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# Nickel-Catalyzed C–H Activation of Purine Bases with Alkyl Halides

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Zhixiong Ruan,[a] Debasish Ghorai,[a,b] Giuseppe Zanoni,[b] and Lutz Ackermann[a,b]*

**C–H alkylations of purine nucleosides were achieved by means of most user-friendly nickel catalysis with ample substrate scope and high levels of chemo, site and regio control, which among others enabled the direct fluorescent labeling of purines in terms of late stage diversification.**

## Introduction

Purines represent a privileged structural motif found in various compounds of relevance to biology with *inter alia* anti-retroviral, anti-cancer and anti-malaria activities (Figure 1a).[1] Thus, the preparation of non-natural purine analogs by chemical syntheses has attracted considerable attention, with notable recent progress by means of transition metal-catalyzed C–H[2] functionalization.[3] Despite of undisputed advances,[4]Hocek/Fairlamb these transition-metal catalyzed chelation-assisted C–H transformations have in large been dominated by the use of expensive precious 4d and 5d transition metal catalysts.[4a-h, 5] In contrast, recent focus has shifted towards cost-effective base metals[6] with considerable progress in arene C–H activation by naturally abundant nickel, featuring major contributions by Chatani,[7] Ge,[8] Ackermann,[9] and Shi,[10] among others. However, nickel-catalyzed arene C–H activation was unfortunately thus far largely limited to benzamide substrates bearing *N,N*-bidentate directing group,[6c] and C–H alkylations[11] of purines have proven elusive. Within our own program on nickel-catalyzed C–H alkylation,[9a] we have now developed the first protocol for nickel-catalyzed C–H alkylations of 6-anilinopurines, on which we report herein. Notable features of our general strategy include (*a*) the use of inexpensive nickel(II) catalysts for C–H alkylations of highly valuable purine bases *via* purinyl six-membered metallacycle, (*b*) an unparalleled broad substrate scope including both primary and secondary alkyl halides, (*c*) direct fluorescent labeling on nuclobases, and (*d*) considerable mechanistic insights. It is particularly noteworthy that the unique catalyst-guided C–H functionalization selectively occurred at the aniline motif, while the C–H functionalization process was not governed by C–H dissociation energies,[12] or the C–H acidity[13] at the C8 position (Figure 1b).

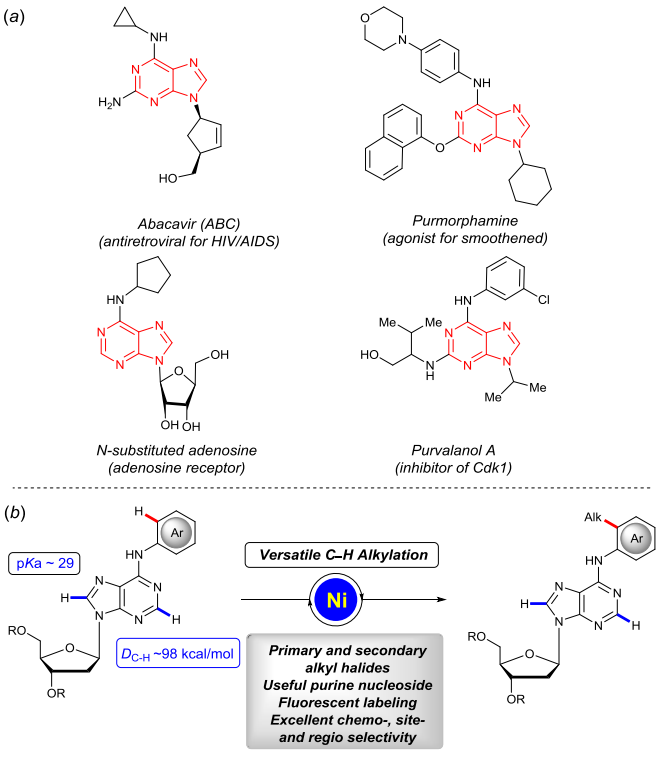


**Figure 1.** Nickel-catalyzed C–H activation of bioactive purine bases.

## Results and Discussion

At the outset of our studies, we probed a representative set of ligands for the envisioned nickel(II)-catalyzed C–H alkylation of 6-anilinopurine **1a** with secondary alkyl bromide **2a** in 1,4-dioxane as the solvent (Table 1). While typical phosphine, N-heterocyclic carbene,[14] or bipyridine ligands failed to improve the yield of desired product **3aa** (entries 1–4), the vicinal diamine D*t*BEDA (**4**) was identified as being the ligand of choice (entry 5). The conversion of

