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Visible Light-Mediated (Hetero)aryl Amination Using Ni(II) Salts and Photoredox Catalysis in Flow: A Synthesis of Tetracaine

Boyoung Y. Park, Michael T. Pirnot, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States
Supporting Information Placeholder

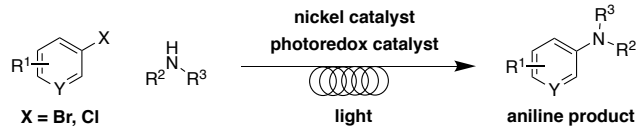
ABSTRACT: We report a visible light-mediated flow process for C–N cross-coupling of (hetero)aryl halides with a variety of amine coupling partners through the use of a photoredox/nickel dual catalyst system. Compared to the method in batch, this flow process enables a broader substrate scope, including less-activated (hetero)aryl bromides and electron-deficient (hetero)aryl chlorides, and significantly reduced reaction times (10 to 100 minutes). Furthermore, scale up of the reaction, demonstrated through the synthesis of tetracaine, is easily achieved, delivering the C–N cross-coupled products in consistently high yield of 84% on up to a 10 mmol scale.

Introduction

Anilines are a common class of fine chemicals frequently employed as pharmaceutical agents and agrochemicals and have applications in a variety of other fields. Due to the prevalence of these compounds, a number of transformations have been developed over the years to prepare them. They are often accessed through the use of copper and palladium catalysts, by coupling aryl halides or pseudohalides with amines.[1,2] Additionally, nucleophilic aromatic substitution (S_NAr) is a commonly employed method for forming anilines from activated aryl electrophiles.[3]

We reported the development of a complementary C–N cross-coupling method in collaboration with the MacMillan lab at Princeton and researchers at Merck in 2016 (Figure 1).[4,5] This method hinged on a dual nickel and photoredox catalyst system for coupling aryl bromides with a variety of amine coupling partners. Attractive features of this process in comparison to classical Ni-catalyzed C–N coupling reactions,[6,7] include the use of mild reaction conditions, inexpensive Ni(II) salts, and organic bases, such as DABCO, which also presumably serves as a ligand for the reaction. In 2016, scientists at AstraZeneca also reported iridium photoredox and nickel catalysis for the cross-coupling of primary aryl amines with aryl halides.[8]

Recent reports have detailed the attractive features of transferring a photochemical reaction to flow.[9-12] Due to the high molar extinction coefficients of most photocatalysts, photoredox-catalyzed transformations carried out on a preparative scale in batch are frequently "photon-limited," in accordance with the Beer-Lambert law.[13] Thus, we considered that the development of this C–N cross-coupling reaction in flow would be a means of reducing reaction times and expanding the substrate scope due to increased photon concentration through decreasing the path length and increasing the surface area of the reaction vessel. Herein we report a rapid and efficient photoredox/nickel-catalyzed (hetero)aryl amination with an array of aryl bromides/chlorides and amine coupling partners. Importantly, residence times in all cases are short (10 to 100 minutes), and facile scale-up to 10 mmol scale was readily realized.



Advantages to Photo-C-N:	Additional Advantages in Flow:
- relatively efficient reaction conditions	- short residence times
- use of mild organic bases	- expanded substrate scope
- simple amines serve as ligand	- easy setup and scale-up

Figure 1. Photoredox and nickel-catalyzed aniline formation: comparison of batch and flow processes.

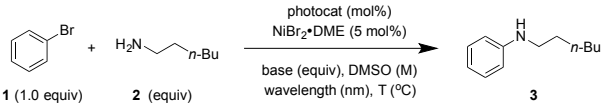
Results and Discussion

Our initial experiments directly adapted the reaction conditions in batch from our previous report for aryl amination to continuous flow conditions. This protocol used $Ir[dF(CF)_3ppy]_2(dtbbpy)PF_6$ as the photocatalyst, $NiBr_2$•DME as the nickel salt, and DMA as the reaction solvent. In addition, a Vapourtec E-series integrated flow chemistry system with an appended UV-150 photochemical reactor was used, due to its ready application to flow photochemical processes (see the Supporting Information for details). However, implementation of these batch conditions to a flow process resulted in clogging of the reactor due to precipitation of crystalline products and salts.[14] To overcome this issue, DMSO, another solvent commonly used in photoredox methodology, was used to increase the solubility of these precipitates.

Further optimization of this flow process is detailed in Table 1. For the aryl amination of bromobenzene (**1**) with hexylamine (**2**), conducting the reaction in flow with a residence time of 30 minutes at 55 °C resulted in a modest yield of 11% (Table 1, entry 1). An increase in temperature from 55 °C to 80 °C improved the yield of the desired product to 24% (entry 2). Although there was no significant improvement seen by increasing the concentration (entry 3), a higher concentration (0.5 M) was used for the optimized conditions in order to afford the same amount of desired products in a shorter time. A slight increase in the yield of **3** was observed by lowering the photocatalyst loading (0.002 mol%) with concomitant suppression of competitive protodehalogenation (entry 4).[15] The yield of the desired product was increased to 64% by utilizing MTBD (7-methyl-1,5,7-diazabicyclo-[4.4.0]deca-5-ene) as the base (entry 5). Unfortunately, the use of MTBD is not practi-

cal due to its relatively high cost. Further optimization of photocatalyst and amine loadings did not improve the yield when $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was employed as the photocatalyst.

Table 1. Optimization of the aryl amination reaction.[a]



1 (1.0 equiv) **2** (equiv) **3**

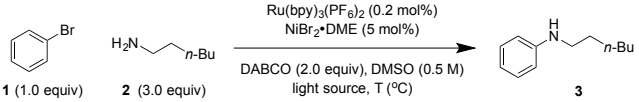
Entry	t_R (min)	photocat (mol%)	**2** (equiv)	base (equiv)	nm	T (°C)	*c* (M)	Yield of **3** (%)
1	30	Ir (0.02)	1.5	DABCO (1.8)	420	55	0.27	11
2	30	Ir (0.02)	1.5	DABCO (1.8)	420	80	0.27	24
3	30	Ir (0.02)	1.5	DABCO (1.8)	420	80	0.5	28
4	30	Ir (0.002)	1.5	DABCO (1.8)	420	80	0.5	32
5	30	Ir (0.002)	1.5	MTBD (1.0)	420	80	0.5	64
6	30	Ru (0.05)	1.5	DABCO (1.8)	420	80	0.5	36
7	30	Ru (0.05)	3.0	DABCO (1.8)	420	80	0.5	50
8	30	Ru (0.1)	3.0	DABCO (1.8)	420	80	0.5	58
9	60	Ru (0.1)	3.0	DABCO (2.0)	420	80	0.5	68
10	60	Ru (0.1)	3.0	DABCO (2.0)	450	80	0.5	69
11	**60**	**Ru (0.2)**	**3.0**	**DABCO (2.0)**	**450**	**80**	**0.5**	**78 (76)[b]**
12	60	Ru (0.1)	3.0	DABCO (2.0)	470	80	0.5	64
13	30	Ru (0.1)	3.0	DABCO (2.0)	-	80	0.5	<1
14[c]	30	Ru (0.1)	3.0	DABCO (2.0)	450	80	0.5	<1
15	30	-	3.0	DABCO (2.0)	450	80	0.5	<1
16[c]	30	-	3.0	DABCO (2.0)	450	80	0.5	<1

[a] Yields determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3-benzodioxole as the internal standard. Ir = $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$. Ru = $Ru(bpy)_3(PF_6)_2$. [b] Yields are of material isolated by silica gel chromatography. [c] Reaction run in the absence of $NiBr_2$•DME.

