CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201901065

Link to VoR: http://dx.doi.org/10.1002/chem.201901065

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FULL PAPER

ortho-Alkylation of Pyridine *N*-oxides with Alkynes by Photocatalysis: Pyridine *N*-oxide as Redox Auxiliary

Jonathan P. Markham, Ban Wang, Edwin D. Stevens, Stuart C. Burris and Yongming Deng*

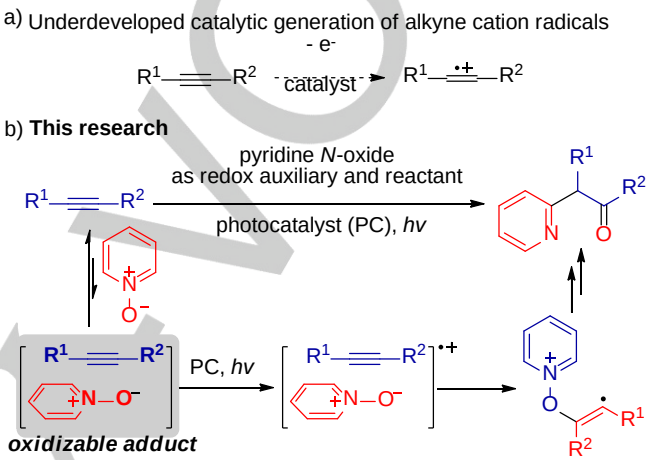
Dedicated to Professor Hong Wang on the occasion of her 50th birthday

Abstract: A photocatalyzed *ortho*-alkylation of pyridine *N*-oxide with ynamides and arylacetylenes has been developed, yielding a series of *α*-(2-pyridinyl) benzyl amides/ketones. Mechanistic studies, including electrochemical studies, radical-trapping experiments, and Stern–Volmer fluorescence quenching studies demonstrate pyridine *N*-oxide serves as both a redox auxiliary and radical acceptor to achieve the mild photocatalytic single-electron oxidation of carbon-carbon triple bonds with the generation of cationic vinyl radical intermediate.

Introduction

Over the past decade, the development of photocatalysis in organic synthesis has enabled the invention of new activation modes for organic substrates and delivered a wide variety of nontraditional bond-forming protocols and synthetic methodologies.[1] The Nicewicz group and others demonstrate a series of photocatalyzed *anti*-Markovnikov hydrofunctionalization reactions through alkene cation radicals, which are generated from alkene *via* photocatalyzed single-electron oxidation.[2] Most recently the study of photocatalyzed single-electron oxidation of aromatic substrates to arene cation radicals delivers arene C-H functionalization and substitution reactions.[3]

Alternatively, alkyne cation radicals, which can be directly generated from carbon-carbon triple bond by single-electron oxidation, presents an appealing intermediate for the construction of carbon−carbon and carbon−heteroatom bonds (Scheme 1a).[4] However, the achievement of alkyne single-electron oxidation and its application in synthetically meaningful organic transformations has yet to be accomplished in a catalytic manner.[5] This dearth of methods is a result of the high oxidation potential of carbon−carbon triple bonds, that requires a potent oxidant to generate alkyne cation radicals.[6] In addition, the exceptionally high reactivity of alkyne cation radicals makes them challenging intermediates for the development of selective and meaningful organic synthesis.[5,6] Reported approaches for the direct single-electron oxidation of alkynes is limited to γ-irradiation[7] or the use of strongly oxidizing conditions.[8] These conditions often result in unselective, low yielding side reactions



Scheme 1. Underdeveloped catalytic single-electron oxidation of alkyne (a), and this research: photocatalyzed *ortho*-alkylation of pyridine *N*-oxide with alkynes (b). (PC = photocatalyst)

and dimerizations.[7a,b,8] The development of requisite methodologies to achieve catalytic single-electron oxidation of alkynes and the correlated organic transformations under mild conditions is of great interest and in demand, yet challenging. Herein, we present a strategy to address this long-standing challenge by using pyridine *N*-oxide as a redox auxiliary to allow the mild photocatalytic single-electron oxidation of carbon-carbon triple bonds (Scheme 1b). Based on this strategy, we have developed a visible-light photocatalyzed *ortho*-alkylation of pyridine *N*-oxide with alkynes, in which the pyridine *N*-oxide also serves as an oxygen transfer agent and radical acceptor. The reaction proceeds on a range of ynamides, aryl alkynes and substituted pyridine *N*-oxides that yields a series of *α*-(2-pyridinyl) benzyl amides/ketones which are important skeletons in many biologically active natural products and pharmaceuticals.[9]

The use of a redox trigger to alter the requisite electrochemical potential of trifluoroacetic anhydride (TFAA) for the development of a photocatalyzed trifluoromethylation reaction was recently reported by Stephenson (Scheme 2a).[10] In this study, a reducible adduct formed through an acylation between TFAA and the redox trigger, pyridine *N*-oxide, enable the access to CF_3 radical by photocatalysis. We wondered whether it would be possible to append a redox auxiliary in concert with alkynes to assemble an oxidizable alkyne adduct. This could allow the single-electron oxidation at a less-forcing potential that falls into the redox potential window of readily accessible photocatalysts (Scheme 2b). As part of the implementation of this research,

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.2018xxxxx.

