C–S Bond Formation

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Pd-Catalyzed Synthesis of Ar–SCF_3 Compounds under Mild Conditions**

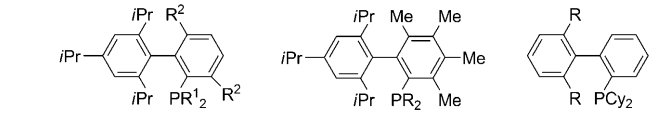
*Georgiy Teverovskiy, David S. Surry, and Stephen L. Buchwald**

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 efficient access to a diverse array of functionalized aromatic products, such as 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 by 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.

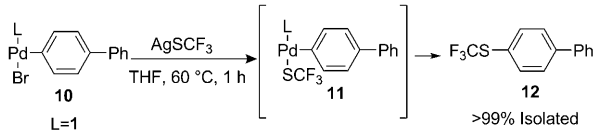
Recent reports from our group regarding novel ligands including BrettPhos (**1**), *t*BuBrettPhos (**2**), XPhos (**3**), and 3,4,5,6-tetramethyl(*t*Bu)XPhos (**4**; Scheme 1), have allowed the successful coupling of weak nucleophiles traditionally thought to be reluctant participants in the transmetalation or reductive elimination steps of a typical Pd^0/Pd^{II} catalytic cycle. Specifically, using these catalyst systems has allowed 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 the formation of a $C_{aromatic}$–SCF_3 bond.



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: PCy_3
7: R = O*i*Pr (RuPhos)
8: R = OMe (SPhos)
9: BINAP

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

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** by 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**).



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

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 $^-SCF_3$ to **10** under catalytic conditions. Thus, we elected to examine the use of a number of alternative previously reported $^-SCF_3$ sources (Table 1).[3c,e]

Clark and Adams'[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 one 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

[*] G. Teverovskiy, Dr. D. S. Surry, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

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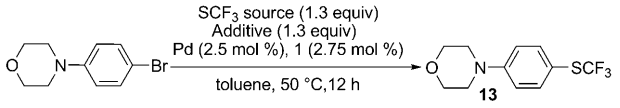
Table 1: Examination of different SCF_3 sources.[a]



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	$AgSCF_3$	$PhEt_3NI$	>99

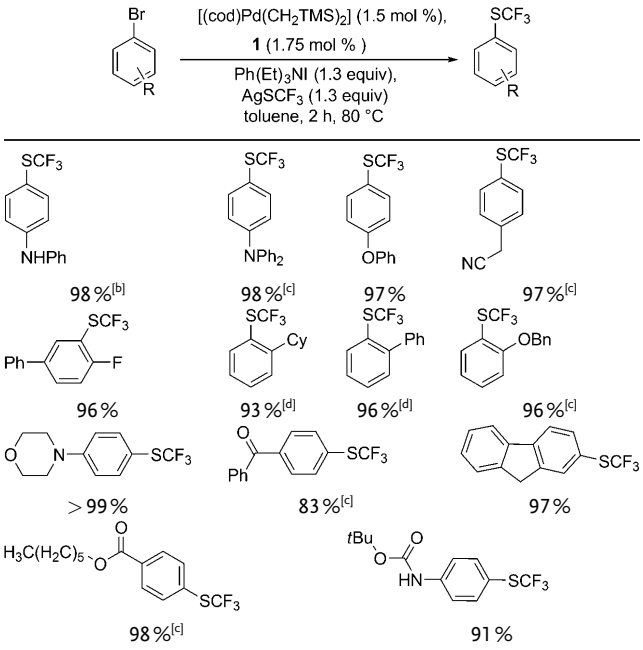
[a] $[(cod)Pd(CH_2TMS)_2]$ (2.5 mol%), PhMe (4 mL); all reactions were run on 0.2 mmol scale and all reported yields are based on GC data.

done by Clark and Adams, it is presumed that the iodide anion binds to $AgSCF_3$ to 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 catalytic turnover, the corresponding chloride analogues 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 (Table 2).[12] Our survey revealed that only dialkylbiarylphosphine-based ligands were successful at carrying out this transformation, while other ligands such as **5** or **6** did not perform well even with higher catalyst loadings.

