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Photocatalytic Visible-Light-Induced Nitrogen Insertion via Dual C(sp^3)−H and C(sp^2)−H Bond Functionalization: Access to Privileged Imidazole-based Scaffolds

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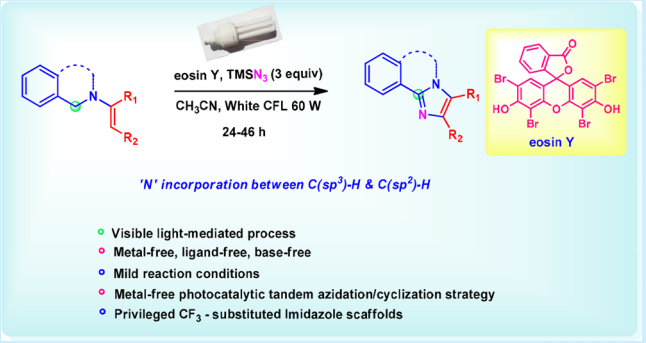
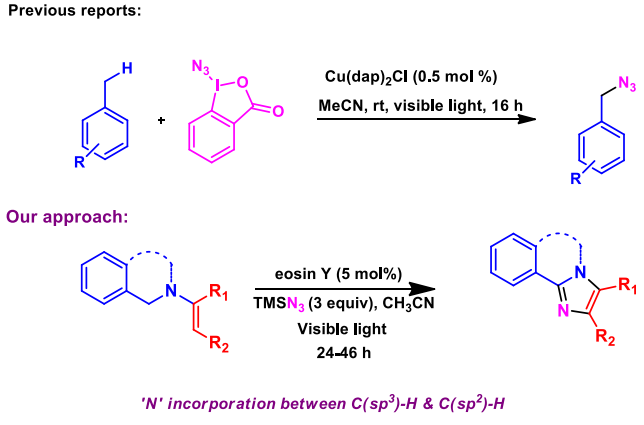
ABSTRACT: Here we have demonstrated a visible-light-mediated metal-free organic-dye-catalyzed dehydrogenative N-insertion leading to highly substituted imidazoles and privileged dihydroisoquinoline-based imidazole derivatives via C(sp^3)−H and C-(sp^2)−H bond functionalization. A sustainable, convenient, metal-free azidation/C−H aminative cyclization approach in the absence of stoichiometric oxidants is presented. This protocol involves a rare photoinduced iminyl radical as a key intermediate for the "N" insertion.

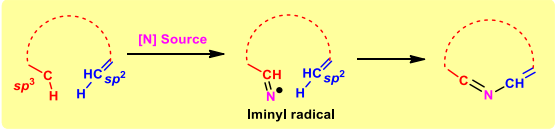


Photochemical reactions have vast potential in green chemistry. Nature's ability to convert solar power in photosynthesis has hugely influenced the scientific community to mimic nature in the development of photoredox systems in all areas of science, including organic chemistry.[1] Visible-light-promoted photoredox catalysis has become one of the promising tools for selective organic transformations, with potential to unlock distinct reaction pathways due to its unique features such as mild conditions, trace or no byproducts, and economical and ecological friendliness in organic synthesis.[2] Photoactive catalysts have emerged as an attractive and sustainable tool for C−H activation for C−C/C−X bond formation via visible-light-induced single-electron transfer (SET) processes.[3] This cutting-edge platform allows the photoexcitation of photocatalysts with visible light and chemical energy conversion, prompting an SET event, to generate reactive free-radical intermediates for synthetically valuable transformations.[4] Conspicuously, MacMillan and coworkers engaged photoredox catalysis to activate native functional groups toward C−C/C−X bond formation and have widely explored visible-light photocatalysis with transition metals and organocatalysts via SET, hydrogen-atom transfer (HAT), radical decarboxylative coupling via dual catalysis (Ni/Ir), and reductive quenching cycles to develop numerous efficient methods for plenteous C(sp^3)−H bond functionalization.[5]

Scheme 1. Photoredox Approach for Benzylic C−H Azidation and Our Strategy



Scheme 2. Hypothesized Approach for "N" Insertion via C(sp^3)−H and C(sp^2)−H Functionalization



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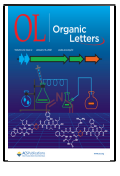

