Purinyl *N*-directed aroylation of 6-arylpurine ribo- and 2'-deoxyribonucleosides, and mechanistic insights†‡

Mahesh K. Lakshman,[a,b]* Casina T. Malinchak,[a, b] Nathaniel Shank,[c] Michelle C. Neary,[d] and Lothar Stahl[e]

[a]*Department of Chemistry and Biochemistry, The City College of New York, 160 Convent Avenue, New York, NY 10031, USA*

[b]*The Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, 365 Fifth Avenue, New York, NY 10016, USA*

[c]*Department of Chemistry and Biochemistry, Georgia Southern University, 11935 Abercorn Street, Savannah, GA 31419, USA*

[d]*Department of Chemistry, Hunter College, 695 Park Avenue, New York, NY 10065, USA*

[e]*Department of Chemistry, University of North Dakota, 151 Cornell Street Stop 9024, Grand Forks, ND* 58202, USA

†A working version of this article is deposited at ChemRxiv (**https://doi.org/10.26434/chemrxiv-2024-n4cj7-v2**)

‡Electronic supplementary information (ESI) available: experimental procedures, structural characterizations, copies of NMR spectra, and NMR FID files. CCDC 2333365 and 2333366. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d4ob00689e)**

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

N-directed C–H bond activation offers facile, economical approaches to diverse functionalizations at remote locations.[1–6] In the context of *N*-directed acylations, aldehydes are convenient, widely available π-acceptors for reactions of metalated intermediates generated by *N*-directed C–H bond activation processes.[6–9] In the initial report, *N*-directed acylations with aryl aldehydes were conducted in xylene (at 120–130 °C), with air as the terminal oxidant.[10] Under these conditions, alkyl aldehydes and *p*-anisaldehyde did not yield products. A subsequent report showed *t*-BuOOH to be a suitable oxidant for reactions of benzo[*h*]quinoline with both alkyl and aryl aldehydes.[11] This oxidant has been applicable to a variety of nitrogenated substrates.[12–19] Beyond aldehydes, other reagents that have found application in *N*-directed aroylation reactions[8] include α-oxocarboxylic acids,[20] alcohols,[21] α-diketones,[22] toluene derivatives,[23,24] carboxylic acids,[25] benzyl amines,[26] styrenes,[27,28] phenyl acetylenes,[28,29] benzylic oxiranes,[29] mandelic acids,[30] benzylic halides,[31,32] and *N*-phenyl-*N*-tosylbenzamides.[33]

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.[34] 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.[35,36] Although purines have been a subject of C–H bond activation reactions, by comparison, the literature on purine nucleosides is quite limited.[37–40] 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.[41] Thus, in general, reactions, and metal-catalyzed reactions in particular, can be challenging with these substrates, in comparison to purines.[42–44] A summary of the significant carbo functionalizations by *N*-directed C–H bond activation of 6-arylpurine nucleosides is shown in Fig. 1.[35,45–51] 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.[37]

