Hydrogen-Bond-Assisted Controlled C−H Functionalization via Adaptive Recognition of a Purine Directing Group

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Ⓢ *Supporting Information*

ABSTRACT: We have developed the Rh-catalyzed selective C−H functionalization of 6-arylpurines, in which the purine moiety directs the C−H bond activation of the aryl pendant. While the first C−H amination proceeds via the N1-chelation assistance, the subsequent second C−H bond activation takes advantage of an intramolecular hydrogen-bonding interaction between the initially formed amino group and one nitrogen atom, either N1 or N7, of the purinyl part. Isolation of a rhodacycle intermediate and the substrate variation studies suggest that N1 is the main active site for the C−H functionalization of both the first and second amination in 6-arylpurines, while N7 plays an essential role in controlling the degree of functionalization serving as an intramolecular hydrogen-bonding site in the second amination process. This pseudo-Curtin−Hammett situation was supported by density functional calculations, which suggest that the intramolecular hydrogen-bonding capability helps second amination by reducing the steric repulsion between the first installed ArNH and the directing group.
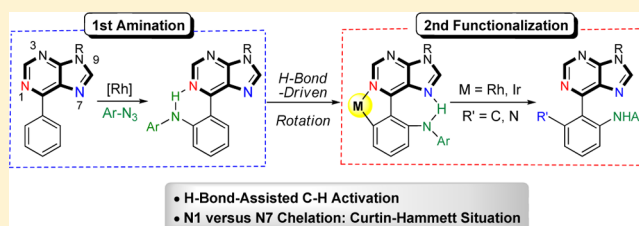
INTRODUCTION

Transition-metal-catalyzed C−H bond activation and subsequent functionalizations are of great synthetic utility in various research areas since it enables the direct introduction of functional groups without relying on the conventional prefunctionalization approaches.[1] With an appropriate combination of metal catalysts and chelate groups, a range of direct C−H functionalizations has been successfully developed including alkenylation,[2] arylation,[3] amination,[4] hydroxylation,[5] and halogenation.[6] In spite of these remarkable recent advances, the degree of functionalization (mono vs di) is often difficult to control (Scheme 1a). This selectivity issue becomes more critical when two different groups need to be introduced.

Recently, we have developed the transition-metal-catalyzed direct intermolecular C−H amination of arenes and alkenes using organic azides as the nitrogen source (Scheme 1b).[7] The reaction is characterized to have broad substrate scope and high functional group tolerance. Reaction conditions are mild, releasing molecular nitrogen as the single byproduct. A wide range of azides could efficiently be employed to include variants of sulfonyl, aryl, alkyl, and acyl azides.[8] In addition, we have optimized three catalytic systems based on rhodium,[7a−c] ruthenium,[7d] and iridium,[7e,f] each of which displays a unique reactivity pattern depending on the combination of substrates and azides.

During the course of these studies, we observed an interesting aspect that the degree of amination depends on

Scheme 1
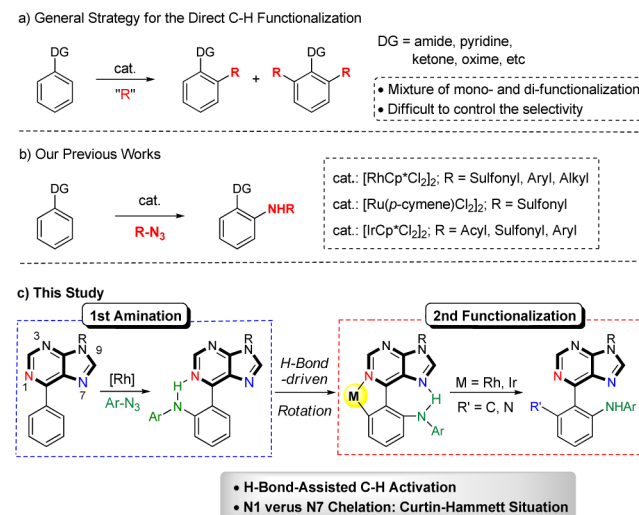
substrates and catalysts employed. For example, most substrates bearing conventional chelation groups are exclusively mono-aminated even when excessive equivalents of azides are used without formation of diaminated products. In sharp contrast, the degree of amination with 6-arylpurines was found to be

controlled to deliver either mono- or diaminated products depending on the stoichiometry of azides. We initially hypothesized that the unique structural feature of a purinyl group is responsible for this outcome. Described herein are our detailed experimental and theoretical studies to validate the working hypothesis in the direct functionalization of 6-arylpurines, especially focusing on the selectivity issue in the amination (Scheme 1c).

An additional motivation for the current work is the high synthetic utility of purine building blocks in medicinal chemistry.[9−12] Compounds containing purine skeleton are widely present in nature with interesting biological activities which are originated presumably through the hydrogen-bonding-based molecular interactions.[9] In addition, 6-arylpurine derivatives are of particular importance since they exhibit high potency of antimycobacterial, cytostatic, and anti-HCV activities (Scheme 2).[10] In this study, the propensity of purine

**Scheme 2. Medicinal Applications of Purine Derivatives**
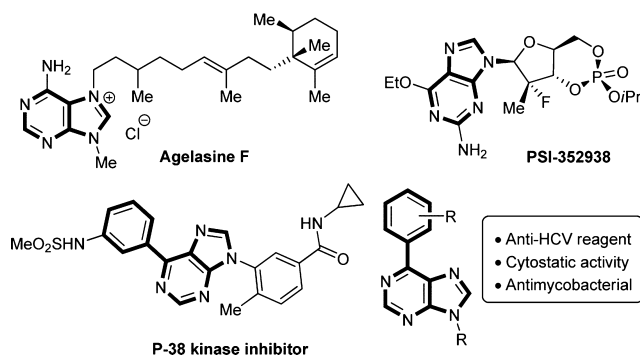
to have H-bonding interaction was used as a key component in controlling the degree of catalytic mono- versus difunctionalization reactions. DFT calculations were carried out to validate the proposed hypothesis and interpret the data.

