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Application of the Photoredox Coupling of Trifluoroborates and Aryl Bromides to Analog Generation Using Continuous Flow

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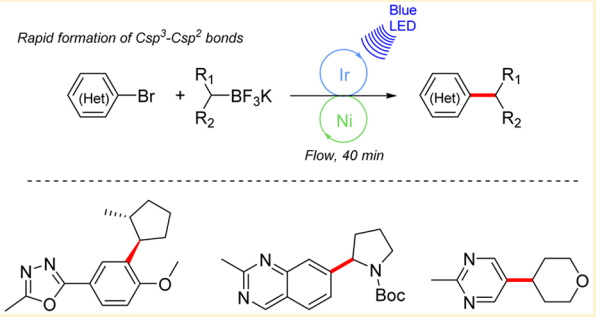
Supporting Information

ABSTRACT: A method for the coupling of aryl bromides with potassium alkyl trifluoroborates, via nickel/photoredox dual catalysis, has been developed for use in continuous flow. This operationally simple protocol is able to form Csp^3–Csp^2 bonds with significantly reduced reaction times and a broader substrate scope than when conducted in batch. The utility of this method for rapid analog synthesis has been demonstrated by the synthesis of a small library of alkyl-substituted quinazolines.



In recent years, nickel/photoredox dual catalysis has emerged as a powerful technology for the formation of carbon–carbon and carbon–heteroatom bonds.[1,2] The single-electron transmetalation mechanism employed by these reactions enables the formation of bonds that are difficult to access with traditional transition metal-catalyzed cross coupling reactions, which proceed via a two-electron transmetalation mechanism. Nickel/photoredox dual catalysis has been shown to be particularly effective for the formation of Csp^3–Csp^2 bonds that are often inaccessible or difficult to form with transition metal-catalyzed reactions, such as Suzuki-Miyaura couplings.[3] The formation of these bonds is highly desirable in a medicinal chemistry setting because increased sp^3 character of a compound has been shown to correlate with increased solubility and improved chances for clinical success.[4]

One reaction of particular interest in this area is the cross-coupling of aryl bromides with potassium alkyl trifluoroborates, catalyzed by nickel and an iridium-based photocatalyst in the presence of visible light.[5] This reaction, pioneered by Molander et al., is very powerful and allows for the synthesis of a variety of interesting compounds. There are, however, several aspects of the reaction that could be improved to make it better suited for use in a medicinal chemistry environment. The sensitivity of the reaction necessitates thorough exclusion of oxygen. This need for thorough degassing, combined with the need to remove tetrahydrofuran after preforming the ligated nickel complex, results in a reaction that can be operationally inconvenient to set up, especially when performing multiple parallel reactions, which is often desirable in medicinal chemistry. Using traditional batch photochemistry, space could quickly become an issue if attempting to set up a large number of such reactions in parallel, because each reaction must be efficiently irradiated with light for up to 24 h. Additionally, these reactions are typically cooled with fans or circulating water, which also makes the setup of multiple reactions inconvenient. Another characteristic of these reactions that can complicate parallel synthesis is the fact that they are usually quite dilute (0.05 M),[5] so the reaction volumes to obtain appreciable amounts of material are relatively high. Finally, scale-up of a promising compound is difficult using batch photochemistry because of limited light penetration into larger reaction vessels. Therefore, scale-up of compounds often either requires much longer reaction times or the performance of multiple small-scale reactions in parallel.

With these limitations in mind, we hypothesized that using continuous-flow photochemistry could significantly mitigate many of the barriers for the effective use of nickel/photoredox dual catalysis in analog synthesis. This would be especially useful in a medicinal chemistry setting. In continuous-flow photochemical reactions, a reaction solution is pumped through transparent, narrow tubing that is irradiated with light. Because the surface-area-to-volume ratio of the flow reactor is significantly higher than that of a traditional batch reaction vessel, much more efficient irradiation of the reaction mixture can be achieved. Other photochemical reactions have been successfully conducted in continuous-flow, resulting in significantly reduced reaction times, increased reproducibility, and facile scale-up.[6] If realized, these improvements would make couplings of aryl bromides with potassium alkyl trifluoroborates much more amenable to regular use in medicinal chemistry laboratories. It should be noted that this type of transformation has been done with boronic esters in flow.[7] Boronic esters were used because of their increased solubility in low boiling point solvents, however, the procedure was limited to the coupling of benzyl and allyl boronic esters. Our goal was to develop a flow procedure with the following

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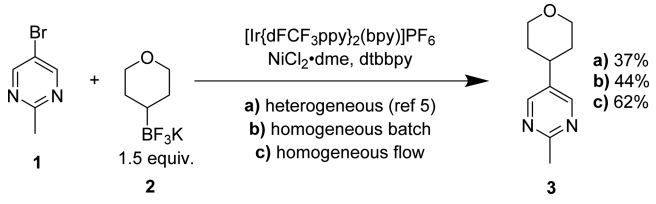
characteristics: (1) can allow for the rapid synthesis of small sets of molecules (parallel synthesis) with minimal exclusion of oxygen; (2) can easily and quickly supply enough highly pure material for initial screening and pharmacokinetic studies (≥10 mg from 0.25 mmol aryl bromide); (3) have a broad substrate scope (for both coupling partners); and (4) be efficient and high yielding enough to supply additional material. These criteria should be satisfied in a flow procedure. In addition, we hypothesized that, because of a significant increase in light exposure, a flow procedure might have the added advantage of rescuing or improving reactions that work poorly in batch.

