Organic Photoredox Catalyzed Direct Hydroamination of Ynamides with Azoles

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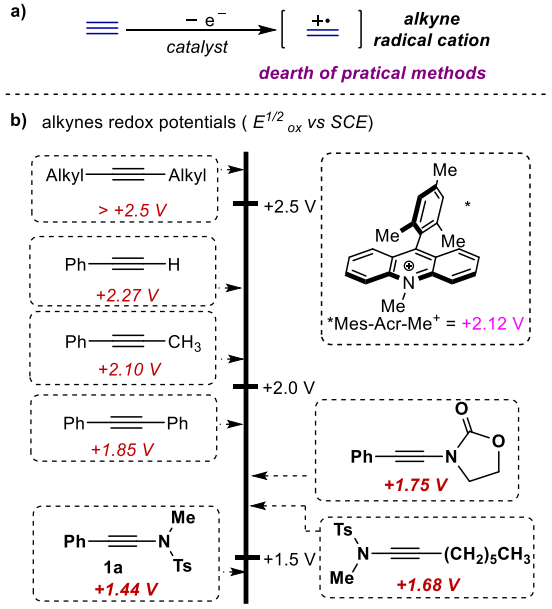
Abstract. Disclosed herein is a novel photoinduced selective hydroamination of ynamides with nitrogen heteroaromatic nucleophiles. By using an organocatalytic photoredox system, a direct method to construct a diverse of (*Z*)-α-azole enamides from ynamides and pyrazoles, as well as triazoles, benzotriazoles, indazoles, and tetrazoles, is developed, thus providing a concise route to heterocyclic motifs common in medicinal agents. Based on the mechanistic studies, the hydroamination is postulated to operate via a mechanism in which the single-electron oxidation of ynamide and the intermediacy of an alkyne radical cation, is responsible for the observed reactivity.

Keywords: photocatalysis; ynamide; nitrogen heterocycles; hydroamination; radical cation

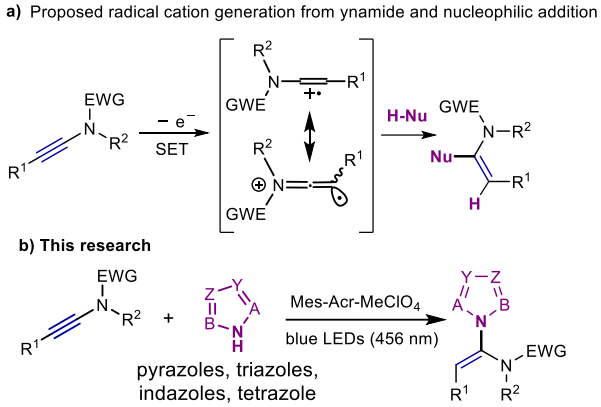
The development of alkyne transformations extending from non-catalytic, transition-metal or acid catalyzed additions and cyclizations, to metathesis, metalations, and radical addition reactions, has been a long-standing and one of the essential research objectives in organic synthesis.[1] Conceptually, a single-electron oxidation event of carbon-carbon triple bond could lead to the generation of an alkyne radical cation, which presents a synthetically attractive intermediate.[2] Such a species might offer a new range of versatile reactivities complementary to the current alkyne chemistry (Scheme 1a), for example, a new approach for alkyne functionalization. However, reported methods for alkyne radical cation generation are limited to γ-irradiation or the use of strongly oxidizing conditions;[2b-d,3] and its catalytically generation and applications in synthetically meaningful reactions still remain scarce. It is surmised that such challenge is a result of two major reasons: 1) general alkynes, as known, typically possessing high oxidation potential (Scheme 1b, over + 2.0 V),[4] require potent oxidants to achieve the single-electron oxidation, which limits the synthetic application; 2) the exceptionally high reactivity of alkyne cation radicals makes them challenging intermediates for the development of controllable and selective transformations.[2,3]

Recently, our group developed a novel photocatalytic strategy for the generation of reactive and controllable β-oxypyridinium radical through mild visible-light photoredox catalyzed single-electron oxidation of an alkyne/pyridine N-oxide system.[5] During these studies, it was found that ynamides, subgroups of alkynes, exhibited significantly lower oxidation potentials than aliphatic and aryl alkynes (Scheme 1b, Figure S1 and S2).[5] In this context, we envisaged that ynamide could serve as an ideal substrate for alkyne radical cation generation by single-electron oxidation under mild reaction conditions, such as using visible-light photoredox catalyst.[6] We rationalize that the strong polarization of ynamide introduced by the electron-donating ability



Scheme 1. Single electron oxidation of alkynes and their redox potentials.

