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Photoredox Enables the Construction of 1,1-Difluoroalkene Carbonyl Mimics

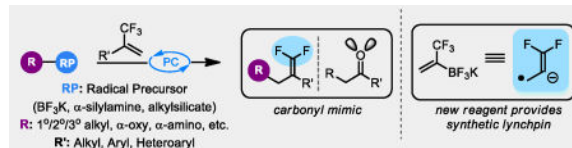
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Abstract

We describe a facile, scalable route to access functional group-rich *gem*-difluoroalkenes. Using visible-light activated catalysts in conjunction with an arsenal of carbon-radical precursors, an array of trifluoromethyl-substituted alkenes undergoes radical defluorinative alkylation. Non-stabilized primary, secondary, and tertiary radicals can be used to install functional groups in a convergent manner that would otherwise be challenging *via* two-electron pathways. The process readily extends to other perfluoroalkyl-substituted alkenes. In addition, we report the development of an organotrifluoroborate reagent to expedite the synthesis of the requisite trifluoromethyl-substituted alkene starting materials.

Graphical Abstract



CF₃ today, CF₂ tomorrow: We describe a facile, scalable route to access functional group-rich *gem*-difluoroalkenes. Using visible-light activated catalysts in conjunction with an arsenal of C-radical precursors, an array of trifluoromethyl-substituted alkenes undergo radical defluorinative alkylation. Non-stabilized primary, secondary, and tertiary radicals can be used to install functional groups in a convergent manner that would otherwise be challenging to access *via* two-electron pathways. The process readily extends to other perfluoroalkyl-substituted alkenes. In addition, we report the development of an organotrifluoroborate reagent to expedite synthesis of the requisite trifluoromethyl-substituted alkene starting materials.

Keywords

Photoredox; Organofluorine; Alkenes; Alkylation; Radicals

Optimizing oral bioavailability is an important facet of developing molecules for use as therapeutic agents.^[1] Although ketone functional groups can be vital for binding and

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substrate recognition,^[2] they are uncommon in pharmaceutical compounds because of their reduction to the corresponding alcohol during phase I metabolism by mammalian NAD(P)H-dependent reductases.^[3] This process facilitates inactivation and excretion, which leads to diminished bioavailability.^[3]

Consequently, efforts have been made to identify carbonyl mimics that preserve the electronics and geometry of the C=O unit but are less susceptible to *in vivo* metabolism.^[4] The *gem*-difluoroethylene moiety, an isopolar analog that may still engage in hydrogen bonding,^[5] is one example. Replacement of a carbonyl with the corresponding *gem*-difluoroalkene has been demonstrated to provide bioactive substrates that are still recognized by their target; however, only a few examples have been reported in the literature.^[6] In the case of *exo*-difluoroethylene artemisinin, the prolonged *in vivo* antimalarial activity may arise from resistance to metabolic processes (Figure 1).^[6a] Additionally, this motif has proved beneficial in several niche applications.^[7]

One reason that this potentially valuable carbonyl mimic has not been more extensively evaluated may be that conventional routes to construct the *gem*-difluoroethylene motif typically involve a functional group interconversion that relies upon highly reactive intermediates, organometallic reagents, or harsh conditions, thus hampering their applicability (Scheme 1a).^[8] Although several convergent methods exist, they do not lend themselves to late-stage functionalization or to the incorporation of sensitive functional groups (Scheme 1b).^[8]

Our laboratory has demonstrated that the regulated generation of carbon-centered radicals from bench-stable progenitors *via* photoredox catalysis proceeds under very mild conditions.^[9] The reactions of these radicals occur readily at room temperature and typically have a broader substrate scope than analogous two-electron pathways because radicals are not prone to acid/base processes. Thus, we anticipated that the radical alkylation of trifluoromethylalkenes would facilitate a convergent synthesis of functional group-rich *gem*-difluoroalkenes.

