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Dual C−F, C−H Functionalization via Photocatalysis: Access to Multifluorinated Biaryls

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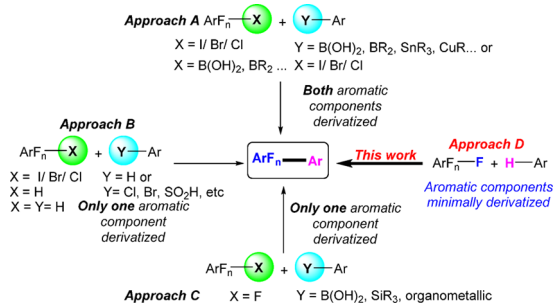
Supporting Information

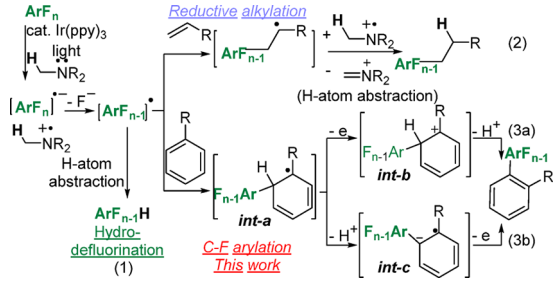
ABSTRACT: Multifluorinated biaryls are challenging to synthesize and yet are an important class of molecules. Because of the difficulty associated with selective fluorination, this class of molecules represent a formidable synthetic challenge. An alternative approach to selective fluorination of biaryls is to couple an arene that already possesses C−F bonds in the desired location. This strategy has been regularly utilized and relies heavily on traditional cross-coupling strategies that employ organometallics and halides (or pseudohalides) in order to achieve the coupling. Herein we report conditions for the photocatalytic coupling via 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 containing between two and five C_{aryl}−F bonds via the synergistic use of photocatalysis and S_NAr chemistry.

Fluorinated biaryls are an important class of molecules with many examples in drugs,[1a,b] agrochemicals,[1c,d] functional materials such as liquid crystals,[1e,f] organic light-emitting diodes (OLEDs),[1g,h] water-splitting sensitizers,[1i] and electron transport materials.[1j,k] While cross-coupling methods have made biaryls generally accessible, currently far fewer methods exist that lead to the important class of partially fluorinated biaryls. The synthesis of fluorinated biaryls has been approached from several directions. One method is traditional cross-coupling of a fluorine-containing arene possessing either a halogen or an organometallic group with a partner substituted with a complementary reactive group (approach A, Scheme 1).[2] Alternatively, methods characterized by the use of less-functionalized molecules (i.e., H[3] on one or both partners) have also been developed (approach B).[4] Typically, activated multifluorinated arenes are derived from the C−F bond in one to three steps, i.e., C−F to C−H[5a] to C−halogen[5b,c] to C−organometallic.[5d,e] Consequently, efforts have been made in the area direct C_{Ar}−F functionalization,[6] which have been focused primarily on overcoming the difficulties associated with C−F functionalization (approach C). Among these challenges, C−F bonds tend to be both kinetically and thermodynamically robust, and they often form strong metal−fluoride bonds, resulting in

Scheme 1. Strategies To Access Fluorinated Biaryls



Scheme 2. Photocatalytic C−F Functionalization



stable catalytic intermediates and leading to sluggish catalyst turnover. If all of 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 bond of the fluoroarene and a C−H bond of 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.[7] In 2014 we showed that catalytic amounts of *fac*-Ir(ppy)$_3$ in the presence of light and an amine reductant result in highly efficient hydrodefluorination (HDF) (eq 1 in Scheme 2) with excellent regioselectivity and functional group tolerance,[8] suggesting that it might provide a novel route for direct C−F functionalization. Indeed, in 2015 we showed that the same reactive intermediate could be intercepted with an alkene (eq 2), which then underwent a subsequent reduction of

