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Chemoselective Radical Dehalogenation and C–C Bond Formation on Aryl Halide Substrates Using Organic Photoredox Catalysts

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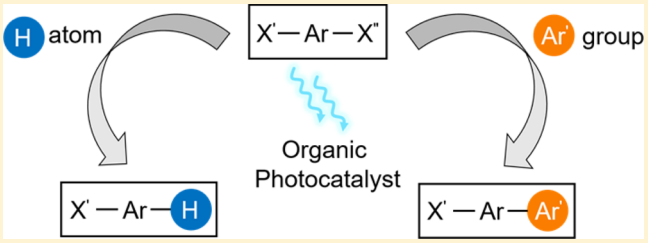
Supporting Information

ABSTRACT: Despite the number of methods available for dehalogenation and carbon–carbon bond formation using aryl halides, strategies that provide chemoselectivity for systems bearing multiple carbon–halogen bonds are still needed. Herein, we report the ability to tune the reduction potential of metal-free phenothiazine-based photoredox catalysts and demonstrate the application of these catalysts for chemoselective carbon–halogen bond activation to achieve C–C cross-coupling reactions as well as reductive dehalogenations. This procedure works both for conjugated polyhalides as well as unconjugated substrates. We further illustrate the usefulness of this protocol by intramolecular cyclization of a pyrrole substrate, an advanced building block for a family of natural products known to exhibit biological activity.



INTRODUCTION

Reductive dehalogenation and carbon–carbon (C–C) cross-coupling reactions with aryl halides are widely utilized in the synthetic organic community as they facilitate the construction of a range of valuable products. Standard methods in this field utilize metal catalysts, which present certain inherent limitations such as high cost or toxicity (e.g., catalytic Pd, Ni, and Rh or stoichiometric Bu_3SnH and SmI_2), as well as harsh and toxic reaction conditions (e.g., pressurized H_2, N_2H_4, and $HSiR_3$ as reductants).[1−3] For these challenges to be addressed, recent developments employing mild, photochemical-based procedures have been reported with many photocatalysts being rare earth metal based.[4,5] To avoid the use of expensive metal catalysts, there has been a concerted effort toward implementing organic photocatalysts, including perylenediimide (PDI)[6] and eosin Y.[7]

These photoredox-based reductions proceed via a carbon-centered radical intermediate that is subsequently trapped using a H atom source or, in many cases, a radical trapping species to form C–C bonds.[8] This includes aryl–aryl bond formations as well as radical cyclizations and atom transfer radical additions.[6,9−12] Such a versatile transformation warrants the development of photocatalytic systems that can chemoselectively activate carbon–halogen bonds (C–X), giving potential for taking a single synthetic derivative bearing multiple C–X bonds and synthesizing a large library of complex targets. Currently, there are very few reports demonstrating the concept of chemoselective dehalogenations, and these are limited to metal-based nonphotocatalyzed systems.[13−16]

Our group recently reported the use of 10-phenylphenothiazine (PTH, **1**) for photomediated, controlled radical polymerizations and radical dehalogenation of aryl and alkyl halides (Figure 1).[17−19] PTH was found to be a highly reducing organic photocatalyst ($E_{1/2}^*$ = −2.1 V vs SCE) with the ability to access a variety of unactivated carbon–halogen bonds that were inaccessible with previous metal-free systems.[19] This

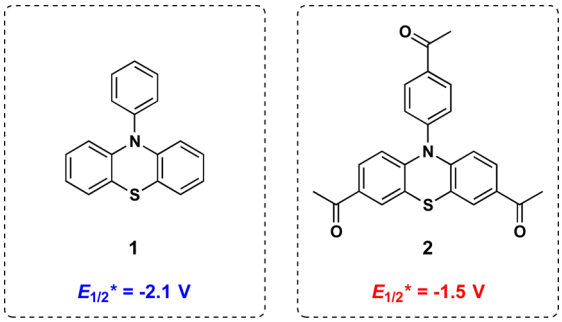


Figure 1. Structure and reduction potential of PTH (**1**) and tris-acetyl-PTH (**2**).