The requisite radical for such an alkylation event can be readily generated *via* the single electron oxidation of carbon-radical precursors such as those depicted in Scheme 2. Following radical addition, the resulting α -CF₃ radical would likely undergo SET reduction by the reduced state of the photocatalyst,^[10] generating a carbanion. Although protonation is viable, we anticipated the known propensity for such anions to undergo E1cB-type fluoride elimination^[11] to predominate and provide the desired *gem*-difluoroalkene *via* a radical/polar crossover process. Indeed, such a radical process is viable for the addition of acyl and stabilized α -amino radicals to trifluoromethyl styrenes, but a general method for the utilization of 1°, 2°, and 3° radicals does not exist.^[12] Moreover, we reasoned that using an array of radical precursors would impart several benefits such as additive-free reactions at near neutral pH, the ability to use inexpensive photocatalysts, and the opportunity to install a wide range of functional groups.

To evaluate the tenability of this approach, a trifluoromethyl styrene bearing two readily manipulated functional handles (**1a**), in conjunction with three classes of radical precursors

that produce a byproduct that can efficiently sequester fluoride upon homolytic fragmentation, were subjected to a range of photoredox conditions. Pleasingly, both the inexpensive organometallic photocatalyst, Ru(bpy)₃(PF₆)₂, and the organic photocatalyst 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)^[13] facilitated the desired transformation without the need for additives (Scheme 2). Control studies verified that each component of the reaction mixture was necessary.

Next, the scope of this process was evaluated. Various aminomethyl moieties were introduced *via* the corresponding α -trimethylsilylamines (Table 1). These amines readily undergo desilylative fragmentation following single electron oxidation of the nitrogen's lone pair.^[14] Difluoroalkenes bearing cyclic and acyclic amines were isolated in good yields.

Potassium organotrifluoroborates also served as competent precursors for a variety of 1°, 2°, and 3° carbon-centered radicals using the organic photocatalyst 4CzIPN. Cyclic secondary radicals provided the desired *gem*-difluoroalkenes in good yields. An acyclic, secondary radical bearing an unprotected alcohol at the radical center was also well-tolerated (**3k**). Products resulting from the addition of primary α -thio- and α -oxy-radicals were obtained in reasonable yields (**3l–3n**). The addition of a 3° radicals also proceeded smoothly (**3g, 3p**, and **3q**). These difluoroalkenes would be challenging to construct using conventional approaches, which is a testament to the functional group tolerance of this approach.

Given their unique ability to furnish non-stabilized 1° radicals, alkylbis(catecholato)silicates were next examined.^[15] A variety of functional groups were installed with ease. Protected secondary amines (**3w, 3x**), a lactam (**3y**), a carbazole (**3u**), and a free aniline (**3t**) were all tolerated under the standard reaction conditions. The distinct advantage of this approach is well illustrated here: many of the alkylbis(catecholato)silicates examined have protic functional groups and, further, all have Brønsted acidic ammonium counter-ions. The absence of appreciable protonation (i.e., generation of an alkyl-CF₃) during this process indicates that SET reduction/fluoride elimination is a fast process. In addition, a pyridine (**3v**), an acetate (**3s**) and an ether (**3r**) were also successfully incorporated. Lastly, a secondary norbornane ring (**3z**) was introduced in good yield.

The generality of the radical scope prompted us to evaluate the trifluoromethylalkene scope. Styryl systems bearing a 1,3-benzodioxole (**4a**), an acetamide (**4b**), a phenol (**4c**), and a cyclic amide (**4d**) were all effectively transformed to their corresponding *gem*-difluoroalkenes. An exocyclic, disubstituted *gem*-difluoroalkene (**4k**) was obtained from a trifluoromethylalkene derived from α -tetralone. Heteroaromatics such as quinoline (**4g**), indole (**4f**), indazole (**4i**), and an aminopyridine (**4h**) were well-tolerated. In a select case, appreciable formation of the undesired alkyl-CF₃ by-product was observed (**4j**, 82:18 alkene/alkane). Although we are unsure why this particular substrate deviated substantially from all other cases, it may result from a resonance stabilized, longer-lived anion.