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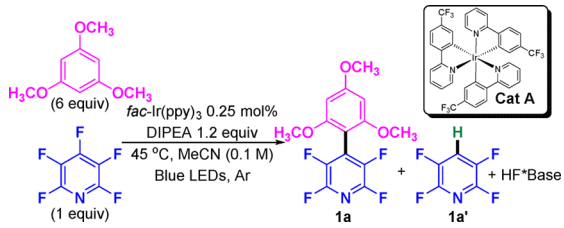
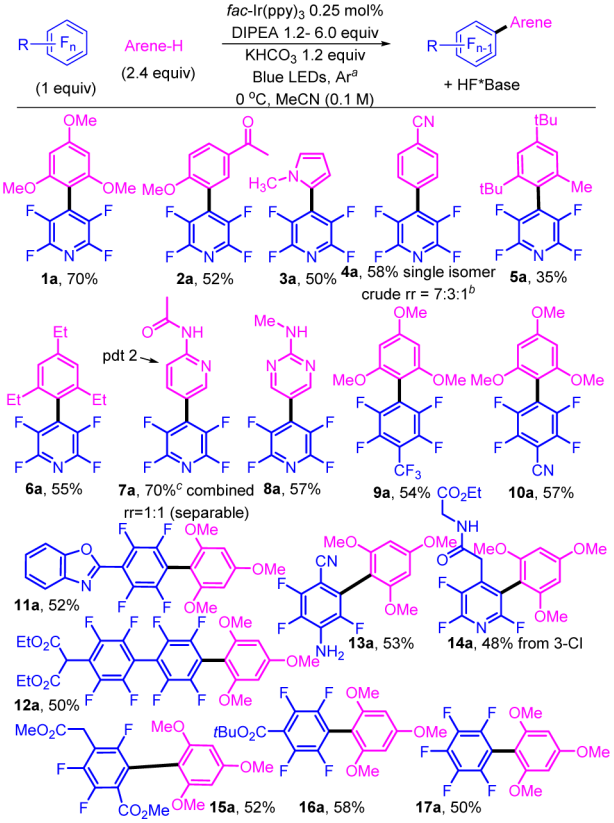
Table 1. Optimization of the Reaction Conditions



entry	modification	1a:1a′	conv. 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_3N instead of DIPEA	4:1	47/66	5/19[b]
7	without DIPEA	na	<5	2/17
8	DIPEA (0.5 equiv)	6:1	22/79	2/17[b]
9	DIPEA (3.0 equiv)	3:1	40/61	2/17[b]
10	iPr_2Nn-hept instead of DIPEA	< 5%		21
11	arene−H (1.2 equiv)	2:1	57	17[b]
12	arene−H (3.0 equiv)	3.5:1	66	17[b]
13	0 °C, arene−H (3.0 equiv)	6:1	75	19[b]
14	0 °C, arene−H (2.4 equiv), DIPEA (0.4 equiv), $KHCO_3$ (1.2 equiv)	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	nd[d]	24
17	in air	na	11	19
18	in the dark	na	nd	19

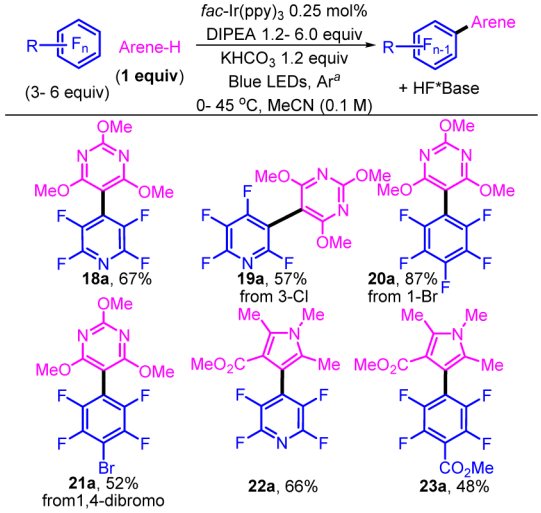
[a]Determined by ^{19}F NMR analysis. [b]Reaction complete. [c]<20% conv. to undesired products. [d]Not detected.

