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$PMes_3$-Promoted Ruthenium-Catalyzed Meta C-H Nitration of 6-Arylpurines

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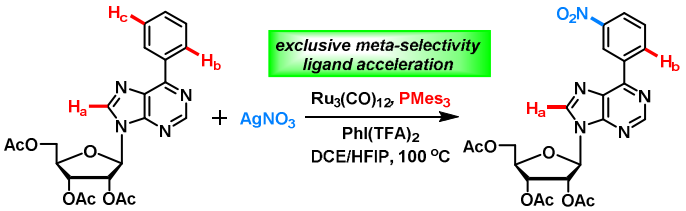


ABSTRACT: To address the challenge of *meta* nitration of 6-arylpurine substrates, a versatile ruthenium catalyzed *meta* C-H nitration is developed. The use of sterically hindered phosphine ligand is crucial for the catalytic efficiency, and a wide class of 6-arylpurines and nucleosides were found suitable for this process providing corresponding exclusively *meta* nitrated products in good yields.

INTRODUCTION

Purine and nucleoside analogues possess a wide range of biological activities, and are used as prototypes for the development of anti-HIV, anti-inflammatory and anticancer agents (Figure 1).[1] Among them, 6-arylpurine derivatives represent an important class and have attracted great interest for their synthesis and diverse functionalization.

Generally, Suzuki cross-coupling reaction of 6-chloropurine with various arylboronic acids represents the universal method for the construction of 6-arylpurines.[2] However, each analogue has to be accessed by means of de novo synthesis in the case of polysubstituted 6-arylpurine through multiple steps. Therefore, development of methods for direct late-stage modifications of 6-arylpurines is daunting.

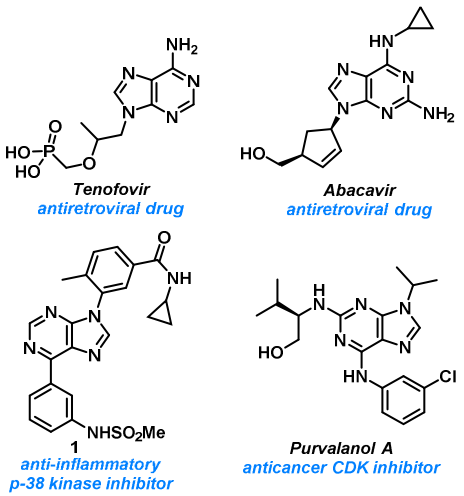
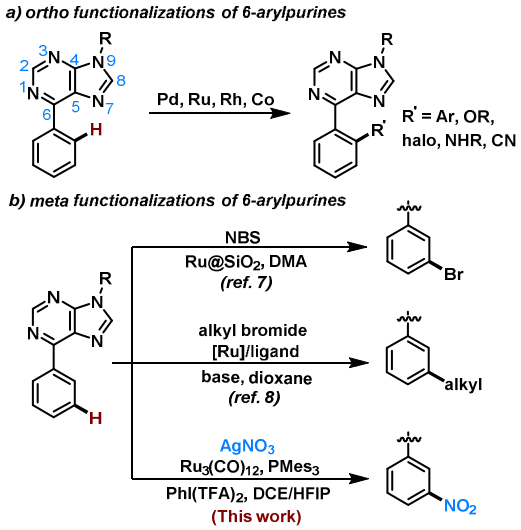


Figure 1. Representative Biologically Active Purine Derivatives.

In the past decades, directing group (DG)-assisted site-selective C-H activation/functionalization has achieved great progress for construction or modification of complex natural products and pharmaceutical molecules.[3-4] In contrast to the widely used pyridyl DG, the purine scaffold as an intrinsic DG is rather challenging due to: 1) multiple potential chelating sites (three additional nitrogen atoms) that may deactivate the catalyst; and 2) easily generation of undesired C-H functionalization at the highly nucleophilic C8 position of the purine core. Despite these limitations, several *ortho* C-H functionalizations on the aryl component of 6-arylpurines have been accomplished (Scheme 1a).[5] In 2011, Guo[5a] and Lakshman[5b] respectively developed Pd and Ru catalysis for *ortho* C-H arylation of 6-arylpurines.

Subsequently, the two research groups also described *ortho* C-H oxidation using purine as the DG.[5c,e] Recently, Pd(II) or Co(III)-catalyzed C-H halogenations were accomplished using *N*-halosuccinimide as the halogenating agent by the Guo[5c] and Pawar[5i] groups, respectively. In addition, Chang et al reported *ortho* cyanation[5h] and mono-amination[5d,f] of 6-arylpurines. In the meantime, *N*-heterocycle-assisted *ortho*-ruthenation strategy has been successfully established for the *meta* C-H functionalization of arenes.[6] Very recently, Ackermann developed the first *meta* C-H bromination of 6-arylpurine bases using the heterogeneous Ru@SiO_2 catalyst,[7] and subsequently they also found that *meta*-selective alkylation was achieved by ruthenium(II/III) catalysis (Scheme 1b).[8]



Scheme 1. Site-Selective C-H Functionalizations of 6-Arylpurines.

Using the catalytic C-H nitration to readily construct the C-N bond with high site-selectivity by avoiding the use of strong acid condition remains an important strategy in modern organic synthesis.[9] Although *ortho* and *meta* C-H functionalizations of 6-arylpurines have achieved success in the past few years, to the best of our knowledge, methods for *meta* C-H nitration of 6-arylpurines have not been established yet. Recently, we developed the first Ru(0)-catalyzed *meta* C-H nitration

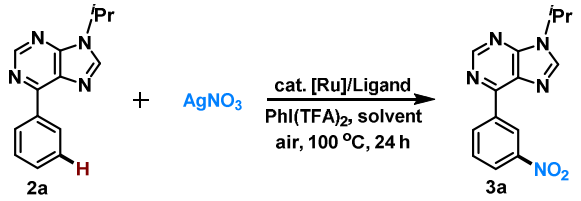
of arenes,[10] unfortunately, this protocol is inapplicable to *meta* nitration of 6-arylpurines. Subsequently, we also established the second-generation ruthenium catalytic system for *meta*-selective nitration of acetophenone oxime substrates,[11] however, only a small amount of *meta* product was observed in the case of 6-arylpurine. Therefore, a more versatile approach for *meta* nitration of the challenging substrate 6-arylpurines is needed. Herein, we described a tertiary phosphine ligand promoted ruthenium-catalyzed *meta* C-H nitration strategy (Scheme 1b), which allows selective *meta* nitration of 6-arylpurines and nucleosides.

