HETEROCYCLES, Vol. 104, No. 10, 2022, pp. 1792 - 1808. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 19th July, 2022, Accepted, 10th August, 2022, Published online, 24th August, 2022
DOI: 10.3987/COM-22-14722

RUTHENIUM(II)-CATALYZED *ortho* HYDROXYMETHYLATION OF 6-ARYLPURINES WITH PARAFORMALDEHYDE VIA PURINE-DIRECTED C-H ACTIVATION

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Abstract – A Ru-catalyzed *ortho* C-H hydroxymethylation of 6-arylpurines has been developed. A wide range of functional groups were tolerated, providing the hydroxymethylated products in good or excellent yields using the readily available paraformaldehyde as a C1 synthon. Moreover, this protocol could be carried out in the presence of water and air, without stoichiometric undesirable waste under mild reaction conditions.

INTRODUCTION

Purine motif is a unique *N*-heterocycle structure in biochemistry and medicinal chemistry, due to the wide existence in pharmaceuticals, bioactive compounds and natural products. Particularly, 6-arylpurines and analogues displayed potential antitumor,[1-7] antibacterial,[8] antivirus (anti-HCV,[9-15] anti-HIV[16,17]) and anti-

inflammatory[18-20] activities (Figure 1). Therefore, the development of efficient method to access various 6-arylpurines is highly desirable.

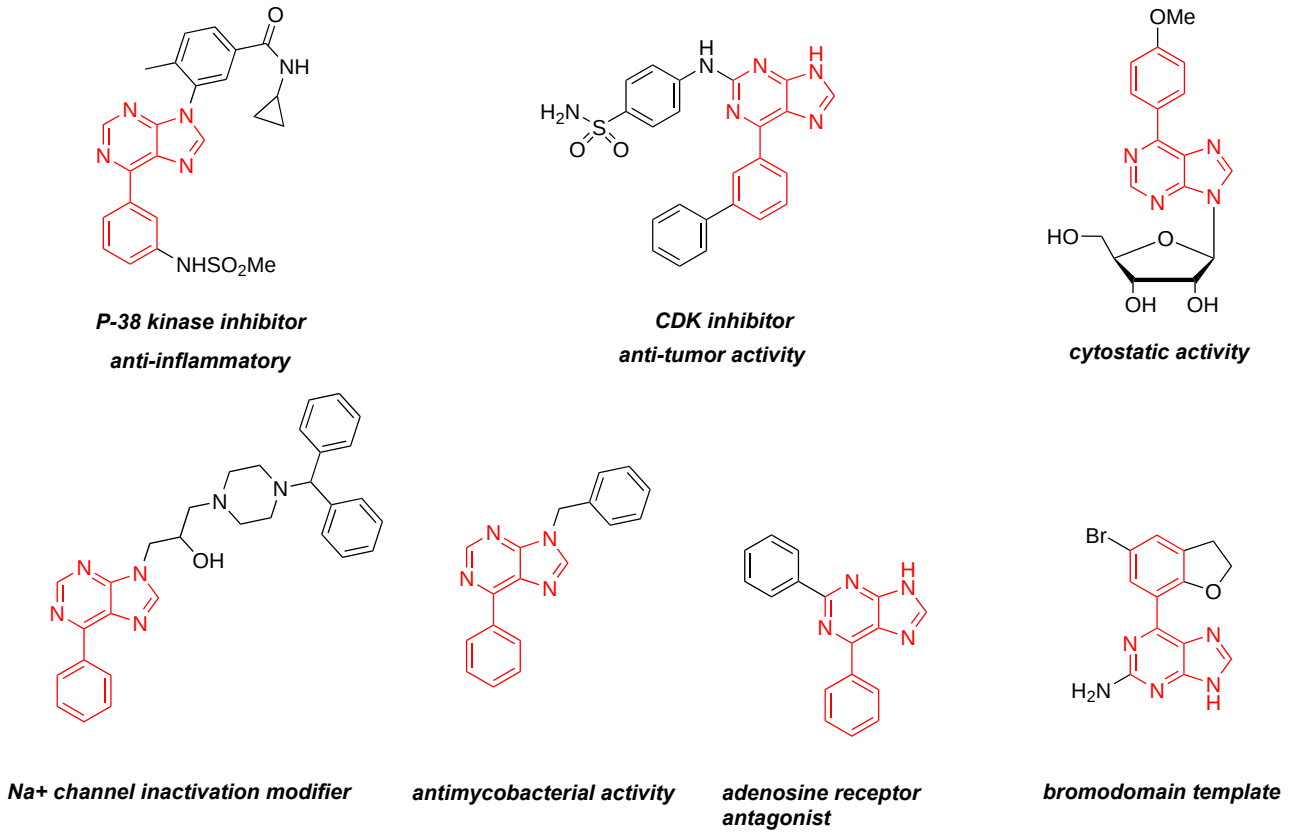
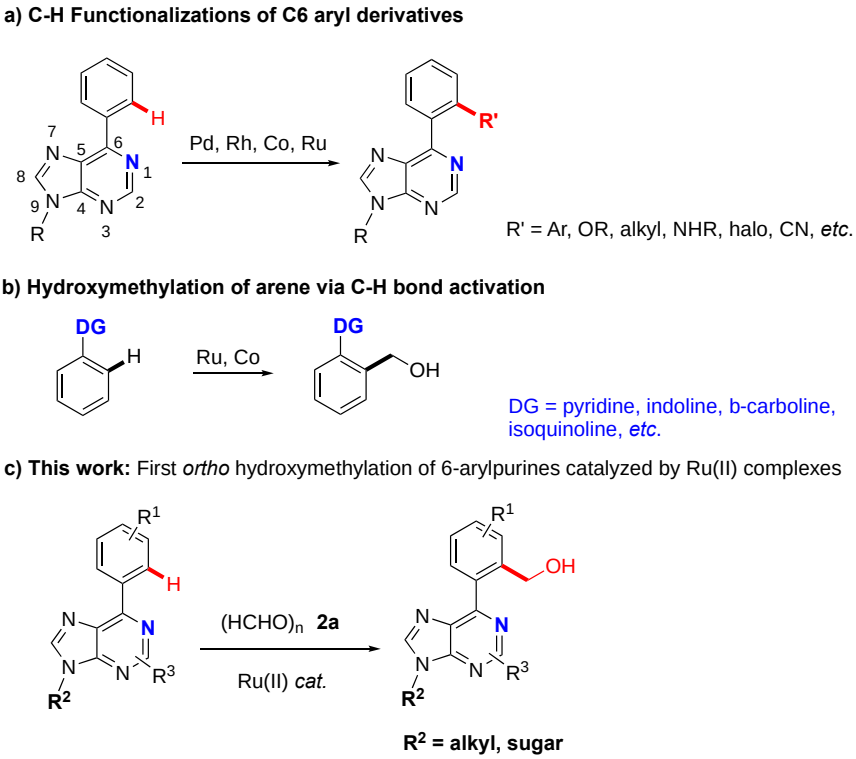


