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Combined Photoredox and Carbene Catalysis for the Synthesis of γ -Aryloxy Ketones

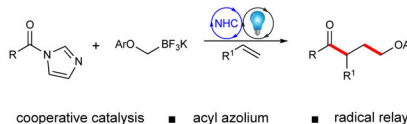
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Abstract

N-heterocyclic carbenes (NHCs) have emerged as catalysts for the construction of C–C bonds in the synthesis of substituted ketones under single-electron processes. Despite these recent reports, there still remains a need to increase the utility and practicality of these reactions by exploring new radical coupling partners. Herein, we report the synthesis of γ -aryloxyketones via combined NHC/photoredox catalysis. In this reaction, an α -aryloxymethyl radical is generated via oxidation of an aryloxymethyl potassium trifluoroborate salt, which is then added into styrene derivatives to provide a stabilized benzylic radical. Subsequent radical-radical coupling reaction with an azolium radical affords the γ -aryloxy ketone products.

Graphical Abstract



Keywords

N-heterocyclic carbene; acyl azolium; photochemistry; potassium trifluoroborate; radical relay

N-Heterocyclic carbenes (NHCs) have traditionally been used as organocatalysts to achieve umpolung (polarity reversal) reactivity in two-electron processes.^[1] The majority of these reactions involve the Lewis basic NHC adding into an aldehyde to generate a Breslow intermediate, which can then act as a nucleophile to react with various sp^2 -derived electrophiles (e.g., carbonyl groups, imines, conjugate acceptors).^[2] More recently, there has been an increase in reports that utilize NHCs as single-electron operators for radical-radical coupling reactions.^[3] These NHC-mediated radical reactions are typically based on a single-electron oxidation of the electron-rich Breslow intermediate to yield an azolium radical species, which could undergo radical-radical coupling with numerous radical sources.^[4] However, the opposite pathway involving single-electron reduction of an acyl azolium species remains underexplored.^[5]

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In 2020, we reported a single-electron reduction of an acyl azolium intermediate derived from activated carboxylic acids.^[6] The resulting azolium radical species could then undergo radical-radical coupling with an oxidatively generated radical derived from alkyl and benzyl Hantzsch esters to access ketones (Figure 1A). This report highlighted new radical-based NHC reactivity because, a) it allowed for the direct alkylation of the azolium intermediate through an alternative method, and b) included the ability to incorporate aliphatic acid substrates. We have expanded this radical coupling platform^[7] to include bis-catecholato silicates,^[8] and developed an alkoxyacylation reaction utilizing potassium trifluoroborate salts (Figure 1B).^[9] Potassium alkyltrifluoroborates offer several attractive features over other oxidative radical precursors including bench stability, chromatography-free synthesis, and high atom economy.^[10]

Studer and coworkers have expanded this reductive alkylation NHC catalysis further with their ability to perform a three-component radical relay with acyl fluorides, olefins, and trifluoromethyl radicals (Figure 1C).^[11] This work, along with our reports, served as inspiration to develop a complimentary three-component reaction that utilizes oxidatively generated radicals not yet examined in azolium reductive alkylations. We sought to develop this three-component NHC/photoredox catalyzed reaction by surveying aryloxymethyl radicals derived from aryloxymethyltrifluoroborates (Figure 1D).^[12] These starting materials are readily accessible and produce a radical that is stabilized by electron donation from the oxygen atom.^[13] This 3-component reaction has the ability to generate a 1,4-dioxygenation pattern. While 1,3-^[14] and 1,5-dioxygenation^[15] patterns are quite common due to their traditional bond disconnection approach, the 1,4-dioxygenation pattern is generally obtained through Umpolung reactivity via a Stetter reaction.^[16] Herein we report the synthesis of γ -aryloxy ketones through combined NHC/photoredox catalysis.