Moving beyond styryl systems, a variety of 2-trifluoromethyl-1,3-enynes also underwent successful alkylation without concomitant addition to the alkynyl moiety. Substrates bearing groups such as a protected piperidine (**4l**), a tertiary propargylic alcohol (**4m**), or a protected furanose (**4n**) were readily transformed into the corresponding 1,1-difluoro-1,3-enyne. Also,

3° and α-amino radicals added to non-styryl alkyltrifluoromethylalkenes in good yields (**4o**, **4p**). Finally, the reaction was not limited to trifluoromethyl alkenes. Both CF₂H- and CF₂CF₃-substituted alkenes provided monofluoro- and (fluoro)trifluoromethylalkenes, respectively, (**4q**, **4r**).

To assess the utility of the described defluorinative alkylation further, the process was scaled to 3 mmol using 4CzIPN for practical reasons [~\$5/mmol vs \$125/mmol for Ru(bpy)₃(PF₆)₂] (Figure 2). This modification did not compromise the yield, and the product obtained from this scale-up was then further elaborated *via* Ni/photoredox dual catalysis to forge a Csp²–Csp³ bond.^[16] The combination of these two modes enables rapid diversification and illustrates the relative stability of *gem*-difluoroalkenes under conditions where additional radicals are generated.

Finally, during the course of our studies it became clear that most methods to synthesize trifluoromethyl styrenes in a convergent manner relied on the Pd-catalyzed coupling of low-boiling 2-bromo-3,3,3-trifluoro-1-propene with various organoboron compounds.^[17] The umpolung approach, wherein the organometallic partner bears the 3,3,3-trifluoro-1-propenyl moiety, is virtually unknown.^[18] This relates to the known instability of the corresponding organometallic (i.e., organolithium, -magnesium, etc.).^[19] Thus, development of the corresponding potassium 1-trifluoromethylethenyltrifluoroborate would not only enable this umpolung approach to be executed with ease on commercially ubiquitous (hetero)aryl bromides, but also provide an easily handled, eminently stable source of the trifluoromethylvinyl fragment. A reliable protocol for the synthesis of this crystalline, bench-stable species was established, enabling multi-gram quantities to be prepared over three steps (see Supporting Information for details). This organotrifluoroborate was subjected to standard Suzuki cross-coupling conditions with an aryl bromide whose boron-substituted counterpart is prohibitively expensive. The desired trifluoromethyl alkene **1s** was obtained in a good yield (76%) and was next subjected to radical alkylation to furnish the corresponding *gem*-difluoroalkene **4t** in 77% yield (Figure 3). These results indicate that potassium trifluoromethylvinyltrifluoroborate serves as a unique synthon with the potential for enabling the construction of a diverse array of trifluoromethyl-substituted styrenes and subsequently for the rapid assembly of *gem*-difluoroalkenes.