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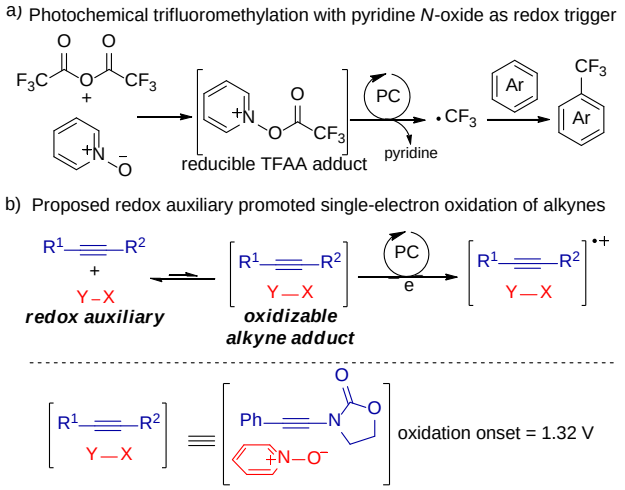

Scheme 2. a) Stephenson's photocatalyzed trifluoromethylation. b) Proposed single-electron oxidation of carbon-carbon triple bond with redox auxiliary.

we took into account aspects of the non-covalent electrostatic interactions between a polarized alkyne and a polarized or charged substance, which has been long recognized.[11] Such electrostatic interaction initializes the halogen addition step in the alkynyl *halo*-Prins reaction[12] and stimulates the step-wise cycloadditions of triple bonds and dipoles.[13] We postulated that the non-covalent interactions may drive the reversible assembly of a polarized alkyne and a polarized or charged redox auxiliary to the oxidizable adduct. In this regard, ynamide, possessing strongly polarized triple bond with amide substituent,[14] was identified as the model substrate. Additionally, we proposed that the use of an auxiliary bearing electron rich substructure could serve as an electron donor to enhance the electrostatic interactions with the electron poor triple bond of ynamide. Furthermore, it would reduce the oxidation potential of the overall adduct. Noteworthy, the exceedingly high oxidation potentials of heteroaromatic *N*-oxides (pyridine *N*-oxide, E^{ox} = 4.37 vs Li/Li$^+$) help to suppress the direct oxidation of themselves.[15] Herein, pyridine *N*-oxide bearing a formally negatively charged oxygen,[16] emerged to be the potential redox auxiliary for this investigation.

Results and Discussion

Our inquiry began with the voltammetry measurements of a ynecarbamate**1a**/pyridine *N*-oxide system (Figure 1). The acetonitrile solution of mixed **1a** and **2a** (**1a**:**2a** = 1:1) exhibits an oxidation onset near 1.32 V vs SCE, which is significantly lower than the observed irreversible oxidation for **1a** at $E_{1/2}^{ox}$ = 1.75 vs SCE (oxidation onset at 1.62 V). We rationalize that this reduced milder oxidation onset can be attributed to the formation of an ynamide/pyridine *N*-oxide oxidizable adduct; while the labile non-covalent electrostatic interaction between ynamide and pyridine *N*-oxide results in the unapparent oxidation potential for the adduct. We are aware of the possibility that the oxidizable adduct could be an electron donor–acceptor (EDA) complex[17] of ynamide and pyridine *N*-oxide. However, no visible color change was observed, and no charge-transfer band was detected by UV-*vis* absorption analysis of the ynamide and pyridine *N*-oxide system. This result implies a weak non-chromogenic interaction between **1a** and pyridine *N*-oxide. An ^{1}H NMR study of the combination also indicated a possible association (Figure S2), but their precise interaction remains unknown. The π-π interaction between the phenyl group/triple bond of ynamide **1a** and pyridine *N*-oxide is also possible.[18]

