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Purinyl N1-Directed Aromatic C−H Oxidation in 6-Arylpurines and 6-Arylpurine Nucleosides

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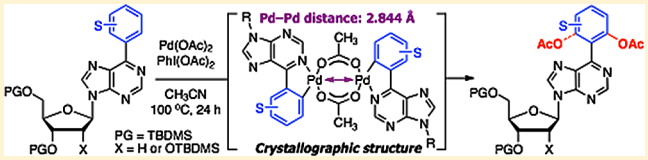
Supporting Information

ABSTRACT: Palladium-catalyzed C−H bond activation and oxidation of C6 arylpurines as well as C6 arylpurine nucleosides can be accomplished using $Pd(OAc)_2/PhI(OAc)_2$ in CH_3CN. Despite the presence of four nitrogen atoms in the purine moiety as well as the polyoxygenated saccharide and a labile glycosidic bond in the nucleosides, these reactions can be effectively conducted. Notably, the generally more labile 2′-deoxyribonucleosides also undergo reaction. The reaction conditions can be tuned to yield either monoacetoxylated or diacetoxylated products predominantly. In the course of these investigations, a dimeric Pd^{II}-containing cyclopalladated C6 naphthylpurine derivative has been obtained and crystallographically characterized. This compound is competent in catalyzing the oxidization with $PhI(OAc)_2$, indicating its plausible intermediacy in the chemistry. The X-ray structure of a monoacetoxylated product from this reaction has also been obtained.



INTRODUCTION

Purines and purine nucleosides are highly important biomolecules that have found wide applications in biology, in biochemistry, and as pharmaceutical agents.[1] Therefore, the ability to functionalize and, in particular, conduct otherwise difficult transformations on these entities has important consequences. Purines and purine nucleosides are generally challenging substrates for metal-catalyzed reactions, due to the presence of the polynitrogenated heterocycles, which can sequester metals and thereby hinder catalytic pathways. With nucleosides, this is additionally complicated by the presence of multiple oxygen atoms as well as a labile glycosidic bond. Furthermore, purine 2′-deoxyribonucleosides are more labile in comparison to their ribo analogues.

In contemporary organic synthesis, a simple but powerful approach to diverse modification of organic molecules involves transition-metal-mediated C−H bond activation and functionalization. Although a wide range of such transformations are catalyzed by Pd, the use of other metals such as Cu, Fe, and Rh is documented as well.[2−4] Of relevance to this communication, a recent review has focused on Pd-catalyzed C−O bond formation.[5]

Despite the potential difficulties posed by purines and purine nucleosides, these substrates have become increasingly interesting for C−H bond activation and functionalization. For example, C8 arylation reactions of xanthines with aryl halides have been conducted using CuI[6] or $Pd(acac)_2/CuI$,[7] and C−H/C−H cross-coupling of xanthines has been accomplished using $Pd(OAc)_2/Cu(OAc)_2$.[8] N9-alkyl adenine derivatives have been subjected to C8 arylation reactions with aryl halides using $Pd(OH)_2/CuI$.[9,10] More importantly, adenosine and 2′-deoxyadenosine have also been used as substrates in C−H bond activation studies, leading to C-8 arylated products.[11−13] Particularly notable is the ability to conduct this type of chemistry on 2′-deoxyadenosine, which is quite a sensitive substrate.[13]

There is sparse literature on N-directed C−H bond activation of purines and purine nucleosides and fewer studies still on the highly labile 2′-deoxyribonucleosides.[14−17] We have recently reported Ru-catalyzed C−H bond activation and arylation of 6-arylpurine 2′-deoxyribonucleosides under nonacidic conditions.[15] Acidic reaction media, which can be used in reactions of purines and ribonucleosides, are precluded due to the acid sensitivity of the glycosidic bond in the 2′-deoxyribonucleosides. More recently, C−H bond activation has been applied to the synthesis of polycycles containing fused purines and purine ribonucleosides,[16] and N-directed sulfonamidation of two purines as well as two purine ribonucleosides has been accomplished.[17] Herein, we discuss our results on the purinyl N1-directed Pd-catalyzed C−H bond activation and monohydroxylation of 6-arylpurines, 6-arylpurine ribonucleosides, and 2′-deoxy derivatives, under broadly applicable nonacidic conditions. We also demonstrate that these substrates can be subjected to bis oxidation by slight modification of the conditions. Importantly, we have isolated and characterized, for the first time, a palladated dimer from a C6 arylpurine and investigated its plausible role in the catalytic process.

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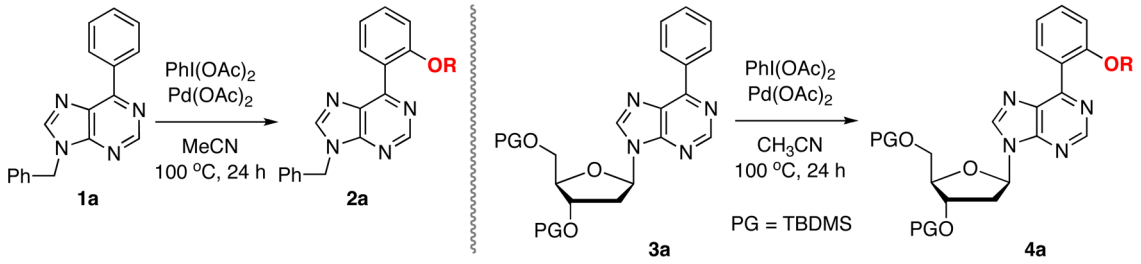
Table 1. Optimization of Reaction Conditions for C−H Bond Activation and Oxidation



entry	substrate	conditions	solvent	R	result[a]
1	**1a**	5 mol % $Pd(OAc)_2$ 1.2 molar equiv $PhI(OAc)_2$	MeCN	H[b]	63% yield
2	**1a**	10 mol % $Pd(OAc)_2$ 1.2 molar equiv $PhI(OAc)_2$	MeCN	H[b]	63% yield
3	**1a**	5 mol % $Pd(OAc)_2$ 1.5 molar equiv $PhI(OAc)_2$	MeCN	H[b]	78% yield
4	**1a**	5 mol % $Pd(OAc)_2$ 1.5 molar equiv $PhI(OAc)_2$	PhH	H[b]	73% yield
5	**1a**	5 mol % $Pd(OAc)_2$ 1.5 molar equiv $PhI(OAc)_2$	MeOH	Me	66% yield of $\mathbf{2a}^{Me}$ (31% recovered **1a**)
6	**3a**	5 mol % $Pd(OAc)_2$ 1.5 molar equiv $PhI(OAc)_2$	AcOH	H	no discernible product[c]
7	**3a**	5 mol % $Pd(OAc)_2$ 1.2 molar equiv $PhI(OAc)_2$	MeCN	H[b]	incomplete
8	**3a**	10 mol % $Pd(OAc)_2$ 1.5 molar equiv $PhI(OAc)_2$	MeCN	H[b]	57% yield

[a]Where reported, yield is of isolated and purified product. [b]After deacetylation with NaOMe/MeOH. [c]Under conditions reported in ref 18 (5 mol % of $Pd(OAc)_2$, 1.5 mol equiv of $PhI(OAc)_2$, Ac_2O, AcOH, 120 °C, 5 h).

RESULTS AND DISCUSSION

Although C−H bond activation and oxidation of N9-alkyl C6-arylpurines were reported in a previous communication, only a single nucleoside was evaluated.[18] There, oxidation of 6-phenyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine gave mono- as well as diacetoxylated products in a ∼2.1:1 ratio (combined 77% yield).[18] This substrate, being a ribonucleoside and bearing electron-withdrawing acetate protecting groups on the saccharide, proved to be relatively stable in acetic acid at 120 °C. These conditions, however, are likely to be incompatible with more sensitive substrates. Thus, we undertook an evaluation of reaction conditions that would be broadly applicable to purines, to purine ribonucleosides, and importantly to the 2′-deoxy derivatives. In fact, the last species are expected to be limiting cases. Table 1 shows the results from this screening.

Using 5 mol % of $Pd(OAc)_2$/1.2 molar equiv of $PhI(OAc)_2$ in MeCN, complete consumption of **1a** was observed. However, in addition to the desired monoacetoxy product, the phenol arising by hydrolysis was also observed. In order to eliminate the need for separation, product yields were assessed after deacetylation with NaOMe/MeOH. This first reaction (entry 1) gave a respectable 63% product yield, and this remained unaltered upon only increasing the amount of $Pd(OAc)_2$ to 10 mol % (entry 2). However, the product yield improved to 78% when the amount of $PhI(OAc)_2$ was increased to 1.5 molar equiv while retaining 5 mol % $Pd(OAc)_2$ (entry 3). Changing the solvent to PhH did not change the outcome significantly (entry 4), although the reaction in MeCN appeared a little cleaner by TLC (UV visualization). Use of MeOH as solvent led to the clean formation of the monomethyl ether $\mathbf{2a}^{Me}$ (66% yield), although **1a** was not fully consumed (entry 5).

Not unexpectedly, a reaction of deoxyribonucleoside **3a** conducted in AcOH led to no discernible product formation (entry 6). However, in MeCN and with 5 mol % of $Pd(OAc)_2$/1.2 molar equiv of $PhI(OAc)_2$ the reaction proceeded but was incomplete. When the $Pd(OAc)_2$ loading was increased to 10 mol % with 1.5 mol molar equiv of $PhI(OAc)_2$, complete consumption of **3a** occurred and **4a** was obtained in 57% yield after acetate cleavage. These results indicate that (a) C6 arylpurines and C6 arylpurine nucleosides can be subjected to C−H bond activation and oxidation, (b) the catalyst loading for reactions of the nucleosides is likely to be higher than that for the purine (we have observed differences in the Ru-catalyzed arylation reactions of C6 phenylpurines and C6 arylpurine nucleosides[15]), (c) the lower yield with the 2′-deoxyribonucleoside is possibly due to its higher lability, but the reaction is satisfactory, (d) under the conditions tested no discernible bis oxidation of the purine or the nucleoside was observed, in contrast to the prior result,[18] and (e) acid additive/solvent is not necessary, which broadens the scope of the method to acid-sensitive compounds.

Next, the general utility of these conditions for the C−H bond activation and oxidation of a range of C6 arylpurines and purine nucleosides was considered (Scheme 1). The four N9-benzyl C6-arylpurines **1a−d** were tested, and each gave monohydroxylated products (after deacetylation) uneventfully and in generally good yields. Interestingly, the C6 naphthyl derivative **1d** underwent regioselective oxidation at C3 and not at C1, as evidenced by the presence of three well-resolved singlets in the ^{1}H NMR spectrum (two purinyl and one naphthyl at δ 10.00, 8.97, and 8.20 ppm).

The four C6 arylpurine 2′-deoxyribonucleosides **3a−d** also underwent acetoxylation readily, yielding the monooxidation products **4a−d**. Oxidation of **3b** had to be conducted with 0.85 molar equiv of $PhI(OAc)_2$ because uncharacterized side products were observed when 1.5 molar equiv was used. Here 22% of **3b** was recovered for a 53% isolated yield of **4b** (not based on recovered **3b**). As was the case with **1d**, the C6 naphthyl derivative **3d** again yielded **4d** as the only regioisomer.

