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Letter

Photocatalyst-Free, Visible-Light-Mediated C(sp^3)–H Arylation of Amides via a Solvent-Caged EDA Complex

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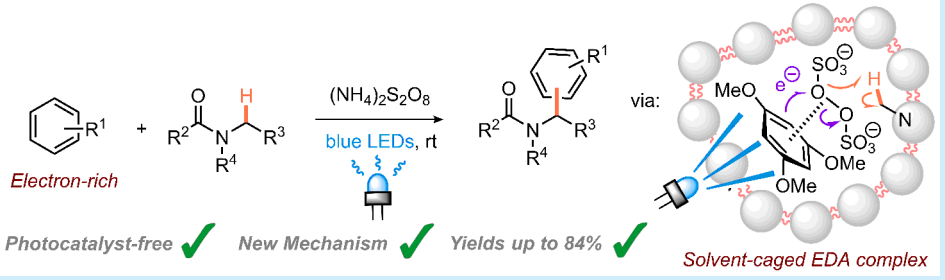

ABSTRACT: A photocatalyst-free and mild visible light photochemical procedure for C(sp^3)–H arylation of amides is described. The reaction proceeds via an electron donor–acceptor (EDA) complex between an electron-rich arene substrate and electron-poor persulfate oxidant. C(sp^3)–H arylation of the amide occurs selectively with the most electron-rich arene of the substrate. Mechanistic studies corroborate the reaction taking place in a solvent cage holding components in a close proximity.

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Amides and lactams are an important class of functional groups commonly found in polymers, peptides/proteins, functional materials, and biologically active scaffolds.[1−6] Commendable efforts have been invested in the synthesis of these moieties beyond the classic condensation of activated carboxylic acids with amines, varying from transamidation reactions to using ligase enzymes.[7−12] However, many of these reactions introduce limiting requirements, such as (i) the use of stoichiometric coupling agents to form activated intermediates or (ii) the condensation of amines with preactivated carboxylic acids. An alternative, valuable approach is the functionalization of existing simple amides. New synthetic opportunities for the direct C(sp^3)–H functionalization of simple amides have emerged, such as (i) radical chemistry using transition metal catalysis[13−15] and (ii) transition-metal-free, nonradical pathways using Lewis or Brønsted acid[16] or base catalyzed chemistry, the latter of which is an active research area of our group[17] and others.[18]

Hydrogen atom transfer (HAT) enables the direct functionalization of C(sp^3)–H amide bonds, circumventing the otherwise high oxidation potentials of primary (E_p^{ox} = +2.0 V), secondary (E_p^{ox} = +1.8 V), and tertiary (E_p^{ox} = +1.2–1.5 V) amides (vs SCE) that generally prohibits their engagement via single electron transfer (SET).[19] Although direct oxidation at the α-positions of amides can be achieved via Shono-type electrochemical anodic oxidation to *N*-acyliminium ions,[20] the α-amido radical intermediate cannot be utilized and undergoes electrochemical oxidation. In a seminal report, Stephenson utilized the combination of SET and HAT to generate *N*-acyliminium ions in a photocatalyzed Friedel–Crafts amidoalkylation of electron-rich arenes (Figure 1).[19] Subsequently, Ji employed benzaldehyde-mediated photoredox oxidative cross-dehydrogenative-coupling (CDC) transformations for amidoalkylation of benzothiazole using ammonium persulfate.[21] Zhu reported a nonphotochemical variant that works with a lower amide loading at 70 °C.[22]

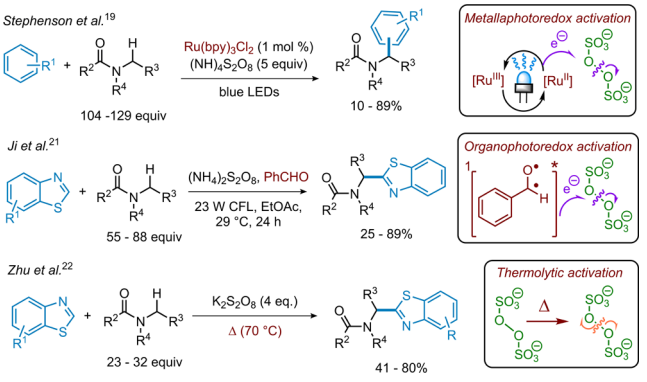

Figure 1. Previous approaches to C(sp^3)–H arylation of amides involving persulfate.