■ RESULTS AND DISCUSSION

Control of the Degree in the Amination of 6-Arylpurines. When the previously developed conditions of the Rh-catalyzed direct C−H amination were applied to 2-phenylpyridine (**1**),[7a] a monoaminated product (**3**) was exclusively obtained after 24 h without forming a diaminated compound (**4**) even when excess amounts (3 equiv) of aryl azide (**2**) were used (Scheme 3a).[13] In contrast, it was surprising to see that the amination of 6-phenylpurine (**5**) took

**Scheme 3. C−H Amination of Arenes with Different DGs**
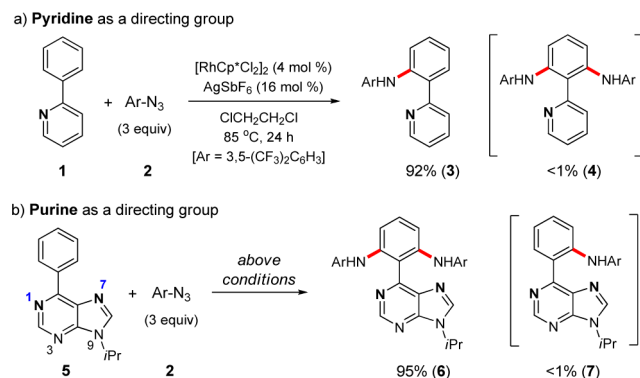
place in an opposite manner; a diaminated product (**6**) was exclusively generated, while a monoaminated compound (**7**) was not observed under otherwise identical conditions (Scheme 3b).

A main difference between two chelates, 2-pyridyl and purinyl group, is the presence of additional nitrogen atoms in the purine moiety. In particular, in addition to N1, N7 in purine may work as an additional coordinating site to the rhodium metal center during the course of the C−H activation process.

Since N3 and N9 are remote from the reacting site of a phenyl pendant, it is reasonable to assume that these two nitrogen atoms are not involved in the amination pathway. As a result, two paths can be presupposed in the C−H bond activation process to generate the corresponding cyclometalates (Scheme 4). A rhodacycle intermediate **I** will be formed from

Scheme 4. Two Modes in the First C−H Amination
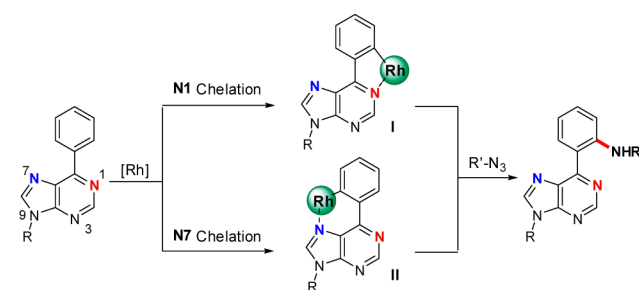
the N1-chelation-assisted C−H bond activation. Alternatively, a rhodacycle **II** generated via N7-chelation assistance is another possibility. It should be addressed that the C−H amination product will be the same irrespective of the chelation mode.

To gain insights into the mechanistic details, a series of experiments were carried out (Scheme 5). First, we obtained a rhodacycle (**8**) in 65% yield upon treatment of 6-aryl-(N-isopropyl)purine (**5**) with 0.5 equiv of [RhCp*Cl₂]₂ and 2.7 equiv of NaOAc.[14] A solid structure of **8** was determined by an X-ray crystallographic analysis, in which the formation of a

Scheme 5. Preparation and Reactivity of a Rhodacycle (8) Derived from 6-Arylpurine (5)
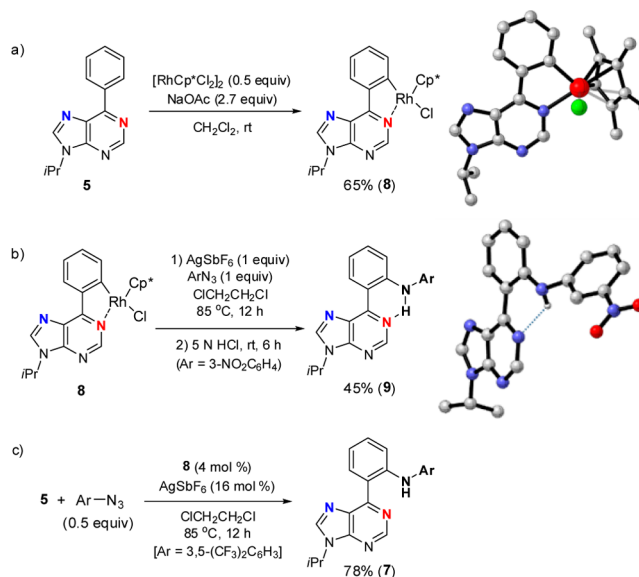
rhodacycle derived from the N1 atom was clearly shown (Scheme 5a). When the isolated rhodacycle was reacted with 3-nitrophenyl azide, a monoaminated product (9) could be obtained after protonolysis (Scheme 5b). The fact that chemical shift of amino NH in 9 appeared at 11 ppm, being shifted by 3−5 ppm relative to a typical diarylamino peak,[15] strongly indicates the presence of H-bonding. Indeed, a solid structural analysis of 9 confirmed an intramolecular hydrogen bonding; 2.02 Å of the NH···N bond length with 121.9° bond angle between those three atoms. In addition, the direct C−H amination of 5 was efficiently catalyzed by 8 (4 mol %) in the presence of a silver additive, suggesting that a cationic rhodacycle is indeed involved in the catalytic amination process.