RESULTS AND DISCUSSION

We initiated our optimization studies with 9-isopropyl-6-phenylpurine (**2a**) as the model substrate and $AgNO_3$ as the nitrating agent, the desired *meta* nitration product **3a** was obtained only in 35% yield (Table 1, entry 1). In order to improve the catalytic efficiency, we firstly investigated various monodentate phosphorous ligands.[8,12] To our delight, tris(2,4,6-trimethylphenyl)phosphine ($PMes_3$) was found to increase the yield of *meta* nitrated product **3a** up to 57% (entry 7). We then tested several NHC ligands, but unfortunately, no better result was obtained (entries 11-12). Through screening the loadings of $PMes_3$, we found that using 0.3 equivalent of ligand gave **3a** in slightly higher yield (entry 13). To increase the solubility of the reaction mixture, we tried to add a number of alcohols as the co-solvent (entries 15-17). The results showed that the use of DCE/HFIP as the mixture solvent improved the yield of **3a** up to 64%. Through prolonging the reaction time to 48 h, the yield of **3a** was further increased (74%, entry 18). It is worth noting that **3a** was not detected in the presence of $RuCl_2(PPh_3)_4$ as the catalyst (entry 19). When the reaction was carried out under O_2

or N_2 atmosphere, the yield of **3a** significantly dropped (entries 20-21). Therefore, the reaction conditions in entry 18 were selected as the standard condition.

Table 1. Optimization of the Reaction Conditions[a]



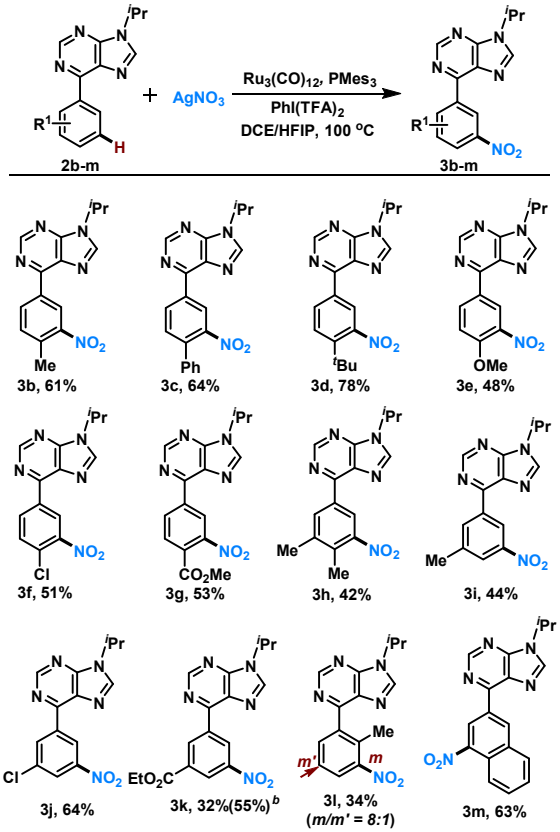
entry	ligand (x equiv)	solvent	yield[b] (%)
1	-	DCE	35
2	PPh_3 (0.2)	DCE	41
3	P(*o*-tol)$_3$ (0.2)	DCE	55
4	P(*o*-furyl)$_3$ (0.2)	DCE	11
5	P(*p*-OMeC$_6$H$_4$)$_3$ (0.2)	DCE	39
6	P(*p*-CF$_3$C$_6$H$_4$)$_3$ (0.2)	DCE	50
7	$PMes_3$ (0.2)	DCE	57
8	PCy_3 (0.2)	DCE	21
9	X-Phos (0.2)	DCE	25
10	BrettPhos (0.2)	DCE	25
11	IMes·HCl (0.2)	DCE	trace
12	IPr·HCl (0.2)	DCE	24
13	$PMes_3$ (0.3)	DCE	60
14	$PMes_3$ (0.4)	DCE	57
15	$PMes_3$ (0.3)	DCE/^{t}BuOH	14
16	$PMes_3$ (0.3)	DCE/HFIP	64
17	$PMes_3$ (0.3)	DCE/MeOH	n.d.
18[c]	**$PMes_3$ (0.3)**	**DCE/HFIP**	**74**
19[c,d]	$PMes_3$ (0.3)	DCE/HFIP	n.d.
20[c,e]	$PMes_3$ (0.3)	DCE/HFIP	62
21[c,f]	$PMes_3$ (0.3)	DCE/HFIP	53

[a]Reaction conditions: **2a** (0.10 mmol), $AgNO_3$ (0.18 mmol), $Ru_3(CO)_{12}$ (7.5 mol%), $PhI(TFA)_2$ (1.1 equiv) in solvent (1 mL DCE, 100 μL alcohol) at 100 °C for 24 h. [b]Isolated yield. [c]For 48 h. [d]Using $RuCl_2(PPh_3)_4$ as the catalyst. [e]Under O_2 protection. [f]Under N_2 protection. n.d. = not detected.

With the optimized reaction condition for *meta* nitration of 6-arylpurines in hand, we then explored a variety of substituted arylpurines in Scheme 2. For the *para* substituted substrates, electron-neutral arylpurines gave the desired *meta* nitrated

products **3b-d** in 61-78% yields, whereas both electron-rich and electron-deficient ones were found to react sluggishly and afforded the corresponding products **3e-g** in slightly lower yields (48-53%). It was found that when one of the two *meta* positions was substituted, the nitration reaction exclusively proceeded on the other *meta* position and products **3h-3k** were afforded in 32-64% yields. For *ortho*-methyl substituted substrate, the *meta* nitration prefers the sterically bulkier position and gave the products in total 34% yield. Regrettably, only trace of corresponding *meta* products were obtained in the cases of *ortho*-chloro or methoxy substituted substrates. In addition, the present nitration approach was also applicable to naphthyl purine and the exclusive *meta* nitration product **3m** was obtained in 63% yield.

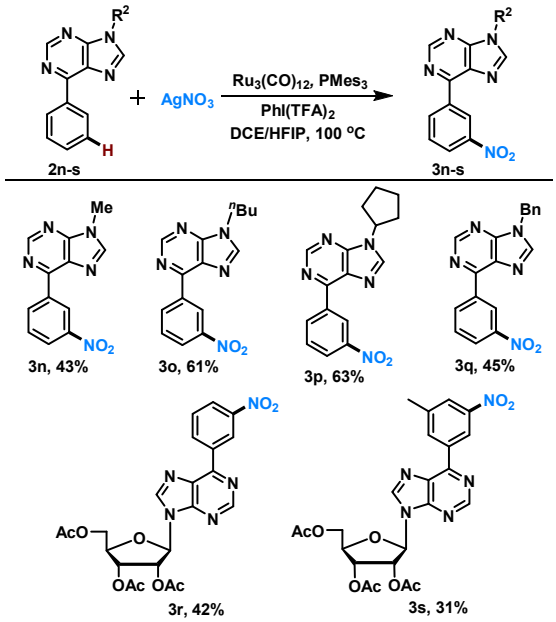
Scheme 2. Scope of Substituted Arylpurines[a]



[a]Reaction conditions: **2b-m** (0.10 mmol), $AgNO_3$ (0.18 mmol), $Ru_3(CO)_{12}$ (7.5 mol%), $PMes_3$ (30 mol%), $PhI(TFA)_2$ (1.1 equiv) in DCE/HFIP (1.1 mL, 10/1, v/v) at 100 °C for 48 h in a sealed tube. [b]Yield based on the recovered starting material is listed in parenthesis.

