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Communication

Nitration

Pd^{II}-Catalyzed Purine-Directed Ortho Nitration of 6-Arylpurines by C(sp^2)–H Activation: A Practical Approach to Synthesize 6-(2-Nitroaryl)-Purine Derivatives

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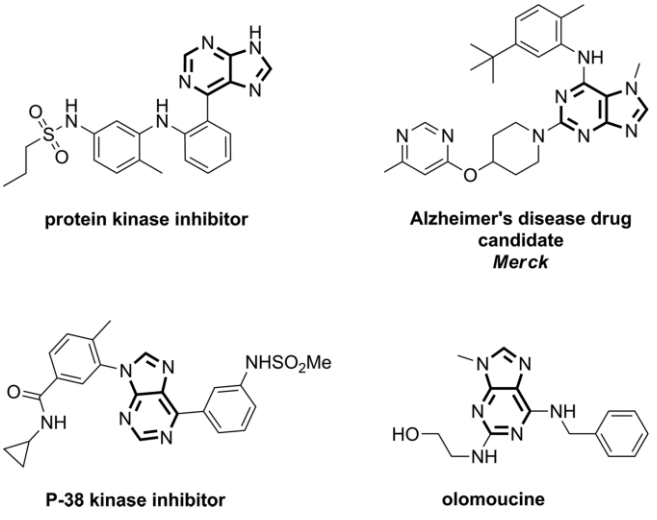
Abstract: Herein we report a method for Pd^{II}-catalyzed purine-directed *ortho* nitration of 6-arylpurines via C(sp^2)–H activation by using *t*BuONO/O_2 as nitration agent. This procedure is highly efficient and produces a range of 6-(2-nitroaryl)-purine derivatives with good chemoselectivity and functional-group tolerance. The utility of the method is further illustrated in the synthesis of antibacterial agent.

Introduction

Aromatic nitro compounds are widespread in the field of material and pharmaceutical science.[1] They are important synthetic precursors for other useful functional groups.[2] The classical electrophilic aromatic nitration to prepare aromatic nitro compounds uses corrosive nitric acid as nitration agent and suffers from poor chemoselectivity and functional-group tolerance.[3] Direct C(sp^2)–H bond activation/nitration have become attractive synthetic solution to this problem and many excellent examples have been reported in the literature.[4]

The purine skeleton, which is an inherent scaffold of RNA and DNA, has received much attention of scientists due to its importance in biochemistry and pharmaceutical industry.[5] Particularly, the arylpurine derivatives have exhibited broad biological activities as antiviral (Hepatitis C), anticancer, and antimycobacterial agents (Scheme 1).[6] Due to their biological significance and applications, chemists have developed synthetic methods to functionalize arylpurines. An important method is the metal-catalyzed C(sp^2)–H activation/functionalization because it simplifies the overall synthetic procedure.[7] Functionalization of arylpurines by C(sp^2)–H acetoxylation, acylation, allylation, arylation, cyanation, halogenation, trifluoromethylthiolation, olefination, and amination have been reported recently.[8]

Nevertheless, *ortho* nitration of 6-arylpurines by C(sp^2)–H activation has never been disclosed. Herein, we report a method of Pd^{II}-catalyzed purine-directed *ortho* nitration of 6-arylpurines by C(sp^2)–H activation. This method is operated under mild conditions by using *t*BuONO/O_2 as nitration source. It is highly efficient and produces a variety of 6-(2-nitroaryl)-purine derivatives with good chemoselectivity and functional group tolerance.



Scheme 1. Purine-based bioactive molecules.

Results and Discussion

In a program directed to develop new C–H activation reactions,[9] we have become interested in investigating of *ortho* nitration of 6-arylpurines by using purine as intrinsic directing group. If successful, this transformation could produce a variety of 6-(2-nitroaryl)-purine derivatives in a straightforward manner. Our study was commenced with nitration of 9-benzyl-6-phenyl-