Table 2. Reaction Scope with Limiting Perfluoroarene



[a]The reaction mixture was degassed by bubbling with Ar for 10 min. [b]The yield is for the isomer shown. The minor regioisomers (meta and ortho) were not separated, assigned, or counted for yield. [c]The yield is the total for the separated isomers.

Table 3. Reaction Scope with Limiting Arene−H



[a]The reaction mixture was degassed by bubbling with Ar for 10 min.

the presumed alkyl radical.[9] We were curious whether the incipient radical formed as a result of C−C bond formation could be oxidized rather than reduced, leading to an alkene.[9] In view of 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 (eq 3).

From the outset,[10] several obvious challenges associated with the desired reaction were apparent (eq 3): the need to achieve an oxidation of ***int-a*** under reducing conditions,[11] the regioselectivity of the C−C coupling event with respect to the Ar−H bond, and competing HDF. Oxidation of ***int-a*** could occur prior to deprotonation (eq 3a) or afterward (eq 3b). The dominant path may depend the natures of both arene partners. Nonetheless, we began our investigation with conditions that had facilitated HDF[8] using pentafluoropyridine with the addition of 6 equiv of trimethoxybenzene, which removed the possibility of regioisomers (Table 1, entry 1). We were pleased to see that the desired C−C-coupled product was indeed formed as the major product in reasonable yield along with a significant amount of the HDF product. By optimization we hoped to increase the yield and simultaneously decrease the amount 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);[12] while a subtle improvement in product ratio was observed, the reaction was noticeably slower. Next, we evaluated both the structure of the amine[13] and its loading as reaction parameters (entries 6−10). While Et_3N worked reasonably well, it led to byproducts stemming from N-perfluoarylation,[14] which were substantially decreased by the use of more sterically cumbersome diisopropylethylamine (DIPEA). Varying the amount of amine revealed two key features (entries 8−10). First, both a reduction and an oxidation occur in the same reaction, which begs the question of whether the amine might just serve as an initiator. While the amine does demonstrate

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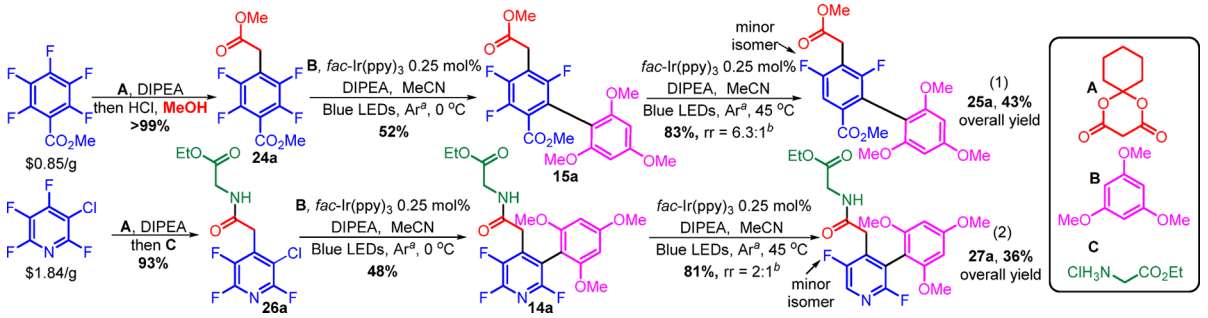
Scheme 3. Utility of C−F Functionalization To Access Complex Multifluorinated Biaryls



[a]The reaction mixture was degassed by bubbling with Ar for 10 min. [b]The yield is for the isolated product. The regioisomeric ratio (rr) was determined by ^{1}H NMR analysis of the isolated product.