Subsequently, diverse *N*-substituted purines were investigated under the standard conditions (Scheme 3). In the case of *N*-methyl, -butyl, -cyclopentyl and -benzyl 6-phenylpurines, the yields of corresponding products **3n-q** were lower than that of *N*-isopropyl analog **3a** (43-63% *vs* 74%). More appealingly, we found that nucleoside analogues protected by acetylation were also suitable for current *meta* C-H nitration and provided the corresponding products **3r-s** in 31-42% yields, which would be potentially useful for antiviral or anticancer drug screening.[13] It should be noted that the unprotected acyclovir side chain and 2'-deoxyribose of 6-arylpurines are not tolerated under present standard conditions.

Scheme 3. Scope of *N*-Substituted Purines[a]

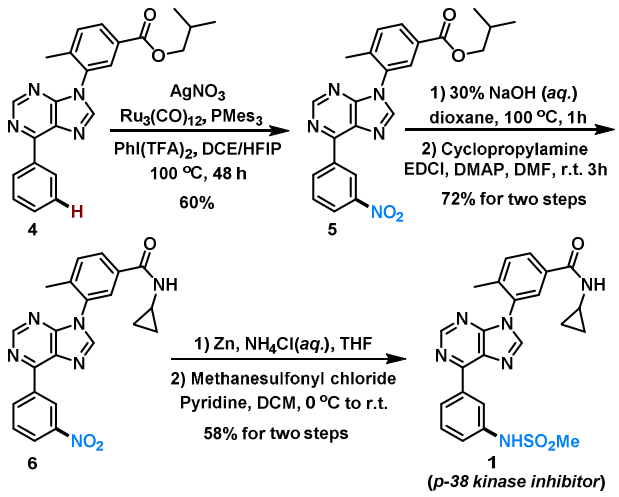


[a]Reaction conditions: **2n-s** (0.10 mmol), $AgNO_3$ (0.18 mmol), $Ru_3(CO)_{12}$ (7.5 mol%), $PMes_3$ (30 mol%), $PhI(TFA)_2$ (1.1 equiv) in DCE/HFIP (1.1 mL, 10/1, v/v) at 100 °C for 48 h in a sealed tube.

To demonstrate the utility of the current approach, we tried to shorten the route for synthesis of the anti-inflammatory p-38 kinase inhibitor **1**[1d] using the current *meta*

nitration of arylpurines as the key step (Scheme 4). Firstly, the key intermediate **5** was conveniently prepared through *meta* C-H nitration of phenylpurine **4** in 60% yield. Subsequent hydrolysis with aqueous NaOH and condensation with cyclopropylamine furnished the amide precursor **6** in 72% yield for two steps. Zn-reduction followed by sulfonylation completed the target inhibitor **1** in 58% overall yield in two-step. It is worth noting that intermediate **6** could not be directly accessed through *meta* C-H nitration method because of the intolerance of amide moiety. This concise five-step process with 25% overall yield (from **4**) provides an alternative route for the synthesis of anti-inflammatory agent **1** and would be conveniently used to generate more derivatives.

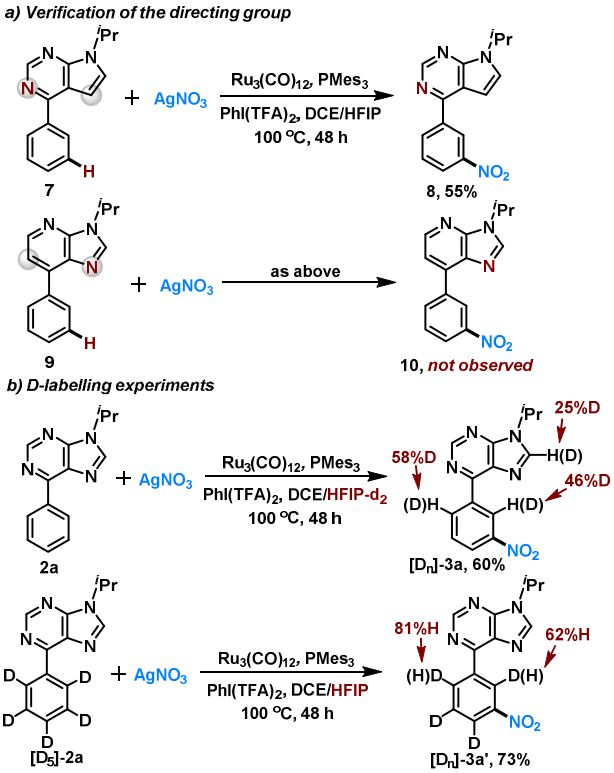
Scheme 4. Synthesis of p-38 Kinase Inhibitor 1



To gain more insight on the details of the *meta* nitration of 6-arylpurines, we firstly conducted the reaction with two model substrates **7** and **9**, in which the N1 or N7 nitrogen atom is removed. Only *meta* nitration product **8** was observed in 55% yield under the standard condition, indicating that N1 is responsible for the reaction (Scheme 5a). Furthermore, isotope-labelling experiments were also carried out with substrates **2a** and **[D_5]-2a**, the *ortho* D/H exchanged products **[D_n]-3a** and **[D_n]-3a'**

were isolated in 60% and 73% yield, respectively. These results disclosed that *ortho* C-H ruthenation process is reversible (Scheme 5b).

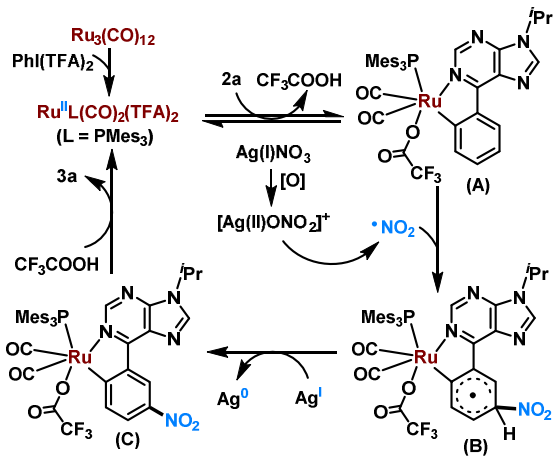
Scheme 5. Primary Mechanism Studies



Based on these results and our previous reports,[11] a proposed mechanism is shown in Scheme 6. Initially, the active Ru(II) catalyst was generated by the oxidation of Ru(0) by $PhI(TFA)_2$, then the resulting Ru(II) species was coordinated to the N1 of the purine moiety and the *ortho* C-H bond of **2a** was activated to provide the Ru(II) species **A**, which could not be isolated and was proposed according to our previous work.[11] The nitrogen dioxide radical, produced by the oxidation of nitrate ion, selectively attacked the *para* position of C-Ru bond to form the species **B**. We have tried to detect the possible TEMPO-NO_2 product through TLC sprayed with potassium permanganate, however, no relative product was isolated. The generation of NO_2 radical was proposed according to the previous literatures[10,11]. Subsequently,

the reductive dehydrogenation occurred to deliver the Ru(II) complex **C**, which then went through ligand exchange with CF_3COOH to release the desired product **3a**. Meanwhile, the active Ru(II) catalyst was regenerated for the next catalytic cycle.

