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Authors: Matthieu Jouffroy and Jongrock Kong

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Direct C–H Carbamoylation of Nitrogen Containing Heterocycles

Matthieu Jouffroy* and Jongrock Kong*

Abstract: *Nucleophilic radical additions at innately electrophilic C_{sp}^2 centers are perfectly suited for the direct functionalization of heterocycles. Using bench stable and commercially available alkyl oxamate and oxamic acid derivatives in combination with photoredox catalysis, we report a direct carbamoylation of heterocycles yielding amide functionalized pharmacophores in a single step. The reaction conditions reported are compatible with structurally complex heterocyclic substrates of pharmaceutical interest. Notably, derivatives containing functional groups incompatible with standard amidation reactions such as carboxylic acids and unprotected amines were found to be amenable to this reaction paradigm.*

In addition to being ubiquitous in proteins,[1] amide linkages are also crucial in their synthetic counterparts such as nylon, hydrogels, artificial silks, and other biocompatible derivatives.[2] Furthermore, amide bonds are not limited to polymers and are widely present in pharmacologically active substances,[3] estimated to be found in 25% of marketed drugs.[4] Indeed, a recent survey found that amide formation is the most commonly used reaction by medicinal chemists due to its suitability for quickly performing structure–activity relationship (SAR) studies.[5]

The "natural" bond disconnection to introduce an amide group onto a desired core involves the formation of a C–N bond from a carboxylic acid and an amine.[6] Extensive methodology including many novel coupling reagents have been developed to enable the formation of challenging amide bonds under mild reaction conditions.[7] In many cases, specifically in pharmaceutical applications, the carboxylic acid partner may not be readily available and will require several synthetic steps to be prepared, rendering this approach inefficient and time-consuming. A highly appealing but non-obvious disconnection strategy to access amides expeditiously would be to forge the C–C bond between a carbamoyl group and an unfunctionalized C–H bond on a heterocycle, avoiding the steps required for the preparation of the carboxylic acid derivative. Unfortunately, examples of this highly desirable transformation are scarce in the literature (Figure 1).[8]

The development of a mild and broadly applicable direct C–H carbamoylation method would allow for the introduction of structural diversity without the need for pre-functionalization. These kinds of transformations are the most employed for the acceleration of drug discovery because they obviate the need of *de novo* synthesis of individual targets.[9] Among the various

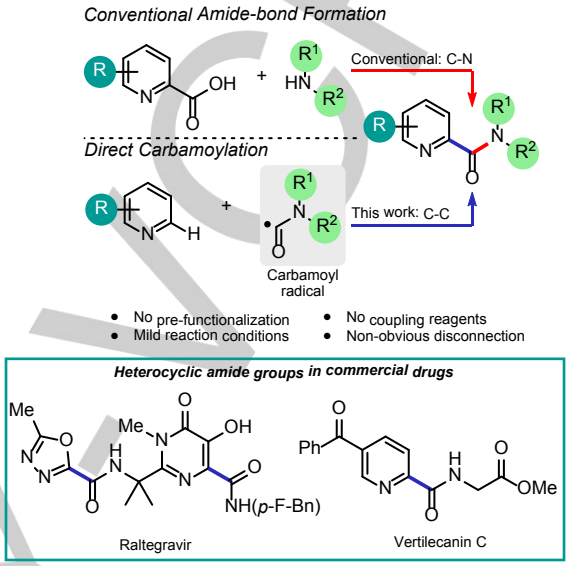

Figure 1. Accessing amide-functionalized *N*-heterocycles: classical disconnection *vs* direct C–H carbamoylation.

strategies that might be used, addition-elimination of radical nucleophiles at innately electrophilic C_{sp}^2 centers—also known as the Minisci reaction —is a common reaction manifold that has grown exponentially in recent years.[10] We therefore envisioned performing a direct C–H functionalization of heterocycles using carbamoyl radicals, to generate amide-functionalized pharmacophores in a single step.

The Minisci group reported such transformations by using oxamic acids as a carbamoyl radical source, together with persulfate salts as the oxidant and a silver-based catalyst.[11] This work, reported three decades ago, constitutes the only example of a direct C–H carbamoylation of heterocycles yielding *N*-alkyl amide-functionalized products. However, the utility of this reaction has been limited due to the relatively harsh reaction conditions reported (silver catalyst, excess oxidant and carbamoyl precursor, high temperature), poor functional group tolerance and often modest yields.[12] In recent years, several photoredox variants of the Minisci reaction have been developed, resulting in dramatically increased reaction yields and robustness,[13] leading us to hypothesize that this novel paradigm could be applied to our desired transformation. Herein, we report a visible light promoted direct C–H carbamoylation of nitrogen containing heterocycles.

