DOI: 10.1002/adsc.201400362

Highly *ortho*-Selective Trifluoromethylthiolation Reactions using a Ligand Exchange Strategy

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Received: April 10, 2014; Revised: April 30, 2014; Published online: August 1, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400362.

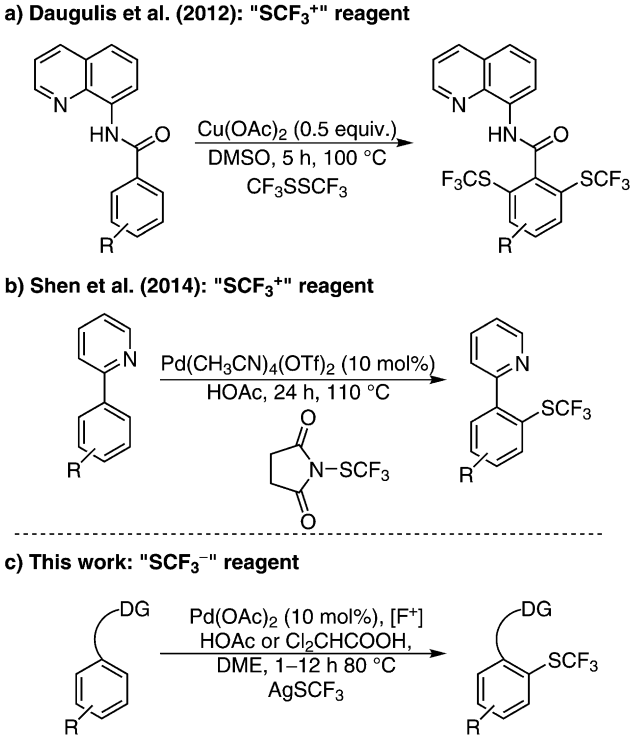
Abstract: The trifluoromethylthio group ($-SCF_3$) is a highly privileged modifier for drug molecules. Direct C–H trifluoromethylthiolation reactions are highly valuable synthetic tools for the late-stage modification of drug candidates, which have so far been underexplored. We report a palladium-catalyzed *ortho*-selective mono-trifluoromethylthiolation reaction of arenes. The reaction proceeds through a key ligand exchange pathway using readily available silver trifluoromethylthiolate ($AgSCF_3$). Acetic acid was found to be crucial to minimize oxidative dimerization of the starting materials and to facilitate the "SCF_3^-" transfer. We expect this strategy to have broad applications in C–H functionalization reactions using a stand-alone oxidant and various anions.

Keywords: C–H activation; C–S bond formation; fluorine; palladium; trifluoromethylthiolation

Introduction

The trifluoromethylthio group ($-SCF_3$) is a highly privileged functionality for pharmaceutical and agrochemical agents.[1] The linkage of a strong electron-withdrawing, lipophilic and metabolically stable CF_3 group with a highly polarizable and bio-friendly sulfur atom makes SCF_3 an ideal modifier (Hansch lipophilicity constant $\pi = 1.44$)[2] for small molecules to cross lipid membranes and affect intracellular targets.[1b] Therefore, intensive research has been carried out to develop synthetic methods to prepare SCF_3 containing molecules, especially $ArSCF_3$ compounds. Classical approaches for the synthesis of $ArSCF_3$ include halogen-fluorine exchange reactions of polyhalogenomethyl thioethers[3] and the trifluoromethylation of sulfur-containing compounds such as disulfides, thiocyanates, and thiols.[4] More recently, efforts have been focused on direct introduction of the SCF_3 group using SCF_3 reagents,[5] which would be highly suitable for late-stage modification of drug candidates. A number of straightforward protocols have been developed for the replacement of aryl Grignard reagents,[6a] aryl halides or boronic acids with an SCF_3 reagent in the presence of palladium,[6b] nickel[6c] or copper.[6d–h] In addition, a Friedel–Crafts type of trifluoromethylthiolation using electrophilic arenes and an "SCF_3^+" reagent has also been reported.[7] However, the more appealing C–H trifluoromethylthiolation strategy has been underexplored.

Compared to other C–H thiolation reactions, the metal-catalyzed $Ar-SCF_3$ coupling would be more challenging due to the attenuated nucleophilicity of the SCF_3 anion.[8] We envisioned that reductive elimination of an aryl–Pd(IV) species bearing an SCF_3 ligand would be a highly probable process.[9] There are two plausible ways to generate the aryl–Pd(IV)–SCF_3 complex: oxidation of an aryl–Pd(II) using an "SCF_3^+" reagent, and ligand exchange of an aryl–Pd(IV)–X (X = a leaving group) using an "SCF_3^-" species. In 2012, Daugulis and co-workers reported a copper-catalyzed, direct trifluoromethylthiolation of aryl C–H bonds using a chelating 8-aminoquinoline or picolinamides as directing auxiliaries (Scheme 1, a).[10a] Nevertheless, the reactions required high catalyst loading (0.5 equiv.) and an expensive/volatile "SCF_3^+" reagent (CF_3SSCF_3). In addition, mono-trifluoromethylthiolation could not be achieved for most substrates. Very recently, Shen and co-workers reported a palladium-catalyzed trifluoromethylthiolation of 2-phenylpyridine derivatives using an oxidative "SCF_3^+" reagent (Scheme 1, b),[10b] which required separate synthesis. By contrast, $Ar-SCF_3$ coupling using the more readily available "SCF_3^-" species



