

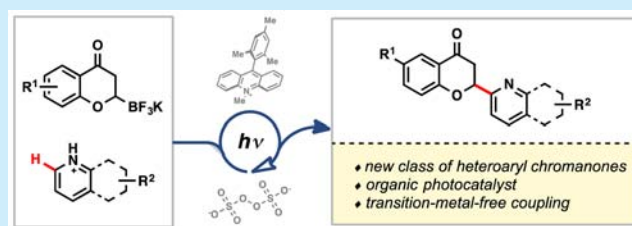
Organocatalyzed, Photoredox Heteroarylation of 2-Trifluoroboratochromanones via C–H Functionalization

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Supporting Information

ABSTRACT: Heteroarylation via C–H functionalization has been synthetically challenging, but such transformations represent an atom-economical and highly convergent route toward complex molecules. Reported herein is a photoredox-catalyzed coupling between 2-trifluoroborato-4-chromanones and various heteroarenes through a Minisci pathway. Mesitylacridinium perchlorate, an organic photocatalyst, proved to be a better photocatalyst than transition-metal counterparts for such transformations. To highlight the utility of this approach, a library of unprecedented heteroaryl-substituted chromanones was generated that was composed of numerous, specifically substituted molecules containing a broad range of functional groups.

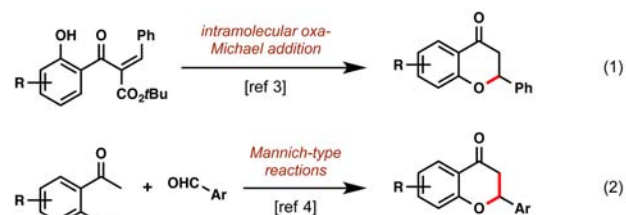


For decades, chromanones have captured the attention of the synthetic community because of their prevalence in natural products and in unnatural, biologically relevant compounds.¹ Although there are a large number of 2-aryl-substituted chromanones reported in the literature, there remain significant gaps among certain subclasses of these molecules. For example, there are less than 30 reported 2-quinolinyl-substituted 4-chromanones and no examples of 2-isoquinolinyl-substituted 4-chromanones. To date, 2-aryl-4-chromanones are primarily accessed through a chalcone precursor that is subsequently cyclized to form the pyranone ring under acidic, basic, or photochemical conditions (Scheme 1).² Although these routes are effective for providing targeted substructures, accessing a diverse array of aryl- or heteroaryl-substituted chromanones is challenging using a late-stage cyclization pathway.

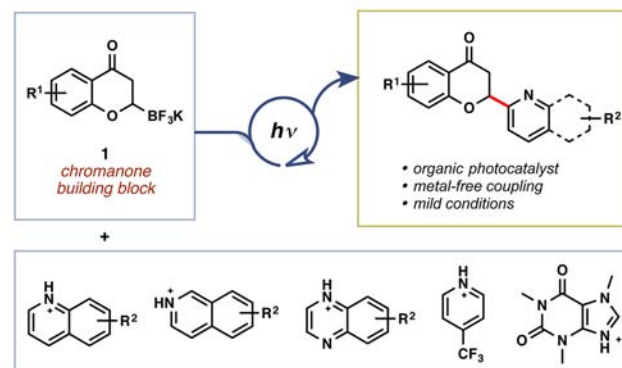
Inspired by these shortcomings, a photocatalyzed Minisci reaction was envisioned. Thus, we sought to deviate from the dual catalytic manifold into a singular photocatalytic cycle. Combining photoredox catalysis and C–H functionalization of heteroarenes represents a more sustainable approach to molecule construction that is being employed with increasing frequency.³ Until recently, Minisci reactions typically required superstoichiometric amounts of oxidant for radical generation under forcing conditions.⁴ Notably, our laboratory demonstrated trifluoroborates to be viable radical sources under “classical” Minisci reaction conditions, requiring either manganese or silver oxidant.^{4f,g} Radical intermediates have been accessed via photocatalysis in a significantly milder manner, but limitations remain, including the need for excess radical precursor,^{3d} expensive photocatalysts,^{3e} or complex radical precursors that limit substrate scope.^{3e} Keeping these limitations in mind, alkyltrifluoroborates appeared to be an attractive alternative given the precedent for single-electron oxidation of trifluoroborates via photoredox catalysis reported by Akita and co-

