# Red-light – Blue-light chromoselective C(sp$^2$)-X bond activation by organic helicenium based photocatalysis

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**ABSTRACT:** Chromoselective bond activation has been achieved in the organic helicenium ($^n$Pr-DMQA$^+$) based photoredox catalysis. Consequently, control over chromoselective C(sp$^2$)-X bond activation in multi-halogenated aromatics has been demonstrated. $^n$Pr-DMQA$^+$ can only initiate halogen atom transfer (XAT) pathway under red-light irradiation to activate low energy accessible C(sp$^2$)-I bonds. In contrast, blue-light irradiation initiates consecutive photoinduced electron transfer (conPET) to activate more challenging C(sp$^2$)-Br bonds. Comparative reaction outcomes have been demonstrated in α-arylation of cyclic ketones with red and blue-lights. Furthermore, red-light-mediated selective C(sp$^2$)-I bonds have been activated in iodobromoarenes keeping the bromo functional handle untouched. Finally, the strength of the chromoselective catalysis has been highlighted with two-fold functionalization using both photo to transition-metal and photo to photo-catalyzed transformations.

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Controllable selective synthesis in photoredox catalysis is a captivating and formidable research area,[1] particularly concerning light switching techniques.[2] The ability to access various catalytic pathways by simply adjusting the irradiation wavelength is often attributed to the distinct excited states of formed intermediates, photosensitizers, and other factors.[3] Enzymes demonstrate exceptional selectivity, thanks to their specific cavities and electron transfer properties involving hydride transfer, electron bifurcation, multiple optical excitations, and more.[4, 5] Similarly, metal-organic capsules[6-9] as well as covalent organic frameworks[10-12] have drawn significant interest due to their high symmetry, stability,[13] and diverse chemical properties, making them powerful platforms for regulating selectivity through the engineering of their catalytic cavities. Nevertheless, exploring modifications in light-controlled electron transfer pathways and kinetics to control reaction selectivity remains relatively uncharted territory, and only a few visible light switchable catalytic methods have been previously reported.[12, 14, 15] Most notable instances of molecular photocatalysts are Rhodamine-6G (450 nm/530 nm),[16] Eosin Y (370 nm/521 nm),[17] and PTH (365/420 nm)[18] (**Figure 1a**). In general, such controllable access of different redox potentials and/or mechanisms have been demonstrated within the close proximity of blue and green wavelengths.[14] However, recent surge in red and deep-red-light photocatalysis[19, 20] set forth an opportunity to approach highly coveted red/blue chromoselective photoredox catalysis.

Aryl halides, which are a prevalent resource in the realm of organic chemistry for a wide range of arylation reactions,[21] offer an ideal platform to investigate chromoselective photoredox catalysis thanks to the wide range of reduction potential and BDE spanning across these class of molecules. Generally, aryl halide functionalization has benefited from the establishment of robust transition metal-based catalytic techniques to attain the desired arylation outcomes.[22, 23] Recent times have also witnessed the introduction of novel methodologies, including photoredox,[24-26] electrochemical,[21, 27, 28] and enzymatic catalysis.[4, 29, 30]. In the context of organic photocatalyzed C-X bond activation, consecutive photoelectron transfer (conPET)[31] and halogen atom transfer (XAT) mechanisms are often the main pathways involved.[32] PDI, acridine and carbazole based photocatalysts are some prominent examples to undergo two photon excitation mechanism resulting in highly photoreducing behavior able to activate strong C(sp$^2$)-X bonds.[31, 33-36] Contemporary works from Leonori and colleagues have demonstrated tertiary amine-based XAT initiated by 4CzIPN under blue-light irradiation[37, 38] is a powerful alternative method, albeit mostly for C(sp$^3$)-X bonds.[32, 38, 39] Metal-based red-light mediated aryl halide activation has also been recently reported.[40, 41] Within this frame of reference, we have investigated a photoredox approach for α-arylation of ketones, catalyzed by electron-rich acridiniums, under green-light irradiation (**Figure 1b left**).[42] The resulting α-arylated cyclic ketone scaffolds hold significant medicinal relevance and serve as pivotal synthons for an array of pharmaceutical agents and bioactive natural products,[43] making metal-free strategies very appealing.[44-46] Yet, this methodology was limited to aryl iodides, and relatively difficult substrates such as aryl bromides were not efficiently activated. Our in-depth mechanistic studies revealed concurrent involvement of the enamine-based XAT mechanism and the classic photoredox single electron transfer (SET) pathway leading to C(sp$^2$)-X bond activation.[42, 47]

