JOC The Journal of Organic Chemistry

C-H Amination of Purine Derivatives via Radical Oxidative Coupling

Zheng Luo, Ziyang Jiang, Wei Jiang, and Dongen Lin

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 06 Mar 2018

ACS Publications

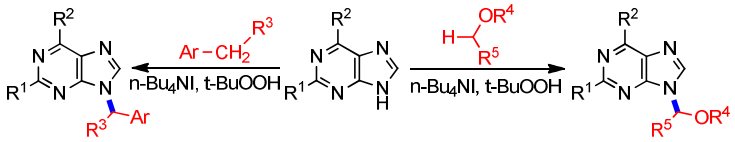
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

C-H Amination of Purine Derivatives *via* Radical Oxidative Coupling

Zheng Luo, Ziyang Jiang, Wei Jiang, Dongen Lin*

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China

e-mail: denlin@scut.edu.cn



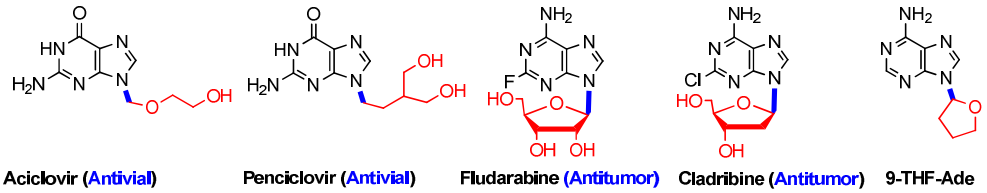
ABSTRACT: An oxidative coupling reaction between purines and alkyl ethers/benzyl compounds was developed to synthesize a series of N-9 alkylated purine derivatives using n-Bu_4NI as a catalyst and t-BuOOH as an oxidant. This protocol uses commercially available, inexpensive catalysts and oxidants, and has a wide range of substrates with simple operation.

Introduction

The purine ring skeleton, a basic framework for many biologically important compounds, is actively investigated in biological and pharmaceutical chemistry. The purine pharmacophore is found in many antiviral and antitumor drug molecules.[1] Therefore, the synthesis of nucleoside drug molecules and the further modification of a diverse range of purines and nucleosides with potential pharmaceutical activity has attracted the interest of synthetic chemists. For example, substitution at the N9 of purine by pentose rings and alkyl derivatives via a C-N glycosidic linkage, affords non-natural nucleosides, which can interfere with the expression of viral genes and obstruct tumor cell replication.[2] Many

modified or functionalized purine nucleosides exhibit important effect in the aspect of biological medicine including the antivirals, Aciclovir and Penciclovir, and anticancer agents, Fludarabine and Cladribine.[3] 9- (Tetrahydrofuryl)adenine (9-THF-Ade) is an inhibitor of adenylyl cyclase (**Figure** 1).[4]

Figure 1. Nucleoside-based bioactive compounds



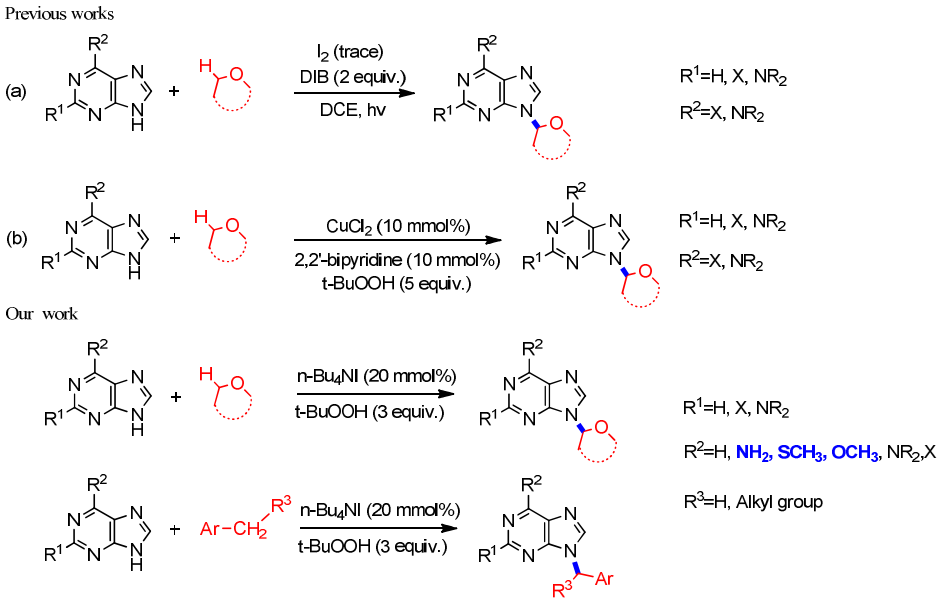
The synthesis of purine nucleoside derivatives has always been an important research topic in organic chemistry due to its marvelous bio-and pharmacological activities. Traditionally, N-alkylation of purines are realized by nucleophilic substitution of alkylating agents, such as halogenated compounds, mesylate or tosylate.[5] Although these alkylating partners have proven to be efficient, they often need multistep pre-synthesis, which leads to a lower atom economy and limited application. For example, 9-THF-Ade was obtained through 4 steps using adenine and 1,4-dichloro-2-butyne as starting material.[6] The reaction steps are rather tedious.

Developing a simple and convenient route to synthesize purine derivates, will help people synthesize drugs containing the purine skeleton, and provide a protocol to obtain purine structures with potential medicinal application. In the past decades, C-N bond formations via cross-dehydrogenative coupling of C-H and N-H bonds have been developed under transition metal catalyzed conditions.[7] However, heavy metal residues in pharmaceutical products and its impact on health have caused public concern. Therefore, metal-free catalysts have received significant attention.

In recent years, with the rapid developments of free radical chemistry, radical oxidative coupling reactions have emerged as a powerful tool in organic synthesis.[8] Remarkably, iodide ions can catalyze the radical oxidative coupling reactions.[9] Many groups have reported the C-N formation of the azole compounds via radical oxidative coupling reaction.[10] Moreover, substituents such as amino could be tolerated under certain radical oxidative coupling conditions.[11]

Hence, the application of the radical oxidative coupling strategy in the study of purine derivatives has attracted much attention by organic chemists. For example, in 2011, Guo's group reported an efficient and elegant synthesis of N-9 alkylated purine derivatives using a DIB/I_2 catalyzed reaction via an intermolecular hydrogen abstraction reaction between the purine ring and an alkyl ether.[12] In 2013, Liu's group discovered a novel route to N-alkoxyalkylated nucleobases by the direct coupling of saturated ethers employing a copper catalyst regulated by the ligand 2,2'-bipyridine.[13] Both of them synthesized a series of purine N9 alkylated derivatives with good yield. Despite the undisputable advances in these papers, there is no mention that the natural purines, such as adenine, could be applied into their catalyzed system to provide the corresponding N-9 alkylated products. In these two reports, adenine's $-NH_2$ was protected by BOC. Therefore, development of a novel protocol to alkylate purine derivatives is necessary. Based on the literature[9,10] and our previous work,[14] we proposed that radical oxidative coupling with iodide ions as a catalyst could be an efficient way to synthesize purine derivatives containing non-protected functional groups. Herein, we report a novel method for the metal-free amination of alkyl ethers or benzyl compounds to form 9-alkylpurine derivatives by using n-Bu_4NI as the catalyst and t-BuOOH as the affordable and nontoxic oxidant (**Scheme 1**).