To commence our investigation, we surveyed various acyl azolium precursors, including acyl imidazoles and acyl fluorides, and multiple photocatalysts. The well-established NHC precursor **Az-1** was chosen as the azolium catalyst while cesium carbonate was selected as the base to be analyzed.^[7, 11] While the desired product **4** was observed using both acyl imidazoles and acyl fluorides, we opted to pursue conditions using acyl imidazole **1a** due to their ease of preparation and handling.^[17] These initial hit conditions provided the desired product in 29% yield using acyl imidazole **1a**, aryloxymethyl trifluoroborate salt **2a**, styrene (**3a**) as the olefin, cesium carbonate as the base, NHC precursor **Az-1**, and the organophotocatalyst 4-CzIPN (**PC-1**) (Table 1, Entry 1). A brief screen of NHC precursors confirmed that **Az-1** was the best azolium catalyst to efficiently afford the γ -aryloxy ketone **4** (Entries 1 and 2, see Supporting Information for more details). It was also found that CsOAc slightly increased the yield compared to other inorganic and organic bases (Entries 2–4). Tuning the electronics of the aryloxymethyl trifluoroborate salt to a more electron rich substrate **2a** as well as making styrene the limiting reagent provided a marked increase in yield (Entries 5–8). Finally, reducing the overall concentration of the reaction provided the product in 90% isolated yield (Entry 9). Interestingly, substituting benzoyl fluoride for the acyl donor under the optimized conditions resulted in trace product detected (Entry 10).

With our optimized conditions in hand, we first examined the scope of the reaction by altering the substitution on the trifluoroborate (Table 2A). Electronic effects proved to be

crucial in this reaction, as the methoxy-derived aryloxymethyl trifluoroborate was uncovered to be the best borate salt (in terms of product yield) while the methyl substituted and neutral phenol derivatives only provided product in moderate yields (**4b,4c**). The bulkier and more electron-rich naphthlene derived borate salt also afforded the desired product **4d** in 63% yield. Interestingly, various halogenated aryloxymethyl trifluoroborates were well-tolerated in this reaction in greater than 60% yield (**4e–4g**). As expected, the electron-withdrawing trifluoromethyl-substituted aryloxymethyl salt produced the product **4h** in only 14% isolated yield. Replacing the trifluoromethyl group with an ester group (–CO₂Et) failed to afford the respective product, presumably due to the increased oxidation potential of the substrate.

Next, we explored the reaction scope by modifying the substitution on the acyl imidazole (Table 2B). A variety of electron-donating and electron-withdrawing substituents were tolerated on the acyl imidazole. The methoxy-substituted aryl acyl imidazole provided ketone **4i** in 66% yield. Methyl groups at the *meta*- and *para*-position of the aryl acyl imidazole afforded the desired products **4j–4k** in good yield. Changing the substitution to a more electron-withdrawing cyano group also allowed formation of the γ -aryloxyketone **4l**. However, the halogenated acyl imidazoles only delivered **4m** and **4n** in 22% and 38% yield, respectively. While aliphatic substrates have been used in direct coupling reactions via NHC/photoredox cooperative catalysis, they have not yet been employed in a 3-component radical-relay NHC/photoredox catalyzed process.^[7, 18] Much to our delight, these reaction conditions were able to tolerate various aliphatic derived acyl imidazoles to generate the ketone products **4o–4q** in low-to-good yields.

Lastly, we wanted to examine the scope with respect to the alkene (Table 2C). An electron-rich *para*-methoxy styrene was able to provide the desired ketone **4s** while using **2b** as the trifluoroborate in 50% yield. Gratifyingly, we were also able to use the electron-rich methoxy styrene while changing substitution on the trifluoroborate to afford a series of ketones **4t–4w** in low-to-moderate yields. Use of *meta*-methyl styrene generated the ketones with the *para*-methoxy trifluoroborate salt as well as the naphthyl-derived trifluoroborate salt in 67% and 55% yield, respectively. Surprisingly, α -methyl-substituted styrene and more sterically hindered 1,1-diphenylethylene afforded the corresponding ketones **4z–4ab** in good yield, showcasing the ability of this methodology to generate quaternary centers. Unfortunately, when the olefins cyclohexene and ethyl vinyl ether were subjected to our reaction conditions, no desired product was observed.