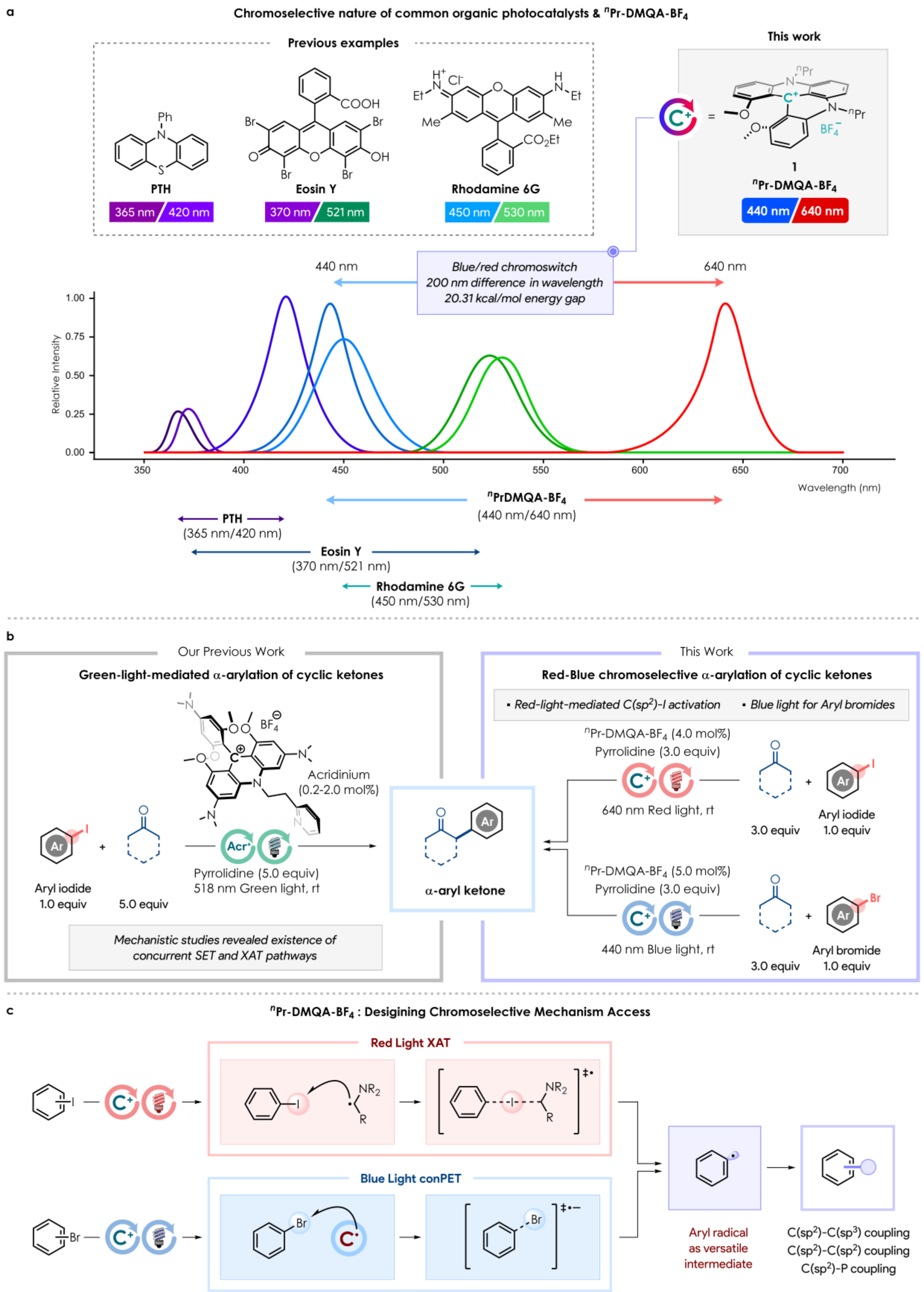


**Figure 1:** **a**. Selected examples of chromoselective organic photocatalysts and comparison with helicenium based ⁿPr-DMQA-BF₄ photocatalyst. **b**. Previous report and current development of metal-free photocatalytic α-arylation of cyclic ketones from our research group. **c**. Light-controlled activation of different mechanistic pathways by ⁿPr-DMQA-BF₄ photocatalyst.

