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Citation: Teverovskiy, Georgiy, David S. Surry, and Stephen L. Buchwald. "Pd-Catalyzed Synthesis of Ar-SCF₃ Compounds under Mild Conditions." *Angewandte Chemie International Edition* 50, no. 32 (August 1, 2011): 7312-7314.

As Published: <http://dx.doi.org/10.1002/anie.201102543>

Publisher: Wiley Blackwell

Persistent URL: <http://hdl.handle.net/1721.1/81964>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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Published in final edited form as:

Angew Chem Int Ed Engl. 2011 August 1; 50(32): 7312–7314. doi:10.1002/anie.201102543.

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

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The unique chemical properties of aryl trifluoromethyl sulfides (ArSCF₃) have been known for over 60 years.^[1] The capacity of SCF₃ to act as a lipophilic electron-withdrawing group has resulted in the incorporation of ArSCF₃ 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 CF₃SH (b.p. = -36 °C)^[6] can be difficult to handle in a laboratory setting, several SCF₃ 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–SCF₃ coupling might be complicated by the reduced nucleophilicity of the SCF₃ 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–SCF₃ 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 AgSCF₃ (Scheme 2). We were surprised when this procedure did not provide the expected transmetalation complex but instead led directly to the Ar–SCF₃ product **12** (presumably via **11**).

**We thank the National Institutes of Health (NIH) for financial support of this project (GM-58160). We thank BASF for a gift of Pd compounds, FMC Lithium for a gift of *t*Bu₂PCl and Nippon Chemical for a gift of Cy₂PCl and unrestricted support. G.T. would also like to thank the DoD for the NDSEG Fellowship (32 CFR 168a). The Varian NMR instrument used was supported by the NSF (CHE-980861).

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

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 $(\text{COD})\text{Pd}(\text{CH}_2\text{TMS})_2$ (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 $^-\text{SCF}_3$ to **10** under catalytic conditions. Thus, we elected to examine the use of a number of alternative previously reported $^-\text{SCF}_3$ sources (Table 1).^[3c, e]

Clark's^[3d] work on the use of $(\text{Bu})_4\text{NI}$ and AgSCF_3 for $\text{S}_\text{N}\text{Ar}$ 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 $(\text{Bu})_4\text{NI}$ to the reaction mixture increased the yield of **13** from 0 % to 55 % (Table 1). Further examination of different ammonium salts revealed that $\text{Ph}(\text{Me})_3\text{NI}$ was more effective than $(\text{Bu})_4\text{NI}$ and that switching to a more soluble ammonium salt, $\text{Ph}(\text{Et})_3\text{NI}$, 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 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 for catalytic turnover, the corresponding chloride analogs were ineffective.

With the optimal combination of $\text{Ph}(\text{Et})_3\text{NI}$ 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).

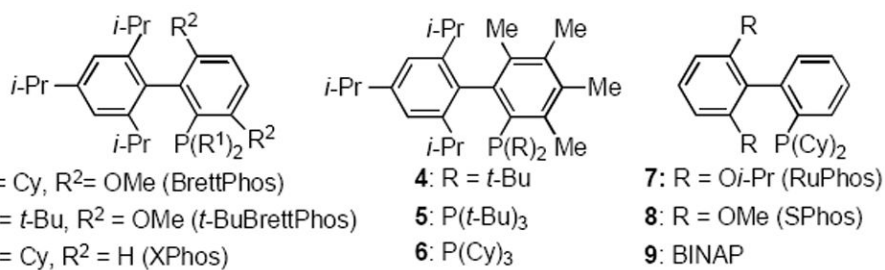
In summary, we have developed a general method for the Pd-catalyzed Ar- SCF_3 bond-forming reaction. Using this method, a wide range of aryl bromides were converted into their corresponding aryl trifluoromethyl sulfides. Additionally, we have been successful in generating a variety of heterocyclic aryl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

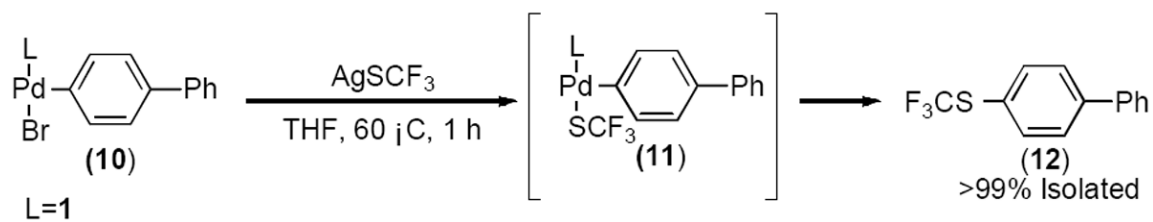
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References

