Chemodivergence made possible by micellar photocatalysis: C-H arylation vs. *N*-dealkylation of chlorinated benzamides in aqueous media

Martyna Cybularczyk-Cecotka,[a] Jędrzej Predygier,[a] Stefano Crespi,[b] Joanna Szczepanik,[a] and Maciej Giedyk*[a]

[a] Institute of Organic Chemistry Polish Academy of Sciences; Kasprzaka 44/52, 01-224 Warsaw, Poland;
[b] Faculty of Science and Engineering, University of Groningen, Nijenborgh 4, 9747 AG Groningen, Netherlands;
Email: maciej.giedyk@icho.edu.pl

Abstract

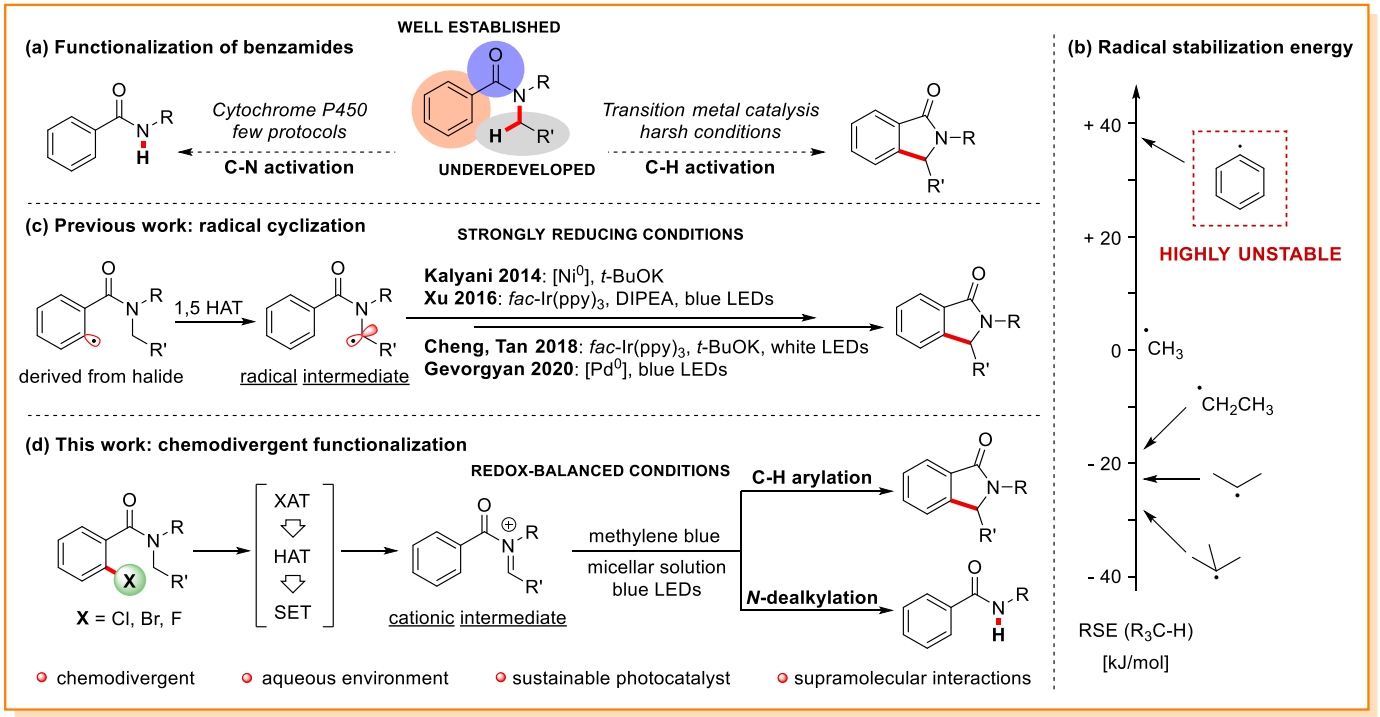
Micellar photocatalysis has recently provided new opportunities for the activation of strong carbon-chlorine bonds and enabled the valorization of cheap and readily available chlorinated starting materials. Thus far, however, it has mainly explored strongly reducing conditions, which restrict the available chemical space to radical or anionic reactivity. Here, we demonstrate a radical-polar crossover process involving cationic intermediates, which enable chemodivergent functionalization of chlorinated benzamide derivatives in aqueous solutions. The reaction can be guided towards either C-H arylation or *N*-dealkylation by simple adjustment of reaction parameters such as the amount of water, the type of surfactant or the amine. The system operates under mild conditions where methylene blue is used as a photocatalyst and blue light emitting diodes are the light source. Tuning the reaction environment not only affects the selectivity of the ionic process, but also alters the mechanism of substrate activation - different forms of the photocatalyst are involved in each of the two reactions.

Introduction

The functionalization of benzamide structures, due to their presence in various compounds of biological or functional importance, remains a vibrant area of synthetic chemistry.[1–3] While the modifications within the aromatic ring or carbonyl group are well developed,[4,5] the repertoire of reactions occurring at *N*-alkyl substituents is limitted (Scheme 1a). It includes C-H activation followed by cyclization to isoindoline – a processes, which requires harsh reaction conditions such as the use of lithium diisopropylamide,[6,7] *t*-BuOK,[8] or stoichiometric amounts of tetrabutylammonium persulfate and TEMPO[9]. Recently, Martin and Montgomery showed that C−H arylation and alkylation at *N*-substituenat can be achieved with the use of dual Ni/photoredox catalysis.[10] Another late-stage functionalization pathway leads to the *N*-dealkylation of secondary and tertiary benzamides. This thermodynamically challenging reaction is mediated in nature by Cytochrome P450,[11–13] but chemical methods are scarce and very limited in scope.[14–16]

We wondered if the reactivity of benzamide *N*-units could be promoted by combining the benefits of confined aqueous environment with the use of chlorine atoms as sacrificial directing groups.[17,18] We wished to achieve target reactivity through initial C-Cl activation followed by intramolecular 1,5 hydrogen-atom transfer (1,5-HAT).[19] Our previous reports,[29–31] as well as the work of others,[32–36] showed that micellar photocatalysis is an attractive tool for the activation of stable organic halides. It enables pre-organization of the components in the reaction mixture and provides high hydration energy of the released halide anions. The use of aryl halides, however, presents a challenge as the desired free radical intermediates are highly unstable (Scheme 1b).