In the second amination stage, as in the first amination, two nitrogen atoms (N1 or N7) might be involved in the chelation-assisted C−H bond activation (Scheme 6). In this process, we

## Scheme 6. Plausible Pathways of the Second Amination
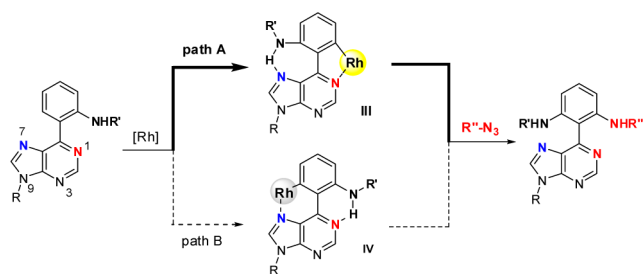
postulated that an intramolecular H-bonding between an initially formed arylamino NH group and a purinyl nitrogen (either N1 or N7) would play an important role in facilitating the rhodacycle formation leading to III or IV, respectively.[16] In fact, there are a number of examples to utilize hydrogen bonding as a key motif to control reactivity and/or selectivity in Michael addition,[17] epoxidation,[18] hydrogenation,[19] cyclo-addition,[20] Diels−Alder,[21] and aldol reaction.[22] We also reported hydrogen-bond-directed stereoselective synthesis of Z-enamides via Pd-catalyzed oxidative amidation of conjugated olefins,[23] in which an intramolecular H-bonding between an amido proton and carbonyl oxygen was proposed as a key driving force to obtain an excellent level of stereoselectivity.

However, only a few reports of utilizing an in situ formed H-bonding are known in the C−H bond activation process. For example, Lassaletta et al. elegantly demonstrated that an iridium complex can catalyze diborylation and sequential functionalization of arenes bearing hydrazone as a directing group.[24] They proposed that an intramolecular H-bonding makes the reaction more facile. In addition, one recent example has been revealed by Glorius and co-workers in the chelation-assisted direct amidation of arenes using aroyloxycarbamates as the nitrogen source under a rhodium catalytic system.[25] In this study, the observation that diamidated products were sometimes obtained for certain substrates was explained by assuming a H-bonding interaction between a directing group and the first-formed amide NH. However, detailed experimental or theoretical studies were not presented in their communication.

Although we could not obtain a single crystal of a postulated rhodacycle (III or IV in Scheme 6) suitable for the X-ray crystallographic analysis, its in situ generation was confirmed by a mass spectroscopic analysis (ESI-HRMS, Scheme 7a). On the other hand, the second amination of 10 was found to be facile under the present rhodium catalytic system to give a

Scheme 7. Detection of a Rhodacycle in the Second Amination
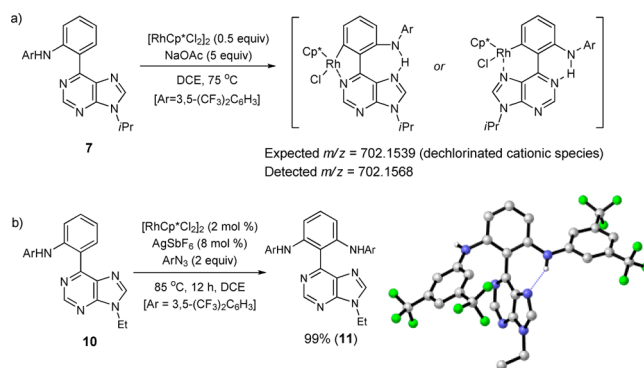
diaminated product (11) in a quantitative yield (Scheme 7b). A solid structure of 11 revealed an interesting aspect: while a purinyl nitrogen atom N7 participates in an *intramolecular* H-bonding with one of the produced amino NH atoms, N1 exhibits an *intermolecular* interaction with another NH bond of a neighboring molecule 11.[26]

In order to examine which nitrogen atom of N1 and N7 is more responsible for the second amination (paths A and B in Scheme 6), we designed two model substrates, in which either N1 or N7 of the purine skeleton was removed. A substrate (12) devoid of the N1 atom was completely unreactive to the amination conditions (Scheme 8a), indicating that N1 in the

Scheme 8. Tests of Two Model Substrates 12 and 13
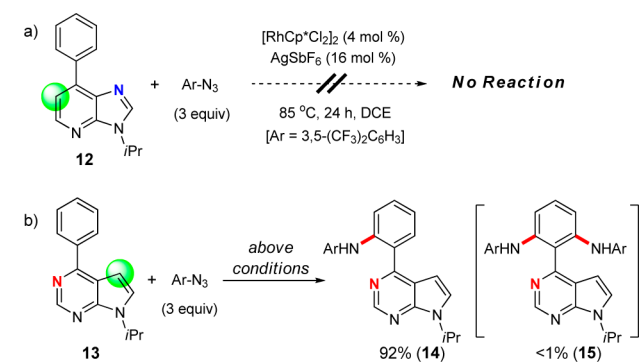
purine moiety is essential for the C−H bond activation process mediated by a rhodium metal species. On the other hand, a substrate 13 that does not bear the N7 atom in the purine skeleton underwent the reaction, but giving rise to only monoaminated product 14 (Scheme 8b). It was intriguing that, even when excessive amounts of aryl azide (3 equiv) were employed, diamination of 13 did not proceed.[27] This result strongly suggests that N7 displays a role in the second amination process presumably through an intramolecular H-bonding with the first-formed amino NH hydrogen atom (Scheme 6, path A).