*[a] Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstraße 2, 37077 Goettingen, Germany.*
*[b] Department of Chemistry, University of Pavia, Viale Taramelli, 10, 27100 Pavia, Italy*
*E-mail: Lutz.Ackermann@chemie.uni-goettingen.de.*

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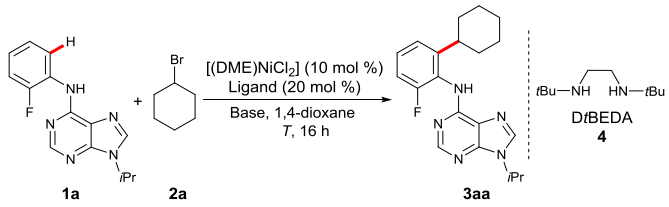
substrate **1a** was not achieved with $Na_2CO_3$ and $K_2CO_3$ as the base (entries 6 and 7). It is noteworthy that the C−H functionalization proceeded in a similar manner in the absence of an additional ligand, albeit with reduced efficacy (entry 8). The reaction temperature could be reduced (entry 9), while a control experiment verified the essential role of the nickel catalyst (entry 10).

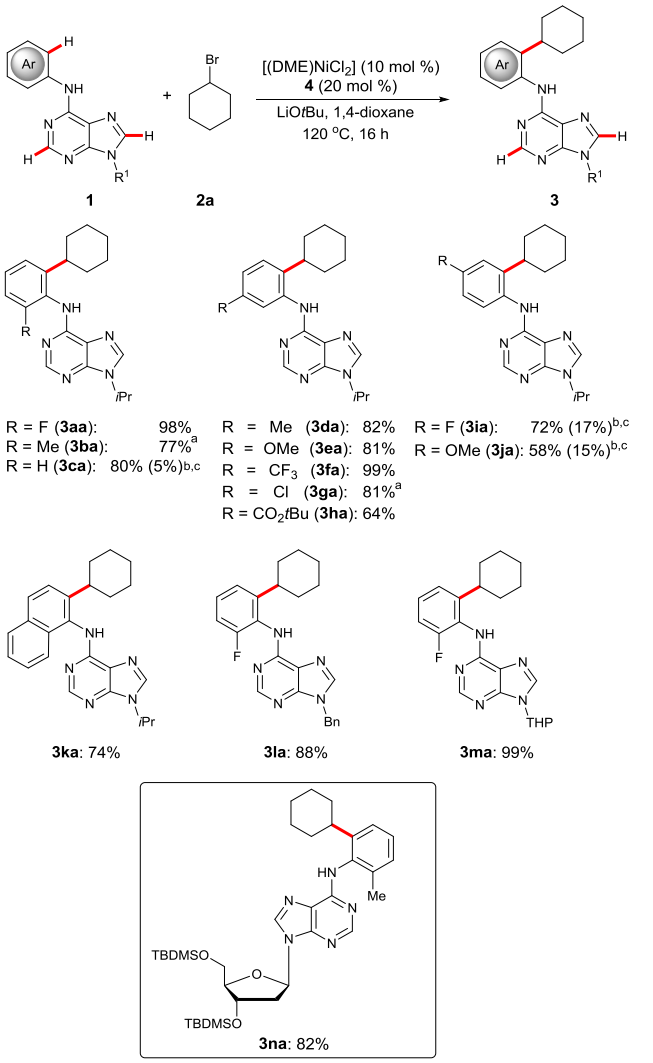
**Table 1.** Optimization of C−H alkylation with purine **1a**.[a]




| Entry | Ligand | Base | *T* [°C] | **3aa** [%] |
|---|---|---|---|---|
| 1 | $PPh_3$ | LiO*t*Bu | 120 | 47 |
| 2 | IPr·HCl | LiO*t*Bu | 120 | 70 |
| 3 | IMes·HCl | LiO*t*Bu | 120 | trace |
| 4 | D*t*BBPY | LiO*t*Bu | 120 | 0 |
| **5** | **D*t*BEDA (4)** | **LiO*t*Bu** | **120** | **98** |
| 6 | D*t*BEDA (**4**) | $Na_2CO_3$ | 120 | 0 |
| 7 | D*t*BEDA (**4**) | $K_2CO_3$ | 120 | 0 |
| 8 | - | LiO*t*Bu | 120 | 68 |
| 9 | D*t*BEDA (**4**) | LiO*t*Bu | 100 | 85 |
| 10 | D*t*BEDA (**4**) | LiO*t*Bu | 120 | 0[b] |

[a] Reaction conditions: **1a** (0.30 mmol), **2a** (2.0 equiv), [(DME)$NiCl_2$] (10 mol %), ligand (20 mol %), base (2.0 equiv), 1,4-dioxane (1.5 mL), under $N_2$, 16 h. [b] Without [Ni]. D*t*BBPY = 4,4'-di-*tert*-butyl-2,2'-dipyridyl.