Figure 1. Related biologically active 6-arylpurine derivatives

Although purine derivatives and purine nucleoside analogues could be obtained via multiple steps,[3-6,8,21] the development of methods for direct late-stage modifications of 6-arylpurines provide an alternative protocol to access a series of 6-arylpurines efficiently. In the past decades, transition-metal catalyzed C-H functionalization of 6-arylpurines have been widely developed (Scheme 1a). Initially, Guo[22] and Lakshman[23] groups reported Pd- and Ru-catalyzed direct *ortho* arylation of 6-arylpurines and 6-arylpurine nucleosides, respectively. Subsequently, Pd-catalyzed *ortho* C-H monoacetoxylation or bisacetoxylation of 6-arylpurines and 6-arylpurine nucleosides using $PhI(OAc)_2$ as oxidant was developed by Guo[24] and Lakshman[25] groups. Moreover, Chang[26,27] and Jiao[28] reported Rh- or Co-catalyzed *ortho* direct C-H amidation of arenes using sulfonyl azides, acetoxycarbamates or 1,4,2-dioxazol-5-ones as the amino source. The Rh-catalyzed direct *ortho* C-H amination was also developed[29,30] by employing organic azides or anthranil as the amination reagent. Co-Catalyzed *ortho* C-H allylation and alkenylation were reported by Matsunaga[31] and Yu.[32] Chang,[33] Jiao[34] and Matsunaga[35] developed *ortho* C-H cyanation, acylation and trifluoromethylthiolation, respectively. Recently, Guo[36] developed a monoselective *ortho* arylation of 6-arylpurines, and then Qin[37] accessed *ortho* nitration products by a Pd(II)-catalyzed functionalization. In

addition, Osipov[38] developed a method for C-H alkylation of 6-arylpurines installing the CF_3 and carboxylate functional groups, and Lin[39] developed a Rh-catalyzed alkenylation of 6-arylpurines. Very recently, Xu[40] used sulfoxonium ylides as carbene precursors to developed a C-H acylmethylation of 6-arylpurines.

On the other hand, hydroxymethylated compounds are highly attractable products in materials, pharmaceuticals and organic synthesis. Paraformaldehyde is a common source of C1 synthon, which is cheap, maneuverable, and tractable.[41] In 2015, Krische[42] group reported the transition-metal catalyzed hydromethylation of allenes, 1,3-dienes and alkynes. Lately, our group[43] and the group of Ding[44] found that hydroxymethyl group could be readily installed via a C-H functionalization with paraformaldehyde using pyridine as a directing group. Subsequntly, Zhou,[45] Kim[46] and Shankaraiah[47] reported Ru-catalyzed *ortho* C-H hydroxymethylation employing indolines, β-carbolines and isoquinolines as directing groups, respectively. Recently, Loh[48] and Chen[49] successful developed the C-H hydroxymethylation of indoles and isoprenes via Co-catalyzed reactions (Scheme 1b).



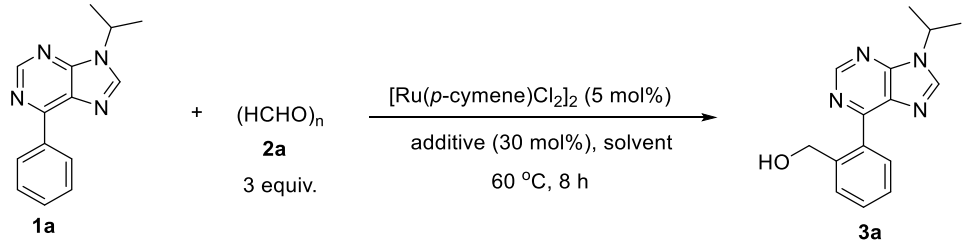
Scheme 1. Transition-metal-catalyzed *ortho* C-H functionalizations of 6-arylpurines

With our continuing interest in the sustainable organic synthesis, especially, C-H hydroxymethylation procedure,[43,45,50] we herein report the first ruthenium(II)-catalyzed *ortho* hydroxymethylation of 6-arylpurines with paraformaldehyde as the coupling partner (Scheme 1c). Notably, this catalytic reaction could be carried out under mild reaction conditions, providing excellent chemical yields with good functional group tolerance.

RESULTS AND DISCUSSION

Our investigation started with 9-isopropyl-6-phenyl-9*H*-purine (**1a**) and paraformaldehyde (**2a**) as model substrate. When using $[RuCl_2(p\text{-cymene})]_2$ as catalyst and $Zn(OTf)_2$ as additive, the desired hydroxymethylated product **3a** was obtained in 55% yield (Table 1, entry 1). The structure of **3a** was confirmed by an X-ray crystallographic analysis (CCDC 1995350). The use of $Zn(OAc)_2$ significantly increased the yield of **3a** to 80% (entry 3). Through screening the solvent (entries 3-9), we found that TFE was the optimal choice (entry 6), giving **3a** in 89% yield. Next, we investigated several acetate as addictive (entries 10-11), and the yield of **3a** was further improved up to 95% when using NaOAc as the additive (entry 10). To our delight, the loading of catalyst could be further reduced to 2.5 mol% (entry 12). **3a** was obtained in less than 5% yield in the absence of NaOAc (entry 13), suggesting that NaOAc was crucial in this reaction. Notably, the reaction proceeded smoothly in water, providing **3a** in 80% yield (entry 14).

Table 1. Optimization of reaction conditions[a]