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initial work demonstrated that catalyst **1** can be used for dehalogenations, is tolerant of oxygen, and can be synthesized in a single step from commercially available materials. Herein, we apply this metal-free photoredox strategy to the chemoselective activation of aryl groups bearing multiple carbon−halogen bonds through catalyst design, specifically tuning the reduction potential of the PTH scaffold. This approach can be applied to selective dehalogenation as well as selective C−C bond formation (Figure 2).

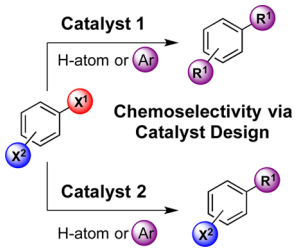

Figure 2. Representative scheme of (a) chemoselective dehalogenation and (b) chemoselective C−C bond formation on a polyhalogenated substrate using an organic photoredox catalyst (X = halides, Ar = aryl group, R = H atom or aryl group).

RESULTS AND DISCUSSION

In developing a catalyst to enable chemoselective reactivity, we hypothesized that incorporating electronically deficient groups on the PTH scaffold could lower the excited state reduction potential of catalyst **1**. Thus, a tris-acetyl-PTH catalyst (**2**) substituted with electron-withdrawing groups on each aryl ring para to the nitrogen was synthesized by subjecting **1** to a Friedel−Crafts acylation with $AlCl_3$ in acetic anhydride. This slight structural modification was found to have a significant influence on the excited state reduction potential ($E_{1/2}^{*} = -1.5$ V vs SCE, see Figure 1) as compared to the originally employed photocatalyst. Furthermore, although visible light was not employed in this study, catalyst **2** was found to absorb well into the visible regime, giving the opportunity to use more mild sources of irradiation while still reducing unactivated substrates.

After observing such a large difference in catalyst reduction potential, we next sought to understand whether or not these values translated into actual changes in reactivity. Thus, a representative aryl iodide (**S1**), bromide (**3**), and chloride (**5**) were chosen as test candidates for dehalogenations using our previously optimized conditions, and reaction progress was monitored using ^{1}H NMR.[19] First, iodobenzene was combined with tributylamine, formic acid, and catalyst **1**, and within 1 h, near complete conversion of the starting material to the dehalogenated product was observed (see Figure S1). In contrast, when catalyst **2** was used under the same reaction conditions, little to no reaction was observed after 1 h. However, at 72 h, both catalysts quantitatively reduced the substrate, which was an encouraging initial result as it suggested differing rates of reactivity. Next, 3-bromopyridine (**3**) was examined, and a similar behavior occurred with the rate of debromination using **1** being significantly faster (4 h, 78%) than when **2** was used (4 h, 14%) (Figure 3a). Again, quantitative conversion of the substrate to the desired product could be achieved using both catalysts with prolonged reaction times (see Figure S2). Next, a more challenging substrate bearing a C−Cl bond with an activating ester group was examined (Figure 3b). In this case, **1** led to quantitative dechlorination within 24 h, but the use of **2** was noticeably slower, reaching only 6% yield within the same time frame and still exhibiting low conversion after 72 h (21%) (see Figure S2). Importantly, these results are within expectations for the relative reduction potentials of the catalysts, as iodides and bromides are known to have lower reduction potentials than chlorides.[20] Encouraged by these results, it was hypothesized that these different reaction rates would lead to selective dehalogenation on substrates with multiple carbon−halogen bonds.

To test chemoselective dehalogenation mediated by **2**, we first examined benzene derivative **7**, which is substituted with four different halogens: iodide, bromide, chloride, and fluoride. The optimized reaction conditions for reductive dehalogenation from the previously reported study were used.[19] After 5 h of irradiation in the presence of **2**, selective deiodination led to **8**, which was obtained in 96% yield with only 4% of deiodinated and debrominated product **9** being formed (Figure 4a). In contrast, when catalyst **1** was used, no selectivity for the formation of **8** and **9** was observed (41 and 59% yield, respectively) within the same 5 h time frame. However, after 48 h, the use of **1** as photocatalyst afforded **9** in 90% yield,