One limitation of continuous flow chemistry is the requirement that the reaction be a homogeneous solution. The batch conditions for the model reaction illustrated in Scheme 1a employ cesium carbonate as a base, which is not fully soluble in dioxane, precluding the direct use of these conditions in flow. Using the coupling of 5-bromo-2-methylpyrimidine **1** with potassium tetrahydropyran-3-trifluoroborate **2** as a test system, we endeavored to find homogeneous conditions in which the reaction still worked with minimal effort to exclude oxygen. Batch reactions were run in a crystallization dish surrounded by strips of blue LEDs, similar to the setup described by Yu and Wang.[8] As shown in Scheme 1b, replacement of cesium carbonate with 2,6-lutidine in a solvent mixture of 1:4 (v/v) DMA:dioxane resulted in a homogeneous solution (Figure 1) that produced **3** in comparable yield to the original heterogeneous conditions described by Molander et al.[5] When carried out in flow (Figure 2), using a Vapourtec E-series apparatus equipped with a 24W blue LED lamp (centered at 450 nm), these conditions resulted in an increased yield and a much shorter reaction time (40 min). In order to ensure relative operational simplicity, the DMA in which the ligated nickel complex was formed was not removed and the reaction was not thoroughly deoxygenated,[9] which could explain the moderate yield of the transformation. Even if the yields of this transformation are moderate, this procedure is operationally simple and should be adequate to supply the quantities of material needed for initial screening. It should also be noted that this particular solvent mixture (1:4 DMA:dioxane) was crucial to ensure a homogeneous reaction mixture throughout the reaction while minimizing the formation of side products, especially in flow. Other solvents systems consisting of different proportions of THF, Me-THF, dioxane, DMA, and DMF (among others) were explored but led to heterogeneous solutions or gave poor conversion to desired product.

Scheme 1. Comparison of (a) Heterogeneous,[5] (b) Homogeneous Batch, and (c) Homogeneous Flow Coupling Conditions[a]



[a](a) $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (2.5 mol%), $NiCl_2$·dme (5 mol%), dtbbpy (5 mol%), Cs_2CO_3 (1.5 equiv), dioxane, 16 h; (b) $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (3 mol%), $NiCl_2$·dme (12 mol%), dtbbpy (12 mol%), 2,6-lutidine (1.6 equiv), 1:4 DMA:dioxane, 16 h; (c) $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (3 mol%), $NiCl_2$·dme (12 mol%), dtbbpy (12 mol%), 2,6-lutidine (1.6 equiv), 1:4 DMA:dioxane, 40 min.

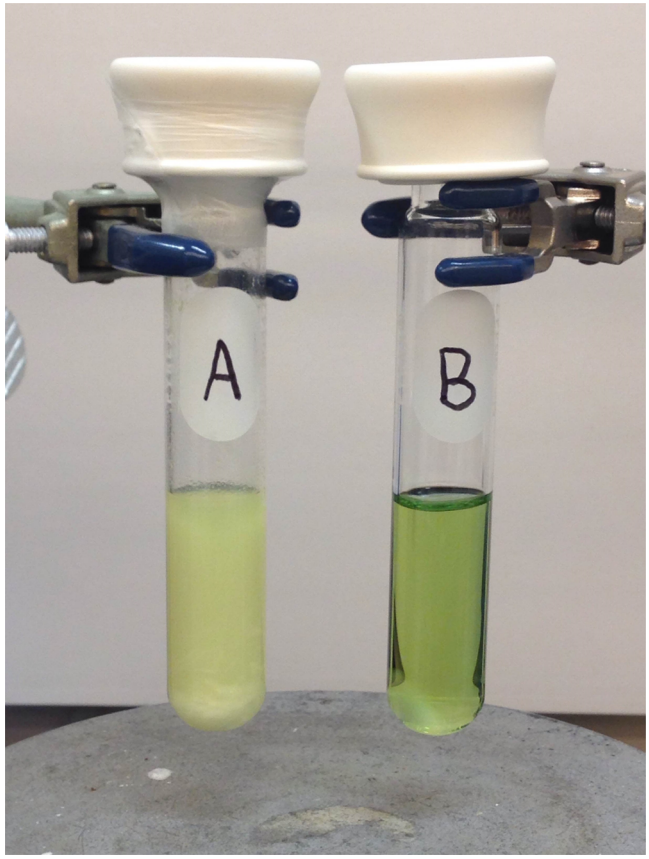


Figure 1. Comparison of (a) heterogeneous[5] and (b) homogeneous reaction mixtures.

