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Communication

Upscaling Photoredox Cross-Coupling Reactions in Batch Using Immersion-Well Reactors

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ABSTRACT: Herein we describe a straightforward approach for the scale-up of photoredox cross-coupling reactions from milligram to multigram scale using immersion-well *batch* reactors with minimal reoptimization of the reaction conditions. This approach can be applied to both homogeneous and, more significantly, *heterogeneous* reaction mixtures. Furthermore, we have used an immersion-well side-loop reactor to perform a reaction on a 400 mmol scale (86 g of aryl bromide).

KEYWORDS: *photoredox, scale-up, cross-coupling, immersion well, side-loop reactor*

INTRODUCTION

Photoredox catalysis (PRC) is a powerful tool that enables novel disconnections, distinct reactivity pathways, and facile access to otherwise difficult to synthesize molecules.[1] With the rapid development of the field, the utility of this technology within the life science industry has become increasingly apparent in recent years. The often-mild reaction conditions make PRC ideal for the preparation of the polar and densely functionalized molecules typically encountered in this industry.[2] Moreover, access to novel scaffolds and the ability to rapidly explore structure−activity relationships (SARs) not readily accessible with other chemical technologies further enhance its potential value. Unfortunately, our experience has demonstrated that despite the apparent uptake of this powerful tool in industrial research laboratories, the challenge of effectively upscaling these reactions even moderately is providing a major hurdle to fully realizing the potential of this important technology, an opinion seemingly shared across the industry.[3]

Key transformations, such as the photoredox-mediated sp^2-sp^3 cross-coupling reactions developed by the groups of MacMillan, Doyle, Molander, and others,[4,5] are incredibly powerful tools for incorporating a diverse range of alkyl groups into polyfunctionalized compounds (Figure 1a). Consequently, they have great potential to become "go-to" reactions for SAR exploration in both drug and agrochemical discovery programs, in a similar vein to the now-pervasive Suzuki−Miyaura palladium-catalyzed cross-coupling reaction. However, the inability to readily scale up these reactions and access the material required (1−100 g) for compound profiling beyond the first in vitro and pharmacokinetic studies is limiting their widespread application.

Flow chemistry is generally considered an ideal solution for upscaling photochemical reactions,[6,7] and numerous examples of contemporary photoredox methods have been demonstrated by the pharmaceutical industry.[8] Photoredox-mediated sp^2-sp^3 cross-coupling reactions have also been performed in continuous flow, with good yields and short residence times reported.[9] However, the typical need for *homogeneous* reaction media and the equipment and knowledge required often render flow solutions unsuitable for upscaling when fast turnaround is required.[10] Moreover, given the large numbers of compounds synthesized in a discovery project, developing individual solutions for the scale-up of a single compound is often not viable for early discovery research projects.[11]

Given the broad applicability and great potential impact of these reactions within the early drug discovery process, we considered that a method enabling the direct scale-up of heterogeneous reactions from the milligram scale to the gram scale was required. To this end, we sought a solution that would enable us to directly reproduce a "Med-Chem" lab synthesis (approximately 100 mg scale) on a 1−100 g scale without the need for significant reoptimization, even if the reaction is heterogeneous in nature.

Our initial multigram-scale reactions, performed using jacketed round-bottom flasks and multiple high-powered blue LED lamps, were unsuccessful. With this setup, it was visibly apparent that most of the light was reflected off the reaction vessel and lost to the surrounding area. Since the challenge of scaling up light-mediated reactions in batch increases exponentially with the reaction volume because of poor light penetration,[12] it was not a surprise that extended reaction times and increased generation of byproducts were observed (Figure 1b).[13] Not to be discouraged, we hypothesized that if we could minimize the photon loss, the reaction efficiency would be restored. Consequently, we turned to a solution

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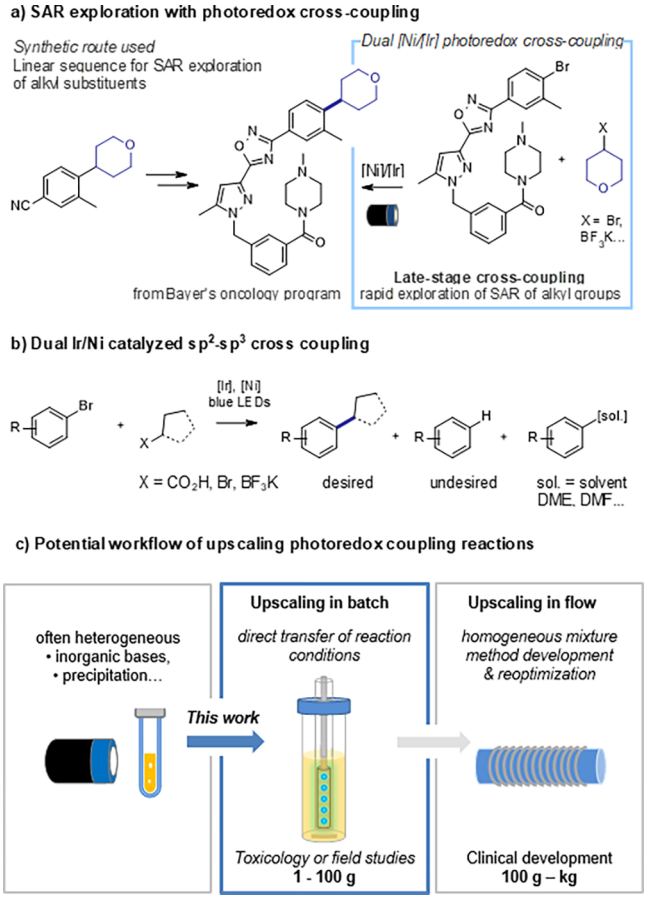

