Dual C–F, C–H Functionalization via Photocatalysis; Access to Multi-Fluorinated Biaryls

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Abstract

Multifluorinated biaryls are challenging to synthesize and yet an important class of molecules. Owing to the difficulty associated with selective fluorination, this class of molecules represent a formidable synthetic challenge. An alternative approach to selective fluorination of biaryls is to couple an arene which already possess C–F bonds in the desired location. This strategy has been regularly utilized, relying heavily on traditional cross-coupling strategies which employ organometallics and halides (or pseudohalides) in order to achieve the coupling. Herein, we report conditions for the photocatalytic coupling via the direct functionalization of the C–F bond of a perfluoroarene and C–H bond of the other arene to provide an expedient route to multifluorinated biaryls. The mild conditions and good functional group tolerance enable a broad scope-including access to the anti-Minisci product of basic heterocycles. Finally, we demonstrate the value of the C–F functionalization approach by utilizing the high fluorine content to systematically build complex biaryls that contain between 2–5 C_{aryl}–F bonds via synergistic use of photocatalysis and S_NAr chemistry.

Graphical Abstract
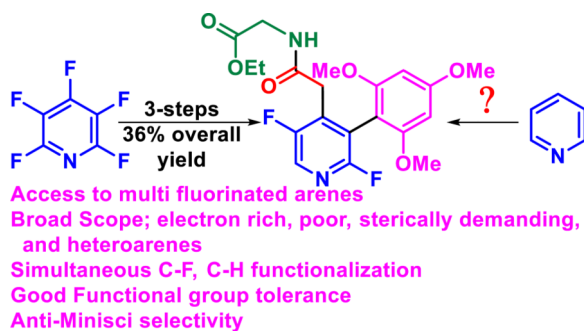
Fluorinated biaryls are an important class of molecules with many examples in drugs,[1,2] agrochemicals,[3,4] functional materials such as liquid crystals,[5,6] organic light-emitting

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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.

diodes (OLEDs),[7,8] water splitting processes,[9] as well as electron transport materials.[10,11] While cross-coupling methods have made biaryls generally accessible, currently, far fewer methods exist which lead to the important class of partially fluorinated biaryls. Synthesis of fluorinated biaryls have been approached from several directions. Including, traditional cross-coupling of a fluorine containing arene that either possess a halogen or an organometallic group while the partner is substituted with a complimentary reactive group (**Approach A**, Scheme 1).[12–19] Alternatively, methods characterized by the use of less functionalized molecules (i.e. H[20] on one or both partners) have also been developed (**Approach B**).[21–23] Typically, activated multifluorinated arenes are derived from the C–F bond in 1–3 steps, i.e. C–F to C–H[24] to C–halogen[25,26] to C–organometallic.[27,28] Consequently, efforts have been made in the area direct C_{Ar}–F functionalization,[29–32] which have been focused primarily with overcoming the difficulties associated with C–F functionalization (**Approach C**). To mention a few of the challenges; C–F bonds tend to be both kinetically and thermodynamically robust, they often form strong metal fluoride bonds which result in stable catalytic intermediates and lead to sluggish catalyst turnover. If all these issues are circumvented the method must contend with a C–F regioselectivity issue-since polyfluorinated arenes contain multiple C–F bonds. In this work (**Approach D**), we sought to form a new biaryl C–C bond directly from a C–F from the fluoroarenes and a C–H from the arene partner. It was expected that realizing this goal, would provide rapid access to new fluorinated chemical space.

While the synthetic advantages of the dual C–F, C–H biaryl formation are manifold, achieving such a goal would require solutions for the aforementioned issues. Photocatalysis has been shown to be capable of reductive cleavage of Ar-X groups, i.e. Ar-X to Ar-H.[33–37] In 2014,[38] we showed that catalytic amounts of *fac*-Ir(ppy)$_3$ in the presence of light and an amine reductant resulted in a highly efficient hydrodefluorination (HDF) (eqn 1, Scheme 2) with excellent regioselectivity and functional group tolerance, suggesting that it might provide a novel route for direct C–F functionalization. Indeed in 2015,[39] we showed that the same reactive intermediate could be intercepted with an alkene (eqn 2) which then underwent a subsequent reduction of the presumed alkyl radical. We were curious to know whether the incipient radical-formed as a result of C–C bond formation, could be oxidized rather than reduced leading to an alkene.[39] Given their propensity to regain aromaticity after temporary loss, arenes were a logical place to start, since we could use rearomatization to our advantage to help facilitate the oxidation (eqn 3).

