assist deprotonation at C8 in adenosine. A base-assisted deprotonation reaction leads to the in situ generation of an organocuprate (path A, Scheme 6), which then participates in transmetallation with the Pd(II) intermediate species in the catalytic cycle. Isomerisation and reductive elimination reveal the arylated adenosine, regenerating Pd(0) in the process. Aggregation of Pd(0) species (and potential Cu species) emerges as an issue during the latter stages of the reaction, where the concentration of iodobenzene is low, a point supported by the formation of metal containing nanoparticles vide supra.

4. Conclusion

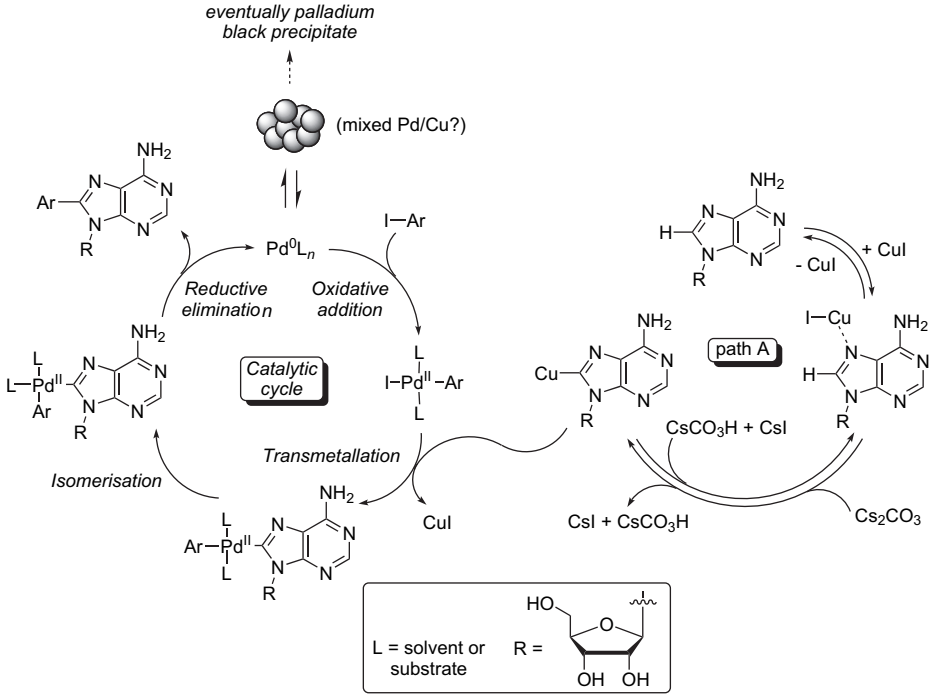
In summary, valuable reaction conditions for the direct aryl functionalisation of unprotected adenosines have been developed. Deglycosylation has been identified as a major issue using similar conditions to those described previously for protected adenines and other direct arylation processes. The above synthetic protocol allows C8-arylated adenosines to be obtained in one step. In Suzuki–Miyaura cross-couplings there is an absolute requirement for the prefunctionalisation of adenosine (bromination), which subsequently requires the use of an organoboronic acid. A pragmatic point to consider is that stoichiometric quantities of CuI are required for direct arylation of adenosine. Thus, one has to remain open-minded about what type of C8-aryl functionalisation might be required for a given target and/or application—Suzuki–Miyaura cross-coupling will be a competitive alternative for certain structures. The direct arylation protocol is not intended to replace Suzuki–Miyaura cross-coupling procedures, rather it serves to complement this *key* synthetic methodology.

Further mechanistic studies to confirm links between classical cross-coupling and direct arylation coupling processes are ongoing in our laboratories. Perhaps more generally, some of the observations reported in this study highlight the challenges faced in the palladium catalysis field, particularly in developing practical synthetic methodologies for the production of more challenging molecular architectures, pharmaceutical compounds and other types of fine chemicals.