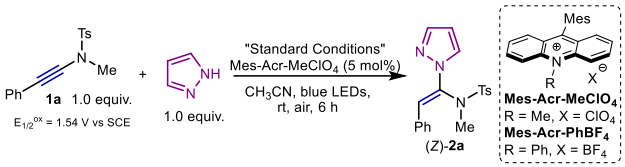
of the nitrogen atom allows milder single-electron oxidation for the respective radical cation generation (Scheme 2a). Moreover, the resultant ynamide radical cation still features a high reactivity, but it is tempered by a keteniminium radical resonance contributor which provides enhanced stability and can also act as an efficient directing group for controllable selective transformations.[7] Considering the electrophilicity nature of radical cation,[8] the facile access to ynamide alkyne radical cations could provide a basis to develop a general system for a range of heteroatom nucleophiles reacting with ynamides. Herein, we report the direct intramolecular hydroamination of ynamides with nitrogen heteroaromatic nucleophiles via photoredox catalyzed radical cation generation (Scheme 2b). This transformation delivers a facile photoredox catalyzed approach for the synthesis of a variety of α-heteroarene substituted enamides, and notably, it provides a new reactivity profile that complements traditional acid or transition metal catalyzed ynamide reactions.



Scheme 2. This research.

Based on our measured redox potential of ynamides as shown in Scheme 1b (Figure S1-S3), we recognized that good candidates for a single electron photoredox catalyst should be capable of oxidizing ynamide in the range +1.5 to +2.0 V. And we envision that the use of a positively charged photoredox catalyst could minimize unproductive back electron transfer to ynamide radical cation via minimization of Coulombic attraction in the reduced (neutral) form of the catalyst.[9] In light of these considerations, acridinium photoredox catalysts, which have been applied in a number of reported transformations relying on single-electron transfer pathways, drew our attention.[10] We predicted that 9-mesityl acridiniums photocatalysts possessing high excited state oxidizing power (Mes-Acr-Me$^+$ $E_{1/2}^{red*}$ = +2.12 V vs SCE)[6d, 11] could conveniently catalyze ynamide radical cation generation, and the reduced form of the acridinium catalyst is a moderate single electron reductant ($E_{1/2}^{ox}$ = −0.57 V vs SCE)[12] that could presumably return electron transfer to radical intermediate.

Table 1. Reaction Condition Optimization.



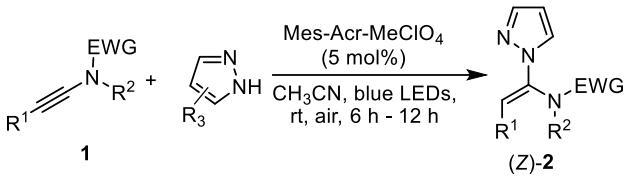
Entry	conditions[a]	yield[b] (%)
1	standard conditions	72
2	no light	<5
3	no photocatalyst	<5
4	protected by N_2	74
5	12 hrs instead of 5 hrs	74[c]
6	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	<5
7	([Ru(bpy)$_3$][PF_6]$_2$	<5
8	Mes-Acr-PhBF_4	70
9	acetone instead of CH_3CN	56
10	toluene instead of CH_3CN	35
11	MeOH instead of CH_3CN	9
12	DMF instead of CH_3CN	<5
13	DCM instead of CH_3CN	78
14	1.2 equiv. pyrazole in DCM	83

