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Visible-Light-Enabled Oxidative Coupling of Alkenes with Dialkylformamides To Access Unsaturated Amides

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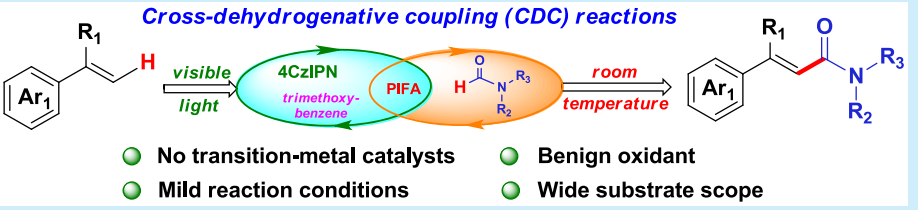
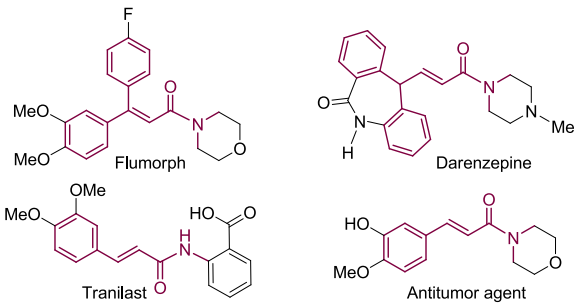
Supporting Information



ABSTRACT: A practical and direct method for oxidative cross-coupling of alkenes with dialkylformamides is established employing visible-light-enabled photoredox catalysis. This strategy allows efficient access to diverse unsaturated amides under mild reaction conditions. The application of an appropriate diaryliodonium salt was demonstrated to be critical to the success of this process. This catalyst system is well tolerant of a variety of useful functional groups.

The unsaturated amide is a highly versatile structural motif present in numerous biologically meaningful molecules, proteins, and functional polymers.[1] For example, they can be employed as antibacterial agents, anticancer agents, and histone deacetylase inhibitors (Scheme 1).[2] Given the significance of these utilities, great effort has been made to explore new, mild, and efficient methods for the preparation of unsaturated amides. Among them, the direct amidation of cinnamic chlorides and amines has emerged as the most frequently adopted route. However, multiple steps and toxic or expensive reagents were commonly required in this method. Strategies trying to address these drawbacks involved the utilization of direct C−H bond functionalizations through photocatalysis or transition-metal-catalysis, in which the need for preactivated reaction substrates could be efficiently bypassed.[3] Within this context, Tsuji and coworkers reported a unique and practical Pd-catalyzed intermolecular addition reaction of formamides to terminal alkynes to synthesize a diverse range of α,β-unsaturated amides, in which Markovnikov addition products were observed as the major product.[3b] This work has subsequently fueled other studies with the purpose of the direct functionalization of the inert sp^2 C−H bond of the formamides. For example, an efficient protocol relying on the intermolecular oxidative coupling reactions of unactivated terminal alkenes and dialkylformamides for the preparation of unsaturated amides was disclosed by Li and coworkers in the presence of the $FeCl_3$/DTBP catalytic system at a high reaction temperature.[3c]

Scheme 1. Unsaturated Amide Moieties in Biological Molecules



Despite these contributions to unsaturated amide synthesis, it is still highly desirable to develop a practical, convenient, and straightforward method that is capable of yielding them with readily available materials, minimal preactivations, and milder reaction conditions. Herein we report our recent achievement in the formation of α,β-unsaturated amides from simple alkenes and dialkylformamides by means of visible-light-promoted photoredox cross-dehydrogenative coupling under mild conditions (Scheme 2).