Some differences were noted in the reactions of the ribonucleosides **5a−c**. With methoxyl precursor **5b**, both mono- and diacetoxylation was observed (ratio of mono- to diacetate ∼3.6:1). On the other hand, with fluoro precursor **5c**, although product **6c** was isolated in a good yield, the reaction remained incomplete and some starting material was isolated along with an uncharacterized impurity. The overoxidation of **5b** and the incomplete reaction of **5c** could be attributable to the electron densities of the two systems. Interestingly, in

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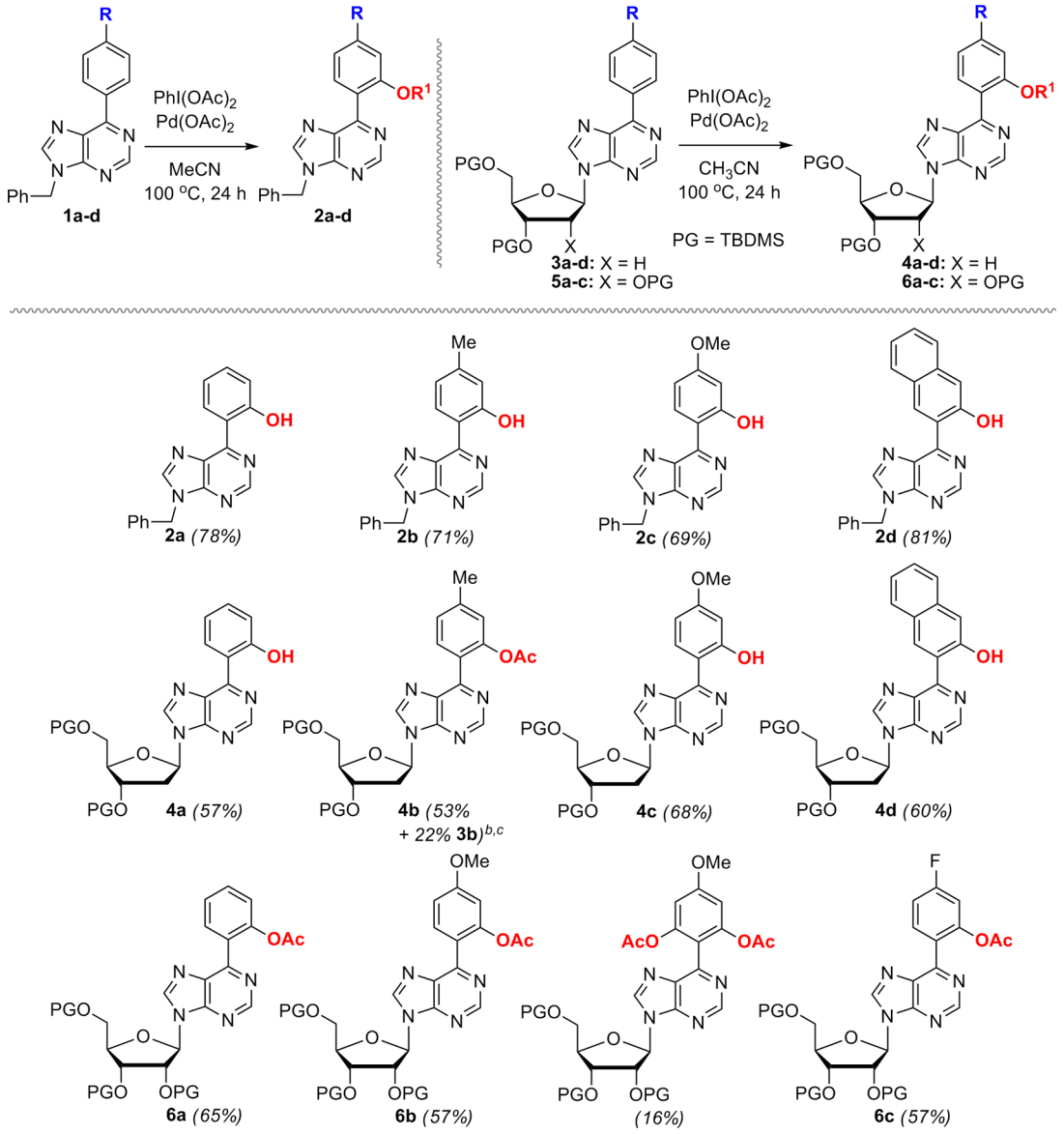
Scheme 1. Monooxidation of Purines and Purine Nucleosides[a]



[a]In the case of the purine and most of the 2′-deoxyribonucleoside derivatives, because partial hydrolysis of the acetoxy group was observed, products were isolated after deacetylation with NaOMe/MeOH. [b]The reaction leading to **4b** was conducted with 0.85 molar equiv of $PhI(OAc)_2$. [c]Product was isolated and characterized as the monoacetate because no significant hydrolysis of the ester was observed at the end of the reaction.

reactions of the ribonucleoside precursors, hydrolysis of the acetate group was not observed, and the products were isolated as the esters.

The unexplored bis oxidation of these substrates was then evaluated. In order to ensure effective conversions, 3 molar equiv of $PhI(OAc)_2$ was used for reactions of both the purines and the nucleosides. The amount of $Pd(OAc)_2$ was increased to 10 mol % for the purine reactions and to 15 mol % for reactions of the nucleosides. The substrates selected for these reactions were **1a−c**, **3a−c**, and **5a−c**. The C6 naphthyl substrates **1d** and **3d** were not included, since it seemed unlikely that they would yield the bis oxidation products on the basis of the results described above: i.e., the regioselective oxidation observed. The results from these experiments are shown in Figure 1.

As can be seen from Figure 1, all substrates underwent reaction and the products could be isolated as the diacetates. Interestingly, the fluorophenyl substrate **5c** gave 39% of the diacetoxylated product **9c** and 32% of monoacetoxylated **6c**. As stated earlier, this result may be attributable to the electron deficiency of the ring undergoing oxidation. Nevertheless, the relatively facile bis oxidation of these complex substrates is feasible under slightly modified conditions.

Having completed these synthetic experiments, attention was focused on the identification of potential reactive intermediate(s) in these transformations, so as to gain an understanding of the plausible mechanism of these oxidations. Heating 9-benzyl-6-(2-naphthyl)-9*H*-purine (**1d**) with stoichiometric $Pd(OAc)_2$ in PhH at 60 °C (2 h) led to the isolation of the dimeric cyclopalladated species **10** (Figure 2) in 40% yield after crystallization.

In prior work we had computationally determined the distances between the *ortho* C−H bond, which undergoes bond activation, and the N1 and N7 atoms in 9-benzyl-6-phenyl-9*H*-

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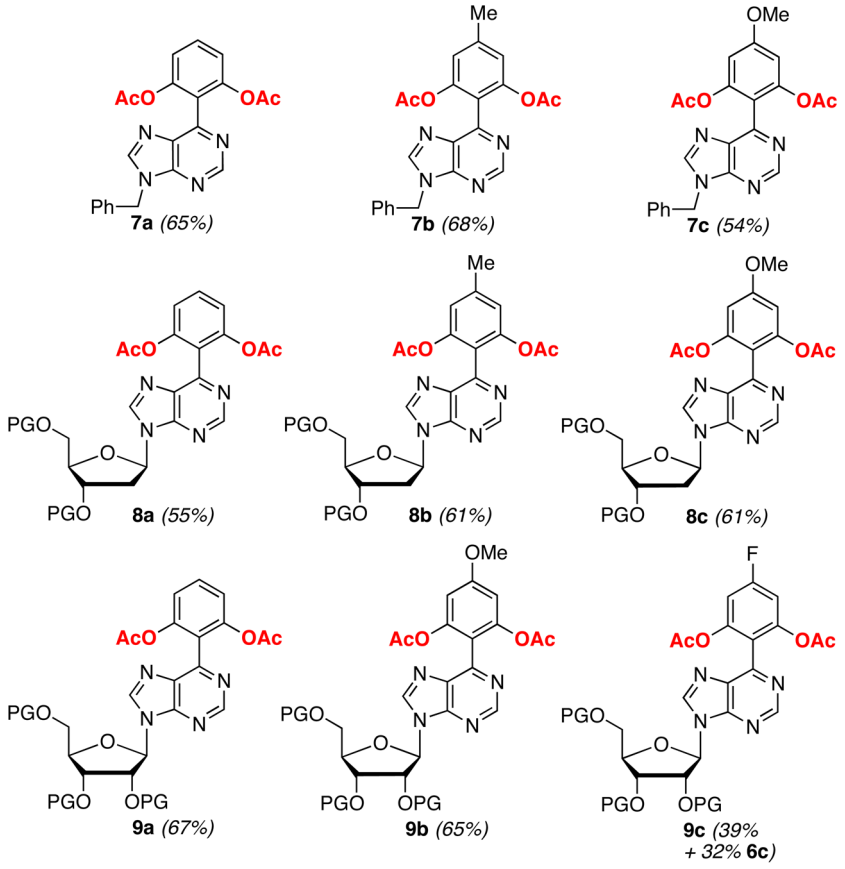

Figure 1. Structures of the bis oxidation products of purines and purine nucleosides.

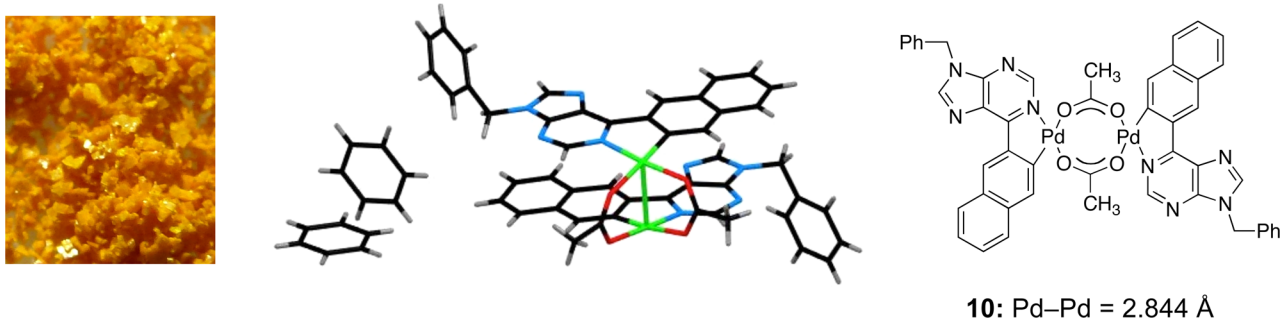

Figure 2. Crystals and crystal structure of dimeric cyclopalladated compound **10** obtained from 9-benzyl-6-(2-naphthyl)-9*H*-purine (**1d**).

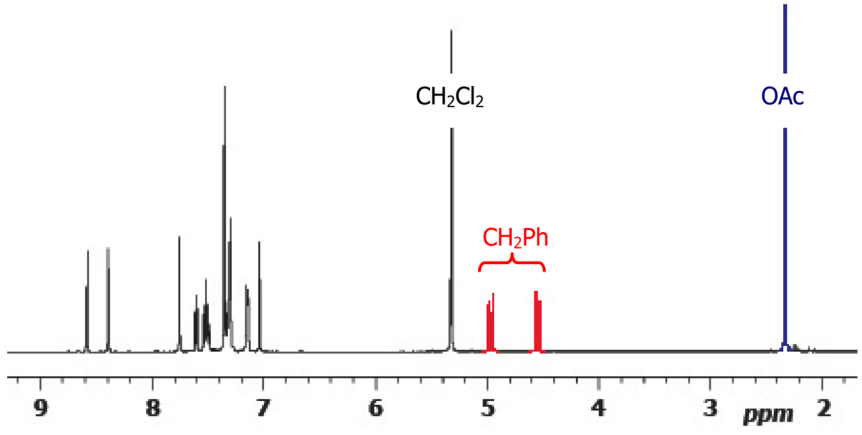

Figure 3. ^{1}H NMR spectrum of palladated complex **10** in CD_2Cl_2.