In most instances, carbamoyl radicals are generated either from formamides *via* homolytic C–H bond cleavage[14] or from oxamic acids[11, 15] and related activated esters[16] *via* single electron transfer (SET) with subsequent loss of CO_2. While formamide derivatives are the most appealing precursors in terms of atom economy, they require in most cases harsh

Dr. M. Jouffroy, Dr. J. Kong
Process Research & Development
Merck & Co., Inc.
126 E. Lincoln Ave., Rahway, NJ 07065 USA
E-mail: matthieu.jouffroy@merck.com
jongrock_kong@merck.com

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.XXXXXXXX

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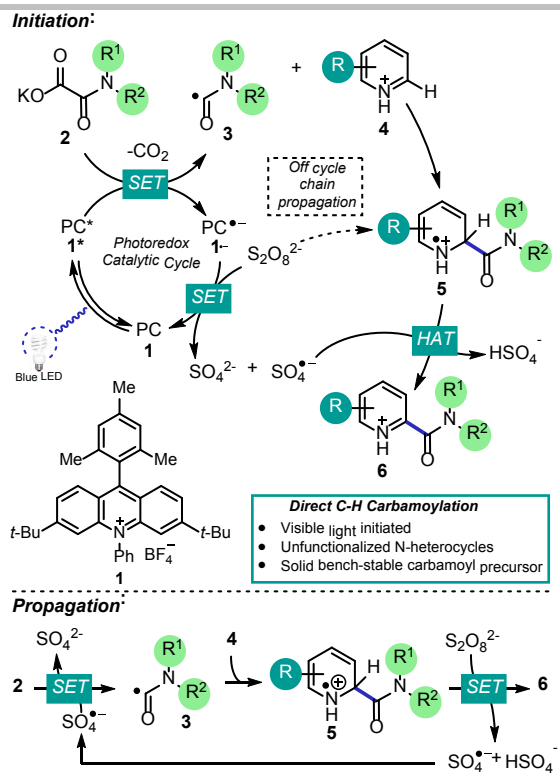


Scheme 1. Proposed Mechanism for the Direct C–H Carbamoylation of Heterocycles.

reaction conditions to generate the desired radicals, resulting in poor selectivity when alkyl formamides are used.[14f] Since we aimed toward the development of a synthetic method that would be easily implemented and compatible with the synthesis of *N*-alkyl amides, we decided to focus on the use of commercially available and bench stable oxamate salts (or the corresponding acids) for the generation of carbamoyl radicals. In addition, these reagents can be easily synthesized from the corresponding amines (see SI).

We envisioned the mechanistic scenario depicted in Scheme 1 for the visible light promoted carbamoylation of heterocycles. Blue LED light activation of an appropriate photocatalyst – in our case 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridin-10-ium tetrafluoro-borate **1** - would permit the latter to reach its excited state **1*** ($E_{1/2}^{red}$ [PC*/PC$^-$] = +2.08 V *vs* SCE in CH_3CN),[17] which is sufficiently oxidizing for SET to occur from the oxamate salt **2**[18] *via* reductive quenching ($E_{1/2}^{red}$ = +1.76 V *vs* SCE in DMSO/H_2O 1:1 for **8**, see SI). Loss of carbon dioxide would then generate the desired nucleophilic carbamoyl radical **3** that should rapidly add to a protonated heteroarene **4** to provide intermediate **5**.[11, 19] Simultaneously, the photocatalyst **1**$^{\bullet}$ ($E_{1/2}^{ox}$ [PC$^{\bullet}$/PC] = +0.59 V *vs* SCE in CH_3CN)[17] could be oxidized by persulfate ($E_{1/2}^{ox}$ = +1.75 V *vs* SCE in MeCN)[13c] to afford the sulfate dianion and the highly oxidizing sulfate radical anion, regenerating photocatalyst **1**.[13h] The latter anion ($E_{1/2}^{ox}$ = +2.36 V *vs* SCE in MeCN) is able to oxidize **5** through hydrogen-atom transfer (HAT), yielding the desired product **6.**