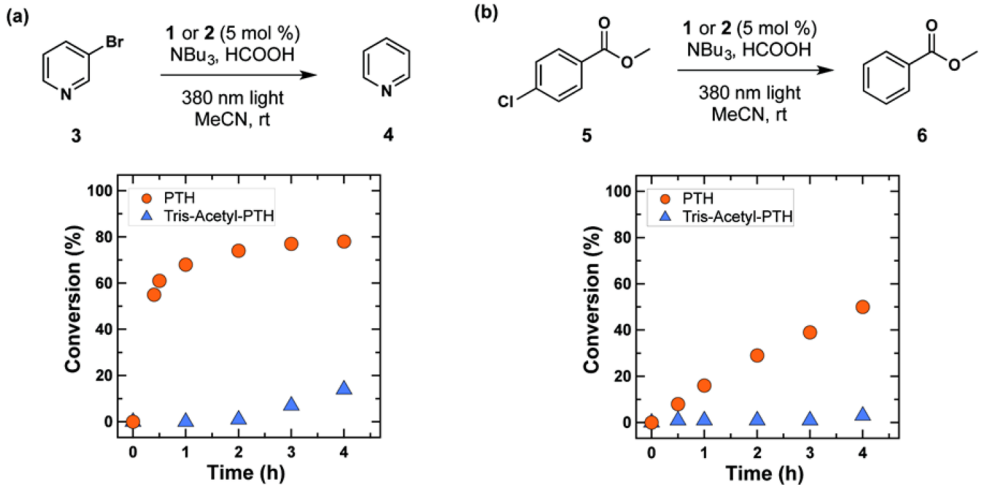

Figure 3. Rate of dehalogenation of (a) 3-bromopyridine (**3**) and (b) methyl 4-chlorobenzoate (**5**) mediated by **1** and **2** for the first 4 h of reaction. ^{1}H NMR yield determined using 1,2,4,5-tetramethylbenzene as an internal standard.

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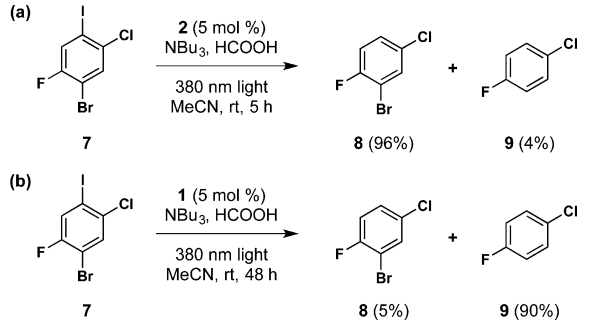

Figure 4. Chemoselective dehalogenation of **7** to its deiodinated product **8** and deiodinated and debrominated product **9** with catalysts **1** and **2**. ^{1}H NMR yield determined using 1,2,4,5-tetramethylbenzene as an internal standard.

demonstrating significant selectivity toward C−I and C−Br bonds over C−Cl and C−F bonds (Figure 4b). Indeed, this initial study using a conjugated multihalogenated substrate gave evidence that different bonds could be selectively activated by catalyst design.

We next examined the reduction of 2-bromo-6-iodobenzonitrile (**10**) and envisioned that inclusion of the electron-withdrawing nitrile functionality would further activate the iodide and bromide, which would help elucidate the tolerance of the iodide selectivity for catalyst **2**. As anticipated, utilizing **2** as a photocatalyst led to deiodinated product **11** in 97% yield with only 3% of **12** after 24 h (Figure 5a). When more reducing

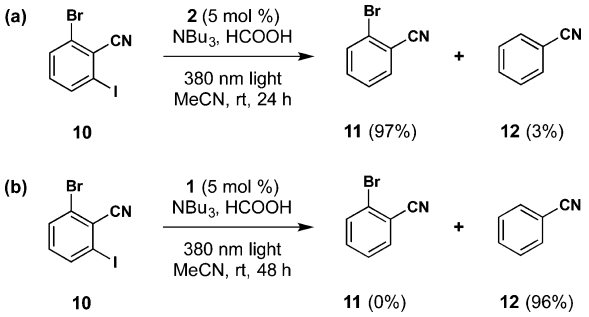

Figure 5. Chemoselective dehalogenation of **10** to its deiodinated product **11** and deiodinated and debrominated product **12** with catalysts **1** and **2**. ^{1}H NMR yield determined using 1,2,4,5-tetramethylbenzene as an internal standard.

photocatalyst **1** was used, fully reduced product **12** was afforded in 83% yield after 24 h and eventually increased to 96% yield after 48 h (Figure 5b). These experiments further highlight that tuning the reduction potential of the PTH scaffold provides a strategy for chemoselective dehalogenation.

