Abstract: Trifluoromethyl-substituted arenes and heteroarenes are widely prevalent in pharmaceuticals and agrochemicals. As a result, the development of practical methods for the formation of aryl–CF₃ bonds has become an active field of research. Over the past five years, transition-metal-catalyzed cross-coupling between aryl–X (X = halide, organometallic, or H) and various CF₃ reagents has emerged as a particularly attractive approach to generating aryl–CF₃ bonds. Despite many recent advances in this area, current methods generally suffer from limitations such as poor generality, harsh reaction conditions, the requirement for stoichiometric quantities of metals, and/or the use of costly CF₃ sources. This Account describes our recent efforts to address some of these challenges by: (1) developing aryltrifluoromethylation reactions involving high oxidation state Pd intermediates, (2) exploiting AgCF₃ for C–H trifluoromethylation, and (3) achieving Cu-catalyzed trifluoromethylation with photogenerated CF₃•.

1 Introduction

Trifluoromethylarenes and heteroarenes are increasingly important structural features of pharmaceuticals and agrochemicals. The incorporation of a trifluoromethyl group into an organic molecule can dramatically impact a variety of properties, including metabolic stability, lipophilicity, and bioavailability. Despite the significance of this functional group in medicinal chemistry, mild, efficient, and functional-group tolerant methods for the formation of aryl/heteroaryl–CF₃ linkages have been limited until very recently.

On the industrial scale, trifluoromethylated arenes are mainly produced by the Swarts reaction, which was developed in 1892. This transformation involves a two-step conversion of toluene derivatives into benzotrifluorides through radical chlorination followed by treatment with an inorganic fluoride (e.g., SbF₅) or anhydrous hydrogen fluoride (Scheme 1).

Scheme 1

This Account describes our efforts in methods development and mechanistic investigations of transition-metal-mediated aromatic trifluoromethylation reactions. When we initiated our work in this area in 2009, three groups had just reported exciting advances in Pd- and Cu-promoted arene trifluoromethylation reactions. For example, in 2006, Grushin demonstrated that (Xantphos)Pd(Ph)(CF₃) undergoes stoichiometric Ph–CF₃ bond-forming reductive elimination to release trifluorotoluene under mild conditions (80 °C, 3 h; Scheme 2). This was the first reported example of selective aryl–CF₃ coupling from a Pd center. The properties of the Xantphos ligand (particularly its large bite angle) were hypothesized to play an important role in this novel transformation.

Scheme 2

A major advance in the area of Cu-promoted trifluoromethylation was made in 2008, when Vicic reported the first example of an isolable, crystallographically characterized Cu¹–CF₃ complex (Scheme 3). This complex, which is supported by an N-heterocyclic carbene ligand, was shown to react with aryl iodides under mild conditions (25 °C, 112 h) to liberate trifluoromethylated products (Scheme 3). While related Cu-mediated trifluoromethylation were known prior to this report,
these previous systems generally involved ill-defined ‘Cu-CF₃’ intermediates.

Scheme 3

A final significant advance that occurred just prior to our entry into the field was a 2009 report by Amii. This work demonstrated the first copper-catalyzed trifluoromethylation of aryl iodides. As shown in Scheme 4, 1,10-phenanthroline (phen) was used as a supporting ligand for Cu in conjunction with TMSCF₃ as the CF₃ source. A variety of electron-deficient aryl iodides underwent trifluoromethylation under these conditions.

Scheme 4

Our goal was to build on these exciting advances by developing new mechanistic pathways for metal-mediated aryl–CF₃ coupling reactions. Over the last three years, we have pursued three different strategies to achieve this goal (Scheme 5). Strategy 1 involves aryltrifluoromethylation via reductive elimination from high-valent Pd IV(aryl)(CF₃) intermediates. Strategy 2 involves exploiting AgCF₃ intermediates to achieve aryl–CF₃ bond-forming. Finally, strategy 3 involves the trifluoromethylation of aryl-Cu intermediates with CF₃•. All three of these approaches are described in detail below.