To demonstrate the utility of our products, we hypothesized that the resulting *para*-methoxy phenyl (PMP) group could be removed to provide γ -hydroxyketones. Thus, exposure of **4a** to oxidative conditions using cerium ammonium nitrate (CAN) afforded the 2,3-dihydrofuran **5** in 58% yield (Scheme 1).^[19] This heterocyclic motif is embedded in many important natural products as well as medicinally relevant molecules and is considered a useful intermediate for other synthetic transformations.^[20] Additionally, employing sodium borohydride as the reducing agent afforded alcohol **6** presumably favoring the Felkin isomer with 11:1 dr and in 96% yield.

To probe the reaction pathway of the overall process, control reactions and radical trapping experiments were performed. No product was observed in the absence of photocatalyst

or light suggesting that this reaction is a photocatalyzed process (Table 1, Entries 10 and 12, respectively). Additionally, the reaction did not proceed in the presence of TEMPO as a radical trap. Instead, the aryloxymethyl TEMPO adduct was observed, indicating that a radical process is likely occurring (Scheme 2A). However, it is important to note that while product was detected in the absence of **Az-1**, it was in much lower quantity, highlighting the importance of the azolium catalyst in this reaction for overall efficiency (Table 1, Entry 11).^[5e] The importance of the azolium can also be displayed in Scheme 2B. Isolated azolium species **7** was synthesized and our optimized conditions were employed. Under these conditions, **4a** was only isolated in 25% yield. While **7** may be a possible intermediate of the reaction, we attribute the decrease in yield due to the steric and electronic effects of the NHC. Based on these results and other combined NHC/photoredox catalysis reports, we propose the following catalytic cycle (Scheme 2C).^[7, 11] The excited state of the photocatalyst (4-CzIPN*) can oxidize the trifluoroborate salt **2** with exposure to LED irradiation. Subsequent fragmentation affords the aryloxymethyl radical **I** and the reduced photocatalyst.^[21] The addition of **I** into styrene generates a stable benzyl radical intermediate **II**. Single-electron reduction of the acyl azolium **III** provides the stabilized azolium radical **IV** while regenerating the ground-state photocatalyst (4-CzIPN).^[22] Based on our previous mechanistic investigations, the steric hindrance and electronic effects from the NHC mesityl group likely guides the final radical-radical coupling between **IV** and **V** to afford the desired γ -aryloxy ketone product **V**.^[7]

In summary, we have developed a three-component NHC/photoredox catalyzed reaction to synthesize γ -aryloxy ketones. This transformation builds on the emerging area of single-electron carbene catalysis by incorporating oxidatively generated aryloxymethyl radicals. A wide variety of γ -aryloxy ketones can be accessed rapidly with good functional group compatibility as well as use highly substituted styrenes to generate quaternary centers adjacent to the carbonyl group. The key-step in this reaction is the reduction of an acyl azolium to yield a stabilized azolium radical, which can then undergo radical-radical coupling with the aryloxymethyl radical. The utility of these products was showcased in the ability to remove the PMP group to afford 2,3-dihydrofurans. Current studies in our laboratory involve exploring new oxidatively generated radical species with NHC/photoredox chemistry and their applications in synthesis.