Scheme 6. Proposed Mechanism



CONCLUSION

In conclusion, we have developed a versatile *meta* C-H nitration of 6-arylpurines under $Ru_3(CO)_{12}$/oxidant catalytic system. Notably, the reactivity was significantly enhanced through employing the sterically hindered phosphine ligand. This protocol could tolerate broad purine substrates as well as nucleosides. Moreover, it also provides a convenient pathway for the synthesis of ongoing p-38 kinase inhibitor and its analogues.

EXPERIMENTAL SECTION

General Information. All reactions were performed in flame-dried glassware, including sealed tubes or Schlenck tubes. Liquids and solutions were transferred with syringes. All solvents and chemical reagents were obtained from commercial sources and used without further purifications. ^1H and ^{13}C NMR spectra were recorded with

tetramethylsilane as an internal reference. Low and high-resolution mass spectra were recorded on EI-TOF (electrospray ionization-time of flight) or ESI-TOF. Flash column chromatography on silica gel (200 - 300 mesh). The column output was monitored by TLC on silica gel (100 - 200 mesh) precoated on glass plates (15 x 50 mm), and spots were visualized by UV light at 254 nM. The following starting materials were synthesized according to previously described methods: 9-isopropyl-6-arylpurine,[2b] 9-butyl or benzyl-6-chloropurine,[14] 9-cyclopentyl-6-chloropurine,[15] (2*R*,3*R*,4*R*,5*R*)-2-(acetoxymethyl)-5-(6-chloro-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyldiacetate.[16]

General Procedure for Synthesis of Meta Nitrated Prodcucts. To a stirred solution of substrates **2, 4** or **7** (0.10 mmol) in DCE/HFIP (1 mL/100 μL), $AgNO_3$ (31 mg, 0.18 mmol), $PhI(TFA)_2$ (47 mg, 0.11 mmol), $Ru_3(CO)_{12}$ (4.8 mg, 7.5 mol%) and $PMes_3$ (12 mg, 30 mol%) were added. The mixture was stirred at 100 ^oC for 48 h. After cooled to room temperature, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified on a preparative TLC with petroleum petroleum ether/ethyl acetate as the eluent to afford the nitrated products **3, 5** or **8**.

Synthesis of Compound 4.[2b,17] a) To a stirred solution of 3-amino-4-methylbenzoic acid (**S1**) (600 mg, 4 mmol) in isobutanol (20 mL), thionyl chloride (1.44 mL, 20 mmol) was added at 0 ^oC. Then the mixture was stirred overnight at 80 ^oC. After the solvent was removed, the residue was purified on a silica gel column (PE/EA = 4/1) to give compound **S2**; b) A microwave vial was charged with 4,6-dichloropyrimidin-5-amine (39 mg, 0.24 mmol), compound **S2** (50 mg, 0.24 mmol), 37% HCl (12 μL) and isobutanol (0.5 mL). The vessel was sealed and heated in a microwave reactor at 150 ^oC for 1 h. After cooled to room temperature, the solvent was removed. The rude product **S3** and one drop of acetic acid were added in triethyl orthoformate (1 mL).

The reaction vessel was placed in a microwave reactor at 120 ^{o}C for 15 min. After the solvent was removed, The residue was purified on a silica gel column (PE/EA = 5/1) to afford product **S4**; c) To a stirred solution of **S4** (344 mg, 1 mmol) in toluene (20 mL), phenylboronic acid (244 mg, 2 mmol), K_2CO_3 (207 mg, 1.5 mmol), $Pd(PPh_3)_4$ (62 mg, 0.05 mmol) were added under N_2 protection. Then the mixture was stirred at 100 ^{o}C for 16 h. After the solvent was removed, the residue was purified on a silica gel column (PE/EA = 5/1) to afford compound **4.**

Synthesis of Compound 6. To a stirred solution of compound **5** (43 mg, 0.1 mmol) in dioxane (1 mL), 30% aqueous NaOH (0.5 mL) was added. Then the mixture was stirred at 100 ^{o}C for 1 h. HCl aqueous solution was added until pH = 3, the mixture was extracted with DCM, and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in DMF (1 mL), EDCI (23 mg, 0.12 mmol), DMAP (1 mg, 0.01 mmol) and cyclopropylamine (14 μL, 0.2 mmol) were added. Then the mixture was stirred overnight at room temperature. After the solvent was removed, the residue was purified by silica gel column chromatography (PE/EA = 1/2) to give compound **6**.

Synthesis of p-38 Kinase Inhibitor 1. A round flask was charged with compound **6** (29 mg, 0.07 mmol), zinc powder (46 mg, 0.7 mmol), saturated aqueous NH_4Cl (1 mL) and THF (1 mL). The mixture was stirred at 80 ^{o}C for 5 h. The solid was removed by filtrated. 30% NaOH was added until pH = 9. The aqueous layer was extracted with EtOAc, and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was used in the next step without further purification. The crude product was dissolved in DCM (1 mL), pyridine (9 μL, 0.11 mmol) and methylsulfonyl chloride (7 μL, 0.08 mmol) were added at 0 ^{o}C. The

mixture was stirred at room temperature for 12 h. After the solvent was removed, the residue was purified on a silica gel column (DCM/MeOH = 50/1) to give compound **1.**

Spectroscopic Data of All New Compounds.

*9-Isopropyl-6-(3-nitrophenyl)pur*ine *(**3a**):* white solid (21 mg, 74%); mp = 171-173 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1H), 9.21 (d, *J* = 7.8 Hz, 1H), 9.06 (s, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.26 (s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 5.02 (p, *J* = 6.9 Hz, 1H), 1.71 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 152.1, 151.7, 148.7, 142.8, 137.6, 135.5, 131.7, 129.6, 125.2, 124.7, 47.6, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{13}N_5O_2$, 283.1069; found, 283.1068.

