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Research Article

Photocatalysis in Aqueous Micellar Media Enables Divergent C−H Arylation and *N*-Dealkylation of Benzamides

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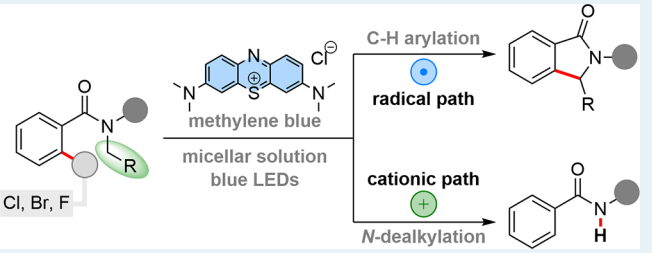
ABSTRACT: Photocatalysis in aqueous micellar media has recently opened wide avenues to activate strong carbon−halide bonds. So far, however, it has mainly explored strongly reducing conditions, restricting the available chemical space to radical or anionic reactivity. Here, we demonstrate a controllable, photocatalytic strategy that channels the reaction of chlorinated benzamides via either a radical or a cationic pathway, enabling a chemodivergent C−H arylation or *N*-dealkylation. The catalytic system operates under mild conditions with methylene blue as a photocatalyst and blue LEDs as the light source. Factors determining the reactivity of substrates, their selectivity, and preliminary mechanistic studies are presented.



KEYWORDS: *photocatalysis, divergence, micelles, aqueous solutions, aryl chlorides, benzamides, C−H arylation, dealkylation*

INTRODUCTION

The benzamide core is widespread in biologically relevant compounds, including antitumor agents,[1] antidepressants,[2] and recently inhibitors of SARS-CoV-2 replication,[3] which renders the functionalization of this structure a vibrant area of research.[4,5] While different strategies targeting the aromatic ring or the carbonyl group of benzamides are well developed,[6,7] the repertoire of methods for direct transformations at the *N*-unit remains limited (Scheme 1a, right).[8−12] To overcome this challenge, several indirect approaches have been investigated. They typically involve reductive activation of the aromatic carbon−halide bond at the position *ortho* to the carbonyl group, followed by intramolecular 1,5-hydrogen-atom transfer (1,5-HAT), giving access to reactive species at a position α to the *N*-atom (Scheme 1b).[13−18] Although they are highly efficient, these methods necessitate strongly reducing reagents or specific catalysts, thereby restricting the available chemical space to radical reactivity—particularly radical cyclization—and precluding the possibility of more general, divergent strategies.

Our previous reports,[19−22] as well as the work of others,[23−28] showed that photocatalysis in aqueous micellar media is an attractive tool for the activation of stable chemical bonds. It can improve the selectivity of processes and prolong the lifetimes of highly energetic intermediates by preorganizing the components in the reaction mixture. Additionally, it provides a high hydration energy of the released ions, thus enhancing the thermodynamic driving force of the process. We hypothesized that these unique features should facilitate the reductive cleavage of C(sp^2)−Cl bonds and, after 1,5-HAT, lead to radicals at *N*-alkyl units. Moreover, thanks to the mild reaction conditions, subsequent oxidation to cations via radical−polar crossover should become feasible. Consequently, the scope of possible transformations of benzamide derivatives could be extended to cationic processes that are important from the viewpoint of a late-stage modification—a prime example of which is the *N*-dealkylation reaction (Scheme 1a, left). This thermodynamically challenging transformation is mediated in Nature by cytochrome P450,[29−31] but chemical methods are scarce and are very limited in scope.[32−34]

This article presents a controllable, photocatalytic strategy that allows channeling the reaction of *o*-chlorobenzamides in two different directions: either C−H arylation or *N*-dealkylation (Scheme 1c). The developed reactions proceed with the intermediacy of *N*-acyliminium radicals or cations, which serve as precursors of highly valuable products: isoindolinones or secondary amides.[35,36] The experimental conditions are exceptionally mild and involve aqueous micellar solutions as the reaction environment, methylene blue as a photocatalyst, and amines as electron donors.