Scheme 5 Three different strategies used in the Sanford group for aryl–CF₃ coupling

2 Part 1. Aryltrifluoromethylation via High-Valent Palladium

Historically, it has proven challenging to achieve aryl–CF₃ bond-forming reductive elimination from Pd⁰ centers. Only two high-yielding examples of this transformation have been reported in the literature, and both involve the use of specialized phosphine ligands to induce the desired reactivity. As described above, Grushin reported Ph–CF₃ coupling from (Xantphos)Pd II(Ph)(CF₃) in 2006 (Scheme 2). More recently, Buchwald has shown that (Brettphos)PdII(aryl)(CF₃) {Brettphos = dicyclohexyl(2′-isopropyl-3,6-dimethoxy-4′,6′-dipropyl-[1,1′-biphenyl]-2-yl)phosphine} also undergoes aryl–CF₃ bond-forming reductive elimination under mild conditions (80 °C, ~30 min).

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Melanie Sanford was born in New Bedford, MA, USA in 1975. She received B.Sc. and M.Sc. degrees in chemistry from Yale University in 1996 and a Ph.D. in chemistry from California Institute of Technology in 2001. After post-doctoral studies at Princeton University, she joined the faculty at the University of Michigan in 2003, where she is currently the Moses Gomberg Collegiate Professor as well as an Arthur F. Thurnau Professor of Chemistry.
Our group aimed to achieve aryl–CF$_3$ coupling from Pd using a different, complementary approach. Rather than modifying the ligands at Pd$^{II}$, we sought to access the desired reactivity by changing the oxidation state of the Pd center from Pd$^{II}$ to Pd$^{IV}$. This idea was predicated on the fact that Pd$^{IV}$ complexes are well known to undergo other reductive elimination reactions (e.g., C–F, C–Cl, C–I, C–N, C–O) that have proven challenging at Pd$^{II}$ centers. To probe the viability of this strategy, we synthesized and characterized by NMR spectroscopy and X-ray crystallography.

Two synthetic routes were used to access these compounds: the $2e^-$ oxidation of pre-formed Pd$^{II}$(aryl)(CF$_3$)$_2$ complexes (Scheme 6a) and the oxidation of Pd$^{II}$(aryl) complexes with CF$_3^+$ reagents (Scheme 6b).

We initially pursued the synthesis of Pd$^{IV}$(aryl)(CF$_3$)$_2$ complexes via the $2e^-$ oxidation of (N~N)Pd$^{II}$(aryl)(CF$_3$)$_2$ (1). As shown in Scheme 7, N-fluoro-2,4,6-trimethyl-pyrindinyl triflate (NFTPT) was selected as the N–N ligand, since its rigid, bidentate structure is known to stabilize Pd$^{IV}$ complexes. As shown in Scheme 7, N-fluoro-2,4,6-trimethyl-pyrindinyl triflate (NFTPT) proved to be particularly effective for the oxidation of 1, yielding 2 in 53% isolated yield. This product was fully characterized by NMR spectroscopy and X-ray crystallography.

The availability of pure samples of 1 and 2 enabled a direct comparison of aryl–CF$_3$ bond formation from dtbpy-ligated Pd$^{II}$ versus Pd$^{IV}$ centers. As shown in Scheme 8, Pd$^{II}$ complex 1 was inert towards thermal reductive elimination, affording $<$5% yield of p-F-Ph–CF$_3$ even after 72 h at 130 °C (mass balance was predominantly recovered starting material). In marked contrast, the analogous Pd$^{IV}$ complex underwent high yielding aryl–CF$_3$ bond-forming reductive elimination over 3 h at just 80 °C (Scheme 8). Notably, products derived from competing aryl–F or aryl–OTf coupling were not observed from 2, presumably due to the low reactivity of these ligands towards reductive elimination. Overall, the results given in Scheme 8 confirmed our original hypothesis that aryl–CF$_3$ coupling can be accelerated by oxidation of a Pd center from Pd$^{II}$ to Pd$^{IV}$.

