

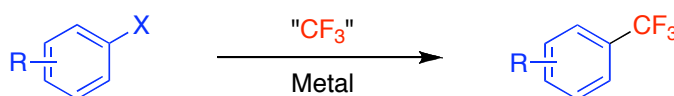
Metal-Mediated Trifluoromethylation of Aryl Halides

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ABSTRACT



Recently the number of relevant organic molecules that contain benzotrifluoride substructures has increased appreciably. Because of this a significant amount of research has been devoted to the discovery of a cost-effective and efficient synthesis of these moieties. This review takes a critical look at recent advances in the metal-mediated trifluoromethylation of aryl halides.

The occurrence of fluorine in natural molecules is low compared to other halogens, however, fluorinated organic compounds have become increasingly important over the past 30 years.¹ It is estimated that 20% of pharmaceuticals and 30 - 40% of agrochemicals contain fluorine. Of these molecules the majority contain benzotrifluorides.² For this reason, a cost-effective, green, and efficient route to benzotrifluorides is highly attractive and a major focus of many research groups.³ This review will focus on the recent advances in the metal-mediated trifluoromethylation of aryl halides.

Benzotrifluorides are traditionally prepared in a two step sequence from toluenes.⁴ Benzotrichlorides are first formed via radical chlorination, followed by treatment with either metal fluorides or anhydrous hydrogen fluoride to afford the desired product (Figure 1). While this method can be used efficiently on scale, it suffers from the need to use highly toxic reagents as well as having a poor substrate scope.

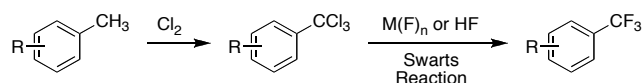


Figure 1. Synthesis of benzotrifluorides.

Due, in part, to the disadvantages of the reactions discussed above a great deal of effort has gone toward finding a method that would convert aryl halides to the corresponding benzotrifluorides. Systems based on copper have received the most attention and have been the most promising for this type of reaction. McLoughlin and Thrower⁵ and Kobayashi and Kumadaki⁶ first reported systems that converted activated aryl halides to benzotrifluorides using CF₃I and copper metal. These methods, however, required high temperatures, superstoichiometric amounts of the metal and showed poor substrate scope. Nevertheless, these seminal publications laid the groundwork for development of the field.

Subsequent work focused on alternate methods for the *in situ* generation of the "CF₃Cu" species. The most widely explored methods involved transmetalation to a copper(I) complex from M(CF₃)₂⁷ or R₃SiCF₃⁸ reagents, or decarboxylation of copper trifluoroacetate complexes

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- 2) Thayer, A.M. *Chem. Eng. News* **2006**, *84*, Number 23, 15.
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- 4) (a) Swarts, F. *Bull. Acad. R. Belg.* **1892**, *24*, 309. (b) Langlois, B. Side-Chain Fluorinated Aromatic Compounds. In *Organofluorine Chemistry*; Banks, R.E.; Smart, B.E.; Tatlow, J.C., Eds.; Plenum Press: New York, 1994; p 221.

5) McLoughlin, V.C.R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921.

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(Figure 2).⁹ These protocols allowed for the trifluoromethylation of aryl iodides or activated aryl chlorides and bromides but still had the drawback of requiring high reaction temperatures and use of stoichiometric quantities of copper. Burton was the first to detect the CuCF_3 complex by NMR and showed that it was unstable at room temperature.^{7b} By adding HMPA this complex could be stabilized but its reactivity was diminished. They concluded from their study that solutions of the CuCF_3 reagent were much more complicated than previously thought and that control and stabilization of this complex would be particularly important for future work in this area.

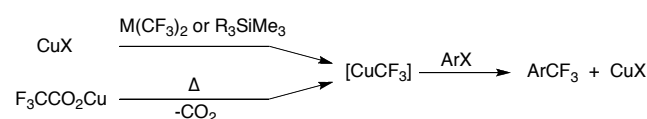


Figure 2. Formation of the “ CF_3Cu ” species.