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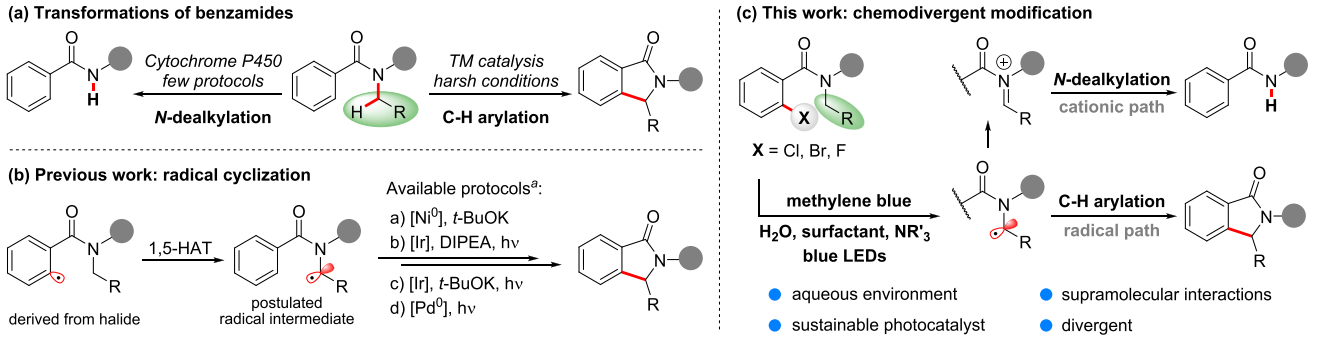
Scheme 1. Strategies for Modification of Benzamide Derivatives



[a]According to ref.[14,16−18]

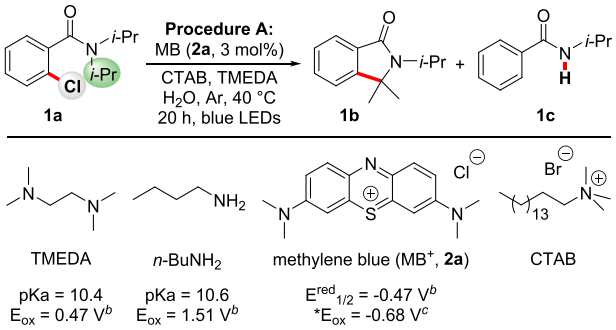
RESULTS AND DISCUSSION

We began our study by exploring the reactivity of 2-chloro-*N*,*N*-diisopropylbenzamide (**1a**) toward the intended intramolecular C−H arylation in aqueous solutions. To this end, we carried out extensive optimization of the reaction conditions with respect to the photocatalyst, surfactant, amine, additives, and the ratio and concentration of reagents, ultimately obtaining the desired product **1b** in 89% yield (see the Supporting Information). Cheap, readily available, and environmentally benign methylene blue (MB, **2a**) was selected as the photocatalyst of choice. The developed method (procedure A) also required tetramethylethylenediamine (TMEDA), cetrimonium bromide (CTAB), and water. We observed the complete solubility of all reaction components at 40 °C and found that 20 h of irradiation with blue LEDs provides an optimal conversion for most substrates. Nevertheless, some of the reagents, e.g., model substrate **1a**, gave 89% of product **1b** after only 5 h (for detailed kinetic studies, see the Supporting Information). Satisfyingly, we also identified compound **1c**, in which one of the *N*-alkyl substituents was removed, as the major side product.

Control experiments have shown that a photocatalyst is necessary for the reaction to occur. They also proved the superiority of MB (**2a**) over other typical catalysts such as $[Ir(ppy)_2(dtbbpy)]PF_6$ (**3**), 4-CzIPN (**4**), and the strongly reducing 10-phenylphenothiazine (PTH; **5**) (Table 1, entries 1−3). Despite the fact that MB (**2a**) displays only weak absorption at 450−500 nm, blue light is necessary, and it cannot be replaced with other visible-light colors (entry 4). In terms of surfactants, zwitterionic SB3-14, which bears a quaternary ammonium group, can be used instead of cationic CTAB without compromising the reaction efficiency (entry 6). Neutral surfactants such as Triton X-100 and the state of the art, tocopherol-based surfactant TPGS-750-M are competent as well and afford product **1b** in 84% and 47% yields, respectively (entries 7 and 8). However, using the anionic sodium dodecyl laurate (SDS) under otherwise unaltered conditions offers only a slight advantage over the reaction carried out in neat water or DMF (entries 5, 9, and 10). We did not observe any desired reaction in the presence of radical trapping agents, including 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO), suggesting the involvement of radical intermediates in the reaction mechanism (entry 11).