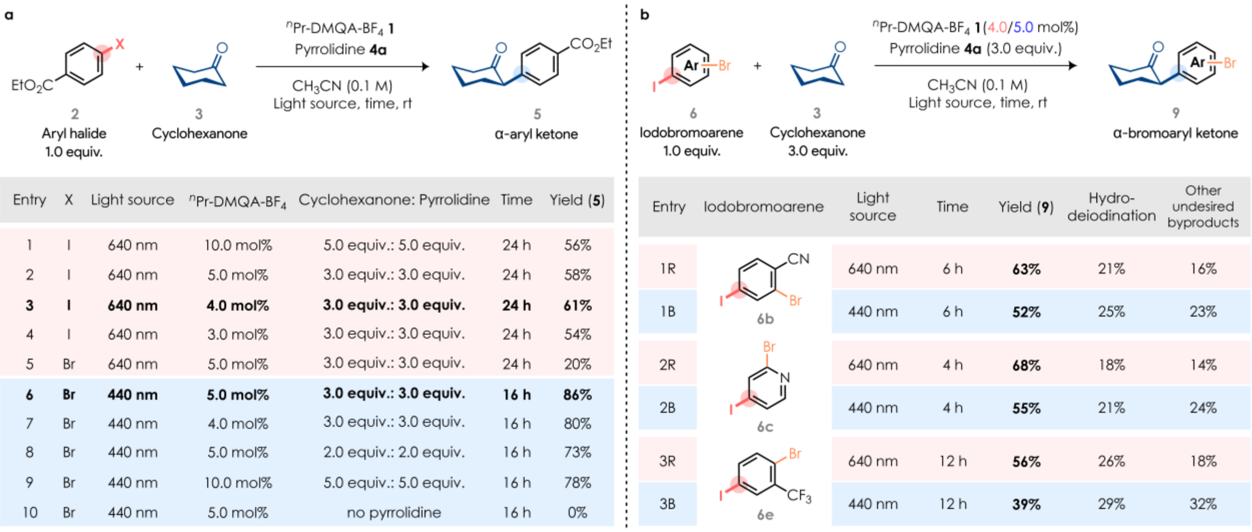
In this interpretation of competitive mechanism, we envisaged that achieving selective mechanistic pathways would be possible by ported that $^{n}$Pr-DMQA-BF$_4$ can be photoexcited at 640 nm red-light region. It can efficiently undergo oxidative quenching cycle with the excited state potential of $E^{*}_{1/2}{}^{ox}$ = +1.1 V vs SCE and generate the neutral helicene radical $^{n}$Pr-DMQA$^{\bullet}$ as the reduced form of the photocatalyst.[48] We now speculate that $^{n}$Pr-DMQA$^{+}$ can readily oxidize amines like pyrrolidine, piperidine, DIPEA or enamines to generate their corresponding α-aminoalkyl radicals, a key intermediate in aryl iodide activation via XAT mechanism (**Figure 1c**). This hypothesis was supported by the Stern-Volmer fluorescence quenching studies of the photocatalyst $^{n}$Pr-DMQA-BF$_4$ in presence of amine (pyrrolidine) and enamine (1-pyrrolidino-1-cyclohexene) (for additional details see supplementary information, section IV. i). In addition to that, generation of the reduced photocatalyst radical $^{n}$Pr-DMQA$^{\bullet}$ has been detected in the EPR spectroscopy when photoexcited in presence of amine or enamine (for additional details see supplementary information, section IV.ii). No reaction was observed in absence of the photocatalyst (Supplementary information, section IV.iii) ruling out an alternative pathway involving photoexcitation of EDA (electron donor-acceptor) complex between enamine and electron deficient aryl halides.[49, 50] Moreover, aryl radical formation was confirmed during the reaction by trapping with triethyl phosphite (Supplementary information, section IV.iii) further supporting the XAT mediated pathway under red-light condition.

In a subsequent study we reported that the *in situ* generated $^{n}$Pr-DMQA$^{\bullet}$ can act as a highly reducing photocatalyst under blue-light (440 nm) irradiation. As a result, irradiation of $^{n}$Pr-DMQA$^{+}$ under blue-light led to consecutive photoelectron transfer (conPET) mechanism able to activate C(sp$^2$)-Br bonds in substrates with reduction potential as low as -3.4 V vs SCE providing corresponding aryl radical (**Figure 1c**).[51]

Within this framework, using our developed α-arylation of cyclic ketones reaction platform, we report the modular photoredox behavior of $^{n}$Pr-DMQA$^{+}$, leading to the red-light-mediated C(sp$^2$)-I bond functionalization of aryl iodides (640 nm) as well as the efficient functionalization of aryl bromides under blue-light irradiation (440 nm) (**Figure 1b right**). Such an extensive difference in wavelength (200 nm) and energy (20.31 kcal/mol) propelled the selectivity of bond activation in multi-halogenated arenes. The dissociation energy of the C(sp$^2$)-X bond play the pivotal role to facilitate the chromoselectivity.[38] Generally, C(sp$^2$)-I bonds have 15.5 kcal/mol lower BDE than the corresponding C(sp$^2$)-Br bonds.[52] On this account, light-dependent mechanism control has been showcased by chromoselective activation of C(sp$^2$)-I bond in iodobromoarenes through C(sp$^2$)-C(sp$^3$), C(sp$^2$)-C(sp$^2$) and C(sp$^2$)-P couplings, while keeping the C(sp$^2$)-Br bond intact as a useful functional handle for a wide array of classic and state of the art reaction scopes.