The defluorinative alkylation protocol developed herein has resulted in the generation of a vast library of functional group-rich *gem*-difluoroalkenes. Installation of numerous complex fragments was achieved from a variety of carbon-radical progenitors, each from its own unique chemical feedstock. This process is readily scaled and can be paired with existing photoredox technology to enhance structural diversity. Finally, an organotrifluoroborate reagent was developed to expedite trifluoromethyl alkene synthesis and provide a new approach to (trifluoromethyl)vinylation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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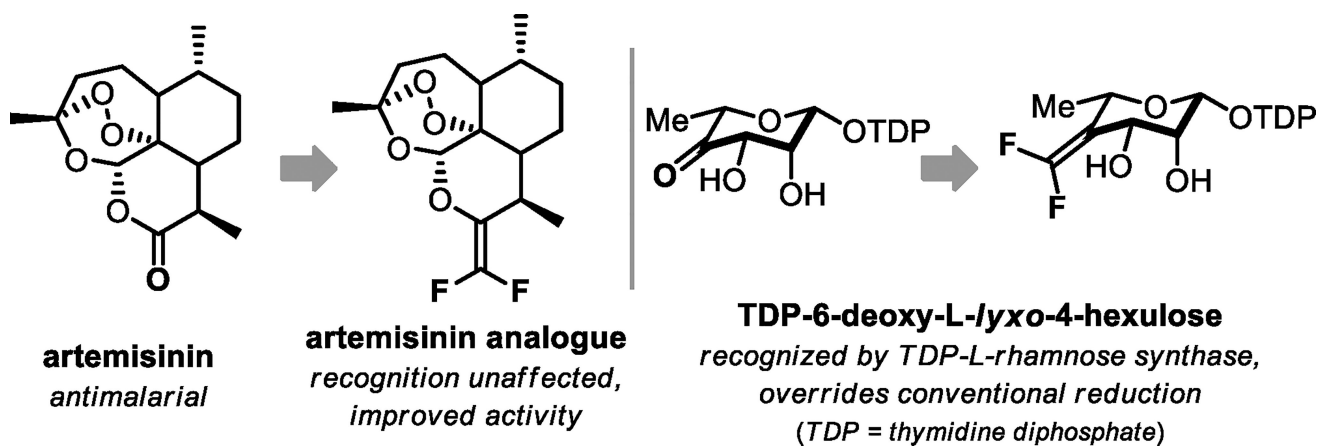


Figure 1.
Representative applications of *gem*-difluoroalkenes.