Figure 1. (a) Photoredox cross-couplings provide a rapid way to explore SAR via late-stage diversification. (b) Cross-coupling product and the byproducts often observed. (c) Potential workflow for upscaling: initial milligram-scale reactions in vials, 10−100 g scale reactions in batch involving minimal optimization of reaction conditions (this work), and large-scale reactions using continuous flow processes.

historically utilized for classical UV photochemistry: immersion-well (IW) reactors (Figure 1c).[14,15]

RESULTS AND DISCUSSION

IW reactors consist of a reaction vessel fitted with an immersion tube that encases the light source.[14] The reaction vessel sits on a magnetic stirrer plate and a magnetic stir bar or disk in the vessel is used for stirring. Thus, reactions can be readily carried out with both homogeneous and heterogeneous reaction mixtures. The IW reactor used (Figure 2a), purchased from Peschl Utraviolet GmbH, has vessels with an internal volume between 150 and 850 mL when the immersion tube is inserted and an optical path of between 6.5 and 27 mm. The volume of the reactor and the optical path length are determined by the combination of the reaction vessel and immersion tube size. The LED light rod used has an emission maximum of 460 nm and a radiant flux of 27 W and is cooled by water to prevent overheating.

To survey the utility of IW reactors for upscaling photoredox cross-couplings reactions, we first examined the decarboxylative coupling of amino acids with aryl halides.[5b] Methyl 4-bromobenzoate was coupled with *N*-Boc-DL-proline under literature conditions on 10, 15, 20, and 30 mmol scales. Surprisingly, consistent yields were observed across all

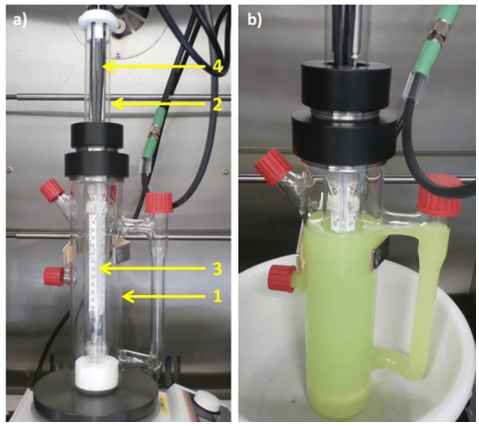

Figure 2. (a) IW reactor. Legend: (1) reaction vessel; (2) immersion tube; (3) LED light rod; (4) hosing for cooling water to cool the LED lamps. (b) Decarboxylative sp^2/sp^3 reaction mixture containing Cs_2CO_3.

reactions, and an isolated yield of 88% was obtained on a 30 mmol scale. This reaction mixture was heterogeneous as cesium carbonate (14 g in the 30 mmol scale reaction) is only sparingly soluble in *N*,*N*-dimethylformamide (DMF) (Figure 2b).

Encouraged by this initial success, we further explored the scale-up of both the decarboxylative cross-coupling and MacMillan's sp^2-sp^3 reductive coupling (Figure 3A,B).[16] In practice, for each reaction a small base/solvent screen (three to five reactions) on a 0.1 mmol scale was first performed to find conditions, as per our standard workflow, and the best conditions were then directly scaled up to 25, 30, or 60 mmol scale. For each reaction, the LCMS trace for the crude reaction mixture of the large-scale reaction was comparable to or even better (cleaner/higher conversion) than that of the corresponding 0.1 mmol scale reaction (see sections 4 and 5 in the Supporting Information (SI)). Furthermore, benzyl chloride and *N*-Boc-DL-proline were coupled on a 30 mmol scale using the IW reactor, enabling the rapid synthesis of a valuable building block (Figure 3C).[17] Additionally, the cross-coupling of alkyltrifluoroborates with aryl halides, which has been extensively developed by Molander and co-workers,[5a] was also readily scaled up to provide >5 g of the desired product (Figure 3D).

Having established that dual Ni/Ir photoredox cross-coupling reactions could be readily scaled up to from the milligram scale to the gram scale in IW reactors, we set a new challenge: *finding a scale-up solution to perform reactions on ∼100 g scale* (approximately 400−500 mmol, 5 L reaction volume).