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purine. In this analysis, the N1···H distance was calculated to be 2.41 Å and the N7···H distance as 2.29 Å.[15] By comparison, in 2-phenylpyridine the corresponding N···H distance is 2.49 Å.[15] Thus, the N1···H distance in the purine derivative is similar to that in 2-phenylpyridine. However, in 9-benzyl-6-phenyl-9*H*-purine the phenyl ring and purine are coplanar,[15] consistent with crystallographic data in the literature.[19] On this basis, we had proposed the involvement of the purinyl N1 atom in the Ru-catalyzed C−H bond activation and arylation.[15]

As seen from Figure 2, despite the presence of four purinyl nitrogen atoms, complex **10**[20] involves the N1 atom. This is the first such structure of a dimeric palladated species resulting from purinyl N-directed C−H bond activation. The crystal structure of a monomeric Ir^{III} complex derived from N9-THP-protected 6-phenylpurine, involving N-directed C−H bond activation, has been recently obtained.[21] Interestingly, the absence of the THP substituent at N9 led to the formation of a dimeric complex involving this nitrogen atom, and no C−H bond activation was observed.[21] This result also demonstrates the precarious reactivity balance in the chemistry of these heterocycles.

In CD_2Cl_2, the proton NMR spectrum of **10** (Figure 3) shows the presence of four one-proton singlets at δ 8.58, 8.39, 7.75, and 7.04 ppm, corresponding to two purinyl resonances as well as two aromatic resonances from the naphthyl moiety, in addition to the remaining naphthyl resonances and the acetate resonance. Here again, these data provide evidence for N-directed palladation at the C3 position of the naphthalene moiety rather than at the C2 position. More interesting, however, is the presence of two doublets at δ 4.97 and 4.55 ppm (J_{gem} = 15.3 Hz) corresponding to the geminal protons of the benzyl group.

Studies have recently been conducted into the mechanism of N-directed C−H bond activation and oxidation. Whereas Pd^{II}/Pd^{IV} redox cycles have been proposed in C−H bond activation processes,[22−27] dinuclear Pd^{III} species have recently emerged as plausible intermediates in these catalytic cycles.[28−31] Such dinuclear complexes would also account for the overall second-order dependence on the Pd concentration, observed in the C−H bond activation−arylation chemistry.[27] Dinuclear complexes are important to the formation and stabilities of high-valent Pd−Pd bonds. In fact, modulation of bridging versus chelating properties of ligands between two Pd centers has been shown to influence the separation of the metal centers in dinuclear Pd complexes, a factor that then influences the ease of one-electron oxidation.[32]

Crystallographic structures of palladium acetate dimers from 2-phenylpyridine, 2-*p*-tolylpyridine, and benzo[*h*]quinoline have been obtained. When the Pd−Pd bond distance in **10** is compared to those in these simpler analogues, it is similar to those in palladated pyridyl dimers[33] and identical with that formed from benzo[*h*]quinoline.[30] It is a reasonable anticipation then that the mechanism of oxidative addition and reductive elimination involving **10** could be similar to that of the less complex heterocycles: that is, a bimetallic process involving Pd^{III}−Pd^{III} bond formation.[29,34]

In order to probe this question, oxidation of 9-benzyl-6-(2-naphthyl)-9*H*-purine (**1d**) was performed using 2.5 mol % of the Pd dimer **10** (based upon the molecular weight of the dimer) as a precatalyst and 1.5 molar equiv of $PhI(OAc)_2$. This reaction gave a high 93% yield of product **12** after a reaction time of 24 h at 100 °C.

We also evaluated comparatively the oxidation reactions catalyzed by $Pd(OAc)_2$ as well as the palladated dimer **10**, and the results of this analysis are shown in Table 2. Dimer **10**

Table 2. Comparison of the Oxidation Reactions Catalyzed by $Pd(OAc)_2$ and Complex 10[a]

entry	substrate	catalyst	time (h)	product: yield (%)[b]
1	**1d**	5 mol % $Pd(OAc)_2$	1	**12**: 86
2	**1d**	2.5 mol % **10**[c]	1	**12**: 91, incomplete reaction[d]
3	**1d**	5 mol % $Pd(OAc)_2$	5	**12**: 82
4	**1d**	2.5 mol % **10**[c]	5	**12**: 91
5	**1d**	2.5 mol % **10**[c]	24	**12**: 93
6	**3a**	10 mol % $Pd(OAc)_2$	5	$\mathbf{4a}^{Ac}$: 61
7	**3a**	2.5 mol % **10**[c]	5	$\mathbf{4a}^{Ac}$: 55, incomplete reaction[e]
8	**3a**	5 mol % of **10**[c]	5	$\mathbf{4a}^{Ac}$: 59, incomplete reaction[f]

[a]1.5 molar equiv of $PhI(OAc)_2$ was used in each reaction. [b]Where reported, the yield is of isolated and purified product. [c]Based upon the molecular weight of the dimer. [d]About 5% of **1d** was recovered, contaminated with an impurity. [e]About 27% of **3a** was recovered, contaminated with a trace amount of an impurity. [f]A trace of **3a** was recovered, contaminated with an impurity.

produced cleaner reactions (TLC analysis) of 9-benzyl-6-(2-naphthyl)-9*H*-purine (**1d**), with generally slightly better product yields (entries 1 versus 2, and 3 versus 4). In the reactions of nucleoside **3a**, use of $Pd(OAc)_2$ led to a completed reaction and gave a 61% yield of monoacetoxy product $\mathbf{4a}^{Ac}$ (entry 6). This is comparable to the result in Scheme 1, where a 57% yield of **4a** was obtained over two steps. On the other hand, use of 2.5 mol % of **10** led to an incomplete reaction, with a significant amount of residual **3a** and 55% yield of $\mathbf{4a}^{Ac}$ (entry 7). Interestingly, increasing the loading of **10** to 5 mol % produced a marginally better 59% yield of $\mathbf{4a}^{Ac}$ and a trace amount of **3a** was left unconverted. As we have observed in Ru-catalyzed arylation chemistry,[15] and as seen in these results, there are subtle reactivity differences between closely related purines and the corresponding nucleosides.

Although a prior report speculated on the plausible intermediacy of palladated purinyl dimers in these oxidations, we provide direct evidence herein.[18] Thus, palladated dimers such as **10**, which can potentially form in the reaction, are competent in catalyzing the oxidation reaction. The plausible involvement of **10** in the catalytic cycle is shown in Scheme 2. The crystal structure of product **12**[35] obtained from the reaction of **1d** (Scheme 2) confirms the structure and addresses the regiochemistry question associated with the oxidation of this substrate.

One notable aspect of these reactions is the role of acetic acid. Typically C−H bond activation processes are conducted in acetic acid, and a linear correlation has been observed between the concentration of acetic acid and the rate of reductive elimination in C−Cl bond-forming processes.[30,34] This has led to the proposal that protonation of one acetate bridge in the Pd^{III}−Pd^{III} dimer occurs, leading to cleavage of one Pd−O bond and formation of a binuclear species with one pentacoordinate Pd. Computations indicate that reductive elimination from such a species is more favorable than in the absence of protonation.[30] Thus, the role of acetic acid solvent may be important in these reactions. However, because of

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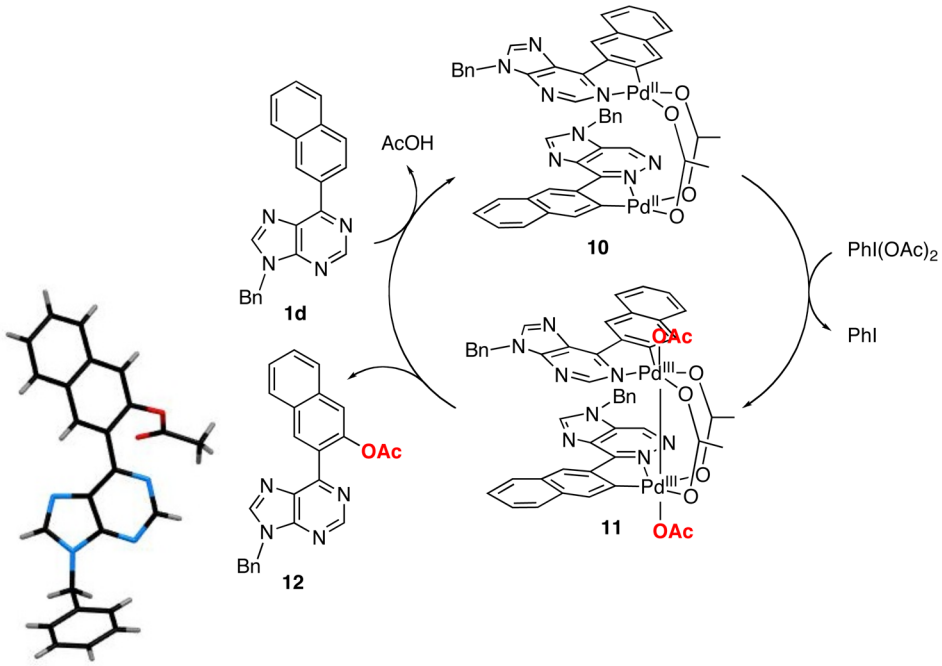
Scheme 2. Plausible Mechanism for the N-Directed Oxidation and Crystallographic Structure of the Acetoxylation Product 12



instability of the nucleoside and/or protecting groups in hot acetic acid, the reactions herein were conducted in MeCN. Thus, the reductive elimination step in the present cases either proceeds via a (slower) acid-independent pathway[30] or simply by the small amounts of acetic acid produced in the cyclopalladation step. Notably, the 24 h reaction times do not appear to be detrimental to the nucleosides.

In order to decipher the electron density differences between the four purinyl nitrogen atoms, natural bond order (NBO) analysis was performed by the B3LYP density functional method with the triple-ζ basis set 6-311++G(d,p). These calculations show that the N1 and N3 atoms in both 9-benzyl-6-phenyl-9*H*-purine and 6-phenyl-9-(2′-deoxy-β-D-ribofuranosyl)-9*H*-purine carry greater electron densities than the N7 and N9 atoms (Figure 4). Thus, on the basis of these computations,

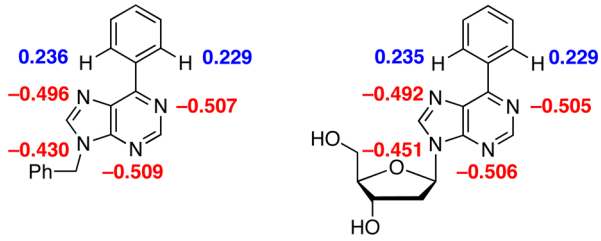


Figure 4. NBO analyzed natural charges on the nitrogen and two aryl hydrogen atoms in 9-benzyl-6-phenyl-9*H*-purine and 6-phenyl-9-(2′-deoxy-β-D-ribofuranosyl)-9*H*-purine.

greater interactions of the metal with the N1 and N3 atoms can be postulated in comparison to the N7 and N9 atoms, with the N1-metal interactions leading to the reaction cascade. However, all of the nitrogen atoms can in principle interact with the metal center. Despite this, as demonstrated herein, both mono- and diacetoxylation reactions can be accomplished, conceivably with the involvement of the purinyl N1 atom.

