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# Palladium-Catalyzed Trifluoromethylthiolation of Aryl C−H Bonds

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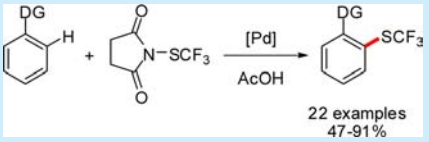
Supporting Information

**ABSTRACT:** A method for monotrifluoromethylthiolation of arenes via palladium-catalyzed directed C−H bond activation was described. The reaction was compatible with a variety of functional groups. Initial mechanistic studies disclosed that the turnover limiting step of the catalytic cycle did not involve C−H activation.




The trifluoromethylthio group ($CF_3S$−) is a privileged functional group used for the design of leading compounds in the field of agrochemical and pharmaceuticals,[1] mainly due to its high lipophilicity that makes the trifluoromethylthiolated drug compounds easier to cross lipid membranes.[2] As a result, the development of new trifluoromethylthiolation methods has attracted great interest in synthetic organic chemistry.[3] While earlier studies for trifluoromethylthiolation typically involved halogen−fluorine exchange reactions of polyhalogenomethyl thioether or the trifluoromethylation of sulfur-containing compounds via a single-electron transfer (SET) mechanism,[4] recent focus has been shifted toward developing more environmentally benign and functional-group-tolerant methods using a transition-metal catalyst[5] or eletrophilic $CF_3S$-substituted reagents.[6] For instance, Buchwald and Vicic reported trifluoromethylthiolation of aryl halides under mild conditions catalyzed by a Pd- or Ni-catalyst, respectively.[5a,b] Qing, Vicic, and Duan reported a Cu-catalyzed oxidative trifluoromethylthiolation of arylboronic acids with in situ formed nucleophilic $CF_3S$ reagent or $[NMe_4][SCF_3]$.[5c−e,l] Weng et al. reported several stable trifluoromethylthiolated Cu complexes that reacted with aryl halides to form the corresponding products in excellent yields.[5f] We and Rueping independently reported a Cu-catalyzed trifluoromethylthiolation of arylboronic acids with an eletrophilic $CF_3S$-substituted reagent.[5h−j] More recently, Gooßen et al. reported a Sandmeyer trifluoromethylthiolation of arenediazonium salts with NaSCN and $TMSCF_3$ under mild conditions.[5m]

Despite these great achievements, the trifluoromethylthio group was typically placed into the position of the C−X (X = halides or boron) bond of the prefunctionalized arenes. Therefore, a new strategy that is capable of direct trifluoromethylthiolation of nonactivated arenes via C−H activation is highly desirable.[7] While several transition-metal catalyzed fluorinations[8] and trifluoromethylations[9] of arenes have been reported, to the best of our knowledge, the only known method for C−H bond activation ditrifluoromethylthiolation of arenes using a substoichiometric amount of Cu was reported by Daugulis et al.,[10] which employed the toxic and volatile $CF_3SSCF_3$[11] as the $CF_3S$ source. In addition, under the Cu-catalyzed conditions, selective monotrifluoromethylthiolation of arenes could not be achieved.

Inspired by Sanford's pioneering work on Pd-catalyzed selective chlorination of aromatic C−H bonds by using an electrophilic chlorinating reagent (NCS),[12] and considering that the $CF_3S$ group is generally referred to as a pseudohalide,[13] we envisioned that a highly selective monotrifluoromethylthiolation of the arene C−H bonds might be realized by using compound **1a** or **1b**, structural analogs of NCS under Pd-catalyzed conditions. Herein, we reported the first monotrifluoromethylthiolation of arene C−H bonds that is compatible with various functional groups.

