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Visible light-promoted alkylation of imines using potassium organotrifluoroborates†

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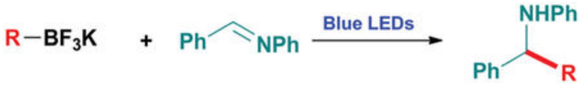
Abstract

A mild, redox-neutral, alkylation of imines with potassium alkyltrifluoroborates is described. The reaction proceeds under photoredox conditions at ~30 °C with primary, secondary, and tertiary alkyltrifluoroborates, leading to alkylation products in moderate to good yield in most cases. Aryl-, vinyl-, and cyclopropyl-trifluoroborates failed to react under the reported conditions.

Graphical Abstract



Addition of organometallic reagents to imines is a general, well-established method for the synthesis of α-alkylated and arylated amines.[1] Despite the attractiveness of this method, there are some drawbacks. For example, many organometallic compounds require special handling methods due to their water- and/or air-sensitivity,[2] and do not exhibit sufficient tolerance toward most functional groups. Methods based on radical addition to imines circumvent many of these issues, but often require stoichiometric amounts of strong oxidants or reductants.[3]

Recently, the use of photoredox catalysis to promote key bond-forming steps in organic synthesis has emerged as an alternative to classical radical chemistry, and has become a practical means to achieve a number of important synthetic transformations.[4] This approach relies on a catalyst that absorbs light in the visible range; the photoexcited catalyst subsequently mediates the formation of a radical from an organic substrate through a single-electron-transfer (SET) event (*i.e.*, oxidative or reductive quenching of the photocatalyst). The resulting species may then participate in an additional SET event to regenerate the ground state photocatalyst and close the catalytic cycle. The organic radicals thus generated can engage in downstream reactions leading to the final product(s). The photocatalysts

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†Electronic supplementary information (ESI) available: Experimental procedures, and compound ^{1}H- and ^{13}C-NMR spectra.

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Conflicts of interest
There are no conflicts to declare.

involved are often ruthenium or iridium polypyridyl complexes,[4] but may also be organic molecules.[5]

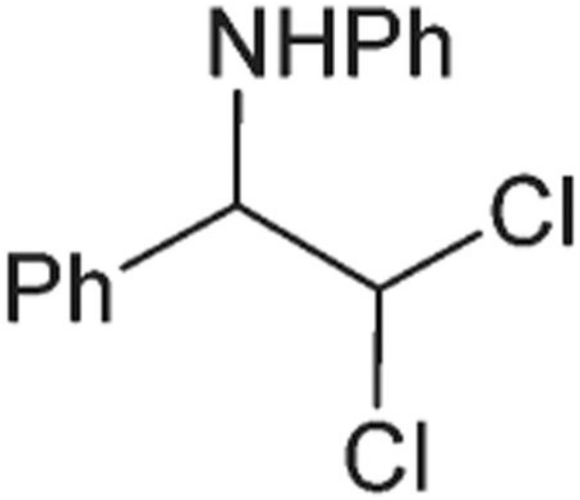
Potassium alkyltrifluoroborates have been shown to be viable radical precursors in several visible light-promoted protocols.[6] For example, Akita's laboratory has reported radical couplings with TEMPO,[7] as well as alkylations[7,8] and thioalkylations[9] of α,β-unsaturated carbonyls and related compounds, and Molander's group has developed a clever single-electron transmetalation approach to Csp^2–Csp^3 cross-coupling,[10] both using alkyl radicals derived from photo-oxidation of potassium alkyltrifluoroborates. Given their advantages as synthetic reagents, such as their stability, availability, ease of preparation, and functional group tolerance,[11] our research group became interested in exploring their utility in visible light-promoted alkylations of C=N bonds. Non-photoredox additions of potassium aryl- and allyltrifluoroborates to imines[12] are well-known, but there seem to be no accounts involving the direct addition of ordinary primary, secondary, or tertiary alkyl trifluoroborates to these substrates. And while there appear to be no reports to date of photoredox alkylations of imines using potassium organotrifluoroborates as alkyl radical precursors, reports of similar approaches employing alkyl bis(catecholato) silicates[13] and 4-alkyl-1,4-dihydropyridines[14] as alkyl radical precursors have appeared recently. In this communication, we report the results of a preliminary study employing potassium organotrifluoroborates as alkyl radical precursors in a mild, visible light-promoted, redox-neutral alkylation of imines.