CONCLUSIONS

In summary, we have demonstrated that purines as well as purine nucleosides (ribo and 2′-deoxyribo derivatives) undergo N-directed C−H bond activation and oxidation via the use of $Pd(OAc)_2$/$PhI(OAc)_2$ in MeCN as solvent. This is despite the four nitrogen atoms of the purine, which can all coordinate to the metal, the labile glycosidic bond, and the multiple oxygen atoms of the saccharide moiety. Use of AcOH as solvent is precluded because 2′-deoxyribonucleosides are not stable to acidic conditions at elevated temperature. Thus, any rate-enhancing effect of acidic solvent or additive is limited to the AcOH produced upon cyclometalation. Despite this, satisfactory reactions are observed. A dimeric cyclopalladated species has been obtained from 9-benzyl-6-(2-naphthyl)-9*H*-purine, and its structure has been established by crystallographic as well as NMR analyses. In this species among the four nitrogen atoms of the purine, the N1 atom is coordinated to the metal center. This appears to be consistent with prior computational results, which implicate this nitrogen atom in Ru-catalyzed C−H bond activation processes as well. The cyclopalladated species catalyzes the oxidation of 9-benzyl-6-(2-naphthyl)-9*H*-purine with $PhI(OAc)_2$. This is the first case wherein a cyclopalladated Pd^{II} dimer resulting from a purine has been isolated, characterized, and implicated in C−H bond activation processes. Other studies on metal-mediated C−H bond activation are currently ongoing in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Considerations. Thin-layer chromatography was performed on aluminum-foil-backed TLC plates of 200 μm thickness, and column chromatographic purifications were performed on 200−300 mesh silica gel. MeCN was distilled over CaH_2, and commercially available anhydrous MeOH was used. $Pd(OAc)_2$ and all other reagents were obtained from commercial sources and were used without further purification. The 6-arylpurine and 6-arylpurine nucleoside precursors were synthesized by minor modifications of published procedures.[36,37] ^{1}H NMR spectra were recorded at 500

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MHz in deacidified $CDCl_3$ (deacidification is done by percolating through a bed of basic alumina and $NaHCO_3$) and are referenced to the residual solvent resonance. ^{13}C NMR spectra were recorded at 125 MHz in $CDCl_3$ and are referenced to the solvent resonance. ^{19}F NMR spectra were recorded at 282 MHz using $CDCl_3$ as the lock solvent and $CFCl_3$ as the internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are in hertz (Hz). Proton assignments indicated were made on the basis of COSY spectra of representative compounds and comparisons with the literature. HRMS analyses were performed using a TOF analyzer; the ionization methods are provided in the compound characterization.

General Procedure for the Mono C−H Bond Oxidation of 6-Aryl-9-benzyl-9*H*-purine. In an oven-dried, nitrogen gas flushed vial equipped with a stirring bar was placed the 6-aryl-9-benzyl-9*H*-purine (0.10 mmol) in anhydrous MeCN (1.0 mL). To this solution was added $Pd(OAc)_2$ (5 mol %) followed by $PhI(OAc)_2$ (1.5 molar equiv). The reaction mixture was flushed with nitrogen gas, sealed with a Teflon-lined cap, and heated at 100 °C for 24 h. The crude reaction mixture was then filtered through a short plug of silica, and the filtrate was evaporated. The residue was dissolved in anhydrous MeOH (2 mL), NaOMe (2 molar equiv) was added, and the mixture was stirred for 3 h at room temperature. After the completion of the reaction (monitored by TLC), the MeOH was evaporated, the residue was redissolved in CH_2Cl_2, and this solution was washed with 5% aqueous HCl (1 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography.

General Procedure for the Bis C−H Bond Oxidation of 6-Aryl-9-benzyl-9*H*-purine. In an oven-dried, nitrogen gas flushed vial equipped with a stirring bar was placed the 6-aryl-9-benzyl-9*H*-purine (0.10 mmol) in anhydrous MeCN (1.0 mL). To this solution was added $Pd(OAc)_2$ (10 mol %) followed by $PhI(OAc)_2$ (3 molar equiv). The reaction mixture was flushed with nitrogen gas, sealed with a Teflon-lined cap, and heated at 100 °C for 24 h. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography.

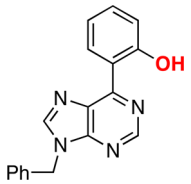
General Procedure for the Mono C−H Bond Oxidation of 6-Arylpurine 2′-Deoxyribonucleosides. In an oven-dried, nitrogen gas flushed vial equipped with a stirring bar was placed the 6-arylpurine 2′-deoxyribonucleoside (0.10 mmol) in anhydrous MeCN (0.5 mL). To this solution was added $Pd(OAc)_2$ (10 mol %) followed by of $PhI(OAc)_2$ (1.5 molar equiv). The reaction mixture was flushed with nitrogen gas, sealed with a Teflon-lined cap, and heated at 100 °C for 24 h. The crude reaction mixture was filtered through a short plug of silica gel, and the filtrate was evaporated. The residue was dissolved in anhydrous MeOH (2 mL), NaOMe (2 molar equiv) was added, and the mixture was stirred for 3 h at room temperature. After the completion of the reaction (monitored by TLC), the MeOH was evaporated, the residue was redissolved in CH_2Cl_2, and this solution was washed with 5% aqueous HCl (1 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography.

Note: 0.85 molar equiv of $PhI(OAc)_2$ was used for the oxidation substrate **3b**.

Note: in the mono C−H bond oxidation reactions of 6-arylpurine ribonucleosides, the procedure is exactly the same as for the 2′-deoxyribo analogues, except that deacetylation using NaOMe was not necessary and the products were isolated as the monoacetates.

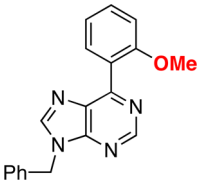
General Procedure for the Bis C−H Bond Oxidation of 6-Arylpurine 2′-Deoxyribonucleosides and 6-Arylpurine Ribonucleosides. In an oven-dried, nitrogen gas flushed vial equipped with a stirring bar was placed the 6-arylpurine 2′-deoxyribonucleoside or 6-arylpurine ribonucleoside (0.10 mmol) in anhydrous MeCN (1.0 mL). To this solution was added $Pd(OAc)_2$ (15 mol %) followed by $PhI(OAc)_2$ (3 molar equiv). The reaction mixture was flushed with nitrogen gas, sealed with a Teflon-lined cap, and heated at 100 °C for 24 h. After the completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography.

2-(9-Benzyl-9*H*-purin-6-yl)phenol (2a).



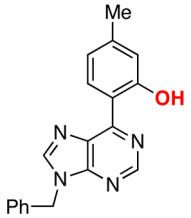
Chromatography using CH_2Cl_2 followed by 0.5% acetone in CH_2Cl_2 gave 23.7 mg (78% yield) of a light yellow solid. R_f (SiO_2/10% acetone in CH_2Cl_2) = 0.60. ^1H NMR (500 MHz, $CDCl_3$): δ 9.37 (d, 1H, Ar-H, J = 7.8 Hz), 8.95 (s, 1H, Ar-H), 8.18 (s, 1H, Ar-H), 7.44−7.33 (m, 6H, Ar-H), 7.09 (d, 1H, Ar-H, J = 8.3 Hz), 7.04 (t, 1H, Ar-H, J = 7.8 Hz), 5.51 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 155.8, 151.9, 149.8, 143.9, 134.9, 133.5, 132.4, 129.2, 128.7, 127.8, 119.2, 118.2, 117.3, 47.3. HRMS (ESI): calcd for $C_{18}H_{15}N_4O$ $[M + H]^+$ 303.1240, found 303.1243.

9-Benzyl-6-(2-methoxyphenyl)-9*H*-purine (2a^{Me}).



In an oven-dried, nitrogen gas flushed vial equipped with stirring bar was placed 9-benzyl-6-phenyl-9*H*-purine (28.6 mg, 0.10 mmol) in anhydrous MeOH (1.0 mL). To this solution was added $Pd(OAc)_2$ (1.12 mg, 5 μmol, 5 mol %) followed by $PhI(OAc)_2$ (48.3 mg, 0.15 mmol, 1.5 molar equiv). The reaction mixture was flushed with nitrogen gas, sealed with a Teflon-lined cap, and heated at 100 °C for 24 h. After 24 the solvent was evaporated under reduced pressure and the crude material was purified by chromatography on a silica gel column using 5% acetone in CH_2Cl_2 to afford 21.0 mg (66% yield) of a light brown solid. R_f (SiO_2/10% acetone in CH_2Cl_2) = 0.14. ^1H NMR (500 MHz, $CDCl_3$): δ 9.12 (s, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 7.69 (d, 1H, Ar-H, J = 6.8 Hz), 7.45 (t, 1H, Ar-H, J = 7.8), 7.39−7.33 (m, 5H, Ar-H), 7.13−7.08 (m, 2H, Ar-H), 5.48 (s, 2H, CH_2), 3.85, (s, 3H, OMe). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 156.5, 152.5, 152.0, 144.5, 135.3, 132.5, 132.0, 131.8, 129.4, 128.8, 128.4, 128.2, 124.6, 120.9, 112.2, 56.2, 47.6. HRMS (ESI): calcd for $C_{19}H_{17}N_4O$ $[M + H]^+$ 317.1397, found 317.1396.

2-(9-Benzyl-9*H*-purin-6-yl)-5-methylphenol (2b).



Chromatography using CH_2Cl_2 followed by 1% acetone in CH_2Cl_2 gave 22.4 mg (71% yield) of a yellow solid. R_f (SiO_2/10% acetone in CH_2Cl_2) = 0.55. ^1H NMR (500 MHz, $CDCl_3$): δ 9.24 (d, 1H, Ar-H, J = 7.8 Hz), 8.88 (s, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 7.38−7.31 (m, 5H, Ar-H), 6.89 (s, 1H, Ar-H), 6.85 (d, 1H, Ar-H, J = 8.3 Hz), 5.48 (s, 2H, CH_2), 2.38 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 156.0, 151.9, 149.9, 144.9, 143.9, 135.2, 132.4, 129.4, 129.1, 128.9, 128.1, 120.7, 118.7, 114.8, 47.5, 22.0. HRMS (ESI): calcd for $C_{19}H_{17}N_4O$ $[M + H]^+$ 317.1397, found 317.1420.

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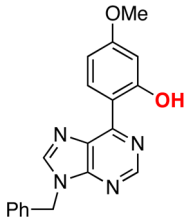
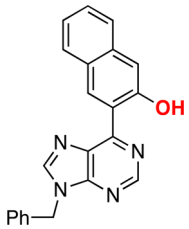
2-(9-Benzyl-9*H*-purin-6-yl)-5-methoxyphenol (2c).



