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Synthesis of Cycloalkyl Substituted 7-Azaindoles via Photoredox Nickel Dual Catalytic Cross-Coupling in Batch and Continuous Flow

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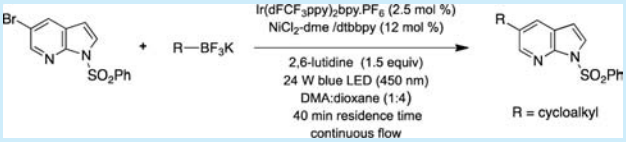
Supporting Information

ABSTRACT: An efficient photoredox/Ni dual catalytic C_{sp^2}–C_{sp^3} cross-coupling protocol in a continuous-flow regime to synthesize a variety of regioisomeric cycloalkyl substituted 7-azaindoles has been developed. These transformations proceed efficiently under mild conditions (blue LED light irradiation at 30 °C over 40 min residence time in mixed solvent systems). Reactions are easy to perform and afford most of the desired 2-, 3-, 4-, 5-, and 6-cycloalkyl substituted 7-azaindoles in moderate-to-good yield.



Azaindoles exhibit significant biological activities and are utilized as a core in a variety of drug discovery programs.[1] Although azaindoles occur rarely in nature, there has been considerable synthetic interest in azaindoles as indole bioisosteres wherein the additional nitrogen atom present in the 6-membered ring confers unique properties distinct from analogous indoles.[1] When compared to other fused bicyclic heterocycles, the azaindole core frequently demonstrates improved solubility, lipophilicity, target binding, pharmacokinetic properties, and ADMET profiles.[1] Therefore, azaindoles have been recognized as privileged structures in medicinal chemistry and drug discovery programs. The most commonly studied 7-azaindole isomer is represented by more than 100 000 reported structures in the literature, and the commercial availability of 7-azaindoles is amplified over other azaindole isomers.[1] Two drugs containing a 7-azaindole core recently gained FDA approval,[2] and several other 7-azaindole-containing drugs are in various stages of clinical development[2] (Figure 1).

We were interested in introducing cycloalkyl moieties into the 7-azaindole pharmacophore with the goal of improving drug likeness by reducing aromatic ring counts and increasing F_{sp^3}. The most common method used to introduce cycloalkyl groups onto the azaindole core involves two chemical steps: Suzuki–Miyaura coupling of an alkenyl boronic acid with a bromo azaindole followed by hydrogenation of the resulting alkene. The hydrogenation step often requires harsh reaction conditions[3] (Scheme 1). Direct Suzuki–Miyaura C_{sp^2}–C_{sp^3} coupling of the bromo azaindole with an alkyl boronic acid may be ineffective due to the formation of byproducts associated with β-hydride elimination.[4] In conventional C_{sp^2}–C_{sp^3} coupling, reactivity profiles are inversely proportional to carbon–boron bond strength, therefore greatly reducing efficient cross-coupling of C_{sp^3} alkylboron nucleophiles with aryl bromides.[5]

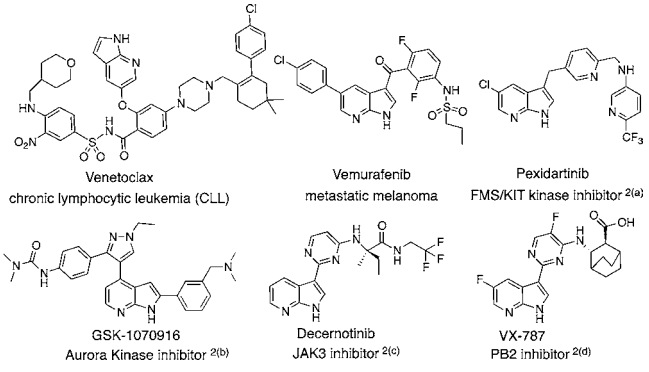
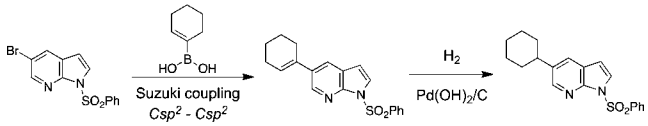


Figure 1. Examples of drugs containing 7-azaindoles.

