C–H Bond Activation

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Direct Arylation of 6-Phenylpurine and 6-Arylpurine Nucleosides by Ruthenium-Catalyzed C–H Bond Activation**

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C–H bond activation represents an efficient approach to molecular functionalization.[1,2] In directed C–H bond activation, Lewis basic sites are exploited to draw the catalyst proximal to the reactive center. We have been interested in the C–H bond activation and arylation of nucleobases and nucleosides using the nitrogen atoms of the purine itself as the Lewis basic sites. In this context, 6-arylpurine has embedded 2-phenylpyridine and 4-phenylpyrimidine motifs. 2-Arylpyridines, and benzo[*h*]quinoline, which can be considered as containing a rigidified 2-phenylpyridine structure, have been the subject of C–H bond activation/arylation strategies using Pd, Ru, Rh, and Fe.[3–6] However, any metal-catalyzed conversion of purines and purine nucleosides is a challenging proposition owing to the presence of four nitrogen atoms in the nucleobases, plus additional oxygen atoms in the sugar unit; all of these heteroatoms could participate in metal sequestration and deactivation of catalytic processes.

As shown in Scheme 1, the N1 nitrogen atom of purine is well positioned to direct C–H bond activation. Alternatively, N7 can also function in a similar capacity. To gain preliminary insight, energy minimization was performed, using DFT at the B3LYP/6-311++G(2d,2p) level of theory, on 2-phenylpyridine as well as 9-benzyl-6-phenyl-9*H*-purine. The distances between the metal-directing nitrogen atom and the *ortho*-hydrogen atom on the phenyl ring were calculated from the energy-minimized structures, and are shown in Figure 1.

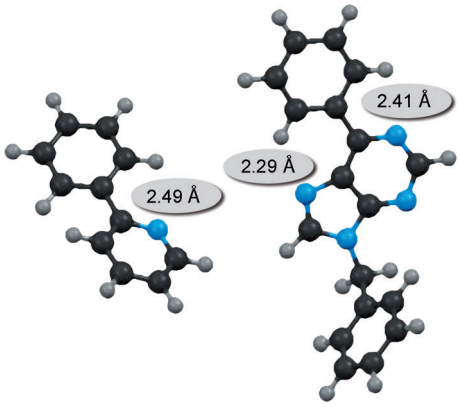
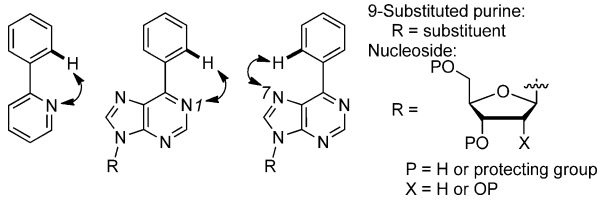


Figure 1. Energy-minimized structures of 2-phenylpyridine (left) and 9-benzyl-6-phenyl-9*H*-purine (right).



Scheme 1. N-directed C–H bond activation in 2-phenylpyridine, and two plausible modes of N-directed C–H bond activation in *C*6-aryl purines and nucleosides.