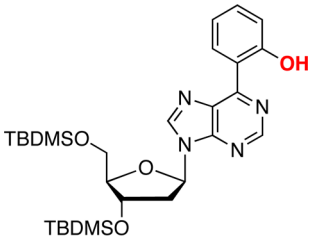
Chromatography using CH_2Cl_2 followed by 2% acetone in CH_2Cl_2 gave 23.0 mg (69% yield) of an off-white solid. R_f (SiO_2/10% acetone in CH_2Cl_2) = 0.54. ^1H NMR (500 MHz, $CDCl_3$): δ 9.30 (d, 1H, Ar-H, J = 8.8 Hz), 8.80 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 7.38−7.30 (m, 5H, Ar-H), 6.58 (dd, 1H, Ar-H, J = 2.4 Hz, 8.8 Hz), 6.54 (d, 1H, Ar-H, J = 2.9 Hz), 5.44 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3, 164.2, 155.7, 151.6, 149.8, 143.6, 135.2, 133.9, 129.4, 128.8, 128.6, 128.0, 110.7, 107.8, 101.7, 55.3, 47.3. HRMS (ESI): calcd for $C_{19}H_{17}N_4O_2$ $[M + H]^+$ 333.1346, found 333.1349.

3-(9-Benzyl-9*H*-purin-6-yl)naphthalen-2-ol (2d).



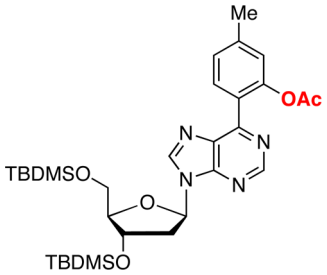
Chromatography using CH_2Cl_2 followed by 0.5% acetone in CH_2Cl_2 gave 28.5 mg (81% yield) of a yellow solid. R_f (SiO_2/10% acetone in CH_2Cl_2) = 0.62. ^1H NMR (500 MHz, $CDCl_3$): δ 10.00 (s, 1H, Ar-H), 8.97 (s, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 7.95 (d, 1H, Ar-H, J = 8.3 Hz), 7.68 (d, 1H, Ar-H, J = 8.3 Hz), 7.47 (t, 1H, Ar-H, J = 7.3 Hz) 7.41−7.33 (m, 6H, Ar-H), 7.30 (t, 1H, Ar-H, J = 7.6 Hz), 5.49 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 155.7, 152.3, 150.0, 144.6, 136.8, 135.1, 130.1, 129.7, 129.5, 128.9, 128.6, 128.1, 127.9, 126.2, 123.5, 119.6, 112.1, 47.6. HRMS (ESI): calcd for $C_{22}H_{17}N_4O$ $[M + H]^+$ 353.1397, found 353.1395.

6-[2-Hydroxyphenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (4a).



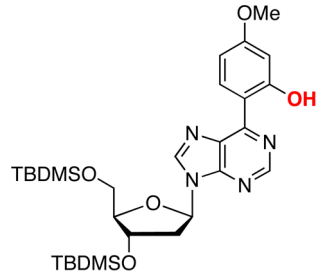
Chromatography using 50% CH_2Cl_2 in hexanes followed by 80% CH_2Cl_2 in hexanes gave 31.6 mg (57% yield) of a yellowish green oil. R_f (SiO_2/5% EtOAc in CH_2Cl_2) = 0.60. ^1H NMR (500 MHz, $CDCl_3$): δ 9.41 (dd, 1H, Ar-H, J = 1.71, 8.0 Hz), 8.88 (s, 1H, Ar-H), 8.50 (s, 1H, Ar-H), 7.42 (ddd, 2H, Ar-H, J = 1.5, 6.8, 8.5 Hz), 7.07−7.03 (m, 2H, Ar-H), 6.58 (app t, 1H, H-1′, J_{app} = 6.3 Hz), 4.67−4.64 (m, 1H, H-3′), 4.07 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.89 (dd, 1H, H-5′, J = 4.4, 11.2 Hz), 3.80 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.67 (app quint, 1H, H-2′, J_{app} = 6.5 Hz), 2.52 (ddd, 1H, H-2′, J = 3.9, 5.9, 13.2 Hz), 0.93 and 0.92 (2 s, 18H, *t*-Bu), 0.12 and 0.10 (2 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 155.7, 151.3, 149.4, 142.6, 133.5, 132.5, 129.9, 119.2, 118.2, 117.3, 88.1, 84.5, 71.9, 62.7, 41.4, 25.9, 25.7, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. HRMS (ESI): calcd for $C_{28}H_{45}N_4O4Si_2$ $[M + H]^+$ 557.2974, found 557.2976.

6-[2-Acetoxy-4-methylphenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (4b).



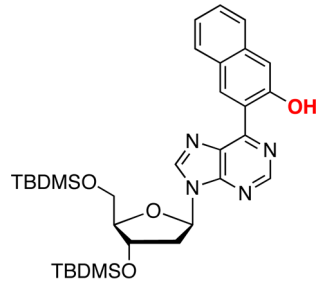
Chromatography using CH_2Cl_2, followed by 1% and then 2% acetone in CH_2Cl_2 gave 32.4 mg (53% yield) of a yellow gum. R_f (SiO_2/5% acetone in CH_2Cl_2) = 0.39. ^1H NMR (500 MHz, $CDCl_3$): δ 8.97 (s, 1H, Ar-H), 8.37 (s, 1H, Ar-H), 8.12 (d, 1H, Ar-H, J = 7.8 Hz), 7.23 (d, 1H, Ar-H, J = 7.8 Hz), 7.08 (s, 1H, Ar-H), 6.55 (t, 1H, H-1′, J = 6.6 Hz), 4.66−4.64 (m, 1H, H-3′), 4.05 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.88 (dd, 1H, H-5′, J = 4.1, 11.2 Hz), 3.79 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.71 (app quint, 1H, H-2′, J_{app} = 6.5 Hz), 2.49−2.44 (ddd + s, 4H, H-2′, CH_3, J = 3.6, 5.9, 12.7 Hz), 2.18 (s, 3H, OAc), 0.93 and 0.90 (2 s, 18H, *t*-Bu), 0.12, 0.08, and 0.07 (3 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 154.8, 152.1, 151.7, 148.9, 143.1, 142.3, 132.6, 132.5, 127.2, 125.3, 124.6, 88.2, 84.7, 72.3, 63.0, 41.3, 29.9, 26.2, 25.9, 21.6, 21.5, 18.6, 18.2, −4.4, −4.6, −5.1, −5.2. HRMS (ESI): calcd for $C_{31}H_{49}N_4O_5Si_2$ $[M + H]^+$ 613.3236, found 613.3210.

6-[2-Hydroxy-4-methoxyphenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (4c).



Chromatography using 80% CH_2Cl_2 in hexanes gave 39.7 mg (68% yield) of a light yellow oil. R_f (SiO_2/5% EtOAc in CH_2Cl_2) = 0.60. ^1H NMR (500 MHz, $CDCl_3$): δ 9.33 (d, 1H, Ar-H, J = 8.8 Hz), 8.79 (s, 1H, Ar-H), 8.42 (s, 1H, Ar-H), 6.62 (dd, 1H, Ar-H, J = 2.4, 8.8 Hz), 6.57−6.55 (m, 2H, Ar-H, H-1′), 4.66−4.63 (m, 1H, H-3′), 4.06 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.90−3.87 (m + s, 4H, H-5′, OMe), 3.79 (dd, 1H, H-5′, J = 3.4, 11.2 Hz), 2.66 (app quint, 1H, H-2′, J_{app} = 6.5 Hz), 2.49 (ddd, 1H, H-2′, J = 3.9, 5.9, 13.2 Hz), 0.93 and 0.91 (2 s, 18H, *t*-Bu), 0.12 and 0.10 (2 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 155.5, 150.9, 149.3, 142.0, 133.8, 129.1, 110.6, 107.5, 101.6, 88.1, 84.4, 71.9, 62.7, 55.3, 41.4, 25.9, 25.7, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. HRMS (ESI): calcd for $C_{29}H_{47}N_4O_5Si_2$ $[M + H]^+$ 587.3080, found 587.3079.

6-[3-Hydroxy-2-naphthenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (4d).



Chromatography using 50% CH_2Cl_2 in hexanes, followed by 80% CH_2Cl_2 in hexanes and finally CH_2Cl_2, gave 36.7 mg (60% yield) of a golden yellow solid. R_f (SiO_2/5% acetone in CH_2Cl_2) = 0.52. ^1H NMR (500 MHz, $CDCl_3$): δ 10.06 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H), 8.57 (s, 1H, Ar-H), 7.98 (d, 1H, Ar-H, J = 8.2 Hz), 7.69 (d, 1H, Ar-H, J =

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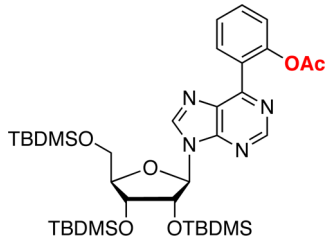
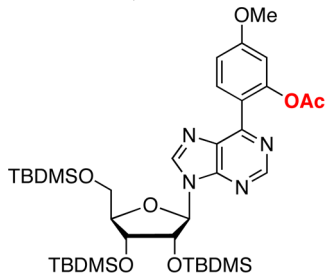
8.2 Hz), 7.47 (t, 1H, Ar-H, J = 7.8 Hz), 7.37 (s, 1H, Ar-H), 7.31 (t, 1H, Ar-H, J = 7.8 Hz), 6.60 (t, 1H, H-1′, J = 6.3 Hz), 4.69−4.66 (m, 1H, H-3′), 4.08 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.91 (dd, 1H, H-5′, J = 4.4, 11.2 Hz), 3.82 (dd, 1H, H-5′, J = 3.4, 11.2 Hz), 2.69 (app quint, 1H, H-2′, J_{app} = 6.3 Hz), 2.54 (ddd, 1H, H-2′, J = 3.9, 6.3, 13.2 Hz), 0.94 and 0.93 (2 s, 18H, *t*-Bu), 0.13 and 0.12 (2 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1, 155.1, 151.5, 149.3, 143.3, 136.7, 135.1, 130.4, 129.6, 128.5, 127.8, 126.0, 123.1, 119.2, 112.0, 88.3, 84.7, 71.8, 62.7, 41.5, 25.9, 25.7, 18.4, 18.0, −4.6, −4.8, −5.4, −5.5. HRMS (ESI): calcd for $C_{32}H_{47}N_4O_4Si_2$ $[M + H]^+$ 607.3130, found 607.3132.

6-[2-Acetoxyphenyl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-9*H*-purine (6a).