At this stage of the project, we examined the use of DABCO, a widely available and inexpensive organic base, and $Ru(bpy)_3(PF_6)_2$, a common and more economical photocatalyst, for our reaction protocol. A variety of conditions were examined, including the number of equivalents of amine used (Table 1, entries 6 and 7), photocatalyst loading (entries 7, 8 and 11), residence time (entries 8 and 9) and wavelength of visible light (entries 9, 10, and 12). The optimized conditions (0.2 mol% $Ru(bpy)_3(PF_6)_2$, 3 equiv hexylamine, 450 nm light with a residence time of 60 minutes) afforded the desired C–N cross-coupled product **3** in 76% isolated yield (entry 11). In particular, a wavelength of 450 nm was selected due to better overlap with the absorption profile (λ_{max} = 452 nm) of $Ru(bpy)_3^{2+}$.[16] Control experiments were also performed in the absence of light, Ni(II) salt, or $Ru(bpy)_3(PF_6)_2$. Under otherwise optimized conditions, less than 1% yield of product was observed when any of these were omitted (entries 13-16). It is important to note that the reaction time for this cross-coupling under batch conditions was previously reported to be 19 hours in the presence of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as a photocatalyst with the use of MTBD as a base on a 1 mmol scale.[4]

For comparison of batch and continuous flow process, the cross-coupling of bromobenzene (**1**) with hexylamine (**2**) was explored at 55 °C[17] with these two methods on a 10 and 50 mmol scale under the optimized reaction conditions (Table 2). In the flow process, a total reaction time of 4.2 hours and 15.3 hours (entries 2 and 4), respectively, is required with the same residence time used earlier (60 minutes) due to a longer collection time of the desired product. In addition, there is no difference in yield between a 10 and a 50 mmol scale using this continuous flow process (entries 2 and 4). In contrast, yields are significantly lower when run in batch, especially when the reaction was run on a 50 mmol scale (entry 3 and 5).

Table 2. Comparison of batch and continuous flow process.[a]



1 (1.0 equiv) **2** (3.0 equiv) **3**

Entry	scale	type	light source	residence time	total reaction time	T (°C)	Yield of **3** (%)[a]
1	10 mmol	flow	450 nm blue light	1.0 h	4.2 h[b]	80	78
2	10 mmol	flow	450 nm blue light	1.0 h	4.2 h[b]	55	42
3	10 mmol	batch	34 W blue LED	N/A	4.2 h	55	32
4	50 mmol	flow	450 nm blue light	1.0 h	15.3 h[b]	55	41
5	50 mmol	batch	34 W blue LED	N/A	15.3 h	55	9

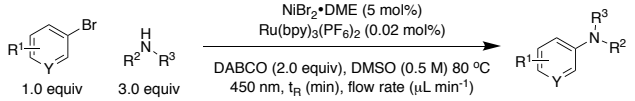
[a] Yields determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3-benzodioxole as the internal standard. [b] Total reaction time includes the injection of the reaction solution, running of the reaction, and collection of the crude material (See the Supporting Information for details).

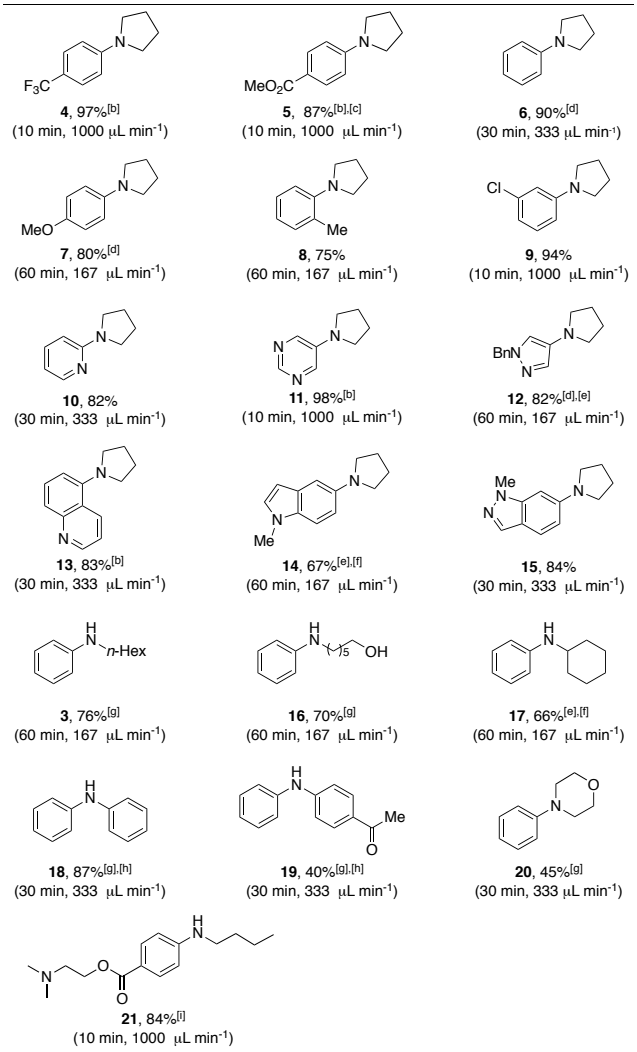
To assess the generality of this flow process, the substrate scope of the aryl electrophile was explored using pyrrolidine, which is the most common five-membered nonaromatic nitrogen heterocycle in pharmaceuticals,[18] as the amine coupling partner using a lower concentration of photocatalyst (0.02 mol%) (Table 3).[19] Electron-poor (**4** and **5**), electron-neutral (**6**), and electron-rich (**7**) aryl bromides were all found to be competent coupling partners. In addition, an *ortho*-substituted aryl bromide (**8**) also readily reacted to form the desired product with good efficiency. Longer residence times were required when the arene was more electron-rich or sterically hindered. For example, the coupling of pyrrolidine with 4-bromobenzotrifluoride (**4**) and methyl-4-bromobenzoate (**5**) took place with a residence time of 10 minutes, while longer residence times were required for bromobenzene (**6**, 30 minutes), 4-bromoanisole (**7**, 60 minutes) and 2-bromotoluene (**8**, 60 minutes). In addition, lowered photocatalyst loadings proved more successful with electron-rich and electron-neutral aryl halides, presumably because competitive protodehalogenation is diminished. 1-bromo-3-chlorobenzene is also sucessfully converted to C–N cross coupled product **9** in a chemoselective manner. In addition, it was found that a variety of heteroaryl bromides, including a pyridine (**10**), a pyrimidine (**11**), a pyrazole (**12**), a quinoline (**13**), an indole (**14**) and an indazole (**15**), effectively engaged in heteroaryl amination in moderate to excellent yields (67% to 98% yield). Unfortunately, an unprotected bromopyrazole failed to give product under these reaction conditions.[20]

The substrate scope of amine coupling partners was then explored to gain further insight into the generality of this C–N cross-coupling reaction. A variety of primary amines, including hexylamine, 6-amino-1-hexanol, and cyclohexylamine were found to efficiently couple with bromobenzene (**1**) to afford respective adducts **3**, **16**, and **17** in moderate to good isolated yields (66 to 76%). Unfortunately, acyclic secondary amines, such as diethylamine, were not effectively transformed to product. When aniline was tested as a substrate, C–N cross-coupled product **18** was not observed under these conditions. In line with our previous report,[4] we hypothesized that this is due to aniline lacking α-hydrogens, which could prevent generation of the active Ni(0) species from the Ni(II) precatalyst through β-hydride elimination. The use of added

dicyclohexylamine and diethylamine as hydride sources provided diphenylamine (**18**) in 38% and 67% isolated yields, respectively. Switching to Et_3N (2.0 equiv) as the hydride source delivered **18** in 87% isolated yield. A previously reported photoredox/nickel-catalyzed C–N cross-coupling system also details the use of Et_3N for high efficiencies in their protocol.[8] In addition, the reactions of electron-deficient anilines proceeded in poor yield, presumably because C–N cross-coupling product **19** is a photosensitizer (see the Supporting Information for details). Morpholine also coupled, delivering adduct **20** in moderate yield. Lastly, tetracaine **21**, which is a local anesthetic, was obtained via C–N cross coupling reaction in 84 % isolated yield with a residence time of only 10 minutes.