To develop the red-light-mediated α-arylation of carbonyls we employed ethyl-4-iodobenzoate with cyclohexanone under 640 nm red-light (Table 1a and supplementary table S1). The reaction was attempted with 10 mol% $^{n}$Pr-DMQA-BF$_4$ as photocatalyst and 5.0 equivalent excess of cyclohexanone and pyrrolidine in acetonitrile solvent. Full conversion of starting aryl iodide was observed within 24 h of red-light irradiation with a 56% α-arylated product **5** (Table 1a entry 1). Decreasing the catalyst loading, ketone and amine equivalence improved the yield (Table 1a entry 2-3). Optimal reaction condition was found in presence of 4.0 mol% of $^{n}$Pr-DMQA-BF$_4$ which in combination with 3.0 equivalent of cyclohexanone and pyrrolidine furnished the desired α-arylated product in 61% yield (Table 1a entry 3). Further lowering the catalyst to 3.0 mol% resulted in incomplete reaction within 24 h irradiation time with a slightly diminished yield of 54% (Table 1a entry 4 and supplementary table S1). With optimized red-light reaction condition identified, we attempted α-arylation of cyclohexanone with aryl bromide.

**Table 1: a) Reaction optimization for red and blue-light mediated α-arylation of cyclic ketones. b) Reaction condition for chromoselective alpha-arylation of iodobromoarenes.**



| Entry | X | Light source | $^{n}$Pr-DMQA-BF$_4$ | Cyclohexanone: Pyrrolidine | Time | Yield (**5**) |
|---|---|---|---|---|---|---|
| 1 | I | 640 nm | 10.0 mol% | 5.0 equiv.: 5.0 equiv. | 24 h | 56% |
| 2 | I | 640 nm | 5.0 mol% | 3.0 equiv.: 3.0 equiv. | 24 h | 58% |
| **3** | **I** | **640 nm** | **4.0 mol%** | **3.0 equiv.: 3.0 equiv.** | **24 h** | **61%** |
| 4 | I | 640 nm | 3.0 mol% | 3.0 equiv.: 3.0 equiv. | 24 h | 54% |
| 5 | Br | 640 nm | 5.0 mol% | 3.0 equiv.: 3.0 equiv. | 24 h | 20% |
| **6** | **Br** | **440 nm** | **5.0 mol%** | **3.0 equiv.: 3.0 equiv.** | **16 h** | **86%** |
| 7 | Br | 440 nm | 4.0 mol% | 3.0 equiv.: 3.0 equiv. | 16 h | 80% |
| 8 | Br | 440 nm | 5.0 mol% | 2.0 equiv.: 2.0 equiv. | 16 h | 73% |
| 9 | Br | 440 nm | 10.0 mol% | 5.0 equiv.: 5.0 equiv. | 16 h | 78% |
| 10 | Br | 440 nm | 5.0 mol% | no pyrrolidine | 16 h | 0% |

| Entry | Iodobromoarene | Light source | Time | Yield (**9**) | Hydro-deiodination | Other undesired byproducts |
|---|---|---|---|---|---|---|
| 1R | 6b | 640 nm | 6 h | **63%** | 21% | 16% |
| 1B | | 440 nm | 6 h | **52%** | 25% | 23% |
| 2R | 6c | 640 nm | 4 h | **68%** | 18% | 14% |
| 2B | | 440 nm | 4 h | **55%** | 21% | 24% |
| 3R | 6e | 640 nm | 12 h | **56%** | 26% | 18% |
| 3B | | 440 nm | 12 h | **39%** | 29% | 32% |

*Yields reported here are calculated from $^1$H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard. For detailed optimization see the supplementary tables S1-S3.*