We began our study by examining the reaction of potassium benzyltrifluoroborate (**1a**) with benzalaniline (**2**). Based on a survey of reduction potentials for potential photocatalysts,[4b] we chose to employ [4,4′-bis(*tert*-butyl)-2,2'-bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]iridium(III) hexafluorophosphate (***Ir-dF(CF_3)-dtb***) in our experiments, since, in its excited state, it is likely to be strong enough ($E_{1/2}(\mathrm{Ir}^*/\mathrm{Ir}^-)$ = +1.21 V *vs.* SCE[15,16]) to generate the alkyl radical from a variety of potassium alkyltrifluoroborates. While the reduction potential of the excited photocatalyst is clearly sufficient to oxidize benzyl and allyl trifluoroborates (~+1 V (ref. 7)), primary and secondary substrates were seen as potentially problematic due to their higher reduction potentials (~+1.5 V for $c\text{-}C_6H_{11}BF_3K$ and ~+1.8 V for $PhCH_2CH_2BF_3K$).[7] In spite of this, encouraging results from Molander's group have demonstrated that thermodynamically unfavorable single-electron oxidation, driven by irreversible C–B bond cleavage, is possible in these cases.[10]

We quickly found that irradiation of an argon-sparged dichloromethane solution of **1a, 2,** and ***Ir-dF(CF_3)-dtb***, mounted between 2 16 W 450 nm LED floodlights for 18 h resulted in a 70% (isolated) yield of **3a** (reactor assembly and LED emission spectrum shown in Fig. S1 and S2 of the ESI†). GC/MS of the reaction mixture showed that **2** was completely consumed, and only a small amount bibenzyl, resulting from homocoupling of the benzyl radical generated from **1a**, was detected. Essentially no 1,2-bis(phenylamino)-1,2-diphenylethane, resulting from a potential α-amino radical derived from **2**,[17] was detected. Control experiments established the need for both catalyst and light; these results are shown in Table 1.

[†] Electronic supplementary information (ESI) available: Experimental procedures, and compound ^{1}H- and ^{13}C-NMR spectra.

Building on these initial results, we screened a number of potassium organotrifluoroborates for suitability in this protocol. As shown in Table 2, use of a wide range of potassium alkyltrifluoroborates led to moderate to good yields when reacted with **2;** addition of a proton donor (entry 1) gave a slightly better yield of product. As expected, product yields seem to be related to trifluoroborate reduction potential; thus, organotrifluoroborates that have lower reduction potentials (*i.e.*, those that form more stable radicals and thus are more easily oxidized) result in higher yields of product (entries 1–3 and 7). Given the much higher reduction potential of primary alkyltrifluoroborates, it was somewhat surprising to find that potassium phenethyltrifluoroborate (E_{red} = +1.83 V (ref. 7)) was a competent radical source, although the reaction proceeded much more slowly. As shown in entry 6, only a 17% yield of amine **3f** was produced after 46 h, but GC/MS analysis of the reaction mixture showed that only about 30% of **2** had been consumed during this time. Extending the reaction time to 1 week (168 h) led to complete consumption of **2** and a respectable 41% yield of **3f**. Potassium α-benzyloxymethyltrifluoroborate (**1h**) also reacted smoothly in the protocol (entry 8), leading to a reasonable yield of the vicinal amino ether **3h**. Aryl- and vinyltrifluoroborates did not react (entries 9 and 10); potassium cyclopropyltrifluoroborate (entry 4) was also not suitable in this protocol. These failures can be rationalized in terms of relative radical stabilities, which are related to R–H bond dissociation energies (BDEs).[18] Vinyl-H, aryl-H, and cyclopropyl-H BDEs are generally >440 kJ mol^{-1}, while alkyl-H BDEs are generally <420 kJ mol^{-1},[19] reflecting the greater stability of alkyl radicals as compared to vinyl, aryl, or cyclopropyl radicals. Consistent with this trend, potassium cyclobutyltrifluoroborate (**1e**) could be used in the protocol (cyclobutyl-H BDE = 404 kJ mol^{-1}),[19] leading to an acceptable yield of **3e** (entry 5). Unfortunately, **3e** could only be isolated as an inseparable mixture with a second product in a 12 :1 molar ratio. The chemical shifts of the impurity signals, along with the HRMS of the second product seem consistent with compound **4** below, apparently derived from reaction of **2** with the dichloromethane solvent, probably *via* generation of the dichloromethyl radical.[20]