Experimental Section

General information

All reactions were carried out under an argon or nitrogen atmosphere in oven-dried glassware with magnetic stirring. All solvents were purified by passing through a bed of activated alumina, dried over 3Å molecular sieves, and then degassed using freeze-pump-thaw method (3–4 cycles). Purification of reaction products was carried out by flash chromatography on Biotage Isolera 4 systems with Ultra-grade silica cartridges. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light. ¹H NMR spectra were recorded on AVANCE III 500 MHz w/ direct cryoprobe (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data are reported as (s = singlet, d

= doublet, t = apparent triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration.) Proton-decoupled ^{13}C NMR spectra were recorded on an AVANCE III 500 MHz w/ direct cryoprobe (126 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl_3 at 77.16 ppm). Mass spectra were obtained on a WATERS Acquity-H UPLC-MS with a single quad detector (ESI) or an Agilent 7890 gas chromatograph equipped with a 5975C single quadrupole EI-MS. High-resolution mass spectrometry (HRMS) was obtained using an Agilent 6201 MSLC-TOF (ESI). All photocatalytic reactions were carried out in a SynLED Parallel Photoreactor (465–470 nm) purchased from Sigma-Aldrich. $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ (IrdF) was purchased from Strem Chemicals and used without purification. 4-CzIPN was prepared according to the literature procedure. The spectra of 10 known prepared BF_3K substrates (**2a-2k**) were matched with the literatures data.

General synthetic procedure for the synthesis of acyl imidazoles (**1**)

The appropriate acid (10 mmol, 1.0 equiv) was dissolved in dry dichloromethane (0.3 M), and CDI (carbonyldiimidazole, 15 mmol, 1.5 equiv) was added slowly (caution, exothermic). The resulting mixture was stirred overnight at room temperature. Upon completion, the solution was transferred to a separatory funnel and washed with deionized water (2×25 mL), and then the organic layer was dried over Na_2SO_4 . Concentration under reduced pressure afforded the acyl imidazole, which was used in the following reaction without further purification.

General synthetic procedure for BF_3K salts (**2**)

A solution of potassium *tert*-butoxide (3.0 equiv) in anhydrous THF at 0 °C under N_2 was treated with phenol (3.0 equiv). The reaction mixture was stirred at 0 °C for 15 min and then was allowed to warm to room temperature over 30 min. Potassium bromomethyltrifluoroborate (1.0 equiv) was added in one batch at 0 °C. The resulting reaction mixture was stirred at room temperature for 23 h and 4.5 M KHF_2 (2.1 equiv) solution was added. The reaction mixture was stirred at room temperature for 30 min, and the white suspension was added with benzene/toluene (2–3 times). The solvent was removed, and the resulting solid was washed with Et_2O followed by hot acetone to yield the pure BF_3K salts.

General synthetic procedure for light-driven carbene-catalyzed reactions

All reactions were set up inside a glovebox under N_2 atm. To an oven-dried 2-diam vial containing a stir bar was added the respective BF_3K salts (**2**, 5.0 equiv), respective styrene (**3**, 1.0 equiv), respective acyl imidazole (**1**, 3.0 equiv), CsOAc (2.0 equiv), **Az-1** (15 mol%) and **PC-1** (5 mol%). Acetonitrile (0.05 M) was added, and the reaction vial was capped and taken out of the glovebox. Parafilm was wrapped around the cap to prevent air from entering. The vials were placed in a SynLED Parallel Photoreactor (blue LEDs) and the reaction mixture was stirred for 24 h. The reaction progress was monitored by GCMS or LCMS. After the reaction was deemed complete, the reactions were diluted with ethyl acetate and passed through a Celite pad. The yellow filtrate was collected and concentrated.