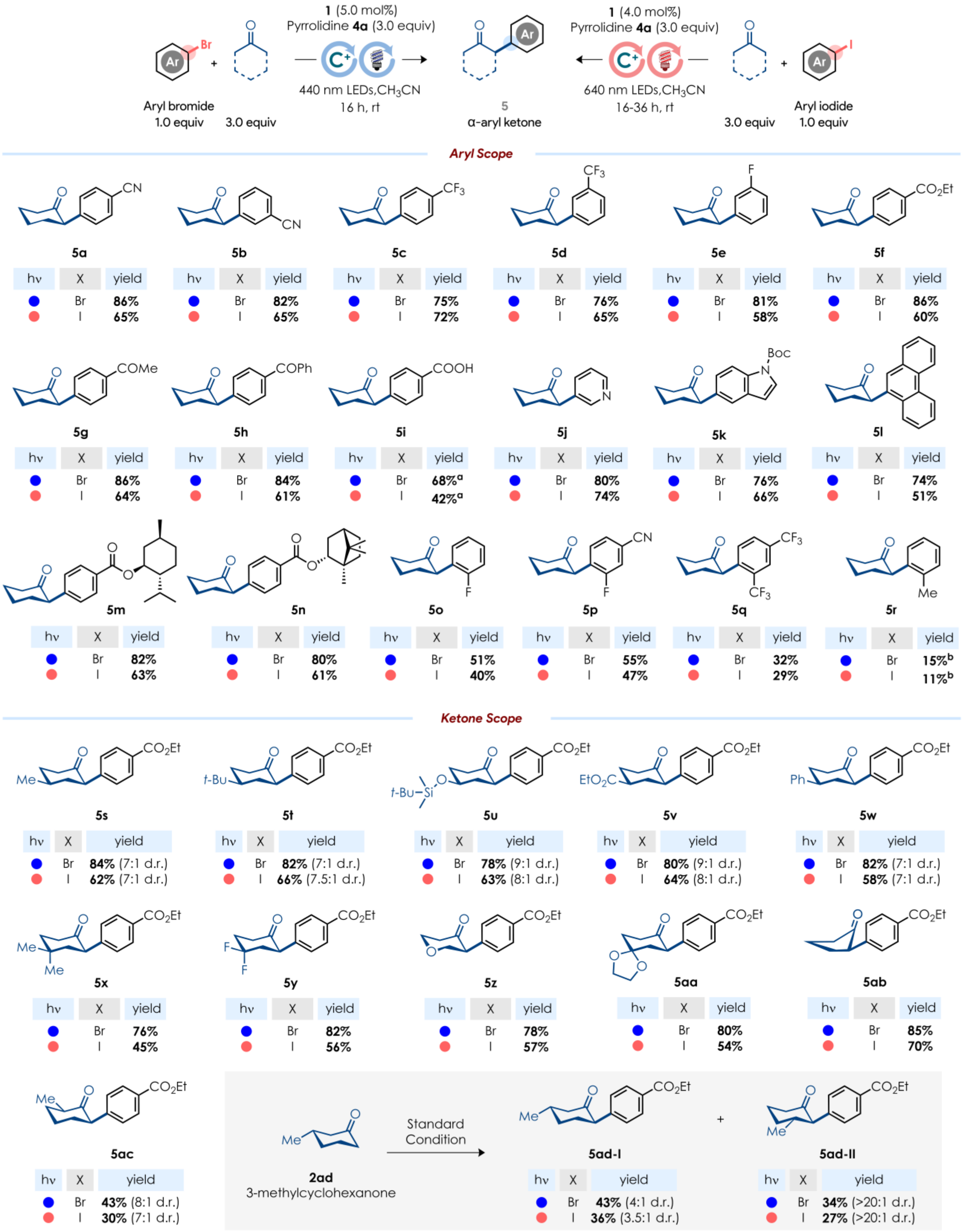


**Figure 2:** Substrate scope for blue and red-light mediated α-arylation of cyclic ketones. For detailed reaction conditions see the experimental section of the supplementary information. [a]DMSO was used as solvent. [b] Not isolated, $^1$H NMR yield calculated using 1,3,5-trimethoxybenzene as the internal standard.

Under red-light irradiation the C(sp$^2$)-Br bond activation was found to be significantly thwarted resulting only in 20% yield and 64% unreacted aryl bromide (Table 1a entry 5 and supplementary table S1). However, switching irradiation wavelength to 440 nm blue-light to activate bromoarene through conPET resulting in an improved yield of 86% in 16 h (Table 1a entry 6).

Changing the catalyst loading, dropping the ketone-pyrrolidine equivalence and swapping pyrrolidine with any other cyclic or acyclic secondary amine resulted in diminished yields (Table 1a entry 7-9 and supplementary table S1). Consistent with our mechanistic understandings, omission of light, catalyst or secondary amine additive halts the reaction immediately (Table 1a entry 10 and supplementary table S1). Within this frame of observations, we investigated the selective C(sp$^2$)-I bond activation of iodobromoarenes with red-light-mediated photoredox catalysis (Table 1b). On that account, we attempted exploring the α-arylation reaction with three different iodobromoarenes (**6b**, **6c**, **6e**). In all three cases, superior product yields were observed under mild red-light irradiation over blue-light (Table 1b entry 1-3). In consistent with our hypothesis of selective C(sp$^2$)-I bond activation under red-light, higher amount of hydro-

