Visible Light Photocatalysis for the Generation and Use of Reactive Azolyl and Polyfluoroaryl Intermediates
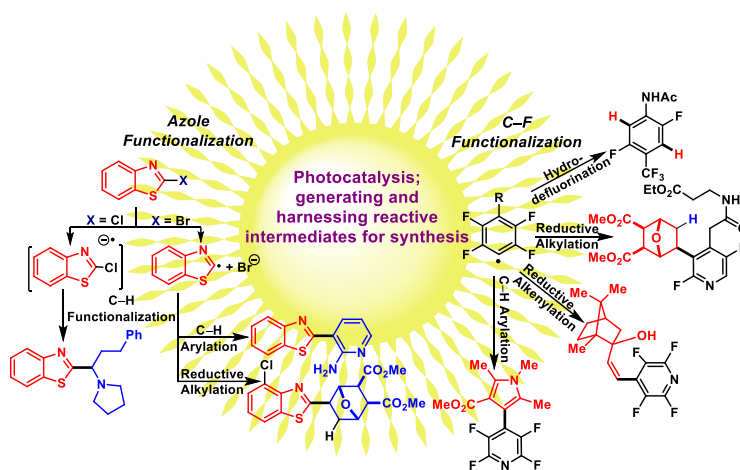
Amandeep Arora, and Jimmie D. Weaver*

Department of Chemistry, Oklahoma State University, Stillwater, OK 74078.

Conspectus

Photocatalysis offers several mechanistically unique pathways that are not rivaled by mainstream catalysis. Primarily, the ability to convert photochemical energy into single electron oxidation and reduction events provides a new dimension for chemists to consider when choosing how to activate a molecule or approach a complex synthesis. Since most organic molecules do not absorb light in the visible region, they are impervious to direct visible light photochemistry which provides an opportunity for photocatalysis in which a visible light absorbing compound can serve as a mediator. In this review, we discuss the consequences of catalyst mediated, photoinduced electron transfer to several classes of reducible arenes. While the bulk of the work discussed within this review utilizes iridium-based photocatalysts, in principle the chemistry is not limited to this class of photocatalyst and the principles should be more general. Instead, this account focuses largely on the consequences of single electron transfer to poly- and perfluorinated arenes and 2-halo azoles. Electron transfer converts these stable molecules into reactive intermediates whose behavior often depends entirely on the identity of the halogen which undergoes substitution. The result is both diverse chemistry and an alternative way of thinking about the chemical reactivity of these motifs. Specifically, we discuss our efforts and others to develop strategies for the generation of radicals or radical anions from perfluoroarenes and azoles and the behavior of these intermediates as implied by reactions in which they participate. The divergent pathway is illustrated by 2-bromoazoles which yield azolyl radicals and can be utilized for addition to pi-bonds while use of the 2-chloroazoles substrate leads to an entirely different reaction profile. Under the right reaction conditions, the reactive and transient intermediates are useful coupling partners and often provide unrivaled access to new chemical space. The odd electron species can form challenging bonds with minimal prefunctionalization of the coupling partner. For instance, some of the intermediates can be utilized for C–H functionalizations to selectively make crowded amines or to synthesize biarenes substituted at every ortho position. While photocatalysis is not the only manner of accomplishing electron transfer, the catalytic generation of the reactive species in which the concentration of the transient odd electron species is kept low, provides a synthetic handle that can be used to improve reaction outcomes. This is elegantly demonstrated in a number of examples in which redox sensitive groups, located on

substrates, survive the reaction. In addition, the underlying basic concepts associated with radical anion fragmentation are reviewed and provide the backdrop for discussion throughout the account.

1. INTRODUCTION

A general aim of catalysis is to reduce energy barriers and convert stable molecules into reactive intermediates capable of undergoing bond reorganization. Photocatalysis can activate molecules through several mechanistically distinct pathways that complement the field of catalysis. As such, synthetic photocatalysis has emerged as a powerful way of creating new bonds that were not feasible with existing techniques. One of the foremost questions that arises in photoredox catalysis is whether an electron can be transferred to a substrate. To some extent, this can be answered by assessing the redox potentials of the substrate and the possible electron donors, though other phenomena can also influence the feasibility of electron transfer. A secondary and more specific question one can ask is, if an electron is transferred, how does the resulting radical anion behave? It could fragment rapidly to generate a radical. If not, it could behave as a radical or an anion. Alternatively, bond formation could precede fragmentation altogether. In an attempt to answer these types of questions, we began to systematically investigate both the nature of the reactive intermediates that could be generated by photocatalytic electron transfer and conditions necessary for bond formation. We hoped that systematic study of a few model substrates would provide general and thorough understandings that when strategically applied would allow rapid and facile syntheses. Herein, we will discuss some of the fundamental phenomena of electron transfer that surround photocatalytic C_{aryl}–F and azole–X functionalizations. Additionally, the intermediates are compared to those proposed by others.

2. PERFLUOROARYL RADICALS

2.1. Radical Anion Fragmentation

Although perfluoroarenes are kinetically and thermodynamically robust, having short bonds of herculean strength (ca. 1.35 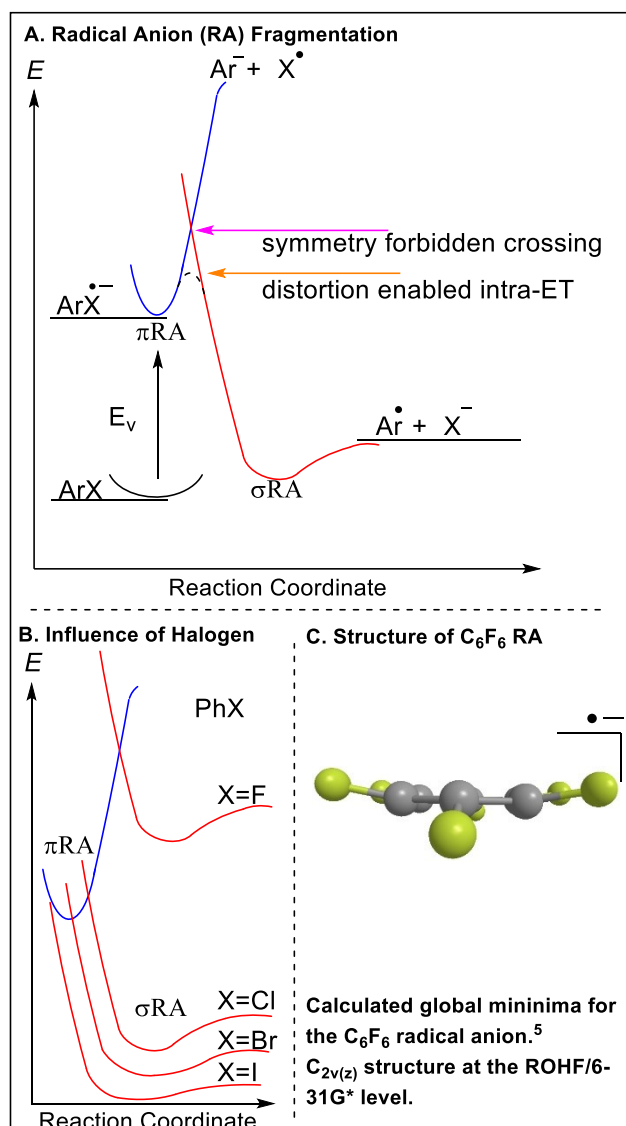Å, 145 kcal/mol for C–F of C_6F_6)[1] the relatively low lying LUMOs are a target for exploitation. For instance, the reduction potential is significantly more negative for C_6H_6 ($E_{1/2 \ red}$=-3.42 vs. SCE) than C_6F_6 ($E_{1/2 \ red}$=-2.81 vs. SCE). In absolute terms, perfluoroarenes are not easily reduced because electron transfer from common reductants would be endothermic. A brief review of radical anion fragmentation is in order.[2-4]

Often the π* orbital is the LUMO to which an electron can be added (Scheme 1A). However, for planar π-type radical anions, monomolecular fragmentation is symmetry forbidden.[2] For fragmentation to occur, a symmetry forbidden dissociative electron transfer to a σ* orbital must occur. Fortunately, the symmetry restriction is lifted by distortion of the radical anion from planarity. The barrier to intramolecular-ET correlates to the intersection of the π* and σ* orbitals.

For unstabilized phenyl, a more negative reduction potential corresponds to an increase in the energy of the π* energy level, i.e. the blue line is raised in energy (Scheme 1B). This results in a decreased barrier to intramolecular electron transfer, which leads to faster halogen extrusion.[4] The influence of the leaving group is seen as sequentially larger halogens are fragmented, the barrier to intra-ET becomes smaller until it is nonexistent. This is a consequence of decreasing σ* orbital energy.

Polyfluorinated arenes are peculiar in regards to the rate of fragmentation. Namely, the LUMO (π* orbital) decreases in energy as the degree of fluorination increases, and yet the rate of fragmentation increases. For instance, a difference of six orders of magnitude is seen in the reductive C–F fragmentation of $C_6F_5CO_2^-$ (k_f=1.2 x 10^9 S^{-1}) and m-$FC_6H_4CO_2^-$ (k_f < 3 x 10^3 S^{-1}).[1]

Scheme 1. Energy Diagram for RA fragmentation and Hexafluorobenzene RA Structure

2

A. Radical Anion (RA) Fragmentation

E

$Ar^{-} + X^{\bullet}$

symmetry forbidden crossing

distortion enabled intra-ET

$ArX^{\bullet -}$

πRA

E_v

$Ar^{\bullet} + X^{-}$

ArX

σRA

Reaction Coordinate

B. Influence of Halogen

E

PhX

X=F

πRA

σRA X=Cl

X=Br

X=I

Reaction Coordinate

C. Structure of C_6F_6 RA

$\bullet -$

Calculated global minima for the C_6F_6 radical anion.[5] $C_{2v(z)}$ structure at the ROHF/6-31G* level.

