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CuI Controlled C–C and C–N Bond Formation of Heteroaromatics through C(sp^3)–H Activation

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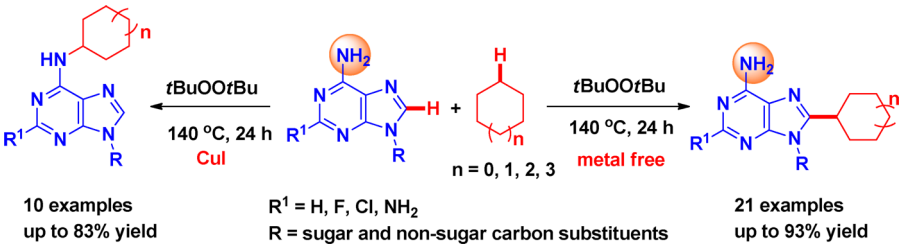
ABSTRACT



A new method for C–C and C–N bond formation of heteroaromatics and C(sp^3)–H alkanes was developed with high regioselectivity. The reaction occurred on C8 to give 8-cylcoakylpurines by C–C bond formation only promoted by *t*BuOO*t*Bu, while it occurred on the amino group to give *N*6-alkylated purines by C–N bond formation when 2 equiv of CuI were added. A reaction mechanism was also proposed based on our preliminary experimental data.

C–H Bond direct functionalization is one of the hot topics in current organic chemistry[1] which enables the efficient construction of carbon–carbon or carbon–heteroatom bonds as a highly atom-economical and direct approach.[2] In the past few decades, this area has received a great deal of interest from chemists and has been widely explored. Among various C–H bond activation types, many efforts have been made in the direct functionalization of C(sp^3)–H bonds which is more challenging owing to their low reactivity and the lack of a coordination site for the transition-metal catalyst.[3] C(sp^3)–H bond activation can

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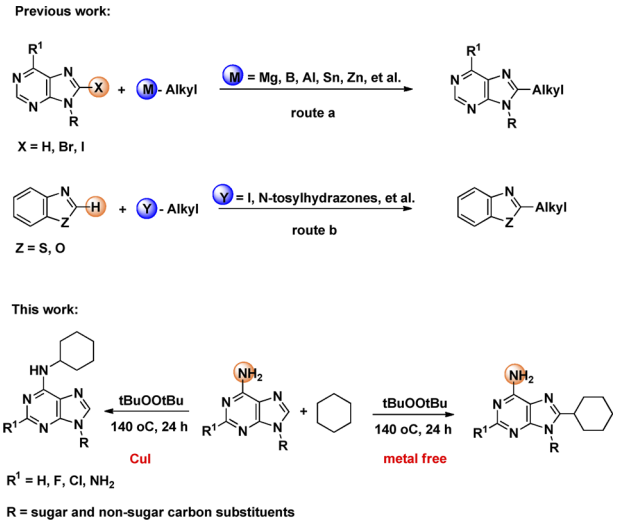
be classified as three types: (1) C(sp^3)−H bond activation with the assistance of a directing group in the presence of transition metals to form versatile functionalized products, including arylation, olefination, alkylation, etc.;[4,5] (2) C(sp^3)−H bond activation adjacent to heteroatoms, double bonds, phenyl or electron withdrawing groups,[6−8] which produces a stable intermediate and is relatively reactive because of the high acidity of the H atom; (3) the C(sp^3)−H bond activation of cycloalkanes to form C−O,[9] C−N,[10] or C−C[11] bonds, which is still rare by virtue of the lower reactivity of C(sp^3)−H bonds in cycloalkanes. Li's group[12a−d] and others[12e] have done elegant work in this field using a transition-metal catalyst (such as Ru, Sc, Fe, etc.) both for activating the C(sp^3)−H bond and subsequent coupling to form C−Y (Y = O, N, C) bonds. The progress of the metal-free C(sp^3)−H bond activation was also achieved between pyridine *N*-oxide and cycloalkanes promoted by *t*BuOO*t*Bu, although the nitrogen heteroaromatics needed to be preactivated and the regioselectivity of the reaction were not satisfactory.[13] Recently, anilines also took part in C(sp^3)−H bond amination through N−Cu(I) coordination.[10d]

