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Redox-activated amines in C(sp^3)-C(sp) and C(sp^3)-C(sp^2) bond formation enabled by metal-free photoredox catalysis

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ABSTRACT The amino group represents one of the most prevalent structural motifs in organic chemistry. Therefore, application of amines as alkylating agents in synthesis is highly compelling. Herein, we present a metal-free photoredox strategy for the formation of C(sp^3)-C(sp) and C(sp^3)-C(sp^2) bonds from redox-activated primary amine derivatives. The developed reaction of 2,4,6-triphenylpyridinium salts with alkynyl *p*-tolylsulfones, leading to functionalized alkynes, is easily scalable, offers broad substrate scope, high chemoselectivity, and mild conditions. Its potential is also highlighted by diversification of complex molecular scaffolds. Additionally, the approach proved to be also suitable for synthesis of (*E*)-alkenes from vinyl phenyl sulfones. Mechanistic studies contribute to the elucidation of unexpected differences in reactivity of primary and secondary alkyl substituted pyridinium salts.

KEYWORDS: photoredox, pyridinium, catalysis, amine, alkyne, deaminative

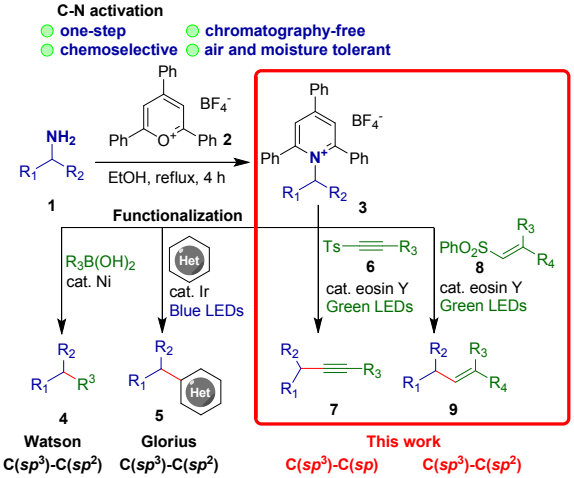
INTRODUCTION

The amine functionality is widely represented in various areas of chemical science - from feedstock molecules, to natural products and complex pharmaceuticals.[1] In 1884, Sandmeyer disclosed potential of primary aryl amines as valuable synthetic intermediates by their straightforward transformation into aryl diazonium salts.[2] Owing to its feasibility of harnessing aforementioned advantages in synthesis, this strategy rapidly became one of the cornerstones in organic chemistry.[3] On the other hand, due to the low stability of alkyl diazonium salts, development of a complementary approach employing amines as alkylating agents represents a longstanding challenge. Recent studies in this area led to transition-metal catalyzed methods for the formation of C(sp^3)-C(sp^3) and C(sp^3)-C(sp^2) bonds using alkyl amine derivatives such as diazo compounds,[4] ammonium[5] or pyridinium salts.[6,7] Conversely, to the best of our knowledge, a general deaminative alkynylation strategy via the formation of C(sp^3)-C(sp) bond has not been described yet.

Alkynes found numerous applications in chemical biology,[8] medicinal chemistry,[9] and material sciences.[10] In recent years, they have been prominently featured in cycloaddition reactions broadly utilized for connecting biologically relevant molecules.[11,12] In organic synthesis, alkynes are versatile building blocks due to their ability to act both as nucleophiles and electrophiles as well as to undergo oxidation and reduction.[11] Classic methods for their synthesis such as Corey-Fuchs[13] or Seyferth-Gilbert reactions[14] are associated with the use of strong bases and therefore are rarely applicable to late-stage functionalization or diversifications of complex molecules. This issue has been recently addressed by Baran's[15] and Weix's groups[16] which reported elegant Ni-catalyzed decarboxylative cross-coupling procedures. In addition, decarboxylative[17] and deboronative[18] alkynylation under mild conditions are accessible by visible-light photoredox

catalysis. In this context, complementary deaminative strategy would open new vistas in chemical sciences by harnessing molecular scaffolds exclusive to alkyl amines for the synthesis of C(sp^3) -C(sp) bonds.

We wondered whether the activation/functionalization approach, applied for over a century for aromatic compounds, could be adapted to synthesis of functionalized alkynes from alkyl amines. In this line, Watson[6] and Glorius[7] showed that Katritzky salts (2,4,6-triphenylpyridinium salts, **3**)[19] can be employed as alkyl radicals precursors in nickel- or photoredox-iridium-catalyzed deaminative alkylation of arenes and heteroarenes (Scheme 1). These redox-active species are easily prepared from unactivated primary amines **1** and commercially available pyrylium salts **2** via straightforward, chromatography-free procedure (Scheme 1).[19] We envisioned that alkyl radicals, generated from Katritzky salts **3** via visible-light photoredox catalysis, could be trapped by electrophilic alkyne and alkene derivatives[17,20] leading to the formation of internal alkynes **7** and alkenes **9**.