Computational Insights. To gain additional insights into the role played by N1 and N7 in the C−H amination process, density functional theory calculations were carried out using B3LYP functional[28,29] as implemented in the Q-CHEM quantum chemistry package.[30] Stuttgart relativistic small core (SRSC)[31] effective core potential basis set was used for rhodium and for all other atoms, and 6-31G* basis set was employed in geometry optimization and 6-311G** in single-

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point energy calculations. The -R, -R′, and -R″ groups of model substrates in the calculations were CH_3, C_6H_5, and C_6H_5, respectively (Schemes 4 and 6) to reduce the computational cost. Stationary points were confirmed by frequency calculations, showing all positive vibrations for minima and one imaginary vibration for transition states.

The wave function generated from the gas-phase-optimized geometry of purines was used for the molecular electrostatic potential (MESP) analysis. The MESP of a molecule at a point is formally defined as the work done in bringing a unit positive test charge from infinity to that point; the more negative value meaning the higher electron density. It is a real physical property that can be determined experimentally by X-ray diffraction techniques or rigorously calculated using eq 1, where Z_A is the charge on nucleus A located at R_A, $\rho(r')$ is the electron density of the molecule, and r' is the dummy integration variable.[32,33] The first and second terms on the right-hand side of the equation represent the bare nuclear and electronic contributions, respectively, and the sign of $V(\mathbf{r})$ depends on whether the nuclear or electronic effects are dominant in a particular region. All reported free energies involve zero-point vibrational corrections and thermal corrections to the Gibbs free energy on the gas-phase-optimized geometries at 298.15 K.

$$V(\mathbf{r}) = \sum_A^N \frac{Z_A}{|\mathbf{r} - R_A|} - \int \frac{\rho(r')\mathrm{d}^3 r'}{|\mathbf{r} - r'|} \tag{1}$$

We denote V_{min} as the lowest MESP value (the highest electron density) in space (**A**) in Figure 1, which indicates that
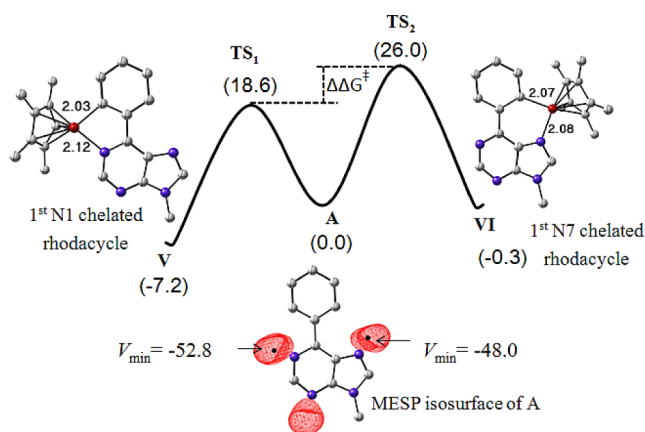

Figure 1. Relative energies of metal chelates expected to be formed in the first amination. Values in the parentheses are the relative free energies (kcal/mol). The MESP minimum V_{min} values are also given in kcal/mol. Distances are given in Å. Color code: gray, C; blue, N; and red, Rh. Hydrogen atoms are omitted for clarity.

N1 moiety (V_{min} = −52.8 kcal/mol) has a higher electron density compared to that of N7 moiety (V_{min} = −48.0 kcal/mol). A simpler Mulliken charge analysis (−0.36 e⁻ for N1 versus −0.35 e⁻ for N7) was qualitatively consistent with the more physical MESP analysis. It was also observed that the metal chelate formed after the first C−H activation is stabilized more when the metal chelation occurs at N1 (**V** in Figure 1) than at N7 (**VI** in Figure 1) by an amount of 6.9 kcal/mol of energy, similar to the electrostatic potential energy difference between the two nitrogen sites (4.8 kcal/mol). This similarity suggests that the relative stability of N1-chelated complex and N7 counterpart arises mainly from the difference in electrostatic

interactions between N1 and Rh versus N7 and Rh. The remaining difference between the net energy difference (6.9 kcal/mol) and the electrostatic component (4.8 kcal/mol) would be due to the dispersion interactions, the steric repulsion, and orbital interactions associated with metal chelation. **V** and **VI** are expected to be generated by the C−H activation process (via **TS₁** and **TS₂**, respectively) and their relative activation energies ($\Delta\Delta G^{\ddagger}$ = 7.4 kcal/mol) favor 99.9% of **V** in excess according to eq 2, where $\Delta\Delta G^{\ddagger}$ is the difference in the activation energies to form the rhodacycles (Figure 1). This result as well as the thermodynamic energy difference (6.9 kcal/mol) between **V** versus **VI** are consistent with the experimental data of a rhodacycle (**8**) shown in Scheme 5a.

$$\frac{[\text{N1-rhodacycle}]}{[\text{N7-rhodacycle}]} = e^{\Delta\Delta G^{\ddagger}/RT} \tag{2}$$