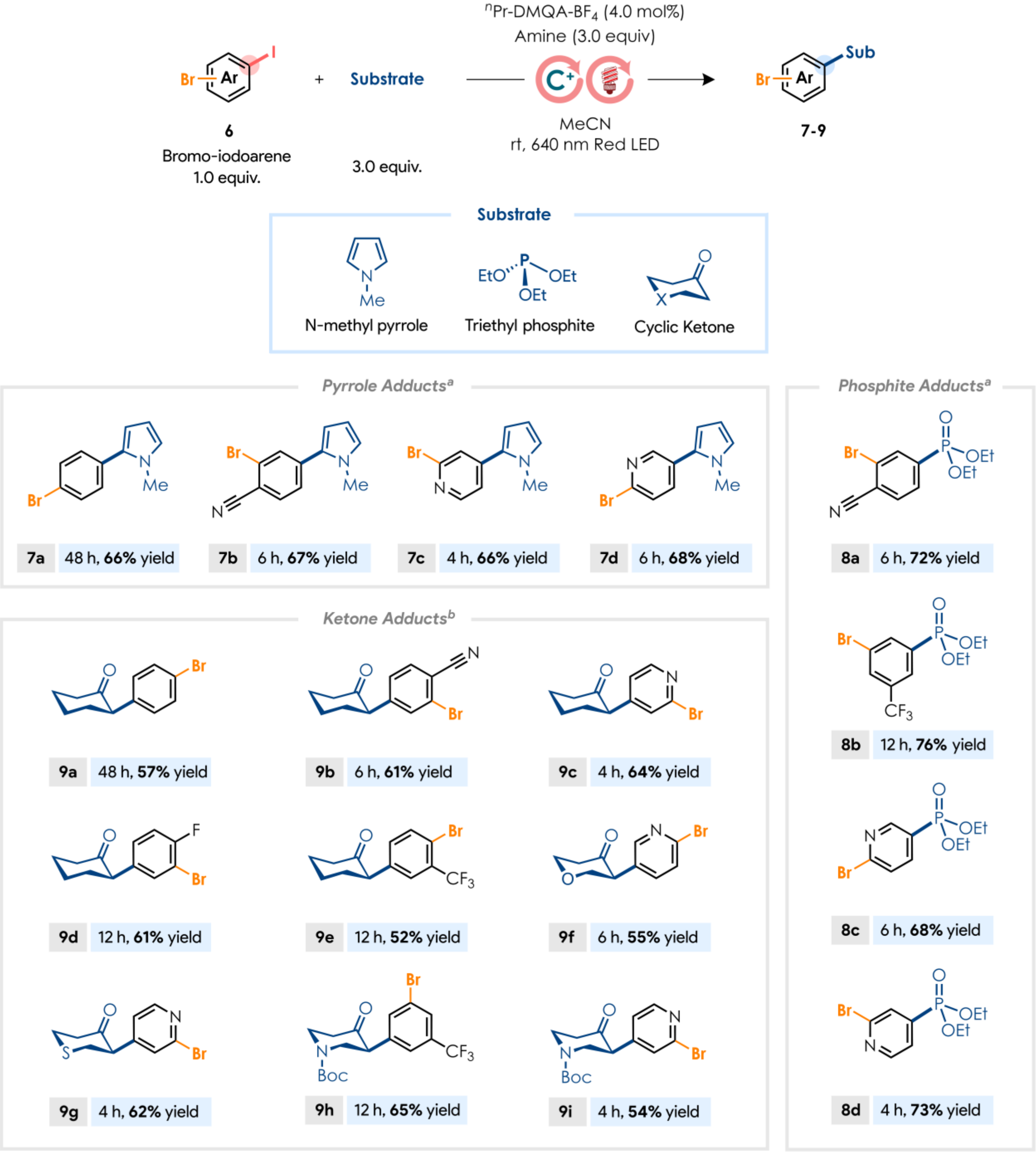


**Figure 3:** Red light selective C(sp$^2$)-I bond activation in iodobromoarenes. $^a$DIPEA was used as amine additive, $^b$Pyrrolidine was used as amine additive.

deiodinated and other undesired byproducts were observed under blue-light irradiation. Overall, these comparative studies highlighted the strength of the red-light photoredox methodology in the context of efficient selective functionalization.

With these optimal conditions for the alpha-arylation of cyclic ketones in hand, we examined the scope with respect to the aryl bromide component under 440 nm blue-light and aryl iodides under 640 nm red-light. As shown in **Figure 2**, medicinally significant functional groups like nitrile, trifluoromethyl and fluorine substituted arylbromides were initially evaluated as these groups are commonly employed to modulate the bioavailability in pharmaceutical developments. In such instances, the corresponding alpha-arylated products were generated in very good yields (**5a-5e**, blue, 75-86% yield). Substitution in para or meta position did not affect the product yield neither in nitrile (**5a** and **5b**, blue, 86% and 82% yield) nor in trifluoromethyl containing substrates (**5c** and **5d**, blue, 75% and 76% yield). Furthermore, *para*-substituted bromoarenes containing most commonly useful functional groups like ester, carbonyl and free acid were well accommodated, furnishing alpha-arylated adducts in very good yields (**5f-5i**, blue, 68-86% yield). In addition to that, heteroaromatic and polyaromatic bromoarenes like bromopyridine, bromoindole and 9-bromophenanthrene were also found to be excellent substrates for this transformation (**5j** and **5l**, blue, 74-80% yield). Similar to these observations, aryl iodides under red-light condition furnished the corresponding products in moderate to good yields (**5a-5l**, red, 42-74% yield). In all instances, the functional group tolerance and the reaction yields are generally found to be consistent with the outcomes observed with blue-light activation of bromo arenes. Furthermore, as a demonstration that this method can be extended to the installation of multiple chiral centers containing arenes, corresponding α-arylated cyclic ketones from natural product containing arenes can be synthesized in excellent efficiencies both in blue (**5m** and **5n**, 82 and 80% yield) and red-light condition (**5m** and **5n**, 63 and 61% yield). Finally, the versatility of this method was probed on challenging ortho-substituted aryl halides. Electron deficient arenes performed moderately (**5o-5q**, 29-55% yield) while electron rich substrates appeared unsuitable (**5r**, 11-15% yield) for this method.