Once again, the central challenge was maintaining a short optical path length to enable efficient light penetration when upscaling the reaction, and therefore, we could not simply increase the size of the reaction vessel. Instead, we investigated whether the reactions could be further scaled up using an IW reactor with a side loop as a circulating batch system (Figure 4). To this end, the IW reactor vessels (internal volume = 250 mL or 1 L, optical path length = 5 or 10 mm, respectively) and a side-loop tank (a storage tank for the reaction mixture that is in excess of the reactor vessel) were coupled with a pump to circulate the reaction mixture. The reaction mixture is circulated using a magnetic drive pump from the bottom of the loop tank through the pump and into the bottom of the IW

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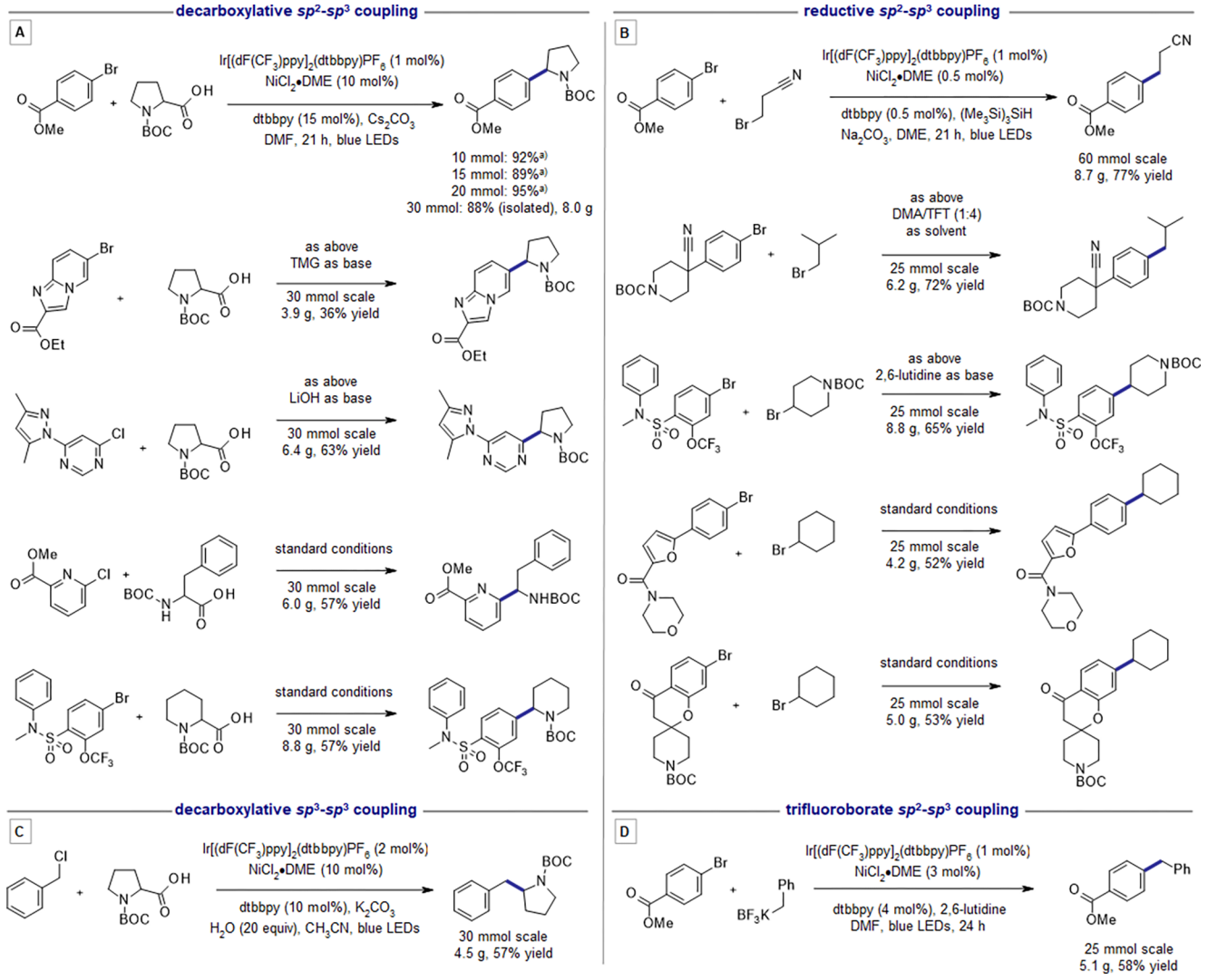

Figure 3. (A) Decarboxylative coupling. (B) sp^2/sp^3 reductive coupling. (C) Decarboxylative coupling with benzyl chloride. (D) Cross-coupling of alkyltrifluoroborate salt. [a]Yields were determined by LCMS calibrated with a standard. Abbreviations: ppy, 2-phenylpyridine; dtbbpy, 4,4′-di-*tert*-butyl-2,2′-dipyridyl; TMG, 1,1,3,3-tetramethylguanidine; DME, 1,2-dimethoxyethane; DMA, *N*,*N*-dimethylacetamide; TFT, α,α,α-trifluorotoluene; BOC, *tert*-butoxycarbonyl.

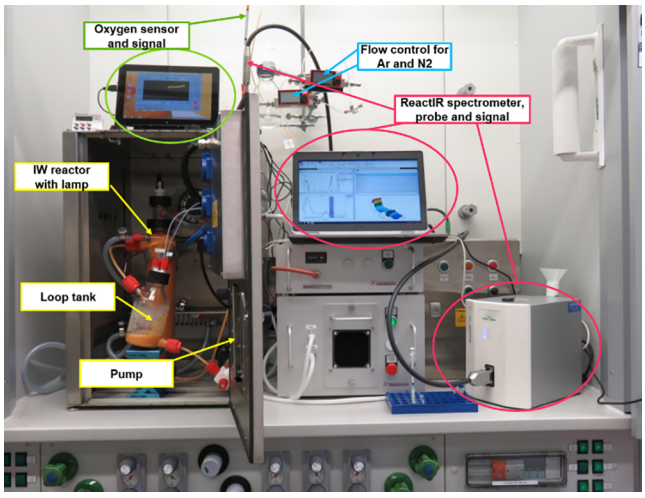

Figure 4. IW side-loop reactor setup running a reductive coupling on a 40 mmol scale.

reactor. The solution is then pumped through the reactor, where it is irradiated, and then back into the top of the loop tank; there is no irradiation in the loop tank. PTFE tubing (internal diameter of 4 mm or 12 mm) connects the loop tank, pump, and reactor. Overall, this is a highly modular solution that can be readily adapted to a wide range of scales simply by changing the volume of the loop tank as desired.