Scheme 1. Previous and present approaches for the alkylation of 9H-purine derivatives

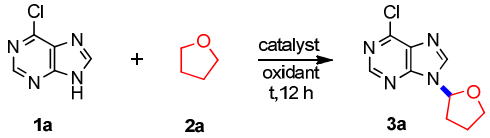


Results and Discussion

We initially investigated the oxidative coupling reaction between commercially available 6-chloropurine and tetrahydrofuran (THF) under various catalytic conditions. Purines when treated with tetrahydrofuran in the presence of n-Bu_4NI (20%) and TBHP in aqueous (3 equiv.) at 80 ^oC produced the desired product in 68% yield (**Table 1**, entry 1). Encouraged by this result, we examined different organic catalysts. Substituting n-Bu_4NI with n-Bu_4NBr or n-Bu_4NCl gave unsatisfactory results (entries 2 and 3). Other iodine catalysts, KI and I_2 when used instead of n-Bu_4NI, afforded, respectively, (61%) and (4%) yields (entries 4 and 5). Further optimization showed that a lower yield was obtained by reducing the catalyst amount to 5 or 10 mol% (entry 6 or 7). The use of other oxidants, $K_2S_2O_8$, di-tert-butyl peroxide (DTBP) and 2, 3-dichloro-5, 6-dicyano-1, 4-benzequinone (DDQ), was completely unproductive (entries 8-11). Moreover, increasing the quantity of oxidant TBHP from 3 to 5 equiv., reduced the yield slightly to 66% (entry 12). A much lower yield was obtained when 8 equiv.

of TBHP was used (entry 13). A cooperative combination of oxidant (TBHP) and catalyst (n-Bu_4NI) is essential for the success of this method, as the reaction failed in the absence of either of them (entries 14 and 15). When the reaction was performed at 70 °C, 90 °C and 100 °C, the desired products were isolated in 60% , 82% and 50% yield (entries 16-18). THF served the dual role of a reactant and solvent. Decreasing the quantity of the solvent, reduced the yield of product (entries 19 and 20). On the basis of the above results, the best oxidative coupling conditions involved 4 mmol THF, 20 mol% n-Bu_4NI, and 3 equiv. TBHP at 90 °C.

Table 1. Optimization of the Reaction Parameters[a]



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

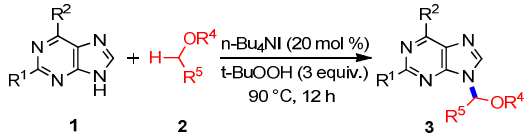
entry	cat.(mol%)	oxidant[b] (equiv..)	t(℃)	yield(%)[c]
1	n-Bu_4NI (20)	TBHP (3)	80	68
2	n-Bu_4NCI (20)	TBHP (3)	80	0
3	n-Bu_4NBr (20)	TBHP (3)	80	0
4	KI (20)	TBHP (3)	80	61
5	I_2 (20)	TBHP (3)	80	<5
6	n-Bu_4NI (5)	TBHP (3)	80	56
7	n-Bu_4NI (10)	TBHP (3)	80	52
8	n-Bu_4NI (20)	$K_2S_2O_8$(3)	80	0
9	n-Bu_4NI (20)	DDQ (3)	80	0
10	n-Bu_4NI (20)	H_2O_2 (3)	80	0
11	n-Bu_4NI (20)	DTBP (3)	80	0
12	n-Bu_4NI (20)	TBHP (5)	80	66
13	n-Bu_4NI (20)	TBHP (8)	80	40
14	----------	TBHP (3)	80	<5
15	n-Bu_4NI (20)	----------	80	0
16	n-Bu_4NI (20)	TBHP (3)	70	60
17	**n-Bu_4NI (20)**	**TBHP (3)**	**90**	**82**
18	n-Bu_4NI (20)	TBHP (3)	100	50
19[d]	n-Bu_4NI (20)	TBHP (3)	90	45
20[e]	n-Bu_4NI (20)	TBHP (3)	90	62

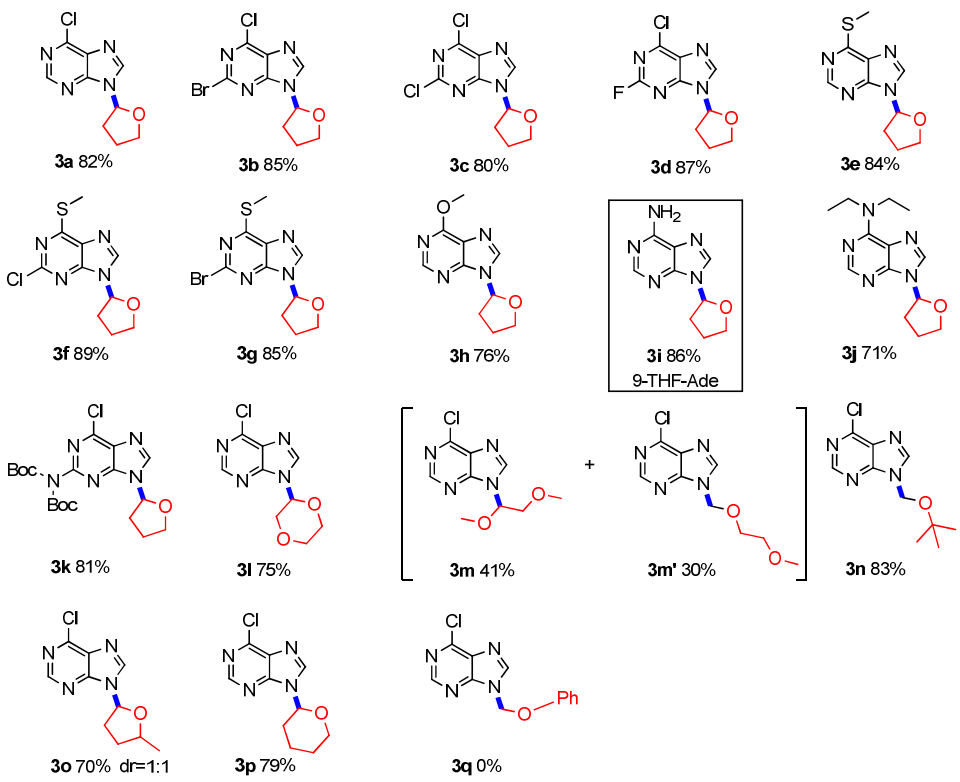
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (4 mmol), 90 °C, 12 h, air. [b]TBHP (70% in water), H_2O_2 (30% in water), DTBP (98%). [c]Isolated yield. [d]**2a** (2 mmol). [e]**2a** (3 mmol).

With the optimized conditions in hand (**Table** 1, entry 17), we investigated the scope of this oxidative coupling by reacting THF with a series of purines. As shown in **Scheme 2**, purine rings bearing halide substituents (2-F, 2-Cl and 2-Br) all formed the corresponding purine products with good yields (**3b-3d**, 80-87%). Purine rings substituted at the 6 position with electron-donating groups (-OMe, -NEt_2, -$NBoc_2$) afforded moderate yields (**3h**, **3j-3k**, 71-81%). Even the easily oxidized methylthio group could be tolerated under the oxidative conditions (**3e-3g**, 84-89%). It is worth mentioning that adenine, one of the natural purines, can also be used in these reaction conditions yielding the desired product (**3i**, 86%). Gratifyingly, this direct oxidative coupling reaction occurred on the N9 position of the purines, rarely on N7 or other functional groups of the purine, suggesting excellent regioselectivity.

Next, scope studies were carried out between 6-chloropurine and various ethers under the optimized conditions. We noticed that both cyclic and chain ethers were suitable reaction substrates for this transformation (**3l-3p**, 30-83%). It worth noting that the oxidative coupling reaction of dimethoxyethane and 6-chloropurine gave the coupled products in a separable regioisomeric mixture with a total yield of 71% (**3m** and **3m'**). From the result, we conclude that the secondary carbon is more reactive than the primary carbon.[10a,e]

Scheme 2. Substrate Scope of the Purines and Ethers [a]





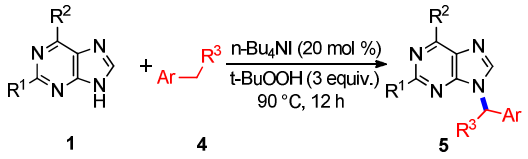
[a]Reaction conditions: **1** (0.2 mmol), **2** (4 mmol), TBAI (20 mol%), TBHP (3 equiv.), under air at 90 °C for 12 h. Isolated yield are shown.