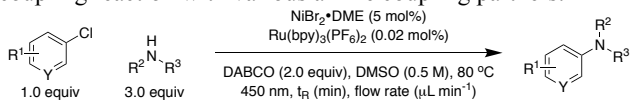
Table 3. (Hetero)aryl bromide substrate scope of C–N cross-coupling reaction with various amine coupling partners.[a]

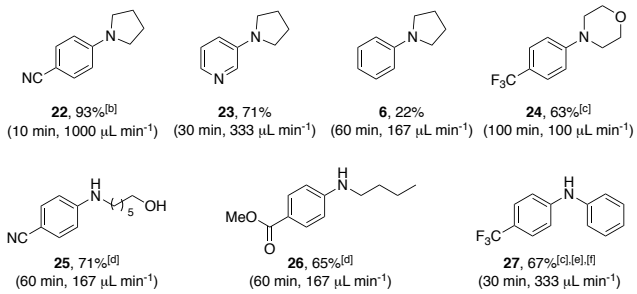




[a] All yields represent the average of isolated yields from two runs performed with 1 mmol of (hetero)aryl bromide. [b] 1.5 equiv of amine used. [c] 0.3 M concentration used. [d] 0.002 mol% $Ru(bpy)_3(PF_6)_2$ used. [e] 5.0 equiv of amine used. [f] 1.0 equiv MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) used as the base. [g] 0.2 mol% $Ru(bpy)_3(PF_6)_2$ used. [h] 2.0 equiv Et_3N included. [i] 2.0 equiv of amine used.

Table 4. (Hetero)aryl chloride substrate scope of C–N cross-coupling reaction with various amine coupling partners.[a]



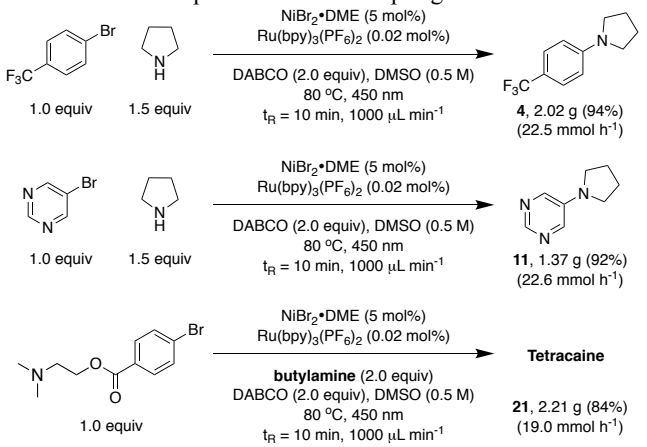


[a] All yields represent the average of isolated yields from two runs performed with 1 mmol of (hetero)aryl chloride. [b] 1.5 equiv of pyrrolidine used. [c] 0.2 mol% $Ir(ppy)_2(dtbbpy)(PF_6)$ used. [d] 0.2 mol% $Ru(bpy)_3(PF_6)_2$ used. [e] 2.0 equiv Et_3N included. [f] 0.3 M concentration used.

Aryl chlorides are attractive coupling partners for cross-coupling reactions relative to aryl bromides due to their lower cost and wider availability. In continuing efforts to broaden the scope of electrophilic coupling partners for this cross-coupling strategy, the reactions of a variety of aryl- and heteroaryl chlorides were explored with several amine coupling partners as displayed in Table 4. We found that 4-chlorobenzonitrile and 3-chloropyridine are cleanly and efficiently converted to **22** and **23**, respectively, demonstrating the feasibility of using electron poor aryl chlorides and heteroaryl chlorides. Control experiments indicated that in the absence of light, Ni(II) precatalyst, or $Ru(bpy)_3(PF_6)_2$, only trace quantities (less than 5% yield) of the product were formed, indicating that this reaction was not operating through a S_NAr mechanism under these conditions. The coupling of 4-chlorobenzotrifluoride with morpholine and aniline likewise provided cross-coupled products **24** and **27** in 63% and 67%, in the presence of $Ir(ppy)_2(dtbbpy)(PF_6)$ as a photocatalyst. 4-Chlorobenzonitrile and methyl-4-chlorobenzoate could also be successfully coupled with 6-amino-1-hexanol and butylamine, delivering C–N cross-coupling products **25** and **26**, respectively. Unfortunately, the C–N cross-coupling of chlorobenzene with pyrrolidine only provided the desired product **6** in 22% isolated yield. To date, this method is currently practically limited to the transformations of electron-poor aryl chlorides, while electron-neutral and electron-rich aryl chlorides were found to generally be poor substrates. This is in contrast to classical nickel- and palladium-catalyzed aminations in which aryl chlorides are often excellent substrates.[1,6]

Representative reactions were also performed on a 10 mmol scale, delivering cross-coupled products **4**, **11** and tetracaine, **21**, in high yields (Scheme 1). For example, 2.02 g and 1.37 g of C-N cross-coupled products **4** and **11** were obtained in 25 minutes (22.5 mmol h^{-1} and 22.6 mmol h^{-1}), respectively. Furthermore, tetracaine was synthesized by the C–N cross-coupling of 2-(dimethylamino)ethyl 4-bromobenzoate **21S**, in the presence of 0.02 mol% photocatalyst and butylamine loading (2.0 equiv), in high isolated yield with a short residence time (10 minutes). This highlights the excellent material throughput and potential practical utility of this continuous flow process.

Scheme 1. Scale-up of C–N cross-coupling reaction.[a]



[a] Yields represent isolated yields with 10 mmol of (hetero)aryl bromides.

Conclusions

In summary, we report the translation of a photoredox and nickel-catalyzed (hetero)aryl amination to continuous flow conditions using air stable Ni(II) salts. Short residence times were generally observed (10 to 100 minutes), likely due to the improved surface-area-to-volume ratio provided by a continuous flow set-up. This protocol enables rapid and efficient conversion of both (hetero)aryl bromides and electron-deficient chlorides to anilines. Several reactions were also shown to scale well to 10 mmol scale, demonstrating the possible applicability of this method.

Experimental Section

General reagent information: Nickel(II) bromide ethylene glycol dimethyl ether ($NiBr_2$•DME), Tris(2,2′-bipyridine)ruthenium(II) hexafluorophosphate [$Ru(bpy)_3(PF_6)_2$], 1,4-Diazabicyclo[2.2.2]octane (DABCO) and anhydrous DMSO in Sure/Seal™ bottles were purchased from Sigma-Aldrich. All other reagents were obtained from commercial sources such as Acros Organics, Alfa Aesar, Combi-Blocks, Matrix Scientific and Sigma-Aldrich. 5-bromopyrimidine, 1-benzyl-4-bromo-1H-pyrazole, 5-bromoquinoline, 5-bromo-1-methyl-1H-indole, 6-bromo-1-methyl-1H-indazole, 2-bromobenzo[b]thiophene, 4'-aminoacetophenone were purified by flash column chromatography before use. Compounds were purified by flash column chromatography using 40-63 μm silica gel (SiliCycle SiliaFlash® F60).

