JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

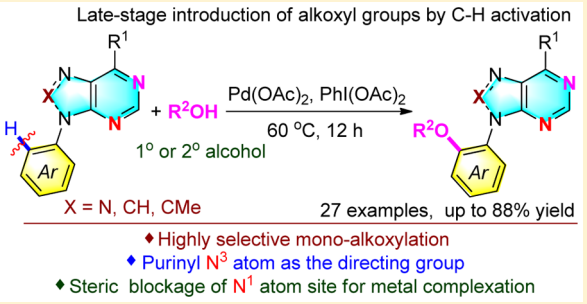
Purinyl N^3-Directed Palladium-Catalyzed C−H Alkoxylation of N^9-Arylpurines: A Late-Stage Strategy to Synthesize N^9-(*ortho*-Alkoxyl)arylpurines

Mingwu Yu, Zhiqian Wang, Miao Tian, Chenghu Lu, Shunlai Li, and Hongguang Du*

Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, P. R. China

Supporting Information

ABSTRACT: A palladium-catalyzed alkoxylation of N^9-arylpurines with primary or secondary alcohols has been developed successfully, which is a rare C−H activation reaction of polynitrogenated purines and offers a late-stage strategy to synthesize N^9-(*ortho*-alkoxyl)-arylpurines. Although there are more than four nitrogen atoms present in the purine moiety, the reaction can be effectively conducted by sterically blocking the N^1 site for catalyst coordination and first employing the purinyl N^3 atom as a directing group.



N^9-(*ortho*-Alkoxyl)arylpurines with unique *ortho*-alkoxylaryl substitution at the N-9 position have attracted much attention from medicinal and synthetic chemists since they exhibit broad bioactivities in biochemical and medicinal chemistry, such as anti-CRF,[1] CHIKV inhibitors,[2] anti-mTOR,[3] and PDE4 inhibitors[4] (Figure 1).

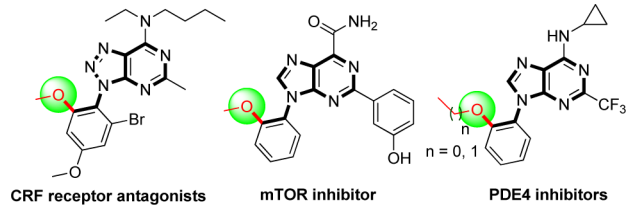
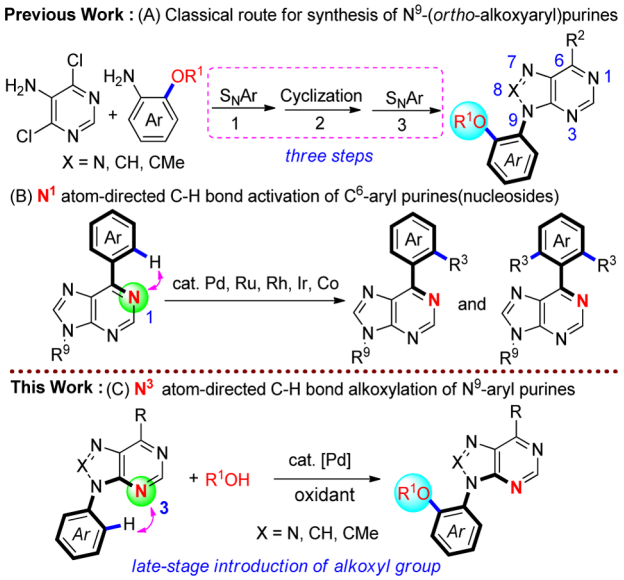


Figure 1. Purine pharmaceuticals containing N^9-(*ortho*-alkoxyl)aryl substitution.

Till now, the traditional method to synthesize these important compounds mostly includes three steps by employing 4-amino-2,6-dichloropyrimidine as raw materials (Scheme 1, A).[1−5] Unfortunately, this multistep approach leads to the complicated operation with long time and relatively low yields and requires (*ortho*-alkoxyl)arylamines that are sometimes not easy to obtain. Disappointingly, due to that the C−O bond was introduced into the framework in the first step, the whole route must be repeated again from the first step when the compound with a new 9-*ortho*-alkoxylaryl substituent needs to be synthesized. Meanwhile, with the advantage of operational convenience, high yields, and so on, the concept of late-stage functionalization has achieved great success in current organic synthesis chemistry. Thus, it is quite significantly demanded to develop a late-stage alkoxylation method, in which the alkoxyl groups can be flexibly and freely modified on the N^9-aryl substituent.

Scheme 1. Synthesis of N^9-(*ortho*-Alkoxyl)arylpurines and N^1-Directed C−H Activation



On the other hand, transition-metal-catalyzed C−H functionalizations with the aid of directing groups (e.g., oxime ether,[6] acylamino,[7] 2-pyridyloxyl,[8] triazole,[9] cyano,[10] iminophosphorane[11]) have achieved great success in constructing C−heteroatom bonds.[12] However, the metal-catalyzed C−

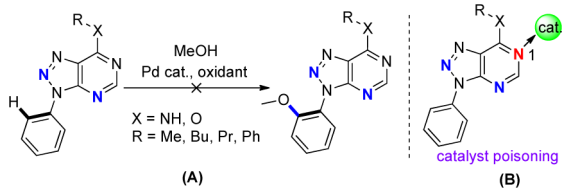
Received: January 22, 2016
Published: March 25, 2016

DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435−3442

H bond activation of purines(nucleosides) still remains severely underdeveloped and challenging because the four nitrogen atoms in purine backbones all can strongly participate in metal sequestration and thereby impede catalyst pathways, especially for the N^1 atom. Till now, sparse purines/nucleosides (e.g., C6-arylpurines/purine nucleosides) were applied to form diverse C−heteroatom bonds by using Pd,[13] Ru,[14] Rh,[15,16] Ir,[16] and Co[17] complexes as catalysts (Scheme 1, B). Among these reactions, only the purinyl N^1 atom was usually used as the Lewis basic sites. To our best knowledge, there were seldom if ever reports on the purinyl N^3-directed C−H bond activation of purines. With these developments and challenges in mind, we disclosed that the palladium-catalyzed direct alkoxylation of N^9-arylpurines can be readily accomplished by using purinyl N^3 atoms as a directing group, which provide a late-stage functionalization strategy to synthesize N^9-(*ortho*-alkoxyl)-arylpurines (Scheme 1, C).

Initially, various 6-mono-alkylamino/alkoxyl-9-phenyl-8-aza-purines[18] were applied to the reaction in the presence of palladium catalyst under diverse conditions according to the literatures,[7−10,19] but all the attempts failed and most starting materials were recovered (Scheme 2, A). This is probably due to catalyst poisoning by the strong coordination of the N^1 nitrogen atoms (Scheme 2, B).[20]

Scheme 2. Methoxylation of 6-Mono-alkylamino/alkoxyl-9-phenyl-8-azapurines and Catalyst Poisoning



In view of the success of C−H functionalization of C6-arylpurine, we conclude that the N^1 atom has more ability to coordinate with the metal catalyst than other nitrogen atoms, and thus we must achieve robust control of positional selectivity in the experiment. Then, we envisioned that dialkylamino groups with the outspread carbon chain at the C-6 position could always shield the N^1 atoms, and thus possibly prevent catalyst poisoning.[21] With this hypothesis in mind, 9-phenyl-6-dipropylamino-8-azapurine (**1a**) was chosen as the substrate to react with methanol in the presence of palladium catalyst. To our delight, the desired product was obtained in an excellent yield up to 92% (Table 1, entry 4) by using 4 equiv of $PhI(OAc)_2$ as oxidant; however, other oxidants, i.e., K_2S_2O8, AgOAc, and DTBP, gave low yields (Table 1, entries 1−3, 5, and 6). Furthermore, other palladium catalysts, such as $PdCl_2$, $Pd(PPh_3)_2Cl_2$, and $Ph(PPh_3)_4$, were explored, and the results showed that they were less effective to the reaction than $Pd(OAc)_2$ (Table 1, entries 7−9). Therefore, $Pd(OAc)_2$ and $PhI(OAc)_2$ were chosen as catalyst and oxidant, respectively. Moreover, the yield reduced dramatically when mixed solvents were tested, which revealed that a low concentration of alcohol was unfavorable for the reaction (Table 1, entries 10 and 11). After extensive screening of different parameters (Table 1, entries 12−17), we finally found the best yield of **2a** was obtained by employing 3.5 equiv of $PhI(OAc)_2$ and 5 mol % equiv of $Pd(OAc)_2$ in MeOH at 60 °C for 12 h (Table 1, entry 17). It is noted that no dimethoxylated product (**2a′**) was observed under the reaction conditions.