Scheme 1. Synthetic Routes toward 2-Aryl-4-chromanones

Previous Methods



This Work: Transition-Metal-Free Minisci Coupling



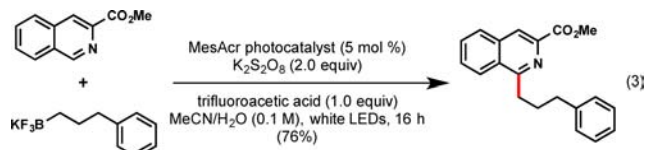
workers.⁵ Therefore, a robust method was sought to harness the reactivity of 2-trifluoroborato-4-chromanones as radical precursors to construct a wide range of 2-heteroaryl-4-chromanones

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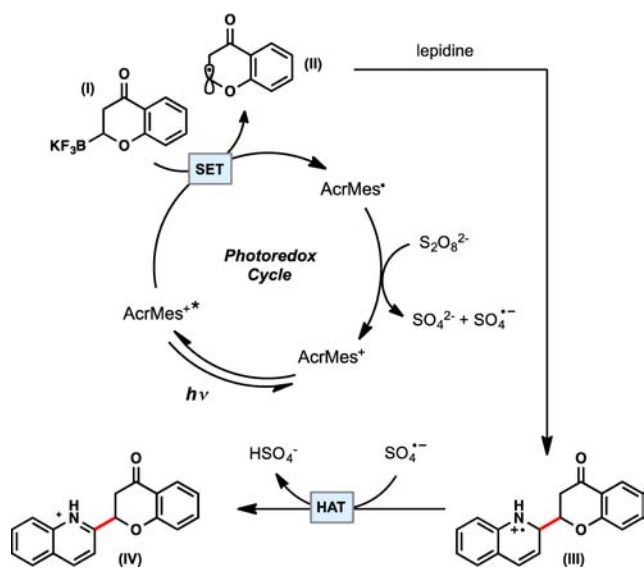
in a photocatalytic fashion that would address the shortcomings of previously reported methods.

In this vein, we recently developed a protocol for alkylation of heteroarenes in which primary, secondary, and tertiary alkyltrifluoroborates could be used in photoredox Minisci chemistry,⁶ allowing alkylation of numerous heteroarenes. The chemistry made use of an organic photocatalyst (a mesityl acridinium dye) and an inexpensive, mild oxidant and required only 1 equiv of alkyltrifluoroborate as an alkyl radical precursor (eq 3). We set out to parlay this development into a method for



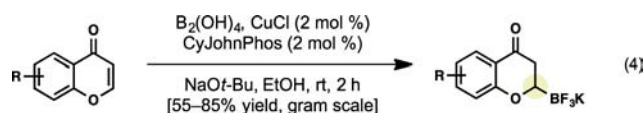
the construction of heteroaromatic flavanones. A mechanistic scenario (Scheme 2) was envisioned in which the excited state of

Scheme 2. Proposed Mechanism



a suitable photocatalyst possessed a redox potential sufficiently high to induce a single-electron oxidation of the trifluoroboratochromanone (I) to afford the α -alkoxy radical (II). The stabilized radical (II) would add to the heteroarene, activated by a Bronsted acid. An appropriate oxidant would be required to regenerate the ground-state photocatalyst as well as to rearomatize intermediate III via hydrogen atom transfer (HAT).

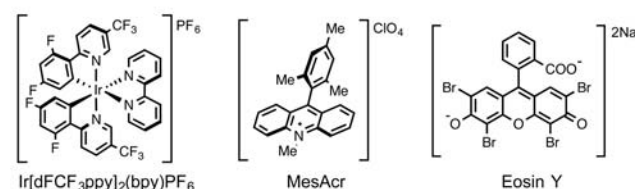
As alluded to above, access to the requisite 2-trifluoroborato-4-chromanones was achieved through a conjugate borylation reaction previously reported by our group (eq 4).⁷ Using this process, a variety of chromanones were acquired with excellent tolerance of functional groups and diverse substitution patterns.