Halogenated benzamides have already been recognized as promissing substrates in the radical C-H arylation to isoindoline (Scheme 1c). In 2013 Kalyani and co-workers reported the cyclization of *o*-chlorinated and *o*-brominated benzamides using either $Ni(COD)_2$ or 1,10-phenanthroline in the presence of stoichiometric amount of *t*-BuONa.[20] The initially developed method was later improved by the same authors, which allowed to lower the temperature from 145 °C to rt.[21] A similar approach, was developed by Kumar and co-workers, who prepared isoindolinones from respective *o*-iodo and *o*-bromo derivatives in metal-free conditions.[22] Xu and co-workers applied photoinduced single electron-transfer (PET) from excited *fac*-$Ir(ppy)_3$ photocatalyst to *o*-iodobenzamides in the presence of *i*-Pr_2NEt, which was postulated to act as both redox mediator and base.[23] The same, strongly reducing *fac*-$Ir(ppy)_3$ photocatalyst was later used by Cheng, Tan and co-workers to activate analogous fluorides.[24] In this case, however, the presence of *t*-BuOK, a non-hydrogen-donating electron donor, was required. Recently, Gevorgyan and co-workers showed that intramolecular C-H arylation can also be mediated by photoexcited Pd(0) species, which are able to generate hybrid aryl Pd-radical intermediates from *o*-triflates.[25] Abovementioned existing methods, however, share a common need for strongly reducing reagents or catalysts. This excludes the possibility of oxidation of the intermediate alkyl radical, and thus limits the number of potential transformations, leading only to radical cyclization products.



Scheme 1. Strategies for functionalization of benzamide derivatives.

Recent discoveries show that selective activation of stable organic halides can be realized in much milder conditions than previously thought. In this context, Leonori and co-workers used halogen-atom-transfer (XAT) to photogenerated α-aminoalkyl radicals.[26] König and co-workers established the consecutive photoinduced electron transfer (conPET) strategy as an efficient approach to improve the reducing properties of otherwise mild photoredox catalysts.[27,28] We recognized that such relatively redox-balanced methodologies, combined with strongly environment-dependent supramolecular interactions, may not only promote the activation of stable C(sp^2)-Cl bonds but also guide the selectivity

of the catalytic protocol (Scheme 1d). Herein we present the photocatalytic modifications of *o*-chlorobenzamides, which lead to either intramolecular C-H arylation to isoindolines or to *N*-dealkylation products. To achieve the required chemodivergence, we optimized the composition of structured solutions and examined the role of individual components in catalytic cycles. This allowed to lead each of two reactions along a different mechanistic pathway in a highly controllable and operationally simple manner.

Results and Discussion

Intramolecular C-H arylation

At first, we verifyied the feasibility of the intramolecular C-H arylation of *o*-chlorinated benzamides in aqueous environment. Satisfyingly, initial experiements showed that the cyclization of *o*-chlorobenzamide **1a** is possible under mild reaction condition: the use of 10-phenylphenothiazine (**3**) in micellar solution containing substrate **1a**, sodium dodecyl laurate (SDS) and DIPEA provided the desired isoindoline **1b** in 24%.

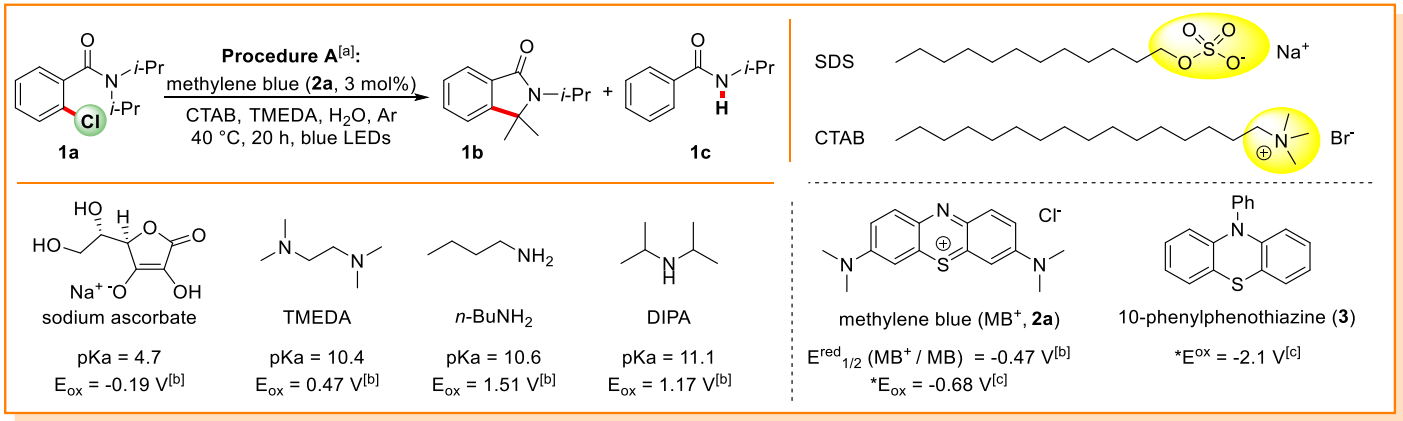
We performed extensive optimization of the reaction conditions with respect to the photocatalyst, surfactant, amine, additives, the ratio and concentration of reagents (see SI). Methylene blue (**2a**) turned out to be the photocatalyst of choice, allowing for the formation of the desired product **1b** in 89% yield. The developed conditions, called Procedure A, also included tetramethylethylenediamine (TMEDA) , cetrimonium bromide (CTAB), and water. Full solubility of all reaction components at 40 °C was observed. We found that 20 hours of irradiation with blue LEDs provides optimal conversion for the majority of substrates, although some of them, e.g. model substrate **1a** gave 89% of product **1b** after only 5 h (for detailed kinetic studies see SI). Unexpectedly, we also identified compound **1c,** in which one of the *N*-alkyl substituent was removed, as the major by-product.

Control experiments have shown that a photocatalyst is necessary and proved the superiority of methylene blue (**2a**) over such common mediators as rhodamine 6G (**4**), $[Ir(ppy)_2(dtbbpy)]PF_6$ (**5**) or strongly reducing 10-phenylphenothiazine (**3**) (Table 1, entries 2-5). CTAB can be replaced by other surfactants e.g. Triton X-100 provides product **1b** in 84% yield (entry 8) and zwitterionic SB3-14 in 90% yield (entry 9). The use of SDS, however, under otherwise unaltered conditions offers little advantage compared to the reaction carried out in pure water (entries 6, 7). The desired transformation can also be performed in DMF instead of the aqueous micellar solution, but with a significantly lower yield (entries 10, 11). Despite the fact that methylene blue (**2a**) displays only weak absorption at 450-500 nm, exposure to blue light is necessary and it cannot be replaced with other light-colour (entries 12-14). The reaction can be carried out in the atmosphere of air, but with the lower yield of the product **1b** (64%, entry 20). In contrast, no desired reaction was observed in a presence od radical trapping agents, including 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO), which indicates the presence of radical intermediates in the reaction mechanism (entry 21).

The developed C-H arylation reaction highly depends on the sacrificial electron donor (entries 15-19). Although its presence of electron donor is indespensible (entry 15), TMEDA can be easily replaced with another tertiary amine Et_3N without disturbing the reaction outcome. (entry 16). The conversion of substrate **1a** remains high when primary or secondary amines are used, but the proportion of dealkylation product **1c** raises substantially (entries 17, 18). We found such a change in selectivity

intriguing, as all the aforementioned amines display similar pKa and differ mostly in redox properties. Compound **1c** is also a major product of a reaction performed in the presence of sodium ascorbate, which is a relatively strong reductant, but not a XAT reagent (entries 19).