With the optimal conditions in hand, the alkoxylation reaction was next extended to other 9-aryl-6-dipropylamino-8-azapurines, as shown in Table 2. Using methanol as the coupling partner, a series of ortho-monomethoxylation products were obtained in moderate to good yields, and none of the dimethoxylated products was observed (**2b−2j**). The results also indicated that substrates with electron-donating groups (Me, OMe) gave higher yields than those with electron-withdrawing groups (F, Cl). It is interesting that the methoxylation selectively took place on the side with smaller steric hindrance for substrates with a meta-substituent on the phenyl rings (**2f−2i**). Another interesting result is that the methoxylation of 9-(naphthalen-2-yl)-6-dipropylamino-8-aza-purine occurred on the 3′-position instead of the 1′-position (**2j**). It was not surprising that no methoxylated product (**2k**) was formed when the substrate (**1k**) with *ortho*-Me in the phenyl ring was applied to the reaction possibly because *ortho*-Me hindered the formation of the palladium-mediated intermediate, and the similar "ortho-substituent" effect also occurred in other C−H functionalizations.[7b,22]

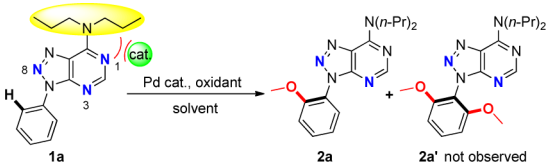
Subsequently, we turned our attention to the effect of other substrates with various substituents at different positions (C-6, C-8, and C-2) in purine moieties (Table 3). To further evaluate the effect of the steric hindrance of dialkylamino groups at the C-6 position, the substrates with various dialkylamino groups, i.e., $N(n\text{-}Bu)_2$, $N(Et)_2$, $N(Me)_2$, $N(Boc)_2$, N(Boc)Me, and piperidin-1-yl, at the C-6 position were applied to the reaction, and we found that most of the reactions proceeded successfully (**2l−2o**), except for **2m′** and **2n′**. Despite only one directing N^3 atom, the reactions of N^9-aryl-6-dipropylaminopurines with various meta- or para-substituents (i.e., Cl, MeO, and Me) on the benzene ring also afforded desired products in moderate yields (**2p−2u**). It is interesting that, when 9-phenyl-6-dipropylaminopurine (**1p**) was used, the first dimethoxylated product (**2p′**) was isolated in a yield of 16% besides monomethoxylated product (**2p**). Furthermore, this alkoxylation reaction also worked well for C-8-Me substituted purines (**2t**, **2u**). However, substrates **2v** or **2v′** with C-2-Me substituted failed to react with methanol under the standard conditions possibly because the 2-Me group sterically blocks the formation of the Pd-intermediate. Intriguingly, some other primary alcohols and a secondary alcohol (i.e., ethanol, propanol, isopropanol) were also employed as the alkoxylation reagents (Table 3). Although the desired ortho-alkoxylation products (**3b−3h**) were isolated successfully, the yields decreased significantly presumably due to the steric hindrance. Furthermore, after replacement of alcohols with $KOSiMe_3$ (OH equivalent), no desired product (**3h′**) was formed and all the raw material was recovered. Notably, only trace ethoxylated product (**3a**) was detected and most of the substrate was recovered, but the exact reason is still unclear.

To test the scalability of the current method, the methoxylation of substrate **1a** (5 mmol, 1.48 g) was carried out on a gram scale, and the product **2a** was isolated in 86% yield (Scheme 3), which was comparable to the yield in Table 1, entry 17 (74 mg scale).

To obtain insights into the role that nitrogen atoms played in this alkoxylation process, we carried out the theory calculation and controlled experiments (Scheme 4). The electron density differences among the nitrogen atoms were obtained by natural bond order (NBO) analysis, which was performed by the

DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435−3442

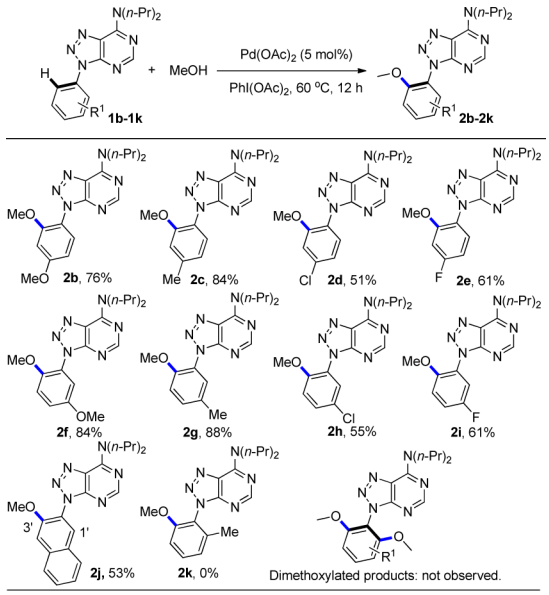
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidant (equiv)	temp. (°C)	time (h)	**2a**, yield (%)[b]
1	$Pd(OAc)_2$	$K_2S_2O_8$ (2)	80	24	trace[c]
2	$Pd(OAc)_2$	AgOAc (2)	80	24	0[c]
3	$Pd(OAc)_2$	$Cu(OAc)_2$ (2)	80	24	0[c]
4	$Pd(OAc)_2$	$PhI(OAc)_2$ (4)	80	24	92
5	$Pd(OAc)_2$	THBP (3)	80	24	trace[c]
6	$Pd(OAc)_2$	DTBP (3)	80	24	0[c]
7	$PdCl_2$	$PhI(OAc)_2$ (4)	80	24	87
8	$Pd(PPh_3)_2Cl_2$	$PhI(OAc)_2$ (4)	80	24	80
9	$Pd(PPh_3)_4$	$PhI(OAc)_2$ (4)	80	24	74
10	$Pd(OAc)_2$	$PhI(OAc)_2$ (4)	80	24	trace[c,d]
11	$Pd(OAc)_2$	$PhI(OAc)_2$ (4)	80	24	27[e]
12	$Pd(OAc)_2$	$PhI(OAc)_2$ (4)	80	12	90
13	$Pd(OAc)_2$	$PhI(OAc)_2$ (4)	60	12	95
14	$Pd(OAc)_2$	$PhI(OAc)_2$ (3.5)	60	12	95
15	$Pd(OAc)_2$	$PhI(OAc)_2$ (3.0)	60	12	91
16	$Pd(OAc)_2$	$PhI(OAc)_2$ (2.0)	60	12	45
17[f]	$Pd(OAc)_2$	$PhI(OAc)_2$ (3.5)	60	12	94 (87)[g]

[a]Unless otherwise mentioned, all of the reactions were carried out with **1a** (0.25 mmol), methanol (2 mL), catalyst (10 mol %), and oxidant in a sealed tube under an air atmosphere. DTBP, di-*tert*-butyl peroxide; THBP, *tert*-butyl hydroperoxide (70% solution in water). [b]Yield was determined by ^{1}H NMR with 4-nitro-2,6-dichloropyrimidine as internal standard. [c]Yield was estimated by TLC. [d]Mixed solvent MeOH/dioxane (v/v 1:3, 2 mL) was used. [e]Mixed solvent MeOH/CH_3CN (v/v 1:3, 2 mL) was used. [f]$Pd(OAc)_2$ (5 mol %) was used. [g]Isolated yield.