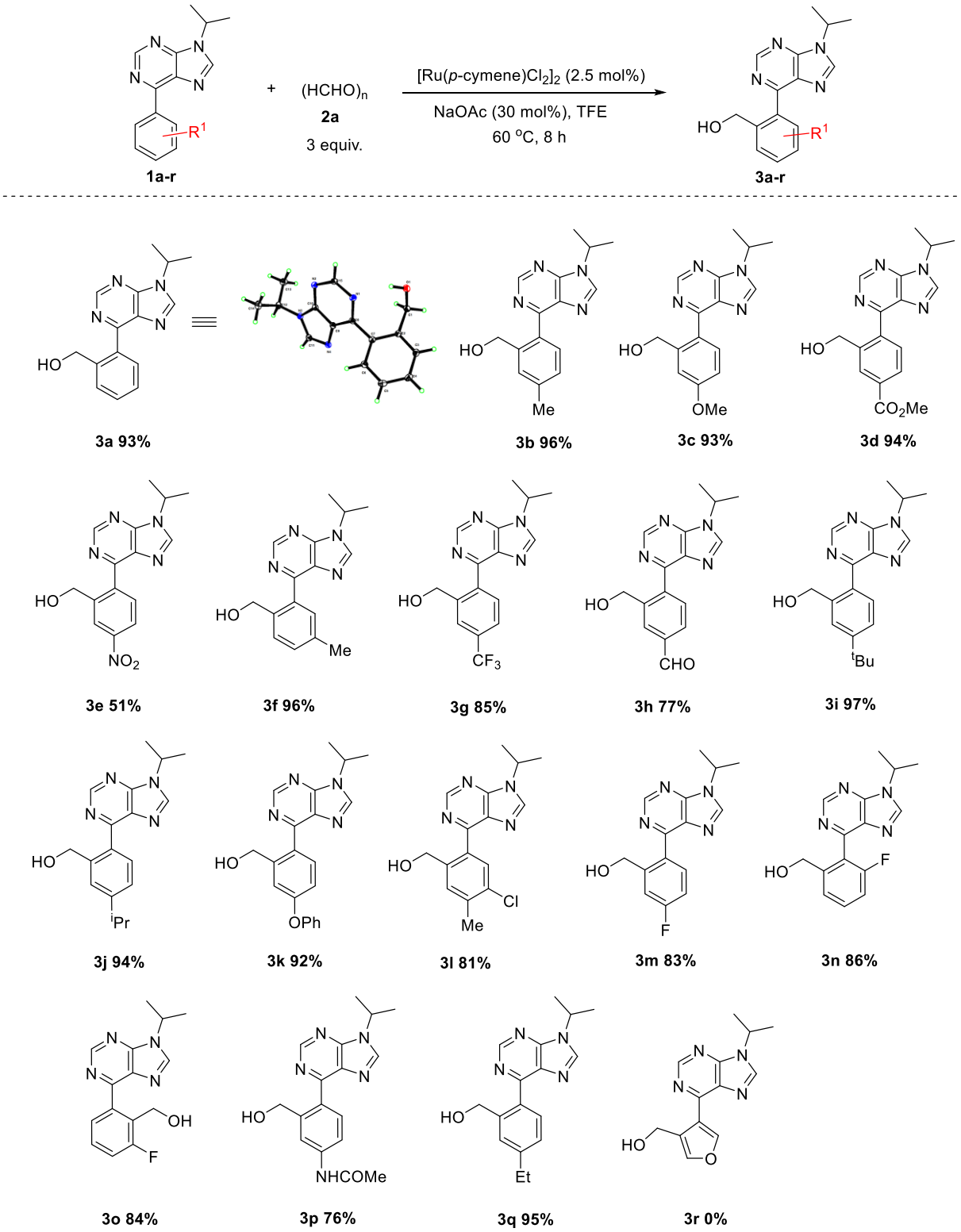


1a **3a**

entry	catalyst	additive	solvent	yield **3a** (%)[b]
1	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OTf)_2$	DCE	55
2	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(TFA)_2$	DCE	77
3	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OAc)_2$	DCE	80
4	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OAc)_2$	MeOH	56
5	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OAc)_2$	toluene	15
6	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OAc)_2$	TFE	89
7	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OAc)_2$	DMF	0
8	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OAc)_2$	MeCN	0
9	$[Ru(p\text{-cymene})Cl_2]_2$	$Zn(OAc)_2$	HFIP	58
10	**$[Ru(p\text{-cymene})Cl_2]_2$**	**NaOAc**	**TFE**	**95**
11	$[Ru(p\text{-cymene})Cl_2]_2$	CsOAc	TFE	8
12[c]	**$[Ru(p\text{-cymene})Cl_2]_2$**	**NaOAc**	**TFE**	**95**
13	$[Ru(p\text{-cymene})Cl_2]_2$		TFE	<5
14	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc	H_2O	80[d]

[a] Conditions: **1a** (0.2 mmol), **2a** (3 equiv.), catalysts (5 mol%), and additive (30 mol%) in the solvent (2 mL) at 60 °C for 8 h in a round bottom flask. [b] Isolated yield. [c] The loading of catalyst $[Ru(p\text{-cymene})Cl_2]_2$ was decreased to 2.5 mol%. [d] The reaction was performed for 24 h.

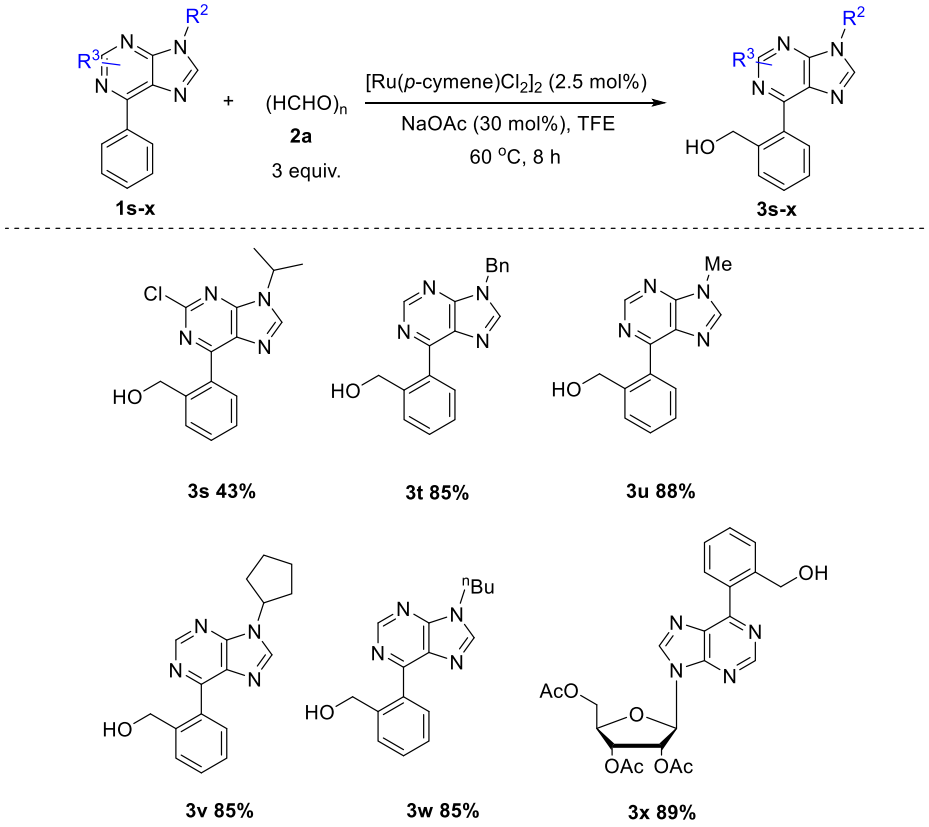
With the optimized conditions in hand, the substrate scope was next investigated (Scheme 2). Electron-rich arylpurines reacted with paraformaldehyde smoothly to give the corresponding *ortho* hydroxymethylated products **3b-c**, **3f**, **3i-k**, and **3p-q** in good to excellent yields.



Scheme 2. Scope of substituted arylpurines. Reaction conditions: **1a-r** (0.2 mmol), **2a** (3 equiv.), catalysts (2.5 mol%), additive (30 mol%) in TFE (2 mL) at 60 °C for 8 h in a round bottom flask.

