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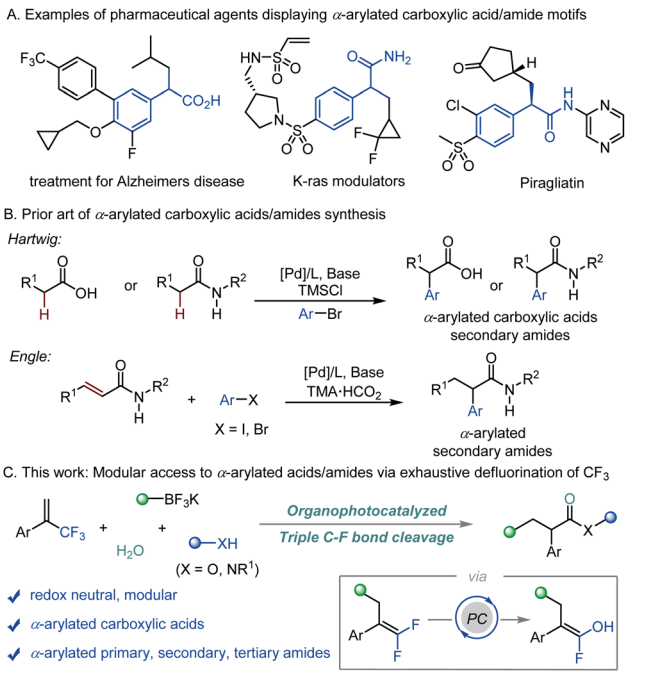
Modular synthesis of α-arylated carboxylic acids, esters and amides *via* photocatalyzed triple C–F bond cleavage of methyltrifluorides†

Sifan Li,[ab] Paul W. Davies *[b] and Wei Shu *[a]

α-Arylated carboxylic acids, esters and amides are widespread motifs in bioactive molecules and important building blocks in chemical synthesis. Thus, straightforward and rapid access to such structures is highly desirable. Here we report an organophotocatalytic multicomponent synthesis of α-arylated carboxylic acids, esters and amides from exhaustive defluorination of α-trifluoromethyl alkenes in the presence of alkyltrifluoroborates, water and nitrogen/oxygen nucleophiles. This operationally simple strategy features a unified access to functionally diverse α-arylated carboxylic acids, esters, and primary, secondary, and tertiary amides through backbone assembly from simple starting materials enabled by consecutive C–F bond functionalization at room temperature. Preliminary mechanistic investigations reveal that the reaction operates through a radical-triggered three-step cascade process, which involves distinct mechanisms for each defluorinative functionalization of the C–F bond.

Introduction

α-Arylated carboxylic acids and amides are ubiquitous substructures and indispensable building blocks in chemical synthesis.[1] The wide existence of such structural motifs in biologically active molecules[2] (Scheme 1A) has inspired much effort to develop efficient methods towards the synthesis of α-arylated carboxylate derivatives.[3] Pioneered by Buchwald and Hartwig, methods relying on the use of transition-metal catalyzed α-arylation of enolates with aryl halides have been extensively developed.[4] Later, metal-catalyzed cross-coupling of α-halo carbonyl electrophiles with aryl nucleophiles has also been described.[5] However, these methods are typically not applicable to direct arylation of aliphatic carboxylic acids and amides with acidic N–H bonds.[6] To address this issue, Hartwig a reported an elegant Pd-catalyzed α-arylation of carboxylic acids and secondary amides through the *in situ* formation of the corresponding disilyl intermediates in the presence of a base and TMSCl (Scheme 1B).[7] In 2020, Engle's group described the synthesis of α-arylated amides enabled by Pd-catalyzed α-selective hydroarylation of acrylamides (Scheme 1B).[8] These methods suffer from the use of transition metals, multi-step synthesis of advanced starting materials, and/or harsh conditions. Different approaches for the non-transition metal catalyzed synthesis of α-arylated amides have also been reported. Nevado, Greaney, Clayden and Studer have independently reported aryl migration strategies,[9] while Miyata and Maulide have each shown the umpolung α-arylation of



Scheme 1 Significance and synthetic design for α-arylated carboxylic acids and amides.