Experimental and computational mechanistic studies indicate that aryl–CF$_3$ coupling from 2 proceeds via pre-equilibrium triflate dissociation (step 1) followed by aryl–CF$_3$ bond-formation from cationic intermediate 3 (step 2, Scheme 9). These results led us to propose that replacing the dtbpy ligand with N,N$_2$N$_2$N$_4$-tetramethylethylenediamine (tmeda) would result in an acceleration of this C–C bond-forming event. Importantly, literature precedent has shown that the use of more flexible tmeda increases the rate of C–C coupling from the related Pd$^{IV}$ complexes (N~N)Pd$^{IV}$(CH$_3$)$_2$(Ph)(I) (N~N = bpy versus tmeda). DFT calculations of analogues of 2 were consistent with this hypothesis, predicting that both triflate dissociation and aryl–CF$_3$ coupling would be faster with tmeda. Experimental studies confirmed that the Pd$^{IV}$ tmeda complex 5 is significantly more reactive than 2, as substitution of tmeda for dtbpy enables aryl–CF$_3$ coupling to proceed at room temperature rather than 80 °C (Scheme 9).

This work provides the basis for the development of many different types of Pd$^{IV}$-catalyzed aryl–CF$_3$ cross-coupling reactions. A potential catalytic cycle for such transformations is outlined in Scheme 10. Step 1 involves formation of a Pd$^{IV}$(aryl) complex, which could occur, for example, by C–H activation (X = H) or transmetalation (X = B, Sn, Si). Subsequent reaction with TMSCF$_3$ (step 2) would yield Pd$^{II}$(aryl)(CF$_3$)$_2$ (A). Two-electron oxidation of A (step 3) followed by aryl–CF$_3$ bond-forming reductive elimination (step 4) would then furnish the trifluoromethylated product and regenerate the catalyst. This approach is already being adopted to achieve synthetically useful trifluoromethylation reactions. For example, a recent report by Liu and co-workers exploited...
this strategy in the Pd-catalyzed C–H trifluoromethylation of indoles (Scheme 11). While detailed mechanistic investigations of this transformation have not yet been conducted, the combination of aryl–H (indole), TMSCF₃, and an oxidant [PhI(OAc)₂] was proposed to react via a cycle very similar to that depicted in Scheme 10. A related pathway has also been proposed for the Pd-catalyzed aryltrifluoromethylation of alkenes. Numerous analogous transformations can be envisioned, and we anticipate that this approach could find widespread utility for Pd-catalyzed trifluoromethylation sequences.

We initially examined the feasibility of using this transformation in the context of the cyclopalladated dimer [{bzq}Pd{II}(OAc)]₂ (6). This complex was selected for study for two reasons. First, it contains a rigid cyclometalated σ-aryl ligand, which should stabilize high-valent Pd oxidation products. Second, it is believed to be a catalytically relevant intermediate in C–H functionalization reactions of benzo[h]quinoline. As such, studies of its reactivity could potentially be directly applicable to the development of catalytic ligand-directed C–H trifluoromethylation reactions.

The reaction of 6 with CF₃⁺ reagents 7–9 in AcOH afforded the Pd{IV} complex 10 (Scheme 13). This complex was fully characterized by NMR spectroscopy and by X-ray crystallography.

Complex 10 was stable at room temperature, but it decomposed at 60 °C to form the aryl–CF₃ coupled product 11 (Scheme 14). However, under all of the conditions examined, the formation of 11 was sluggish, showed an induction period, and proceeded in only modest yield (56% in AcOH), with poor mass balance. While we have not yet been able to completely explain these results, we have identified additives that ameliorate many of these issues.

The lessons learned from these stoichiometric studies have proven to be highly relevant to Pd-catalyzed ligand-
directed C–H trifluoromethylation reactions. In an elegant recent paper, Yu and co-workers achieved the Pd-catalyzed C–H trifluoromethylation of a variety of aromatic substrates using 9 as the CF$_3^+$ source (Scheme 15). The optimal conditions for these transformations [using a chlorinated solvent in the presence of a Brønsted acid (TFA) and a Lewis acid (Cu(OAc)$_2$)] are remarkably similar to those identified in our stoichiometric reactions with 6 and 11.$^{18}$ This suggested the possibility that PdIV complex 10 might be an intermediate under Yu’s catalytic reactions. Consistent with this proposal, the use of 10 as catalyst provided nearly identical yield to that obtained with Pd(OAc)$_2$. Furthermore, analysis of the initial rates with Pd(OAc)$_2$ versus 10 showed that the PdIV complex is a kinetically competent catalyst for C–H trifluoromethylation.$^{17}$

Overall, these studies demonstrate the viability of catalytic cycles such as that depicted in Scheme 16 for Pd$^{IV}$-catalyzed trifluoromethylation. This cycle involves initial generation of Pd$^{II}$ intermediate B via C–H activation or transmetalation (step i). Oxidation of B with CF$_3^+$ (step ii) and subsequent C–CF$_3$ coupling (step iii) then releases the trifluoromethylated product. We anticipate that this pathway could prove broadly useful for a number of different Pd-catalyzed transformations for introducing CF$_3$ groups into organic molecules.

