C–F Alkylation; Access to Multi-Fluorinated Arenes

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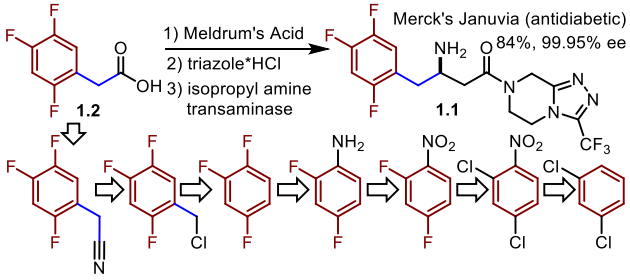
Supporting Information Placeholder

ABSTRACT: C–F functionalizations that provide C–C bonds are challenging synthetic transformations. Herein, we disclose conditions for the photocatalytic reductive alkylation of highly fluorinated arenes. Importantly, ubiquitous alkenes are used as the coupling partner and the mild reaction conditions allow a broad scope of functionality to be tolerated. Furthermore, we demonstrate that commercially available, highly fluorinated arenes can be utilized to access elaborate arenes that contain between 2-5 C_{aryl}–F bonds via synergistic use of photocatalysis and underutilized S_NAr chemistry.

Partially fluorinated arenes make up an extremely important class of molecules within the pharmaceutical[1] and crop science[2] industries. In 2013, the FDA approved 27 new small molecule entities.[3] Of these, 9 contain C–F bonds and 4 (Adempas, Gilotrif, Tafinlar, Tivicay) contain aryl C–F bonds. Aryl fluorides share a similar importance in the crop protection sciences with important aromatic fluorides such as Tefluthrin, Lufenuron, Clodinafop, and Saflufenacil.[4] However, closer inspection of drugs containing fluoroarenes reveals a disturbing trend.[5] Namely, fluoroarenes typically share only a single C–C bond with the rest of the drug molecule and, in practice, serve as terminating groups (i.e. found on the periphery).[6] This fact may stem from the biology but a more likely cause is the limitations of synthetic chemistry and the difficulty associated with placing fluorine atoms in the desired locations. Despite their simple appearance, partially fluorinated molecules often involve lengthy synthetic sequences such as the case for the trifluorophenacetic acid used by Merck in the synthesis of Januvia (Scheme 1). Due to the difficulty associated with their synthesis, only a relatively small number of multi-fluorinated aryl building blocks are available and typically provide only a single site for connecting to the desired molecule.

Scheme 1. Synthesis of Januvia's Fluorinated Precursor

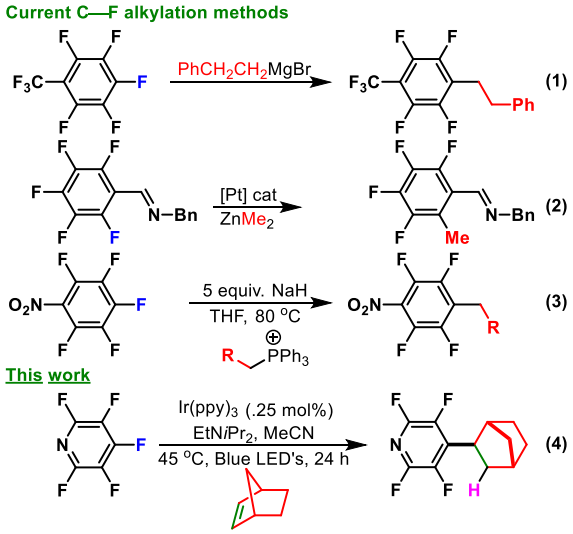


We reasoned that highly fluorinated arenes, which are readily available by exhaustive fluorination or the halex process[7]-many of which are commercially available, could help remedy this issue by providing the carbon framework with the desired fluorine atoms already in place. The undesired fluorine atoms could then serve as functional group handles to transform the molecule into the desired product; thus, effectively serving as a synthetic linchpin and providing access to fluorinated molecules not previously possible.

While the strategy is conceptually simple, there are several significant challenges associated with this approach. Specifically, the C–F bonds are remarkably strong,[8] short,[9] and not significantly polarizable[10]-making them both kinetically and thermodynamically robust. Furthermore, even if the bond is broken and fluoride formed, it often forms strong metal–F bonds which can lead to sluggish catalyst turnover, making metal-catalyzed processes difficult. Finally, if all these issues are circumvented, the regioselectivity of the C–F functionalization could still be problematic given that the arene contains multiple C–F bonds.