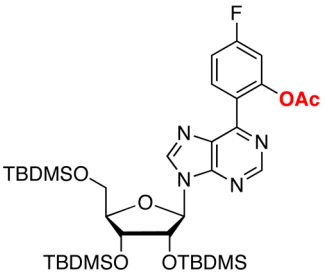
Chromatography using 9% EtOAc in hexanes gave 47.5 mg (65% yield) of a light brown solid. R_f (SiO_2/40% EtOAc in hexanes) = 0.63. ^1H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H, Ar-H), 8.45 (s, 1H, Ar-H), 8.15 (d, 1H, Ar-H, J = 7.8 Hz), 7.54 (t, 1H, Ar-H, J = 7.8 Hz), 7.43 (t, 1H, Ar-H, J = 7.6 Hz), 7.29 (d, 2H, Ar-H, J = 7.8 Hz), 6.16 (d, 1H, H-1′, J = 5.4 Hz), 4.72 (t, 1H, H-2′, J = 4.6 Hz), 4.35 (t, 1H, H-3′, J = 3.9 Hz), 4.17 (app q, 1H, H-4′, J_{app} = 3.2 Hz), 4.04 (dd, 1H, H-5′, J = 3.5, 11.4 Hz), 3.82 (dd, 1H, H-5′, J = 2.7, 11.5 Hz), 2.16 (s, 3H, OAc), 0.96, 0.95, and 0.79 (3 s, 27H, *t*-Bu), 0.14, 0.13, 0.12, −0.03, and −0.24 (5 s, 18H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 154.5, 152.1, 152.0, 149.0, 143.8, 132.6, 131.5, 128.1, 126.2, 124.1, 88.5, 85.8, 76.0, 72.2, 62.7, 26.3, 26.0, 25.8, 21.5, 21.5, 18.7, 18.3, 18.0, −4.2, −4.4, −4.5, −4.8, −5.2. HRMS (ESI): calcd for $C_{36}H_{61}N_4O_6Si_3$ $[M + H]^+$ 729.3893, found 729.3880.

6-[2-Acetoxy-4-methoxyphenyl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-9*H*-purine (6b).



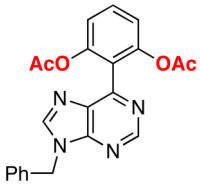
Chromatography using 10% EtOAc in hexanes gave 43.5 mg (57% yield) as a light yellow gum. R_f (SiO_2/20% EtOAc in hexanes) = 0.30. ^1H NMR (500 MHz, $CDCl_3$): δ 8.95 (s, 1H, Ar-H), 8.42 (s, 1H, Ar-H), 8.28 (d, 1H, Ar-H, J = 8.8 Hz), 6.97 (dd, 1H, Ar-H, J = 2.2, 8.5 Hz), 6.80 (d, 1H, Ar-H, J = 2.4 Hz), 6.14 (d, 1H, H-1′, J = 5.4 Hz), 4.71 (t, 1H, H-2′, J = 4.6 Hz), 4.35 (t, 1H, H-3′, J = 3.7 Hz), 4.16 (app q, 1H, H-4′, J_{app} = 3.2 Hz), 4.04 (dd, 1H, H-5′, J = 4.1, 11.5 Hz), 3.87 (s, 3H, OMe), 3.81 (dd, 1H, H-5′, J = 2.7, 11.5 Hz), 2.21 (s, 3H, OAc), 0.95, 0.94, and 0.79 (3 s, 27H, *t*-Bu), 0.14, 0.13, 0.11, −0.03, and −0.23 (5 s, 18H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 162.3, 154.3, 152.0, 150.5, 143.5, 133.9, 132.2, 120.5, 112.4, 109.8, 88.5, 85.9, 76.0, 72.2, 62.7, 55.8, 26.3, 26.1, 25.8, 21.5, 18.7, 18.3, 18.1, −4.2, −4.4, −4.5, −4.8, −5.1. HRMS (ESI): calcd for $C_{37}H_{63}N_4O_7Si_3$ $[M + H]^+$ 759.3999, found 759.4014.

6-[2-Acetoxy-4-fluorophenyl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-9*H*-purine (6c).



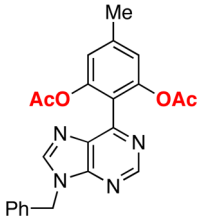
Chromatography using 7% EtOAc in hexanes gave 42.3 mg (57% yield) of a light brown gum. R_f (SiO_2/20% EtOAc in hexanes) = 0.49. ^1H NMR (500 MHz, $CDCl_3$): δ 8.98 (s, 1H, Ar-H), 8.45 (s, 1H, Ar-H), 8.22 (dd, 1H, Ar-H, J = 6.3, 8.8 Hz), 7.15 (td, 1H, Ar-H, J = 2.4, 8.3 Hz), 7.05 (dd, 1H, Ar-H, J = 2.4, 9.3 Hz), 6.16 (d, 1H, H-1′, J = 4.9 Hz), 4.69 (t, 1H, H-2′, J = 4.9 Hz), 4.34 (t, 1H, H-3′, J = 3.9 Hz), 4.16 (app q, 1H, H-4′, J_{app} = 3.2 Hz), 4.04 (dd, 1H, H-5′, J = 3.9, 11.2 Hz), 3.82 (dd, 1H, H-5′, J = 2.4, 11.2 Hz), 2.12 (s, 3H, OAc), 0.96, 0.94, and 0.79 (3 s, 27H, *t*-Bu), 0.15, 0.14, 0.11, −0.03, and −0.24 (5 s, 18H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 165.0, 163.0, 153.7, 152.2 (d, J = 5.9 Hz), 152.0, 150.3 (d, J = 11 Hz), 143.9, 134.1 (d, J = 9.6 Hz), 132.5, 124.5, 113.6 (d, J = 21.5 Hz), 112.0 (d, J = 24.3 Hz), 88.5, 85.9, 76.1, 72.2, 62.7, 26.3, 26.0, 25.8, 21.5, 18.7, 18.3, 18.0, −4.2, −4.4, −4.5, −4.8, −5.1. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −108.38 (br). HRMS (ESI): calcd for $C_{36}H_{60}FN_4O_6Si_3$ $[M + H]^+$ 747.3799, found 747.3825.

2-(9-Benzyl-9*H*-purin-6-yl)-1,3-phenylene Diacetate (7a).



Chromatography using CH_2Cl_2 followed by 4% acetone in CH_2Cl_2 gave 26.1 mg (65% yield) of a light brown solid. R_f (SiO_2/5% acetone in CH_2Cl_2) = 0.43. ^1H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H, Ar-H), 8.06 (s, 1H, Ar-H), 7.54 (t, 1H, Ar-H, J = 8.3 Hz), 7.39−7.32 (m, 5H, Ar-H), 7.22 (d, 1H, Ar-H, J = 8.3 Hz), 5.48 (s, 2H, CH_2), 1.96 (s, 6H, OAc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 152.2, 151.8, 151.5, 149.4, 144.8, 135.0, 132.8, 130.5, 129.2, 128.7, 127.8, 121.6, 120.9, 47.4, 20.9. HRMS (ESI): calcd for $C_{22}H_{19}N_4O_4$ $[M + H]^+$ 403.1401, found 403.1401.

2-(9-Benzyl-9*H*-purin-6-yl)-5-methyl-1,3-phenylene Diacetate (7b).



Chromatography using CH_2Cl_2 followed by 5% acetone in CH_2Cl_2 gave 28.5 mg (68% yield) of a light brown solid. R_f (SiO_2/5% acetone in CH_2Cl_2) = 0.33. ^1H NMR (500 MHz, $CDCl_3$): δ 9.05 (s, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 7.39−7.29 (m, 5H, Ar-H), 7.03 (s, 2H, Ar-H), 5.46 (s, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.95 (s, 6H, OAc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 152.4, 152.0, 151.9, 149.3, 144.7, 141.7, 135.3, 133.0, 129.4, 128.9, 128.0, 121.8, 119.0, 47.5, 21.7, 21.2. HRMS (ESI): calcd for $C_{23}H_{21}N_4O_4$ $[M + H]^+$ 417.1557, found 417.1539.

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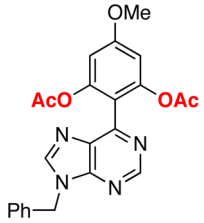
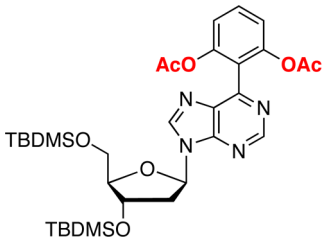
2-(9-Benzyl-9*H*-purin-6-yl)-5-methoxy-1,3-phenylene Diacetate (7c).



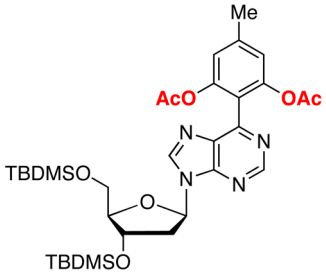
Chromatography using CH_2Cl_2 followed by 6% acetone in CH_2Cl_2 gave 23.4 mg (54% yield) of a fluffy, light brown solid. R_f (SiO_2/10% acetone in CH_2Cl_2) = 0.32. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.04 (s, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 7.39−7.31 (m, 5H, Ar-H), 6.77 (s, 2H, Ar-H), 5.47 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 1.96 (s, 6H, OAc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 161.3, 152.0, 151.5, 150.2, 144.5, 129.2, 128.7, 127.8, 107.2, 55.8, 47.4, 21.1. HRMS (ESI): calcd for $C_{23}H_{21}N_4O_5$ $[M + H]^+$ 433.1506, found 433.1509.

6-[2,6-Diacetoxyphenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (8a).



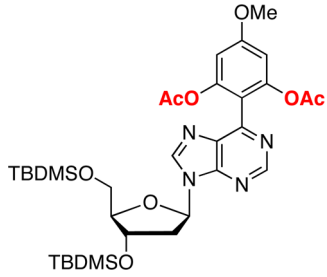
Chromatography using CH_2Cl_2 followed by 1%, 2%, and 3% acetone in CH_2Cl_2 gave 36.1 mg (55% yield) of a pale yellow solid. R_f (SiO_2/5% acetone in CH_2Cl_2) = 0.36. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (s, 1H, Ar-H), 8.38 (s, 1H, Ar-H), 7.53 (t, 1H, Ar-H, J = 8.3 Hz), 7.22 (d, 2H, Ar-H, J = 8.3 Hz), 6.56 (t, 1H, H-1′, J = 6.6 Hz), 4.66−4.64 (m, 1H, H-3′), 4.05 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.87 (dd, 1H, H-5′, J = 4.4, 11.2 Hz), 3.79 (dd, 1H, H-5′, J = 3.4, 11.2 Hz), 2.70 (app quint, 1H, H-2′, J_{app} = 6.6 Hz), 2.47 (ddd, 1H, H-2′, J = 3.4, 5.8, 12.7 Hz), 1.97 (s, 6H, OAc), 0.93 and 0.90 (2 s, 18H, *t*-Bu), 0.12, 0.08, and 0.07 (3 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 151.7, 151.3, 149.4, 143.6, 133.5, 130.6, 121.3, 120.9, 88.1, 84.4, 72.0, 62.8, 41.2, 25.9, 25.8, 21.0, 18.4, 18.0, −4.7, −4.8, −5.4, −5.5. HRMS (ESI): calcd for $C_{32}H_{49}N_4O_7Si_2$ $[M + H]^+$ 657.3134, found 657.3137.

6-[2,6-Diacetoxy-4-methylphenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (8b).