To further investigate the potential of this approach, we prepared a substrate bearing activated C−I and C−Br bonds on separate rings with a carbon spacer. In contrast to the previous substrate (**10**), we envisioned that this newly prepared bis-ester (**13**) would allow for examination of the reduction of the C−I bond without affecting the electronics of the other ring containing the C−Br bond (Figure 6). It was found that with **2**, deiodinated product **14** could be isolated in 84% yield after 48 h. With the use of **1**, both the iodide and bromide could be reduced to give **15** in 60% isolated yield in only 24 h.

Having demonstrated successful chemoselective dehalogenation on substrates with multiple C−X bonds with this methodology, we turned our attention to C−C bond forming reactions. Inspired by the work of König and co-workers,[6] we examined the C−C cross coupling of 4-bromobenzonitrile (**16**) with pyrrole in DMSO and found that desired product **17** could be isolated in 56% yield (Figure 7a). The key component in

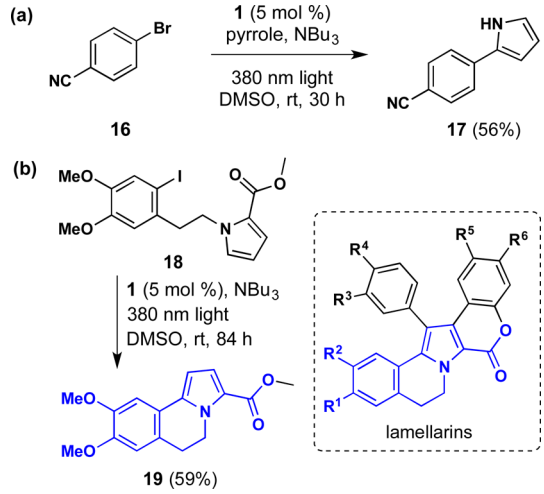

Figure 7. C−C bond forming reactions of (a) **16** with pyrrole and (b) intramolecular cyclization of **18** toward the core of the lamellarins.

C−C bond formation was the use of a large excess of pyrrole to out-compete the H atom abstraction from tributylamine and facilitate trapping of the aryl radical. In addition, using a highly polar solvent, DMSO, significantly aided the C−C bond formation, presumably due to its ability to solvate the charged radical pairs of the catalyst and the substrate.[21]

Following intermolecular aryl−aryl cross coupling with pyrrole derivatives mediated by **1**, we explored the utility of the PTH-based photoredox system for intramolecular cyclization. In particular, we examined a system based on the lamellarins, which are polyaromatic marine alkaloids containing condensed pentacyclic skeletons and are known to show biological activity toward tumor cells (Figure 7b).[22,23] First, an electron-rich aryl iodide with a tethered pyrrole methyl ester (**18**) was prepared according to a literature procedure.[24] Using the same reaction conditions as for the coupling of 4-bromobenzonitrile, only excluding the trapping agent, the lamellarin core (**19**) was isolated in 59% yield.

Having successfully demonstrated C−C bond formation with PTH photocatalyst **2**, we sought to conduct C−C cross

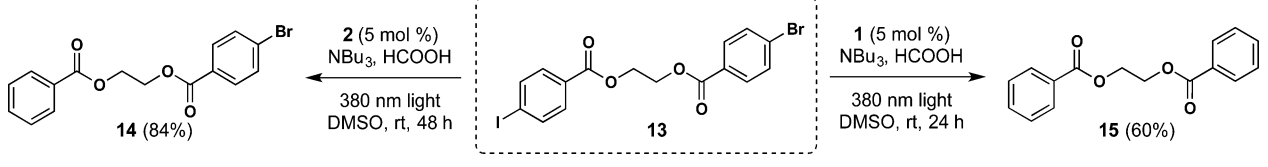

Figure 6. Selective dehalogenation of **13** with catalysts **1** and **2**.

