Cross-Coupling

DOI: 10.1002/anie.201004051

Transition-Metal-Catalyzed Trifluoromethylation of Aryl Halides**

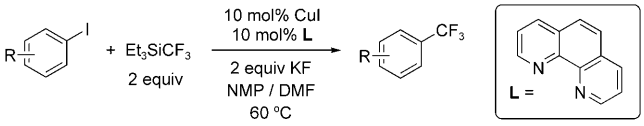
*Rylan J. Lundgren and Mark Stradiotto**

copper · cross-coupling · fluorine · homogeneous catalysis · palladium

The incorporation of trifluoromethyl groups into organic molecules can serve to dramatically alter many of the physical properties of such compounds, including lipophilicity, metabolic stability, and conformational behavior.[1] For these reasons, trifluoromethyl groups are featured in many important pharmaceuticals and pesticides, such as fluoxetine (Prozac), celecoxib (Celebrex), and lansoprazole (Prevacid). Despite the widespread importance of $ArCF_3$ units in medicinal and materials chemistry, no general catalytic method for the selective installation of trifluoromethyl groups into functionalized arenes currently exists.[2]

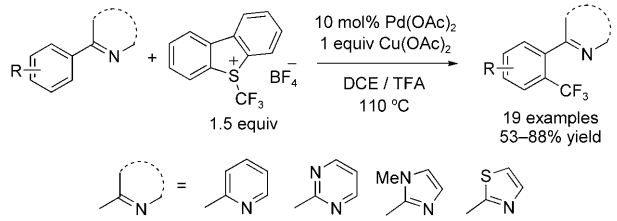
Whereas electrophilic or radical trifluoromethylation reagents have been employed with success in many applications,[3] nucleophilic trifluoromethylation appeared poised to provide progress towards facile, catalytic arene trifluoromethylation analogous to well-established, metal-catalyzed cross-coupling reactions.[4] Unfortunately, the use of nucleophilic "CF_3^-" sources presents difficulties, which has limited their use in metal-catalyzed reactions. The commonly employed Ruppert's reagent (Me_3SiCF_3),[2,5] which upon exposure to fluoride sources generates trifluoromethyl anion, is prone to decomposition leading to the formation of more stable difluorocarbene and fluorosilicon compounds. Thus, when using (trifluoromethyl)silanes, more wasteful and less efficient methods employing stoichiometric copper to generate Cu^I–CF_3 species[6] have been utilized most commonly for arene trifluoromethylations.

Amii and co-workers developed a catalytic aryl iodide trifluoromethylation protocol by employing a CuI/1,10-phenanthroline catalyst system (Scheme 1).[7] The increased electron density at Cu (compared to CuI), resulting in higher nucleophilicity at the CF_3 ligand, combined with the stabilizing and solubilizing effect of the diamine ligand, allowed for rapid Ar–CF_3 bond formation to proceed from the presumed Cu–CF_3 species before significant decomposition of Et_3SiCF_3 in the presence of KF occurred. Other Cu sources such as CuBr or CuCl, or the use of TMEDA (TMEDA = *N,N,N′,N′*-tetramethylethylenediamine) or bipyridine ligands provided lower conversions into the desired product. Although this report represented a significant step forward for Cu-mediated trifluoromethylations, good conversions into the desired products were only observed with electron-poor aryl iodides and with 2-iodoheterocycles.



Scheme 1. Copper-catalyzed cross-coupling of aryl iodides and (trifluoromethyl)silanes. DMF = *N,N′*-dimethylformamide, NMP = *N*-methylpyrrolidone.

Although a classical Pd^0/Pd^{II} cross-coupling cycle would dramatically increase the scope and utility of arene trifluoromethylation reactions,[4] the development of such a process was not reported until very recently.[8,9] Although the generation of $[Pd^{II}(Ar)(CF_3)]$ complexes had been reported in the literature,[4,10] C–C bond formation through reductive elimination appeared to be a major challenge, because of the strength of the Pd–CF_3 bond. Recently, Yu and co-workers elegantly circumvented this problem through the development of a Pd^{II}-catalyzed C–H trifluoromethylation reaction utilizing a dibenzothiophenium reagent (Scheme 2).[11] By employing 10 mol% $Pd(OAc)_2$ in 1,2-dichloroethane with trifluoroacetic acid, good yields were observed for 2-phenylpyridine substrates having electron-donating groups or moderately electron-withdrawing groups, including chloro-func-



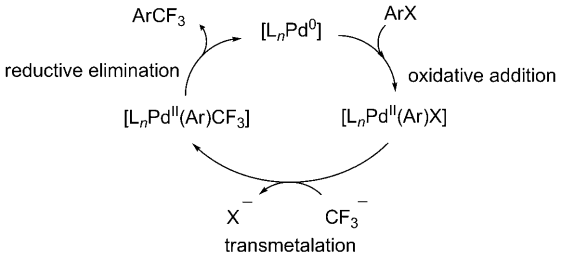
Scheme 2. Palladium(II)-catalyzed *ortho*-trifluoromethylation of arenes. DCE = 1,2-dichloroethane, TFA = trifluoroacetic acid.

