C-H alkylation of heterocycles via light-mediated palladium catalysis

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Abstract: *Methods enabling direct C-H alkylation of heterocycles are of fundamental importance in the late-stage modification of natural products, bioactive molecules, and medicinally relevant compounds. However, there is a scarcity of a general strategy for the direct C-H alkylation of a variety of heterocycles using commercially available alkyl surrogates. We report an operationally simple palladium-catalyzed direct C-H alkylation of heterocycles using alkyl halides under the visible light irradiation with good scalability and functional group tolerance. Our studies suggest that the photoinduced alkylation proceeds through cascade of events comprising, site-selective alkyl radical addition, base-assisted deprotonation, and oxidation. A combination of experiments and computations was employed for the generalization of this strategy, which was successfully translated towards the modification of natural products and pharmaceuticals.*

Direct C-H alkylation reactions of heterocycles are of high relevance for the introduction three-dimensional aliphatic frameworks onto the heterocycle skeletons. Such direct alkylation reactions overcome limitations of prefunctionalization of starting materials and would ideally allow the direct employment of readily available heterocycles and alkyl halides to furnish sp³-rich building blocks. The latter are highly demanded in modern drug discovery to improve on the properties of drug molecules.[1-3] For example, sp³-rich building blocks are essential to increase molecular complexity, to improve target binding and/or selectivity, or to improve ADME properties (adsorption, distribution, metabolism, excretion) of small molecule drugs (**1a**,**b**, Scheme 1a).[3] A generalized method that allows the introduction of alkyl groups onto existing heterocyclic frameworks from simple, commercially available precursors thus represents an imperative approach to address modern demands in the search of state-of-the-art drug molecules.

Until today, different approaches in accessing radical intermediates and their application in the functionalization of heterocycles have been described,[4] e.g. proceeding via the introduction of alkyl radicals via Minisci-type reactions (Scheme
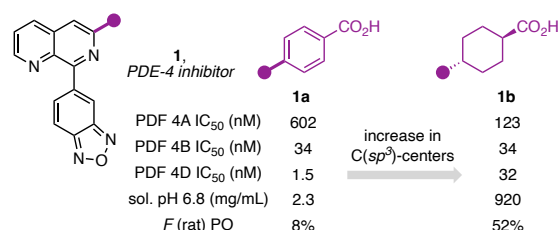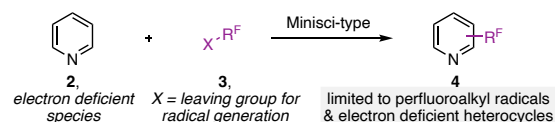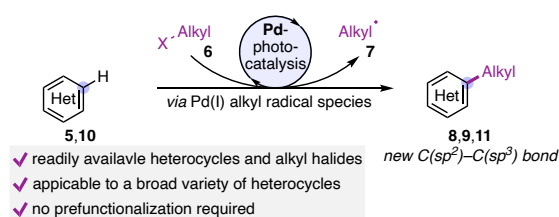

Scheme 1. Sp³-rich compounds in drug discovery and radical alkylation chemistry.

1b), via halogen atom transfer reactions, or via hydrogen atom transfer.[5-7] Alternatively, C-H alkylation with activated and synthetically modified alkyl precursors, such as alkyl N-(acyloxy)phthalimides, 1,4-dihydropyridines, alkyl peroxides, and redox-active oxime esters are known as well.[8,9] However, the direct introduction of carbon-centered radicals from simple precursors such as alkyl halides is significantly more demanding. In this context, we considered to access such radical

intermediates via visible light-induced palladium catalysis (Scheme 1c).[10,11] Visible light-induced palladium catalysis has recently attracted the interest of synthetic chemists and commonly proceeds through the intermittent formation of a Pd(I) alkyl radical species, which can engage, e.g. in Heck-type couplings, 1,2-difunctionalization reactions, or annulation reactions.[11] Based on our interest in the functionalization of heterocycles,[12,13] we were considering that such strategy could be employed to transfer an alkyl radical onto an existing heterocyclic framework. Following rearomatization, such process should lead to formal C-C coupling reactions between a heteroaromatic C(sp^2) and an aliphatic C(sp^3) atom.