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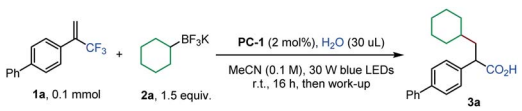
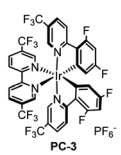
amides.[10] Despite these significant advances, a straightforward and unified method providing rapid access to α-arylated carboxylic acids, and primary, secondary, and tertiary amides from readily available precursors is highly desirable.

Over the past decade, photoredox catalysis has served as a powerful platform for numerous challenging organic transformations. Notably, manipulation of strong C–F bonds in multifluorinated compounds under photoredox conditions has attracted considerable attention due to the potential applications in accessing novel bond forming strategies and for the degradation of fluorinated pollutants.[11] Great efforts have been devoted to the cleavage of one or two of the C–F bonds in α-trifluoromethyl alkenes for the synthesis of di- or monofluoroalkenes, respectively.[12,13] To date, no example of the consecutive cleavage of three C–F bonds in α-trifluoromethyl alkenes to access versatile products has been reported. Here we report an organophotoredox-catalyzed triple defluorination of α-trifluoromethyl alkenes to furnish a variety of functionally diverse α-arylated carboxylic acids, and primary, secondary, and tertiary amides in the presence of alkyltrifluoroborates, water and nitrogen/oxygen nucleophiles (Scheme 1C). This metal-free protocol consists of a defluorinative alkylation, defluorinative hydroxylation, and defluorinative amination/hydroxylation cascade, providing access to α-arylated carboxylate derivatives *via* assembly of the carbon skeleton from simple starting materials under redox-neutral conditions.

Table 1 Optimization studies[a]



Entry	Deviation from standard conditions	Yield of **3a**[b] (%)
1	None	88 (80)
2	**PC-2** instead of **PC-1**	44
3	**PC-3** instead of **PC-1**	16
4	DCM instead of MeCN	43
5	Et_2O instead of MeCN	37
6	1,4-Dioxane instead of MeCN	0
7	10 μL of H_2O	56
8	100 μL of H_2O	76
9	W/O **PC-1**	0
10	W/O H_2O	0
11	W/O work-up	53

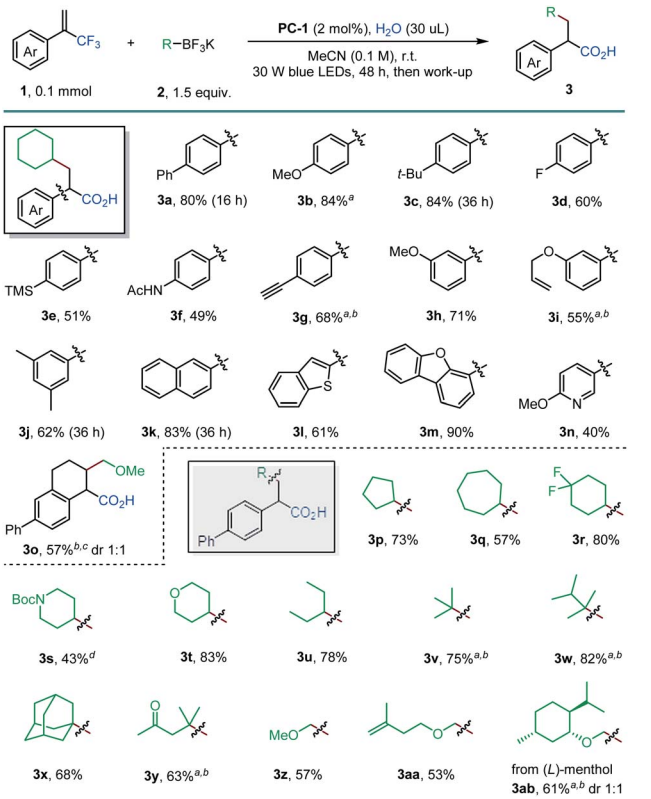


[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), **PC-1** (0.002 mmol), and H_2O (30 μL) in MeCN (0.1 M) under 30 W blue LED irradiation at room temperature for 16 h, then NaOH/HCl work-up. [b] Yields were determined by ^1H NMR of the crude reaction mixture with mesitylene as the internal standard, and isolated yield is shown in parentheses.