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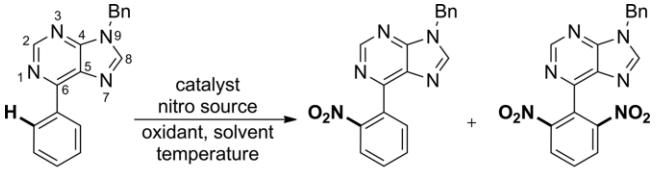
9*H*-purine **1a** as the model reaction (Table 1). Treatment of **1a** with $NaNO_2$ in the presence of $Cu(OAc)_2$ under air did not afford the desired mono-nitrated product **2a** (Table 1, entry 1). With $Pd(OAc)_2$ as catalyst, the reaction with either $AgNO_2$ or $NaNO_2$ as nitration agent in the presence of $K_2S_2O_8$ did not produce any amount of **2a** (Table 1, entries 2–4). However, when *t*BuONO was used as nitration agent under O_2, the reaction provided **2a** in 30 % yield (Table 1, entry 5). Solvent effects were then screened (Table 1, entries 6–11). It was found that benzotrifluoride was the best solvent, affording **2a** in 90 % yield along with 5 % of the di-nitrated product **3a** (Table 1, entry 9). Other solvents such as DCE, MeCN, anisole, PhCl or *o*-dichlorobenzene were inferior to benzotrifluoride. Afterwards, we investigated the effects of base additives on the reaction efficiency. It was shown that bases such as Na_2CO_3, K_2CO_3, KOAc or Cs_2CO_3 were detrimental to the reaction (Table 1, entries 12–15). After that, we screened different palladium catalysts (Table 1, entries 16–18). We found that $Pd(OAc)_2$ remained to be the best catalyst. Ultimately, the optimal reaction conditions were $Pd(OAc)_2$ (10 mol-%), *t*BuONO (2.0 equiv.) under 1 atm O_2 in benzotrifluoride (0.1 M) at 110 °C. It was worth to note that the reaction conditions were highly chemoselective in that the nitration on **1a** occurred exclusively on *ortho* position of phenyl group without formation of C-2 or C-8 nitrated product.

With the optimal reaction conditions in hands, we investigated the scope of 6-arylpurines (Table 2). To our delight, nitrations of substrates with either electron-donating or electron-withdrawing *ortho*-substituted phenyl groups proceeded smoothly to furnish the desired products in good yields (Table 2, **2ba**–**2ca**). In addition, *para*-substituted 6-arylpurines bearing either electron-deficient groups like F, Cl, Br, CO_2Me, OCF_3, or electron-rich groups such as *t*Bu, MeO, Me, and TMS also performed well under the reaction conditions, affording the corresponding products in good to excellent yields (Table 2, **2da**–**2ha**, **2ia**–**2la**). Moreover, substrates with either electron-withdrawing or electron-donating *meta*-substitutions also afforded the nitration products without incident under the reaction conditions (Table 2, **2ma**–**2pa**). The sterically hindered substrates were also tolerated to afford the product in good yield (Table 2, **2qa**–**2ra**). It is worth to note that the reaction conditions tolerated useful functional groups such as Br and CO_2Me that could be utilized as handles for further transformations.

Afterwards, we examined the effect of N9-substitutions of 6-phenylpurines on the nitration (Table 3). Nitrations of substrates bearing N9-alkyl substitutions such as methyl, butyl and isopropyl groups were well tolerated to give the products in moderate to good yields (Table 3, **2sa**–**ua**). In addition, the nitration of substrates that contained either aryl or benzyl group as N9-substitution proceeded smoothly in moderate to good yields (Table 3, **2va**–**wa**). It is worth to note that the benzyl group of the product **2wa** could be removed to release the free nitrogen atom for further derivatizations. Purine nucleosides are a class

Table 1. Optimization of reaction conditions.[a]