Scheme 1. Katritzky salts as redox-activated amines in C-C bond formation reactions.

Herein, we report an unprecedented metal-free, photo-catalytic approach for deaminative formation of C(sp^3)-C(sp) and C(sp^3)-C(sp^2) bonds (Scheme 1). In addition to its mild conditions,

this reaction tolerates a broad range of starting materials and exhibit excellent chemoselectivity. The feasibility of this method in late-stage functionalization and synthesis of pharmaceuticals is highlighted by diversification of several complex drug-like molecules.

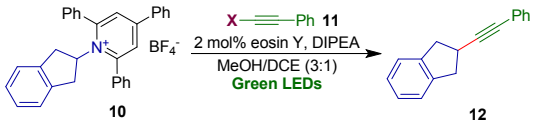
RESULTS AND DISCUSSION

Model Studies To attain an access to C(sp^3)-C(sp) bonds from primary amines, we explored reactivity of Katritzky salts **3** in reaction with alkynyl derivatives **11**. Our studies commenced with the choice of a photocatalytic system. Glorius et al. reported that ruthenium and iridium polypyridyl complexes generate alkyl radicals from pyrdinium salts **3** via light-induced reductive single-electron transfer process.[7] Encouraged by an increasing interest in the use of organic photocatalysts[21] and considering reduction potential values of Katritzky salts **3** ($E_{1/2}$ = ca. -0.95 V vs. Ag/AgCl in MeOH, see SI), we hypothesized that similar outcome should be possible with nontoxic and inexpensive organic dyes. Such an approach merging unique capabilities of photoredox catalysis with benefits of "metal-free" catalytic system would be advantageous for development of sustainable transformations. To this end, using pyridinium salt **10**, we performed fluorescence-quenching studies of a series commonly employed in photoredox catalysis xanthene dyes (with redox potentials $E_{1/2}(PC^+/PC^*)$ < -0.95 V): eosin Y, rose bengal, erythrosin B and rhodamine 6G.[21] Pleasingly, compound **10** quenched the fluorescence of all of the aforementioned dyes, with eosin Y being quenched the most efficiently ($k_q = 8.1 \cdot 10^{10}$ $s^{-1} \cdot M^{-1}$) (see SI).

Following the evaluation of a catalyst, we sought to establish a suitable alkyne acceptor (Table 1). After considerable optimization studies, we found that alkynyl bromides and *p*-tolylsulfones enabled the desired reaction, with the latter providing the highest yield of desired product **12** (entries 2 and 3). Unsurprisingly, terminal alkynes did not furnish product **12** (entry 1). Control

experiments identified the catalyst, light, and the sacrificial reductant (DIPEA) as essential components of the reaction (entries 7, 8, 9). Comparison of the studied catalysts under the optimal conditions showed that eosin Y performed superior to other organic dyes (see SI) and equally with transition-metal-based catalysts (entries 5, 6). Importantly, the use of both anhydrous solvents and inert atmosphere was not required (entry 10) (for optimization details see SI).

Table 1. Model studies.[a]



Entry	Catalyst	X	Light	Yield (%)[b]
1	eosin Y	H	green	0
2	eosin Y	Br	green	34
3	eosin Y	Ts	green	86 (84)[c]
4	eosin Y	BI	green	0
5	$Ru(bpy)_3Cl_2 \cdot 6H_2O$	Ts	blue	80
6	$[Ir(ppy)_2(dtbbpy)]PF_6$	Ts	blue	85
7	none	Ts	white	0
8	eosin Y	Ts	none	0
9[d]	eosin Y	Ts	green	0
10[e]	eosin Y	Ts	green	79 (78)[c]

[a]Reaction conditions: alkyne **11** (0.10 mmol), pyridinium salt **10** (1.4 equiv.), catalyst (2.0 mol%), DIPEA (3.25 equiv.), MeOH/DCE (3:1, *c* = 0.033 M), ambient temperature (20-22 °C), 16 h, under Ar atmosphere, light source: LED tape (for more details see SI). [b]GC yield. [c]Isolated yield. [d]Without DIPEA. [e]Air atmosphere. BI – benziodoxole, DCE – 1,2-dichloroethane.

