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Visible-Light-Induced Remote C(sp^3)−H Pyridylation of Sulfonamides and Carboxamides

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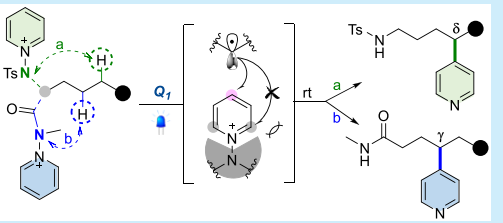
Supporting Information

ABSTRACT: Visible-light-induced site-selective C(sp^3)−H pyridylation of amides has been accomplished using *N*-amidopyridinium salts. The N-centered radicals generated by the single-electron reduction of *N*-amidopyridinium substrates undergo 1,5-hydrogen atom transfer to form alkyl radical intermediates. Excellent C4-selectivity in radical trapping with pyridinium salts is observed for the alkyl radicals to provide *δ*-pyridyl sulfonamides and *γ*-pyridyl carboxamides. The utility is demonstrated by offering a practical approach for the late-stage functionalization of complex amide derivatives.

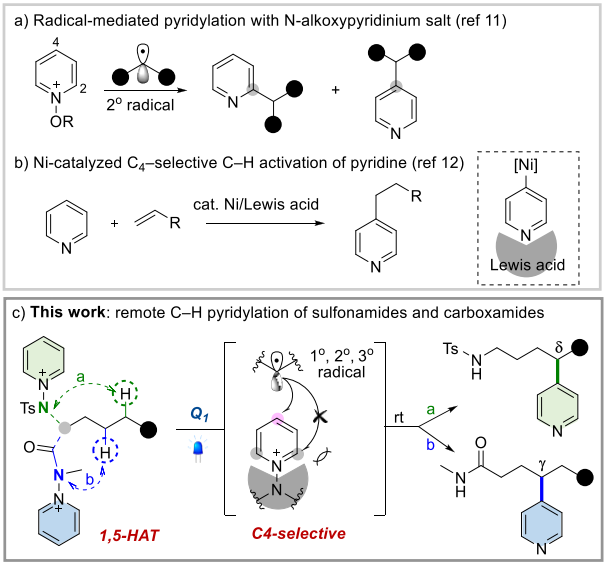


The site-selective functionalization of unactivated C(sp^3)−H bonds in the presence of multiple reaction sites constitutes a long-standing challenge in synthetic chemistry and late-stage transformations.[1] Due to its ubiquity and versatility, the amino group is an attractive functionality capable of directing transformations and for the subsequent elaboration of amine-containing targets.[2] Inspired by the Hofmann−Löffler−Freytag reaction,[3] photocatalytic[4] remote C−H functionalization has been widely used by a facile and selective 1,5-hydrogen atom transfer (HAT) reaction[5] where pendant N-centered radicals cleave inert aliphatic C−H bonds. This photochemical approach enables C−H functionalization of previously inaccessible distant C−H bonds in the nitrogen-containing compounds even in complex molecular settings under mild and environmentally benign conditions.[6] Despite the great success in HAT catalysis, the remote and regioselelctive C−H pyridylation in the aliphatic chain of amides has not been explored.

Pyridine derivatives are extensively found in a large number of biologically active natural products, pharmaceuticals, and fine chemicals.[7] Consequently, considerable effort has been directed toward chemical modification of the pyridine core.[8,9] Recently, *N*-alkoxypyridinium salts[10] have been used as versatile pyridine surrogates with increased levels of selectivity and reactivity.[11] However, these approaches have faced limited success due to the regioselectivity issue regarding two competing sites (C2 vs C4) on the *N*-alkoxypyridinium salts (Scheme 1a). Hiyama and Ong reported bimetallic catalysis for the C4-selective C−H bond activation of the pyridine core by employing nickel/Lewis acid cooperative catalysis (Scheme 1b).[12] In this innovative system, a bulky $AlMe_3$ Lewis acid coordinates at the pyridine nitrogen to allow for the C4-selective synthesis of alkyl or alkenylpyridines.