This acceleration is further perplexing in light of the fact that the C–F bonds strengthen with the degree of fluorination. For instance, the C–F BDE for fluorobenzene is 117 kcal/mol while hexafluorobenzene is 145 kcal/mol.[1]
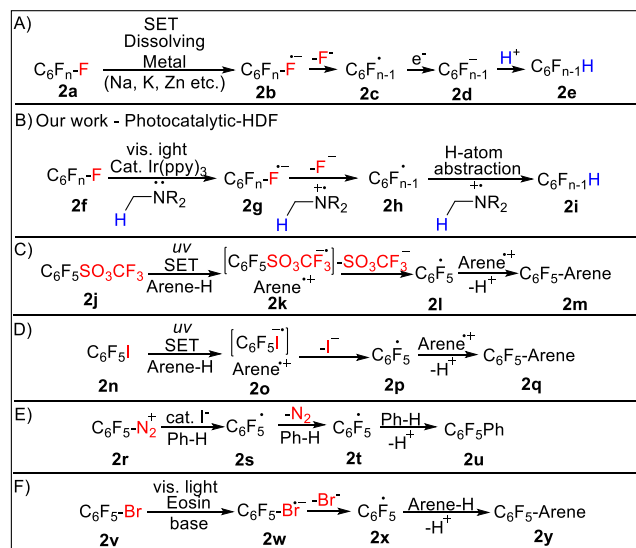
Acceleration of the fragmentation is attributable to the exaggerated nonplanarity of the radical anion[5] (Scheme 1C). In fact, in the case of highly fluorinated arenes there is significant orbital mixing of the π* and σ* orbitals. The degree of contribution to the MO by the C–F σ* orbitals is dependent upon the number and location of the fluorine atoms on the arene. Fragmentation is expected to occur at the site of the largest σ*-contribution. For a given arene, both the rate and regioselectivity of the fragmentation event can be predicted by the energy difference between the $\prod$ and $\sum$* states, in which $\prod$ represents the π-state of the planar radical anion and $\sum$* represents the SOMO located on the C–F σ* orbitals.[1]

2.2 Access to the Perfluoroaryl Radical

Experimentally, the most extensively studied reductive fragmentation of perfluoroarenes has been accomplished via solvated electrons with dissolving metals (Scheme 2A).[1,6-14] The generally accepted mechanism in this reaction is electron transfer to give the metastable nonplanar radical anion **2b**. **2b** undergoes unimolecular fragmentation to generate a σ-radical **2c**. The radical is easily reduced[15] to the perfluoroaryl anion **2d**, which undergoes protonation from the medium to give the hydrodefluorination (HDF) product. In 2014, we showed[16] that visible light and catalytic Ir(ppy)₃, (*fac*-tris-[2-phenylpyridinato-C^2, N] iridium (III)) could also accomplish the HDF of perfluoroarenes (2B). In stark contrast, when photocatalysis is used to facilitate the electron transfer no second reduction event is observed (i.e., **2c** to **2d**), providing an opportunity to access the perfluoroaryl radical. There was no evidence of protonation of a perfluoroaryl anion and deuterium labeling showed that the amine was the source of the hydrogen atom. These results suggest the perfluoroaryl radical is the bond-forming intermediate. Several other sources of perfluoroaryl radicals have been investigated, including ultraviolet light induced electron transfer from perfluorophenyl-perfluoroalkylsulfonates (2C)[17] and iodides (2D),[18] iodide induced decomposition of perfluoroaryl diazoniums (2E),[19] and recently the photocatalytic fragmentation of perfluoroaryl bromides[20] (2F).
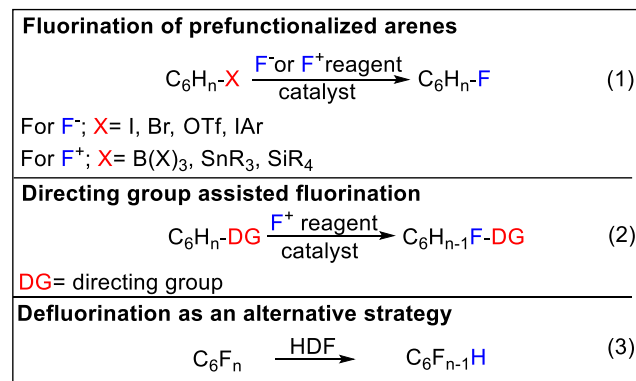
Scheme 2. Synthetic Strategies to Access the Perfluoroaryl Radical

3

2.3 Photocatalytic Hydrodefluorination (HDF)

Partially fluorinated arenes are important structural motifs[21,22] in pharmaceutical, agrochemical, and industrially relevant molecules. Despite the remarkable ability of fluorine to dramatically improve the properties of a molecule, no natural fluoroaromatic sources have yet been identified.**[23]** Thus, synthesis of arylfluorides is necessary. While it is not the aim of this account

Scheme 3. Fluorination vs. defluorination strategies to multifluorinated arenes

Fluorination of prefunctionalized arenes

$$C_6H_n\text{-}X \xrightarrow[\text{catalyst}]{F^- \text{ or } F^+ \text{reagent}} C_6H_n\text{-}F \qquad (1)$$

For F^-; X= I, Br, OTf, IAr
For F^+; X= $B(X)_3$, SnR_3, SiR_4

Directing group assisted fluorination

$$C_6H_n\text{-}DG \xrightarrow[\text{catalyst}]{F^+ \text{ reagent}} C_6H_{n-1}F\text{-}DG \qquad (2)$$

DG= directing group

Defluorination as an alternative strategy

$$C_6F_n \xrightarrow{\text{HDF}} C_6F_{n-1}H \qquad (3)$$

to discuss the strategies to realize regioselective fluorination, typically they rely on the substitution of prefunctionalized arylhalides, organometallics, or directed C–H fluorination (Scheme 3). However, in the case of multiple fluorines on one aryl ring, the installation of the fluorines becomes a daunting synthetic challenge and does little to provide greater access to the motif.
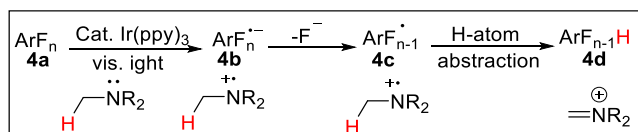
In contrast, perfluorinated arenes, in which all hydrogens of the parent arenes have been replaced with fluorines, are actually simpler synthetic targets since the selectivity issue has been removed. In fact, a significant number of perfluoro(hetero)arenes are commercially available and are relatively inexpensive. An attractive alternative approach to partially fluorinated arenes is to start with fully fluorinated arenes in which the desired C–F bonds are already in place. The focus then shifts from making C–F bonds to selective functionalization of C–F bonds either by (HDF) or to other selective C–F functionalizations to give more complex fluorinated molecules.[24]

The potential advantages of C–F functionalization strategies are significant and have also been championed by others.[25-29] However, in practice there are a number of obstacles that make it a challenging transformation, and has arguably prevented its widespread adoption. First, the shortness of the C–F bond gives it a degree of kinetic robustness against insertion processes. Secondly, if a catalyst does successfully insert into the bond, it often makes thermodynamically strong metal–F bonds, resulting in catalytically sluggish intermediates. A third issue faced by C–F functionalization is that of regioselectivity, since perfluoroarenes contain multiple C–F bonds of nearly equal length and strength.
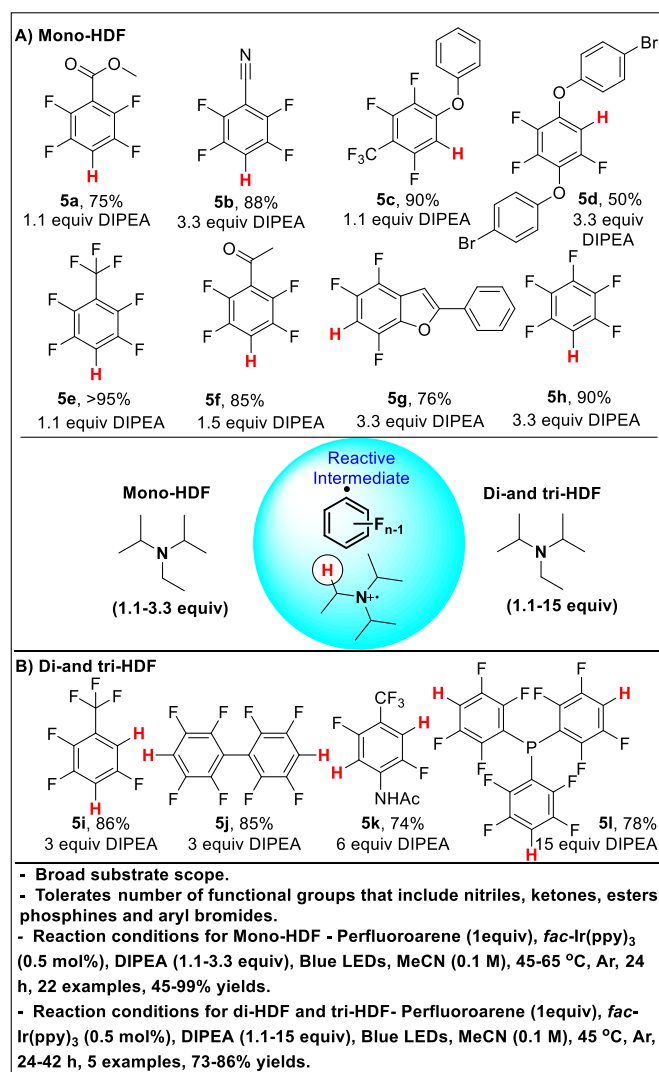
Photocatalytic activation circumvents these issues. A detailed assessment of redox potentials suggests that the photocatalytic cycle could take place via either an oxidative or a reductive quenching pathway, and likely varies as the substrate potentials change. Ultimately, a visible light photon is absorbed by the photocatalyst which in turn converts this energy into an electron transfer. In analogy to the dissolving metal reductions, it is believed that an electron is added to the low lying LUMO of perfluoroarene, resulting in an unstable radical anion (**4b**),[30-32] which undergoes fluoride extrusion to generate a perfluoroaryl radical (**4c**).[32] In the case of photocatalytic HDF, the radical undergoes HAT from the amine or its radical cation, to give the reduced product (**4d**). The amine serves as both the reductant and the H-atom source.