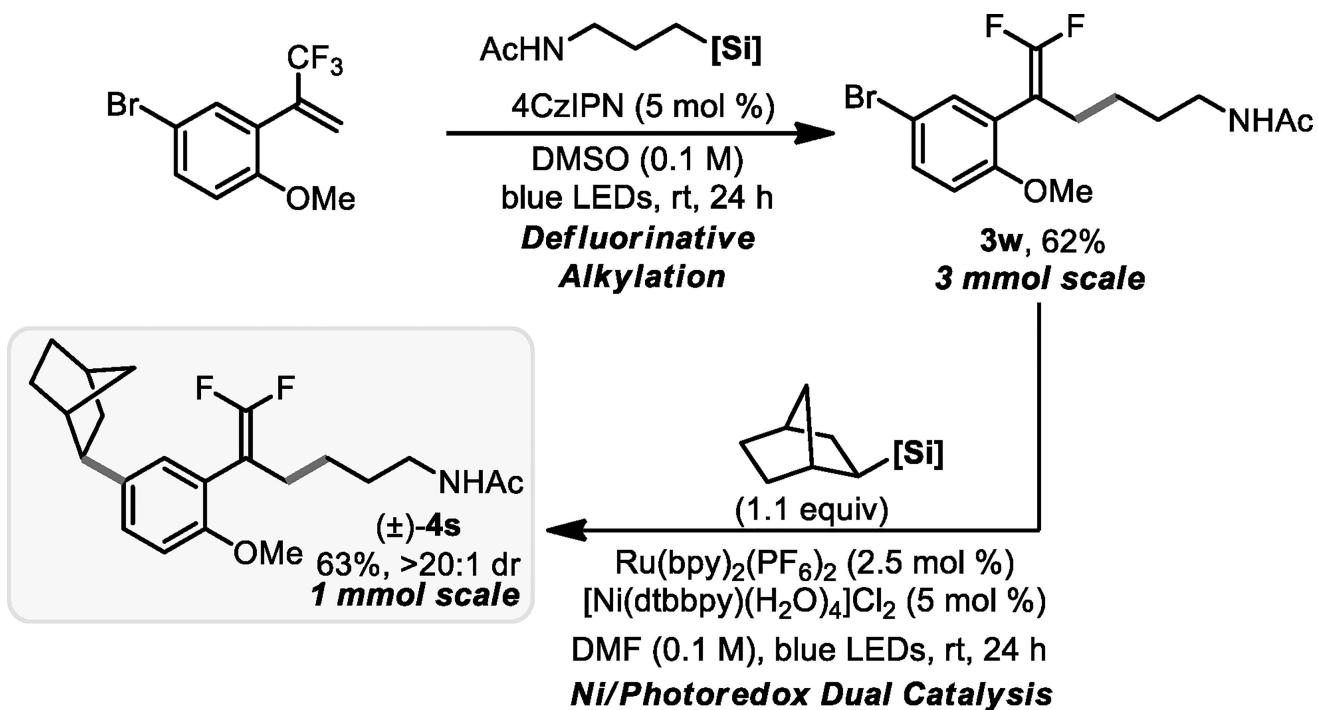


Figure 2.
Scale-up of defluorinative alkylation with subsequent cross-coupling.