5. Experimental

5.1. General details

Proton (^1H, 400 MHz) NMR spectra were recorded on an Oxford AS400 spectrometer. Samples were prepared using approximately 10 mg of compound dissolved in 0.7 ml of DMSO-d_6. Chemical shifts were referenced to residual undeuterated DMSO in DMSO-d_6 at δ=2.5 ppm. All spectra were reprocessed using MestRec version 4.9.9.6 on a PC (SineBell apodization was used to obtain detailed proton spin–spin coupling patterns and constants). Carbon (^{13}C, 100.6 MHz) NMR spectra were recorded on the same NMR spectrometer. MS (mass spectrometry) spectra were recorded on a Bruker Daltronics micrOTOF machine with electrospray ionisation



Scheme 6. Proposed mechanism for the direct arylation of adenosine mediated by Pd/Cu in the presence of Cs_2CO_3.

(ESI). The mass to charge ratio, *m*/*z*, of the protonated molecular ion is reported with any major fragments formed. IR (infrared) spectra were recorded on a Perkin–Elmer Paragon 1000PC FT-IR spectrometer. UV–vis (ultraviolet–visible) spectroscopy was performed on a Jasco V-560 UV–vis spectrophotometer and temperature controlled at 20 °C using a water bath; spectra were taken in DMSO as approximately 50 μM solutions in a quartz cuvette (λ_{max} is reported). Melting points (mp) were recorded using a Stuart digital SMP3 machine. Reaction progress was monitored by TLC (thin layer chromatography) on a silica gel matrix on aluminium, or plastic supported plates, with a fluorescent indicator at 254 nm. High Performance Liquid Chromatography (HPLC) was used to monitor the progress of the direct arylation reactions using an Agilent 1100 system with a DAD (diode array detector) and a Zorbax Eclipse XDB-C18 5 μm reverse-phase column. Samples for HPLC analysis (50 μl) were removed by gas-tight syringe and added directly to MeOH (2 ml). An aliquot of this solution (100 μl) was then added to water (2 ml), which had been filtered through a MILLEX®GP filter unit (0.22 μm, Millipore Ltd.). An aliquot of the aqueous sample (50 μl) was analysed directly by HPLC using mixtures of HPLC grade water and methanol as the eluants, while monitoring the absorbance of the effluent at 254 nm. Common abbreviations used: EtOAc=ethyl acetate; DMF=*N*,*N*-dimethylformamide; MeOH=methanol). Commercial chemicals were purchased from Sigma–Aldrich or Alfa Aesar.

5.2. Transmission electron microscopy (TEM)

Metal containing nanoparticles were characterised using a FEI Tecnai 12 Biotwin High Contrast Electron Microscope operated at 120 keV. Prior to imaging, the samples were resuspended in ethanol and pipetted onto a gold grid.

5.3. X-ray photoelectron spectrometry

XPS measurements were performed using a Kratos AXIS HSi instrument equipped with a charge neutraliser and Mg Kα X-ray source. Spectra were recorded at normal emission using an analyser pass energy of 20 eV and a X-ray power of 144 W. Spectra were energy referenced to the valence band and adventitious carbon. Quantification was performed using appropriate elemental relative sensitivity factors.

5.4. General procedure for direct arylation

Adenosine (1.0 equiv, 500 mg, 1.87 mmol), Cs_2CO_3 (2.5 equiv, 1.53 g, 4.68 mmol), CuI (3.0 equiv, 1.07 g, 5.61 mmol), $Pd(OAc)_2$ (5 mol %, 21 mg, 94 μmol) and the aryl iodide (2.0 equiv, 3.74 mmol) were added to a vacuum dried Schlenk tube. The reaction vessel was evacuated under high vacuum at 25 °C with stirring and then flushed with N_2 (three cycles). DMF (10 ml) was then added and the reaction was heated in an oil bath at 120 °C, and stirred continuously for 13 h. The mixture was then allowed to cool to 25 °C and 1 M HCl solution (10 ml) added. The pH was then adjusted to 6.5 with 1 M NaOH and the aqueous solution extracted with ^{i}PrOH/EtOAc (1:9, v/v, 5×50 ml) mixture. The organic extracts were combined, dried ($MgSO_4$), filtered and reduced in vacuo to yield a thick gum, which was dried under high vacuum to give a powder. This powder was re-dissolved/suspended in MeOH (20 ml), reduced in vacuo and adsorbed onto silica gel (approximately 0.5 g). A short silica gel column

(approximately 10 g) was eluted using CH_3OH/CH_2Cl_2 (2:98 v/v, moving in stepwise increments to 10:90 by gradient elution). The fractions containing the product were combined and the solvents removed in vacuo. The final pure product was isolated and dried under high vacuum.