Scheme 4. Proposed Mechanism for the Photocatalytic-HDF

The use of *fac*-Ir(ppy)$_3$ to accomplish HDF effectively circumvents a number of problems that have plagued the HDF community. Namely, *fac*-Ir(ppy)$_3$ is an 18-electron complex with no open coordination site, which decreases the chances of problematic iridium–F bond formation. Fragmentation regioselectivity relies on electronic control by the substrate and has proven to be excellent in most cases.

Scheme 5. A) Scope of mono-HDF. B) Di- and tri-HDF

The scope of the reaction is remarkably broad (Scheme 5) and tolerates many functional groups that would not be expected to survive dissolving metal reductions, highlighting the utility of the method. Remote aryl bromides

remain intact, demonstrating selective reduction of the arene with a more positive reduction potential. Subsequent reduction and fragmentation events can be induced, and sufficient differences in the rates of the mono-, di- or tri-HDF exist such that the products can be selectively accessed.
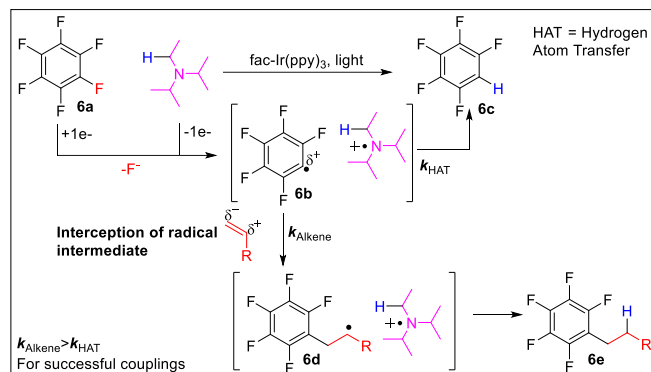
2.4 Photocatalytic C–F Alkylation

Others have recognized the potential of C–F functionalization, and several methodologies have been developed for C–F alkylation. Methods include imine directed Pt-catalyzed addition of zincates,[33] nucleophilic addition of magnesiates,[34] and C–F substitution of phosphonium ylides.[35] Having provided functional access to the perfluoroaryl radical via photocatalysis, we were curious to learn if it could be exploited for C–F alkylation reactions, and to benchmark the reactivity of the perfluoroaryl radical. The use of catalytically generated radicals for C–C bond formation is attractive, not only because they have relatively small energy barriers preventing addition to π-bonds,[36] but also because the energy barriers correlate strongly with the thermodynamics of addition. Given the expected exothermicity, the implication is that bond formation should be facile and we hoped to react unactivated and sterically congested π-bonds. Little was known about the nucleo-/electrophilicity of the radical and the scope of the reaction provides some insight. Because an amine is needed as an electron source, competitive HDF was expected to remain an issue common to all photocatalytic C–F functionalizations.

For the development of the photocatalytic C–F alkylation[37] it was necessary that the perfluoroaryl radical (vide supra) be intercepted with an alkene faster than HAT. Though the structure of the amine has the potential to affect the relative rates of the different processes involved, we found the simplest strategy to increase the yield of the desired product was to increase the alkene concentration in the reaction. Addition of the perfluoroaryl radical to an alkene generates an sp^3–hybridized alkyl radical and was expected to be exothermic (Scheme 6). Given alkenes' ubiquity, this was a satisfactory solution.

5

Furthermore, the majority of the alkene could be recovered unchanged from the reaction mixture.
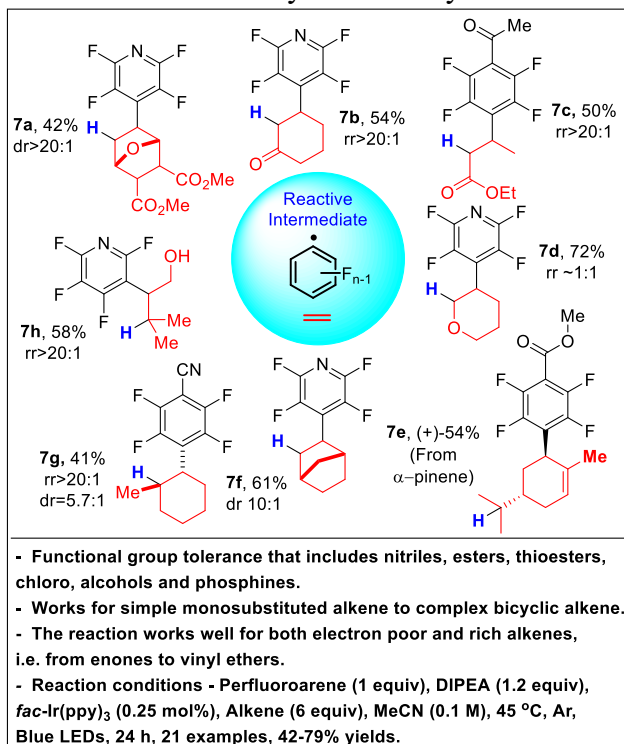
Scheme 6. Possible mechanism of C–F alkylation

The reaction works well for both electron poor and rich alkenes (Scheme 7). The radical adds unselectively to both termini of electron rich alkenes but adds with high selectivity to electron deficient alkenes. These results evidence a highly reactive and electrophilic perfluoroaryl radical. This results in an early transition state with neutral or electron rich alkenes that is insensitive to the electronics, leading to unselective addition. However, in the case of the electron poor alkenes, the rate is retarded and the transition state is later, resulting in a more selective addition.

The addition takes place selectively at the less substituted carbon. If both termini are similarly substituted, the addition is not selective. The reaction shows remarkable functional group tolerance. Stereochemically dense alkenes undergo facile addition and highlight the ability of alkenes to rapidly increase the structural complexity of the perfluoroarene.

Scheme 7. Photocatalytic C–F alkylation

- Functional group tolerance that includes nitriles, esters, thioesters, chloro, alcohols and phosphines.
- Works for simple monosubstituted alkene to complex bicyclic alkene.
- The reaction works well for both electron poor and electron rich alkenes, i.e. from enones to vinyl ethers.
- Reaction conditions - Perfluoroarene (1 equiv), DIPEA (1.2 equiv), *fac*-Ir(ppy)$_3$ (0.25 mol%), Alkene (6 equiv), MeCN (0.1 M), 45 °C, Ar, Blue LEDs, 24 h, 21 examples, 42-79% yields.