We initially studied the reaction of benzo[*h*]quinoline with compound **1a**, **1b**,[14] or **1c**, an electrophilic trifluoromethylthio-substituted reagent developed in our group,[5h] in the presence of different Pd catalysts in different solvents. Compounds **1a** and **1b** can be easily synthesized in excellent yields by the reaction of NBS or *N*-bromophthalimide with $AgSCF_3$ in anhydrous $CH_3CN$ at rt.[5j]

After several rounds of attempts, it was found that the desired trifluoromethylthiolated product was formed in 14% yield for the reaction of benzo[*h*]quinoline with **1a** in HOAc at 100 °C when $Pd(OAc)_2$ was used as the catalyst. Under the otherwise identical conditions, reactions with **1b** or **1c** generated the trifluoromethylthiolated product in much lower yields (6% and <1%, respectively). The trifluoromethylthiolated compound **3a** was isolated and fully characterized by $^1H$, $^{19}F$, $^{13}C$ NMR spectroscopies and MS spectra, and the structure was further confirmed by X-ray diffraction of its single crystals.

Encouraged by these initial promising results, we further optimized the reaction conditions by using different Pd catalysts and stoichiometries of the reagents in different solvents under different reaction temperatures. It was found that reactions of benzo[*h*]quinoline with compound **1a** in other solvents such as $CH_3CN$, 1,2-dichloroethane, DMF, dioxane, or NMP occurred in <1% yield (Table 1, entries 2−6). Using trifluoroacetic acid as the solvent did not affect the yield of the product, while using pivalic acid led to a much lower yield (Table 1, entries 7−8). Reactions using $PdCl_2$ or $Cu(OAc)_2$ as the catalyst also occurred in <1% yield (Table 1, entries 9−10). Switching the Pd catalyst to

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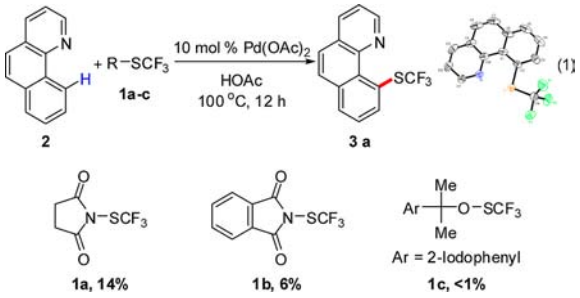
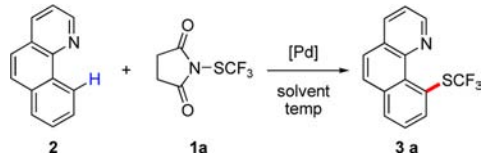



**Table 1. Optimization of the Conditions for Pd-Catalyzed Trifluoromethylthiolation of Arenes**[a]




| entry | [Pd] | solvent | temp (°C) | time (h) | additive | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | AcOH | 100 | 12 | - | 14 |
| 2 | $Pd(OAc)_2$ | $CH_3CN$ | 100 | 12 | - | < 1 |
| 3 | $Pd(OAc)_2$ | $ClCH_2CH_2Cl$ | 100 | 12 | - | < 1 |
| 4 | $Pd(OAc)_2$ | DMF | 100 | 12 | - | < 1 |
| 5 | $Pd(OAc)_2$ | dioxane | 100 | 12 | - | < 1 |
| 6 | $Pd(OAc)_2$ | NMP | 100 | 12 | - | < 1 |
| 7 | $Pd(OAc)_2$ | $CF_3COOH$ | 100 | 12 | - | 13 |
| 8 | $Pd(OAc)_2$ | $^tBuCOOH$ | 100 | 12 | - | 1 |
| 9 | $PdCl_2$ | AcOH | 100 | 12 | - | <1 |
| 10 | $Cu(OAc)_2$ | AcOH | 100 | 12 | - | <1 |
| 11 | $Pd(O_2CCF_3)_2$ | AcOH | 100 | 12 | - | 17 |
| 12 | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 100 | 12 | - | 26 |
| 13 | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 12 | - | 40 |
| 14 | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 12 | DMSO | 42 |
| 15 | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 12 | NMP | 40 |
| 16 | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 12 | BQ | 26 |
| 17 | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 12 | $K_2S_2O_8$ | 34 |
| 18[c] | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 12 | - | 62 |
| 19[c] | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 24 | - | 71 |
| 20[d] | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 120 | 24 | - | 73 |
| 21[d] | $Pd(CH_3CN)_4(OTf)_2$ | AcOH | 110 | 24 | - | 84 |