The reductive coupling of methyl 4-bromobenzoate with 3-bromopropanenitrile was selected to test this setup. Prior to further upscaling, a small base screen was performed to identify the optimal base for the reaction, and 2,6-lutidine was found to be superior to Na_2CO_3 (see SI section 8.1 for details). While the reaction mixture was initially homogeneous, formation of a precipitate (presumably the HBr salt of the base) upon irradiation caused the reaction mixture to become heterogeneous within 15 min. The coupling was initially tested in the side-loop reactor on a 40 mmol scale (reaction volume = 500 mL, internal volume of IW reactor vessel = 250 mL, flow rate = 9 L/min) using an LED light rod with a radiant flux of 47 W (λ_{max} = 420 nm). Through close monitoring of the reaction using calibrated LCMS, it was determined that the reaction

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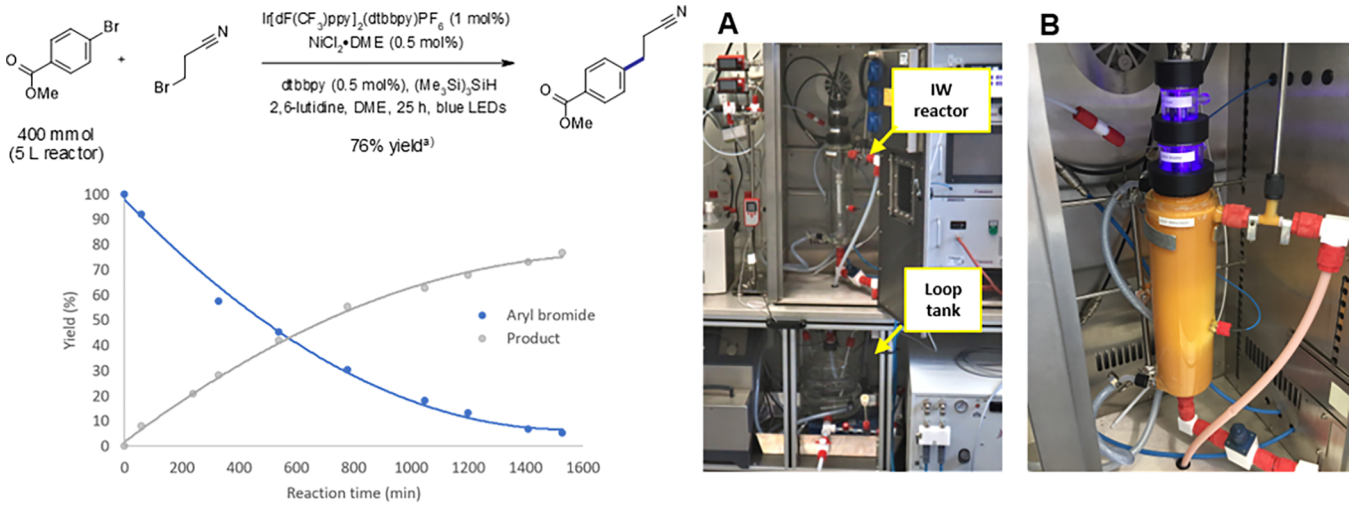

Figure 5. Photoredox sp^2-sp^3 reductive couplings performed in an IW side-loop reactor setup on a 400 mmol scale with a radiant flux of 47 W (λ_{max} = 420 nm). (left) Time course of the reaction. (right) Photograps of (A) the reactor setup and (B) the IW reaction under irradiation. [a]Determined by LCMS calibrated with a standard.

reached completion after 8 h of irradiation (87% yield, 4.4 mmol/h) (see SI section 8.2 for details).

With this promising result in hand, we further scaled up this reaction 10-fold to 400 mmol scale (86 g of methyl 4-bromobenzoate, reaction volume = 5 L). The reaction was performed in a 1 L IW reactor combined with a 5 L looping tank (Figure 5, photo A) and gave the desired product in 76% yield. Minimal incident light is lost when this IW setup is used (see Figure 5, photo B), thus resulting in efficient irradiation of the reaction mixture and high yields (yield = 12.2 mmol/h). Detailed investigation of the reactor design and profiling of the reaction parameters, including light penetration, stirring efficiency, and photon flux, are still required. To that end, analysis of more powerful light sources is currently ongoing to determine whether the reaction time can be further decreased.

■ CONCLUSION

We have demonstrated that immersion-well reactors are an effective solution for upscaling photoredox cross-coupling reactions in batch. Because of the reduced loss of incident photons achieved through the use this reaction setup, we have found that reaction conditions developed on a milligram scale can be applied on a multigram scale. More specifically, four different photoredox-catalyzed carbon−carbon cross-couplings have been investigated on 10−400 mmol scale. By sharing our solution to this challenge, we hope that chemists working in both the life science industry and academia will recognize that these highly valuable cross-coupling reactions can be readily applied on preparative scale in batch.