The resulting residue was purified by column chromatography (5%–10% ethyl acetate in hexanes) on silica gel.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

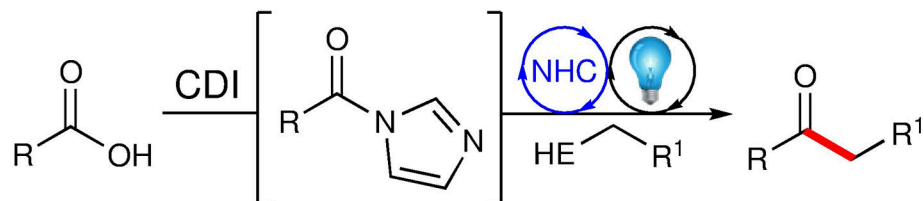
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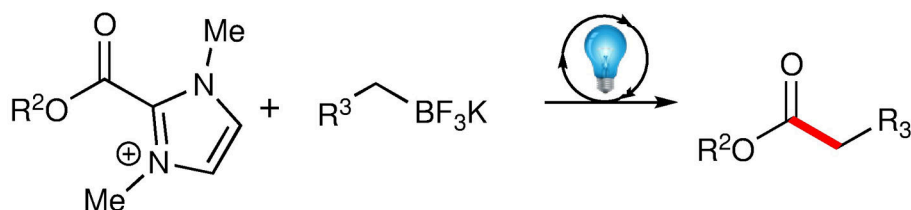
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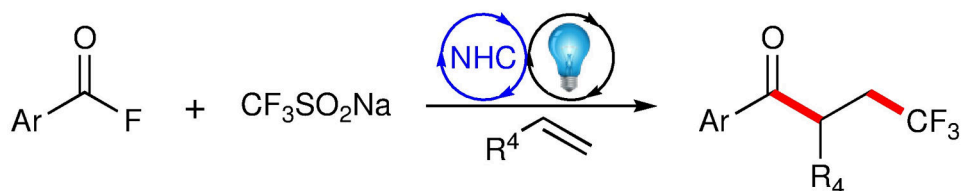
A. Alkylation of Acyl Azoliums