It was not until recently that a well-defined “ CuCF_3 ” reagent was utilized for the trifluoromethylation of aryl iodides. Vicic showed that treatment of the *N*-heterocyclic carbene (NHC) copper complex **1** with CF_3SiMe_3 (Ruppert’s reagent) yielded the first isolable copper(I)-trifluoromethyl complex **2** (Figure 3).¹⁰ In solution **2** showed no evidence of aggregation and was stable at room temperature. When it was treated with PhI at ambient temperature for 44 h, a 33% yield of the PhCF_3 product was observed. Me_3SiF was determined to be the major byproduct in this reaction, suggesting that the silylated NHC in complex **2** could be the cause of the modest yields obtained for these processes.

This prompted the authors to explore NHC ligands with saturated backbones, as this should prevent incorporation

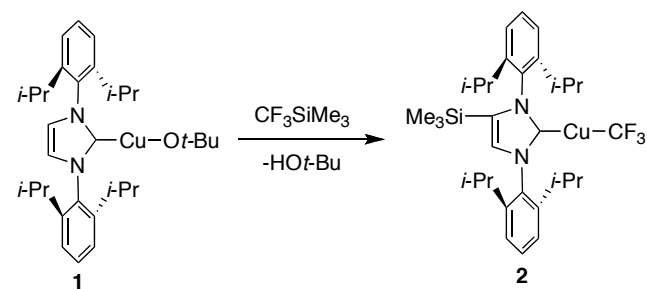


Figure 3. Synthesis of complex **2**.

- 7) (a) Kondratenko, N.V.; Vechirko, E.P.; Yagupolskii, L.M. *Synthesis* **1980**, 932. (b) Wiemers, D.M.; Burton, D.J. *J. Am. Chem. Soc.* **1986**, *108*, 832. (c) Clark, J.H.; McClinton, M.A.; Blade, R.J. *J. Chem. Soc., Chem. Commun.* **1988**, 638.
- 8) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, 32, 91.
- 9) (a) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. *Chem. Lett.* **1981**, 1719. (b) Carr, G.E.; Chambers, R.D.; Holmes, T.F.; Parker, D.G. *J. Chem. Soc. Perkin Trans. 1* **1988**, 921.

of TMS in the corresponding copper complex. Exposing **3**, which contained the saturated *SI*Pr (1,3-di-*i*-propylimidazolin-2-ylidene) ligand, to CF_3SiMe_3 afforded the desired copper- CF_3 complex **4** with no incorporation of TMS (Figure 4). When **4** was allowed to react with aryl iodides at room temperature the benzotrifluoride products were obtained in excellent yields. Because **4** was air-sensitive it was more convenient to generate it *in situ* from **3** in the presence of CF_3SiMe_3 . Although this was much more effective than previous methods for this transformation it was still limited to aryl iodides and required a full equivalent of the metal.

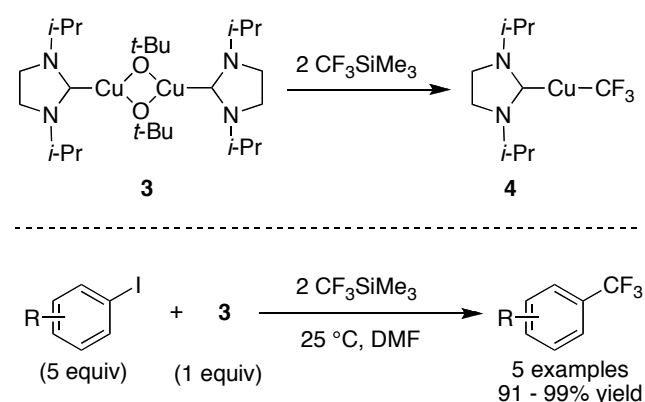


Figure 4. Synthesis of **4** and trifluoromethylation of aryl iodides with **3**.

Vicic next investigated the use of SIMes (1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) as the supporting ligand for these reactions.¹¹ It was postulated that the SIMes copper- CF_3 complexes would show novel reactivity because SIMes is much larger than the *SI*Pr ligand that was used in the previous study. When (SIMes) Cu-OtBu was treated with CF_3SiMe_3 the desired complex **5** was obtained in high yield (Figure 5). Unexpectedly, in solution at room temperature **5** was shown to be in equilibrium with a new species, which was identified as the cuprate salt **6**. Using **6**, aryl iodides and aryl bromides could be converted to benzotrifluorides in good to excellent yields. This complex showed higher reactivity in these reactions than **4**. It was also observed that the rate of trifluoromethylation of PhI increased with decreasing concentration of **6**. By decreasing the concentration the equilibrium would be shifted toward complex **5**. This suggested that **5** was the active species in these reactions and not the cuprate **6**. Formation of discrete “ CuCF_3 ” complexes by Vicic led to much more active systems for the trifluoromethylation of aryl iodides and aryl bromides but stoichiometric amounts of copper were still required.

