Purinyl *N*-Directed Aroylation of 6-Arylpurine Ribo- and 2'-Deoxyribonucleosides, and Mechanistic Insights

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Abstract

The purinyl ring contains four embedded nitrogen atoms of varying basicities. Selective utilization of these ring nitrogen atoms can lead to relatively facile remote functionalization, yielding modified purinyl motifs that are otherwise not easily obtained. Herein, we report previously undescribed *N*-directed aroylation of 6-arylpurine ribo and the more labile 2'-deoxyribonucleosides. Kinetic isotope analysis as well as reaction with a well-defined dimeric, palladated 9-benzyl 6-arylpurine provided evidence for *N*-directed cyclometallation as a key step, with a plausible rate-limiting C–H bond cleavage. Radical inhibition experiments indicate the likely intermediacy of aroyl radicals. The chemistry surmounts difficulties often posed in the functionalization of polynitrogenated and polyoxygenated nucleosidic structures that possess complex reactivities and a labile glycosidic bond that is more sensitive in the 2'-deoxy substrates.

Introduction

The Friedel-Crafts acylation and reactions of organometallics with acylating agents or nitriles constitute classical approaches for acylation of aromatic systems.[1–4] Whereas carboxylic acids or their derivatives can be utilized, through the addition of organometallic reagents, over-addition leading to tertiary alcohols is a problem. One solution to this problem has been the Weinreb

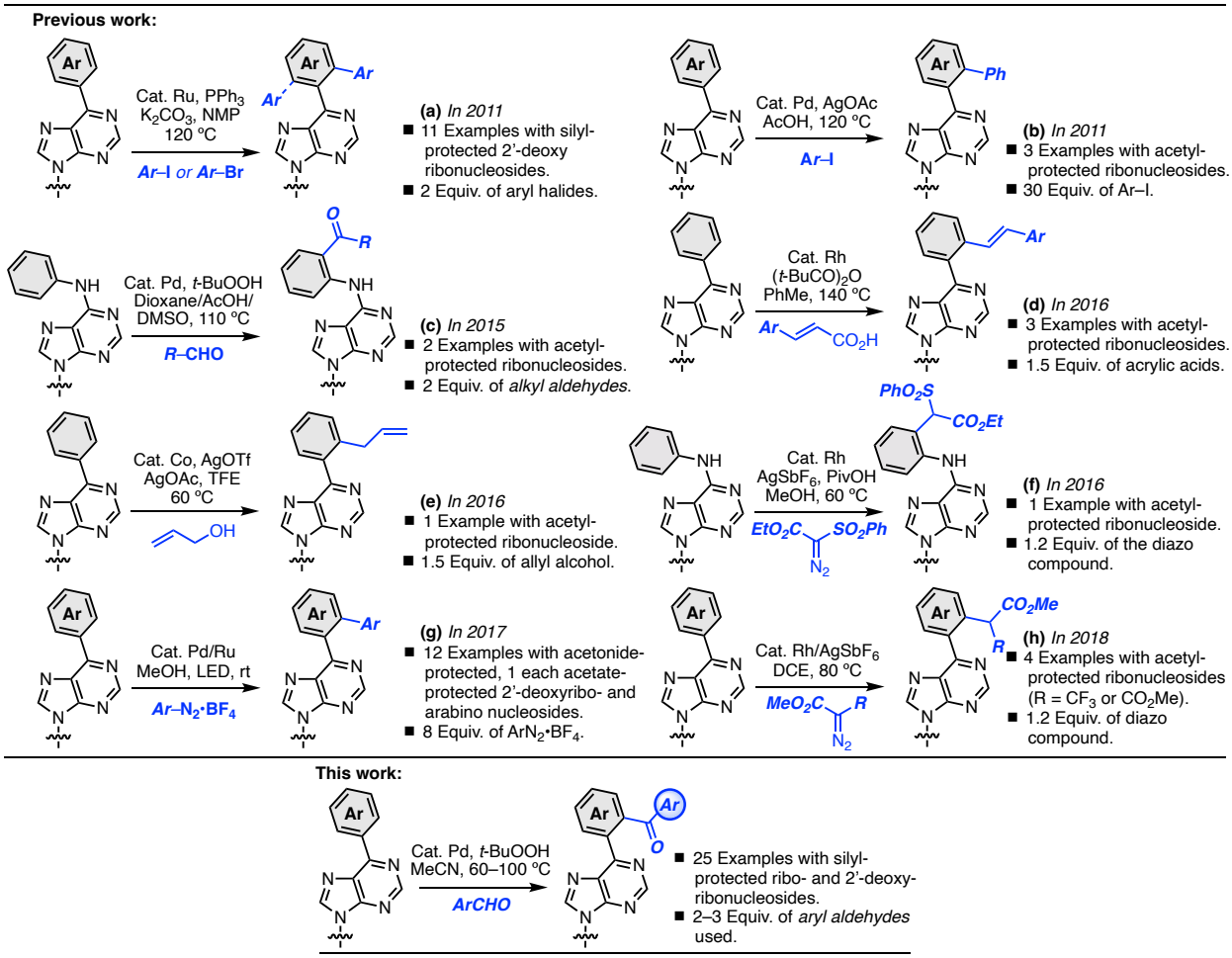
amide methodology.[5–7] Another has been cross coupling reactions of acyl halides, thiol esters, amides, anhydrides and in situ formed mixed anhydrides with a variety of organometallic and organoboron reagents.[6–30] More recently, photocatalytic methods have emerged for acylation reactions.[31–36]

