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Deaminative Strategy for the Visible Light-Mediated Generation of Alkyl Radicals

Felix J. R. Klauck⁺, Michael J. James⁺ and Frank Glorius^{*}

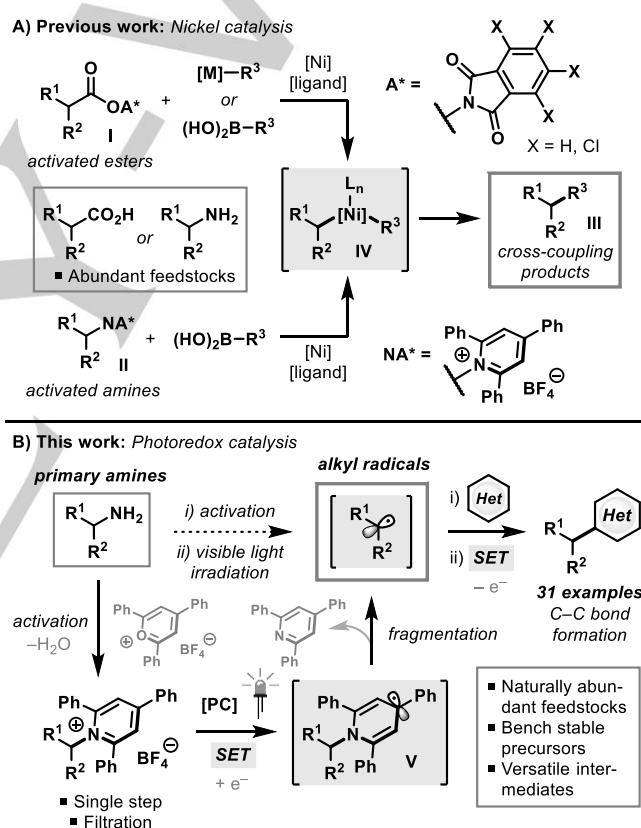
Abstract: A deaminative strategy for the visible light-mediated generation of alkyl radicals from redox-activated primary amine precursors is described. Abundant and inexpensive primary amine feedstocks, including amino acids, were converted in a single step into redox-active pyridinium salts and subsequently into alkyl radicals by reaction with an excited-state photocatalyst. The broad synthetic potential of this protocol was demonstrated in the alkylation of a number of heteroarenes under mild and operationally simple conditions.

Methods for the generation of alkyl radicals are highly important processes that enable the formation of new C–C and C–X bonds in ways that would not be possible by traditional two-electron pathways.^[1] Furthermore, methods which can use naturally abundant and inexpensive feedstocks to generate alkyl radicals are of high interest in modern synthetic organic chemistry.^[2] In particular, decarboxylative methods using carboxylic acids as radical precursors have been the focus of recent attention,^[3] especially with redox-active NHPI esters **I** (Scheme 1A);^[4] these bench stable solids have enabled a range of powerful cross-coupling reactions to be performed under nickel catalyzed conditions.^[5]

Primary amines are another feedstock of similar natural abundance to carboxylic acids,^[6] and so naturally, a number of methods have been developed to exploit them as synthetic intermediates in two-electron processes.^[7] Primary amines also feature prominently in numerous biologically active natural products^[8] and drug molecules,^[9] and as such, a range of methods exist for their synthesis.^[10] All of these features strengthen demand to utilize this functionality as a synthetic handle in single-electron C–C and C–X bond forming reactions. To this end, Watson and co-workers recently reported that bench stable Katritzky salts **II**,^[11] which are readily formed in one step by the condensation of a primary amine with a commercially available pyrylium salt, can engage in elegant nickel catalyzed cross-coupling reactions with boronic acids (Scheme 1A, **II** → **III**).^[12] While this cross-coupling reaction is presumed to proceed via the formation of an alkyl radical species, the open-shell intermediate is inaccessible for direct functionalization as it is immediately captured by the nickel catalyst in a formal oxidative addition process (**II** → **IV**).

Inspired by this work, we envisioned that Katritzky salts could also be used to generate reactive alkyl radicals under visible light-mediated conditions (Scheme 1B). Here, an open-shell species could be generated following a single-electron reduction

of a Katritzky salt **II** ($E_{1/2} = -0.93$ V vs. SCE in DMF)^[13] and the fragmentation of the resultant dihydropyridine radical **V**, a process driven by the reformation of the aromatic pyridine ring. This work would represent a significant advance in the field of photoredox catalysis, as while alkyl radicals can be prepared from a variety of different precursors, the photocatalytic generation of an alkyl radical species via the cleavage of a C–N bond is still a conceptually limited process.^[14,15] Thus, a general method for the deaminative formation of alkyl radicals would enable a powerful new retrosynthetic disconnection that would allow inexpensive primary amine precursors to be converted into complex high-value compounds.



