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Photochemistry

C–H Alkylation of Heterocycles via Light-Mediated Palladium Catalysis

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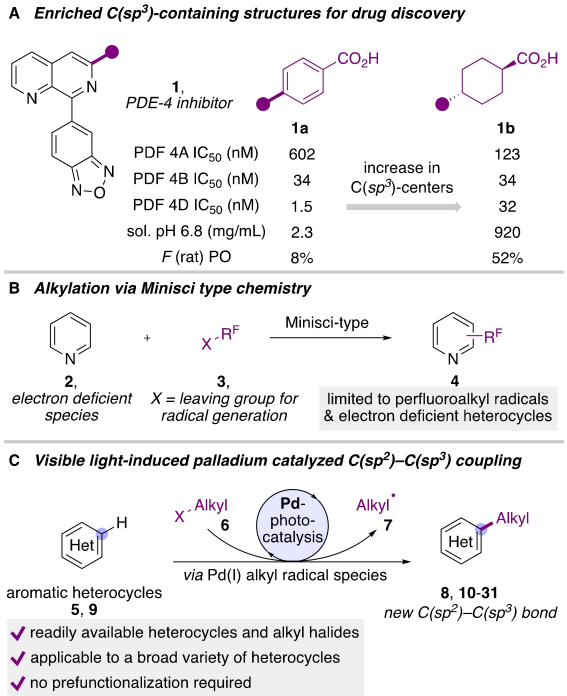
Abstract: Methods enabling direct C–H alkylation of heterocycles are of fundamental importance in the late-stage modification of natural products, bioactive molecules, and medicinally relevant compounds. However, there is a scarcity of a general strategy for the direct C–H alkylation of a variety of 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 a 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 of 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 sp^3-rich building blocks. The latter are highly demanded in modern drug discovery to improve on the properties of drug molecules.[1–3] For example, sp^3-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 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



Scheme 1. (**A**) Sp^3-rich compounds in drug discovery and radical alkylation chemistry. (**B**) Alkalyation via Minisci chemistry. (**C**) C–H alkylation of aromatic heterocycles via light-induced palladium catalysis.

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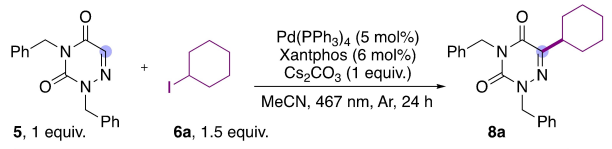
palladium catalysis (Scheme 1c).[10,11] Visible light-induced palladium catalysis has recently attracted the interest of synthetic chemists and commonly proceeds through the intermittent formation of a Pd(I) alkyl radical species, which can engage, e.g. in Heck-type couplings, 1,2-difunctionalization 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 palladium source, solvent(Table 1, entries 4, 5) and reaction stoichiometry (entry 6 and Table S1)—under optimized conditions the alkylated azauracil **8a** could be isolated in near quantitative yield. Control reactions in the absence of light, base, or Pd source showed that no reaction occurred and all starting materials remained untouched (entry 7). Xantphos as a ligand proved important and a significant reduction of the reaction yield was observed without ligand (entry 8). The sensitivity 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).

