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Pd(II)-Catalyzed *Ortho* Arylation of 6-Arylpurines with Aryl Iodides via Purine-Directed C–H Activation: A New Strategy for Modification of 6-Arylpurine Derivatives

Hai-Ming Guo,*,† Li-Li Jiang,† Hong-Ying Niu,‡ Wei-Hao Rao,† Lei Liang,† Run-Ze Mao,† De-Yang Li,† and Gui-Rong Qu*,†

College of Chemistry and Environmental Science, Key Laboratory of Green Chemical Media and Reactions of Ministry of Education, Henan Normal University, Xinxiang, 453007, China, and School of Chemistry and Chemical Engineering, Henan Institute of Science and Technology, Xinxiang 453003, China

guohm518@hotmail.com; quguir@sina.com

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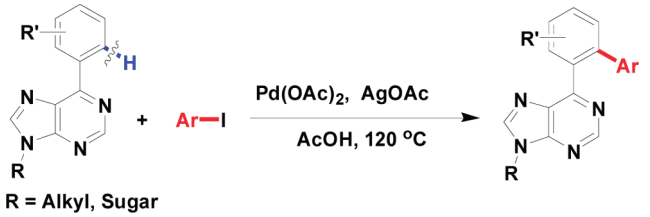
ABSTRACT



Purine is utilized as a new directing group for the Pd-catalyzed monoarylation of 6-arylpurines with simple aryl iodides via C–H bond activation in good yields, providing a complementary tool for the modification of 6-arylpurines (nucleosides). Most importantly, purine can be used as a building block for nucleoside derivatives, and the use of purine as a directing group helps avoid additional synthetic steps.

In recent years, significant advances in the transition-metal-catalyzed construction of C–C bonds have been made,[1] which provides a useful tool for synthesizing complex organic compounds and constructing some pharmaceutical scaffolds.[2] Traditionally, the formation of biaryl linkages involves standard cross-coupling reactions[3] (i.e., Suzuki–Miyaura, Stille, Hiyama, Kumada, and Negishi reactions). Despite their widespread application, these coupling reactions are usually conducted under fairly harsh reaction conditions utilizing catalysts comprised of expensive organometallic reagents and complex auxiliary ligands, which in some instances may limit their practical applications in synthesis. To overcome these drawbacks, organic chemists have developed a transition-metal-catalyzed

† Henan Normal University.
‡ Henan Institute of Science and Technology.

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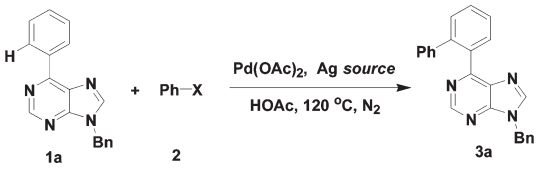
direct arylation of a C−H bond to construct a variety of C−C bonds.[4] However, selective direct arylation of substrates with similar C−H bonds tends to require various auxiliary ligands.

Over the past decade, more effort has been devoted to substrate-directed metal-catalyzed C−H bond arylation[5] as a complementary tool for standard cross-coupling reactions. Consequently, most nitrogen-containing groups and carboxyl groups have been explored for directing metal-catalyzed C−H bond arylation. The majority of the directing groups, which are necessary for the selective transformation, often are difficult to attach or remove, thus limiting these methodologies to particular types of substrates.[5d,e] Extending these methodologies to include other substrates seems to be urgent. Meanwhile, aryl boronic acids[6] and diaryliodonium salts[7] were extensively applied to the arylation of heteroaromatic substrates. However, aryl boronic acids are expensive or require multistep preparation, and diaryliodonium salts are not atom economic and generate waste and purification problems. Furthermore, direct arylation of Ar−H via C−H bond activation has been known to suffer from over-functionalization or regioselectivity issues.[8,5g]

C6-Arylpurine nucleosides are of particular importance since they have displayed anti-HCV, cytostatic, and anti-mycobacterial activities,[9] and continued methodological efforts have been made in recent years. Purine contains four nitrogen atoms and belongs to a special class of aromatic heterocycles. To our knowledge, there have been no reports of purine-directed palladium-catalyzed C−H bond activation thus far. During the ongoing course of our study on the modification of purine analogues[10] and according to the reports on transition-metal-catalyzed arylation of substrate-directed C−H bond, we choose purine as a directing group for C−H bond arylation with aryl iodides, since purine may offer a nitrogen atom for effectively participating in cyclopalladation. Purine is more challenging than simple pyridine since it possesses three additional nitrogen atoms that could potentially bind and poison the catalyst.[11] Most importantly, this directing group is a useful building block for the desired nucleoside derivatives. This functionalization is highly regiospecific, thus making the process simple and more synthetically desirable. This C−H functionalization approach offers an alternative strategy for modification of 6-arylpurine derivatives, providing access to molecules that may have great importance in medicinal chemistry.[12]