With several 2-trifluoroborato-4-chromanones in hand, the development of the Minisci coupling reaction conditions was carried out using 4-bromoquinoline as a reaction partner (Table 1). A variety of photocatalysts were screened that possessed

Table 1. Photoredox/C–H Activation Optimization^a

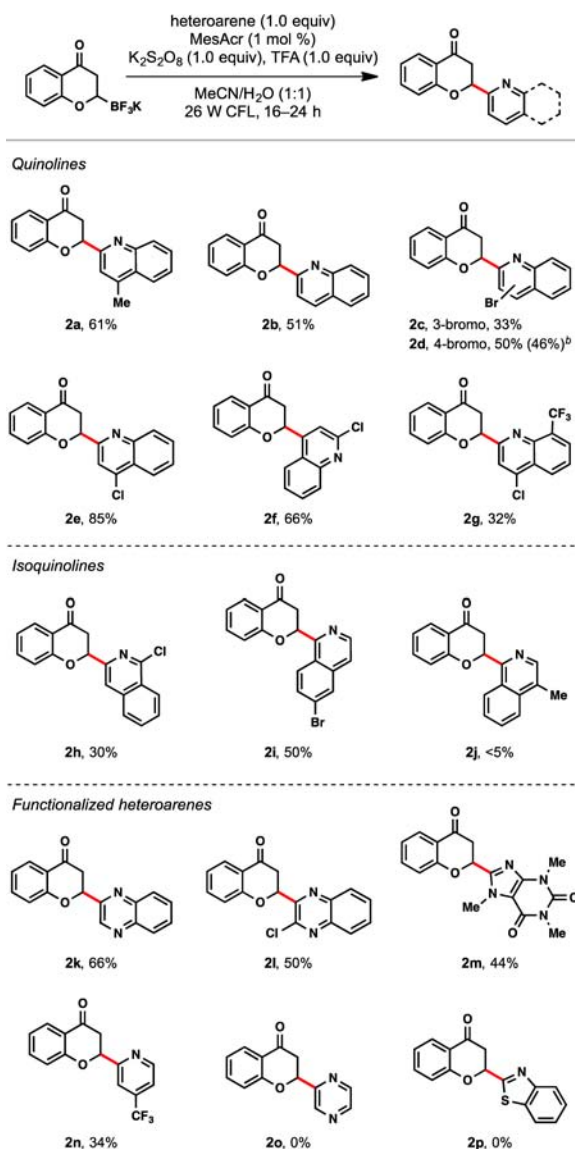
entry	photocatalyst (mol %)	K ₂ S ₂ O ₈ (equiv)	TFA (equiv)	yield (%)
1	Ir[dFCF ₃ ppy] ₂ (bpy)PF ₆ (2)	2.0	2.0	43
2	Eosin Y (2)	2.0	2.0	40
3	MesAcr (2)	2.0	2.0	55
4	MesAcr (1)	2.0	2.0	57
5	MesAcr (0.5)	2.0	2.0	42
6	MesAcr (1)	1.0	2.0	58
7	MesAcr (1)	1.0	1.0	60
8	MesAcr (1)	1.0	none	32
9	MesAcr (1)	none	1.0	21
10	none	1.0	1.0	0
11	MesAcr (1), no light	1.0	1.0	trace



^aOptimization reactions were performed on a 0.1 mmol scale. Yields were obtained via HPLC using a calibration curve.