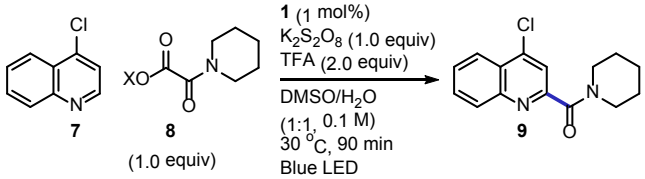
As often observed in photoredox catalysis,[20] off-cycle radical chain processes may also occur in this reaction (Scheme 1, bottom).[13c] Indeed, intermediate **5** could be oxidized by the persulfate anion, generating the sulfate radical anion that is able to perform a SET oxidation from oxamate **2** (or by HAT from the conjugate acid) to generate the carbamoyl radical **3**.[15d][21] Combined with the photoredox cycle mentioned above as a radical initiation cycle, this radical chain propagation would afford the desired product **6** efficiently.[22][23]

We decided to investigate the direct C–H carbamoylation of 4-chloroquinoline **7** using potassium piperidine oxamate **8** as the carbamoyl radical source (Table 1). *N*-alkyl and *N*,*N*'-dialkyl oxamates could produce the corresponding carbamoyl radicals upon oxidation, and therefore we investigated photocatalysts possessing matching oxidation potentials. We focused on inexpensive and metal-free organocatalysts and found that photocatalysts of the mesityl-phenylacridinium family performed well under our conditions, with **1** affording the best results (see SI). Indeed, when combined with potassium persulfate (1.0 equiv) and trifluoroacetic acid (2.0 equiv) in a DMSO/H_2O mixture (1:1) under blue LED irradiation, product **9** was obtained in excellent yield (Table 1, Entry 1).

The relative stoichiometry and nature of all reagents, as well as other reaction parameters were investigated (see SI). In particular, the choice of solvent mixture and reaction internal temperature were found to be critical to ensure maximum yield (Table 1, Entries 2 and 3). Initial reaction screens carried out using the standard CH_2Cl_2/H_2O and MeCN/H_2O mixtures gave only modest yields, but a dramatic increase was observed when switching to DMSO/H_2O. Crucially, it was found that maintaining the reaction's temperature at 30 ±2 °C using a fan allowed us to obtain consistent results.

Gratifyingly, a similar yield was obtained when using the corresponding oxamic acid instead of potassium oxamate (with 1.0 instead of 2.0 equivalents of TFA), opening up a wider range of commercially available reagents (Table 1, Entry 4). Control experiments showed that the reaction failed to proceed in the absence of light or oxidant (Table 1, Entries 5-7), and with diminished yields without TFA (Table 1, Entry 8).Interestingly, in the absence of photocatalyst we observed formation of product **9** and full consumption of oxamate **8** (Table 1, Entry 9). However, the yield was low and a significant amount of side products were generated. We rationalized that visible light could mediate decomposition of persulfate as proposed by Ji and co-

Table 1. Optimization of the Reaction Conditions and Control Experiments[a]



Entry	Deviation from standard conditions	Yield of **9** (%)[b]
1	None (X = K)	90
2	MeCN/H_2O as solvent mixture	40
3	No temperature control (~45 °C)	72
4	Acid (X = H) and 1.0 equiv of TFA	95
5	No light, mixture heated to 30 °C	0
6	No light, mixture heated to 80 °C	6
7	No $K_2S_2O_8$	5
8	No TFA	18
9[c]	No photocatalyst	35

[a] Conditions: **7** (0.10 mmol, 1.0 equiv), **8** (1.0 equiv), **1** (1 mol%), $K_2S_2O_8$ (1.0 equiv), TFA (2.0 equiv), DMSO/H_2O (1:1, 0.1 M). [b] Yields determined by HPLC using a calibration curve made with pure product **9** as reference. [c] Prolonged reaction time allows to reach full conversion of **8**, but several side products were observed (51% yield after 16 h).

