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Functionalization of Pyridinium Derivatives with 1,4-Dihydropyridines Enabled by Photoinduced Charge Transfer

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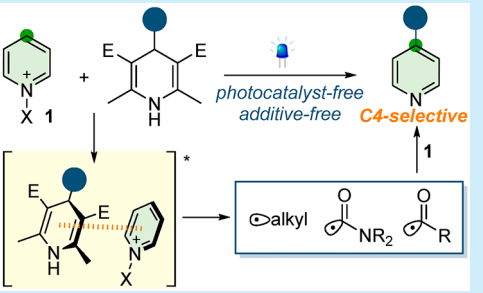
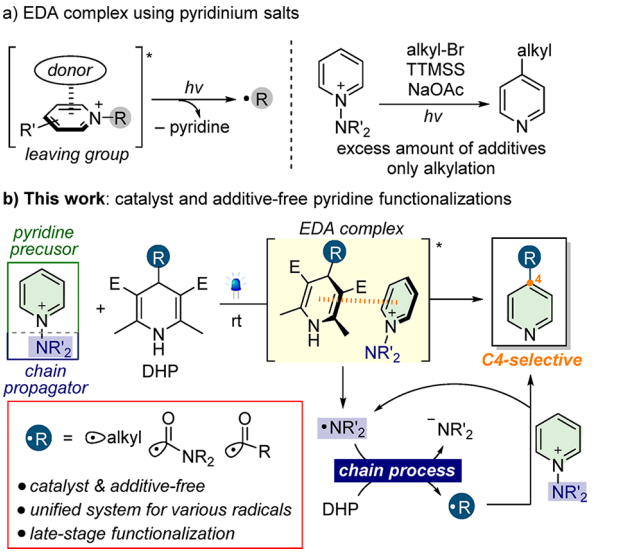
ABSTRACT: By exploiting electron donor–acceptor (EDA) complexes between 1,4-dihydropyridines and *N*-amidopyridinium salts under visible light irradiation, we discovered that photoinduced intermolecular charge transfer induces a single-electron transfer event without requiring a photocatalyst for the facile functionalization of pyridines. The generality of this method is amenable to various types of 1,4-dihydropyridines radical precursors to generate structurally different radicals such as alkyl, acyl, and carbamoyl radicals, ultimately providing facile access to synthetically valuable C4-functionalized pyridines. A broad range of functional groups are well accommodated under mild and metal-free conditions, and the synthetic utility of the present method is showcased by the late-stage functionalization of a variety of biologically relevant pyridine-based compounds, pharmaceuticals, and peptide feedstocks.



The pyridine scaffolds are core units of various pharmaceuticals, natural products, and agrochemicals.[1] Accordingly, various synthetic techniques, such as Minisci-type cross-coupling reactions, have been developed to rapidly functionalize the pyridine motifs. Despite the fascinating advances in the acid-activated pyridine functionalizations, the reactions using unblocked pyridines frequently resulted in mixtures of undesired byproducts due to competitive overalkylation and poor site selectivity.[2] Recently, pyridinium salts have drawn much attention in radical chemistry as versatile pyridine surrogates, which offers direct access to monofunctionalized pyridine derivatives.[3] In particular, a high degree of regioselectivity can be achieved by changing the energy levels of orbitals of pyridines and the steric effects of the activators. In light of these benefits, pyridinium salts have found widespread use in a number of visible-light-mediated radical reactions, in which single-electron transfer (SET) manifolds are required.[4]

Photochemical strategies involving charge transfer in photon-absorbing electron donor–acceptor (EDA) complexes have emerged as powerful tools to promote a wide range of radical-based transformations that bypass the need for an external photocatalyst.[5] In such protocols, Aggarwal[6a] and Glorius[6b] reported photoactive Katritzky pyridinium salt-based EDA complexes with electron donors such as diborons, Hantzsch esters, and indoles. The generated alkyl radicals subsequently undergo a series of deaminative cross-coupling reactions with high efficiency (Scheme 1a).[6] In addition, the Lakhdar group used amines as electron donors to the pyridinium salts for the facile generation of reactive radicals via EDA complexes, which undergo a hydrogen atom transfer (HAT) process.[7a,b] We recently disclosed a photochemical cross-coupling between *N*-amidopyridinium salts and alkyl bromides to yield various C4-alkylated pyridines.[7c] Driven by the need for a unified reaction system to install various functionalities including alkyl, acyl, and