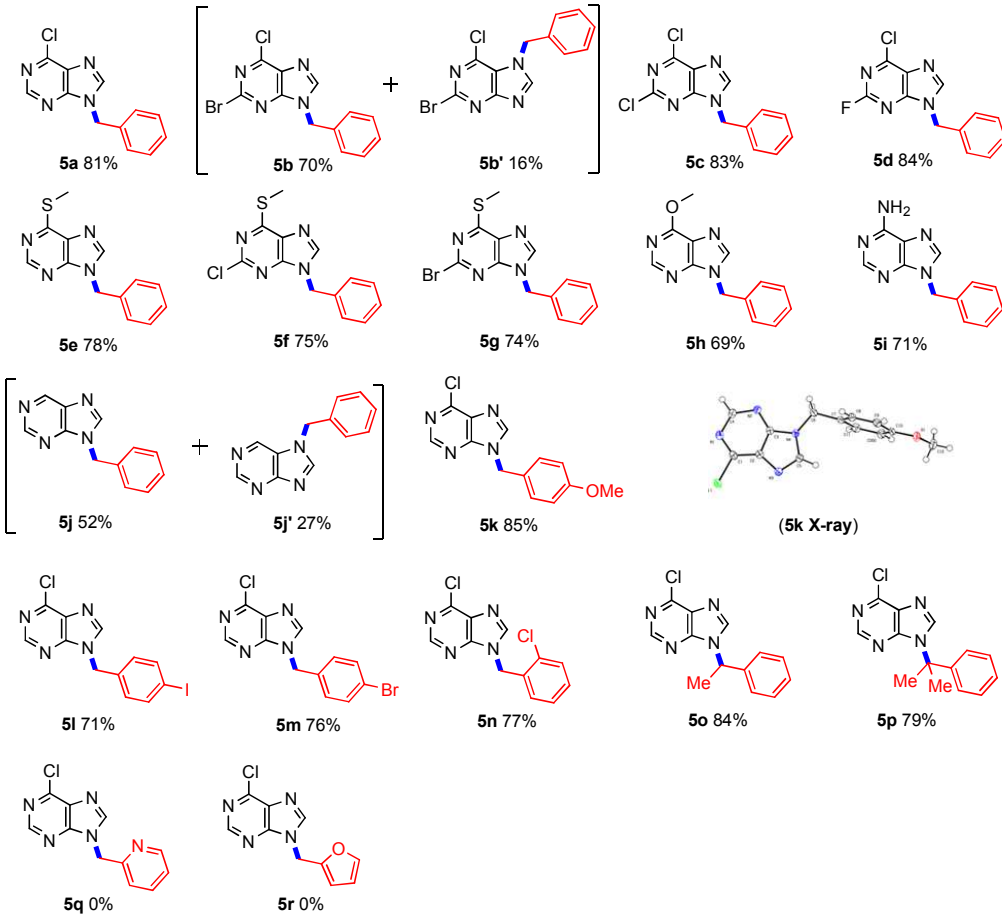
However, the reaction of 6-chloropurine with anisole did not generate the corresponding product. To our surprise, we obtained the product **5k** from the reaction between p-methyl anisole and 6-chloropurine, which occurred at the benzyl site. Subsequently, we studied the scope of various purines with toluene. As shown in **Scheme 3**, purine substrates bearing electron-donating groups such as 6-SMe, 6-OMe and electron-withdrawing groups such as 2-F, 2-Cl and 2-Br all could be smoothly converted to the corresponding products in moderate to good yields (**5b-5h**, 16-84%). Even the adenine with NH_2 could be used in the reaction system and generated the corresponding product (**5i**, 71%). In addition, the structure of **5k** was unambiguously assigned by its single crystal X-ray analysis (see SI for more details).[15] However some purine substrates yielded isomers of the desired products under these oxidative coupling conditions. For example, products **5b** and **5b'** were obtained in 70% and 16% yield

when 2-bromo-6-chloro-9H-purine reacted with toluene. It worth noting that purine without any substituent afforded isomers of the desired products **5j** and **5j'** in 52% and 27% yield.

To further explore the potential of our methodology, a variety of benzylic C-H bonds of substrates were investigated. We were delighted to find that toluene derivatives with electron-donating substituents furnished higher yields of desired products than electron-withdrawing substituents (**5k-5n**, 71-85%). Moreover, the coupling reaction proceeded successfully when employing benzylic substrates with steric hinderance (**5o-5p**, 79-84%). However, in the reactions of the 6-chloropurine with 2-methylpyridine and 2-methylfuran under the standard conditions, there were no coupling products detected.

Scheme 3. Substrate Scope of the Purines and Aromatic Compounds[a]

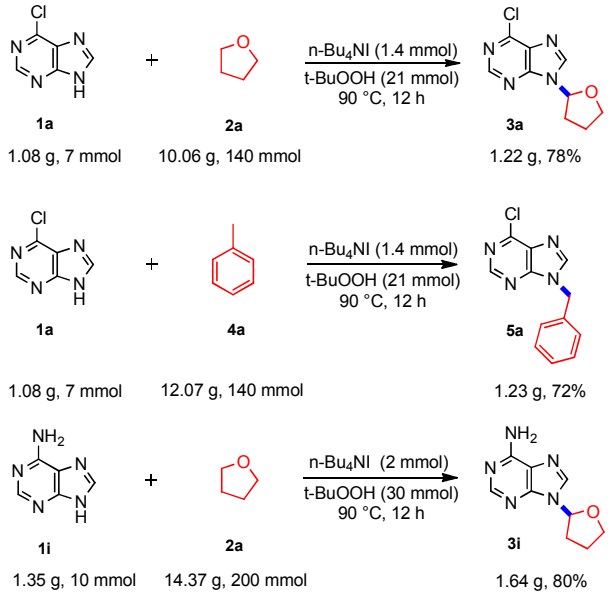




[a]Reaction conditions: **1** (0.2 mmol), **4** (4 mmol), TBAI (20 mol%), TBHP (3 equiv.), under air at 90 °C for 12 h. Isolated yield are shown.

In addition, the satisfactory results (78% yield or 72% yield) were obtained when the reaction was performed on a gram-scale. We also conducted the reaction of adenine with THF on a gram-scale under standard reaction conditions, producing 9-THF-Ade in 80% yield, suggesting that 9-THF-Ade could be synthesized with no other wasteful byproducts except H_2O and t-BuOH. It is the first example of a one-step synthesis of 9-THF-Ade in good yield with unprotected adenine and the readily accessible starting material THF. It makes the method quite attractive for its economical and environmental significance (**Scheme 4**).

