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Pd-Catalyzed Synthesis of Ar–SCF3 Compounds Under Mild Conditions**

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The unique chemical properties of aryl trifluoromethyl sulfides ($ArSCF_3$) have been known for over 60 years.[1] The capacity of SCF_3 to act as a lipophilic electron-withdrawing group has resulted in the incorporation of $ArSCF_3$ components into a number of pharmaceutical and agrochemical agents.[2] Unfortunately, direct access to this important class of compounds is complicated by a lack of efficient, safe and general methods.[1a, 3]

Significant advances in Pd-catalyzed cross-coupling processes have allowed for efficient access to a diverse array of functionalized aromatic products, including aryl sulfides.[4] While the coupling of many aromatic or aliphatic thiols with aryl halides has been achieved with very high efficiency,[5] the analogous transformation to form aryl trifluoromethyl sulfides has not been reported. As gaseous CF_3SH (b.p. = -36 °C)[6] can be difficult to handle in a laboratory setting, several SCF_3 salts have been developed, however, most of these decompose under standard cross-coupling conditions.[3c]

It has been postulated that reductive elimination of Ar–SR from a palladium center is initiated via a nucleophilic attack on the electrophilic hydrocarbyl group by the metal-bound thiolate.[7] Thus, metal-catalyzed Ar–SCF_3 coupling might be complicated by the reduced nucleophilicity of the SCF_3 anion[2b] as compared to a standard thiolate.

Recent reports from our group regarding novel ligands including BrettPhos (**1**), *t*-BuBrettPhos (**2**), XPhos (**3**) and 3,4,5,6-tetramethyl(*t*-Bu)XPhos (**4**) (Scheme 1), have allowed for the successful coupling of weak nucleophiles traditionally thought to be reluctant participants in the transmetalation or reductive elimination steps of a typical Pd(0)/Pd(II) catalytic cycle. Specifically, using these catalyst systems has allowed for the direct formation of diaryl ether,[8] aryl fluoride,[9] aryl trifluoromethyl,[10] and aryl nitro compounds[11] from their corresponding aryl halides or pseudo halides. In light of these results, we hypothesized that a similar Pd-based system might allow for the formation of an aromatic C–SCF_3 bond.

As we suspected that reductive elimination from putative intermediate **11** would be rate limiting in any catalytic process, we began our investigation by attempting its preparation from oxidative addition complex **10** via treatment with $AgSCF_3$ (Scheme 2). We were surprised when this procedure did not provide the expected transmetalation complex but instead led directly to the Ar–SCF_3 product **12** (presumably via **11**).

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Given this finding, we attempted to convert 4-(4-bromophenyl)morpholine to the corresponding trifluoromethyl sulfide using $AgSCF_3$ and a catalytic quantity of **1** and $(COD)Pd(CH_2TMS)_2$ (Table 1). However, under these conditions, none of **13** was observed. We surmised that failure to observe the coupled product might be due to the inefficient transfer of $^{\ominus}SCF_3$ to **10** under catalytic conditions. Thus, we elected to examine the use of a number of alternative previously reported $^{\ominus}SCF_3$ sources (Table 1).[3c, e]

Clark's[3d] work on the use of $(Bu)_4NI$ and $AgSCF_3$ for S_NAr reactions with aryl halides indicated to us that the addition of a quaternary ammonium salt might be beneficial. Consistent with this hypothesis, the addition of 1 equivalent of $(Bu)_4NI$ to the reaction mixture increased the yield of **13** from 0 % to 55 % (Table 1). Further examination of different ammonium salts revealed that $Ph(Me)_3NI$ was more effective than $(Bu)_4NI$ and that switching to a more soluble ammonium salt, $Ph(Et)_3NI$, provided a nearly quantitative yield of the desired product (Table 1). Based on work done by Clark, it is presumed that the iodide anion binds to $AgSCF_3$ in order generate an anionic "ate" complex. We hypothesize that a large diffuse cation further aids in the solubility of this complex. It is worth noting that while the use of quaternary ammonium iodides and bromides allowed for catalytic turnover, the corresponding chloride analogs were ineffective.