On the basis of our recent studies[4] on the direct functionalization of the inert sp^3 C−H bond by photoredox catalysis[5,6] (Scheme 3), we envisioned that the diaryliodonium salt[7] possessing strong electron-donating properties as well as large steric bulk aromatic group seems to be feasibly functioned as a reliable and safe single-electron oxidant in

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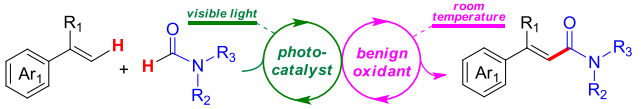
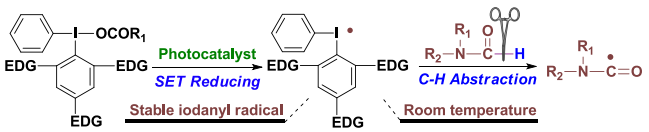
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Photocatalytic Oxidative Coupling Strategy for the Synthesis of Unsaturated Amides



Scheme 3. Visible-Light-Enabled Diaryliodonium-Salt-Induced sp^2 C−H Functionalization

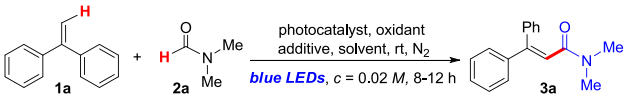


the inert sp^2 C−H bond activation because it can be expediently converted to the relatively stable iodanly radical with the synergistic actions of visible-light irradiation and a photocatalyst through a single electron transfer (SET) process. Subsequently, the in-situ-generated iodanyl radical would be able to undergo an H-abstraction event on dialkylformamide, thereby converting it into the corresponding carbonyl radical species.

The initial oxidant screenings, carried out on a readily available model substrate **1a**, indicated that the in-situ-generated diaryliodonium salt should be a promising starting point, and the corresponding results are illustrated in Table 1. We discovered that 63% yield of the desired product **3a** was obtained in the solvent of DMF in the presence of an organic fluorophore 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) ($E_{1/2}^{red}$(*P/P$^-$) = +1.35 V, $E_{1/2}^{ox}$(P/P$^-$) = −1.21 V vs SCE)[8] (0.02 equiv) and PIFA/1,3,5-trimethoxybenzene (**A**) (2.0 equiv, 0.333 mmol) under blue LED irradiation for 10 h at room temperature (entry 1). Subsequently, other similar arenes such as 1,3-dimethoxybenzene (**B**), anisole (**C**), and 1,3,5-trimethylbenzene (**D**) were used in place of 1,3,5-trimethoxybenzene (**A**) under other otherwise identical reaction conditions, but the product was produced in lower yield (entries 2−4). Notably, complicated mixtures were observed only when the 1,3,5-trimethoxybenzene was purposefully removed from the reaction system (entry 5). Gratifyingly, when a base K_2CO_3 (2 equiv) was added to the reaction system, the yield of **3a** was improved to 79% (entry 6). Thus a range of bases involving Cs_2CO_3, Na_2CO_3, and Na_2HPO_3, were subsequently screened under various conditions, but all of which were found to have a negative influence on the cinnamide formation (entries 7−9). Furthermore, the choice of oxidant was also revealed to be crucial because the utilization of PhI(OAc)$_2$ (PIDA), acetoxybenziodoxole (BI-OAc), $K_2S_2O_8$, or even *t*-BuOOH (TBHP) resulted in either reductions or complete inhibitions in reactivities (entries 10−13). Subsequent attempts employing eosin Y or Ru(bpy)$_3$Cl$_2$ as an alternative photocatalyst also could not efficiently improve the reactivity (entries 14 and 15). Finally, reactions carried out in the absence of a photocatalyst, oxidant, or visible light distinctly pointed to complete inhibitions in reactivities (entries 16−18).

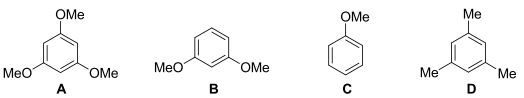
After efficient conditions for α,β-unsaturated amide formation were determined, we next explored the substrate scope of this transformation (Scheme 4). It was found that a