As described above (Scheme 6), it can be assumed that either N1 or N7 site is available for the chelation-assisted second C−H amination process by a rotation of the monoaminated product (via **TS_rot** in Figure 2; $\Delta G^{\ddagger}$ = 9.9 kcal/mol). It was calculated that two conformers of a monoaminated molecule (**B** and **C** in Figure 2) differ in energy by only 3.1 kcal/mol. The H-bonding between the introduced ArNH and nitrogen atom of N1 or N7 (**B** and **C**, respectively) is expected to assist the second amination by reducing steric repulsion between ArNH and the directing group. During the course of generating the corresponding rhodacycle, the N1-assisted metal chelate (**VII**) was calculated to be more stable than the N7 counterpart (**VIII**) by 4.7 kcal/mol. The higher stability of **VII** is expected to arise from the stronger electrostatic interaction of the metal center to the electron-rich N1 site in **C** compared to the N7 site in **B** by −7.3 kcal/mol (V_{min} = −55.0 versus −47.7 kcal/mol), which is then offset by the less favorable intramolecular H-bonding energy of **C** (NH-N7) compared to **B** (NH-N1) by 3.1 kcal/mol ΔG^0 in Figure 2. This simple decomposition of the relative stability of rhodacycles into electrostatic metal−nitrogen interaction (−7.3 kcal/mol) and intramolecular H-bonding interaction (3.1 kcal/mol) yields **VII** more stable than **VIII** by 4.2 kcal/mol, in good agreement with the actual difference in free energy, 4.7 kcal/mol.

It is interesting to note that the presence of the first aminated group increases the electron density at N1 in **C**, whereas it slightly decreases that at the N7 site in **B** when compared to the initial substrate (Figure 1). Even though the relative population of **B** seems to be higher than that of **C**, it is actually the relative activation energy in a process leading to the rhodacycles that determine their actual proportion (*Curtin−Hammett principle*). **VII** and **VIII** are expected to be given by the second C−H activation process (via **TS₃** and **TS₄**, respectively), and their relative activation energies ($\Delta\Delta G^{\ddagger}$ = 3.6 kcal/mol) favor 99.5% of **VII** in excess according to eq 2, where $\Delta\Delta G^{\ddagger} = \Delta G_C^{\ddagger} + \Delta G^0 - G_B^{\ddagger}$ (Figure 2). This indicates that **VII** (second N1-chelated rhodacycle) will be a major intermediate to initiate the second amination. In other words, it is clear that the N1 site is more favored over N7 for both the first and second amination as this is proved by experiment (no product in the case of substrate **12**) and theory (explained more clearly on the basis of Curtin−Hammett principle). Although both **VII** and **VIII** have intramolecular H-bonding interactions shown as the dotted line in Figure 2, lower activation barrier and hence preferred reaction path for **VII** relative to **VIII** is perhaps due to the higher stability of a planar five-membered rhodacycle for **VII**
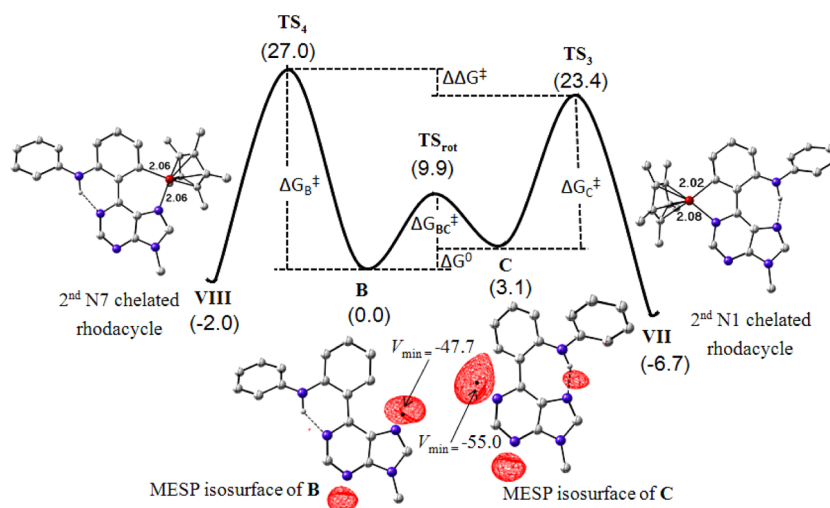
Figure 2. Relative energies of metal chelates expected to be formed in the second amination. Values in the parentheses are the relative free energies (kcal/mol). V_{min} values are also given in kcal/mol. Distances are given in Å. Color code: gray, C; blue, N; ivory, H; and red, Rh. Less important hydrogen atoms are omitted for clarity.

compared to a less stable puckered six-membered rhodacycle for **VIII**.