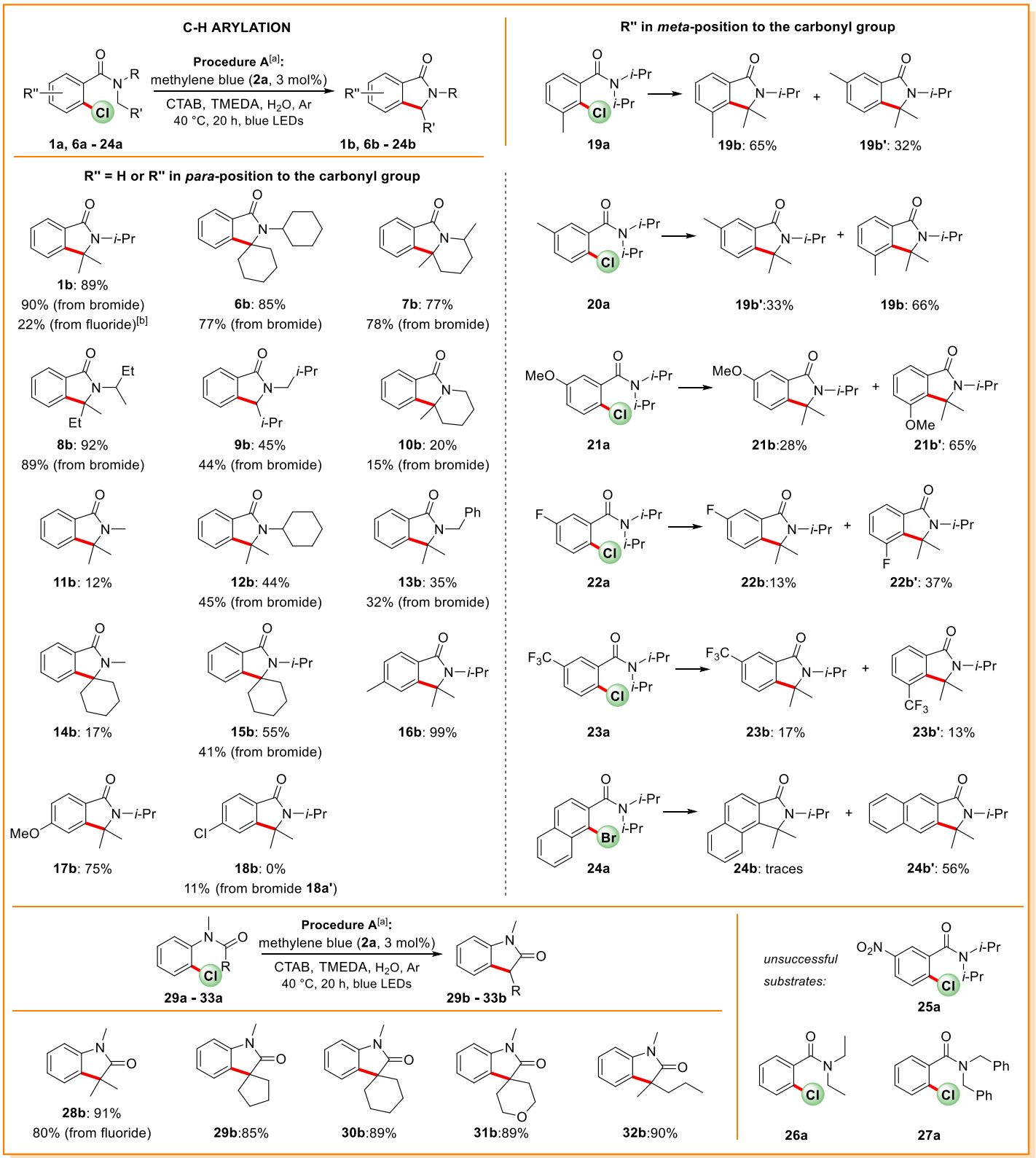
Table 1. Controll experiments[a]



No.	Deviation from optimized conditions	Yield 1b [%]	Yield 1c [%]	No.	Deviation from optimized conditions	Yield 1b [%]	Yield 1c [%]
1	-	89	4		**LIGHT**		
	PHOTOCATALYST			12	no light	0	0
2	no photocatalyst	0	0	13	green LEDs	2	0
3	10-phenylphenothiazine (**3**)	1	0	14	red LEDs	0	0
4	rhodamine 6G (**4**)	5	0		**ELECTRON DONOR**		
5	$[Ir(ppy)_2(dtbbpy)]PF_6$ (**5**)	11	0	15	no electron donor	0	0
	SURFACTANT			16	Et_3N	87	8
6	no surfactant	31	6	17	*n*-$BuNH_2$	32	37
7	SDS	36	7	18	DIPA	45	37
8	Triton X-100	84	4	19	sodium ascorbate	27	48
9	SB3-14	90	4		**MISCELLANEOUS**		
10	DMF instead of $CTAB_{aq}$	33	1	20	air instead of argon	64	12
11	DMF with CTAB instead of $CTAB_{aq}$	44	0	21	addition of TEMPO[d]	traces	0

[a] Optimized reaction conditions: substrate **1a** (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. Yields were calculated using GC analysis. *n*-Dodecane was used as internal standard. [b] according to ref[37] vs. SCE. [c] according to ref[38] vs. SCE. [d] 3 equiv of TEMPO were added.

The developed conditons were then employed in the intramolecular C-H arylation of a series of *o*-chlorinated benzamides **1a, 6a – 24a** (Scheme 2). In general, substrates **1a**, **6a – 8a** having two identical substituents on the nitrogen atom provided highest yields of desired isoindolines **1b**, **6b – 8b**, exceeding 80%. High preference for the functionalization of tertiary C-H bonds was observed e.g. substrate **9a** bearing isobutyl groups yielded product **9b** in 45%, while analogue **8a** with *s*-butyl substituents gave compound **8b** in twice higher yield. Substrates **26a** and **27a** with less bulky *N*,*N*-diethyl- and *N*,*N*-dibenzyl amides displayed no reactivity. In the case of the mixed substituents on the *N*-atom (substrates **10a – 15a**), the reaction only took place at the tertiary carbon center, even when an alternative benzyl position was available (product **13b**). We found that *o*-brominated starting materials could be used in place of chlorides without significantly affecting the results.



Scheme 2. Scope of intramolecular C-H arylation of *o*-chlorobenzamides. [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] 10 mol% of methylene blue (**2a**) was used instead of 3 mol%.

The reactivities of substrates strongly depend on the substituents at the phenyl ring. While *o*-chlorobeznamides **18a**, **22a**, **23a** bearing electron-withdrawing substitutents (including halides) displayed lower reactivity, the presence of electron-donating groups facilitated the desired reaction.