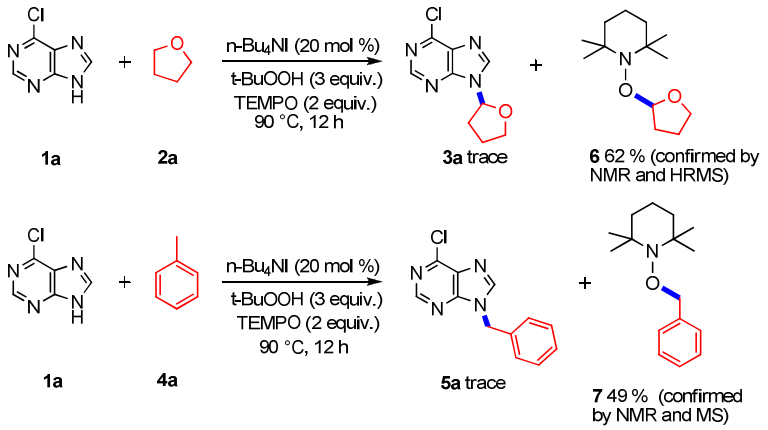
Scheme 4. Gram-scale oxidative coupling reaction



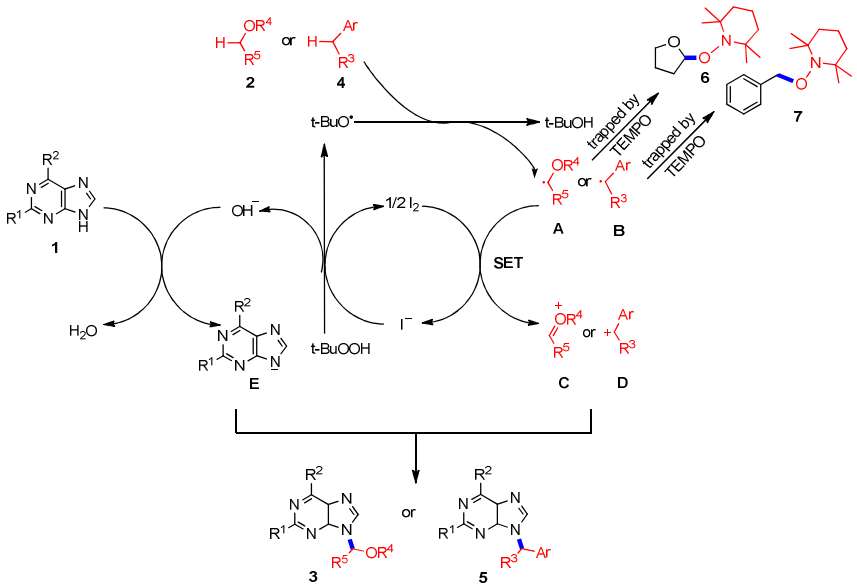
To elucidate the mechanism of this coupling reactions, several control experiments were carried out. Initially, when a radical inhibitor, BHT (2,6-di-tert-butyl-4-methylphenol) or TEMPO (2,2,6,6-tetra-methyl-piperidine-N-oxyl) was added into the reaction, the formation of the desired product was greatly supressed. We detected the radical trapped products by MS, isolated them by flash chromatography, and obtained the THF−TEMPO and toluene-TEMPO coupled products **6** and **7** in 62% and 49% yield (**Scheme 5**). These results indicated that this oxidative coupling reaction involved a radical pathway. Replacing n-Bu_4NI with I_2 gave very little desired product, suggesting that n-Bu_4NI plays an important role in the reaction. The mechanism of the oxidative coupling reaction has not been fully explained but a plausible mechanism is proposed based on our above experimental results and literature reported.[10e,16] As shown in **Scheme 6**, initially, the oxidation of n-Bu_4NI by t-BuOOH generates the tert-butoxyl radical, iodine, and a hydroxyl anion.[17] Then, tert-butoxyl radical abstracts hydrogen atoms from the ethers **2** or benzyl compounds **4** to give radical **A** and **B**, which were further oxidized to an oxonium intermediate **C** or a benzyl cation **D** via a single electron transfer process.[9e,16a,c]

Next, purines **1** is deprotonated by the hydroxyl anion to provide anionic species **E**,[16a] Finally, the nucleophilic reaction of purine **E** with the oxonium intermediate **C** and the benzyl cation **D** forms the corresponding desired product **3** or **5**.

Scheme 5. Coupling in the Presence of a Free-radical Scavenger



Scheme 6. Proposed Reaction Mechanism



Conclusions

In conclusion, an n-Bu_4NI-catalyzed direct oxidative coupling reaction of alkyl ethers and benzyl compounds with purine derivatives has been developed. The reactions of substrates containing various functional groups proceeded smoothly to give the desired products in moderate to good yield. This protocol provides an efficient and green way for the preparation of compounds containing the purine ring structural unit. These compounds have potential in biological and pharmaceutical application. Further investigations to study the synthetic utility of this reaction are currently in progress.

Experimental Section

General Information. All reactions were carried out in flame-dried sealed tubes with magnetic stirring under an air atmosphere unless otherwise noted. All alkyl ethers and benzyl compounds were purchased from commercial suppliers and used without further purification, unless otherwise stated. C6 substituted purines were synthesized from 6-chloropurine according to Huang's method.[18] C2 and C6 substituted purines were synthesized from 2-amido-6-chloropurine according to Hu's method.[19] Purifications of reaction products were carried out by flash chromatography using Qingdao Haiyang Chemical Co. Ltd silica gel (300-400 mesh). Infrared spectra (IR) were recorded on a Brucker TENSOR 27 FTIR spectrophotometer and are reported as wave number (cm^{-1}). Infrared spectra were recorded by preparing a KBr pellet containing the title compound. ^1H, ^{13}C, ^{19}F NMR spectra were recorded on 400 MHz, 100 MHz and 376 MHz spectrometer, respectively. ^1H NMR and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0 and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as external standard. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized

are designated as multiple (m). High resolution mass spectra (HRMS) were recorded on an IF-TOF spectrometer (Micromass). Crystal data were obtained by employing graphite monochromated Mo - Kα radiation (λ = 1.54178 Å) at 293(2) K and operating in the φ-ω scan mode. The structure was solved by direct methods SHELXS-97.

General Procedure for the direct alkylation of purines. Purine substrates **1** (0.2 mmol), TBAI (0.04 mmol, 14.77 mg), dried ethers **2** or benzyl compounds **4** (4 mmol) and TBHP (0.6mmol, 70% in water) were successively added into a sealed tube. The reaction mixture was stirred at 90 ^{o}C for 12 hours. After completion of reaction，the reaction tube was allowed to cool to room temperature and quenched by the addition of a saturated solution of sodium bisulfite (3 mL). The mixture was extracted with ethyl acetate (3×8 mL), the combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was then purified by flash column chromatography on silica gel to afford the desired product **3** or **5**.

6-chloro-9-(tetrahydrofuran-2-yl)-9H-purine **3a**. The product **3a** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow solid (36.7 mg, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.19 (s, 1H), 6.29 (dd, *J*=6.2, 3.0, 1H), 4.24 (dd, *J*=14.6, 6.8, 1H), 4.03 (q, *J*=7.6, 1H), 2.60 – 2.44 (m, 2H), 2.17 – 2.07 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.8, 151.0, 150.9, 143.4, 132.4, 86.6, 70.0, 32.5, 24.2. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_9H_9ClN_4NaO$: 247.0357, found: 247.0359.

2-bromo-6-chloro-9-(tetrahydrofuran-2-yl)-9H-purine **3b**. The product **3b** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a light yellow solid (51.2 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 6.29 (t, *J* = 4.7 Hz, 1H), 4.29 (dd, *J* = 13.9, 7.5 Hz, 1H), 4.07 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.56 – 2.51 (m, 2H), 2.18 – 2.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$)

δ 152.0, 151.4, 143.8, 142.9, 131.9, 86.8, 70.1, 32.7, 24.2. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_9H_8BrClN_4NaO$: 324.9462, found: 324.9460.

2,6-dichloro-9-(tetrahydrofuran-2-yl)-9H-purine **3c**. The product **3c** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a light yellow solid (41.4 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 6.29 (t, *J* = 4.7 Hz, 1H), 4.29 (dd, *J* = 13.9, 7.5 Hz, 1H), 4.07 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.56 – 2.51 (m, 2H), 2.18 – 2.11 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.8, 152.1, 151.7, 144.0, 131.5, 86.8, 70.1, 32.7, 24.1. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_9H_8Cl_2N_4NaO$: 280.9967, found: 280.9964.

