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Synthesis of $(MeCN)_2Pd(CF_3)OTs$, a General Precursor to Palladium(II) Trifluoromethyl Complexes $LPd(CF_3)X$

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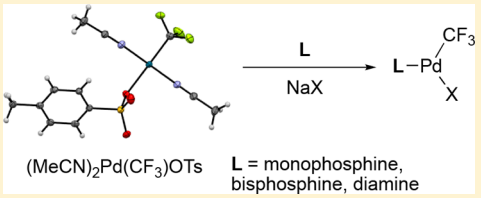
Supporting Information

ABSTRACT: In palladium-catalyzed aryl−trifluoromethyl cross-coupling reactions, reductive elimination is often the rate-limiting step. Stoichiometric studies of reductive elimination have proved effective in evaluating the ability of various ligands to facilitate this challenging elementary step. However, the difficulty of synthesizing palladium trifluoromethyl complexes has hindered the use of this strategy. To address this deficiency, we herein report the synthesis of $(MeCN)_2Pd(CF_3)OTs$, an air- and moisture-stable solid that can be used as a common precursor to access various $LPd(CF_3)X$ complexes. From this complex we were able to prepare palladium trifluoromethyl complexes bearing many monophosphine, bisphosphine, and diamine ligands that are known to help facilitate $Ar-CF_3$ and $vinyl-CF_3$ reductive elimination. Further, we found that the anionic ligand (X) could be readily changed by modifying the NaX or AgX salt used.



In recent years, the trifluoromethyl group has received significant attention from scientists in both the pharmaceutical and agrochemical industries due to its effect on many properties of organic molecules, such as lipophilicity, bioavailability, and metabolic stability.[1] The selective incorporation of trifluoromethyl groups on arenes has also been shown to advantageously influence the HOMO−LUMO gap in various photovoltaic materials and photocatalysts.[2] Due to the prevalence and importance of this functional group, numerous transition-metal-mediated systems have been developed to facilitate aryl−CF_3 bond formations.[3] In the context of Pd-mediated trifluoromethylation, many research groups have systematically studied the steric effects,[4] electronic effects,[5] and denticity[6] of ligands that can help promote this challenging reductive elimination. On the basis of these stoichiometric studies, $Pd^{0/II}$-catalyzed trifluoromethylation of arenes using BrettPhos-, RuPhos-, and tri-*tert*-butylphosphine ($P(^tBu)_3$)-ligated palladium complexes has been realized.[7]

Stoichiometric trifluoromethylation studies typically require transmetalation of a "CF_3^-" equivalent with a Pd oxidative-addition complex. Unfortunately, the difficulty of forming complexes bearing $Pd-CF_3$ bonds in this way has been a major limiting factor in the study of the reactivity of the resultant palladium trifluoromethyl complexes. As reported by Naumann, during transmetalation with a CF_3 anion source, monodentate ligands and weakly bidentate ligands will often dissociate, leading to the undesired formation of palladate complexes.[8] This significantly limits the scope of ligands that can be employed in stoichiometric studies of reductive elimination processes. To address this limitation, we employed a known, but lesser used, alternative strategy to access $LPd(CF_3)Ar$ complexes starting from the synthesis of a Pd complex which incorporates the $Pd-CF_3$ bond but which bears labile ligands that can be subsequently easily displaced by the desired ancillary ligand. Since the desired dative ligand is installed in the final step, this strategy has the potential to overcome the current limitations in ligand scope that would otherwise arise from its displacement by CF_3^-. Specifically, our method would produce compounds of the general formula $LPd(CF_3)X$ following ligand exchange, where L is a desired ancillary dative ligand and X is an anionic ligand, such as a halide. Not only could these complexes potentially be used to study various aryl−trifluoromethyl reductive eliminations but they could also ultimately be used as reagents for late-stage trifluoromethylation.