Purine nucleobases and nucleosides display a wide range of biological activities (cytostatic, antiviral, antagonists of GnRH, etc.).[14,15] C8-Alkyl substituted purines and *N*6-alkylated adenine derivatives possess unique biological activities and are widely reported in the literatures.[16−18] The traditional method for the synthesis of 8-alkyl purine derivatives is the transition-metal catalyzed coupling of 8-*H* or 8-halo purines with alkyl metals (Scheme 1, route a).[19] 2-Alkyl benzothiazole or benzoxazoles were synthesized through coupling of benzothiazole or benzoxazoles with alkyl halides[20] or *N*-tosylhydrazones[21] catalyzed by a transition-metal catalyst (Scheme 1, route b). As for the synthesis of *N*6-alkylated adenine derivatives, the orthodox method is amination of 6-substituted purines with various amines.[22]

Scheme 1. Strategies for the Alkylation of Heteroaromatics



Herein, we wish to report a double activation of heteroaromatics and C(sp^3)−H alkanes with high regioselectivities. Metal-free conditions gave C−C bond formation products, and adding CuI gave C(sp^3)−H bond amination products.

Initially, we started our study by using 2′,3′,5′-tri-*O*-acetyladenosine (**1a**) and cyclohexane (**2a**) as model substrates to optimize the reaction conditions (see the Supporting

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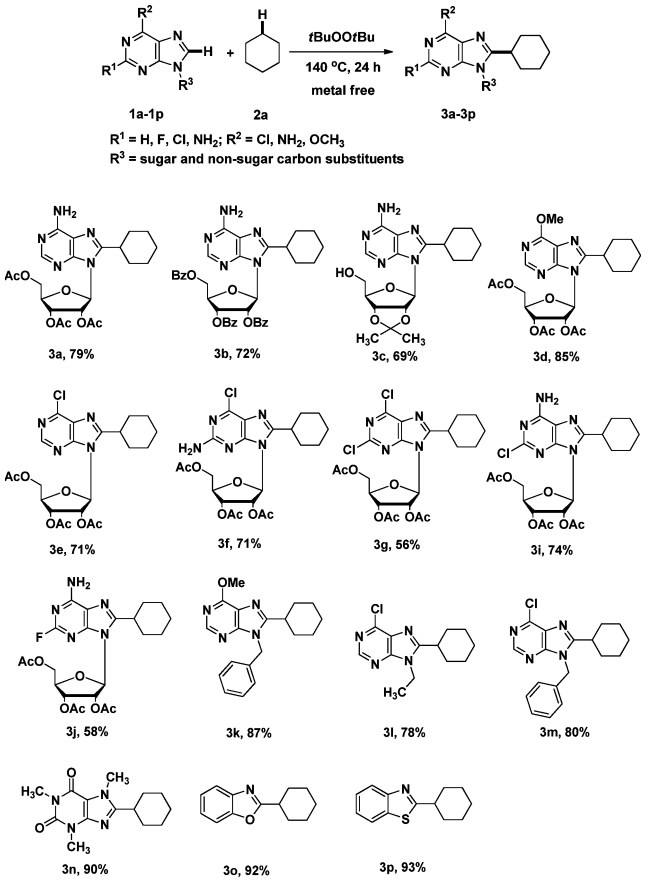
Information). The optimized reaction conditions involved in *t*BuOO*t*Bu as the oxidant at 140 °C for 24 h without solvent under air.

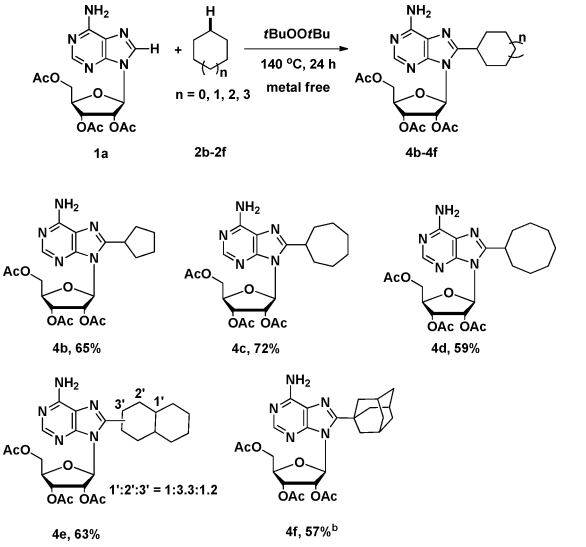
Scheme 2. Cross-Coupling of Heteroaromatics (**1**) with Cyclohexane (**2a**)[a]



[a] The reactions were carried out with **1a** (0.25 mmol), **2a** (10 mL), *t*BuOO*t*Bu (0.5 mmol), 140 °C, 24 h, under air.