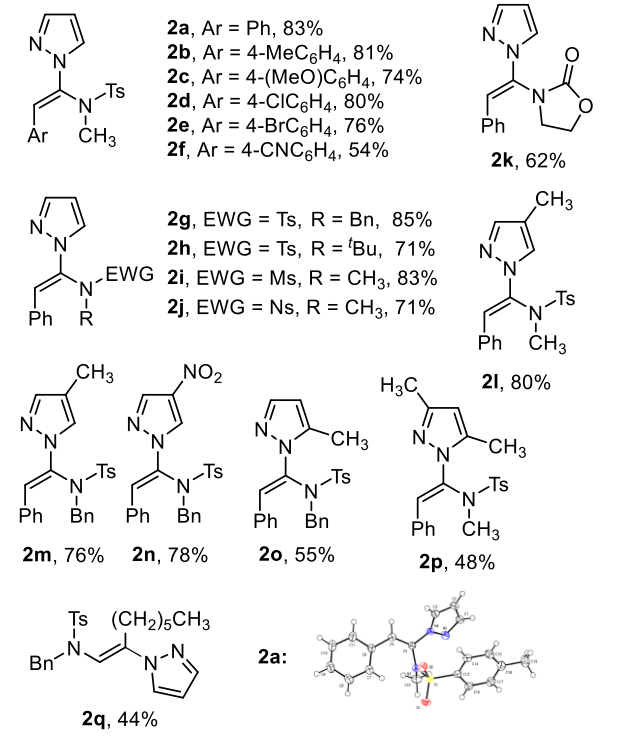
[a] Reaction conditions: **1a** (0.20 mmol), pyrazole (0.20 mmol), and 5 mol% of photocatalyst were dissolved in dry solvent (2.0 ml) under blue LED lamps (~400−520 nm, λ_{max} = 456 nm, 34 W) for 6 h. [b] Yield of isolated product **2a** based on the limiting reagent **1a**. [c] Combined yield of (*Z*)- and (*E*)-**2a**, *Z:E* = 3:1. CH_3CN = acetonitrile, DCM = dichloromethane, DMF = dimethylformamide.

To test the principle, we subjected ynesulfonamide **1a** ($E_{1/2}^{ox}$ = +1.44 V vs SCE) and pyrazole (1.0 equiv) to 5 mol% of 9-mesityl-10-methylacridinium perchlorate (Mes-Acr-MeClO_4) in acetonitrile under irradiation with 450 nm LEDs at room temperature. The desired hydroamination adduct (Z)-**2a** was obtained in 72% yield in 6 hours with high syn addition selectivity (Z/E = 11:1). The structure of (Z)-α-pyrazole enamide **2a** was unambiguously identified spectroscopically and confirmed by X-ray crystallography.[13] Only unconverted starting materials were recovered when the reactions were carried out without photocatalyst or photoirradiation (Table 1, entries 2 and 3). It is worthy that inert gas protection is not necessary for the reaction (entry 4). Increasing reaction time to 12 hours did not improve the production of **2a**, instead, photoinduced $Z \rightarrow E$ isomerization was observed (entry 5, 12 hrs, *Z/E* = 2.1:1). Systematic examination of the reaction variants, including photocatalysts and solvents, were performed. Neither iridium (Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6),nor ruthenium ([Ru(bpy)$_3$][PF_6]$_2$) photocatalysts were effective catalysts for this reaction (entries 6 and 7). Mes-Acr-PhBF_4 is comparable to Mes-Acr-MeClO_4 giving **2a** in 70% yield (entry 8). The use of toluene or acetone also delivered the formation of **2a**, albeit in low to moderate yield (entries 9 and 10). Methanol and dimethylformamide were not suitable solvents for this transformation (entries 11 and 12). The optimized

reaction condition was identified as the use of Mes-Acr-$MeClO_4$ in dichloromethane with 1.2 equiv. of pyrazole (entry 14), providing the best results to date (5 hours, 83% yield, Z/E = 12:1).

