Micellar photocatalysis enables divergent C-H arylation and *N*-dealkylation of benzamides via *N*-acyliminium cations

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Abstract

Micellar photocatalysis has recently opened new 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 radical-polar crossover process involving cationic intermediates, which enables chemodivergent modification of chlorinated benzamide derivatives *via* either C-H arylation or *N*-dealkylation. The catalytic system operates under mild conditions employing methylene blue as a photocatalyst and blue LEDs as the light source. Factors determining the reactivity of substrates and preliminary mechanistic studies are presented.

Introduction

The benzamide core is widespread in biologically relevant compounds, including anti-tumor agents,[1] antidepressants,[2] or recently inhibitors of SARS-CoV-2 replication,[3] which renders functionalisation 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 (Fig. 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 *o*-position to the carbonyl group, followed by intramolecular 1,5-hydrogen-atom transfer (1,5-HAT), giving access to reactive species at α–position to *N*-atom (Fig 1b).[13–18] Although highly efficient, these methods necessitate strongly reducing reagents or specific catalysts, thereby restricting the available chemical space to radical reactivity - particularly radical cyclisation - and precluding the possibility of more general, divergent strategies.

Our previous reports,[19–22] as well as the work of others,[23–27] showed that micellar photocatalysis is an attractive tool for the activation of stable chemical bonds under mild reaction conditions. It can improve selectivity of processes and prolong the lifetimes of highly energetic intermediates by pre-organizing the components in the reaction mixture. Additionally, it provides high hydration energy of the released ions, thus enhancing the thermodynamic driving force of the process. We hypothesised that these unique features should facilitate the formation of radicals at *N*-alkyl units and also enable their subsequent oxidation to cations *via* radical-polar crossover. Consequently, the scope of possible transformations of benzamide derivatives could be extended to cationic processes that are important from the viewpoint of the late-stage modification – a prime example of which is the *N*-dealkylation reaction (Fig. 1a left). This thermodynamically challenging transformation is mediated in nature by Cytochrome P450[28–30] but chemical methods are scarce and very limited in scope.[31–33]

In this article, we present highly controllable, photocatalytic strategy for divergent modifications of *o*-chlorobenzamides via either C-H arylation or *N*-dealkylation (Fig. 1c). The developed reactions proceed with the intermediacy of *N*-acyliminium cations, which serve as precursors of highly valuable products: isoindolinones or secondary amides.[34,35] The experimental conditions are exceptionally mild and involve aqueous micellar solutions as the reaction environment and methylene blue as a photocatalyst.

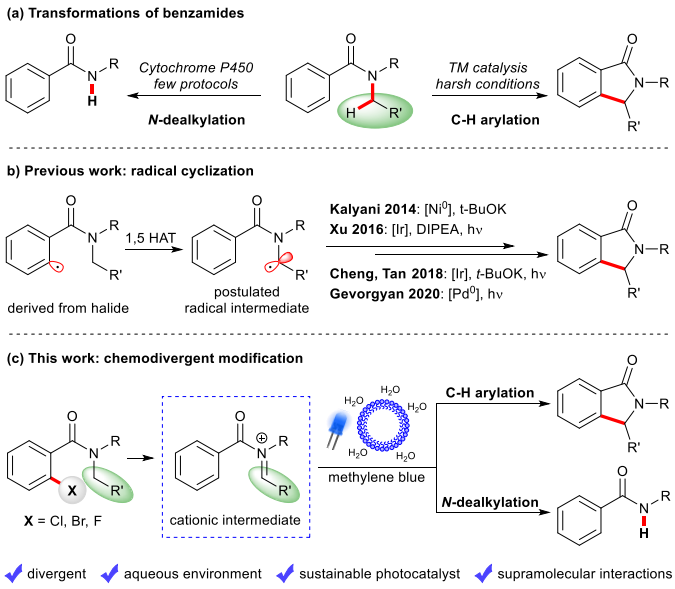


Fig. 1 Strategies for modification of benzamide derivatives.