To date, only four methods exist to form complexes of this type (Scheme 1). The first approach, reported independently by Stone and Klabunde, involves the oxidative addition of CF_3X to Pd^0 precursors.[9] This approach provided important evidence for the formation of stable complexes that contained $Pd-CF_3$ linkages. Stone's method, however, was only demonstrated using triphenylphosphine (PPh_3) or 1,2-bis-(diphenylphosphino)ethane (dppe) as the ancillary ligand, and Klabunde's method utilized vapor diffusion of Pd metal, which is challenging to carry out in most laboratories. Sanford greatly improved upon this approach by using trifluoroacetic anhydride (TFAA) as the CF_3 source in the synthesis of $LPd(CF_3)OTFA$ complexes.[10] As part of this study of the mechanism of Pd-mediated $Ar-CF_3$ coupling, it was found that this complex could undergo transmetalation with diaryl zinc reagents to form $LPd(CF_3)Ar$ complexes. Furthermore, other fluoroalkyl complexes could be easily accessed by variation of the anhydride used in the synthesis. While Sanford's work is currently the most general means of accessing various palladium fluoroalkyl complexes, this approach requires elementary steps that involve an unstable

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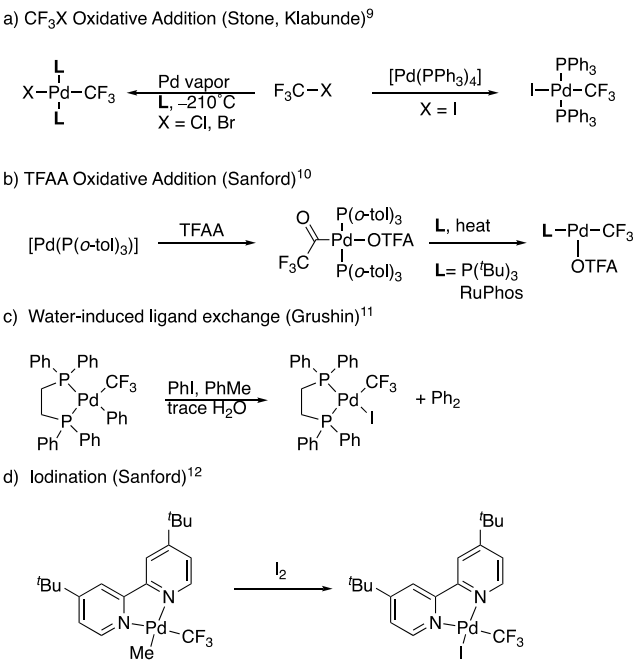
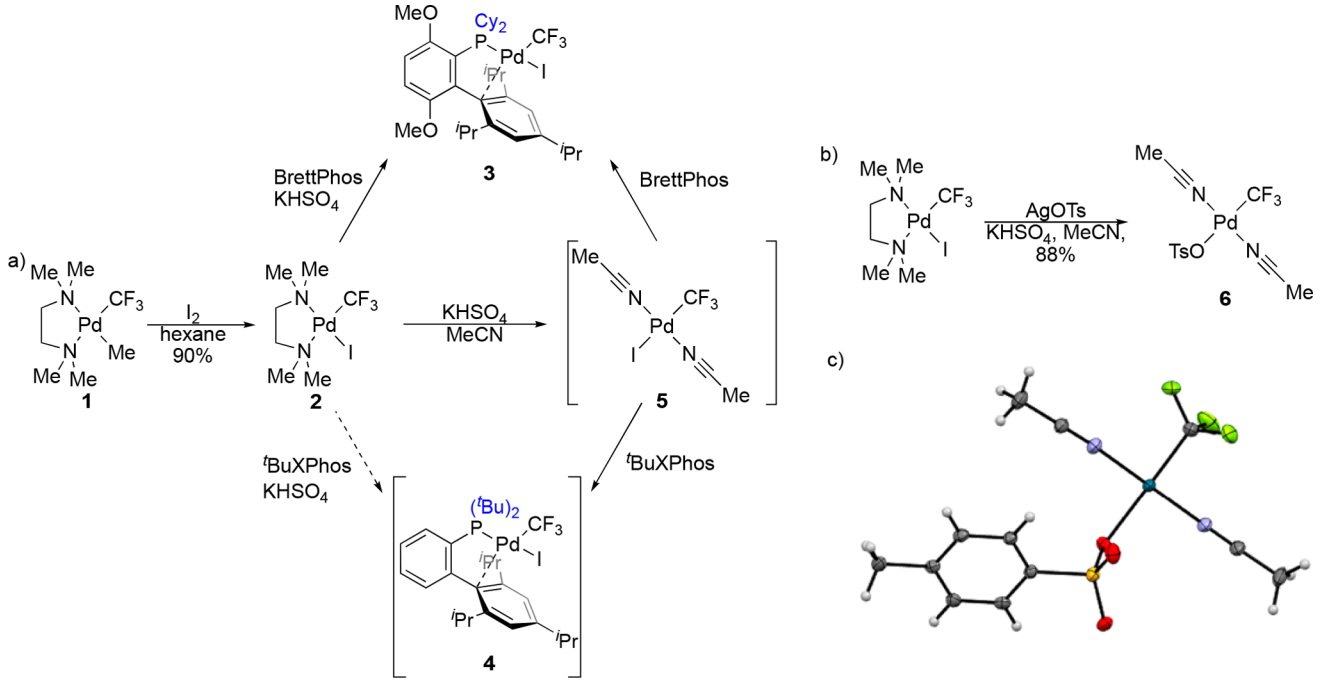
Scheme 1. Current Synthetic Approaches To Access LPd(CF_3)X Complexes