Scheme 1. C4-Selective Pyridine Functionalization with Various 1,4-DHPs by an EDA Complex Activation Strategy



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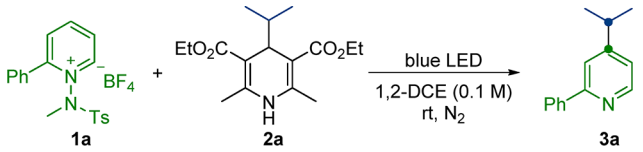
carbamoyl groups, we sought to explore novel reactivity by exploiting new types of electron donors that enable the effective installation of interesting feedstock functional groups into pyridines in a controllable manner, thus providing a potential opportunity to enable pyridine functionalization. The utilization of naturally abundant aldehydes is an appealing method to enable the direct conversion of readily available chemicals into value-added products. 1,4-Dihydropyridines (DHPs) easily prepared from aldehydes in a single step can undergo oxidative fragmentation to afford a broad range of C-centered radicals, such as alkyl, acyl, and carbamoyl radicals, which can engage in cross-coupling reactions.[8] Inspired by the aforementioned studies on EDA-mediated cross-coupling reactions, we speculated that the radical generated by the SET process could then engage in cross-coupling reactions with *N*-amidopyridinium salts (Scheme 1b), which would offer an opportunity for the facile functionalization of pyridines via a productive radical chain process. Herein, we report an efficient method for the C4-selective functionalization of pyridines[9] by leveraging EDA complex activation between the *N*-amidopyridinium salts and 1,4-DHPs upon visible light irradiation. The generality of this method is amenable to various types of alkyl, acyl, and carbamoyl radicals derived from 1,4-DHPs to provide facile access to synthetically challenging C4-functionalized pyridines under metal-free and mild reaction conditions.

We first sought to confirm the postulated photochemically active EDA complexes between pyridinium salts and 1,4-DHPs (see Figure S9 in Supporting Information). A significant red shift was observed when pyridinium salt **1a** and 1,4-DHP **2a** were combined, revealing that the shift in absorption wavelength is likely attributed to the association of these two species. Next, we conducted computational simulation using time-dependent density functional theory (TDDFT)[10] and observed a calculated peak at 437 nm. This predicted peak is composed of a charge transfer excitation from the donor π orbital of the 1,4-DHPs to the acceptor π^* orbital of the pyridinium salt. After observing the possibility of an EDA complex between pyridinium salts and 1,4-DHPs, we further investigated continuous variations of each component by employing Job's analysis using UV/vis absorption measurements, suggesting that the donor–acceptor complex consists of **1a** and **2a** in a 1:1 ratio. In addition, by NMR analysis, we observed that the ^{1}H NMR signal of **2a** and **1a** shifted downfield and upfield, respectively. The above experiments and observations demonstrated the formation of the EDA complex between pyridinium salts and 1,4-DHPs.

After confirmation of the formation of the donor–acceptor complex between *N*-amidopyridinium salts and 1,4-DHPs, our optimization began by monitoring the reactivity of pyridinium salt **1a** with DHP **2a** under blue LED irradiation, as summarized in Table 1. After screening key parameters, we observed that the desired product **3a** was formed in a 1,2-DCE solvent system at room temperature in 76% yield without the need for an external photocatalyst or additives (entry 1). Among the various solvent systems, 1,2-DCE was determined to be the best, and other solvents showed slightly diminished yields (entries 2–4). Not surprisingly, toluene and THF did not lead to any conversion because of poor pyridinium salt solubility (entries 5 and 6). It should be noted that a comparable product yield was obtained at a longer wavelength (approximately 525 nm) under green LED irradiation, further supporting the formation of the EDA complex in this reaction system (entry 7), considering the shorter wavelength absorption of each pyridinium salt **1a** and

Table 1. Reactions between *N*-Amidopyridinium Salts and 1,4-DHPs[a]



entry	variations from standard conditions	yield (%)[b]
1	none	76
2	MeCN instead of 1,2-DCE	66
3	DCM instead of 1,2-DCE	67
4	chloroform instead of 1,2-DCE	65
5	toluene instead of 1,2-DCE	trace
6	THF instead of 1,2-DCE	trace
7	green LED instead of blue LED	68
8	in dark	0
9	with TEMPO	0

[a]Reaction conditions: **1a** (0.1 mmol) and **2a** (1.5 equiv) at rt under light irradiation using a blue LED at rt for 16 h under N_2. [b]Yields were determined by ^{1}H NMR. TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.