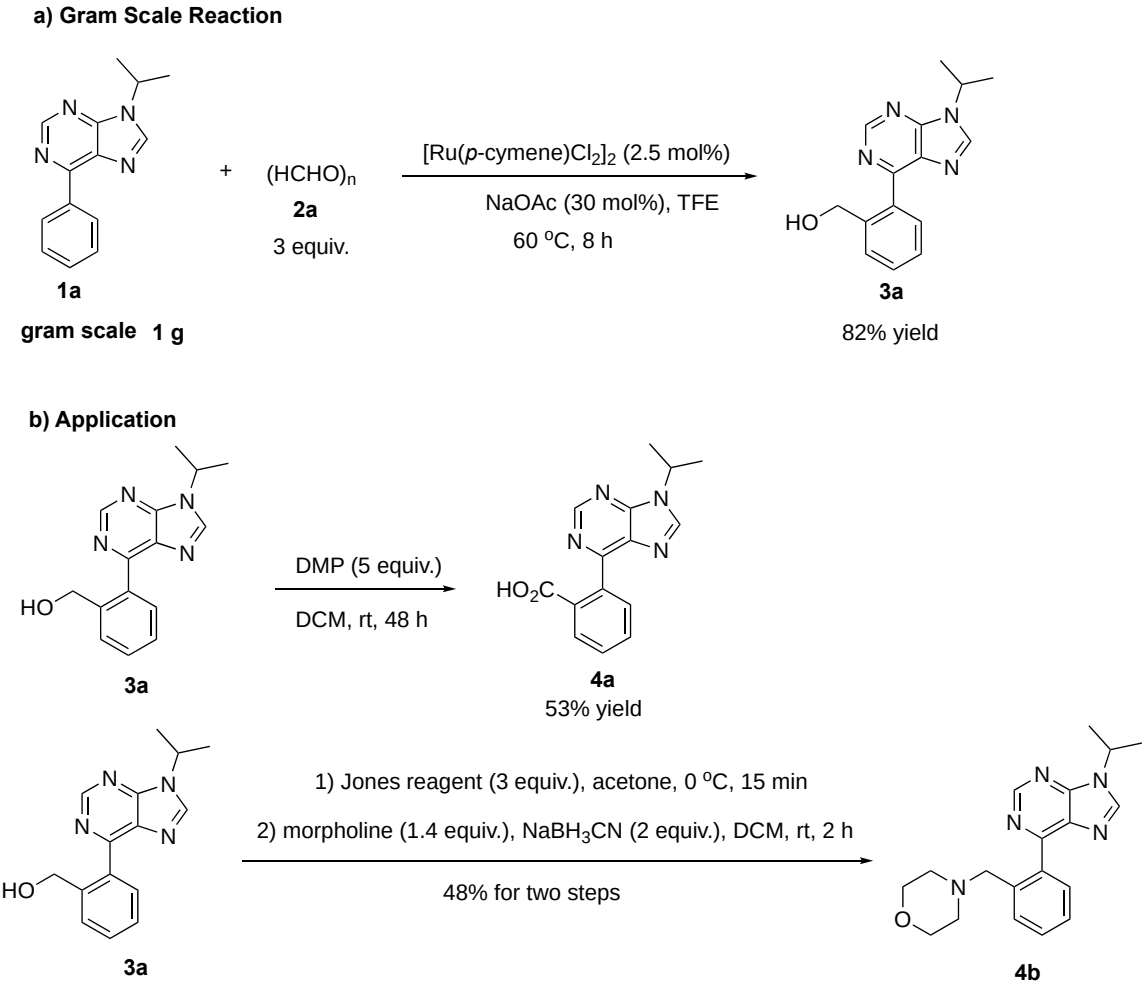
Among them, the alkyl substituted arylpurines afforded the desired products **3b**, **3f**, **3i**, **3j**, **3q** in more than 90% yields. Electron-deficient arylpurines also provided the products **3d**, **3g-h**, and **3m-o** in good yield, except the nitro substituted arylpurine **3e**. For *meta*-substituted substrates, the C-H hydroxymethylation reaction showed excellent regioselectivity in favor of the sterically more accessible C-H bond (**3f** and **3l**) and electron-deficient fluorine substitution resulted in opposite regioselectivity (**3o**). Evidently, Shankaraiah[47] et al, have also reported the similar directing effect. To our delight, the functional groups such as ester (**3d**), nitrile (**3e**), halogen (**3l** and **3m**), amide (**3p**) and even aldehyde (**3h**) were all nicely tolerated, enabling further functionalization. Unfortunately, when furan-substituted purine (**3r**) was used, no desired product was observed.

Subsequently, various *N*-substituted arylpurines were explored under the standard conditions (Scheme 3). *N*-Benzyl, *N*-methyl, *N*-cyclopentyl, and *N*-butyl-6-arylpurines (**3t-w**) were also productive substrates. 2-Chloro-9-isopropyl-6-phenylpurine also provided the corresponding product **3s** in 43% yield, enabling further functionalization. Notably, purine nucleoside analog effectively underwent this C-H hydroxymethylation reaction to give the corresponding product **3x** in good yield (89%), suggesting that this reaction might possess potential values in the field of purine nucleoside drug research.



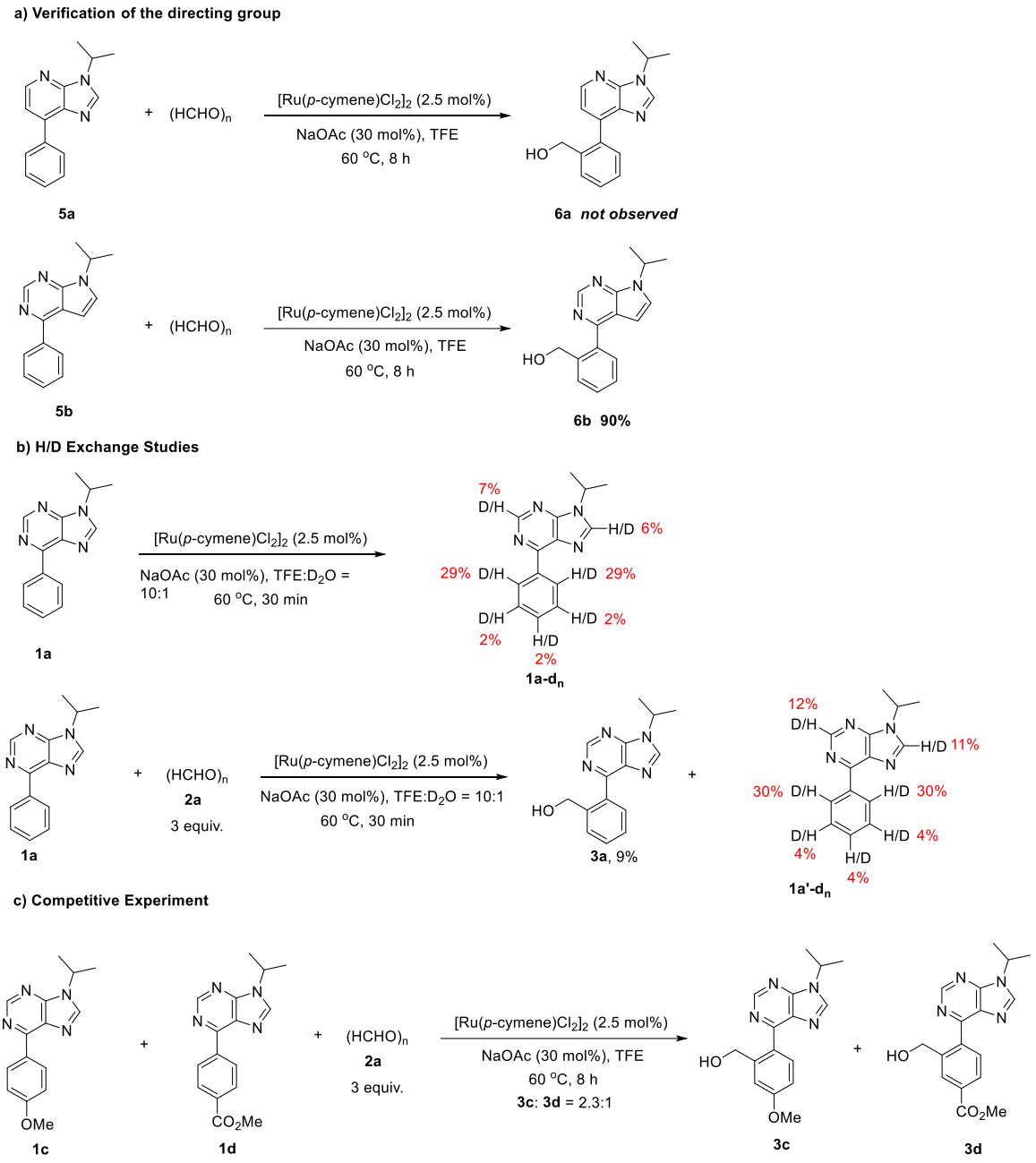
Scheme 3. Scope of *N*-substituted purines[a]. [a] Reaction conditions: **1s-x** (0.2 mmol), **2a** (3 equiv.), catalysts (2.5 mol%), additive (30 mol%) in TFE (2 mL) at 60 °C for 8 h in a round bottom flask.