3 Part 2. Aryltrifluoromethylation Using AgCF$_3$

Our second approach to uncovering new pathways for arene trifluoromethylation has been to explore metal catalysts beyond Pd and Cu. Our initial efforts in this area focused on Ag for three reasons. First, Ag$^+$ has the same electronic configuration as Cu$^+$, which suggests the possibility of similar reactivity. Second, Ag$^+$ salts have recently been used as catalysts for related organometallic reactions, including the fluorination of arylstannanes with F$^+$ reagents.$^{19}$ These examples suggest the possibility that organometallic Ag complexes can participate in aryl–X bond-forming transformations. Third, AgCF$_3$ is readily synthetically accessible (although its reactivity with organic substrates had not previously been explored extensively)$^{20}$.

We first examined the reaction between AgCF$_3$ and iodo-benzene. PhI was selected as a substrate because it is known to react with CuCF$_3$ complexes to generate trifluorotoluene (Scheme 17a).$^{1f}$ Very surprisingly, treatment of AgCF$_3$ with PhI did not yield the expected cross-coupled product PhCF$_3$. Instead, this reaction afforded a mixture of three isomeric C–H trifluoromethylation products (iodobenzotrifluorides) (Scheme 17b)$^{21}$ This is a particularly exciting result because it shows that moving to a different metal (from Cu to Ag) results in completely complementary reactivity.
different trifluoromethylated analogues in a single operation. This is exemplified in the formation of 12 as a mixture of four isomers from the trifluoromethylation of Tricor (a commercial cholesterol-lowering drug).

While detailed mechanistic studies have not yet been conducted, several pieces of evidence implicate a pathway involving homolysis of the Ag–CF₃ bond to generate Ag⁰ and CF₃• followed by C–H functionalization via radical aromatic substitution. First, a Ag mirror is observed at the bottom of the flask at the end of these reactions, which is indicative of the reduction of AgI to Ag⁰. Additionally, the high reactivity with electron-rich aromatics is consistent with the intermediacy of an electrophilic CF₃ radical. Finally, the addition of one equivalent of 2,2,6,6-(tetramethylpiperidin-1-yl)oxyl (TEMPO) to this transformation resulted in a dramatic reduction of the yield, suggesting the possibility that this additive is trapping the key CF₃• intermediate.

Overall these efforts demonstrate the viability of Ag as a promoter for C–H trifluoromethylation. The AgCF₃-mediated transformations proceed under mild conditions and are complementary to analogous reactions of CuCF₃. In addition, this work adds to a growing body of evidence suggesting that CF₃• is a potently reactive species that can function as a radical source for (hetero)aryl C–H trifluoromethylation reactions. For example, Baran and MacMillan have recently demonstrated the C–H trifluoromethylation of complex molecules with CF₃• generated from either NaSO₂CF₃/–BuOOH (Baran) or CF₃SO₂Cl/Ru(phen)₃²⁺/visible light (MacMillan). All of these transformations serve as valuable methods for the trifluoromethylation of aromatic/heteroaromatic substrates under mild and functional-group-tolerant conditions.

4 Part 3. Cu-Catalyzed Aryltrifluoromethylation with CF₃•

A third objective of our efforts in this area has been to identify new pathways for Cu-catalyzed boronic acid trifluoromethylation. Prior work had demonstrated that this transformation can be achieved via transfer of nucleophilic CF₃⁻ [derived from, for example, TMSCF₃ or K(MeO)₃B(CF₃)] or electrophilic CF₃⁺ (derived, for example, from 7–9) to the Cu catalyst (Scheme 19). These two approaches are limited by the relatively high cost of some CF₃⁻/CF₃⁺ reagents, limited functional group tolerance in the presence of these highly nucleophilic/electrophilic reagents, and the requirement for high temperatures in some systems. We reasoned that these limitations could potentially be addressed by accessing an alternative mechanistic manifold in which CF₃ transfer to the metal center occurs via CF₃• (Scheme 19). As discussed above in Part 2, CF₃• can effect C–H trifluoromethylation via radical aromatic substitution. Thus, a key challenge for this approach is to identify a system in which reaction of CF₃• with the metal catalyst is faster than competing uncatalyzed C–H trifluoromethylation. We selected Cu-based catalysts based on the fact that they are susceptible to rapid 1e⁻ oxidation reactions.