The C−H bond activation barrier for the second amination seems to be comparable to the first amination for both substrates 2-phenylpyridine (**1**) and 9-methyl-6-phenylpurine (**A**, Figure 1). In fact, for **1**, the activation barrier for the second amination reaction (20.8 kcal/mol) is even slightly lower than the first amination reaction (21.2 kcal/mol), implying that as long as there is enough rhodacycle formation after the first amination, we would observe the second amination eventually for 2-phenylpyridine also. It is expected that a rotation of the directing group around the central C−C bond should occur prior to the second amination to form a more stable rhodacycle at the N1 site, and this may bring steric repulsion between the directing group and the initially installed ArNH group for certain substrates such as 2-phenylpyridine (**1**). In this case, the rotated isomer is less stable than its unrotated isomer by 3.8 kcal/mol (Table 1) due to the loss of intramolecular H-

Table 1. Free Energy Difference and Population Ratio of Rotational Isomers for Monoaminated Compounds at 358 K[a]

substrate	ΔG (kcal/mol)	[rotated]/[unrotated]
1	3.8	1:200
A	3.1	1:80
13a	5.1	1:1300

[a]**13a** is an analogue of **13** in which the N-iPr group is replaced by N-CH₃ for the computational simplicity.

bonding and the creation of the steric repulsion accordingly. In case of 9-methyl-6-phenylpurine (**A**), however, the rotated form still retains the stability by newly formed H-bonding between the N7 and ArNH group, and thus the energy difference between rotated versus unrotated isomers is reduced to 3.1 kcal/mol. These free energy differences correspond to the equilibrium population ratio of rotated (active) versus unrotated (inactive) conformations to be 1:200 and 1:80 for **1** and **A**, respectively, at 358 K. It is assumed that a longer reaction time would be required for **1** than that of **A** in order to have sufficient population of the rotated isomers mentioned

above to form a diaminated product. Indeed, it is observed that when the reaction time was extended to 48 h, diamination of **1** also occurred albeit in low yield (6%), supporting the active role of H-bonding in the product selectivity.[13] Similarly, for **13a**, the equilibrium population ratio of rotated versus unrotated monoamino product is 1:1300, suggesting that the diaminated product will hardly be obtained under optimized or even extended reaction time conditions.[27]

Detailed additional analyses of the reaction mechanism for various substrates, currently under investigation, would undoubtedly be helpful to offer further insights, but all of the present experimental and computational results point quite conclusively to the fact that the H-bonding is actively assisting the second amination by lowering the steric repulsion and facilitating the regeneration of the N1 site by rotation.

Substrate Scope. On the basis of the above mechanistic studies and computational calculations, we envisioned that an orthogonal strategy can be designed to afford various types of direct C−H functionalization products starting from 6-arylpurines (Scheme 9). As hinted from the result of Scheme 3, optimal procedures to deliver mono- or symmetric diaminated products were predicted to be plausible by tuning the stoichiometry of azide reactants. Sequential diamination at the arene pendant by employing two different azides will provide unsymmetrical diamination products. In addition, we

Scheme 9. Orthogonal C−H Functionalization Approaches
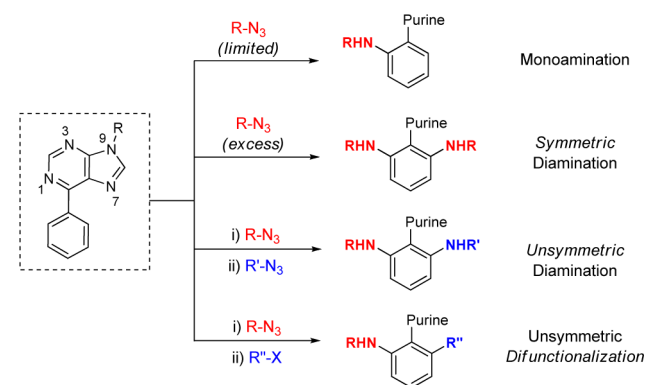
also envisaged to develop an unsymmetric difunctionalization procedure by applying an initial amination followed by a reaction with different organic electrophiles. It should be addressed that the diversity attainable through the present C−H functionalization strategy can be attributed to the unique structural property of the purinyl group.

As the proof of concept, we examined the substrate scope of 6-arylpurines in the mono- versus symmetric diamination reaction (Table 2). Two procedures differ only in the

Table 2. Substrate Scope of Arenes in 6-Arylpurines

16 (yield, %)[c]	R[1]/R[2]	17 (yield, %)[c]
99 (**16a**)	R[1] = iPr, R[2] = 4-Me	86 (**17a**)
99 (**16b**)	R[1] = iPr, R[2] = 4-CF$_3$	72 (**17b**)
99 (**16c**)	R[1] = iPr, R[2] = 4-Cl	95 (**17c**)
93 (**16d**)	R[1] = iPr, R[2] = 4-CO$_2$Me	90 (**17d**)
88 (**16e**)	R[1] = iPr, R[2] = 4-Ac	93 (**17e**)
99 (**16f**)	R[1] = iPr, R[2] = 4-OMe	94 (**17f**)
82 (**16g**)	R[1] = iPr, R[2] = 4-OBn	76 (**17g**)
52 (**16h**)	R[1] = iPr, R[2] = 4-OH	58 (**17h**)
45 (**16i**)	R[1] = iPr, R[2] = 4-CHO	63 (**17i**)
91 (**16j**)	R[1] = iPr, R[2] = 4-NO$_2$	98 (**17j**)
99 (**16k**)	R[1] = iPr, R[2] = 3-Me	
87 (**16l**)	R[1] = Bn, R[2] = H	90 (**17l**)
96 (**10**)	R[1] = Et, R[2] = H	84 (**11**)
83 (**16m**)	R[1] = n-Bu, R[2] = H	92 (**17m**)

[a]Conditions A: 6-arylpurine (2 equiv), aryl azide (0.2 mmol), [RhCp*Cl$_2$]$_2$ (2 mol %), and AgSbF$_6$ (8 mol %) for 12 h. [b]Conditions B: substrate (0.2 mmol), aryl azide (3 equiv), [RhCp*Cl$_2$]$_2$ (4 mol %), and AgSbF$_6$ (16 mol %) for 24 h. [c]Isolated yield.

stoichiometry of two reactants and reaction time: while azide was used as a limiting reagent for the monoamination (conditions A), excessive azides were employed with longer reaction time to obtain doubly aminated products (conditions B).

