Catalyst-Free Deaminative Functionalizations of Primary Amines by Photoinduced Single-Electron Transfer

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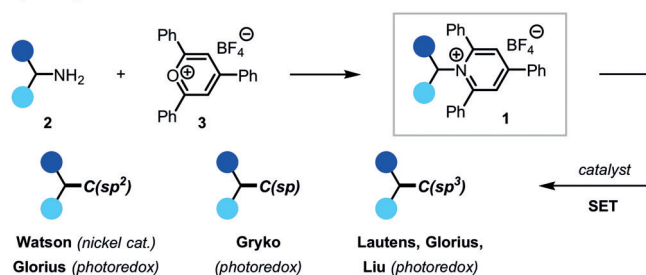
Abstract: The use of pyridinium-activated primary amines as photoactive functional groups for deaminative generation of alkyl radicals under catalyst-free conditions is described. By taking advantage of the visible light absorptivity of electron donor–acceptor complexes between Katritzky pyridinium salts and either Hantzsch ester or Et₃N, photoinduced single-electron transfer could be initiated in the absence of a photocatalyst. This general reactivity platform has been applied to deaminative alkylation (Giese), allylation, vinylation, alkynylation, thioetherification, and hydrodeamination reactions. The mild conditions are amenable to a diverse range of primary and secondary alkyl pyridiniums and demonstrate broad functional group tolerance.

Visible light photochemistry in organic synthesis has witnessed a surge in research activity over the last decade.[1] This is largely due to a growing appreciation of the synthetic utility of photoredox catalysts, which, upon photoexcitation, function as single-electron or energy transfer catalysts to provide access to free-radical intermediates.[2] An alternative strategy, that circumvents the need for catalysis, is direct photoexcitation of a substrate, which has classically been performed using UV light.[3] However, recent developments have taken advantage of the visible light absorptivity of specific functional groups that act as photoactive handles to enable photoinduced electron transfer (PET).[4] Although direct photoexcitation is possible with a number of different functional groups,[5] such reactions more commonly take advantage of electron donor–acceptor (EDA) complexes, whose absorption spectra display a bathochromic shift relative to their constituent parts, thus enabling photoexcitation with visible light.[6]

These strategies have enabled the development of a broad range of radical transformations that proceed through visible light-mediated PET under catalyst-free conditions. However, such reactions are typically limited to the generation of perfluoroalkyl or stabilized alkyl radicals.[5,7,8] Access to non-stabilized alkyl radicals under such conditions is considerably more challenging,[9,10] with only a single report by Melchiorre and co-workers that generates secondary alkyl radicals by direct photoexcitation of 4-alkyl-1,4-dihydropyridine derivatives.[11] We sought an alternative functional group that could act as a versatile photoactive handle for catalyst-free generation of non-stabilized carbon-centered radicals. One possibility was Katritzky *N*-alkylpyridinium salts **1**, which are easily prepared from primary amines **2** by reaction with 2,4,6-triphenylpyrylium **3**, are air and moisture stable, and allow selective deaminative transformations of abundant amino groups (Scheme 1 A).[12] While these redox active amines have recently been applied to a number of radical-mediated transformations, they usually rely on catalysis to promote single-electron transfer (SET)-induced deamination.[13,14]

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A) Catalyzed SET-induced deaminative functionalizations

B) Catalyst-free photoinduced deaminative transformations
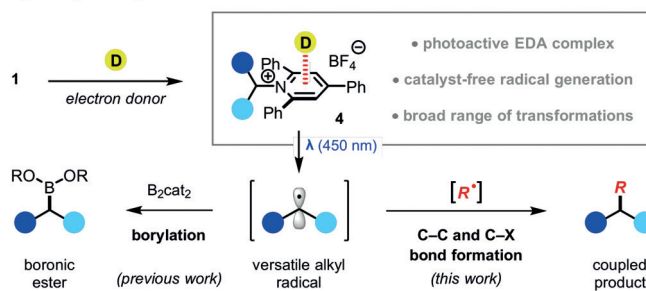
Scheme 1. Radical-mediated transformations of Katritzky pyridinium salts.