Carbonylation reactions constitute another approach to the synthesis of ketones, and sp^2 nitrogen atoms in heterocyclic substrates are effective site directors for such reactions.[37–40] In the development of CO-free carbonylations, Pd-catalyzed reactions of nitrogenated substrates with DEAD led to regioselective ethoxy carbonylations,[41] and Ru- or Pt-catalyzed reactions of pyridine-ring-containing substrates (benzo[*h*]quinoline, 2-aryl pyridines, and (2-aryloxy)pyridines) with carbamoyl chlorides, alkyl chloroformates, and acyl chlorides led to the corresponding remote regioselective functionalizations.[42–44] Ru-mediated carbonylation and reaction with aryl iodides[45] and $Ru_3(CO)_{12}$ mediated C–$N(Me)_2$ bond cleavage followed by carbonylation with CO and ArB(nep) have both also led to remote aroylations.[46]

The utility of aldehydes as π-acceptors in *N*-directed acylations requires a terminal oxidation, and whereas air was initially reported,[47] *t*-BuOOH has been a suitable oxidant in a variety of such acylation reactions.[48–56] Beyond aldehydes, other reagents have been utilized for *N*-directed aroylation reactions.[57] For example, acylations of 2-aryl pyridines have been conducted with α-oxocarboxylic acids,[58] alcohols,[59] α-diketones,[60] toluene derivatives,[61,62] carboxylic acids,[63] benzyl amines,[64] styrenes,[65,66] phenyl acetylenes,[66,67] benzylic oxiranes,[67] mandelic acids,[68] benzylic halides,[69,70] and *N*-phenyl-*N*-tosylbenzamides.[71]

Nucleosides are a significantly important family of biomolecules, and the nucleoside scaffold has provided a rich diversity of compounds impacting broad-ranging areas, such as biological, medicinal, and pharmaceutical fields.[72] Thus, facile approaches to nucleoside modifications are of significant interest. Within such contexts and among various metal-catalyzed reactions, purinyl nitrogen atom-directed "*ortho*-C–H" bond activation and functionalization has been a goal of ours.[73,74] Although purines have been a subject of C–H bond activation reactions, by comparison, the literature on purine nucleosides is quite limited.[75–78] In nucleosides, beyond the multiple metal coordinating nitrogen atoms in the purines themselves, there are multiple oxygen atoms in the saccharide, and a labile glycosidic bond that renders them prone to deglycosylation. 2'-

Deoxyribosides are more prone to deglycosylation than the ribo analogues and nucleoside stability also depends upon a number of factors such as structure, temperature, and pH.[79] Thus, in general, reactions, and metal-catalyzed reactions in particular, can be challenging with these substrates, in comparison to purines.[80–82] A summary of the significant carbo functionalizations by *N*-directed C–H bond activation of 6-arylpurine nucleosides is shown in Scheme 1.[73,83–89] A vast majority of previous work explore 2',3',5'-tri-*O*-acetyl-protected ribonucleoside substrates, which generally display higher stabilities as compared to the 2'-deoxy analogues and silyl-protected derivatives. A recent review summarizes C–N, C–S, and *meta*-functionalizations of purines and purine nucleosides.[75]