Table 2. Ortho-Methoxylation of 9-Aryl-6-dipropylamino-8-azapurines[a,b]



[a]Unless otherwise mentioned, all of the reactions were carried out with 9-aryl-6-dipropylamino-8-azapurine (0.5 mmol), methanol (4 mL), $Pd(OAc)_2$ (5 mol %), and $PhI(OAc)_2$ (1.75 mmol) at 60 °C for 12 h in a sealed tube under an air atmosphere. [b]Isolated yield.

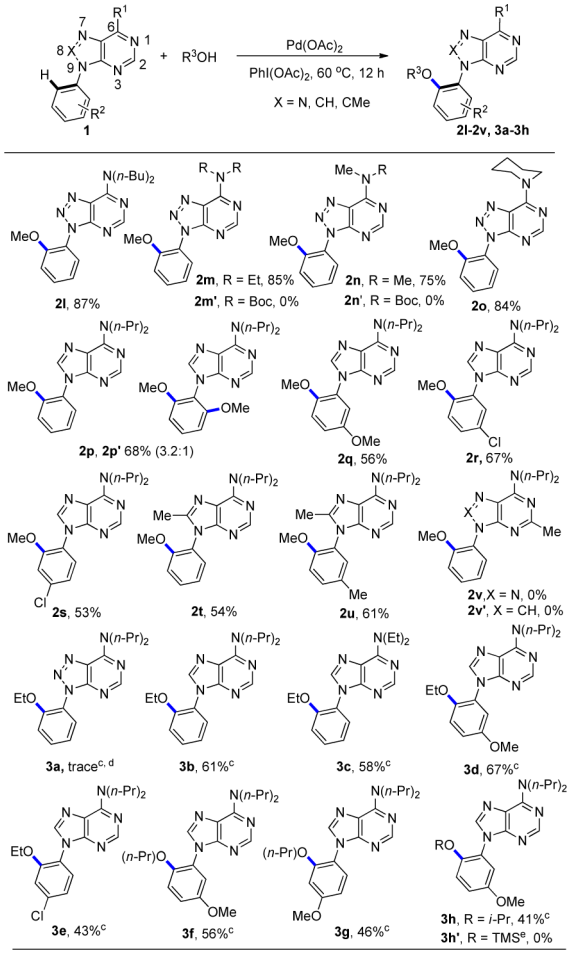
B3LYP density functional method with the basis set 6-311++G (d,p). The calculations show that N^1 and N^3 atoms carry more electron densities than N^7, N^8, N^9, and C^6-N atoms (Scheme 4, A). Thus, we postulate that the interactions of the metal with N^1 and N^3 atoms are greater than those with N^7, N^8, N^9, and C^6-N atoms, and the N^1−metal interactions most likely lead to the catalyst poisoning in our reaction. In principle, all the nitrogen atoms can interact with the metal center, so it is very essential to figure out which atoms (N^3, N^8) are the real directing atoms. Then, the controlled experiments were carried out (Scheme 4, B and C). To our surprise, even for the substrates (**1p**, **1t**) without an N^8 atom, the reactions also could proceed well, which indicated that the N^8 atom was not the essential directing atom (Scheme 4, B). Further, no desired product was isolated when substrate (**1w**) with lacking the N^3 atom was applied to the reaction (Scheme 4, C). This important phenomenon indicated that the sole directing atom was the N^3 atom, but not the N^8 atom.

On the basis of the literatures[23] and our experimental results, a plausible mechanism involving the purinyl N^3 atoms is outlined in Scheme 5. First, the reaction may involve the formation of a C−Pd bond to generate the N^3-Pd(II) intermediate **A**. Then, the oxidation of intermediate **A** will form Pd(IV) intermediate **B**. Finally, the formation of the C−O bond affords the alkoxylated product and regenerates the catalyst via reductive elimination.

In conclusion, we have developed a palladium-catalyzed high regioselective alkoxylation of N^9-arylpurines at the aromatic ring, in which $PhI(OAc)_2$ and alcohols are employed as the oxidant and the alkoxylation reagents, respectively. Notably, this reaction is a rare C−H activation reaction of polynitrogenated purines using N^3 atoms of purine itself as the directing groups. The reaction is available for both primary and secondary alcohols, though the yields were not good enough for some alcohols and substrates. We discovered that the C^6-dialkylamino groups succeed to avoid catalyst poisoning by sterically blocking purinyl N^1 atoms to coordinate with the

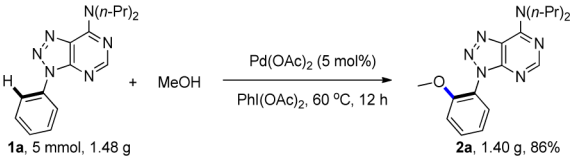
DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435−3442

Table 3. Ortho-Alkoxylation of 9-Arylpurines with Alcohols[a,b]



[a]Unless otherwise mentioned, all of the reactions were carried out with 9-aryl-6-dialkoxylaminopurine (0.5 mmol), alcohol (4 mL), $Pd(OAc)_2$ (5 mol %), and $PhI(OAc)_2$ (1.75 mmol) at 60 °C for 12 h in a sealed tube under an air atmosphere. [b]Isolated yield. [c]10 mol % $Pd(OAc)_2$ and 10 equiv of AcOH were added. The reaction was carried out at 45 °C for 12 h. [d]**3a** was detected by LC-MS. [e]TMS = trimethylsilyl.

Scheme 3. Gram-Scale Synthesis of Product (2a)

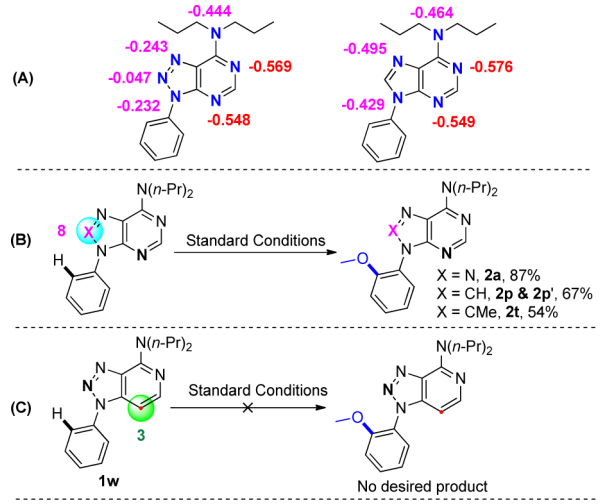


catalyst. Additionally, this strategy provides an alternative and late-stage approach to synthesize N^9-(*ortho*-alkoxyl)arylpurines in medicinal and synthetic chemistry.