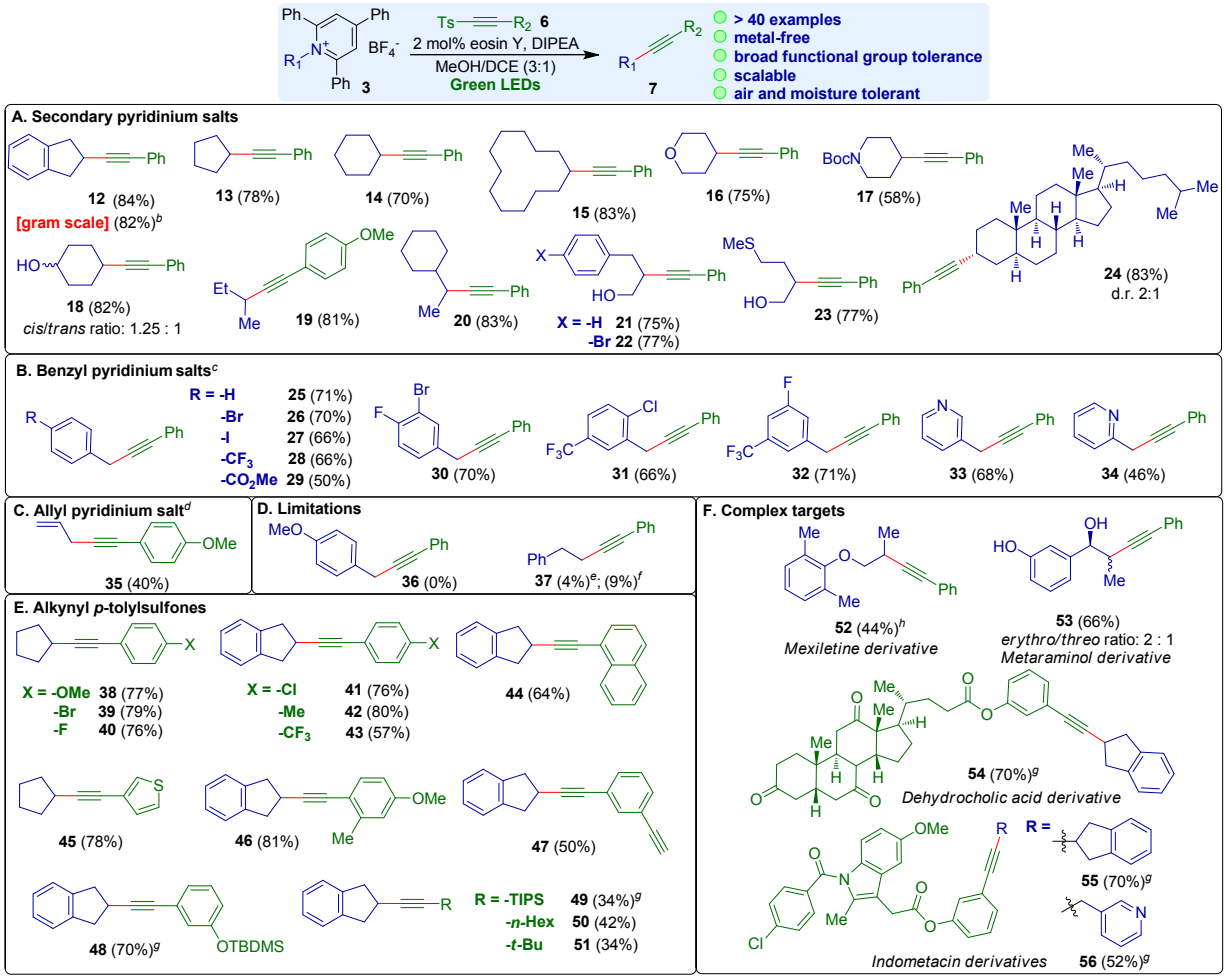
Scope and Limitations With the optimized conditions in hand, we explored scope and limitations of the developed reaction. To this end, a range of pyridinium salts **3** were prepared

and tested (Scheme 2A-D).[19] Substrates derived from secondary alkyl, primary benzyl and allyl tethered primary amines smoothly underwent the examined transformation. The reaction proved to be suitable for the synthesis of simple cyclic (**12**-**15**), heterocyclic (**16**), and acyclic (**19**, **20**) alkynes. Importantly, products bearing a range of functional groups including: carbamate (**17**), unprotected hydroxyl group (**18**, **21**, **22**, **23**), sulfide (**23**), halogens (**26**, **27**, **28**), ester (**29**), basic nitrogen atom (**33**, **34**), and alkene (**35**) were easily obtained, highlighting utility of the developed method in synthesis of valuable building blocks. For example, bromo- (**26**) and iodoarenes (**27**) are favorable substrates in metal-catalyzed cross-coupling reactions,[22] while 1,4-enynes, such as **35**, are applicable in rapid synthesis of complex carbon frameworks via Pt-catalyzed cycloisomerization.[23] Moreover, merging this strategy with well-established methods for amine synthesis can be used to transform different functional groups into alkynes. In this line, halogenated compound **30** was obtained from corresponding nitrile, while steroid **24** was derived from commercially available 5α-cholestan-3-one.