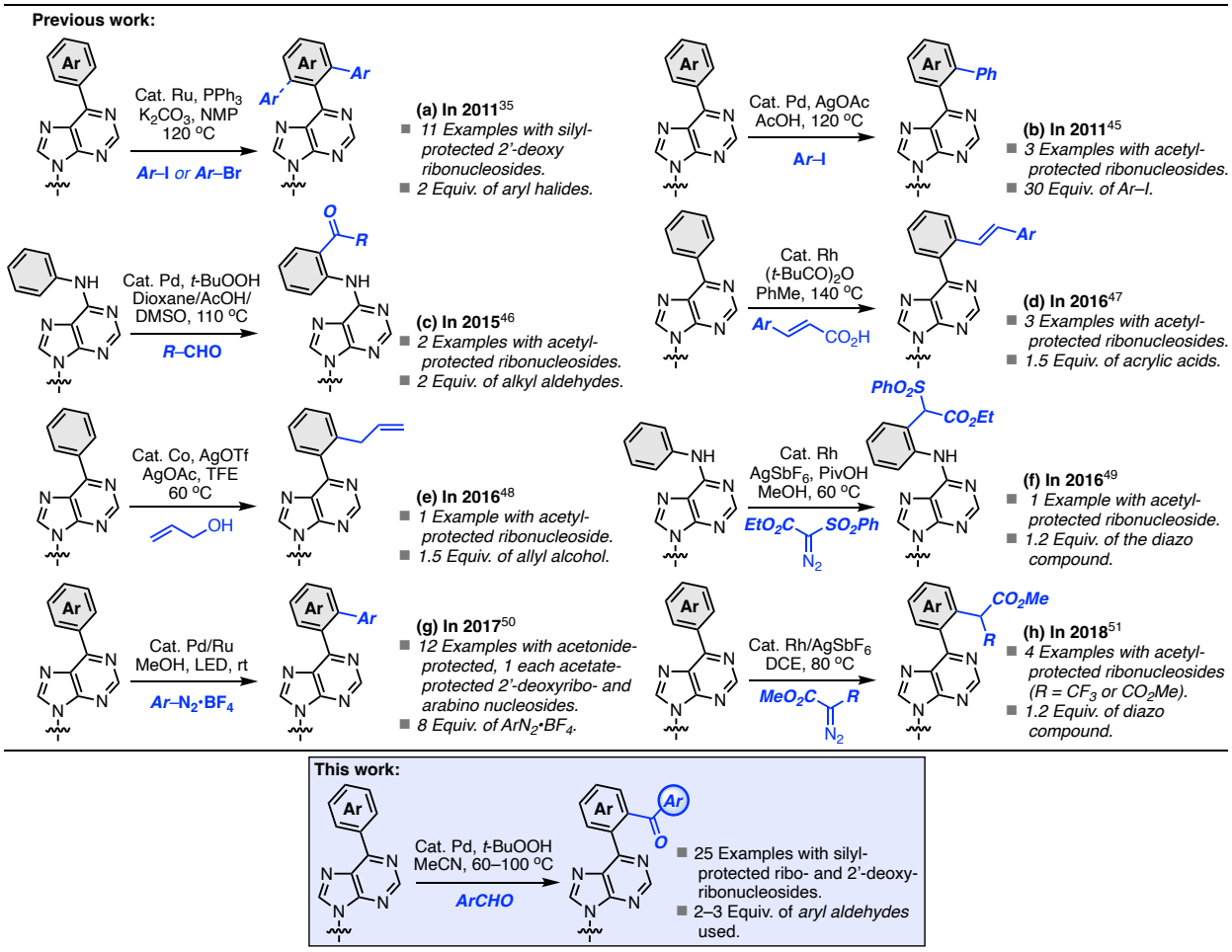


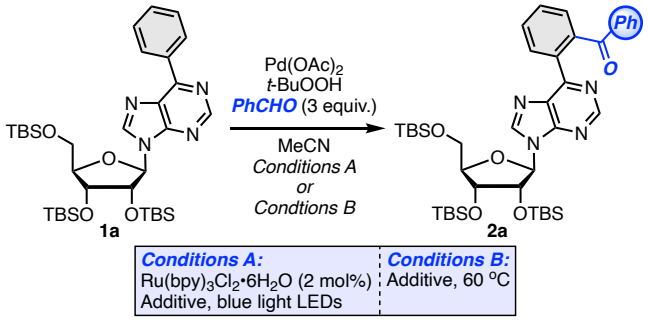
Fig. 1 Examples of *N*-directed *ortho*-carbo functionalization of 6-aryl- and 6-anilinopurine nucleosides.

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 a photochemical approach, involving Pd^{II}/Ir^{III} cocatalysis with an amino acid additive.[52] Although MeCN was selected as solvent, based upon our prior work on *N*-directed oxidations,[36] this solvent

could benefit reactions where radical intermediates are anticipated. Unlike in reactions of polar intermediates, solvent effects in radical reactions are less expected. However, significant solvent influences on radical reactions are known.[53,54] Of relevance here, hydroxyl radical is less reactive in MeCN for H-atom abstractions.[55] Also, in unrelated radical reactions, we have found MeCN to have a beneficial effect on reaction outcomes.[56] Results from the initial screening 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]

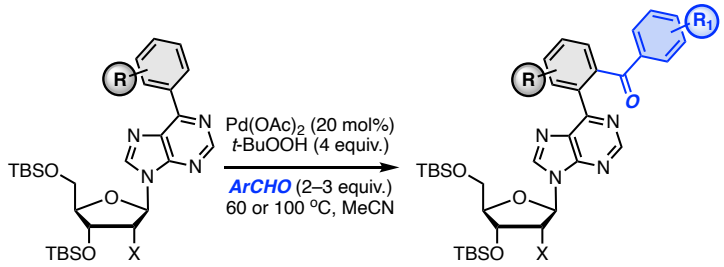


Entry	Pd (mol%)	Additive (mol%)	LED (W)	Time	Yield[b]
Photoredox (Conditions A)					
1	20	Boc-Val-OH (20)	48	24 h	*64%*
2	20	Boc-Val-OH (20)	36	24 h	*65%*
3	20	Boc-Val-OH (20)	24	24 h	*56%*
4	20	Boc-Val-OH (20)	24	24 h	Inc[c,d]
Thermal (Conditions B)					
5	20	Boc-Val-OH (20)	–	1 h	74%
6	10	Boc-Val-OH (10)	–	18 h	78%
7	20	Boc-Val-OH (20)	–	18 h	Inc[d,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 (Inc). [e] The reaction was conducted in PhCl.