■ EXPERIMENTAL METHODS

Synthesis of *tert*-Butyl 2-(4-Methoxycarbonylphenyl)-pyrrolidine-1-carboxylate on a 30 mmol Scale. To the reaction flask fitted with a stirring magnet were added methyl 4-bromobenzoate (30 mmol, 6.45 g), 1-*tert*-butoxycarbonyl-pyrrolidine-2-carboxylic acid (45 mmol, 9.69 g), Cs_2CO_3 (45 mmol, 14.7 g), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.3 mmol, 337 mg), $NiCl_2$·DME (3 mmol, 659 mg), and dtbbpy (3.6 mmol, 966 mg). The immersion tube was fitted into the reactor, and DMF (400 mL) was added to the flask. The mixture was degassed by bubbling argon through the solution for 20 min, and then the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S2). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (8.0 g, 88% yield). The data were in accordance with those previously reported.[5b]

Synthesis of Ethyl 6-(1-*tert*-Butoxycarbonylpyrrolidin-2-yl)imidazo[1,2-*a*]pyridine-2-carboxylate on a 30 mmol Scale. To the reaction flask fitted with a stirring magnet were added ethyl 6-bromoimidazo[1,2-*a*]pyridine-2-carboxylate (30 mmol, 8.07 g), 1-*tert*-butoxycarbonylpyrrolidine-2-carboxylic acid (45 mmol, 9.69 g), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.3 mmol, 337 mg), $NiCl_2$·DME (3 mmol, 659 mg), and dtbbpy (4.5 mmol, 1.21 g). The immersion tube was fitted into the reactor, and DMF (400 mL) was added to the flask, followed by TMG (45 mmol, 5.63 mL). The mixture was degassed by bubbling argon through the solution for 20 min, and then the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, then the crude reaction mixture was analyzed by LCMS (Figure S3 SI). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (3.9 g, 36% yield) as a mixture of rotamers (1:1 A:B). ^1H NMR (600 MHz, DMSO-d_6) δ ppm 8.68−8.63 (m, 1H), 7.63−7.54 (m, 1H), 7.47−7.38 (m, 1H), 6.82−6.70 (m, 1H), 5.40−5.29 (m, 1H), 4.41−4.34 (m, 2H), 3.66−3.63 (m, 1H),

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3.49−3.46 (m, 1H), 2.48−2.31 (m, 1H), 1.98−1.89 (m, 1H), 1.88−1.72 (m, 2H), 1.42 (s, 9H, A), 1.38−1.31 (m, 3H), 1.04 (m, 9H, B). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 163.3, 154.0, 153.5, 145.8, 142.1, 141.0, 136.6, 136.5, 127.1, 116.4, 116.3, 115.6, 115.4, 109.5, 109.1, 79.7, 79.1, 60.79, 57.3, 57.0, 47.2, 46.9, 31.3, 30.0, 28.6, 28.1, 23.8, 23.3, 14.8 (five signals overlapping). HRMS (ES-TOF) m/z calcd for $C_{19}H_{25}N_3O_4H$ $[M + H]^+$ 360.1918, found 360.1909.

Synthesis of *tert*-Butyl 2-[6-(3,5-Dimethylpyrazol-1-yl)pyrimidin-4-yl]pyrrolidine-1-carboxylate on a 30 mmol Scale. To the reaction flask fitted with a stirring magnet were added 4-chloro-6-(3,5-dimethylpyrazol-1-yl)-pyrimidine (30 mmol, 6.26 g), 1-*tert*-butoxycarbonylpyrrolidine-2-carboxylic acid (45 mmol, 9.69 g), LiOH (45 mmol, 1.08 g), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.3 mmol, 337 mg), $NiCl_2$·DME (3 mmol, 659 mg), and dtbbpy (4.5 mmol, 1.21 g). The immersion tube was fitted into the reactor, and DMF (400 mL) was added to the flask. The mixture was degassed by bubbling argon through the solution for 20 min, and then the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, then the crude reaction mixture was analyzed by LCMS (Figure S4). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (6.4 g, 63%) as a mixture of rotamers (3:2 A:B). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.98−8.93 (m, 1H, A+B), 7.72 (s, 1H, A), 7.68 (s, 1H, B), 6.22 (s, 1H, A+B), 4.86−4.75 (m, 1H A+B), 3.58−3.44 (m, 2H, A+B), 2.67 (s, 3H, A+B), 2.44−2.28 (m, 1H, A+B), 2.21 (s, 3H, A+B), 1.96−1.81 (m, 3H, A+B), 1.44−1.36 (m, 9H, B), 1.14 (m, 9H, A). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 173.4 (A), 172.6 (B), 158.8 (A), 158.6 (B), 157.5(0) (B), 157.4(5) (A), 153.6 (B), 153.1 (A), 151.1 (A), 151.0 (B), 142.4 (B), 142.3 (A), 111.0 (B), 110.9 (A), 106.3 (A), 106.2 (B), 78.9 (B), 78.5 (A), 61.5 (A), 61.2 (B), 47.1 (B), 46.9 (A), 33.2 (A), 32.1 (B), 28.0 (B), 27.7 (A), 26.27, 23.4 (B), 22.9 (A), 15.0 (B), 13.4 (A) (one signal overlapping). HRMS (ES-TOF) m/z calcd for $C_{18}H_{25}N_5O_2H$ $[M + H]^+$ 343.2081, found 343.2082.