Fluorination serves to activate the ring toward reduction by lowering the LUMO (C_6H_6 $E_{1/2red}$ = -3.42 compared to C_6F_6 $E_{1/2red}$ = -2.81 vs. SCE).[37] Remarkably, even as the fluorine content is utilized for functionalization (not HDF), photocatalytic C–F functionalization remains viable, though noticeably slower. It is not clear whether the sluggishness is because of difficulty forming the radical anion or its decomposition. When on the same arene, the C–Cl undergoes preferential fragmentation to a C–F and serves as a convenient way to synthesize isomers (Scheme 8A).
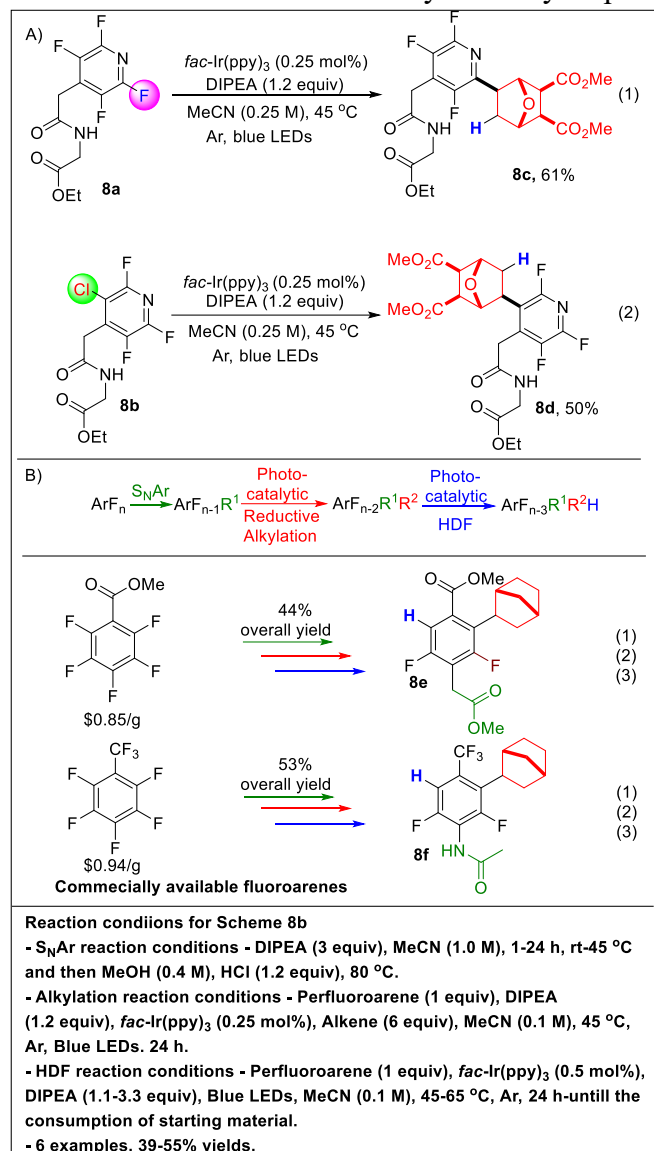
The utility of the method was demonstrated using inexpensive perfluoroarenes which were subjected to a 3-step sequence (8B, **8e-8f**). The inexpensive starting material, brevity, and multiple opportunities to diversify highlight the utility of the polyfluoroaryl radical for discovery chemistry.

2.5. Photocatalytic Arylation of Perfluoroarenes

Considering the importance of partially fluorinated biarenes, a number of groups have developed different strategies to synthesize fluorinated biarenes.[20, 38-43] We postulated that the extreme reactivity of the perfluoroaryl radical

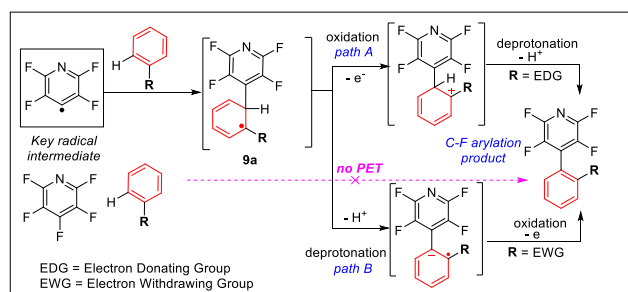could be exploited to streamline synthesis of fluorinated biarenes via dual C–F, C–H functionalization.

Scheme 8. Perfluoroarenes as a synthetic lynchpin

Reaction condiions for Scheme 8b
- S$_N$Ar reaction conditions - DIPEA (3 equiv), MeCN (1.0 M), 1-24 h, rt-45 °C and then MeOH (0.4 M), HCl (1.2 equiv), 80 °C.
- Alkylation reaction conditions - Perfluoroarene (1 equiv), DIPEA (1.2 equiv), fac-Ir(ppy)$_3$ (0.25 mol%), Alkene (6 equiv), MeCN (0.1 M), 45 °C, Ar, Blue LEDs. 24 h.
- HDF reaction conditions - Perfluoroarene (1 equiv), fac-Ir(ppy)$_3$ (0.5 mol%), DIPEA (1.1-3.3 equiv), Blue LEDs, MeCN (0.1 M), 45-65 °C, Ar, 24 h-untill the consumption of starting material.
- 6 examples, 39-55% yields.

Perfluoroaryl radicals are reactive intermediates which are capable of addition to the π-bonds of even tri-substituted alkenes.[37] In this regard, arenes can also be viewed as a π-nucleophile which can undergo addition to the perfluoroaryl radical.[20,44] Again, several insights concerning the generation, nature, and use of the perfluoroaryl radical can be gained by evaluation of the reaction of arene–Hs with this radical.[44] Addition of a perfluoroaryl radical to the arene results in a cyclohexadienyl radical (**9a**, Scheme 9). While there are a number ways that **9a** might be utilized, the simplest would be to undergo a net oxidation event to regain aromaticity. The exact

path to oxidation of **9a** is likely substrate dependent. With electron rich arene–Hs, *path A* becomes more likely, whereas, with electron poor arene–Hs deprotonation likely precedes oxidation, *path B*. A photoinduced electron transfer (PET) mechanism[18] from the C–H arene to the perfluoroarene can be eliminated based on the transparency of the arenes (even mixed), by evaluation of the substrate scope, which includes electron deficient arenes, and from the observation of significant quantities (in the unoptimized reaction) of the HDF product. These observations are not consistent with a PET mechanism.[18]
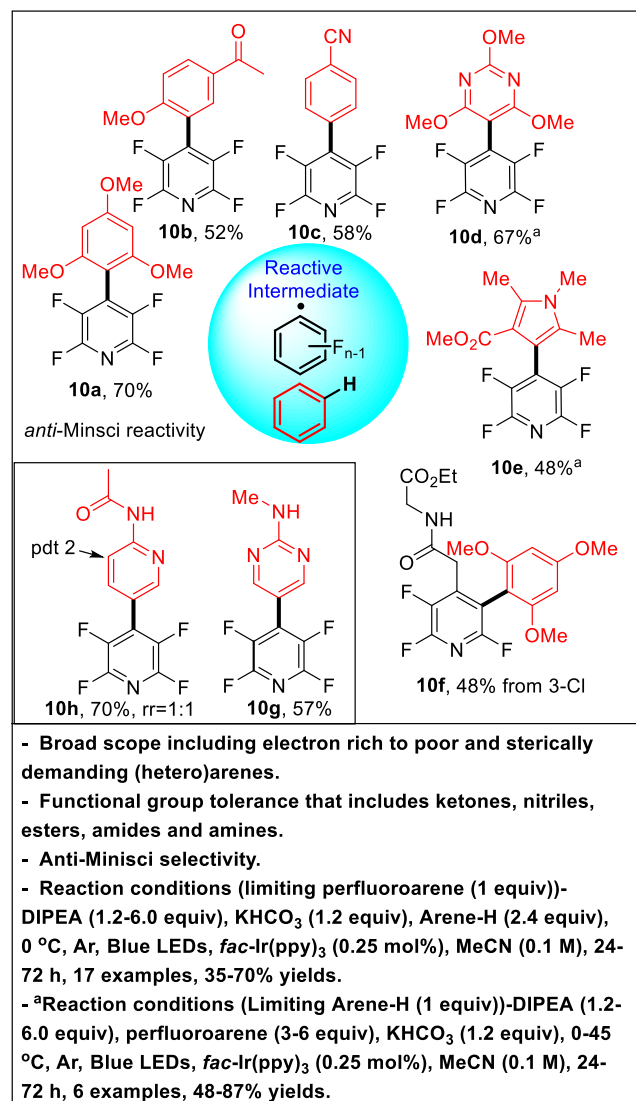
Scheme 9. Possible mechanism of C–F arylation

Ultimately, in both potential mechanisms a proton and an electron are generated as a result of aromatization. As a result, we found that the amine concentration could be lowered, thereby minimizing competitive HDF. Investigation revealed that sub-stoichiometric amounts of amine along with stoichiometric amounts of KHCO$_3$ were optimal for production of the multifluorinated biarene (Scheme 10).
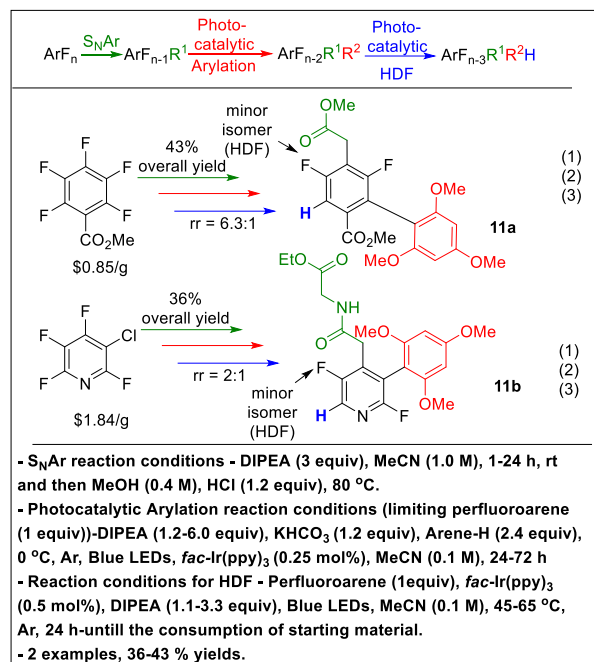
The scope of the reaction is broad, and the ability of the perfluoroaryl radical to make highly hindered bonds is remarkable. The reaction works with both electron rich and electron poor arene–Hs, though in general it was faster with electron rich arenes. Interestingly, anti-Minisci selectivity was observed (**10g** and **10f**) and is likely a result of both the nonacidic conditions typical of the Minisci-reaction, and the electrophilic nature of the perfluoroaryl radical.