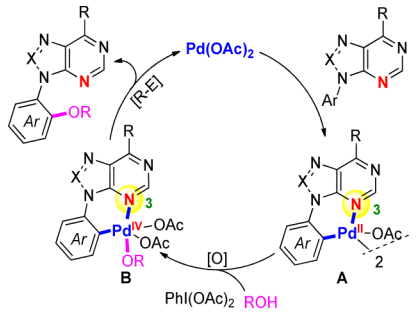
EXPERIMENTAL SECTION

General Information. Commercially available reagents were used without further purification. Melting points were determined on a hot-stage melting point apparatus (uncorrected). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard, and the chemical shifts (δ) are reported in parts per million (ppm). The obtained signal multiplicities were distinguished with the common abbreviations s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), br s (broad singlet), quint (quintet), sex (sextet), and m (multiplet). IR spectra were recorded on an FT-IR instrument. HRMS measurements were carried out on an LC/MSD QTOF mass spectrometer.

Scheme 4. NBO Analyzed Natural Charges and Controlled Experiments



Scheme 5. Plausible Reaction Mechanism



All the substrates were prepared according to the method in previous reports.[24]

General Procedure for the Palladium-Catalyzed Purine-Directed C–H Alkoxylation of N^9-Arylpurines. Under an ambient atmosphere, a mixture of purine **1**(0.5 mmol), $Pd(OAc)_2$(0.025 mmol, 0.05 equiv), $PhI(OAc)_2$ (1.75 mmol, 3.5 equiv), and alcohol (4 mL) was stirred at 60 °C for 12 h in a seal tube. After the reaction was completed, the mixture was evaporated in vacuo. The residue was purified by flash column chromatography on a silica gel using petroleum ether/EtOAc (10:1 to 3:1) as the eluent to give the desired products **2**.

*9-(2-Methoxylphenyl)-6-dipropylamino-8-azapurine (**2a**).* Yield 140 mg, 87%; white solid, mp 84–85 °C; R_f = 0.24 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.52–7.48 (m, 1H), 7.44–7.42 (m, 1H), 7.13–7.10 (m, 2H), 4.23 (t, J = 7.6 Hz, 2H), 3.78 (s, 3H), 3.75 (t, J = 7.6 Hz, 2H), 1.84 (sext, J = 7.6 Hz, 2H), 1.76 (sext, J = 7.6 Hz, 2H), 1.05 (t, J = 7.6 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 154.7, 154.5, 151.0, 131.5, 128.5, 124.6, 123.8, 120.9, 112.6, 56.1, 52.0, 50.1, 21.7, 20.6, 11.4, 11.1. FTIR (film, cm^{-1}): 3014, 2935, 2875, 2841, 1597, 1559, 1507, 1469, 1335, 1282, 1069, 1046, 755, 696. ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{23}N_6O$ m/z 327.1928, found 327.1933.

*9-(2,4-Dimethoxylphenyl)-6-dipropylamino-8-azapurine (**2b**).* Yield 135 mg, 76%; oil; R_f = 0.14 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 6.65–6.62 (m, 2H), 4.24 (t, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.77–3.74 (m, 5H), 1.85 (sext, J = 7.6 Hz, 2H), 1.75 (sext, J = 7.6 Hz, 2H), 1.06 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 156.6, 155.8, 154.5, 151.2, 129.2, 124.6, 116.9, 104.8, 99.9,

DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435–3442

56.0, 55.7, 52.0, 50.1, 21.7, 20.6, 11.4, 11.1. FTIR (film, cm^{-1}): 3023, 2963, 2932, 2874, 1596, 1559, 1524, 1323, 1211, 1163, 1071, 835. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{25}N_6O_2$ m/z 357.2034, found 357.2032.

9-(2-Methoxyl-4-methylphenyl)-6-dipropylamino-8-azapurine ***(2c)***. Yield 143 mg, 84%; oil; R_f = 0.25 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.94−6.92 (m, 2H), 4.24 (t, J = 8.0 Hz, 2H), 3.77 (s, 3H), 3.76 (t, J = 8.0 Hz, 2H), 2.45 (s, 3H), 1.85 (sext, J = 8.0 Hz, 2H), 1.77 (sext, J = 8.0 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 154.5, 154.4, 151.1, 142.1, 128.1, 124.6, 121.5, 121.2, 113.4, 56.0, 52.0, 50.1, 21.9, 21.7, 20.6, 11.4, 11.1. FTIR (film, cm^{-1}): 3026, 2963, 2930, 2874, 1596, 1558, 1511, 1465, 1379, 1326, 1069. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{25}N_6O$ m/z 341.2084, found 341.2087.

9-(4-Chloro-2-methoxylphenyl)-6-dipropylamino-8-azapurine ***(2d)***. Yield 93 mg, 51%; white solid, mp 93−94 °C; R_f = 0.37 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.13−7.12 (m, 2H), 4.23 (t, J = 7.6 Hz, 2H), 3.80 (s, 3H), 3.76 (t, J = 7.6 Hz, 2H), 1.85 (sext, J = 7.6 Hz, 2H), 1.77 (sext, J = 7.6 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 155.2, 154.4, 151.0, 137.2, 129.2, 124.5, 122.4, 121.0, 113.4, 56.3, 52.0, 50.1, 21.6, 20.6, 11.4, 11.1. FTIR (film, cm^{-1}): 3054, 2962, 2929, 2874, 1597, 1559, 1505, 1326, 1066, 871, 796. ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{22}ClN_6O$ m/z 361.1538, found 361.1540.

9-(4-Fluoro-2-methoxylphenyl)-6-dipropylamino-8-azapurine ***(2e)***. Yield 105 mg, 61%; white solid, mp 92−93 °C; R_f = 0.31 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.43−7.39 (m, 1H), 6.86−6.82 (m, 2H), 4.23 (t, J = 7.6 Hz, 2H), 3.79 (s, 3H), 3.76 (t, J = 7.6 Hz, 2H), 1.86 (sext, J = 7.6 Hz, 2H), 1.77 (sext, J = 7.6 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5 (d, $^1J_{C\text{-}F}$ = 248.5 Hz), 156.7, 156.1 (d, $^3J_{C\text{-}F}$ = 10.7 Hz), 154.5, 151.1, 129.7 (d, $^3J_{C\text{-}F}$ = 10.9 Hz), 124.5, 119.9 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 107.6 (d, $^2J_{C\text{-}F}$ = 23.1 Hz), 100.9 (d, $^2J_{C\text{-}F}$ = 26.9 Hz), 56.3, 52.0, 50.1, 21.7, 20.6, 11.4, 11.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −106.87. FTIR (film, cm^{-1}): 3020, 2963, 2931, 2875, 1596, 1560, 1522, 1466, 1327, 1303, 1155, 1068, 1030, 837; ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{22}FN_6O$ m/z 345.1834, found 345.1831.

9-(2,5-Dimethoxylphenyl)-6-dipropylamino-8-azapurine ***(2f)***. Yield 149 mg, 84%; oil; R_f = 0.14 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.07−7.06 (m, 2H), 7.01 (t, J = 2.0 Hz, 1H), 4.24 (t, J = 8.0 Hz, 2H), 3.80−3.74 (m, 8H), 1.86 (sext, J = 7.6 Hz, 2H), 1.77 (sext, J = 7.6 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 154.5, 153.7, 151.0, 148.8, 124.6, 124.1, 117.1, 114.0, 113.8, 56.8, 55.9, 52.0, 50.1, 21.7, 20.6, 11.4, 11.1. FTIR (film, cm^{-1}): 3011, 2962, 2931, 2874, 2833, 1596, 1559, 1512, 1438, 1379, 1253, 1220, 1069, 866, 747. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{25}N_6O_2$ m/z 357.2034, found 357.2035.