B. Alkoxyacylation of Trifluoroborates



C. Acyltrifluoromethylation of olefins



D. γ - Aryloxy Ketone Synthesis (this work)

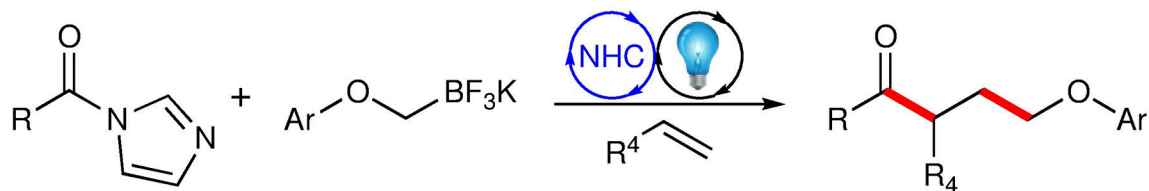
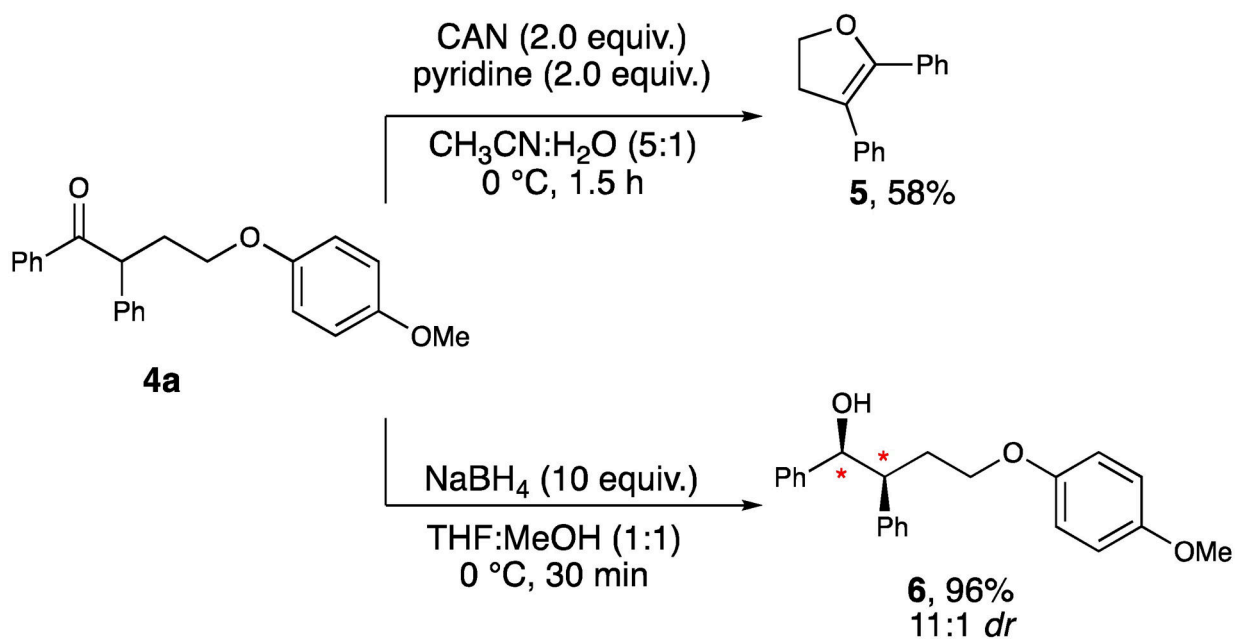
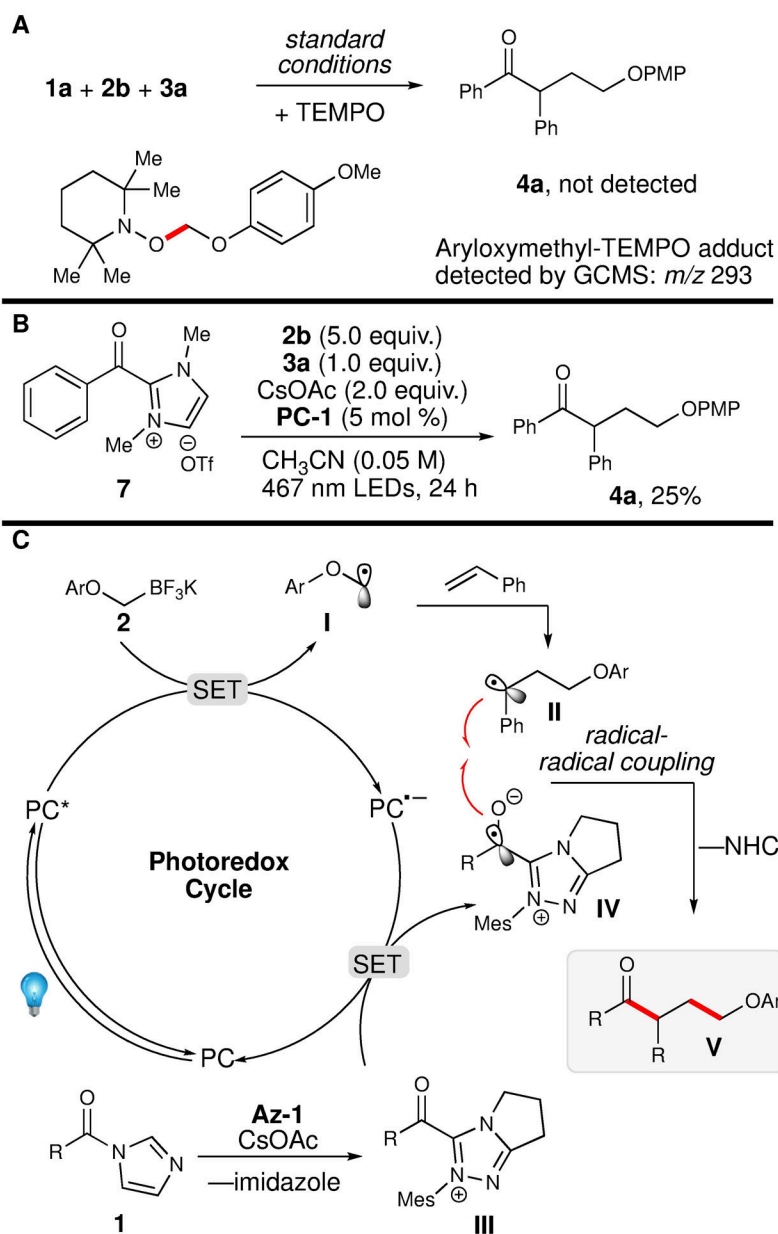