Scheme 10. Photocatalytic C–F arylation

Scheme 11. Photocatalytic access to diversely substituted multifluorinated biarenes

Conditions were also optimized such that the arene–H can be the limiting reagent, adding to the versatility of the method. The synthetic potential of C–F functionalization was demonstrated by subjecting commercially available perfluoroarenes to a simple sequence of S_NAr,[45] photocatalytic-arylation,[44] and finally photocatalytic-HDF[16] which yielded complex multifluorinated biarenes (Scheme 11).
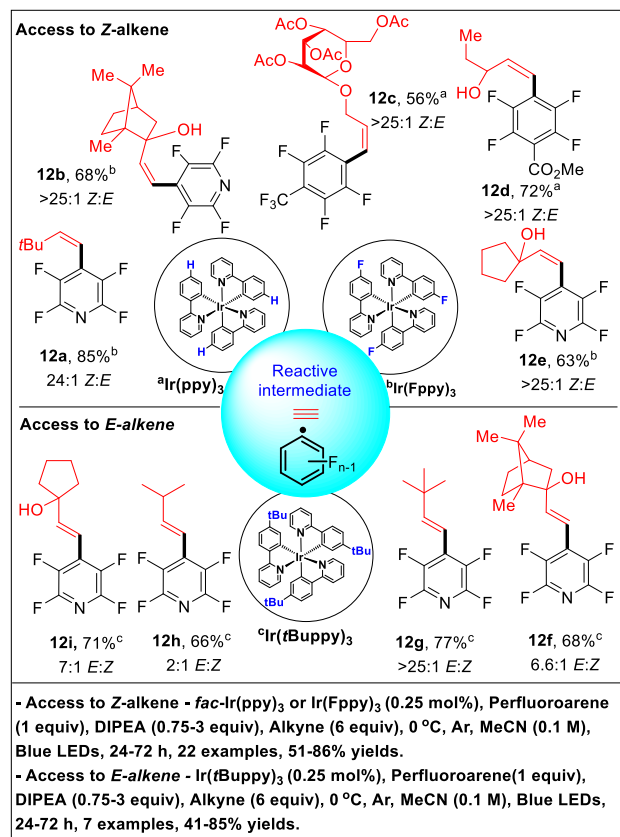
2.6. Photocatalytic Alkenylation of Perfluoroarenes

In addition to alkenes and arenes, the perfluoroaryl radical is also capable of undergoing addition to π–bonds of alkynes.[46] Given that radical addition to alkenes is faster than the related alkynes,[36] it is somewhat surprising that the perfluoroaryl radical does not undergo subsequent addition to the generated alkene. It should be noted that in contrast to neutral and nucleophilic radicals, highly electrophilic radical addition to alkynes has not been studied in depth,[36] but appears to be sufficiently fast to outcompete the corresponding addition to the alkene product. The slow rate for the subsequent perfluoroaryl radical addition to the bulky styrenoid product may be a consequence of the non-coplanar conformer it assumes with the alkene. Consequently, any incipient radical formed from the product alkene would not benefit from orbital overlap with the aryl ring. Alternatively, it may simply be a consequence of poor electronic matching. While an important aspect of this work pertains to the involvement of the catalyst structure in the outcome of the alkene geometry which conveniently provides access to both isomers, it is beyond the scope of this review.

Scheme 12. Photocatalytic *Z*- or *E*-alkenylation

Access to Z-alkene

12b, 68%[b]
>25:1 Z:E

12c, 56%[a]
>25:1 Z:E

12d, 72%[a]
>25:1 Z:E

12a, 85%[b]
24:1 Z:E

12e, 63%[b]
>25:1 Z:E

Reactive intermediate

[a]**Ir(ppy)₃** [b]**Ir(Fppy)₃**

Access to E-alkene

12i, 71%[c]
7:1 E:Z

12h, 66%[c]
2:1 E:Z

[c]**Ir(tBuppy)₃**

12g, 77%[c]
>25:1 E:Z

12f, 68%[c]
6.6:1 E:Z

- **Access to Z-alkene** - *fac*-Ir(ppy)₃ or Ir(Fppy)₃ (0.25 mol%), Perfluoroarene (1 equiv), DIPEA (0.75-3 equiv), Alkyne (6 equiv), 0 °C, Ar, MeCN (0.1 M), Blue LEDs, 24-72 h, 22 examples, 51-86% yields.
- **Access to E-alkene** - Ir(tBuppy)₃ (0.25 mol%), Perfluoroarene(1 equiv), DIPEA (0.75-3 equiv), Alkyne (6 equiv), 0 °C, Ar, MeCN (0.1 M), Blue LEDs, 24-72 h, 7 examples, 41-85% yields.
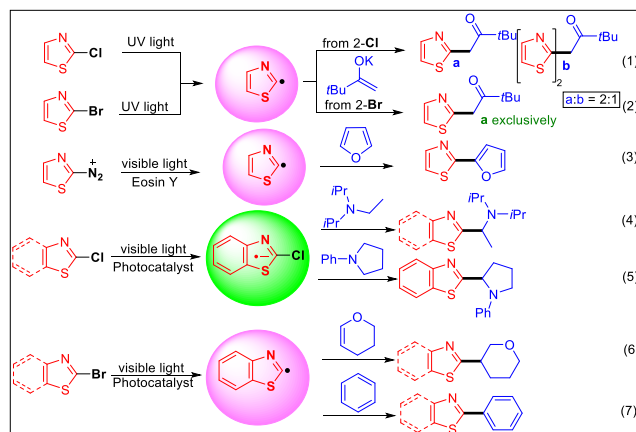
3. REACTIVE AZOLE INTERMEDIATES

3.1. Generation and Nature of the Reactive Azoles

Substituted azoles are an important class of molecules[47] that appear in natural products, drugs, and functional materials. As such, there is much interest in their rapid functionalization. While much attention[47] has been given to the late-transition metal catalyzed cross-couplings, as well as the use of lithiated azoles, far less attention has been paid to the reactive species of electron transfer. Herein, we discuss the generation of apparently different azolyl intermediates and their enabling bond forming ability.

Wolfe demonstrated that UV irradiation of both 2-chloro- and 2-bromothiazole led to a reactive azole species. He proposed a common 2-azolyl radical, despite different product outcomes (eqn 1 and 2, Scheme 13), which presumably arose from electron transfer from the potassium enolates.[48] Ranu showed that 2-diazoniums could be used as a source of 2-azolyl radicals via photocatalytic reduction.[49,50] MacMillan[51,52] and we[53] have shown that 2-chloroazoles can also be

activated with Ir-based photocatalysts and visible light. Furthermore, we have shown that under similar conditions, 2-bromoazoles give intermediates with unique reactivity.[54,55]

Scheme 13. Strategies for forming reactive azole species
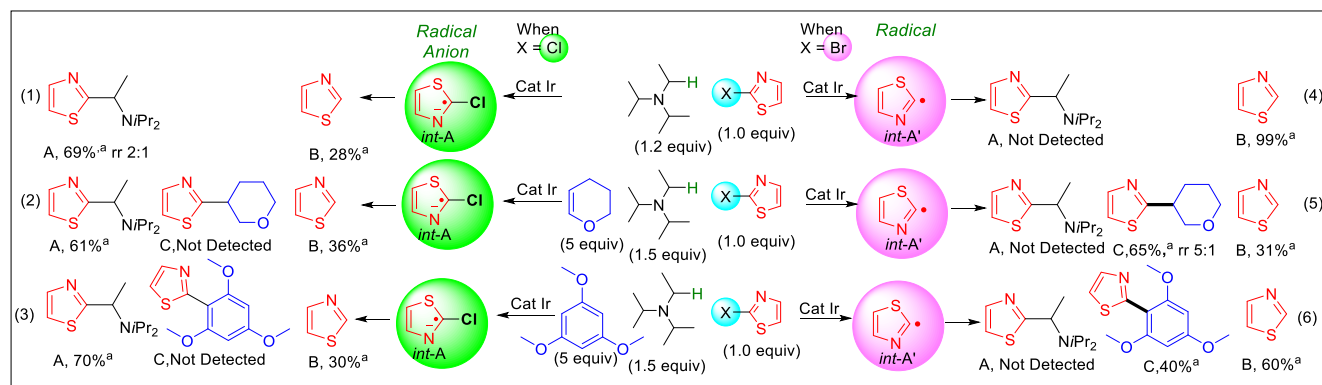

All of these results can be understood as a consequence of electron transfer to the azole core and differential rates of fragmentation. Simple analysis of the electronics, as in Scheme 1A and 1B, suggests that the presence of heteroatoms in the azole ring serve to lower the LUMO, making it easier to reduce than benzene.[56] Thus, the π* will drop in energy such that πRA becomes a viable intermediate. The lifetime of the πRA will then depend on the nature of the leaving group. Of those investigated, the 2-chloro substrate is expected to give rise to the longest-lived πRA followed by the 2-bromo and the 2-diazonium πRAs. The diazoniums may undergo a concerted electron transfer fragmentation process.

The heteroatoms of the azole structure present some noteworthy features. First, azoles are basic heterocycles capable of hydrogen bonding, and there is some evidence that the electron transfer process can be facilitated by hydrogen bonding (vide infra). Second, the azole displays regiospecificity rather than halogen selectivity. Herein, we will provide evidence and applications of the different reactive azoles that can be generated via photocatalysis for C–C bond forming reactions.