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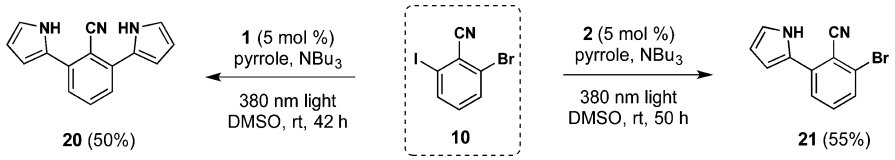

Figure 8. Selective C−C cross coupling reactions of a conjugated polyhalide with pyrrole.

coupling reactions in a chemoselective manner. A substrate bearing C−I and C−Br bonds with an activating nitrile group (**10**) was chosen as the model compound and subjected to the same reaction conditions with an excess amount of pyrrole in the presence of catalyst **1** or **2** (Figure 8). In the reaction with **1**, disubstituted pyrrole **20** was obtained in 50% yield after 42 h. Of particular note, when **2** was used as the photocatalyst, only the C−I bond was activated, leading to the formation of monosubstituted pyrrole **21** in 55% yield. This result demonstrated that selective bond formation was achieved by the preferential reduction of the more highly accessible C−I bond over the corresponding C−Br bond, producing an aryl radical, which in turn was trapped by pyrrole.

In conclusion, we have developed a new metal-free photoredox catalyst based on the PTH scaffold to perform mild and efficient chemoselective dehalogenation and C−C bond forming reactions. We observed that the less reducing catalyst, tris-acetyl-PTH (**2**), can selectively activate C−I bonds, whereas the more reducing PTH catalyst (**1**) can activate both C−I and C−Br bonds. We believe that this protocol will provide a simple, mild, and efficient method for chemoselective dehalogenation and C−C coupling reactions. Further investigation exploring a range of substrates to further elucidate the scope of this methodology is currently underway.

EXPERIMENTAL SECTION

General Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of argon using reagent-grade solvents. All commercially obtained reagents were used as received. Reactions were performed at room temperature (rt, approximately 23 °C) unless stated otherwise. LED strips (380 nm) were purchased from Elemental LED (see www.elementalled.com). Reactions were placed next to the 380 nm source under vigorous stirring while cooling with compressed air. The light intensity was measured to be 1.8 μW/cm^2. Thin-layer chromatography (TLC) was conducted with Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde or potassium permanganate. Flash column chromatography was performed using normal-phase silica gel (60 Å, 230−240 mesh, Merck KGA). ^{1}H NMR spectra were recorded at 400, 500, or 600 MHz and are reported relative to deuterated solvent signals (7.26 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. For quantitative ^{1}H NMR to monitor yields, a 15 s relaxation delay parameter was used with 1,2,4,5-tetramethylbenzene as the internal standard. ^{13}C NMR spectra were recorded at 100 or 125 MHz and are reported relative to deuterated solvent signals (77.16 ppm). Data for ^{13}C NMR spectra are reported as follows: shift (δ ppm). High-resolution mass spectra (HRMS) were obtained using a TOF mass spectrometer, and infrared (IR) spectra were obtained using a Fourier transform infrared spectrometer with an ATR accessory.

*1,1′-(10-(4-Acetylphenyl)-10H-phenothiazine-3,7-diyl)bis(ethan-1-one) (**2**).* To a 100 mL round-bottom flask with stir bar were added CS_2 (4.4 mL) and $AlCl_3$ (871 mg, 6.5 mmol, 5.9 equiv). The mixture was cooled to 0 °C, and a mixture of acetic anhydride (0.51 mL, 5.4 mmol, 4.9 equiv) and phenyl phenothiazine (300 mg, 1.1 mmol, 1 equiv) in CS_2 (2.7 mL) was slowly added dropwise via dropping funnel, resulting in the immediate appearance of a dark purple color. The reaction was allowed to warm slowly to room temperature, stirred for 19 h, and poured over ice water (30 mL), resulting in the immediate appearance of a yellow color. HCl (3 M, 7 mL) was then added dropwise with stirring. The mixture was washed with toluene (3 × 50 mL), and the combined organic layers were washed successively with deionized water, sat. aq $NaHCO_3$, deionized water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a yellow solid, which was purified by column chromatography with toluene/EtOAc (17:3) to afford **2** (289 mg, 66% yield). Mp 231−233 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27−8.22 (m, 2H), 7.58 (d, J = 2.0 Hz, 2H), 7.51−7.47 (m, 2H), 7.41 (dd, J = 8.7, 2.1 Hz, 2H), 6.09 (d, J = 8.6 Hz, 2H), 2.71 (s, 3H), 2.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 195.7, 146.2, 144.0, 137.7, 132.8, 131.5, 130.9, 128.2, 127.2, 119.9, 115.7, 26.9, 26.3; IR (ATR) 3104, 3056, 2993, 2922, 1664, 1568, 1475, 1237, 961, 822 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{24}H_{19}NO_3S$ 401.1086, found 401.1083.