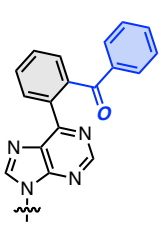
To ensure that the photoredox reactions were not influenced by local heating, a fan was used to dissipate any heat generated. This reaction (entry 4) remained incomplete, with a significant amount of residual precursor **1a**. We determined that the temperature of a reaction under 24 W LEDs was *ca.* 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

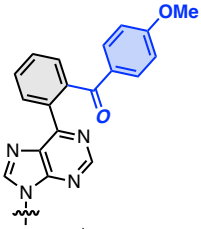


1a–e: X = OTBS
3a,b: X = H

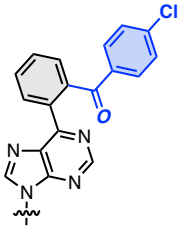
2a–t: X = OTBS
4a–e: X = H



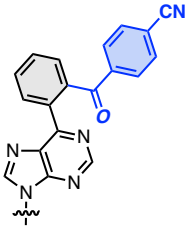
2a: *77%*[a,b]
1.5 h @ 60 °C



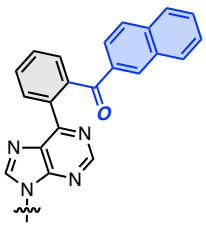
2b: *76%*[a,b] (*67%*[c])
1.5 h @ 60 °C



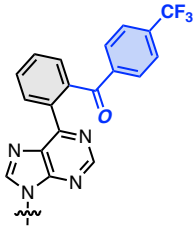
2c: *36%*[b]
2 h @ 60 °C



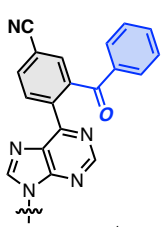
2d: *46%*[b]
2 h @ 60 °C



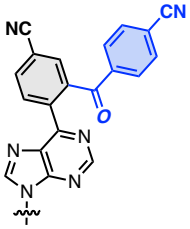
2e: *57%*[b]
3 h @ 60 °C



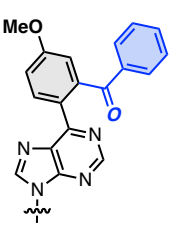
2f: *19%*[b]
3.5 h @ 60 °C



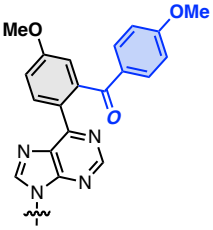
2g: *47%*[a,b]
3 h @ 100 °C



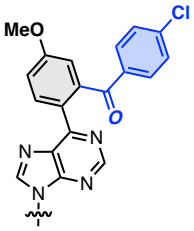
2h: *46%*[b]
4 h @ 100 °C



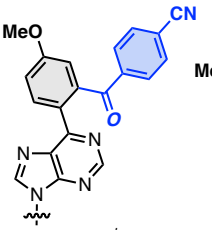
2i: *67%*[a,b]
2.5 h @ 60 °C



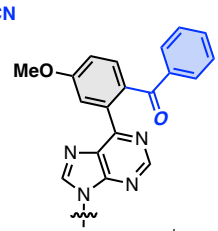
2j: *52%*[a,b]
3 h @ 60 °C



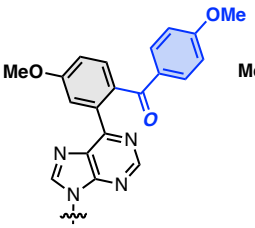
2k: *43%*[b]
4 h @ 60 °C



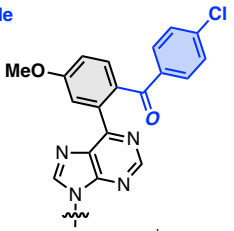
2l: *30%*[b]
3.5 h @ 60 °C



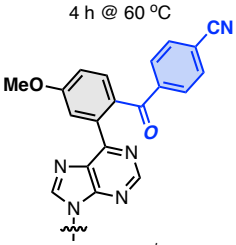
2m: *77%*[a,b]
7.5 h @ 60 °C



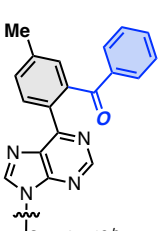
2n: *44%*[a,b]
4 h @ 60 °C



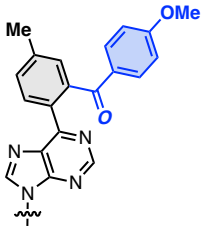
2o: *61%*[b]
4 h @ 60 °C



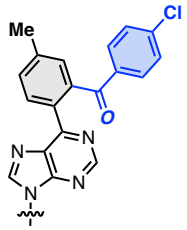
2p: *47%*[b]
2 h @ 60 °C



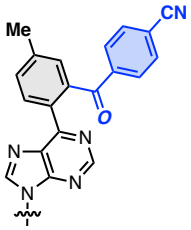
2q: *67%*[a,b]
2.5 h @ 60 °C



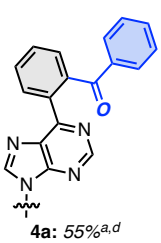