Table 2. Scope of ynamides and pyrazoles.[a)]

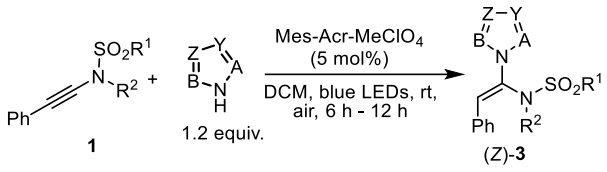


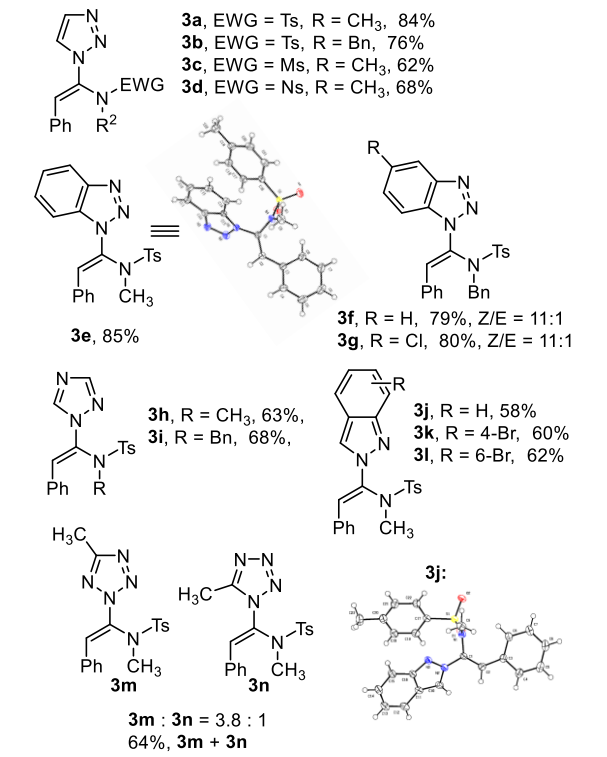


[a)] For experimental details, see supporting information.

Having identified a viable catalyst system, we investigate the substrate generality of ynamides and pyrazoles for the photoredox catalyzed intramolecular hydroamination reaction. A variety of ynesulfonamide with various substitution patterns and functional groups were examined in the reaction with pyrazole (Table 2). Ynesulfonamides bearing electronically distinct aryl substituents ranging from electron-rich (**2b** and **2c**) to electron-deficient (**2d**, **2e**, and **2f**) provided the desired (*Z*)-α-pyrazole enamides in good yields and high selectivity (*Z*/*E* > 10:1). The reactions of *N*-Bn- and *N*-^{t}Bu-ynesulfonamides with pyrazole generated products **2g** and **2h** smoothly in high yields. It is noteworthy that the photoinduced $Z \rightarrow E$ isomerization of (*Z*)-α-pyrazole enamide **2h** was not observed with prolonged reaction time (up to 18 hours), presumably because of resistance to isomerization caused by steric effect of bulky *tert*-butyl group. *N*-Mesyl and *N*-nosylynamides gave high yields of the corresponding products **2i** and **2j** as well. 3-(Phenylethynyl)-2-oxazolidinone ($E_{1/2}^{ox}$ = +1.75 V vs SCE) was a suitable substrate as well, yielding product **2k** in 69% yield with high *Z*/*E* selectivity (> 15:1). The scope with respect to substituted pyrazoles was then explored. In contrast to the high reactivity of 4-substituted pyrazoles (**2l**, **2m**, and **2n**), reaction yields of 3-substituted pyrazoles were significantly diminished (**2o** and **2p**), and steric interactions are probably responsible for the poor activity of the 3-substituted substrates. The reaction was further tested with alkyl substituted ynamide. Employment of hexyl substituted ynamide gave β-pyrazole enamide **2q** as a major product albeit with a lower isolated yield.