General analytical information: All compounds were characterized by ^{1}H NMR, ^{13}C NMR and ^{19}F NMR (when applicable). New compounds were also characterized by IR spectroscopy, melting point (if solids), elemental analysis or high-resolution mass spectrometry (HRMS). Copies of the ^{1}H, ^{13}C and ^{19}F spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals of residual chloroform (7.26 ppm) in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm) and all were obtained with ^{1}H decoupling. ^{19}F spectra were calibrated from an external standard (α,α,α-trifluoromethyltoluene: −63.72 ppm). All IR spectra were taken on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. HRMS spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer. Melting points were determined on an EZ-Melt melting point apparatus.

General equipment information: Vapourtec E-Series Integrated Flow chemistry System (Vapourtec Ltd, part # 50-1307) and UV-150 photochemical reactor (Vapourtec Ltd, part # 50-1453) were used. 2 mL and 10 mL of UV-150 reactor (bore and wall, 1.3 x 0.15 nm, Vapourtec Ltd, part # 50-1289 and 50-1287) were used. 420 nm (Vapourtec Ltd, part # 50-1445), 450 nm (Vapourtec Ltd, part # 50-1448) and 470 nm LED lamp (Vapourtec Ltd, part # 50-1449) were used. (The blue LED lamps were positioned 1 cm away from the reactor without the use of filters) The temperature was monitored with an external surface sensor. An organometallic chemistry kit (Vapourtec Ltd, part # 50-1311) was also used. This kit consists of a series of tubes and needles that enable reagents to be aspirated from bottles sealed with septa while inert gas is supplied into the bottles to replace the volume removed. (*We thank Vapourtec Ltd. for the generous loan of the Vapourtec system used in this research. We are grateful to Dr. Stacey Crane for training. We also thank Dr. Duncan Guthrie for technical support.)* Kessil blue LED (40 W, 12V, 450 nm) was used for batch reaction.

General experimental information for flow setup

(For solid aryl halide coupling partners): A screw-cap reaction tube (20 mm × 150 mm, Fisher Scientific, part # 14-959-37C) was capped with a Teflon/silicone septum screw cap (Fisher Scientific, part # 033407G) and insert (Fisher Scientific, part # 03394B). The reaction tube was charged with $NiBr_2$•DME (5 mol%), $Ru(bpy)_3(PF_6)_2$ (0.2 mol%), aryl halide (3 or 5 mmol, 1 equiv) and DABCO (2 equiv). The reaction tube was recapped, the septum was punctured with a needle attached to a Schlenk line and the tube was evacuated and backfilled with argon (this process was repeated a total of three times). Addition of DMSO was followed by addition of the amine coupling partner (1.5, 3 or 5 equiv) via syringe. The reaction mixture was sonicated for 5 min. *Note: 0.02 or 0.002 mol% of $Ru(bpy)_3(PF_6)_2$ was added by using a stock solution (4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO, [0.001 M]) via syringe after addition of DMSO.*

(For liquid aryl halide coupling partners): A screw-cap reaction tube (20 mm × 150 mm, Fisher Scientific, part # 14-959-37C) was capped with a Teflon/silicone septum screw cap (Fisher Scientific, part # 033407G) and insert (Fisher Scientific, part # 03394B). The reaction tube was charged with $NiBr_2$•DME (5 mol%), $Ru(bpy)_3(PF_6)_2$ (0.2 mol%) and DABCO (2 equiv). The reaction tube was recapped, the septum was punctured with a needle attached to a Schlenk line, and the tube was evacuated and backfilled with argon (This process was repeated a total of three times). DMSO was added, followed by aryl halide (3 or 5 mol, 1 equiv) and amine coupling partner (1.5, 3 or 5 equiv) via syringe. The reaction mixture was sonicated for 5 min. *Note: 0.02 or 0.002 mol% of*

$Ru(bpy)_3(PF_6)_2$ was added by using a stock solution (4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO, [0.001 M]) via syringe after addition of DMSO.

The reaction solution was pumped through the reactor at a flow rate of 100 – 1000 μL min^{-1} (residence time of 10 – 100 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. 1 mmol or 10 mmol of the crude reaction mixture (step 9) was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel (SiliCycle SiliaFlash® F60) (see the Supporting Information for details).

_N_-hexylaniline (3)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 0.006 mmol, 0.2 mol%) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (6 mL) was followed by addiiton of bromobenzene (0.32 mL, 3 mmol, 1 equiv) and 1-hexylamine (1.19 mL, 9 mmol, 3 equiv) via syringe. Total volume of the reaction mixture was 8.4 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 μL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.80 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a colorless oil. (run 1: 131 mg, 74% yield; run 2: 138 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 7.6, 7.6 Hz, 2H), 6.70 (dd, J = 7.2, 7.2 Hz, 1H), 6.62 (d, J = 8.0 Hz, 2H), 3.61 (bs, 1H), 3.12 (t, J = 7.2 Hz, 2H), 1.63 (p, J = 7.2 Hz, 2H), 1.49 – 1.28 (m, 6H), 0.93 (t, J = 6.8 Hz, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 148.7, 129.3, 117.2, 112.8, 44.1, 31.8, 29.7, 27.0, 22.8, 14.2. IR (neat, cm^{-1}): 3409, 1601, 1505, 745, 690. Anal. Calcd. For $C_{12}H_{19}N$: C, 81.30; H, 10.80. Found: C, 81.37; H, 10.96.

1-(4-(trifluoromethyl)phenyl)pyrrolidine (4)

(1 mmol scale) The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 1 mL of this stock solution was added to the reaction vessel. Lastly, 4-bromobenzotrifluoride (0.7 mL, 5 mmol, 1 equiv) and pyrrolidine (0.63 mL, 7.5 mmol, 1.5 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 12.2 mL (5 mmol). The reaction solution (10.0 mL) was pumped through the reactor at a flow rate of 1000 μL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.44 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a white solid. (run 1: 200 mg, 93% yield; run 2: 204 mg, 95% yield). *(Note: the title compound should not be dried under high vacuum due to volatility)*

(10 mmol scale) The reaction with $NiBr_2$•DME (201 mg, 0.65 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (2.24 mg, 0.0026 mmol, 0.02 mol%) and DABCO (2.92 g, 26 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (26 mL) was followed by addition of 4-bromobenzotrifluoride (1.82 mL, 13 mmol, 1 equiv) and pyrrolidine (1.63 mL, 19.5 mmol, 1.5 equiv) via syringe. Total volume of the reaction mixture was 37.4 mL (13 mmol). The reaction solution (32.0 mL) was pumped through the reactor at a flow rate of 1000 μL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (28.8 mL, 10 mmol) from steady state was collected in a 100 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a white solid. (2.02 g, 94% yield). *(Note: the title compound should not be dried under high vacuum due to volatility)* Melting point: 95.5 – 96.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.6 Hz, 2H), 6.58 (d, J = 8.6 Hz, 2H), 3.34 (dd, J = 6.6, 6.6 Hz, 4H), 2.11 − 2.03 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 149.9, 126.4 (q, J = 4 Hz), 125.6 (q, J = 268 Hz), 116.6 (q, J = 32 Hz), 111.1, 47.6, 25.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −60.47. IR (neat, cm^{-1}): 1610,1326,1088, 1065, 815. Anal. Calcd. For $C_{11}H_{12}F_3N$: C, 61.39; H, 5.62. Found: C, 61.38; H, 5.55.