sufficiently high excited-state redox potentials to oxidize the trifluoroboratochromanones ($E_{\text{red}} \approx +1.11$ V).⁸ Although Ir[dFCF₃ppy]₂(bpy)PF₆ ($E^*_{1/2} = +1.21$ V)⁹ and Eosin Y ($E^*_{1/2} = +0.79$ V)¹⁰ proved to be viable catalysts, Fukuzumi's mesitylacridinium perchlorate organophotocatalyst ($E^*_{1/2} = +2.20$ V),¹¹ recently used by Akita and co-workers,¹² provided superior yields. Using an organic photocatalyst is particularly advantageous because of the substantially lower cost relative to transition metal counterparts.¹³ Furthermore, both oxidant and protic acid loadings were lowered to 1 equiv without affecting the yield. Control studies were performed to confirm the need for acid (entry 8), terminal oxidant (entry 9), and photocatalyst (entry 10). Stern–Volmer relationship studies are consistent with the reductive quenching of the photocatalyst by the trifluoroborate (see the Supporting Information). Interestingly, the Stern–Volmer plot exhibited an exponential fluorescence quenching trend, suggesting a static quenching pathway.¹⁴ Additional ¹⁹F NMR experiments supported a static quenching pathway, where a distinct chemical shift was observed when photocatalyst was added to a solution of alkyltrifluoroborate.¹⁵ The observed shift in fluorine signals of the trifluoroborate suggests formation of a preassociation complex between the alkyltrifluoroborate and MesAcr before the single-electron transfer occurs. Quantum yield studies in a related study have indicated that this is not a radical-chain process as evidenced by a ϕ of 0.31.⁶ Finally, a control was run in the absence of light (entry 11) to demonstrate that the catalyst is active only in its photoexcited state.¹⁶

With suitable conditions in hand, the substrate scope for the heteroarene partners was explored (Scheme 3). Lepidine, a prototypical substrate in Minisci chemistry,⁴ was first used as a reacting partner. As expected, 2a was obtained regioselectively in relatively high yield (61%). Product 2b was obtained along with trace amounts of regioisomers but was primarily selective *ortho* to the nitrogen. Steric sensitivity was probed with 3-bromoquinoline, affording a lower yield of 2c (33%). When 4-bromoquinoline,

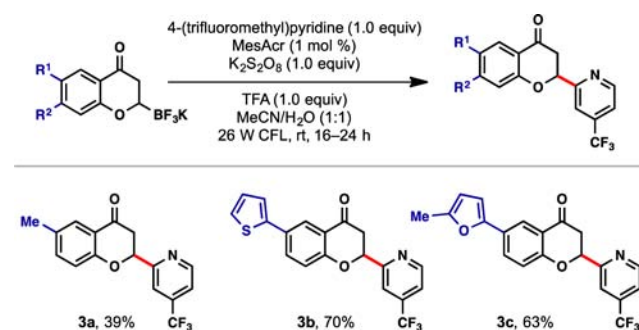
Scheme 3. Heteroarene Scope^a

^aReactions were performed with heteroarene (1.0 equiv), trifluoroborate (1.5 equiv), MesAcr (1 mol %), K₂S₂O₈ (1.0 equiv), and trifluoroacetic acid (1.0 equiv) in MeCN/H₂O (1:1) on a 0.5 mmol scale. ^bIsolated yield for a 1.0 g scale reaction.

line was used, the yield of **2d** improved to 50%. Notably, when the reaction was performed on gram scale, the yield was a comparable 46% yield. Conversion was significantly higher with 4-chloroquinoline, which provided an excellent yield of **2e**. 2-Chloroquinoline was next explored, and selective addition to the 4-position was observed (**2f**). With a more decorated chloroquinoline, 4-chloro-8-(trifluoromethyl)quinoline, a modest 32% yield was achieved. Halogenated isoquinolines were next explored to access products possessing functional handles for further diversification. 1-Chloroisoquinoline afforded a lower 30% yield (**2h**), but when the halide was appended on the adjacent ring, the yield improved to 50% (**2i**). Alkyl substitution at the C4 position resulted in <5% conversion, suggesting electron-withdrawing groups enhance the electrophilicity of the isoquinoline moieties. The scope was further explored with substrates containing more heteroatoms. Quinoxaline yielded monosubstituted product **2k** in 66% yield. A slightly lower yield