Similar to aryl halides, different cyclic ketones were also evaluated using optimal conditions. A series of substituted cyclohexanone-derived substrates were readily coupled to

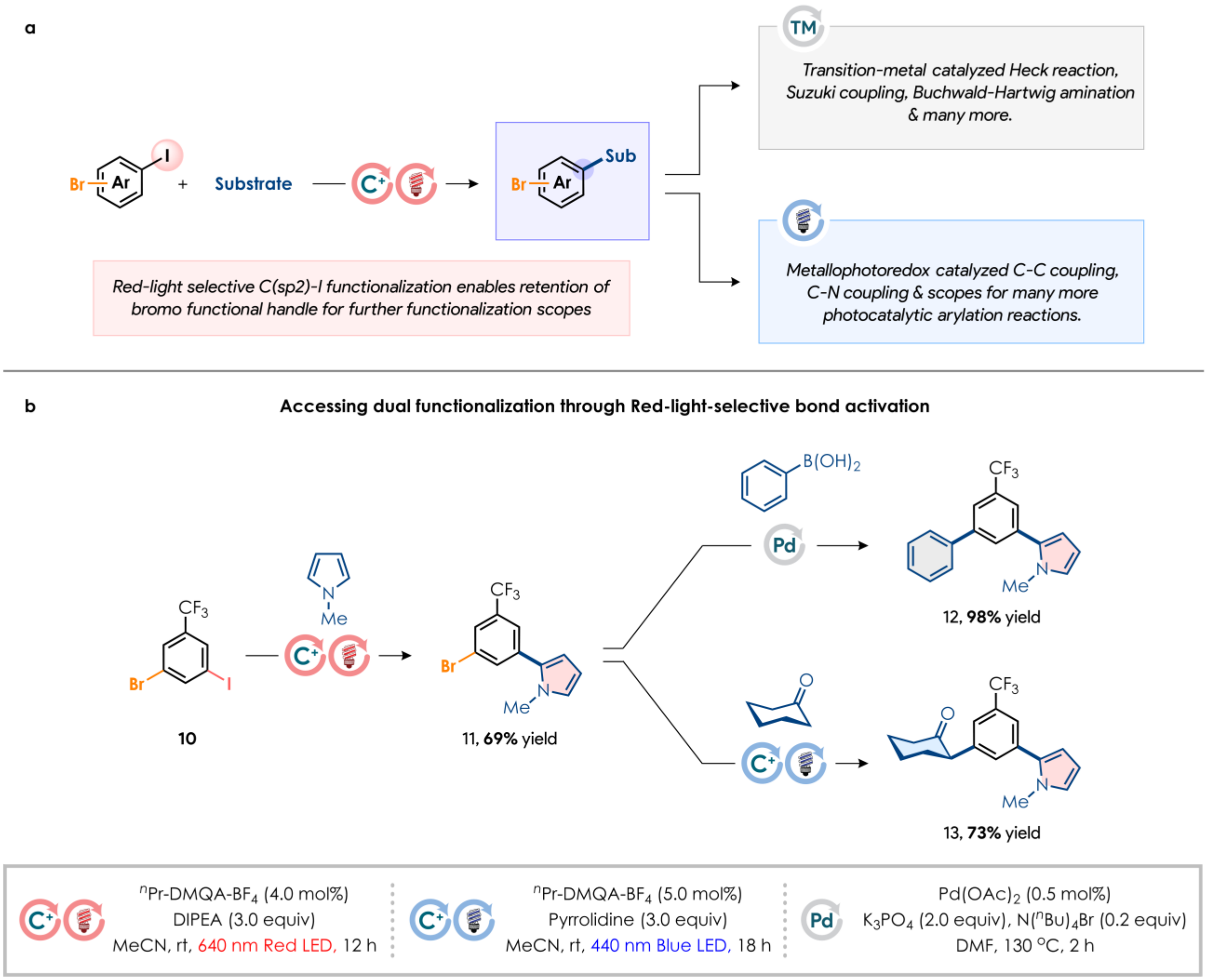


**Figure 4:** Consecutive functionalization of multihalogenated arenes through red-light selective C(sp$^2$)-I bond activation.

the 4-ethylbenzoate moieties. As described earlier, ethyl-4-bromobenzaote was employed under blue-light condition and ethyl-4-iodobenzaote was employed under red-light condition to screen numerous cyclic ketones. It is of note that incorporation of both alkyl and aryl substituents at positions 4 of the cyclohexanone ring were well-tolerated in both reaction conditions (**5s**-**5w**, blue, 78–84% yield and red, 58–66% yield). As expected, the presence of single substituent at the 4-position in the cyclohexanone ring induced higher levels of diastereoselectivity in products. Disubstituted cyclohexanones at the 4-position of the ring also successfully transformed to the corresponding alpha-arylated derivatives in good yield (**5x** and **5y**, blue, 76% and 82% yield; red, 45% and 56% yield). Spirocyclic cyclohexanone derivative and heteroatom containing cyclic ketone were also well tolerated in optimal reaction condition (**5z** and **5aa**, blue, 78% and 80% yield: red, 57% and 54% yield). Further, cyclopentanone was also found to be an efficient ketone substrate for this transformation with excellent outcomes (**5ab**, blue, 85% yield and red, 70% yield). Interestingly, sterically hindered 2-methyl cyclohexanone formed the desired α-arylated product, albeit in a compromised yield (**5ac**, blue, 43% yield and red, 30% yield). Finally, 3-methylcyclohexanone **2ad** furnished two isolable regio-isomeric products (**5ad-I**; blue, 43% yield and red, 36% yield; **5ad-II**; blue, 34% yield and red, 27% yield).