With the optimal combination of $Ph(Et)_3NI$ and $AgSCF_3$ realized, we re-examined various other previously reported ligands, which have enjoyed a measure of success in Pd-catalyzed cross-coupling reactions.[12] Our survey revealed that only dialkylbiarylphosphine based ligands were successful carrying out this transformation, while other ligands such as **5** or **6** did not perform well even with higher catalyst loadings.

Accordingly, we were successful in converting electron-rich, -neutral and -deficient aryl bromides to their respective aryl trifluoromethyl sulfides in 2 hours at 80 °C using 1.5 - 3.5 mol % of Pd and 1.65 – 3.85 mol % of **1**. Electron-neutral and electron-rich substrates were coupled more efficiently than their electron-poor analogs. This effect has previously been noted in the coupling of aryl halides with $NaNO_2$.[11] Substrates containing acid-sensitive functional groups, such as BOC-protected anilines and nitriles, were tolerated and coupled in high yield along with substrates containing ketones, esters, and free NH groups of anilines (Table 3). Aryl bromides containing bulky *ortho*-groups, e.g., *o*-cyclohexyl and *o*-phenyl groups, could also be coupled successfully, although they required the use of the smaller ligand XPhos (**3**) (Table 3).

Heteroaryl bromides such as those containing indoles, pyridines, quinolines, thiophenes and furans, were also viable substrates (Table 4). Unfortunately, attempts to extend this methodology to the coupling of aryl chlorides or aryl triflates were unsuccessful. We are currently working to understand and overcome these limitations.

Finally, to demonstrate the utility of this method, we prepared an intermediate in the reported synthesis of Toltrazuril,[13] an antiprotozoal agent. Intermediate **14** can be assembled from readily available starting materials in an overall yield of 88%. The key C–SCF_3 bond-forming process proceeded in 95% yield (Scheme 3).

In summary, we have developed a general method for the Pd-catalyzed Ar–SCF_3 bond-forming reaction. Using this method, a wide range of aryl bromides were converted into their corresponding aryl trifluoromethyl sulfides. Additionally, we have been successful in generating a variety of heterocyclic aryl trifluoromethyl sulfides from heteroaryl bromide precursors. Due to the utility of Ar–SCF_3 compounds as biologically active agents, and the mild reaction conditions employed, we expect this method to be immediately implemented in the discovery of novel compounds with pharmaceutical and agrochemical applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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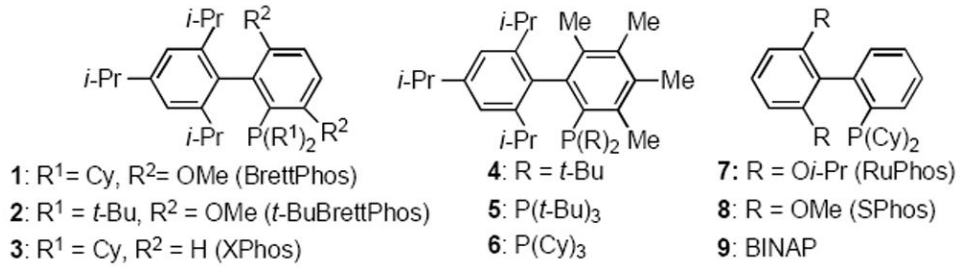
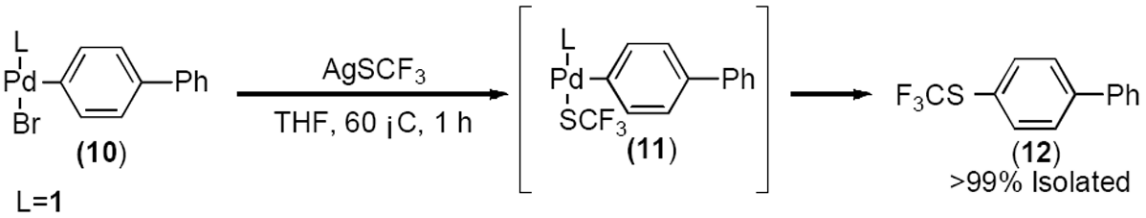