We recently reported a catalyst-free deaminative borylation reaction that proceeds through EDA complex formation between **1** and bis(catecholato)diboron (B₂cat₂) (Scheme 1 B).[15] Subsequent PET and fragmentation provided efficient access to non-stabilized alkyl radicals that were intercepted by the diboron reagent. We reasoned that the 2,4,6-triphenylpyridinium moiety in **1** could be complexed

with other electron-donors to generate EDA complex **4**,[16] thus providing a photoactive handle capable of generating non-stabilized alkyl radicals for application in a diverse range of C−C or C−X bond forming reactions (Scheme 1 B). Herein, we report that Katritzky pyridinium salts are versatile substrates for photoinduced deaminative functionalizations of primary amines under catalyst-free conditions.

Our investigations began by studying the use of pyridiniums **1** in Giese reactions with electron-deficient alkenes (Table 1). Such reactions are well-developed using photocatalysis, but there are few reports of photoinduced reactions under catalyst-free conditions.[17] Given the overall transformation is reductive, a stoichiometric reductant was required. We selected Hantzsch ester (**5**) as this would act as a reductant but could also function as an electron-donor to form the key EDA complex with **1**.[10c,d] Gratifyingly, irradiation ($\lambda_{max} = 450$ nm) of a mixture of 4-aminopiperidine-derived pyridinium **1a**, Hantzsch ester, and methyl acrylate in DMA yielded the desired Giese adduct **6** in 77% yield (Table 1). Control experiments confirmed the necessity of light and **5** for successful reaction, and alternative reductants, such as Et₃N, gave no desired product.[18]

These optimized conditions were subsequently applied to a broad range of Michael acceptors (Table 1). Giese products

from reactions with substituted acrylates (**7**), acrylonitrile (**8**), methyl vinyl ketone (**9**), *N*-phenylacrylamide (**10**), and phenyl vinyl sulfone (**11**) were formed in good to excellent yields. Aldehydes were tolerated (**12–14**), although the substituted enals methacrolein (**13**) and tiglic aldehyde (**14**) required higher temperatures for successful reaction. Interestingly, vinyl silanes and boronic esters were also suitable substrates, providing products **15** and **16**, respectively, albeit in low yield. Finally, methyl propiolate underwent the Giese reaction to give alkene product **17** as a mixture of *E* and *Z* isomers.

With respect to the pyridinium salts, a variety of cyclic (**18** and **19**) and acyclic (**20**) secondary alkyl substrates reacted efficiently. The Giese product from a γ-amino alcohol-derived pyridinium could be cyclized by treatment with acid to generate lactone **21**. Alternatively, *t*-butyl acrylate could be used in place of methyl acrylate to inhibit lactonization, allowing isolation of norephedrine-derived alcohol **22**. Pharmaceutical and natural product derivatives were also readily accessed, as exemplified by the formation of product **23**, from the anti-arrhythmic drug mexiletine, and **24**, from the steroid tigogenin.

While primary benzylic pyridiniums yielded products **25–27** in good yields, primary non-benzylic substrates failed to undergo the deaminative Giese reaction. However, we found

Table 1: Giese reaction substrate scope.[a]

[a] General conditions: Pyridinium (0.2 mmol, 1.0 equiv), Michael acceptor (1.3 equiv) and **5** (3.0 equiv) in DMA (0.5 M) at 40°C for 16 h. Yields are of isolated products after flash column chromatography. [b] Isolated as the alcohol after reduction with NaBH₄. [c] Reaction performed at 60°C for 40 h. [d] Isolated as the alcohol after oxidation with NaBO₃. [e] Using 1.8 equiv of vinylboronic acid pinacol ester. [f] Lactonization was promoted by treatment with Amberlyst®. [g] Reactions performed at 60°C in DMA (0.25 M) with the addition of Et₃N (3.0 equiv). DMA = *N,N*-dimethylacetamide. TBS = *tert*-butyldimethylsilyl.

that adding Et$_3$N to the reaction mixture and increasing the reaction temperature to 60 °C had a dramatic effect on the outcome of the reaction and enabled the isolation of adduct **28**, albeit in low yield. Switching from benzyl acrylate to the more activated alkene methyl 2-phenylacrylate provided further improvements and enabled isolation of product **29** in 47 % yield. Despite the yield being moderate, this result is notable as it is a rare example of a photoinduced Giese reaction of a non-stabilized primary alkyl radical under mild and catalyst-free conditions. With these new conditions, a range of non-benzylic primary alkyl pyridiniums reacted to give the Giese products (**29–35**) in moderate to good yields. Furthermore, the functional group tolerance of the methodology was highlighted by generating products bearing primary sulfonamide (**31**), pyridine (**32**), thiophene (**33**), and silyl ether (**35**) moieties.