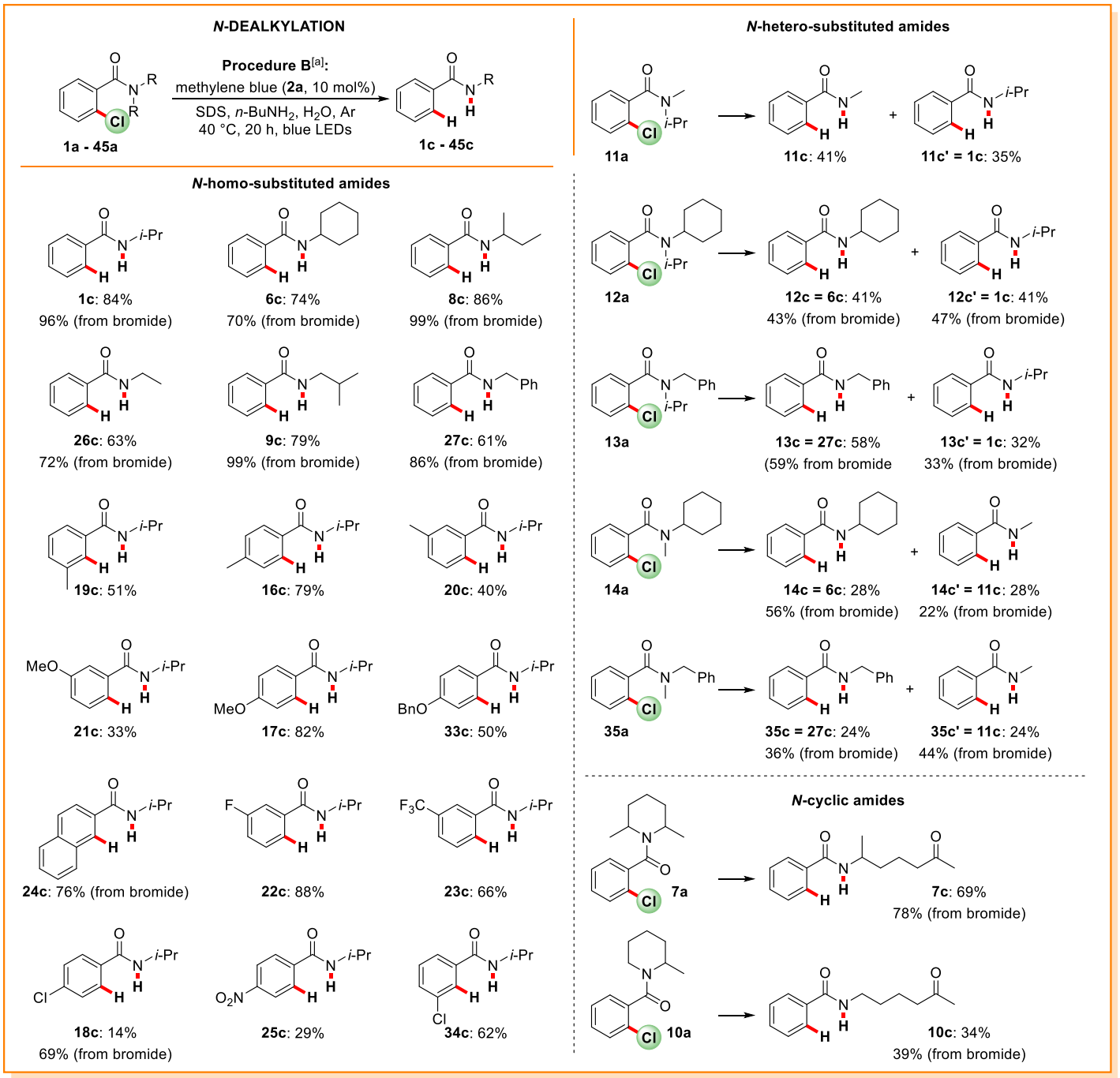
Interestingly, this contrasts with the reduction potentials of these compounds (see SI) and suggests that single-electron reduction is either not involved in the C-Cl activation process or, at least, that it is not a rate limiting step. The distribution of products obtained from substrates **19a** – **24a** showed that the cyclization at the carbon atom closer to the substituent is preferred. The exception was the naphthyl-based substrate **24a** for which cyclization at position *3* was mainly observed. In addition to functionalization of benzamides, we also employed Procedure A in the α-arylation of *N*-substituted anilides **28a** – **32a**.[25,39] The reaction proceeded smoothly and provided a series of oxindoles **28b** – **32b** in 85% - 90% yields. Pleasingly, the developed system proved competent for the transformation of *o*-fluorinated anilide, which gave the oxindole **28b** in 80% yield.

<u>*N*-Dealkylation</u>

Recognizing the importance of late-stage modification of stable amides and the current lack of mild and efficient protocols, we next took closer look at the intriguing *N*-dealkylation side reaction. Separate optimization allowed to establish Procedure B, which utilizes slightly different reagent ratios, an anionic instead of a cationic surfactant (SDS instead of CTAB), and *n*-$BuNH_2$ in place of TMEDA. It should be emphasized that despite these adjustments, the photocatalyst and the general reaction conditions remain the same as for intramolecular C-H arylation. We used them to carry out scope studies, which included various tertiary amides bearing two identical or two different alkyl substituents at the nitrogen atom (Scheme 3). In the later case, the mixture of two possible *N*-dealkylation products was always obtained. However, unlike in the cyclization process, we did not observe a consistent preference for the reaction to occur at tertiary *N*-substituents over secondary and methyl groups. For example, substrate **13a** possessing *i*-Pr and benzyl groups at nitrogen atom gave a mixture of products in which the removal of *i*-Pr predominated (58% of product **13c** vs 32% of product **13c'**). In the same time, an analogue **11a** with *i*-Pr and methyl substituents provided the mixture of secondary amides **11c** and **11c'** in similar yields (41% and 35% respectively). *N*,*N*-diethylamide **26a** and *N*,*N*-dibenzylamide **27a**, both of which were inert under the conditions of Procedure A, gave desired dealkylation products **26c** and **27c** in satisfactory 63% and 61% yields. The bromides gave higher yields of dealkylation products than the chlorides, although the observed differences were moderate, ranging from 10-20%.

Another major difference with respect to the C-H arylation protocol was the influence of substitutents at the phenyl ring. In the case of Procedure B, the presence of electron-donating groups hampered the reactivity, while electron-withdrawing substituents such as fluorine atom in substrate **22a** was neutral and allowed for product **22c** in 88%, similarily to the unsubstituted model substrate **1a**. The highest effect was observed for substituents at *orto*- and *para*-position to the chlorine atom, while the impact of *meta*-substituents was negligible (compare products **21c** and **17c**: 33% vs. 82% or **19c**, **16c** and **20c**: 51% vs. 79% vs. 40%). The relatively low yields obtained from substrates **18a** and **25a** were due to numerous side reaction and not due to low reactivity, as was the case in the cyclization process.