From the outset,[40] several obvious challenges associated with the desired reaction were apparent (eqn 3, Scheme 2); the need to achieve an oxidation of ***int-a*** under reducing conditions,[41] the regioselectivity of the C–C coupling event with respect to the aryl–H, and competing HDF. Oxidation of ***int-a*** could occur prior to deprotonation (3a) or afterwards (3b). The dominant path may depend the nature of both the arene partners. Nonetheless, we began our investigation with conditions that had facilitated the HDF[38] using pentafluoropyridine with the addition of 6 equivalents of trimethoxybenzene which removed the possibility of regioisomers (Entry 1, Table 1). We were pleased to see that the desired C–C coupled product was indeed formed as the major product in reasonable yields along with a significant amount of the HDF product. By optimization we hoped to increase the yield and

simultaneously decrease the equivalents of the arene-H coupling partner. A survey of solvents (Entries 2–4) showed that both DMF and DMSO provided the desired product, albeit in lower yields than MeCN, while DCM and THF resulted in low yields of only undesired products. Next we screened photocatalysts for the ability to influence the product ratio and yield (Entry 5),[42] while a subtle improvement in product ratio was observed, the reaction was noticeably slower. Next, we evaluated both the structure of the amine[43] as well as the loading of the amine (Entries 6–10) as reaction parameters. While Et$_3$N worked reasonably well, it led to products stemming from N-perfluoroarylation[44] byproducts which were substantially decreased by use of more sterically cumbersome diisopropyl ethyl amine (DIPEA). When the amount of amine was varied, two key features were revealed (Entries 8–10). First, despite the fact that both a reduction and oxidation occur in the same reaction which begs the question whether the amine might just serve as an initiator. While the amine does demonstrate superstoichiometric activity (entry 8), the reaction becomes inefficient. Secondly, too much amine results in increased amounts of HDF product, **1a'**. Previously, we have shown that the use of less soluble amines could retard the rate of photocatalytic reduction.[45] However, in this case, less soluble *i*Pr$_2$N*n*-hept (Entry 10, 0.15 M, max conc. in MeCN vs 1.3 M for DIPEA, both at rt) dramatically slowed the rate of the reaction. Next, we looked at the effect of reducing the amount of trimethoxybenzene, in hopes that we could approach near stoichiometric ratios (Entries 11–12). As expected, diminishing the amount of arene-H led to increased amounts of HDF-product, **1a'**. Next, we investigated the effect of temperature. We were pleased to see that dropping the temperature led to an improved **1a**: **1a'** ratio (Entries 12 vs. 13). Finally, we suspected that the amine was serving two roles, both as a reductant that initiates the C–F fragmentation as well as a base to scavenge the HF which is formed in the reaction. In order to address this, we added KHCO$_3$ (Entry 14) which allowed us to simultaneously lower the loading of both the amine and trimethoxybenzene and achieve the best ratio of **1a:1a'**. Finally, controls were run (entries 15–18) which indicated the necessity of light, catalyst, and amine as well as the sensitivity towards air.

Using conditions from entry 14 we evaluated the scope of the reaction (Table 2). We were pleased to see that good to modest yields could be obtained with electron rich arenes with a variety of perfluoroarenes (**1a, 9a–17a**) as well as acetophenones (**2a**), pyrroles (**3a**), and nitriles (**4a**). The ability of the perfluoroaryl radical to form highly congested C–C bonds (**5a** and **6a**) is noteworthy. The Minisci reaction is commonly employed to functionalize basic heterocycles.[46] Interestingly, we observe anti-Minisci selectivity (**7a** and **8a**), likely owing to the fact that basic heterocycle is not protonated under these conditions as is typical in the Minisci reaction. Substrates **11a** and **12a** suggest that the method can be used to access extended aryl systems and that even moderately acidic protons are tolerated under the reaction conditions. **13a** indicates that the second site of photocatalytic C–F functionalization occurs ortho to the nitrile. **14a** shows the preference for the 3-Cl fragmentation compared to the fluorines and allows access to complimentary regioisomers. Comparison of **15a** and **16a** demonstrate that both the 2- and 4- positions are accessible on the perfluorobenzoate system.[38,39,47] Hexafluorobenzene, devoid of electron withdrawing functional groups, which would facilitate reduction, also undergoes arylation (**17a**). In general, the scope is broad in terms of fluoroarene while the arene-H benefits from substitution or polarizing functional groups.