With flow-compatible conditions in hand, we set out to test this reaction on more challenging and pharmacologically relevant substrates. By testing our conditions on challenging substrates that had not worked in batch, we hoped to ensure that our conditions had a broad substrate scope. The coupling of sterically hindered *o*-methoxy aryl bromide **4** with potassium trifluoroborate **2** gave only trace conversion to product under both traditional heterogeneous and the homogeneous batch conditions. However, when the same procedure was carried out in flow, this reaction showed approximately 90% consumption of starting material by LC-MS in 40 min and gave **5** in 46% isolated yield (Scheme 2). The fact that this procedure rescued this reaction, which was completely ineffective in batch, led us to believe that the procedure should have a good substrate scope. This observation also suggests that light exposure is an important consideration when attempting this transformation on difficult substrates.

To ensure that the utility of this continuous-flow reaction with **4** was not limited to installing the tetrahydropyran moiety, and to obtain accurate steady-state yields, we tested couplings with several other potassium trifluoroborates on a 1 mmol scale. All three compounds were obtained in moderate to good yield and excellent purity (Scheme 3).

Following the successful synthesis of this small selection of analogues, we sought to demonstrate the utility of this technology on a larger set. This experiment was designed to demonstrate the value of this protocol for rapid analog synthesis. To simplify reaction setup for library synthesis, a

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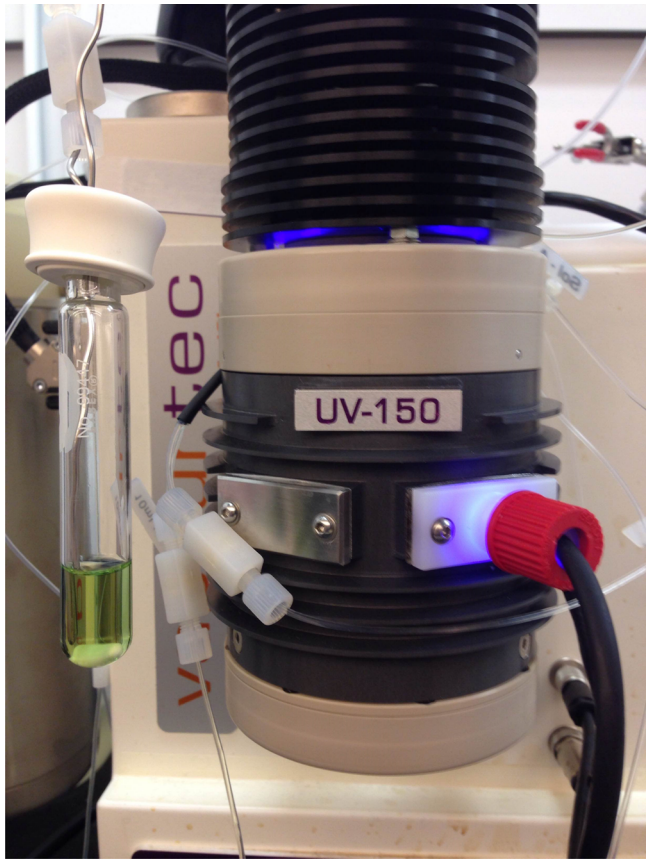


Figure 2. Flow reactor equipped with blue LED lamp (centered at 450 nm).

stock solution in DMA of aryl bromide **9**, $NiCl_2$·dme, dtbbpy, $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$, and 2,6-lutidine was first prepared. Aliquots of this solution were then added to a diverse selection of commercially available potassium trifluoroborates to form solutions that were diluted with dioxane before being run through the flow reactor (all steps were done with minimal effort to exclude oxygen[9]). With the goal of quickly producing 10 mg of each compound (from a 5 mL, 0.25 mmol solution), the crude reaction mixtures were concentrated (the residual DMA was efficiently and conveniently removed on a Biotage V-10 apparatus) and purified by automated mass-directed reverse-phase HPLC. The largest pure fraction was collected to afford product in pure form (>95% by LCMS). As shown in Scheme 4, secondary, cyclic, benzylic, heteroatom-containing, and 2-substituted alkyl trifluoroborates all reacted to produce sufficient material (≥10 mg after purification) in 5 mL (0.25 mmol) reactions. Conceivably, larger sets of analogs could be easily prepared with this procedure using flow systems equipped with liquid handlers and a fraction collector.[10] Overall, the substrate scope for this reaction is robust, with the limitation that this procedure was found to be ineffective for the coupling of primary alkyl trifluoroborates. This observation is not surprising since these substrates are also ineffective in batch.[3]

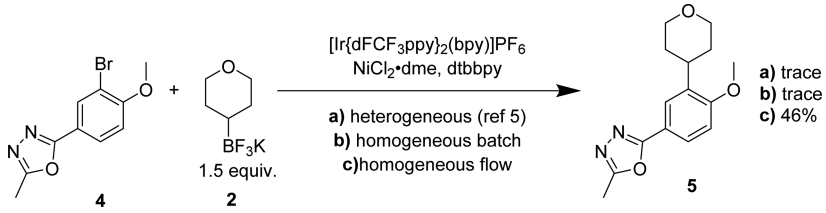
A significant advantage of using continuous-flow over batch photochemistry for the synthesis of a library is the ability to easily scale-up a compound of interest. To demonstrate this, 7-bromo-2-methylquinazoline **9** was coupled with potassium cyclobutyltrifluoroborate **19** to afford **13** (Scheme 5). The reaction was conducted on sufficient scale to collect 15 mL of steady-state reaction, which afforded **13** in 54% yield, for a productivity of 81 mg/hour. Assuming similar yields, to achieve the same amount of product (1.3 g) in 16 h, 48 individual 5 mL batch reactions would have to be set up in parallel. This reaction also demonstrated the significant yield increase that can be obtained when automated purification is not used, due to the fact that only the largest fraction-containing product was isolated.