5.4.1. 8-Phenyladenosine

Light yellow solid (410 mg, 65%), mp 142–143 °C (decomp.); UV–vis λ_{max} 289 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (br s, 1H), 7.76 (m, 2H), 7.60 (m, 3H), 7.54 (br s, 2H), 5.83 (dd, J=3.4, 9.2, 1H), 5.76 (d, J=7.0, 1H), 5.49 (d, J=6.5, 1H), 5.18 (ddd, J=4.7, 7.0, 6.5, 1H), 5.15 (d, J=4.4, 1H), 4.16 (ddd, J=1.9, 4.7, 4.4, 1H), 3.94 (ddd, J=1.9, 3.5, 3.5, 1H), 3.70 (ddd, J=3.4, 3.5, 12.3, 1H), 3.56 (ddd, J=3.5, 9.2, 12.3, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.2, 152.0, 150.9, 149.7, 130.1, 129.6, 129.4, 128.7, 119.2, 89.0, 86.7, 71.2, 71.1, 62.3; ESI-MS m/z 344 [100% $(MH)^+$], 212 [5.6% $(M-\beta$-D-ribose+2H$)^+$]; HR (MH^+) 344.1354 (calcd for $C_{16}H_{18}O_4N_5$ 344.1353).

5.4.2. 8-p-Tolyladenosine

Light pink solid (570 mg, 85%), mp 144–147 °C (decomp.); UV–vis λ_{max} 290 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (br s, 1H), 7.64 (d, J=8.1, 2H), 7.47 (br s, 2H), 7.40 (d, J=8.1, 2H), 5.83 (dd, J=3.5, 9.4, 1H), 5.74 (d, J=7.1, 1H), 5.47 (d, J=6.7, 1H), 5.17 (ddd, J=5.0, 6.7, 7.1, 1H), 5.14 (d, J=4.7, 1H), 4.16 (ddd, J=1.9, 4.7, 5.0, 1H), 3.93 (ddd, J=1.9, 3.7, 3.6, 1H), 3.69 (ddd, J=3.5, 3.6, 12.5, 1H), 3.54 (ddd, J=3.7, 9.4, 12.5, 1H), 2.41 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.1, 151.9, 151.1, 149.8, 139.9, 129.5, 129.3, 126.5, 119.5, 89.1, 86.6, 71.2, 71.1, 62.3, 21.0; ESI-MS m/z 358 [100% $(MH)^+$], 226 [31.2% $(M-\beta$-D-ribose+2H$)^+$]; HR (MH^+) 358.1508 (calcd for $C_{17}H_{20}O_4N_5$ 358.1510).

5.4.3. 8-p-Methoxyphenyladenosine

Light grey solid (487 mg, 70%), mp 162–164 °C (decomp.); UV–vis λ_{max} 291 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (br s, 1H), 7.60 (d, J=8.9, 2H), 7.47 (br s, 2H), 7.14 (d, J=8.9, 2H), 5.85 (dd, J=3.4, 9.3, 1H), 5.75 (d, J=6.9, 1H), 5.47 (d, J=6.6, 1H), 5.17 (ddd, J=5.0, 6.9, 6.6, 1H), 5.15 (d, J=4.6, 1H), 4.16 (ddd, J=1.9, 5.0, 4.6, 1H), 3.94 (ddd, J=1.9, 3.5, 3.5, 1H), 3.85 (s, 3H), 3.69 (ddd, J=3.4, 3.5, 12.3, 1H), 3.56 (ddd, J=3.5, 9.3, 12.3, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 160.6, 156.0, 151.7, 150.9, 149.7, 131.1, 121.5, 119.0, 114.2, 89.0, 86.6, 71.2, 71.1, 62.3, 55.3; ESI-MS m/z 374 [100% $(MH)^+$], 242 [1.3% $(M-\beta$-D-ribose+2H$)^+$]; HR (MH^+) 374.1461 (calcd for $C_{17}H_{20}O_5N_5$ 374.1459).