9-(2-Methoxyl-5-methylphenyl)-6-dipropylamino-8-azapurine ***(2g)***. Yield 150 mg, 88%; oil; R_f = 0.23 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.24 (t, J = 7.6 Hz, 2H), 3.78−3.74 (m, 5H), 2.36 (s, 3H), 1.86 (sext, J = 7.6 Hz, 2H), 1.77 (sext, J = 7.6 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 154.5, 152.6, 151.0, 132.0, 130.5, 128.9, 124.6, 123.4, 112.6, 56.2, 52.0, 50.1, 21.7, 20.6, 20.4, 11.4, 11.1. FTIR (film, cm^{-1}): 3032, 2962, 2929, 2873, 1596, 1558, 1516, 1465, 1333, 1281, 1070, 810, 748. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{25}N_6O$ m/z 341.2084, found 341.2089.

9-(5-Chloro-2-methoxylphenyl)-6-dipropylamino-8-azapurine ***(2h)***. Yield 99 mg, 55%; white solid, mp 89−90 °C; R_f = 0.20 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.50−7.46 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 4.23 (t, J = 7.6 Hz, 2H), 3.80 (s, 3H), 3.76 (t, J = 7.6 Hz, 2H), 1.85 (sext, J = 7.6 Hz, 2H), 1.77 (sext, J = 7.6 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 154.5, 153.4, 151.0, 131.3, 128.5, 125.6, 124.5, 113.7, 56.4, 52.0, 50.1, 21.6, 20.6, 11.4, 11.1. FTIR (film, cm^{-1}): 3062, 3011, 2963, 2930, 2874, 1597, 1558, 1504, 1463, 1380, 1333, 1065, 796. ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{22}ClN_6O$ m/z 361.1538, found 361.1539.

9-(5-Fluoro-2-methoxylphenyl)-6-dipropylamino-8-azapurine ***(2i)***. Yield 105 mg, 61%; white solid, mp 108−110 °C; R_f = 0.23 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.27−7.22 (m, 2H), 7.10−7.06 (m, 1H), 4.23 (t, J = 7.6 Hz, 2H), 3.79 (s, 3H), 3.76 (t, J = 7.6 Hz, 2H), 1.86 (sext, J = 7.6 Hz, 2H), 1.76 (sext, J = 7.6 Hz, 2H), 1.07 (t, J = 7.6 Hz, 3H), 1.00 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 156.3 (d, $^1J_{C\text{-}F}$ = 240.2 Hz), 154.5, 151.1(d, $^4J_{C\text{-}F}$ = 2.6 Hz), 151.0, 124.5, 124.1 (d, $^3J_{C\text{-}F}$ = 10.1 Hz), 117.8 (d, $^2J_{C\text{-}F}$ = 22.5 Hz), 115.8 (d, $^2J_{C\text{-}F}$ = 25.2 Hz), 113.6 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 56.7, 52.0, 50.2, 21.7, 20.6, 11.4, 11.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ −122.08. FTIR (film, cm^{-1}): 3041, 2963, 2932, 2875, 1596, 1560, 1510, 1334, 1266, 1067, 875, 749. ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{22}FN_6O$ m/z 345.1834, found 345.1835.

9-(3-Methoxynaphthalen-2-yl)-6-dipropylamino-8-azapurine ***(2j)***. Yield 100 mg, 53%; white solid, mp 129−130 °C; R_f = 0.28 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.96 (s, 1H), 7.83−7.80 (m, 2H), 7.54−7.50 (m, 1H), 7.42−7.38 (m, 1H), 7.39 (s, 1H), 4.26 (t, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.77 (t, J = 7.6 Hz, 2H), 1.87 (sext, J = 7.6 Hz, 2H), 1.78 (sext, J = 7.6 Hz, 2H), 1.08 (t, J = 7.6 Hz, 3H), 1.01 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 154.5, 152.4, 151.4, 135.1, 128.3, 128.2, 128.0, 127.9, 126.7, 124. 69, 124.67, 124.6, 107.7, 56.1, 52.0, 50.1, 21.7, 20.6, 11.4, 11.1; FTIR (film, cm^{-1}): 3059, 2962, 2928, 2873, 1596, 1558, 1488, 1466, 1331, 1252, 1067, 748. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{25}N_6O$ m/z 377.2084, found 377.2083.

6-Dibutylamino-9-(2-methoxylphenyl)-8-azapurine ***(2l)***. Yield 154 mg, 87%; oil; R_f = 0.27 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.54−7.49 (m, 1H), 7.46−7.43 (m, 1H), 7.15−7.11 (m, 2H), 4.28 (t, J = 7.6 Hz, 2H), 3.82−3.78 (m, 5H), 1.81 (quint, J = 7.6 Hz, 2H), 1.73 (quint, J = 7.6 Hz, 2H), 1.51 (sext, J = 7.6 Hz, 2H), 1.41 (sext, J = 7.6 Hz, 2H), 1.00 (q, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 154.7, 154.4, 151.0, 131.5, 128.5, 124.6, 123.8, 120.9, 112.6, 56.1, 50.2, 48.1, 30.5, 29.5, 20.3, 20.1, 14.0. FTIR (film, cm^{-1}): 3011, 2958, 2932, 2872, 1597, 1559, 1507, 1468, 1325, 1281, 1146, 1069, 754. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{27}N_6O$ m/z 355.2241, found 355.2246.

6-Diethylamino-9-(2-methoxylphenyl)-8-azapurine ***(2m)***. Yield 126 mg, 85%; white solid, mp 125−127 °C; R_f = 0.14 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.55−7.50 (m, 1H), 7.46−7.43 (m, 1H), 7.16−7.12 (m, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.86 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 1.44 (t, J = 6.8 Hz, 3H), 1.33 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 154.7, 154.0, 151.0, 131.6, 128.5, 124.5, 123.8, 120.9, 112.7, 56.1, 44.7, 42.7, 13.7, 12.6. FTIR (film, cm^{-1}): 3041, 2973, 2932, 2868, 2836, 1598, 1560, 1506, 1324, 1278, 1069, 755. ESI-HRMS $[M + H]^+$ calcd for $C_{15}H_{19}N_6O$ m/z 299.1615, found 299.1617.

9-(2-Methoxylphenyl)-6-dimethylamino-8-azapurine ***(2n)***. Yield 101 mg, 75%; white solid, mp 131−133 °C; R_f = 0.33 (PE/EA = 1:1, v/v). ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.55−7.51 (m, 1H), 7.46−7.44 (m, 1H), 7.16−7.12 (m, 2H), 3.94 (s, 3H, OCH_3), 3.79 (s, 3H, NCH_3), 3.41 (s, 3H, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 155.0, 154.6, 151.0, 131.6, 128.5, 125.1, 123.6, 120.9, 112.6, 56.0, 40.1, 37.6. FTIR (film, cm^{-1}): 3014, 2932, 2833, 1608, 1564, 1508, 1471, 1428, 1334, 1257, 1068, 756, 690. ESI-HRMS $[M + H]^+$ calcd for $C_{13}H_{15}N_6O$ m/z 271.1302, found 271.1301.

9-(2-Methoxylphenyl)-6-(piperidin-1-yl)-8-azapurine ***(2o)***. Yield 130 mg, 84%; white solid, mp 132−135 °C; R_f = 0.11 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.54−7.50 (m, 1H), 7.45−7.43 (m, 1H), 7.15−7.12 (m, 2H), 4.68 (br s, 2H), 4.07 (br s, 2H), 3.79 (s, 3H), 1.81 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 154.8, 153.8, 151.3, 131.7, 128.6, 124.8, 123.8, 121.0, 112.7, 56.1, 48.7, 45.1, 26.5, 26.0, 24.7. FTIR (film, cm^{-1}): 3015, 2933, 2854, 1596, 1559, 1505, 1332, 1274, 1022, 755. ESI-HRMS $[M + H]^+$ calcd for $C_{16}H_{19}N_6O$ m/z 311.1615, found 311.1618.