2r: *49%*[a,b]
4 h @ 60 °C



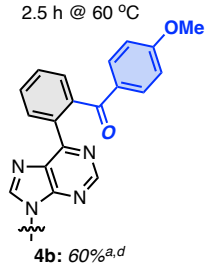
2s: *61%*[b]
4.5 h @ 60 °C



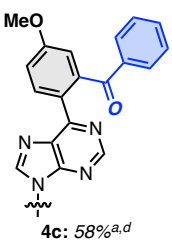
2t: *62%*[b]
4 h @ 60 °C



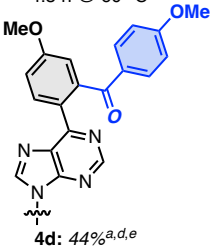
4a: *55%*[a,d]
1.5 h @ 60 °C



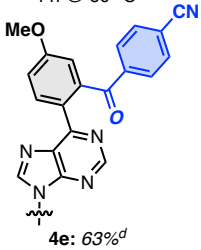
4b: *60%*[a,d]
2 h @ 60 °C



4c: *58%*[a,d]
2 h @ 60 °C



4d: *44%*[a,d,e]
2 h @ 60 °C



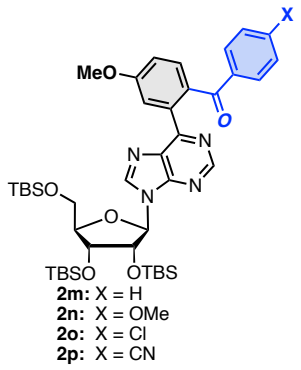
4e: *63%*[d]
2.5 h @ 60 °C

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

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 (**2o**) in this comparison, whereas that with *p*-NC-PhCHO was similar (**2p**). With a *p*-anisyl or *p*-tolyl substituent on thepurine 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 participated well although the yields were slightly lower in four of the five examples (**4a**–**d**). In all cases, the crude reaction material was loaded onto a silica column and eluted with PhMe to remove non-nucleosidic materials. With the

deoxyribonucleosides, product separation was rendered easier when the reactions were performed with a lower excess of the aldehyde (2 equiv.). 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 alleviated difficulties in the removal of a byproduct in the aroylation reaction (*p*-anisic acid). One product, **2s**, was conventionally crystallized from PhH, and its structure was obtained by X-ray analysis (Fig. 2, please see the Supporting Information for additional structural data).

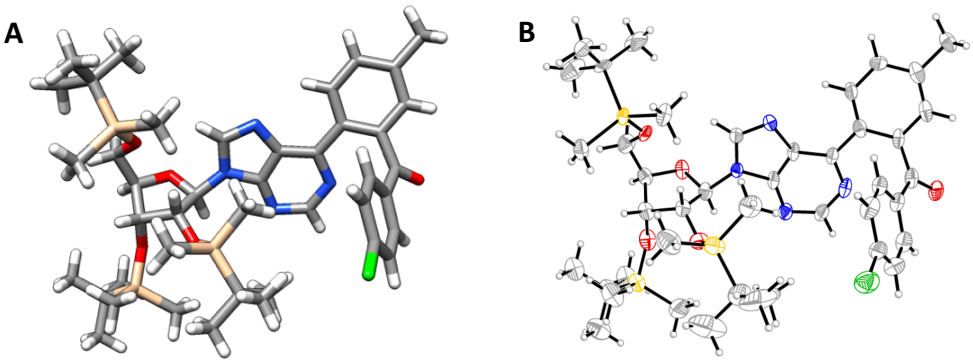
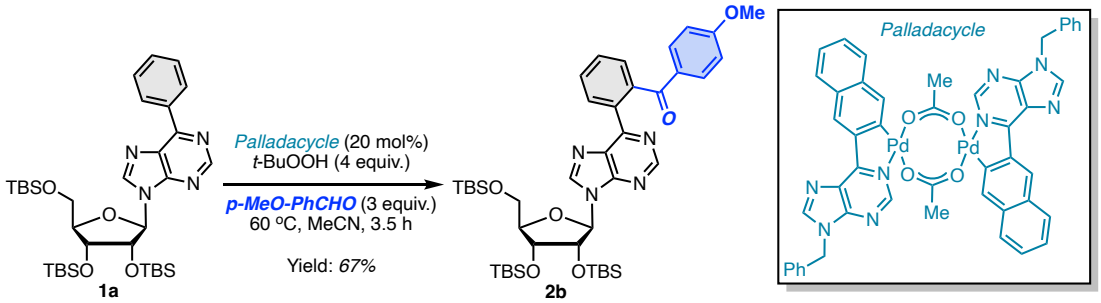


Fig. 2 X-ray crystal structure of compound **2s** (CCDC 2333365). Panel **A**: capped sticks. Panel **B**: ORTEP (atomic displacement parameters are shown at the 30% probability level and disorder at the 3' silyl group is omitted for clarity).