With the optimized reaction conditions in hand, the scope of the reaction with respect to purine derivatives was investigated (Scheme 2). A number of modified purines and purine nucleosides, including a nonsugar carbon substituent at *N*9, were subjected to the optimized reaction conditions, affording the desired 8-cyclohexyl purine derivatives in moderate to high isolated yields (56–93%, **3a**–**3p**). When the hydroxyl group on the 5′ position of the sugar cycle was not protected, the yield of the product was somewhat low compared with those protected in the sugar cycle (**3a** vs **3c**). Purine derivatives with stronger electron-donating groups (NH_2, OCH_3) at the C6 or C2 position could furnish the desired products in better yields, but those with electron-withdrawing substituents such as Cl or F gave lower yields (**3d** vs **3e**, **3f** vs **3g**, and **3a** vs **3i**–**3j**). The type of substituent at *N*9 also had an obvious impact on the yield. The *N*9 alkyl-substituted substrates gave higher yields, while the sugar-substituted substrates gave slightly lower yields (**3d** vs **3k**, and **3e** vs **3l**–**3m**). The 2-position of 6-chloro-2-iodo-2′,3′,5′-tri-*O*-acetylpurineside was hydrogenated to give **3e** in 62% yield, and the mechanism was unclear. It was worth mentioning that all of the coupling reaction exclusively occurred on the C8 position of the purines, not on the C2 or other functional groups, giving excellent regioselectivities. In addition to purines and purine nucleosides, we were pleased to find that other nitrogen heteroaromatics (e.g., xanthine, benzothiazole, and benzoxazole) could also react with cyclohexane at C(sp^3)–H and give the products in high yields (**3n**–**3p**).

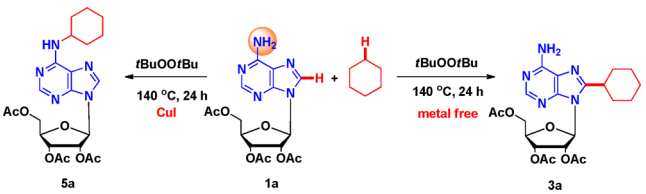
Scheme 3. Cross-Coupling of **1a** with Various Cycloalkanes (**2**)[a]



[a] Unless otherwise mentioned, all of the reactions were carried out with **1a** (0.25 mmol), **2** (10 mL), *t*BuOO*t*Bu (0.5 mmol), 140 °C, 24 h, under air. [b] Benzene (5.0 mL) was used as solvent, and 2.5 mmol of **2f** were used.

The tolerance of this reaction to a range of cycloalkanes was examined (Scheme 3) afterward. In a similar manner to the reaction of **2a**, cyclopentane (**2b**), cycloheptane (**2c**), and cyclooctane (**2d**) reacted smoothly with **1a** to give the desired products (**4b**–**4d**). Decahydronaphthalene (**2e**) gave an unseparated mixture, and the ratio of 1′:2′:3′ was 1:3.3:1.2 (**4e**). Adamantane (**2f**) only reacted at 3° CH to