We then employed these newly developed conditions in the intramolecular C−H arylation of a series of *o*-chlorinated benzamides **1a** and **6a−21a** (Table 2). In general, starting materials **1a** and **6a−8a** having two identical substituents on

Table 1. Control Experiments[a]



entry	variation from standard conditions	yield of **1b** (%)	yield of **1c** (%)
1	none	89	4
2	no photocatalyst	0	0
3	$[Ir(ppy)_2(dtbbpy)]PF_6$ (**3**), 4-CzIPN (**4**) or PTH (**5**) instead of MB (**2a**)	traces	0
4	no light or green or red LEDs	traces	0
5	no surfactant	31	6
6	SB3-14 instead of CTAB	90	4
7	Triton X-100 instead of CTAB	84	4
8	TPGS-750-M instead of CTAB	47	3
9	SDS instead of CTAB	36	7
10	DMF instead of micellar solution	33	1
11	addition of TEMPO[c]	traces	0
12	no electron donor	0	0
13	*n*-$BuNH_2$, DIPA instead of TMEDA	32−45	37

[a]Standard reaction conditions: substrate **1a** (0.2 mmol, 100 mM), methylene blue (MB, **2a**; 3 mol %), CTAB (0.3 mmol, 150 mM), TMEDA (0.6 mmol, 300 mM), water (2 mL), 40 °C, 451 nm, 20 h. Yields were calculated using GC analysis. *n*-Dodecane was used as an internal standard. [b]According to ref 37 vs SCE. [c]3 equiv of TEMPO was added.

the nitrogen atom provided the highest yields of the desired isoindolinones **1b** and **6b−8b**, exceeding 80%. We observed a marked preference for the functionalization of tertiary C−H bonds: e.g., substrate **9a** bearing isobutyl groups yielded 45% of product **9b**, while the analogous **8a** with *s*-butyl substituents gave compound **8b** in 2-fold higher yield. In the cases of two different substituents on the *N*-atom (**10a−14a**), the reaction only occurred at the tertiary carbon center, even when an alternative benzyl position was available (product **12b**). We found that *ortho*-brominated substrates could replace the chlorides without significantly affecting the results.

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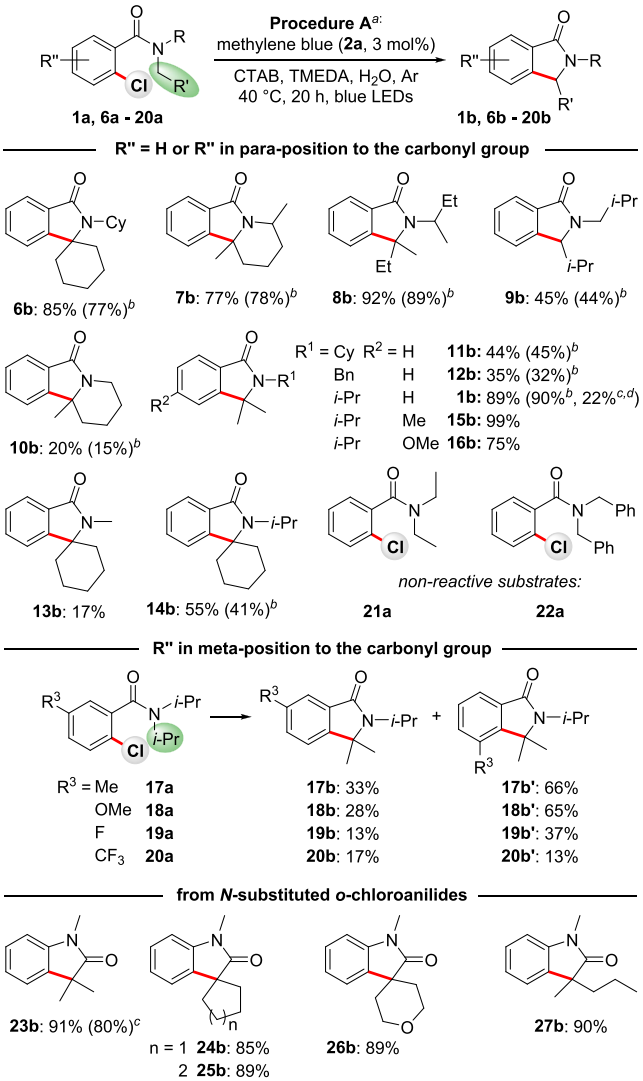
Table 2. Scope of Intramolecular C−H Arylation of *o*-Chlorobenzamides[a]