6-chloro-2-fluoro-9-(tetrahydrofuran-2-yl)-9H-purine **3d**. The product **3d** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white liquid (42.1 mg, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 6.33 – 6.27 (m, 1H), 4.32 (dd, *J* = 14.7, 6.7 Hz, 1H), 4.10 (dd, *J* = 15.8, 7.5 Hz, 1H), 2.61 – 2.53 (m, 2H), 2.23 – 2.16 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.0 (d, *J* = 218 Hz), 152.7 (d, *J* = 10 Hz), 152.5 (d, *J* = 9 Hz), 144.1 (d, *J* = 3 Hz), 131.1 (d, *J* = 5 Hz), 86.8, 70.1, 32.5, 24.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -49.3. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_9H_8ClFN_4NaO$: 265.0263, found: 265.0270.

6-(methylthio)-9-(tetrahydrofuran-2-yl)-9H-purine **3e**. The product **3e** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow solid (39.7 mg, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.06 (s, 1H), 6.32 (dd, *J* = 6.4, 3.1 Hz, 1H), 4.28 (dd, *J* = 14.8, 6.6 Hz, 1H), 4.07 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.72 (s, 3H), 2.57 – 2.46 (m, 2H), 2.18 – 2.11 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 151.8, 147.4, 140.6, 132.1, 86.1, 69.7, 32.4, 24.3, 11.7. **HRMS (ESI)** calcd for $[M + H]^+$: $C_{10}H_{13}N_4OS$: 237.0805, found:237.0803.

2-chloro-6-(methylthio)-9-(tetrahydrofuran-2-yl)-9H-purine **3f**. The product **3f** was purified with

silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (48.2 mg, 89% yield). **Mp** 113-115 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.30 – 6.26 (m, 1H), 4.28 (dd, *J* = 14.9, 6.5 Hz, 1H), 4.07 (dd, *J* = 15.7, 7.5 Hz, 1H), 2.72 (s, 3H), 2.54 – 2.49 (m, 2H), 2.17 – 2.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8, 153.5, 148.8, 141.1, 131.0, 86.2, 69.9, 32.7, 24.2, 12.1. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{10}H_{11}ClN_4NaOS$: 293.0234, found: 293.0238. **IR (KBr)**: 3131, 2903, 1698, 1555, 1480, 1389, 1319, 1211, 1079, 794 cm^{-1}.

2-bromo-6-(methylthio)-9-(tetrahydrofuran-2-yl)-9H-purine **3g**. The product **3g** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (53.6 mg, 85% yield). **Mp** 253-254 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.28 (t, *J* = 4.7 Hz, 1H), 4.28 (dd, *J* = 14.8, 6.5 Hz, 1H), 4.07 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.72 (s, 3H), 2.54 – 2.50 (m, 2H), 2.18 – 2.12 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8, 148.7, 144.1, 140.9, 131.4, 86.2, 69.9, 32.7, 24.2, 12.1. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_{10}H_{11}BrN_4NaOS$: 336.9729, found: 336.9730. **IR (KBr)**: 3133, 2904, 1658, 1523, 1443, 1379, 1309, 1109, 1068, 673 cm^{-1}.

6-methoxy-9-(tetrahydrofuran-2-yl)-9H-purine **3h**. The product **3h** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (33.5 mg, 76% yield). **Mp** 170-172 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.96 (s, 1H), 6.29 – 6.24 (m, 1H), 4.21 (dd, *J* = 14.2, 7.2 Hz, 1H), 4.11 (s, 3H), 4.00 (dd, *J* = 15.6, 7.4 Hz, 1H), 2.51 – 2.42 (m, 2H), 2.14 – 2.03 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.0, 152.0, 151.2, 140.2, 122.2, 86.0, 69.7, 54.2, 32.4, 24.3. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_{10}H_{12}N_4NaO_2$: 243.0852, found: 243.0856. **IR (KBr)**: 3224, 3130, 2904, 1600, 1560, 1434, 1343, 1201, 1106 cm^{-1}.

9-(tetrahydrofuran-2-yl)-9H-adenine **3i**. The product **3i** was purified with silica gel chromatography (petroleum ether/ethyl acetate/ammonium hydroxide=15:5:1) as a yellow solid (35.2 mg, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.85 (s, 1H), 6.23 (dd, *J* = 6.3, 3.1 Hz, 1H), 5.91 (s, 2H), 4.21 (dd, *J* = 14.6, 6.6 Hz, 1H), 3.99 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.51 – 2.36 (m, 2H), 2.09 – 2.03 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.5, 153.0, 149.3, 138.5, 120.3, 85.9, 69.6, 32.5, 24.3. **HR-MS (ESI)** calcd for $[M + H]^+$: $C_9H_{12}N_5O$: 206.1036, found: 206.1037.

N, N-diethyl-9-(tetrahydrofuran-2-yl)-9H-purin-6-amine **3j**. The product **3j** was purified with silica gel chromatography (petroleum ether/ethyl acetate/ammonium hydroxide=15:5:1) as a light yellow liquid (37.1 mg, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.75 (s, 1H), 6.25 – 6.20 (m, 1H), 4.18 (dd, *J* = 14.8, 6.5 Hz, 1H), 3.99 – 3.92 (m, 5H), 2.45 – 2.37 (m, 2H), 2.07 – 2.00 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.6, 152.4, 149.7, 136.0, 120.1, 85.4, 69.4, 42.9, 32.3, 24.2, 13.5. **HRMS (ESI)** calcd for $[M + H]^+$: $C_{13}H_{20}N_5O$: 262.1662, found: 262.1666. **IR (KBr)**: 3208, 3126, 2930, 1676, 1588, 1449, 1384, 1285, 1070 cm^{-1}.

2-(di-t-butyloxycarbonylamino)-6-chloro-9-(tetrahydrofuran-2-yl)-9H-purine **3k**. The product **3k** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (71.3 mg, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 6.23 (dd, *J* = 6.4, 3.1 Hz, 1H), 4.22 (dd, *J* = 14.9, 6.5 Hz, 1H), 4.01 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.54 – 2.40 (m, 2H), 2.12 – 2.04 (m, 2H), 1.38 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.7, 151.6, 151.1, 150.6, 144.3, 130.7, 86.8, 83.6, 70.0, 32.5, 27.9, 24.2. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_{19}H_{26}ClN_5NaO_5$: 462.1515, found: 462.1524.

6-chloro-9-(1,4-dioxan-2-yl)-9H-purine **3l**. The product **3l** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (36.1 mg, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.48 (s, 1H), 5.98 (dd, *J* = 5.2, 2.9 Hz, 1H), 4.15 (dd, *J* = 12.0, 2.7 Hz, 1H), 4.04 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.87 – 3.80 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.3, 151.5, 151.3, 143.8, 131.5, 77.7, 68.3, 66.3, 64.2. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_9H_9ClN_4NaO_2$:

263.0306, found: 263.0307.

6-chloro-9-(1,2-dimethoxyethyl)-9H-purine **3m**. The product **3m** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (19.8 mg, 41% yield). **Mp** 62-63 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.36 (s, 1H), 5.88 (t, *J* = 4.7 Hz, 1H), 3.90 (dd, *J* = 10.5, 5.1 Hz, 1H), 3.80 (dd, *J* = 10.5, 4.2 Hz, 1H), 3.36 (d, *J* = 11.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.2, 152.1, 151.2, 143.9, 131.5, 84.6, 72.8, 59.7, 57.3. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_9H_{11}ClN_4NaO_2$: 265.0463, found: 265.0466. **IR (KBr)**: 3123, 3112, 2916, 1648, 1592, 1453, 1393, 1223, 1108, 729 cm^{-1}.