Scheme 1. Introduction of Cycloalkyl Groups to 7-Azaindole Using a Conventional Two-Step Method



Visible light photoredox catalysis has emerged as a powerful innovative methodology for transmetalation involving a single electron transfer (SET) to generate a wide variety of new chemical entities.[6] This area has made tremendous progress in organic synthesis in the past decade.[6] In recent years, many research groups have focused on developing dual catalytic systems that combine photoredox catalysis with a second transition metal assisted activation mode. In this area, Molander and MacMillan concurrently developed novel photoredox/nickel dual catalytic systems for conventionally challenging C_{sp^2}–C_{sp^3} cross-couplings. Molander demonstrated the cross-coupling of potassium organotrifluoroborates with aryl halides,[5]

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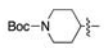
while MacMillan demonstrated the decarboxylative cross-coupling of α-amino acids with aryl halides.[7] Molander's group has recently documented very challenging photoredox/nickel dual catalytic $C_{sp^2}-C_{sp^3}$ couplings of secondary alkyltrifluoroborates with a variety of aryl bromides under very mild conditions (ambient temperature, visible light, no strong base).[8] These new protocols have significantly increased the success rate of challenging $C_{sp^2}-C_{sp^3}$ cross-coupling reactions. Application of the SET strategy to secondary alkyltrifluoroborates was considered challenging because of their relatively high reduction potentials (+1.50 V vs SCE) when compared to photoexcited Ir catalyst, $Ir(dFCF_3ppy)_2(bpy)PF_6$ (+1.32 V vs SCE).[8] This thermodynamically challenging oxidation of secondary alkyltrifluoroborates can, however, occur to generate a secondary alkyl radical which can enter the cross-coupling cycle.[8]

Encouraged by Molander's results,[8] we became interested in applying photoredox/Ni dual catalytic cross-coupling methodology to synthesize a variety of 7-azaindoles bearing cycloalkyl substitutions. *N*-Protection of the bromo 7-azaindoles was required for successful cross-coupling,[8] and the benzenesulfonyl group was selected, as it confers much greater stability than *t*-Boc protection. An investigation of the cross-coupling process was studied by treating compound **1**[3] with a diverse set of commercially available potassium trifluoroborates under conditions slightly modified from those reported by Molander.[8] The results are summarized in Table 1. Molander's original

Table 1. Potassium Trifluoroborate Scope in Photoredox/Ni Dual Catalytic Cross-Coupling under Batch Conditions

1 2a-2h 3a-3h

compd no	R	light source[a]	yield[b]
3a		A	60%
		B	69%
3b		A	60%
		B	64%
3c		A	58%
		B	64%
3d		B	44%
3e		A	59%
		B	54%
3f		A	14%
		B	trace
3g	 (±)-*trans*	A	51%
		B	50%
3h	 (±)-*trans*	A	trace
		B	trace

[a]Light source **A** = 2 × 26 W CFL; light source **B** = 6 × 4 W blue LED. [b]Isolated yields.

batch conditions involved the formation of a ligated nickel complex ($NiCl_2$·dtbbpy) in THF first and then removal of THF, followed by photoredox coupling in dioxane. We carried out formation of the ligated nickel complex, followed by photoredox coupling in THF. Both methods produced similar yields. For example, **3a** and **3b** were isolated in yields of 60% and 57% respectively, using Molander's original conditions while **3a** and **3b** were isolated in 60% yield using our modified conditions. Our modified procedure is more convenient and less time-consuming than previously reported procedures.[8] $Ir(dFCF_3ppy)_2(bpy)PF_6$,[8] THF, and Cs_2CO_3 were used as the photocatalyst, solvent, and base, respectively. The reaction mixture was exposed to either two 26 W CFL light bulbs or six 4 W blue LED light strips for 24 h to obtain the desired coupling products in moderate-to-good yields (**3a**–**e** and **3g**). Notably, the light source (CFL or blue LED) did not significantly affect the isolated yield of the coupling products except **3f**. However, some trifluoroborates produced desired coupling products in poor yields under these batch conditions (**3f** and **3h**).