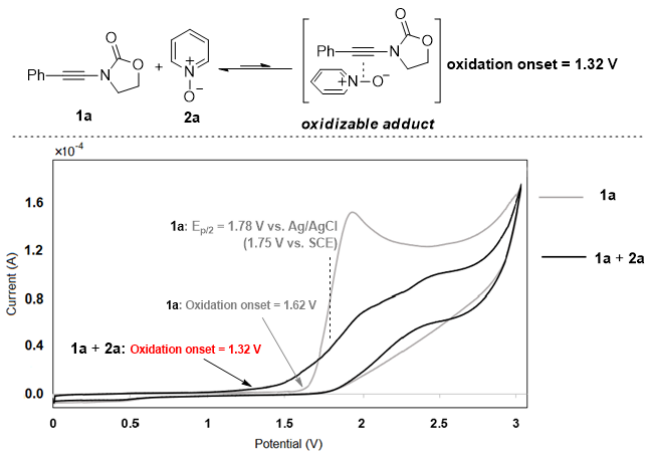

Figure 1. Voltammetry measurements of ynamide **1a**/pyridine *N*-oxide system. Cyclic voltammetry measurements of ynamide **1a** (0.01 M in MeCN) and the mixed solution of ynamide **1a** (0.01 M in MeCN)/pyridine *N*-oxide **2a** (0.01 M in MeCN) were performed with a PARSTAT 2263 Advanced Electrochemical System. Measurements were performed with a glassy carbon working electrode, Pt auxiliary electrode, Ag/AgCl reference electrode, Bu_4NPF_6 electrolyte (0.1 M in MeCN), and analytes (ynamide **1a**, 0.01 M or **1a**: **2a** = 1:1, 0.01M for each) with a sweep rate of 10 mV s^{-1}. (MeCN = acetonitrile)

The mild oxidation potential of the ynamide/pyridine *N*-oxide system (oxidation onset at 1.37 V vs SCE) suggests the accessibility for the single-electron oxidation process by utilizing photocatalysts, such as methylene blue ($E^*_{1/2}{}^{red}$ = 1.56 vs SCE).[1d] As shown in Scheme 3, we proposed that the photocatalytically generated radical cation **I** of the oxidizable ynamide/pyridine *N*-oxide adduct could lead to a distonic cation vinyl radical intermediate **II(a)** or **II(b)** *via* nucleophilic attack by the oxygen of pyridine *N*-oxide. We predict that the site selective generation of cationic vinyl radical **II(a)** would be favored due to the resonance stabilization of phenyl group towards the vinyl radical. Guided by recent photocatalyzed Minisci reactions[19] and Miura along with Murakami's study on the photocatalyzed *ortho*-alkylation/cleavage reaction of pyridine *N*-oxides with alkenes,[20] we predicted that an intramolecular Minisci-type pathway would then afford the aminyl radical cation **III**. Alternatively, the direct concerted reaction from **I** to **III** is also possible. Following simultaneous or successive-stepped 1,2-electron shift, *β*-N-O bond scission and proton transfer would be driven by aromatization to deliver the resonance-stabilized radical **IV** from **III**. The radical **IV** would undergo a second SET event with the oxidized photo-system and a proton transfer to regenerate the

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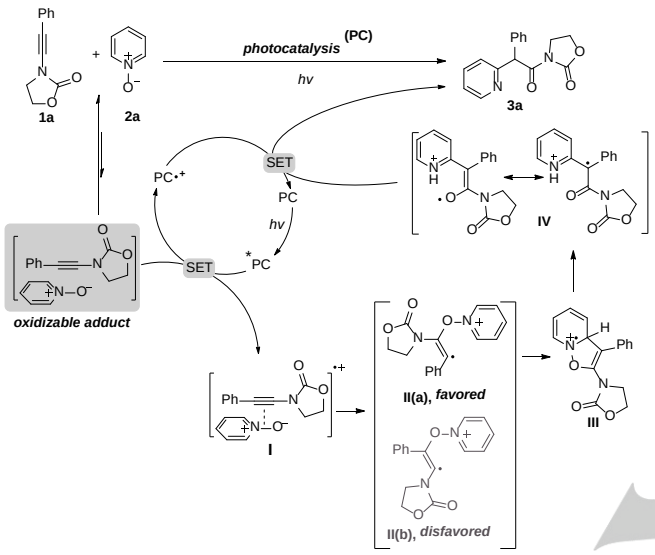
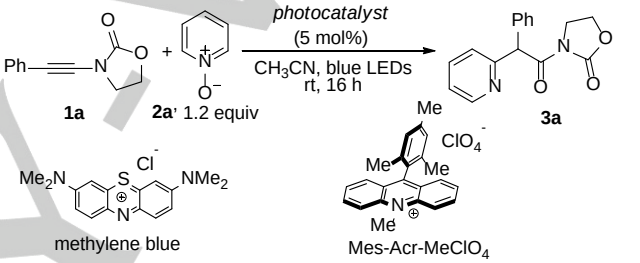
photocatalyst ground-state and furnish *α*-(2-pyridinyl) benzyl amide product **3a**. In this proposed transformation, pyridine *N*-oxide not only serves as a redox auxiliary to enable the challenging photocatalyzed single-electron oxidation process, but also functions as an oxygen transfer agent and a trap of the highly reactive vinyl radical intermediate to suppress the undesired dimerization and further oxidation.