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The field of PhotoRedox Catalysis (PRC) evolved rapidly over the past two decades inspired by photocatalytic reactions using Ru(II)- or Ir(III)-bipyridyl complexes.[23−28] A paradigm shift toward the use of organic dye and first-row transition metal photocatalysts has provided an alternative to the use of unsustainable, toxic, and expensive Ru- and Ir-based photocatalysts.[29−31] Another recently trending concept in PRC completely obviates the need for an exogenous "photocatalyst" to harness visible photon energy as chemical energy. This approach leverages the photoactivity of a ground state assembly of an electron donor and an electron acceptor, referred to as an electron donor−acceptor (EDA) complex. While the electron donor (D) and acceptor (A) may be colorless on their own, their charge transfer interaction results in a bathochromic shift to afford a visible light absorbing colored species that, upon photoexcitation, affords reactive intermediates (radical anions and cations) via SET (Figure 2).[32−34] Although the substitution of photocatalysts by EDA

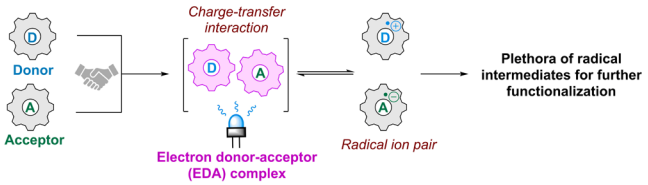


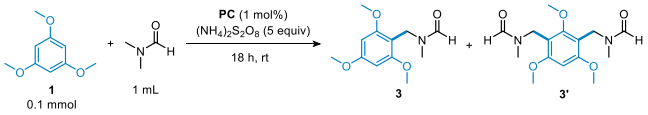
Figure 2. Formation of radical ion pairs via an EDA complex after complexation and photoexcitation.

complexes represents a "greener" solution for C−H functionalization, their prediction of occurrence and photophysical characterization is more challenging.[35] Moreover, their properties highly depend upon the individual components which restricts their substrate scope of applications. Herein, we disclose a photocatalyst-free visible-light-mediated aryl functionalization of amides via an EDA complex.

Our initial investigation focused on finding a nontoxic and cheap organophotocatalyst as an alternative to $Ru(bpy)_3Cl_2$ ($E_{1/2}{}^{*(II)/(III)}$ = −0.81 V vs SCE) in the photochemical Friedel−Crafts amidoalkylation reaction.[19] 1,3,5-Trimethoxybenzene (1,3,5-TMB) **1** was selected as an electron-rich arene and ammonium persulfate as an oxidant. Finding similar yields for several different organophotocatalysts screened prompted us to conduct a control reaction in the absence of any photocatalyst, which was just as efficient. This observation was surprising, since such a control reaction in the hands of Stephenson and co-workers gave <5% conversion. We hypothesized an EDA complex was responsible. We speculated that a combination of (i) our LEDs likely being higher power than those employed in "early" PRC papers and (ii) our reaction configuration placing reactors in closer proximity to the LEDs may have resulted in an overall greater radiant flux to the reaction to enable such reactivity. Although LED specifications were not available in that paper, other publications from the group around the same time period (2011−2012) suggested common use of a 1 W input power blue LED strip spread around a beaker at some (approximately a few centimeters) distance from the reaction (∼5 mL).[36−38] In contrast, each LED herein had an optical power of ∼0.85 W and reactions (1 mL) were placed directly atop of LEDs for the highest possible light penetration.

From entry 4 (Table 1) as a starting point, we began a detailed optimization study (see Supporting Information (SI)).

Table 1. Organophotocatalyst Screening and Control Reactions



Entry	Organophotocatalyst	^{1}H NMR conversion **1a** (%)	^{1}H NMR yield **3aa** (%)	^{1}H NMR yield **4aa** (%)
1	4CzIPN (441 nm)	95	47	3
2	Mes-Acr-BF_4^- (441 nm)	92	65	3
3	Eosin Y	83	58	3
4	**No PC (441 nm)**	**92**	**54**	**3**
5[a]	No PC (441 nm)	94	77	6
6[a]	No PC (dark)	77	39	1

[a]Reaction conditions: 0.135 M, $(NH_4)_2S_2O_8$ (5 equiv), 24 h.