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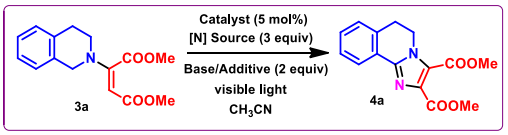
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (5 mol %)	[N] source	base/additive	light source	time (h)	yield (%)[b]
1	rose Bengal	$TMSN_3$	–	60W bulb	48	50
2	**eosin Y**	**$TMSN_3$**	–	**60W bulb**	**48**	**70**
3	rhodamine B	$TMSN_3$	–	60W bulb	48	48
4	riboflavin	$TMSN_3$	–	60W bulb	48	55
5	$Ru(bpy)_3Cl_2$	$TMSN_3$		60W bulb	48	40
6	$Ir(ppy)_3$	$TMSN_3$		60W bulb	48	35
7	eosin Y	IBA-N_3	–	60W bulb	48	45
8	eosin Y	NaN_3	–	60W bulb	48	30
9	eosin Y	$TMSN_3$	–	3W blue LED	48	45
10	eosin Y	$TMSN_3$	–	other light source	48	10–20[c]
11	eosin Y	$TMSN_3$	Et_3N	60W bulb	48	20
12	eosin Y	$TMSN_3$	DIPEA	60W bulb	48	30
13	eosin Y	$TMSN_3$	$CBrCl_3$	60W bulb	36	60
14	eosin Y	$TMSN_3$	CCl_4	60W bulb	60	65
15	eosin Y	$TMSN_3$	–	dark	48	ND

[a]Reaction conditions: **3a** (0.36 mmol), [N] source (1.08 mmol), and 2 mL of CH_3CN solvent. [b]Isolated yields after column chromatography. [c]Other light sources afforded green LED (20%), red LED (trace), CFL variable wattages (11W, 15W, 18 W) around 20%, sunlight (10%). ND = not detected.

Photocatalytic transformation has mostly been reported using metal complexes such as ruthenium and iridium polypyridyl complexes;[6] however, transition-metal-based photocatalysts demonstrate disadvantages such as low sustainability, potential toxicity, and high cost. Most recently, some of the organic dyes like rose bengal, eosin Y, rhodamine B, and riboflavin have been recognized as superior alternatives due to their easy accessibility, low cost, and low toxicity.[7] In organic dyes, eosin Y has been widely used in visible-light-promoted organic transformations involving SET.[8] On the contrary, the photoredox-catalyzed C–H functionalization has been extensively developed, especially for the C–H bond adjacent to the nitrogen atom, leading to the synthesis of N-heterocycles.[9]

In the past few decades, C–H activation leading to C–N bond formation has emerged as a powerful tool for the synthesis of nitrogen-containing bioactive molecules and pharmaceutically important compounds.[10,11] Very recently, radical chemistry has gained importance due to its sustainable features, and, in particular, "N" radical species have gained importance in their applicability in C–N bond formation,[12] specifically with photo/electrotechniques. Among them, iminyl radicals represent valuable synthons among N-centered radicals.[13] Therefore, various approaches have been developed starting from vinyl-azides, oximes, and cyanide derivatives. Keeping sustainability in view, light-induced photoredox strategies for generating these radicals are of immense focus. Recently, the formation of an α-azidyl radical has been a promising approach for iminyl radical generation and α-C–N bond construction. Yu et al. have reported light-induced *N*-bromosuccinimide (NBS)-mediated iminyl radical cyclization to quinazolinones from α-azidyl benzamide *via* an α-azidoradical.[14] Later on, they reported an interesting "N" insertion protocol utilizing the iminyl radical strategy, leading to quinoxalines via the light-induced tandem azidation/cyclization of *N*-arylenamines,[15] featuring step-economic operation in which two C–N bonds were formed in one step. Greaney et al. reported benzylic C–H azidation using the Zhdankin reagent as an azide source in the presence of a copper photoredox catalyst (Scheme 1).[16] In a continuation of our recent interests in photoredox catalysis for C–H functionalization[17] and azide-based chemistry,[18] we envisaged that it would be of great importance to investigate a light-induced "N" insertion strategy via iminyl radical cyclization involving dual C(sp^3)–H and C(sp^2)–H amination (Scheme 2).

