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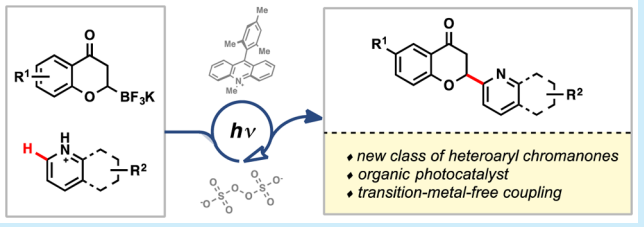
Organocatalyzed, Photoredox Heteroarylation of 2-Trifluoroboratochromanones via C−H Functionalization

Jennifer K. Matsui and Gary A. Molander*

Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

Supporting Information

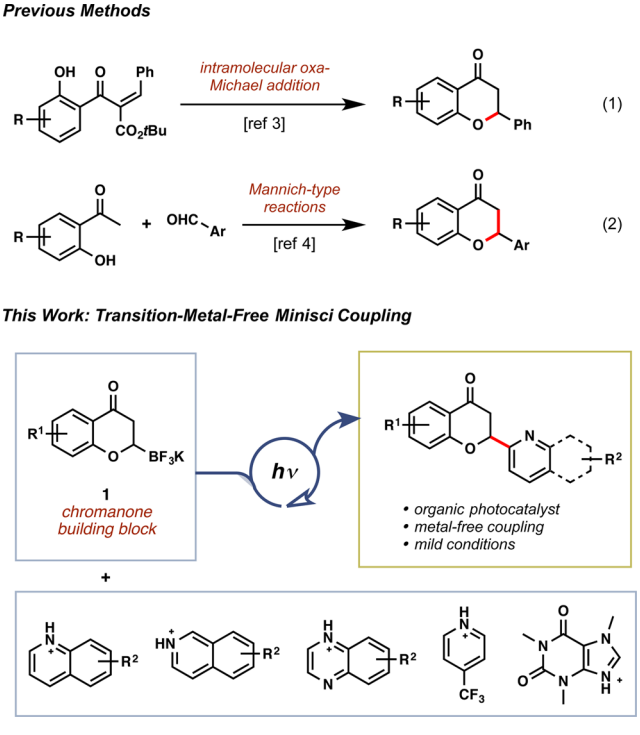
ABSTRACT: Heteroarylation via C−H functionalization has been synthetically challenging, but such transformations represent an atom-economical and highly convergent route toward complex molecules. Reported herein is a photoredox-catalyzed coupling between 2-trifluoroborato-4-chromanones and various heteroarenes 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 super-stoichiometric 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-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

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



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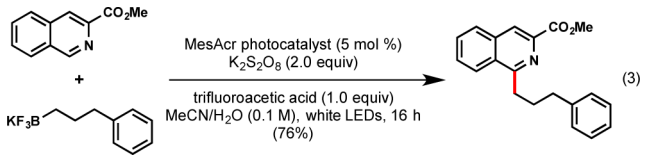
in a photocatalytic fashion that would address the shortcomings of previously reported methods.

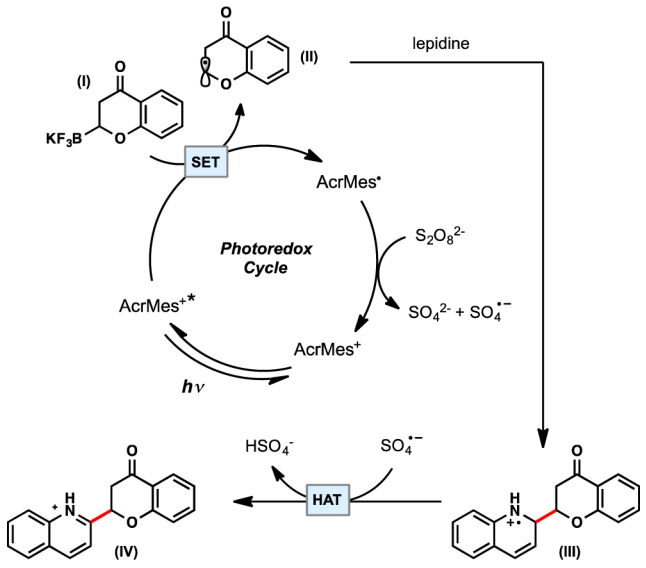
In this vein, we recently developed a protocol for alkylation of heteroarenes in which primary, secondary, and tertiary alkyltrifluoroborates could be used in photoredox Minisci chemistry,[6] allowing alkylation of numerous heteroarenes. The chemistry made use of an organic photocatalyst (a mesityl acridinium 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