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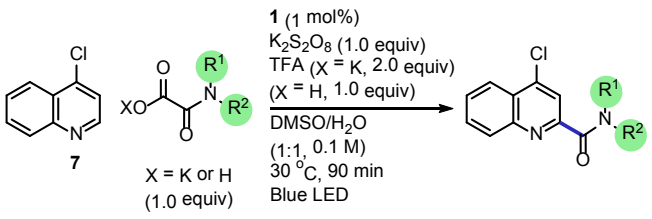
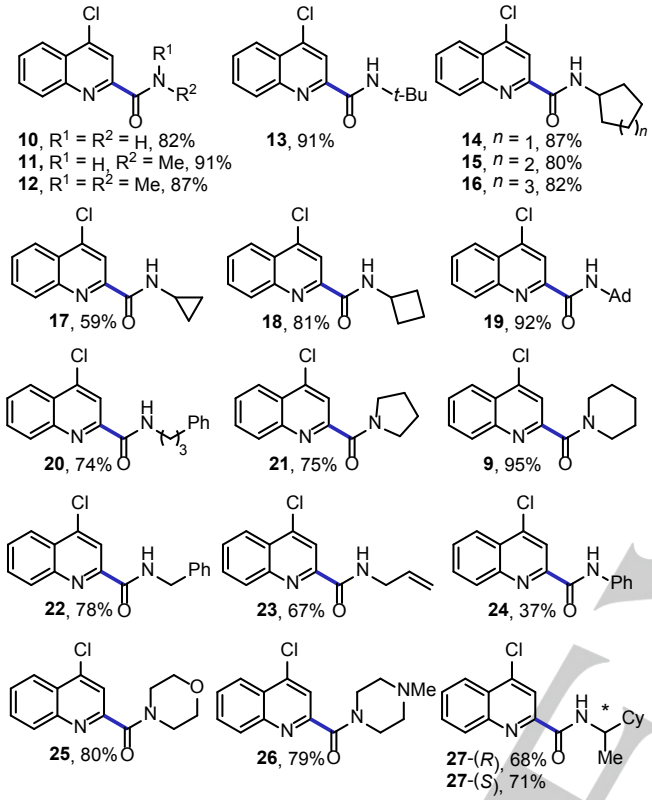
Table 2. Direct C–H Carbamoylation of 4-Chloroquinoline with Various Carbamoyl Moieties[a]





[a] Isolated yields. Conditions: **7** (0.50 mmol, 1.0 equiv), potassium alkyl oxamate or oxamic acid (1.0 equiv), **1** (1 mol%), $K_2S_2O_8$ (1.0 equiv), TFA (X = K: 2.0 equiv; X = H: 1.0 equiv), DMSO/H_2O (1:1, 0.1 M).

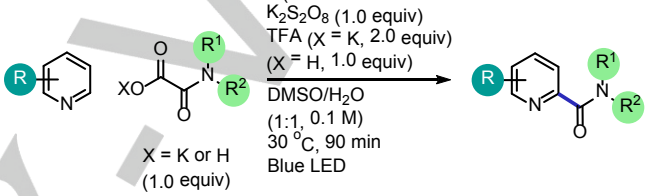
workers,[14f] [22] generating the sulfate radical anion responsible of oxidizing the oxamate, and consequently leading to the desired carbamoylation reaction (see Scheme 1, propagation).[24]

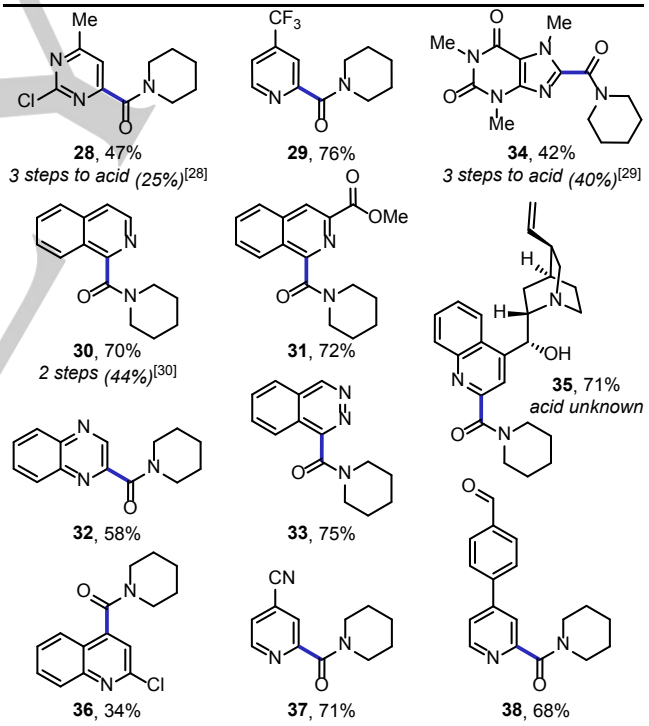
Next, we explored the substrate scope of the direct C–H carbamoylation, first focusing on the oxamate part (Table 2). Varying the electronics of the substituents on nitrogen and were delighted to obtain the desired products in often excellent yields. Indeed, *N*-alkyl and *N,N'*–dialkyl carbamoyl groups were perfectly tolerated and no activation of the C–H bonds adjacent to nitrogen was observed.[14f, 25] Sterically encumbered amines, which are very often problematic to couple even using the most elaborate coupling reagents, proceeded uneventfully (Table 2, Entries **13** and **19**). Because epimerization is a common phenomenon in standard amide bond forming reactions, we decided to assess chiral starting materials and were pleased to observe that no racemization occurred, affording the corresponding product in almost identical optical purity as the starting material (Table 2, Entry **27-(*R*)** and **(*S*)**).[26]