Next, we investigated the scenario in which the arene-H would be the more valuable coupling partner by switching the limiting reagent to the arene-H and using the perfluoroarene in excess (Table 3). We were pleased to see that the reaction worked under these conditions and allowed the formation of fully substituted biaryls. Trisubstituted pyrimidines underwent addition to give the C–H coupled product (**18a–21a**). Tetra-substituted pyrroles also coupled with the expected C–F selectivity (**22a** and **23a**) to give biologically relevant pentasubstituted pyrroles (i.e. see Lipitor®), suggesting it may be possible to use this method to accomplish late-stage modifications of biologically active molecules. conditions. **19a–21a** in which substitution of C–Cl or C–Br bonds occurs indicate a halogen-fragmentation pattern consistent with that of radical anion fragmentation observed by Bunnett[48,49] and Rossi,[50] (i.e. I>Br>Cl>F). This selectivity is both an inherent limitation as well as an opportunity to build complimentary regioisomers. Importantly, use of the fluorinated arene in excess protects the bromine of product **21a** from subsequent reduction of the C–Br, providing opportunity for further elaboration by other methods. In general, the biggest limitation of the method is the use of arene-H's that are either highly substituted or polarized as this reduces the number of isomers that are formed.

In addition to the esoteric reasons to develop C–F functionalization chemistry, it also has the potential to be the most rapid and versatile method for accessing multifluorinated arenes which would be useful in discovery chemistry efforts involving fluorinated aromatics.[51–54] Specifically, it starts with readily available perfluorinated arenes which have all of the difficult to install fluorines in the desired positions.

The challenge then becomes selectively functionalizing the unwanted fluorines to build the desired molecule. To demonstrate this concept and its feasibility, we started with commercially available perfluoroarenes and subjected them to a series of both photocatalytic and S_NAr functionalizations. This allowed us to rapidly obtain multifluorinated benzoates and pyridines that would be otherwise very difficult to synthesize by any method, thus allowing access to new fluorinated chemical space (Scheme 3). Addition of a Meldrum's acid derivative followed by decomposition in the presences of a nucleophile gave near quantitative yields of the product of α-perfluoroarylation (**24a** and **26a**).[55] Photocatalytic arylation then desymmetrizes the molecules (**15a** and **14a**). The total fluorine content can then be reduced to generate hard to access difluorinated arenes (**25a**) and heteroarenes (**27a**). The regiochemistry of the HDF appears to be dominated by the electronics, i.e. proximity to the electron withdrawing functional group, but other competing influences lead to formation of regioisomers. On radical anions of benzene systems, halogen fragmentation is preferred at the position opposite of a substituent, which we believe gives rise to the minor isomer of **25a**. Hydrogen bonding may be an even stronger influence on the selectivity as the amide is essential to obtaining the minor regioisomer of **27a**. We have previously observed similar switches of selectivity with NHAc perfluoroarenes.[38] Understanding the subtle and potential exploitable phenomena concerning C–F selectivity is the topic of an ongoing investigation in our group.

In conclusion, we have generated and utilized the perfluoroaryl radical-generated by photocatalyst *fac*-Ir(ppy)$_3$, blue light, and an amine, to form a new C–C bond via dual C–F, C–H functionalization. This allows access a wide array of multifluorinated biaryls. From a

synthetic perspective, this reaction has the potential for significant impact given the single step coupling of such broadly accessible starting materials, the mild conditions, and functional group tolerance of the method. From a mechanistic perspective, we have shown that the perfluoroaryl radical is capable of adding to pi-systems of a wide range of arenes, including some that give anti-Minisci selectivity, followed by oxidation and rearomatization. Given these initial findings, we expect that this chemistry will facilitate investigation into new fluorinated chemical space and therefore enable a number of research efforts.