Table 1. Optimization of the Reaction Conditions



entry	PC (2 mol %)[a]	oxidant (equiv)[b]	additive (equiv)	solvent	yield (%)[c]
1	4CzIPN	PIFA/**A** (2.0)	none	DMF	63
2	4CzIPN	PIFA/**B** (2.0)	none	DMF	45
3	4CzIPN	PIFA/**C** (2.0)	none	DMF	trace
4	4CzIPN	PIFA/**D** (2.0)	none	DMF	trace
5	4CzIPN	PIFA (2.0)	none	DMF	decomp
6	**4CzIPN**	**PIFA/A (2.0)**	**K_2CO_3 (2.0)**	**DMF**	**79**
7	4CzIPN	PIFA/**A** (2.0)	Na_2CO_3 (2.0)	DMF	72
8	4CzIPN	PIFA/**A** (2.0)	Cs_2CO_3 (2.0)	DMF	56
9	4CzIPN	PIFA/**A** (2.0)	Na_2HPO_4 (2.0)	DMF	73
10	4CzIPN	PIDA/**A** (2.0)	K_2CO_3 (2.0)	DMF	decomp
11	4CzIPN	BI-OAc/**A** (2.0)	K_2CO_3 (2.0)	DMF	trace
12	4CzIPN	$K_2S_2O_8$/**A** (2.0)	K_2CO_3 (2.0)	DMF	trace
13	4CzIPN	TBHP/**A** (2.0)	K_2CO_3 (2.0)	DMF	decomp
14	eosin Y	PIFA/**A** (2.0)	K_2CO_3 (2.0)	DMF	64
15	Ru(bpy)$_3$Cl$_2$	PIFA/**A** (2.0)	K_2CO_3 (2.0)	DMF	67
16	none	PIFA/**A** (2.0)	K_2CO_3 (2.0)	DMF	trace
17	4CzIPN	none	K_2CO_3 (2.0)	DMF	NR
18[d]	4CzIPN	PIFA/**A** (2.0)	K_2CO_3 (2.0)	DMF	NR

Structures of **A-D**:



[a]4CzIPN = 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene. [b]PIFA = PhI(OCOCF$_3$)$_2$; PIDA = PhI(OAc)$_2$; BI-OAc = acetoxy-benziodoxole; TBHP = *t*-BuOOH [c]Yield of isolated product. [d]No light.

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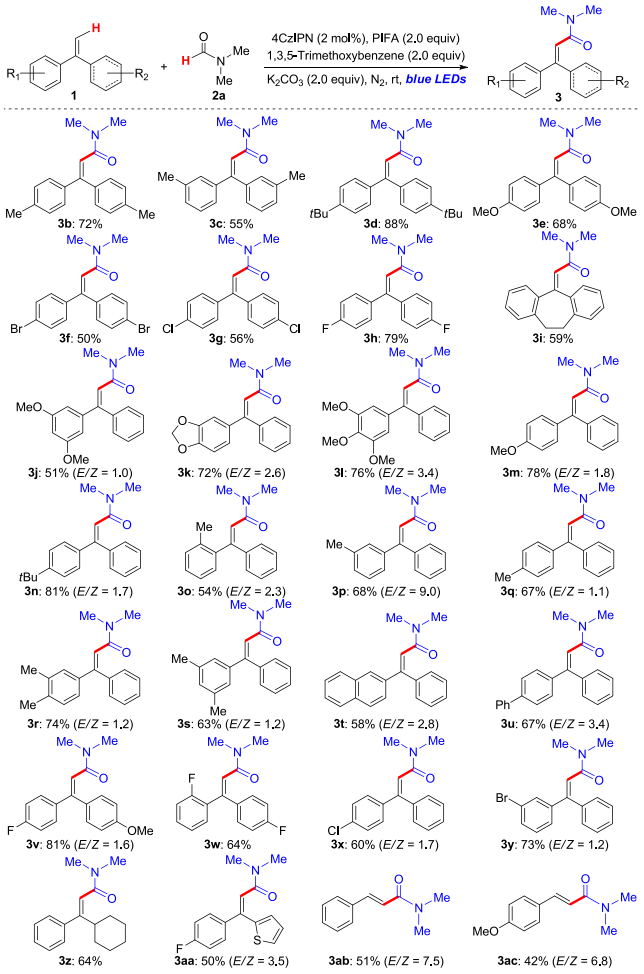
Org. Lett. XXXX, XXX, XXX−XXX