In summary, reaction conditions suitable for continuous flow nickel/photoredox catalyzed couplings of aryl bromides with potassium alkyl trifluoroborates have been developed. This new procedure involves operationally simpler reaction steps, faster reaction times, and significant improvements in reaction scalability. Additionally, this procedure expands the substrate scope of this powerful transformation and allows for rapid analog synthesis.

EXPERIMENTAL SECTION

General Considerations. Dioxane (99.8%, extra dry) was sparged with nitrogen gas for 15 min upon receipt then stored under nitrogen. Nickel(II) chloride ethylene glycol dimethyl ether complex (98%), 4,4′-di-*tert*-butyl-2−2′-dipyridyl (98%) (dtbbpy), and $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ ($dFCF_3ppy$ =2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine) were purchased from Sigma-Aldrich and used as received. Thin layer chromatography (TLC) was performed using 250 μm silica gel plates. TLC plates were visualized using an ultraviolet lamp. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Spectra are internally referenced to residual solvent signals. Data for ^{1}H NMR are reported according to the following conventions: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quintet, br = broad, and combinations thereof), coupling constant J (Hz), integration. Automated mass-directed purification carried out using a binary pump and an injector/fraction collector with a C_8 30 × 150 mm column. Mobile phase A was 10 mM NH_4OH (pH ∼ 10) in water; mobile phase B was acetonitrile. Compounds were purified using an 8 min focused gradient based on the retention time observed in a

Scheme 2. Comparison of Batch and Flow Conditions for Challenging Substrate 4[a]



[a](a) $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (2.5 mol%), $NiCl_2$·dme (5 mol%), dtbbpy (5 mol%), Cs_2CO_3 (1.5 equiv), dioxane, 16 h; (b) $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (3 mol%), $NiCl_2$·dme (12 mol%), dtbbpy (12 mol%), 2,6-lutidine (1.6 equiv), 1:4 DMA:dioxane, 16 h; (c) $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (3 mol%), $NiCl_2$·dme (12 mol%), dtbbpy (12 mol%), 2,6-lutidine (1.6 equiv), 1:4 DMA:dioxane, 40 min.

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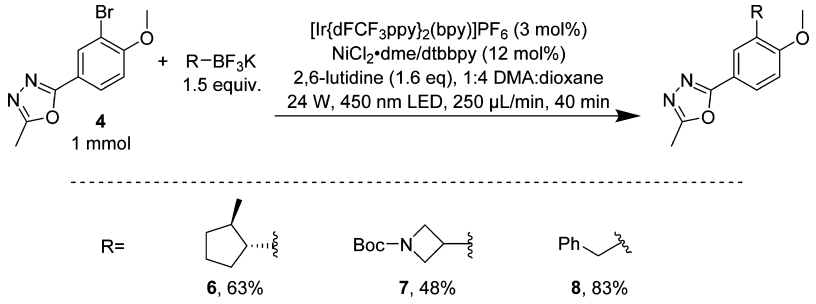
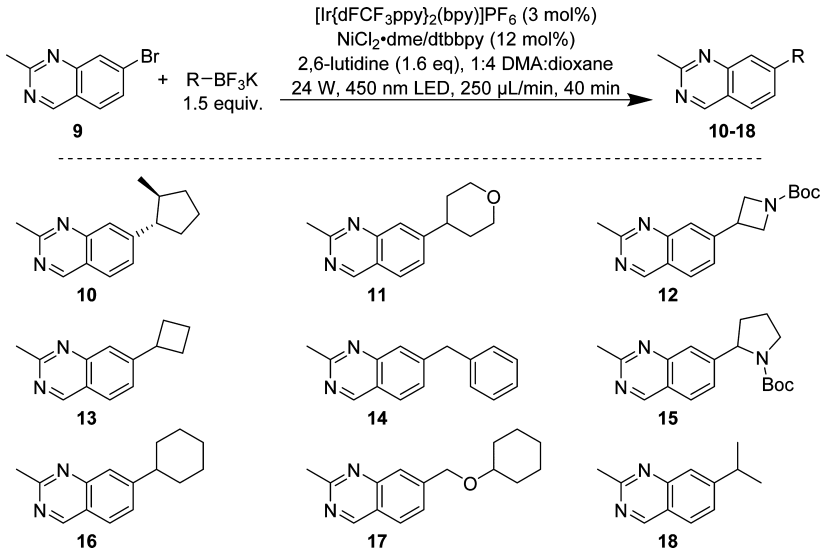
Scheme 3. Continuous-Flow Photoredox Couplings; Steady-State Yields

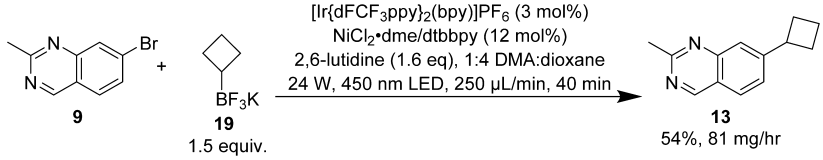


Scheme 4. Library Synthesized Using Continuous-Flow Nickel/Photoredox Coupling[a]



[a]10-35 mg of each product obtained in pure form.