While secondary alkyl substituted pyridinium salts furnished products in good to excellent yields under optimized conditions, benzyl derivatives required a higher excess of a Katritzky salts, due to the concurrent dimerization of benzyl radicals. Noteworthy, regarding the benzylation of alkynes, the developed method is complementary to the recently reported Ni-catalyzed decarboxylative alkynylation reactions,[15,16] which are unsuitable for the synthesis of this type of products.

Based on Katritzky's works, poor reactivity of electron rich benzyl salts (**36**) can be explained by their diminished stability due to activation towards the competing nucleophilic substitution.[24] For primary alkyl substituted substrates, the reaction proceeded remarkably slow, giving only traces of product **37** even after prolonged reaction time. Moreover, the reaction of amino ester

derived pyridinium salts **3** with alkynyl sulfones **6** led to formation of inseparable mixtures of β,γ-alkynyl esters and isomeric allenes.



Scheme 2. Scope of deaminative alkynylation.[a]

[a]Reaction conditions: alkyne **6** (0.25 mmol), pyridinium salt **3** (1.4 eqiuv.), eosin Y (2.0 mol%), DIPEA (3.25 equiv.), MeOH/DCE (3:1, *c* = 0.033 M), ambient temperature (20-22 °C), 16 h, under Ar atmosphere, light source: green LEDs tape. All reported yields are mean values of isolated yields from at least two independent experiments. [b]5.0 mmol scale, reaction time: 40 h. [c]Pyridinium salt **3** (2.0 equiv.), DIPEA (3.75 equiv.). [d]Pyridinium salt **3** (3.0 equiv.), DIPEA (4.5 equiv.). [e]GC yield, reaction time: 48 h. [f]GC yield, at 60 °C. [g]In DCE (c = 0.033 M). [h]Pyridinium salt **3** (0.25 mmol), alkyne **6** (5 equiv.).

Continuing with the evaluation of the reaction scope, several alkynyl *p*-tolylsulfones **6** were prepared from terminal[17a] and silyl protected alkynes[25] via the literature procedures (Scheme 2E).

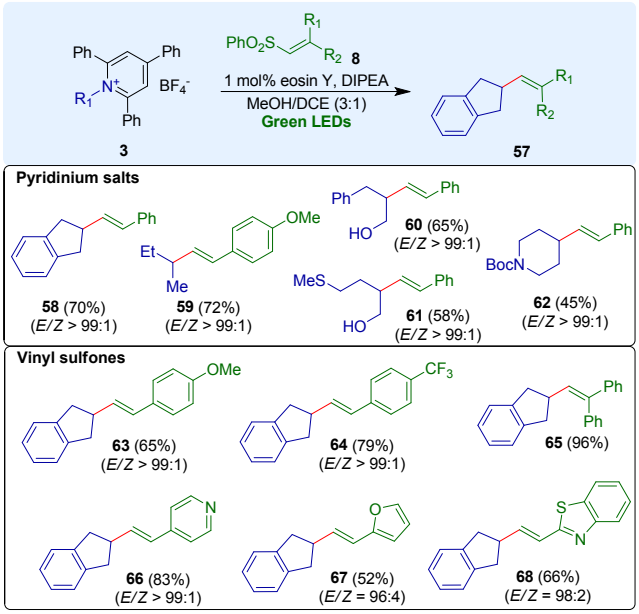
Phenyl derivatives with electron-donating (**38**, **42**) as well as mildly electron-withdrawing substituents (**39**, **40**, **41**) reacted equally well. The presence of a strongly electron-withdrawing substituent as in **43** reduced the reaction yield. Additionally, the reaction outcome was not affected by the substitution pattern on the aromatic ring, as demonstrated by the excellent yields of the *para* (**42**), *meta* (**47**) and *ortho* (**46**) substituted products. Furthermore, heteroaryl alkyne derivatives were well tolerated under the studied conditions (**45**). The preference of alkyl radicals for the reaction with electrophilic alkynyl *p*-tolylsulfones compared with terminal alkynes, permits the synthesis of unsymmetrical dialkynes via regioselective functionalization (**47**). Finally, silyl (**49**) and alkyl (**50**, **51**) substituted alkynes were also possible to obtain in workable yields, without additional optimization.