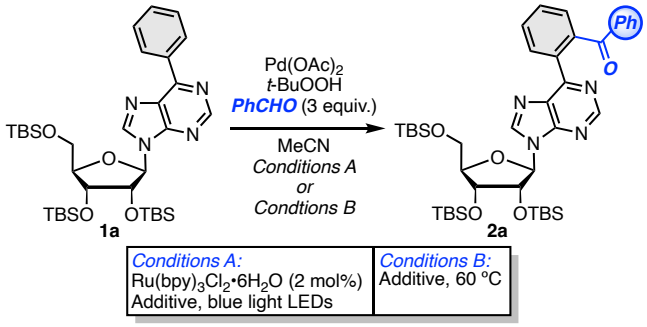


Scheme 1. Examples of *N*-directed *ortho*-functionalization of 6-aryl- and 6-anilinopurine nucleosides.

Results and Discussion

In prior studies on acylation of acetyl-protected 6-anilinopurine ribonucleosides (Scheme 1(c)), aryl aldehydes could not be used because they were observed to undergo ready oxidation to carboxylic acids. Thus, we were drawn to the unknown purinyl *N*-directed *ortho* aroylation of 6-arylpurine ribo and 2'-deoxyribonucleosides. Our initial efforts were based upon photochemical approaches and specifically Pd^{II}/Ir^{III} cocatalysis.[90,91] These initial results are shown in Table 1. Using Boc-Val-OH as an additive, reactions of **1a** and PhCHO under 48 and 36 W blue light LEDs proceeded to give product **2a** in comparably good yields (entries 1 and 2). However, use of 24 W LEDs led to a decreased yield (entry 3).

Table 1. Photochemical and thermal conditions tested for the aroylation[a]