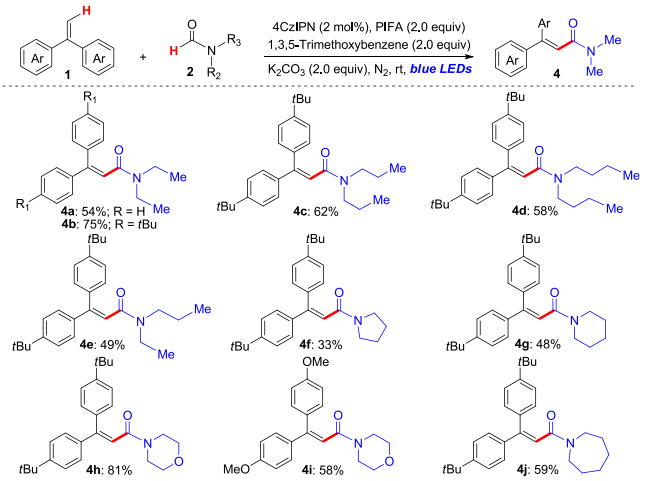
Scheme 4. Reactivity Screenings on Alkenes 1



series of different alkenes were well tolerated in addition to the 1,1-diphenylethylene **2a** under the optimal reaction conditions, proceeding smoothly to afford the corresponding α,β-unsaturated amide product **3** in good yield (42−88%). When symmetrical 1,1-diarylethylenes were used, neither the substitution patterns (**1b** and **1c**) nor the electronic characteristics (**1d**−**h**) on the aryl rings seemed to have an obvious influence on the reactivities. The alkene **1l** with a tricyclic moiety could be efficiently converted to the corresponding product. Furthermore, we found that a range of frequently encountered electron-donating substituents such as methoxyl (**1j**−**m**), *tert*-butyl (**1n**), methyl (**1o**−**s**), 2-naphthalenyl (**1t**), and phenyl (**1u**) on the aromatic ring in the unsymmetrical diarylethylenes were well tolerated, smoothly furnishing the corresponding products in good yield (51−81%) and with E/Z isomeric ratios ranging from 1.0 to 9.0. The successful generation of **3v**−**y** containing intact carbon−halogen bonds would provide a useful platform for further required synthetic editing. It should be noted that the 1,1-diaryl moieties in the substrates were not a structural requisite for the cross-dehydrogenative coupling previously outlined. Monoaryl substrates were also revealed to work with comparable efficiency, thus notably extending the synthetic utilization of this method. For example, the alkenes with a cycloalkyl and thienyl group could undergo this process to give **3z** and **3ab**, respectively. Furthermore, simple styrenes, such as **1ab** and **1ac**, were found to be successful under our conditions, albeit in relatively low isolated yield.

This technology could be readily extended to the scope of other dialkylformamides **2** under the optimal reaction conditions, and the results are illustrated in Scheme 5. The

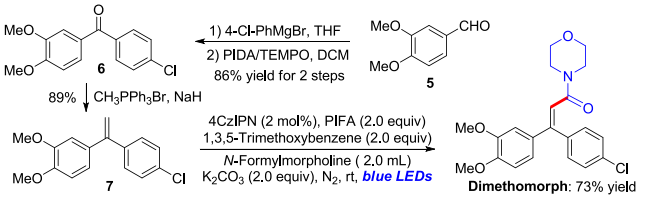
Scheme 5. Reactivity Screenings on Dialkylformamides 2



corresponding α,β-unsaturated amides **4** were generally furnished in moderate-to-good isolated yield (30−81%). The formamides carrying an ethyl (**2a**), propyl (**2b**), or butyl (**2c**) are comparably efficient in these instances. It was found that cyclic formamide derivatives also proceeded smoothly to afford the corresponding products in good isolated yield (**4f**−**j**). These results, in conjunction with the aforementioned observations, further demonstrated that this established method would be widely applicable to substances carrying different functionalities.

The synthetic application of this method was further manifested through the straightforward preparation of pharmaceutically active molecules. For example, the 1,1-diarylethylene **7**, derived in three steps through a sequence of 1,2-addition, oxidation, and olefination of **5**, was able to efficiently couple to *N*-formylmorpholine under the standard reaction conditions to expediently furnish the familiar bactericide dimethomorph in good yield (Scheme 6).