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Since addition of potassium allyltrifluoroborate (**1b**) to certain imines previously had been shown to occur in the presence of Lewis acids,[12b] the reaction of **1b** was also examined in the absence of both catalyst and light (entry 2); no product was produced in either case, further validating the need for both in the protocol.

Based on literature precedent, thermodynamic considerations and the absence of homocoupling products derived from benzalaniline, we postulate that this reaction proceeds by a closed-cycle radical addition mechanism as shown in Scheme 1. Irradiation of the iridium catalyst should give an excited-state species which is able to oxidize an organotrifluoroborate to radical intermediate **A**. Radical addition of **A** to the imine should produce N-centered radical **B.** ***Ir-dF(CF_3)-dtb***, in its reduced state ($E_{1/2}$(Ir^{III}/Ir^{II}) = −1.37 V (ref. 15)), will likely be strong enough to convert **B** to amide ion **C**,[21] thus closing the catalytic cycle. A similar mechanism has recently been proposed for radical alkylations of imines with alkyl silicates.[13b]

However, many visible-light photoredox reactions which are postulated as closed-cycle mechanisms may actually proceed via radical chain processes, since a group transfer event in a radical chain process generates the same intermediate as an electron transfer event.[22] To screen for this possibility, we performed a “light–dark” experiment, alternating between irradiation and non-irradiation, and analyzing the extent of product formation after each period. These results are shown in Fig. 1. Based on these data, it appears that product formation only occurs during periods of illumination, and does not occur to any appreciable extent during periods of no illumination. It should be noted that after about 60% conversion to product, the reaction mixture was left in the dark overnight (~16 h), during which time no additional product formation was observed. After that period, product formation resumed upon further illumination. These results are consistent with a closed cycle mechanism, although further study (*i.e.*, determination of the quantum yield) is necessary to completely rule out a radical chain process.[23]