To shed light on the mechanism of this catalyst-free Giese reaction, we analyzed the reaction components by UV/Vis absorption spectroscopy. DMA solutions of secondary alkyl pyridinium **36** and Hantzsch ester (**5**) were both found to absorb in the visible region (> 400 nm) (Figure 1 A). However, a mixture of **36** and **5** displayed a significant red-shift in absorbance, confirming formation of the postulated EDA complex. A similar shift was observed with a mixture of primary alkyl pyridinium **37** and **5** (Figure 1 B). Interestingly, a mixture of **37**, **5**, and Et$_3$N showed a further bathochromic shift, suggesting the formation of a ternary EDA complex, which could contribute to the enhanced reactivity observed with primary alkyl pyridiniums upon addition of Et$_3$N. The formation of alkyl radical intermediates was confirmed by a radical clock experiment with cyclopropylmethyl pyridinium **38**, during which ring-opening occurred to give alkene **39** as the only observable product (Figure 1 C).

These results suggest a mechanism comprised of initial formation of an EDA complex **40** between the electron-deficient pyridinium **1** and electron-rich Hantzsch ester (**5**) (Figure 2). Subsequent PET leads to dihydropyridine radical cation **41** and radical **42**, which fragments to triphenylpyridine
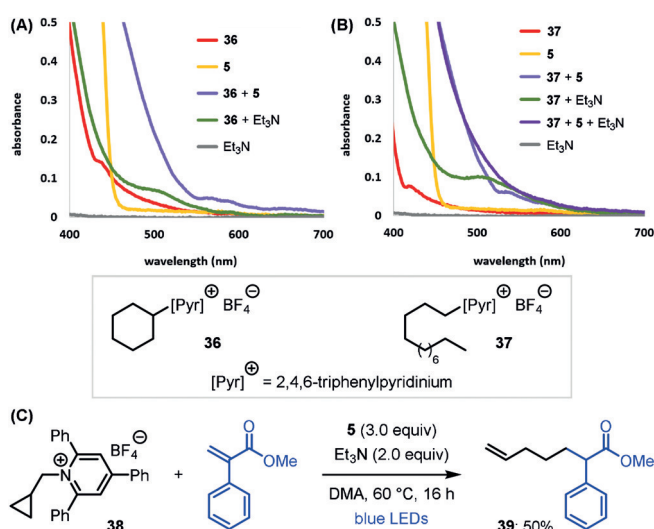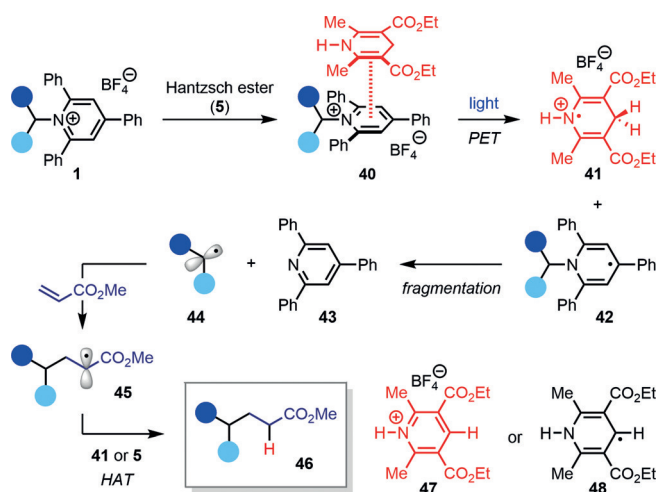

Figure 2. Proposed mechanism.