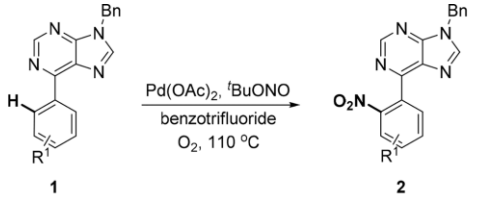


1a **2aa** **3aa**

Entry	Catalyst	Nitro source	Solvent	Yield[b]
				2aa/3aa
1[c]	$Cu(OAc)_2$	$NaNO_2$	MeOH	0:0
2[d]	$Pd(OAc)_2$	$AgNO_2/K_2S_2O_8$	dichloroethane	0:0
3[d]	$Pd(OAc)_2$	$AgNO_2/K_2S_2O_8$	toluene	0:0
4[e]	$Pd(OAc)_2$	$NaNO_2/K_2S_2O_8$	toluene	0:0
5	$Pd(OAc)_2$	*t*BuONO/O_2	toluene	30:0
6	$Pd(OAc)_2$	*t*BuONO/O_2	dichloroethane	41:15
7	$Pd(OAc)_2$	*t*BuONO/O_2	MeCN	0:0
8	$Pd(OAc)_2$	*t*BuONO/O_2	anisole	0:0
9	$Pd(OAc)_2$	*t*BuONO/O_2	benzotrifluoride	90:5[f]
10	$Pd(OAc)_2$	*t*BuONO/O_2	PhCl	78:21
11	$Pd(OAc)_2$	*t*BuONO/O_2	*o*-dichlorobenzene	0:0
12[g]	$Pd(OAc)_2$	*t*BuONO/O_2	benzotrifluoride	10:0
13[h]	$Pd(OAc)_2$	*t*BuONO/O_2	benzotrifluoride	15:0
14[i]	$Pd(OAc)_2$	*t*BuONO/O_2	benzotrifluoride	0:0
15[j]	$Pd(OAc)_2$	*t*BuONO/O_2	benzotrifluoride	0:0
16	$PdCl_2$	*t*BuONO/O_2	benzotrifluoride	6:0
17	$Pd(MeCN)_2Cl_2$	*t*BuONO/O_2	benzotrifluoride	75:12
18	$Pd(PPh_3)_2Cl_2$	*t*BuONO/O_2	benzotrifluoride	45:10

[a] General procedure: **1a** (0.20 mmol), nitro source (0.40 mmol), and catalyst (10 mol-%) in solvent (2.0 mL) at 110 °C for 12–24 h with TLC control. [b] Determined by analysis of crude mixture with CH_2Br_2 as internal standard by ^1H NMR spectroscopy (400 MHz). [c] $Cu(OAc)_2$: 3.0 equiv., $NaNO_2$: 2.0 equiv., 2.0 equiv. of K_2HPO_4 was added. [d] $AgNO_2$: 2.0 equiv., $K_2S_2O_8$: 2.0 equiv. [e] $NaNO_2$: 2.0 equiv., $K_2S_2O_8$: 2.0 equiv. [f] Isolated yield. [g] 2.0 equiv. of Na_2CO_3 was added. [h] 2.0 equiv. of K_2CO_3 was added. [i] 2.0 equiv. of KOAc was added. [j] 2.0 equiv. of Cs_2CO_3 was added.

Table 2. Substrate scope of 9-benzyl-6-arylpurines.[a,b]



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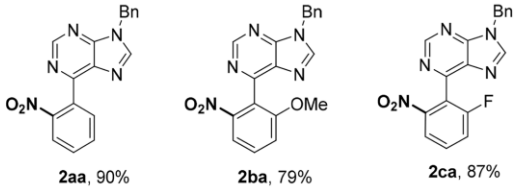
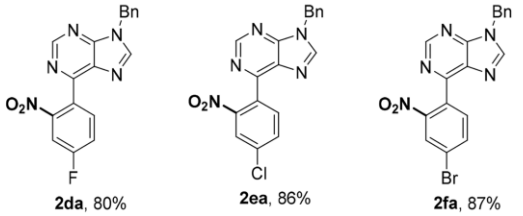
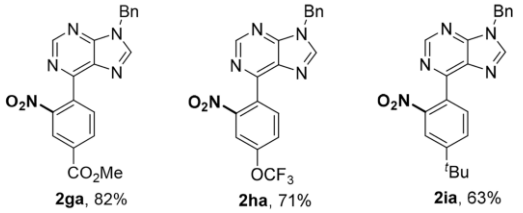