1: R^1= Cy, R^2= OMe (BrettPhos)
2: R^1 = *t*-Bu, R^2 = OMe (*t*-BuBrettPhos)
3: R^1 = Cy, R^2 = H (XPhos)

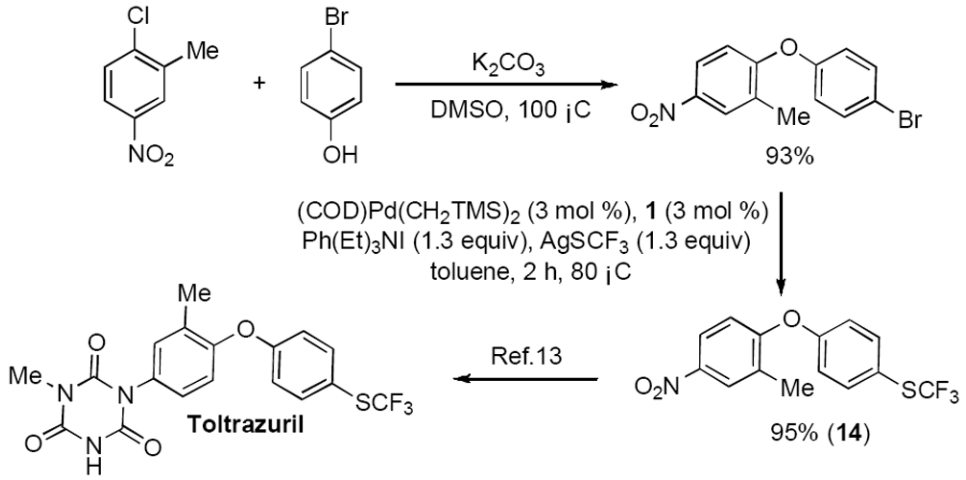
4: R = *t*-Bu
5: P(*t*-Bu)$_3$
6: P(Cy)$_3$

7: R = O*i*-Pr (RuPhos)
8: R = OMe (SPhos)
9: BINAP

Scheme 1.
Various ligands used in Pd-catalyzed cross-coupling reactions.



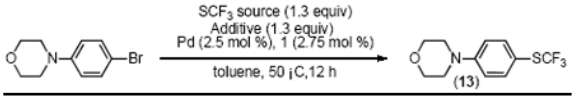
Scheme 2.
Formation of $ArSCF_3$ via transmetalation and reductive elimination from an isolated LPdAr(Br) complex.



Scheme 3.
Synthesis of Toltrazuril intermediate.

Table 1

Examination of different SCF_3 sources.[a]

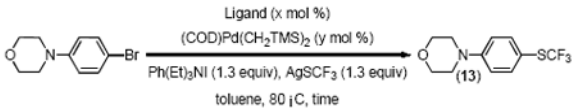


Entry	SCF_3 Source	Additive	Yield [%]
1	$CsSCF_3$	none	10
2	$AgSCF_3$	none	0
3	$(Me)_4NSCF_3$	None	20
4	$AgSCF_3$	$(Me)_4NI$	0
5	$AgSCF_3$	$(Bu)_4NCl$	0
6	$AgSCF_3$	$(Bu)_4NBr$	56
7	$AgSCF_3$	$(Bu)_4NI$	55
8	$AgSCF_3$	$Ph(Me)_3NI$	80
9	$AgSCF_3$	$Ph(Et)_3NI$	>99

[a] $(COD)Pd(CH_2TMS)_2$ (2.5 mol %), PhMe (4 mL); all reactions are run on 0.2 mmol scale and all reported yields are based on GC data

Table 2

Examination of various ligands commonly employed in Pd-catalyzed reactions.[a]



Entry	Ligand	Time (h)	Yield (%)
1	**1**	1	>99[b]
2	**2**	1.5	60[b]
3	**3**	1	84[b]
4	**7**	2	36[c]
5	**8**	2	3[c]
6	**5**	2	29[d]
7	**6**	2	0[d]
8	**9**	2	0[d]
9	**4**	2	<1[c]

[a] PhMe (4 mL); all reactions are run on 0.2 mmol scale and all reported yields are based on GC data.