We next turn our attention to study the scope of the heteroaryl component (Table 3). A range of heterocycles was found to be compatible with the developed conditions for direct C–H carbamoylation affording the desired product in moderate to good yields. In most cases, the mass balance of the reaction was unreacted heteroarene, which could be isolated and resubjected to the same reaction conditions. In addition to quinoline (Table 2), other bicyclic systems such as isoquinoline, quinoxaline, phthalazine or caffeine performed well in the reaction (Table 3, **30-36**). Of note is the Cinchona alkaloid **35** that not only shows the remarkable tolerance of the reaction towards protic (OH) and basic (tertiary amine) functional groups, but also the reaction's selectivity for addition of the carbamoyl radical to the heteroarene rather than the exogenous vinyl functionality. The synthesis of such derivatives is of particular interest for applications in phase transfer catalysis and the methodology described here could be used to fine-tune a catalyst so as to achieve improved yields and enantioselectivity.[27]

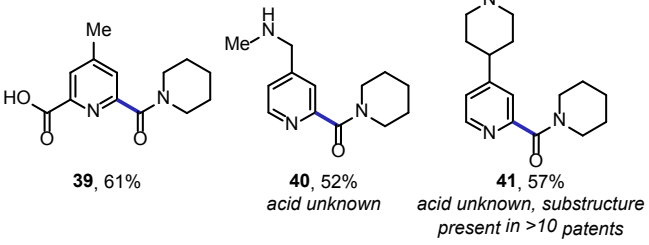
One obvious limitation of traditional approaches to amide formation is that the carboxylic acid precursors required are often not accessible. This is exemplified by the preparation of

Table 3. Scope of the Direct C–H Carbamoylation of Heterocycles[a]





Challenging substrates in conventional amidation



[a] Isolated yields. Conditions: heteroarene (0.50 mmol, 1.0 equiv), potassium alkyl oxamate or oxamic acid (1.0 equiv), **1** (1 mol%), $K_2S_2O_8$ (1.0 equiv), TFA (X = K: 2.0 equiv; X = H: 1.0 equiv), DMSO/H_2O (1:1, 0.1 M).

amides **28**, **29**, **37** and **38**, which are easily prepared from commercially available starting materials using our carbamoylation methodology, but would be harder to access *via* traditional amide bond forming methods as the necessary carboxylic acids are not readily available.

In order to challenge the method we developed, we decided to test substrates known to be incompatible even when using state-of-the-art amide bond forming reactions. Normally, substrates that bear either free amines or several carboxylic acids are particularly problematic in traditional amide couplings and would lead to the formation of oligomers among other side-products. However in our case, no electrophilic carboxylic acid intermediates are formed, allowing us to isolate compounds **39-41** without the use of protecting groups.[31] This unusual functional group tolerance might find application in the late-stage functionalization of drug candidates, allowing for the introduction of amide groups to complex molecules in a single step under mild reaction conditions.

In summary, we report a visible light photoredox-mediated reaction, which enables direct C–H carbamoylation of heterocycles by means of a radical addition to a non-functionalized C_{sp}^2 center. Of particular importance is the tolerance of this reaction protocol to functional groups such as carboxylic acids and unprotected amines that are typically incompatible with standard amide coupling reagents. By allowing the direct formation of *N*-alkyl and *N,N'*-dialkyl amide functionalized heterocycles in a rapid, robust and transition metal free manner, we believe that this non-obvious bond disconnection should find rapid adoption in both academia and industry.

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Keywords: carbamoylation, C-H functionalization, photoredox catalysis, heterocycles, alkyl oxamate.

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