New Organotrifluoroborate Reagent Enables an Umpolung Approach

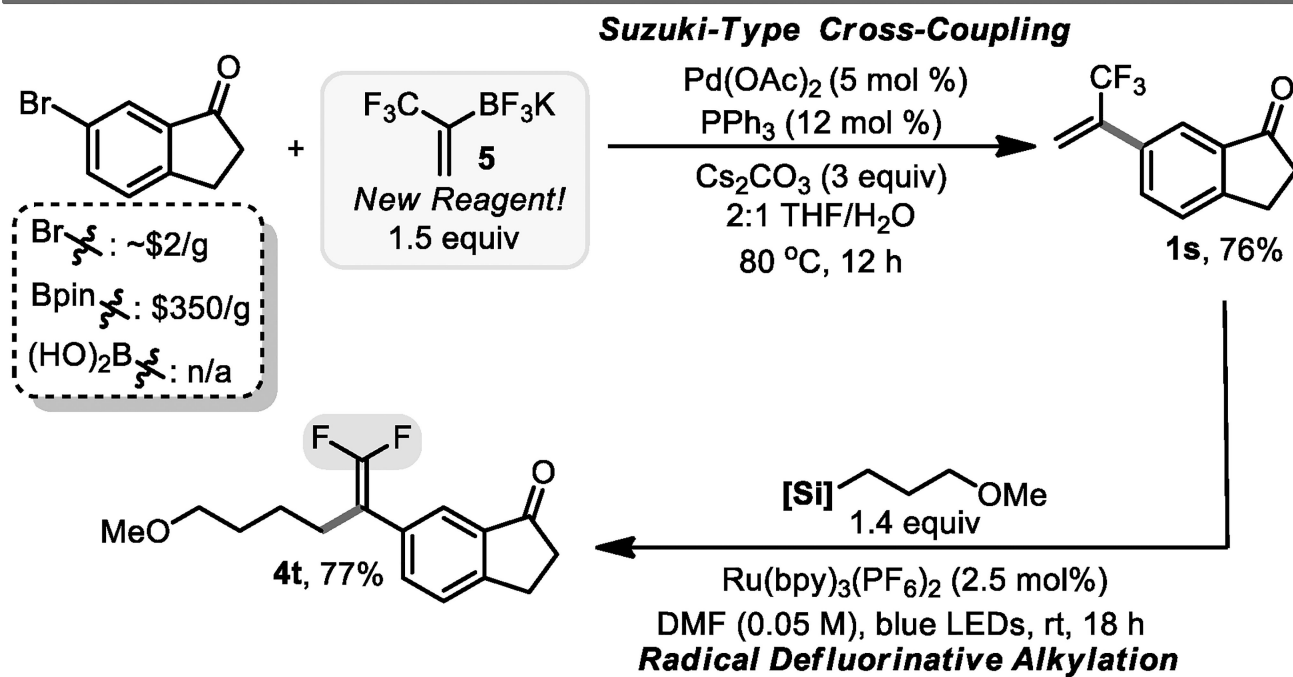
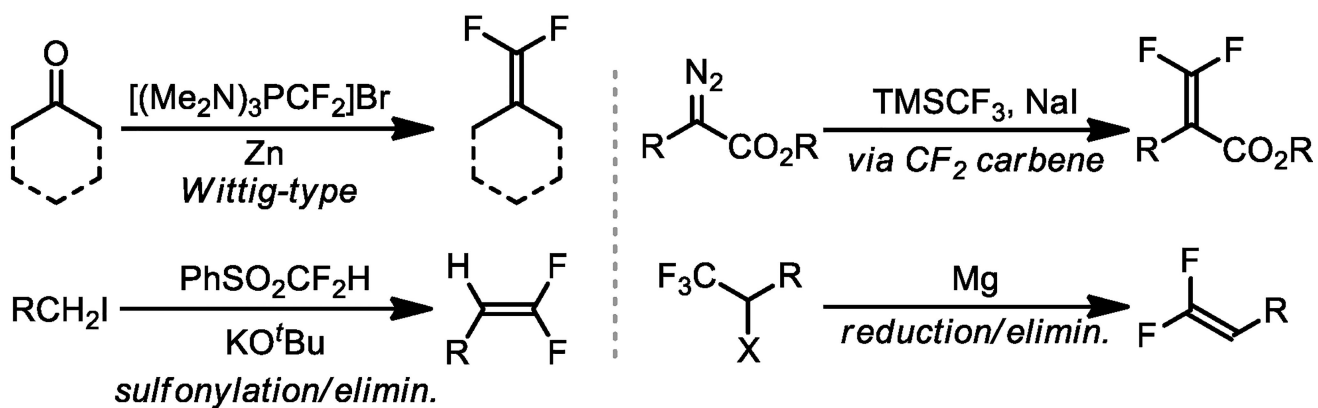
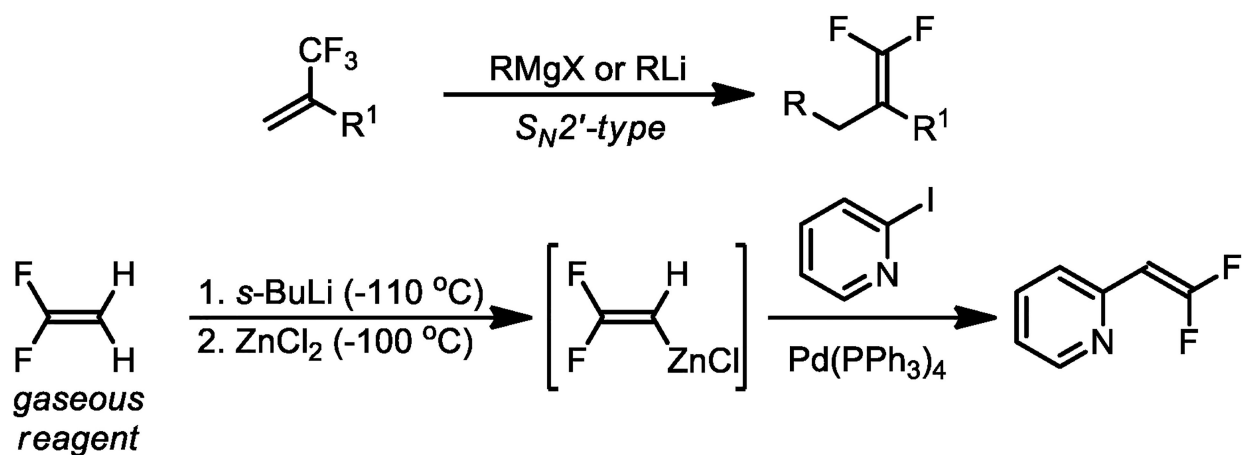