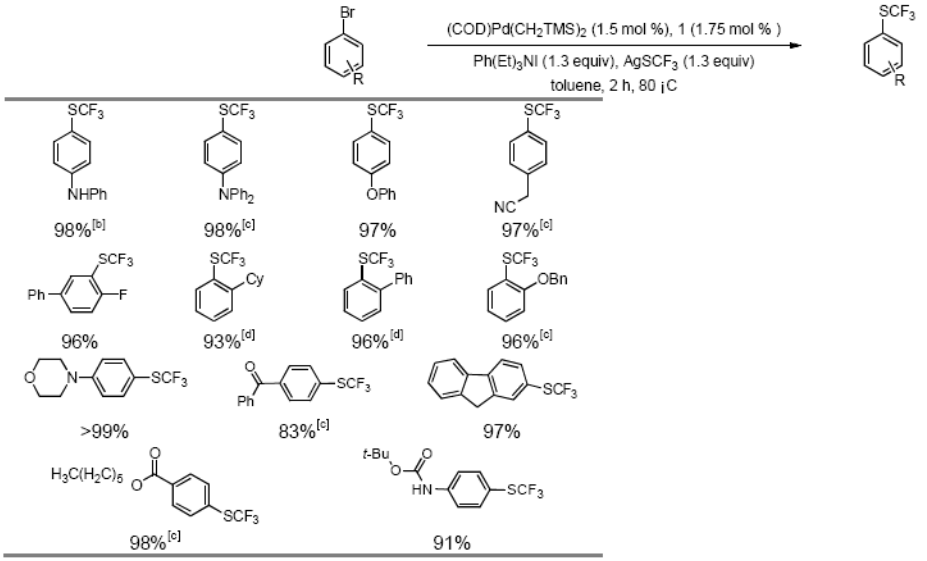
[b] 1.15 mol % Pd, 1.27 mol % L.

[c] 1.5 mol % Pd, 1.65 mol % L.

[d] 2.5 mol % Pd, 2.75 mol % L

Table 3

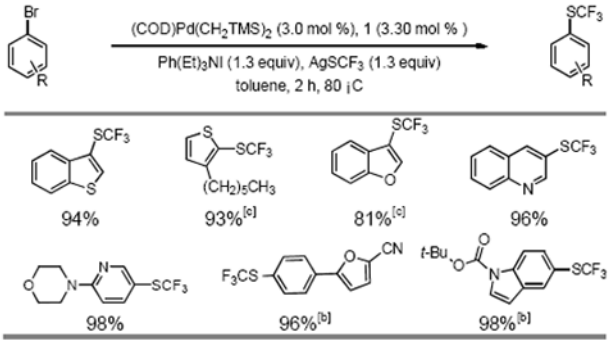
Pd-catalyzed coupling of aryl bromides.[a]



[a] ArBr (1 mmol), PhMe (5 mL); isolated yields, average of two runs. [b] 3.0 mol % Pd, 3.3 mol % **1**. [c] 2.0 mol % Pd, 2.2 mol % **1**. [d] 3.0 mol % Pd, 3.3 mol % **3**.

Table 4

Pd-catalyzed formation of heteroaryl–SCF_3 compounds.[a]



[a] ArBr (1 mmol), PhMe (5 mL); isolated yields, average of two runs. [b] 1.5 mol % Pd, 1.65 mo l% **1**. [c] 3.5 mol % Pd, 3.85 mol % **1**.