5.4.4. 8-p-Acetophenyladenosine

Brown solid (348 mg, 48%), mp 154–156 °C (decomp.); UV–vis λ_{max} 316 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (br s, 1H), 8.16 (d, J=8.2, 2H), 7.91 (d, J=8.2, 2H), 7.65 (br s, 2H), 5.79 (1H, m, 1H), 5.75 (d, J=7.1, 1H), 5.50 (d, J=6.8, 1H), 5.21–5.16 (br m, 2H), 4.17 (m, 1H), 3.96 (m, 1H), 3.71 (m, 1H), 3.56 (m, 1H), 2.66 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 197.5, 156.3, 149.9, 149.8, 137.5, 133.4, 129.8, 128.4, 119.4, 89.1, 86.7, 71.2, 70.9, 62.1, 26.8 (15 of a possible 16 carbon resonances observed); ESI-MS m/z 386 [100% $(MH)^+$], 254 [31.2% $(M-\beta$-D-ribose+2H$)^+$]; HR (MH^+) 386.1450 (calcd for $C_{18}H_{20}O_5N_5$ 386.1459).

5.4.5. 8-p-Fluorophenyladenosine

Light brown solid (296 mg, 44%), mp 151–153 °C (decomp.); UV–vis λ_{max} 288 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (br s, 1H), 7.80 (m, 2H), 7.56 (br s, 2H), 7.45 (m, 2H), 5.78 (m, 1H), 5.71 (d, J=7.2, 1H), 5.48 (d, J=6.0, 1H), 5.15 (m, 2H), 4.17 (m, 1H), 3.95 (m, 1H), 3.70 (m, 1H), 3.55 (m, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 163.1 (d, J_{CF}=248), 155.5, 151.6, 150.3, 149.6, 132.0 (d, J_{CF}=9), 125.7, 119.0, 115.9 (d, J_{CF}=22), 89.1, 86.7, 71.2, 70.9, 62.1; ESI-MS m/z 362 [100% $(MH)^+$], 230 [55.1% $(M-\beta$-D-ribose+2H$)^+$]; HR (MH^+) 362.1257 (calcd for $C_{16}H_{17}O_4N_5F$ 362.1259).

5.4.6. 8-p-Hydroxybenzyladenosine

Extended elution from the silica gel column was required. Light yellow solid (370 mg, 70%), mp 173–176 °C (decomp.); UV–vis λ_{max} 290 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (br s, 1H), 7.71 (d, J=8.4, 2H), 7.52 (d+br s, J=8.4, 4H), 5.85 (dd, J=3.4, 9.3, 1H), 5.75 (d, J=7.0, 1H), 5.48 (d, J=6.6, 1H), 5.38 (t, J=5.7, 1H), 5.18 (ddd, J=5.2, 6.6, 7.0, 1H), 5.16 (d, J=4.2, 1H), 4.61 (d, J=5.7, 2H), 4.17 (m, 1H), 3.94 (ddd, J=1.8, 3.7, 3.6, 1H), 3.70 (ddd, J=3.4, 3.6, 12.2, 1H), 3.55 (ddd, J=3.7, 9.3, 12.2, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.1, 151.9, 151.0, 149.7, 144.7, 129.4, 127.6, 126.5, 119.0, 89.0, 86.6, 71.1, 71.1, 62.4, 62.3; ESI-MS m/z 374 [100% $(MH)^+$], 242 [29.5% $(M-\beta$-D-ribose+2H$)^+$]; HR (MH^+) 374.1471 (calcd for $C_{17}H_{20}O_5N_5$ 374.1459).

5.4.7. 8-p-Aminophenyladenosine

The reaction mixture was extracted with the organic solvent 10 times; an extended elution from the silica gel column was required. Brown solid (282 mg, 42%), mp 176–180 °C (decomp.); UV–vis λ_{max} 311 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (br s, 1H), 7.43 (d, J=8.6, 2H), 7.36 (br s, 2H), 6.68 (d, J=8.6, 2H), 5.89 (dd, J=3.4, 9.5, 1H), 5.80 (d, J=7.2, 1H), 5.66 (br s, 2H), 5.46 (d, J=6.5, 1H), 5.15 (m+d, J=4.2, 2H), 4.17 (m, 1H), 3.93 (m, 1H), 3.70 (ddd, J=3.4, 3.4, 12.5, 1H), 3.55 (ddd, J=3.5, 9.5, 12.5, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 155.7, 152.2, 151.2, 150.5, 149.7, 130.7, 119.0, 115.8, 113.3, 89.0, 86.5, 71.1, 71.1, 62.4; ESI-MS m/z 359 [100% $(MH)^+$], 227 [60.4% $(M-\beta$-D-ribose+2H$)^+$]; HR (MH^+) 359.1454 (calcd for $C_{16}H_{19}O_4N_6$ 359.1462).