(3)

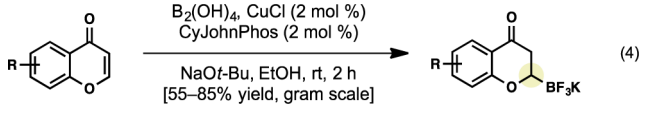
the construction of heteroaromatic flavanones. A mechanistic scenario (Scheme 2) was envisioned in which the excited state of

Scheme 2. Proposed Mechanism



a suitable photocatalyst possessed a redox potential sufficiently high to induce a single-electron oxidation of the trifluoroborotochromanone (**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).

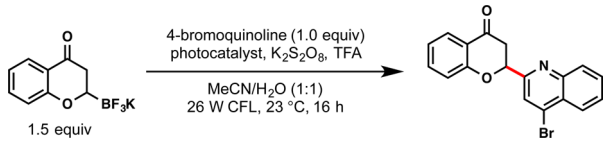
As alluded to above, access to the requisite 2-trifluoroborato-4-chromanones was achieved through a conjugate borylation reaction previously reported by our group (eq 4).[7] Using this process, a variety of chromanones were acquired with excellent tolerance of functional groups and diverse substitution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



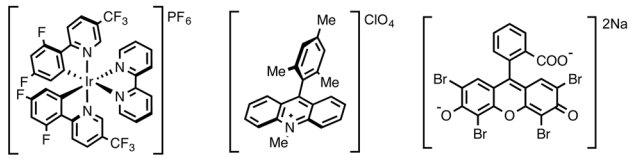
(4)

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 %)	$K_2S_2O_8$ (equiv)	TFA (equiv)	yield (%)
1	$Ir[dFCF_3ppy]_2(bpy)PF_6$ (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



$Ir[dFCF_3ppy]_2(bpy)PF_6$ MesAcr Eosin Y

[a]Optimization 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 ($E_{red} \approx +1.11$ V).[8] Although $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ ($E^*_{1/2} = +1.21$ 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 ^{19}F 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-bromoquino-

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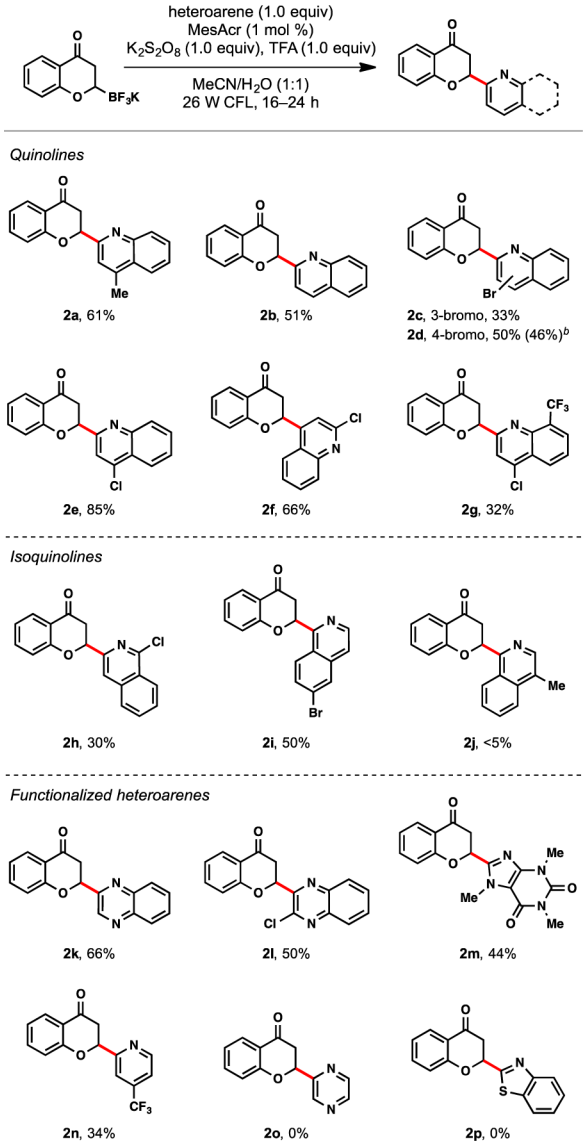
Scheme 3. Heteroarene Scope[a]