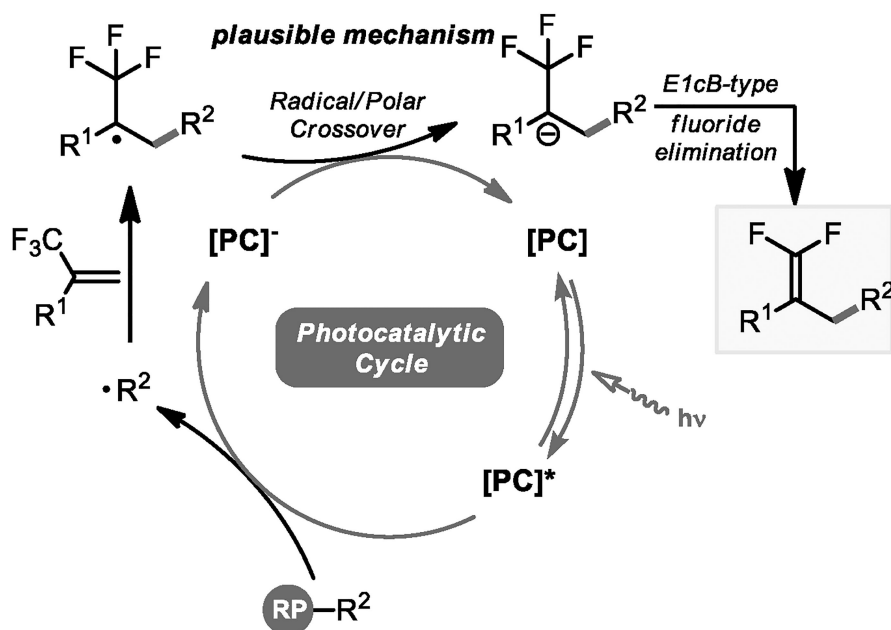
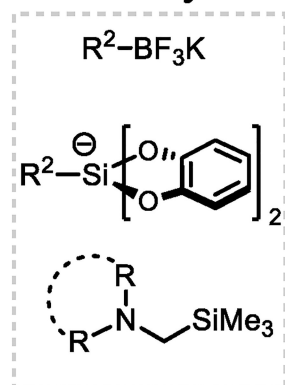
Figure 3. Development and implementation of an organotrifluoroborate for trifluoromethyl-substituted styrene synthesis.

(a) Functional Group Interconversion**(b) Convergent Approaches**

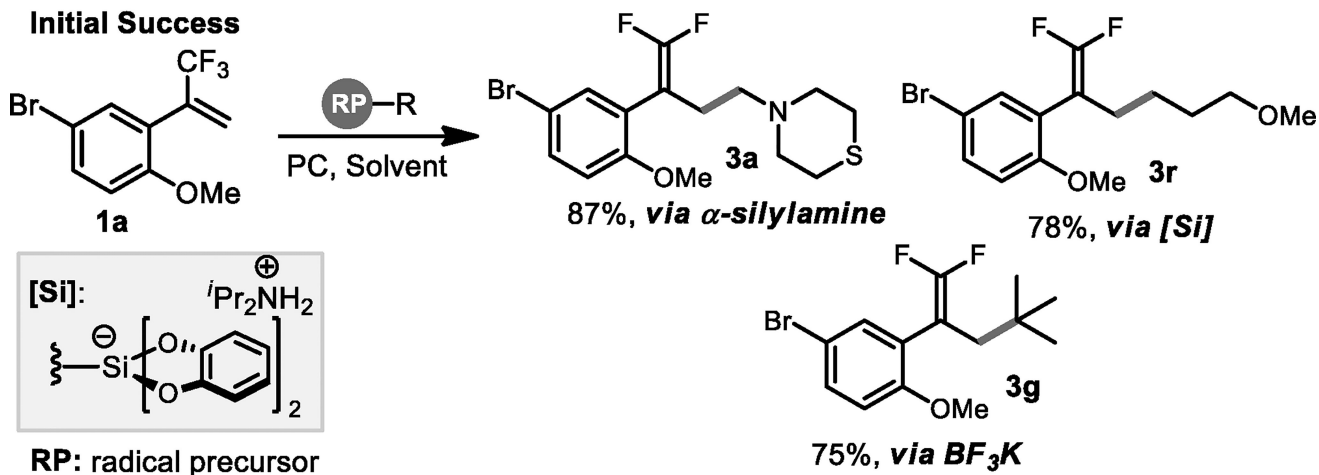
Scheme 1.
 Typical routes to *gem*-difluoroalkenes.