43 and alkyl radical **44**. Addition of **44** to methyl acrylate generates radical **45**, which undergoes hydrogen atom transfer (HAT) with dihydropyridine radical cation **41** (BDFE = 31 kcal mol^{-1})[19] or **5** (BDFE = 69 kcal mol^{-1})[19] to form Giese product **46** (BDFE ≈ 96 kcal mol^{-1})[20] and pyridinium **47** or dihydropyridine radical **48**, respectively.[21]

Encouraged by the results of the Giese reaction, we proceeded to investigate other catalyst-free transformations. Pleasingly, with only slight modification to the reaction conditions,[18] allylation reactions with allyl sulfone **49** were also found to be efficient (Table 2).[14c] A range of secondary alkyl pyridiniums underwent the catalyst-free deaminative allylation to give products **50–57** in moderate to good yields. As with the Giese reaction, although primary benzylic pyridiniums yielded the allylation product **58** under these conditions, non-benzylic primary alkyl pyridiniums **59–68** required the addition of Et$_3$N for successful reaction. The allylation reaction was found to tolerate a diverse range of functional groups, including alcohols (**53**), nitriles (**60**), sulfonamides (**61**), unprotected indoles (**63**), olefins (**65**), and secondary carbamates (**67**), and was also applied to various pharmaceuticals (**57** and **66**) and natural product derivatives (**55**, **56**, **67**, and **68**). Furthermore, the use of other allyl sulfone reagents enabled the preparation of styrene derivative **69** and alkenylboronic ester **70**.

During our UV/Vis absorbance studies of pyridinium **36** we found that it also forms an EDA complex with Et$_3$N (Figure 1 A). Thus, we were curious as to whether these photoinduced reactions could be performed with Et$_3$N in place of Hantzsch ester. While the Giese reaction proceeded with low yield, the allylation reaction proceeded smoothly to generate **50** in 71 % when using 6.0 equiv of Et$_3$N in place of Hantzsch ester (Scheme 2).[18] An identical result was also obtained when Et$_3$N was replaced by iPr$_2$NEt. This result is intriguing given that these conditions are very similar to the photoredox-catalyzed conditions recently reported by Liu and co-workers, which differ only by the use of an iridium photocatalyst.[14c] We also investigated other addition–elimination reactions with unsaturated sulfone reagents and found that alkynylation and vinylation reactions also proceeded

Figure 1. Mechanistic studies. A) Spectrophotometry of pyridinium **36**. B) Spectrophotometry of pyridinium **37**. C) Radical clock experiment.
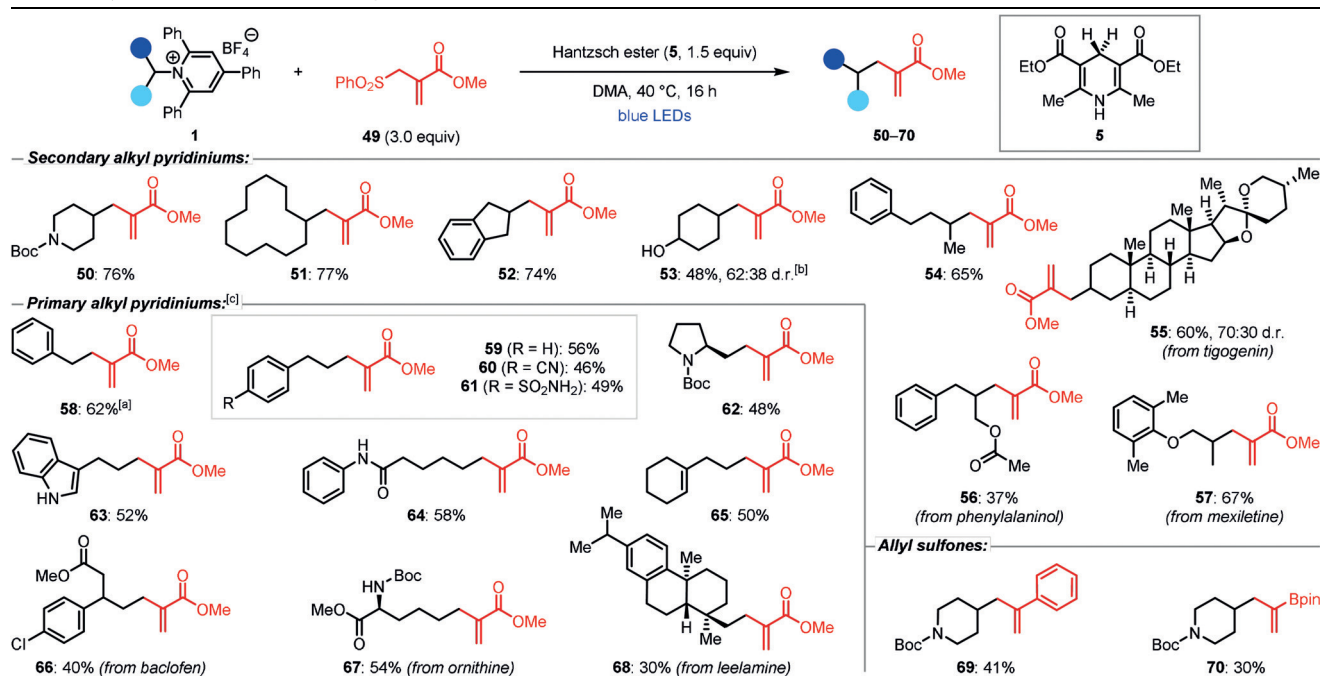
Table 2: Allylation reaction substrate scope.[a]