Nonetheless, some progress has been made in the area of selective C–F alkylation of highly fluorinated arenes.[11] For instance, Li has demonstrated that magnesiates are sufficiently nucleophilic to add uncatalyzed to perfluorinated arenes (eqn 1, Scheme 2).[12] The Love group has developed a benzyl imine directed Pt-catalyzed methylation reaction (eqn 2).[13] More recently, Wu has shown that phosphonium ylides are capable of undergoing C–F substitution (eqn 3).[14] These methods are important examples of selective C–F functionalization. However, they have significant limitations with regards to functional group tolerance, ortho only functionalization of aldehyde derivatives, or are limited to primary alkyl group transfers. Consequently, there is still a pressing need for the development of novel strategies to alkylate C–F bonds.

Scheme 2. C–F Alkylation Strategies



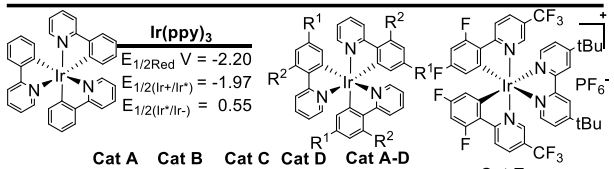
In 2014, we demonstrated that visible light photocatalysis could be used to perform selective hydrodefluorination of perfluoroarenes.[15] This method proved ideal for avoiding many of the challenges facing metal-catalyzed methods for C–F functionalization. Specifically, the catalyst, *fac*-Ir(ppy)$_3$, is an 18-

electron complex that is tris-cyclometalated and coordinatively saturated and provides little opportunity to form problematic M–F bonds.

The reaction was postulated to take place by an electron transfer to the arene which typically resulted in a selective C–F bond fragmentation event. Furthermore, the method was mild and functional group tolerant. Thus, we were eager to see if the intermediate could be utilized to form a C–C bond (eqn 4, Scheme 2) which would help us realize our larger goal of making perfluoroarenes a useful synthetic linchpin. We chose to initiate our investigation with alkenes, which we envisioned could serve as a surrogate for an alkyl group. The use of alkenes was attractive in comparison to sp^3-hybridized coupling partners because they would require no prefunctionalization and between natural compounds and synthetic methods, would provide enormous substrate variety. Herein, we report our progress towards achieving this goal via reductive alkylation of polyfluorinated arenes with alkenes.

Table 1. Optimization of Reaction Conditions.

Entry	Modifications	Conv.[a]	1a/1a'	Time
1.	None	100%	2.6	8 h
2.	THF, DCM, or Toluene instead of MeCN	0%	na	8 h
3.	$MeNO_2$, DMF instead of MeCN	100%	na[b]	2 d
4.	DMSO instead of MeCN	99%	1.7	8 h
5.	1.2 equiv cyclohexene	73%	0.8	2.2 h
6.	2.4 equiv cyclohexene	57%	1.5	2.2 h
7.	3.6 equiv cyclohexene	59%	1.8	2.2 h
8.	4.8 equiv cyclohexene	58%	2.1	2.2 h
9.	6.0 equiv cyclohexene	68%	1.8	2.2 h
10.	10.0 equiv cyclohexene	39%	2.5	2.2 h
11.	$Ir(ppy)_3$[c]	100%	2.8	20 h
12.	**Cat A**	92%	3.2	20 h
13.	**Cat B**	100%	2.8	20 h
14.	**Cat C**	68%	2.8	20 h
15.	**Cat D**	52%	2.7	20 h
16.	**Cat E**	69%	2.3	20 h
17.	$Ir(ppy)_3$ (0.5 mol%)	72%	3.2	5.5 h
18.	$Ir(ppy)_3$ (0.25 mol%)	73%	2.8	5.5 h
19.	$Ir(ppy)_3$ (0.125 mol%)	35%	2.9	5.5 h



	Cat A	Cat B	Cat C	Cat D
(R^1, R^2) =	(*t*Bu,H)	(CF3, H)	(F,H)	(F,F)
$E_{1/2Red}$ V =	-2.27,	-2.13,	-2.13,	-1.82
$E_{1/2(Ir+/Ir*)}$ =	-1.90,	-1.65,	-1.86,	-1.23
$E_{1/2(Ir*/Ir-)}$ =	0.32,	0.63,	0.73,	0.39

a. Determined by ^{19}F NMR b. unidentified products formed. c. run in the catalyst screen experiment.