DHP **2a**. The necessity of light for a successful reaction was confirmed by the control experiment (entry 8).

With the operationally simple optimized conditions, the generality of the current method was explored (Figure 1). First, various pyridinium substrates bearing electron-deficient or electron-donating substituted C2-aryl groups were alkylated to provide desired products (**3a**–**3c**). A thienyl-substituted substrate was compatible with the optimized reaction conditions (**3d**). Unsubstituted and C3-substituted pyridinium salts were also readily alkylated to afford the corresponding C4-alkylated products **3f** and **3g** with complete regioselectivity. Likewise, valuable bicyclic **3h** and bipyridinium derivatives **3i** could be successfully synthesized. Encouraged by the success of the pyridinium salts, we tested the reactivity of a quinoline derivative. Pleasingly, the quinolinium salt could also be used as an efficient electron acceptor in a productive EDA complex to afford the desired product **3j**. Next, we evaluated the scope of 1,4-DHP radical precursors to investigate the reactivity of differently substituted alkyl radicals. This method worked well with a series of amino acid-derived 1,4-DHPs, such as phenylalanine, leucine, and proline, to deliver the desired products **3k**, **3l**, **3m**, and **3n**, respectively. The alkyl radical, having an internal alkene from melonal that is often used in the perfume industry, provided desired product **3o**. Cyclic alkyl radicals were successfully coupled with pyridinium salts (**3p**, **3q**, and **3r**). Notably, unprotected and protected hydroxyl groups were intact in these reaction conditions (**3s** and **3t**). In addition, bromide was tolerable under the current conditions to provide product **3u**, thus allowing further modification. Sterically hindered *tert*-butyl (**3v**) and benzyl radicals (**3w**) efficiently engaged in the couplings. Next, we attempted to extend this pyridine functionalization protocol to the C4-selective carbamoylation and acylation of pyridine to further expand scope generality. With respect to carbamoyl and acyl radicals, we were pleased to observe that diverse 1,4-DHPs were successfully employed as effective cross-coupling partners with **1** by using our standard reaction conditions. For example, a series of carbamoyl and acyl radicals efficiently participated in the reaction with various *N*-amidopyridinium salts, affording cross-coupled products (**3x**–**3am**). The reactions successfully

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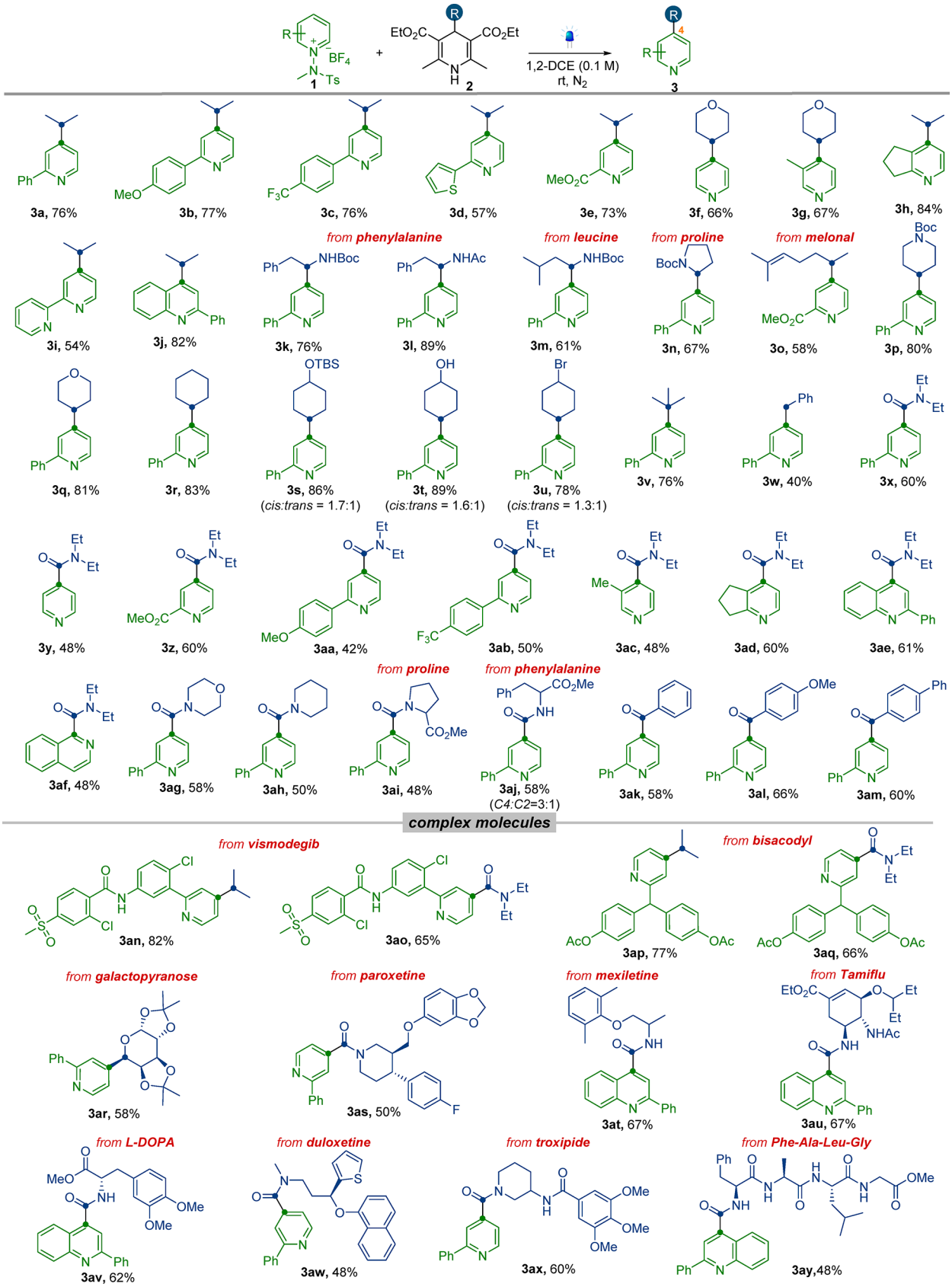