Drawing inspiration from these studies, we hypothesized that N-substituents on pyridinium salts could exhibit a similar

Scheme 1. Strategy for Remote C−H Pyridylation at the C4-Position of Pyridine Core



effect of a bulky Lewis acid to avoid an unfavorable clash at the C2 position between the N-substituents and the translocated alkyl radical, as depicted in Scheme 1c. In designing a strategy to enable remote C−H pyridylation, we speculated that sulfonamide- and carboxamide-based pyridinium substrates would offer an opportunity to activate different remote positions (e.g., amino acids) via a radical relay mechanism. In the process, the N-centered radicals[6] formed from a single-electron transfer (SET) reduction trigger an intramolecular

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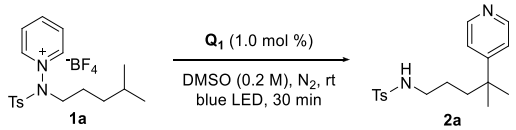
1,5-HAT to generate δ-radical sulfonamides or γ-radical carboxamides, providing impressive synthetic versatility for subsequent installation of pyridyl moiety. Herein, we report a photocatalytic remote C(sp^3)−H pyridylation that addresses the regioselectivity issue of the two competing sites (C2 vs C4) through C4−H activation of the pyridine core to provide synthetically valuable δ-pyridyl sulfonamides and γ-pyridyl carboxamides. This approach significantly broadens the synthetic scope of amide-directed remote C(sp^3)−H functionalization and has the potential to simplify installation of the pyridyl group across a wide range of complex sulfonamides and carboxamides under mild, metal-free conditions.

To verify the validity of our proposed approach, we investigated the remote C(sp^3)−H pyridylation of sulfonamides using *N*-amidopyridinium salt **1a** as a model substrate at room temperature (Table 1). After an extensive survey of the reaction parameters, we were pleased to find that a promising result was obtained under blue LED irradiation using 3-phosphonated quinolinone $\mathbf{Q_1}$[10b,11c,g] (1 mol %) as the photoredox catalyst, leading to the remote pyridylation of the C−H bond at the δ position. Under these conditions, the desired product **2a** was produced in 95% yield as a single isomer. Increasing the $\mathbf{Q_1}$ loading (2.5 mol %) provided a comparable yield (entry 2, 92%). Among the screened solvents, DMSO was more effective than any of the others tested. Of the various photocatalysts tested, $\mathbf{Q_1}$ displayed the best activity. We examined the influence of the light source, and the blue LED was found to be the best light source. A series of control experiments carried out in the absence of light or photocatalyst confirmed that the current reaction is driven by a photocatalytic process (entries 7 and 8). To examine the role of a photocatalyst $\mathbf{Q_1}$, a series of Stern−Volmer quenching experiments were performed with *N*-amidopyridinium salt **1a**, revealing the feasibility of the oxidative quenching cycle (see the Supporting Information for details). The addition of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) completely inhibited the formation of **2a**, indicating that a radical process was involved. To demonstrate the robustness of this method, the reaction was carried out on the 1 mmol scale, leading to 83% of **2a** under the standard conditions.

Table 1. Optimization of the Reaction Conditions[a]