Consistent with known X-ray structures of 2-phenylpyridine derivatives,[7] the aryl rings in 2-phenylpyridine are not coplanar. The distance between the pyridyl nitrogen atom and the *ortho*-hydrogen atom of the aryl ring in this case is 2.49 Å. By comparison, in the energy-minimized structure of 9-benzyl-6-phenyl-9*H*-purine, the *C*6-aryl group is coplanar with the purine ring. We next compared the computed structure of 9-benzyl-6-phenyl-9*H*-purine to the crystallographic structures of 9-benzyl-6-phenyl-8-(*p*-tolyl)-9*H*-purine and 8,8′-bis(9-benzyl-6-phenyl)-9*H*-purine.[8] In both compounds, the *C*6-phenyl group is coplanar with the purinyl system. We also evaluated the distance between N1 and the *ortho*-hydrogen atom of the *C*6-aryl group for these cases. In 9-benzyl-6-phenyl-8-(*p*-tolyl)-9*H*-purine, this distance is 2.43 Å whereas the distance to N7 is 2.34 Å. Similar distances of 2.43 Å and 2.36 Å, respectively, were obtained for 8,8′-bis(9-benzyl-6-phenyl)-9*H*-purine. These data closely match the DFT-derived distances for 9-benzyl-6-phenyl-9*H*-purine shown in Figure 1. Given the similar distances between the nitrogen atom and the aryl hydrogen atom in 9-benzyl-6-phenyl-9*H*-purine and 2-phenylpyridine, we reasoned that C–H bond activation in purines and nucleosides should be feasible. In support of this hypothesis, serendipitously, undesired arylation of the *C*6-phenyl group has been observed in the Pd/Cu-mediated C8 arylation of 9-benzyl-6-

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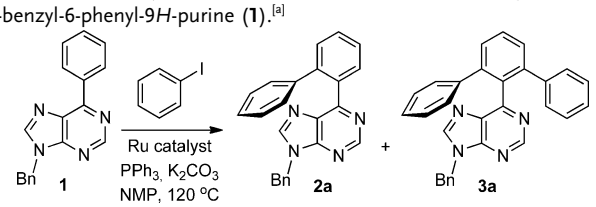
phenyl-9*H*-purine with iodobenzene or *p*-iodotoluene (2–10 equiv).[8]

In initial experiments, [{$RuCl_2$(benzene)}$_2$] (**A**) and [{$RuCl_2$(*p*-cymene)}$_2$] (**B**) were selected as catalysts for assessing the C–H bond activation of 9-benzyl-6-phenyl-9*H*-purine (**1**), and 2 equivalents of iodobenzene were used to ensure complete consumption of **1**. Results from a preliminary screen of reaction conditions are shown in Table 1. Notably, 5 mol% of catalyst **A** in combination with 40 mol% of PPh_3 resulted in full conversion (Table 1, entries 1–4), and catalyst **A** appeared marginally superior to catalyst **B** (Table 1, entries 4 and 5). Replacement of K_2CO_3 with Cs_2CO_3 led to a slower reaction (Table 1, entries 6 and 7), and the mono/diarylation ratio was substantially altered. This indicates an unknown but crucial role of the base in these C–H bond activation processes.

Table 1: Preliminary evaluation of the C–H bond activation process for 9-benzyl-6-phenyl-9*H*-purine (**1**).[a]



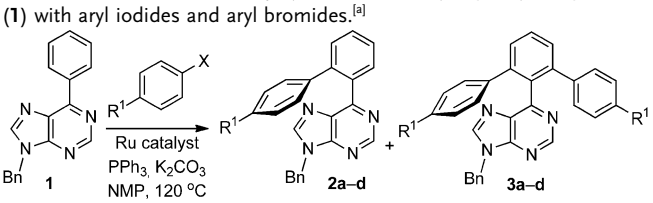
Entry	Catalytic system[b]	Result[c]
1	**A** (2.5 mol%), PPh_3 (20 mol%), K_2CO_3 (3 equiv)	**1**/**2a**/**3a** = 83:15:2[d]
2	**B** (2.5 mol%), PPh_3 (20 mol%), K_2CO_3 (3 equiv)	**1**/**2a**/**3a** = 83:15:2[d]
3	**A** (5 mol%), PPh_3 (20 mol%), K_2CO_3 (3 equiv)	**1**/**2a**/**3a** = 63:34:3[d]
4	**A** (5 mol%), PPh_3 (40 mol%), K_2CO_3 (3 equiv)	**2a**:76% **3a**:17%
5	**B** (5 mol%), PPh_3 (40 mol%), K_2CO_3 (3 equiv)	**1**/**2a**/**3a** = 3:84:13[d]
6	**A** (5 mol%), PPh_3 (40 mol%), Cs_2CO_3 (3 equiv)	**1**/**2a**/**3a** = 7:52:41[d]
7[e]	**A** (5 mol%), PPh_3 (40 mol%), Cs_2CO_3 (3 equiv)	**2a**:56% **3a**:36%