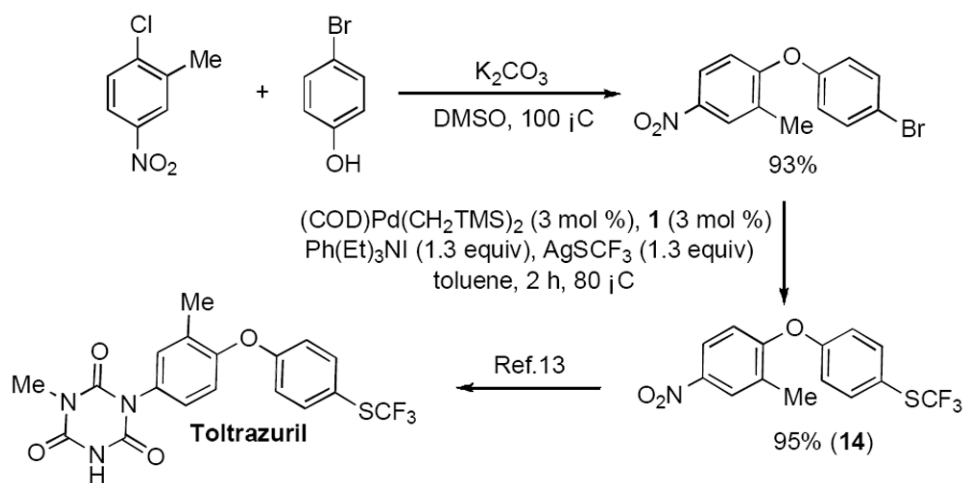
1. a) Manteau B, Pazenok S, Vors JP, Leroux FR. *J Fluorine Chem.* 2010; 131:140. b) Jeschke P. *Pest Manag Sci.* 2010; 66:10. [PubMed: 19701961]
2. a) Leo A, Hansch C, Elkins D. *Chem Rev.* 1971; 71:525. b) Yagupolskii LM, Il'chenko AY, Kondratenko NV. *Russ Chem Rev.* 1974; 43:32. c) Leroux F, Jeschke P, Schlosser M. *Chem Rev.* 2005; 105:827. [PubMed: 15755078]
3. a) Kieltsch I, Eisenberger P, Togni A. *Angew Chem Int Ed.* 2007; 46:754. b) Pooput C, Medebielle M, Dolbier WR. *Org Lett.* 2004; 6:301. [PubMed: 14723553] c) Tyrra W, Naumann D, Hoge B, Yagupolskii YL. *J Fluorine Chem.* 2003; 119:101. d) Adams DJ, Clark JH. *J Org Chem.* 2000; 65:1456. [PubMed: 10814109] e) Clark JH, Jones CW, Kybett AP, Mcclinton MA, Miller JM, Bishop D, Blade RJ. *J Fluorine Chem.* 1990; 48:249. f) Wakselman C, Tordeux M. *J Chem Soc Chem Comm.* 1984:793. g) Yagupolskii LM, Kondratenko NV, Sambur VP. *Synthesis.* 1975:721. h) Adams DJ, Goddard A, Clark JH, Macquarrie DJ. *Chem Commun.* 2000:987. i) Boiko VN, Shchupak GM, Yagupolskii LM. *Zh Org Khim.* 1977; 13:1057.
4. a) Surry DS, Buchwald SL. *Chemical Science.* 2011; 2:27. [PubMed: 22432049] b) Cacchi S, Fabrizi G. *Chem Rev.* 2005; 105:2873. [PubMed: 16011327] c) Miyaura, N. *Metal-Catalyzed Cross-Coupling Reactions.* Second ed. de Meijere, A.; Diedrech, F., editors. Wiley-VCH; Weinheim: 2004.
5. Fernández-Rodríguez MA, Shen Q, Hartwig JF. *J Am Chem Soc.* 2006; 128:2180. [PubMed: 16478149]
6. Zack NR, Shreeve JM. *Synthetic Commun.* 1974; 4:233.
7. Mann G, Baranano D, Hartwig JF, Rheingold AL, Guzei IA. *J Am Chem Soc.* 1998; 120:9205.
8. Burgos CH, Barder TE, Huang X, Buchwald SL. *Angew Chem Int Ed.* 2006; 45:4321.
9. Watson DA, Su MJ, Teverovskiy G, Zhang G, Garcia-Fortanet J, Kinzel T, Buchwald SL. *Science.* 2009; 325:1661. [PubMed: 19679769]
10. Cho EJ, Senecal TD, Kinzel T, Zhang Y, Watson DA, Buchwald SL. *Science.* 2010; 328:1679. [PubMed: 20576888]
11. Fors BP, Buchwald SL. *J Am Chem Soc.* 2009; 131:12898. [PubMed: 19737014]
12. a) Barder TE, Walker SD, Martinelli JR, Buchwald SL. *J Am Chem Soc.* 2005; 127:4685. [PubMed: 15796535] b) Milne JE, Buchwald SL. *J Am Chem Soc.* 2004; 126:13028. [PubMed: 15469301] c) Wolfe JP, Buchwald SL. *J Am Chem Soc.* 1996; 118:7215. d) Hartwig JF, Kawatsura M, Hauck SI, Shaughnessy KH, Alcazar-Roman LM. *J Org Chem.* 1999; 64:5575. [PubMed: 11674624] e) Reddy NP, Tanaka M. *Tetrahedron Lett.* 1997; 38:4807.
13. Günther A, Mohrmann K-H, Stubbe M, Ziemann H, Bayer AG. 1986 DE3516630.