acyl–palladium complex and a subsequent decarbonylation that can only proceed with a limited number of ancillary ligands. Grushin reported a water-induced transformation of dppe-bound (dppe)Pd(CF_3)Ph into (dppe)Pd(CF_3)I in the presence of iodobenzene.[11] While this reaction works exceptionally well for dppe-bound Pd complexes, the corresponding reaction does not occur with diamine ligands or biarylphosphines (such as BrettPhos); in the latter case, reductive elimination of Ar–CF_3 occurs. Finally, Sanford, Mayer, and coworkers reported the synthesis of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine-bound (TMEDA)Pd(CF_3)(Me), which can undergo ligand exchange with 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbbpy), followed by iodination to form (dtbbpy)Pd(CF_3)I.[12] While the dtbbpy-ligated Pd complex was the target of their particular study, we postulated that the initial TMEDA-bound Pd complex could be utilized as a general starting point for the synthesis of many other LPd(CF_3)X complexes, as Grushin has developed an efficient technique for selective abstraction and sequestration of TMEDA from various palladium complexes with the assistance of potassium bisulfate ($KHSO_4$).[11]

Synthesis of Pd–CF_3 Precursors: (TMEDA)Pd(CF_3)I and (MeCN)$_2$Pd(CF_3)OTs. Starting with (TMEDA)Pd(CF_3)(Me) (**1**),[12] iodination cleanly forms (TMEDA)Pd(CF_3)I (**2**) in excellent yield (Scheme 2, footnote *a*). While direct ligand exchange of **2** with BrettPhos failed to form (BrettPhos)Pd(CF_3)I (**3**), addition of excess $KHSO_4$ to a mixture of **2** and BrettPhos led to clean removal of TMEDA and complete formation of **3**. However, this ligand exchange strategy was not found to be general, as the same procedure with bulkier di-*tert*-butylphosphine ligands such as ^{t}BuXPhos failed to deliver any product. Analysis of the crude reaction mixture by ^{31}P NMR indicated that protonated ^{t}BuXPhos was produced exclusively, with no evidence of the desired complex **4**. Thus, a proton transfer between $KHSO_4$ and basic phosphines was limiting the scope of ligands that could be utilized in this process. While attempting to circumvent this issue by separating the TMEDA abstraction and desired ligand association steps, we found that by simply treating **2** with $KHSO_4$ in acetonitrile (MeCN) led to complete formation of *trans*-(MeCN)$_2$Pd(CF_3)I (**5**), as assessed by ^{19}F NMR. While only metastable, **5** could be

Scheme 2. Synthesis of Pd–CF_3 Precursors and Evaluation of Ligand Exchange



[a]See the Supporting Information for detailed experimental procedures for the synthesis of **1**–**3**. [b]Synthesis of the stable Pd–CF_3 precursor (MeCN)$_2$Pd(CF_3)OTs (**6**). See the Supporting Information for a detailed experimental procedure for the synthesis of **6**. [c]ORTEP diagram for **6**. Hydrogen atoms have been omitted for clarity, and ellipsoids are shown at 50% probability.