Based on our earlier work,[15] we expect the reaction to take place via electron transfer from the photocatatlyst to the perfluoroarene, which results in a C–F fragmentation to generate fluoride and a perfluoroaryl radical. We hoped that this radical could be enticed to undergo C–C bond formation with an alkene rather than H-atom transfer. It is worth noting, that most systems used for the generation of aryl radicals (typically from aryl-iodides and -bromides) are subject to rapid secondary reduction to give an aryl anion and are typically limited to fast cyclizations which can compete with reduction.[16] Given our novel reduction system, we hoped that the undesirable over-reduction could be avoided, allowing the generation of a fluoroaryl radical that could undergo productive C–C formation. Thus, we set about developing the reductive alkylation of highly fluorinated arenes with alkenes.

We began the optimization using pentafluoropyridine and cyclohexene (Table 1). Starting with conditions that facilitated the photocatalytic hydrodefluorination[15] (HDF) we screened solvents (entry 2-4). When toluene, THF, or DCM were used as the reaction solvent, no reaction occurred (entry 2). The use of nitromethane or dimethylformamide led to unidentified products. While use of DMSO led to product formation but a decrease in the relative amount of alkylated (**1a**) to HDF product (**1a'**).

We next evaluated the effect of the concentration of the alkene on the reaction outcome (entries 5-10). At low alkene concentration the reaction proceeded noticeably faster, but gave greater amounts of the reduced fluoroarene. While high alkene concentration (10 equivalents, entry 10) gave the best product ratio, we ultimately chose 6 equivalents as a compromise between the two extremes.

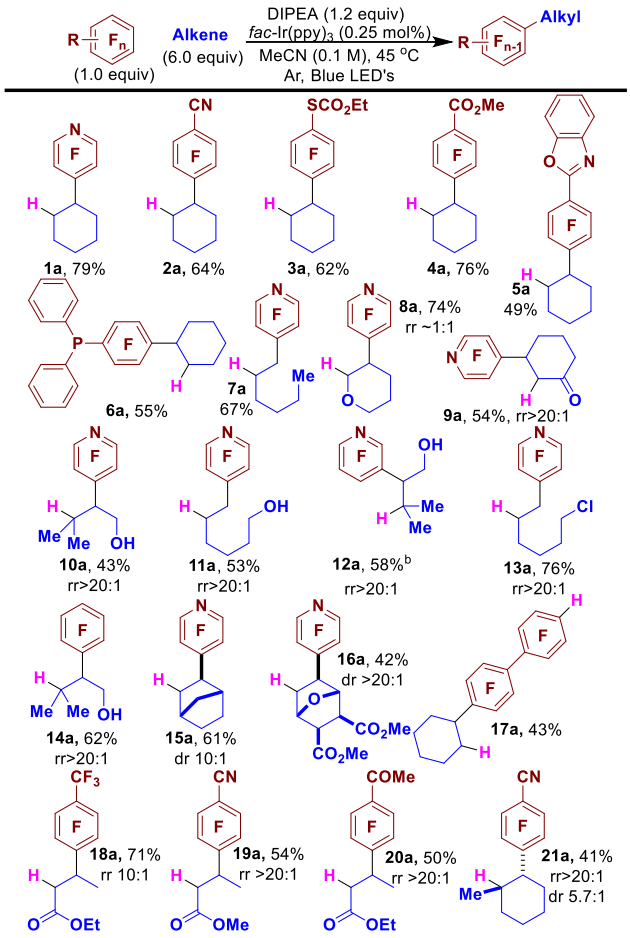
Lastly, we investigated the nature and concentration of the photocatalyst (entries 11-19). The catalyst ranged from strongly reducing to strongly oxidizing. Interestingly, the reaction proceeded with all the photocatalysts and resulted in only minor changes to the product distribution. However, the relative rates of the reaction were not uniform. Conceivably, $Ir(ppy)_3$ and **Cat A** could be proceeding through an oxidative quenching path, despite a slight underpotential (C_5F_5N -2.12, $E_{1/2}$ V).[17] While a reductive quenching event ($EtNiPr_2$ +0.68 $E_{1/2}$ V)[18] seems more probable for **Cat B** and **Cat C** and almost certain for **Cat D** and **Cat E**. Together these results suggest that multiple mechanistic pathways are feasible. Given the relatively small difference observed in the best performing photocatalysts, we opted to use the more common $Ir(ppy)_3$ catalyst. Finally, we evaluated the photocatalyst loading. We found that the loading could be dropped to 0.25 mol% before the rate suffered. Thus, we began to explore the scope of the reaction using DIPEA (1.2 equiv), alkene (6.0 equiv), $Ir(ppy)_3$ (0.25 mol%) in MeCN (0.1 M) with visible light irradiation with blue LED strips.