Amides **7a** and **10a**, which are derivatives of cyclic amines, undergo ring-opening to respective ketones **7c** and **10c** with the insertion of oxygen atom taking place at the more substituted carbon atom. This reaction is not only of interest as a method for the synthesis of protected aminoketones, but also provides important mechanistic clues: it indicates that the developed *N*-dealkylation reaction likely proceeds through the hydrolysis of intermediate *N*-acylimine or *N*-acyliminium cation.

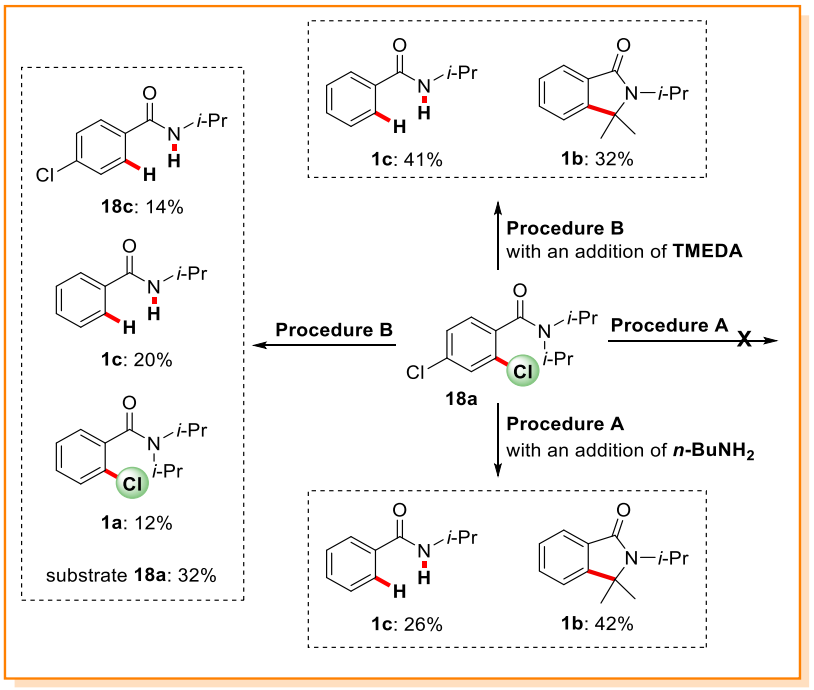


Scheme 3. Scope of *N*-dealkylation of *o*-chlorobenzamides. [a] Reaction conditions: substrate (0.1 mmol, 20 mM), methylene blue (**2a**, 10 mol%), SDS (0.25 mmol, 50 mM), *n*-$BuNH_2$ (0.6 mmol, 60 mM), water (5 mL), 40 °C, 451 nm, 20 h. Average isolated yield obtained from two separate reactions are given.

Origin of chemoselectivity: mechanistic studies

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 cyclization or dealkylation. We began by studying the reactivity of the dichlorosubstituted substrate **18a** under various reaction conditios (Scheme 4a). The compound **18a** provided mixture of dehalogenation and/or dealkylation products **1a**, **1c** and **18c** when Procedure B, involving SDS and *n*-butylamine, was employed. In the same time, it remained perfectly inert under the conditions of Procedure A. Such a drastic difference in reactivity indicates two different activation pathways operating under Procedures A and B. Interestingly

alternative experiments: 1) the addition of external *n*-butylamine to Procedure A or 2) the addition of external TMEDA to Procedure B gave a similar mixture comprising products **1b** and **1c**. Figuratively, this means that *n*-butylamine 'unlocks' the substrate **18a**, while TMEDA opens the cyclization pathway.

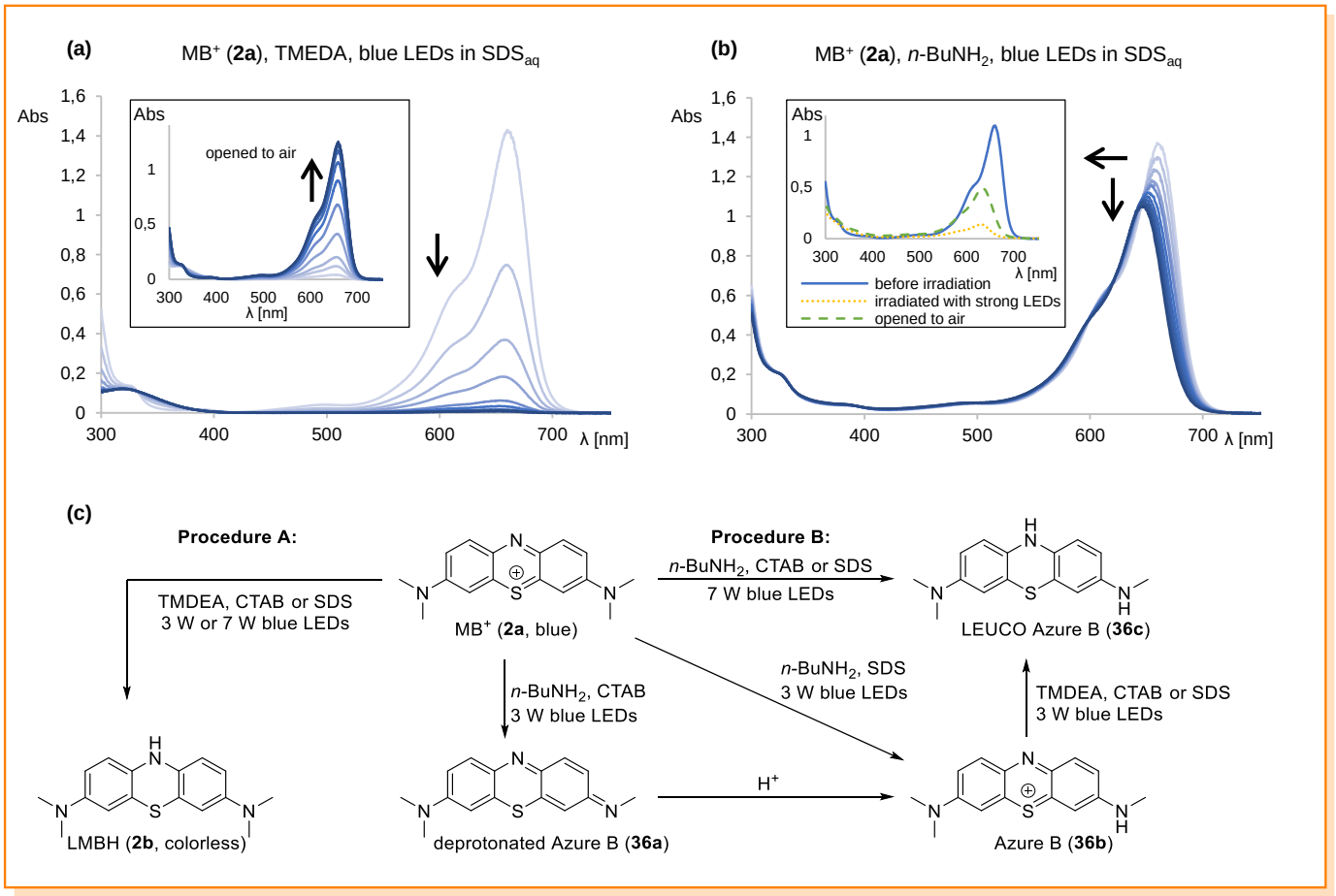


Scheme 4. Reactivity of dichlorinated benzamide **18a** under various reaction conditions: distribution of products.