In recent years, continuous flow chemistry has emerged as an expedient technology.[9] Photochemical transformations in continuous flow reactors often result in increased yields, reduced reaction time, and convenient scale-up as a result of efficient energy transfer between the light source and the reaction vessel.[10] Generally, the high surface area to volume ratio of flow reactors permits intense and uniform irradiation of the reaction mixture for a specific time period, hence avoiding over-irradiation of the solution.[11] An efficient photon penetration of the reaction medium is important for optimizing photoredox reaction efficiency. Therefore, continuous flow technology is ideally suited for large scale photoredox reactions. Merck has recently developed process scale photoredox flow reactors for this purpose.[6]

We anticipated that the photoredox/Ni dual catalytic cross-coupling protocol in a continuous flow reactor would increase yields, reduce reaction times, and facilitate scale-up. We chose to initiate our investigation of photoredox/Ni dual catalytic cross-coupling of compound **1** with potassium THP trifluoroborate **2a** in a continuous flow reactor. The inorganic base, Cs_2CO_3 in this case, was first replaced with a soluble organic base, such as 2,6-lutidine, to keep the reaction mixture homogeneous. The reaction solvents, such as THF, 2-methyl-THF, dioxane, DMF, and DMA, led to poor yields of desired coupling product **3a**. The choice of solvents played a critical role in our continuous flow cross-coupling to generate the desired coupling product, **3a**, as the major product. As has been recently reported, solvent participation in the reaction can lead to solvent addition products, complicating the desired outcome.[12] Our most successful results were achieved when mixed solvents were used in continuous flow. In general solvent addition byproducts were lower when using 1,4-dioxane due to the higher C–H bond dissociation energy than observed with THF,[12a] while addition of DMA not only helped provide a homogeneous solution suitable for flow but also appeared to suppress solvent interference. A similar mixed solvent combination was reported by Baran to be optimal for the Ni-catalyzed cross-coupling of active esters with aryl boronic acids.[13] With these modifications in place, **3a** was formed as a major product in 71% yield in 40 min residence time when a mixture of DMA and dioxane (1:4) was used. With optimized reaction conditions in hand (2,6-lutidine, DMA:dioxane (1:4), 24W blue LED (450 nm), 30 °C, 40 min residence time) we investigated further cross-couplings of trifluoroborates used in batch with compound **1** in continuous flow. The results are summarized in Scheme 2. Coupling products **3b**, **3c**, **3e**, **3f**, and **3g** were obtained with similar yields as our modified batch conditions but in a short reaction time (40 min residence time vs 24 h in batch) in continuous flow. However, coupling products **3d** and **3h** were isolated with an increased yield in continuous flow compared to modified batch conditions. Compound **3d** was isolated in 58% yield in continuous flow

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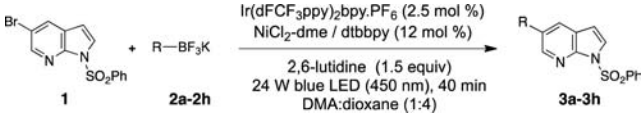
Scheme 2. Scope of Trifluoroborates in Phototoredox/Ni Dual Catalytic Cross-Coupling in Continuous Flow with *N*-Benzylsulfonyl-5-bromo-7-azaindole[a]



[a]**3a**: R = 4-THP, 71%; **3b**: R = cyclohexyl, 65%; **3c**: R = 4-Boc-piperidyl, 65%; **3d**: R = cyclobutyl, 58%; **3e**: R = cyclopentyl, 51%; **3f**: R = cycloheptyl, 16%; **3g**: R = *trans*-2-methylcyclopentyl, 41%; **3h**: R = *trans*-2-methylcyclohexyl, 16%.

and 44% in batch while compound **3h** was isolated in 16% yield in continuous flow and 0% in batch. Cyclobutyl, cyclopentyl, and cyclohexyl trifluoroborates produced desired coupling products **3d**, **3e**, and **3b** in good yields whereas cycloheptyl trifluoroborate produced the desired coupling product **3f** in poor yield in continuous flow. Furthermore, sterically hindered trifluoroborates such as 2-methylcyclopentyl and 2-methylcyclohexyl produced the desired (*trans*)-coupling products **3g** and **3h** exclusively in 41% and 16% respectively. After discovering new homogeneous continuous flow conditions (mixed solvent system, organic base, 24 W blue LED) we set up several control experiments in batch for comparison. Under these conditions, compounds **3b**, **3c**, **3d**, and **3f** were isolated in yields of 35%, 45%, 18%, and 0%, respectively, in batch after 24 h, at 30 °C while these compounds were isolated in 65%, 65%, 58%, and 16% yield respectively in continuous flow in 40 min. These control experiments clearly indicated that our new homogeneous conditions increased the yields of the desired coupling products and substantially reduced the reaction time (40 min vs 24 h) only in the continuous flow.