Methyl 4-(pyrrolidin-1-yl)benzoate (5)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), methyl-4-bromobenzoate (645 mg, 3 mmol, 1 equiv) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9.4 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.6 mL of this stock solution was added to the reaction vessel. Lastly, pyrrolidine (0.38 mL, 4.5 mmol, 1.5 equiv) was added via syringe to the reaction vessel. Total volume of the reaction mixture was 11.6 mL (3 mmol). The reaction solution (10.0 mL) was pumped through the reactor at a flow rate of 1000 μL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (3.87 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (5% to 15% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 185 mg, 90% yield;

run 2: 175 mg, 85% yield). Melting point: 141.4 – 142.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.88 (m, 2H), 6.52 – 6.48 (m, 2H), 3.85 (s, 3H), 3.36 – 3.33 (m, 4H), 2.04 – 2.01 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.7, 151.0, 131.5, 116.4, 110.8, 51.6, 47.7, 25.6. IR (neat, cm^{-1}): 1692, 1609, 1276, 1176, 1105, 768. Anal. Calcd. For $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.28; H, 7.18.

1-phenylpyrrolidine (6)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9.9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.1 mL of this stock solution was added to the reaction vessel. Lastly, bromobenzene (0.53 mL, 5 mmol, 1 equiv) and pyrrolidine (1.26 mL, 15 mmol, 3.0 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 13.2 mL (5 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 μL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.64 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a colorless oil. (run 1: 132 mg, 90% yield; run 2: 132 mg, 90% yield). *(Note: the title compound should not be dried under high vacuum due to volatility)* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 6.70 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.61 (d, *J* = 7.6 Hz, 2H), 3.36 – 3.30 (m, 4H), 2.09 – 2.00 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 148.1, 129.2, 115.5, 111.8, 47.7, 25.6. IR (neat, cm^{-1}): 1593, 1505, 1366, 743, 689. Anal. Calcd. For $C_{10}H_{13}N$: C, 81.58; H, 8.90. Found: C, 81.33; H, 9.00.

1-(4-methoxyphenyl)pyrrolidine (7)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9.9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.1 mL of this stock solution was added to the reaction vessel. Lastly, 4-bromoanisole (0.63 mL, 5 mmol, 1 equiv) and pyrrolidine (1.26 mL, 15 mmol, 3.0 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 13.2 mL (5 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 μL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.64 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 5% diethyl ether/hexanes) to provide the title compound as a white solid. (run 1: 142 mg, 80% yield; run 2: 142 mg, 80% yield). Melting point: 46.0 − 46.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 9.0 Hz, 2H), 6.55 (d, *J* = 9.0 Hz, 2H), 3.77 (s, 3H), 3.25 (dd, *J* = 5.6, 5.6 Hz, 4H), 2.05 – 1.96 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 150.9, 143.4, 115.2, 112.7, 56.2, 48.4, 25.5. IR (neat, cm^{-1}): 1511, 1234, 1178, 1043, 813. Anal. Calcd. For $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.67; H, 8.64.

1-(*o*-tolyl)pyrrolidine (8)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (5.4 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.6 mL of this stock solution was added to the reaction vessel. Lastly, 2-bromotoluene (0.75 mL, 3 mmol, 1 equiv) and pyrrolidine (0.75 mL, 9 mmol, 3 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 8.4 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 μL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.80 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a colorless oil. (run 1: 121 mg, 75% yield; run 2: 121 mg, 75% yield). *(Note: the title compound should not be dried under high vacuum due to volatility)* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.89 (dd, *J* = 7.2, 7.2 Hz, 1H), 3.24 (dd, *J* = 6.4, 6.4 Hz, 4H), 2.39 (s, 3H), 2.01 – 1.95 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 149.5, 131.8, 128.8, 126.4, 120.4, 115.9, 51.1, 25.1, 20.7. IR (neat, cm^{-1}): 1599, 1492, 1309, 751, 716. Anal. Calcd. For $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 81.67; H, 9.55.

1-(3-chlorophenyl)pyrrolidine (9)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 1 mL of this stock solution was added to the reaction vessel. Lastly, 1-bromo-3-chlorobenzene (0.59 mL, 5 mmol, 1 equiv) and pyrrolidine (1.26 mL, 15 mmol, 3 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 13.0 mL (5 mmol). The reaction solution (10.0 mL) was pumped through the reactor at a flow rate of 1000 μL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.60 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography

using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a colorless oil. (run 1: 174 mg, 96% yield; run 2: 167 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.4, 8.4 Hz, 1H), 6.64 – 6.61 (m, 1H), 6.54 (dd, *J* = 2.4, 2.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.31 – 3.24 (m, 4H), 2.05 – 1.98 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 149.0, 135.0, 130.1, 115.2, 111.5, 110.0, 47.7, 25.6. IR (neat, cm^{-1}): 1593, 1496, 1370, 989, 754, 679. Anal. Calcd. For $C_{10}H_{12}ClN$: C, 66.12; H, 6.66. Found: C, 66.36; H, 6.62.

2-(pyrrolidin-1-yl)pyridine (10)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 1 mL of this stock solution was added to the reaction vessel. Lastly, 2-bromopyridine (0.48 mL, 5 mmol, 1 equiv) and pyrrolidine (1.26 mL, 15 mmol, 3 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 12.8 mL (5 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 μL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.56 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (10% to 20% EtOAc/hexanes) to provide the title compound as a colorless oil. (run 1: 122 mg, 82% yield; run 2: 122 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.6 Hz, 1H), 7.39 (dd, *J* = 8.6, 6.6 Hz, 1H), 6.47 (dd, *J* = 6.6, 6.6 Hz, 1H), 6.31 (d, *J* = 8.6 Hz, 1H), 3.42 (dd, *J* = 6.4, 6.4 Hz, 4H), 2.02 – 1.94 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 157.4, 148.2, 136.9, 111.1, 106.5, 46.7, 25.6. IR (neat, cm^{-1}): 1595, 1496, 1481, 1441, 766. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{13}N_2$ 149.1073; Found: 149.1068.

5-(pyrrolidin-1-yl)pyrimidine (11)

(1 mmol) The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%), 5-bromopyrimidine (795 mg, 5 mmol, 1 equiv) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 1 mL of this stock solution was added to the reaction vessel. Lastly, pyrrolidine (0.63 mL, 7.5 mmol, 1.5 equiv) was added via syringe to the reaction vessel. Total volume of the reaction mixture was 12.2 mL (5 mmol). The reaction solution (10.0 mL) was pumped through the reactor at a flow rate of 1000 μL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.44 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (50% to 80% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 146 mg, 98% yield; run 2: 148 mg, 99% yield).

(10 mmol) The reaction with $NiBr_2$•DME (171 mg, 0.55 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (1.9 mg, 0.0022 mmol, 0.02 mol%), 5-bromopyrimidine (1.76 g, 11.1 mmol, 1 equiv) and DABCO (2.48 g, 22.2 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (22.2 mL) was followed by addition of pyrrolidine (1.39 mL, 16.6 mmol, 1.5 equiv) via syringe. Total volume of the reaction mixture was 27.0 mL (11.1 mmol). The reaction solution (25.0 mL) was pumped through the reactor at a flow rate of 1000 μL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (24.4 mL, 10 mmol) from steady state was collected in a 100 mL vial. The crude residue was diluted with water (30 mL), and extracted with diethyl ether (5 x 50 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo* The crude material was purified by flash column chromatography (50% to 80% EtOAc/hexanes) to provide the title compound as a white solid. (1.37 g, 92% yield). Melting point: 75.5 − 76.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 8.53 (s, 1H), 8.03 (s, 2H), 3.30 (dd, *J* = 6.6, 6.6 Hz, 4H), 2.08 – 2.00 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) NM146.5, 141.0, 139.3, 46.8, 25.2. IR (neat, cm^{-1}): 1569, 1438, 1198, 728, 622. Anal. Calcd. For $C_8H_{11}N_3$: C, 64.40; H, 7.43. Found: C, 64.19; H, 7.57.