Consequently, to show the utility of the developed methodology for diversification of drug molecules two commercially available drugs bearing a primary amino group, mexiletine (anti-arrhythmic) and metaraminol (antihypotensive) were converted into the corresponding Katritzky salts and subjected to the title transformation. Initially, the derivatization of mexiletine proved to be challenging due to the concurrent β-fragmentation of the resulting alkyl radical. However, the use of an excess of alkynyl derivative (5 equiv.) provided product **52** in satisfactory 44% yield. Conversely, the metaraminol derivative smoothly underwent alkynylation giving compound **53** with full retention of the configuration at the stereogenic center adjacent to reaction site. These examples highlight the possibility of application of the reaction to rapidly access complex structural motifs.

Furthermore, to examine applicability of our approach in late-stage functionalization, drug-like alkynyl *p*-tolylsulfones were synthesized from complex substrates: dehydrocholic acid (steroid) and indometacin (non-steroidal anti-inflammatory drug). Steroidal derivative **54** bearing reactive

ketone groups and multiple stereogenic centers was obtained in excellent yield as a single enantiomer. Similarly, highly functionalized indometacin derivative proved to be a suitable coupling partner for both secondary (**55**) and benzylic Katritzky salts (**56**), underscoring mild conditions and high chemoselectivity of the developed method.

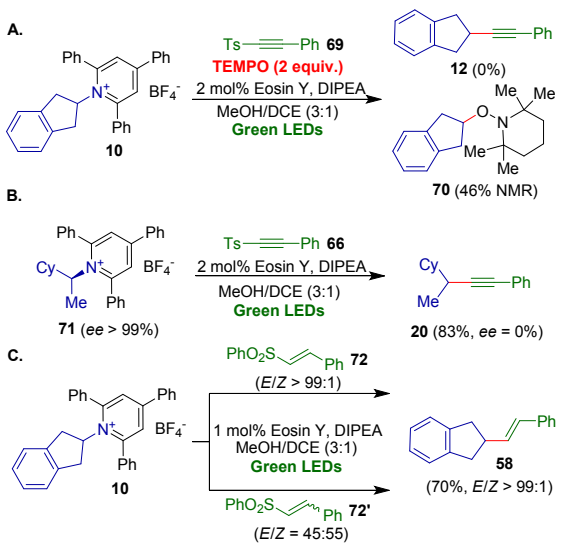
The successful development of deaminative alkynylation prompted us to further explore the possibility of constructing other types of C-C bonds via the studied approach. Pleasingly, vinyl sulfones **8** proved to be suitable acceptors of alkyl radicals under previously developed conditions, leading to functionalized alkenes (Scheme 3). The reaction provided a range of aryl (**58-65**) and heteroaryl (**66**, **67**, **68**) substituted olefins with excellent diastereoselectivity leading to theromodynamically favoured (*E*)-alkenes. Moreover, 1,1-disubstitued substrate provided product **65** in significantly higher yield, presumably due to better stabilization of intermediate benzyl radical. Most importantly, the ability to access alkenes from unstabilized (secondary) alkyl radicals makes this reaction complementary to recently published Ni-catalysed cross-coupling of benzylic Katritzky salts with vinyl boronic acids.[6c]



Scheme 3. Scope of deaminative alkynylation.[a]

[a]Reaction conditions: alkene **8** (0.25 mmol), pyridinium salt **3** (2.0 eqiuv.), eosin Y (1.0 mol%), DIPEA (2.5 equiv.), MeOH/DCE (3:1, *c* = 0.033 M), ambient temperature (20-22 °C), 40 h, under Ar atmosphere, light source: green LEDs tape. *E/Z* ratios were established based on GC-MS analysis of crude reaction mixtures.

Mechanistic Consideration To gain mechanistic insight into our photocatalytic system, several experiments were conducted. Based on Watson's[6] and Glorius's work,[7] a radical mechanism is postulated. To corroborate this hypothesis, the reaction of pyridinium salt **10** with alkyne **69** in the presence of TEMPO [(2,2,6,6-tetramethylpiperindin-1-yl)oxyl] was performed (Scheme 4A). Expectedly, the addition of a radical trap had a detrimental effect on the reaction outcome due to the formation of the alkylated TEMPO derivative **70** (detected by LR-MS and NMR). Moreover, the reaction with enantiomerically pure pyridinium salt **71** gave racemic product **20**, which is typical for reactions proceeding via readily epimerizable radical intermediates (Scheme 4B). The alkenylation reactions with pure *E*-isomer as well as a mixture geometric isomers of vinyl sulfone **72** led to comparable results both in terms of the product **58** yield and stereochemical outcome, which is characteristic for the reactions proceeding via radical addition-elimination mechanism (Scheme 4C).[24b,24c,26]



Scheme 4. Mechanistic experiments.