Scheme 1. a) Previous work on nickel catalyzed cross-coupling reactions; b) The deaminative visible light-mediated generation of alkyl radicals.

Herein, we describe the realization of this approach for the deaminative generation of alkyl radicals from redox-activated primary amines under mild, visible light-mediated conditions. The feasibility of this approach and the synthetic utility of the resultant alkyl radicals was demonstrated by a number of C–C bond forming heteroarene alkylation reactions.

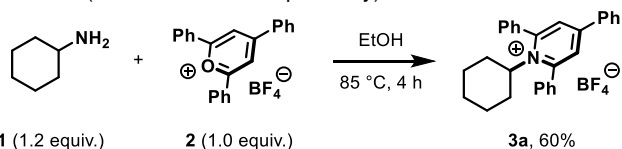
Our studies began with the condensation of cyclohexylamine **1** with 2,4,6-triphenylpyrylium tetrafluoroborate **2** to afford cyclohexyl Katritzky salt **3a** on a gram-scale after a simple filtration. Katritzky salt **3a** was then submitted to luminescence quenching studies with several common photocatalysts (see supporting information),^[16] of which iridium-based photocatalysts

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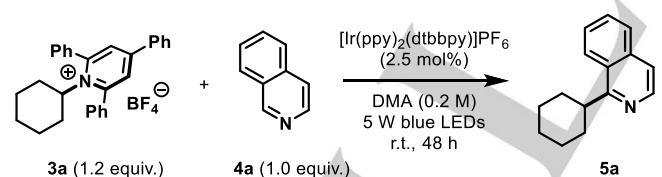
fac-Ir(ppy)₃ and [Ir(ppy)₂(dtbbpy)]PF₆ were most efficiently quenched (>99% and 83% respectively).



Scheme 2. Synthesis of cyclohexyl Katritzky salt **3a**.

Having established that Katritzky salt **3a** could effectively quench the luminescence of an excited-state photocatalyst, we sought to develop an appropriate reaction to establish a proof of concept and to demonstrate the synthetic utility of this method. Thus, we turned our attention towards the formation of a C–C bond between the nucleophilic cyclohexyl radical and an electron-deficient heteroarene, such as isoquinoline **4a**.^[17] Pleasingly, after optimization studies (see supporting information), the desired alkylated product **5a** could be prepared in excellent yield by irradiating a solution of isoquinoline **4a** with just 1.2 equivalents of the cyclohexyl Katritzky salt **3a** and [Ir(ppy)₂(dtbbpy)]PF₆ (2.5 mol%) in DMA (*N,N*-dimethylacetamide, 0.2 M) with visible light for 48 h ($\lambda_{\text{max}} = 455\text{ nm}$, blue LEDs)^[18] (table 1, entry 1). A shorter reaction time was insufficient to effectively form the product **5a** (entry 2), as was using the more efficiently quenched photocatalyst, *fac*-Ir(ppy)₃ (entry 3), suggesting that the formation of the alkyl radical might be hindered by a competing back electron transfer process. Minimal reaction was also observed in the absence of a photocatalyst or light (entries 4 & 5) and all reactivity was completely suppressed with the addition of TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl, entry 6). A TEMPO-alkyl radical adduct was also detected by ESI-MS analysis during these studies, strongly suggesting that an alkyl radical intermediate is indeed formed in this reaction (for further mechanistic studies, including Stern-Volmer quenching studies and quantum yield determination see supporting information).

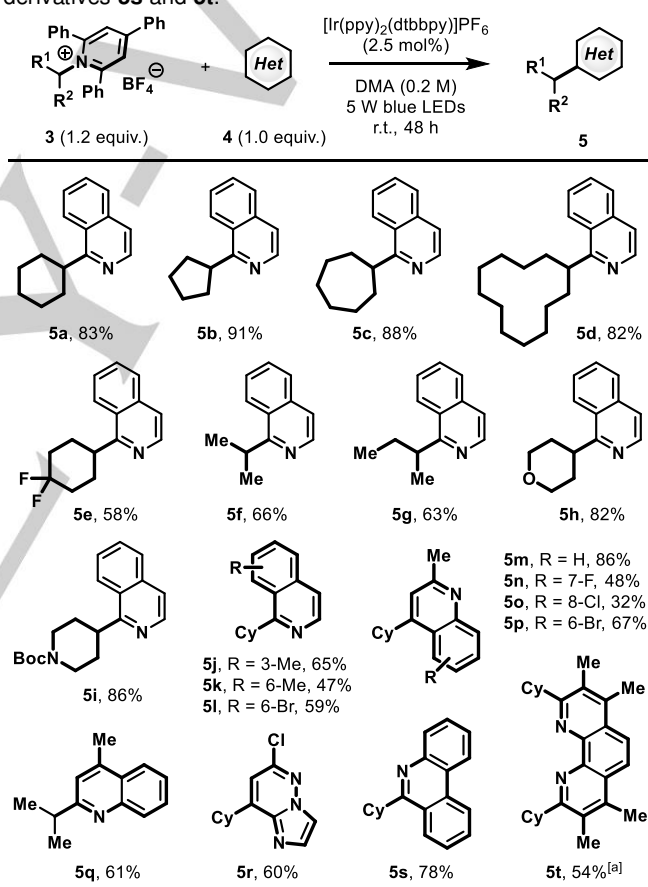
Table 1. Visible light-mediated deaminative C–H alkylation of isoquinoline **4a**.