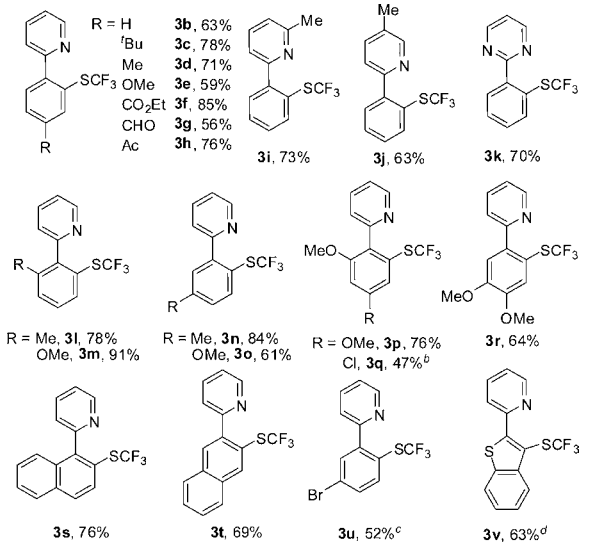
[a]Reaction conditions: benzo[*h*]quinoline (0.05 mmol), compound **1a**, **1b**, or **1c** (0.075 mmol), Pd catalyst (10 mmol %) in solvent (1.0 mL) under conditions indicated. [b]The yields were determined by $^{19}F$ NMR with an internal standard. [c]3.0 equiv of **1a** were used. [d]4.0 equiv of **1a** were used.

$Pd(O_2CCF_3)_2$ or $Pd(CH_3CN)_4(OTf)_2$ led to an increase in the yield to 17% and 26%, respectively (Table 1, entries 11−12). The yield was improved to 40% when the reaction temperature was increased to 120 °C (Table 1, entry 13). The addition of different additives such as DMSO, NMP, BQ, or $K_2S_2O_8$ had a negligible effect on the reaction (Table 1, entries 14−17). Interestingly, when the amount of **1a** was increased to 3.0 equiv, the yield of the product was increased significantly to 62% after 12 h and 71% after 24 h (Table 1, entries 18−19). When 4.0 equiv of **1a** were used in 110 °C, the yield was further improved to 84% (Table 1, entries 20−21). Under the otherwise identical conditions, the reaction of compound **2** with 4.0 equiv of **1b** only led to a 39% yield. Previously, Yu reported a Pd-catalyzed C−H trifluoromethylation protocol; however, under Yu's reaction conditions,[9a,b] <1% of the desired trifluoromethylthiolation product was observed.

We next studied the effect of the directing group on the Pd-catalyzed trifluoromethylthiolation of arenes with different directing groups (see Table S1 for more details). The directing groups were very important for the yields of the reactions. It was found that when pyridine was used as the directing group, the reactions proceeded smoothly to generate the corresponding monotrifluoromethylthiolated products in good yields. When *o*-methyl oxime was used as the directing group, the yield of the product decreased to 25% under otherwise identical conditions. The reaction occurred much slowly while pyrimidine was used as the directing group and required 24 h at 150 °C to full conversion to give the product in 70% yield. Other directing groups such as oxazoline, dimethylamine, acetoamide, or 8-aminoquinoline were not effective for Pd-catalyzed trifluoromethylthiolations.