*9-Isopropyl-6-(4-methyl-3-nitrophenyl)purine (**3b**):* white solid (18 mg, 61%); mp = 179-181 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (d, *J* = 1.8 Hz, 1H), 9.08 – 8.97 (m, 2H), 8.23 (s, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.27 (s, 1H), 5.01 (p, *J* = 6.8 Hz, 1H), 2.70 (s, 3H), 1.70 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 152.0, 151.8, 149.7, 142.6, 135.9, 135.2, 133.6, 133.0, 131.5, 125.8, 47.5, 22.6, 20.6; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{15}N_5O_2$, 297.1226; found, 297.1226.

*9-Isopropyl-6-(2-nitro-[1,1'-biphenyl]-4-yl)purine (**3c**):* white solid (23 mg, 64%); mp = 144-146 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (d, *J* = 1.7 Hz, 1H), 9.13 (dd, *J* = 8.2, 1.7 Hz, 1H), 9.06 (s, 1H), 8.25 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.39 (m, 5H), 5.01 (q, *J* = 6.8 Hz, 1H), 1.71 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 152.1, 151.4, 149.7, 142.7, 138.0, 137.0, 136.2, 132.9, 132.2, 131.7, 128.8, 128.5, 127.9, 125.2, 47.6, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{20}H_{17}N_5O_2$, 359.1382; found, 359.1382.

*6-(4-(tert-Butyl)-3-nitrophenyl)-9-isopropylpurine (**3d**):* white solid (26.5 mg, 78%); mp = 119-121 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (d, *J* = 0.9 Hz, 1H), 8.92 (dd, *J* = 8.5, 1.9 Hz, 1H), 8.88 (d, *J* = 1.9 Hz, 1H), 8.20 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 1H),

5.05 – 4.96 (m, 1H), 1.69 (d, *J* = 6.8 Hz, 6H), 1.47 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 152.0, 151.6, 151.5, 143.6, 142.5, 134.9, 131.5, 131.4, 128.9, 125.0, 47.5, 35.9, 30.6, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{18}H_{21}N_5O_2$, 339.1695; found, 339.1692.

*9-Isopropyl-6-(4-methoxy-3-nitrophenyl)purine (**3e**):* white solid (15 mg, 48%); mp = 201-203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (d, *J* = 2.2 Hz, 1H), 9.11 (dd, *J* = 8.9, 2.2 Hz, 1H), 8.99 (s, 1H), 8.21 (s, 1H), 7.24 (s, 1H), 4.99 (p, *J* = 6.8 Hz, 1H), 4.06 (s, 3H), 1.69 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 152.3, 152.0, 151.6, 142.3, 140.0, 135.2, 131.1, 128.6, 127.2, 113.3, 56.7, 47.4, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{15}N_5O_3$, 313.1175; found, 313.1174.

*6-(4-Chloro-3-nitrophenyl)-9-isopropylpurine (**3f**):* white solid (16 mg, 51%); mp = 139-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, *J* = 2.0 Hz, 1H), 9.08 (dd, *J* = 8.5, 2.0 Hz, 1H), 9.03 (s, 1H), 8.24 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 5.01 (p, *J* = 6.8 Hz, 1H), 1.70 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 152.0, 150.4, 148.4, 142.9, 135.9, 133.7, 132.0, 131.6, 129.0, 126.6, 47.6, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{12}ClN_5O_2$, 317.0680; found, 317.0678.

*Methyl 4-(9-isopropylpurinyl)-2-nitrobenzoate (**3g**):* white solid (18 mg, 53%); mp = 126-128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, *J* = 1.6 Hz, 1H), 9.23 (dd, *J* = 8.2, 1.6 Hz, 1H), 9.07 (s, 1H), 8.26 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 5.08 – 4.98 (m, 1H), 3.97 (s, 3H), 1.71 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 152.8, 152.0, 150.3, 148.7, 143.2, 139.8, 133.6, 131.9, 130.1, 128.5, 124.9, 53.4, 47.7, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{15}N_5O_4$, 341.1124; found, 341.1125.

*6-(3,4-Dimethyl-5-nitrophenyl)-9-isopropylpurine (**3h**):* white solid (13 mg, 42%); mp = 164-166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 9.02 (s, 1H), 8.84 (s, 1H), 8.22 (s, 1H), 5.04 – 4.96 (m, 1H), 2.50 (d, *J* = 13.0 Hz, 6H), 1.69 (d, *J* = 6.8 Hz,

6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 152.02, 151.95, 151.5, 142.5, 139.8, 134.0, 133.8, 133.2, 131.5, 123.1, 47.4, 30.9, 22.6, 20.8, 15.5; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{17}N_5O_2$, 311.1382; found, 311.1381.

*9-Isopropyl-6-(3-methyl-5-nitrophenyl)purine (**3i**):* white solid (13 mg, 44%); mp = 139-141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 9.05 (s, 1H), 8.97 (s, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 5.02 (p, *J* = 6.8 Hz, 1H), 2.64 – 2.58 (m, 3H), 1.70 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 151.99, 151.96, 148.7, 142.8, 140.1, 137.3, 135.9, 131.7, 125.7, 122.2, 47.5, 22.6, 21.5; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{15}N_5O_2$, 297.1226; found, 297.1227.

*6-(3-Chloro-5-nitrophenyl)-9-isopropylpurine (**3j**):* white solid (20.5 mg, 64%); mp = 143-145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 – 9.69 (m, 1H), 9.25 (t, *J* = 1.7 Hz, 1H), 9.06 (s, 1H), 8.34 (t, *J* = 2.1 Hz, 1H), 8.27 (s, 1H), 5.08 – 4.98 (m, 1H), 1.71 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 152.0, 150.1, 149.1, 143.2, 138.9, 135.7, 135.2, 131.7, 125.3, 122.9, 47.7, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{12}ClN_5O_2$, 317.0680; found, 317.0681.

*Ethyl 3-(9-isopropylpurin-6-yl)-5-nitrobenzoate (**3k**):* white solid (11.5 mg, 32%); mp = 172-174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (t, *J* = 1.9 Hz, 1H), 9.83 (t, *J* = 1.5 Hz, 1H), 9.09 (s, 1H), 8.99 (t, *J* = 1.9 Hz, 1H), 8.29 (s, 1H), 5.02 (q, *J* = 6.8 Hz, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 1.71 (d, *J* = 6.8 Hz, 6H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 152.7, 152.1, 150.7, 148.8, 143.2, 138.1, 135.9, 132.7, 131.8, 128.4, 126.0, 62.1, 47.6, 22.6, 14.4; HRMS (EI): m/z [M^+] calcd for $C_{17}H_{17}N_5O_4$, 355.1281; found, 355.1284.