Product yields were good to excellent in general, and the functional group tolerance was also found to be satisfactory. Electronic variation on substrates did not much influence the reactivity and selectivity: all examined substrates bearing electron-donating or electron-withdrawing groups underwent the selective amination with high efficiency. Variation of N9 substituents in the purine moiety was flexible, thus allowing a range of different amino groups. Interestingly, a substrate bearing a *meta*-substituent underwent the first amination at the sterically more accessible position in quantitative yield (**16k**), but the second amination did not proceed mainly due to the steric congestion.

The scope of aryl azides was subsequently explored again to validate our orthogonal approach (Table 3). As shown in our previous study,[7b] aryl azides bearing electron-withdrawing substituents such as trifluoromethyl, ester, nitro, sulfonyl, or acetyl groups at the *para*- or *meta*-position underwent the desired mono- and diamination in good to excellent yields. As proved in Table 2, the functional group compatibility was also

Table 3. Scope of Aryl Azides

18 (yield, %)[c]	R	19 (yield, %)[c]
90 (**18a**)	4-CF$_3$	92 (**19a**)
85 (**18b**)	3-CF$_3$	95 (**19b**)
66 (**18c**)	4-CO$_2$Me	98 (**19c**)[d]
64 (**18d**)	3-CO$_2$Me	96 (**19d**)
99 (**9**)	3-NO$_2$	90 (**19e**)
82 (**18f**)	4-SO$_2$Me	99 (**19f**)[d,e]
74 (**18g**)	4-C(O)CH$_3$	75 (**19g**)[d,e]
95 (**7**)	3,5-(CF$_3$)$_2$	95 (**6**)

[a]Conditions A: **5** (2 equiv), aryl azide (0.2 mmol), [RhCp*Cl$_2$]$_2$ (2 mol %), and AgSbF$_6$ (8 mol %) for 12 h. [b]Conditions B: **5** (0.2 mmol), aryl azide (3 equiv), [RhCp*Cl$_2$]$_2$ (4 mol %), and AgSbF$_6$ (16 mol %) for 24 h. [c]Isolated yield. [d]With 5 equiv of aryl azide. [e]Cl$_2$CHCHCl$_2$ was used as a solvent.

excellent, and **5** was aminated in high efficiency with a wide range of aryl azides.

After successful exploration of the substrate scope with 6-arylpurines and aryl azides, we turned our attention to a different type of directing groups to examine our working hypothesis on the H-bonding-assisted C−H functionalizations (Table 4). A phenyl group substituted at the 2-position of

Table 4. Direct Amination of Various Phenylheterocycles

entry	20 (yield, %)[c]	DG (Directing Group)	21 (yield, %)[c]
1	53% (**20a**) + 20% (**21a**)		88% (**21a**)
2	52% (**20b**) + 14% (**21b**)		92% (**21b**)
3	70% (**20c**)[d]		65% (**20c**) <1% (**21c**)

[a]Conditions A: substrate (3 equiv), aryl azide (0.2 mmol), [RhCp*Cl$_2$]$_2$ (4 mol %), and AgSbF$_6$ (16 mol %) for 12 h. [b]Conditions B: substrate (0.2 mmol), aryl azide (3 equiv), [RhCp*Cl$_2$]$_2$ (4 mol %), and AgSbF$_6$ (16 mol %) for 24 h. [c]Isolated yield. [d]With 2 equiv of substrate.

pyrimidine and quinazoline underwent the catalytic C−H amination in excellent yields, leading to the corresponding diaminated products (**21a** and **21b**, respectively) under conditions B. However, the monoamination was not selective unlike the above 6-arylpurine derivatives, and a mixture of mono- and diaminated products was obtained under conditions A using azide as a limiting reagent. For example, a reaction of 2-phenylpyrimidine afforded a mixture of **20a** and **21a** (2.7:1) under these conditions (entry 1). A similar pattern was also observed with 2-phenylquinazoline to give a mixture of mono- and diaminated products (3.7:1, entry 2) under the conditions

A. Based on our above experimental results and theoretical interpretations, the formation of diaminated compounds albeit in minor under conditions A may be ascribed to the presence of an additional nitrogen atom in the directing groups that can form favorable rhodacycle. It is assumed that this nitrogen readily allows the formation of a rhodacycle for the second amination since a presumed H-bonding between an initially formed amino NH and one of two "equivalent" nitrogen atoms in these directing groups does not need to be broken, nor the rotation required as in 6-arylpurines. Indeed, a solid structure of a monoaminated compound (**20a**) reveals a H-bonding while a free nitrogen atom is also available in the pyrimidinyl group for the formation of a rhodacycle eventually leading to the second amination (Figure 3a). The molecular skeleton of aminated 2-
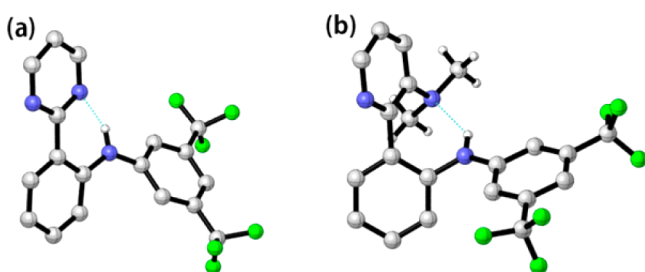

Figure 3. X-ray structure of **20a** (a) and **20c** (b).

phenylpyrimidine (**20c**) is revealed to be almost planar (dihedral angle of 6°) in the X-ray structure, implying that the formation of a rhodacycle for the second amination would be facile, maintaining the intramolecular hydrogen bond. We believe that this would be an origin being responsible for the different selectivity between 6-arylpurines which requires rotation for second amination and arylpyrimidines (and arylquinazolines) which does not require such a rotation.