On the basis of the results summarized in Table 1, the reaction conditions of entry 21 in Table 1 were chosen to study the scope of the Pd-catalyzed trifluoromethylthiolation of arenes with a directing group, and the results are summarized in Scheme 1. 2-

**Scheme 1. Scope of the Pd-Catalyzed Trifluoromethylthiolation of Arenes**[a]




[a]Reaction conditions: benzo[*h*]quinoline (0.5 mmol), compound **1a** (2.0 mmol), $Pd(CH_3CN)_4(OTf)_2$ (10 mmol %) in AcOH (10 mL) at 110 °C for 24 h, isolated yield. [b] 6.0 equiv of **1a** were used at 130 °C for 30 h. [c] 6.0 equiv of **1a** were used at 150 °C for 24 h. [d] The reaction was conducted at 150 °C for 24 h.

Pyridylbenzene substituted with various electron-withdrawing or -donating groups generally reacted with **1a** to give the corresponding trifluoromethylthiolated products in moderate to good yields. For instance, the reaction of 2′-pyridyl-2-methoxybenzene afforded the desired product in 91% yield, whereas reactions of the *m*- and *p*-OMe substituted substrates gave the corresponding products in moderate 61% and 59% yields, respectively (Scheme 1, **3m**, **3e**, and **3o**). Furthermore, the Pd-catalyzed trifluoromethylthiolation of arenes is tolerant of a variety of functional groups, such as ester, aldehyde, enolizable ketone, and halides that include chloride and bromide (Scheme 1, **3f−h**, **3q**, and **3u**). It is worth noting that bromide was not compatible in the Pd- or Ni-catalyzed coupling of aryl halides with nucleophilic trifluoromethylthio reagents.[5a,b] Importantly, in all of these cases, no ditrifluoromethylthiolated side products were observed as determined by $^{19}F$ NMR spectra of the crude mixture of the reactions.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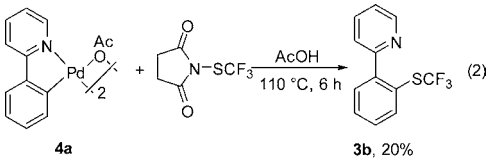
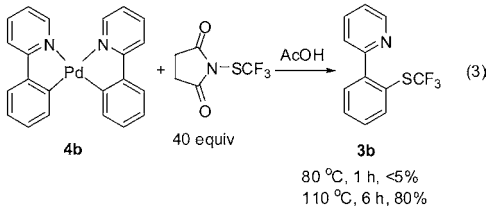
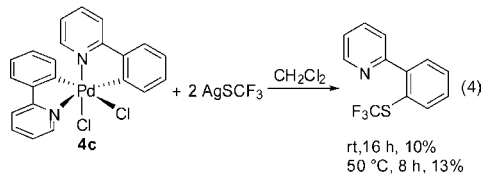
To gain some insights into the reaction, we carried out some preliminary mechanistic investigations of this coupling process. A stoichiometric reaction of known palladacycle **4a** or **4b** with **1a** after 6 h at 110 °C generated the trifluoromethylthiolated product in 20% and 80% yields, respectively, while no product was observed if the reactions were conducted at rt (eqs 2−3). To



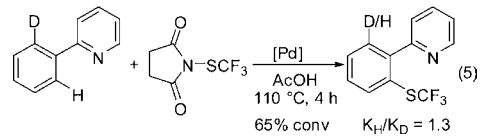

mimic the catalytic reaction where the ratio of substrate to Pd catalyst was 40/1, 40 equiv of **1a** were used in these stoichiometric reactions. These experiments suggested that the trifluoromethylthiolated arenes could be formed from reactions of cyclometalated complexes with **1a** at elevated temperature.