**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 1Examination of different SCF₃ sources.^[a]

Entry	SCF ₃ Source	Additive	Yield [%]
1	CsSCF ₃	none	10
2	AgSCF ₃	none	0
3	(Me) ₄ NSCF ₃	None	20
4	AgSCF ₃	(Me) ₄ NI	0
5	AgSCF ₃	(Bu) ₄ NCl	0
6	AgSCF ₃	(Bu) ₄ NBr	56
7	AgSCF ₃	(Bu) ₄ NI	55
8	AgSCF ₃	Ph(Me) ₃ NI	80
9	AgSCF ₃	Ph(Et) ₃ NI	>99

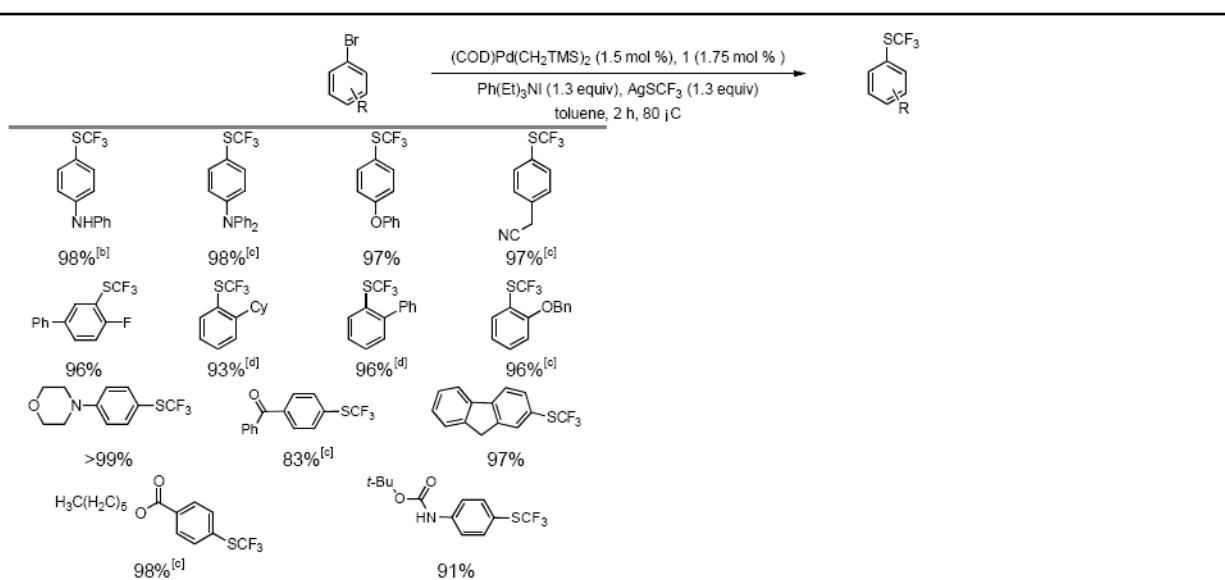
^[a](COD)Pd(CH₂TMS)₂ (2.5 mol %), PhMe (4 mL); all reactions are run on 0.2 mmol scale and all reported yields are based on GC data

Table 2Examination 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 4Pd-catalyzed formation of heteroaryl-SCF₃ compounds.^[a]