Figure 1.
Previous examples of combined NHC/photoredox processes.



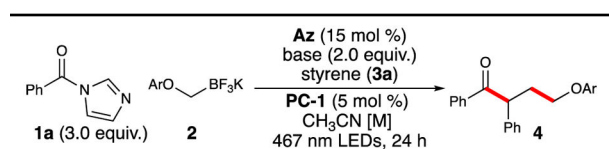
Scheme 1.
Synthetic transformations with **4a**.



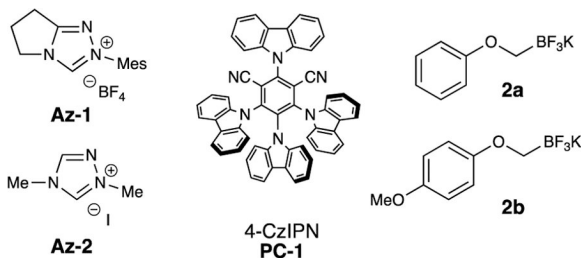
Scheme 2.
Mechanistic studies and proposed mechanism.

Table 1.

Optimization of reaction conditions.



| entry | Az | Base | [M] | 2 | Yield (%) ^{a,b} |
|-------|----|---------------------------------|------|----|--------------------------|
| 1 | 1 | Cs ₂ CO ₃ | 0.1 | 2a | 29 |
| 2 | 2 | Cs ₂ CO ₃ | 0.1 | 2a | 20 |
| 3 | 1 | CsOAc | 0.1 | 2a | 32 |
| 4 | 1 | K ₂ CO ₃ | 0.1 | 2a | 22 |
| 5 | 1 | CsOAc | 0.1 | 2b | 48 ^c |
| 6 | 1 | CsOAc | 0.05 | 2b | 48 ^c |
| 7 | 1 | CsOAc | 0.1 | 2b | 68 ^d |
| 8 | 1 | CsOAc | 0.05 | 2b | 97 (90) ^d |
| 9 | 1 | CsOAc | 0.05 | 2b | trace ^e |
| 10 | 1 | CsOAc | 0.05 | 2b | 0 ^f |
| 11 | - | CsOAc | 0.05 | 2b | (30) |
| 12 | 1 | CsOAc | 0.05 | 2b | 0 ^g |



[a] Reaction conditions unless otherwise stated: **1a** (0.3 mmol), **2** (0.1 mmol), **Az** (0.015 mmol), base (0.2 mmol), styrene **3a** (0.3 mmol), PC (5 μmol), and solvent (0.1 M) for 24 h.

[b] ¹H NMR yield using 1,3,5-trimethoxybenzene as internal standard (0.33 equiv.) and yield of isolated product is given in parenthesis.

[c] **1a** (0.3 mmol), **2** (0.2 mmol), **3a** (0.1 mmol).

[d] **1a** (0.3 mmol), **2** (0.5 mmol), **3a** (0.1 mmol).

[e] same conditions as [d] except benzoyl fluoride used as acyl starting material (0.3 mmol).

[f] absence of **PC-1**.

[g] no light.