*9-Isopropyl-6-(2-methyl-3-nitrophenyl)purine (**3l**):* white solid (9 mg, 30%); mp = 106-108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.19 (s, 1H), 7.97 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.85 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 5.02 (p, *J* =

6.8 Hz, 1H), 2.50 (s, 3H), 1.72 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 152.0, 151.7, 151.4, 143.1, 138.2, 134.7, 132.8, 131.9, 126.5, 125.2, 47.7, 22.6, 16.9; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{15}N_5O_2$, 297.1226; found, 297.1219.

*9-Isopropyl-6-(2-methyl-5-nitrophenyl)purine (**3l'**):* colorless oil (1.2 mg, 4%); mp = 117-119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.62 (d, *J* = 2.5 Hz, 1H), 8.25 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.20 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 5.02 (p, *J* = 6.8 Hz, 1H), 2.57 (s, 3H), 1.72 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 152.0, 151.9, 146.2, 145.3, 143.0, 136.2, 132.5, 132.1, 126.1, 124.1, 47.7, 22.6, 21.0; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{15}N_5O_2$, 297.1226; found, 297.1226.

*9-Isopropyl-6-(4-nitronaphthalen-2-yl)purine (**3m**):* pale yellow solid (21 mg, 63%); mp = 165-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 2H), 9.05 (s, 1H), 8.57 (d, *J* = 8.7 Hz, 1H), 8.27 (s, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 5.03 (q, *J* = 6.7 Hz, 1H), 1.71 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 152.0, 151.5, 147.0, 142.7, 136.3, 134.4, 132.2, 131.7, 130.6, 130.2, 127.7, 125.9, 124.2, 123.2, 47.5, 22.6; HRMS (EI): m/z [M^+] calcd for $C_{18}H_{15}N_5O_2$, 333.1226; found, 333.1233.

*9-Methyl-6-(3-nitrophenyl)purine (**3n**):* white solid (11 mg, 43%); mp = 245-247 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 9.22 (d, *J* = 7.8 Hz, 1H), 9.10 (s, 1H), 8.38 (d, *J* = 10.0 Hz, 1H), 8.19 (s, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 151.8, 148.7, 148.6, 145.6, 137.4, 135.5, 131.2, 129.6, 125.3, 124.8, 30.0; HRMS (EI): m/z [M^+] calcd for $C_{12}H_9N_5O_2$, 255.0756; found, 255.0760.

*9-Butyl-6-(3-nitrophenyl)purine (**3o**):* white solid (18 mg, 61%); mp = 122-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.0 Hz, 1H), 9.22 (dt, *J* = 7.9, 1.3 Hz, 1H), 9.07 (s, 1H), 8.37 (ddd, *J* = 8.2, 2.4, 1.1 Hz, 1H), 8.19 (s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H),

4.36 (t, *J* = 7.2 Hz, 2H), 1.95 (q, *J* = 7.5 Hz, 2H), 1.40 (dd, *J* = 14.9, 7.4 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 152.3, 151.7, 148.7, 145.1, 137.5, 135.4, 131.3, 129.6, 125.2, 124.7, 43.9, 31.9, 19.9, 13.5; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{15}N_5O_2$, 297.1226; found, 297.1223.

*9-Cyclopentyl-6-(3-nitrophenyl)purine (**3p**):* white solid (19.5 mg, 63%); mp = 151-153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 9.21 (d, *J* = 7.8 Hz, 1H), 9.06 (s, 1H), 8.37 (d, *J* = 8.2 Hz, 1H), 8.24 (s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 5.14 – 5.03 (m, 1H), 2.37 (dt, *J* = 10.9, 5.1 Hz, 2H), 2.14 – 1.97 (m, 4H), 1.87 (dd, *J* = 10.2, 5.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 152.1, 151.6, 148.7, 143.4, 137.6, 135.4, 131.7, 129.6, 125.2, 124.7, 56.4, 32.7, 23.9; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{15}N_5O_2$, 309.1226; found, 309.1226.

*9-Benzyl-6-(3-nitrophenyl)purine (**3q**):* white solid (15 mg, 45%); mp = 186-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 9.22 (d, *J* = 7.8 Hz, 1H), 9.11 (s, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 8.17 (s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.37 (q, *J* = 4.7 Hz, 5H), 5.52 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 152.6, 151.9, 148.7, 144.9, 137.4, 135.5, 134.9, 131.2, 129.6, 129.3, 128.8, 127.9, 125.3, 124.7, 47.5; HRMS (EI): m/z [M^+] calcd for $C_{18}H_{13}N_5O_2$, 331.1069; found, 331.1048. Spectral data matched the previous report.[18]

*(2R,3R,4R,5R)-2-(Acetoxymethyl)-5-(6-(3-nitrophenyl)purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (**3r**):* white solid (21 mg, 42%); mp = 73-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H), 9.20 (d, *J* = 8.1 Hz, 1H), 9.08 (s, 1H), 8.44 – 8.34 (m, 2H), 7.75 (t, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 5.2 Hz, 1H), 6.02 (t, *J* = 5.4 Hz, 1H), 5.71 (t, *J* = 5.1 Hz, 1H), 4.54 – 4.36 (m, 3H), 2.17 (d, *J* = 7.0 Hz, 6H), 2.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 152.7, 152.4, 148.7, 143.4, 137.1, 135.5,

131.9, 129.7, 125.5, 124.8, 86.6, 80.5, 73.1, 70.6, 63.0, 20.8, 20.6, 20.4; HRMS (EI): m/z [M^+] calcd for $C_{22}H_{21}N_5O_9$, 499.1339; found, 499.1342.

*(2R,3R,4R,5R)-2-(Acetoxymethyl)-5-(6-(3-methyl-5-nitrophenyl)purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (**3s**):* colorless oil (16 mg, 31%); mp = 162-164 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 9.06 (s, 1H), 8.96 (s, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 6.31 (d, *J* = 5.2 Hz, 1H), 6.02 (t, *J* = 5.4 Hz, 1H), 5.75 – 5.68 (m, 1H), 4.53 – 4.39 (m, 3H), 2.61 (s, 3H), 2.17 (d, *J* = 6.6 Hz, 6H), 2.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 152.64, 152.61, 152.4, 148.7, 143.3, 140.3, 136.8, 135.9, 131.9, 126.0, 122.3, 86.6, 80.5, 73.1, 70.6, 63.0, 30.9, 21.5, 20.8, 20.5, 20.4; HRMS (EI): m/z [M^+] calcd for $C_{23}H_{23}N_5O_9$, 513.1496; found, 513.1495.

*Isobutyl 3-amino-4-methylbenzoate (**S2**):* white solid (546 mg, 66%); mp = 33-35 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.7, 1.8 Hz, 1H), 7.35 (d, J = 1.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 4.07 (d, J = 6.6 Hz, 2H), 3.66 (s, 2H), 2.21 (s, 3H), 2.07 (dt, J = 13.4, 6.7 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.9, 144.5, 130.4, 129.3, 127.5, 119.9, 115.5, 70.8, 27.9, 19.3, 17.6; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{18}NO_2$, 208.1332; found, 208.1331.