Figure 1. Substrate scope of the functionalization of pyridines. Reaction conditions: **1** (0.1 mmol) and **2** (0.15 mmol) at rt under light irradiation using a blue LED for 16−24 h under N_2. Yields of isolated products.

proceeded with the proline- and phenylalanine-derived DHPs to yield desired products **3ai** and **3aj**.

Encouraged by the results that take place under extremely mild reaction conditions, this method was next employed for the

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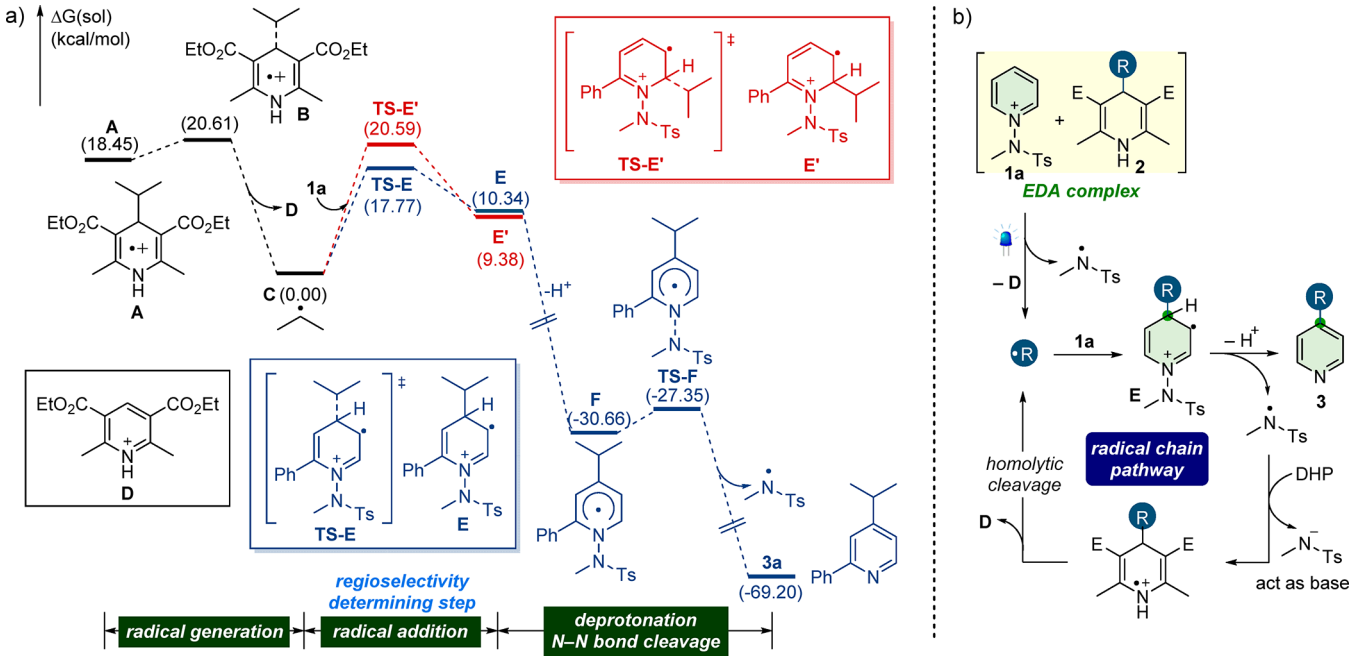