Initially, we looked at a series of perfluoroarenes with cyclohexene to evaluate the generality of the scope with regard to arene. We found that moderate to good yields could be obtained directly from a number of perfluoroarenes including pyridine (**1a**), benzonitrile (**2a**), thiocarbonates (**3a**), esters (**4a**), heterocyclic substituted (**5a**), and even phosphines (**6a**). We were concerned that the intermediate radical might be too reactive to be selective, but we found that differences in the substitution pattern of the alkenes led to excellent selectivity, with addition occurring at the less substituted carbon (**7a**, **10a**, **11a**, **12a**, and **13a**). The reaction proceeds smoothly in the presence of electron rich dihydropyran (**8a**) as well as with electron poor cyclohexenone (**9a**) which gives a single regioisomer. **12a** is derived from 3-chloro tetrafluoropyridine and demonstrates the orthogonal reactivity of the photocatalytic functionalization and S_NAr chemistry which is selective for the 4-F in the perfluoropyridine system. **12a** is also noteworthy because no 5-exo-trig cyclization product is detected and highlights the mild reaction conditions. Furthermore, the primary alkyl chloride is well tolerated (**13a**).

Complex alkenes are available from synthetic methods and nature and we were eager to test the reaction to see if we could use them to easily incorporate complex 3-dimensional alkyl groups via the reductive alkylation. We found norbornene to be an excellent substrate (**15a**) as well as the furan derived [4+2] adduct (**16a**) which contains several sensitive functional groups and base labile stereocenters.

Reaction with acrylates provides the saturated β-fluoroarylated esters (**18a**-**20a**).). Reaction with methyl cyclohexene provides the *trans*-1,2-disubstituted cyclohexane with moderate stereoinduction (**21a**, 5.7:1 dr). Decafluorobiphenyl undergoes a rapid second photocatalytic C–F fragmentation event and allows facile access to the product of tandem reductive alkylation and HDF (**17a**) which can be further elaborated by traditional methods that utilize the enhanced acidity of the Ar–H.[19]

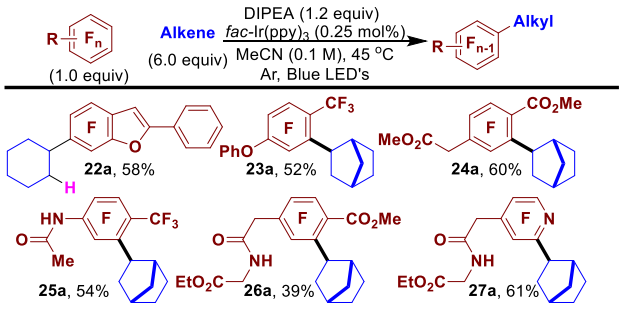
Table 2. Scope of the C–F Reductive Alkylation



a. Yields correspond to isolated product. The regioisomeric ratio (rr) and diastereomeric ratio (dr) were determined by ^{1}H NMR of the crude reaction mixture after workup.

We expected that highly fluorinated nature of the arenes should facilitate elaboration of the structure by SNAr reactions as well as the photocatalytic reaction. The fluorines serve to activate the arene towards electron addition ($E_{1/2\ red}$ C_6H_6 = -3.41[20] and $E_{1/2\ red}$ C_6F_6 = -2.41[21]). Consequently, we were concerned that substitution of the fluorines would might make the photochemical reactions to sluggish to be useful. Nonetheless, we next began to look at substrates in which at least one fluorine had already been used to synthesize the desired substrate (Table 3). When the acetophenone derived benzofuran was exposed to cyclohexene we obtained the trifluorinated, alkyl substituted **22a** in good yield.