superstoichiometric activity (entry 8), the reaction becomes inefficient. Second, too much amine results in increased amounts of the HDF product **1a′**. We previously showed that the use of less-soluble amines could retard the rate of photocatalytic reduction.[15] 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 reaction. Next, we looked at the effect of reducing the amount of trimethoxybenzene in hopes that we could approach near-stoichiometric ratios (entries 11 and 12). As expected, diminishing the amount of arene−H led to increased amounts of **1a′**. Next, we investigated the effect of temperature. We were pleased to see that dropping the temperature led to an improved **1a**:**1a′** ratio (entry 12 vs 13). Finally, we suspected that the amine plays two roles: as a reductant that initiates the C−F fragmentation and as a base to scavenge the HF formed in the reaction. In order to address this, we added $KHCO_3$ (entry 14), which allowed us to simultaneously lower the loadings of both the amine and trimethoxybenzene and achieve the best **1a**:**1a′** ratio. Finally, controls were run (entries 15−18) and indicated the necessity of light, catalyst, and amine as well as the sensitivity toward air.

Using the conditions from Table 1, 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 and a variety of perfluoroarenes (**1a**, **9a**−**17a**) as well as with 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.[16] Interestingly, we observed anti-Minisci selectivity (**7a** and **8a**), likely because the 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 over that of the fluorines, allowing access to complementary regioisomers. Comparison of **15a** and **16a** demonstrates that both the 2- and 4-positions of the perfluorobenzoate system are accessible.[8,9,17] Hexafluorobenzene, devoid of electron-withdrawing functional groups, which would facilitate reduction, also undergoes arylation (**17a**). In general, the scope is broad in terms of the 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 making it the limiting reagent and using excess perfluoroarene (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**). Tetrasubstituted pyrroles also coupled with the expected C−F selectivity (**22a** and **23a**) to give biologically relevant pentasubstituted pyrroles (e.g., see Lipitor), suggesting that it may be possible to use this method to accomplish late-stage modifications of biologically active molecules. **19a**−**21a**, in which substitution of the C−Cl or C−Br bond occurs, indicate a halogen fragmentation pattern consistent with that of radical anion fragmentation observed by Bunnett[18] and Rossi[19] (i.e., I > Br > Cl > F). This selectivity is both an inherent limitation and an opportunity to build complementary regioisomers. Importantly, use of the fluorinated arene in excess protects the bromine of product **21a** from subsequent reduction of the C−Br bond, providing the opportunity for further elaboration by other methods. In general, the biggest limitation of the method is the use of arene−H compounds 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.[20] Specifically, it starts with readily available perfluorinated arenes that have all of the difficult-to-install fluorines at the desired positions. The challenge then becomes selective functionalization of 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 very difficult to synthesize by any other method, thus allowing access to new fluorinated chemical space (Scheme 3). Addition of a Meldrum's acid derivative followed by decomposition in the presence of a nucleophile gave a near-quantitative yields of the products of α-perfluoroarylation (**24a** and **26a**).[21] Photocatalytic arylation then desymmetrized the molecules (**15a** and **14a**). The total fluorine content could 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 the formation of regioisomers. On radical anions of benzene systems, halogen fragmentation is preferred at the

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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 obtain the minor regioisomer of **27a**. We previously observed similar switches of selectivity with NHAc perfluoroarenes.[8] Understanding the subtle and potentially 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 the 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 to 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 the functional group tolerance of the method. From a mechanistic perspective, we have shown that the perfluoroaryl radical is capable of adding to π 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 investigations of new fluorinated chemical space and therefore enable a number of research efforts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13450.

Experimental procedures and additional data (PDF)

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Notes

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

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(10) The first step of the reaction is transfer of an electron to the perfluoroarene. Reductive and oxidative quenching are nearly equally endothermic (0.17−0.16 V vs SCE) in the case of pentafluoropyridine, DIPEA, and Ir(ppy)$_3$. Extrusion of F^- is likely an irreversible step that could drive the reaction. With other less-reducible perfluoroarenes, reductive quenching is likely operative. See ref 9 for more discussion.

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

(12) More photocatalysts were screened but none gave better results (see the Supporting Information for details).

(13) More amines were screened but none gave better results than DIPEA (see the Supporting Information for details).

(14) The ^{19}F NMR shifts are consistent with those of 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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