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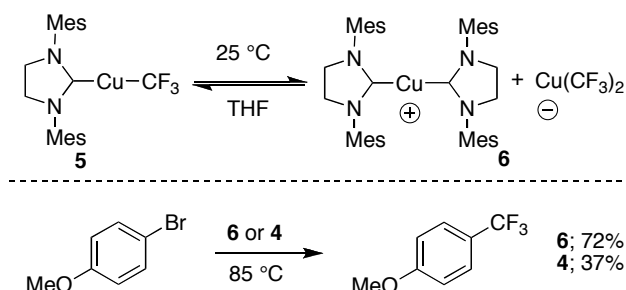
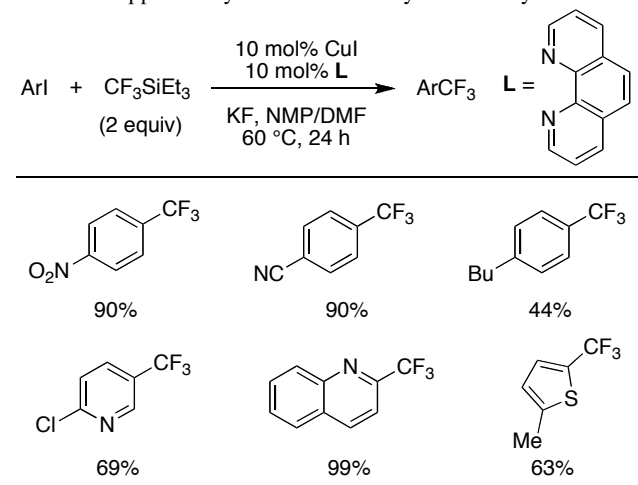


Figure 5. Equilibrium between **5** and **6** and comparison of trifluoromethylation using **4** and **6**.

Amii hypothesized that trifluoromethylation reactions of aryl iodides using R_3SiCF_3 reagents and copper had not been rendered catalytic because the decomposition of the R_3SiCF_3 reagent was faster than the regeneration of the CuX salt.¹² He reasoned that copper(I)-diamine complexes, which have been shown to be highly active in other cross-coupling processes,¹³ could accelerate both the formation of the benzotrifluoride product and the regeneration of the CuX complex; this could conceivably allow these reactions to be performed with catalytic amounts of metal. Using 10 mol% CuI , 10 mol% 1,10-phenanthroline, 2 equiv CF_3SiEt_3 , and 2 equiv KF in NMP/DMF at 60 °C aryl iodides were successfully trifluoromethylated in moderate to excellent yields (Table 1). Unfortunately, this method is only effective with electron-deficient aryl iodides, however, it is still a noteworthy advance in this area because it represents the first trifluoromethylation of aryl halides that is truly catalytic in copper.

Table 1. Copper-catalyzed trifluoromethylation of aryl iodides.



A considerable amount of attention has been devoted to the use of palladium for the conversion of aryl halides to benzotrifluorides. In 1982 Kitazume and Ishikawa reported that they could convert iodobenzene to benzotrifluoride using CF_3I , zinc powder, and a catalytic amount of $Pd(PPh_3)_4$.¹⁴ They proposed that the zinc and CF_3I underwent oxidative addition to form CF_3ZnI , which would

act as a CF_3^- source in the catalytic cycle. This was the first catalytic trifluoromethylation of aryl halides and is still the only Pd -catalyzed method for this transformation reported to date. Even though this method was only shown to trifluoromethylate iodobenzene, it demonstrated that the conversion of aryl halides to benzotrifluorides using a Pd catalyst was possible and has inspired continued research in this area.