Entry	Variation from standard conditions ^[a]	Yield [%] ^[b]
1	none	88 (83) ^[c]
2	16 h reaction time	62
3	<i>fac</i> -Ir(ppy) ₃ instead of [Ir(ppy) ₂ (dtbbpy)]PF ₆	<5
4	no photocat.	9
5	no light	0
6	TEMPO (2.0 equiv.)	0

[a] Conditions: **4a** (0.10 mmol), **3a** (0.12 mmol), and [Ir(dtbbpy)(ppy)₂](PF₆) (2.5 mol%) and DMA (0.2 M) under argon. [b] Yields determined by calibrated GC-FID analysis using mesitylene as internal standard. [c] Isolated yield on a 0.3 mmol scale in parentheses.

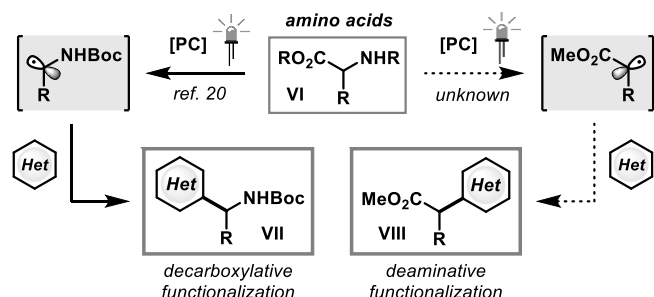
With the optimized conditions in hand, we sought to establish the generality of this strategy for the generation of alkyl radicals and their application in C–C bond forming reactions. Thus, a wider range of Katritzky salts was prepared for examination as in scheme 2. To our delight, a range of cyclic, acyclic and heterocyclic Katritzky salts could all be used to form alkylated isoquinolines **5a–i** in generally excellent yield (scheme 3). Other substituted heterocycles were also well-tolerated in this process, with alkylated isoquinolines **5j–l** and quinolines **5m–q** afforded in typically good yield. The synthetic value of these reactions was further demonstrated with the efficient formation of imidazopyridazine derivative **5r** (related derivatives have undergone clinical trials against myeloproliferative diseases).^[19] Prominent ligand architectures were also efficiently alkylated with this method, such as in phenanthridine and phenanthroline derivatives **5s** and **5t**.^[20]



Scheme 3. Scope of the deaminative C–H alkylation of heteroarenes. Reactions performed on a 0.30 mmol scale in 1.5 mL of solvent. [a] Performed with 3.0 equiv. of **3**.

Having demonstrated the effectiveness of this approach for the generation of relatively simple cyclic and acyclic alkyl radicals, we sought to challenge this process for the generation of more complex alkyl radical species using one of the most well-known naturally abundant feedstocks – amino acids. Amino acids have previously been used as radical precursors in photoredox catalyzed decarboxylative processes (Scheme 4, **VI** → **VII**),^[21] and as such, a deaminative protocol (**VI** → **VIII**) would offer a

powerful complementary approach for the chemoselective generation of alkyl radicals from the same precursors.



Scheme 4. Overview of amino acids as radical precursors in photoredox catalysis.