To probe if the trifluoromethylthiolating product could be produced from reductive-elimination of a Pd(IV) complex, we studied the stoichiometric reaction of complex **4c** with $AgSCF_3$ (eq 4). No $CF_3S$-substituted Pd(IV) complex was able to be

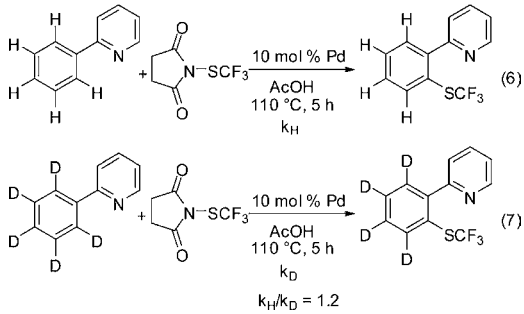



isolated at rt. Instead, reactions of complex **4c** with $AgSCF_3$ in $CH_2Cl_2$ at rt generated the reductive-elimination product in 10% yield after 16 h, with some unidentified trifluoromethylthiolated species. Increasing the reaction temperature to 50 °C resulted in only a slightly increased yield. These experiments indicated that the trifluoromethylthiolated arenes could be generated from trifluoromethylthiolated Pd(IV) species, albeit in low yields.

To probe if the C−H activation step is the rate-limiting step, two sets of experiments were further conducted. In the first experiment, an intramolecular competition reaction was studied, and it was found that the C−H bond compared to the C−D bond was only slightly favored to be activated (eq 5).




In the second set of experiments, two parallel reactions of 2-pyridylbenzene and 2′-pyridyl-2,3,4,5,6-pentadeuterated benzene with **1a** in the presence of $[Pd(CH_3CN)_4(OTf)_2]$ in acetic acid were conducted and the reactions were monitored in real time by $^{19}F$ NMR. In both experiments, an induction period was observed and, after 1 h, the reaction proceeded much faster. Yet, the rate for the reaction of 2-pyridylbenzene was only slightly faster than those for 2′-pyridyl-2,3,4,5,6-pentadeuterated benzene (eqs 6−7). These results clearly suggested that the turnover limiting step of the catalytic trifluoromethylthiolation reaction did not involve C−H bond activation.




Based on these preliminary results and previous studies by others,[12,15,16] we propose a mechanism that was initiated by cyclopalladation of 2-pyridylbenzene with $Pd(CH_3CN)_4(OTf)_2$, followed by oxidative addition of the N−$SCF_3$ bond to form a trifluoromethylthio-substituted Pd(III) or Pd(IV) intermediate, and reductive-elimination to form the product and regenerated the Pd(II) species (Figure 1). However, detection of the

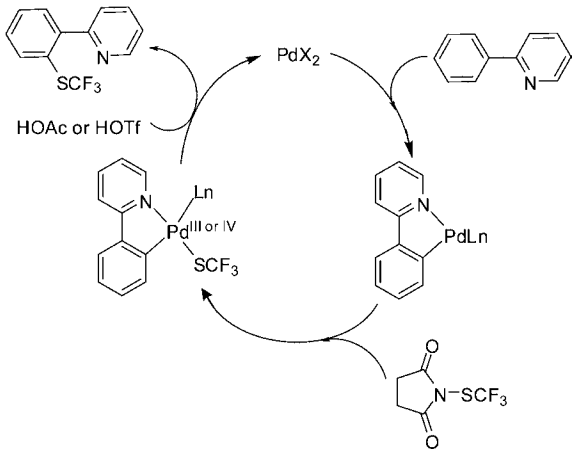



**Figure 1.** Proposed mechanism for Pd-catalyzed C−H trifluoromethylthiolation.

oxidative-addition product in the catalytic cycle remains elusive at this stage. In addition, we could not rule out another pathway, in which the Pd−C bond cleavage/C−$SCF_3$ formation proceeded by electrophilic substitution.

In conclusion, a Pd(II)-catalyzed intermolecular highly selective C−H monotrifluoromethylthiolation was developed for the first time. The reaction was compatible with a variety of functional groups. Initial mechanistic studies disclosed that the C−H activation step was not the rate-limiting step. The isolation of the trifluoromethylthio-substituted high-valent Pd complexes, further elucidation of the mechanism of the catalytic reaction, and expansion of the scope of the reaction are currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

All experimental procedures and spectroscopic data of compounds **3a−v**, X-ray crystallography data for **3a**. This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### Notes

The authors declare no competing financial interest.

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