Dynamic light scattering (DLS) proved the presence of micelles in the reaction mixtures, with hydrodynamic radius changing upon the addition of reacting compounds, which indicated the partial incorporation of substrate **1a** and amines inside the hydrophobic core. With the help of the UV-Vis measurements, we excluded dimers dimers or higher aggregates as potential catalytically active species under developed conditions (see SI). Cyclic voltammetry (CV) measurements showed that the reduction of halogenated substrates **1a**, **18a** and **18a'** is facilitated in micellar system compared to a benchmark solution in MeCN (see SI). For instance, cathodic peak potential of substrate **1a** in the aqueous solution of CTAB is E_{pc1} = -2,28 vs. SCE, which is more then 0.4 V less negative then in MeCN. Nevertheless, the obtained values significantly exceed the reducing capability of methylene blue (**2a**), either in ground ($E^{red}_{1/2}(MB^+/MB)$ = -0.47 V vs. SCE) or excited state ($^*E_{ox}$ = -0.68 V vs. SCE).[37,38] They are also not affected by the presence of amine in the mixture (see SI). These observations exclude a classical variant of PET for the reductive activation of chlorides. Alternative mechanism could involve the generation of alkyl radical at α-position to nitrogen atom through either single electron oxidation within the amide group or hydrogen-atom abstraction. These two pathways, however, were rulled out as no reactivity for substrates lacking the chlorine atoms was observed, even in the presence of external oxidant (see SI). Morover, we did not detect any products with halogen atoms intact in any of the reactions studied. Finally, Stern-Volmer experiment showed that fluorescence quenching is triggered only by the addition of amines, and not by substrates (see SI). The abovementioned results led us to conclude that the observed reactivity of the substrates under standard reaction conditions is likely the result of XAT- or conPET-type activation of the carbon-halogen bond.

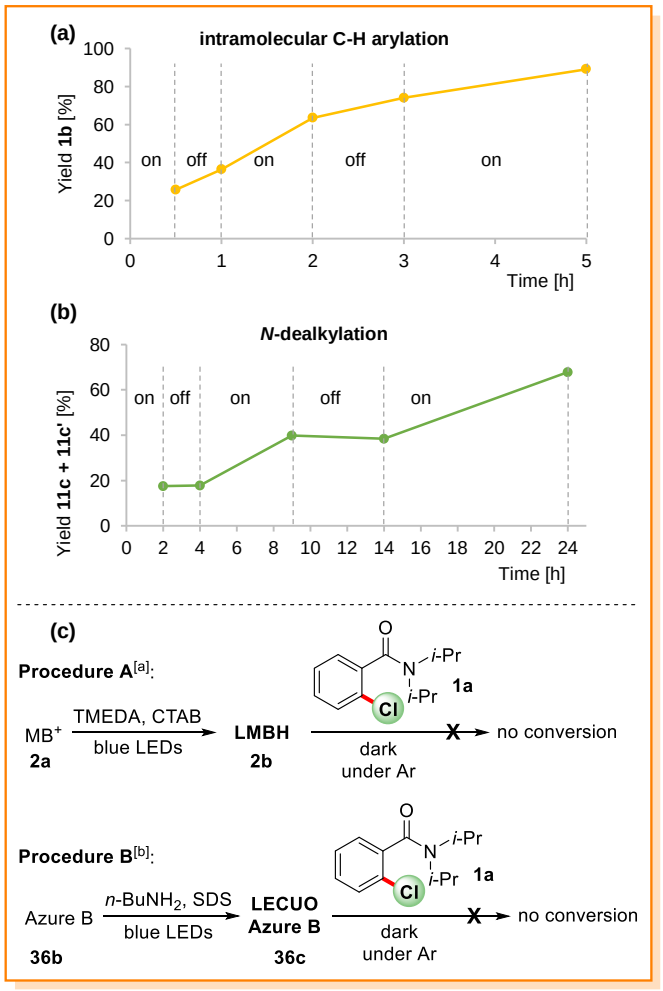
To better investigate the fate of the catalyst **2a** under reaction conditions of Procedures A and B, we performed time-dependent UV-Vis measurements in which the solution containing photocatalyst and

amine was irradiated with blue light and the absorbance was measured in 2 min. intervals. Despite the fact that UV-Vis spectra show only weak absorption at the blue region, reductive quenching of the catalyst **2a** with amines was confirmed. The presence of TMEDA led to the characteristic disappearance of the bands in the 450-700 nm region, indicating the two-electron reduction of the photocatalyst and the formation of colorless leuco-methylene blue (**2b**, Scheme 5a). This species readily returned to the parent oxidized form **2a** upon opening the cuvette to air. The behavior of the photocatalyst **2a** in the presence of *n*-BuNH$_2$ turned out to be more complex. Irradiation with single 3 W blue LED in aqueous SDS caused the spectral change with maximum shifting from 664 nm to 645 nm, which indicated the irreversible transformation of methylene blue (**2a**) to Azure B in its protonated, monomeric form **36b**, without further reduction (Scheme 2b, see SI for more details). However, when stronger 7 W light, closely resembling the standard reaction conditions, was provided, the two-electron reduction of Azure B (**36b**) to its leuco-form **36c** was observed (Scheme 2b – inset). Both photocatalyst **2b** and **36c** display small but detectable absorption in the blue light range and their consecutive excitation can be considered (see SI). Possible transformations of methylene blue **2a** under our conditions are depicted on Scheme 5c.



Scheme 5. Mechanistic investigatins: Time-dependent UV–Vis absorption spectra of methylene blue (**2a**, 0.015 mM) in aqueous SDS solution upon light irradiation (455 nm, 3 W) over 20 min at 25 °C: (a) in the presence of TMEDA (1.5 mM); In the inset: changes of the absorption spectra upon opening the cuvette to air in the darkness. (b) in the presence of *n*-BuNH$_2$ (60 mM); In the inset, changes of the absorption spectra upon irradiation with strong (7W) LEDs and then opening to air. (c) Fate of the photocatalyst **2a** under various reaction conditions.

Light ON/OFF experiments revealed a significantly different conversion plot for the two studied reactions: in the case of C-H arylation, a steady increase in yield of product **1b** was observed, even in the darkness, demonstrating substantial contribution of the chain propagation (Scheme 6a). This is in line with recent results from Leonori and co-workers, who showed efficient radical-propagation pathway for the addition of aryl halides to electron-rich heterocycles.[40] On the contrary, step-like shape of the graph was observed for *N*-dealkylation with no increase in yield in the dark periods (Scheme 6b). While this does not exclude the radical propagation mechanism,[41] it confirms that the light is a critical parameter for efficient formation of products **11c** and **11c'**. Inspired by the recent report by Barham and co-workers, who showed that C(sp^3)–H arylation of amides can be realized *via* the formation of solvent-caged electron donor-acceptor (EDA) complexes,[42] we investigated the mixtures of reaction components using CV, NMR and UV-Vis spectroscopy. However, no alterations in the ground- or excited state properties of substrates **1a** and **18a'** were found (see SI).