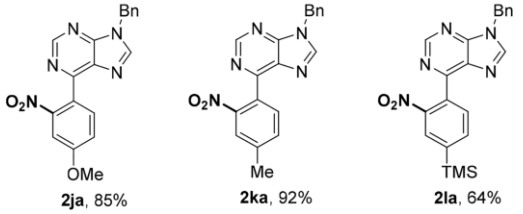
2aa, 90% **2ba**, 79% **2ca**, 87%



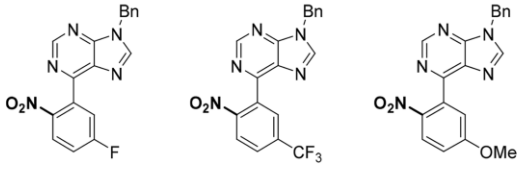
2da, 80% **2ea**, 86% **2fa**, 87%



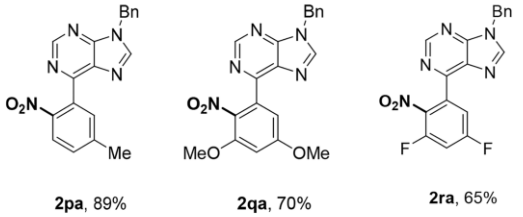
2ga, 82% **2ha**, 71% **2ia**, 63%



2ja, 85% **2ka**, 92% **2la**, 64%



2ma, 78% **2na**, 53% **2oa**, 78%

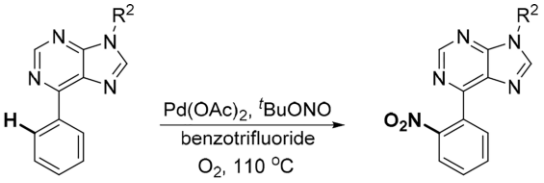


2pa, 89% **2qa**, 70% **2ra**, 65%

[a] Reaction conditions: **1** (0.20 mmol), *t*BuONO (0.40 mmol), and $Pd(OAc)_2$ (10 mol-%) under 1 atm O_2 in benzotrifluoride (2.0 mL) at 110 °C for 12–24 h with TLC control. [b] Isolated yield.

of important structures that have demonstrated important biological activity as anti-HIV/HBV agents.[10] We examined the nitration of purine nucleoside substrate **1x** under the reaction conditions. We were pleased to find that the reaction afforded the nitration product **2xa** in 80 % yield.

Table 3. Substrate scope of N9-substituted 6-phenylpurines.[a,b]



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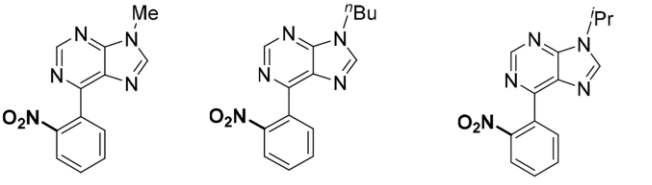
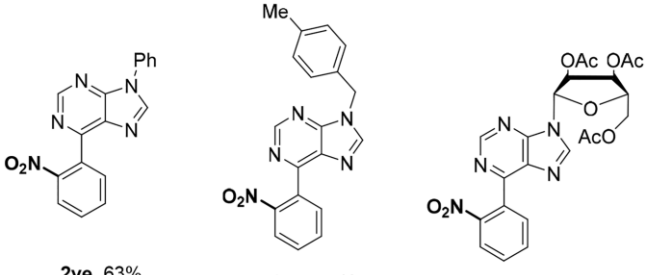


2sa, 60% **2ta**, 83% **2ua**, 65%

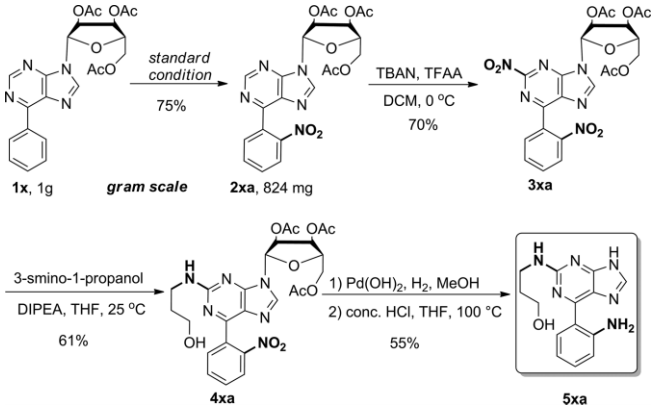


2ve, 63% **2wa**, 81% **2xa**, 80%

[a] Reaction conditions: **1** (0.20 mmol), *t*BuONO (0.40 mmol), and $Pd(OAc)_2$ (10 mol-%) under 1 atm O_2 in benzotrifluoride (2.0 mL) at 110 °C for 12–24 h with TLC control. [b] Isolated yield.