To address this challenge, we considered the light-mediated, palladium-catalyzed C-H alkylation reaction of azauracil **5** (Table 1).[8b,c,14] In the presence of Pd(PPh$_3$)$_4$ and XantPhos as ligand, we could observe a high yielding C-H alkylation reaction of azauracil **5** using a slight excess of cyclohexyl iodide **6a** or cyclohexyl bromide as alkylating reagent (Table 1, entries 1,2). Cyclohexyl chloride gave no reaction (entry 3). Further optimization steps involved the influence of solvent, palladium source and reaction stoichiometry (Table 1, entries 2,3, Table S1) – under optimized conditions the alkylated azauracil **8a** could be isolated in near quantitative yield (entry 4). Control reactions in the absence of light, base, or Pd source showed that no reaction occurred and all starting materials remained untouched (entry 5). Xantphos as a ligand proved important and had a significant influence on the reaction yield (entry 6). The robustness screen showed that deviations from the optimized reaction conditions still gave satisfactory yields of the reaction product. The most critical parameters were found to be the addition of water, longer wavelength, or the reaction in air (see Scheme S1).
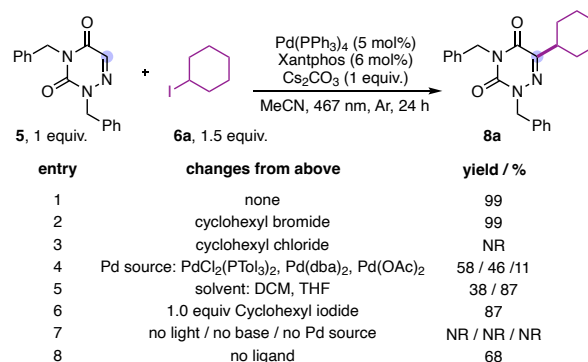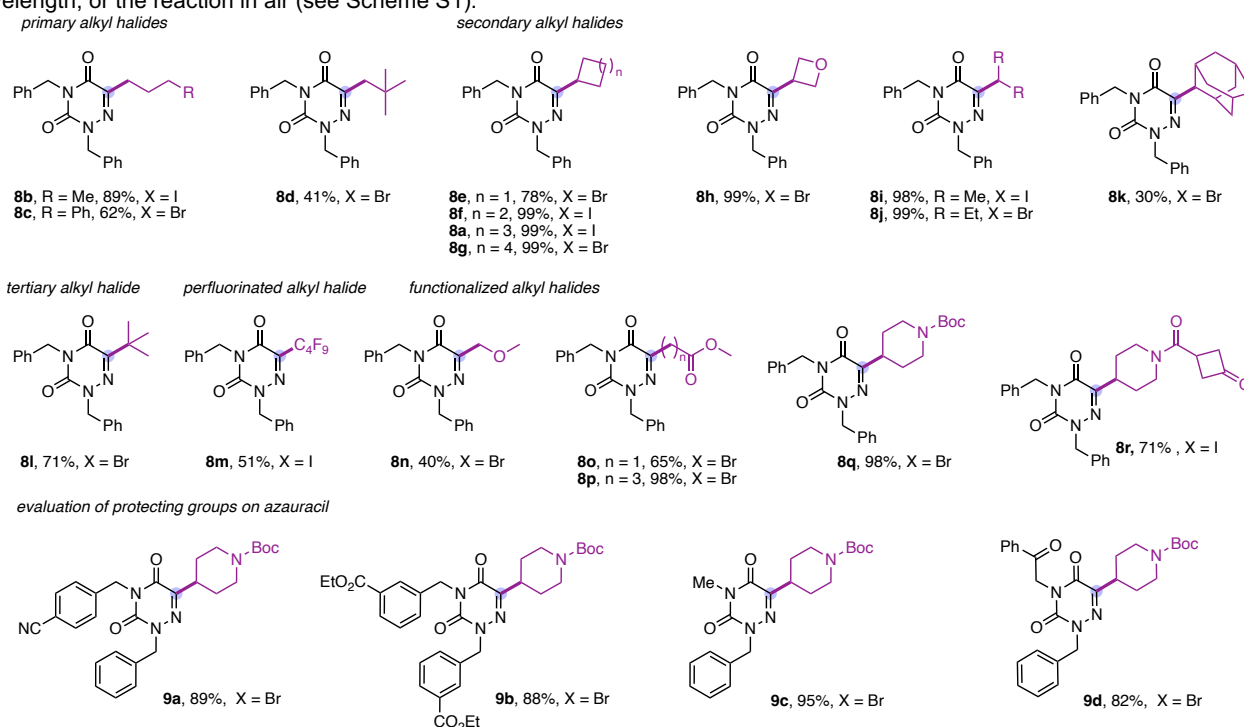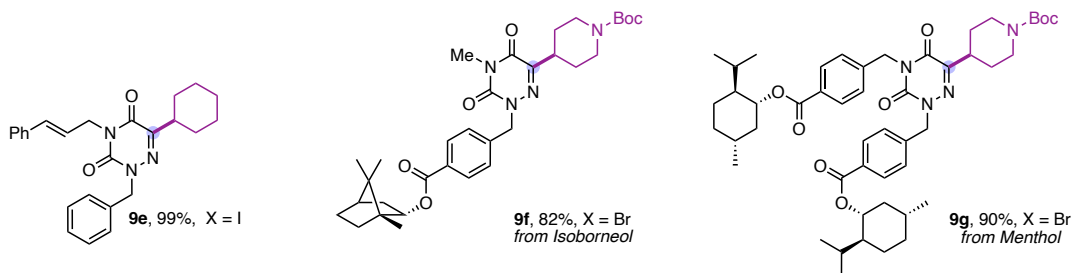