For further demonstrate the synthetic utility of this methodology, several reactions were performed (Scheme 4). This reaction could be readily scaled up with comparable efficiency on a gram scale (Scheme 4a). Acid **4a** could be obtained in moderate yield and the amine **4b** could be obtained through oxidation/reductive amination reaction in moderate yield (Scheme 4b).



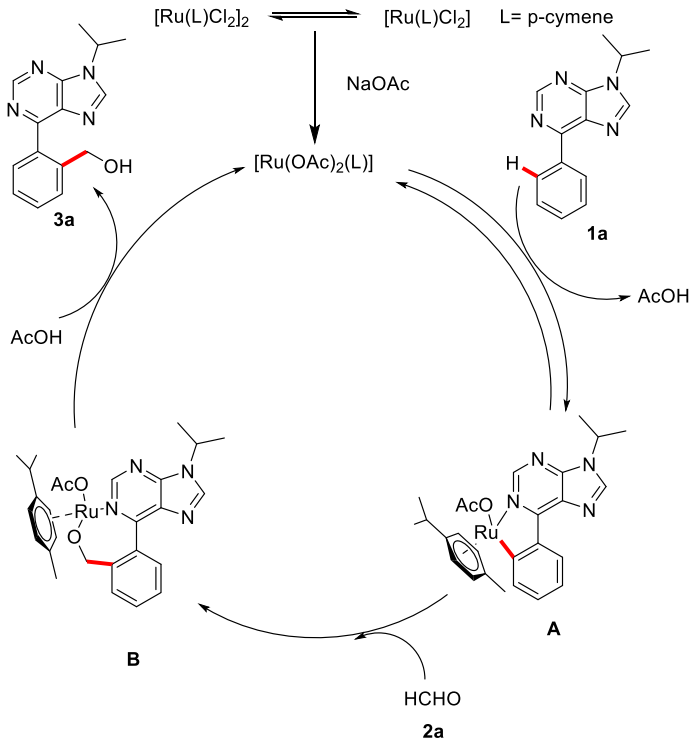
Scheme 4. Gram scale reaction and applications

To gain more insights into the details of reaction mechanism, a series of control experiments were investigated. Substrates **5a** and **5b** were investigated in the standard conditions (Scheme 5a). Only substrates **5b** afforded the corresponding product **6b** in 90% yield, indicating that N1 is important for this reaction. H/D exchange experiments were performed in the presence of co-solvent D_2O (Scheme 5b). The *ortho* H/D exchange was observed in the isolated starting materials, indicating that the *ortho* C-H functionalization is reversible. The competitive experiment was performed between **1c** and **1d**, and the ^{1}H NMR analysis revealed that the ratio of **3c** and **3d** was 2.3:1 (Scheme 5c), suggesting that the electron-donating substrates inherently react preferentially. This observation can be rationalized in terms of an electrophilic C-H ruthenation.



Scheme 5. Primary mechanism studies

On the basis of previous reports and these preliminary studies, a plausible catalytic cycle was shown in Scheme 6. An active Ru(II) species was generated by the presence of NaOAc, which was coordinated with the purine skeleton and the *ortho* C-H of **1a** activated to form the five-membered complex **A**. Complex **A** was transformed into seven-membered ruthenacycle intermediate **B** through nucleophilic addition to formaldehyde. Subsequently, desired product **3a** was released by the protonation of AcOH and the active Ru(II) species was regenerated for next catalytic cycle.



Scheme 6. Plausible mechanism

CONCLUSION

In conclusion, we developed a method for highly site-selective *ortho* hydroxymethylation of 6-arylpurines via Ru(II)-catalyzed. Notably, purine derivatives with broad functional groups as well as purine nucleosides were subjected to the C-H activated reaction in good yields. This protocol could be carried out in the presence of water and air, without stoichiometric undesirable waste, thus offering an environmentally benign method for synthesis of hydroxymethylated arylpurine derivatives. Further investigation of the detailed mechanism and applications are proceeding in our laboratory.

EXPERIMENTAL

General. Unless otherwise noted, reactions involving oxygen or moisture sensitive reagents were performed in pre-dried glassware under argon. Catalysis reaction were carried out in round bottom flask. Chemicals were purchased from commercial suppliers and used without further purification. Column chromatograph purification was used 200-300 mesh silica gel. All reactions were monitored by thin layer chromatography on Huanghai silica gel plates (HSGF254) and visualized under UV light at 254 nm. NMR spectra were performed at 400 or 500 MHz (^{1}H NMR), 125, 126 or 151 MHz (^{13}C NMR) and recorded on Bruker AVANCE III 400 and Bruker AVANCE III 500 instruments, chemical shifts (δ) are given in ppm. Coupling constant (*J*) are provided in Hz. High resolution mass spectrometry were recorded by the Center for Mass Spectrometry, Shanghai Institute of Material Medica.

Starting Materials. All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated. The substances **1a-x, 5** were synthesized according to the reported literatures.[26,51-54]

General Synthetic Procedure for Synthesizing Compounds 3 (taking 3a as an example). To a 10 mL round bottom flask was added **1a** (0.2 mmol, 47.6 mg, 1 equiv.), **2a** (0.6 mmol, 18 mg, 3 equiv.), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3 mg, 2.5 mol%), NaOAc (0.06 mmol, 8.2 mg, 30 mol%) and TFE (2.0 mL, 0.1 M) under air. The mixture was heated at 60 ^oC for 8 h in an oil bath. After completion, the resulting mixture was filtered, and then washed by acetone. The filtrate was concentrated in *vacuo* to give the crude product. The residue was purified by silica gel column chromatograph (PE/EA = 1/1) to afford the product **3a** in 93% yield.