Synthesis of Methyl 6-[1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]pyridine-2-carboxylate on a 30 mmol Scale. To the reaction flask fitted with a stirring magnet were added methyl 6-chloropyridine-2-carboxylate (30 mmol, 5.15 g), 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoic acid (45 mmol, 11.9 g), Cs_2CO_3 (45 mmol, 14.7 g), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.3 mmol, 337 mg), $NiCl_2$·DME (3 mmol, 659 mg), and dtbbpy (4.5 mmol, 1.21 g). The immersion tube was fitted into the reactor, and DMF (400 mL) was added to the flask. The mixture was degassed by bubbling argon through the solution for 20 min, and then the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S5). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (6.0 g, 57% yield) as a mixture of rotamers (9:1 A:B). ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 8.00−7.93 (m, 2H, A+B), 7.64 (d, J = 7.5 Hz, 1H, A+B), 7.51 (d, J = 7.5 Hz, 1H, A+B), 7.29−7.24 (m, 4H, A+B), 7.19−7.21 (m, 1H, A+B), 4.93−4.90 (m, 1H, A), 4.83−4.77 (m, 1H, B), 3.91 (s, 3H, A+B), 3.13 (dd, J = 13.7, 4.9 Hz, 1H, A+B), 2.95 (dd, J = 13.7, 10.4 Hz, 1H, A+B), 1.30 (s, 9H, A), 1.12 (s, 9H, B). ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 165.3, 162.7, 155.2, 146.7, 138.5, 138.1, 129.2, 128.1, 126.2, 124.5, 123.3, 78.0, 57.3, 52.4, 40.5, 28.2. HRMS (ES-TOF) m/z calcd for $C_{20}H_{24}N_2O_4H$ $[M + H]^+$ 357.1809, found 357.1811.

Synthesis of *tert*-Butyl 2-{3-Trifluoromethoxy-4-[methyl(phenyl)sulfamoyl]phenyl}piperidine-1-carboxylate on a 30 mmol Scale. To the reaction flask fitted with a stirring magnet were added 4-bromo-2-hydroxy-*N*-methyl-*N*-phenylbenzenesulfonamide (30 mmol, 12.3 g), 1-*tert*-butoxycarbonylpiperidine-2-carboxylic acid (45 mmol, 10.3 g), Cs_2CO_3 (45 mmol, 14.7 g), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.3 mmol, 337 mg), $NiCl_2$·DME (3 mmol, 659 mg), and dtbbpy (4.5 mmol, 1.21 g). The immersion tube was fitted into the reactor, and DMF (400 mL) was added to the flask. The mixture was degassed by bubbling argon through the solution for 20 min, and then the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S6). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (8.8 g, 57% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.75 (d, J = 8.2 Hz, 1H), 7.40−7.37 (m, 1H), 7.34−7.30 (m, 2H), 7.28−7.25 (m, 1H), 7.21 (s, 1H), 7.19−7.17 (m, 2H), 5.31−5.28 (m, 1H), 3.95−3.91 (m, 1H), 3.28 (s, 3H), 2.70 (t, J = 3.3 Hz, 1H), 2.23−2.19 (m, 1H), 1.87−1.79 (m, 1H), 1.60−1.53 (m, 2H), 1.47−1.39 (m, 1H), 1.36 (s, 9H), 1.19−1.14 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 154.5, 149.9, 145.4, 140.5, 132.0, 129.0, 128.0, 127.2, 126.1, 125.2, 118.6, 120.2 (q, J = 261.00 Hz), 79.3, 53.0, 38.2, 28.0, 27.8, 24.3, 18.7 (one signal overlapping). HRMS (ESI-TOF) m/z calcd for $C_{24}H_{29}F_3N_2O_5SH$ $[M + H]^+$ 515.1822, found 515.1822.

Synthesis of Methyl 4-(2-Cyanoethyl)benzoate on a 60 mmol Scale. To the reaction flask fitted with a stirring magnet were added methyl 4-bromobenzoate (60.0 mmol, 12.9 g), Na_2CO_3 (120 mmol, 12.7 g), and Ir[dF(CF_3)-ppy]$_2$(dtbbpy)PF_6 (0.6 mmol, 673 mg), followed by DME (600 mL). A stock solution of $NiCl_2$·DME (0.3 mmol, 65.9 mg) and dtbbpy (0.3 mmol, 80.5 mg) in DME (20 mL) was prepared and added to the reaction mixture. 3-Bromopropanenitrile (120 mmol, 9.92 mL) was added to the reaction mixture, and the mixture was degassed by bubbling argon through the solution for 20 min. After the reaction mixture was degassed, TTMSS (60 mmol, 18.5 mL) was added, and the

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flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S7). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (8.7 g, 77% yield). The data were in accordance with those previously reported.[18]