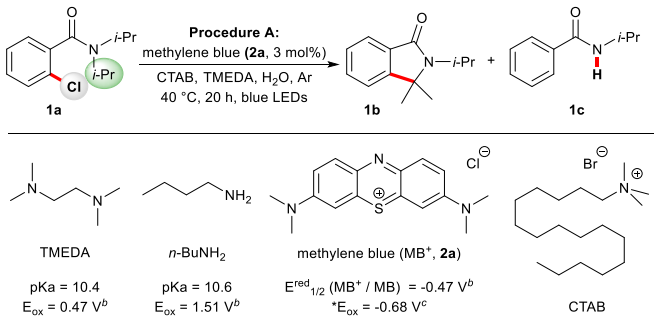
Results and Discussion

We began our study with exploring the reactivity of 2-chloro-*N*,*N*-diisopropylbenzamide (**1a**) towards 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, the ratio and concentration of reagents, ultimately obtaining the desired product **1b** in 89% yield (see SI). Cheap, readily available and environmentally bening 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 complete solubility of all reaction components at 40 °C and found that 20 hours of irradiation with blue LEDs provide optimal conversion for most substrates. Nevertheless, some of the reagents, e.g., model substrate **1a**, gave 89% of product **1b** after only five hours (for detailed kinetic studies, see SI). 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 as $[Ir(ppy)_2(dtbbpy)]PF_6$ (**3**), 4-CzIPN (**4**), or 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 colours (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 or state-of-the-art, tocopherol-

based surfactant TPGS-750-M are competent as well and afford product **1b** in 84% and 47% yield, respectively (entries 7, 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, 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).

Table 1 Control experiments[a]



No.	Variation from standard conditions	Yield **1b**%	Yield **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

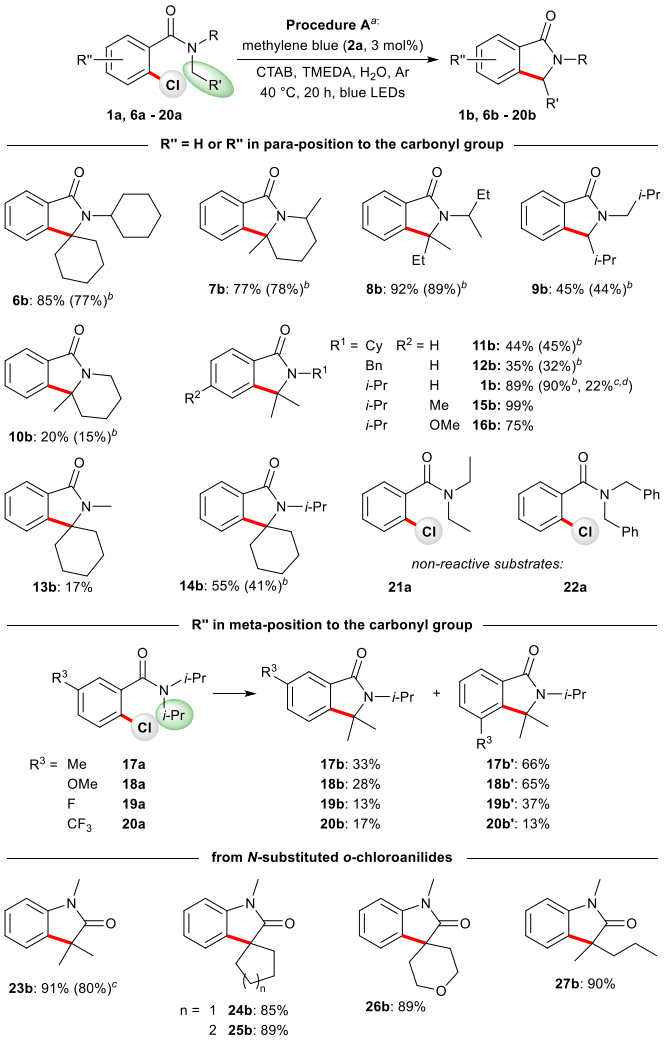
[a] Conditions: substrate **1a** (0.2 mmol, 100 mM), methylene blue (MB, **2a**, 3 mol%), CTAB (0.3 mmol, 150 mM), TMEDA (0.6 mmol, 300 mM), water (2 mL), 40 °C, 451 nm, 20 h. Yields calculated using GC analysis. *n*-Dodecane was used as internal standard. [b] according to ref[36] vs. SCE. [c] 3 equiv of TEMPO were added.

We then employed these newly developed conditions in the intramolecular C-H arylation of a series of *o*-chlorinated benzamides **1a, 6a – 21a** (Table 2). In general, starting materials **1a**, **6a – 8a** having two identical substituents on the nitrogen atom provided the highest yields of the desired isoindolinones **1b**, **6b – 8b**, exceeding 80%. We observed a marked preference for the functionalisation of tertiary C-H bonds, e.g. substrate **9a** bearing *i*-butyl groups yielded 45% of product **9b**, while the analogous **8a** with *s*-butyl substituents gave compound **8b** in two-fold higher yield. In cases of two different substituents on the *N*-atom (**10a – 14a**), the reaction only occurred at the tertiary carbon centre, even when an alternative benzyl position was available (product **12b**). We found that *o*-brominated substrates could replace the chlorides without significantly affecting the results.