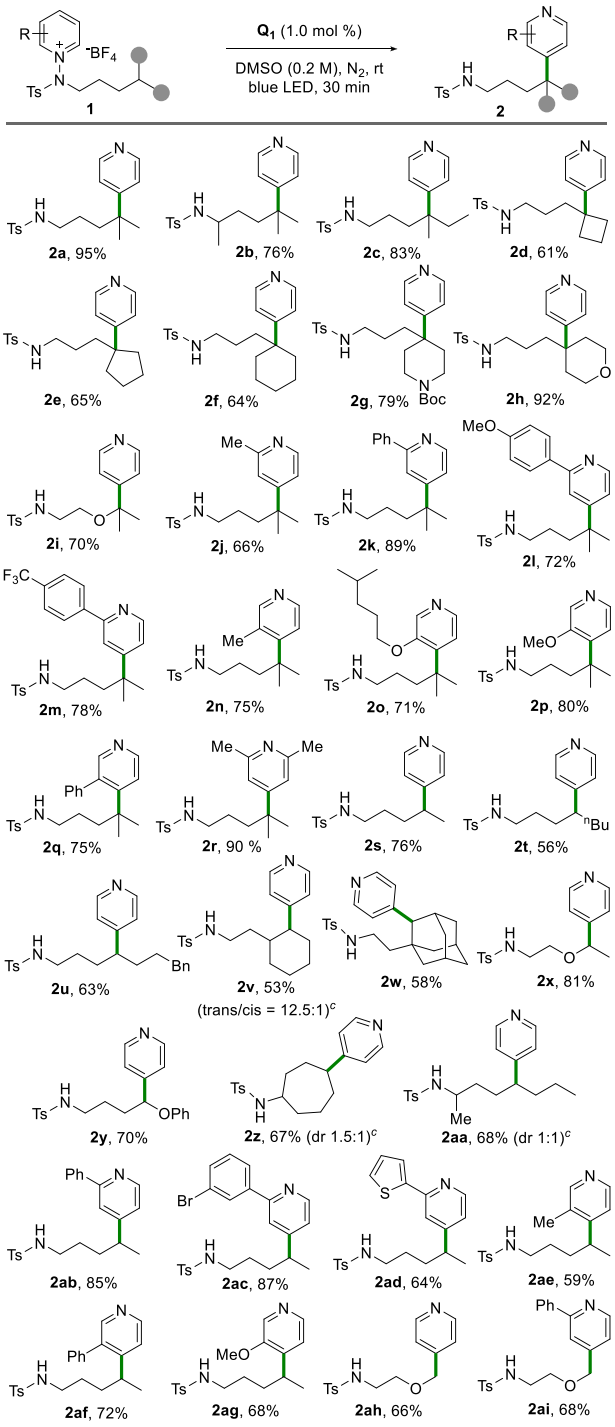


entry	variation from the standard conditions	yield[b] (%)
1	none	95 (83[c])
2	$\mathbf{Q_1}$ (2.5 mol %)	92
3	$Ru(bpy)_3Cl_2$ instead of $\mathbf{Q_1}$	82
4	$Ir(ppy)_3$ instead of $\mathbf{Q_1}$	36
5	Eosin Y instead of $\mathbf{Q_1}$	80
6	addition of $NaHCO_3$ (1.2 equiv)	87
7	without visible light irradiation	NR
8	without $\mathbf{Q_1}$	NR
9	addition of TEMPO (1.0 equiv)	NR

[a]Reaction conditions: **1a** (0.1 mmol), photocatalyst in DMSO (0.5 mL) under irradiation using 10 W blue LEDs at rt for 30 min under N_2. [b]Yield was determined by ^1H NMR spectroscopy. [c]1 mmol scale. $\mathbf{Q_1}$ = 3-(diphenylphosphoryl)-6-methoxy-1-methylquinolin-2(1*H*)-one, DMSO = dimethyl sulfoxide.

With these very simple reaction conditions, we explored the scope of *N*-amidopyridinium substrates to evaluate the utility and generality of the current cascade reaction. As summarized in Scheme 2, sulfonamide substrates containing various groups were successfully employed in the reaction and provided δ-C(sp^3)−H pyridylated products under the optimized reaction conditions. Remarkably, we observed that radical trapping

Scheme 2. Exploration of Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.1 mmol) and $\mathbf{Q_1}$ (1.0 mol %) in DMSO (0.5 mL) using 10 W blue LEDs at rt for 30 min under N_2. [b]Yields of isolated products. [c]The ratio was determined by ^1H NMR spectroscopy.