Synthesis of *tert*-Butyl 4-Cyano-4-(4-isobutylphenyl)-piperidine-1-carboxylate on a 25 mmol Scale. To the reaction flask fitted with a stirring magnet were added *tert*-butyl 4-(4-bromophenyl)-4-cyanopiperidine-1-carboxylate (25.0 mmol, 9.13 g), Na_2CO_3 (50 mmol, 5.30 g), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.25 mmol, 280 mg), followed by α,α,α-trifluorotoluene (240 mL) and DMA (40 mL). A stock solution of $NiCl_2$·DME (0.125 mmol, 27.5 mg) and dtbbpy (0.125 mmol, 33.6 mg) in DMA (20 mL) was prepared and added to the reaction mixture. 1-Bromo-2-methylpropane (75 mmol, 8.02 mL) was added to the reaction mixture, and the mixture was degassed by bubbling argon through the solution for 20 min. After the reaction mixture was degassed, TTMSS (25 mmol, 7.71 mL) was added, and the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S8). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (6.2 g, 72% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.44 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.2 Hz, 2H), 4.20−4.03 (m, 2H), 3.01 (br s, 2H), 2.47−2.45 (m, 2H), 2.11 (br d, J = 12.3 Hz, 2H), 1.96−1.77 (m, 3H), 1.42 (s, 9H), 0.86 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 153.6, 141.1, 137.0, 129.5, 125.3, 121.6, 79.1, 43.9, 41.7, 35.0, 29.5, 28.0, 22.1 (one signal overlapping). HRMS (ESI-TOF) m/z calcd for $C_{21}H_{30}N_2O_2Na$ $[M + Na]^+$ 365.2199, found 365.2186.

Synthesis of *tert*-Butyl 4-{3-Trifluoromethoxy-4-[methyl(phenyl)sulfamoyl]phenyl}piperidine-1-carboxylate on a 25 mmol Scale. To the reaction flask fitted with a stirring magnet were added 4-bromo-2-hydroxy-*N*-methyl-*N*-phenylbenzenesulfonamide (25.0 mmol, 10.3 g), *tert*-butyl 4-bromopiperidine-1-carboxylate (75.0 mmol, 19.8 g), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.25 mmol, 280 mg), followed by DME (600 mL). A stock solution of $NiCl_2$·DME (0.125 mmol, 27.5 mg) and dtbbpy (0.125 mmol, 33.6 mg) in DME (20 mL) was prepared and added to the reaction mixture. The mixture was degassed by bubbling argon through the solution for 20 min. After the reaction mixture was degassed, TTMSS (25 mmol, 7.71 mL) was added, and the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S9). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (8.8 g, 65% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.69−7.66 (m, 1H), 7.44−7.41 (m, 2H), 7.36−7.31 (m, 2H), 7.28−7.24 (m, 1H), 7.20−7.16 (m, 2H), 4.12−4.02 (m, 2H), 3.26 (s, 3H), 2.88 (tt, J = 12.2, 3.4 Hz, 1H), 2.84−2.71 (m, 2H), 1.79−1.75 (m, 2H), 1.49 (qd, J = 12.2, 4.4 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 154.3, 153.8, 145.1, 140.5, 131.7, 129.0, 127.8, 127.1, 126.0, 125.6, 119.7, 119.6 (q, J = 259.21 Hz), 78.6, 54.9, 41.2, 38.1, 32.0, 28.1. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{29}F_3N_2O_5SNa$ $[M + Na]^+$ 537.1641, found 537.1637.

Synthesis of [5-(4-Cyclohexylphenyl)-2-furyl]-(morpholino)methanone on a 25 mmol Scale. To the reaction flask fitted with a stirring magnet were added [5-(4-bromophenyl)-2-furyl](morpholino)methanone (25.0 mmol, 8.41 g), bromocyclohexane (75.0 mmol, 9.02 g), Na_2CO_3 (50 mmol, 5.30 g), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.25 mmol, 280 mg), followed by DME (600 mL). A stock solution of $NiCl_2$·DME (0.125 mmol, 27.5 mg) and dtbbpy (0.125 mmol, 33.6 mg) in DME (20 mL) was prepared and added to the reaction mixture. The mixture was degassed by bubbling argon through the solution for 20 min. After the reaction mixture was degassed, TTMSS (25 mmol, 7.71 mL) was added, and the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S10). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (4.2 g, 52% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.68 (m, J = 8.2 Hz, 2H), 7.31 (m, J = 8.2 Hz, 2H), 7.13 (d, J = 3.5 Hz, 1H), 7.04 (d, J = 3.5 Hz, 1H), 3.87−3.69 (m, 4H), 3.69−3.63 (m, 4H), 2.56−2.52 (m, 1H), 1.79 (br d, J = 11.3 Hz, 4H), 1.70 (br d, J = 12.3 Hz, 1H), 1.46−1.31 (m, 4H), 1.23 (br d, J = 12.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 158.1, 154.5, 148.1, 145.8, 127.3, 127.0, 124.1, 118.2, 106.4, 66.2, 43.5, 33.7, 26.2, 25.5 (one signal overlapping). HRMS (ESI-TOF) m/z calcd for $C_{21}H_{25}NO_3H$ $[M + H]^+$ 340.1909, found 340.1907.