Scheme 3. Proposed mechanism. SET = single-electron transfer.

Our examination of the proposed *ortho*-alkylation reaction began with methylene blue (5 mol%) catalyzed reaction of **1a** and pyridine *N*-oxide **2a** with blue LED light irradiation (34 W, λ_{max} = 450 nm, ~400–520 nm) at room temperature (Table 1, entry 1). As proposed, the desired product **3a** was generated smoothly in 49% yield with excellent site selectivity for the triple bond (> 20:1). The use of 9-mesityl-10-phenyl acridinium perchlorate (Mes-Acr-$MeClO_4$) could improve the yield of **3a** to 87% (entry 2), which is identified as the optimized condition. Neither ruthenium ($[Ru(bpy)_3][PF_6]_2$, $[Ru(bpz)_3][PF_6]_2$), nor iridium photocatalysts ($Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$) were effective catalysts for this transformation (Table S1). Only unconverted starting materials were recovered when the mixture was heated at 80°C for three days without the photocatalyst or photoirradiation (Table 1, entries 3 to 5). Noteworthy, the product **3a** was formed in 48% yield under sunlight irradiation however with longer reaction time (entry 6). Solvent screening was also performed (entries 7 to 9, Table S1). The use of aprotic solvent dichloromethane and 1,2-dichloroethane (entries 7 and 8) also delivered the formation of **3a** in moderate yields. However, when methanol was employed as the solvent (entry 9), the reaction was significantly suppressed. Such results support the proposed pre-association of ynamide and pyridine *N*-oxide which is favored in aprotic solvents, while the use of protic solvent weakens the non-covalent interactions.[11,17] Instead of using pyridine *N*-oxide, the reaction of pyridine and **1a** was performed in the presence of Mes-Acr-$MeClO_4$ (entry 10), and only unreacted **1a** was recovered without any detectable transformation. Although there is no reported study and evidence indicating the feasibility of a 1,3-dipolar cycloaddition of pyridine *N*-oxide and disubstituted ynamide possessing internal triple bond, we recognize that **3a** might be generated from the speculate cycloaddition product through an *N*-*O* bond cleavage process. To address this possible alternative, the examination of Lewis acid catalysts, including $Cu(OTf)_2$, $Yb(OTf)_3$, and $Zn(OTf)_2$, were examined (entry 11, and Table S1). Except for recovery of **1a**, neither desired product **3a**, nor the cycloaddition product was detected. While we cannot definitively rule out the 1,3-dipolar cycloaddition pathway, we favor theproposed photocatalytic pathway (Scheme 3) based on the aforementioned results and latter mechanism studies.

Table 1. Exploration of Reaction Conditions.



Entry	variation from the standard conditions[a]	yield[b] (%)
1	methylene blue	49
2	Mes-Acr-$MeClO_4$	87
3	no light	<5
4	no photocatalyst	<5
5	no photocatalyst at 80 °C for 2 days[c]	<5
6	sunlight and 6 days[c]	48
7	DCM instead of CH_3CN[c]	58
8	DCE instead of CH_3CN[c]	64
9	MeOH instead of CH_3CN[c]	8
10	pyridine instead of pyridine N-oxide[c]	<5
11	$Cu(OTf)_2$ instead of photocatalyst	<5

[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.) **2** (0.24 mmol, 1.2 equiv.), and 5mol% of photocatalyst were dissolved in dry CH_3CN (2.0 ml) under blue LED lamps (~400–520 nm, λ_{max} = 450 nm, 34 W, more information at Kessil.com) for 16 h. [b] Yield of isolated product **3a** based on the limiting reagent **1a**. [c] Mes-Acr-$MeClO_4$ was applied as photocatalyst. CH_3CN = acetonitrile, DCM = dichloromethane, DCE = 1,2-dichloroethane.