Scheme 5. Scale-Up in Continuous-Flow



preprep analytical screen.. The largest fraction containing product was isolated. High-resolution mass spectra were acquired on a Orbitrap mass spectrometer following chromatography on a UPLC system or by direct transfusion. The samples were dissolved in MeOH at a concentration of approximately 0.2 mg/mL and infused with a flow rate of 5 μL/min. Electrospray ionization in positive ion mode was employed with a spray voltage of 4.0 kV. The mass resolution was set to 35 000.

General Procedures. *A. General Procedure for Homogeneous Batch Reactions.* To a 16 × 100 mm Pyrex culture tube containing a Teflon-coated stir bar were added $NiCl_2$·dme (6.6 mg, 0.03 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (8.0 mg, 0.03 mmol), and *N*,*N*-dimethylacetamide (1.0 mL). The tube was sealed with a rubber septum and the contents were stirred under nitrogen for 5 min; a deep blue-green solution formed. Aryl bromide (0.25 mmol), potassium alkyl trifluoroborate (0.375 mmol), 2,6-lutidine (46 μL, 0.4 mmol), and $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (7.6 mg, 0.0075 mmol) were then added in succession. The contents of the reaction were stirred to dissolve as much solid as possible, then 1,4-dioxane (4 mL) was added. The reaction was filtered into a second 16 × 150 mm Pyrex culture tube, sealed with a rubber septum, briefly evacuated, and backfilled with nitrogen. The reaction was allowed to stir for 16 h in the center of a crystallization dish lined with six 4 W blue LED strips (reaction tube located approximately 6 cm from the LEDs), cooling with a fan to approximately 23 °C. The crude reaction mixture was concentrated using a Biotage V-10 apparatus, then purified on silica gel

B. General Procedure for Singleton Flow Reactions. To a 20 × 150 mm Pyrex culture tube containing a Teflon-coated stir bar were added $NiCl_2$·dme (26 mg, 0.12 mmol), 4,4′-di-*tert*-butyl-2−2′-bipyridine (32 mg, 0.12 mmol), and *N*,*N*-dimethylacetamide (4.0 mL). The tube was sealed with a rubber septum and the contents were stirred under nitrogen for 5 min; a deep blue-green solution formed. Aryl bromide (1.0 mmol), potassium alkyl trifluoroborate (1.5 mmol), 2,6-lutidine (185 μL, 1.6 mmol), and $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (30 mg, 0.03 mmol) were then added in succession. The contents of the reaction were stirred to dissolve as much solid as possible, then 1,4-dioxane (16 mL) was added. The reaction was sealed with a rubber septum, briefly evacuated, and backfilled with nitrogen. A Vapourtec E series flow reactor fitted with a UV-150 photoreactor (10 mL) was pre-equilibrated with 1:4 (v/v) DMA:dioxane and the temperature was maintained at 30 °C. The entire 20 mL reaction solution was pumped through the reactor at a flow rate of 250 μL/min (residence time of 40 min), irradiating with a 420−450 nm (peak 450 nm) 24 W LED lamp. After the entire reaction solution had entered the reactor, it was

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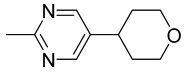
followed with 1:4 (v/v) DMA:dioxane at the same flow rate. The pressure was kept around 1.4 bar using a variable back-pressure regulator. Fifteen milliliters of steady-state reaction was collected. The crude reaction mixture was concentrated using a Biotage V-10 apparatus, then purified by silica gel flash column chromatography, eluting with a gradient of ethyl acetate in heptane to afford product in pure form.

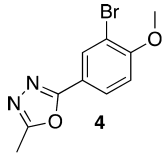
C. General Procedure for Library Flow Reactions. To a 16 × 100 mm Pyrex culture tube containing a Teflon-coated stir bar were added $NiCl_2$·dme (33 mg, 0.15 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (40 mg, 0.15 mmol), and *N*,*N*-dimethylacetamide (5.0 mL). The tube was sealed with a rubber septum and the contents were stirred under nitrogen for 5 min; a deep blue-green solution formed. Aryl bromide (1.25 mmol), 2,6-lutidine (230 μL, 2.0 mmol), and [Ir-{dFCF$_3$ppy}$_2$(bpy)]PF_6 (38 mg, 0.038 mmol) were then added in succession. The contents of the reaction were stirred to dissolve as much solid as possible. One milliliter aliquots of this solution were then added to five separate 16 × 100 mm Pyrex culture tubes containing different potassium alkyl trifluoroborates (0.375 mmol). Reactions were stirred to dissolve, then 1,4-dioxane (4 mL) was added to each tube. Reactions were filtered into second 16 × 100 mm Pyrex culture tubes, sealed with rubber septa, briefly evacuated, and backfilled with nitrogen. Each reaction was run through the flow reactor separately (as in general procedure B), concentrated using a Biotage V-10 apparatus, then purified using automated mass-directed purification in order to obtain products in pure form.