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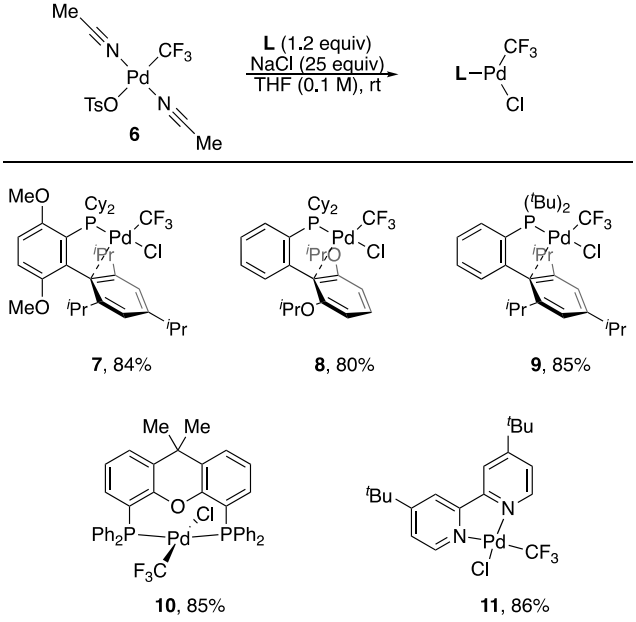
treated with ^{t}BuXPhos to form the desired (^{t}BuXPhos)Pd(CF$_3$)I (**4**) without the formation of protonated ^{t}BuXPhos. Upon further optimization, we found that the addition of silver(I) *p*-toluenesulfonate (AgOTs) to the reaction mixture containing **2** with $KHSO_4$ in MeCN resulted in the formation of *trans*-(MeCN)$_2$Pd(CF$_3$)OTs (**6**), an air- and moisture-stable complex, in 88% yield (Scheme 2, footnote *b*). This reaction was readily scaled to 10 mmol. Single-crystal X-ray diffraction confirmed a square-planar palladium complex wherein the acetonitrile ligands are *trans* to each other (Scheme 2, footnote *c*).

Synthesis of Cl Complexes: LPd(CF$_3$)Cl. Starting from **6**, we synthesized and isolated several Pd−CF$_3$ complexes bearing ancillary ligands that were previously reported to facilitate Ar−CF$_3$ reductive elimination. While simply allowing each ligand to react with **6** overnight led to complete conversion to the desired product by ^{19}F and ^{31}P NMR, the resulting tosylate complexes were often challenging to isolate and each required unique purification conditions. Although these complexes could be used directly and further modified without isolation and purification, we sought to pursue general conditions that would lead to Pd−CF$_3$ complexes that were easily isolable with minimal modification of the purification procedure for each ligand. Accordingly, we found that stirring **6** with a desired ligand and excess sodium chloride in THF cleanly formed the chloride complex LPd(CF$_3$)Cl (Scheme 3). These complexes

Scheme 3. Synthesis of LPd(CF$_3$)Cl Complexes[a]