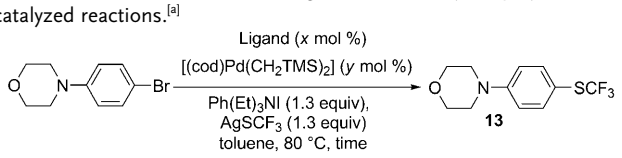
Accordingly, we were successful in converting electron-rich, -neutral, and -deficient aryl bromides to their respective aryl trifluoromethyl sulfides in 2 h at 80 °C using 1.5–3.5 mol% of Pd and 1.65–3.85 mol% of **1**. Electron-neutral and electron-rich substrates were coupled more efficiently than their electron-poor analogues. This effect has previously been noted in the coupling of aryl halides with $NaNO_2$.[11] Substrates containing acid-sensitive functional groups, such as *tert*-butyoxycarbonyl(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, for example, *o*-cyclohexyl and *o*-phenyl groups, could also be coupled successfully, although they required the use of the smaller ligand XPhos (**3**) (Table 3).

Table 3: Pd-catalyzed coupling of aryl bromides.[a]



[a] ArBr (1 mmol), PhMe (5 mL); yield of isolated product, 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 2: Examination of various ligands commonly employed in Pd-catalyzed reactions.[a]



Entry	Ligand	*t* [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]

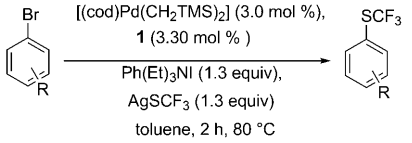
[a] PhMe (4 mL); all reactions were run on 0.2 mmol scale and all reported yields are based on GC data. [b] 1.15 mol% Pd, 1.27 mol% L. [c] 1.5 mol% Pd, 1.65 mol% L. [d] 2.5 mol% Pd, 2.75 mol% L.

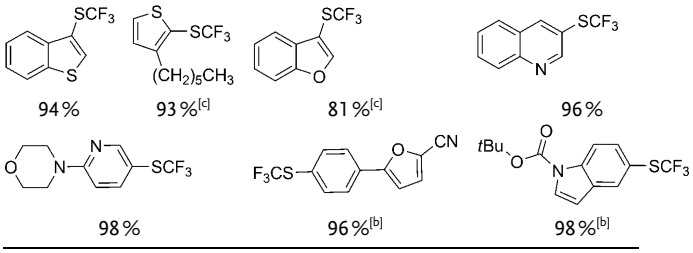
Heteroaryl bromides, such as those containing indoles, pyridines, quinolines, thiophenes, and furans, were also viable substrates (Table 4). Unfortunately, attempts to extend this methodology to the coupling of aryl chlorides or aryl triflates were unsuccessful. We are currently working to understand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

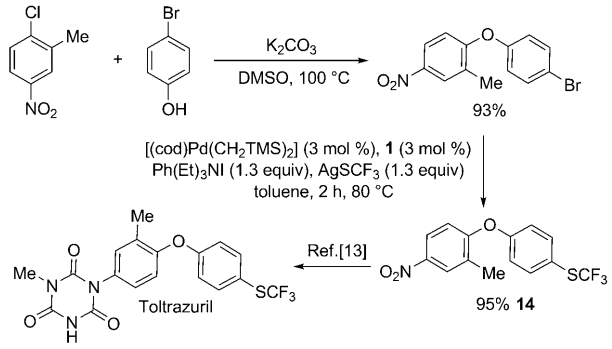
In summary, we have developed a general method for the Pd-catalyzed Ar–SCF_3 bond-forming reaction. Using this method, a wide range of aryl bromides were converted into their corresponding aryl trifluoromethyl sulfides. Additionally, we have been successful in generating a variety of heterocyclic aryl trifluoromethyl sulfides from heteroaryl bromide precursors. Due to the utility of Ar–SCF_3 com-

Table 4: Pd-catalyzed formation of heteroaryl–SCF_3 compounds.[a]





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



Scheme 3. Synthesis of Toltrazuril intermediate.

pounds 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.

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