Photoredox catalysis enables a mild, convergent route to *gem*-difluoroalkenes

radical precursor library



Initial Success



Scheme 2.

A convergent route to *gem*-difluoroalkenes *via* radical alkylation.

Table 1

Defluorinative Alkylation Scope: Perfluoroalkyl-Substituted Alkenes and Radical Precursors.^{[a],[b]}

Radical Precursor Scope	α -Silylamine Scope
<p>1, 1.0 equiv 2, 1.4 equiv Radical Precursor</p> <p>4CzIPN or Ru(bpy)₃(PF₆)₂ DMF or DMSO blue LEDs, rt</p> <p>3</p>	<p>3a, X = S: 87% 3b, X = O: 65% 3c, X = CHCO₂Me: 71%</p> <p>3d, 73%</p> <p>3e, R = Cy: 48% 3f, R = CH₂CH₂OMe: 76%</p>
BF ₃ K Scope	
<p>3g, 75%</p> <p>3h, 86%</p> <p>3i, 80%</p> <p>3j, 56%, 4.8:1 dr</p> <p>3k, 87%</p> <p>3l, 53%</p>	<p>3m, 56%</p> <p>3n, 42%</p> <p>3o, 85%</p> <p>3p, 74%</p> <p>3q, 59%</p>
Silicate Scope	
<p>3r, 78%</p> <p>3s, 53%</p> <p>3t, 65%</p> <p>3u, 67%</p> <p>3v, 58%</p> <p>3w, R = Ac, 69% 3x, R = Boc, 44%</p> <p>3y, 65%</p> <p>(±)-3z, 88% >20:1 dr</p>	
CF ₃ Alkene Scope	
<p>1, 1.0 equiv 2, 1.4 equiv Radical Precursor</p> <p>photocatalyst (2.5-5 mol %) Blue LEDs, rt</p> <p>4</p>	<p>4a, 78%, [SI]</p> <p>4b, 81%, [SI]</p> <p>4c, 76%, [SI]</p> <p>4d, 96%, [SI]</p> <p>4e, 80%, [SI]</p> <p>4f, 68%, [BF₃K]</p> <p>4g, 82%, [BF₃K]</p> <p>4h, 82%, [BF₃K]</p> <p>4i, 89%, [BF₃K]</p> <p>4j, 79%, 82:18,^[c] [BF₃K]</p> <p>4k, 69%, [BF₃K] 1:1.4 dr</p> <p>4l, 66%, [SI]</p> <p>4m, 60%, [SI]</p>
<p>4n, 49%, [SI]</p> <p>4o, 81%,^[d] [BF₃K]</p> <p>4p, 90%, [BF₃K]</p>	<p>From Other Perfluoroalkenes</p> <p>4q, 68%, [SI] 5.7:1 E/Z^[e]</p> <p>4r, 57%, [SI] 1.6:1 E/Z^[e]</p>

^[a] All values indicate isolated yields.

^[b] General reaction conditions: radical precursor (1.4 equiv), perfluoroalkyl-substituted alkene (1 equiv, 0.25–0.5 mmol scale), Ru(bpy)₃(PF₆)₂ (2.5 mol %) or 4CzIPN (5 mol %) DMF or DMSO (0.05–0.1 M), rt, 18–36 h at rt, irradiating with blue LEDs (6 to 40 W), see Supporting Information for details.

[c] Ratio of *gem*-difluoroalkene to trifluoromethyl alkane by ^{19}F NMR.

[d] 1.2 equiv of LiBF_4 added

[e] Identity of major and minor isomers determined by ^1H - ^{19}F HOESY, see Supporting Information for details.

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