[a]Reaction conditions unless specified otherwise: substrate (0.2 mmol, 100 mM), methylene blue (**2a**, 3 mol %), CTAB (0.3 mmol, 150 mM), TMEDA (0.6 mmol, 300 mM), water (2 mL), 40 °C, 451 nm, 20 h. Average isolated yields obtained from two separate reactions are given. [b]Bromide used as a substrate. [c]Fluoride used as a substrate. [d]10 mol % of methylene blue (**2a**) was used instead of 3 mol %.

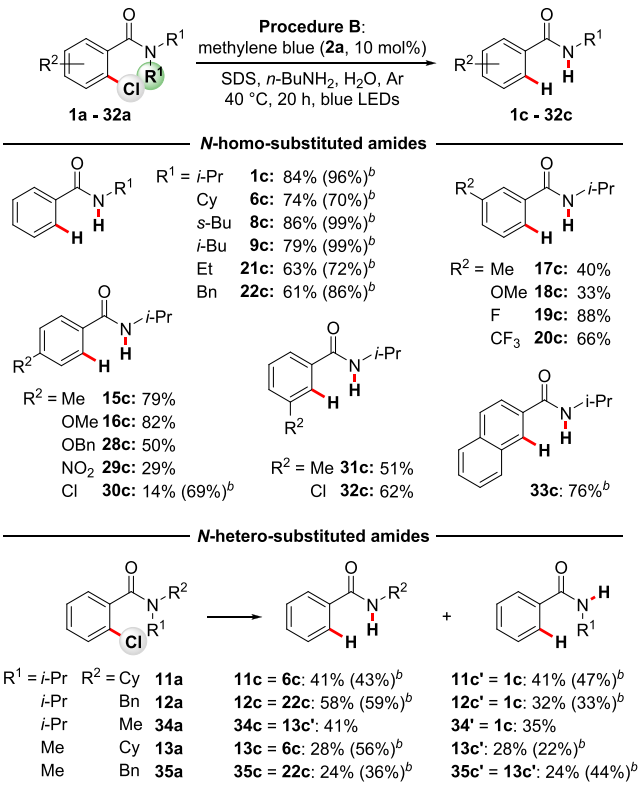
The reactivity of the starting materials strongly depends on the electron density at the phenyl ring. While *o*-chlorobenzamides **19a** and **20a** possessing electron-withdrawing substituents (including halides) reacted slowly, the presence of electron-donating groups facilitated the desired process. Interestingly, this is in contrast to the reduction potentials of these compounds (see the Supporting Information) and suggests that single-electron reduction is either not involved in the C−Cl activation or, at least, that it is not a rate-limiting step. The distribution of products obtained from substrates **17a**−**19a** showed that cyclization at the carbon atom closer to the substituent is preferred. The exception was the electron-deficient substrate **20a**, for which both isomeric products were obtained in similar amounts.

Gratifyingly, as with the modification of benzamides, Procedure A also works for the α-arylation of *N*-substituted anilides **23a**−**27a**.[18,38] The reaction proceeded smoothly and provided the series of oxindoles **23b**−**27b** in 85−90% yields. Pleasingly, the developed system proved competent for the transformation of *o*-fluorinated anilide, which gave oxindole **23b** in 80% yield.