(2-(9-Isopropyl-9*H*-purin-6-yl)phenyl)methanol (3a). Yield: 93%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.22 – 8.14 (m, 2H), 7.57 – 7.52 (m, 1H), 7.51 – 7.45 (m, 2H), 6.28 (s, 1H), 4.97 (hept, *J* = 6.8 Hz, 1H), 4.50 (s, 2H), 1.66 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.97, 151.78, 151.35, 142.79, 140.96, 134.72, 132.58, 132.24, 131.52, 130.83, 128.05, 64.23, 47.71, 22.55; HRMS (ESI) Calcd for $C_{15}H_{17}N_4O$ $[M+H]^+$ 269.1397, found 269.1398.

(2-(9-Isopropyl-9*H*-purin-6-yl)-5-methylphenyl)methanol (3b). Yield: 96%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.18 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 6.39 (s, 1H), 4.98 (hept, *J* = 6.8 Hz, 1H), 4.48 (d, *J* = 3.6 Hz, 2H), 2.41 (s, 3H), 1.66 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.11, 151.72, 151.33, 142.52, 141.26, 140.94, 132.76, 132.36, 132.19, 131.91, 128.81, 64.35, 47.66, 22.60, 21.43; HRMS (ESI) Calcd for $C_{16}H_{18}N_4NaO$ $[M+Na]^+$ 305.1373, found 305.1380.

(2-(9-Isopropyl-9*H*-purin-6-yl)-5-methoxyphenyl)methanol (3c). Yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 8.19 (s, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 7.03 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.99 (hept, *J* = 6.8 Hz, 1H), 4.52 (s, 2H), 3.89 (s, 3H), 1.69 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.60, 156.81, 151.72, 151.36, 143.22, 142.37, 134.77, 131.98, 127.23, 116.98, 113.61, 64.68, 55.56, 47.69, 22.69; HRMS (ESI) Calcd for $C_{16}H_{19}N_4O_2$ $[M+H]^+$ 299.1503, found 299.1509.

Methyl 3-(hydroxymethyl)-4-(9-isopropyl-9*H*-purin-6-yl)benzoate (3d). Yield 94%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.23 (s, 1H), 8.27 – 8.21 (m, 2H), 8.12 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.14 (br, 1H), 4.99 (hept, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 2.6 Hz, 2H), 3.92 (s, 3H), 1.67 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.49, 155.82, 152.01, 151.47, 143.24, 141.27, 138.91, 132.71, 132.59, 132.42, 131.89, 128.99, 63.93, 52.38, 47.88, 22.58; HRMS (ESI) Calcd for $C_{17}H_{19}N_4O_3$ $[M+H]^+$ 327.1452, found 327.1458.

(2-(9-Isopropyl-9*H*-purin-6-yl)-5-nitrophenyl)methanol (3e). Yield 51%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.45 (d, *J* = 2.3 Hz, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.33 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.28 (s, 1H), 5.04 (hept, *J* = 6.8 Hz, 1H), 4.61 (s, 2H), 1.72 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ

154.48, 152.28, 151.65, 148.78, 143.72, 142.89, 140.69, 133.83, 132.52, 126.36, 122.82, 63.68, 48.13, 22.67; HRMS (ESI) Calcd for $C_{15}H_{16}N_5O_3$ $[M+H]^+$ 314.1248, found 314.1253.

(2-(9-Isopropyl-9*H*-purin-6-yl)-4-methylphenyl)methanol (3f). Yield 96%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.18 (s, 1H), 7.93 (d, *J* = 1.3 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.28 (dd, *J* = 7.7, 1.3 Hz, 1H), 5.51 (br, 1H), 4.95 (hept, *J* = 6.8 Hz, 1H), 4.44 (s, 2H), 2.40 (s, 3H), 1.64 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.18, 151.62, 151.35, 142.63, 138.08, 137.71, 134.59, 132.88, 132.18, 131.50, 131.48, 63.76, 47.63, 22.50, 21.25; HRMS (ESI) Calcd for $C_{16}H_{18}N_4NaO$ $[M+Na]^+$ 305.1373, found 305.138.

(2-(9-Isopropyl-9*H*-purin-6-yl)-5-(trifluoromethyl)phenyl)methanol (3g). Yield 85%,^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.32 (d, *J* = 8.2 Hz, 1H), 8.24 (s, 1H), 7.84 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 6.15 (br, 1H), 5.02 (hept, *J* = 6.8 Hz, 1H), 4.56 (s, 2H), 1.70 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.49, 152.13, 151.58, 143.35, 141.85, 138.12, 133.11, 132.49, 132.44 (q, *J* = 32.7 Hz), 128.37 (q, *J* = 3.3 Hz), 124.87 (q, *J* = 3.2 Hz), 123.90 (q, *J* = 272.5 Hz), 63.89, 48.00, 22.64; HRMS (ESI) Calcd for $C_{16}H_{16}F_3N_4O$ $[M+H]^+$ 337.1271, found 337.1275.

3-(Hydroxymethyl)-4-(9-isopropyl-9*H*-purin-6-yl)benzaldehyde (3h). Yield 77%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.07 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.27 (s, 1H), 8.08 (d, *J* = 1.5 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.23 (br, 1H), 5.03 (hept, *J* = 6.8 Hz, 1H), 4.60 (s, 2H), 1.71 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.82, 155.57, 152.16, 151.66, 143.52, 141.95, 140.33, 137.63, 133.42, 132.95, 132.48, 128.74, 63.90, 48.08, 22.67; HRMS (ESI) Calcd for $C_{16}H_{17}N_4O_2$ $[M+H]^+$ 297.1346, found 297.1346.

(5-(*tert*-Butyl)-2-(9-isopropyl-9*H*-purin-6-yl)phenyl)methanol (3i). Yield 97%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.18 (s, 1H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.52 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.41 (t, *J* = 7.2 Hz, 1H), 4.96 (hept, *J* = 6.8 Hz, 1H), 4.52 (d, *J* = 7.2 Hz, 2H), 1.65 (d, *J* = 6.8 Hz, 6H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.15, 154.30, 151.79, 151.32, 142.58, 140.78, 132.63, 132.26, 131.93, 128.67, 125.33, 64.88, 47.70, 35.00, 31.28, 22.67; HRMS (ESI) Calcd for $C_{19}H_{25}N_4O$ $[M+H]^+$ 325.2023, found 325.2031.

(5-Isopropyl-2-(9-isopropyl-9*H*-purin-6-yl)phenyl)methanol (3j). Yield 94%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.18 (d, *J* =8.0 Hz, 2H), 7.39 (d, *J* = 1.7 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.38 (t, *J* = 7.2 Hz, 1H), 4.96 (hept, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 7.2 Hz, 2H), 2.96 (hept, *J* = 6.8 Hz, 1H), 1.65 (d, *J* = 6.8 Hz, 6H), 1.27 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.19, 152.07, 151.78, 151.33, 142.56, 141.09, 132.91, 132.29, 132.24, 129.91, 126.28, 64.63, 47.69, 34.20, 23.87, 22.66; HRMS (ESI) Calcd for $C_{18}H_{23}N_4O$ $[M+H]^+$ 311.1866, found 311.1876.