Table 3. Scope of ynamides and azoles.[a)]

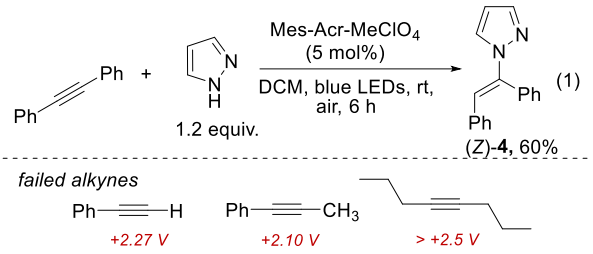




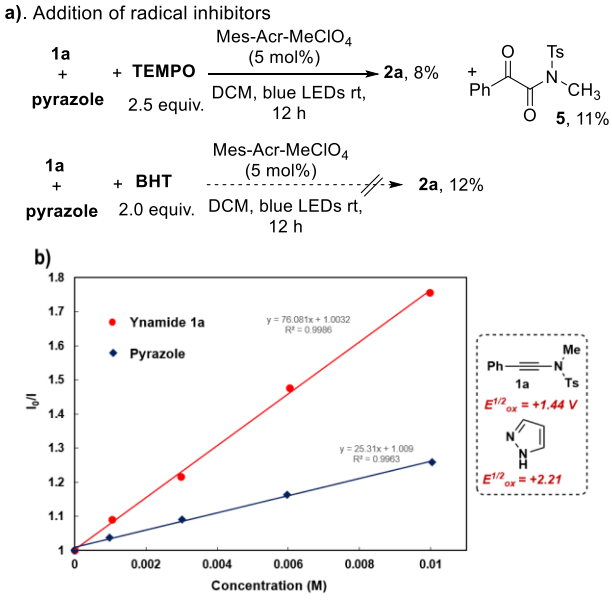
[a)] For experimental details, see supporting information.

Azoles are a privileged structural motif in many bioactive and pharmaceutical compounds and have versatile applicability as building blocks for synthesis and catalysis.[14] We were able to employ a diverse range of *N*-heterocyclic nucleophiles directly coupled to ynamide in our reaction protocol, thus providing access to potentially valuable nitrogen heterocycles bearing enamide moiety (Table 3). In addition to pyrazoles, good reactivities between ynamides and triazoles, benzotriazoles, indazoles, and tetrazoles were observed. Products with substitution at N1 of 1,2,3-triazoles and benzotriazoles were yielded as the major regioisomer as expected (**3a-3g**), which is a

result of the statistical advantage and increased electron density of N1/N3 over N2.[11a, 15] The reaction selectivity and product structure were unambiguously identified spectroscopically and confirmed by X-ray crystallography for **3e**.[16] Indazole gave a single N2 regioisomeric product (**3j-3l**), which is confirmed by X-ray crystallography analysis of product **3j**.[17] Exclusive (*Z*)-α-tetrazole enamides **3m** and **3n** were produced from the reaction of 5-methyl-1*H*-tetrazole in a 3.8:1 N2:N1 *N*-regioisomeric ratio, congruent with prior observations of hydroheteroarylation of ynamides with 2*H*-tetrazoles under thermal conditions.[18] The reaction class presented here should be of potential interest to the biomedical community as a tool for bioactive molecular synthesis and lead-drug candidate discovery.



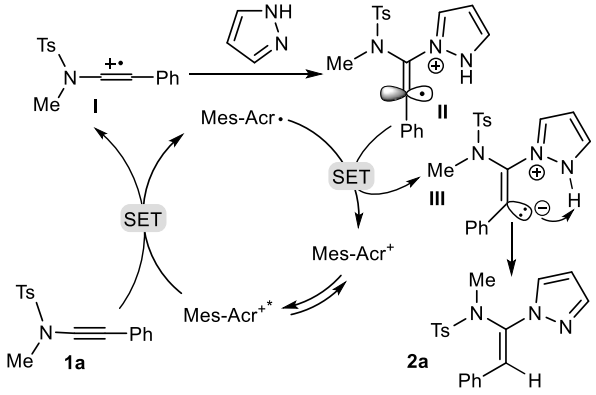
Along with ynamides, we further investigated the reactions of general alkynes. Based on our electrochemical studies of alkynes, we expect that diphenylacetylene ($E_{1/2}^{ox}$ = +1.85 V vs SCE) should be compatible with this hydroamination reaction. Indeed, the reaction of diphenylacetylene produced the desired alkenylpyrazole **4** in 60% yield (eq. 1).[19] Because of the high redox potential, acetylene, 1-phenyl-1-propyne, and 4-octyne are not reactive.[4] Furthermore, a gram-scale reaction of ynesulfonamide **2f** with pyrazole produced the expected enamide product in 72% isolated yield demonstrating the synthetic practicability of this transformation.