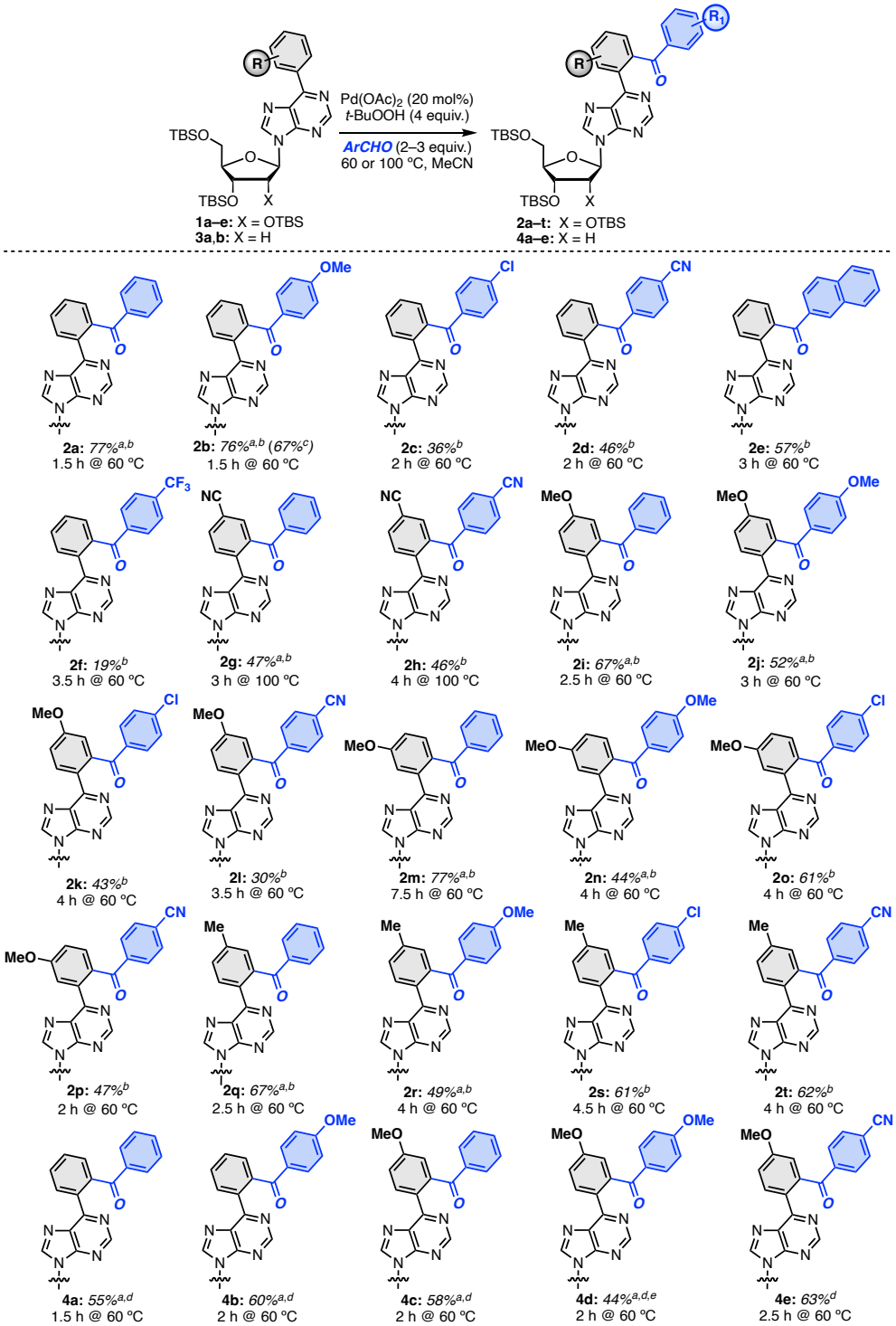


Entry	Pd (mol%)	Additive (mol%)	LED (W)	Time	Yield[b]
Photoredox (Conditions A)					
1	20	Boc-Val-OH (20)	48	24 h	*64%*
2	20	Boc-Val-OH (20)	36	24 h	*65%*
3	20	Boc-Val-OH (20)	24	24 h	*56%*
4	20	Boc-Val-OH (20)	24	24 h	Inc[c,d]
Thermal (Conditions B)					
5	20	Boc-Val-OH (20)	–	1 h	74%
6	10	Boc-Val-OH (10)	–	18 h	78%
7	20	Boc-Val-OH (20)	–	18 h	Inc[e]
8	20	Ac-Val-OH (20)	–	1 h	*60%*
9	20	Boc-Ile-OH (20)	–	1 h	*66%*
10	20	Ac-Ile-OH (20)	–	1 h	*52%*
11	20	None	–	1.5 h	*77%*

[a]Reactions were conducted in a vial, charged with nucleoside **1a** (0.1 mmol), *t*-BuOOH (5–6 M in decane, 4 equiv.), freshly distilled PhCHO, and in a nitrogen atmosphere. [b]Yields are of isolated and purified product. [c]A fan was used to dissipate any heat. [d]Reaction was incomplete. [e]The reaction was conducted in PhCl.

To ensure that the photoredox reactions were not influenced by local heating, a fan was used to dissipate any heat generated. This reaction (entry 4) remained incomplete, with a significant amount of residual precursor **1a**. We determined that the temperature of a reaction under 24 W LEDs was *ca.* 60 °C. On the basis of these collective observations, thermal conditions were evaluated, using 20 mol% $Pd(OAc)_2$. Notably, the very first attempt resulted in a very good yield of product **2a** (entry 5). However, halving the amount of catalyst increased the reaction time significantly, without a major yield improvement (entry 6). In order to eliminate any possible undesired outcomes with other reactants under long reactions times, experimentation was continued with 20 mol% of $Pd(OAc)_2$. A switch from MeCN to PhCl as solvent led to a significant amount of residual precursor **1a** after 18 h (entry 7). Other amino acid additives also led to successful product formation, but with decreased yields (entries 8–10). Finally, and interestingly, eliminating the amino acid additive was not significantly detrimental, and a very good yield of product **2a** was obtained with only a slightly increased reaction time (entry 11).