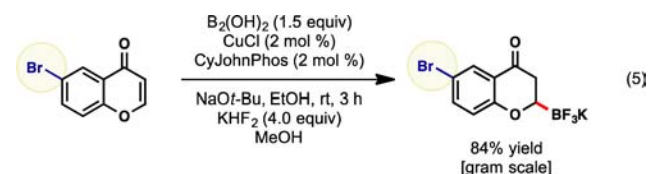
of **2l** was observed with 2-chloroquinoxaline. Caffeine, another nitrogen-rich heteroarene, also provided a modest yield of the alkylated product (**2m**). Pyridine moieties, a common pharmacophore in medicinal chemistry,¹⁷ were next probed. After screening various para-substituted pyridines, 4-(trifluoromethyl)pyridine yielded **2n** in a modest yield. Other, more electron-rich systems (e.g., substituted pyrazine **2o** and benzothiazole **2p**) could not be accessed. Typically, more electrophilic radicals such as CF₃ provide higher yields in reactions with such electron-rich heteroarenes.^{3a}

Finally, functionalized trifluoroboratochromanones were coupled with a variety of heteroarenes. Alkyl substitution (Scheme 4) yielded results similar to those of the unfunctionalized trifluoroborate (**3a**). Surprisingly, heteroaryl substitution on the aryl ring led to markedly higher yields (**3b,c**).

Scheme 4. Trifluoroborate Scope^a

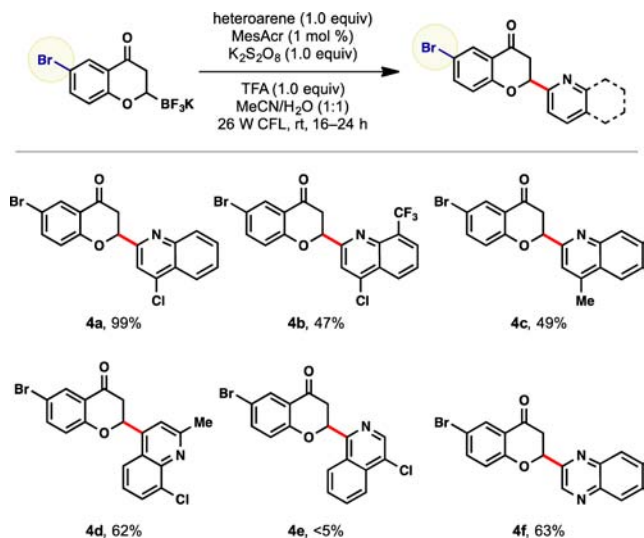
^aReactions were performed with heteroarene (1.0 equiv), trifluoroborate (1.5 equiv), MesAcr (1 mol %), K₂S₂O₈ (1.0 equiv), and trifluoroacetic acid (1.0 equiv) in MeCN/H₂O (1:1) on a 0.5 mmol scale.

Decorating the aryl ring with a halide was an attractive feature for further functionalization on the chromanone core. Starting from the commercially available 6-bromochromone, copper-catalyzed β borylation afforded the desired trifluoroborate in 84% yield on a multigram scale (eq 5).



Because 6-bromo-2-trifluoroboratochromanone has potential for elaboration on the aryl ring, an array of substrates was explored to confirm that the reactivity was similar to that of **1a** (Scheme 5). Coupling the bromo-substituted trifluoroboratochromanone with 4-chloroquinoline resulted in a markedly higher yield (**4a**). Other functionalized quinolines resulted in more modest yields (**4b–d**). Isoquinoline **4e** could not be accessed utilizing this protocol, but quinoxaline **4f** was generated in 63% yield.

In conclusion, a new class of 2-heteroaryl-substituted 4-chromanones has been accessed via sustainable photoredox-catalyzed coupling with a variety of heteroarene partners. An inexpensive organophotocatalyst was utilized to provide markedly higher yields relative to precious metal photocatalysts. This reaction proceeds chemo- and regioselectively, providing a viable method for radical-induced C–H functionalization of

Scheme 5. Bromochromanone Scope^a

^aReactions were performed with heteroarene (1.0 equiv), 6-bromo-2-trifluoroboratochromanone (1.5 equiv), MesAc (1 mol %), $K_2S_2O_8$ (1.0 equiv), and trifluoroacetic acid (1.0 equiv) in MeCN/ H_2O (1:1) on a 0.5 mmol scale.

activated heteroarenes. The net result is an efficient, robust, and reasonably general route to a class of compounds that, as a class, is underrepresented in the current literature.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00196.

Experimental details and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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