With the optimized nickel(II) catalyst in hand, we probed its versatility in the C–H alkylation of differently substituted purine derivatives **1** (Scheme 1). The nickel-catalyzed C–H functionalization proved widely applicable and enabled highly chemo-selective transformations of *ortho*- and *para*-substituted arenes **1**. *meta*-Substituted anilines **1d-1h** delivered the desired products **3** with excellent positional selectivity control, which was governed by steric interactions. Moreover, the robustness of the versatile nickel catalyst was reflected by fully tolerating both electron-rich groups as well as synthetically meaningful electron-deficient functional groups, such as fluoro, chloro and ester substituents. Substrates displaying different *N*-substituents afforded the C–H alkylated products **3ka-3ma** in high yields. Furthermore, the robustness of the nickel(II)-catalyzed C–H alkylation was also illustrated by the efficient functionalization of purine nucleoside **3na**.

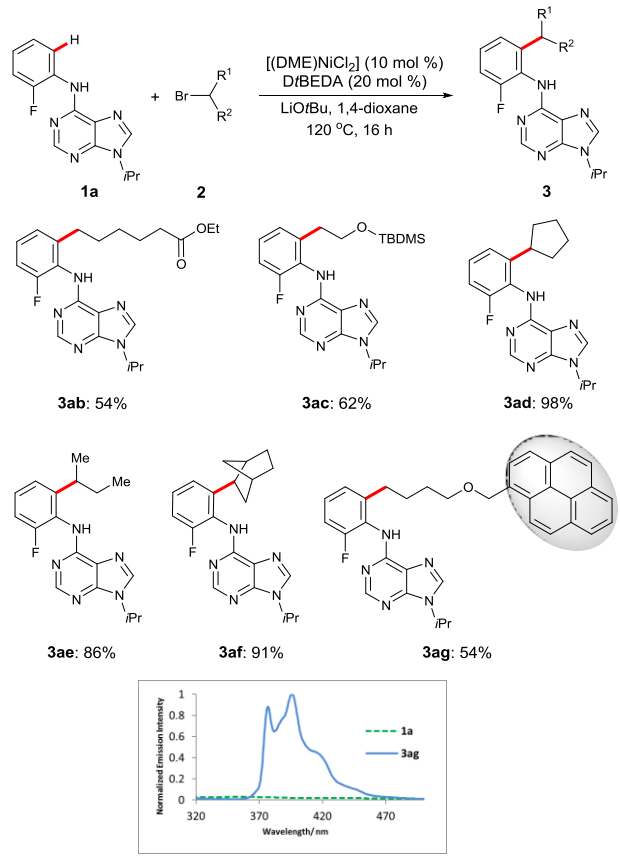



**Scheme 1**. C–H alkylation of purine nucleoside **1**. [a] [Ni] (5.0 mol %). [b] **2** (1.1equiv). [c] Isolated yields of dialkylated products **3'** in parenthesis.

Subsequently, we probed the scope of viable primary and secondary alkyl bromides **2** in the nickel-catalyzed C–H transformation manifold (Scheme 2). The robustness of our method was highlighted by successful C–H alkylations with various functionalized primary alkyl halides **2** displaying ester or ether groups, among others. Furthermore, the inexpensive nickel catalyst could not only be used for reactions with cyclic alkyl halide **2d**, but also the acyclic electrophile **2e**, furnishing the desired product **3ae** in a chemoselective manner. Notably, the C–H alkylation with a norbornyl bromide **2f** delivered the *exo* product **3af** with retention of configuration.

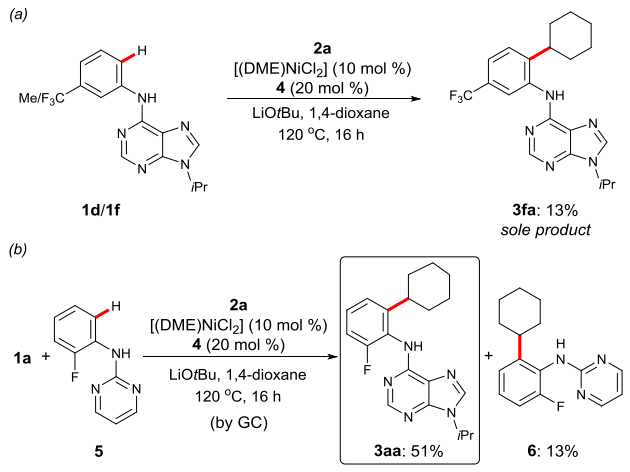
Interestingly, the remarkable synthetic utility of our nucleobase C–H functionalization was demonstrated by introducing a pyrene fluorescent label in a user-friendly fashion, highlighting the potential for the fluorescent labeling of nucleobases.[15]