Synthesis of *tert*-Butyl 7-Cyclohexyl-4-oxospiro-[chromane-2,4′-piperidine]-1′-carboxylate on a 25 mmol Scale. To the reaction flask fitted with a stirring magnet were added *tert*-butyl 7-cyclohexyl-4-oxospiro-[chromane-2,4′-piperidine]-1′-carboxylate (25.0 mmol, 9.91 g), bromocyclohexane (75.0 mmol, 9.02 g), Na_2CO_3 (50 mmol, 5.30 g), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.25 mmol, 280 mg), followed by DME (600 mL). A stock solution of $NiCl_2$·DME (0.125 mmol, 27.5 mg) and dtbbpy (0.125 mmol, 33.6 mg) in DME (20 mL) was prepared and added to the

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reaction mixture. The mixture was degassed by bubbling argon through the solution for 20 min. After the reaction mixture was degassed, TTMSS (25 mmol, 7.71 mL) was added, and the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S11). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (5.0 g, 53% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.53 (d, J = 2.2 Hz, 1H), 7.45 (dd, J = 8.5, 2.2 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 3.78−3.63 (m, 2H), 3.23−3.01 (m, 2H), 2.80 (s, 2H), 1.85 (br d, J = 13.2 Hz, 2H), 1.80−1.73 (m, 4H), 1.69 (br d, J = 12.3 Hz, 1H), 1.60 (br t, J = 10.4 Hz, 2H), 1.42−1.30 (m, 13H), 1.27−1.10 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 191.5, 156.8, 153.7, 140.2, 135.2, 122.8, 119.9, 118.1, 78.7, 77.6, 46.7, 42.5, 33.8, 28.0, 26.2, 25.4 (two signals overlapping). HRMS (ESI-TOF) m/z calcd for $C_{24}H_{33}NO_4Na$ $[M + Na]^+$ 422.2299, found 422,2302.

Synthesis of *tert*-Butyl 2-Benzylpyrrolidine-1-carboxylate on a 30 mmol Scale. To the reaction flask fitted with a stirring magnet were added 1-*tert*-butoxycarbonylpyrrolidine-2-carboxylic acid (45 mmol, 9.69 g), K_2CO_3 (60 mmol, 8.29 g), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.6 mmol, 673 mg), $NiCl_2$·DME (3 mmol, 659 mg), and 4,4′-dimethoxy-2,2′-bipyridine (3.0 mmol, 649 mg). The immersion tube was fitted into the reactor, and acetonitrile (300 mL) was added to the flask, followed by chloromethylbenzene (30 mmol, 3.45 mL). The mixture was degassed by bubbling argon through the solution for 20 min, and then degassed water (600 mmol, 10.8 mL) was added and the flask was sealed (*note: this setup is not gastight—the CO_2 generated is released through the seals, preventing pressure buildup!*). The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S12). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (4.5 g, 57% yield). The data were in accordance with those previously reported.[17]

Synthesis of Methyl 4-Benzylbenzoate on a 40 mmol Scale. To the reaction flask fitted with a stirring magnet were added methyl 4-bromobenzoate (40 mmol, 8.60 g), potassium benzyltrifluoroborate (50 mmol, 9.90 g), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.4 mmol, 449 mg), $NiCl_2$·DME (1.2 mmol, 264 mg), and dtbbpy (1.6 mmol, 429 g). The immersion tube was fitted into the reactor, and DMF (400 mL) was added to the flask, followed by 2,6-lutidine (140 mmol, 16.3 mL). The mixture was degassed by bubbling argon through the solution for 20 min, and then the flask was sealed. The reaction mixture was placed in the PhotonCabinet, and the lamp was placed inside the immersion tube. The reaction mixture was irradiated for 21 h, and then the crude reaction mixture was analyzed by LCMS (Figure S13). Following the reaction, water (200 mL) was added, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with water and brine, dried with Na_2SO_4, and filtered. The reaction mixture was concentrated and purified by silica gel column chromatography on a gradient column to provide the pure product (5.1 g, 58% yield). The data were in accordance with those previously reported.[5a]

Synthesis of Methyl 4-(2-Cyanoethyl)benzoate on a 400 mmol Scale in the Side-Loop Reactor. To the reaction flask fitted with immersion tube and the connected side loop with PTFE tubing (internal diameter = 12 mm) were added methyl 4-bromobenzoate (400 mmol, 86.0 g), 2,6-lutidine (800 mmol, 85.7 g), and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (4.0 mmol, 4.49 g), followed by DME (4.59 L). A solution of $NiCl_2$·DME (2 mmol, 439 mg) and dtbbpy (2 mmol, 537 mg) in DME (300 mL) was prepared and added to the reaction mixture. 3-Bromopropanenitrile (800 mmol, 66.2 mL) was added to the reaction mixture, and the mixture was degassed by bubbling nitrogen through the solution for 10 min. After the reaction mixture was degassed, the pump was started to circulate the reaction mixture. TTMSS (400 mmol, 99.4 g) was added, and the mixture was degassed for a further 45 min. The reaction mixture was irradiated for 25 h and monitored with calibrated LCMS. The reaction mixture was circulated using an IWAKI magnet pump (MD-55F-X magnet-driven impeller pump) at a flow rate of 10 mL/min. After 25 h, the product was observed in 76% yield based on calibrated LCMS analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00070.

Diagrams of the reactor setups, copies of ^{1}H and ^{13}C NMR spectra for products, and HPLC traces of reaction mixtures (PDF)

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Notes

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■ ABBREVIATIONS

PRC, photoredox catalysis; IW, immersion-well; LED, light-emitting diode; SAR, structure−activity relationship

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