Using the conditions in entry 11 of Table 1, a variety of products were prepared (Scheme 1) from the ribosyl precursors **1a**–**e** (X = OTBS) and the 2'-deoxyribosyl precursors **3a** and **3b** (X = H). For reactions with PhCHO and *p*-MeO-PhCHO, the aldehydes were distilled prior to use. The reaction appears to be sensitive to substituents on both the 6-arylpurine nucleoside as well as the aldehyde, although the outcome seems to be a balance between substituents R and R_1. With 6-phenylpurine riboside (R = H), reactions with PhCHO and *p*-MeO-PhCHO proceeded quite efficiently (**2a**, **2b**). Presence of electron-withdrawing *p*-Cl and *p*-CN groups on the benzaldehyde lowered the product yields (**2c**, **2d**), whereas 2-naphthaldehyde gave a good product yield (**2e**). The reduction in product yield was most dramatic with *p*-CF_3-PhCHO (**2f**). Presence of a strongly electron-withdrawing substituent on the 6-arylpurine moiety (R = CN) led to incomplete reactions at 60 °C. Increasing both the nucleoside concentration from 0.1 to 0.2 M and the reaction temperature to 100 °C, led to successful aroylation reactions (**2g**, **2h**). With substrate **1c**, bearing a *p*-OMe group on the 6-arylpurinyl unit, product yields with PhCHO, *p*-MeO-PhCHO and *p*-NC-PhCHO (**2i**, **2j**, **2l**) were all lower as compared to reactions of substrate **1a**. However, *p*-Cl-PhCHO gave a better product yield (**2k** *versus* **2c**). Relocation of the methoxy group to the *m*-position on the 6-arylpurine prolonged reaction times with PhCHO and *p*-MeO-PhCHO, and while the product



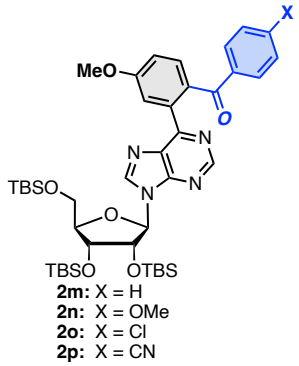
[a]The aldehyde was distilled just prior to use. [b]Reaction was conducted with 3 equiv. of the aldehyde. [c]Yield from 2 × 0.5 mmol scale reactions, 3.5 h reaction time. [d]Reaction was conducted with 2 equiv. of the aldehyde. [e]Because of a minor inseparable byproduct, the aroylated product was desilylated with $Et_3N•3HF$ in THF, at rt. The yield is over two steps.

Scheme 1. Products from the aroylation reactions of TBS-protected ribo- and 2'-deoxyribonucleoside substrates.

yield with the former (**2m**) was similar to that with 6-phenylpurine riboside, that with the latter was lower (**2n**). Interestingly, *p*-Cl-PhCHO gave a better product yield in this comparison (**2o**), whereas that with *p*-NC-PhCHO was similar (**2p**). With a *p*-anisyl or *p*-tolyl substituent on the purine nucleus, product yields with PhCHO and *p*-MeO-PhCHO were similar (compare **2i** to **2q** and **2j** to **2r**). With a *p*-tolyl substituent on the purine, product yields with *p*-Cl-PhCHO and *p*-NC-PhCHO were higher (**2s**, **2t**) within the series and as compared to other comparable reactions, with the exception of product **2o**. The highest product yield with *p*-NC-PhCHO was obtained with a *p*-tolyl substituent on the purine (**2t**). One reaction with precursor **1a** was scaled up to the 1 mmol scale and this also resulted in a good yield of product **2b**.

Products **2m**–**p** are notable. Although precursor **1d**, with a meta-methoxy group on the C6 aryl ring, presents two potential aroylation sites, reactions occurred at the *p*-position to the methoxy group. This could be readily ascertained by an analysis of the remaining C6 aryl proton resonances post aroylation. These data are shown in Table 2.

Table 2. Chemical shifts and coupling constants of the protons in the arylpurine unit of compounds **2m**–**p**.[a,b]



Compound	*d* ppm (*J* Hz)	*d* ppm (*J* Hz)	*dd* ppm (*J* Hz)
2m	δ = 8.06 (2.0)	δ = 7.57 (8.5)	δ = 7.14 (8.4, 2.2)
2n	δ = 7.98 (1.7)	δ = 7.57 (8.4)	δ = 7.10 (8.4, 1.8)
2o	δ = 8.04 (1.9)	δ = 7.57 (8.4)	δ = 7.14 (8.5, 2.2)
2p	δ = 8.18 (2.2)	δ = 7.55 (8.5)	δ = 7.13 (8.5, 2.3)

[a]Spectra were obtained at 500 MHz in $CDCl_3$. [b]*d* = Doublet, *dd* = doublet of doublet.