9-(2-Methoxylphenyl)-6-dipropylaminopurine ***(2p)***. Yield 85 mg, 52%; white solid, mp 124−126 °C; R_f = 0.18 (PE/EA = 3:1, v/v). ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.91 (s, 1H), 7.53−7.51 (m, 1H), 7.44−7.40 (m, 1H), 7.14−7.08 (m, 2H), 3.94 (br s, 4H), 3.81 (s,

DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435−3442

3H), 1.77 (sext, J = 7.2 Hz, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.8, 153.0, 151.2, 139.3, 129.9, 128.0, 123.4, 121.1, 119.2, 112.3, 55.8, 50.5, 21.5, 11.3. FTIR (film, cm^{-1}): 3029, 2962, 2930, 2873, 1583, 1557, 1522, 1503, 1464, 1337, 1265, 1079, 751. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{24}N_5O$ m/z 326.1975, found 326.1978.

*9-(2,6-Dimethoxylphenyl)-6-dipropylaminopurine (**2p'**).* Yield 28 mg, 16%; white solid, mp 140−141 °C; R_f = 0.35 (PE/EA = 1:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.66 (s, 1H), 7.38 (t, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 2H), 3.91 (br s, 4H), 3.73 (s, 6H), 1.78 (sext, J = 7.2 Hz, 4H), 1.00 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 154.4, 152.8, 151.6, 139.7, 130.6, 119.1, 111.9, 104.6, 56.1, 50.5, 21.5, 11.4. FTIR (film, cm^{-1}): 3068, 2962, 2933, 2873, 2842, 1585, 1528, 1503, 1481, 1380, 1259, 1113, 781, 751. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{26}N_5O_2$ m/z 356.2081, found 356.2083.

*9-(2,5-Dimethoxylphenyl)-6-dipropylaminopurine (**2q**).* Yield 99 mg, 56%; white solid, mp 122 °C; R_f = 0.15 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.91 (s, 1H), 7.12 (d, J = 2.8 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.95 (dd, J = 2.8, 9.2 Hz, 1H), 3.93 (br s, 4H), 3.80 (s, 3H), 3.75 (s, 3H), 1.77 (sext, J = 7.2 Hz, 4H), 1.00 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.8, 153.0, 151.1, 148.0, 139.2, 123.9, 119.2, 114.9, 113.8, 113.6, 56.5, 55.9, 50.5, 21.5, 11.4. FTIR (film, cm^{-1}): 3018, 2962, 2931, 2872, 2836, 1584, 1557, 1509, 1479, 1381, 1223, 1044, 791. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{26}N_5O_2$ m/z 356.2081, found 356.2083.

*9-(5-Chloro-2-methoxylphenyl)-6-dipropylaminopurine (**2r**).* Yield 120 mg, 67%; white solid, mp 64−66 °C; R_f = 0.26 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.88 (s, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 2.4, 8.8 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 3.93 (br s, 4H), 3.80 (s, 3H), 1.76 (sext, J = 7.2 Hz, 4H), 1.00 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 153.1, 152.6, 151.0, 138.8, 129.6, 128.0, 125.8, 124.3, 119.0, 113.4, 56.2, 50.5, 21.4, 11.3. FTIR (film, cm^{-1}): 3029, 2961, 2929, 2872, 1582, 1556, 1502, 1379, 1291, 1077, 820. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{23}ClN_5O$ m/z 360.1586, found 360.1589.

*9-(4-Chloro-2-methoxylphenyl)-6-dipropylaminopurine (**2s**).* Yield 95 mg, 53%; white solid, mp 184−186 °C; R_f = 0.42 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.87 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 3.99 (br s, 4H), 3.81 (s, 3H), 1.76 (sext, J = 7.2 Hz, 4H), 1.00 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 154.3, 153.0, 151.1, 138.9, 135.3, 128.8, 122.1, 121.2, 119.1, 113.1, 56.2, 50.5, 21.4, 11.3. FTIR (film, cm^{-1}): 3014, 2961, 2922, 2867, 1598, 1557, 1504, 1462, 1379, 1252, 1022, 830, 645. ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{23}ClN_5O$ m/z 360.1586, found 360.1589.

*8-Methyl-9-(2-methoxylphenyl)-6-dipropylaminopurine (**2t**).* Yield 92 mg, 54%; oil; R_f = 0.11 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.48−7.43 (m, 1H), 7.29−7.27 (m, 1H), 7.13−7.07 (m, 2H), 3.99 (br s, 2H), 3.87 (br s, 2H), 3.75 (s, 3H), 2.32 (s, 3H), 1.75 (sext, J = 7.2 Hz, 4H), 0.99 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 153.6, 152.9, 152.2, 147.6, 130.7, 129.5, 123.3, 121.2, 118.7, 112.4, 55.7, 50.2, 21.5, 14.1, 11.3. FTIR (film, cm^{-1}): 3038, 2962, 2931, 2873, 1587, 1562, 1464, 1373, 1296, 1047, 752. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{26}N_5O$ m/z 340.2132, found 340.2134.

*8-Methyl-9-(2-methoxyl-5-methylphenyl)-6-dipropylaminopurine (**2u**).* Yield 108 mg, 61%; oil; R_f = 0.15 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.24 (dd, J = 2.0, 8.4 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 3.99 (br s, 2H), 3.87 (br s, 2H), 3.70 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 1.75 (sext, J = 7.2 Hz, 4H), 0.98 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 152.9, 152.8, 152.2, 147.6, 131.1, 130.7, 129.9, 122.9, 118.7, 112.3, 55.8, 50.2, 21.5, 20.4, 14.1, 11.3. FTIR (film, cm^{-1}): 3032, 2961, 2931, 2872, 1587, 1562, 1514, 1461, 1375, 1257, 1092, 809, 744. ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{28}N_5O$ m/z 354.2288, found 354.2291.

Under an ambient atmosphere, a mixture of purine **1** (0.3 mmol), $Pd(OAc)_2$(0.03 mmol, 0.1 equiv), $PhI(OAc)_2$ (1.05 mmol, 3.5 equiv), and alcohol (1.5 mL) was stirred at room temperature for 1 h in a seal tube. Then, the temperature was slowly ramped to 45 °C over 2 h for another 12 h. Then, the mixture was evaporated in vacuo. The residue was purified by flash column chromatography on a silica gel using petroleum ether/EtOAc (10:1 to 3:1) as the eluent to give the desired products **3**.

*9-(2-Ethoxylphenyl)-6-dipropylaminopurine (**3b**).* Yield 62 mg, 61%; oil; R_f = 0.30 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.96 (s, 1H), 7.55 (dd, J = 1.6, 8.0 Hz, 1H), 7.40−7.36 (m, 1H), 7.12−7.06 (m, 2H), 4.06 (q, J = 7.2 Hz, 2H), 3.95 (br s, 4H), 1.77 (sext, J = 7.2 Hz, 4H), 1.29 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.0, 152.9, 151.1, 139.4, 129.6, 127.8, 123.6, 121.0, 119.1, 113.4, 64.4, 50.4, 21.4, 14.6, 11.3. FTIR (film, cm^{-1}): 3029, 2961, 2926, 2873, 1583, 1557, 1503, 1458, 1264, 1078, 750. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{26}N_5O$ m/z 340.2132, found 340.2134.