[*] R. J. Lundgren, Prof. Dr. M. Stradiotto
Department of Chemistry, Dalhousie University
Halifax, Nova Scotia B3H 4J3 (Canada)
Fax: (+1) 902-494-7190
E-mail: mark.stradiotto@dal.ca

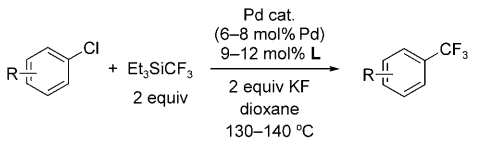
[**] We are grateful to the NSERC of Canada, Dalhousie University, and the Killam Trusts for their support and Prof. G. K. S. Prakash (University of Southern California) for providing information regarding R_3SiCF_3 reagents.

tionalized substrates. Pyrimidine, imidazole, or thiazole could be used as alternative directing groups. However, the reaction relies on a stoichiometric amount of a copper-based oxidant and strictly requires heterocyclic directing groups.

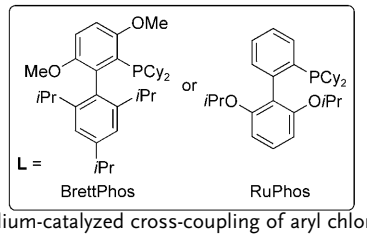
Very recently, a landmark report from Buchwald and co-workers has detailed the Pd-catalyzed trifluoromethylation of aryl chlorides by use of judiciously selected ancillary ligands.[8] Stoichiometric reactions of a [**L**Pd^{II}(Ar)Br] (**L** = BrettPhos) complex with Et_3SiCF_3 in the presence of CsF in THF at 65 °C resulted in the formation of an $ArCF_3$ product in 28 % yield, indicating the feasibility of C–C reductive elimination from [**L**Pd^{II}(Ar)CF_3] complexes under conditions relevant to catalysis (Scheme 3). Additional optimization, namely the use of KF in dioxane at 130 °C, allowed the catalytic trifluoromethylation of 4-*n*-butyl-chlorobenzene in 80 % yield when using 3 mol % [{Pd(allyl)Cl}$_2$] and 9 mol % ligand (Scheme 4). Importantly, the developed methodology ap-



Scheme 3. Proposed Pd^0/Pd^{II} catalytic cycle for the cross-coupling of aryl halides and trifluoromethyl anion.



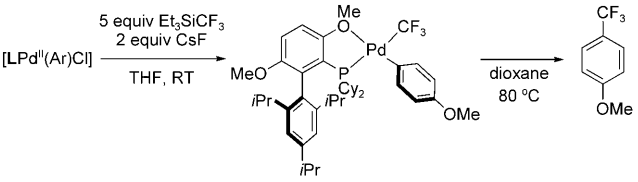
>20 examples 70–94% yield, including heterocyclic examples



Scheme 4. Palladium-catalyzed cross-coupling of aryl chlorides and trifluoromethyl anion derived from Et_3SiCF_3. dba = dibenzylideneacetone; Pd cat.: [{Pd(allyl)Cl}$_2$] or [Pd(dba)$_2$].

pears to exhibit broad substrate scope. Electron-rich and electron-poor aryl chloride substrates reacted with good to excellent yields when using 6–8 mol % Pd, including examples with ester, acetal, amide, nitrile, ether, or tertiary amine functionality. A number of trifluoromethylated heterocycles could be prepared by using similar catalytic protocols, including indole, carbazole, quinoline, and benzofuran frameworks. The versatility within Buchwald's biaryl ligand class[12] was demonstrated by the use of RuPhos (Scheme 4) instead of BrettPhos for more bulky, 2-substituted aryl chlorides. The steric profile of the RuPhos ligand is apparently more suitable when employing sterically demanding substrates.

Persuasive evidence for a Pd^0/Pd^{II} catalytic cycle was also gained by a study of the synthesis and reactivity of relevant Pd intermediates. [**L**Pd^{II}(Ar)Cl] (**L** = BrettPhos) species, generated from the oxidative addition of aryl chloride to **L**Pd^0, underwent reaction with Et_3SiCF_3 and KF in approximately 40 % yield to generate [**L**Pd^{II}(Ar)CF_3] at room temperature (Scheme 5). These complexes were characterized by use of



Scheme 5. Preparation and reductive elimination from a [LPd^{II}(Ar)CF_3] complex.

solution NMR spectroscopy, as well as X-ray crystallography. Notably, a Pd–OMe interaction with the ligand is observed in the solid state, rather than coordination from the *ipso*-carbon atom of the lower flanking ring. Upon heating in dioxane, reductive elimination generated the corresponding (trifluoromethyl)benzene under first-order kinetics. Additionally, when similar reactions were conducted in the presence of aryl chloride, the catalytic cycle was closed by the formation of [**L**Pd^{II}(Ar)Cl], by oxidative addition of the resultant **L**Pd^0 species.

With the recent reports of catalytic aryl halide trifluoromethylation described herein, the stage is now set for continued optimization of such reactions to increase the scope of this transformation. Future efforts to employ a wider range of aryl (pseudo)halides under milder reaction conditions should render such reactions well-suited for application in the synthesis of potential new medicines and organic materials. Additionally, catalyst development and the use of more environmentally friendly CF_3 sources should reduce the environmental and economic impact of utilizing such trifluoromethylation reactions.

Received: July 2, 2010
Published online: September 28, 2010

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