The reactivity of the starting materials strongly depends on the electron density at the phenyl ring. While *o*-chlorobenzamides **19a**, **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 SI) 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 the cyclisation 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 a similar amount.

Gratifyingly, as with the modification of benzamides, Procedure A also works for the α-arylation of *N*-substituted anilides **23a** – **27a**.[18,37] The reaction proceeded smoothly and provided a 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.

Table 2 Scope of intramolecular C-H arylation of *o*-chlorobenzamides [a]

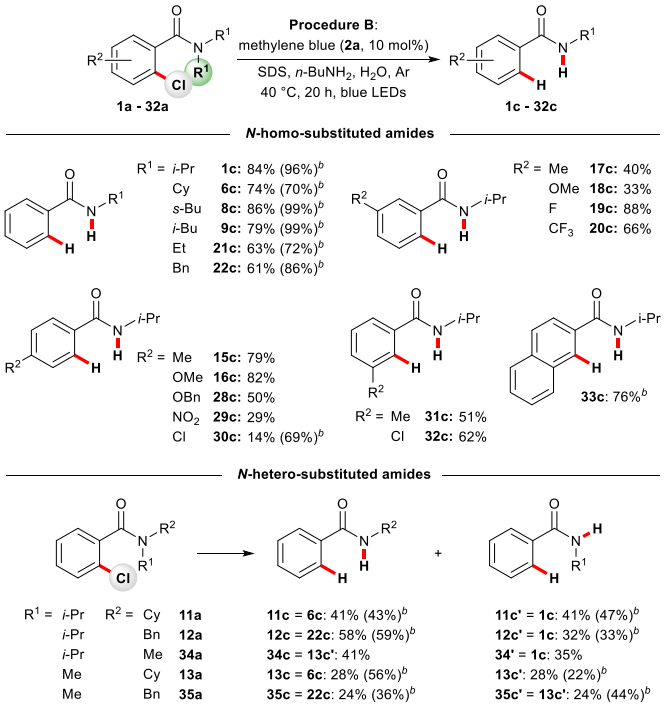


[a] Reaction conditions: substrate (0.2 mmol, 100 mM), methylene blue (**2a**, 3 mol%), CTAB (0.3 mmol, 150 mM), TMEDA (0.6 mmol, 300 mM), water (2 mL), 40 °C, 451 nm, 20 h. Average isolated yield obtained from two separate reactions are given. [b] Bromide used as a substrate. [c] Fluoride used as a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

Although the presence of the sacrificial electron donor in the reaction mixture is indispensable (Table 1, entry 12), the conversion of substrate **1a** remains high also 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 the amines mentioned above display similar pK_a 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 to alter the reaction course, so that the *N*-dealkylation product now became the predominant one. Compared 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 SI). 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**, **35a**) we always obtained a mixture of two possible *N*-dealkylation products. However, unlike in the cyclisation approach, we did not observe 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. The bromides were more reactive than the chlorides, although the observed differences in yields were moderate, ranging from 10-20%.

Table 3 Scope of *N*-dealkylation of *o*-chlorobenzamides [a]



[a] Reaction conditions: 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 yield obtained from two separate reactions are given. [b] Bromide used as a substrate.

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 fluorine atom in compound **19a** were neutral and allowed for product **19c** in 88%, similarly to the unsubstituted model substrate **1a**. While the highest effect was observed for substituents at *o*- and *p*-position to the chlorine atom, the impact of *m*-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 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 towards cyclisation or dealkylation (Fig. 2). 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 compared to a benchmark solution in MeCN (see SI). The cathodic peak potential of substrate **1a** in the aqueous solution of CTAB is E_{pc1} = -2,28 vs. SCE, which is more than 0.4 V less negative than in MeCN. Nevertheless, the obtained values significantly exceed the reducing capability of methylene blue (**2a**), either in the ground ($E^{red}_{1/2}(MB^+/MB)$ = -0.47 V vs. SCE) or excited state ($^*E_{ox}$ = -0.68 V vs. SCE).[36,38] These observations exclude a classical, one-photon variant of PET for the reductive activation of chlorides. With the aid of additional synthetic and analytical experiments, we could also rule out other pathways such as single electron oxidation within the amide group, hydrogen-atom abstraction, or formation of solvent-caged[39] electron donor-acceptor (EDA) complexes (see SI for details).