5.4.8. 8-m-Trifluoromethylphenyladenosine

Light yellow solid (507 mg, 66%), mp 163–167 °C (decomp.); UV–vis λ_{max} 296 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (br s, 1H), 8.09 (s, 1H), 8.04 (d, J=7.8, 1H), 7.95 (d, J=7.8, 1H), 7.86 (t, J=7.8, 1H), 5.77 (dd, J=3.6, 9.1,

1H), 5.70 (d, *J*=7.0, 1H), 5.50 (d, *J*=6.5, 1H), 5.15 (d, *J*=4.6, 1H), 5.14 (ddd, *J*=5.0, 7.0, 6.5, 1H), 4.14 (ddd, *J*=1.9, 4.6, 5.0, 1H), 3.93 (ddd, *J*=1.9, 3.6, 3.6, 1H), 3.69 (ddd, *J*=3.6, 3.6, 12.4, 1H), 3.53 (ddd, *J*=3.6, 9.1, 12.4, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.3, 152.4, 149.9, 149.3, 133.4, 130.4, 130.1, 129.6 (q, J_{CF}=33), 126.7, 126.2, 123.8 (q, J_{CF}=272), 119.2, 89.1, 86.9, 71.3, 71.0, 62.2; ESI-MS *m/z* 412 [100% $(MH)^+$]; HR (MH^+) 412.1234 (calcd for $C_{17}H_{17}O_4N_4F_3$ 412.1227).

5.4.9. 8-p-Trifluoromethylphenyladenosine

Brown solid (572 mg, 75%), mp 187–189 °C (decomp.); UV–vis λ_{max} 301 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (br s, 1H), 7.99 (br s, 4H), 7.63 (br s, 2H), 5.79 (dd, *J*=3.5, 9.1, 1H), 5.72 (d, *J*=7.1, 1H), 5.49 (d, *J*=6.8, 1H), 5.20 (d, *J*=4.7, 1H), 5.17 (ddd, *J*=5.0, 6.8, 7.1, 1H), 4.16 (ddd, *J*=1.8, 4.7, 5.0, 1H), 3.96 (ddd, *J*=1.8, 3.7, 3.7, 1H), 3.71 (ddd, *J*=3.5, 3.7, 12.3, 1H), 3.53 (ddd, *J*=3.7, 9.1, 12.3, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 149.7, 149.3, 133.2, 130.4, 130.1 (q, J_{CF}=32), 129.91, 125.64, 125.60, 125.48, 123.8 (q, J_{CF}=273), 89.04, 86.81, 71.19, 70.87, 62.09; ESI-MS *m/z* 412 [100% $(MH)^+$], 280 [2.8% $(M-\beta\text{-D-ribose}+2H)^+$]; HR ($MH^+$) 412.1236 (calcd for $C_{17}H_{17}O_4N_4F_3$ 412.1227).

5.4.10. N6-o-Nitrophenyladenosine

Orange solid (370 mg, 51%), mp 121–124 °C (decomp.); UV–vis λ_{max} 283 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (br s, 1H), 8.65 (s, 1H), 8.41 (s, 1H), 8.40 (dd, *J*=1.2, 8.4, 1H), 8.12 (dd, *J*=1.5, 8.3, 1H), 7.78 (ddd, *J*=1.4, 7.2, 8.4, 1H), 7.33 (ddd, *J*=1.2, 7.4, 8.4, 1H), 5.97 (d, *J*=5.9, 1H), 5.54 (d, *J*=6.1, 1H), 5.25 (d, *J*=4.8, 1H), 5.22 (dd, *J*=5.1, 6.1, 1H), 4.64 (dd, *J*=5.9, 11.0, 1H), 4.18 (ddd, *J*=3.4, 4.9, 4.9, 1H), 3.98 (ddd, *J*=3.7, 3.7, 3.7, 1H), 3.69 (ddd, *J*=4.5, 4.5, 12.0, 1H), 3.56 (ddd, *J*=3.9, 6.6, 12.0, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 151.6, 151.0, 149.8, 141.9, 140.0, 134.7, 133.6, 125.4, 124.5, 123.7, 121.0, 87.8, 85.8, 73.6, 70.4, 61.4; ESI-MS *m/z* 389 [100% $(MH)^+$], 344 [3.8% $(M-NO_2+2H)^+$], 257 [17.0% $(M-\beta\text{-D-ribose}+2H)^+$]; HR ($MH^+$) 389.1196 (calcd for $C_{16}H_{17}O_6N_5$ 389.1204).