Results and discussion

Our initial study focused on the reaction of α-trifluoromethyl alkene **1a** with cyclohexyltrifluoroborate **2a** to test the feasibility of this proposal (Table 1).[14] After evaluation of various parameters, the desired α-arylated carboxylic acid **3a** was obtained in 80% yield using acridinium **PC-1** as a photocatalyst with H_2O in acetonitrile. Other photocatalysts could mediate the transformation, albeit in lower efficiencies (Table 1, entries 2 and 3). Replacing acetonitrile with CH_2Cl_2 or Et_2O gave **3a** in diminished yields, and **3a** was not detected when 1,4-dioxane was used as the solvent (Table 1, entries 4–6). Varying the amount of H_2O led to lower yields of **3a** (Table 1, entries 7 and 8). Control experiments revealed that photocatalyst **PC-1** and H_2O were both necessary for this reaction while a reduced yield was obtained when the base/acid work-up was not performed (Table 1, entries 9–11).[15]

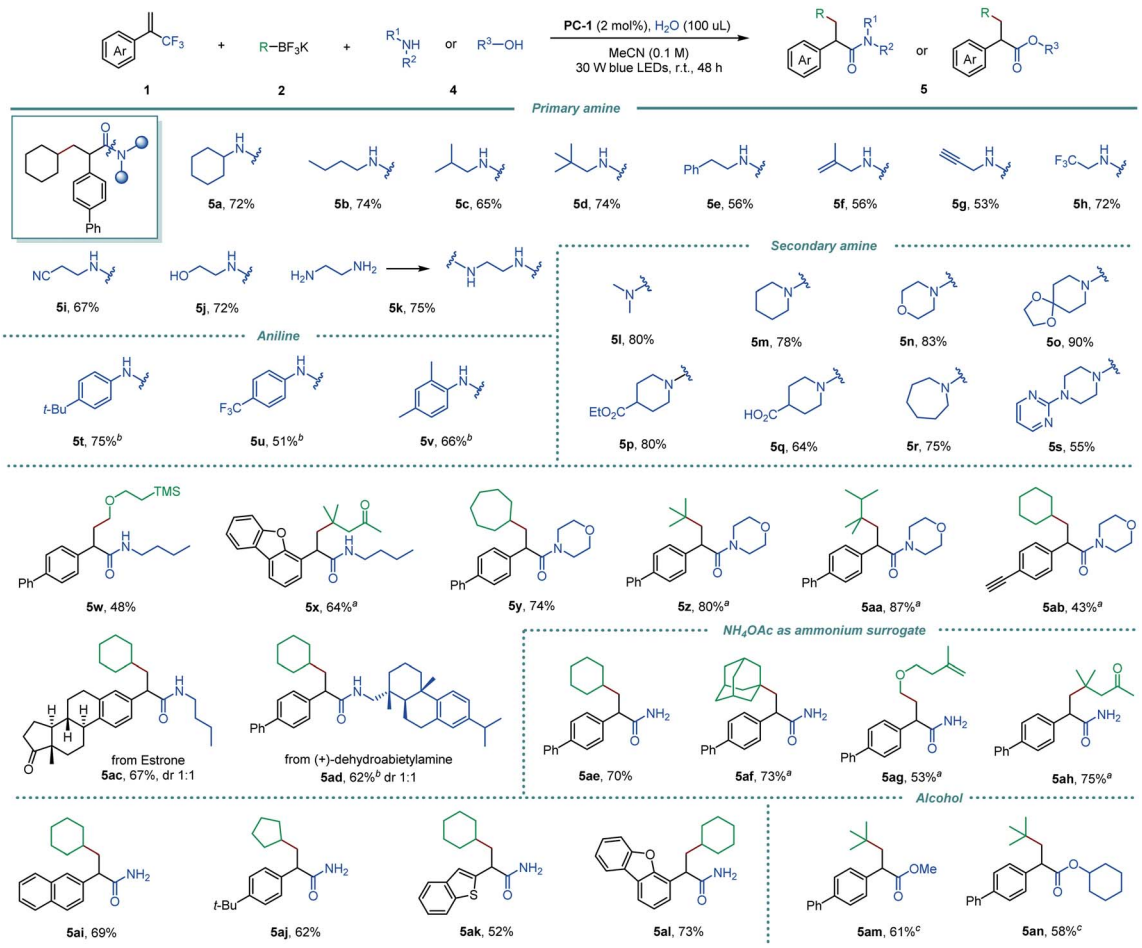
With the optimized reaction conditions in hand, the scope of α-trifluoromethyl alkenes **1** and alkyltrifluoroborates **2** was investigated (Scheme 2). *para*-Substituted styrenyl methyltrifluorides were well-tolerated in the exhaustive defluorinative reaction, forming the desired α-arylated carboxylic acid in 49–84% yields (**3a–3g**). Electron-donating groups (**3b** and **3c**) and