(2-(9-Isopropyl-9*H*-purin-6-yl)-5-phenoxyphenyl)methanol (3k). Yield 92%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 8.20 (s, 1H), 7.42 – 7.36 (m, 2H), 7.20 – 7.15 (m, 2H), 7.13

– 7.08 (m, 3H), 6.49 (t, *J* = 7.0 Hz, 1H), 5.01 (hept, *J* = 6.8 Hz, 1H), 4.49 (d, *J* = 7.0 Hz, 2H), 1.70 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.85, 156.51, 156.06, 151.83, 151.38, 143.47, 142.60, 134.81, 132.10, 130.06, 129.23, 124.33, 120.78, 120.15, 117.34, 64.38, 47.77, 22.68; HRMS (ESI) Calcd for $C_{21}H_{21}N_4O_2$ $[M+H]^+$ 361.1659, found 361.1666.

(4-Chloro-2-(9-isopropyl-9*H*-purin-6-yl)-5-methylphenyl)methanol (3l). Yield 81%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.24 (d, *J* = 4.3 Hz, 2H), 7.43 (s, 1H), 5.55 (br, 1H), 5.00 (hept, *J* = 6.8 Hz, 1H), 4.47 (s, 2H), 2.44 (s, 3H), 1.69 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.58, 151.89, 151.50, 142.95, 139.41, 139.08, 134.19, 134.05, 133.67, 132.95, 132.10, 63.61, 47.85, 22.65, 20.08; HRMS (ESI) Calcd for $C_{16}H_{18}ClN_4O$ $[M+H]^+$ 317.1164, found 317.117.

(5-Fluoro-2-(9-isopropyl-9*H*-purin-6-yl)phenyl)methanol (3m). Yield 83%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.26 (dd, *J* = 8.6, 5.8 Hz, 1H), 8.21 (s, 1H), 7.26 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.17 (td, *J* = 8.6, 2.7 Hz, 1H), 6.33 (br, 1H), 4.99 (hept, *J* = 6.8 Hz, 1H), 4.49 (s, 2H), 1.68 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.99 (d, $^1J_{C\text{-}F}$ = 252.5 Hz), 156.01, 151.88, 151.51, 143.92 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 142.98, 134.99 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 132.11, 130.85 (d, $^4J_{C\text{-}F}$ = 2.9 Hz), 118.44 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 115.15 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 63.97, 47.90, 22.66; HRMS (ESI) Calcd for $C_{15}H_{16}FN_4O$ $[M+H]^+$ 287.1303, found 287.1302.

(3-Fluoro-2-(9-isopropyl-9*H*-purin-6-yl)phenyl)methanol (3n). Yield 86%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.21 (s, 1H), 7.50 (q, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.7Hz, 1H), 7.21 (t, *J* = 9.0 Hz, 1H), 5.00 (hept, *J* = 6.8 Hz, 1H), 4.35 (s, 2H), 4.16 (br, 1H), 1.69 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.56 (d, $^1J_{C\text{-}F}$ = 251.3 Hz), 152.52, 151.59, 151.50, 143.25, 142.83, 133.41, 132.13 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 126.47 (d, $^4J_{C\text{-}F}$ = 2.7 Hz), 122.81 (d, $^2J_{C\text{-}F}$ = 14.3 Hz), 115.88 (d, $^2J_{C\text{-}F}$ = 22.4 Hz), 63.68, 47.92, 22.63; HRMS (ESI) Calcd for $C_{15}H_{16}FN_4O$ $[M+H]^+$ 287.1303, found 287.1308.

(2-Fluoro-6-(9-isopropyl-9*H*-purin-6-yl)phenyl)methanol (3o). Yield 84%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.21 (s, 1H), 7.51 (td, *J* = 7.9, 5.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 9.1 Hz, 1H), 5.00 (hept, *J* = 6.8 Hz, 1H), 4.35 (s, 2H), 1.70 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.59 (d, $^1J_{C\text{-}F}$ = 251.4 Hz), 152.58, 151.64, 151.52, 143.19, 142.84, 133.49, 132.12 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 126.53 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 122.94 (d, $^2J_{C\text{-}F}$ = 14.4 Hz), 115.92 (d, $^2J_{C\text{-}F}$ = 22.4 Hz), 63.75, 47.90, 22.65; HRMS (ESI) Calcd for $C_{15}H_{16}FN_4O$ $[M+H]^+$ 287.1303, found 287.1297.

N-(3-(Hydroxymethyl)-4-(9-isopropyl-9*H*-purin-6-yl)phenyl)acetamide (3p). Yield 76%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.95 (s, 1H), 8.73 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.43 (t, *J* = 6.0 Hz, 1H), 4.91 (hept, *J* = 6.8 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 2H), 2.10 (s, 3H), 1.60 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.63, 155.83, 151.22, 150.93, 144.40, 142.84, 140.79, 132.41, 131.50, 127.99, 118.25, 116.66, 61.69, 47.10, 24.13, 21.94; HRMS (ESI) Calcd for $C_{17}H_{20}N_5O_2$ $[M+H]^+$ 326.1612, found 326.1614.

(5-Ethyl-2-(9-isopropyl-9*H*-purin-6-yl)phenyl)methanol (3q). Yield 95%,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.18 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.38 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 6.38 (t, *J* = 7.0 Hz, 1H), 4.97 (hept, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 6.7 Hz, 2H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.66 (d, *J* = 6.8 Hz, 6H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.17, 151.75, 151.34, 147.52, 142.56, 141.04, 132.88, 132.22, 132.14, 131.26, 127.69, 64.49, 47.68, 28.85, 22.65, 15.38; HRMS (ESI) Calcd for $C_{17}H_{21}N_4O$ $[M+H]^+$ 297.171, found 297.1713.

(2-(2-Chloro-9-isopropyl-9*H*-purin-6-yl)phenyl)methanol (3s). Yield 43%,^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.16 (d, *J* = 7.3 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.51 (dt, *J* = 14.8, 7.3 Hz, 2H), 5.50 (t, *J* = 7.3 Hz, 1H), 4.97 (hept, *J* = 6.8 Hz, 1H), 4.53 (d, *J* = 7.4 Hz, 2H), 1.66 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.82, 153.33, 153.30, 143.30, 141.01, 133.71, 132.53, 131.87, 131.48, 131.26, 128.24, 64.04, 47.92, 22.64; HRMS (ESI) Calcd for $C_{15}H_{15}ClN_4NaO$ $[M+Na]^+$ 325.0827, found 325.0825.

(2-(9-Benzyl-9*H*-purin-6-yl)phenyl)methanol (3t). Yield 85%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.27 – 8.22 (m, 1H), 8.13 (s, 1H), 7.60 – 7.54 (m, 1H), 7.54 – 7.48 (m, 2H), 7.42 – 7.32 (m, 5H), 6.22 (br, 1H), 5.49 (s, 2H), 4.53 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.17, 152.26, 151.93, 144.86, 141.10, 134.94, 134.61, 132.73, 131.81, 131.65, 131.02, 129.33, 128.86, 128.13, 128.08, 64.33, 47.61; HRMS (ESI) Calcd for $C_{19}H_{17}N_4O$ $[M+H]^+$ 317.1397, found 317.1399.