5.4.11. 8-m-Nitrophenyladenosine

Yellow solid (245 mg, 34%), mp 203–207 °C (decomp.); UV–vis λ_{max} 280 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (dd, *J*=1.7, 2.2, 1H), 8.44 (ddd, *J*=1.0, 2.2, 8.0, 1H), 8.21 (ddd, *J*=1.0, 1.7, 8.0, and overlapping br s, 2H), 7.91 (t, *J*=8.0, 1H), 7.65 (br s, 2H), 5.79 (dd, *J*=3.7, 9.1, 1H), 5.74 (d, *J*=7.0, 1H), 5.53 (d, *J*=6.5, 1H), 5.20 (d, *J*=4.9, 1H), 5.15 (ddd, *J*=5.1, 6.5, 7.0, 1H), 4.17 (ddd, *J*=2.0, 4.9, 5.1, 1H), 3.97 (ddd, *J*=2.0, 3.7, 3.7, 1H), 3.70 (ddd, *J*=3.7, 3.7, 12.4, 1H), 3.56 (ddd, *J*=3.7, 9.1, 12.4, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.4, 152.5, 149.9, 148.6, 147.9, 135.6, 130.8, 130.6, 124.8, 124.3, 119.2, 89.1, 86.9, 71.4, 70.9, 62.1; ESI-MS *m/z* 389 [100% $(MH)^+$], 257 [94.3% $(M-\beta\text{-D-ribose}+2H)^+$]; HR ($MH^+$) 389.1204 (calcd for $C_{16}H_{17}O_6N_5$ 389.1204).

5.4.12. 8-p-Nitrophenyladenosine

Yellow solid (311 mg, 43%), mp 233–238 °C (decomp.); UV–vis λ_{max} 249 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, *J*=8.9, 2H), 8.19 (s, 1H), 8.04 (d, *J*=8.9, 2H), 7.66 (br s, 2H), 5.76 (dd, *J*=3.7, 9.1, 1H), 5.74 (d, *J*=7.0, 1H), 5.50 (d, *J*=6.7, 1H), 5.21 (d, *J*=4.6, 1H), 5.16 (ddd, *J*=5.1, 6.7, 7.0, 1H), 4.17 (ddd, *J*=2.0, 4.6, 5.1, 1H), 3.97 (ddd, *J*=2.0, 3.7, 3.7, 1H), 3.71 (ddd, *J*=3.7, 3.7, 12.4, 1H), 3.57 (ddd, *J*=3.7, 9.1, 12.4, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.4, 152.6, 150.0, 148.7, 148.1, 135.4, 130.9, 123.9, 119.4, 89.1, 86.9, 71.3, 70.8, 62.1; ESI-MS *m/z* 389 [100% $(MH)^+$], 257 [44.7% $(M-\beta\text{-D-ribose}+2H)^+$]; HR ($MH^+$) 389.1191 (calcd for $C_{16}H_{17}O_6N_5$ 389.1204).

5.4.13. 8-1-Napthyladenosine

Light yellow solid (735 mg, 99%), mp 173–177 °C (decomp.); UV–vis λ_{max} 286 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (br s, 1H), 8.17 (t, *J*=5.0, 1H), 8.07 (dd, *J*=1.5, 8.1, 1H), 7.73 (m, 1H), 7.69 (m, 2H), 7.61 (ddd, 1.3, 6.8, 8.1, 1H), 7.55 (ddd, *J*=1.5, 6.8, 8.3, 1H, overlapping with br s, 2H), 5.89 (br m, 1H), 5.36 (d, *J*=7.3, 1H), 5.32 (br m, 1H), 5.06 (br m, 1H), 4.97 (d, *J*=4.1, 1H), 4.05 (m, 1H), 3.83 (m, 1H), 3.67 (ddd, *J*=3.5, 3.5, 12.3, 1H), 3.54 (ddd, *J*=3.2, 9.3, 12.3, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.3, 152.2, 149.4, 149.4, 133.1, 131.8, 130.5, 128.4, 127.3, 126.9, 126.7, 125.4, 125.2, 119.4, 89.5, 86.7, 71.1, 71.1, 62.3 (19 resonances of a possible 20 observed); ESI-MS *m/z* 394 [100% $(MH)^+$], 262 [23.1% $(M-\beta\text{-D-ribose}+2H)^+$]; HR ($MH^+$) 394.1512 (calcd for $C_{20}H_{20}O_4N_5$ 394.1510).