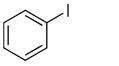
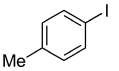
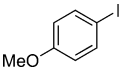
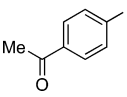
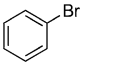
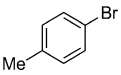
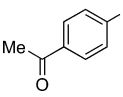
[a] Reaction conditions: **1** (0.2 M) in anhydrous NMP, iodobenzene (2 equiv), 120 °C, 24 h. [b] **A**: [{$RuCl_2$(benzene)}$_2$], **B**: [{$RuCl_2$(*p*-cymene)}$_2$]. [c] Yields are of the isolated and purified products. [d] The reaction was incomplete. The ratio was determined from ^{1}H NMR spectra by the integration of the benzyl CH_2 resonances, which appear at $\delta = 5.49$ ppm for **1**, $\delta = 5.41$ ppm for **2a**, and $\delta = 5.32$ ppm for **3a**. [e] The reaction time was 32 h. Bn = benzyl, NMP = *N*-methylpyrrolidone.

We evaluated the use of aryl iodides and aryl bromides for the direct arylation of 9-benzyl-6-phenyl-9*H*-purine (**1**) under the optimal reaction conditions developed in Table 1. Results from these experiments are shown in Table 2.

Results in Table 2 indicate that reactions can be accomplished with both aryl iodides and aryl bromides, in yields of 75–99% (combined for mono- and diarylated products). Yields of reactions with aryl bromides were respectable (Table 2, entries 5–7) but a little lower than those with aryl iodides.

Table 2: C–H bond activation/arylation of 9-benzyl-6-phenyl-9*H*-purine (**1**) with aryl iodides and aryl bromides.[a]



Entry	Aryl halide	Yield [%][b]	**2**/**3**
1		**2a**: 76 **3a**: 17	4.5:1
2		**2b**: 81 **3b**: 18	4.5:1
3[c]		**2c**: 79 **3c**: 14	5.6:1
4		**2d**: 82 **3d**: trace	NA[d]
5		**2a**: 72 **3a**: 12	6:1
6		**2b**: 73 **3b**: 17	4.3:1
7		**2d**: 75 **3d**: trace	NA[d]

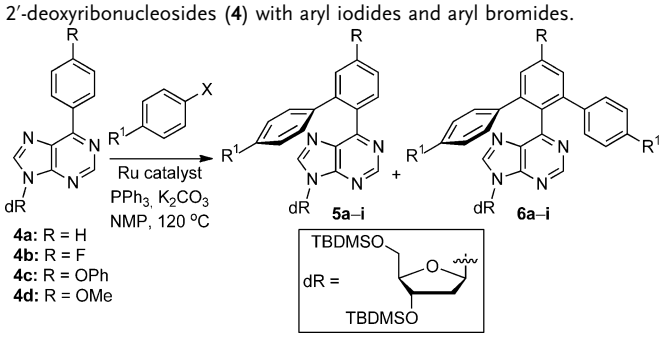
[a] Reaction conditions: **1** (0.2 M) in anhydrous NMP, aryl halide (2 equiv), [{$RuCl_2$(benzene)}$_2$] (5 mol%), PPh_3 (40 mol%), K_2CO_3 (3 equiv), 120 °C. [b] Yields are of isolated and purified products. [c] The reaction was conducted using 10 mol% of [{$RuCl_2$(benzene)}$_2$] and 80 mol% of PPh_3. [d] Not applicable since only a trace of the diaryl product was detected.