In an attempt to introduce a second aroyl moiety into a mono aroyl product, compound **2a** was exposed to PhCHO, *t*-BuOOH, and catalytic $Pd(OAc)_2$. This did not result in any conversion even after 24 h, and compound **2a**, albeit not very clean, was reisolated. In contrast to Ru-catalyzed arylation[35] and Pd-catalyzed oxidation of 6-arylpurine nucleosides,[36] where a second functionalization was possible, a second aroylation appears difficult.



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

The next focus was on understanding some of the mechanistic details of the aroylation reactions. On the basis of other literature reports[11,14,16] and our prior results[36] a $Pd^{II}/Pd^{III \text{ or } IV}$

catalytic cycle was anticipated. Ideally, formation of an aroylation product from a palladated nucleoside species, under the reaction conditions, would offer direct evidence for involvement of such a species in the reaction pathway. However, as in past efforts,[36] we were unable to isolate a well-defined palladacycle from $Pd(OAc)_2$ and a nucleoside precursor. Thus, we chose to evaluate an aroylation reaction using a purinyl palladacycle we have previously prepared and characterized (Scheme 2).[36] It was hypothesized that if a nucleoside palladacycle is formed *en route* to product, then this preformed palladacycle could become involved in the formation of the requisite palladated nucleoside. In prior work, this palladacycle gave effective C–H bond oxidation. 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.

Generally, reactions of aryl aldehydes with *t*-butoxyl radical are anticipated to yield aroyl radicals. In this context, the bond dissociation energy of the aldehydic C–H bond in PhCHO has been reported as 89 ± 3 kcal mol^{-1},[57] and homolysis of the O–O bond in *t*-BuOOH to yield *t*-butoxyl radical was calculated to be 46.0 kcal mol^{-1}.[58] In thermal Pd-mediated directed aroylation reactions with aryl aldehydes, intermediacy of aroyl radicals has been demonstrated by the isolation of TEMPO-adducts.[14,59–61] To ascertain if radical intermediate(s) are involved in the present reactions, two radical trapping experiments were performed, one using 2 equiv. of 1,1-DPE and the other with 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. Although we were unable to isolate and/or identify any radical-trapped byproducts in both cases, the yield suppression is consistent with the formation of an aroyl radical.

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 Fig. 3. From these data the k_H/k_D was estimated to be 2.25 (average of two runs).

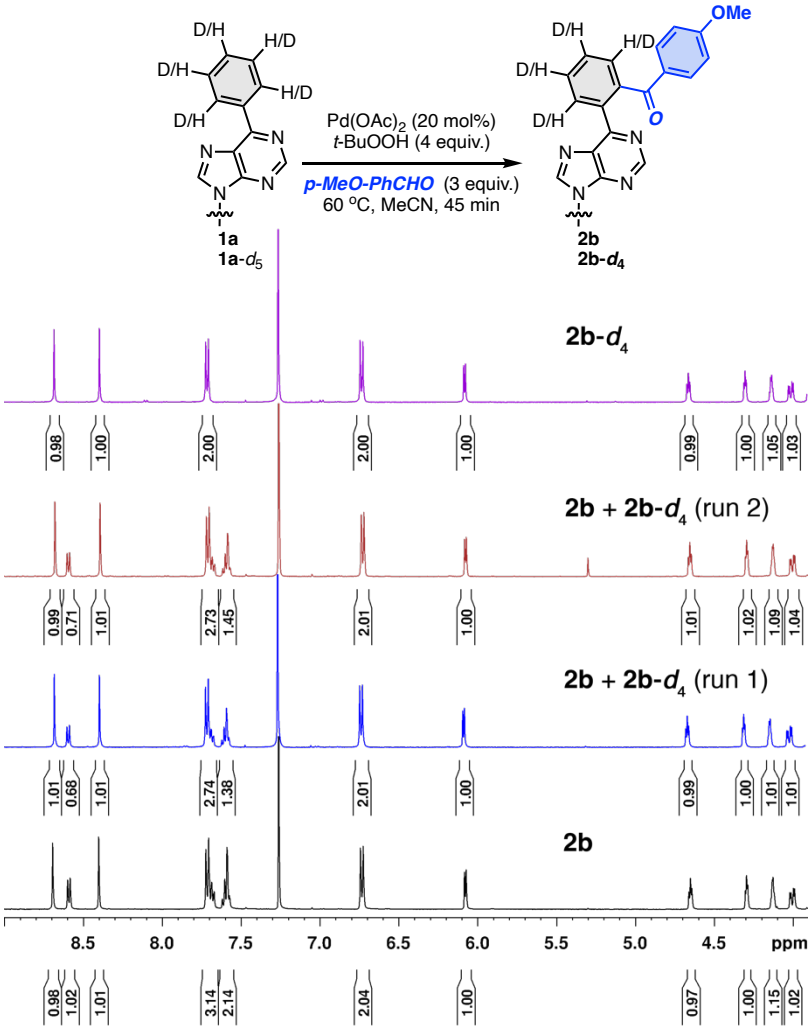
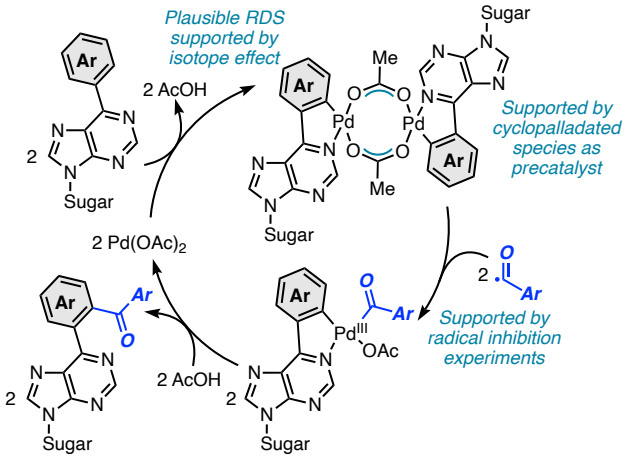