Although the presence of a sacrificial electron donor in the reaction mixture is indispensable (Table 1, entry 12), the conversion of substrate **1a** also remains high when primary or secondary amines are used instead of tertiary TMEDA. In these cases, however, the proportion of dealkylation product **1c** increases dramatically (entry 13). We found such a change in selectivity intriguing, as all of the amines mentioned above display similar pK_a values and, apart from the number of N−H protons, differ mainly in redox properties.

We took a closer look at the *N*-dealkylation reaction and carried out separate optimization studies. They allowed alteration of the reaction course, so that the *N*-dealkylation product now became the predominant one. In comparison to Procedure A, the developed conditions (dubbed Procedure B) involve slightly different reagent ratios, an anionic instead of a cationic surfactant (SDS instead of CTAB), and *n*-BuNH_2 in place of TMEDA (for full optimization see the Supporting Information). Subsequently, we examined the scope of various tertiary benzamides bearing two identical or two different alkyl substituents at the nitrogen atom (Table 3). In the latter case (substrates **11a**−**13a**, **34a**, and **35a**) we always obtained a mixture of two possible *N*-dealkylation products. However, unlike the case for the cyclization approach, we did not observe

Table 3. Scope of *N*-Dealkylation of *o*-Chlorobenzamides[a]



[a]Reaction conditions unless specified otherwise: substrate (0.1 mmol, 20 mM), methylene blue (**2a**, 10 mol %), SDS (0.25 mmol, 50 mM), *n*-BuNH_2 (0.6 mmol, 60 mM), water (5 mL), 40 °C, 451 nm, 20 h. Average isolated yields obtained from two separate reactions are given. [b]Bromide used as a substrate.

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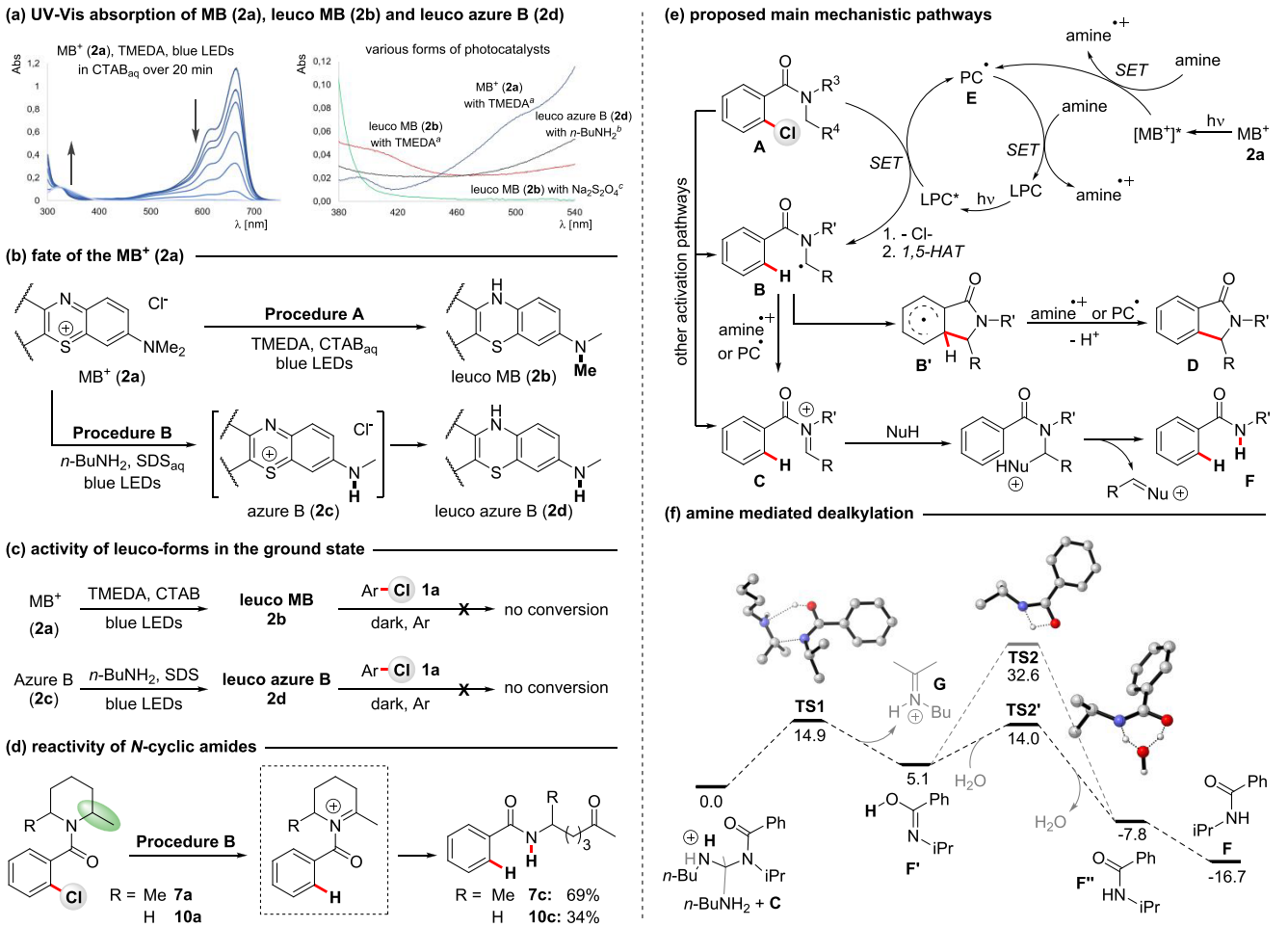