Scheme 2 Reaction scope for the triple defluorinative formation of α-arylated carboxylic acids. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **PC-1** (0.002 mmol), and H_2O (30 μL, 17 equiv.) in MeCN (0.1 M) under 30 W blue LED irradiation at room temperature, then NaOH/HCl work-up. Isolated yields after flash chromatography are reported. [a] 50 μL of H_2O was used. [b] 5 mol% of **PC-1** was used. [c] Reaction was run on 0.2 mmol scale. [d] 100 μL of H_2O was used.

a fluoride substituent (**3d**) are compatible under the reaction conditions. Terminal ethynyl-substituted α-arylated carboxylic acid **3g** was obtained in 68% yield when an α-trifluoromethyl alkene with a 4-(trimethylsilyl)ethynylphenyl group was used. Cleavage of the silyl group is likely due to the release of fluoride anions during the reaction. 3-Methoxy, 3-allyloxy and 3,5-dimethyl groups were well-tolerated (**3h–3j**). The use of fused aryl and heteroaryl vinylmethyltrifluorides allowed the incorporation of naphthyl (**3k**), benzothiophenyl (**3l**) and dibenzofuranyl (**3m**) substituted carboxylic acids in good yields (61–90%). Notably, α-pyridinyl carboxylic acid (**3n**) was effectively obtained in this reaction. A cyclic alkene was also transformed into α,β-cyclic-α-arylated carboxylic acid **3o** in 57% yield. However, α-trifluoromethyl alkenes with electron-withdrawing arenes failed to deliver the corresponding α-arylated carboxylic acids, with the reaction stalling at the corresponding *gem*-difluoroalkenes.[16] A wide range of alkyltrifluoroborates (**2**) were found to be suitable for this reaction. Five-, six- and seven-membered cyclic secondary alkyl groups (**3p**, **3q**, and **3r**) with diverse substitution patterns can be readily incorporated by this route. Piperidine (**3s**) and tetrahydropyran (**3t**) motifs can also be introduced in this exhaustive defluorination reaction (43% and 83% yield, respectively). Acyclic secondary (**3u**) and tertiary alkyl radical precursors (**3v–3x**) participated in this reaction with good efficiencies (68–82%). The formation of a 1,6-keto acid **3y** showcased a new approach to this desirable functional motif. Primary α-alkoxymethyltrifluoroborates can also be used, providing access to γ-alkoxy acids (**3z–3ab**).