In summary, we have developed a mild, visible light-promoted protocol for the alkylation of imines using potassium organotrifluoroborates. Moderate to good yields of amine products are obtained with a wide variety of these substrates, including ordinary primary, secondary, and tertiary alkyl examples. Further optimization of the methodology, as well as investigations into the scope and mechanism of the transformation are ongoing in our laboratory, and the results will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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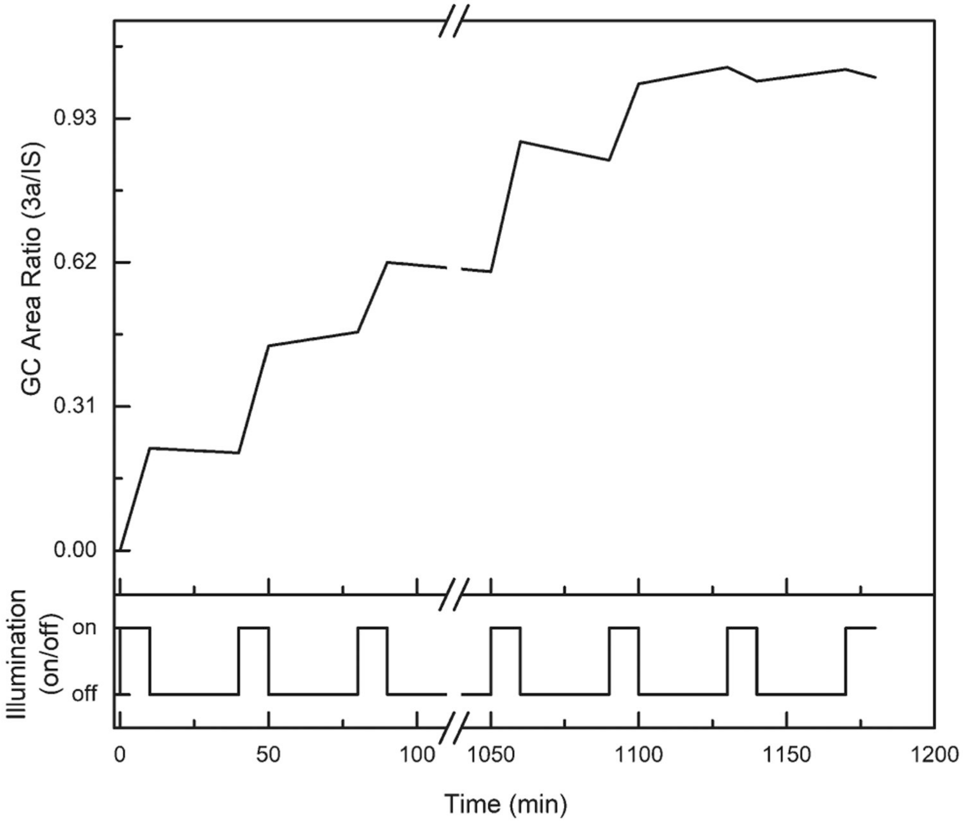
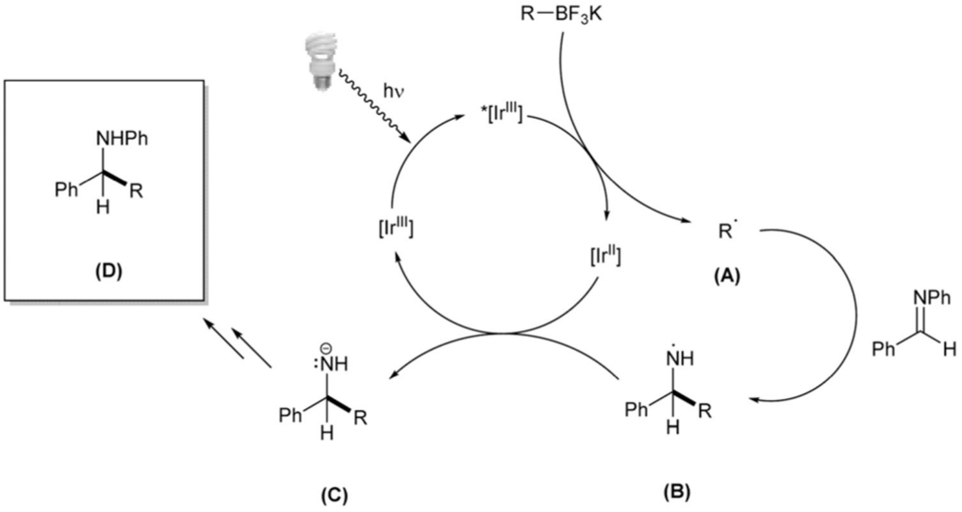


Fig. 1.

Light–dark experiment results. Top: Time course for the appearance of **3a**, measured as GC area ratio of **3a** to that of an internal standard (decane). Bottom: Illumination of reaction mixture *vs*. time. Experimental details can be found in the ESI.†

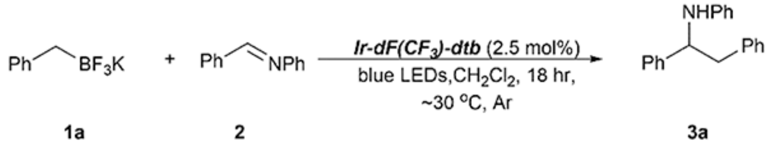


Scheme 1.