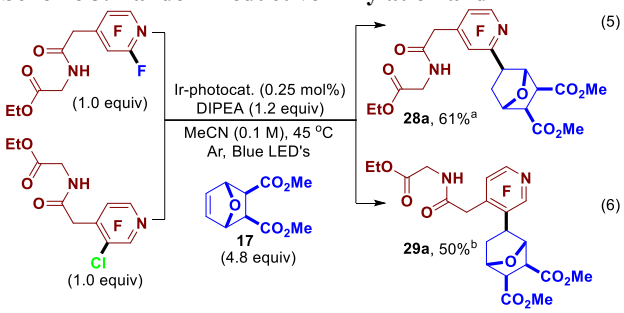
Table 3. Trifluorinated Arenes.



Ocatfluorotoluene and methylbenzoate both undergo smooth nucleophilic addition at the 4-position and then can undergo photocatalytic reductive alkylation at the position ortho to the trifluoromethyl or ester group (**23a**, **24a**, **25a**, and **26a**) to rapidly provide complex multi-fluorinated arenes that contain aryl ethers, esters, amides and even amino acid derivatives. Similarly, pentafluoropyridine can undergo substitution at the 4-position and then be photocatalytically coupled at the 2-position (**27a**).

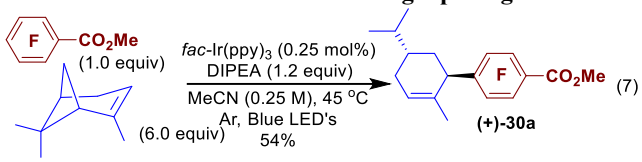
As mentioned, the inherent regioselectivity of the photocatalytic C–F fragmentation event can be overridden by the addition of a chlorine to a different location on the ring. Importantly, this reactivity pattern is orthogonal to that of SNAr chemistry. Thus, by judicious choice of starting material (pentafluoropyridine vs. 3-chlorotetrafluoropyrine) we were able to access complimentary regioisomers (**28a** and **29a**, Scheme 3) in reasonable yields which highlights the synthetic versatility of this approach.

Scheme 3. Tandem Reductive Alkylation and HDF



Interestingly, when vinyl cyclobutane, α-pinene, was used an optically active ring-opened trisubstituted cyclohexene was obtained rather than the standard reductively alkylated product (**30a**, Scheme 4). Presumably, this comes from perfluoroaryl radical addition to the less substituted terminus of the alkene followed by ring-opening and finally reduction exocyclic radical.[22]

Scheme 4. Tandem Addition and Ring Opening



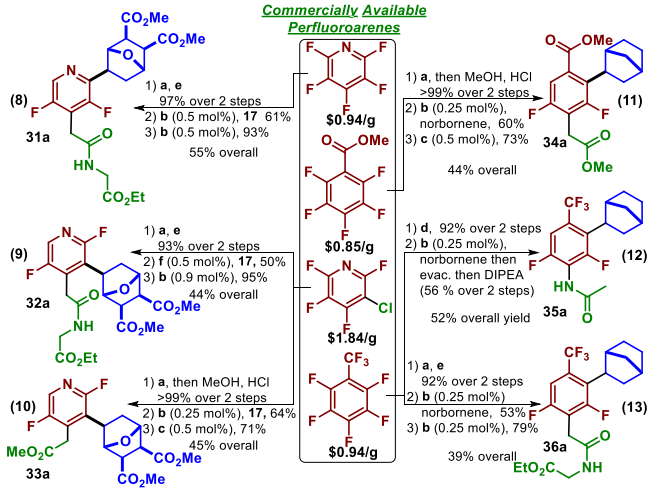
Finally, having explored the scope of the reaction we sought to demonstrate that perfluoroarenes possess significant synthetic potential that can provide both access to multi-fluorinated arenes and simultaneously serve as synthetic linchpins that allow a high level of structural complexity to be built directly from the core of the fluorinated molecule.

To demonstrate this, we developed a simple and general sequence of SNAr and elaboration, followed by photocatalytic reductive alkylation and finally photocatalytic hydrodefluorination (HDF). This sequence provides access to a diverse and elaborate set of multi-substituted,difluorinated arenes and heteroarenes in reasonable yields, 39%-55% with excellent regiocontrol starting from just a few inexpensive polyfluorinated arenes (Scheme 5).