To examine the role of a photocatalyst, Stern-Volmer quenching experiments were performed (Figure 1). Although both Katritzky salts **3** and tertiary amines quenched the luminescence of eosin Y, the significantly higher quenching constant for pyridinium salt **73** ($k_q = 3.8 \cdot 10^{10}$ $s^{-1} \cdot M^{-1}$) compared with DIPEA ($k_q = 2.3 \cdot 10^{9}$ $s^{-1} \cdot M^{-1}$) indicates that the oxidative quenching cycle is favored. Additionally, a light on/off experiment proved the exclusive light-dependence of the reaction (see SI).

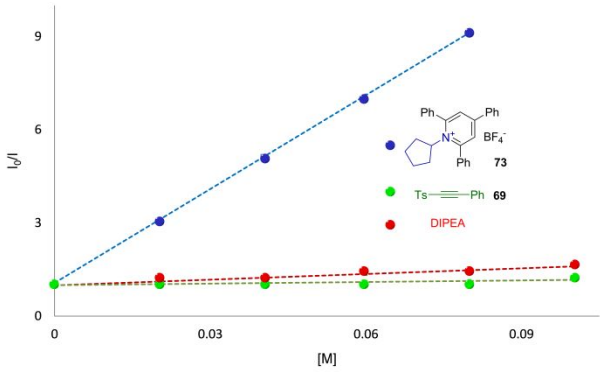
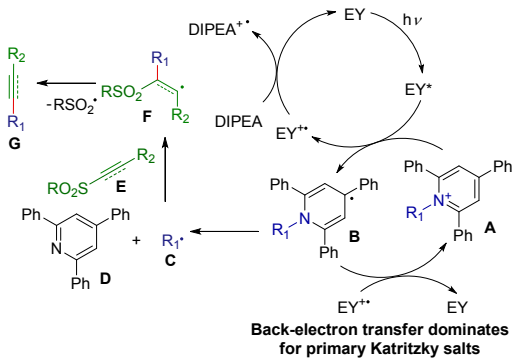


Figure 1. Stern-Volmer fluorescence quenching of eosin Y (*c* = 2.0 μM) in MeOH.

Based on the presented experimental evidences and reported results,[7,17a,17c] we propose the reaction mechanism shown in Scheme 5. Photoexcited eosin Y (EY*) reduces pyridinium salt **A** via single-electron transfer, followed by fragmentation of the resultant dihydropyridine radical **B** generating alkyl radical **C** and rearomatized pyridine derivative **D**. Simultaneously, to maintain the catalytic cycle, $EY^{+\cdot}$ is reduced to the initial form by DIPEA. Subsequent α-addition of radical **C** to acceptor **E** furnishes intermediate **F** that rapidly eliminates arylsulfonyl radical giving product **G**. The *E*-selectivity of the alkenylation reaction arises during the β-elimination step and is dictated by the thermodynamic and steric factors.[26]



Scheme 5. Proposed reaction mechanism.

The intriguingly significant difference in the reactivity of secondary and primary alkyl substituted Katritzky salts can be explained based on voltammetric (Figure 2) and kinetic (Figure 3) experiments. For primary alkylic (**74**), secondary alkylic (**10**) and benzylic (**75**) pyridinium salts, fully-reversible, semi-reversible, and irreversible reduction waves are respectively observed, illustrating the relative stability of the dihydropyridine radicals **B**. Similarly, the rates of substrates conversion under optimized conditions follows the order benzyl > secondary > primary. These results indicate that the fragmentation rate of dihydropyridine radical **B** strongly depends on the stability of the resulting alkyl radical **C**. While benzyl- and secondary alkyl-substituted pyridinium salts produce alkyl radicals at a sufficient rate, primary derivatives lead to persistent dihydropyridine radicals, which preferentially undergo reoxidation to pyridinium salts (Scheme 5).

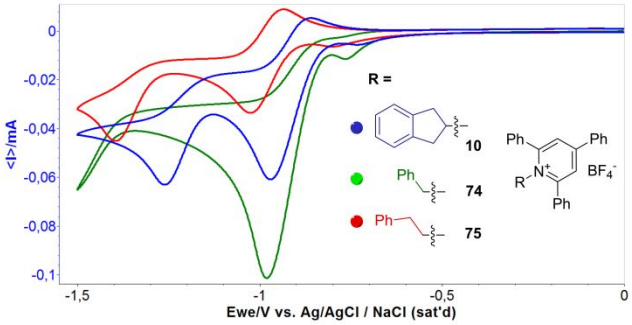


Figure 2. Cyclic voltammograms of Katritzky salts **10**, **74** and **75** (c = 10 mM) in dry MeOH.