6-chloro-9-((2-methoxyethoxy) methyl)-9H-purine **3m'**. The product **3m'** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (14.5 mg, 30% yield). **Mp** 54-56 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.23 (s, 1H), 5.69 (s, 2H), 3.68 – 3.63 (m, 2H), 3.47 – 3.43 (m, 2H), 3.27 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.5, 152.1, 151.4, 145.3, 131.5, 73.6, 71.5, 69.4, 59.1. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_9H_{11}ClN_4NaO_2$: 265.0463, found: 265.0459. **IR (KBr)**: 3214, 3068, 2927, 1623, 1562, 1438, 1379, 1212, 1100, 754 cm^{-1}.

9-(tert-butoxymethyl)-6-chloro-9H-purine **3n**. The product **3n** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow solid (40.0 mg, 83% yield). **Mp** 63-64 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.27 (s, 1H), 5.64 (s, 2H), 1.18 (s, 9H). **^{13}CNMR** (100 MHz, $CDCl_3$) δ 152.0, 151.2, 150.8, 145.3, 131.4, 76.2, 67.5, 27.7. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_{10}H_{13}ClN_4NaO$: 263.0670, found: 263.0672. **IR (KBr)**: 3136, 3014, 2879, 1639, 1573, 1462, 1365, 1238, 1100, 648 cm^{-1}.

6-chloro-9-(5-methyltetrahydrofuran-2-yl)-9H-purine **3o**. The product **3o** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow solid (33.4 mg, 70% yield), a mixture

of two diastereomers (dr=1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.30 (s, 0.5H), 8.24 (s, 0.5H), 6.36 (s, 0.5H), 6.30 (s, 0.5H), 4.66 – 4.57 (m, 0.5H), 4.40 – 4.27 (m, 0.5H), 2.68– 2.61 (m, 1H), 2.57 – 2.54 (m, 1H), 2.31 (dd, *J* = 12.8, 6.5 Hz, 0.5H), 2.21 (dd, *J* = 10.0, 4.7 Hz, 0.5H), 1.80 – 1.71 (m, 1H), 1.44 (d, *J* = 5.9 Hz, 1.5H), 1.33 (d, *J* = 5.9 Hz, 1.5H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 151.8, 151.8, 151.0, 150.9, 150.9, 150.8, 143.6, 143.4, 132.4, 132.4, 86.5, 86.2, 78.7, 77.7, 33.4, 32.3, 31.8, 31.4, 20.9, 20.7. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_{10}H_{11}ClN_4NaO$: 261.0514, found: 261.0518.

6-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purine **3p**. The product **3p** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a green solid (37.7 mg, 79% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.28 (s, 1H), 5.72 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.12 (dd, *J* = 12.7, 2.7 Hz, 1H), 3.72 (dd, *J* = 11.5, 8.8 Hz, 1H), 2.14 – 2.00 (m, 3H), 1.76 – 1.59 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.0, 151.1, 151.0, 143.1, 131.7, 82.6, 68.9, 31.8, 24.8, 22.6. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{10}H_{11}ClN_4NaO$: 261.0514, found: 261.0513.

9-benzyl-6-chloro-9H-purine **5a**. The product **5a** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (39.6 mg, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.07 (s, 1H), 7.13 – 7.05 (m, 5H), 5.29 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.9, 151.8, 150.6, 145.4, 134.6, 131.3, 129.0, 128.5, 127.8, 47.7. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{12}H_9ClN_4Na$: 267.0408, found: 267.0412.

9-benzyl-2-bromo-6-chloro-9H-purine **5b. T**he product **5b** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (39.mg, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.32 – 7.22 (m, 5H), 5.34 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.1, 151.6, 145.4, 143.3, 134.0, 131.0, 129.4, 129.1, 128.1, 48.1. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{12}H_8BrClN_4Na$: 344.9513, found: 344.9519.

7-benzyl--2-bromo-6-chloro-7H-purine **5b'**. The product **5b'** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (8.9mg, 16% yield). **Mp** 145-148 ^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.41 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.20 – 7.17 (m, 2H), 5.68 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6, 150.2, 143.6, 143.5, 134.1, 129.5, 129.1, 127.1, 122.2, 50.9. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{12}H_8BrClN_4Na$: 344.9513, found: 344.9514. **IR (KBr)**: 3105, 2924, 1646, 1599, 1528, 1476, 1453, 1169, 796, 744, 703, 626 cm^{-1}.

9-benzyl-2,6-dichloro-9H-purine **5c**. The product **5c** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (53.7 mg, 83% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.42 – 7.31 (m, 5H), 5.43 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.2, 153.2, 151.9, 145.6, 134.0, 130.7, 129.4, 129.1, 128.1, 48.1; **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{12}H_8Cl_2N_4Na$: 301.0018, found: 301.0014.

9-benzyl-6-chloro-2-fluoro-9H-purine **5d**. The product **5d** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white liquid (44 mg, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.32 – 7.22 (m, 5H), 5.31 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.4 (d, *J* = 219 Hz), 153.7 (d, *J* = 17Hz), 152.8 (d, *J* = 18Hz), 145.6 (d, *J* = 3Hz), 134.0, 130.2 (d, *J* = 5Hz), 129.4, 129.1, 128.1, 48.1; **^{13}F NMR** (376 MHz, $CDCl_3$) δ -49.2. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{12}H_8ClFN_4Na$: 285.0314, found: 285.0312.

9-benzyl-6-(methylthio)-9H-purine **5e**. The product **5e** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a light yellow solid (40.0 mg, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.95 (s, 1H), 7.37 – 7.28 (m, 5H), 5.43 (s, 2H), 2.75 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.8, 152.2, 148.4, 142.4, 135.2, 131.3, 129.1, 128.6, 127.8, 47.4, 11.8. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{13}H_{12}N_4NaS$: 279.0675, found: 279.0678.

9-benzyl-2-chloro-6-(methylthio)-9H-purine **5f**. The product **5f** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow solid (43.6 mg, 75% yield**). Mp** 118-119 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.28 – 7.19 (m, 5H), 5.28 (s, 2H), 2.64 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.0, 153.9, 149.8, 142.8, 134.7, 130.2, 129.2, 128.7, 128.0, 47.5, 12.1. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{13}H_{11}ClN_4NaS$: 313.0285, found: 313.0287. **IR (KBr)**: 3099, 2924, 1634, 1579, 1490, 1426, 1409 , 1381, 1235, 1150, 803, 765, 707 cm^{-1}.

9-benzyl-2-bromo-6-(methylthio)-9H-purine **5g**. The product **5g** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (49.43 mg, 74% yield). **Mp** 130-133 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.39 – 7.28 (m, 5H), 5.38 (s, 2H), 2.74 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.9, 149.8, 144.5, 142.6, 134.7, 130.6, 129.2, 128.8, 128.0, 47.5, 12.2. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{13}H_{11}N_4BrNaS$: 356.9780, found: 356.9784. **IR (KBr)**: 3098, 2923, 1642, 1571, 1494, 1454, 1409 , 1378, 1144, 1079, 744, 705, 665 cm^{-1}

9-benzyl-6-(methoxy)-9H-purine **5h**. The product **5h** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a light yellow solid (33.1 mg, 69% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.92 (s, 1H), 7.41 – 7.28 (m, 5H), 5.44 (s, 2H), 4.22 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.1, 153.8, 152.3, 142.0, 135.2, 129.1, 128.6, 127.8, 121.4, 54.3, 47.5. **HRMS (ESI)** calcd for $[M + H]^+$: $C_{13}H_{13}N_4O$: 241.1084, found: 241.1088.

9-benzyl-9H-adenine **5i.** The product **5i** was purified with silica gel chromatography (petroleum ether/ethyl acetate/ammonium hydroxide=15:5:1) as a white solid (31.9 mg, 71% yield). **^{1}H NMR** (400 MHz, DMSO-d6) δ 8.25 (s, 1H), 8.15 (s, 1H), 7.35 – 7.22 (m, 7H), 5.37 (s, 2H). **^{13}C NMR** (100 MHz, DMSO-d6) δ 156.5, 153.1, 150.0, 141.3, 137.6, 129.1, 128.2, 128.0, 119.1, 46.6. **HRMS (ESI)** calcd for $[M + H]^+$: $C_{12}H_{12}N_5$: 226.1087, found: 226.1085.