Starting with pentafluoropyridine (eqn 8, Scheme 5) the Meldrum's acid adduct[23] is formed and then decomposed in the presence of the glycine*HCl salt to afford the amide in high yield. The tetrafluoropyridine product is then sequentially subjected to photocatalytic reductive alkylation and HDF to arrive at **31a** in 55% overall yield. Using the 3-chlorotetrafluoropyridine analog allows synthesis of the regioisomer (**32a**) in 44% yield. The ability to easily access both isomers could potentially facilitate structural activity relationship studies. The commercially available Meldrum's acid adducts are a versatile functional group handle that can quickly provide other motifs such as esters which can undergo similar sequences (**33a**). This sequence can be extended to other perfluoroarenes such as methyl benzoate (eqn 11) and octafluorotoluene (eqns 12 and 13). Synthesis of **35a** required a total of only 0.25 mol% $Ir(ppy)_3$ to carry out both photocatalytic steps. At the completion of the alkylation step, the excess alkene was removed from the reaction mixture by vacuum. Upon addition of solvent, amine, light, and degassing the photocatalytic-HDF reaction began. In some cases a purification step is required to

remove impurities before progressing, but even then, substantial amounts of material (**36a**) can be obtained in this short synthetic sequence.

Scheme 5. Perfluoroarenes as Synthetic Linchpins



a. Cyclohexyl Meldrum's acid, DIPEA, MeCN. b. Ir(ppy)$_3$ (X mol%), Blue LEDs, DIPEA. c. Cat B (X mol%) Blue LEDs, DIPEA. d. NH_4OH, 1,4-dioxane then Ac_2O, C_6H_6, cat. $HClO_4$. e. Glycine-HCl (MeCN). f. Cat-A (X mol%), Blue LEDs, DIPEA.

In conclusion, we have provided a new strategy for the alkylation of C–F bonds in highly fluorinated arenes. The reaction takes place with low catalyst loadings, utilizes simple unactivated alkenes, and displays excellent functional group tolerance. Importantly, it suggests that photocatalytic electron transfer can serve as convenient method for generating fluoroaryl radicals directly from the C–F bonds, greatly reducing the need for synthetic manipulations in order to achieve fluorinated arenes. We have demonstrated that this chemistry, when used synergistically with S_NAr chemistry, can lead to elaborate molecules that would be otherwise difficult, if possible, to synthesize. We expect this chemistry should substantially aid the discovery processes given the current unmet need for multi-fluorinated arenes and the rapid and flexible nature of this chemistry.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, additional optimization experiments, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare a competing financial interest in that they hold a patent United States Serial No.: 62/043,650 concerning the structure and method for the Meldrum's acid adducts.

ACKNOWLEDGMENT

The research results discussed in this publication were made possible in total or in part by funding through the award for project number HR-14-072, from the Oklahoma Center for the Advancement of Science and Technology, and by NSF (CHE-1453891) and by OSU-startup funds. We thank KAT for help in editing the manuscript.

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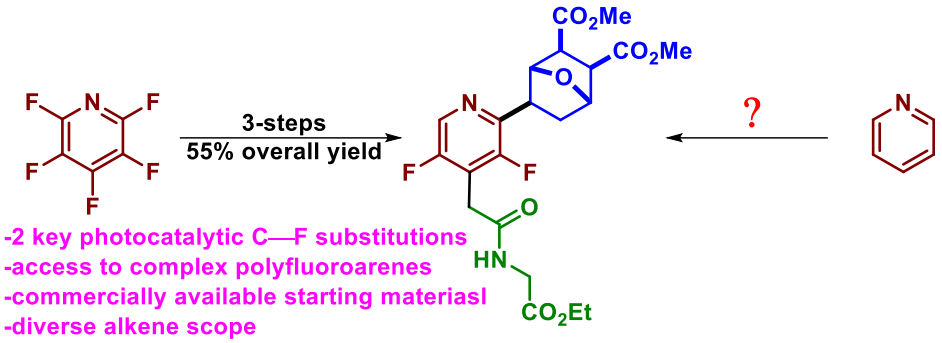

-2 key photocatalytic C—F substitutions
-access to complex polyfluoroarenes
-commercially available starting materiasl
-diverse alkene scope
-excellent functional group tolerance