entry	changes from above	yield / %
1	none	99
2	cyclohexyl bromide	99
3	cyclohexyl chloride	NR
4	Pd source: PdCl$_2$(PTol$_3$)$_2$, Pd(dba)$_2$, Pd(OAc)$_2$	58 / 46 / 11
5	solvent: DCM, THF	38 / 87
6	1.0 equiv Cyclohexyl iodide	87
7	no light / no base / no Pd source	NR / NR / NR
8	no ligand	68

Table 1. Reaction optimization.

With the optimized conditions in hand, we next embarked on the evaluation of the substrate scope (Scheme 2). Tertiary, secondary and primary alkyl halides were tolerated under the present reaction to give alkylated azauracils **8b-8l** in good to high yield. Even the sterically demanding neopentyl bromide was found compatible to give **8d** in moderate yield. Next, examples of perfluorinated alkyl halides (**8m**) and alkyl halides bearing functional groups such as ethers, protected amines, or esters (**8n-8r**) were evaluated, which all gave the desired alkylation products in high yield. Last, different N-protecting groups on azauracil were evaluated, which only had a minor effect on the reaction product yield (**9a-9g**).


primary alkyl halides

8b, R = Me, 89%, X = I
8c, R = Ph, 62%, X = Br

8d, 41%, X = Br

secondary alkyl halides

8e, n = 1, 78%, X = Br
8f, n = 2, 99%, X = I
8a, n = 3, 99%, X = I
8g, n = 4, 99%, X = Br

8h, 99%, X = Br

8i, 98%, R = Me, X = I
8j, 99%, R = Et, X = Br

8k, 30%, X = Br

tertiary alkyl halide

8l, 71%, X = Br

perfluorinated alkyl halide

8m, 51%, X = I

functionalized alkyl halides

8n, 40%, X = Br

8o, n = 1, 65%, X = Br
8p, n = 3, 98%, X = Br

8q, 98%, X = Br

8r, 71% , X = I

evaluation of protecting groups on azauracil

9a, 89%, X = Br

9b, 88%, X = Br

9c, 95%, X = Br

9d, 82%, X = Br

**Scheme 2 continued.** Investigations on the basic substrate scope.

In a next step, we embarked on the computational analysis of the reaction mechanism for an understanding of key reaction steps in this C-H alkylation reaction (Scheme 3A). Following the current working hypothesis on visible light-mediated palladium catalysis,[15] this analysis indicates that the reaction proceeds through formation of a palladium(I) alkyl radical intermediate **7a**, which reacts via **TS1** to the radical intermediate **INT1**. The subsequent oxidation of **INT1** can occur via single electron transfer to the intermediate Pd(I) complex. Experimental validation was carried out by on/off experiments. The on/off experiment shows that the reaction is occurring exclusively in the