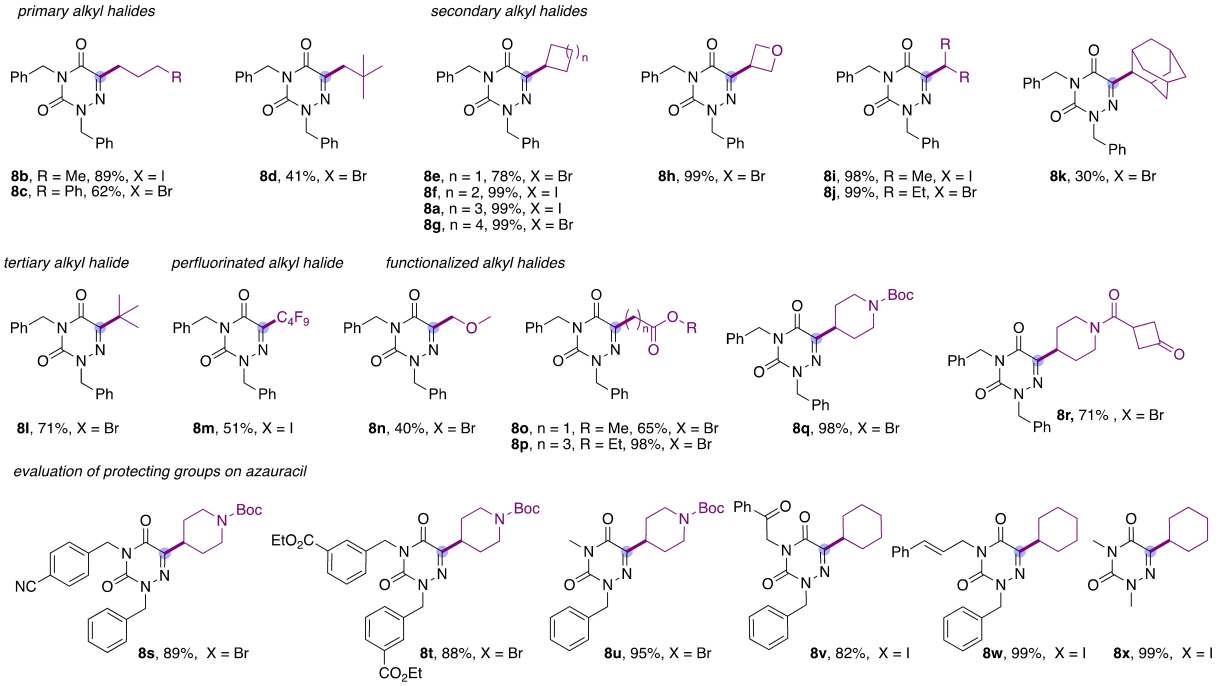
Table 1: Reaction optimization. Xantphos = (9,9-Dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane), NR = No reaction.



5, 1 equiv. **6a**, 1.5 equiv. **8a**

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: CH_2Cl_2, 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

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. A slightly reduced product yield was observed, when studying an example of a perfluorinated alkyl halides (**8m**). A range of different alkyl halides bearing functional groups such as protected amines, or esters (**8o–8r**) were evaluated, which all gave the desired alkylation products in high yield. Limitations were found with the electron-rich, stabilized primary alkyl halides, which led to a



Scheme 2. Investigations on the basic substrate scope. *Reaction conditions*: Azauracil (0.2 mmol, 1 eq.), alkyl halide (0.3 mmol, 1.5 eq., halide as indicated), $Pd(PPh_3)_4$ (5 mol%), XantPhos (6 mol%), MeCN (2 mL) were irradiated under Ar atmosphere with 2x 40 W (Kessil PR160 L) at room temperature.

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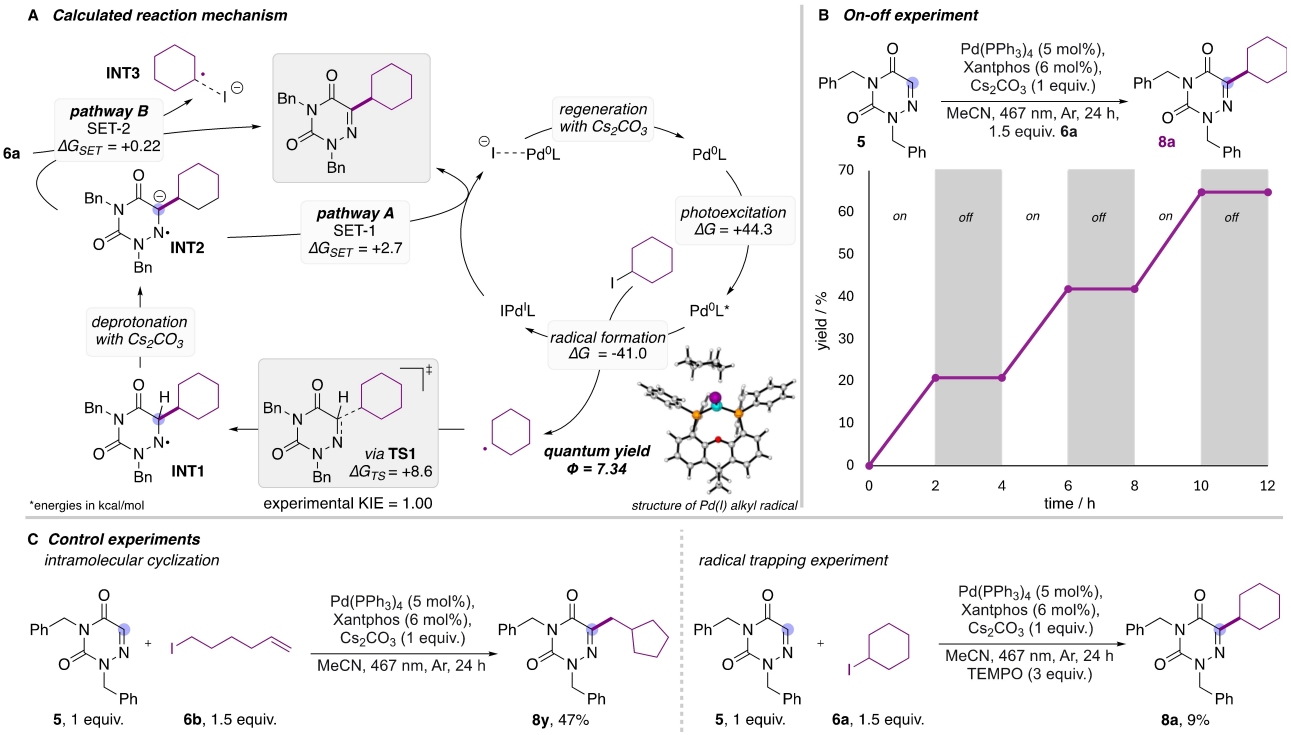
slight reduction in product yield (**8c**, **8n**). Last, different N-protecting groups on azauracil were evaluated, which only had a minor effect on the reaction product yield (**8s–x**).