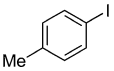
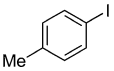
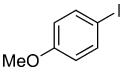
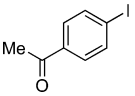
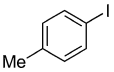
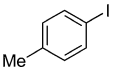
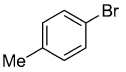
We next explored arylations of the more complex 2′-deoxynucleoside substrates, which are quite labile and prone to facile deglycosylation.[9] The requisite 6-arylpurine 2′-deoxyribonucleosides (6-aryl 2′-deoxynebularines) are readily available by our previously reported procedures.[10] Results from the nucleoside arylation reactions are shown in Table 3.

The results in Table 3 indicate that the procedure is readily applicable to the sensitive 2′-deoxyribonucleoside substrates. However, 10 mol% of the Ru catalyst was needed to obtain complete consumption of the precursor. In contrast to the reactions of purine **1**, for which a 1:8 ratio of Ru catalyst/PPh_3 was needed for complete reaction (Table 1 entry 4), use of a 1:4 and 1:8 ratio of the Ru catalyst/PPh_3 led to full conversion of **4a** (Table 3 entries 1–4), but there were some differences in the reaction results. With iodobenzene, increasing the amount of PPh_3 resulted in a better yield and better mono/diarylation ratio (Table 3, entry 1 versus entry 2). With *p*-iodotoluene, again a better ratio of mono/diarylation was observed with more PPh_3, although the yield of the monoarylation remained almost the same (Table 3, entry 3 versus entry 4). Arylation reactions with electron-rich *p*-iodoanisole and electron-deficient *p*-iodoacetophenone were both successful (Table 3, entries 5 and 6, respectively). Interestingly, for reasons currently unknown, when R = F (**4b**) or OPh (**4c**), more diarylation was observed in reactions

with iodobenzene (Table 3, entries 7 and 9). The same trend was also observed when using catalyst **B** for the arylation of **4c** with iodobenzene (Table 3, entry 10). In contrast, for **4d** (R = OMe), greater monoarylation was observed (Table 3, entries 11 and 12). As with purine **1**, aryl bromides were also reactive (Table 3, entries 13 and 14).

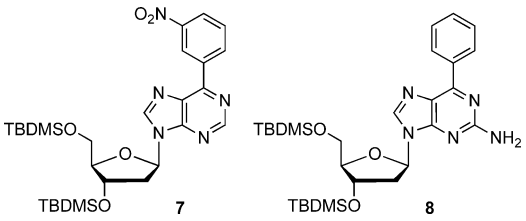
Table 3: C–H bond activation/arylation of 3′,5′-di-*O*-silyl 6-arylpurine 2′-deoxyribonucleosides (**4**) with aryl iodides and aryl bromides.



Entry	R	Aryl halide	Yield [%][a]	5/6
1[b]	H		**5a**: 46 **6a**: 23	2:1
2[c]	H		**5a**: 65 **6a**: 14	4.6:1
3[b]	H		**5b**: 52 **6b**: 16	3.2:1
4[c]	H		**5b**: 54 **6b**: 7	7.7:1
5[c]	H		**5c**: 53[d] **6c**: 7	7.6:1
6[c]	H		**5d**: 62 **6d**: 15	4.1:1
7[c]	F		**5e**: 31 **6e**: 44	1:1.5
8[c]	F		**5f**: 42 **6f**: 20	2.1:1
9[c]	OPh		**5g**: 29 **6g**: 53	1:1.8
10[e]	OPh		**5g**: 24 **6g**: 72	1:3
11[c]	OMe		**5h**: 39 **6h**: 16	2.4:1
12[c]	OMe		**5i**: 46 **6i**: 17	2.7:1
13[c]	H		**5a**: 36 **6a**: 18	2:1
14[c]	H		**5b**: 57 **6b**: 18	3.2:1

[a] Yields are of the isolated and purified products. [b] Reaction conditions: **4a** (0.2 M) in anhydrous NMP, aryl halide (2 equiv), [{$RuCl_2$(benzene)}$_2$] (10 mol%), PPh_3 (40 mol%), K_2CO_3 (3 equiv), 120°C, 30 h. [c] Reaction conditions: **4a**–**d** (0.2 M) in anhydrous NMP, aryl halide (2 equiv), [{$RuCl_2$(benzene)}$_2$] (10 mol%), PPh_3 (80 mol%), K_2CO_3 (3 equiv), 120°C. [d] Owing to the similar R_f values of the products, a trace of the diarylated product was present. [e] Reaction conditions were the same as [c] except that [{$RuCl_2$(*p*-cymene)}$_2$] was used in place of [{$RuCl_2$(benzene)}$_2$].