We then questioned whether amines could be compatible in the reaction, thus allowing the direct formation of amides from vinylmethyltrifluorides *via* triple C–F bond functionalizations. Pleasingly, the desired α-arylated amides were obtained efficiently *via* exhaustive defluorinative C–N coupling (Scheme 3), despite the competing potential for single-electron oxidation of amines by the excited-state photocatalyst.[17] Primary amines with a wide range of functional groups and structural elements worked well (**5a–5j**). Alongside linear and branched substituents (**5a–5e**), allylic (**5f**) and propargyl (**5g**) amines were good substrates. Moreover, trifluoromethyl and nitrile containing primary amines delivered the corresponding α-arylated amides **5h** and **5i** in 72% and 67% yields, respectively. Notably, free amino alcohol was compatible in the reaction, furnishing the



Scheme 3 Reaction scope for the triple defluorinative formation of α-arylated amides and esters. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **4** (0.15 mmol, 0.20 mmol for NH_4OAc, and 0.50 mmol for alcohol), **PC-1** (0.002 mmol), and H_2O (100 μL) in MeCN (0.1 M) under 30 W blue LEDs irradiation at room temperature. Isolated yields are reported. [a] 5 mol% of **PC-1** was used. [b] MeCN : CH_2Cl_2 = 3 : 1. [c] 10 μL of H_2O was used.

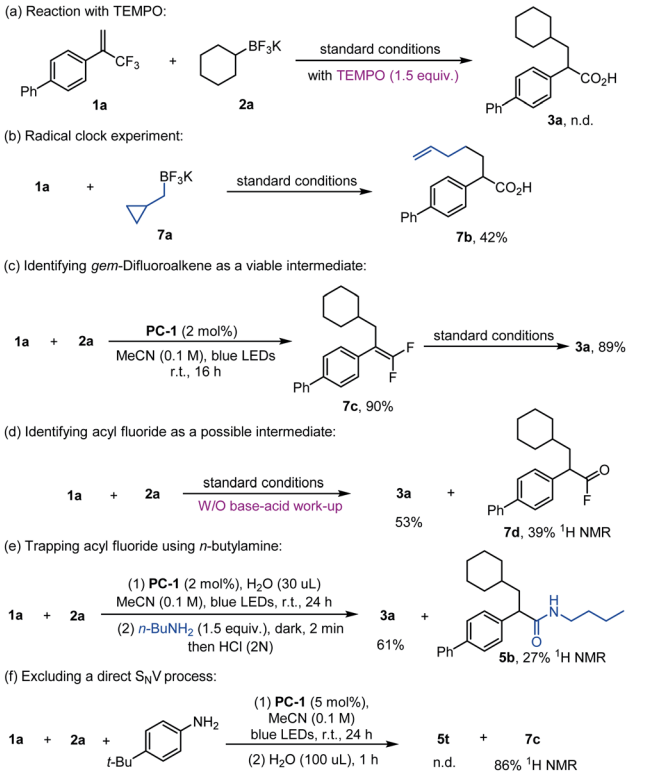
corresponding hydroxyl amide **5j** in 72% yield. Interestingly, a diamide product **5k** was formed in 75% yield when 1,2-diaminoethane was used. Acyclic and cyclic secondary amines were also shown to be suitable coupling partners in this reaction (**5l–5s**, 55–90% yields), including piperidines bearing ketal (**5o**), ester (**5p**), free carboxylic acid (**5q**), morpholine (**5n**) and a piperazine derivative (**5s**). Electron-rich and electron-deficient anilines participated smoothly in the reaction, affording **5t–5v** in 51–75% yields. Various alkyltrifluoroborates including primary, secondary, and tertiary alkyl groups, and silyl and ketone groups were also good precursors for the triple defluorinative amide formation (**5w–5aa**, 48–87% yields). The desilylated amide **5ab** was obtained in 43% yield when α-trifluoromethyl alkene with a 4-(trimethylsilyl)ethynylphenyl group was used. In addition, structurally complex substrates derived from natural products, such as estrone and (+)-dehydroabietylamine, were readily incorporated in this reaction, affording **5ac** and **5ad** in 67% and 62% yields, respectively.

Next, the feasibility of transforming α-trifluoromethyl alkenes into primary amides by cleaving three C–F bonds was also tested. Ammonium acetate was identified as a readily available and cost-effective ammonia surrogate, allowing efficient access to a series of primary amides (**5ae–5al**, 52–75% yields). This protocol is also suitable for the synthesis of α-arylated esters by using alcohols as nucleophiles, affording **5am** and **5an** in good yields (61% and 58% yield, respectively).