Compound Characterization Data.



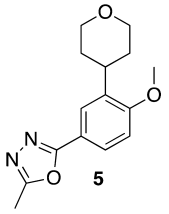
3

*2-Methyl-5-(tetrahydro-2H-pyran-4-yl)pyrimidine (**3**).* Synthesized using General Procedure A to afford 19.5 mg faint yellow amorphous solid (42%). Also synthesized using General Procedure B to afford 83 mg faint yellow amorphous solid (62%). Characterization data presented is for batch synthesized using General Procedure A, but both batches match. ^{1}H NMR (400 MHz, MeOD) δ 8.61 (s, 2H), 4.11−4.00 (m, 2H), 3.64−3.50 (m, 2H), 2.97−2.82 (m, 1H), 2.66 (s, 3H), 1.89−1.72 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 166.9, 157.1, 137.3, 68.9, 37.6, 34.1, 25.0. HRMS (ESI) *m*/*z* calc. for $C_{10}H_{14}N_2O$ (M+H) 179.1179, found 179.1178.



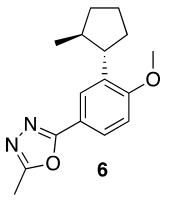
4

*2-(3-Bromo-4-methoxyphenyl)-5-methyl-1,3,4-oxadiazole (**4**).* To a 500 mL round-bottomed flask fitted with a Telfon-coated stir bar were added 3-bromo-4-methoxybenzoic acid (4.84 g, 20.95 mmol) and acetohydrazide (7.77 g, 104.8 mmol), followed by phosphorus oxychloride (105 mL). The reaction was stirred at 100 °C for 4 h under nitrogen. The reaction was cooled to 0 °C and water (100 mL) was slowly added to quench the reaction. Methylene chloride (100 mL) was added and the reaction was allowed to stir for 12 h. The reaction mixture was filtered to remove a white solid, which was discarded. Phases were separated and the organic layer was extracted with water (2 × 25 mL). Combined aqueous layers were neutralized by the slow addition of 2 M NaOH solution until pH 7; a white solid precipitated. Precipitate was isolated by filtration and dried under vacuum to give 1.994 g as a tan amorphous solid (35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 2.1 Hz, 1H), 7.97 (dd, *J* = 6.3, 3.1 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 3.97 (s, 3H), 2.60 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.7, 162.7, 157.9, 130.5, 127.5, 117.2, 113.3, 111.3, 56.67, 10.6. HRMS (ESI) *m*/*z* calc. for $C_{10}H_9BrN_2O_2$ (M +H) 268.9920, found 268.9917.



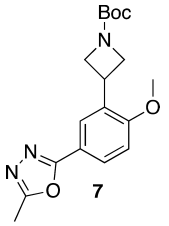
5

*2-(4-Methoxy-3-(tetrahydro-2H-pyran-4-yl)phenyl)-5-methyl-1,3,4-oxadiazole (**5**).* Synthesized using General Procedure B on a 0.25 mmol scale to afford 31.8 mg white amorphous solid (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.83 (m, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 4.09 (dd, *J* = 10.9, 3.9 Hz, 2H), 3.90 (s, 3H), 3.58 (td, *J* = 11.7, 2.3 Hz, 2H), 3.28−3.16 (m, 1H), 2.60 (s, 3H), 1.93−1.71 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 163.2, 159.7, 135.0, 126.4, 125.6, 116.7, 110.7, 68.7, 55.7, 34.7, 32.6, 11.3. HRMS (ESI) *m*/*z* calc. for $C_{15}H_{18}N_2O_3$ (M+H) 275.1390, found 275.1388.



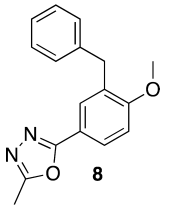
6

*(±)-2-(4-Methoxy-3-(2-methylcyclopentyl)phenyl)-5-methyl-1,3,4-oxadiazole (**6**).* Synthesized using General Procedure B to afford 133 mg faint yellow amorphous solid (63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.80 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 2.94 (td, *J* = 10.0, 8.2 Hz, 1H), 2.60 (s, 3H), 2.19−1.93 (m, 3H), 1.86−1.71 (m, 2H), 1.70−1.55 (m, 1H), 1.41−1.24 (m, 1H), 0.93 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 163.2, 160.7, 134.9, 126.0, 125.9, 116.3, 110.7, 55.7, 46.6, 41.3, 34.8, 33.9, 23.9, 18.7, 11.2. HRMS (ESI) *m*/*z* calc. for $C_{16}H_{20}N_2O_2$ (M+H) 273.1598, found 273.1596.