Figure 1. Mechanistic studies. (a, left) Time-dependent UV−vis spectra of MB^+ (**2a**, 0.015 mM) in a CTAB solution of TMEDA (1.5 mM) upon irradiation (455 nm) over 20 min. (a, right) UV−vis spectra of MB^+ (**2a**), leuco MB (**2b**), and leuco azure B (**2d**). Forms **2b** and **2d** were generated upon irradiation (455 nm) over 10 min. Legend: (*a*) in the presence of TMEDA (1.5 mM) in $CTAB_{aq}$ (50 mM); (*b*) in the presence of *n*-$BuNH_2$ (1.5 mM) in SDS_{aq} (50 mM); (*c*) in the presence of $Na_2S_2O_4$ (1.5 mM) in $CTAB_{aq}$ (50 mM). (b) Transformations of methylene blue (**2a**) in the presence of amines. (c) Substrate **1a** treated with leuco-form **2b** or **2d** in darkness. (d) Reactions of *N*-cyclic benzamides **7a** and **10a**. (e) Proposed mechanism. PC denotes the photocatalyst: methylene blue (**2a**) or azure B (**2c**). LPC denotes leuco-form **2b** or **2d** interacting with an amine. (f) Computed pathway of the dealkylation mechanism of **C** mediated by the presence of *n*-$BuNH_2$. All energies reported are Gibbs free energies (in kcal mol^{-1}) obtained at the PW6B95-D3BJ/def2-QZVP//r^2SCAN-3c level of theory.

a consistent preference for the reaction to occur at tertiary *N*-substituents over secondary and methyl groups. *N,N*-Diethylamide **21a** and *N,N*-dibenzylamide **22a**, both of which were inert under the conditions of Procedure A, provided the desired dealkylation products **21c** and **22c** in satisfactory 63% and 61% yields, respectively. The bromides were more reactive than the chlorides, although the observed differences in yields were moderate, ranging from 10 to 20%.

Another major difference with respect to the C−H arylation protocol was the influence of substituents at the phenyl ring. In the case of Procedure B, the presence of electron-donating groups hampered the reactivity. Electron-withdrawing substituents such as a fluorine atom in compound **19a** were neutral and allowed for product **19c** in 88% yield, similarly to the unsubstituted model substrate **1a**. While the highest effect was observed for substituents at positions *ortho* and *para* to the chlorine atom, the impact of *meta* substituents was negligible (compare products **16c** and **18c**, 82% vs 33% or **15c**, **17c**, and **31c**, 79% vs 40% vs 51%). The relatively low yields obtained from substrates **29a** and **30a** were due to numerous side reactions rather than low reactivity.