Secondary alkyl pyridiniums:

50: 76% **51**: 77% **52**: 74% **53**: 48%, 62:38 d.r.[b] **54**: 65% **55**: 60%, 70:30 d.r. *(from tigogenin)*

Primary alkyl pyridiniums:[c]

58: 62%[a] **59** (R = H): 56% **60** (R = CN): 46% **61** (R = SO₂NH₂): 49% **62**: 48%

63: 52% **64**: 58% **65**: 50% **56**: 37% *(from phenylalaninol)* **57**: 67% *(from mexiletine)*

66: 40% *(from baclofen)* **67**: 54% *(from ornithine)* **68**: 30% *(from leelamine)*

Allyl sulfones:

69: 41% **70**: 30%

[a] General conditions: Pyridinium (1.0 equiv), allyl sulfone (3.0 equiv), and **5** (1.5 equiv) in DMA (0.4 M) at 40°C for 16 h. Yields are of isolated products after flash column chromatography. [b] Isolated after acetyl protection of the alcohol. [c] Reactions performed at 60°C with **5** (2.5 equiv) and Et₃N (3.0 equiv).

under our catalyst-free conditions, generating alkyne **71** and alkene **72** in good yields. Again, these conditions are similar to previously reported photoredox-catalyzed protocols by Gryko and co-workers but proceed efficiently in the absence of a photocatalyst.[14b] Finally, we found that by replacing the unsaturated sulfones with other sulfur-based reagents, under otherwise identical conditions, high yielding hydrodeamination and deaminative thioetherification reactions were also possible, providing good yields of *N*-Boc-piperidine **73** and thioether **74**, respectively.
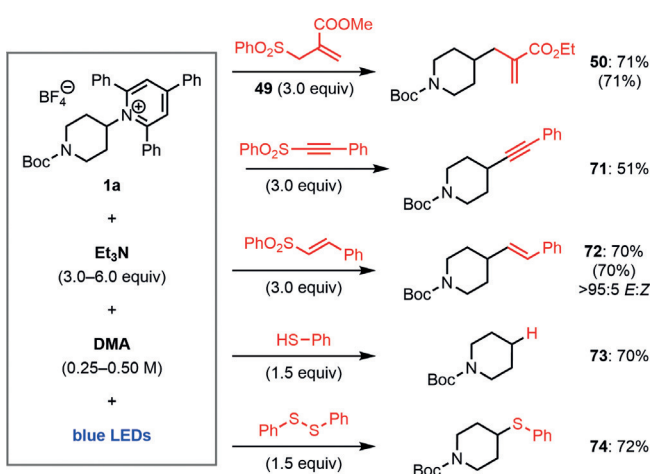
In conclusion, we have described the development of a general catalyst-free deaminative protocol for the generation of non-stabilized alkyl radicals, proceeding through visible light photoexcitation of EDA complexes of *N*-alkylpyridinium salts. The radicals were shown to undergo a range of transformations, including Giese, allylation, vinylation, alkynylation, HAT, and thioetherification reactions. The mild conditions, high functional group tolerance and ease of synthesis of the pyridinium substrates make this a useful catalyst-free approach to alkyl radical formation.

Conflict of interest

The authors declare no conflict of interest.

Scheme 2. Deaminative transformations promoted by Et₃N. Reactions performed at 60°C. Yields in parentheses are for reactions performed using *i*Pr₂NEt in place of Et₃N.

50: 71% (71%)
71: 51%
72: 70% (70%) >95:5 E:Z
73: 70%
74: 72%

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