Using catalyst **A**, we then examined the C–H bond activation/arylation of *m*-nitrophenyl nucleoside derivative **7**[10] and 2-amino-6-phenylpurine nucleoside **8**[11] (Scheme 2) with iodobenzene. In the case of **7**, no product formation was seen but some precursor decomposition occurred, thus indicating very electron-deficient aromatic rings, not surprisingly, are resistant to arylation (see the mechanism in Scheme 3). Substrate **8**, which is structurally similar to **4a**, but has a *C*2-amino group, remained largely intact and showed no product formation. It appears therefore that the presence of the amino group abolishes any reactivity.



Scheme 2. Nucleoside substrates that did not yield arylation products. TBDMS = *tert*-butyldimethylsilyl.

Since in previous experiments 2 equivalents of aryl halide were used to achieve complete consumption of the purine or nucleoside precursor, we evaluated the arylation of **1** and **4a** with a variety of stoichiometries of iodobenzene; all other reaction conditions remained the same. These results are shown in Table 4. With purine **1**, incomplete reaction was observed with 1 equiv of iodobenzene, but substantially more monoarylated product **2a** was formed (Table 4, entry 1).

Table 4: Reactions of **1** and **4a** using various stoichiometries of iodobenzene.

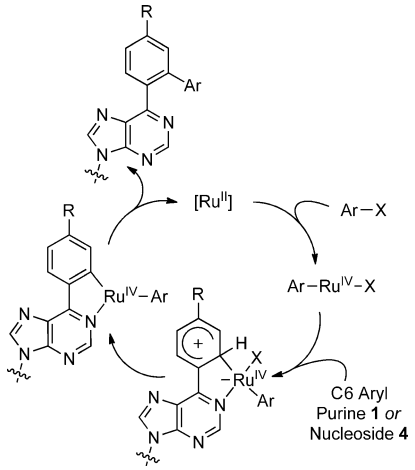
Entry	Substrate	Mol% of PhI	*t* [h]	Yield [%][a]	Mono/diaryl products
1[b]	**1**	100	24	**2a**: 91 **3a**: 2	**2a**/**3a** = 45:1[c]
2[b]	**1**	120	24	**2a**: 80 **3a**: 12	**2a**/**3a** = 6.7:1
3[b]	**1**	400	24	**2a**: 60 **3a**: 30	**2a**/**3a** = 2:1
4[b]	**1**	400	48	**2a**: 59 **3a**: 32	**2a**/**3a** = 1.8:1
5[d]	**4a**	120	30	**5a**: 62 **6a**: 10	**5a**/**6a** = 6.2:1
6[d]	**4a**	400	30	**5a**: 62 **6a**: 12	**5a**/**6a** = 5.2:1
7[d]	**4a**	400	60	**5a**: 53 **6a**: 13	**5a**/**6a** = 4.1:1

[a] Yields are of isolated and purified products. [b] Reaction conditions: **1** (0.2 M) in anhydrous NMP, PhI (see Table), [{$RuCl_2$(benzene)}$_2$] (5 mol%), PPh_3 (40 mol%), K_2CO_3 (3 equiv), 120°C. [c] Reaction was incomplete, 4% of **1** was recovered. [d] Reaction conditions: **4a** (0.2 M) in anhydrous NMP, PhI (see Table), [{$RuCl_2$(benzene)}$_2$] (10 mol%), PPh_3 (80 mol%), K_2CO_3 (3 equiv), 120°C.