With the optimized conditions, substrate generality was investigated for the photocatalyzed *ortho*-alkylation of various heteroaromatic *N*-oxides and ynamides (Table 2). Those with *ortho*, *meta*, or *para* alkyl and halogen substituents on the pyridine *N*-oxide reacted smoothly with **1a**, generating the corresponding products in good yields (77−93%, **3a**-**3e**) with excellent site selectivities. The reactions of pyridine *N*-oxides with para electron-withdrawing substituents furnished products **3f** and **3g** with lower yields. The scope with respect to ynecarbamates with various aryl substituents was examined in the reactions of 2-methylpyridine *N*-oxide (**2b**), affording the corresponding products (**3h** to **3l**). Structure of product **3j** was identified

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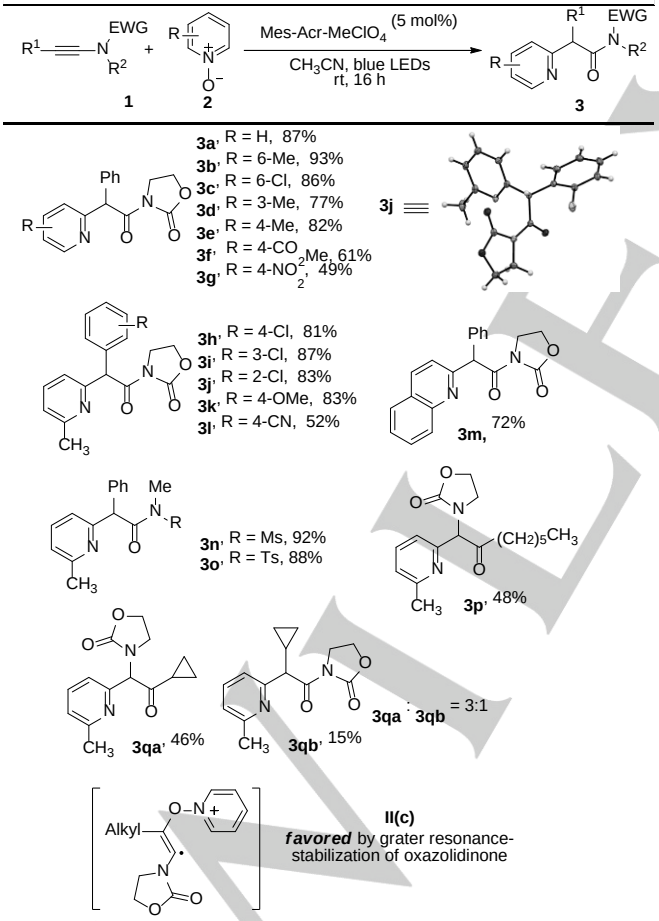
spectroscopically and confirmed by X-ray diffraction analysis.[21] *N*-Oxide of quinoline was also compatible with this transformation (**3m**, 72%). In addition to ynecarbamates, ynesulfonamides were ideal reagents as well, yielding products **3n** and **3o** with high yield. The reaction was further tested with alkyl substituted ynamides. Notably, employment of hexyl substituted ynamide completely switched the site selectivity of the triple bond to preferentially producing **3p** albeit with a lower isolated yield. We rationalize that the grater resonance-stabilization that occurs in the oxazolidinone group towards the proposed distonic cation vinyl radical intermediate **II(c)** may account for the switched site selectivity, when compared to the alkyl group. When cyclopropyl substituted ynamide was subjected to the reaction, **3qa** with switched site selectivity was also isolated as the major product. While **3qb** with carbonyl group adjacent to the oxazolidinone group was also obtained with 15% yield. No three-member ring-opening product is observed. We suspected that the *ortho*-addition of the highly reactive vinyl radical to the pyridinium ring is faster than the ring-opening and radical migration process.[22]

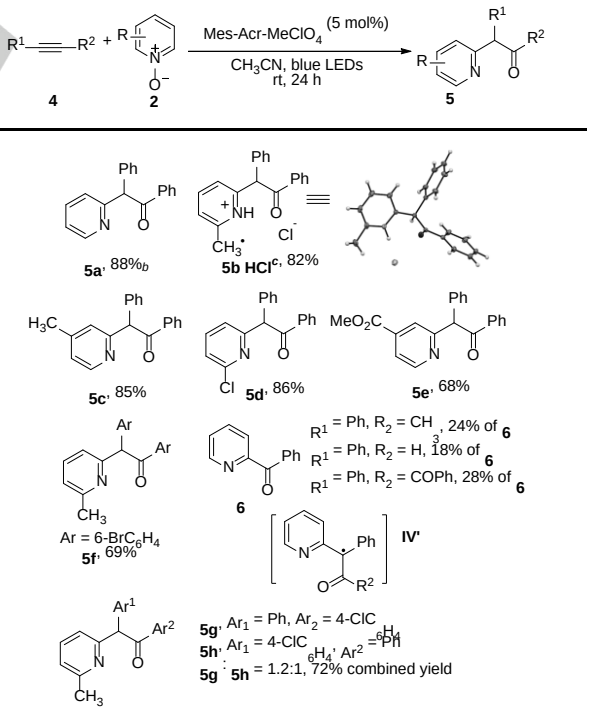
Table 2. Scope of ynamides and pyridine *N*-oxides.[a]



[a] For experimental details, see supporting information.