presence of light and that no reaction is observed, when the light is switched off and provides evidence that radical chain reactions are not playing a role in this transformations (Scheme 3B). When using the radical probe 6-iodo-hex-1-ene (**6b**), we could observe exclusive formation of product **8s**, which results from intramolecular radical cyclization followed by radical addition to the azauracil heterocycle (Scheme 3C). In the presence of TEMPO as radical trapping reagent, the reaction yield significantly dropped, consistent with a mechanism involving radical intermediates (Scheme 3D).
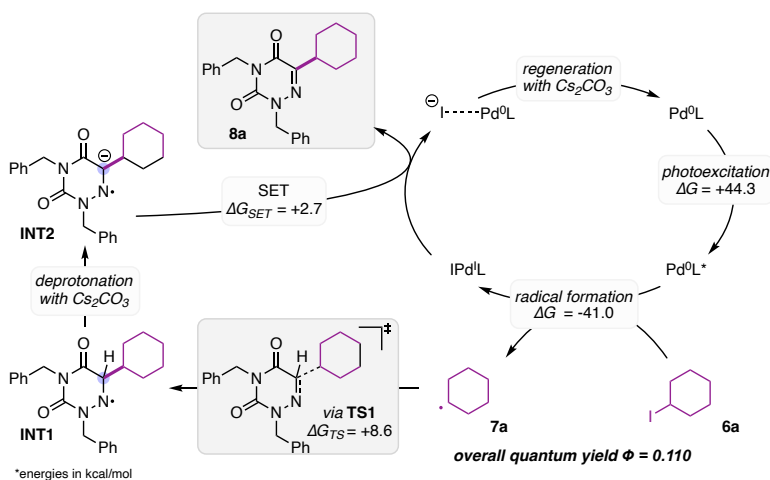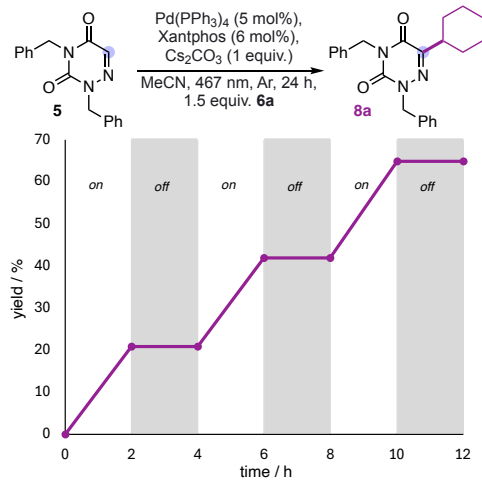
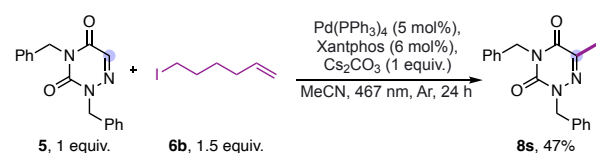**Scheme 3.** Combined computational and experimental studies on the reaction mechanism.

We next embarked on a combined experimental and computational screening of a more generalized set of heterocycles with the aim of building a basis for a predictive computational substrate screening.[15b,16] Such computational substrate screening methods are of high relevance to reduce synthetic efforts and to build a structure reactivity relationship.

Taken together, such data can be used in a next step to facilitate screening of generalized limitations of substrate scope.
For this purpose, we embarked on the analysis of a selected set of 5- and 6-membered ring N-heterocycles and one example of an O-heterocycle. For each data point, we conducted the C-H alkylation reaction of the heterocycle with cyclohexyl iodide to