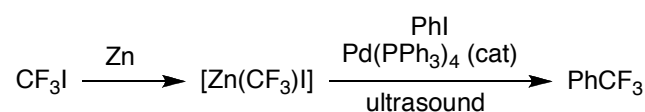


Figure 6. Pd -catalyzed trifluoromethylation of iodobenzene.

In 2004 Hartwig and Culkin systematically studied $C-C$ bond-forming reductive elimination from palladium(II) complexes.¹⁵ They found that at 40 °C complex **7** [$(dppbz)Pd(CH_3)(o\text{-tol})$] underwent facile reductive elimination to give the xylene product in high yield (Figure 7). In contrast, when complex **8**, a congener of **7** where the methyl group is replaced with a CF_3 substituent, was heated to 130 °C for days, no reductive elimination was observed. This showed that reductive elimination of CH_3Ar from a $Pd(II)$ center was much more favorable than for the corresponding reductive elimination to form CF_3Ar . The general recalcitrance to form $ArCF_3$ bonds by reductive elimination further compounds the difficulty in developing a general Pd catalyst for this transformation.

Two years later Grushin and Marshall prepared $(dpe)Pd(CF_3)Ph$ (**9**) in an attempt to show that reductive elimination from these $Pd(II)$ complexes to make benzotrifluorides was possible (Figure 8).¹⁶ In order to model a catalytic system for the production of benzotrifluorides, they heated **9** in the presence of PhI ,

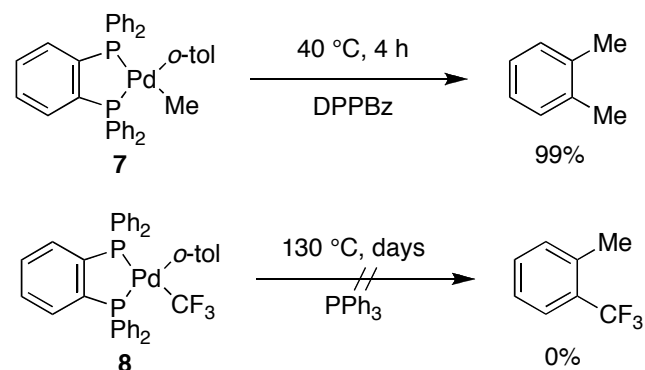


Figure 7. Comparison of the reductive elimination for methyl and trifluoromethyl substituents from $Pd(II)$ aryl complexes.

- Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909.
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- Culkin, D.A.; Hartwig, J.F. *Organometallics* **2004**, *23*, 3398.

postulating that after reductive elimination the resulting Pd(0) species would be trapped by the PhI. To their surprise, only biphenyl and **10** were formed and no Ph-CF₃ was observed. They hypothesized that a small amount of H₂O could facilitate the reduction of **9** to give the Pd(0) complex **11**. This could then undergo an oxidative addition with PhI to provide **12**, which would then be converted to **13** and **10** via a transmetalation with another equivalent of **9**. Complex **13** could then undergo reductive elimination to produce biaryl and regenerate **11**. While this report described an interesting mechanistic study, it provided no precedent for the reductive elimination from an aryl trifluoromethyl Pd(II) complex to yield a benzotrifluoride product.

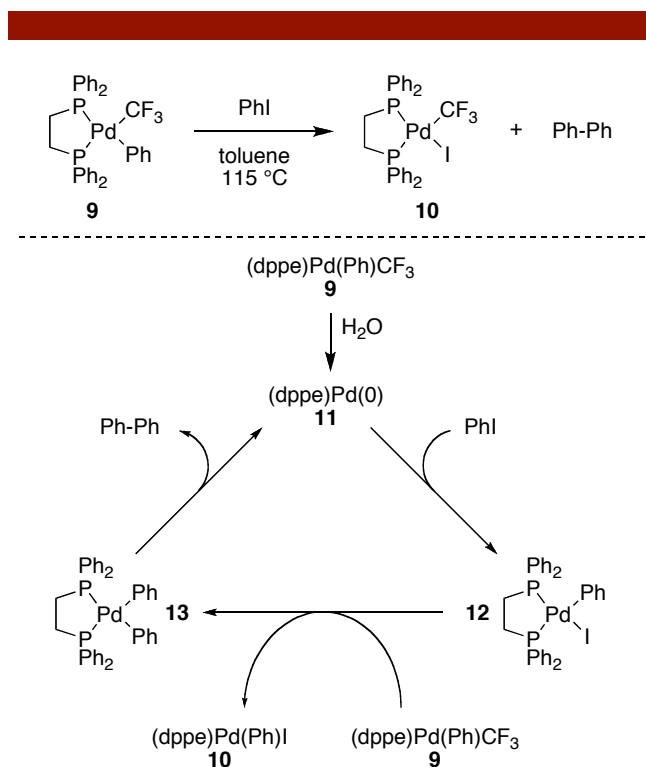


Figure 8. Decomposition of **9** to form biphenyl and **10**.