However, with 120 mol% of iodobenzene the result was nearly the same as that obtained with 200 mol% (Table 4, entry 2 versus Table 2, entry 1). Increasing the amount of iodobenzene to 400 mol% yielded a greater proportion of the diarylated product **3a**, but complete conversion to the diarylated **3a** did not occur (Table 4, entry 3). Doubling the reaction time did not increase diarylation either (Table 4, entry 4). The stoichiometry of iodobenzene had very little effect on the mono/diarylation ratio of the nucleoside precursor **4a** (Table 4, entries 5–7 and Table 2, entry 2), although a prolonged reaction time (60 h) was detrimental and led to a lower yield (Table 4, entry 7).

While this work was in progress, a complementary Pd-catalyzed C–H bond activation of 6-arylpurines and three acetate-protected 6-arylpurine ribonucleosides was reported.[12] It is therefore reasonable to offer a comparison of the two approaches. In contrast to the reactions reported here, those catalyzed by Pd required 30 equiv of aryl iodide, with reaction times from 48 hours (nucleosides) to 60 hours (purines), at 120 °C.[12] Thus, the present reaction conditions use substantially less of the aryl halide and generally provide faster reactions. Pd catalysis results in only monoarylation,[12] plausibly because of the slow reactions, whereas under Ru catalysis both mono and diaryl products are formed. Use of AcOH as the solvent at 120 °C and a N_2 atmosphere have been stated as crucial for the Pd-catalyzed reactions.[12] Exposure to AcOH at elevated temperature may be unsuitable for acid-sensitive substrates such as the deoxyribonucleosides described here. Also, an inert atmosphere is strictly necessary for Pd-catalyzed reactions. Plausibly, this is to suppress undesired dimerization of the purine, as dimerization has been observed previously when air was introduced into Pd-catalyzed arylation reactions.[8] Most notably, aryl bromides can be used in the Ru-catalyzed chemistry, whereas aryl bromides and chlorides were unreactive under Pd catalysis.[12]

In analogy to reactions of 2-arylpyridines,[4d] a possible mechanism involving the purinyl N1 atom is depicted in Scheme 3. The monoarylated products could reenter the catalytic cycle resulting in diarylation. Consistent with an N-directed electrophilic attack by the aryl/Ru^{IV} complex onto the *C*6-aryl ring, no reaction was observed with the *m*-nitrophenyl nucleoside derivative **7**. This is because reaction would have to occur at the electron-deficient *para* or *ortho* positions to the nitro group.



Scheme 3. Possible mechanism for the C–H bond activation/arylation of 6-arylpurine and 6-arylpurine 2′-deoxyribonucleosides.

Owing to interest in oxidative C–H cross-coupling processes,[3c,13–17] we evaluated whether the purinyl nitrogen directed C–H bond activation could be used to promote C–H cross-coupling.[18] This reaction gave dimerized 8,8′-bis(9-benzyl-6-phenyl)-9*H*-purine[8] in ca. 20% yield, thus indicating a facile dimerization of **1** under oxidative conditions (50% of **1** was recovered).

We have demonstrated that Ru-catalyzed C–H bond activation/arylation can be accomplished with purines and deoxyribonucleosides. Both aryl iodides and aryl bromides are reactive, leading to densely functionalized products in relatively few steps. Metal-catalyzed approaches, such as that described here, provide facile routes to novel entities that are otherwise not easily accessed. This is important in the context of the high biological value placed on purine and nucleoside derivatives. Further work is currently ongoing in our laboratories on these and related chemical processes, including understanding the role, if any, of the purinyl N7 atom.

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[18] Purine **1** was exposed to 10 mol% of $Pd(OAc)_2$, 2 equiv of Ag_2CO_3, 0.5 equiv of 1,4-benzoquinone, 4 equiv of DMSO, and 53 equiv of benzene, at 100 °C for 24 h.

