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"Applications of *N*–Centered Radicals Generated from Electrochemical Initiation of Stable Organic Precursors"
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During the course of the funded research, we discovered an interesting mode of reactivity involving unprotected amino acids and Selectfluor. Our work involving the electrochemical reduction of *N*-centered radical precursors led us to investigate the reduction of Selectfluor to produce a diazobicyclo radical cation, known to participate in the amino fluorination of alkenes and cyclopropanes. Through the study of this process we were able to develop a C–H fluorination reaction for simple aromatic compounds containing at least one benzylic C–H bond (Figure 1). Although Selectfluor may be reduced directly via electrochemistry, for synthetic utility we optimized a protocol involving Ag(I) salts as radical initiators. Interestingly, based simply on the analysis of reduction potentials, Selectfluor (E^o = -0.04 V) should not be capable of generating Ag(II) from Ag(I) via single-electron transfer, which typically requires a strong oxidant such as $S_2O_8^{2-}$ (E^o = 2.01 V). *In situ* reaction monitoring via ReactIR confirmed that Ag(I) salts alone are not capable of reducing Selectfluor (Figure 2). However, unprotected amino acid additives facilitated rapid Selectfluor reduction, presumably via a single-electron process. In addition, oxidative decarboxylation of the amino acids via the Ag(II) generated during the reaction provides an α-aminoalkyl radical species capable of C–H abstraction for a variety of benzylic substrates. Subsequent radical fluorination via Selectfluor provided an additional equivalent of the dazabicyclo radical cation to continue the chain radical process. The most straightforward explanation for the activation of the Ag(I)/Selectfluor system is to invoke glycine as a ligand for Ag(I), lowering its oxidation potential and allowing for single-electron oxidation from Selectfluor to produce Ag(II). We explored this possibility experimentally by measuring the onset oxidation potential of $AgNO_3$ in the presence of various additives. As shown in Figure 3, the oxidation potential of $AgNO_3$ (Figure 3a) is lowered in the presence of nitrogen-containing additives capable of strong ligation. The addition of glycine to a solution of $AgNO_3$ led to a significant decrease in the onset oxidation potential for the Ag(I)/Ag(II) couple (Figure 3b). Conversely, when Boc-glycine was added to a solution of $AgNO_3$, a negligible shift in oxidation potential was observed, owing to the fact that the Boc group is deactivating, decreasing the nitrogen atom's ability to bind to Ag(I) (Figure 3c). In fact, no fluorination is observed using Boc-glycine as an additive and *in situ* ReactIR shows that Selectfluor reduction is not possible under these conditions. These experiments suggest that lowering the oxidation potential of the Ag(I) catalyst through nitrogen binding is important for decarboxylation. This effect can be further illustrated by employing pyridine as a ligand for Ag(I). As shown in

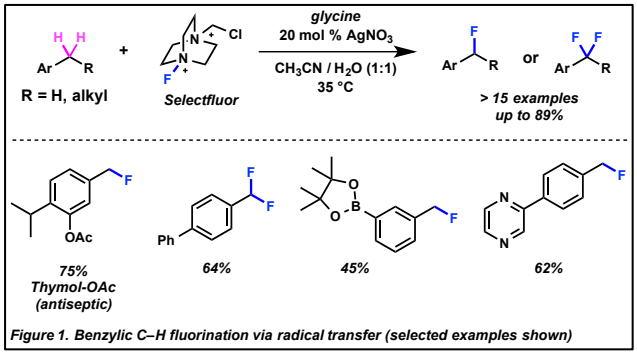

Figure 1. Benzylic C–H fluorination via radical transfer (selected examples shown)