Scheme 3. Control experiments for elucidation of the mechanism.

In addition to the aforementioned electrochemical studies, control experiments and Stern–Volmer fluorescence quenching studies were performed to gain further mechanistic insight into this photoredox catalyzed hydroamination reaction of ynamides with nitrogen heteroaromatic nucleophiles. When the radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT) was subjected to the reaction of **1a** and pyrazole under the standard condition, the hydroamination reaction was substantially suppressed, suggesting the involvement of radical intermediates (Scheme 3a). Stern–Volmer fluorescence quenching studies (Scheme 3b) of the ynesulfonamide **1a** and pyrazole systems showed that the irradiated photocatalyst was quenched by **1a** (K_{sv} = 75.08) rather than pyrazole (K_{sv} = 25.31). Taken together the cyclic voltammetry measurements of ynamide **1a** ($E_{1/2}^{ox}$ = +1.44 V vs SCE) and pyrazole ($E_{1/2}^{ox}$ = +2.21 V vs SCE), it is feasible that the generation of ynamide cation radical **I** from photocatalyzed single-electron oxidation of ynesulfonamide **1a** may initial this photoinduced transformation.

Herein, in accord with the experimental evidence and literature support,[5,11] a plausible mechanism is depicted in Scheme 4 using the reaction of **1a** and pyrazole as an example. It is proposed that a reductive quenching of photoexcited Mes-Acr+* by **1a** leads to ynamide cation radical **I** and the reduced Mes-Acr•. The resultant intermediate **I** undergoes regioselective nucleophilic addition with pyrazole giving vinyl radical intermediate **II** that could be stabilized by the adjacent aromatic resonance contribution. It is proposed that the cationic vinyl radical **II** is reduced by Mes-Acr• leading to the formation of a vinyl anion intermediate **III** and photocatalyst regeneration. We envisioned that, in this reaction, the vinyl anion is immediately quenched by intramolecular proton transfer producing pyrazole enamide **2a**. The observed syn addition selectivity is rationalized by rapid proton transfer and proximity effect. The mechanism of this reaction is currently the subject of detailed investigations undertaken by our group.



Scheme 4. Proposed reaction mechanism.

In sum, a photoredox catalyzed hydroamination of ynamide with various heteroaromatic compounds including pyrazoles, triazoles, and tetrazoles has been developed. By accessing reactive ynamide radical cation intermediate, this protocol provides convenient metal-free access to a variety of valuable α-heteroarene substituted enamides. Notably, this research disclosed a photocatalytic strategy for synthetically attractive alkyne radical cation generation from readily available ynamides, which provide a solution, at least in part, for the generation of highly reactive alkyne radical cation species, and therein holding the promise to advance this underdeveloped research area. Further investigation of the reaction mechanism and the synthetic applications are currently underway.

Experimental Section

Typical procedure for the hydroamination reaction: A magnetic stir bar, ynamide (1.0 equiv), pyrazole (1.2 equiv), and acridinium catalyst (Mes-Acr-MeClO$_4$, 5.0 mol%) were added to a flame-dried 2-dram vial containing a magnetic stir bar. Dichloromethane [1.0 M] were then introduced via syringe. The vial was fitted with a septum cap and placed on a magnetic stirring plate irradiated with a blue LED lamp (456 nm) at room temperature. The course of the reaction was monitored by TLC and, upon completion, the solvent was removed and the crude reaction mixture purified by silica gel chromatography.

Acknowledgements

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