(2-(9-Methyl-9*H*-purin-6-yl)phenyl)methanol (3u). Yield 88%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.27 – 8.23 (m, 1H), 8.15 (s, 1H), 7.61 – 7.56 (m, 1H), 7.56 – 7.50 (m, 2H), 6.24 (br, 1H), 4.53 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.06, 152.58, 151.80, 145.61, 141.10, 134.65, 132.71, 131.81, 131.67, 131.03, 128.16, 64.36, 30.10; HRMS (ESI) Calcd for $C_{13}H_{12}N_4NaO$ $[M+Na]^+$ 263.0903, found 263.0898.

(2-(9-Cyclopentyl-9*H*-purin-6-yl)phenyl)methanol (3v). Yield 85%,^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.23 – 8.18 (m, 1H), 8.17 (s, 1H), 7.59 – 7.52 (m, 1H), 7.52 – 7.45 (m, 2H), 5.04 (p, *J* = 7.4 Hz, 1H), 4.50 (s, 2H), 2.41 – 2.27 (m, 2H), 2.12 – 1.90 (m, 4H), 1.90 – 1.76 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.95, 152.19, 151.36, 143.36, 140.99, 134.74, 132.59, 132.28, 131.55, 130.85, 128.07, 64.26, 56.47, 32.68, 23.96; HRMS (ESI) Calcd for $C_{17}H_{18}N_4NaO$ $[M+Na]^+$ 317.1373, found 317.1376.

(2-(9-Butyl-9*H*-purin-6-yl)phenyl)methanol (3w). Yield 85%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.26 – 8.21 (m, 1H), 8.14 (s, 1H), 7.60 – 7.53 (m, 1H), 7.53 – 7.47 (m, 2H), 4.52 (s, 2H), 4.33 (t, *J* = 7.4 Hz, 2H), 1.94 (p, *J* = 7.4 Hz, 2H), 1.40 (h, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.03, 152.27, 151.65, 145.04, 141.08, 134.71, 132.70, 131.93, 131.64, 130.98, 128.13, 64.35, 44.02, 32.02, 20.04, 13.60; HRMS (ESI) Calcd for $C_{16}H_{18}N_4NaO$ $[M+Na]^+$ 305.1373, found 305.138.

2-(Acetoxymethyl)-5-(6-(2-(hydroxymethyl)phenyl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3x). Yield 89%,^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.30 (s, 1H), 8.20 – 8.13 (m, 1H), 7.56 – 7.51 (m, 1H), 7.50 – 7.43 (m, 2H), 6.28 (d, *J* = 5.0 Hz, 1H), 5.98 (t, *J* = 5.3 Hz, 1H), 5.93 (t, *J* = 7.2

Hz, 1H), 5.66 (t, *J* = 5.0 Hz, 1H), 4.48 (d, *J* = 7.1 Hz, 2H), 4.47 – 4.33 (m, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.23, 169.54, 169.37, 157.55, 151.82, 151.66, 143.40, 140.99, 134.19, 132.65, 132.43, 131.49, 131.03, 127.98, 86.62, 80.41, 73.07, 70.53, 64.10, 62.97, 20.72, 20.49, 20.37; HRMS (ESI) Calcd for $C_{23}H_{25}N_4O_8$ $[M+H]^+$ 485.1667, found 485.1675.

Gram Scale Reaction (Synthesis of Compound 3a). To a 250 mL round bottom flask were added **1a** (1 g, 4.2 mmol, 1 equiv.), **2a** (378 mg, 12.6 mmol, 3 equiv.), [Ru(*p*-cymene)Cl_2]$_2$ (64 mg, 0.105 mmol, 2.5 mol%), NaOAc (177 mg, 1.3 mmol, 30 mol%) and TFE (42.0 mL, 0.1 M) under air. The mixture was heated at 60 °C for 8 h in an oil bath. After completion, the reaction mixture was cooled to room temperature, filtered and then washed by acetone. The filtrate was concentrated and purified by silica gel column chromatography using petroleum ether and EtOAc as eluent to afford product **3a** (926 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.22 – 8.14 (m, 2H), 7.57 – 7.52 (m, 1H), 7.51 – 7.45 (m, 2H), 6.28 (s, 1H), 4.97 (hept, *J* = 6.8 Hz, 1H), 4.50 (s, 2H), 1.66 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.97, 151.78, 151.35, 142.79, 140.96, 134.72, 132.58, 132.24, 131.52, 130.83, 128.05, 64.23, 47.71, 22.55; HRMS (ESI) Calcd for $C_{15}H_{17}N_4O$ $[M+H]^+$ 269.1397, found 269.1398.

Synthesis of Compound 4a. To a solution of **3a** (167 mg, 0.62 mmol) in DCM (5 mL) at 0 °C was added Dess-Martin periodnane (1.315 g, 3.1 mmol, 5 equiv.). The mixture was stirred at ambient temperature over 48 h. The reaction mixture was filtered through Celite, extracted with DCM (×3) and concentrated in vacuo. The crude product was purified by column chromatograph on silica gel (DCM/acetone) to give product **4a** (93 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.66 (br, 1H), 9.09 (s, 1H), 8.45 (s, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 4.1 Hz, 2H), 7.65 – 7.58 (m, 1H), 4.99 (hept, *J* = 6.8 Hz, 1H), 1.65 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.89, 151.75, 149.64, 145.28, 132.41, 132.12, 131.70, 131.61, 131.29, 131.14, 130.69, 48.95, 22.34; HRMS (ESI) Calcd for $C_{15}H_{15}N_4O_2$ $[M+H]^+$ 283.119, found 283.1197.

Synthesis of Compound 4b. To a stirred solution of **3a** (200 mg, 0.75 mmol) in acetone (8 mL) at 0 °C was added 1M Jones reagent (2.3 mL, 2.3 mmol, 3 equiv.). The mixture was stirred at 0 °C for 15 min. After that, the reaction was quenched with isopropanol, extracted with DCM (5 mL × 3), washed with brine and dried over anhydrous Na_2SO_4 to give the solution of crude product without further purification. Subsequently, to a solution of the crude product in DCM at 0 °C was added morpholine (91 mg, 1.05 mmol, 1.4 equiv.) and $NaBH_3CN$ (94 mg, 1.5 mmol, 2 equiv.). The reaction was stirred at room temperature over 2 h. The mixture was concentrated in vacuo and purified by column chromatograph on silica gel (DCM/acetone) to afford product **4b** (124 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.10 (s, 1H), 7.66 – 7.61 (m, 1H), 7.54 – 7.49 (m, 1H), 7.44 – 7.37 (m, 2H), 4.97 (hept, *J* = 6.8 Hz, 1H), 3.74 (s, 2H), 3.20 (s, 4H), 2.10 (s, 4H), 1.67 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.75, 151.74, 151.06, 141.97, 137.63, 135.61, 132.60, 130.70, 130.13, 129.48, 127.32, 66.90, 60.80, 52.92, 47.51, 22.67; HRMS (ESI) Calcd for $C_{19}H_{24}N_5O$ $[M+H]^+$ 338.1975, found 338.1984.

ACKNOWLEDGEMENTS

This work is financially supported by National Natural Science Foundation of China (No. 81973166) and Shanghai Natural Science Foundation Program (22ZR1474100).

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