Consequently, a variety of natural and unnatural amino acid methyl esters were converted into the required Katritzky salts **3**. Pleasingly, our previously developed conditions were still sufficient to generate the desired electrophilic radicals, which were capable of alkylating electron-rich heteroarenes (Scheme 5).^[22,23] Thus, with minor modifications to the reaction stoichiometry (see supporting information) a number of C2-alkylated indole products **6a–g** was prepared in modest to good yield. The scope of this reaction with respect to the heteroarene was also investigated with an alanine derived Katritzky salt, which was used to successfully form C2/3-alkylated indoles **6h–j** and C2-alkylated pyrrole **6k** without any additional optimization. It should be noted that these reactions also failed to proceed in

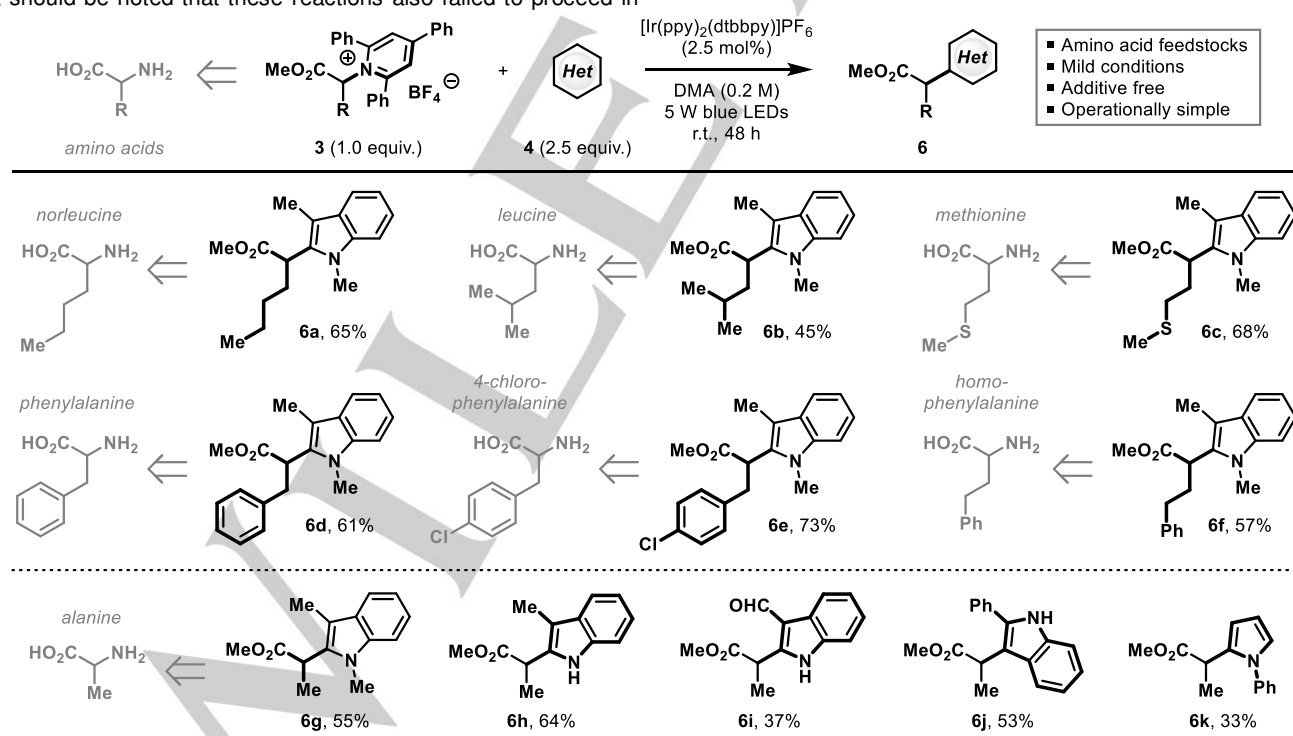
the absence of photocatalyst or light, excluding S_N mechanisms for the formation of the observed products (see supporting information).

In conclusion, we have developed a mild and efficient visible light-mediated protocol for the deaminative generation of alkyl radicals. Highly abundant primary alkyl amines, including amino acids, were readily converted into redox-active Katritzky salts, which were subsequently used as radical precursors for the alkylation of both electron-rich and -deficient heteroarenes. We believe this work will be of significant interest to the synthetic community and will enable the formation of new C–C and C–X bonds from a significantly enlarged source of alkyl radicals.

Acknowledgements

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Keywords: alkyl radicals • deamination • redox-active • photoredox catalysis • amino acids



Scheme 5. Scope of the amino acid-based deaminative C–H alkylation of heteroarenes. Reactions performed on a 0.30 mmol scale in 1.5 mL of solvent.

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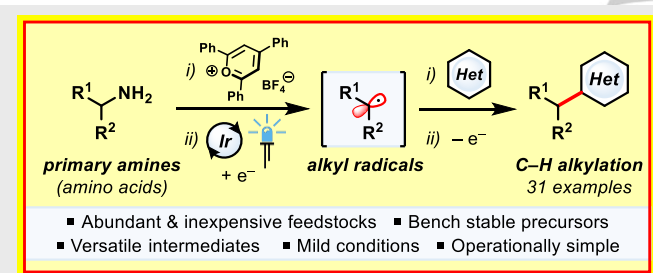
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Layout 2:

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