*2-Hydroxyethyl 4-Iodobenzoate (**S2**).* To a solution of ethylene glycol (2.0 mL, 35.863 mmol, 2.0 equiv), triethylamine (1.0 mL, 7.175 mmol, 2.0 equiv), and DMAP (0.0239 g, 0.196 mmol, 0.05 equiv) in CH_2Cl_2 (36 mL) at 0 °C was added 4-iodobenzoyl chloride (0.9795 g, 3.676 mmol, 1.0 equiv). The solution was warmed to room temperature and stirred for 12 h. The reaction was then quenched with an ammonium chloride solution (1 M, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography with hexanes/EtOAc (gradient from 4:1 to 1:1) as the eluant to afford **S2** (0.83 g, 78%) as a colorless solid. Mp 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 20.0, 8.0 Hz, 4H), 4.46−4.42 (m, 2H), 3.96−3.92 (m, 2H), 2.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 137.9, 131.2, 129.4, 101.2, 66.9, 61.4; IR (ATR) 3497, 2958, 2916, 2873, 1695, 1584, 1378, 1274, 1083 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_9H_9IO_3$ 291.9596, found 291.9594.

*2-((4-Bromobenzoyl)oxy)ethyl 4-Iodobenzoate (**13**).* To a solution of **S2** (0.8323 g, 2.850 mmol, 1.0 equiv), triethylamine (0.900 mL, 6.457 mmol, 2.3 equiv), and DMAP (10.0 mg, 0.082 mmol, 0.03 equiv) in CH_2Cl_2 (12 mL) at 0 °C was added 4-bromobenzoyl chloride (1.110 g, 5.058 mmol, 1.8 equiv). The solution was warmed to room temperature and stirred for 12 h. The reaction was then quenched with an ammonium chloride solution (1M, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography with toluene/EtOAc (gradient from 100:0 to 99:1) as the eluant to afford **13** (1.35 g, 99%) as a colorless solid. Mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 4.65 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.8, 138.0, 132.0, 131.3, 131.2, 129.3, 128.7, 128.5, 101.3, 63.0; IR (ATR) 3083, 3033, 2960, 1709, 1583, 1258, 1101, 1010 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{16}H_{12}BrIO_4$ 473.8964, found 473.8968.

*2-(Benzoyloxy)ethyl 4-Bromobenzoate (**14**).* A vial equipped with a magnetic stir bar and fitted with a Teflon screw cap septum was charged with **13** (47.5 mg, 0.100 mmol, 1.0 equiv), tris-acetyl-PTH (2.0 mg, 0.095 mmol, 0.05 equiv), formic acid (19 μL, 0.504 mmol, 5.0 equiv), tributylamine (120 μL, 0.504 mmol, 5.0 equiv), and DMSO (1 mL). The reaction mixture was sparged for 15 min with argon and then vigorously stirred in front of 380 nm LEDs while cooling with compressed air to maintain ambient temperature. After 48 h, the reaction mixture was diluted with EtOAc (10 mL) and quenched with H_2O (30 mL). After the layers were separated, the aqueous layer was

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extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography with hexanes/EtOAc (gradient from 99:1 to 7:1) as the eluant to afford **14** (29.2 mg, 84%) as a colorless solid. Mp 41−44 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 6.9 Hz, 2H), 7.91 (d, J = 8.6 Hz, 2H), 7.61−7.53 (m, 3H), 7.44 (t, J = 7.8 Hz, 2H), 4.66 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.8, 133.3, 131.9, 131.3, 129.8, 128.8, 128.6, 128.54, 128.46, 63.1, 62.7; IR (ATR) 3064, 2955, 2920, 1717, 1590, 1451, 1398, 1259, 1096 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{16}H_{13}BrO_4$ 347.9997, found 347.9990.