Herein we disclose a visible-light-promoted "N" insertion leading to highly substituted imidazole derivatives by a tandem azidative/cycloamination strategy. Imidazole scaffolds shows high biological activity and exist in many pharmaceuticals and natural products.[19]

To check our hypothesis, we choose **3a** as a model substrate and treated it with rose bengal in CH_3CN in the presence of $TMSN_3$ under a 60W CFL bulb, resulting in the complete disappearance of the starting material within 48 h to the desired product **4a** (50% yield, Table 1, entry 1). We screened the reaction with different photocatalysts such as eosin Y, rhodamine B, riboflavin, $Ru(bpy)_3Cl_2$, and $Ir(ppy)_3$, which resulted in moderate to good yields (35–70%) of **4a** (Table 1, entries 2–6). For sp^3 C–H azidation, we investigated different azide sources like IBA-N_3 and NaN_3, which afforded a moderate yield of the product **4a** (45 and 30%, Table 1, entries 7 and 8). Subsequently, we switched the light source to blue LEDs, which, however, significantly decreased the yield (38%, Table 1, entry 9). Trying our protocol with other light sources afforded a poor yield of the product **4a** (Table 1, entry 10). With further testing with bases and additives, there was no improvement in the yield of the product (Table 1, entries 11–14). Importantly, when the reaction was conducted in the dark, no conversion was observed, indicating that photocatalysis is crucial for the transformation (Table 1, entry 15). Finally, the reaction with eosin Y in CH_3CN in the presence of $TMSN_3$ under 60W CFL bulb proved to be the best among all optimized conditions.

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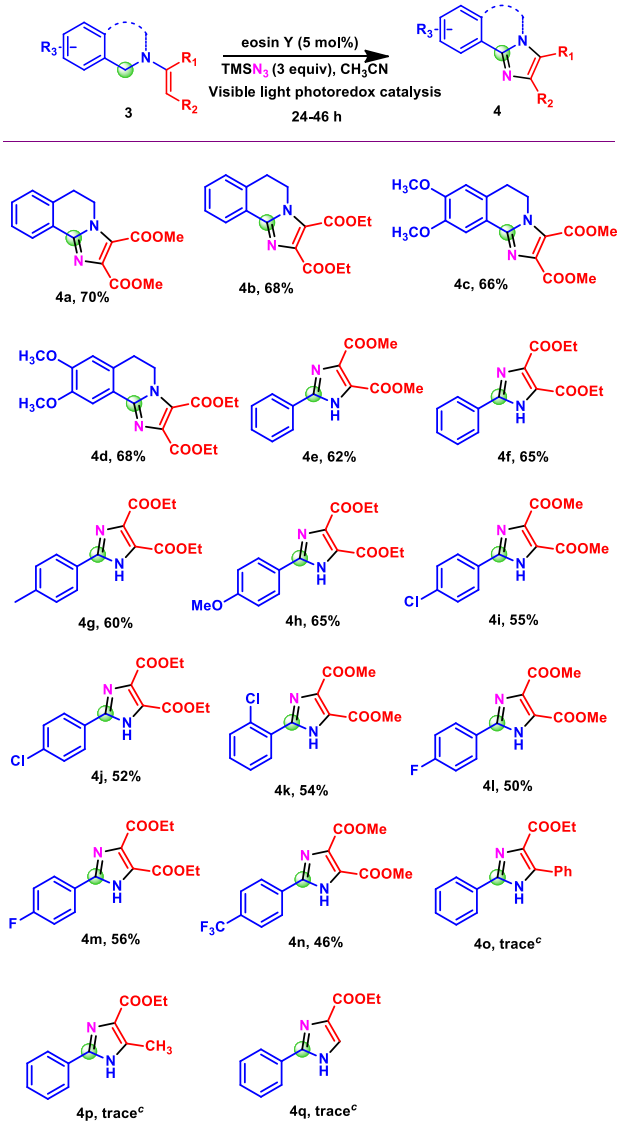
Scheme 3. Scope of *N*-Benzylenamine Esters in Visible-Light-Induced "N" Incorporation[a,b]