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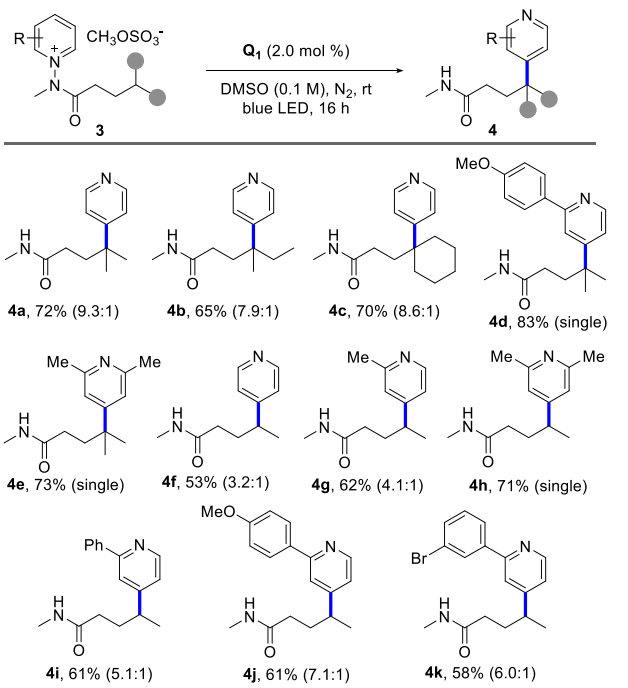
occurs exclusively at the C4 position of the pyridine core in all investigated cases with primary (**2ah**−**2ai**), secondary (**2s**−**2ag**), and tertiary alkyl (**2a**−**2r**) C(sp^3)−H bonds, highlighting the advantage of the current strategy over the previous results obtained from the use of *N*-alkoxypyridinium salts.[9] Variation at the aliphatic chains has little influence on reaction efficiency, and substrates with different substitution patterns were suitable to deliver the corresponding products **2a**, **2c**, **2s**, **2t**, and **2u**. The current protocol could also be adapted for the functionalization of the internal cycloalkyl C−H bond. For example, C−H bonds in cyclohexane and cycloheptane could be activated to provide an efficient approach for the decoration of the cycloalkyl skeleton (**2v** and **2z**). The reaction was further expanded to an interesting example of a substrate containing a sterically bulky adamantyl group, effectively yielding the product **2w**. The reaction worked well with substrates bearing an oxygen atom adjacent to the reaction position (**2i**, **2x**, **2y**, **2ah**, and **2ai**). Substrates bearing cyclic motifs, such as cyclobutane, cyclopentane, cyclohexane, *N*-Boc-piperidine, and tetrahydropyran, were all tolerated, providing the products **2d**, **2e**, **2f**, **2g**, and **2h**. Moreover, the scope could be expanded to α-branched sulfonamides, which afforded the corresponding secondary sulfonamide products **2b** and **2aa**. The utility of the present method was further broadened by the reaction with primary C(sp^3)−H bonds (**2ah** and **2ai**). With respect to the scope of pyridyl groups, we were pleased to observe that substrates possessing methyl, substituted aryl, alkoxy, or thienyl groups on the pyridine core could be incorporated into the δ-C(sp^3)−H to afford the corresponding products (**2j**−**2n**, **2ab**−**2ag**). Notably, the method accommodates sterically bulky groups at the C3 position of pyridine, affording the C4-selective products (**2n**, **2o**, **2p**, **2q**, **2ae**, **2af**, and **2ag**). The reaction is also applicable to the 2,6-disubstituted pyridinium substrate (**2r**).

Next, we turned our attention to evaluating the remote C−H pyridylation of carboxamides. To our delight, the protocol could be successfully applied to a variety of carboxamide and pyridinium substrates, leading to the remote functionalization of the C−H bond at the γ position, and the results are summarized in Scheme 3. Interestingly, both secondary and tertiary C−H bonds could also be selectively functionalized at the C4 position of the pyridine core with modest to good regioselectivity. Together with the excellent scope of sulfonamides, the strategy would potentially broaden the synthetic application of the remote C−H pyridylation strategy.

To further demonstrate the broad synthetic utility of this method, we investigated the late-stage functionalization of various complex biomolecules as illustrated in Scheme 4. Specifically, derivatives of bisacodyl[13] and abiraterone[14] were successfully employed to furnish the desired products (**2aj**, **2ak**, and **2am**). In addition, the reaction of a pentoxifylline[15] derivative was employed under standard reaction conditions to afford the product **2al** in 62% yield with excellent C4-regioselectivity of the pyridine core. Significantly, the strategy could be applied to unnatural amino acid derivatives for the C−H activation of different positions. For instance, site-specific C−H functionalization offers a significant advantage by installing a pyridyl group at the δ- or γ-positions of L-norleucine[16] (**2an** and **4l**). This late-stage functionalization exhibits a wide tolerance for biologically relevant functionalities and highlights the potential utility of this method in medicinal chemistry and chemical biology.

Scheme 3. Carboxamide Substrate Scope[a−c]



[a]Reaction conditions: **1** (0.1 mmol) and $\mathbf{Q_1}$ (2 mol %) in DMSO (1.0 mL) using 10 W blue LEDs at rt for 16 h under N_2. [b]Isolated yields. [c]The C2/C4 ratio was determined by ^{1}H NMR spectroscopy.