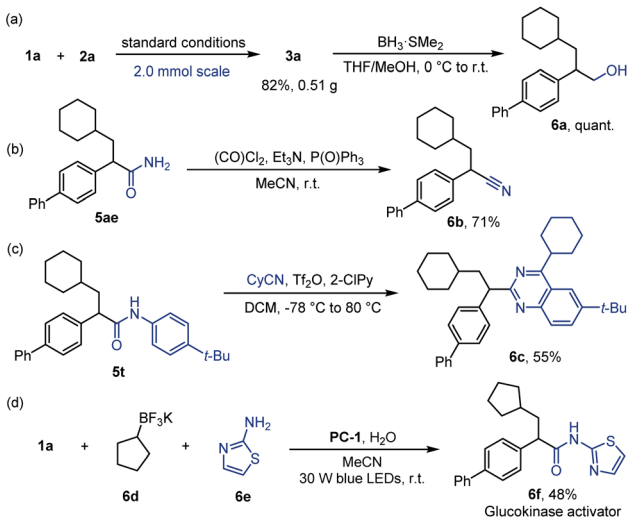
To further demonstrate the utility of this protocol, product **3a** was prepared on a 2.0 mmol scale in 82% yield (Scheme 4a). This new transformation allows for ready access into other useful motifs, such as β-arylated alcohol **6a** in quantitative yield (Scheme 4a), α-arylated nitrile **6b** in 71% yield (Scheme 4b) and quinazoline **6c** in 55% yield (Scheme 4c). In addition, one-step synthesis of glucokinase activator **6f** from simple precursors was achieved, illustrating the great potential of this protocol to facilitate rapid analogue evaluation in medicinal chemistry (Scheme 4d).[18]

Control experiments were conducted to probe the reaction mechanism (Scheme 5). Addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) into the reaction completely inhibited the formation of **3a**, whilst the use of the radical precursor **7a** led to the ring-opening product **7b** in 42% yield (Scheme 5a and b). Conducting the reaction in the absence of H_2O did not yield the product **3a**, and *gem*-difluoroalkene **7c** was obtained in 90% yield instead. Moreover, **7c** was productive under the standard reaction conditions to afford **3a** in good yield (Scheme 5c), suggesting that *gem*-difluoroalkene might be the intermediate of this reaction. When **1a** and **2a** were subjected to the standard conditions without a NaOH/HCl work-up procedure, acid **3a** was formed in 53% yield alongside acyl fluoride **7d** in 39% yield as detected by NMR spectroscopy and HRMS (Scheme 5d). Further evidence for the formation of an electrophilic acyl fluoride intermediate was obtained by replacing NaOH in the reaction work-up protocol with *n*-butylamine which led to the formation of **3a** in 61% yield and amide **5b** in 27% yield (Scheme 5e). *gem*-Difluoroalkene **7c** was formed rather than amide **5t** when H_2O was excluded from the standard reaction conditions for the amide formation, indicating that water was required for the second defluorination step (Scheme 5f). These results support the involvement of alkyl radical species during the reaction, indicating that *gem*-difluoroalkene is an intermediate in this transformation that is converted into acyl fluoride species and not subject to a direct S_NV process.[19]

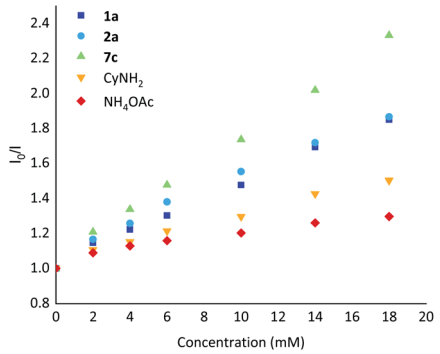
Stern–Volmer luminescence quenching studies were also performed using representative substrates **1a** and **2a**, cyclohexylamine ($CyNH_2$), ammonium acetate and the intermediate *gem*-difluoroalkene **7c** (Scheme 6). The results showed that *gem*-difluoroalkene **7c** quenched the excited photocatalyst



Scheme 5 Control experiments.