*6-Diethylamino-9-(2-ethoxylphenyl)purine (**3c**).* Yield 54 mg, 58%; white solid, mp 102−104 °C; R_f = 0.21 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.99 (s, 1H), 7.56 (dd, J = 1.6, 7.6 Hz, 1H), 7.41−7.36 (m, 1H), 7.13−7.07 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 4.06 (br s, 4H), 1.34 (t, J = 7.2 Hz, 6H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 153.0, 152.9, 151.1, 139.6, 129.7, 127.8, 123.6, 121.0, 119.1, 113.4, 64.5, 43.1, 14.6, 13.6. FTIR (film, cm^{-1}): 3032, 2976, 2929, 1585, 1558, 1503, 1459, 1284, 1081, 964, 838, 752. ESI-HRMS $[M + H]^+$ calcd for $C_{17}H_{22}N_5O$ m/z 312.1819, found 312.1820.

*9-(2-Ethoxyl-5-methoxylphenyl)-6-dipropylaminopurine (**3d**).* Yield 74 mg, 67%; oil; R_f = 0.24 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.97 (s, 1H), 7.15 (d, J = 3.2 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 6.91 (dd, J = 3.2, 9.0 Hz, 1H), 3.98 (q, J = 7.2 Hz, 2H), 3.96 (br s, 4H), 3.80 (s, 3H), 1.77 (sext, J = 7.2 Hz, 4H), 1.24 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 153.7, 152.9, 151.0, 147.0, 139.3, 124.4, 119.1, 115.1, 114.7, 113.5, 65.4, 55.8, 50.4, 21.4, 14.7, 11.3. FTIR (film, cm^{-1}): 3029, 2962, 2933, 2873, 1584, 1557, 1480, 1293, 1223, 1044, 850, 791. ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{28}N_5O_2$ m/z 370.2238, found 370.2235.

*9-(4-Chloro-2-ethoxylphenyl)-6-dipropylaminopurine (**3e**).* Yield 48 mg, 43%; white solid, mp 120−122 °C; R_f = 0.51 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.92 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.09 (dd, J = 2.0, 8.4 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 4.06 (q, J = 6.8 Hz, 2H), 3.94 (br s, 4H), 1.77 (sext, J = 7.2 Hz, 4H), 1.31 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.5, 153.0, 151.0, 138.9, 135.0, 128.6, 122.2, 121.2, 119.1, 113.9, 64.9, 50.5, 21.5, 14.5, 11.3. FTIR (film, cm^{-1}): 3041, 2963, 2930, 2873, 1584, 1502, 1464, 1382, 1267, 1077, 980. ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{25}ClN_5O$ m/z 374.1742, found 374.1745.

*9-(5-Methoxyl-2-propoxylphenyl)-6-dipropylaminopurine (**3f**).* Yield 64 mg, 56%; oil; R_f = 0.30 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.95 (s, 1H), 7.14 (d, J = 3.2 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 6.92 (dd, J = 3.2, 9.0 Hz, 1H), 3.98 (s, 4H), 3.86 (t, J = 6.8 Hz, 2H), 3.80 (s, 3H), 1.77 (sext, J = 7.2 Hz, 4H), 1.61 (sext, J = 6.8 Hz, 2H), 1.00 (t, J = 7.2 Hz, 6H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.7, 152.9, 151.1, 147.3, 139.3, 124.4, 119.1, 115.0, 114.8, 113.5, 71.3, 55.8, 50.4, 22.5, 21.4, 11.3, 10.4. FTIR (film, cm^{-1}): 3029, 2963, 2933, 2874, 1584, 1557, 1508, 1464, 1381, 1222, 1041, 865, 803. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{30}N_5O_2$ m/z 384.2394, found 384.2396.

*9-(4-Methoxyl-2-propoxylphenyl)-6-dipropylaminopurine (**3g**).* Yield 53 mg, 46%; oil; R_f = 0.22 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.86 (s, 1H), 7.41 (d, J = 9.2 Hz, 1H), 6.63−6.60 (m, 2H), 3.94 (br s, 4H), 3.91 (t, J = 6.8 Hz, 2H), 3.85 (s, 3H), 1.78 (sext, J = 7.2 Hz, 4H), 1.65 (sext, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 6H), 0.84 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 154.5, 152.9, 151.4, 139.6, 128.5, 125.1, 116.8, 104.7, 100.7, 70.3, 55.7, 50.3, 22.3, 21.4, 11.3, 10.4. FTIR (film, cm^{-1}): 3035, 2963, 2932, 2874, 1584, 1558, 1510, 1463, 1379, 1203, 1080, 978, 792. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{30}N_5O_2$ m/z 384.2394, found 384.2393.

DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435−3442

*9-(5-Methoxyl-2-i-propoxylphenyl)-6-dipropylaminopurine (**3h**).* Yield 43 mg, 41%; oil; R_f = 0.32 (PE/EA = 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.98 (s, 1H), 7.16 (d, J = 2.8 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 6.91 (dd, J = 2.8, 9.2 Hz, 1H), 4.25 (hept, J = 6.0 Hz, 1H), 3.98 (br s, 4H), 3.80 (s, 3H), 1.76 (sext, J = 7.2 Hz, 2H), 1.14 (d, J = 6.0 Hz, 6H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 154.1, 152.9, 150.9, 145.9, 139.5, 125.9, 119.1, 118.2, 114.9, 133.2, 73.1, 55.8, 50.4, 22.0, 21.5, 11.3. FTIR (film, cm^{-1}): 3035, 2964, 2932, 2873, 1584, 1557, 1505, 1464, 1293, 1222, 1039, 843. ESI-HRMS $[M + H]^+$ calcd for $C_{21}H_{30}N_5O_2$ m/z 384.2394, found 384.2396.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00148.

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dhg@mail.buct.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (Grant 21272022). We also thank Dr. Ning Chen for providing some helpful advice in our experiments and Dr. Baodong Zhao for theory calculations.

■ REFERENCES

(1) (a) Chorvat, R. J.; Bakthavatchalam, R.; Beck, J. P.; Gilligan, P. J.; Wilde, R. G.; Cocuzza, A. J.; Hobbs, F. W.; Cheeseman, R. S.; Curry, M.; Rescinito, J. P.; Krenitsky, P.; Chidester, D.; Yarem, J. A.; Klaczkiewicz, J. D.; Hodge, C. D.; Aldrich, P. E.; Wasserman, Z. R.; Fernandez, C. H.; Zaczek, R.; Fitzgerald, L. W.; Huang, S.-M.; Shen, H. L.; Wong, Y. N.; Chien, B. M.; Quon, C. Y.; Arvanitis, A. *J. Med. Chem.* **1999**, *42*, 833. (b) Miller, D. C.; Klute, W.; Brown, A. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6108.

(2) (a) Gigante, A.; Canela, M.-D.; Delang, L.; Priego, E.-M.; Camarasa, M.-J.; Querat, G.; Neyts, J.; Leyssen, P.; Pérez-Pérez, M.-J. *J. Med. Chem.* **2014**, *57*, 4000. (b) Pérez Pérez, M. J.; Gigante Martinez, A.; Canela Gomez, M. D.; Leyssen, P.; Neyts, J. Patent WO 2014/170368 A1, Oct 23, 2014.

(3) Mortensen, D. S.; Mederos, M. M. D.; Sapienza, J. J.; Albers, R. J.; Clareen, S. S.; Schwarz, K. L.; Parnes, J. S.; Riggs, J. R.; Papa, P. W.; Hegde, S. G.; McKenna, J. M. Patent US8383634 B2, Feb 26, 2013.

(4) Tehim, A.; Hopper, A. T.; Liu, R.; Hess, H.-J. E.; Rong, Y. Patent US2010/0004236 A1, Jan. 7, 2010.