We have studied the consequences of photocatalytically mediated electron transfer from tertiary amines to 2–halo substituted azoles, which provide a number of insights about the different

Scheme 14. Different proposed azole intermediates and their chemistry

Reactions Conditions = Cat Ir = Ir(ppy)$_3$ (0.25 mol%), MeCN, 45 °C, Blue LEDs. [a]Yields are based on NMR.
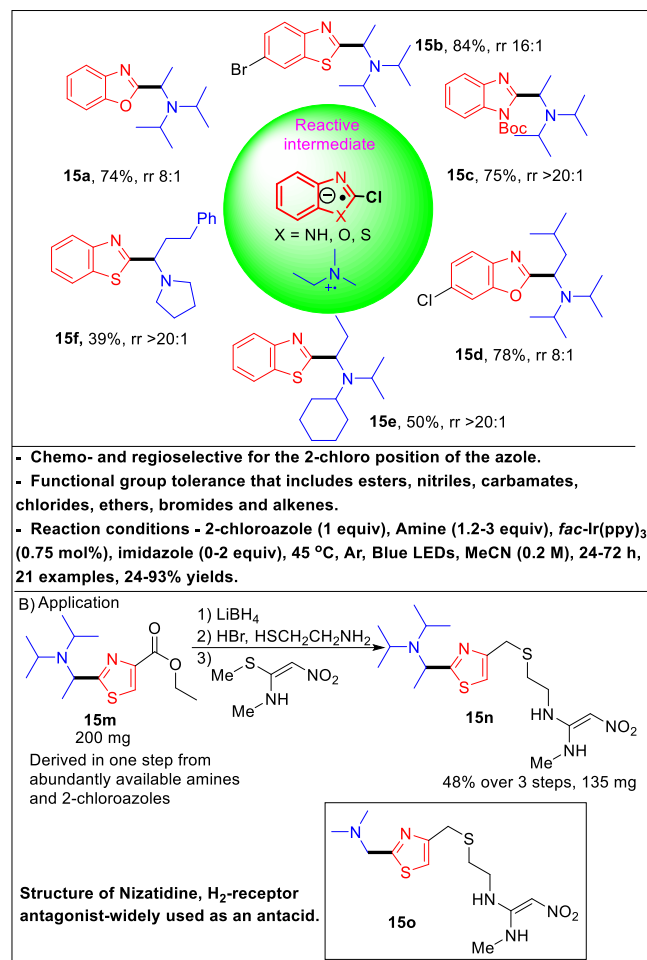
azolyl intermediates (Scheme 14). The reactivity depends completely upon the identity of the halogen. For instance, 2-chloroazoles undergo C–H functionalization of tertiary aliphatic amines (eqn 1), even in the presence of alkenes (eqn 2) and arenes (eqn 3). In stark contrast, 2-bromoazoles undergo complete reduction (eqn 4) in the presence of tertiary amines. When possible this intermediate undergoes addition to π–bonds, resulting in alkylation (eqn 5) and arylation (eqn 6).[54] The apparent change is likely due to the difference in the rate of unimolecular fragmentation of the radical anion, which is expected to be greater for the bromoazole than the chloroazole.[2,4] We have developed several methods that take advantage of the different reactivity of these accessible intermediates.

3.2. Photocatalytic C–H Functionalization; Access to α-Azolyl Carbinamines.

The development of the photocatalytic coupling of aliphatic amines and 2-chloroazoles (Scheme 14)[53] allows shortened synthetic sequences and vastly expands the chemical space of practically accessible 2-azolyl carbinamines. The methodology shows broad azole scope. The reaction displays complete chemo- and regio-selectivity for the 2–chloro position over a 7-bromo. There is a strong preference for the sterically more accessible C–H even though it is not the weakest C–H bond, which increases with the size of the azole. This suggests kinetic control over the C–H selectivity.

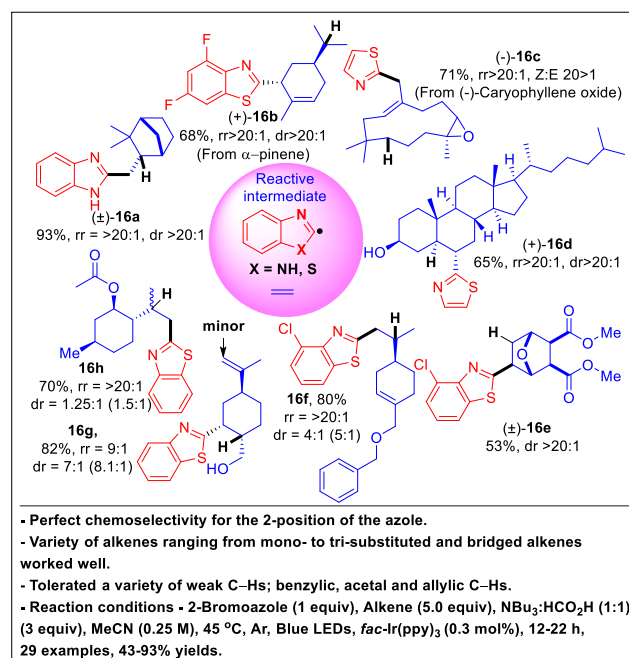Scheme 15. A) Photocatalytic azolylation of amines B) Application towards nizatidine-analog.

- Chemo- and regioselective for the 2-chloro position of the azole.
- Functional group tolerance that includes esters, nitriles, carbamates, chlorides, ethers, bromides and alkenes.
- Reaction conditions - 2-chloroazole (1 equiv), Amine (1.2-3 equiv), fac-Ir(ppy)$_3$ (0.75 mol%), imidazole (0-2 equiv), 45 °C, Ar, Blue LEDs, MeCN (0.2 M), 24-72 h, 21 examples, 24-93% yields.

The reaction displays a strong preference for acyclic methylene C–Hs over the endocyclic C–Hs (15f). Benzimidazoles, which are harder to reduce than other azoles required N-boc protection (15c). The utility of the methodology to rapidly access analogs was demonstrated by applying it to the synthesis of a previously unknown nizatidine-analog (15n).

10

Given the above facts, we propose that an azolyl radical anion, not a radical, is responsible for the α-C–H functionalization of *tert*-aliphatic amines. Interestingly, MacMillan published a highly related method that formed a similar bond to *N, N*-dialkylarylamines.[51] In MacMillan's case, a long-lived α-amino radical is likely involved, however, it seems reasonable that the same azole intermediate may be involved.

3.3. Photocatalyzed Reductive Alkylation of Azoles

Returning to the exploration of electron transfer to azoles, we began to assess the reactivity pattern of the intermediate generated from 2-bromoazoles. It was found that in the presence of an amine, photocatalyst, and visible light irradiation, an electron transfer to the 2-bromoazole generated a reactive intermediate that is most consistent with an azolyl radical. It underwent smooth addition to unactivated π–bonds of alkenes (Scheme 14, eqn 5) but only reacted with amines to abstract an H-atom (eqn 4). A major issue was the amount of simple azole reduction product. This problem plagues many intermolecular radical additions, and any solution should be of broad interest. While the amine is a necessary component, low concentrations gave less of the undesired reduction product. This could be achieved either by incremental addition of the amine, or alternatively by use of a low solubility amine. Meanwhile, the rate of reduction and HAT were only negligibly affected by amine concentration. While much discussion within this review has assumed a facile electron transfer to the arene-π*, under conditions of low amine concentrations, the rate of reduction of the arene may become limiting and the properties of the photocatalyst influence the overall rate of reaction. The optimal conditions for photocatalytic alkylation of azoles are shown in Scheme 16. The use of formic acid in the reaction was found to be vital to the reaction, but the exact role it plays is still unclear. The scope of the reaction is broad but does not include oxazoles. The azolyl radical demonstrated a strong preference for the less substituted terminus and, to a lesser degree, the more electron rich terminus. Interestingly, some evidence for H-bonding with the radical was shown.

Scheme 16. Photocatalytic alkylation of azoles

- Perfect chemoselectivity for the 2-position of the azole.
- Variety of alkenes ranging from mono- to tri-substituted and bridged alkenes worked well.
- Tolerated a variety of weak C–Hs; benzylic, acetal and allylic C–Hs.
- Reaction conditions - 2-Bromoazole (1 equiv), Alkene (5.0 equiv), NBu$_3$:HCO$_2$H (1:1) (3 equiv), MeCN (0.25 M), 45 °C, Ar, Blue LEDs, *fac*-Ir(ppy)$_3$ (0.3 mol%), 12-22 h, 29 examples, 43-93% yields.
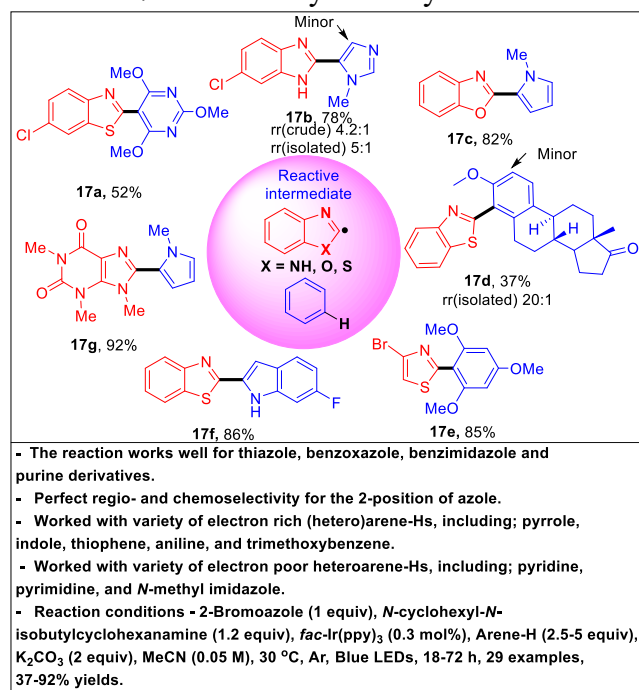
Vinyl cyclobutanes undergo azolylation followed by ring-opening then HAT (**16b** and **16c**). The azolyl radical must undergo addition faster than HAT, which may be because the hydrogen atom donor and azolyl radical are not well matched electronically. Addition to the tri-substituted olefin of cholesterol (**16d**) takes place smoothly, illustrating the potential of azolylation for late stage functionalization. Given the ubiquity of alkenes, this is a powerful strategy for alkylation of azoles.