To further extend the reaction scope and the compatibility of the proposed alkyne activation strategy by applying pyridine *N*-oxide as a redox auxililary, the reactions of arylacetylenes and pyridine *N*-oxides were then explored (Table 3). A voltammetry measurement of the diphenylacetylene/pyridine *N*-oxide system was also carried out (Figure S3). Notably, a weak irreversible oxidation potential for the diphenylacetylene/pyridine *N*-oxide system was detected at $E_{1/2}^{ox}$ = 1.52 vs SCE, as well with an observable oxidation onset near 1.4 V vs SCE, that is significantly lower than the oxidation protentional of diphenylacetylene ($E_{1/2}^{ox}$ = 1.85 vs SCE).[23] We postulated that a possible π-π interaction between pyridine *N*-oxide and arylacetylene may deliver the formation of an oxidizable adduct. Pyridine *N*-oxides possessing methyl, chloro, or ester substituents were suitable substrates, affording the *α*-(2-pyridinyl) benzyl ketone products in good yields (**5a** to **5e**) at a prolonged reaction time (24 h). Bis(4-bromophenyl)acetylene also reacted smoothly with **2a** generating product **5f** with moderate yield. However, when phenylacetylene, 1-phenyl-1-propyne or diphenylpropynone was employed in the reaction with **2a**, only 2-benzoylpyridine **6** was obtained with low yield, which may be formed through further oxidation of radical intermediate **IV'** with involvement of another pyridine *N*-oxide as oxygen transfer agent. When 1-chloro-4-(phenylethynyl)benzene was applied, the regioisomers **5g** and **5h** (**5g** : **5h** = 1.2 : 1) were both obtained with combined 72% yield.

Table 3. Scope of arylacetylenes.[a]



[a] For experimental details, see supporting information.

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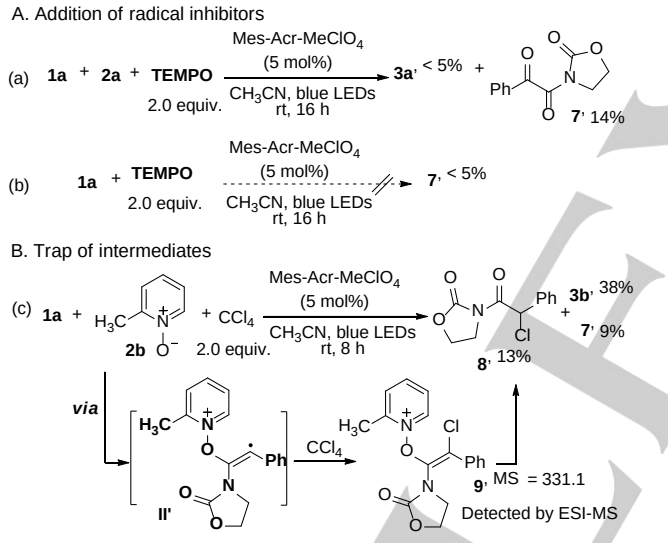
To gain mechanistic insight into this transformation, radical inhibition and tapping experiments were conducted (Scheme 4, Scheme S1-S3). Upon the addition of the radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT), the alkylation reaction was substantially suppressed (Scheme 4a, S2). *α*-Keto imide **7** was isolated in 14% yield from the reaction of **1a**, **2a**, and TEMPO (Scheme 4a). While only unconverted **1a** was recovered from the reaction of ynamide **1a** and TEMPO under the standard condition without formation of **7** (Scheme 4b). These experiments not only suggest the involvement of radical intermediates in this transformation, but also indicate the indispensability of pyridine *N*-oxide for photocatalytic single-electron oxidation of alkynes. Furthermore, CCl_4 was employed to trap the reactive radical species (Scheme 4c). In the presence of CCl_4 (2 equiv), the *α*-chloro imide **8** was isolated in 13% yield along with the desired product **3b** in 38% yield. Noteworthy, the chlorinated intermediate **9** was successfully detected by ESI-MS analysis of the reaction mixture, which accounts for the generation of **8**. These results clearly point to the involvement of a distonic cation vinyl radical intermediate **II'**, which is consistent with our mechanistic proposal (Scheme 3).