*Isobutyl 3-(6-chloropurin-9-yl)-4-methylbenzoate (**S4**):* white solid (47 mg, 57% for two steps); mp = 132-134 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.23 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.00 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 4.13 (d, J = 6.6 Hz, 2H), 2.21 (s, 3H), 2.09 (dd, J = 13.7, 7.1 Hz, 1H), 1.01 (d, J = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 152.8, 152.2, 151.9, 145.0, 140.6, 132.5, 132.0, 131.5, 131.3, 130.2, 128.6, 71.5, 27.9, 19.2, 18.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{18}ClN_4O_2$, 345.1113; found, 345.1106.

*Isobutyl 4-methyl-3-(6-phenylpurin-9-yl)benzoate (**4**):* white solid (332 mg, 86%); mp = 94-96 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.85 (d, J = 6.1 Hz, 2H),

8.23 (s, 1H), 8.16 (d, J = 7.9 Hz, 1H), 8.04 (s, 1H), 7.58 (p, J = 8.1, 7.1 Hz, 4H), 4.13 (d, J = 6.6 Hz, 2H), 2.24 (s, 3H), 2.12 – 2.00 (m, 1H), 1.01 (d, J = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.3, 155.6, 153.2, 152.9, 144.0, 140.9, 135.5, 133.1, 131.8, 131.3, 130.98, 130.70, 130.04, 129.87, 128.77, 71.44, 27.87, 19.20, 18.41; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{23}N_4O_2$, 387.1816; found, 387.1816.

*Isobutyl 4-methyl-3-(6-(3-nitrophenyl)purin-9-yl)benzoate (**5**):* white solid (26 mg, 60%); mp = 107-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (t, *J* = 2.0 Hz, 1H), 9.28 (d, *J* = 7.8 Hz, 1H), 9.09 (s, 1H), 8.46 – 8.40 (m, 1H), 8.29 (s, 1H), 8.18 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.04 (d, *J* = 1.7 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 4.13 (d, *J* = 6.7 Hz, 2H), 2.25 (s, 3H), 2.08 (dt, *J* = 13.5, 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.2, 153.3, 153.2, 152.6, 148.7, 144.9, 140.8, 137.2, 135.5, 132.8, 131.9, 131.2, 130.9, 130.2, 129.8, 128.8, 125.6, 124.9, 71.5, 27.9, 19.2, 18.4; HRMS (EI): m/z $[M^+]$ calcd for $C_{23}H_{21}N_5O_4$, 431.1594; found, 431.1584.

*N-Cyclopropyl-4-methyl-3-(6-(3-nitrophenyl)purin-9-yl)benzamide (**6**):* white solid (30 mg, 72% for two steps); mp = 208-210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, *J* = 2.0 Hz, 1H), 9.28 (d, *J* = 7.5 Hz, 1H), 9.07 (s, 1H), 8.42 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.27 (s, 1H), 7.90 – 7.74 (m, 3H), 7.54 (d, *J* = 8.1 Hz, 1H), 6.30 (s, 1H), 2.91 (tt, *J* = 7.1, 3.6 Hz, 1H), 2.23 (s, 3H), 0.90 (q, *J* = 6.9 Hz, 2H), 0.69 – 0.58 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.1, 153.3, 153.2, 152.6, 148.7, 144.9, 139.2, 137.2, 135.6, 134.0, 133.0, 132.0, 130.9, 129.8, 128.1, 126.6, 125.6, 124.8, 23.3, 18.2, 6.9; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{22}H_{17}N_6O_3$, 413.1368; found, 413.1363.

*N-Cyclopropyl-4-methyl-3-(6-(3-(methylsulfonamido)phenyl)purin-9-yl)benzamide (**1**):* white solid (18.7 mg, 58% for two steps); mp = 214-216 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.03 (s, 1H), 9.00 (s, 1H), 8.91 (s, 1H), 8.74 – 8.68 (m, 2H), 8.51 (d, *J*

= 4.2 Hz, 1H), 7.98 (dd, *J* = 10.5, 1.9 Hz, 2H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 3.08 (s, 3H), 2.89 – 2.82 (m, 1H), 2.16 (s, 3H), 0.72 – 0.64 (m, 2H), 0.59 – 0.52 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.5, 153.4, 153.2, 152.9, 147.0, 139.4, 138.9, 136.8, 133.7, 133.3, 131.6, 130.6, 130.2, 128.8, 127.3, 125.8, 123.0, 120.6, 23.6, 18.0, 6.2; ESI-MS (m/z) 461 $(M-H)^-$; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_{23}H_{21}N_6O_3S$, 461.1401; found, 461.1401. Spectral data matched the previous report.[1d]

*7-Isopropyl-4-(3-nitrophenyl)pyrrolo[2,3-d]pyrimidine (**8**):* white solid (15.5 mg, 55%); mp = 113-115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.99 (s, 1H), 8.51 (d, *J* = 7.8 Hz, 1H), 8.37 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 3.7 Hz, 1H), 6.85 (d, *J* = 3.7 Hz, 1H), 5.24 (p, *J* = 6.7 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3, 151.3, 151.1, 148.7, 140.2, 134.6, 129.8, 126.5, 124.4, 123.7, 116.0, 99.6, 46.2, 22.7; HRMS (EI): m/z $[M^+]$ calcd for $C_{15}H_{14}N_4O_2$, 282.1117; found, 282.1109.

ASSOCIATED CONTENT

Supporting Information

H/D exchange experiments and ^{1}H and ^{13}C NMR spectra for all new compounds. 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) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192. (b) Harrigan, P. R.; Stone, C.; Griffin, P.; Nájera, I.; Bloor, S.; Kemp, S.; Tisdale, M.; Larder, B.; the CNA2001 Investigative Group. *J. Infect. Dis.* **2000**, *181*, 912. (c) Naumann, T.; Matter, H. *J. Med. Chem.* **2002**, *45*, 2366. (d) Dong, Q.; Wang, J.; Lan, J.; Lang, H. *WO 2005063766A2* **2005**. (e) Pozniak, A. *Int. J. Clin. Pract.* **2008**, *62*, 1285. (f) Picaud, S.; Strocchia, M.; Terracciano, S.; Lauro, G.; Mendez, J.; Daniels, D. L.; Riccio, R.; Bifulco, G.; Bruno, I.; Filippakopoulos, P. *J. Med. Chem.* **2015**, *58*, 2718. (g) Sharma, S.; Mehndiratta, S.; Kumar, S.; Singh, J.; Bedi, P. M. S.; Nepali, K. *Recent Pat. Anti-Canc.* **2015**, *10*, 308.

(2) (a) Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817. (b) Čerňa, I.; Pohl, R.; Klepetářová, B.; Hocek, M. *J. Org. Chem.* **2008**, *73*, 9048.