Supplementary Material

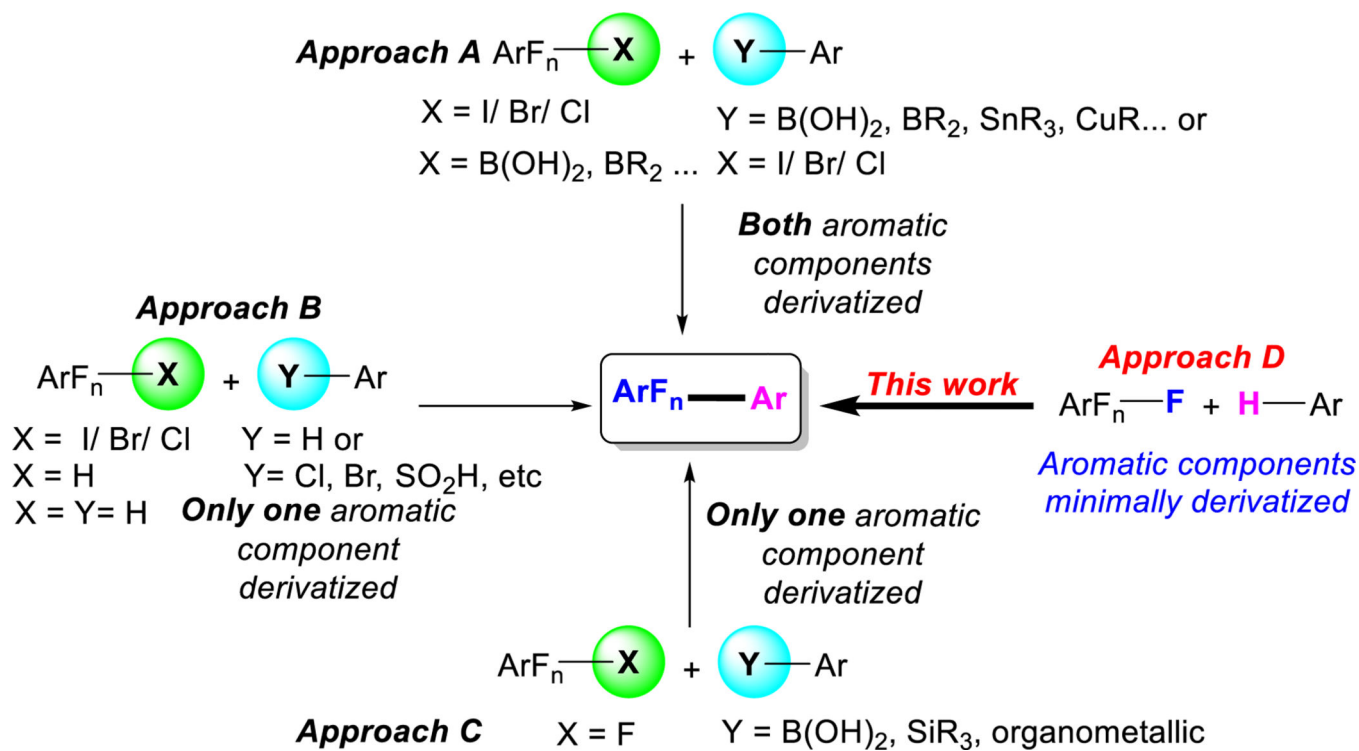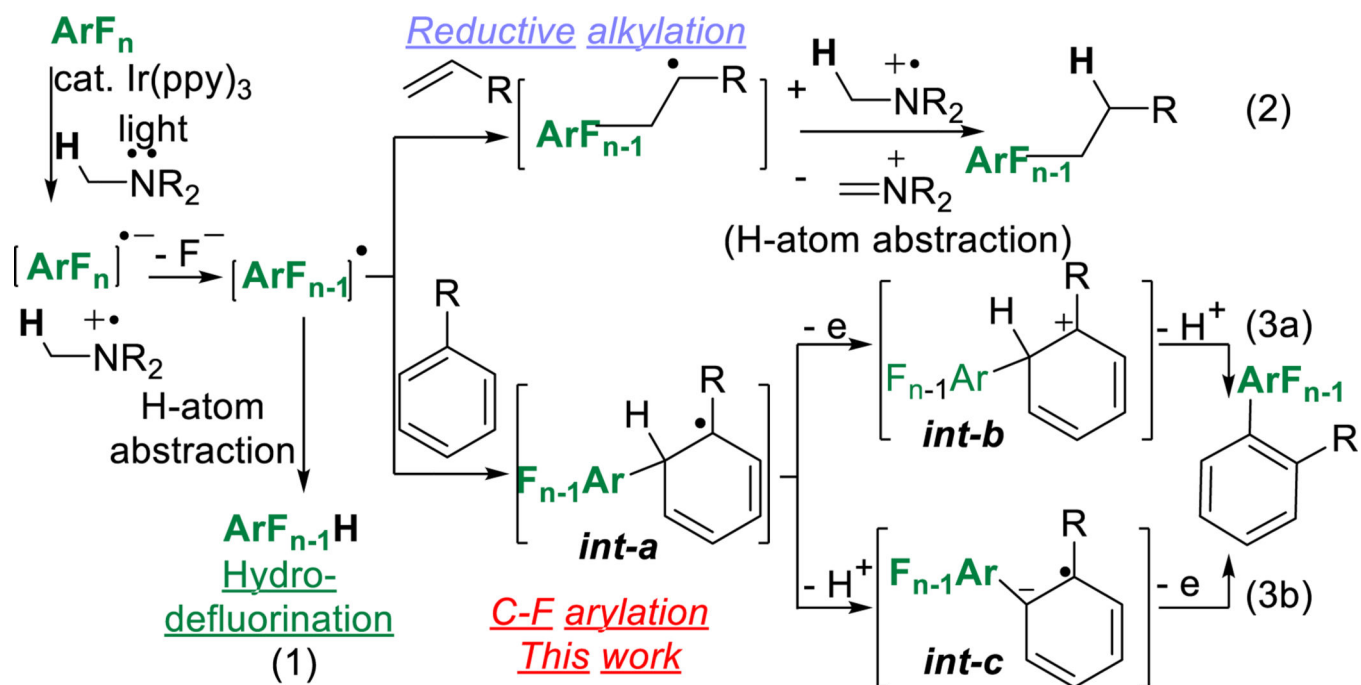Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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40. The first step of the reaction is transfer of an electron to the perfluoroarene. Energetically speaking both reductive and oxidative quenching are nearly equally endothermic (0.17-0.16 V vs. SCE) in the case of pentafluoropyridine, DIPEA, and $Ir(ppy)_3$. Fluoride extrusion is likely an irreversible step that could serve to drive the reaction. With other, less reducible perfluoroarenes reductive quenching is likely operative. See reference 39 for more discussion.