Scheme 4. Mechanistic study.

We have sought to obtain further evidence for the proposed alkyne activation stratergy by using pyridine *N*-oxide as a redox auxililary. The Stern–Volmer fluorescence quenching studies of alkyne alone and in combination with pyridine *N*-oxide using the preferred Mes-Acr-$MeClO_4$ photocatalyst were perfomed. As revealed in Figure 2a, the emission quenching of the excited state of the photocatalyst was significantly enhanced by the ynamide **1a**/pyridine *N*-oxide **2a** combination system (K_{sv} = 104.050), compared to the solo **1a** test (K_{sv} = 48.707). Similar observations can also be noticed for the diphenylacetylene **4a**/ pyridine *N*-oxide **2a** system (K_{sv} = 92.836 *vs* K_{sv} = 41.247 for **4a** alone). This finding indicates that the addition of pyridine *N*-oxide promotes the photocatalyzed oxidative process of alkynes. Although the direct photocatalyzed single-electron oxidation of alkyne process cannot be ruled out, taken together with the electrochemical study (Figure 1) and radical quenching experiments (Scheme 4b), the function of pyridine *N*-oxide as a redox auxiliary to facilitate single-electron oxidation of carbon-carbon triple bonds is operative and indispensabile.

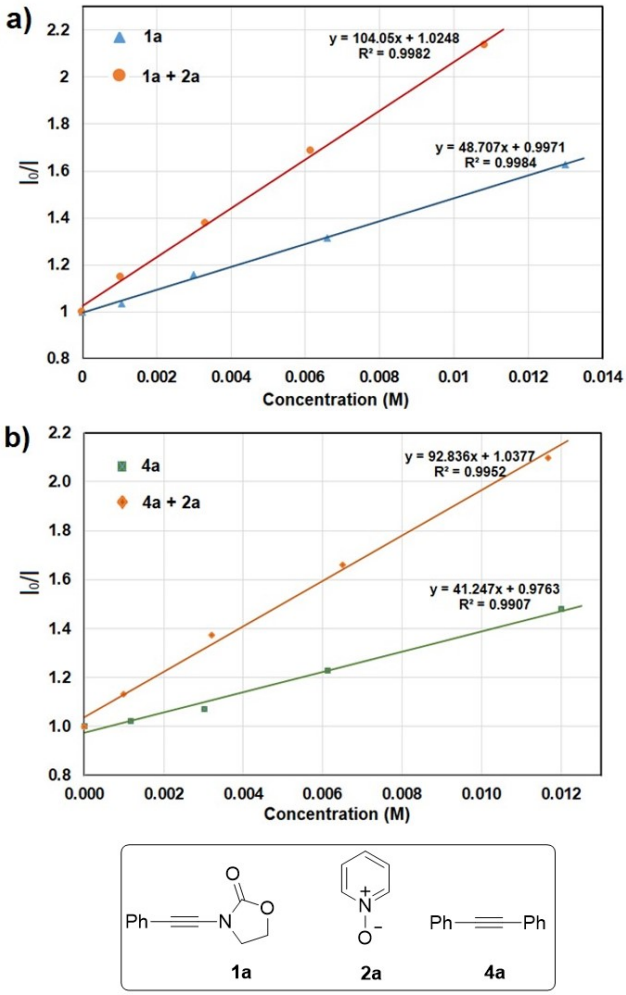
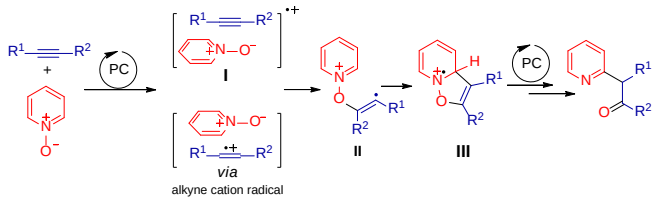


Figure 2. a) Stern–Volmer emission quenching studies of ynamide **1a** and **1a**/pyridine *N*-oxide **2a** system. b) Stern–Volmer emission quenching studies of diphenylacetylene **4a** and **4a**/pyridine *N*-oxide **2a** system. y = I_0/I, x = K_{SV}, error <5% (estimated from multiple trials). Stern–Volmer equation: $I_0/I = 1 + K_{sv}[Q]$; I_0 and I are the fluorescence intensity in the absence and presence of quencher *Q*, K_{SV} is the Stern-Volmer constant, and [*Q*] is the concentration of quencher alkyne.