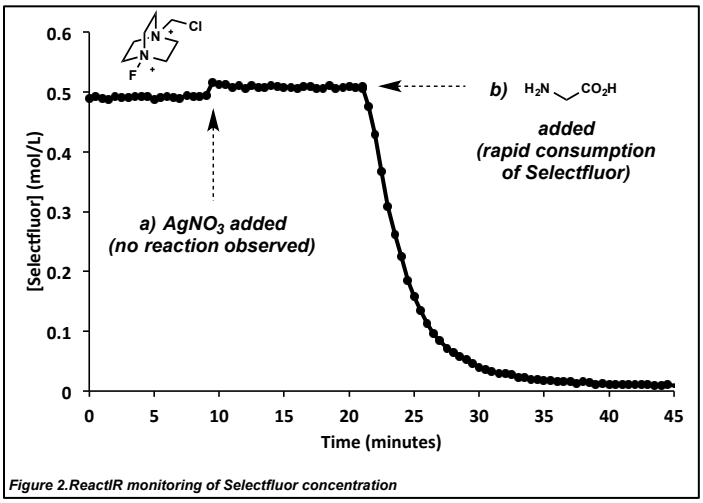

Figure 2.ReactIR monitoring of Selectfluor concentration

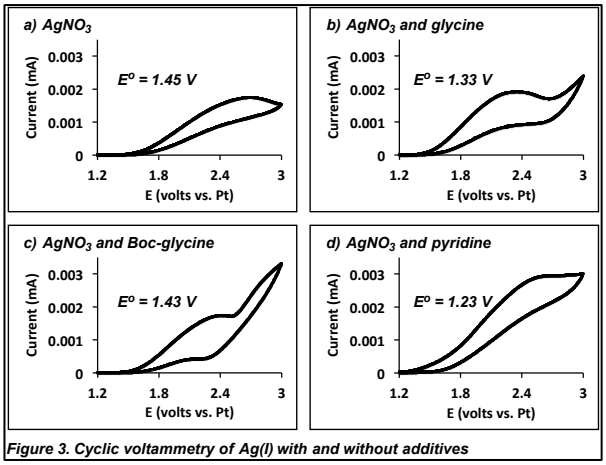

Figure 3. Cyclic voltammetry of Ag(I) with and without additives

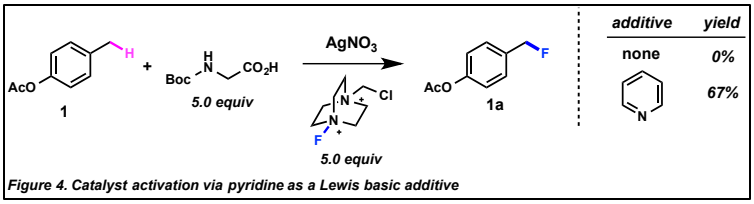

Figure 4. Catalyst activation via pyridine as a Lewis basic additive

Figure 3d, a dramatic shift in onset oxidation potential is observed for Ag(I) in the presence of pyridine, suggesting that oxidation to Ag(II) by Selectfluor is possible. Whereas Boc-glycine is incapable of promoting radical fluorination on its own, the addition of 200 mol% pyridine enabled the fluorination of **1** in 67% isolated yield using Boc-glycine as a hydrogen atom transfer reagent (Figure 4). This important result confirms that nitrogen binding to Ag(I) is critical for oxidation to Ag(II) with Selectfluor. The development of this chemistry, enabled by funding through the ACS-PRF, allowed our lab to further explore radical reactions that could be mediated by Ag(I) catalysts, Selectfluor, and Lewis basic nitrogen additives. In one example, we discovered that aromatic heterocycle alkylation could be promoted when simple carboxylic acids were used in place of amino acids. In the absence of abstractable C–H bonds, direct addition to aromatic heterocycles is favored, and the substrate itself likely served to activate the Ag(I) catalyst. Figure 5 shows that many heterocycles are suitable substrates for radical alkylation, and a variety of carboxylic acids serve as radical precursors. An analogous strategy could also be employed to promote radical arylation from aryl boronic acids and esters, and a broad scope of substrates were suitable partners for the chemistry.

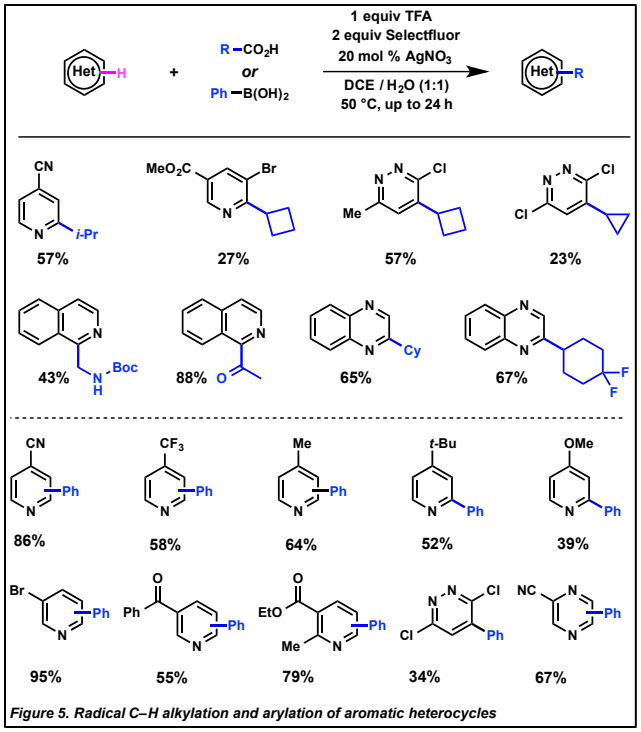

Figure 5. Radical C–H alkylation and arylation of aromatic heterocycles

As shown above, work completed through support by the ACS-PRF has led to several new areas of research within my lab. Multiple projects have resulted in publications that have served as the cornerstone for successful research proposals soliciting additional external funds. In addition, several student fellowships were secured based on work completed during the ACS-PRF project period. Additional funding and student fellowships have had a directly positive impact on my career, and the ACS-PRF grant served as a springboard for these. Several students received diverse scientific training; from chemical synthesis and method development, to chemical kinetics and physical organic chemistry. Through the support of the ACS, two students involved in the fluorination project described above traveled to the ACS National conference to present their work.