Fig. 3 500 MHz partial ^{1}H NMR spectra (in $CDCl_3$) of products **2b**, **2b-*d*$_4$**, and **2b** + **2b-*d*$_4$**.

In principle, either the *N*1 or the *N*7 atom of the purine, or both, could be involved in coordination to the metal, then proceeding to the C–H bond activation step. Any of these processes would result in the products. In our prior work, by DFT computation we had shown the purinyl *N*1 to aryl C–H distance to be similar to that of the comparable atoms in 2-phenylpyridine (the distance between the *N*7 atom and the aryl C–H was much shorter).[35] Therefore, we had

proposed involvement of the purinyl *N*1 atom in such bond activations. Subsequently, we had calculated the electron densities on the purinyl nitrogen atoms in 6-phenylpurine 2'-deoxyriboside and the order was *N*3 > *N*1 > *N*7 > *N*9.[36] Consistent with these data, metalated complexes obtained from 6-arylpurines and nucleosides with $[IrCl_2Cp^*]_2$, $[RhCl_2Cp^*]_2$, and $OsH_6(iPr_3P)_2$ all involve the purinyl *N*1 atom.[62–65] Similarly, the cyclopalladated complex obtained from $Pd(OAc)_2$[36] used here (Scheme 2) also involves the *N*1 atom in the metalation. From the collective data above, we propose that *N*1 atom-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, straightforward conditions. No special equipment or catalysts are necessary. 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 remotely aroylate purine ribo and 2'-deoxyribonucleoside analogues by an *N*-directed C–H bond activation strategy.

Author Contributions

M.K.L. conceptualized this work, assisted with troubleshooting, wrote the manuscript, reanalyzed all the ^{1}H NMR data, and prepared the ESI based upon the Ph.D. thesis of C.T.M. C.T.M. performed the benchwork and 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 ESI.

Conflicts of Interest

There are no conflicts to declare.

Acknowledgments

We gratefully acknowledge support of this work by NSF awards CHE-1953574 to M.K.L. and CHE-2018774 to N.S. The X-ray diffractometer used to collect data for compound **2s** was acquired with the support of the Air Force Office of Scientific Research under award number FA9550-20-1-0158. We thank Dr. Padmanava Pradhan for his assistance with some NMR acquisitions and Dr. R. R. Chamala for synthesis of the aroyl purine derivative reported in the ESI. We thank Drs. M. K. Reddy, S. Thunga, and G. Garlapati for a critical reading of the manuscript and ESI.

References

1 T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169.

2 X. F. Wu and H. Neumann, *ChemCatChem*, 2012, **4**, 447–458.

3 B. Liu, A. M. Romine, C. Z. Rubel, K. M. Engle and B.-F. Shi. *Chem. Rev.*, 2021, **121**, 14957–15074.

4 J. H. Docherty, T. M. Lister, G. Mcarthur, M. T. Findlay, P. Domingo-Legarda, J. Kenyon, S. Choudhary and I. Larrosa, *Chem. Rev.*, 2023, **123**, 7692–7660.

5 S. K. Sinha, S. Guin, S. Maiti, J. P. Biswas, S. Porey and D. Maiti, *Chem. Rev.*, 2022, **122**, 5682–5941.

6 J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163–9227.

7 G. Yan, X. Wu and M. Yang, *Org. Biomol. Chem.*, 2013, **11**, 5558–5578.

8 X.-F. Wu, *Chem. Eur. J.*, 2015, **21**, 12252–12265.

9 P. Kumar, S. Dutta, S. Kumar, V. Bahadur, E. V. Van der Eycken, K. S. Vimaleswaran, V. S. Parmar and B. K. Singh, *Org. Biomol. Chem.*, 2020, **18**, 7987–8033.