1-benzyl-4-(pyrrolidin-1-yl)-1*H*-pyrazole (12)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), 1-benzyl-4-bromo-1H-pyrazole (712 mg, 3 mmol, 1 equiv) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (5.94 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.06 mL of this stock solution was added to the reaction vessel. Lastly, pyrrolidine (1.26 mL, 15 mmol, 5 equiv) was added via syringe to the reaction vessel. Total volume of the reaction mixture was 8.6 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 μL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.87 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (30% to 50% EtOAc/hexanes) to provide the title compound as a yellow oil. (run 1: 186 mg, 82% yield; run 2: 186 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 3H), 7.25 – 7.19 (m, 2H), 7.17 (s, 1H), 6.84 (s, 1H), 5.23 (s, 2H), 3.05 (dd, *J* = 6.4, 6.4 Hz, 4H), 1.99 – 1.91 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 137.2, 137.0, 128.6, 127.7, 127.4, 127.3, 113.7, 56.2, 51.0, 24.7. IR (neat, cm^{-1}): 1586, 1402, 1369, 709,

694, 653. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{18}N_3$ 228.1495; Found: 228.1489.

5-(pyrrolidin-1-yl)quinolone (13)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%), 5-bromoquinoline (1.04 g, 5 mmol, 1 equiv) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 1 mL of this stock solution was added to the reaction vessel. Lastly, pyrrolidine (0.63 mL, 7.5 mmol, 1.5 equiv) was added via syringe to the reaction vessel. Total volume of the reaction mixture was 12.8 mL (5 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 µL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.56 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (30% to 50% EtOAc/hexanes) to provide the title compound as a yellow oil. (run 1: 165 mg, 83% yield; run 2: 165 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.42 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.47 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.18 (dd, *J* = 8.6, 4.2 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.27 (dd, *J* = 6.4, 6.4 Hz, 4H), 1.94 – 1.86 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 149.6, 149.5, 147.7, 133.3, 129.4, 122.5, 121.3, 118.6, 110.6, 52.7, 25.0. IR (neat, cm^{-1}): 1570, 1460, 1406, 1317, 790. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{15}N_2$ 199.1230; Found: 199.1222.

1-methyl-5-(pyrrolidin-1-yl)-1*H*-indole (14)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%) and 5-bromo-1-methyl-1H-indole (630 mg, 3 mmol, 1 equiv) was conducted in accordance with the general procedure. DMSO (5.4 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.6 mL of this stock solution was added to the reaction vessel. Lastly, pyrrolidine (1.26 mL, 15 mmol, 5 equiv) and MTBD (0.43 mL, 3 mmol, 1 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 8.2 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 µL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.73 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 µm silica gel without the extraction process. The crude residue was purified by flash column chromatography (5% to 15% diethyl ether/hexanes) to provide the title compound as a white solid. (run 1: 130 mg, 65% yield; run 2: 136 mg, 68% yield). Melting point: 91.2 − 91.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.8 Hz, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.81 (s, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.34 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.32 (dd, *J* = 6.2, 6.2 Hz, 4H), 2.07 − 2.00 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 143.2, 130.6, 129.6, 128.9, 110.0, 109.6, 102.0, 99.7, 49.0, 32.9, 25.4. IR (neat, cm^{-1}): 1496, 1421, 1281, 781, 724, 709. Anal. Calcd. For $C_{13}H_{16}N_2$: C, 77.96; H, 8.05. Found: C, 77.72; H, 8.17.

1-methyl-6-(pyrrolidin-1-yl)-1*H*-indazole (15)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), 6-bromo-1-methyl-1H-indazole (634 mg, 3 mmol, 1 equiv) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (5.4 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.6 mL of this stock solution was added to the reaction vessel. Lastly, pyrrolidine (0.75 mL, 9 mmol, 3 equiv) was added via syringe to the reaction vessel. Total volume of the reaction mixture was 7.8 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 µL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.60 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo* The crude material was purified by flash column chromatography (30% to 50% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 167 mg, 83% yield; run 2: 169 mg, 84% yield). Melting point: 106.0 −106.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 6.59 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.21 (d, *J* = 2.0 Hz, 1H), 3.96 (s, 3H), 3.36 (dd, *J* = 6.0, 6.0 Hz, 4H), 2.09 – 2.00 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 147.3, 142.0, 132.6, 121.4, 116.0, 110.0, 87.4, 48.2, 35.3, 25.6. IR (neat, cm^{-1}): 1620, 1436, 849, 784, 619. Anal. Calcd. For $C_{12}H_{15}N_3$: C, 71.61; H, 7.51. Found: C, 71.50; H, 7.45.

6-(phenylamino)hexan-1-ol (16)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 0.006 mmol, 0.2 mol%), 6-amino-1-hexanol (1.05 g, 9 mmol, 3 equiv) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (6 mL) was followed by addition of bromobenzene (0.32 mL, 3 mmol, 1 equiv) via syringe. Total volume of the reaction mixture was 8.4 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 µL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.80 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (20% to 50% EtOAc/hexanes) to provide the title compound as a colorless oil. (run 1: 131 mg, 68% yield; run 2: 139 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21

– 7.14 (m, 2H), 6.70 (dddd, J = 7.3, 7.3, 1.1, 1.1 Hz, 1H), 6.64 – 6.59 (m, 2H), 3.65 (t, J = 6.5 Hz, 2H), 3.12 (t, J = 7.1 Hz, 2H), 1.68 – 1.54 (m, 4H), 1.48 – 1.38 (m, 4H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.6, 129.3, 117.3, 112.9, 63.0, 44.0, 32.8, 29.7, 27.1, 25.7. IR (neat, cm^{-1}): 3553, 2928, 2856, 1601, 1505, 747, 691. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{20}NO$ 194.1539; Found: 194.1530.

_N_-cyclohexylaniline (17)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 0.006 mmol, 0.2 mol%) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (6 mL) was followed by addition of bromobenzene (0.32 mL, 3 mmol, 1 equiv) and cyclohexylamine (1.72 mL, 15 mmol, 5 equiv) via syringe. Total volume of the reaction mixture was 9.0 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 μL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (3.00 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a colorless oil. (run 1: 119 mg, 68% yield; run 2: 112 mg, 64% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.15 (m, 2H), 6.69 (dd, J = 7.2, 7.2 Hz, 1H), 6.65 – 6.59 (m, 2H), 3.52 (bs, 1H), 3.28 (tt, J = 10.1, 3.7 Hz, 1H), 2.14 – 2.05 (m, 2H), 1.85 −1.75 (m, 2H), 1.73 – 1.63 (m, 1H), 1.48 – 1.34 (m, 2H), 1.33 – 1.12 (m, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.5, 129.4, 116.9, 113.3, 51.8, 33.6, 26.1, 25.2. IR (neat, cm^{-1}): 3399, 2925, 2851, 1600, 1501, 744, 691. Anal. Calcd. For $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.25; H, 9.91.

Diphenylamine (18)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (8.7 mg, 0.01 mmol, 0.2 mol%) and DABCO (1.13 mg, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (10 mL) was followed by addition of bromobenzene (0.53 mL, 5 mmol, 1 equiv), aniline (1.37 mL, 15 mmol, 3 equiv) and Et_3N (1.39 mL, 10 mmol, 2 equiv) via syringe. Total volume of the reaction mixture was 14.6 mL (5 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 μL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.92 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% diethyl ether/hexanes) to provide the title compound as a white solid. (run 1: 147 mg, 87% yield; run 2: 147 mg, 87% yield). Melting point: 51.9 – 52.9 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 4H), 7.18 – 7.15 (m, 4H), 7.06 – 7.02 (m, 2H), 5.73 (bs, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.2, 129.4, 121.1, 117.9. IR (neat, cm^{-1}): 3383, 1587, 1494, 742, 688. Anal. Calcd. For $C_{12}H_{11}N$: C, 85.17; H, 6.55. Found: C, 84.91; H, 6.54.