Proposed mechanism for the visible light-promoted alkylation of imines.

Table 1

Visible light-promoted reaction of potassium benzyltrifluoroborate (**1a**) with benzalaniline (**2a**)[a]



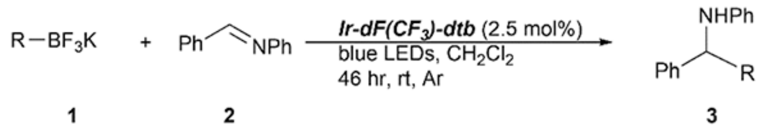
Entry	Catalyst (Y/N)	Light (Y/N)	Yield[b] (%)
1	Y	Y	70
2	N	Y	Trace
3	Y	N	0

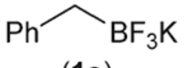
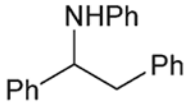
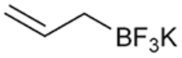
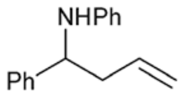
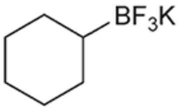
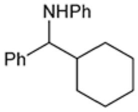
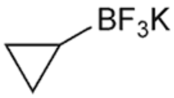
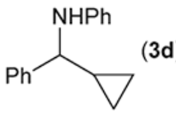
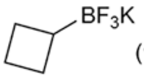
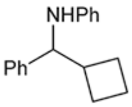
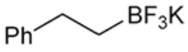
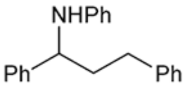
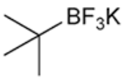
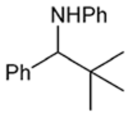
[a] Reaction conditions: **1a** (0.38 mmol), **2** (0.25 mmol), ***Ir-dF(CF3)-dtb*** (0.0063 mmol), CH_2Cl_2 (5 mL), blue LEDs, rt, Ar, 46 h.

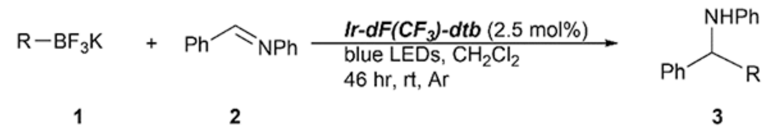
[b] Isolated yield.

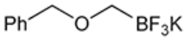
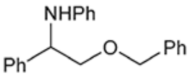
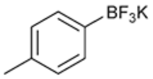
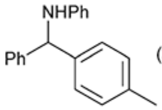
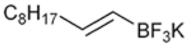
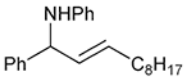
Table 2

Scope of the reaction employing various potassium organotrifluoroborates[a]



Entry	RBF_3K (1)	Product (3)	Yield[b] (%)
1	 (1a)	 (3a)	70 (76[c])
2	 (1b)	 (3b)	70 (0[d]) (0[e])
3	 (1c)	 (3c)	73
4	 (1d)	 (3d)	0
5	 (1e)	 (3e)	48[f,g]
6	 (1f)	 (3f)	17 (41[h])
7	 (1g)	 (3g)	60



Entry	RBF$_3$K (1)	Product (3)	Yield[b] (%)
8	 **(1h)**	 **(3h)**	61
9	 **(1i)**	 **(3i)**	0
10	 **(1j)**	 **(3j)**	0

[a] Reaction conditions: **1** (0.38 mmol), **2** (0.25 mmol), ***Ir-dF(CF$_3$)-dtb*** (0.0063 mmol), CH_2Cl_2 (5 mL), blue LEDs, rt, Ar. 46 h.

[b] Isolated yields.

[c] $(PhO)_2PO_2H$ (0.38 mmol) added to the reaction mixture.

[d] No catalyst.

[e] No light.

[f] Isolated as an inseparable mixture with **4** (**3e : 4** = 10: 1 by NMR).

[g] Calculated yield of **3e** based on NMR purity.

[h] 168 h.