9-benzyl-9H-purine **5j**. The product **5j** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (21.8 mg, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 9.04 (s, 1H), 8.09 (s, 1H), 7.40 – 7.30 (m, 5H), 5.47 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.9, 151.5, 148.7, 145.1, 135.0, 134.0, 129.2, 128.7, 127.9, 47.2. **HR-MS (ESI)** calcd for $[M + H]^+$: $C_{12}H_{11}N_4$: 211.0978, found: 211.0980.

9-benzyl-9H-purine **5j'**. The product **5j'** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (11.3 mg, 27% yield). **Mp** 123-124 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.76 (s, 1H), 8.31 (s, 1H), 7.41 (dd, *J* = 5.1, 1.8 Hz, 3H), 7.27 (dd, *J* = 7.3, 4.2 Hz, 2H), 5.46 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.1, 153.5, 148.0, 140.4, 133.6, 129.5, 129.2, 127.5, 125.3, 50.3. **HRMS (ESI)** calcd for $[M + H]^+$: $C_{12}H_{11}N_4$: 211.0978, found: 211.0979. **IR (KBr)**: 3105, 2923, 1601, 1554, 1520, 1484, 1448, 1208, 731, 697 cm^{-1}.

6-chloro-9-(4-methoxybenzyl)-9H-purine **5k**. The product **5k** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a white solid (46.7 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.08 (s, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.40 (s, 2H), 3.81 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.0, 151.1, 150.8, 150.1, 143.9, 130.6, 128.6, 125.4, 113.6, 54.3, 46.5. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{13}H_{11}ClN_4NaO$: 297.0514, found: 297.0519.

6-chloro-9-(4-iodobenzyl)-9H-purine **5l**. The product **5l** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a light yellow solid (52.6 mg, 71% yield). **Mp** 140-142 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.04 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 5.33 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.3, 151.8, 151.3, 144.8, 138.4, 134.2, 131.5, 129.7, 94.7, 47.4. **HR-MS (ESI)** calcd for $[M + Na]^+$: $C_{12}H_8ClIN_4Na$: 392.9374, found: 392.9376. IR (KBr):

3120, 3081, 2924, 1643, 1592, 1559, 1487, 1442, 1008, 859, 809 , 583 cm^{-1}.

9-(4-bromobenzyl)-6-chloro-9H-purine **5m**. The product **5m** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow solid (49.2 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.12 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.43 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.3, 151.8, 151.3, 144.8, 133.5, 132.5, 131.5, 129.6, 123.1, 47.3. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{12}H_8BrClN_4Na$: 344.9513, found: 344.9516.

6-chloro-9-(2-chlorobenzyl)-9H-purine **5n**. The product **5n** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a light yellow solid (43.4 mg, 77% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.20 (s, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.38 – 7.25 (m, 3H), 5.58 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.1, 151.9, 151.2, 145.2, 133.7, 132.1, 131.4, 130.7, 130.5, 130.2, 127.6, 45.6. **HRMS (ESI)** calcd for $[M + H]^+$: $C_{12}H_9Cl_2N_4$: 279.0199, found: 279.0193.

6-chloro-9-(1-phenylethyl)-9H-purine **5o**. The product **5o** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow liquid (43.0 mg, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.14 (s, 1H), 7.38 – 7.32 (m, 5H), 5.99 (t, *J* = 7.2 Hz, 1H), 2.04 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.9, 151.6, 151.0, 143.5, 139.1, 131.8, 129.2, 128.8, 126.6, 54.7, 20.7. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{13}H_{11}ClN_4Na$: 281.0564, found: 281.0567.

6-chloro-9-(2-phenylpropan-2-yl)-9H-purine **5p**. The product **5p** was purified with silica gel chromatography (petroleum ether/ethyl acetate=3:1) as a yellow solid (43.1 mg, 79% yield). **Mp** 120-124 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.08 (s, 1H), 7.29 – 7.23 (m, 3H), 7.12 (d, *J* = 6.7 Hz, 2H), 2.14 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.0, 151.3, 151.2, 144.0, 143.5, 132.7, 128.9, 128.1, 125.0, 62.8, 29.7 29.2. **HRMS (ESI)** calcd for $[M + Na]^+$: $C_{14}H_{13}ClN_4Na$: 295.0721, found: 295.0723. **IR (KBr)**: 3119, 3068, 2924, 1647, 1592, 1553, 1485, 1433, 1389, 1084, 858, 766,

703 cm^{-1}.

2,2,6,6-Tetramethyl-1-((tetrahydrofuran-2-yl)oxy)piperidine **6**. The product **6** was purified with silica gel chromatography (petroleum ether/ethyl acetate=15:1) as a white solid (62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.37 (s, 1H), 3.86 (dd, J = 13.8, 6.6 Hz, 2H), 2.04 – 1.87 (m, 3H), 1.79 (d, J = 9.8 Hz, 1H), 1.49 (s, 5H), 1.33 (s, 1H), 1.22 (s, 3H), 1.11 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 109.6, 66.6, 60.1, 58.6, 40.1, 39.7, 33.9, 33.4, 31.2, 23.9, 20.5, 20.1, 17.3. HRMS (ESI) Calculated for[$M+H]^+$: $C_{13}H_{26}NO_2$, 228.1958, Found:228.1963

1-(benzyloxy)-2,2,6,6-tetramethylpiperidine **7**. The product **7** was purified with silica gel chromatography (petroleum ether/ethyl acetate=20:1) as a white solid (49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 4.88 (s, 2H), 1.70 – 1.40 (m, 6H), 1.31 (s, 6H), 1.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.3, 127.5, 127.3, 78.8, 60.1, 39.8, 33.1, 20.3, 17.2. MS (EI) Calculated for[$M]^+$ $C_{16}H_{25}NO$,247.19, Found:247.09

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

*E-mail: denlin@scut.edu.cn

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors thank the Science and Technology Program of South China University of Technology for financial support. The authors also thank Professor Gary Histand from the International School of

Advanced Materials, South China University of Technology for helpful discussions.

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all the compounds, copies of ^{19}F NMR spectra of **3d** and **5d** and X-ray crystallography data of **5k** are available in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

(1) (a) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859. (b) Huryn, D. M.; Okabe, M. *Chem. Rev*. **1992**, *92*, 1745. (c) Ichikawa, E.; Kato, K. *Curr. Med. Chem*. **2001**, *8*, 385. (d) Chen, X. C.; Kern, E. R.; Drach, J. C.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. *J. Med. Chem*. **2003**, *46*, 1531. (e) Mahony, W. B.; Domin, B. A.; Daluge, S. M.; Zimmerman, T. P. *Biochem. pharmacol.* **2004**, *68*, 1797. (f) Ferrero, M.; Gotor, V. *Chem. Rev*. **2000**, *100*, 4319. (g) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev*. **1999**, *99*, 779.

(2) (a) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1. (b) Vivet-Boudou, V.; Didierjean, J.; Isel, C.; Marquet, R. *Cell. Mol. Life Sci.* **2006**, *63*, 163. (c) Ueland, P. M. *Pharmacol. Rev.* **1982**, *34*, 223. (d) De Clercq, E.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. *Proc. Natl. Acad. Sci. U. S. A*. **1979**, *76*, 2947. (e) McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem*. **2000**, *43*, 4993.