1-(4-(phenylamino)phenyl)ethan-1-one (19)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (8.7 mg, 0.01 mmol, 0.2 mol%), 4'-aminoacetophenone (2.03 g, 15 mmol, 3 equiv) and DABCO (1.13 mg, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (10 mL) was followed by addition of bromobenzene (0.53 mL, 5 mmol, 1 equiv) and Et_3N (1.39 mL, 10 mmol, 2 equiv) via syringe. Total volume of the reaction mixture was 15.0 mL (5 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 μL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (3.00 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (10% to 30% EtOAc/hexanes) to provide the title compound as a pale yellow solid. (run 1: 87 mg, 41% yield; run 2: 82 mg, 39% yield). Melting point: 95.3 – 96.0 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H), 7.35 (dd, J = 7.6, 7.6 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.09 (dd, J = 7.6, 7.6 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.11 (bs, 1H), 2.53 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.5, 148.5, 140.7, 130.8, 129.7, 129.2, 123.5, 120.8, 114.6, 26.3. IR (neat, cm^{-1}): 3315, 1647, 1569, 1275, 754, 575. Anal. Calcd. For $C_{14}H_{13}NO$: C, 79.59; H, 6.20. Found: C, 79.31; H, 6.19.

4-phenylmorpholine (20)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 0.006 mmol, 0.2 mol%) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (6 mL) was followed by addition of bromobenzene (0.32 mL, 3 mmol, 1 equiv) and morpholine (0.79 mL, 9 mmol, 3 equiv) via syringe. Total volume of the reaction mixture was 8.0 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 μL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.67 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 μm silica gel without the extraction process. The crude residue was purified by flash column chromatography (15% to 30% diethyl ether/hexanes) to provide the title compound as a white solid. (run 1: 75 mg, 46% yield; run 2: 73 mg, 45% yield). Melting point: 52.6 – 53.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 2H), 6.97 – 6.91 (m, 3H), 3.91 – 3.88 (m, 4H), 3.18 (dd, J = 4.8, 4.8 Hz, 4H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 129.2, 120.1, 115.7, 67.0, 49.4. IR (neat, cm^{-1}): 1224, 1118, 924, 769, 699. Anal. Calcd. For $C_{10}H_{13}NO$: C, 73.59; H, 8.03. Found: C, 73.71; H, 8.09.

2-(dimethylamino)ethyl 4-bromobenzoate (21S)

To a solution of 4-bromobenzoyl chloride (6.58 g, 30 mmol, 1 equiv) in CH_2Cl_2 (60 mL, [0.5 M]) in an oven-dried round-bottom flask equipped with a large stir bar was added 2-diethylaminoethanol (3.32 mL, 33 mmol, 1.1 equiv) and Et_3N (4.57 mL, 33 mmol, 1.1 equiv). The reaction mixture was stirred vigorously under nitrogen at rt for 3 h. Water was then added to the reaction mixture. The aqueous layer was separated and extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (40% EtOAc/hexanes to 100% EtOAc) to provide the title compound as a pale yellow oil. (6.68 g, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 4.40 (t, *J* = 5.8 Hz, 2H), 2.68 (t, *J* = 5.8 Hz, 2H), 2.31 (s, 6H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 165.9, 131.8, 131.3, 129.2, 128.1, 63.4, 57.9, 46.0. IR (neat, cm^{-1}): 2769, 1718, 1590, 1266, 1011, 753. Anal. Calcd. For $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19. Found: C, 48.44; H, 5.22.

2-(dimethylamino)ethyl 4-(butylamino)benzoate (21)

(1 mmol) The reaction with $NiBr_2$•DME (61.8 mg, 0.20 mmol, 5 mol%), 2-(dimethylamino)ethyl 4-bromobenzoate (1.09 g, 4 mmol, 1 equiv) and DABCO (904 mg, 8 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (7.2 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 0.8 mL of this stock solution was added to the reaction vessel. Lastly, butylamine (0.79 mL, 8 mmol, 2 equiv) was added via syringe to the reaction vessel. Total volume of the reaction mixture was 10.8 mL (4 mmol). The reaction solution (10.0 mL) was pumped through the reactor at a flow rate of 1000 µL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.70 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (100 % EtOAc) to provide the title compound as a white solid. (run 1: 225 mg, 85% yield; run 2: 219 mg, 83% yield).

(10 mmol) The reaction with $NiBr_2$•DME (201 mg, 0.65 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (2.24 mg, 0.0026 mmol, 0.02 mol%), 2-(dimethylamino)ethyl 4-bromobenzoate (3.54 g, 13 mmol, 1 equiv) and DABCO (2.92 g, 26 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (26 mL) was followed by addition of butylamine (26.3 mL, 26 mmol, 2 equiv) via syringe. Total volume of the reaction mixture was 34.4 mL (13 mmol). The reaction solution (32.0 mL) was pumped through the reactor at a flow rate of 1000 µL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (26.46 mL, 10 mmol) from steady state was collected in a 100 mL vial. The crude residue was diluted with water (30 mL), and extracted with diethyl ether (5 x 50 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (100 % EtOAc) to provide the title compound as a white solid. (2.21 g, 84% yield). Melting point: 39.0 – 41.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.0 Hz, 2H), 6.53 (d, *J* = 9.0 Hz, 2H), 4.39 (t, *J* = 5.8 Hz, 2H), 4.08 (s, 1H), 3.19 – 3.14 (m, 2H), 2.74 (t, *J* = 5.9 Hz, 2H), 2.37 (s, 6H), 1.66 – 1.57 (m, 2H), 1.48 – 1.38 (m, 2H), 1.26 (s, 1H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 166.9, 152.3, 131.7, 117.9, 111.3, 62.4, 58.1, 45.9, 43.1, 31.4, 20.3, 13.9. IR (neat, cm^{-1}): 3370, 1683, 1596, 1341, 1167, 767. Anal. Calcd. For $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15. Found: C, 68.02; H, 9.27.

4-(pyrrolidin-1-yl)benzonitrile (22)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%), 4-chlorobenzonitrile (688 mg, 5 mmol, 1 equiv) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 1 mL of this stock solution was added to the reaction vessel. Lastly, pyrrolidine (0.63 mL, 7.5 mmol, 1.5 equiv) was added via syringe to the reaction vessel. Total volume of the reaction mixture was 12.4 mL (5 mmol). The reaction solution (10.0 mL) was pumped through the reactor at a flow rate of 1000 µL min^{-1} (residence time of 10 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.48 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 µm silica gel without the extraction process. The crude residue was purified by flash column chromatography (5% to 15% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 160 mg, 93% yield; run 2: 160 mg, 93% yield). Melting point: 85.0 – 85.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 3.35 – 3.28 (m, 4H), 2.06 – 2.00 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 150.1, 133.5, 121.1, 111.5, 96.5, 47.6, 25.5. IR (neat, cm^{-1}): 2210, 1605, 1520, 1390, 1174, 813. Anal. Calcd. For $C_{11}H_{12}N_2$: C, 76.71; H, 7.02. Found: C, 76.60; H, 7.02.