5.5. Reaction of adenosine with 1,4-diiodobenzene

The general direct arylation procedure was followed using 0.5 equiv of 1,4-diiodobenzene (308 mg, 0.94 mmol) with respect to adenosine (0.5 g, 1.87 mmol, 1 equiv). The yields are based on 1,4-diiodobenezene (limiting substrate).

5.5.1. Data for 1,4-di-(8′-adenosinyl)benzene

Light brown solid (49 mg, 9%), mp 188–191 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (br s, 2H), 7.75 (m, 2H), 7.60 (m, 2H), 7.56 (br s, 4H), 5.82 (dd, *J*=3.5, 9.2, 2H), 5.76 (d, *J*=7.2, 2H), 5.50 (d, *J*=6.4, 2H), 5.18 (m, 2H), 5.17 (d, *J*=4.4, 2H), 4.16 (m, 2H), 3.94 (ddd, *J*=1.9, 3.5, 3.5, 2H), 3.70 (ddd, *J*=3.5, 3.5, 12.4, 2H), 3.55 (ddd, *J*=3.5, 9.2, 12.4, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.2, 152.0, 150.9, 149.7, 130.1, 129.6, 129.3, 128.7, 89.0, 86.7, 71.2, 71.0, 62.2 (13 of a possible 14 carbon resonances observed); ESI-MS *m/z* 631 [17.9% $(MNa)^+$], 609 [17.4% $(MH)^+$], 477 [94.9% $(M-\beta\text{-D-ribose}+2H)^+$], 345 [100% $(M-2\beta\text{-D-ribose}+3H)^+$], 212 [68.5% $(M-\beta\text{-D-ribose-adenosine}+3H)^+$]; HR ($MH^+$) 631.1982 (calcd for $C_{26}H_{28}O_8N_{10}Na$ 631.1984). A trace quantity of the N^6-phenyl derivative was detected by ESI-MS only at *m/z* 685 [9.8% $(M^{N6\text{-Ph}}H)^+$] and 553 [19.1% $(M^{N6\text{-Ph}}-\beta\text{-D-ribose}+2H)^+$] (this is not visible by NMR spectroscopy).

5.5.2. Data for 8-p-iodophenyladenosine

Light yellow solid (62 mg, 14%), mp 148–150 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6, selected data) δ 8.16 (s, 1H), 7.75 (m, 2H), 7.60 (m, 2H), 7.53 (br s, 2H), 5.83 (dd, J=3.4, 9.4, 1H), 5.75 (d, J=6.6, 1H), 5.49 (d, J=6.4, 1H), 5.18 (m, 1H), 5.16 (d, J=4.2, 1H), 4.16 (m, 1H), 3.94 (ddd, J=1.8, 3.6, 3.6, 1H), 3.69 (ddd, J=3.4, 3.6, 12.5, 1H), 3.54 (ddd, J=3.6, 9.4, 12.5, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.2, 152.0, 150.9, 149.7, 130.1, 129.6, 129.3, 128.7, 119.0, 89.0, 86.7, 71.2, 71.0, 62.3; ESI-MS *m/z* 366 [5.0% $(M-I+H+Na)^+$], 344 [9.2% $(M-I+2H)^+$], 212 [100% $(M-\beta$-D-ribose$-I+3H)^+$].