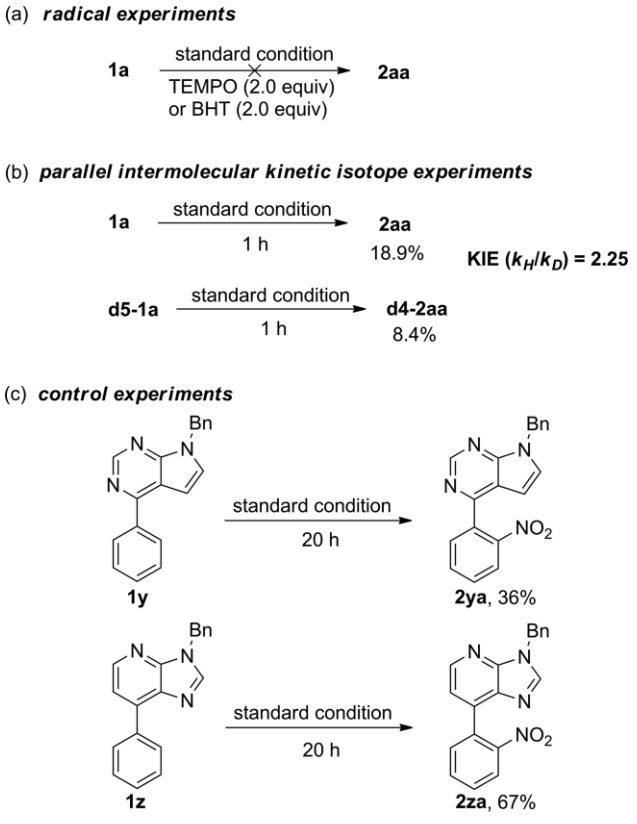
The utility of the method was successfully demonstrated in the synthesis of antibacterial agent **5xa** as shown in Scheme 2.[11] Under the reaction conditions, nitration of **1x** was performed on a gram scale to give **2xa** in 75 % yield. Then, an additional nitro group was introduced at C2 position by treatment of **2xa** with TBAN/TFAA (TBAN = *tetra*-butylammonium nitrate) to provide **3xa** in 70 % yield. Afterwards, the C-2 nitro group of **3xa** was selectively replaced by 3-amino-1-propanol to deliver **4xa**, which was finally transformed into **5xa** by a two-step sequence including hydrogenative reduction and deglycosylation in 55 % overall yield.

To gain insights into the reaction mechanism, a series of control experiments was performed (Scheme 3). The nitration of **1a** was completely inhibited in the presence of radical scavengers, such as BHT or TEMPO, implying that a radical process might be involved for the reaction (Scheme 3, **a**). The kinetic isotope experiments (parallel intermolecular KIE = 2.25, see the Supporting Information) indicated that the cleavage of the