7

*tert-Butyl 3-(2-methoxy-5-(5-methyl-1,3,4-oxadiazol-2-yl)-phenyl)azetidine-1-carboxylate (**7**).* Synthesized using General Procedure B to afford 124 mg thick colorless oil (48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 6.94 (d, J = 8.5 Hz, 1H), 4.29 (m, 2H), 4.10−3.95 (m, 3H), 3.88 (s, 3H), 2.60 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 163.3, 160.1, 156.7, 130.8, 127.2, 125.8, 116.6, 110.7, 79.6, 55.8, 54.7, 29.0, 28.6, 11.2. HRMS (ESI) *m*/*z* calc. for $C_{18}H_{23}N_3O_4$ (M+H) 346.1761, found 346.1760.



8

*2-(3-Benzyl-4-methoxyphenyl)-5-methyl-1,3,4-oxadiazole (**8**).* Synthesized using general procedure B to afford 178 mg white amorphous solid (83%). ^{1}H NMR (400 MHz, DMSO) δ 7.82 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.32−7.15 (m, 6H), 3.98 (s, 2H), 3.88 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 163.1, 160.1, 140.3, 130.7, 129.0, 128.9, 128.5, 126.8, 126.2, 116.4, 110.8, 55.7, 36.0, 11.2. HRMS (ESI) *m*/*z* calc. for $C_{17}H_{16}N_2O_2$ (M+H) 281.1285, found 281.1282.

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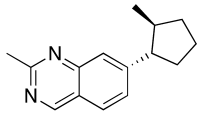
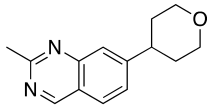


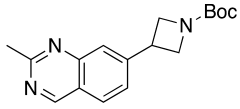
10

*(±)-2-Methyl-7-(2-methylcyclopentyl)quinazoline (**10**).* Synthesized using General Procedure C to afford 16 mg white amorphous solid (28%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.35 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.73 (m, 1H), 7.61 (dd, J = 8.4, 1.6 Hz, 1H), 2.82 (s, 3H), 2.75−2.64 (m, 1H), 2.26−2.14 (m, 1H), 2.14−2.01 (m, 2H), 1.94−1.77 (m, 3H), 1.49−1.34 (m, 1H), 0.95 (d, J = 5.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 165.1, 161.5, 155.4, 151.4, 129.2, 128.8, 125.4, 123.0, 56.3, 44.4, 36.3, 35.9, 25.7, 25.0, 18.7. HRMS (ESI) m/z calc. for $C_{15}H_{18}N_2$ (M+H) 227.1543, found 227.1541.



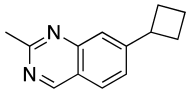
11

*2-Methyl-7-(tetrahydro-2H-pyran-4-yl)quinazoline (**11**).* Synthesized using General Procedure C, except 0.1% trifluoroacetic acid was used rather than NH_4OH as the additive in chromatography. Resulting material was dissolved in methylene chloride, washed with saturated aqueous sodium bicarbonate, concentrated, and repurified using silica gel flash column chromatography, eluting with 0−100% ethyl acetate in heptane to afford 17.1 mg white amorphous solid (29%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.37 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.78−7.73 (m, 1H), 7.65 (dd, J = 8.4, 1.6 Hz, 1H), 4.13−4.03 (m, 2H), 3.68−3.55 (m, 2H), 3.14−3.02 (m, 1H), 2.82 (s, 3H), 1.96−1.83 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 165.3, 161.6, 155.3, 151.5, 129.0, 128.9, 124.5, 123.0, 69.1, 43.1, 34.5, 25.8. HRMS (ESI) m/z calc. for $C_{14}H_{16}N_2O$ (M+H) 229.1335, found 229.1335.



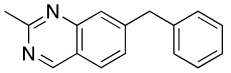
12

*tert-Butyl 3-(2-methylquinazolin-7-yl)azetidine-1-carboxylate (**12**).* Synthesized using General Procedure C to afford 21.5 mg thick colorless oil (28%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.42 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.73 (dd, J = 8.4, 1.5 Hz, 1H), 4.45 (m, 2H), 4.08 (m, 3H), 2.84 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, MeOD) δ 164.3, 160.4, 156.8, 150.0, 150.0, 128.2, 126.4, 123.8, 121.9, 79.9, 55.7, 33.6, 27.3, 24.4. HRMS (ESI) m/z calc. for $C_{17}H_{21}N_3O_2$ (M+H) 300.1707, found 300.1705.



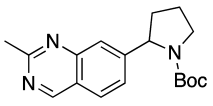
13

*7-Cyclobutyl-2-methylquinazoline (**13**).* Synthesized using General Procedure C, repurified after automated purification using silica gel flash column chromatography, eluting with 0−100% ethyl acetate in heptane to afford 13.4 mg faint yellow amorphous solid (27%[11]). Also synthesized using General Procedure B, except crude material was purified using a RediSep Rf Reversed Phase C18 Column, eluting with 5−60% acetonitrile in water, containing 5 mM ammonium formate as an additive, to afford 81 mg faint yellow amorphous solid (54%). Characterization data presented are for batch synthesized using General Procedure C, but both batches match. ^{1}H NMR (400 MHz, MeOD) δ 9.36 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 3.82 (q, J = 8.7 Hz, 1H), 2.82 (s, 3H), 2.54−2.43 (m, 2H), 2.35−2.09 (m, 3H), 2.01−1.90 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 165.2, 161.6, 155.7, 151.5, 128.8, 128.3, 123.7, 122.8, 41.9, 30.3, 25.7, 19.1. HRMS (ESI) m/z calc. for $C_{13}H_{14}N_2$ (M+H) 199.1230, found 199.1228.