3.4. Photocatalyzed C–H Arylation with Azoles and Heteroarenes

Next, we sought to intercept the azolyl radical with arene C–H bonds, followed by rearomatization.[54] Unlike the azole alkylation reaction, a unique facet of the arylation was the necessary oxidation under generally reducing conditions. Specifically, the amine was both necessary to initiate the photocatalytic reaction but was expected to be unneeded and possibly problematic for the subsequent oxidation. A catalytic amount of a low solubility amine and stoichiometric inorganic base along with decreased reaction temperatures were found to be key to obtaining high yields. The scope of the reaction was explored (Scheme 17). As anticipated the reaction shows perfect

11

regioselectivity for the 2-bromo of the azole rather than other halogens on the same azole.

Scheme 17. Photocatalytic azolylation of arenes

- The reaction works well for thiazole, benzoxazole, benzimidazole and purine derivatives.
- Perfect regio- and chemoselectivity for the 2-position of azole.
- Worked with variety of electron rich (hetero)arene-Hs, including; pyrrole, indole, thiophene, aniline, and trimethoxybenzene.
- Worked with variety of electron poor heteroarene-Hs, including; pyridine, pyrimidine, and *N*-methyl imidazole.
- Reaction conditions - 2-Bromoazole (1 equiv), *N*-cyclohexyl-*N*-isobutylcyclohexanamine (1.2 equiv), *fac*-Ir(ppy)$_3$ (0.3 mol%), Arene-H (2.5-5 equiv), K$_2$CO$_3$ (2 equiv), MeCN (0.05 M), 30 °C, Ar, Blue LEDs, 18-72 h, 29 examples, 37-92% yields.

The 2-azolyl radical adds to a variety of electron rich (hetero)arene C–H bonds and electron deficient heterocycles. Noticeably faster reactions with electron rich arenes evidence the electrophilic character of the 2-azolyl radical. Consequently, anti-Minisci selectivity is again displayed in the addition to electron deficient heteroarenes. Benzimidizoles were less prone to reduction and gave noticeably higher yields. Addition to biologically active mestranol shows the ability to perform selective late-stage functionalization. The ability to functionalize simple C$_{aryl}$–H bonds using only modest amounts of the arene (2.5 or 5 equiv), suggests that the photocatalytic C–H azolylation may be generally useful for synthesis.

4. CONCLUSION AND FUTURE PERSPECTIVE

Photocatalytic electron transfer can lead to reactive radical anions. The exact nature of the arene then dictates the subsequent chemistry, including the regio-, chemo-selectivity, and timing of the fragmentation event. Photocatalysis, while not alone in its ability to generate the reactive species, is unprecedented in its ability to harness these reactive species for synthesis.

While the fragmentation event of monosubstituted perfluoroaryl radical anions have been studied in some detail, virtually no work has been done on elaborate fluorinated scaffolds. If this chemistry is to be valuable for the synthetic community, the ability to predict the regioselectivity of the fragmentation will be paramount. Future efforts should aim to modulate the regioselectivies of C–F.

The azoles are curious as they deviate from normal radical anion fragmentation behavior, displaying overwhelming regiospecificity. A theoretical understanding of this phenomenon as well as a better understanding of the role of the heteroatoms in the formation of the radical and radical anions will provide valuable insight for synthetic planning.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Jimmie.Weaver@okstate.edu
Notes

The authors declare no competing financial interest.

Biographies

Dr. Jimmie D. Weaver. After completing his B.S in chemistry with math and physics minors in 2004 from South Nazarene University, Bethany, Oklahoma, he undertook his graduate studies under the supervision of Professor Jon Tunge at the University of Kansas, obtaining his Ph.D in 2010. After completing his Ph.D, he joined the laboratory of Professor Jonathan Ellman at Yale University as a postdoctoral fellow (2010-2012). He started his independent career at Oklahoma State University in the fall of 2012. Research in his group is focused on the catalytic generation and utilization of reactive intermediates for the purpose of developing useful chemistry. Interest include C–H and C–F functionalization, and cross-couplings of simple molecules, and the

development of unexplored strategies for synthesis such as uphill catalysis.

Amandeep Arora was born in Punjab, India in 1986. She studied pharmaceutical chemistry under the supervision of Dr. M.P. Mahajan during her M.Sc in Guru Nanak Dev University, Amritsar (India) in 2009. After spending next three years in teaching, she joined Oklahoma State University in 2012 and started her graduate studies in the laboratory of Dr. Jimmie Weaver. She has been working on the development of novel methodology that allows access to pharmaceutically and industrially relevant substituted azoles and heteroarenes.

■ ACKNOWLEDGMENTS

 References

(1) Konovalov, V. V.; Laev, S. S.; Beregovaya, I. V.; Shchegoleva, L. N.; Shteingarts, V. D.; Tsvetkov, Y. D.; Bilkis, I.: Fragmentation of Radical Anions of Polyfluorinated Benzoates. *J. Phys. Chem. A* **2000**, *104*, 352-361.

(2) Pierini, A. B.; Vera, D. M. A.: Ab Initio Evaluation of Intramolecular Electron Transfer Reactions in Halobenzenes and Stabilized Derivatives. *J. Org. Chem.* **2003**, *68*, 9191-9199.

(3) Costentin, C.; Robert, M.; Savéant, J.-M.: Fragmentation of Aryl Halide π Anion Radicals. Bending of the Cleaving Bond and Activation vs Driving Force Relationships. *J. Am. Chem. Soc.* **2004**, *126*, 16051-16057.

(4) Saveant, J. M.: Catalysis of chemical reactions by electrodes. *Acc. Chem. Res.* **1980**, *13*, 323-329.

(5) Shchegoleva, L. N.; Beregovaya, I. V.; Schastnev, P. V.: Potential energy surface of C6F6− radical anion. *Chem. Phys. Lett.* **1999**, *312*, 325-332.

(6) Shteingarts, V. D.: Recent advances in practice and theory of polyfluoroarene hydrodehalogenation. *J. Fluorine Chem.* **2007**, *128*, 797-805.

(7) Laev, S. S.; Shteingarts, V. D.; Bilkis, I. I.: On the difference in the results of reductive defluorination of pentafluorobenzoic acid by sodium and zinc in liquid ammonia medium. *Tetrahedron Lett.* **1995**, *36*, 4655-4658.

(8) Selivanova, G. A.; Reshetov, A. V.; Beregovaya, I. V.; Vasil'eva, N. V.; Bagryanskaya, I. Y.; Shteingarts, V. D.: Hydrodefluorination of polyfluoro-2-naphthylamines by Zn in aqueous NH3: A correlation of the product distribution and the computationally predicted regioselectivity of the substrate radical anion fragmentation. *J. Fluorine Chem.* **2012**, *137*, 64-72.

(9) Mashkantsev, D. E.; Beregovaya, I. V.; Shchegoleva, L. N.: Position-dependent fragmentation mechanism for radical anions of fluorinated benzoates. *J. Fluorine Chem.* **2016**, *188*, 171-176.

(10) Shchegoleva, L. N.; Bilkis, I. I.; Schastnev, P. V.: Geometrical and electronic structure of fluoro-substituted benzene radical anions based on quantum chemical analysis of hyperfine interactions. *Chem. Phys.* **1983**, *82*, 343-353.

(11) Gant, K. S.; Christophorou, L. G.: Attachment of slow electrons to hexafluorobenzene. *J. Chem. Phys.* **1976**, *65*, 2977-2981.

(12) Freeman, P. K.; Srinivasa, R.: Photochemistry of polyhaloarenes. 6. Fragmentation of polyfluoroarene radical anions. *J. Org. Chem.* **1987**, *52*, 252-256.

(13) Krasnov, V. I.; Platonov, V. E.; Beregovaya, I. V.; Shohegoleva, L. N.: Transformations of perfluoroxylenes and perfluoro-p-cymene under the action of Zn(Cu)-D-DMF-H2O. *Tetrahedron* **1997**, *53*, 1797-1812.

(14) Laev, S. S.; Shteingarts, V. D.: Reductive dehalogenation of polyfluoroarenes by zinc in aqueous ammonia. *J. Fluorine Chem.* **1999**, *96*, 175-185.