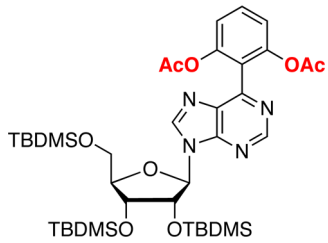
Chromatography using CH_2Cl_2 followed by 3% acetone in CH_2Cl_2 gave 40.9 mg (61% yield) of a light yellow solid. R_f (SiO_2/5% acetone in CH_2Cl_2) = 0.45. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H, Ar-H), 8.36 (s, 1H, Ar-H), 7.03 (s, 2H, Ar-H), 6.59 (app t, 1H, H-1′, J_{app} = 6.6 Hz), 4.64 (m, 1H, H-3′), 4.05 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.87 (dd, 1H, H-5′, J = 4.4, 11.2 Hz), 3.79 (dd, 1H, H-5′, J = 3.4, 11.2 Hz), 2.70 (app quint, 1H, H-2′, J_{app} = 6.6 Hz), 2.49−2.44 (m + s, 4H, H-2′, CH_3), 1.97 (s, 6H, OAc), 0.93 and 0.91 (2 s, 18H, *t*-Bu), 0.12, 0.08, and 0.07 (3 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8, 151.9, 151.4, 149.3, 143.5, 141.8, 133.7, 121.7, 88.3, 84.6, 72.3, 63.1, 41.4, 26.2, 25.9, 21.7, 21.3, 18.6, 18.2, −4.4, −4.6, −5.1, −5.2. HRMS (ESI): calcd for $C_{33}H_{51}N_4O_7Si_2$ $[M + H]^+$ 671.3291, found 671.3298.

6-[2,6-Diacetoxy-4-methoxyphenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (8c).



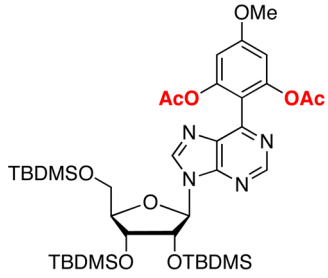
Chromatography using CH_2Cl_2 followed by 3% acetone in CH_2Cl_2 gave 42.0 mg (61% yield) of a pale yellow gum. R_f (SiO_2/5% acetone in CH_2Cl_2/) = 0.41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (s, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 6.77 (s, 2H, Ar-H), 6.55 (app t, 1H, H-1′, J_{app} = 6.6 Hz), 4.64 (m, 1H, H-3′), 4.04 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.89−3.84 (m + s, 4H, H-5′, OMe), 3.79 (dd, 1H, H-5′, J = 3.4, 11.2 Hz), 2.70 (app quint, 1H, H-2′, J_{app} = 6.5 Hz), 2.46 (ddd, 1H, H-2′, J = 3.7, 5.9, 13.2 Hz), 1.96 (s, 6H, OAc), 0.90 and 0.89 (2 s, 18H, *t*-Bu), 0.09, 0.06, and 0.05 (3 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 161.4, 152.0, 151.8, 151.4, 150.5, 143.2, 133.7, 114.5, 107.5, 88.2, 84.6, 72.3, 63.1, 55.9, 41.3, 26.1, 25.9, 21.2, 18.6, 18.2, −4.5, −4.6, −5.3, −5.3. HRMS (ESI): calcd for $C_{33}H_{51}N_4O_8Si_2$ $[M + H]^+$ 687.3240, found 687.3243.

6-[2,6-Diacetoxyphenyl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (9a).



Chromatography using 70% EtOAc in hexanes gave 52.8 mg (67% yield) of a light brown solid. R_f (SiO_2/EtOAc) = 0.24. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (s, 1H, Ar-H), 8.43 (s, 1H, Ar-H), 7.53 (t, 1H, Ar-H, J = 8.3 Hz), 7.22 (d, 2H, Ar-H, J = 8.3 Hz), 6.16 (d, 1H, H-1′, J = 5.9 Hz), 4.72 (t, 1H, H-2′, J = 5.1 Hz), 4.33 (t, 1H, H-3′, J = 3.7 Hz), 4.16 (app q, 1H, H-4′, J_{app} = 3.1 Hz), 4.03 (dd, 1H, H-5′, J = 4.4, 11.2 Hz), 3.82 (dd, 1H, H-5′, J = 2.7, 11.2 Hz), 2.97 (s, 6H, OAc), 0.96, 0.95, and 0.78 (3 s, 27H, *t*-Bu), 0.14, 0.13, 0.11, −0.04, and −0.29 (5 s, 18H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 152.0, 151.8, 151.6, 149.6, 144.1, 133.8, 130.7, 121.7, 121.0, 88.4, 86.1, 75.9, 72.4, 62.8, 26.3, 26.0, 25.8, 21.2, 18.7, 18.3, 18.0, −4.2, −4.3, −4.4, −4.9, −5.2. HRMS (ESI): calcd for $C_{38}H_{63}N_4O_8Si_3$ $[M + H]^+$ 787.3948, found 787.3944.

6-[2,6-Diacetoxy-4-methoxyphenyl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl]-9*H*-purine (9b).

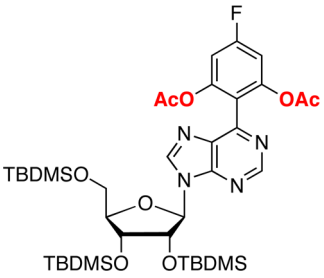


Chromatography using 30% EtOAc in hexanes gave 52.8 mg (65% yield) of a fluffy, yellow solid. R_f (SiO_2/30% EtOAc in hexanes) = 0.28. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar-H), 8.40 (s, 1H, Ar-H), 6.78 (s, 2H, Ar-H), 6.14 (d, 1H, H-1′, J = 5.9 Hz), 4.72 (t, 1H, H-2′, J = 4.9 Hz), 4.33 (t, 1H, H-3′, J = 3.7 Hz), 4.16 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 4.03 (dd, 1H, H-5′, J = 4.1, 11.5 Hz), 3.85 (s, 3H, OMe), 3.82 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 1.98 (s, 6H, OAc), 0.95,

dx.doi.org/10.1021/jo4008282 | J. Org. Chem. 2013, 78, 7423−7435

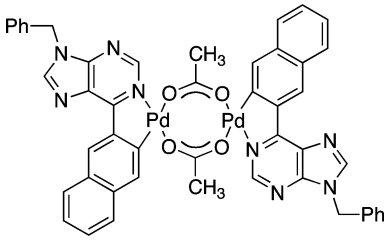
0.94, and 0.78 (3 s, 27H, *t*-Bu), 0.14, 0.13, 0.11, −0.04, and −0.28 (5 s, 18H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 161.5, 151.9, 151.7, 150.4, 143.9, 133.7, 107.5, 88.4, 86.0, 75.9, 72.4, 62.8, 56.0, 26.3, 26.0, 25.8, 21.3, 18.7, 18.3, 18.0, −4.2, −4.3, −4.4, −4.8, −5.1. HRMS (ESI): calcd for $C_{39}H_{65}N_4O_9Si_3$ $[M + H]^+$ 817.4054, found 817.4078.

6-[2,6-Diacetoxy-4-fluorophenyl]-9-[2,3,5-tri-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-9*H*-purine (9c).



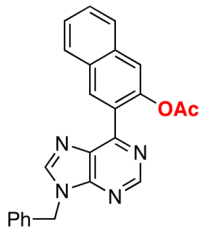
Chromatography using 60% EtOAc in hexanes gave 31.7 mg (39% yield) gave a light brown gum. R_f (SiO_2/70% EtOAc in hexanes) = 0.21. ^1H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H, Ar-H), 8.43 (s, 1H, Ar-H), 7.01 (d, 2H, Ar-H), 6.16 (d, 1H, H-1′, J = 5.9 Hz), 4.70 (t, 1H, H-2′, J = 5.1 Hz), 4.32 (t, 1H, H-3′, J = 3.4 Hz), 4.16 (app q, 1H, H-4′, J_{app} = 3.1 Hz), 4.03 (dd, 1H, H-5′, J = 4.1, 11.5 Hz), 3.82 (dd, 1H, H-5′, J = 2.7, 11.5 Hz), 1.97 (s, 6H, OAc), 0.96, 0.94, and 0.78 (3 s, 27H, *t*-Bu), 0.14, 0.13, 0.11, −0.04, and −0.29 (5 s, 18H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 163.9, 161.9, 152.2, 151.8, 151.1, 150.3 (d, J = 13.3 Hz), 144.1, 133.8, 118.3, 109.4 (d, J = 24.7 Hz), 88.4, 86.1, 76.0, 72.4, 62.9, 60.6, 26.3, 26.0, 25.8, 21.1, 18.7, 18.3, 18.0, −4.2, −4.3, −4.4, −4.8, −5.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.87 (t, J = 7.6 Hz). HRMS (ESI): calcd for $C_{38}H_{62}FN_4O_8Si_3$ $[M + H]^+$ 805.3854, found 805.3851.

Procedure for the Synthesis of Palladated Complex 10.



In an oven-dried, nitrogen gas flushed vial equipped with a stirring bar was placed 9-benzyl-6-naphthyl-9*H*-purine (33.6 mg, 0.10 mmol) in anhydrous benzene (1.0 mL). To this solution was added $Pd(OAc)_2$ (23.0 mg, 0.10 mmol), and the mixture was heated at 60 °C for 2 h. After all the starting material was consumed (monitored by TLC), the solvent was evaporated and the crude product was dissolved in a minimum amount of CH_2Cl_2. The solution was layered with heptane and kept in the freezer overnight to provide 39.9 mg (40% yield) of the palladated complex as yellowish orange crystals. ^1H NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1H, Ar-H), 8.39 (s, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 7.60 (d, 1H, Ar-H, J = 8.3 Hz), 7.53−7.49 (m, 2H, Ar-H), 7.34−7.30 (m, 4H, Ar-H), 7.15−7.14 (m, 2H, Ar-H), 7.04 (s, 1H, Ar-H), 4.97 (d, 1H, benzylic CH, J = 15.3 Hz), 4.55 (d, 1H, benzylic CH, J = 15.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.2, 161.0, 152.5, 151.3, 147.9, 146.1, 142.7, 135.3, 134.0, 130.8, 130.4, 129.8, 129.7, 129.6, 129.1, 128.8, 128.4, 128.2, 128.1, 127.7, 124.6, 47.6, 25.3 (one resonance at 128−129 ppm is from PhH).

3-(9-Benzyl-9*H*-purin-6-yl)-2-naphthyl Acetate (12).



In an oven-dried, nitrogen gas flushed vial equipped with a stirring bar was placed the 9-benzyl-6-(2-naphthyl)-9*H*-purine **1d** (33.6 mg, 0.10 mmol) in CH_3CN (1 mL). To this mixture was added the Pd catalyst (see below and refer to Table 2) followed by $PhI(OAc)_2$ (48.3 mg, 0.15 mmol). The mixture was flushed with nitrogen gas, sealed with a Teflon-lined cap, and heated at 100 °C for an appropriate period of time (see below and refer to Table 2). Evaporation of the solvent and chromatography of the reaction mixture on a silica gel column eluted with 1% acetone in CH_2Cl_2 followed by 7% acetone in CH_2Cl_2 gave **12** as a pale yellowish white solid.

$Pd(OAc)_2$ (1.1 mg, 5 μmol) over 1 h gave 33.8 mg (86% yield) of **12**.

Complex **10** (2.5 mg, 2.5 μmol) over 1 h gave 35.9 mg (91% yield) of **12**.