Scheme 6. Synthetic Elaboration on the Dimethomorph



To get a better understanding about the potential reaction mechanism, some control experiments were subsequently carried out. (See the Supporting Information.) As shown in Scheme 7, 1,3,5-trimethoxybenzene could react efficiently with $PhI(OCOCF_3)_2$ to furnish the diaryliodonium salt through a ligand exchange process. When the in-situ-generated diaryliodonium salt was directly employed as the oxidant, the desired α,β-unsaturated amide **3a** was smoothly produced in comparable yield. Complete inhibition of the reactivity was

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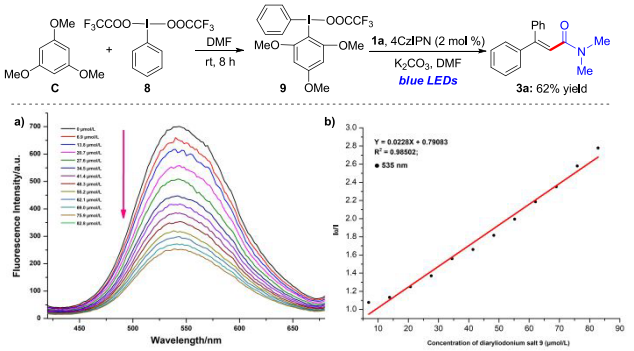
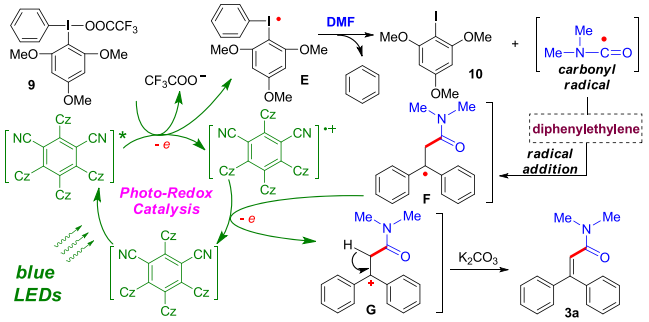
Scheme 7. Experimental Studies on the Reaction Mechanism



noticed when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction system, suggesting that this reaction should include a radical step. Finally, fluorescence quenching (Stern−Volmer) experiments showed that the photoexcited 4CzIPN could be quenched efficiently by diaryliodonium salt, indicating that the diaryliodonium salt presumably participated in a single electron transfer process in this reaction.[9]

On the basis of the above observation and literature reports, a plausible mechanistic network for α,β-unsaturated amide formation was proposed in Scheme 8. Initially, the in-situ-

Scheme 8. Mechanistic Proposal



generated diaryliodonium salt was quenched by the photoexcited state species 4CzIPN to yield the key iodanyl radical **E**. The resulting iodanyl radical **E** would subsequently induce a hydrogen abstraction event on DMF, thus affording the highly active carbonyl radical as well as the 2-iodo-1,3,5-trimethoxybenzene **10**. The carbonyl radical then added to the diphenylethylene to obtain the radical addition adduct **F**, which could further undergo single electron transfer with the radical cation 4CzIPN to give the alkyl cation **G**. Finally, β-hydrogen elimination of alkyl cation **G**, with the assistance of base K_2CO_3, resulted in the formation of the final α,β-unsaturated amide product, **3a**.

In summary, we have developed the first visible-light-enabled formamide oxidation to produce carbonyl radicals employing the in-situ-generated benign oxidant diaryliodonium salt. A variety of alkenes as well as formamides were revealed to be well tolerated under this reaction condition, expediently providing access to functionalized α,β-unsaturated amides in good-to-excellent yield. The identification of a practical method allowing for generations of carbonyl radical intermediates from readily available dialkyl formamides is of central significance to this discovery. Given the widely appreciated importance of cinnamide-type substances in biological and pharmaceutical contexts, we envision that this dual diaryliodonium salt/photoredox catalytic system will find broader applications in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03870.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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