2'-Deoxyribonucleoside precursors **3a** and **3b** also performed admirably although the yields were slightly lower in four of the five examples (**4a**–**d**). Due to the formation of a byproduct, these reactions were performed with 2 equiv. of the aldehyde. The product yield with *p*-NC-PhCHO (**4e**) was highest in this series, comparable to that of ribo product **2t**. In the case of the product from *p*-MeO-PhCHO (**4d**), the yield shown in Scheme 1 is that of the desilylated material. This was done because of the presence of a minor inseparable byproduct formed in the aroylation reaction. One product, **2s**, was conventionally crystallized from PhH, and its structure was

obtained by X-ray analysis (Figure 2, please see the Supporting Information for additional structural data).

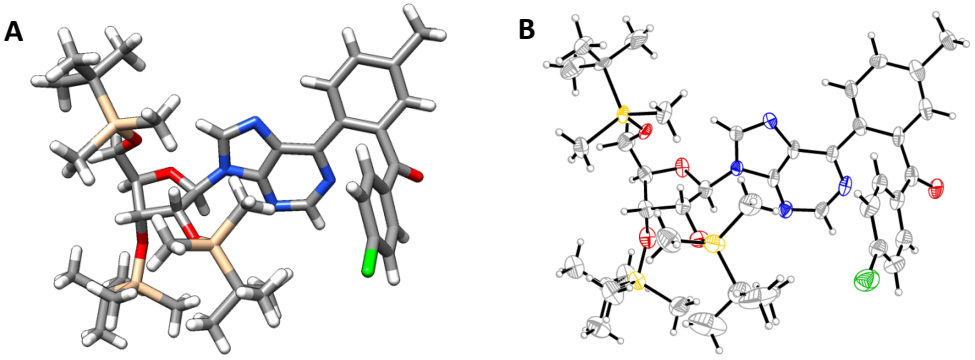
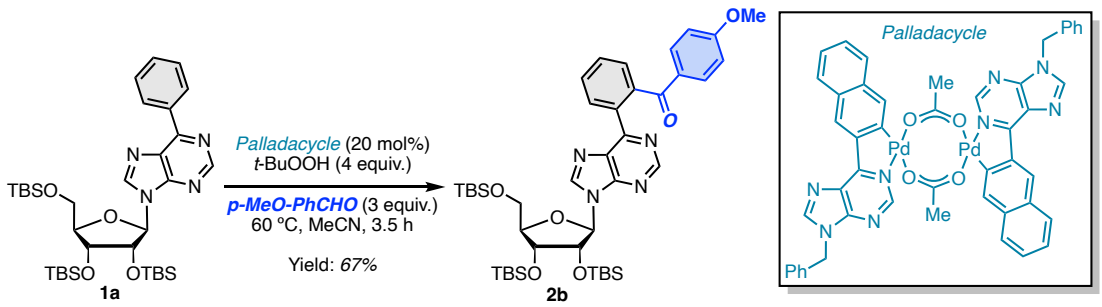


Figure 2. X-ray crystal structure of compound **2s**. Panel **A**: capped sticks. Panel **B**: ORTEP (atomic displacement parameters are shown at the 30% probability level and disorder at the 3' silyl group is omitted for clarity).

The next focus was on understanding some of the mechanistic details of the aroylation reactions. On the basis of our prior experience[74] and other literature reports[48,51,55,60] a $Pd^{II}/Pd^{III\ or\ IV}$ catalytic cycle was anticipated. As in the past,[74] during this work we were unable to isolate a palladacycle from $Pd(OAc)_2$ and a nucleoside precursor for crystallographic structure analysis. Thus, we chose to evaluate an aroylation reaction using a purinyl palladacycle we have previously prepared and characterized (Scheme 2).[74] With 20 mol% of this palladacycle, a 67% yield of product **2b** was obtained from ribonucleoside **1a**, which compares reasonably well to the yield obtained with $Pd(OAc)_2$. This shows that a nucleoside-derived palladacycle is a plausible intermediate in the reaction.