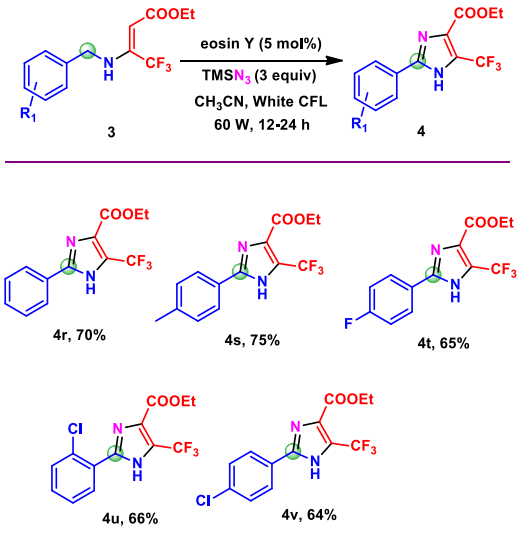


[a]Conditions: **3** (0.36 mmol), eosin Y (0.018 mmol), $TMSN_3$ (1.08 mmol) in dry CH_3CN (2 mL), white CFL 60 W. [b]Yields are reported for compounds isolated after silica gel column chromatography. [c]Detected by HRMS analysis.

Under the optimized conditions, the substrate scope was investigated. Initially we started investigation with tetrahydroisoquinoline (THIQ) enamines generated from THIQs and dialkylbut-2-ynedioate (Scheme 2). THIQ enamines **3a−d** proceeded smoothly to give privileged imidazo-fused dihydroisoquinoline (DHIQ) scaffolds (**4a−d**) in 66−70% yields (Scheme 3). DHIQ is an important core structure of pharmaceuticals and natural products.[20]

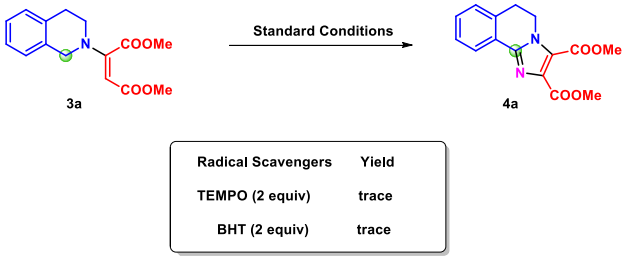
Pleased by the results, we envisioned applying the optimal reaction conditions to other benzylamine-based enamines (**3e** and **3f**), which resulted in the generation of highly substituted imidazoles **4e** and **4f** in moderate yields (62 and 65%). Similarly, electron-donating-group-substituted enamines **3g** and **3h** afforded the products **4g** and **4h** in good yields (60 and 65%). Furthermore, employing weakly electron-donating groups such as −F and −Cl at the ortho and para positions of enamines (**3i−m**) gave the corresponding products **4i−m** in moderate yields (50−56%). Furthermore, the CF_3− substituent on the phenyl ring of enamine (**3n**) was also found to be accomplished for the synthesis of highly substituted imidazole **4n** in moderate yield

Scheme 4. Scope of CF_3-based Enamines[a,b]



[a]Conditions: **3** (0.36 mmol), eosin Y (0.018 mmol), $TMSN_3$ (1.08 mmol) in dry CH_3CN (2 mL), white CFL 60 W. [b]Yields are reported for compounds isolated after silica gel column chromatography.

Scheme 5. Control Experiments



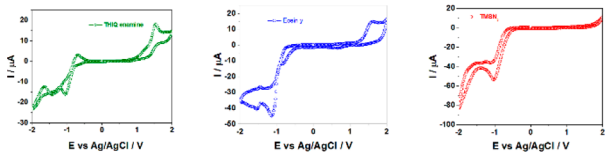
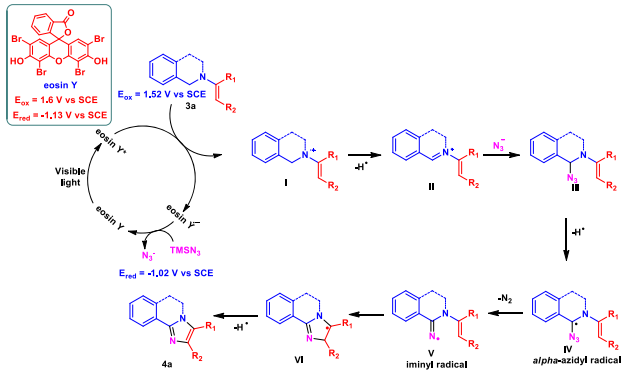


Figure 1. Electrochemical oxidation and reduction curves in dry CH_3CN solution of THIQ enamine (**3a**), eosin Y, and $TMSN_3$ at a scan rate of 100 mV/s.