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] initial photoexcitation of the palladium complex leads to the complex in the triplet state, which reacts with **5a** to initially form a palladium(I) alkyl radical intermediate. The latter can be considered as a palladium(I) species and free alkyl radical **7a**, which reacts via **TS1** to the radical intermediate **INT1** (for details please see ESI Scheme S4 and S5). The subsequent rearomatization of **INT1** can occur via two different mechanisms: a) via single electron transfer to the intermediate Pd(I) complex (Pathway A), or b) via single electron transfer to another molecule of cyclohexyl iodide **6a** (Pathway B). The latter would result in a radical chain mechanism. Experimental validation was carried out by on/off experiments and quantum yield calculations. The quantum yield for the reaction of azauracil **5a** with cyclohexyl iodide **6a** was calculated to be 7.34. Together with the on/off experiments, this suggests that pathway B is favored. We further determined the kinetic isotope effect by performing two parallel reactions of deuterated and non-deuterated dimethyl azauracil. This experiment showed no difference in the reaction yield between the deuterated and non-deuterated heterocycle (KIE = 1.00), confirming that C–H bond cleavage is not involved in the rate determining step (for details please see ESI). When using the radical probe 6-iodo-hex-1-ene (**6b**), we could observe exclusive formation of product **8y**, 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).

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.[14b] 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-heterocyle. For each data point, we conducted the C–H alkylation reaction of the heterocycle with cyclohexyl iodide to 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. We chose this step because it was previously identified as the step with the higher activation free energy compared to the rearomatization step (Scheme 4B). We then compared experimental yield with the activation free energy of the energetically



Scheme 3. Combined computational and experimental studies on the reaction mechanism. (**A**) Computational studies on the mechamism. (**B**) On-off experiment. (**C**) Control experiments.