*Ethane-1,2-diyl Dibenzoate (**15**).* A vial equipped with a magnetic stir bar and fitted with a Teflon screw cap septum was charged with **13** (49.9 mg, 0.100 mmol, 1.0 equiv), PTH (1.4 mg, 0.005 mmol, 0.05 equiv), formic acid (19 μL, 0.504 mmol, 5.0 equiv), tributylamine (120 μL, 0.504 mmol, 5.0 equiv), and DMSO (1 mL). The reaction mixture was sparged for 15 min with argon and then vigorously stirred in front of 380 nm LEDs while cooling with compressed air to maintain ambient temperature. After 48 h, the reaction mixture was diluted with EtOAc (10 mL) and quenched with H_2O (30 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography with hexanes/EtOAc (gradient from 99:1 to 7:1) as the eluant to afford **15** (16.2 mg, 60%) as a colorless solid.[25] Mp 64−66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.4 Hz, 4H), 7.57 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.6 Hz, 4H), 4.67 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 133.3, 129.9, 129.8, 128.6, 62.9; IR (ATR) 3064, 2959, 2914, 1710, 1602, 1451, 1265, 1113 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{16}H_{14}O_4$ 270.0892, found 270.0889.

*4-(1H-Pyrrol-2-yl)benzonitrile (**17**).* To a 1 dram vial was added a solution of **16** (18.2 mg, 0.100 mmol, 1.0 equiv), pyrrole (0.35 mL, 5.00 mmol, 50.0 equiv), **1** (1.4 mg, 0.005 mmol, 0.05 equiv), and tributylamine (0.12 mL, 0.500 mmol, 5.0 equiv) in DMSO (1.0 mL). The solution was purged with argon for 10 min. The vial was placed next to the 380 nm light under vigorous stirring while cooling with compressed air for 24 h. The reaction was then quenched by adding DI water, and the crude product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, and the product was purified by column chromatography using hexane/EtOAc (99:1 to 70:30) to afford **17** (9.4 mg, 56% yield) as yellowish crystals.[26] Mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 6.95 (s, 1H), 6.67 (s, 1H), 6.35 (q, J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 132.9, 130.2, 123.8, 121.1, 119.3, 111.1, 108.9; IR (ATR) 3358, 3103, 3058, 2996, 2923, 2852, 2223, 1606, 1502, 1453, 1418, 1180, 1116, 839 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{11}H_8N_2$ 168.0687, found 168.0682.

*Methyl 1-(2-Iodo-4,5-dimethoxyphenethyl)-1H-pyrrole-2-carboxylate (**18**).* Methyl 2-pyrrolecarboxylate (216 mg, 1.7 mmol, 1.0 equiv) and NaH (60% dispersion, 74 mg, 1.85 mmol, 1.1 equiv) were stirred in dry DMF (3.4 mL) in an ice-bath for 30 min. A solution of 2-iodo-4,5-dimethoxyphenethyl 4-methylbenzenesulfonate[27] (957 mg, 2.1 mmol, 1.2 equiv) in dry DMF (4.3 mL) was added, and the mixture was stirred for 20 h at room temperature. The DMF was then evaporated under reduced pressure, and Et_2O was added. The organic solution was washed with 1 M HCl, saturated $NaHCO_3$, and brine, dried, and concentrated. The residue was purified by column chromatography with hexanes/EtOAc (gradient from 95:5 to 90:10) to afford **18** (485 mg, 68%) as a white solid. Mp 69−71 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.95 (dd, J = 3.9, 1.8 Hz, 1H), 6.56 (t, J = 2.2 Hz, 1H), 6.36 (s, 1H), 6.02 (dd, J = 4.0, 2.5 Hz, 1H), 4.47 (t, J = 6.9 Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 3.11 (t, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 149.2, 148.3, 133.5, 129.5, 121.4, 121.3, 118.6, 112.9, 107.9, 88.0, 56.2, 55.9, 51.2, 49.3, 42.2; IR (ATR) 3101, 2950, 2836, 1698, 1507, 1437, 1330, 1239, 1211, 1107 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{16}H_{18}INO_4$ 415.0281, found 415.0285.