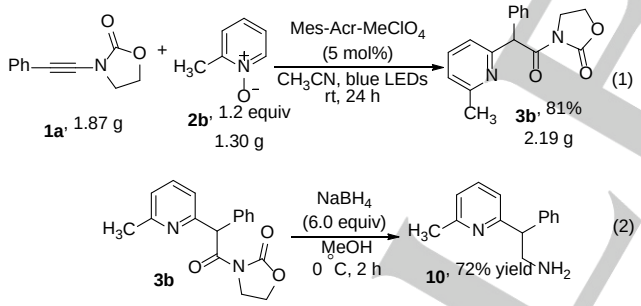
Based on our electrochemical study, radical trapping and quenching experiments, and Stern–Volmer fluorescence quenching studies, a general plausible mechanism of the photocatalyzed *ortho*-alkylation of pyridine *N*-oxide with alkynes is described in Scheme 5. Oxidized by the excited photocatalyst, a cation radial intermediate **I** can be generated from the alkyne/pyridine *N*-oxide adduct; alternatively, the catalytical generation of alkyne cation radical is also possible. Both cation

radical intermediates could lead to the distonic cation vinyl radical intermediate **II** *via* nucleophilic attack by the oxygen of pyridine *N*-oxide. Following Minisci-type reaction leads to the aminyl radical cation **III**. Subsequent 1,2-electron shift, *β*-N-O bond scission, proton transfer, and SET event is driven by aromatization to furnish *α*-(2-pyridinyl) functionalized carbonyl product and achieve photocatalyst turnover.



Scheme 5. The general plausible mechanism of the photocatalyzed *ortho*-alkylation of pyridine *N*-oxide with alkynes. PC = photocatalyst

Efforts devoted to exploring the synthetic practicability of this photocatalyzed reaction demonstrated the ease of access to a gram scale reaction [Eq. (1)]. Furthermore, treatment of **3b** under classic reduction conditions by sodium borohydride gave the 2-(6-methylpyridin-2-yl)-2-phenylethanamine product **10** in 72% yield [Eq. (2)]. This photocatalyzed reaction of ynamides and pyridine *N*-oxides along with the convenient reduction provide access to the arylethylamine compounds, that are an important skeleton in many natural products and bioactive compounds, such as chlorphenamine and disopyramide.



Conclusions

In summary, we have developed a facile and scalable photocatalyzed *ortho*-alkylation of pyridine *N*-oxides with ynamides and arylacetylenes. The protocol provides a convenient access to a variety of *α*-pyridyl functionalized carbonyls, alone with derivatized arylethylamine compounds. Mechanistic insights, including electrochemical study, radical inhibition and tapping experiments, and Stern–Volmer fluorescence quenching studies, reveal that pyridine *N*-oxide serves as a redox auxiliary in concert with ynamides and arylacetylenes to affect a mild photocatalyzed single-electron oxidation process of carbon-carbon triple bonds through a distonic cation vinyl radical intermediate. We expect that this transformation will provide a new strategy of greater value for future applications in alkyne activation and organic synthesis *via* vinyl radicals.

Acknowledgements

Support for this research from Westen Kentucky University and the Chemistry Deparment is gratefully acknowledged. J.P.M. thanks Graduate Student Research Grant from Westen Kentucky University. The authors thank Pauline Norris at Advanced Materials Institute at Westen Kentucky University for ESI-MS analysis.

Keywords: photocatalysis • alkyne • ynamide • pyridine *N*-oxide • alkylation

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10.1002/chem.201901065

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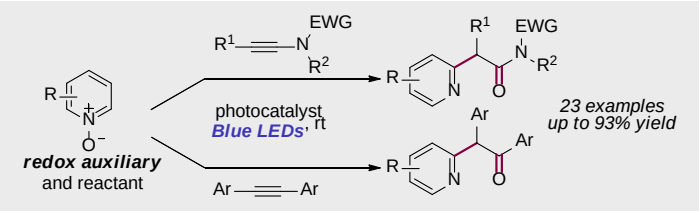

Pyridine *N*-oxide as a redox auxiliary for alkynes: A *ortho*-alkylation of pyridine *N*-oxide with alkynes, including ynamides and arylacetylenes, has been achieved by organic photocatalysis, providing access to a series of α-(2-pyridinyl) benzyl carbonyl compounds. Pyridine *N*-oxide function as both a redox auxiliary and radical acceptor to achieve the challenge photocatalytic single-electron oxidation of carbon-carbon triple bond.

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ortho-Alkylation of Pyridine _N_-oxides with Alkynes by Photocatalysis: Pyridine N-oxide as Redox Auxiliary