After establishing the synthetic capabilities of Procedures A and B, we turned our attention to mechanistic investigations, seeking to explain two key aspects of each method: the nature of C−Cl activation and the source of chemoselectivity toward cyclization or dealkylation (Figure 1). Dynamic light scattering (DLS) proved the presence of micelles in the reaction mixtures, with the hydrodynamic radius changing upon the addition of reacting compounds, which indicated the partial incorporation of substrate **1a** and amines inside the hydrophobic core. Cyclic voltammetry (CV) measurements showed that the reduction of halogenated benzamides is facilitated in the micellar system in comparison to a benchmark solution in MeCN (see the Supporting Information). The cathodic peak potential of substrate **1a** in an aqueous solution of CTAB is $E_{pc1} = -2.28$ vs SCE, which is more than 0.4 V less negative than that in MeCN. Nevertheless, the obtained values significantly exceed the reducing capability of methylene blue (**2a**), in either the ground ($E^{red}_{1/2}(MB^+/MB) = -0.47$ V vs SCE) or excited state ($^*E_{ox} = -0.68$ V vs SCE).[37,39] These observations exclude a classical, one-photon variant of PET for the reductive activation of chlorides. With the aid of additional

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synthetic and analytical experiments, we could also rule out other pathways such as single-electron oxidation within the amide group, hydrogen-atom abstraction, or the formation of solvent-caged[40] electron donor−acceptor (EDA) complexes between the substrates and photocatalyst or amine (see the Supporting Information for details).

A Stern−Volmer experiment showed that fluorescence quenching is triggered only by the addition of amines, not by that of substrates. This was observed upon excitation with blue light or red light, which implies the formation of amine radical cations under both irradiation regimes. These species are known to undergo deprotonation, producing aminoalkyl radicals, which readily participate in halogen-atom-transfer (XAT) processes.[41,42] Our control experiments, however, showed no red-light-induced conversion of chlorinated substrates, thus allowing us to exclude the XAT mechanism.

To better understand the fate of the catalyst **2a**, we performed time-dependent UV−vis measurements in which the solution of the photocatalyst and amine was irradiated with blue light and the absorbance was measured at 2 min intervals (Figure 1a, left). Despite the fact that UV−vis spectra show only weak absorption in the blue region, efficient quenching of the catalyst **2a** by TMEDA occurs. The resulting spectrum is in perfect agreement with the literature data of leuco-methylene blue (**2b**),[43] showing that a stepwise, two-electron reduction of photocatalyst **2a** has occurred. *n*-$BuNH_2$ was also proved to be a suitable quencher, although in this case, an irreversible demethylation occurred concomitantly with the reduction, yielding ultimately the leuco-form of azure B (**2d**) (Figure 1b). Importantly, neither of the leuco-forms **2b** and **2d** react with the model substrate **1a** in darkness, indicating that a single-electron transfer (SET) from ground states does not occur (Figure 1c). It is known, however, that leuco-MB (**2b**) can undergo consecutive excitation, producing strongly reducing triplet-state species.[43,44] Therefore, we studied the spectroscopic properties of leuco-forms **2b** and **2d** generated *in situ* in the micellar solutions. When they are prepared by the reduction of MB^+ (**2a**) and azure B (**2c**) with sodium dithionite, these species display no absorption in the visible range (Figure 1a, right, and the Supporting Information). Detectable absorption in the blue region appears, however, when amines are used as sacrificial reducing agents. Overall, these results indicate the major activation pathway, which involves the interaction of photocatalysts in their leuco-forms **2b** and **2d** with amines followed by excitation and SET to chlorinated substrates. Additionally, the contribution of light-independent processes should also be considered, as indicated by the steady increase of yield in a light ON/OFF experiment (see the Supporting Information).

Ultimately, we turned our attention to the chemoselectivity of our strategy. We hypothesized the presence of cationic intermediates favoring the dealkylation pathway, in line with existing reports on the *N*-dealkylation of amides,[29,33,34] which postulate the attack of water on the cation followed by the cleavage of the respective hemiaminal. To further validate the cationic route for the *N*-dealkylation, we subjected derivatives of cyclic amines **7a** and **10a** to the conditions of Procedure B and observed ring opening to the respective ketones **7c** and **10c**, with the insertion of oxygen atom taking place at the more substituted carbon atom (Figure 1d). In addition to reinforcing our hypothesis, this reaction may also be of interest as a method for the synthesis of protected aminoketones.