Scheme 2. Use of a purinyl palladacycle precatalyst for an aroylation reaction.

To ascertain if radical intermediate(s) are involved in this reaction, two radical trapping experiments were performed using 2 equiv. of 1,1-DPE and TEMPO. With 1,1-DPE, a reaction of substrate **1a** and PhCHO showed both precursor and product **2a**, after a 2 h reaction time. The

yield of product from this reaction was 57%, as compared to 77% in the absence of 1,1-DPE. Use of TEMPO, in place of 1,1-DPE, led to no product formation. However, in both cases we were unable to identify and/or isolate any radical-trapped byproducts. Nevertheless, these results point to the formation of an aroyl radical.

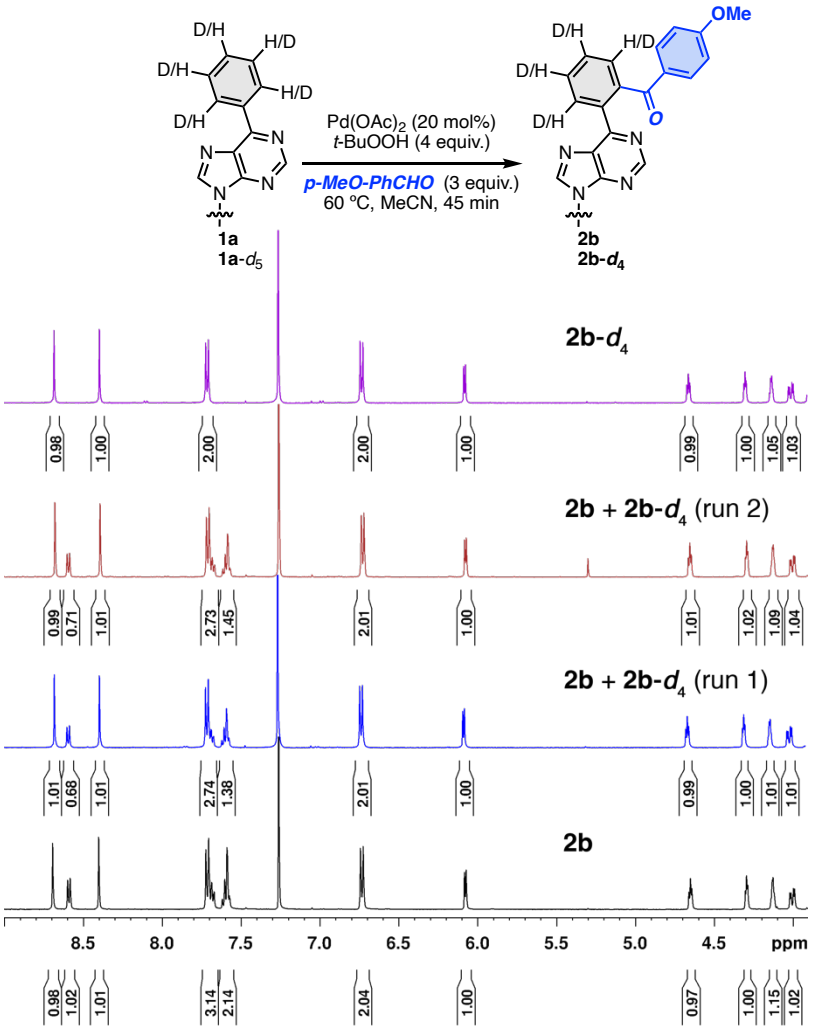
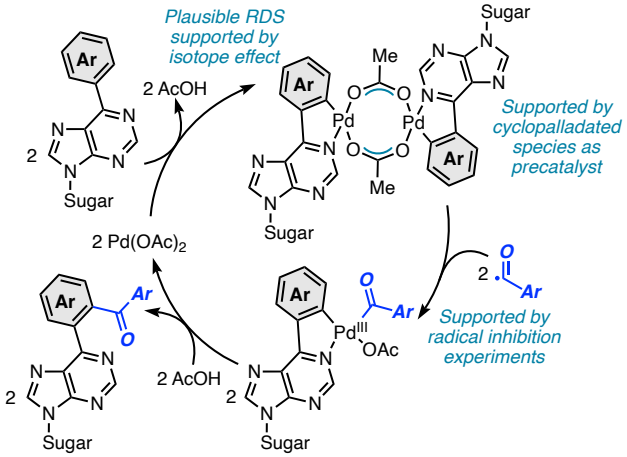


Figure 3. 500 MHz partial ^{1}H NMR spectra (in $CDCl_3$) of products **2b**, **2b**-d_4, and **2b** + **2b**-d_4.