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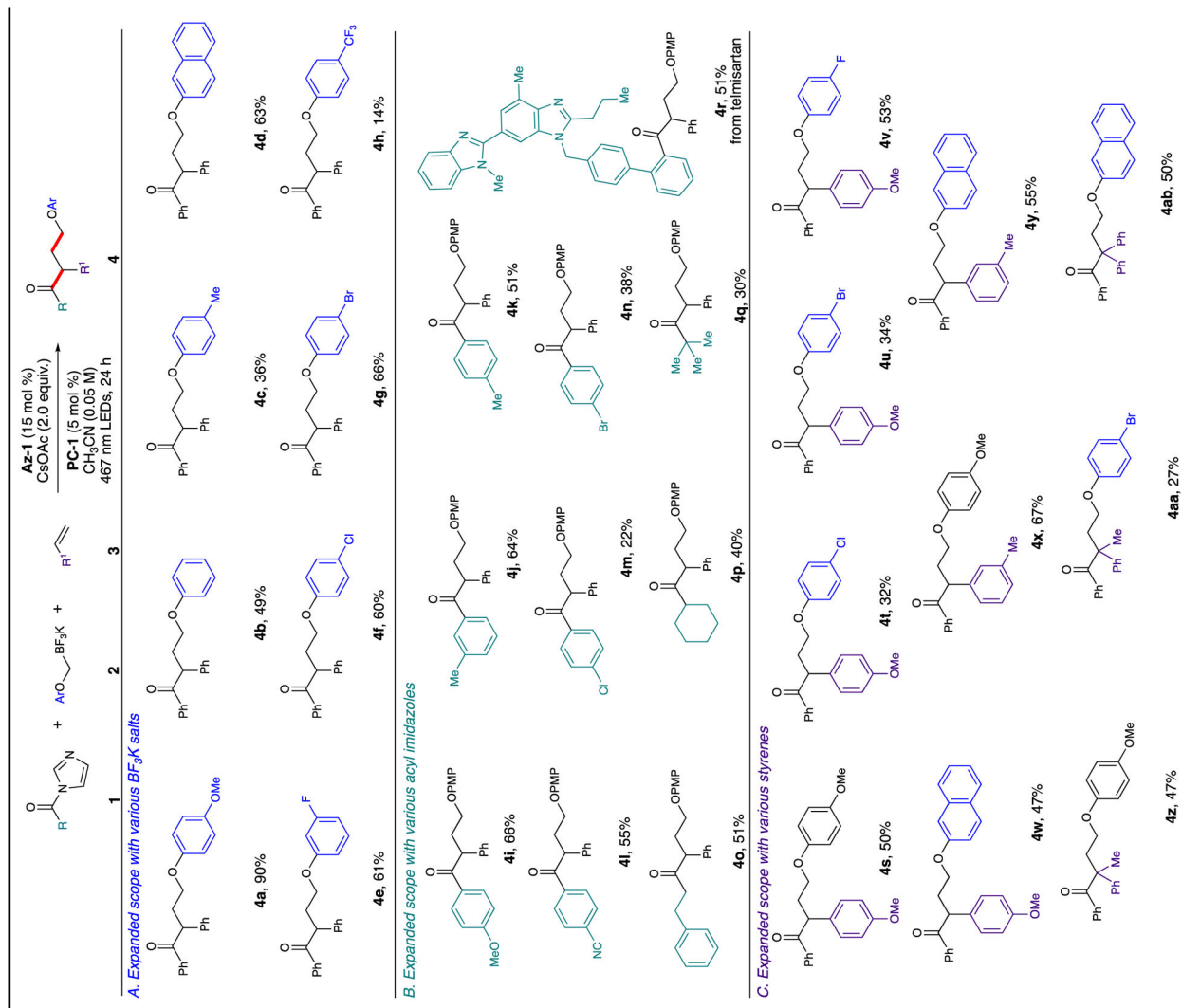
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Table 2.

Substrate scope with respect to the trifluoroborate salt.^{a, b, c}



[a] See the Supporting Information for reaction details.

[b] Yield of isolated product.

[c] PMP = *para*-methoxy phenyl.

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