10 X. Jia, S. Zhang, W. Wang, F. Luo and J. Cheng, *Org. Lett.*, 2009, **11**, 3120–3123.

11 O. Baslé, J. Bidange, Q. Shuai and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 1145–1149.

12 S. K. Santra, A. Banerjee and B. K. Patel, *Tetrahedron*, 2014, **70**, 2422–2430.

13 X.-B. Yan, Y.-W. Shen, D.-Q. Chen, P. Gao, Y.-X. Li, X.-R. Song, X.-Y. Liu and Y.-M. Liang, *Tetrahedron*, 2014, **70**, 7490–7495.

14 J.-H. Chu, S.-T. Chen, M.-F. Chiang and M.-J. Wu, *Organometallics*, 2015, **34**, 953–966.

15 G. Kumar and G. Sekar, *RSC Adv.*, 2015, **5**, 28292–28298.

16 F. Zhao, Z. Chen, Y. Liu, K. Xie and Y. Jiang, *Eur. J. Org. Chem.*, 2016, **2016**, 5971–5979.

17 S. Maiti, L. Burgula, G. Chakraborti and J. Dash, *Eur. J. Org. Chem.*, 2017, **2017**, 332–340.

18 J.-H. Chu, M.-F. Chiang, C.-W. Li, Z.-H. Su, S.-C. Lo and M.-J. Wu, *Organometallics*, 2019, **38**, 2105–2119.

19 J. Liu, S. Jin, Y. Zhou, D. Ni, T. Liu, B. Cui, G. Hu, X. Yu and G. Huang, *Synthesis*, 2020, **52**, 1407–1416.

20 M. Li and H. Ge, *Org. Lett.*, 2010, **12**, 3464–3467.

21 F. Xiao, Q. Shuai, F. Zhao, O. Baslé, G. Deng and C.-J. Li, *Org. Lett.*, 2011, **13**, 1614–1617.

22 W. Zhou, H. Li and L. Wang, *Org. Lett.*, 2012, **14**, 4594–4597.

23 S. Guin, S. K. Rout, A. Banerjee, S. Nandi and B. K. Patel, *Org. Lett.*, 2012, **14**, 5294–5297.

24 Z. Xu, B. Xiang and P. Sun, *RSC Adv.,* 2013, **3**, 1679–1682.

25 J. Lu, H. Zhang, X. Chen, H. Liu, Y. Jiang and H. Fu, *Adv. Synth. Catal.*, 2013, **355**, 529–536.

26 Q. Zhang, F. Yang, Y. Wu, *Chem. Commun.*, 2013, **49**, 6837–6839.

27 A. B. Khemnar and B. M. Bhanage, *Eur. J. Org. Chem.*, 2014, **2014**, 6746–6752.

28 N. Khatun, A. Banerjee, S. K. Santra, A. Behera and B. K. Patel, *RSC Adv.*, 2014, **4**, 54532–54538.

29 Q. Zhang, Y. Wang, T. Yang, L. Li and D. Li, *Tetrahedron Lett.*, 2016, **57**, 90–94.

30 X. Liu, Z. Yi, J. Wang and G. Liu, *RSC Adv.*, 2015, **5**, 10641–10646.

31 G. Zhang, S. Sun, F. Yang, Q. Zhang, J. Kang, Y. Wu and Y. Wu, *Adv. Synth. Catal.*, 2015, **357**, 443–450.

32 A. Behera, W. Ali, S. Guin, N. Khatun, P. R. Mohanta and B. K. Patel, *RSC Adv.*, 2015, **5**, 33334–33338.

33 W. Li, S. Zhang, X. Feng, X. Yu, Y. Yamamoto and M. Bao, *Org. Lett.*, 2021, **23**, 2521–2526.

34 M. K. Lakshman, *Chem. Rec.*, 2023, **23**, e202200182, and references therein.

35 M. K. Lakshman, A. C. Deb, R. R. Chamala, P. Pradhan and R. Pratap, *Angew. Chem., Int. Ed.*, 2011, **50**, 11400–11404.

36 R. R. Chamala, D. Parrish, P. Pradhan and M. K. Lakshman, *J. Org. Chem.*, 2013, **78**, 7423–7435.

37 M. Mondal, T. Begum and P. Bharali, *Catal. Sci. Technol.*, 2018, **8**, 6029–6056.

38 Y. Liang and S. F. Wnuk, *Molecules*, 2015, **20**, 4874–4901.

39 V. Gayakhe, Y. S. Sanghvi, I. J. S. Fairlamb and A. R. Kapdi, *Chem. Commun.*, 2015, **51**, 11944–11960.

40 Z. Chen, X. Kong and B. Xu, *ChemistrySelect*, 2020, **5**, 2465–2468.

41 A. C. Rios, H. T. Yu and Y. Tor, *J. Phys. Org. Chem.*, 2015, **28**, 173–180.

42 E. C. Western, J. R. Daft, E. M. Johnson II, P. M. Gannett and K. H. Shaughnessy, *J. Org. Chem.*, 2003, **68**, 6767–6774.