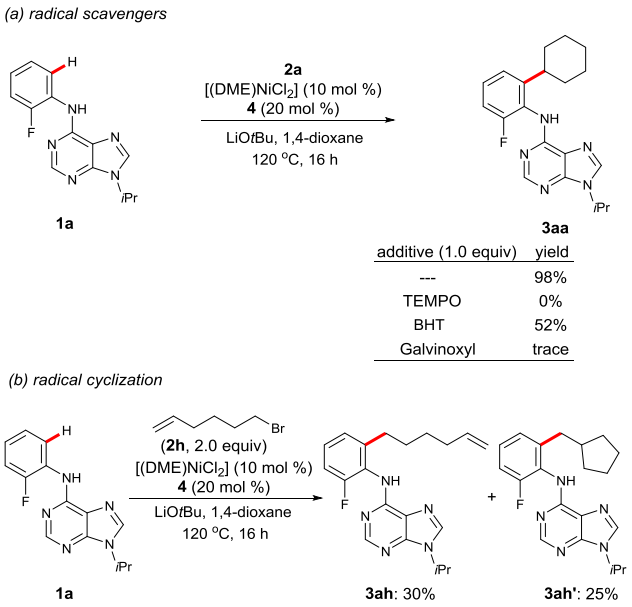

**Scheme 2**. C–H alkylation of purine base **1a** with alkyl halides **2** and fluorescence spectra of purines **1a** and **3ag.**

In consideration of the unique efficiency of the nickel catalysis regime, we became intrigued by rationalizing its mode of action. To this end, intermolecular competition experiments between differently substituted arenes **1** revealed electron-withdrawing groups to react preferentially (Scheme 3a). Moreover, an intermolecular competition experiment between the purinyl and the pyrimidyl groups revealed the former to be more powerful in the nickel-catalyzed C–H activation process (Scheme 3b).



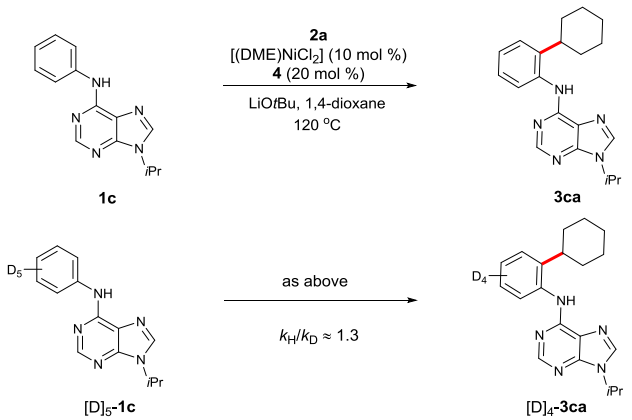

**Scheme 3**. Intermolecular competition experiments.

The nickel-catalyzed C–H functionalization was inhibited by the addition of typically used radical scavengers (Scheme 4a), which can be rationalized in terms of single-electron transfer (SET)-type processes being of key relevance. In good agreement with this hypothesis, the involvement of radical intermediates was confirmed through the partial cyclization of 6-bromohexene (**2h**) (Scheme 4b).[16]




**Scheme 4**. Key mechanistic findings supporting SET-based mechanism.

Moreover, we observed a significant H/D scrambling with labeled substrate [D]$_5$-**1c** and a minor kinetic isotope effect (KIE) of $k_H/k_D \approx 1.3$ in independent experiments, being indicative of a facile C–H metalation event (Scheme 5).[17]




**Scheme 5**. Independent KIE studies.

## Conclusions

In summary, we have developed the first nickel-catalyzed C–H alkylation of purine nucleoside. Thus, 6-anilinopurines were C–H

functionalized with excellent positional selectivity, ample substrate scope and high functional group tolerance, providing access to key structural motifs of numerous bioactive compounds and marketed drugs. The unique synthetic utility of the nickel catalysis regime set the stage for novel strategies of direct nucleobase fluorescent labeling, while mechanistic studies were indicative of a facile C–H nickelation step and a SET-type C–X cleavage event.

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16. This observation is in good agreement with the previously reported one; see Ref. [9a].
17. For detailed information, see the Supporting Information.