Other oxidants were attempted but led to no reaction. Changes in oxidant loading either severely decreased yields (decomposition) or gave no reaction. Efforts to conduct reactions in other aprotic solvents with a lower excess of amide (15 equiv) did not achieve satisfactory yields, consistent with previous reports where amides were required in excess.[19,21,22] Anhydrous conditions were essential while strict degassing was not required. A Design of Experiments (see SI) approach varying overall concentration, temperature, and reaction time found that the optimum conditions affording the best compromise of monoadduct yield and monoadduct selectivity were 0.135 M **1** in DMF, 24 h, rt, and 5 equiv of persulfate, providing 77% (^{1}H NMR) of **3** with 12.8:1 (monoadduct/bisadduct) selectivity. When the optimal reaction conditions were tested in the dark, (i) **3**'s yield was halved, (ii) conversion was decreased, and (iii) the proportion of productive conversion was lower, indicating more decomposition.

With the optimized conditions in hand, the substrate scope was examined first with respect to arene partners (Scheme 1). Where some methoxyarene substrates and derivatives were not converted quantitatively, longer reaction times were examined to improve conversion and monoadduct yield. A number of electron-rich arenes underwent Friedel−Crafts amidoalkylation in moderate to high (24−84%) yields.

Formation of an EDA complex requires compatibility in the electronics and/or sterics of its electron-rich and its electron-poor partners.[35] Lower substrate conversions (and yields of **5** and **10**) were observed for 1,3-dimethoxybenzene and 1,2,3,5-tetramethoxybenzene than 1,3,5-TMB. Substrates such as 1,2,3-TMB and 1,2,4-TMB which have the same number of methoxy groups as **1** gave almost no reaction (see SI). The reaction of 1,4-dimethoxybenzene (1,4-DMB) also failed to proceed. This suggests a balance of electronics is required in forming the EDA complex. Interestingly, a substrate primed for intramolecular amidoalkylation en route to **7** resulted only in intermolecular amidoalkylation. Comparable product yields were obtained for the reactions of **1** with dimethylformamide (DMF), dimethylacetamide (DMA), and *N*-methyl-2-pyrrolidone (NMP). In products **8**, **9**, and **18**, *para*-methoxybenzylic positions were tolerated with no C(sp^3)−H functionalization on the anisole. An exocyclic five-membered amide afforded a

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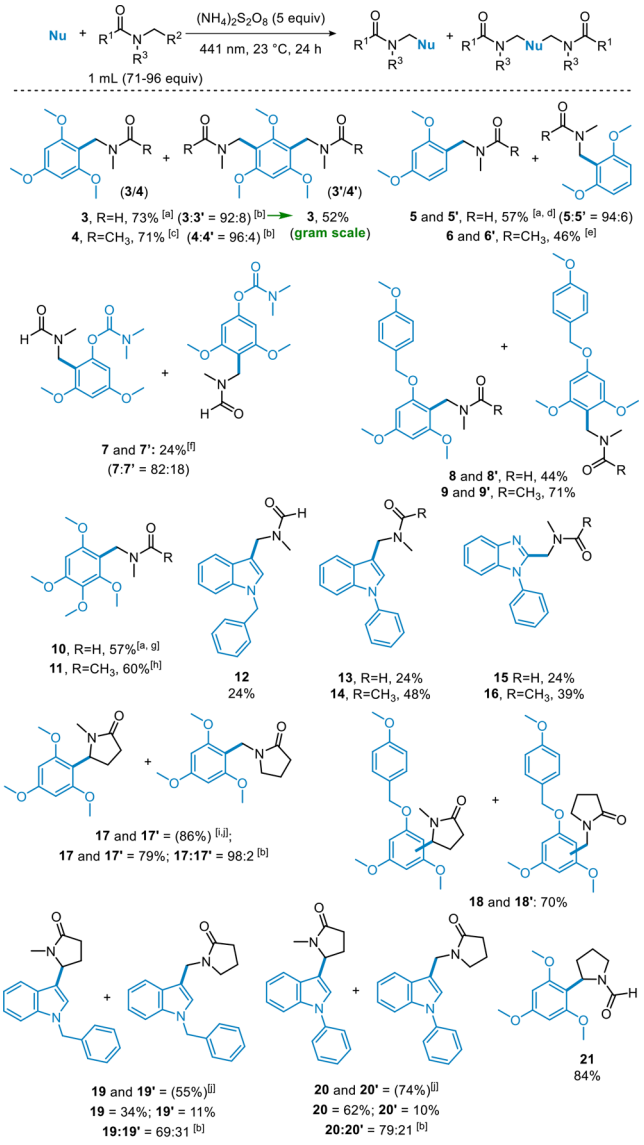
Scheme 1. Substrate Scope[a]