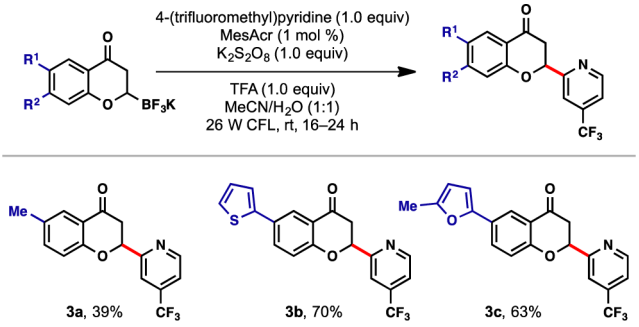


[a]Reactions were performed with heteroarene (1.0 equiv), trifluoroborate (1.5 equiv), MesAcr (1 mol %), $K_2S_2O_8$ (1.0 equiv), and trifluoroacetic acid (1.0 equiv) in MeCN/H_2O (1:1) on a 0.5 mmol scale. [b]Isolated yield for a 1.0 g scale reaction.

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 CF_3 provide higher yields in reactions with such electron-rich heteroarenes.[3a]

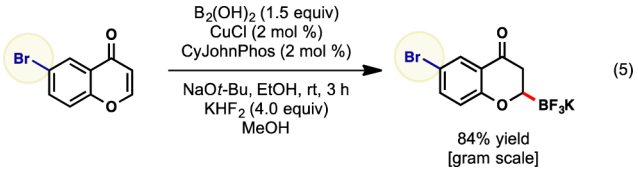
Finally, functionalized trifluoroboratochromanones were coupled with a variety of heteroarenes. Alkyl substitution (Scheme 4) yielded results similar to those of the unfunctionalized trifluoroborate (**3a**). Suprisingly, heteroaryl substitution on the aryl ring led to markedly higher yields (**3b**,**c**).

Scheme 4. Trifluoroborate Scope[a]



[a]Reactions were performed with heteroarene (1.0 equiv), trifluoroborate (1.5 equiv), MesAcr (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.

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).



(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

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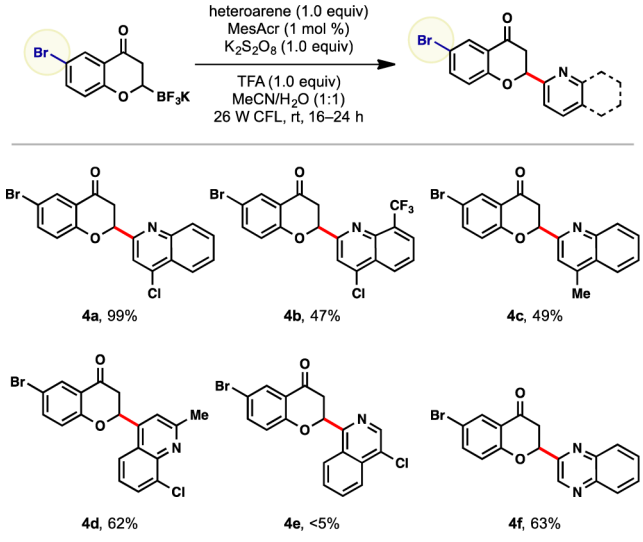
Scheme 5. Bromochromanone Scope[a]



[a]Reactions were performed with heteroarene (1.0 equiv), 6-bromo-2-trifluoroboratochromanone (1.5 equiv), MesAcr (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

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)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: g molandr@sas.upenn.edu.

ORCID

Gary A. Molander: 0000-0002-9114-5584

Notes

The authors declare no competing financial interest.

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