41. Both the reduced $Ir(ppy)_3-$ species (−2.245 V vs. SCE) and the photoexcited $Ir(ppy)_3*$ (−2.012 V vs. SCE) are strongly reducing. Oxidative quenching would produce an $Ir(ppy)_3^+$ (0.738 V vs. SCE) that could most likely oxidize *int-A*. However, given the low concentration of both species, this would be a statistically unlikely event.

42. More photocatalysts were screened but none gave better results, see SI for details.

43. More amines were screened but none gave better results than DIPEA, see SI for details.

44. The 19F NMR shifts are consistent with other N-substituted tetrafluoropyridines observed in our lab which have been observed to undergo N-arylation followed by dealkylation. No further attempts were made to characterize this product.

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Approach A ArF_n—**X** + **Y**—Ar

X = I/ Br/ Cl

X = B(OH)$_2$, BR$_2$ ...

Y = B(OH)$_2$, BR$_2$, SnR$_3$, CuR... or

X = I/ Br/ Cl

Both aromatic components derivatized

Approach B

ArF_n—**X** + **Y**—Ar

X = I/ Br/ Cl

X = H

X = Y= H

Y = H or

Y= Cl, Br, SO$_2$H, etc

Only one aromatic component derivatized

ArF_n —— Ar

This work

Approach D

ArF_n—**F** + **H**—Ar

Aromatic components minimally derivatized

Only one aromatic component derivatized

ArF_n—**X** + **Y**—Ar

Approach C   X = F   Y = B(OH)$_2$, SiR$_3$, organometallic

Scheme 1.
Strategies to Access Fluorinated Biaryls

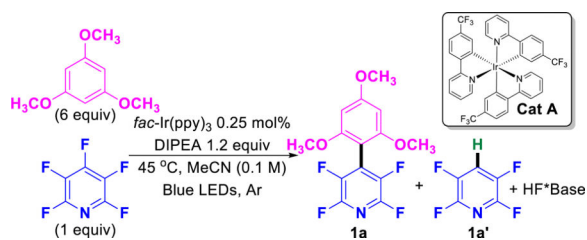**Scheme 2.**
Photocatalytic C-F Functionalization
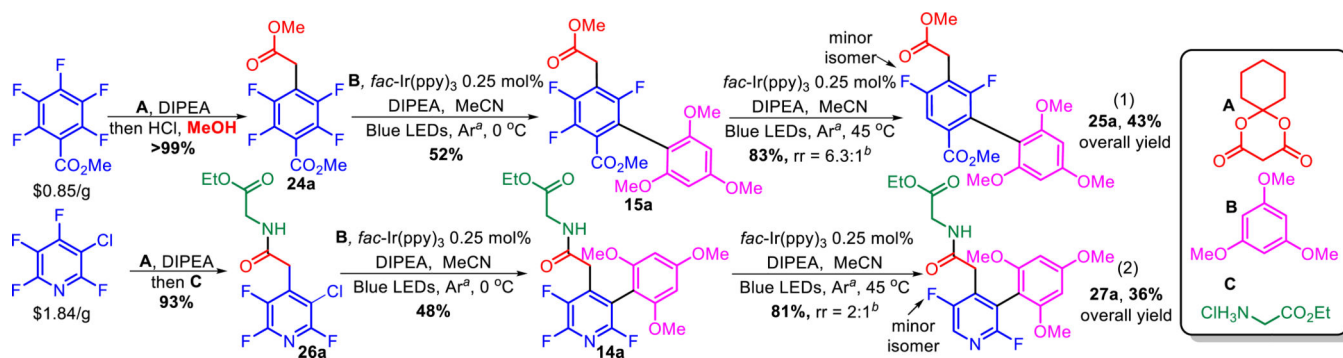
Scheme 3.

The Utility of C–F functionalization to Access Complex Multifluorinated Biaryls

a. The reaction was degassed by bubbling argon for 10 min. b. Yields correspond to isolated product. Regioisomeric ratio (rr) was determined by 1H NMR of the isolated products.
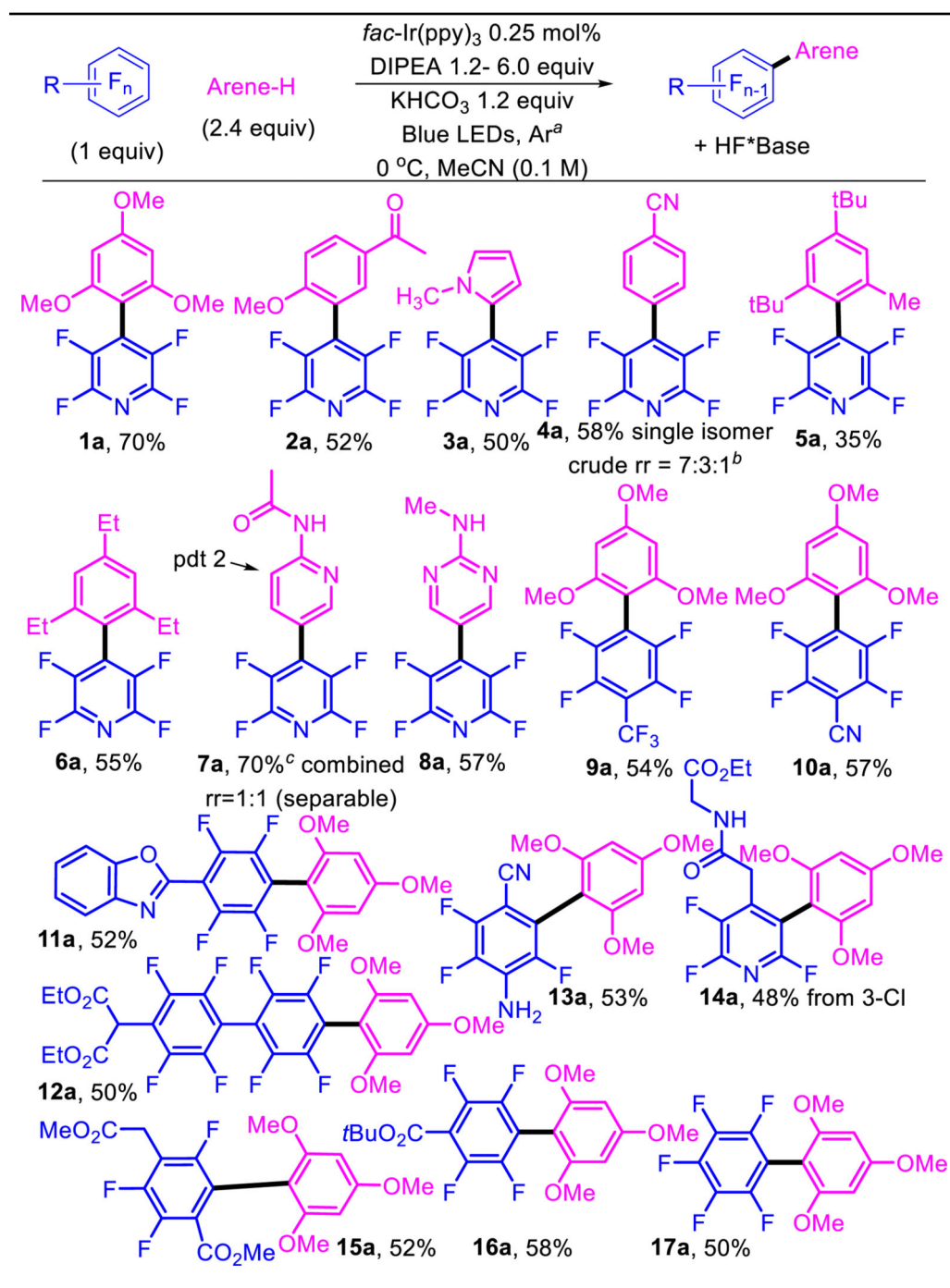
Table 1