Our proposed approach to Cu-catalyzed trifluoromethylation requires a mild and readily available source of CF₃•. We were inspired by several recent reports by MacMillan that used CF₃I as a precursor to CF₃• in the presence of visible light and a photocatalyst. As such, our initial studies focused on the Cu-catalyzed trifluoromethylation of boronic acid derivatives with CF₃I in the presence of Ru(bpy)₃²⁺ (Scheme 20).

Scheme 18 C–H trifluoromethylation reactions with AgCF₃

Scheme 19
Scheme 20

Our investigations revealed that the reaction of 1,1′-biphenyl-4-ylboronic acid with CF₃I in the presence of 20 mol% Cu(OAc), 1 mol% Ru(bpy)₃²⁺, and visible light (two 26 W household light bulbs) affords the trifluoromethylated product 4-(trifluoromethyl)-1,1′-biphenyl in high yield (Scheme 21). Importantly, the reaction proceeds in less than 5% yield when light, Cu, or Ru are excluded from the reaction mixture, indicating that all three of these components are necessary for the major reaction pathway. Furthermore, less than 2% of competing C–H trifluoromethylation of the substrate or product was observed, indicating that the relative rate of the Cu-catalyzed process is faster than radical aromatic substitution.

Scheme 22 summarizes the scope of this transformation. As shown, this method is effective for the trifluoromethylation of a wide variety of aromatic and heteroaromatic boronic acid substrates bearing many common functional groups. Importantly, analogous perfluoroalkylation reactions of boronic acids can also be conducted under these conditions using inexpensive and readily available perfluoroalkyl iodide starting materials.

This work indicates that Cu-catalyzed trifluoromethylation reactions involving CF₃• intermediates can be viable and facile processes. We believe that it is possible (even likely) that many Cu-catalyzed processes that were initially believed to involve CF₃⁻ or CF₃⁺ transfer actually involve radical intermediates. For example, several reports have shown that Ag salts serve as promoters for the Cu-catalyzed trifluoromethylation of aryl iodides. The role of Ag has been proposed to involve mediating transmetalation of CF₃⁻ from Si (in TMSCF₃) to Cu. However, the current results (together with those detailed in Part 2 of this Account) suggest that the role of Ag may be to generate CF₃• in these transformations. In addition, CF₃⁺ reagents can potentially undergo 1e⁻ reduction to form CF₃•, suggesting the possibility that Cu-catalyzed reactions of CF₃⁺ reagents may also involve radical intermediates.

Our preliminary results also have implications for the future development of Cu-catalyzed fluoroalkylation sequences. They suggest that combining aryl-Cu species (generated via transmetalation, C–H activation, oxidative addition, etc) with perfluoroalkyl radicals (generated via
various possible oxidative or reductive pathways) could prove to be broadly effective for the construction of new fluorinated molecules.

5 Outlook

Over the past five years, the field of aromatic trifluoromethylation has experienced an explosion of research activity. In parallel with our own efforts, numerous advances from other research groups around the world\cite{1,2,3} have dramatically expanded the organic chemists’ toolbox for installing CF₃ groups onto arenes and heteroarenes. As discussed above, our contributions to this area have particularly focused on discovering new oxidation states (e.g., Pd⁵⁺), new metals (e.g., Ag), and new re-
action pathways (e.g., the combination of Cu and photogenerated CF₃⁺) for achieving aryl–CF₃ coupling. Moving forward, we anticipate that detailed mechanistic studies of all of these transformations will provide valuable insights for the development of second-generation catalysts. Furthermore, the invention of novel pathways and reagents for these reactions should stimulate advances that further facilitate the assembly of trifluoromethyl-containing molecules.

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References