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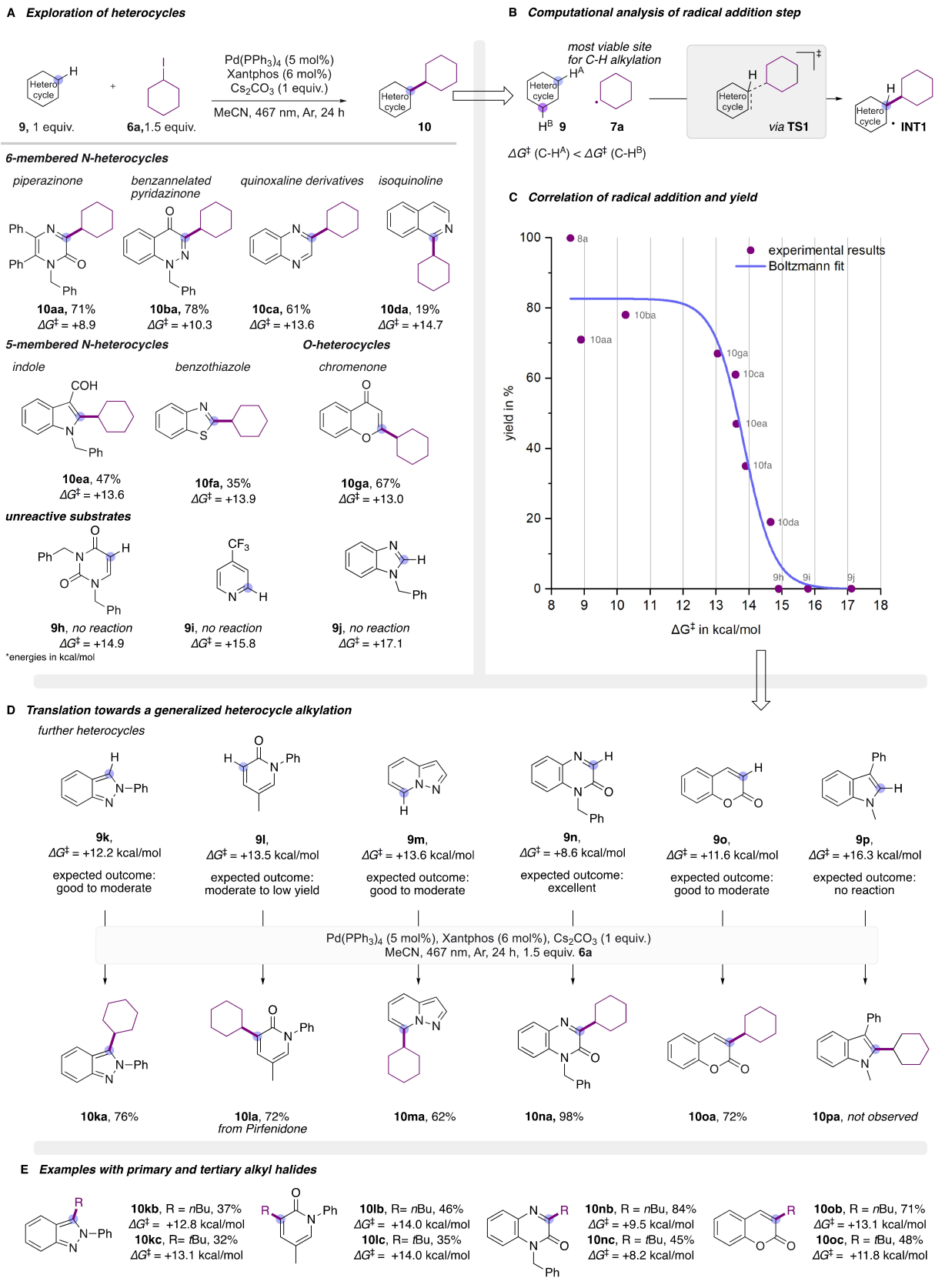

Scheme 4. Development of a predictive model for translation towards a generalized heterocycle C–H alkylation reaction. (**A**) Exploration of heterocycles. (**B**) Computational analysis of key transition states. (**C**) Correlation of key transition state with experimental yield. (**D**) Translation towards a generalized heterocycle alkylation. (**E**) Examples with primary and tertiary alkyl halides.