3-(pyrrolidin-1-yl)pyridine (23)

The reaction with $NiBr_2$•DME (77.2 mg, 0.25 mmol, 5 mol%) and DABCO (1.13 g, 10 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (9 mL) was added to the reaction vessel. A stock solution of $Ru(bpy)_3(PF_6)_2$ (0.001 M) was made by dissolving 4.3 mg of $Ru(bpy)_3(PF_6)_2$ in 5 mL of DMSO. Subsequently, 1 mL of this stock solution was added to the reaction vessel. Lastly, 3-chloropyridine (0.48 mL, 5 mmol, 1 equiv) and pyrrolidine (1.26 mL, 15 mmol, 3 equiv) were added via syringe to the reaction vessel. Total volume of the reaction mixture was 12.8 mL (5 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 333 µL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.56 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was

diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (50% to 80 % EtOAc/hexanes) to provide the title compound as a colorless oil. (run 1: 107 mg, 72% yield; run 2: 104 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.90 (m, 1H), 7.87 – 7.84 (m, 1H), 7.06 – 7.00 (m, 1H), 6.76 – 6.70 (m, 1H), 3.24 – 3.18 (m, 4H), 1.98 – 1.92 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 143.7, 136.7, 134.2, 123.5, 117.7, 47.2, 25.3. IR (neat, cm^{-1}): 3386, 2835, 1583, 1485, 1370, 789, 707. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_{13}N_2$ 149.1073; Found: 149.1067.

4-(4-(trifluoromethyl)phenyl)morpholine (24)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ir(ppy)_2(dtbbpy)(PF_6)$ (5.5 mg, 0.006 mmol, 0.2 mol%) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (6 mL) was followed by addition of 4-chlorobenzotrifluoride (0.40 mL, 3 mmol, 1 equiv) and morpholine (0.79 mL, 9 mmol, 3 equiv) via syringe. Total volume of the reaction mixture was 7.8 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 100 µL min^{-1} (residence time of 100 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.60 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 µm silica gel without the extraction process. The crude residue was purified by flash column chromatography (5% to 15% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 150 mg, 65% yield; run 2: 139 mg, 60% yield). Melting point: 69.5 – 71.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.86 (dd, *J* = 4.8, 4.8 Hz, 4H), 3.23 (dd, *J* = 4.8, 4.8 Hz, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 153.5, 126.5 (*J* = 4 Hz), 124.8 (*J* = 269 Hz), 121.0 (*J* = 33 Hz), 114.4, 66.7, 48.2.^{19}F NMR (376 MHz, $CDCl_3$) δ – 61.36. IR (neat, cm^{-1}): 1612, 1325, 1236, 1098, 924, 825, 650. Anal. Calcd. For $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23. Found: C, 57.34; H, 5.37.

4-((6-hydroxyhexyl)amino)benzonitrile (25)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 0.006 mmol, 0.2 mol%), 4-chlorobenzonitrile (413 mg, 3 mmol, 1 equiv), 6-amino-1-hexanol (1.05 g, 9 mmol, 3 equiv) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. DMSO (6 mL) was added via syringe. Total volume of the reaction mixture was 8.4 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 µL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.80 mL, 1 mmol) from steady state was collected in a 20 mL vial. The crude residue was diluted with water (5 mL), and extracted with diethyl ether (5 x 10 mL), organics dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (50% to 70% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 159 mg, 73% yield; run 2: 151mg, 69% yield). Melting point: 74.5 – 75.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 3.14 (t, *J* = 7.1 Hz, 2H), 1.69 – 1.54 (m, 4H), 1.47 – 1.38 (m, 4H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 151.5, 133.8, 120.7, 112.2, 98.4, 62.9, 43.3, 32.7, 29.2, 26.9, 25.7. IR (neat, cm^{-1}): 3446, 3313, 2213, 1606, 1530, 835. Anal. Calcd. For $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31. Found: C, 71.50; H, 8.32.

Methyl 4-(butylamino)benzoate (26)

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 0.006 mmol, 0.2 mol%), methyl-4-chlorobenzoate (512 mg, 3 mmol, 1 equiv) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (6 mL) was followed by addition of butylamine (0.89 mL, 9 mmol, 3 equiv) via syringe. Total volume of the reaction mixture was 8.2 mL (3 mmol). The reaction solution (6.0 mL) was pumped through the reactor at a flow rate of 167 µL min^{-1} (residence time of 60 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (2.73 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 µm silica gel without the extraction process. The crude residue was purified by flash column chromatography (5% to 15% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 135 mg, 65% yield; run 2: 135mg, 65% yield). Melting point: 104.5 – 105.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 4.16 (bs, 1H), 3.84 (s, 3H), 3.14 (t, *J* = 7.1 Hz, 2H), 1.64 – 1.55 (m, 2H), 1.47 – 1.36 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 167.5, 152.3, 131.6, 118.0, 111.4, 51.6, 43.1, 31.5, 20.3, 13.9. IR (neat, cm^{-1}): 3379, 1682, 1600, 1274, 1171, 770. Anal. Calcd. For $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27. Found: C, 69.77; H, 8.18.

***N*-phenyl-4-(trifluoromethyl)aniline (27)**

The reaction with $NiBr_2$•DME (46.3 mg, 0.15 mmol, 5 mol%), $Ir(ppy)_2(dtbbpy)(PF_6)$ (5.5 mg, 0.006 mmol, 0.2 mol%) and DABCO (676 mg, 6 mmol, 2 equiv) was conducted in accordance with the general procedure. Addition of DMSO (10 mL) was followed by addition of 4-chlorobenzotrifluoride (0.40 mL, 3 mmol, 1 equiv) and aniline (0.82 mL, 9 mmol, 3 equiv) and Et_3N (0.83 mL, 6 mmol, 2 equiv) via syringe. Total volume of the reaction mixture was 12.8 mL (3 mmol). The reaction solution (8.0 mL) was pumped through the reactor at a flow rate of 333 µL min^{-1} (residence time of 30 min), irradiating with a 450 nm LED lamp with the flow wizard program. After the reaction solution had entered the reactor, it was followed with DMSO at the same flow rate. The crude reaction mixture (4.27 mL, 1 mmol) from steady state was collected in a 20 mL vial, and subsequently purified by silica gel flash column chromatography using 40-63 µm silica gel without the extraction process. The crude residue was purified by flash column chromatography (2% to 4% EtOAc/hexanes) to provide the title compound as a white solid. (run 1: 154 mg, 65% yield; run 2: 166 mg, 70% yield). Melting point: 61.9 – 62.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz,

2H), 7.36 (dd, J = 7.6, 7.6, Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.11 – 7.05 (m, 3H). 5.92 (s, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.9, 141.3, 129.7, 126.8 (J = 4 Hz), 124.8 (J = 269 Hz), 123.1, 121.8 (J = 32 Hz), 120.2, 115.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ – 61.4. IR (neat, cm^{-1}): 3396, 1320, 1170, 1097, 1060, 744, 691. Anal. Calcd. For $C_{13}H_{10}F_3N$: C, 65.82; H, 4.25. Found: C, 65.87; H, 4.41.

Supporting Information: Comparison of batch and continuous flow process; experimental information for C–N cross coupling in the presence of adduct 20; 1H, 13C and 19F NMR spectra of all compounds found in the SI.

Keywords: flow process • photochemistry • nickel • ruthenium • C–N cross-coupling • dual catalysis

Corresponding Authors

sbuchwal@mit.edu

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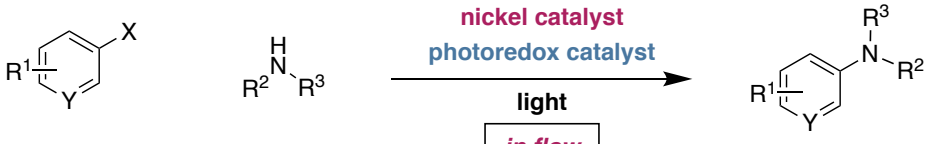
(20) Unreacted starting material remained after the completion of reaction.



aryl halide **amine** **25 exmples** ***up to*** **99% yield**