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obtain a solid experimental basis (Scheme 4A). In parallel, the computational analysis of the radical addition step of a cyclohexyl radical to each of the C-H bonds of the heterocycle was conducted (Scheme 4B). We then compared experimental yield with the activation free energy of the energetically most feasible C-H alkylation reaction (Scheme 4C, for details, see Table S4).
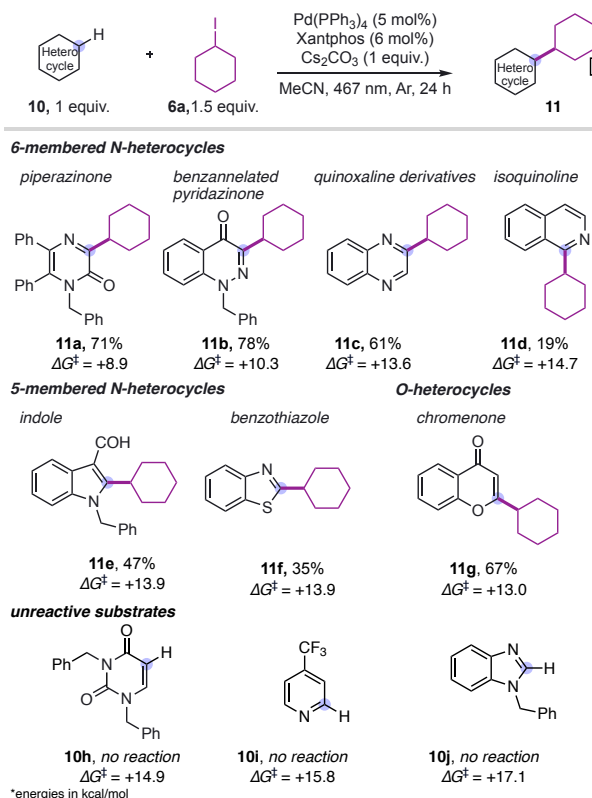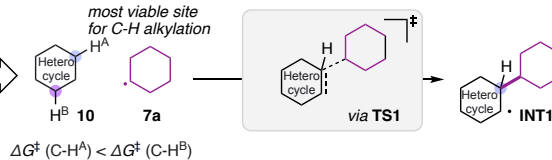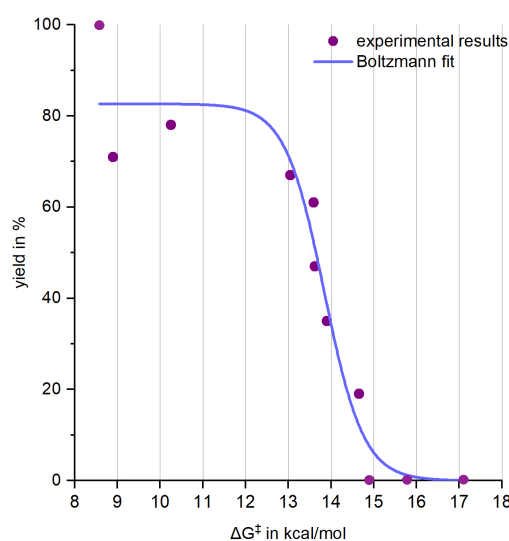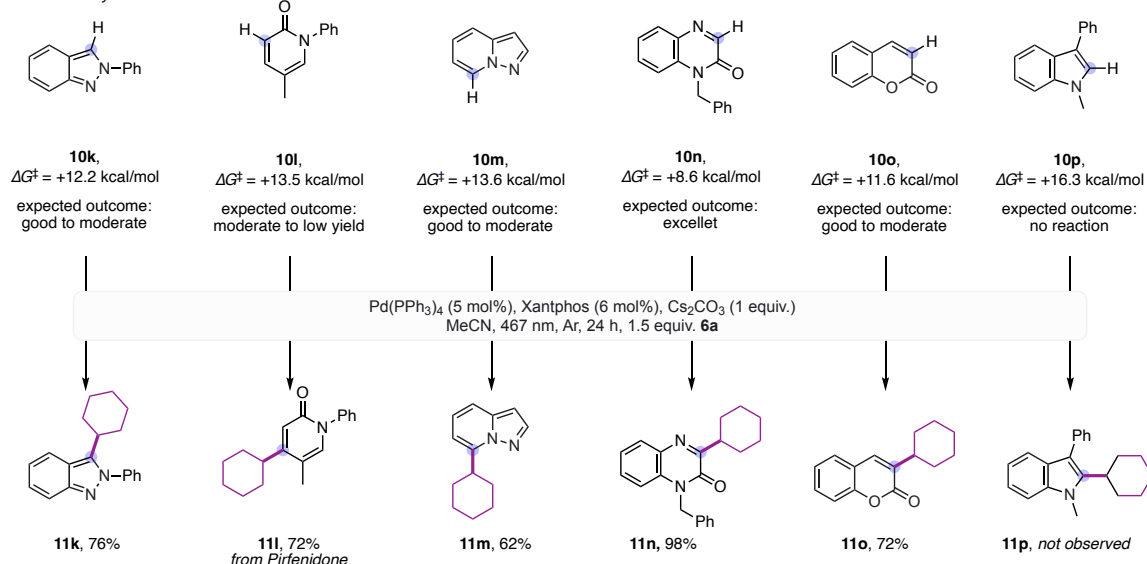

Scheme 4. Development of a predictive model for translation towards a generalized heterocycle C-H alkylation reaction.