[a]: Reactions in dark (NMR yield): **3** = 37%, **5** = 25%, **10** = 3%, **12** = 7%, **13** = 5%; [b]: ratio calculated using NMR of crude product; Reaction time [c] = 22 h; Reaction time [d] = 79 h, [e] = 32 h, [f] = 50 h, [g] = 49 h, [h] = 45 h, [i] = 20 h. [j] combined NMR yield.

[a]Reactions in dark (NMR yield): **3** = 37%, **5** = 25%, **10** = 3%, **12** = 7%, **13** = 5%. [b]Ratio calculated using NMR of crude product. [c]Reaction time = 22 h. [d]79 h. [e]32 h. [f]50 h. [g]49 h. [h]45 h. [I]20 h. [j]Combined NMR yield.

high yield of **21**. Both *N*-alkyl and *N*-aryl indoles as well as *N*-phenylbenzimidazole were tolerated in moderate to good yields, with no C(sp^3)−H functionalization on the *N*-substituent. The nonrequirement of photocatalyst in this reaction indicated that the operating mechanism was different than initially proposed.[19]

Mulliken's charge transfer theory describes that the physical properties of a molecular assembly between an electron-rich and electron-poor partner are different in comparison to the separated starting materials.[33] The observation of color changes within minutes after mixing the colorless starting materials in solvent led us to hypothesize formation of an EDA complex. UV−vis studies of reaction mixtures of reactive substrates (Figure 3 and see SI) revealed the presence of charge-transfer bands ($h\nu_{CT}$) suggestive of their EDA

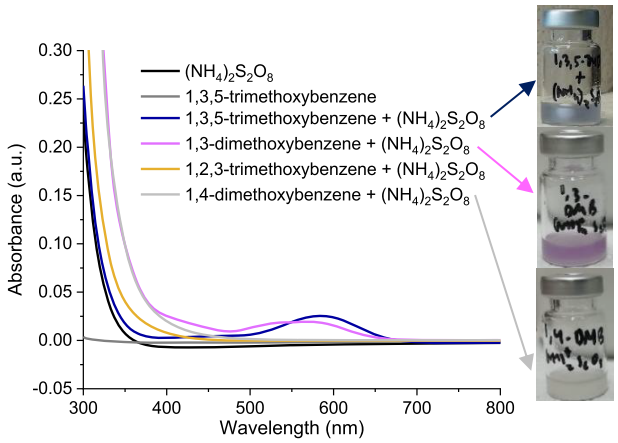


Figure 3. UV−vis spectra and pictures of the reaction mixtures of reactive vs unreactive arenes in DMF (times stated in the SI).

complexes. Consistent with their lack of reactivity, substrates 1,2,3-TMB and 1,4-DMB did not form EDA complexes. A complete absence of trend between product yield and arene oxidation potential revealed by cyclic voltammetry (see SI) confirmed that the thermodynamic driving force for initial SET oxidation was not important to the success of the reaction. The quantum yield of the reaction affording **3** was determined as $\Phi = 0.015 \pm 0.001$, supporting the necessity of extended reaction times (24 h) and evidencing against a radical chain mechanism that was previously suggested as a candidate[19] or is reported elsewhere in PRC reactions.[39]