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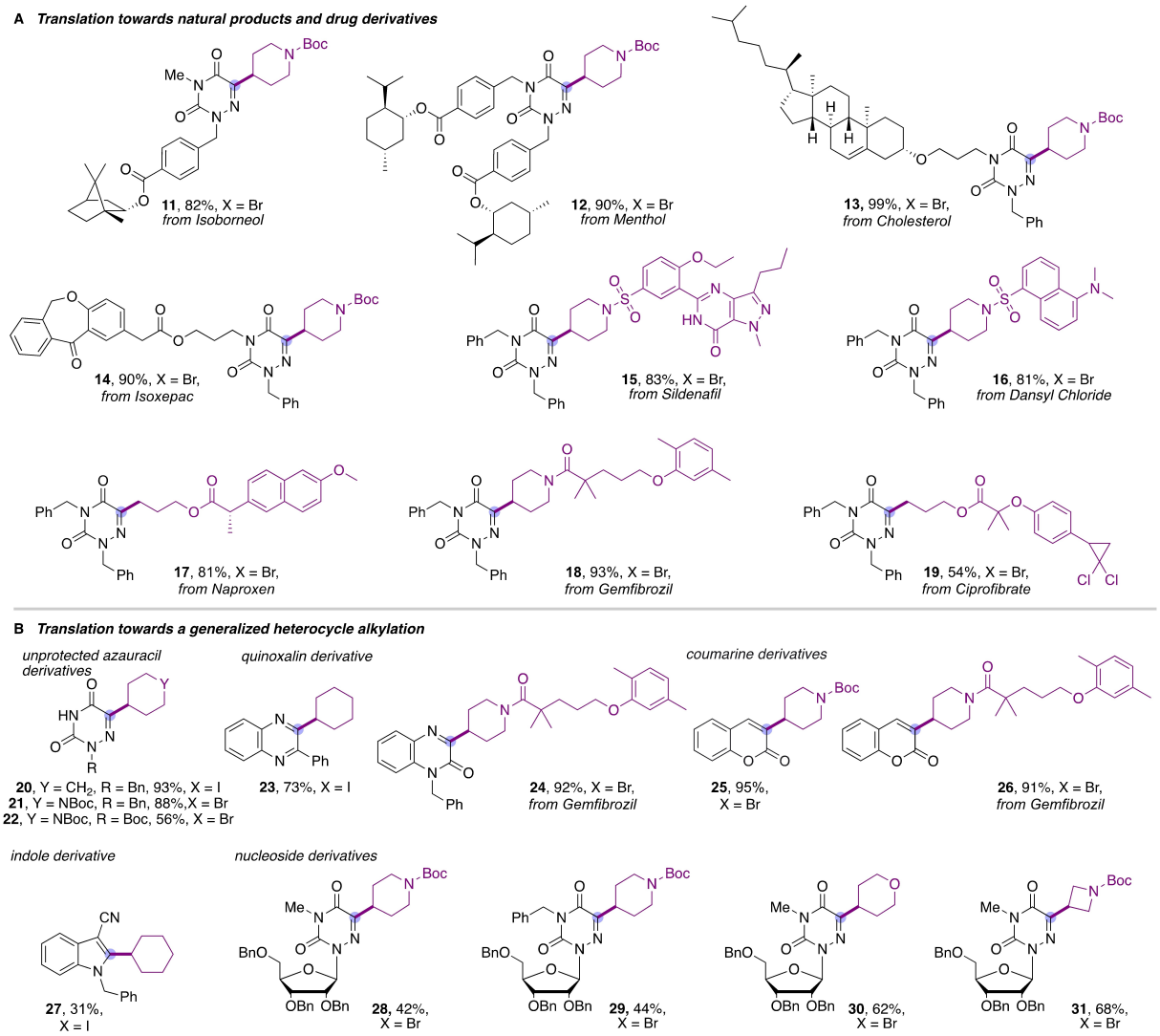

Scheme 5. Applications with natural products, drug molecules and nucleoside synthesis. *Reaction conditions*: Heterocycle (0.2 mmol, 1 eq.), alkyl halide (0.3 mmol, 1.5 eq., halide as indicated), $Pd(PPh_3)_4$ (5 mol%), XantPhos (6 mol%), MeCN (2 mL) were irradiated under Ar atmosphere with 2x 40 W (Kessil PR160 L) at room temperature. (**A**) Natural products and drug derivatives. (**B**) Translation towards generalized appliations.

most feasible C–H alkylation reaction (Scheme 4C, for details, see Table S4).

To our delight, this computational model shows that the computational data on site-selectivity matches with the experimentally observed site-selectivity (for details please see Table S4 in ESI). For example, in the case of chromenone **9g** the radical addition was predicted to the α-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 of heterocycles, of which examples of further suitable heterocycles are shown in Scheme 4D. Computations predict that heterocycles **9k–o** 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 **9p** 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.

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Further computational analysis involved the computational evaluation of primary and tertiary alkyl halides in the radical addition reaction with heterocycles **9k**, **9l**, **9n** and **9o**. In all cases, this analysis suggests facile addition of the alkyl radical to the heterocycle with activation barriers ranging from +8.2 to +14.0 kcal mol^{-1} (Scheme 4E). When performing the respective C–H functionalization with *n*-butyl iodide or *t*-butyl bromide, respectively, the corresponding alkylation products were obtained in moderate to good yield. It is noteworthy that in the case of tertiary alkyl halides, the yields of alkylation products dropped significantly, compared to the alkylation reaction with secondary alkyl halides.

In the next step, we embarked on synthetic applications of this C–H alkylation reaction (Scheme 5). For this purpose, we initially studied examples, where natural products or drugs such as cholesterol or isoxepac were introduced in the side chain of the azauracil heterocycle. In these cases, high yields of the respective C–H alkylation product with N-Boc 4-bromo piperidine were obtained. Further examples then include alkyl halides, where drug molecules were introduced into the side chain (**11**–**19**). 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.

In further studies, the application of heterocycles was further examined. Notably, unprotected azauracil could be demonstrated to successfully undergo C–H alkylation to give **20**–**22**. 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 (**23**–**27**). 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 (**28**–**31**).

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.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Palladium · Photochemistry · Heterocycles · Computational Studies · C–H functionalization

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