To our delight, this computational model shows that the computational data on site-selectivity matches with the experimentally observed site-selectivity. For example, in the case of chromenone **10o** the radical addition was predicted to the α-
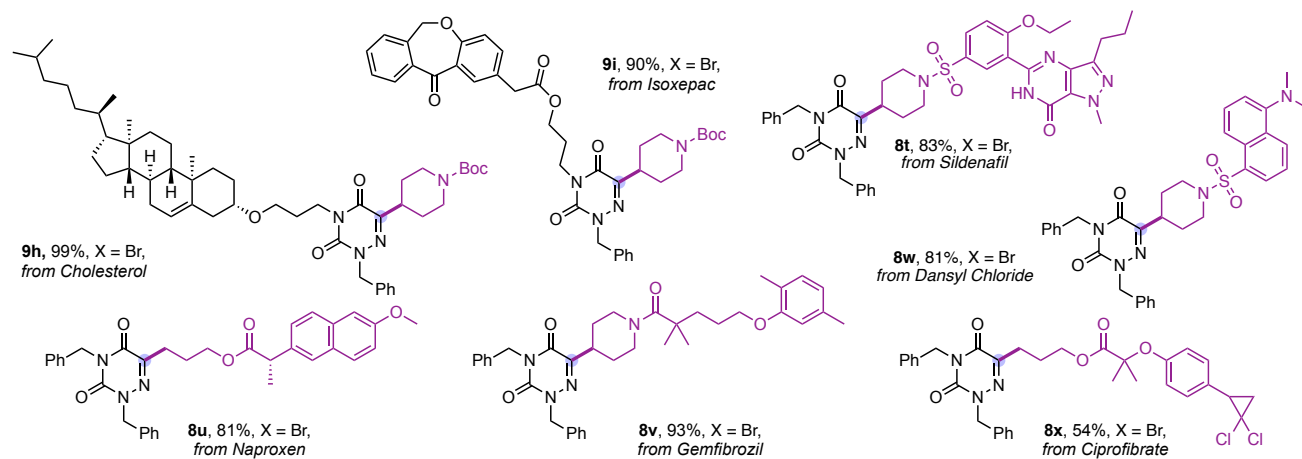
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position of the carbonyl group with an activation free energy of 13.0 kcal mol^{-1}. All other potential sites were calculated to be unfavored by at least 3.1 kcal mol^{-1}. This was then confirmed by experiment with a good yield of 67% and exclusive site-selectivity. Across the whole initial dataset, an activation free energy of approximately 14 kcal mol^{-1} was found to be crucial for a good reaction yield. For the reaction heterocyclic substrates and a cyclohexyl radical with activation free energies of more than 14 kcal mol^{-1} no product of C-H functionalization could be observed experimentally.

This analysis provides a basis for further analysis and broadening of substrate scope. In this context we did the computational examination of a more generalized set heterocycles, of which examples of further suitable heterocycles are shown in Scheme 4D. Computations predict that heterocycles **10k-10o** should react favorably in this C-H alkylation reaction and activation free energies for the preferred site of radical addition were found to be in the range of 8.6 to 13.6 kcal mol^{-1}. Contrarily, indole heterocycle **10p** should not react in this reaction owing to the large activation free energy. The subsequent experimental validation showed that

yield and site-selectivity of the C-H functionalization are in accordance with the computational pre-screening. For example, the 2H-indazole heterocycle, pyridine, quinoxalinone, or coumarin heterocycles were identified as suitable substrates for further evaluation of applications of this heterocycle C-H alkylation reaction.