*Methyl 8,9-Dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (**19**).* To a 2 dram vial was added a solution of **18** (400 mg, 0.96 mmol, 1.0 equiv), **1** (13.3 mg, 0.05 mmol, 0.05 equiv), and tributylamine (1.1 mL, 4.8 mmol, 5.0 equiv) in DMSO (4.8 mL). The solution was purged with argon for 10 min. The vial was placed next to the 380 nm light under vigorous stirring while cooling with compressed air for 84 h. The reaction was then quenched by adding DI water, and the crude product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine and DI water, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the product was purified by column chromatography using hexane/EtOAc (gradient from 100:0 to 70:30) to afford **19** (163 mg, 59% yield) as off-white crystals. Mp 86−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 7.00 (d, J = 4.1 Hz, 1H), 6.73 (s, 1H), 6.42 (d, J = 4.1 Hz, 1H), 4.60 (t, J = 6.8 Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.01 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 148.8, 148.3, 136.5, 124.7, 121.4, 121.1, 118.5, 111.0, 106.9, 103.5, 56.2, 56.1, 51.2, 42.4, 28.7; IR (ATR) 3000, 2954, 2933, 2850, 1694, 1611, 1429, 1243, 1130, 1007, 856, 759 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{16}H_{17}NO_4$ 287.1158, found 287.1160.

*2,6-Di(1H-pyrrol-2-yl)benzonitrile (**20**).* To a 2 dram vial was added a solution of **10** (154 mg, 0.500 mmol, 1.0 equiv), pyrrole (1.75 mL, 25.0 mmol, 50.0 equiv), **1** (6.9 mg, 0.025 mmol, 0.05 equiv), and tributylamine (0.60 mL, 2.5 mmol, 5.0 equiv) in DMSO (2.5 mL). The solution was purged with argon for 10 min. The vial was placed next to the 380 nm light under vigorous stirring while cooling with compressed air for 50 h. The reaction was then quenched by adding DI water, and the crude product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine and DI water, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the product was purified by column chromatography using hexane/EtOAc (gradient from 9:1 to 2:1) to afford **20** (59.0 mg, 50% yield) as an off-white solid. Mp 190−193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 2H), 7.52 (dd, J = 8.6, 7.1 Hz, 1H), 7.44 (d, J = 0.5 Hz, 1H), 7.42 (d, J = 0.9 Hz, 1H), 6.99 (td, J = 2.8, 1.5 Hz, 2H), 6.81 (ddd, J = 3.7, 2.7, 1.5 Hz, 2H), 6.36 (dt, J = 3.7, 2.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 133.2, 128.4, 124.9, 121.2, 120.9, 111.0, 110.4, 101.5; IR (ATR) 3406, 3362, 3121, 2957, 2924, 2853, 2212, 1579, 1468, 1416, 1113, 1088, 1036, 798, 739 cm^{-1}; HRMS (EI) m/z [M − H]$^+$ calcd for $C_{15}H_{10}N_3$ 232.0875, found 232.0868.

*2-Bromo-6-(1H-pyrrol-2-yl)benzonitrile (**21**).* To a 2 dram vial was added a solution of **10** (154 mg, 0.500 mmol, 1.0 equiv), pyrrole (1.75 mL, 25.0 mmol, 50.0 equiv), **2** (10.0 mg, 0.025 mmol, 0.05 equiv), and tributylamine (0.60 mL, 2.5 mmol, 5.0 equiv) in DMSO (2.5 mL). The solution was purged with argon for 10 min. The vial was placed next to the 380 nm light under vigorous stirring while cooling with compressed air for 50 h. The reaction was then quenched by adding DI water, and the crude product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine and DI water, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the product was purified by column chromatography using hexane/EtOAc (gradient from 9:1 to 2:1) to afford **21** (67.1 mg, 55% yield) as an off-white solid. Mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.00 (s, 1H), 6.83 (s, 1H), 6.40−6.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 133.8, 129.9, 127.32, 127.26, 125.6, 121.7, 118.7, 111.6, 110.7, 109.2; IR (ATR) 3388, 3072, 2918, 2852, 2226, 1586, 1558, 1543, 1460, 1125, 1042, 730 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_{11}H_7N_2Br$ 245.9793, found 245.9798.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01034.

NMR conversions for **S1**, **3**, and **5** and proposed mechanism for dehalogenation, and NMR spectra of isolated products **2**, **S2**, **13**−**15**, and **17**−**21** (PDF)

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Notes

The authors declare no competing financial interest.

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