With this in mind, we initially carried out our experiment by choosing 6-phenyl-9-benzylpurine (**1a**) as the substrate and $Pd(OAc)_2$ as the catalyst (Table 1). To our delight, we found the phenylation of **1a** took place in the presence of a catalytic amount of $Pd(OAc)_2$, 5 equiv of PhI, and 2 equiv

Table 1. Monophenylation of 6-Phenyl Purine via Pd-Catalyzed C−H Bond Activation[a]



entry	X (equiv)	Ag source	yield (%)[b]
1	I (5)	AgOAc	15
2	I (10)	Ag_2O	12
3	I (10)	AgOAc	20
4	**I (30)**	**AgOAc**	**82**
5	I (40)	AgOAc	82
6	Cl (30)	AgOAc	N.R.[c]
7	Br (30)	AgOAc	N.R.
8[d]	I (30)	AgOAc	N.R.
9[e]	I (30)	AgOAc	N.R.
10	I (30)	AgOTf	40

[a] Unless otherwise mentioned, all of the reactions were carried out with 0.2 mmol of **1a**, 5 mol % $Pd(OAc)_2$, 0.4 mmol of Ag source, and 0.5 mL of AcOH in a Schlenk tube at 120 °C for 60 h under a N_2 atmosphere. [b] Isolated yields. [c] N.R. = No Reaction. [d] Without N_2 protection. [e] In the absence of AcOH.

(5) For recent reviews about substrate-directed C−H arylation, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Daugulis, O.; Do, H.-Q; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. For other recent examples about substrate-directed C−H arylation, see:(d) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. (e) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270. (f) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331. (g) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (h) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (i) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925.

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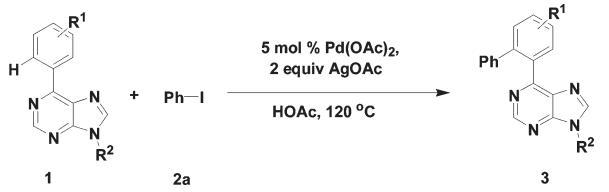
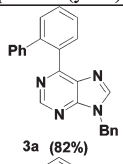
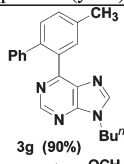
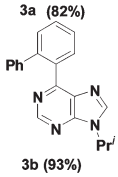
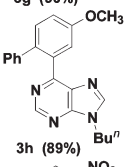
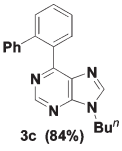
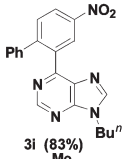
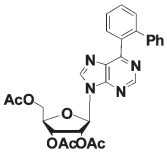
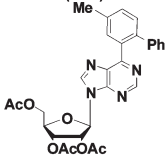
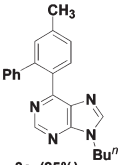
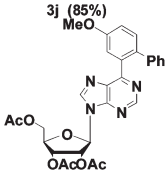
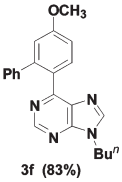
Table 2. Highly Regioselective Monophenylation of Various 6-Arylpurines with PhI[a]



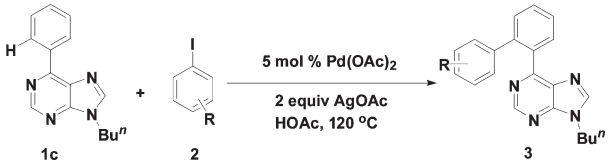
1 2a 3

entry	product (yield)[b]	entry	product (yield)[b]
1	 3a (82%)	7	 3g (90%)
2[c]	 3b (93%)	8	 3h (89%)
3	 3c (84%)	9	 3i (83%)
4[c]	 3d (89%)	10[c]	 3j (85%)
5	 3e (85%)	11[c]	 3k (87%)
6	 3f (83%)		

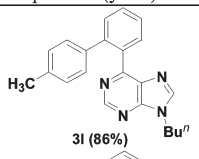
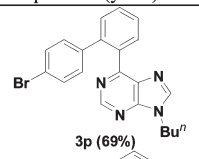
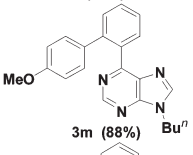
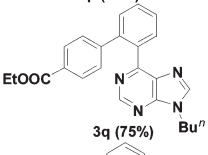
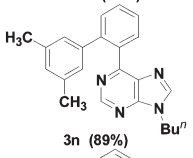
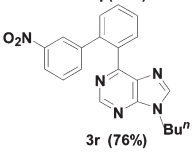
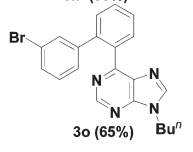
[a] Unless otherwise mentioned, all of the reactions were carried out with 0.2 mmol of **1**, 30 equiv of **2a**, 5 mol % $Pd(OAc)_2$, 0.4 mmol of AgOAc, and 0.5 mL of HOAc in a Schlenk tube at 120 °C for 60 h under a N_2 atmosphere. [b] Isolated yields were reported. [c] The reaction proceeded for 48 h.