Scheme 6. Plausible Reaction Mechanism



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(46%). On the contrary, when we have examined enamines derived from monoactivated alkynes (**3o** and **3p**) and terminal alkynes (**3q**) under optimized conditions, they have afforded a trace amount of corresponding products **4o−q**, which was confirmed by HRMS analysis (Scheme 3). Keeping in view the relevance of imidazole skeletons in pharmaceuticals and biologically important molecules, we have examined the gram-scale reaction of our protocol with **3a**, which furnished a 52% yield of the product **4a**.

To further diversify the skeleton, we have applied our azidation/C−H aminative cyclization approach to enamines derived from 1,3-dicarbonyls (with $-COCF_3$), resulting in the corresponding CF_3-substituted imidazoles **4r−v** in good yields 64−75% (Scheme 4). The trifluoromethyl-substituted heterocycles are very important structural motifs in agrochemicals, pharmaceuticals, organic materials, and tracers for positron emission tomography; furthermore, owing to their metabolic stability, strong electron-withdrawing power, and high lipophilicity, they can increase the strength of a compound's interactions with a target protein.[21]

To understand the probable mechanism of the visible-light-promoted azidation/C−H aminative cyclization strategy, some control experiments were performed, as shown in Scheme 5. When the model reaction was carried out in the presence of TEMPO and BHT as radical scavengers, the reaction was completely inhibited, thus indicating a radical pathway.

To understand the mechanical aspects of this reaction, we measured the oxidation potential (E_{ox}) and reduction potential (E_{red}) based on the cyclic voltammetry (CV) for THIQ-based enamine (**3a**), eosin Y. and $TMSN_3$ at a scan rate of 100 $mV{\cdot}s^{-1}$ (vs Ag/AgCl) (Figure 1). The E_{ox} is calculated to be 1.52 V for **3a**, and the E_{ox} and E_{red} are calculated to be 1.6 and −1.13 V for eosin Y. On the basis of the value of the more oxidation potential value of eosin Y (1.6 V vs SCE), **3a** is oxidized to radical cation **I** *via* the reductive quenching cycle by the SET mechanism. Subsequently, **I** is oxidized to produce the iminium ion **II,** which affords the product **4a** *via* the azidation/C−H aminative cyclization strategy. The E_{red} for $TMSN_3$ is calculated to be −1.02 V vs SCE, and hence $TMSN_3$ is crucial in the oxidation of the eosin Y radical anion to eosin Y to complete the reductive quenching cycle.

On the basis of the controlled experiments, the cyclic voltammetry results, and literature reports, we have formulated a plausible reaction mechanism for the synthesis of 2,4,5-trisubstituted imidazoles, as shown in Scheme 6. Initially, in the presence of white CFL light, eosin Y is photoexcited. The THIQ enamine (**3a**) is oxidized to the THIQ enamine radical cation (**I**) by the SET mechanism *via* a reductive quenching cycle. Subsequently, **I** is oxidized to the intermediate iminium ion (**II**), which is attacked by N_3^- to produce **III**, followed by an oxidation to afford α-azidyl radical **IV**. Subsequently, the extrusion of N_2 from **IV** generates iminyl radical **V**, which undergoes an oxidation to afford final product **4a**.

In conclusion, we have disclosed for the first time a photocatalytic azidative/cycloamination strategy leading to highly substituted imidazoles via $C(sp^3)$−H and $C(sp^2)$−H functionalization. This environmentally friendly methodology features a convenient, mild, step-economic, C−H amination approach without the use of any stoichiometric oxidants, resulting in the formation of two C−N bonds in one synthetic operation. Furthermore, this protocol furnishes interesting $-CF_3$-substituted imidazoles, which would be of great significance as therapeutic agents due to the enhanced physicochemical properties of fluorinated compounds and in imaging. Overall, this sustainable method would open new avenues for industrial applications in making value-added heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03269.

Experimental procedures, ^1H and ^{13}C NMR spectra, and characterization data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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