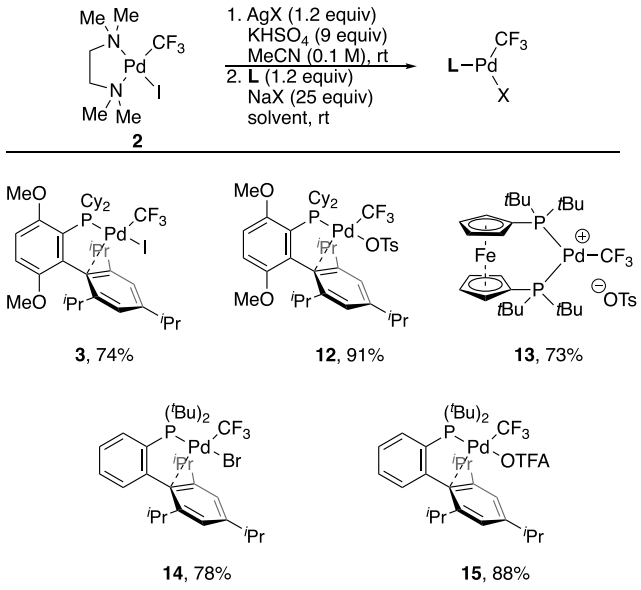


[a]Reaction conditions: **6** (0.5 mmol), **L** (0.6 mmol), and NaCl (12.5 mmol) in THF (5.0 mL) at room temperature overnight; isolated yields reported.

were found to be easily isolable by filtration in air and were typically stable under ambient conditions. Using this approach, we were able to synthesize numerous chloride complexes, including complexes bearing the ancillary ligands BrettPhos (**7**) and RuPhos (**8**), both previously shown to facilitate catalytic trifluoromethylation of aryl chlorides,[7a] ^{t}BuXPhos (**9**), previously shown to facilitate catalytic trifluoromethylation of vinyl triflates,[13] Xantphos (**10**), the ligand used in the first example of stoichiometric reductive elimination to form Ar−CF$_3$,[6a] and dtbbpy (**11**), which has been shown to facilitate aryl trifluoromethylation from high-valent Pd^{IV} centers.[14] However, extremely bulky diadamantylphosphine ligands such as AdXPhos did not react with **6**.

Synthetic Modifications To Access Various X Groups: LPd(CF$_3$)X. After successfully forming the aforementioned chloride complexes, we also wanted to modify the general procedure to generate LPd(CF$_3$)X complexes bearing a variety of anionic ligands X (Scheme 4). In the modified procedure,

Scheme 4. Synthesis of LPd(CF$_3$)X Complexes[a]



[a]Reactions were run with **2** (0.5 mmol) and **L** (0.6 mmol) at room temperature. See the Supporting Information for detailed experimental procedures.

(TMEDA)Pd(CF$_3$)I (**2**) was allowed to react with a silver salt (AgX) and $KHSO_4$ to form the *trans*-bis(acetonitrile) intermediate complex (MeCN)$_2$Pd(CF$_3$)X. Following removal of insoluble TMEDA and silver salts, this acetonitrile complex was allowed to react with a ligand in the presence of a sodium salt (NaX). As previously described, the BrettPhos complex **3** can be synthesized directly from **2**. By simply omitting the use of a sodium salt, BrettPhos and cationic 1,1′-bis(di-*tert*-butylphosphino)ferrocene (DTBPF) tosylate complexes **12** and **13** were formed. By using sodium bromide (NaBr) instead of NaCl, the ^{t}BuXPhos bromide complex **14** could be formed in moderate yield. Finally, by using silver trifluoroacetate (AgOTFA) instead of AgOTs, the ^{t}BuXPhos trifluoroacetate complex **15** could be formed. Thus, using this general strategy, we have been able to synthesize numerous trifluoromethyl complexes of the general formula LPd(CF$_3$)X, where both L and X could be readily modified.

In conclusion, we have developed a new palladium complex, *trans*-(MeCN)$_2$Pd(CF$_3$)OTs, an air- and moisture-stable reagent that can be used as a general precursor for the formation of Pd−CF$_3$ complexes bearing one of many ancillary ligands. This reagent was stable for months at 0 °C in air with no evidence of diminished yields in the subsequent ligand exchange. The variety of complexes accessible by this method could enable broader and more facile stoichiometric studies of C−CF$_3$ reductive elimination. Studies are also underway

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toward the use of these complexes as trifluoromethylation reagents.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and characterization data for new compounds (PDF)

Accession Codes

CCDC 1944264 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): MIT has patents on ligands that are described in this manuscript, from which S.L.B. and former co-workers receive royalty payments.

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