The next assessment was an evaluation of any difference in the C–H *versus* C–D bond abstraction step in the aroylation reactions. For this pentadeuterio derivative **1a**-d_5 was synthesized from (d_5)-PhB(OH)$_2$. Under conditions leading to product **2b**, three aroylation reactions were conducted simultaneously, one each with precursors **1a**, **1a**-d_5 and an equimolar mixture **1a** + **1a**-d_5. The reactions were terminated after 45 min and the products were chromatographically purified, at which time unreacted starting materials were also recovered.

The yield of product **2b** from protiated precursor **1a** was 66% (10% recovered **1a**) and that of product **2b**-d_4 from deuteriated precursor **1a**-d_5 was 56% (18% recovered **1a**-d_5). The ^{1}H NMR spectra of products **2b**, **2b**-d_4, and **2b** + **2b**-d_4 that were obtained (relaxation delay D1 = 5 s) are displayed in Figure 3. From these data the k_H/k_D was estimated to be 2.25 (average of two runs).

From the collective data above, we propose that *N*-directed palladation of the nucleoside, likely produces a Pd^{II}-Pd^{II} dimer, akin to the palladacycle shown in Scheme 2, involving a primary isotope effect. Next, in a Pd^{II} to Pd^{III} oxidation, the acyl radical reacts with this dimer (a Pd^{IV} intermediate cannot be excluded). Formation of radical intermediates is supported by the modest inhibition to abrogation by radical inhibitors. This is followed by a product forming sp^2-acyl bond formation and regeneration of the Pd^{II} catalyst. The overall pathway is represented in Scheme 3.



Scheme 3. A plausible catalytic cycle for the *N*-directed aroylation.

Conclusions

In this work we have demonstrated that a variety of 6-arylpurine ribo and 2'-deoxyribonucleosides undergo *N*-directed C–H bond activation and aroylation with a range of benzaldehydes, under generally mild conditions. Oxidation of the aryl aldehydes to the carboxylic acids does not appear to be a significant problem under the reaction conditions. Despite the presence of four nitrogen atoms that could all sequester Pd, interaction with a single nitrogen atom leads to effective remote C–H bond activation. From a mechanistic standpoint, it appears that cleavage of the C–H bond in the 6-arylpurine moiety, leading to formation of a cyclopalladated species, could be rate limiting. In this context, use of a purine-based Pd^{II} dimer

as precatalyst points to the possible formation of nucleoside-Pd^{II} dimers *in situ*. Formation of aroyl radicals by reaction of the aryl aldehydes with *t*-BuOOH is indicated on the basis of the radical inhibition experiments. A Pd^{II}/Pd^{III} (or Pd^{IV}) redox cycling is then likely responsible for the transformations. Importantly, despite the intermediacy of radical species in the reactions and the presence of O–C–H bonds in the saccharide units, hydrogen atom abstraction, as would be observed in cross-dehydrogenative coupling reactions, does not seem to complicate. One product has been characterized by X-ray crystallographic analysis. In summary, we have demonstrated the ability to readily functionalize complex systems such as purine nucleoside analogues by a *N*-direction C–H bond activation strategy.

Acknowledgments

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Author Contributions

M.K.L. conceptualized this work, assisted with troubleshooting, wrote the manuscript, reanalyzed all the ^{1}H NMR data, and prepared the Supporting Information based upon the Ph.D. thesis of C.T.M. C.T.M. performed the benchwork, performed the initial spectroscopic analyses of the compounds, produced a Ph.D. thesis, then reassessed and recompiled all of the $^{13}C\{^{1}H\}$ NMR data reported here. N.S. obtained the HRMS data for the compounds described herein. M.C.N. performed the X-ray crystallographic analysis of compound **2s**. L.S. obtained the X-ray crystallographic data for the aroyl purine derivative shown in the Supporting Information.

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