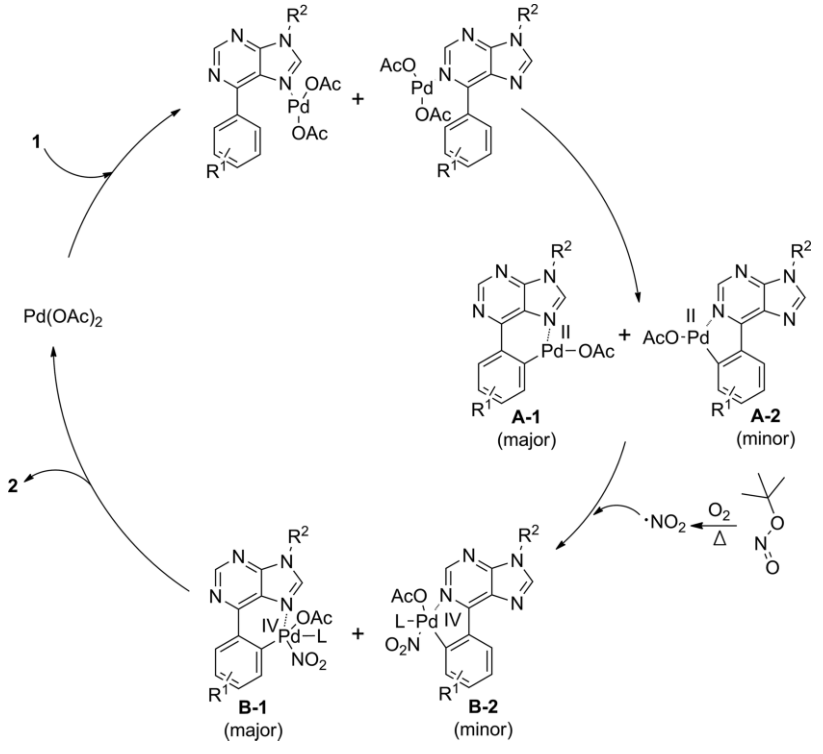


Scheme 2. Synthesis of antibacterial agent **5xa**.

C(sp^2)–H bond of the substrate occurred as the rate-limiting step (Scheme 3, **b**).[12] The purine N1 and N7 atom of **1a** were involved in the reaction presumably as chelating group, because substrate **1y** or **1z**, which had either N1 or N7 absent compared to **1a**, afforded the nitration product **2ya** and **2za** in much lower yield under the reaction condition (36 % and 67 % respectively) (Scheme 3, **c**). Based on the limited data available, a radical pathway involving Pd^{II}/Pd^{IV} catalysis was tentatively proposed as shown in Scheme 4.[4j–4l] In the first step, either the N1 or the N7 atom of substrate **1** coordinate to Pd^{II} followed by cleavage of the C(sp^2)–H bond to either form the six-membered or the five-membered cyclopalladated complex **A-1** or **A-2**. Then, an oxidative addition of **A-1** and **A-2** with $\cdot NO_2$ generated by *t*BuONO/O_2 produced an Pd^{III} intermediate, which was further oxidized by O_2 to give the Pd^{IV} intermediates **B-1** or **B-2**. Finally, a reductive elimination of **B-1** or **B-2** afforded **2** along with regeneration of the Pd^{II} for the next catalytic cycle.



Scheme 3. Control experiments.



Scheme 4. Proposed reaction mechanism.

Conclusion

In conclusion, we have developed an efficient protocol for the *ortho* nitration of 6-arylpurines by Pd^{II}-catalyzed C(sp^2)–H activation using purine as an intrinsic directing group. This approach is operated under mild conditions and uses *t*BuONO/O_2 as nitration agent. It shows good chemoselectivity and functional-group tolerance and produces a variety of 6-(2-nitroaryl)-purine derivatives, which are useful scaffolds in medicinal chemistry. The utility of the method is further illustrated in the synthesis of an antibacterial agent. Further investigation of the detailed reaction mechanism and expanding the reaction scope is currently in progress.

Experimental Section

A 15 mL Schlenk tube was charged with **1** (0.20 mmol), *t*BuONO (2.0 equiv.), and $Pd(OAc)_2$ (10 mol-%) in benzotrifluoride (0.1 M). The Schlenk tube was purged with oxygen and then tightly capped. The mixture was vigorously stirred at 110 °C and the progress of this reaction was monitored by TLC. Upon completion of the reaction, the mixture was filtered through a short pad of Celite. The filtrate was concentrated in vacuo to give a residue, which was purified by flash chromatography to furnish the title compounds **2**.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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Keywords: Palladium · Nitration · Nitrogen heterocycles · *tert*-Butyl nitrite · Radical reactions

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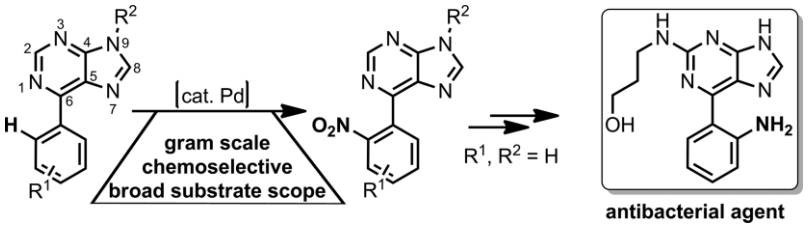

6-(2-Nitroaryl)-purine can be obtained through Pd^{II}-catalyzed C(sp^2)–H activation of 6-arylpurines in the presence of *t*BuONO/O_2. The purine substituent acts as an *ortho* directing group for the nitration.

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