When 3-(*N,N*-dimethylamino)-2-phenylpyridine was allowed to react under conditions A, a monoaminated product (**20c**) was obtained exclusively without diamination (entry 3). Surprisingly, the same result was also observed even under conditions B by using excess amounts of aryl azide. A crystal structure of **20c** showed that a H-bonding is present between the introduced amino NH and NMe$_2$ substituent while the 2-phenylpyridine skeleton is significantly distorted with a dihedral angle of 57° (Figure 3b). It is thus anticipated that the formation of a rhodacycle for the second amination from the first aminated compound (**20c**) would be difficult since the required coplanarity of the 2-phenylpyridine skeleton is not accessible due to the severe steric congestion between the dimethylamino (-NMe$_2$) substituent and installed amino group.

Sequential Arene Functionalization of Arylpurines. In the chelation-assisted direct C−H functionalization, the introduction of *two different groups* at the *ortho*-position relative to the directing groups has been challenging. The key to success in dealing with this issue will be the minimal inhibitory effects of the first installed groups toward the second introduction of functional groups. In this regard, we envisioned to take advantage of the unique controlling property of the purinyl directing group for the formation of unsymmetric diaminated compounds. Indeed, we were pleased to observe that the second amination of monoaminated compound (**7**) was highly facile over a range of azides (Scheme 10). Not only aryl azides (**22a−22e**) bearing various substituents at the *para*- or *meta*-position but also sulfonyl (**22f**) and benzyl azide (**22g**)

Scheme 10. Unsymmetric Diamination[a]
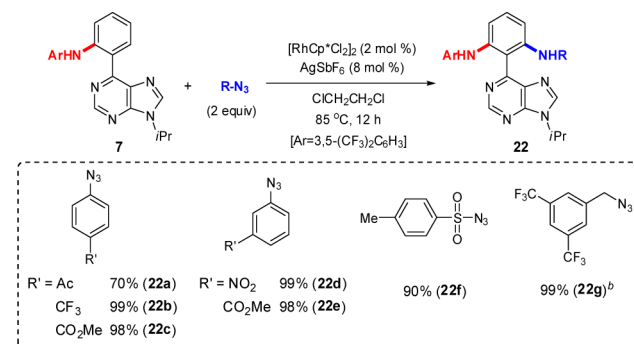
[a]Isolated yield. [b]At 110 °C.

all participated in the second amination reaction with high efficiency.

Sequential C−H functionalization was also briefly tested either with different types of organic electrophiles or using a different metal catalytic system to extend the applicability of the present approach (Scheme 11). We observed that a direct

Scheme 11. Unsymmetric Difunctionalization
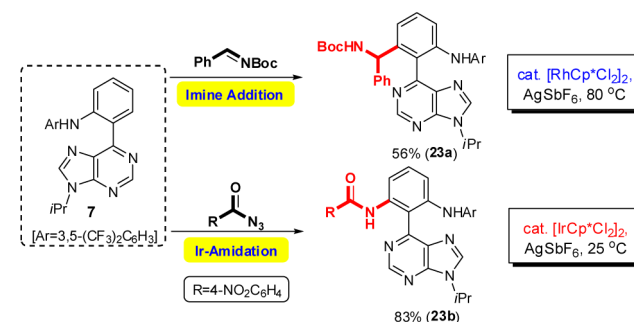
imine addition took place with a monoaminated phenylpurine (**7**) under the slightly modified Ellman's conditions.[34] Although the product yield was moderate, this result is noteworthy in that two different functional groups could be introduced in sequence at our will. We also successfully carried out the Ir-catalyzed amidation of **7** using acyl azide as the coupling partner at room temperature according to our recent protocol.[7e]

■ CONCLUSION

We have described herein the unique structural utility of purine in the metal-catalyzed direct C−H functionalization of an aryl pendant with an emphasis on the selectivity control. Highly selective mono- or double C−H amination was achieved with the assistance of an intramolecular hydrogen-bonding interaction. For the first amination of 6-arylpurines, a rhodacycle was found to form through the chelation assistance of a purinyl N1 atom. Experimental data including the isolation of the rhodacycle and the demonstration of its catalytic activity supported this postulate. The presence of N7, however, was observed to be essential for the second functionalization through an intramolecular H-bonding with the first introduced amino NH moiety. It was also shown that the steric repulsion between the first installed amino group and the directing group is reduced by the H-bond assistance in order to perform the second functionalization. This interpretation was validated by

DFT calculations and well rationalized by taking the Curtin–Hammett principle into account. On the basis of the unique chelation property of a purine moiety, we have developed orthogonal approaches to the selective functionalization of 6-arylpurines either symmetrically or unsymmetrically. The present strategy is anticipated to have a high utility in such areas as catalysis and synthetic chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedure and characterization of new compounds, including ^{1}H, ^{13}C NMR spectra, Cartesian coordinates of computed structures, and CIF files of **8**, **9**, **11**, **20a**, and **20c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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