(3) For selected recent reviews on *ortho* C−H activation, see: (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (b) Chen, D. Y.-K.; Youn, S. W. *Chem. -Eur. J.* **2012**, *18*, 9452. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.;

Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (e) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (f) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (g) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (h) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (i) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498.

(4) For recent reviews on *meta or para* C−H activation, see: (a) Juliá-Hernández, F.; Simonetti, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11458. (b) Frost, C. G.; Paterson, A. J. *ACS Cent. Sci.* **2015**, *1*, 418. (c) Li, J.; De Sarkar, S.; Ackermann, L. *Top. Organomet. Chem.* **2015**, *55*, 217. (d) Sharma, R.; Thakur, K.; Kumar, R.; Kumar, I.; Sharma, U. *Catal. Rev.: Sci. Eng.* **2015**, *57*, 345. (e) Yang, J. *Org. Biomol. Chem.* **2015**, *13*, 1930. (f) Dey, A.; Agasti, S.; Maiti, D. *Org. Biomol. Chem.* **2016**, *14*, 5440.

(5) (a) 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. (b) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11400. (c) 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. (d) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110. (e) Chamala, R. R.; Parrish, D.; Pradhan, P.; Lakshman, M. K. *J. Org. Chem.* **2013**, *78*, 7423. (f) Kim, H. J.; Ajitha, M. J.; Lee, Y.; Ryu, J.; Kim, J.; Lee, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 1132. (g) Liang, Y.; Wnuk, S. F. *Molecules* **2015**, *20*, 4874. (h) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660. (i) Pawar, A. B.; Lade, D. M. *Org. Biomol. Chem.* **2016**, *14*, 3275. (j) Liang, L.; Xie, M.-S.; Wang, H.-X.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *J. Org. Chem.* **2017**, *82*, 5966.

(6) For selected Ru-catalyzed *meta* C-H functionalizations, see: (a) Saidi, O.; Marafie, J.; Ledger, A. E.; Liu, P. M.; Mahon, M. F.; Kociok-Kohn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298. (b) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875. (c) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877. (d) Li, J.; Warratz, S.; Zell, D.; De Sarkar, S.; Ishikawa, E. E.; Ackermann, L. *J. Am. Chem. Soc.* **2015**, *137*, 13894. (e) Teskey, C. J.; Lui, A. Y.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 11677. (f) Yu, Q.; Hu, L.; Wang, Y.; Zheng, S.; Huang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 15284. (g) Li, J.; Korvorapun, K.; De Sarkar, S.; Rogge, T.; Burns, D. J.; Warratz, S.; Ackermann, L. *Nat. Commun.* **2017**, *8*, 15430. (h) Li, G.; Li, D.; Zhang, J.; Shi, D.-Q.; Zhao, Y. *ACS Catal.* **2017**, *7*, 4138.

(7) Warratz, S.; Burns, D. J.; Zhu, C.; Korvorapun, K.; Rogge, T.; Scholz, J.; Jooss, C.; Gelman, D.; Ackermann, L. *Angew. Chem., Int. Ed.* **2017**, *56*, 1557.

(8) (a) Ruan, Z.; Zhang, S.-K.; Zhu, C.; Ruth, P. N.; Stalke, D.; Ackermann, L. *Angew. Chem., Int. Ed.* **2017**, *56*, 2045. (b) Korvorapun, K.; Kaplaneris, N.; Rogge, T.; Warratz, S.; Stückl, A. C.; Ackermann, L. *ACS Catal.* **2018**, 8, 886. (c) Fumagalli, F.; Warratz, S.; Zhang, S.-K.; Rogge, T.; Zhu, C.; Stückl, A. C.; Ackermann, L. *Chem. Eur. J.* **2018**, DOI: 10.1002/chem.201800530.

(9) For selected *ortho* C-H nitration, see: (a) Zhang, L.; Liu, Z.; Li, H.; Fang, G.; Barry, B.-D.; Belay, T. A.; Bi, X.; Liu, Q. *Org. Lett.* **2011**, *13*, 6536. (b) Xie, F.; Qi, Z.; Li, X. *Angew.Chem., Int. Ed.* **2013**, *52*, 11862. (c) Zhang, W.; Lou, S.; Liu, Y.; Xu, Z. *J. Org. Chem.* **2013**, *78*, 5932. (d) Dong, J.; Jin, B.; Sun, P. *Org. Lett.* **2014**, *16*, 4540. (e) Katayev, D.; Pfister, K. F.; Wendling, T.; Gooßen, L. J. *Chem. -Eur. J.* **2014**, *20*, 9902. (f) Liang, Y.-F.; Li, X.; Wang, X. C.; Yan, Y.; Feng, P.; Jiao, N. *ACS Catal.*

2015, *5*, 1956. (g) Pawar, G. G.; Brahmanandan, A.; Kapur, M. *Org. Lett.* **2016**, *18*, 448.

(10) Fan, Z.; Ni, J.; Zhang, A. *J. Am. Chem. Soc.* **2016**, *138*, 8470.

(11) Fan, Z.; Li, J.; Lu, H.; Wang, D.-Y.; Wang, C.; Uchiyama, M.; Zhang, A. *Org. Lett.* **2017**, *19*, 3199.

(12) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232.

(13) For recent reviews on antiviral or anticancer activity of nucleosides, see: (a) Xia, Y.; Qu, F.; Peng, L. *Mini-Rev. Med. Chem.* **2010**, *10*, 806. (b) Len, C.; Enderlin, G. *Molecules* **2015**, *20*, 4967. (c) Toti, K.; Renders, M.; Groaz, E.; Herdewijn, P.; Van Calenbergh, S. *Chem. Rev.* **2015**, *115*, 13484. (d) helton, J.; Lu, X.; Hollenbaugh, J. A.; Cho, J. H.; Amblard, F.; Schinazi, R. F. *Chem. Rev.* **2016**, *116*, 14379.

(14) Kim, B. Y.; Ahn, J. B.; Lee, H. W.; Kang, S. K.; Lee, J. H.; Shin, J. S.; Ahn, S. K.; Hong, C. I.; Yoon, S. S. *Eur. J. Med. Chem.* **2004**, *39*, 433.

(15) Tunçbilek, M.; Ateş-Alagöz, Z.; Altanlar, N.; Karayel, A.; Özbey, S. *Bioorg. Med. Chem.* **2009**, *17*, 1693.

(16) Ali, M. A.; Yao, X.; Li, G.; Lu, H. *Org. Lett.* **2016**, *18*, 1386.

(17) Aguado, L.; Camarasa, M.-J.; Pérez-Pérez, M.-J. *J. Comb. Chem.* **2009**, *11*, 210.

(18) Havelková, M.; Dvořák, D.; Hocek, M. *Synthesis* **2001**, *11*, 1704.