Scheme 4. Effect of CuI



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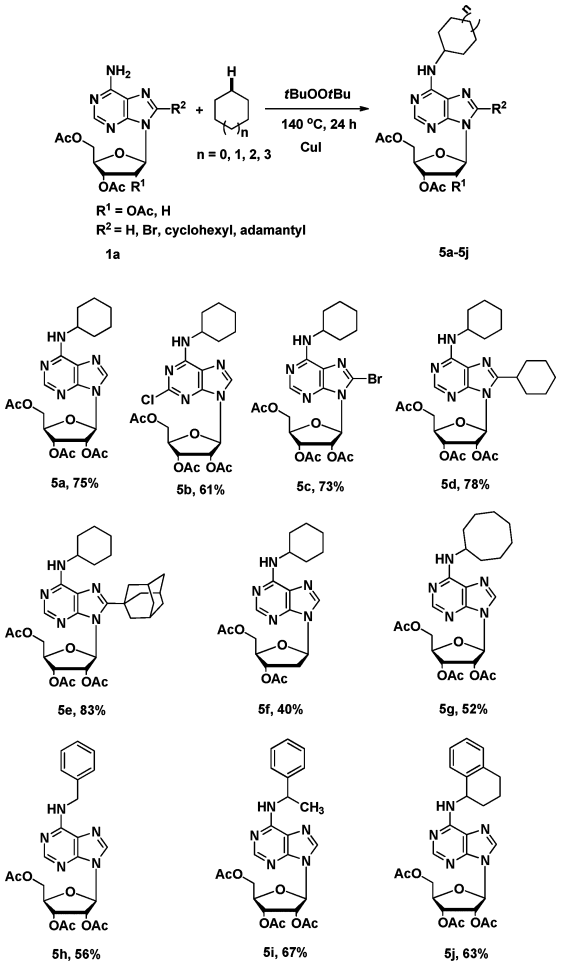
give structurally interesting molecule **4f** in moderate yield. Toluene, phenylethane, or 1,2,3,4-tetrahydronaphthalene gave no product, and the reason was proposed in the subsequent mechanism discussion. The purines were not soluble in *n*-hexane; thus the reaction of purines with *n*-hexane only occurred with a trace yield indicated by TLC.

Scheme 5. C−N Formation of Purines with Various Alkanes (**2**)[a]



[a] 6-Aminopurines (0.25 mmol), **2** (10 mL), *t*BuOO*t*Bu (0.5 mmol), CuI (0.5 mmol), 140 °C, 24 h, under air.

When we added CuI to the reaction mixture of **1a** and **2a**, the formation of the C−N bond was also observed (Scheme 4; see Supporting Information for details). The C−N formation reaction was also extended to a variety of 6-aminopurines (nucleosides) and alkanes (Scheme 5). The 8-alkyl substituted purine nucleosides gave higher yields (**5d**−**5e**), while 8-bromo or 8-H substituted purine nucleosides gave lower yields (**5a**−**5c** and **5f**). Notably, the reaction with toluene, phenylethane, or 1,2,3,4-tetrahydronaphthalene proceeded smoothly in moderate yields (**5h**−**5j**).

A plausible mechanism for this reaction is proposed. It might involve a free-radical process[23] (see the Supporting Information for details). The cyclohexyl free radical reacts at the C8 position of purine by radical addition−oxidation and acquires product **3a**. It should be noted that the reaction was suppressed by a radical scavenger, TEMPO. A significant isotope effect was observed (k_H/k_D = 3.8), suggesting that C−H bond cleavage of cyclohexane is the rate-limiting step. When we added CuI to the reaction, the cyclohexyl radical can be converted into the cyclohexyl cation[10c] which then reacts with the amino group on account of its more electrophilic property.

In conclusion, we have developed a new method to modify purines (nucleosides), benzothiazole, and benzoxazole through C(sp^3)−H activation with alkanes. The reaction exclusively occurred on C8 to give 8-cylcoakylpurines by C−C bond formation under metal-free conditions in the presence of *t*BuOO*t*Bu, while it occurred on the amino group to give N6-alkylated purines by C−N bond formation when CuI was added. The preliminary experimental data showed that the C−C bond formation reaction presumably involves the production of a cycloalkyl radical and subsequent radical addition−oxidation reactions with heteroaromatics. And the C−N bond formation reaction might be through electrophilic attack on the amino group by carbocation which was produced by the oxidation of a carbon radical by CuI. A range of heteroaromatics, including purines, purine nucleosides, benzothiazole, and benzoxazole, might be employed and gave satisfactory yields. Further application of this protocol is being developed, and research about the detailed mechanism is ongoing in our group.

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Supporting Information Available. Experimental details, optimization of the reaction conditions, proposed mechanism, copies of all spectra, and full characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.