Scheme 6. (a) Light on/off investigation of C-H arylation reaction of chloride **1a** under Procedure A. (b) Light on/off investigation of dealkylation reaction of chloride **11a** under Procedure B. (c) Reactivity of aryl chlorides in the presence of LEUCO forms of photocatalysts **2b** and **36c** in the darkness.

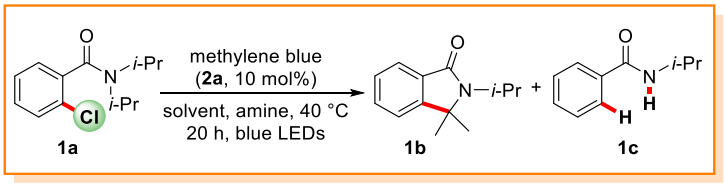
To gain more insights into the nature of C-Cl bond activation, we carried out an experiment in which methylene blue (**2a**) was first quantitavely reduced to give leuco-methylene blue (**2b**) and leuco-Azure B (**36c**) respectively (Scheme 6c). Then, model substrate **1a** was added in the darkness and under strict argon atmosphere and the mixtures were stirred for another 19,5 h. As expected, no conversion was observed in either of the two reactions. This further supports the possible activation pathways: the

consecutive excitation of reduced leuco form of the catalyst[43,44] or, alternatively, generation of α-aminoalkyl radicals and their participation in XAT event, provided the halogenated substrate is present in the reaction mixture.

Ultimately, we turned our attention to the chemoselectivity of the process. The high reactivity of compounds containing electron-donating groups in the cyclization reactions strongly supports the intermediacy of cationic species and corresponds well with the results of the Friedel-Crafts amidoalkylation reaction demonstrated previously by Stephenson and co-workers.[45] It is also in line with existing reports on *N*-dealkylation of amides, which postulate the attack of water on the intermediate cation followed by the cleavage of the respective hemiaminal.[11,15,16] Abovementioned observations indicate that, unlike the majority of reports in which nucleophilic alkyl radical is proposed to initiate cyclization process, in our case the generation of *N*-acyliminium cation occurs first. It is then followed by the electrophilic attack on the phenyl ring or the reaction with nucleophile (water, amine or ascorbate), which ultimately leads to dealkylation. In other words, the unique properties of the catalytic system, which retain the ability to carry out oxidation of *N*-alkyl radicals to *N*-acyliminium cations, open the door to chemodivergency.

To get a more in-depth view on how individual factors affect the chemoselectivity of the process, we carried out a series of reactions under standarized conditions, changing only one parameter at a time (Table 2). The use of DMF as a solvent leads predominantly to C-H arylation product **1b** while the presence of water facilitates dealkylation (entries 7-12). These results correspond well with the proposed hydrolysis of intermediate cation. The selectivity of the process also depends on the surfactant: SDS facilitates dealkylation (ratio **1b** : **1c** = 1:42) while in CTAB the share of the C-H arylation product is relatively larger (ratio **1b** : **1c** = 1:9.4; entry 1 vs 5). Such an effect may result from the Coulombic interactions between the *N*-acyliminium cation generated in the micellar core and the presence of a charged interface. For anionic surfactant such as SDS this is an attractive force, which pulls the *N*-acyliminium cation towards the water-rich Stern layer where fast addition of the molecule of water occurs. Undoubtly, however, the choice of amine has the largest effect on the chemoselectivity as it can completely reverse the outcome of the reaction (entries 1 vs 2, 5 vs 6). Once more, it could be clearly seen that tertiary amine TMEDA promotes cyclization and primary *n*-butylamine leads almost exclusively to dealkylation reaction. The same trend is observed when a different photocatalyst – 10-phenylphenothiazine – is used. In this case compound **1b** remains the main product regardless of the amine used, but the ratio changes from 1.8:1 to 11:1 (entries 3 vs 4). The nature of this dependence has not been fully understood. Yet, literature reports suggests that the formation of highly reactive gem-diamine intermediates from *N*-acyliminium cations or different energies of cyclic transition states at the stage of hemiaminal hydrolysis may play an important role.[46,47]

Table 2. Selectivity studies under standardized conditions[a]