The continuous flow setup is represented in Figure 2 and is illustrated in the Supporting Information. The reaction mixture

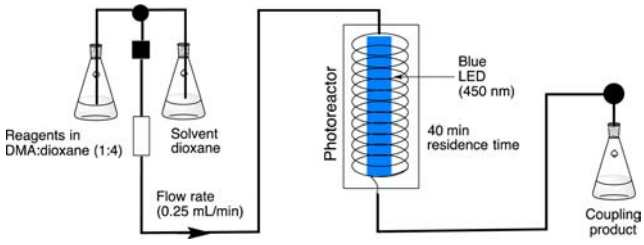


Figure 2. Continuous flow set up for photoredox/Ni dual catalytic cross-coupling.

was first prepared[14] and applied to a Vapourtec E-series UV-150 flow reactor equipped with a 24 W blue LED illuminating a 10 mL reaction loop, at a 0.25 mL/min flow rate.

Next, we focused our attention toward the synthesis of other cycloalkyl substituted 7-azaindole regioisomers using our optimized reaction conditions in continuous flow. The results of the photoredox/Ni dual catalytic cross-coupling of corresponding 2-, 3-, 4-, and 6-bromo-7-azaindoles[15−18] with selected commercially available trifluoroborates in continuous flow are summarized in Figure 3. As expected, all regioisomeric bromo 7-azaindoles produced corresponding coupling products. Both 4- and 6-bromo 7-azaindole produced the corresponding coupling products in moderate-to-good yield (**4a**−**4e** and **5a**−**5e**). However, 2- and 3-bromo-7-azaindoles produced the corresponding coupling products in lower yields

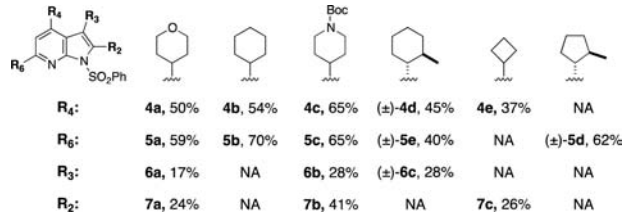


Figure 3. Cycloalkyl substituted 7-azaindoles produced via photoredox/Ni dual catalytic cross-coupling of corresponding 2-, 3-, 4-, and 6-bromo-7-azaindoles in continuous flow.

(**6a**−**6c** and **7a**−**7c**). Under these continuous flow conditions, debrominated azaindoles were isolated as a major byproduct of the cross-coupling of 2- and 3-bromo-7-azaindole. Continuous flow reaction conditions (e.g., flow rate, reaction temperature, and blue LED intensity) can be further optimized to generate desired 2- and 3-cycloalkyl substituted 7-azaindoles in good yield by minimizing the formation of a debrominated azaindole byproduct. The coupling products **5d**, **4d**, **5e**, **6c** derived from 2-methylcyclopentyl and 2-methylcyclohexyl substrates were isolated exclusively as the *trans* diastereomers.

In conclusion, we investigated the photoredox/Ni dual catalytic C_{sp^2}−C_{sp^3} cross-coupling of bromo-7-azaindoles with selected potassium trifluoroborates under batch and continuous flow conditions. The coupling reaction is accelerated in continuous flow, and the coupling products were obtained in similar or improved yields. To the best of our knowledge, this is the first application of continuous flow technology combined with photoredox/Ni dual catalytic cross-coupling of potassium trifluoroborates with bromo azaindoles to synthesize a variety of cycloalkyl substituted azaindoles. These transformations proceed efficiently under very mild conditions (blue LED light irradiation at 30 °C over a 40 min residence time in mixed solvent systems). Reactions are easy to conduct, and most of the desired cycloalkyl substituted 7-azaindoles were obtained in moderate-to-good yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03223.

Detailed experimental procedures and characterization of products (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The reaction mixture for continuous flow experiments was prepared as follows. The ligand $NiCl_2$-dme and dtbbpy was dissolved in DMA (1 mL) in a 10 mL Pyrex tube to form a blue colored solution to which the remaining reagents (2,6-lutidine, cycloalkyl trifluoroborate, bromo-7-azaindole, and photocatalyst) were added. The solution was diluted with 1-4-dioxane (4 mL), and the reaction mixture was filtered into another 10 mL Pyrex tube. The tube was capped, and the solution was purged with N_2. The solution was applied to a Vapourtec E-series UV-150 easy Medchem flow reactor equipped with a 24 W blue LED and 10 mL flow cell eluted at a flow rate of 0.25 mL/min. Further details are available in the Supporting Information.
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