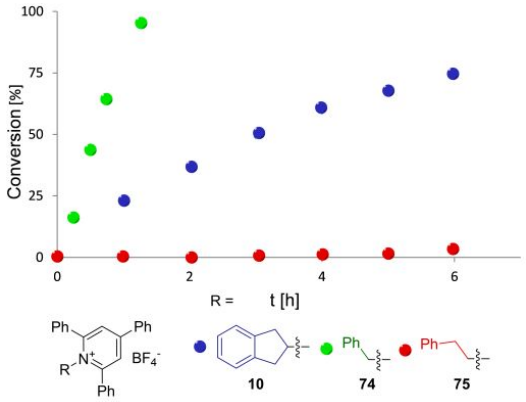


Figure 3. Kinetic study of the conversion of pyridinium salts **10**, **74**, and **75** under reaction conditions.

CONCLUSIONS

In summary, a visible-light-mediated deaminative strategy for the construction of C(sp^3)-C(sp) bond has been developed. This reaction employs an environmentally benign "metal-free" catalytic system. High chemoselectivity, mild conditions, and scalability of the title transformation open new prospects for a straightforward access to complex molecules from prevalent primary amines. Its applicability was demonstrated on the examples of diversification of complex drug derivatives. Additionally, the developed approach proved to be also suitable for synthesis of functionalized alkenes from vinyl sulfones.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge.

Experimental procedures, optimization details and mechanistic studies (PDF file)

^{1}H and ^{13}C NMR spectra for all new compounds (PDF file)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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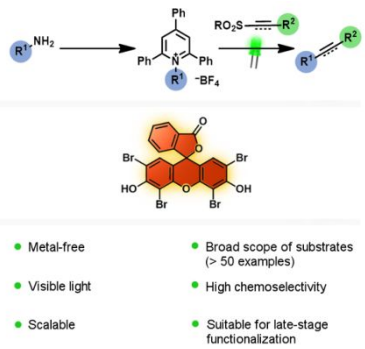

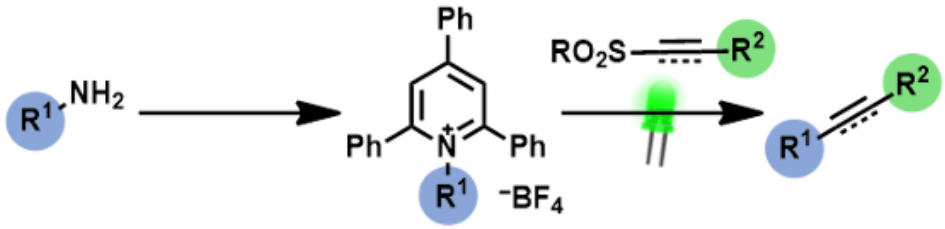

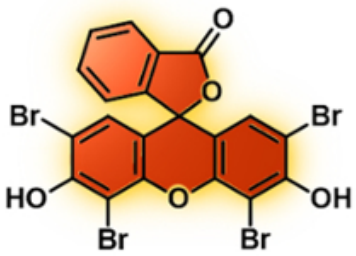

- Metal-free
- Visible light
- Scalable
- Broad scope of substrates (> 50 examples)
- High chemoselectivity
- Suitable for late-stage functionalization

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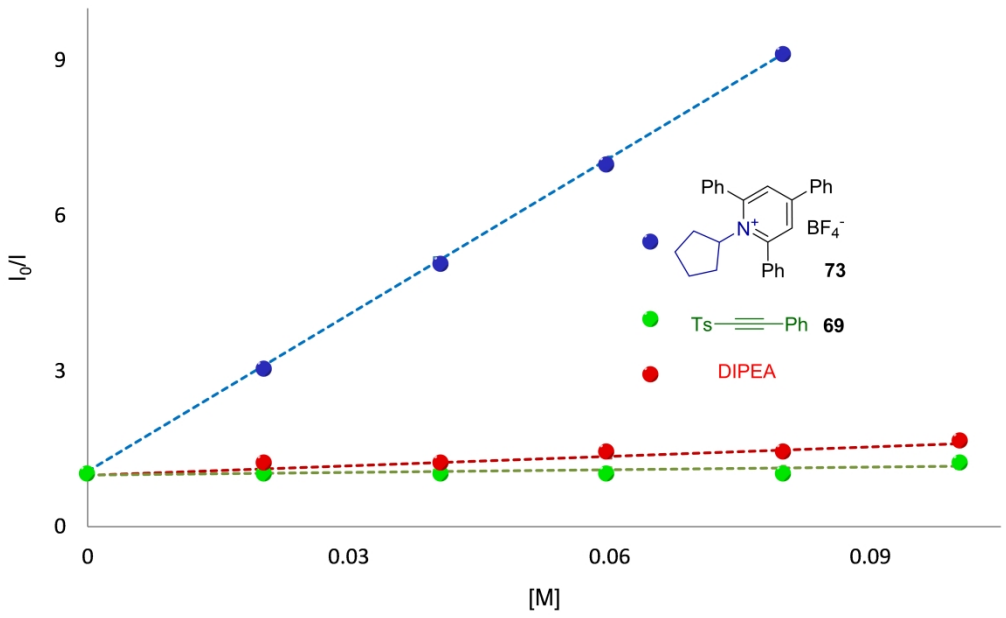