On the basis of the aforementioned considerations, we propose a mechanism for the developed C−H arylation and *N*-dealkylation reactions (Figure 1e). Photocatalyst **2a** is first converted to leuco-form **2b** or **2d** (LPC) with the concomitant formation of an amine radical cation that can be further stabilized by a negatively charged interface. A subsequent interaction of the photocatalyst with an amine and consecutive excitation generates LPC* (approximated $^*E_{ox}$ = −2.22 V vs SCE; see the Supporting Information) that transfers a single electron to substrate **A**.[45,46] The driving force for this process is further increased by irreversible fragmentation of the C−Cl bond, dissociation of a chlorine anion, and its hydration in the aqueous phase.[47] Radical **B**, formed upon 1,5-HAT, can easily cyclize, forming radical **B′**. The reaction is extremely favored ($\Delta G^{\ddagger}$ = 13.4 kcal mol^{-1} and ΔG = −3.5 kcal mol^{-1} at the PW6B95-D3BJ/def2-QZVP//r^2SCAN-3c level of theory) in comparison to alternative mechanisms (see the Supporting Information). Finally, oxidation and deprotonation restore the aromaticity and yield the C−H arylation product **D**.[48,49] A competitive mechanism involves oxidation of **B** to the *N*-acyliminium cation **C** by the neutral form of the photocatalyst **E** or by an amine radical cation. Intermediate **C** is subsequently hydrolyzed, leading to the dealkylated product **F**. In this case, the substrates **17a**−**20a** differing in the substituents at the aromatic ring show an opposite reactivity trend in comparison to the cyclization reaction. The electron-withdrawing groups activate the aryl chloride, and since there is no need for subsequent oxidative rearomatization, they make the overall process more efficient. The choice of amine dictates which of the two paths—inter- or intramolecular—the reaction takes. We also hypothesize that the nature of the amine affects the outcome of the interaction with the cationic species **C** (Figure 1f). In particular, after the attack of *n*-$BuNH_2$ on **C**, which proceeds without kinetic barriers, the ensuing adduct can break with low activation barriers (via **TS1** in Figure 1f, $\Delta G^{\ddagger}$ = 14.9 kcal mol^{-1}), affording the imidic acid **F′** and the iminium cation **G**. This process involves the transfer of one of the protons of the amine to the C═O group of the amide and consequently necessitates a nucleophile with acidic protons, e.g. *n*-$BuNH_2$ or water, to proceed. On the other hand, the characteristics of the micellar environment possibly limit the interaction of **C** with water, rendering the amine as the nucleophile with a higher probability to trap the cation. This reaction is slightly endergonic (ΔG = 5.1 kcal mol^{-1}); however, the formation of the amide (initially **F″** in its *trans* form and finally **F** in the more stable *cis* form) drives the thermodynamics of the transformation. While the imidic acid−amide isomerization is predicted to proceed intramolecularly with relatively high barriers (**TS2**), the presence of a protic molecule (via the transition state **TS2′**) lowers the activation barrier by 18.6 kcal mol^{-1}.

CONCLUSIONS

In summary, we developed a highly controllable micellar array in which successful photocatalysis in water leads to chemodivergent functionalization of benzamide derivatives on the *N*-alkyl unit. In contrast to existing methods, which rely only on the nucleophilic reactivity of α-amino radicals, our transformation allows us to selectively generate either *N*-acyliminium radicals or the highly electrophilic *N*-acyliminium cation as the key intermediates, depending on the reaction conditions. Due to this feature, the process can be selectively guided toward either intramolecular C−H arylation or *N*-

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dealkylation by a simple adjustment of the reaction parameters. The system operates under exceptionally mild and operationally simple conditions with methylene blue as a photocatalyst and water as a solvent.

The decisive role of the amine on the final product formation and the change in the photocatalyst structure at the early stages of the reaction demonstrate how complex the interplay between the components of the aqueous reaction mixtures can be. We believe this work is a crucial step toward employing such subtle interdependences to guide the selectivity of the catalytic processes that are closely related from a mechanistic point of view.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c00468.

Experimental procedures, optimization details, and mechanistic studies and also ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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