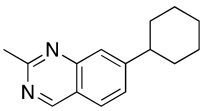
14

*7-Benzyl-2-methylquinazoline (**14**).* Synthesized using General Procedure C to afford 34.5 mg white amorphous solid (58%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.36 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.36−7.18 (m, 5H), 4.23 (s, 2H), 2.80 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 165.3, 161.6, 151.4, 151.2, 141.0, 130.4, 130.2, 129.8, 128.8, 127.6, 126.6, 122.8, 43.1, 25.7. HRMS (ESI) m/z calc. for $C_{16}H_{14}N_2$ (M+H) 235.1230, found 235.1229.



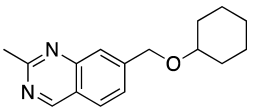
15

*tert-Butyl 2-(2-methylquinazolin-7-yl)pyrrolidine-1-carboxylate (**15**).* Synthesized using General Procedure C to afford 14.8 mg thick faint-yellow oil (19%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.44−9.35 (m, 1H), 8.05 (m, 1H), 7.70 (s, 1H), 7.59 (m, 1H), 5.16−4.98 (m, 1H), 3.68 (m, 2H), 2.83 (s, 3H), 2.57−2.38 (m, 1H), 2.05−1.81 (m, 3H), 1.47 (s, 4H), 1.12 (s, 5H). ^{13}C NMR (101 MHz, MeOD) δ 165.6, 161.7, 156.2, 154.5, 151.3, 129.2, 127.1, 123.8, 123.3, 81.1, 63.1, 62.5, 36.7, 35.6, 28.8, 28.4, 25.7, 24.2. Note: presence of rotamers was observed in both ^{1}H and ^{13}C NMR. HRMS (ESI) m/z calc. for $C_{18}H_{23}N_3O_2$ (M+H) 314.1863, found 314.1863.



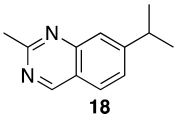
16

*7-Cyclohexyl-2-methylquinazoline (**16**).* Synthesized using General Procedure C, repurified after automated purification using silica gel flash column chromatography, eluting with 0−100% ethyl acetate in heptane to afford 12.5 mg colorless oil (22%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.34 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.60 (dd, J = 8.4, 1.6 Hz, 1H), 2.84−2.71 (m, 4H), 2.01−1.85 (m, 4H), 1.80 (m, 1H), 1.63−1.42 (m, 4H), 1.41−1.22 (m, 1H). ^{13}C NMR (101 MHz, MeOD) δ 165.1, 161.5, 157.5, 151.6, 129.2, 128.7, 124.3, 122.9, 46.4, 35.1, 27.8, 27.1, 25.7. HRMS (ESI) m/z calc. for $C_{15}H_{18}N_2$ (M+H) 227.1543, found 227.1543.



17

*7-((Cyclohexyloxy)methyl)-2-methylquinazoline (**17**).* Synthesized using General Procedure C to afford 16 mg light-yellow amorphous solid (25%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.39 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.91 (s, 1H), 7.66 (dd, J = 8.4, 1.4 Hz, 1H), 4.79 (s, 2H), 3.53−3.44 (m, 1H), 2.83 (s, 3H), 2.05−1.95 (m, 2H), 1.85−1.73 (m, 2H), 1.62−1.51 (m, 1H), 1.50−1.23 (m, 5H). ^{13}C NMR (101 MHz, MeOD) δ 165.4, 161.8, 151.3, 149.2, 128.7, 128.0, 124.9, 123.5, 79.0, 70.1, 33.3, 26.9, 25.8, 25.0. HRMS (ESI) m/z calc. for $C_{16}H_{20}N_2O$ (M+H) 257.1648, found 257.1647.



18

*7-Isopropyl-2-methylquinazoline (**18**).* Synthesized using General Procedure C, repurified after automated purification using silica gel flash column chromatography, eluting with 0−100% ethyl acetate in heptane to afford 10.4 mg colorless oil (22%[11]). ^{1}H NMR (400 MHz, MeOD) δ 9.37 (s, 1H), 8.00 (m, 1H), 7.75 (d, J = 0.8 Hz, 1H), 7.65 (dd, J = 8.4, 1.6 Hz, 1H), 3.17 (m, 1H), 2.82 (s, 3H), 1.37 (m, 6H). ^{13}C NMR (101 MHz, MeOD) δ 165.2, 161.5, 158.5, 151.6, 128.8,

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123.9, 122.9, 36.0, 25.7, 23.8. HRMS (ESI) m/z calc. for $C_{12}H_{14}N_2$ (M +H) 187.1230, found 187.1228.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02408.

^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Yield based on product obtained by automated purification, selecting only the largest fraction. Higher yields are obtainable through manual purification.

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