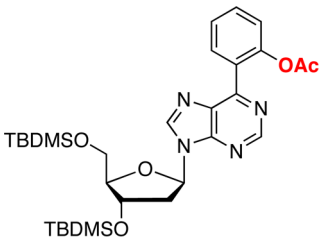
$Pd(OAc)_2$ (1.1 mg, 5 μmol) over 5 h gave 32.5 mg (82% yield) of **12**.

Complex **10** (2.5 mg, 2.5 μmol) over 5 h gave 36.0 mg (91% yield) of **12**.

Complex **10** (2.5 mg, 2.5 μmol) over 24 h gave 36.7 mg (93% yield) of **12**.

R_f (SiO_2/10% acetone in CH_2Cl_2) = 0.40. ^1H NMR (500 MHz, $CDCl_3$): δ 9.09 (s, 1H, Ar-H), 8.80 (s, 1H, Ar-H), 8.11 (s, 1H, Ar-H), 7.98 (d, 1H, Ar-H, J = 7.8 Hz), 7.86 (d, 1H, Ar-H, J = 7.8 Hz), 7.73 (s, 1H, Ar-H), 7.56 (t, 1H, Ar-H, J = 7.6 Hz), 7.51 (t, 1H, Ar-H, J = 7.6 Hz), 7.41−7.35 (m, 5H, Ar-H), 5.51 (s, 2H, CH_2), 2.23 (s, 3H, OAc). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 154.7, 152.4, 152.3, 146.2, 144.8, 135.3, 134.6, 133.9, 132.0, 131.4, 129.3, 129.0, 128.8, 128.0, 127.5, 127.2, 126.3, 121.4, 47.5, 21.5. HRMS (ESI): calcd for $C_{24}H_{19}N_4O_2$ $[M + H]^+$ 395.1503, found 395.1506.

6-[2-Acetoxyphenyl]-9-[2-deoxy-3,5-di-*O*-(*tert*-butyldimethylsilyl)-*β*-D-ribofuranosyl]-9*H*-purine ($4a^{Ac}$).



In an oven-dried, nitrogen gas flushed vial equipped with a stirring bar was placed the 6-phenylpurine 2′-deoxyribonucleoside **3a** (54.1 mg, 0.10 mmol) in CH_3CN (0.5 mL). To this mixture was added the Pd catalyst (see below and refer to Table 2) followed by $PhI(OAc)_2$ (48.3 mg, 0.15 mmol). The mixture was flushed with nitrogen gas, sealed with a Teflon-lined cap and heated at 100 °C for an appropriate period of time (see below and refer to Table 2). Evaporation of the solvent and chromatography on a silica gel column using CH_2Cl_2, followed by 1%, 2%, and 3% acetone in CH_2Cl_2, gave $\mathbf{4a}^{Ac}$ as a yellowish, gummy oil.

$Pd(OAc)_2$ (2.2 mg, 10 μmol) over 5 h gave 36.6 mg (61% yield) of $\mathbf{4a}^{Ac}$.

Complex **10** (2.5 mg, 2.5 μmol) over 5 h gave 33.0 mg (55% yield) of $\mathbf{4a}^{Ac}$.

Complex **10** (5 mg, 5 μmol) over 5 h gave 35.2 mg (59% yield) of $\mathbf{4a}^{Ac}$.

R_f (SiO_2/5% acetone in CH_2Cl_2) = 0.42. ^1H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H, Ar-H), 8.40 (s, 1H, Ar-H), 8.16 (d, 1H, Ar-H, J = 7.8 Hz), 7.53 (t, 1H, Ar-H, J = 7.6 Hz), 7.42 (t, 1H, Ar-H, J = 7.3 Hz), 7.27 (d, 1H, Ar-H, J = 7.8 Hz), 6.56 (t, 1H, H-1′, J = 6.3 Hz), 4.65 (app quint, 1H, H-3′, J_{app} = 2.9 Hz), 4.05 (app q, 1H, H-4′, J_{app} = 3.4 Hz), 3.88 (dd, 1H, H-5′, J = 4.1, 11.0 Hz), 3.79 (dd, 1H, H-5′, J = 2.9, 11.2 Hz), 2.71 (app quint, 1H, H-2′, J_{app} = 6.5 Hz), 2.48 (ddd, 1H, H-2′, J = 3.9, 5.9, 13.2 Hz), 2.17 (s, 3H, OAc), 0.93 and 0.90 (2 s, 18H, *t*-Bu), 0.12, 0.08, and 0.07 (3 s, 12H, $SiCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 154.4, 151.9, 149.1, 143.6, 132.7, 131.6, 127.8, 126.3, 124.1, 88.3, 84.7, 72.2, 63.0, 41.4, 26.2, 25.9, 21.5, 18.6, 18.2, −4.4, −4.6, −5.2, −5.3. HRMS (ESI): calcd for $C_{30}H_{47}N_4O_5Si_2$ $[M + H]^+$ 599.3080, found 599.3080.

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of all products, representative COSY spectra, and X-ray crystallographic data and CIF files for compounds **10** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Herdewijn, P., Ed. *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*; Wiley-VCH: Weinheim, Germany, 2008. (b) Blackburn, G. M., Gait, M. J., Loakes, D., Williams, D. M., Eds. *Nucleic Acids in Chemistry and Biology*, 3rd ed.; RSC Publishing: Cambridge, U.K., 2006. (c) Simons, C. *Nucleoside Mimetics: Their Chemistry and Biological Properties*; Gordon and Breach: Amsterdam, 2001. (d) Kisakürek, M. V., Rosemeyer, H., Eds. *Perspectives in Nucleoside and Nucleic Acid Chemistry*; Verlag Helvetica Chimica Acta and Wiley-VCH: Zürich, Switzerland, and Weinheim, Germany, 2000. (e) Suhadolnik, R. J. *Nucleosides and Nucleic Acids as Biological Probes*; Wiley: New York, 1979.

(2) (a) *Handbook of C−H Transformations: Applications in Organic Synthesis*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vols. *1* and *2*. (b) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; pp 47−79.

(3) For representative reviews, see: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788−802. (b) Bugaut, X.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7479−7481. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740−4761. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215−1292. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (f) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824−889. (g) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540−548. (h) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol* **2011**, *1*, 191−206. (i) You, S.-L.; Xia, J.-B. *Top. Curr. Chem.* **2010**, *292*, 165−194. (j) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269−10310. (k) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (l) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412−9423. (m) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (n) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087−4109. (o) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447−2464. (p) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173−1193. (q) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (r) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35−41. (s) Kalyani, D.; Sanford, M. S. *Top. Organomet. Chem.* **2007**, *24*, 85−116. (t) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041−4047. (u) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382−3388. (v) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72. (w) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (x) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507−514. (y) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639. (z) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932.

(4) Representative reviews are as follows. Cu and Pd catalysis: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062−11087. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074−1086. Fe catalysis: (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293−1314. Co catalysis: (d) Yoshikai, N. *Synlett* **2011**, 1047−1051. Rh catalysis: (e) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212−11222. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624−655. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013−1025. Ru catalysis: (h) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918.

(5) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912−4924.

(6) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296−3300.

(7) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6097−6102.

(8) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822−1824.

(9) Sahnoun, S.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2008**, *49*, 7279−7283.

(10) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Org. Biomol. Chem.* **2009**, *7*, 4271−4278.

(11) Čerňa, I.; Pohl, R.; Hocek, M. *Chem. Commun.* **2007**, 4729−4730.

(12) Storr, T. E.; Firth, A. G.; Wilson, K.; Darley, K.; Baumann, C. G.; Fairlamb, I. J. S. *Tetrahedron* **2008**, *64*, 6125−6137.

(13) Storr, T. E.; Baumann, C. G.; Thatcher, R. J.; De Ornellas, S.; Whitwood, A. C.; Fairlamb, I. J. S. *J. Org. Chem.* **2009**, *74*, 5810−5821.

(14) Guo, H.-M.; Jiang, L.-L.; Niu, H.-Y.; Rao, W.-H.; Liang, L.; Mao, R.-Z.; Li, D.-Y.; Qu, G.-R. *Org. Lett.* **2011**, *13*, 2008−2011.

(15) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11400−11404.

(16) Qu, G.-R.; Liang, L.; Niu, H.-Y.; Rao, W.-H.; Guo, H.-M.; Fossey, J. S. *Org. Lett.* **2012**, *14*, 4494−4497.

(17) Kim, J, Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110−9113.

(18) Guo, H.-M.; Rao, W.-H.; Niu, H.-Y.; Jiang, L.-L.; Meng, G.; Jin, J.-J.; Yang, X.-N.; Qu, G.-R. *Chem. Commun.* **2011**, *47*, 5608−5610.

(19) Čerňa, I.; Pohl, R.; Klepetářová, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389−5392.

(20) Compound **10**: $C_{60}H_{48}N_8O_4Pd_2$; M_w = 1157.86; T = 296(2) K; λ = 0.71073 Å; monoclinic; $P2_1/c$ space group; a = 11.5447(8) Å, b = 21.0130(14) Å, c = 22.4743(15) Å; α = 90°, β = 101.7710(10)°, γ = 90°; V = 5337.4(6) Å^3; Z = 4; calculated density 1.441 Mg/m^3; crystal size 0.27 × 0.23 × 0.11 mm^3; R1 = 0.0998, wR2 = 0.1925 (all data).

(21) Martín-Ortíz, M.; Gómez-Gallego, M.; Ramírez de Arellano, C.; Sierra, M. A. *Chem. Eur. J.* **2012**, *18*, 12603−12608.

(22) Henry, P. M. *J. Org. Chem.* **1971**, *36*, 1886−1890.

(23) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A: Chem.* **1996**, *108*, 35−40.

(24) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301.

(25) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790−12791.

(26) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974−10983.

(27) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234−11241.

(28) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302−309.

(29) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050−17051.

(30) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.,, III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092−14103.
(31) For recent reviews, see: (a) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840−850. (b) Powers, D. C.; Ritter, T. *Top. Organomet. Chem.* **2011**, *35*, 129−156.
(32) Yao, C. L.; He, L. P.; Korp, J. D.; Bear, J. L. *Inorg. Chem.* **1988**, *27*, 4389−4395.
(33) Bercaw, J. E.; Durrell, A. C.; Gray, H. B.; Green, J. C.; Hazari, N.; Labinger, J. A.; Winkler, J. R. *Inorg. Chem.* **2010**, *49*, 1801−1810. Pd−Pd bond distances: in $[(2\text{-phenylpyridine})Pd(\mu\text{-OAc})]_2$, 2.862 Å; in $[(2\text{-}p\text{-tolylpyridine})Pd(\mu\text{-OAc})]_2$, 2.857 Å.
(34) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530−14536.
(35) Compound **12**: $C_{24}H_{18}N_4O_2$; M_w = 394.42; T = 296(2) K; λ = 0.71073 Å; triclinic; $P\bar{1}$ space group; a = 8.102(2) Å, b = 10.608(3) Å, c = 12.154(3) Å; α = 84.335(5)°, β = 84.569(5)°, γ = 70.466(5)°; V = 977.5(5) Å^3; Z = 2; calculated density 1.340 Mg/m^3; crystal size 0.41 × 0.23 × 0.05 mm^3; R1 = 0.0706, *w*R2 = 0.1363 (all data).
(36) Havelková, M.; Dvořák, D.; Hocek, M. *Synthesis* **2001**, 1704−1710.
(37) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779−7787.

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