To better understand the observed excellent C4-regioselectivity, density functional theory (DFT) calculations were carried out (see the SI for computational details), and the reaction energy profile is illustrated in Figure 1. Depending on the reaction sites of the *N*-amidopyridinium salt (C4 vs C2) with an alkyl radical intermediate, the generation of two regioisomeric products is possible, and this radical addition step is responsible for the regiocontrol. This transition state **TS-C2**, leading to the C2-product, is located at 16.4 kcal mol^{-1}, whereas the pathway leading to the experimentally observed C4-product traverses transition state **TS-C4** at 13.6 kcal mol^{-1} (Figure 1a).

The computed structures of these two transition states indicated that the barrier difference of 2.7 kcal mol^{-1} stems mainly from the greater steric demand of the *N*-alkyl tosyl group. As a consequence, these different radical trapping barriers have a profound impact on the regioselectivity, and the C4-substituted regioisomer is predicted to be a major product. On the other hand, the C4-position is preferred by a barrier of 0.81 kcal mol^{-1} in the case of amide substrate **3a** (Figure 1b), which again shows good agreement with the modest regioselectivity experimentally observed.

A possible mechanistic pathway is depicted in Figure 2. Initially, the photolytic N−N bond cleavage of the *N*-amidopyridinium salt **A** by SET of the $\mathbf{Q_1}$* leads to amidyl radical **B** and neutral pyridine. A subsequent 1,5-HAT reaction of *N*-centered radical **B** produces an alkyl radical intermediate **C**. Nucleophilic alkyl radical **C** engages in an intermolecular radical addition to substrate **A** to give a radical cation **D**, leading to the final product and the amidyl radical after deprotonation and the cleavage of the N−O bond. The measured quantum yield (Φ = 41.2) of the model reaction suggests that this radical-chain pathway is quite productive. Alternatively, SET oxidation of **D** completes the catalytic cycle

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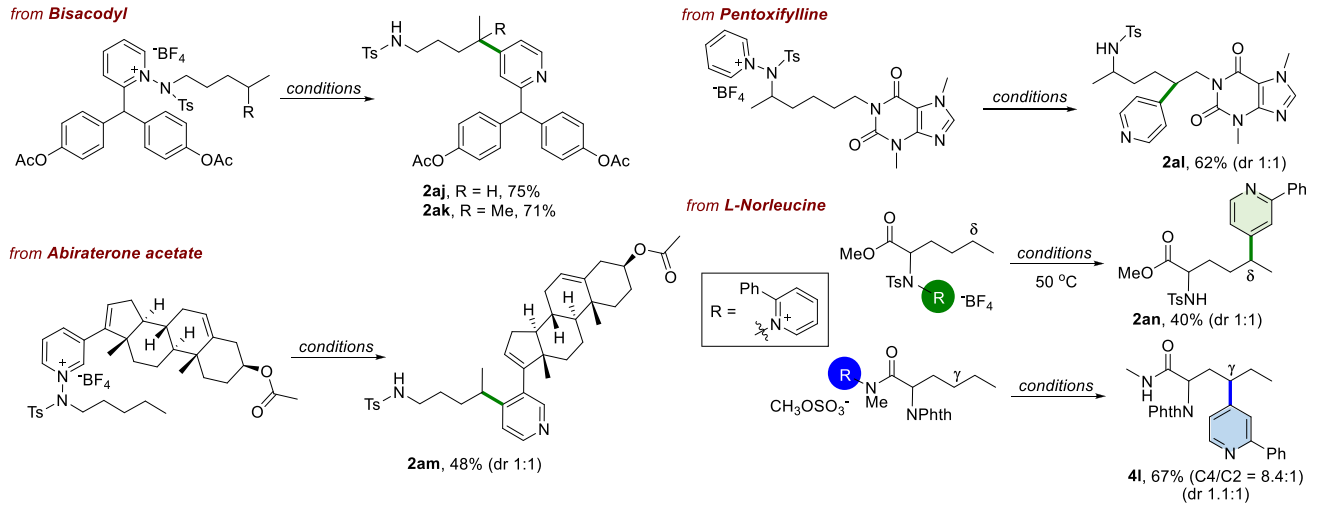
Scheme 4. Late-Stage Functionalization of Complex Molecules