Stern-Volmer experiment showed that fluorescence quenching is triggered only by the addition of amines, and not by substrates. It 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.[40,41] 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 in 2 min. intervals (Fig. 2a, left). Despite the fact that UV-Vis spectra show only weak absorption at 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**),[42] showing that a stepwise, two-electron reduction of photocatalyst **2a** has occurred. *n*-$BuNH_2$ has also proved a suitable quencher, although in this case, the irreversible demethylation occurred concomitantly to the reduction, yielding ultimately the leuco-form of the azure B (**2d**) (Fig 2b). Importantly, neither of the leuco-forms **2b** and **2d** react with the model substrate **1a** in the darkness, indicating that single electron-transfer (SET) from ground states does not occur (Fig. 2c). It is known, however, that leuco MB (**2b**) can undergo consecutive excitation producing strongly reducing triplet-state species.[42,43] Therefore, we studied the spectroscopic properties of leuco-forms **2b** and **2d** generated *in-situ* in the micellar solutions. Indeed, both of them display detectable absorption in the blue region, similar to the native MB^+ (**2a**) (Fig. 2a right). Overall, these results advocate for SET from the excited leuco-forms **2b**

or **2d** to chlorinated substrates as the major activation pathway. Additionally, a contribution of light-independent processes should also be considered, as indicated by the steady increase of yield in the light ON/OFF experiment (see SI).

Ultimately, we turned our attention to the chemoselectivity of our strategy. The high reactivity of electron-rich substrates in the intramolecular cyclisation (Table 2) indicates the intermediacy of cationic species. Such interpretation is also in line with existing reports on the Friedel-Crafts amidoalkylation[44] and *N*-dealkylation of amides,[28,32,33] which postulate the attack of water on the intermediate cation followed by the cleavage of the respective hemiaminal. To further validate the cationic pathway, 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 (Fig. 2d). In addition to reinforcing our hypothesis, this reaction may also be of interest as a method for the synthesis of protected aminoketones.