DFT calculations investigated the kinetic and thermodynamic feasibility of HAT between DMF and the sulfate radical anion (see SI). The reaction profile was, overall, exergonic with an energy barrier of 12.2 kcal/mol. Reactions with a ≤ 20 kcal/mol energy barrier are reported to proceed spontaneously at rt.[40] The calculated bond dissociation enthalpy (BDE) of the H−O bond of the hydrogen sulfate anion was ca. 9 kcal/mol higher than the α-amido C(sp^3)−H bond of DMF, clearly indicating the exothermicity for the HAT step. Based on the previous literature,[19] UV−vis spectra, CV measurements, and DFT calculations, a mechanism is proposed in Scheme 2. An EDA complex [**1**-**I**] is formed between electron-rich donor **1** and the persulfate dianion (an acceptor at its electron-poor O−O bond) which absorbs blue light and is photoexcited to give [**1**-**I**]*. Inside a solvent cage of DMF (**II**), inner-cage SET from **1** to the persulfate dianion followed by O−O cleavage of the latter occurs to afford a sulfate radical anion and $\mathbf{1}^{\bullet+}$ still within the solvent cage (in **III**). The sulfate radical anion engages in HAT with the α-amido C(sp^3)−H bond of DMF to afford its α-amido radical. Inner-cage SET then occurs (in **IV**) to afford the putative *N*-acyliminium ion (in **V**), which is attacked by **1** to give **3**. The product **3** being less electron rich than the starting arene substrate due to the inductive effect of its amide moiety is less facile to SET oxidation, rationalizing monoadduct selectivity. The detrimental effect of H_2O could be due to hydrolysis of the *N*-acyliminium ion within **V** (see SI). The solvent cage mechanism is consistent with several observations: (1) The low quantum yield of <0.02 corroborates the inability of α-amido radicals to diffuse away from the solvent cage to become oxidized by another persulfate molecule (a radical chain mechanism). (2) The substrate en route to **7**/**7′** underwent reaction with DMF instead of its intramolecular arylation, despite the BDE of its α-amido

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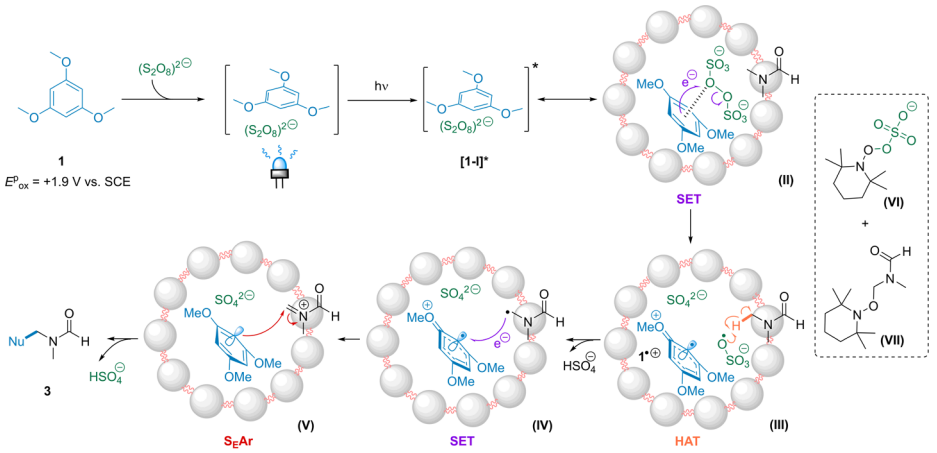
Scheme 2. Proposed Mechanism (Counterions Omitted for Clarity)



C(sp^3)−H bond of substrate being lower (84 kcal/mol) than that of DMF (92 kcal/mol) (see SI) and despite the known rapidity of 6-*endo*-*trig* radical cyclization. (3) Although the intermediacy of the α-amido radical and the sulfate radical anion were confirmed via detection of **VI** and **VII** (see SI) in a radical trapping experiment with TEMPO, 1.25 equiv of TEMPO did not inhibit the reaction at all and as high as 5.5 equiv did not fully inhibit the reaction (conversion = 68%, yield of **3** = 51%). Following EDA complex formation and photoexcitation, these observations strongly suggest that the subsequent steps of the mechanism occur in a confined space with a close proximity to the DMF partner.

In conclusion, we disclose a mild procedure for arene functionalization of amides in absence of an exogenous metal-based or organic photocatalyst. Mechanistic studies suggest the high importance of "preassembly" of the substrate, oxidant, and solvent on the success of the reaction. Further work is ongoing to establish the factors that dictate EDA complexation when certain arenes are similarly electron rich. We are excited by future implications of "preassembly" as an emerging control element in photochemistry and photocatalysis, as well as opportunities to use solvation, in addition to dispersion interactions,[41] hydrogen bonding,[42] and microheterogeneous solutions,[43] to exert control of photochemical outcomes through confined spaces.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00132.

Experimental procedures, characterization data of compounds, reaction optimization including Design of Experiments study, EPR, DFT, quantum yield and cyclic voltammetry mechanistic studies, scalability investigations in batch and flow (PDF)

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Notes

The authors declare no competing financial interest.

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