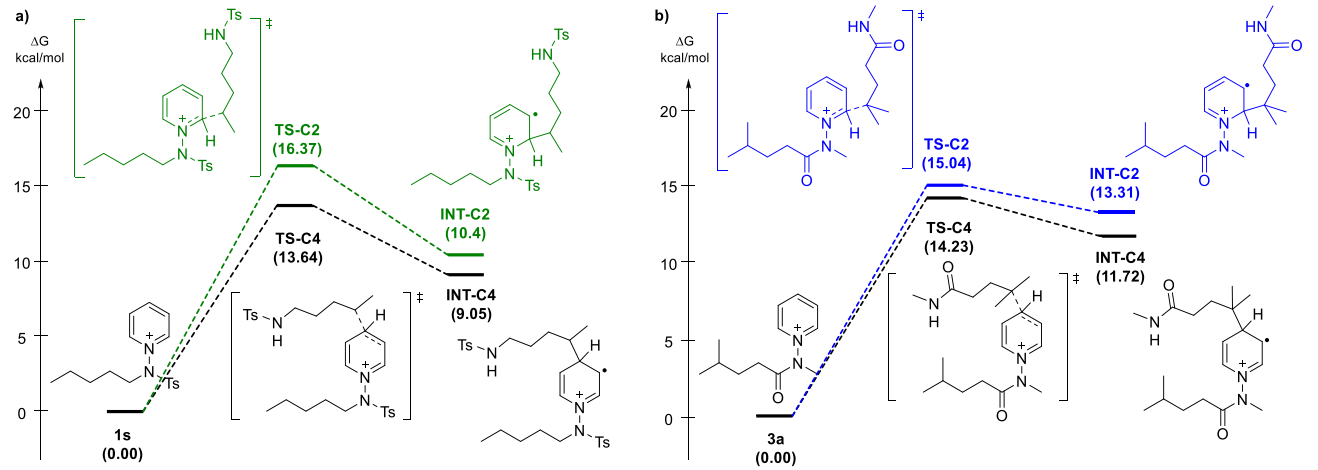


Figure 1. Free-energy profile for the remote C−H pyridylation. Solid black traces represent the *p*-alkylpyridine formation pathway. Blue and green traces represent the *o*-alkylpyridine formation pathway.

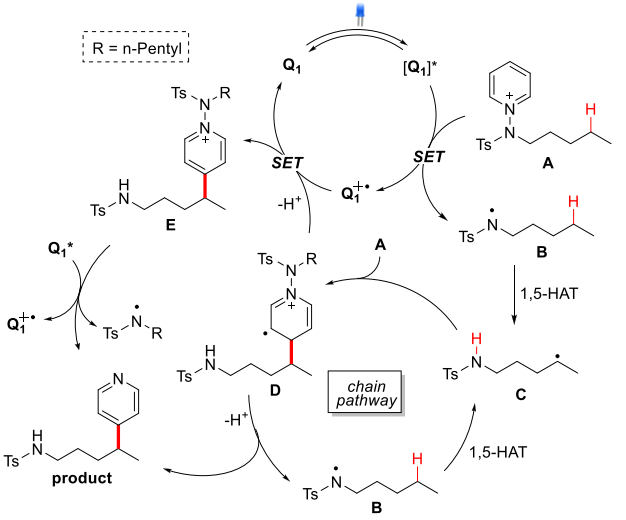


Figure 2. Plausible reaction mechanism.

to provide cation **E**, which undergoes further SET reduction from Q_1* to form product and **B**.

In summary, we developed visible-light-induced site-selective C(sp^3)−H pyridylation of sulfonamides and carboxamides using *N*-amidopyridinium salts under metal-free, mild reaction conditions. In the process, the N-centered radicals formed from a SET reduction trigger a 1,5-HAT reaction to produce *δ*-radical sulfonamides or *γ*-radical carboxamides for subsequent installation of the pyridyl moiety. Remarkably, excellent C4-selectivity in radical trapping with pyridinium salts was observed for all cases investigated with primary, secondary, and tertiary alkyl C(sp^3)−H bonds, ultimately providing synthetically valuable *δ*-pyridyl sulfonamides and *γ*-pyridyl carboxamides. The utility of this powerful method was further demonstrated by offering a practical approach for the late-stage functionalization of complex amide derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03879.

Experimental procedures and characterization of new compounds (^{1}H and ^{13}C NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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