(5) (a) Aguado, L.; Camarasa, M.-J.; Pérez-Pérez, M.-J. *J. Comb. Chem.* **2009**, *11*, 210. (b) Cocuzza, A.; Chidester, D. R.; Culp, S.; Fitzgerald, L.; Gilligan, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1063. (c) Yang, J.; Dang, Q.; Liu, J.; Wei, Z.; Wu, J.; Bai, X. *J. Comb. Chem.* **2005**, *7*, 474.

(6) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141.

(7) (a) Jiang, T.-S.; Wang, G.-W. *J. Org. Chem.* **2012**, *77*, 9504. (b) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476.

(8) (a) Zhang, C.; Sun, P. *J. Org. Chem.* **2014**, *79*, 8457. (b) Xu, Y.; Liu, P.; Li, S.-L.; Sun, P. *J. Org. Chem.* **2015**, *80*, 1269. (c) Dong, J.; Liu, P.; Sun, P. *J. Org. Chem.* **2015**, *80*, 2925. (d) Lou, S.-J.; Chen, Q.; Wang, Y.-F.; Xu, D.-Q.; Du, X.-H.; He, J.-Q.; Mao, Y.-J.; Xu, Z.-Y. *ACS Catal.* **2015**, *5*, 2846.

(9) (a) Tirler, C.; Ackermann, L. *Tetrahedron* **2015**, *71*, 4543. (b) Shi, S.; Kuang, C. *J. Org. Chem.* **2014**, *79*, 6105. (c) He, P.; Tian, Q.; Kuang, C. *Org. Biomol. Chem.* **2015**, *13*, 7146. (d) Tian, Q.; Chen, X.; Liu, W.; Wang, Z.; Shi, S.; Kuang, C. *Org. Biomol. Chem.* **2013**, *11*, 7830.

(10) Li, W.; Sun, P. *J. Org. Chem.* **2012**, *77*, 8362.

(11) Villuendas, P.; Serrano, E.; Urriolabeitia, E. P. *New J. Chem.* **2015**, *39*, 3077.

(12) For selected reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1855. (e) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (f) Wu, X.-F. *Chem.—Eur. J.* **2015**, *21*, 12252. (g) Liu, B.; Shi, B.-F. *Tetrahedron Lett.* **2015**, *56*, 15. (h) Yang, J. *Org. Biomol. Chem.* **2015**, *13*, 1930 and references cited therein.

(13) (a) 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. (b) 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. (c) Chamala, R. R.; Parrish, D.; Pradhan, P.; Lakshman, M. K. *J. Org. Chem.* **2013**, *78*, 7423. (d) Liang, Y.; Wnuk, S. F. *Molecules* **2015**, *20*, 4874.

(14) (a) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11400. (b) Allu, S.; Kumara Swamy, K. C. *Adv. Synth. Catal.* **2015**, *357*, 2665.

(15) (a) Ali, M. A.; Yao, X.; Sun, H.; Lu, H. *Org. Lett.* **2015**, *17*, 1513. (b) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110.

(16) Kim, H. J.; Ajitha, M. J.; Lee, J.; Ryu, J.; Kim, J.; Lee, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 1132.

(17) (a) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660. (b) Patel, P.; Chang, S. *ACS Catal.* **2015**, *5*, 853. (c) Liang, Y.; Liang, Y.-F.; Tang, C.; Yuan, Y.; Jiao, N. *Chem.—Eur. J.* **2015**, *21*, 16395.

(18) Selected substrates are as follows: 9-phenyl-6-butylamino-8-azapurine, 9-phenyl-6-phenylamino-8-azapurine, 9-phenyl-6-methoxyl-8-azapurine, and 9-phenyl-6-propoxyl-8-azapurine.

(19) (a) Kolle, S.; Batra, S. *Org. Biomol. Chem.* **2015**, *13*, 10376. (b) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (c) Eom, D.; Jeong, Y.; Kim, Y. R.; Lee, E.; Choi, W.; Lee, P. H. *Org. Lett.* **2013**, *15*, 5210. (d) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (e) Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203. (f) Péron, F.; Fossey, C.; Sopkova-de Oliveira Santos, J.; Cailly, T.; Fabis, F. *Chem.—Eur. J.* **2014**, *20*, 7507. (g) Gao, T.; Sun, P. *J. Org. Chem.* **2014**, *79*, 9888. (h) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187.

(20) (a) Klečka, M.; Pohl, R.; Klepetářová, B.; Hocek, M. *Org. Biomol. Chem.* **2009**, *7*, 866. (b) Sabat, N.; Slavětínská, L. P.; Hocek, M. *Tetrahedron Lett.* **2015**, *56*, 6860. (c) Qu, G.-R.; Liang, L.; Niu, H.-Y.; Rao, W.-H.; Guo, H.-M.; Fossey, J. S. *Org. Lett.* **2012**, *14*, 4494. (d) Allu, S.; Swamy, K. C. K. *RSC Adv.* **2015**, *5*, 92045. For selected purinyl N^1 atoms metalated complexes, see: (e) Purohit, C. S.; Mishra, A. K.; Verma, S. *Inorg. Chem.* **2007**, *46*, 8493. (f) Ibáñez, S.; Albertí, F. M.; Sanz Miguel, P. J.; Lippert, B. *Inorg. Chem.* **2011**, *50*, 10439. (g) Mihály, T.; Añorbe, M. G.; Albertí, F. M.; Sanz Miguel, P. J.; Lippert, B. *Inorg. Chem.* **2012**, *51*, 10437. (h) Catalan, K. V.; Hess, J. S.; Maloney, M. M.; Mindiola, D. J.; Ward, D. L.; Dunbar, K. R. *Inorg. Chem.* **1999**, *38*, 3904. (i) Montagner, D.; Venzo, A.; Zangrando, E.; Longato, B. *Inorg. Chem.* **2010**, *49*, 2103.

(21) (a) Meiser, C.; Song, B.; Freisinger, E.; Peilert, M.; Sigel, H.; Lippert, B. *Chem.—Eur. J.* **1997**, *3*, 388. (b) Pearson, C.; Beauchamp, A. L. *Inorg. Chem.* **1998**, *37*, 1242.

(22) (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Lee, G. T.; Jiang, X.; Prasad, K.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1921. (c) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717. (d) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1380.

(23) (a) Qian, G.; Hong, X.; Liu, B.; Mao, H.; Xu, B. *Org. Lett.* **2014**, *16*, 5294. (b) Dong, J.; Jin, B.; Sun, P. *Org. Lett.* **2014**, *16*, 4540. (c) Peng, Y.; Zeng, M.; Wang, H.; Zhu, J.; Yang, Q.; Deng, Z.; Yu, C.

DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435−3442

Tetrahedron **2015**, *71*, 9457. (d) Cai, Z.-J.; Yang, C.; Wang, S.-Y.; Ji, S.-J. *J. Org. Chem.* **2015**, *80*, 7928. (e) Xu, N.; Li, D.; Zhang, Y.; Wang, L. *Org. Biomol. Chem.* **2015**, *13*, 9083. (f) Wang, M.; Yang, Y.; Fan, Z.; Cheng, Z.; Zhu, W.; Zhang, A. *Chem. Commun.* **2015**, *51*, 3219. (g) Guo, H.-M.; Rao, W.-H.; Niu, H.-Y.; Jiang, L.-L.; Liang, L.; Zhang, Y.; Qu, G.-R. *RSC Adv.* **2011**, *1*, 961 and references cited therein.

(24) Greenberg, S. M.; Ross, L. O.; Robins, R. K. *J. Org. Chem.* **1959**, *24*, 1314.

DOI: 10.1021/acs.joc.6b00148
J. Org. Chem. 2016, 81, 3435−3442