Aryl trifluoromethyl Pd(II) complexes with strongly chelating bidentate ligands had failed to give the desired reductive elimination products. Grushin and Marshall, therefore, decided to examine complexes with PPh₃ and Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) as supporting ligands.¹⁷ PPh₃ was chosen for study based on Kitazume and Ishikawa's report in which they used Pd(PPh₃)₄ to convert iodobenzene to benzotrifluoride.¹⁴ Xantphos was selected because of its very large bite angle,¹⁸ which is known to accelerate reductive elimination, and its ability to form both *cis*- and *trans*-chelating isomers.¹⁹

Treatment of the aryl fluoride Pd(II) complexes **14** and **15** with CF₃SiMe₃ afforded the desired complexes **16** [(PPh₃)₂Pd(CF₃)Ph] and **17** [XantphosPd(CF₃)Ph] respectively (Figure 9). When **16** was heated to 60 °C in

the presence of PhI or PPh₃ no desired benzotrifluoride product was observed. In contrast, when **17** was heated to 80 °C in the presence of an extra equivalent of free Xantphos, the desired PhCF₃ product was formed in high yield. This was the first example of a reductive elimination of ArCF₃ from a Pd(II) center.

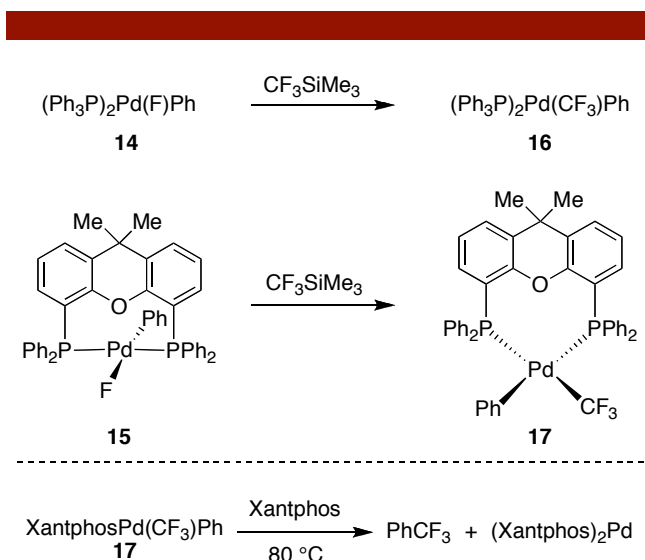


Figure 9. Synthesis of **16** and **17** and reductive elimination from **17** to yield PhCF₃.

In summary, significant effort has gone into developing a metal catalyst for the trifluoromethylation of aryl halides. Systems based on copper have received the most attention for this transformation. Vicic and coworkers have successfully developed (NHC)CuCF₃ reagents that can convert aryl halides to the corresponding benzotrifluorides. These are much more active than previous systems for this reaction but still require stoichiometric amounts of copper and are limited to aryl iodides and activated aryl bromides as substrates. Amii has developed the first copper catalyst, based on diamine ligands, for this transformation. This represented a significant advance but the method is limited to the trifluoromethylation of activated aryl iodides. The development of a Pd catalyst has received considerable attention. While the Kitazume and Ishikawa report establishes that catalysis for this transformation with palladium is possible, their work was limited to iodobenzene as the substrate. Grushin and Marshall were able to demonstrate that reductive elimination to form aryl-CF₃ from a Pd(II) center could take place under mild conditions. This provides support that a Pd catalyst for this transformation could be developed. Although advances have been made in this field, a general catalyst for the conversion of aryl halides and psuedo halides to benzotrifluorides is still needed.

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