In the next step, we embarked on synthetic applications of this C-H alkylation reaction (Scheme 5). For this purpose, we initially studied a 2 examples, where a cholesterol or isoxepac were introduced in the side chain of the azauracil heterocycle. In both cases high yields of the respective C-H alkylation product with N-Boc 4-bromo piperidine were obtained. Further examples then include alkyl halides, were drug molecules were introduced into the side chain (**9h**,**i**, **8t-8x**). Most notably, an analogue of sildenafil could be obtained in high yield, which underlines the good functional group compatibility of this heterocycle C-H alkylation reaction. Similarly, dansyl-protected 4-bromo piperidine reacted in high yield, which showcases the compatibility with other dye molecules.

A *Translation towards natural products and drug derivatives*

B *Translation towards a generalized heterocycle alkylation*
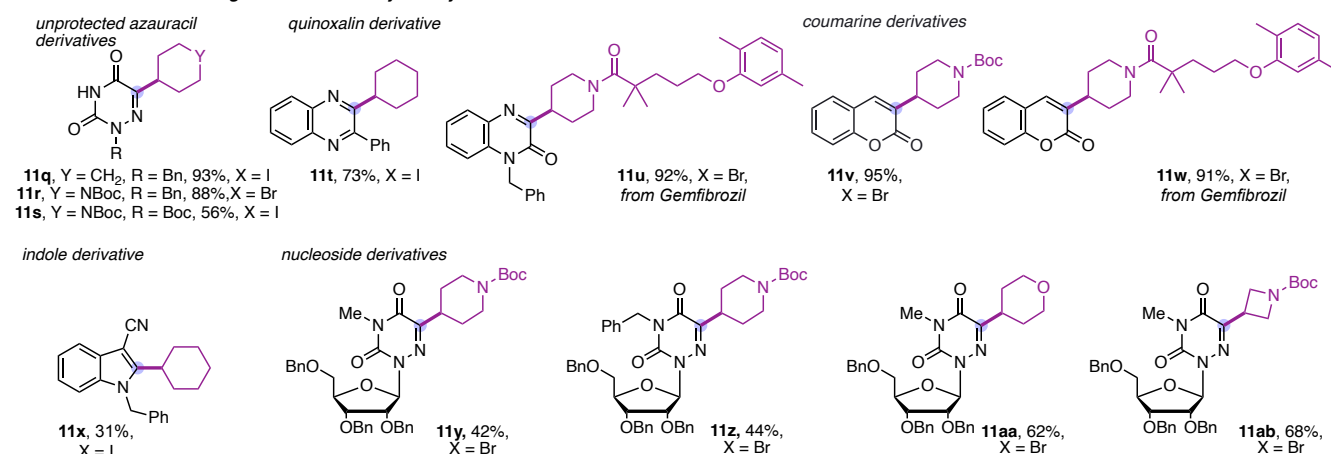
Scheme 5. Applications with natural products, drug molecules and nucleoside synthesis.

In further studies, the application of heterocycles was further examined. Notably, unprotected azauracil could be demonstrated to successfully undergo C-H alkylation to give **11q**,**s**. Similarly,

indole, quinoxaline, or coumarin derivatives were demonstrated in alkylation reactions, e.g. with N-Boc 4-bromo piperidine or with conjugates of drug molecules (**11t-11x**). Most notably, this

method allows the conjugation of coumarin drugs with other drug molecules, such as Gemfibrozil. Last, applications in the synthesis of nucleoside analogues were examined and here, a range of different alkyl halides proved compatible with the present reaction conditions (**11y-11ab**).

In summary, we herein report on the direct C-H alkylation of heterocycles. We describe that a palladium catalyst can be employed in the presence of visible light to access alkyl radical intermediates under mild reaction conditions. Such radical intermediates were shown to undergo high-yielding C-H alkylation reactions of heterocycles. Following an initial screening and control experiments using azauracils, we describe a combined computational and experimental approach to build a model to correlate reaction efficiency with a key transition state of the reaction. We show that the energy barrier of this transition state can be used to assess the viability of more generalized heterocycle C-H alkylation reaction with high predictability on the site of C-H functionalization and reaction outcome. This approach was used to identify a set of further heterocycles that undergo efficient C-H alkylation reactions including applications, e.g. in the functionalization of drug molecules, natural products, or the synthesis of nucleoside analogues.

Supporting Information

The authors have cited additional references within the Supporting Information.

Acknowledgements

Keywords: Palladium • Photochemistry • Heterocycles • Computational Studies • C-H functionalization

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