5.5.3. 8-Phenyl-2′-deoxyadenosine

Light orange solid (514 mg, 84%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.70 (m, 2H), 7.59 (m, 3H), 7.46 (br s, 2H), 6.15 (dd, J=6.2, 8.7, 1H), 5.58 (dd, J=4.0, 8.3, 1H), 5.24 (d, J=4.0, 1H), 4.45 (dddd, J=1.9, 1.9, 4.0, 5.8, 1H), 3.87 (ddd, J=1.9, 4.2, 4.2, 1H), 3.69 (ddd, J=4.0, 4.2, 12.2, 1H), 3.53 (ddd, J=4.2, 8.3, 12.2, 1H), 3.30 (ddd, J=5.8, 8.7, 13.2, 1H), 2.145 (ddd, J=1.9, 6.2, 13.2, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 156.1, 152.0, 150.4, 149.8, 130.1, 129.6, 129.4, 128.8, 119.1, 88.4, 85.7, 71.4, 62.3, 37.2; ESI-MS *m/z* 328 [8.1% $(M+H)^+$], 212 [100% $(M-\beta$-D-ribose$+2H)^+$]; HR (MH^+) 328.1394 (calcd for $C_{16}H_{18}O_3N_5$ 328.1404).

5.5.4. 8-Phenyl-(N6-phenyl)adenosine

Orange solid (32 mg, 4%;) ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.43 (s, 1H), 7.96 (m, 2H), 7.82 (m, 2H), 7.63 (m, 3H), 7.35 (m, 2H), 7.06 (m, 1H), 5.80 (d, J=6.9, 1H), 5.56 (dd, J=4.0, 8.6, 1H), 5.51 (d, J=6.5, 1H), 5.24 (ddd, J=5.0, 6.9, 6.5, 1H), 5.19 (d, J=4.4, 1H), 4.21 (ddd, J=2.0, 5.0, 4.4, 1H), 3.96 (ddd, J=2.0, 4.0, 4.0, 1H), 3.74 (ddd, J=4.0, 4.0, 12.2, 1H), 3.58 (ddd, J=4.0, 8.6, 12.2, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 152.1, 151.9, 151.5, 150.0, 139.3, 130.4, 129.8, 129.6, 129.4, 129.1, 128.8, 128.8, 128.4, 122.9, 121.0, 120.2, 115.4, 89.2, 86.6, 71.1, 70.9, 62.2; ESI-MS *m/z* 420 [100% $(MH)^+$]; HR (MH^+) 420.1667 (calcd for $C_{22}H_{22}O_4N_5$ 420.1666).

5.5.5. N6-Phenyladenosine

Light yellow solid (17 mg, 3%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (br s, 1H), 8.55 (s, 1H), 8.41 (s, 1H), 7.94 (d, J=8.0, 2H), 7.32 (dd, J=7.4, 8.0, 2H), 7.05 (t, J=7.4, 1H), 5.97 (d, J=6.1, 1H), 5.51 (d, J=6.4, 1H), 5.31 (dd, J=4.6, 6.4, 1H), 5.24 (d, J=4.6, 1H), 4.65 (m, 1H), 4.18 (m, 1H), 3.96 (m, 1H), 3.70 (ddd, J=4.0, 4.6, 12.0, 1H), 3.58 (ddd, J=4.0, 6.4, 12.0, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 152.1, 151.9, 140.7, 139.5, 128.3, 122.7, 120.83, 87.8, 85.8, 73.5, 70.5, 61.5 (12 of possible 14 carbon resonances observed); ESI-MS *m/z* 344 [100% $(MH)^+$]; HR (MH^+) 344.1360 (calcd for $C_{16}H_{18}O_4N_5$ 344. 1353).

5.5.6. Deuteration of adenosine at C8

To a reaction vessel containing adenosine (100 mg, 0.37 mmol) and Cs_2CO_3 (306 mg, 0.94 mmol, 2.5 equiv) were added acetone-d_6 and DMF (2 ml, 1:1, v/v). The mixture was heated to 120 °C for 10 h. The reaction was quenched by addition of water (2 ml) and neutralised using dilute (1 M) hydrochloric acid (2 ml), which was then extracted with ethyl acetate/ethanol (9:1, v/v, 4×10 ml). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated in vacuo to give a beige solid (42 mg). ^{1}H NMR (400 MHz, DMSO-d_6, selected peaks) δ 8.35 (s, 0.12H, C8-*H*), 8.13 (s, 1H, C2-*H*); ESI-MS *m/z* 269 [72% $(MH)^+$], 132 [100%]; HR (MH^+) 269.1105 (calcd for $C_{10}H_{13}D_1O_4N_5$ 269.1103).

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