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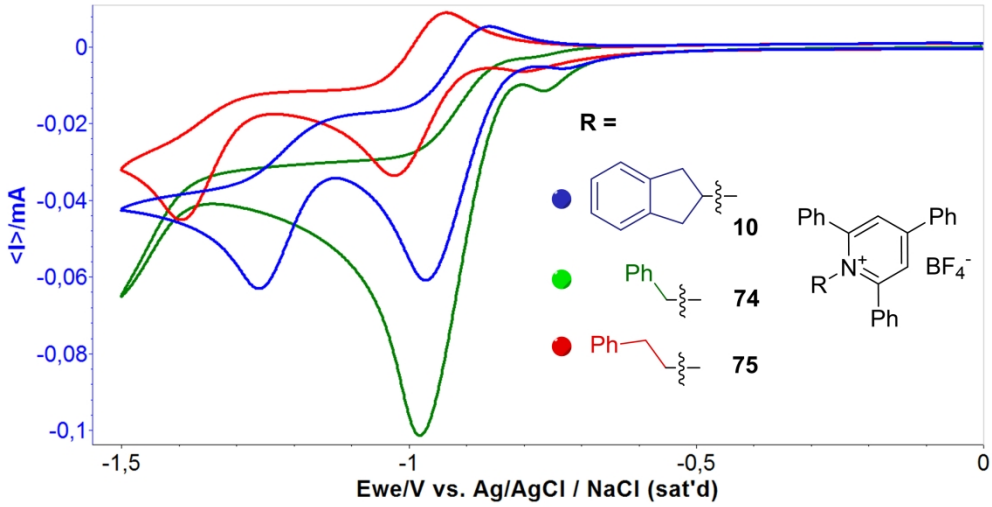

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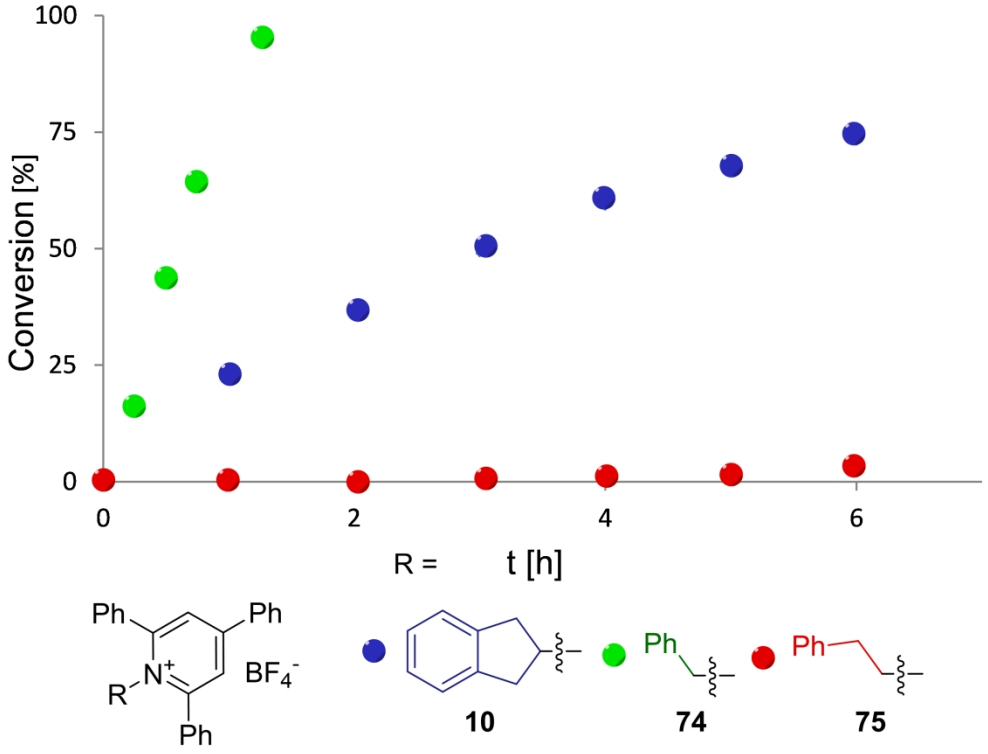

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