of AgOAc as an oxidant but in poor yield (15%, entry 1). Further studies showed that elevated amounts of PhI led to higher yields, but the yield did not increase when the amount of PhI was higher than 30 equiv (entries 4–5). Unfortunately, the phenylation reaction was almost suppressed when PhI was replaced by PhCl or PhBr even under the same reaction conditions (entries 6 and 7). Presumably, the Ph–Cl/Br bond is more difficult to cleave in the course of palladium-mediated oxidative addition. Further investigations showed AgOAc was the best choice among various silver salts in this protocol (entries 1–2 and 10). Importantly, the use of both AcOH and N_2 protection was critical for such success (entries 8 and 9). It was considered that AcOH played three roles in the reaction: (i) it might serve as a good solvent, (ii) it might facilitate the reductive elimination step,[13] and (iii) it might help to overcome the catalyst poison ascribable to multiple nitrogens in purine. It was noteworthy that the monophenylation reaction was selective at the *ortho* site of the C6-phenyl ring, which differed from previous reports[14] that the C8–H bond of purine was prior to be arylated. This indicated such success was predominantly controlled by the N1 atom of purine.

Table 3. Monoarylation of 9-Butyl-6-phenylpurine with Various Aryl Iodides[a]



1c 2 3

entry	product (yield)[b]	entry	product (yield)[b]
1	 3l (86%)	5	 3p (69%)
2	 3m (88%)	6	 3q (75%)
3	 3n (89%)	7	 3r (76%)
4	 3o (65%)		

[a] The reactions were carried out with 0.2 mmol of **1c**, 30 equiv of aryl iodide (**2**), and 0.5 mL of HOAc in a Schlenk tube at 120 °C for 60 h under a N_2 atmosphere. [b] Isolated yields were reported.

With the optimized conditions in hand, this new phenylation protocol was extended to a scope of arylpurines, and the results are shown in Table 2. A series of 6-aryl-9-substituted purines including *i*-Pr (**1b**), *n*-Bu (**1c**), and triacetyl-*β*-ribofuranosyl (**1d**) were subjected to our catalytic system and the corresponding products were obtained in high yields (**3b**–**3d**). Notably, a

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glycosidic bond existing in substrates **1d**, **1j**, and **1k** was well tolerated under the reaction conditions, and the reaction time was relatively short among the tested substrates, which expanded the field of nucleosidic modification. We further investigated the electronic and steric effect on the arylation of 6-arylpurines. Substrates bearing electron-donating groups at their *meta* site such as Me (**1g**), MeO (**1h**) proceeded smoothly to afford the corresponding products **3g** (90%) and **3h** (89%). At the same time, a strong electron-withdrawing group like $-NO_2$ at the *meta* site of C6-phenyl also produced the corresponding product **3i** in 83% isolated yield. For substrates containing the Me (**1e**), MeO (**1f**) group at the *para* site, the corresponding products (**3e**, **3f**) were also obtained in good yield, although somewhat lower than that of the *meta* substituted counterparts (**3g**, **3h**), which might be the result of a slight steric effect arising from the position discrimination.

As showed in Table 3, a variety of aryl iodides were further explored. The reaction with various substituted aryl iodides all proceeded efficiently regardless of their electron-donating (i.e., *p*-Me, *p*-MeO, *m*-dimethyl) and electron-withdrawing (i.e., *m*-Br, *p*-Br, *p*-COOEt, *m*-NO_2) ability. Notably, the bromo and ester substituents were well tolerated under the reaction conditions, which was favorable for further transformation. Remarkably, the selective monoarylation overwhelmingly occurred even though excess aryl iodides were present in the reaction mixture.

In summary, we have developed a new method for a highly regioselective monoarylation of C6-arylpurines via purine-directed C−H bond activation. Multiple-nitrogen-containing purine was first explored as a directing group for Pd-catalyzed C−H bond activation. Notably, this directing group is a useful building block for the desired nucleoside derivatives. The monoarylated products were overwhelmingly obtained by employing simple aryl iodides as arylating agents. A variety of functional groups such as Me−, MeO−, $-NO_2$, −COOEt, and −Br could be well tolerated. Additionally, the approach provides a new access to a variety of arylated purines (nucleosides) which are of great importance in medicinal chemistry. The application of purine as a directing group to construct a C−heteroatom bond and further investigation on the detailed mechanism are underway in our laboratory.

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Supporting Information Available. Typical experimental procedures, characterization of compounds, and compound spectroscopic information. This material is available free of charge via the Internet at http://pubs.acs.org.