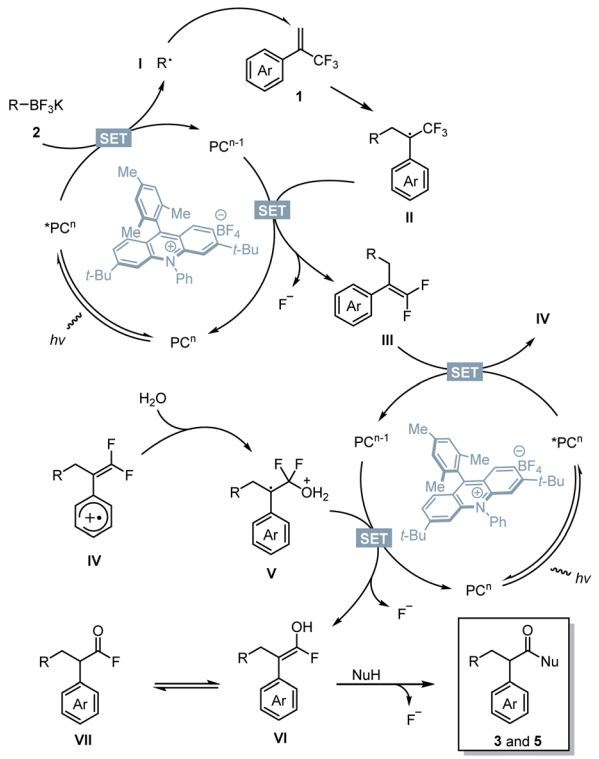
Scheme 4 Synthetic applications.



Scheme 6 Stern–Volmer luminescence quenching studies with **PC-1**.

significantly, and that **2a** and **1a** were also suitable quenchers for the excited photocatalyst.

Based on these results, a possible mechanism is depicted (Scheme 7). Upon blue LED irradiation, the excited acridinium photocatalyst $^*PC^n$ ($E^*_{red} = +2.15$ V) would undergo single electron transfer (SET) with **2** to generate alkyl radical species **I** and reduced photocatalyst PC^{n-1}.[14,20] Radical species **I** underwent radical addition with **1** to generate a benzylic radical **II**. Single-electron reduction of **II** by PC^{n-1} followed by β-fluoride elimination yielded *gem*-difluoroalkenes **III** and the photocatalyst PC^n to complete the first catalytic cycle. After this stage, single-electron oxidation of intermediate **III** by the excited photocatalyst $^*PC^n$ afforded a radical cationic species **IV** and reduced photocatalyst PC^{n-1}.[21] **IV** would be trapped by H_2O to generate intermediate **V**.[22,23] The presence of strongly electron-withdrawing aryl substituents renders this step inefficient. The SET process between PC^{n-1} and **V** followed by second β-fluoride elimination affords the enol intermediate **VI** or its tautomer acyl fluoride species **VII**, and the photocatalyst PC^n. The desired products were then obtained through acyl substitution with oxygen or nitrogen nucleophiles to cleave the third C–F bond.



Scheme 7 Proposed mechanism.

Conclusions

In summary, a photocatalyzed multicomponent triple defluorinative functionalization of α-trifluoromethyl alkenes was achieved to afford a variety of α-arylated carboxylic acids, esters, and primary, secondary, and tertiary amides at room temperature. The reaction operates through three consecutive and distinct C–F bond cleavages opening an avenue for converting methyltrifluorides into synthetically valuable functional groups. α-Trifluoromethyl alkenes, themselves readily prepared in one step from boronic acids,[24] can be combined with alkyltrifluoroborates, water, and alcohols/amines to prepare α-arylated carboxylic acids, esters and amides by the simple alternation of nucleophiles. As a result, these important motifs can now be assembled bearing significant structural and functional group variations in a modular way from simple and readily accessible molecular building blocks.

Data availability

Experimental data has been provided as ESI.†

Author contributions

S. L. discovered the reaction. W. S. and P. W. D. conceived and directed the project. S. L. performed the experiments and analysed the data. S. L., W. S. and P. W. D. prepared the manuscript. All authors discussed the experimental results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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