Figure 2. Free-energy profile and proposed reaction mechanism pathway of the *para*-functionalization of **1a**. (a) Related free-energy profile. (b) Proposed reaction pathway.

late-stage functionalization. To our delight, structurally complex pyridine-based pharmaceutical compounds can be successfully functionalized or prepared with this protocol. Of note, we observed that a diverse range of functional groups were well tolerated, including synthetically important chloro, fluoro, acetate, ether, acetal, ester, amide, sulfonyl, internal alkene, phenoxy, and thienyl groups. Specifically, vismodegib and bisacodyl could be quickly modified with 1,4-DHPs (**3an**–**3aq**), allowing the generation of new drug derivatives.

Additionally, this protocol can be used for the incorporation of pyridines or quinolines into pharmaceuticals such as galactopyranose, duloxetine, paroxetine, mexiletine, L-DOPA, troxipide, and Tamiflu to deliver the corresponding products (**3ar**–**3ax**) with excellent regioselectivity. Late-stage modifications of peptides have been drawing attention for drug discovery,[11] and this robust method was successfully applied to tetra-peptide as exemplified by **3ay** (Phe-Ala-Leu-Gly).

After demonstrating general applicability to a wide range of scope, several control experiments were conducted to gain insight into the mechanistic pathway. The formation of the desired product was suppressed with TEMPO, and a significant amount of alkyl radical-trapped adduct **4** was isolated (Scheme S3). To determine whether the pyridines generated by intermolecular charge transfer could act as coupling substrates, crossover experiments were conducted with a mixture of pyridinium salt **1a** and pyridines. As expected, the reaction took place at the C4 position of the pyridinium salt, producing **3a** (Scheme S4).

With the experimentally observed excellent regioselectivities, we carried out density functional theory (DFT) calculations of alkylation to elucidate the reaction mechanism and regiochemical outcomes (Figure 2a). The reaction is initiated by the formation of an EDA complex from pyridinium salt **1a** and 1,4-DHP upon irradiation with visible light. Single-electron oxidation of 1,4-DHP by **1a** generates radical cation **A**, which produces alkyl radical **C** with a barrier of 2.2 kcal/mol. As shown in Figure 1b, after photoinduced intermolecular electron transfer events of the 1,4-DHPs to **1a**, various alkyl, acyl, or carbamoyl radicals can be generated. Based on the computed energy profile, the intermolecular radical addition to pyridinium salt **1a** determines the regioselectivity, resulting in the formation of two possible regioisomers (C2 vs C4). Consistent with the experimental observations, our calculations show that the transition state **TS-E** C4-addition leading to the intermediate **E** is 2.8 kcal/mol lower in energy than the C2-addition transition state **TS-E′**. Next, subsequent deprotonation of the cationic radical complex **E** and cleavage of the N–N bond ultimately delivers the *para*-functionalized pyridine. In the process, the extruded amidyl radical is reduced by 1,4-DHP to yield a new radical species and initiate a radical chain pathway, which is supported by the measured high reaction quantum yield (Φ = 16.0).[12] The resulting amidyl radical also acts as a base in the deprotonation step to produce the desired product. Taken together, the amido group at the pyridinium salt plays multiple roles as a radical chain propagator, base, and regioselectivity inducer.

In summary, we have developed efficient and catalyst-free pyridine functionalization enabled by the unexplored EDA complex between *N*-amidopyridinium salts and 1,4-DHPs under visible-light promoted conditions. The generality of this transformation was demonstrated through reactions with various types of alkyl, acyl, and carbamoyl radicals to ultimately yield synthetically valuable C4-functionalized pyridines with excellent regiocontrol, thereby expanding the chemical space of privileged pyridine scaffolds under extremely mild and metal-free conditions. The synthetic utility of this method was illustrated by the late-stage modification of a variety of biologically relevant compounds with broad functional group tolerance, which would otherwise be difficult to access.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03347.

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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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