Within this frame of observations, we targeted the selective C($sp^2$)-I bond activation of iodobromoarenes using red-light-mediated photoredox catalysis. On that account, three different aryl functionalization reactions were attempted under red-light irradiation with iodobromoarenes (**Figure 3**). Along with different cyclic ketones, N-methyl pyrrole and triethyl phosphite substrates were employed to demonstrate C($sp^3$)-C($sp^2$), C($sp^2$)-C($sp^2$) and C-P bond formation through selective C($sp^2$)-I bond activation. In case of N-methyl pyrrole and triethyl phosphite arylation, pyrrolidine was substituted with DIPEA as amine additive for improved outcome. Unsubstituted, substituted and heterocyclic bromo-iodobenzenes furnished the desired pyrrole adducts (**7a**-**7d**, 66-68% yield) and phosphite adducts (**8a-8d**, 68-76% yield) in good yields. In both categories, positioning of bromo functionality did not affect the reaction outcomes whether *para* or *meta* to the iodo functional handle. A very similar reaction trend was also observed in case of α-arylation of cyclohexanone with bromo-iodoarenes (**9a-9e**, 52-64% yield). Variation in cyclohexanone *i.e.,* oxygen and sulfur heteroatom containing cyclic ketones were also well accommodated with good outcomes (**9f** and **9g**, 55% and 62% yield). Furthermore, Boc protected 4-piperidone also furnished the desired selective C($sp^2$)-I bond functionalization without any complications (**9h** and **9i**, 65% and 54% yield).

Advantage of keeping a versatile functional handle like bromo on the aryl moiety provides access to a multitude of reaction scopes (**Figure 4a**). In fact, bromoarenes are the go-to starting materials for a great many classic transition-metal catalyzed cross-coupling reactions and expandable to state-of-the-art arylation methodologies.[53-55] Notably, current advancements in catalytic modalities like photo, electro or enzymatic catalysis frequently use the bromo functionalities as feedstock materials. Even the metallophotoredox based dual catalytic C-C and C-N couplings are mostly developed on aryl bromides.[24, 40] Hence, red-light-mediated chromoselective iodobromoarene functionalization facilitates consecutive functionalization modalities in effective efficiencies. Subsequently, our envisaged concept was successfully showcased with 3-bromo-5-iodotrifluoromethylbenzene (**10**) substrate. Under previously described red-light reaction condition, bromoarylated N-methyl pyrrole adduct was isolated in good yield (**11**, 69% yield). This compound **11** with a bromo functional handle was then employed in a ligand-free palladium catalyzed Suzuki reaction condition. Complete conversion to the desired coupling product **12** was achieved within a couple of hours of reaction (**12**, 98% yield).[56] A consecutive photo and transition-metal catalyzed dual functionalization scope was demonstrated in 70% overall yield. Furthermore, blue-light mediated α-arylation of cyclohexanone with compound **12** furnished 73% bis-functionalized product **13**. Such versatility exhibits the potential of consecutive multi-functionalization with only switching the light source that can be highly useful in streamlined process chemistry of industrial setup.

In conclusion, two analogous photoredox methods have been developed with a view to achieving chromoselectivity over photocatalytic bond activation. Efficient aryl bromide functionalization required blue-light irradiation while aryl iodide functionalization has been achieved with red-light mediated reaction conditions. A difference of 200 nm in wavelength and 20.31 kcal/mol in radiation energy smoothly facilitated selective C($sp^2$)-I bond activation in bromo-iodoarenes. Such instances have been illustrated with three different functionalization scopes of C($sp^2$)-I bond selectively preserving the bromo functionality intact. That unveiled the opportunity to explore consecutive dual functionalization using efficient light switch technique.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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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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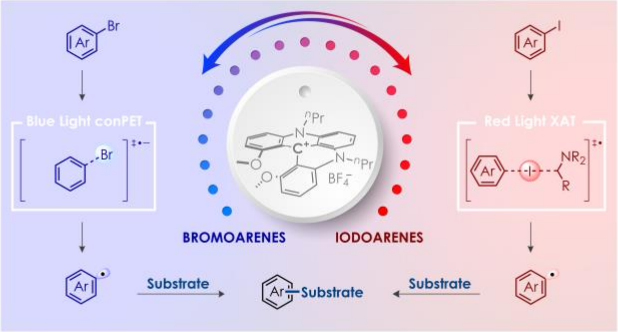
## TOC Graphic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