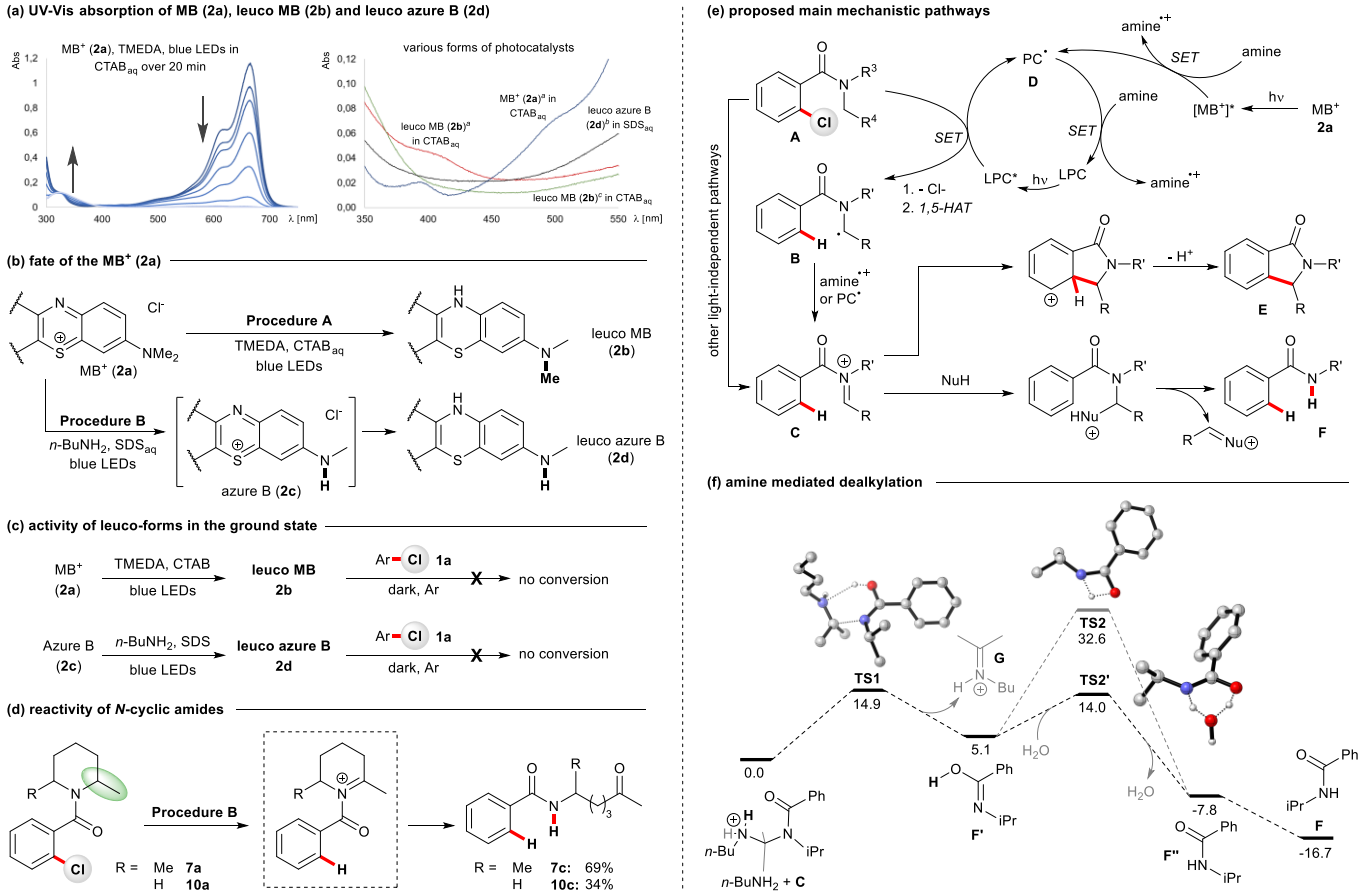


Fig. 2 Mechanistic studies: (a) Left: time-dependent UV-Vis of MB⁺ (**2a**, 0.015 mM) in CTAB solution of TMEDA (1.5 mM) upon irradiation (455 nm) over 20 min. Right: UV–Vis spectra of MB⁺ **(2a)**, leuco MB (**2b**) and leuco azure B (**2d**). Forms **2b** and **2d** generated upon irradiation (455 nm) over 10 min; [a] in the presence of TMEDA (1.5 mM), [b] in the presence of *n*-BuNH$_2$ (1.5 mM), [c] in the presence of sodium ascorbate (1.5 mM). (b) Transformations of methylene blue (**2a**) in the presence of amines. (c) Substrate **1a** treated with leuco-forms **2b** or **2d** in the darkness. (d) Reactions of *N*-cyclic benzamides **7a** and **10a**. (e) Proposed mechanism. PC – photocatalyst: methylene blue (**2a**) or azure B (**2c**). LPC – leuco-form **2b** or **2d**. (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^{2}SCAN-3c level of theory.

Based on the abovementioned consideration, we propose a mechanism for the developed C-H arylation and *N*-dealkylation reactions (Fig. 2e). Photocatalyst **2a** is first converted to leuco-form **2b** or **2d** (LPC)

with a concomitant formation of amine radical cation which can be further stabilised through the interaction with a negatively charged interface. Consecutive excitation of the photocatalyst generates LPC* (approximated $*E_{ox}$ = -2.22 V vs. SCE, see SI) 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 chlorine anion and its hydration in the aqueous phase.[47] A radical **B**, formed upon 1,5-HAT, can be oxidised to the *N*-acyliminium cation **C** by the neutral form of the photocatalyst **D** or by amine radical cation. Finally, electrophilic attack of *N*-acyliminium cation **C** on the aromatic ring yields the C-H arylation product **E**,[44,48] while alternative hydrolysis leads to the desired product **F**. The choice of amine dictates which of the two paths - inter- or intramolecular - the reaction takes. We hypothesize that the nature of the amine affects the outcome of the interaction with the cationic species **C** (Fig. 2f). 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 Fig 2f, $\Delta^{\ddagger}G$ = 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 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 the nucleophile with higher probability to trap the cation. This reaction is slightly endoergonic (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 photomicellar system that catalyses chemodivergent functionalization of benzamide derivatives on the *N*-alkyl unit. In contrast to existing methods, which rely on the nucleophilic reactivity of α–amino radicals, our transformation generates a highly electrophilic *N*-acyliminium cation as the key intermediate. Due to its presence, the process can be selectively guided towards either intramolecular C-H arylation or *N*-dealkylation by simple adjustment of the reaction parameters. The system operates under exceptionally mild, safe and operationally simple conditions employing methylene blue as a photocatalyst.

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

Acknowledgements

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