(15) Andrieux, C. P.; Pinson, J.: The Standard Redox Potential of the Phenyl Radical/Anion Couple. *J. Am. Chem. Soc.* **2003**, *125*, 14801-14806.

(16) Senaweera, S. M.; Singh, A.; Weaver, J. D.: Photocatalytic Hydrodefluorination: Facile Access to Partially Fluorinated Aromatics. *J. Am. Chem. Soc.* **2014**, *136*, 3002–3005.

(17) Chen, Q. Y.; Li, Z. T.: Pentafluorophenylation of aromatics with pentafluorophenyl perfluoro- and polyfluoroalkanesulfonates. A photoinduced electron-transfer cation diradical coupling process. *J. Org. Chem.* **1993**, *58*, 2599-2604.

(18) Chen, Q.-Y.; Li, Z.-T.: Photoinduced electron transfer reactions of pentafluoroiodobenzene with aromatic compounds. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1705-1710.

(19) Kosynkin, D.; Bockman, T. M.; Kochi, J. K.: Thermal (Iodide) and Photoinduced Electron-Transfer Catalysis in Biaryl Synthesis via Aromatic Arylations with Diazonium Salts. *J. Am. Chem. Soc.* **1997**, *119*, 4846-4855.

(20) Meyer, A. U.; Slanina, T.; Yao, C.-J.; König, B.: Metal-Free Perfluorarylation by Visible Light Photoredox Catalysis. *ACS Catal.* **2016**, *6*, 369-375.

(21) Lentz, D.; Braun, T.; Kuehnel, M. F.: Synthesis of Fluorinated Building Blocks by Transition-Metal-Mediated Hydrodefluorination Reactions. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 3328-3348.

(22) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A.: Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315-8359.

(23) O'Hagan, D.; B. Harper, D.: Fluorine-containing natural products. *J. Fluorine Chem.* **1999**, *100*, 127-133.

(24) Kuehnel, M. F.; Lentz, D.; Braun, T.: Synthesis of Fluorinated Building Blocks by Transition-Metal-Mediated Hydrodefluorination Reactions. *Angew. Chem. Int. Ed.* **2013**, *52*, 3328-3348.

(25) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T.: Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation To Access Fluorinated Building Blocks. *Chem. Rev.* **2015**, *115*, 931-972.

(26) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E.: Activation of Carbon-Fluorine Bonds by Metal Complexes. *Chem. Rev.* **1994**, *94*, 373-431.

(27) Amii, H.; Uneyama, K.: C−F Bond Activation in Organic Synthesis. *Chem. Rev.* **2009**, *109*, 2119-2183.

(28) Sun, A. D.; Love, J. A.: Cross coupling reactions of polyfluoroarenes via C-F activation. *Dalton Transactions* **2010**, *39*, 10362-10374.

(29) Weaver, J.; Senaweera, S.: C–F activation and functionalization of perfluoro- and polyfluoroarenes. *Tetrahedron* **2014**, *70*, 7413-7428.

(30) Yim, M. B.; Wood, D. E.: Free radicals in an adamantane matrix. XII. EPR and INDO study of .sigma.*-.pi.* crossover in fluorinated benzene anions. *J. Am. Chem. Soc.* **1976**, *98*, 2053-2059.

(31) Shoute, L. C. T.; Mittal, J. P.: Kinetics and absorption spectra of transients in the radiolysis of hexafluorobenzene in aqueous solution: a pulse radiolysis study. *J. Phys. Chem. A* **1993**, *97*, 379-384.

(32) Rossi, R. A.: Phenomenon of radical anion fragmentation in the course of aromatic SRN reactions. *Acc. Chem. Res.* **1982**, *15*, 164-170.

(33) Sun, A. D.; Love, J. A.: Pt(II)Cl2(DMSO)2-catalyzed cross-coupling of polyfluoroaryl imines. *J. Fluorine Chem.* **2010**, *131*, 1237-1240.

(34) Sun, Y.; Sun, H.; Jia, J.; Du, A.; Li, X.: Transition-Metal-Free Synthesis of Fluorinated Arenes from Perfluorinated Arenes Coupled with Grignard Reagents. *Organometallics* **2014**, *33*, 1079-1081.

(35) Lu, W.; Gao, J.; Yang, J.-K.; Liu, L.; Zhao, Y.; Wu, H.-C.: Regioselective alkyl transfer from phosphonium ylides to functionalized polyfluoroarenes. *Chem. Sci.* **2014**, *5*, 1934-1939.

(36) Fischer, H.; Radom, L.: Factors controlling the addition of carbon-centered radicals to alkenes-an experimental and theoretical perspective. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340-1371.

(37) Singh, A.; Kubik, J. J.; Weaver, J. D.: Photocatalytic C-F alkylation; facile access to multifluorinated arenes. *Chem. Sci.* **2015**, *6*, 7206-7212.

(38) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J.: Palladium-Catalyzed Cross-Coupling of Polyfluoroarenes with Simple Arenes. *Org. Lett.* **2011**, *13*, 276-279.

(39) Wei, Y.; Su, W.: Pd(OAc)₂-Catalyzed Oxidative C−H/C−H Cross-Coupling of Electron-Deficient Polyfluoroarenes with Simple Arenes. *J. Am. Chem. Soc.* **2010**, *132*, 16377-16379.

(40) Lindner, S.; Bräse, S.; Masters, K.-S.: Simple and expedient metal-free CH-

functionalization of fluoro-arenes by the BHAS method – Scope and limitations. *J. Fluorine Chem.* **2015**, *179*, 102-105.

(41)   Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F.: A new application of (polyfluoroorgano)trifluoroborate salts: the palladium-catalysed cross-coupling reaction with substituted benzenediazonium tetrafluoroborates. *J. Fluorine Chem.* **2002**, *117*, 115-120.

(42)   Kinzel, T.; Zhang, Y.; Buchwald, S. L.: A New Palladium Precatalyst Allows for the Fast Suzuki−Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075.

(43)   Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T.: Suzuki−Miyaura Coupling Reaction Using Pentafluorophenylboronic Acid. *Org. Lett.* **2005**, *7*, 4915-4917.

(44)   Senaweera, S. M.; Weaver, J. D.: Dual C–F, C–H Functionalization via Photocatalysis; Access to Multi-Fluorinated Biaryls. *J. Am. Chem. Soc.* **2016**, *138*, 2520-2523.

(45)   Senaweera, S. M.; Weaver, J. D.: Selective Perfluoro- and Polyfluoroarylation of Meldrum's Acid. *J. Org. Chem.* **2014**, *79*, 10466-10476.

(46)   Singh, A.; Fennell, C. J.; Weaver, J. D.: Photocatalyst size controls electron and energy transfer: selectable E/Z isomer synthesis via C-F alkenylation. *Chemical Science* **2016**.

(47)   Badenock, J. C.; Gribble, G. W.: Chapter Four - Metal-Catalyzed Coupling with Heterocycles. In *Adv. Heterocycl. Chem.*; Eric, F. V. S., Christopher, A. R., Eds.; Academic Press, 2016; Vol. Volume 120; pp 99-136.

(48)   Dillender, S. C.; Greenwood, T. D.; Hendi, M. S.; Wolfe, J. F.: Reactions of 2-halothiazoles with ketone enolates and nitrile carbanions. *J. Org. Chem.* **1986**, *51*, 1184-1188.

(49)   Kundu, D.; Ahammed, S.; Ranu, B. C.: Visible Light Photocatalyzed Direct Conversion of Aryl-/Heteroarylamines to Selenides at Room Temperature. *Org. Lett.* **2014**, *16*, 1814-1817.

(50)   Maity, P.; Kundu, D.; Ranu, B. C.: Visible-Light-Photocatalyzed Metal-Free C-H Heteroarylation of Heteroarenes at Room Temperature: A Sustainable Synthesis of Biheteroaryls. *Eur. J. Org. Chem.* **2015**, *2015*, 1727-1734.

(51)   Prier, C. K.; MacMillan, D. W. C.: Amine [small alpha]-heteroarylation via photoredox catalysis: a homolytic aromatic substitution pathway. *Chem. Sci.* **2014**, *5*, 4173-4178.

(52)   McNally, A.; Prier, C. K.; MacMillan, D. W. C.: Discovery of an α-Amino C–H Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science* **2011**, *334*, 1114-1117.

(53)   Singh, A.; Arora, A.; Weaver, J. D.: Photoredox-Mediated C–H Functionalization and Coupling of Tertiary Aliphatic Amines with 2-Chloroazoles. *Org. Lett.* **2013**, *15*, 5390-5393.

(54)   Arora, A.; Weaver, J. D.: Photocatalytic Generation of 2-Azolyl Radicals: Intermediates for the Azolylation of Arenes and Heteroarenes via C–H Functionalization. *Org. Lett.* **2016**.

(55)   Arora, A.; Teegardin, K. A.; Weaver, J. D.: Reductive Alkylation of 2-Bromoazoles via Photoinduced Electron Transfer: A Versatile Strategy to Csp(2)-Csp(3) Coupled Products. *Org. Lett.* **2015**, *17*, 3722-3725.

(56)   Sviatenko, L.; Gorb, L.; Hill, F.; Leszczynska, D.; Leszczynski, J.: Theoretical Study of One-Electron Reduction And Oxidation Potentials of N-Heterocyclic Compounds. *Chem Heterocycl Comp* **2014**, *50*, 311-318.