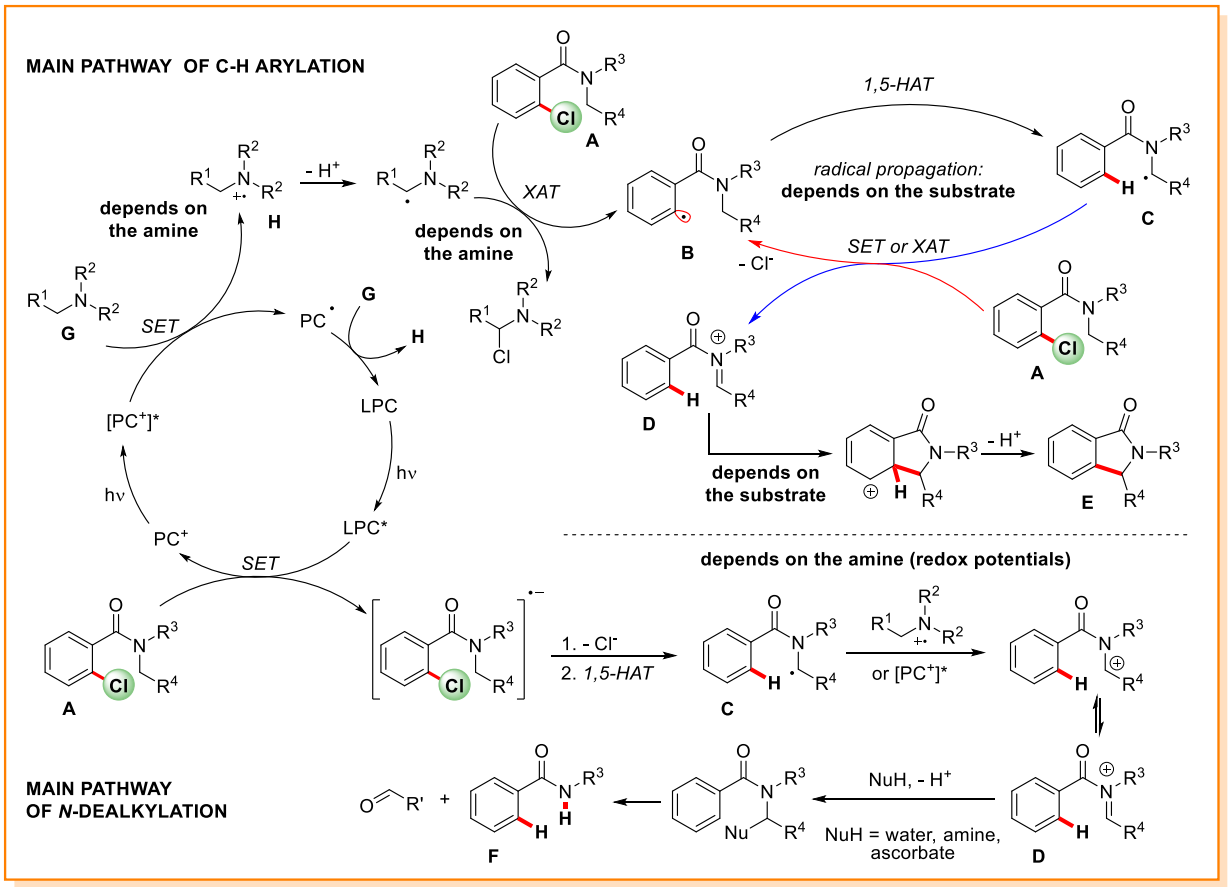


No.	Solvent	Amine	Yield 1b [%]	Yield 1c [%]	Ratio 1b : 1c
1	SDS_{aq}	*n*-$BuNH_2$	2	83	1 : 42
2	SDS_{aq}	TMEDA	67	18	3.7 : 1
3[b]	SDS_{aq}	*n*-$BuNH_2$	18	10	1.8 : 1
4[b]	SDS_{aq}	TMEDA	22	2	11 : 1
5	$CTAB_{aq}$	*n*-$BuNH_2$	7	66	1 : 9.4
6	$CTAB_{aq}$	TMEDA	73	11	6.6 : 1
7	DMF	*n*-$BuNH_2$	63	3	21 : 1
8	DMF	TMEDA	43	0.5	86 : 1
9	DMF : H_2O 9:1	*n*-$BuNH_2$	59	8	7.4 : 1
10	DMF : H_2O 9:1	TMEDA	51	2	26 : 1
11	DMF : H_2O 8:2	*n*-$BuNH_2$	46	16	2.9 : 1
12	DMF : H_2O 8:2	TMEDA	42	2	21 : 1

[a] substrate **1a** (0.1 mmol, 20 mM), methylene blue (**2a**, 10 mol%), surfactant (0.15 mmol, 30 mM), amine (0.2 mmol, 40 mM), solvent (5 mL), 40 °C, 451 nm, 20 h. Yields were calculated using GC analysis. *n*-Dodecane was used as internal standard. [b] 10-Phenylphenothiazine was used instead of methylene blue (**2a**).

Based on the abovementioned consideration, we propose a mechanism for both C-H arylation and *N*-dealkylation reactions (Scheme 7). Intramolecular C-H arylation is believed to occur through a photoinduced XAT process, efficiency of which depends on the electronic and steric structure of the amine.[26] It is then followed by 1,5-HAT in intermediate **B** and radical propagation in which the substrate **A** reacts with a strongly reducing radical intermediate **C**.[45] The driving force for of this process can be further facilitated by irreversible fragmentation of the C-Cl bond and dissociation of chlorine anion.[48] A radical chain process justifices a small photocatalyst loading and explains why substrates bearing electron withdrawing groups display lower reactivity – intermediate radicals **C** are in this case worse reducing agents and hamper the conversion of chlorinated substrates in the catalytic cycle. Finally, electrophilic attack of *N*-acyliminium cation **D** on the aromatic ring and deprotonation/rearomatization yields the C-H arylation product **E**. [45,49]

On the other hand, we postulate the *N*-dealkylation to proceeed through conPET mechanism in which methylene blue (**2a**) is first converted to leuco-form **36c** of Azure B. This is accompanied by a formation of strongly oxidizing radical cation **H**, further stabilized through the interaction with a negatively charged interface. Consecutive excitation of the photocatalyst generates strongly reducing LPC* (approximated $*E_{ox}$ = -2.22 V vs. SCE, see SI) which is able to induce SET to substrate **A**. Upon mesolytic C-Cl bond cleavage and 1,5-HAT a radical **C** forms, which can be oxidized to the *N*-acyliminium cation **D** by radical kation **H** or excited photocatalyst **36b**. Further hydrolysis or aminolysis in aqueous environment leads to the desired product **F**.



Scheme 7. Proposed mechanism for the intramolecular C-H arylation and *N*-dealkylation of chlorinated benzamide derivatives. PC – photocatalyst: methylene blue (**2a**) or Azure B (**36b**).

Conclusions

In summary, we have designed catalytic system comprising aqueous micellar solution of methylene blue and applied it in a photocatalytic, chemodivergent functionalization of benzamide derivatives using chlorine atoms as sacrificial directing groups. We have shown that the reaction can be selectively guided towards either intramolecular C-H arylation or *N*-dealkylation by simple adjustment of reaction parameters such as the amount of water, the type of surfactant or the amine. The system operates under mild, safe and operationally simple conditions. Mechanistic studies suggest that the key to tuneable selectivity lies in its unique ability to provide an intermediate cation on an *N*-alkyl substituent.

Our research shows that structured aqueous solutions can be perfectly compatible with cheap, safe and readily available organic dyes. Additionally, the reported transformation of methylene blue (**2a**) to Azure B (**36b**) at the early stage of the reaction and the decisive role of amine on the final product formation highlight the complex interplay between the reaction components. We believe that this work is an important step towards the long-standing goal of guiding the selectivity of the photocatalytic processes, which are closely related from the mechanistic point of view.

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Keywords: photocatalysis • chemodivergence • micelles • aqueous solutions • aryl chlorides • benzamides • C-H arylation • dealkylation

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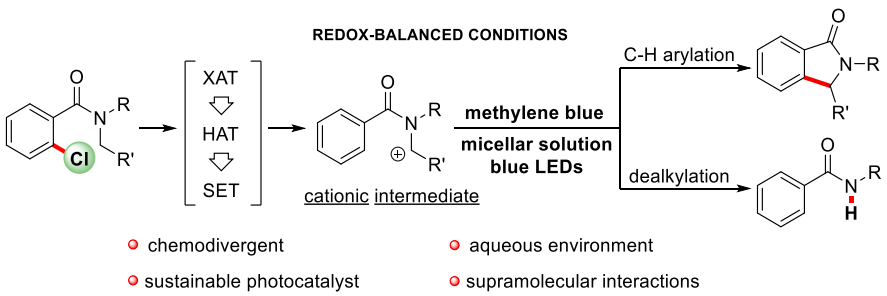

In this article we describe a chemodivergent functionalization of chlorinated benzamide derivatives, which can be selectively guided towards either C-H arylation or dealkylation by simple adjustment of reaction parameters such as the amount of water, the type of surfactant or the amine. The system operates under mild, safe and operationally simple conditions. Mechanistic studies suggest that the key to tuneable selectivity lies in its unique ability to provide an intermediate cation on the *N*-alkyl substituent.