(3) (a) De Clercq, E. *Nucleos. Nucleot. Nucl*. **2004**, *23*, 457. (b) Freeman, S.; Gardiner, J. M.; *Mol. Biotechnol*. **1996**, *5*, 125. (c) Barrio, J. R., Bryant, J. D., Keyser, G. E. *J. Med. Chem*. **1980**, *23*, 572. (d) Novosjolova, I.; Bizdēna, Ē.; Turks, M. *Eur. J. Org. Chem*. **2015**, *17*, 3629. (e) Zhou, X.-X., Littler, E. *Curr. Top. Med. Chem*. **2006**, *6*, 851. (f) Lin, T. S., Luo, M. Z., Liu, M. C.; Pai, B.; Dutschman, G. E.;

Cheng, Y. C. *Biochem. Pharmacol*. **1994**, *47*, 171. (g) Ivo, G.; Thomas, K.; Michael, S.; Francoise, H. G.; Wolfgang, V.; Günther, K. *J. Hepatol*. **1998**, *28*, 504.

(4) (a) De Clercq, E. *Rev. Med. Virol.* **2009**, *19*, 287. (b) Wang, L.; Zhu, K.-Q.; Wu, W.-T.; Chen, Q.; He, M.-Y. *Catal. Sci. Technol*. **2015**, *5*, 2891.

(5) (a) Borrmann, T.; Abdelrahman, A.; Volpini, R.; Lambertucci, C.; Alksnis, E.; Gorzalka, S.; Knospe, M.; Schiedel, A. C.; Cristalli, G.; Müller, C. E. *J. Med. Chem.* **2009**, *52*, 5974. (b) Guo, H.-M.; Wu, Y.-Y.; Niu, H.-Y.; Wang, D.-C.; Qu, G.-R. *J. Org. Chem*. **2010**, *75*, 3863. (c) Chen, S.; Graceffa, R. F.; Boezio, A. A. *Org. Lett.* **2016**, *18*, 16. (d) Arico, J. W.; Calhoun, A. K.; Salandria, K. J.; McLaughlin, L.W. *Org. Lett*. **2010**, *12*, 120. (e) Holý, A.; Dvořáková, H.; Jindřich, J.; Masojídková, M.; Buděšínský, M.; Balzarini, J.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, 39, 4073.

(6) Phadtare, S.; Zemlicka, J. *J. Am. Chem. Soc.* **1989**, *111*, 5925.

(7) (a) Wang, Q.; Su, Y.; Li, L.; Huang, H. *Chem. Soc. Rev*. **2016**, *45*, 1257. (b) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev*. **2013**, *42*, 9283. (c) Martinez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 2801. (d) Sadhu, P.; Punniyamurthy, T. *Chem. Commun.* **2016**, *52*, 2803. (e) Marchetti, L.; Kantak, A.; Davis, R.; DeBoef, B. *Org. Lett.* **2015**, *17*, 358.

(8) (a) Guo, S.; Kumar, P. S.; Yang, M. *Adv. Synth. Catal*. **2017**, *359*, 2. (b) Sun, J.; Zhang, Y.; Mathan, S.; Wang, Y.; Pan, Y. *J. Org. Chem*. **2016**, *81*, 3380. (c) Okugawa, N.; Moriyama, K.; Togo, H. *J. Org. Chem.* **2017**, *82*, 170. (d) Liu, S.; Liu, A.; Zhang, Y.; Wang, W. *Chem. Sci.* **2017**, *8*, 4044. (e) Wang, L.; Cao, J.; Chen, Q.; He, M. *J. Org. Chem*. **2015**, *80*, 4743. (f) Xia, Q.; Chen, W.; Qiu, H. *J. Org. Chem.* **2011**, *76*, 7577. (g) Yang, Q.; Choy, P. Y.; Fu, W. C.; Fan, B.; Kwong, F. Y. *J. Org. Chem*. **2015**, *80*, 11193. (h) Singh, M. K.; Akula, H. K.; Satishkumar, S.; Stahl, L.; Lakshman, M. K. *ACS. Catal*. **2016**, *6*, 1921.

(9) (a) Rajamanickam, S.; Majji, G.; Santra, S. K.; Patel, B. K. *Org. Lett*. **2015**, *17*, 5586. (b) Liu, W.; Liu, C.; Zhang, Y.; Sun, Y.; Abdukadera, A.; Wang, B.; Li, H.; Ma, X.; Zhang, Z. *Org. Biomol. Chem.* **2015**, *13*, 7154. (c) Liu, Z.; Zhang, X.; Li, J.; Li, F.; Li, C.; Jia, X.; Li, J. *Org. Lett.* **2016,** *18*, 4052. (d) Wu, X.-F.; Gong, J.-L.; Qi, X. *Org. Biomol. Chem*. **2014**, *12*, 5807. (e) Xue, Q.; Xie, J.; Li, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 3700. (f) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun*. **2011**, *47*, 10827.

(10) (a) Dian, L.; Wang, S.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Chem. Commun*. **2014**, *50*, 11738. (b) Lv, Y.; Sun, K.; Wang, T.; Wu, Y.; Li, G.; Pu, W.; Mao, S. *Asian. J. Org. Chem*. **2016**, *5*, 325. (c)Yang, Q.; Choy, P. Y.; Wu, Y.; Fan, B.; Kwong, F. Y. *Org. Biomol. Chem*. **2016**, *14*, 2608. (d) Aruri, H.; Singh, U.; Kumar, M.; Sharma, S.; Aithagani, S. K.; Gupta, V. K.; Mignani, S.; Vishwakarma, R. A.; Singh, P. P. *J. Org. Chem*. **2017**, *82*, 1000. (e) Aruri, H.; Singh, U.; Sharma, S.; Gudup, S.; Bhogal, M.; Kumar, S.; Singh, D.; Gupta, V. K.; Kant, R.; Vishwakarma, R. A.; Singh, P. P. *J. Org. Chem*. **2015**, *80*, 1929.

(11) Xia, R.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Org. Lett*. **2012**, *14*, 5546.

(12) Guo, H.-M.; Xia, C.; Niu, H.-Y.; Zhang, X.-T.; Kong, S.-N.; Wang, D.-C.; Qu, G.-R. *Adv*. *Synth. Catal*. **2011**, *353*, 53.

(13) Huang, R.; Xie, C.; Huang, L.; Liu, J. *Tetrahedron* **2013**, 69, 577.

(14) Xu, S.; Luo, Z.; Jiang, Z.; Lin, D. *Synlett* **2017**, *28*, 868.

(15) Single crystal information of **5k**, please see the SI for details.

(16) (a) Wang, L.; Zhu, K.; Chen, Q.; He, M. *J. Org. Chem*. **2014**, *79*, 11780. (b) Liu, Z.; Zhang, X.; Li, J.; Li, F.; Li, C.; Jia, X.; Li, J. *Org. Lett.* **2016**, *18*, 4052. (c) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J*. **2011**, *17*, 4085. (d) Li, L.-T.; Huang, J.; Li, H.-Y.; Wen, L.-J.;

Wang, P.; Wang, B. *Chem. Commun*. **2012**, *48,* 5187. (e) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem*. *Int. Ed*. **2012**, *51*, 3231.

(17) (a) Wong, Y.-C.; Tseng, C.-T.; Kao, T.-T.; Yeh, Y.-C.; Shia, K.-S. *Org. Lett*. **2012**, *14*, 6024. (b) Li, H.; Xie, J.; Xue, Q.; Cheng, Y.; Zhu, C. *Tetrahedron Lett*. **2012**, *53*, 6479. (c) Wang, S.; Wang, J.; Guo, R.; Wang, G.; Chen, S.-Y.; Yu, X.-Q. *Tetrahedron Lett*. **2013**, *54*, 6233.

(18) Huang, L.-K.; Cherng, Y.-C.; Cheng, Y.-R.; Jang, J.-P.; Chao, Y.-L.; Cherng, Y.-J. *Tetrahedron* **2007**, *63*, 5323.

(19) Hu, Y. L.; Liu, X.; Lu, M.; Ge, Q.; Liu, X. B. *J. Korean Chem. Soc*. **2010**, *54*, 429.