43 E. C. Western and K. H. Shaughnessy, *J. Org. Chem.*, 2005, **70**, 6378–6388.

44 T. E. Storr, C. G. Baumann, R. J. Thatcher, S. De Ornellas, A. C. Whitwood, I. J. S. Fairlamb, *J. Org. Chem.*, 2009, **74**, 5810–5821.

45 H.-M. Guo, L.-L. Jiang, H.-Y. Niu, W.-H. Rao, L. Liang, R.-Z. Mao, D.-Y. Li and G.-R. Qu, *Org. Lett.*, 2011, **13**, 2008–2011.

46 S. Allu and K. C. Kumara Swamy, *RSC Adv.*, 2015, **5**, 92045–92054.

47 C. Xu, L. Zhang, J. Xu, Y. Pan, F. Li, H. Li and L. Xu, *ChemistrySelect*, 2016, **1**, 653–658.

48 Y. Bunno, N. Murakami, Y. Suzuki, M. Kanai, T. Yoshino and S. Matsunaga, *Org. Lett.*, 2016, **18**, 2216–2219.

49 S. Allu, M. Ravi and K. C. Kumara Swamy, *Eur. J. Org. Chem.*, 2016, **2016**, 5697–5705.

50 L. Liang, M.-S. Xie, H.-X. Wang, H.-Y. Niu, G.-R. Qu and H.-M. Guo, *J. Org. Chem.*, 2017, **82**, 5966–5973.

51 D. V. Vorobyeva, M. M. Vinogradov, Y. V. Nelyubina, D. A. Loginov, A. S. Peregudov and S. N. Osipov, *Org. Biomol. Chem.*, 2018, **16**, 2966–2974.

52 U. K. Sharma, H. P. L. Gemoets, F. Schröder, T. Noël and E. V. Van der Eycken, *ACS Catal.*, 2017, **7**, 3818–3823.

53 G. A. Russell, *J. Am. Chem. Soc.*, 1958, **80**, 4987–4996.

54 J. M. Tanko and N. K. Suleman, In Energetics of Organic Free Radicals; eds. J. A. M. Simões, A. Greenberg and J. F. Liebman, Chapman & Hall: New York, 1996, pp 224–293.

55 S. Mitroka, S. Zimmeck, D. Troya and J. M. Tanko, *J. Am. Chem. Soc.*, 2010, **132**, 2907–2913.

56 D. Sebastian, P. H. Willoughby and M. K. Lakshman, *Org. Biomol. Chem.*, 2022, **20**, 5735–5746.

57 J. A. Martinho Simões and D. Griller, *Chem. Phys. Lett.*, 1989, **158**, 175–177.

58 P. J. Jones, B. Riser and J. Zhang, *J. Phys. Chem. A.*, 2017, **121**, 7846–7853.

59 A. Banerjee, A. Bera, S. K. Santra, S. Guin and B. K. Patel, *RSC Adv.*, 2014, **4**, 8558–8566.

60 A. Hossain, M. K. Manna, K. Manna and R. Jana, *Org. Biomol. Chem.*, 2017, **15**, 6592–6603.

61 L.-Y. Shao, Z. Xu, C.-Y. Wang, X.-P. Fu, M.-M. Chen, H.-W. Liu and Y.-F. Ji, *Org. Biomol. Chem.*, 2018, **16**, 6284–6294.

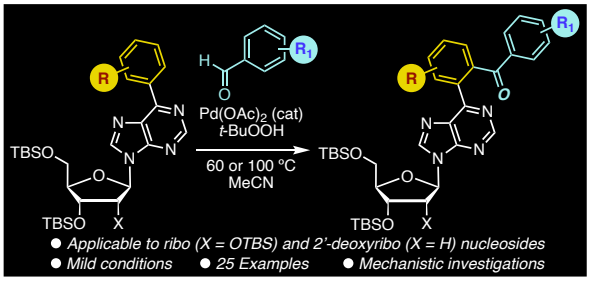
62 M. Martín-Ortíz, M. Gómez-Gallego, C. Ramírez de Arellano and M. A. Sierra, *Chem. Eur. J.*, 2012, **18**, 12603–12608.

63 H. J. Kim, M. J. Ajitha, Y. Lee, J. Ryu, J. Kim, Y. Lee, Y. Jung and S. Chang. *J. Am. Chem. Soc.*, 2014, **136**, 1132–1140.

64 M. Valencia, M. Martín-Ortiz, M. Gómez-Gallego, C. Ramírez de Arellano and M. A. Sierra, *Chem. Eur. J.*, 2014, **20**, 3831–3838.

65 A. Collado, M. Gómez-Gallego and M. A. Sierra, *Eur. J. Org. Chem.*, 2018, **2018**, 1617–1623.

Table of Contents Entry



The purinyl nitrogen atom is an effective metalation director, which in the presence of $Pd(OAc)_2$, *t*-BuOOH, and aryl aldehydes, leads to acylation of the aryl ring at the C6 position of the purine.