Optimization of Reaction Conditions.

entry	modification	1a:1a'	conversion to 1a[a]	time, h
1	none	5:1	47/73%	3/19[b]
2	DMF instead of MeCN	1:2	22/31%	3/19[b]
3	DMSO instead of MeCN	3:1	58/58%	3/19[b]
4	DCM, THF instead of MeCN	na[c]	na[c]	3/19
5	Cat A instead of Ir(ppy)$_3$	6:1	10/52%	4/15[b]
6	Et$_3$N instead of DIPEA	4:1	47/66%	5/19[b]
7	without DIPEA	na	<5%	2/17
8	0.5 equiv of DIPEA	6:1	22/79%	2/17[b]
9	3.0 equiv of DIPEA	3:1	40/61%	2/17[b]
10	iPr$_2$Nn-hept instead of DIPEA	<5%		21
11	1.2 equiv. of arene-H	2:1	57%	17[b]
12	3.0 equiv. of arene-H	3.5:1	66%	17[b]
13	0 °C with 3.0 equiv arene-H	6:1	75%	19[b]
14	0 °C with 2.4 equiv arene-H, 0.4 equiv. DIPEA and 1.2 equiv. KHCO$_3$	13:1	71%	24[b]
15	same as 14 with no DIPEA	na	1%	24
16	same as 14 with no fac-Ir(ppy)$_3$	na	not detected	24
17	in air	na	11%	19
18	in dark	na	not detected	19

[a]Determined by ^{19}F NMR

[b]Reaction complete.

[c]<20% conv. to undesired products.

Table 2

Scope of the photocatalytic C-F arylation (limiting perfluoroarene)

^{c}Yield is the sum of isomers which were separated.

Table 3

Scope of the photocatalytic arylation (limiting arene-H)

Reaction scheme: $R\!-\!\boxed{F_n}$ (3- 6 equiv) + Arene-H (**1 equiv**) → conditions: *fac*-Ir(ppy)$_3$ 0.25 mol%, DIPEA 1.2- 6.0 equiv, KHCO$_3$ 1.2 equiv, Blue LEDs, Ar[a], 0- 45 °C, MeCN (0.1 M) → $R\!-\!\boxed{F_{n-1}}$ Arene + HF*Base

18a, 67%

19a, 57%
from 3-Cl

20a, 87%
from 1-Br

21a, 52%
from 1,4-dibromo

22a, 66%

23a, 48%

[a] The reaction was degassed by bubbling argon for 10 min.