Scheme 1. Directed C–H trifluoromethylthiolation reactions.

has not been established. As a matter of a fact, nearly all analogous Pd-catalyzed C–H fluorination[11] and trifluoromethylation[12] reactions relied on the use of "F^+" "CF_3^+" oxidants, not their cheaper anionic counterparts. Therefore, a mono-selective direct C–H trifluoromethylthiolation reaction using an alternative SCF_3 anion reagent is conceptually interesting and practically attractive, as it would avoid the synthesis of the specialized oxidative "SCF_3^+" reagent and offers a potential general strategy to introduce other nucleophilic functionalities using anionic reagents.

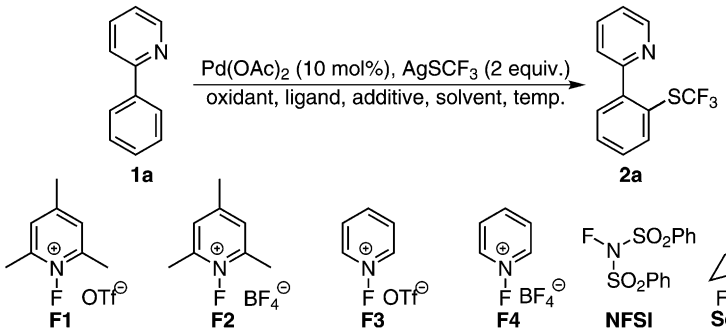
Results and Discussion

Although ligand exchange on a Pd(IV) metal center has been documented, very few types of bond formation have been reported.[13] In most cases, the pivotal ligand exchange on the Pd(IV) center involved Ar–H activation (not an anionic ligand) and was limited to Ar–Ar coupling reactions.[14] One particular challenge is the competing intramolecular reductive elimination on a highly electron-deficient metal center before the intermolecular ligand displacement. The incoming ligand anion must possess a stronger metal binding affinity and a yet faster reductive elimination potential than the leaving species. Alternatively, the ligand exchange could occur prior to the metal oxidation, and the subsequent reductive elimination would become intramolecular.[15] However, it would be very difficult to control the rate of ligand exchange *vs.* oxidation. Following this analysis, we decided to explore the feasibility of using "F^+"-based oxidants. Ar–Pd(IV)–F is known to be slow to undergo Ar–F reductive elimination, which might provide a sufficiently long-lived Ar–Pd(IV) species for the SCF_3 exchange.

We began our initial investigation by examining the reaction of 2-phenylpyridine with $AgSCF_3$ in the presence of $Pd(OAc)_2$ using various oxidants at 60 °C (Table 1, for a comprehensive reaction condition survey, see the Supporting Information). When (diacetoxyiodo)benzene or NBS was used, the *ortho*-acetoxy or *ortho*-bromo product was obtained (Table 1, entries 1 and 2), indicating fast Ar–OAc or Ar–Br elimination in the presence of OAc or "Br^+" oxidant. Although most "F^+" oxidants failed to promote the desired trifluoromethylthiolation (Table 1, entries 3–7), use of Selectfluor led to product **2a** in 32% yield (Table 1, entry 8). The major side product was the dimer of **1a** *via* dehydrogenative homocoupling under most conditions examined. We surmised the formation of the dimer as a result of competitive second C–H insertion, caused by ineffective "SCF_3^-" transfer from silver to palladium. Various ligands were investigated in an attempt to suppress this side reaction (Table 1, entries 9–12; for a comprehensive ligand screen, see the Supporting Information). Unfortunately, either mono-coordinative or bidentate N ligands failed to promote the desired bond formation. Quaternary ammonium salts were reported to facilitate the SCF_3 anion transfer in a Pd(II)-Pd(0)-Pd(II) cycle reported by Buchwald and co-workers.[6b] The starting material was recovered when $(n\text{-}Bu)_4NBr$ was employed (Table 1, entry 14). Eventually, HOAc was identified as the pivotal additive and the desired product **2a** was obtained in 87% yield (Table 1, entry 15). TFA did not promote the desired trifluoromethylthiolation (Table 1, entry 16). After a quick survey of solvents and temperature, the best reaction conditions were identified as $Pd(OAc)_2$ (10 mol%), $AgSCF_3$ (2 equiv.), selectfluor (3 equiv.) and HOAc (5 equiv.) in DME at 80 °C. Rigorous exclusion of air/moisture was not required for this transformation.

With the optimized reaction conditions in hand, we next examined the scope of substituents on the arenes (Table 2). A broad range of functional groups was well tolerated. Substrates with an electron-donating group were particularly effective. The reaction was not affected by acidic protons. A *p*-NHAc substituted substrate gave 76% of the SCF_3 product (Table 2, **2k**), despite NHAc being an excellent directing group (DG) as well. Reactions were noticeably slower when electron-withdrawing groups were present on the aromatic ring, with nitrile being most problematic. 3-(Pyridin-2-yl)benzonitrile resulted only in a trace amount of the SCF_3 product **2o**. One explanation might be the strong coordinating effect of CN towards

Table 1. Survey of reaction conditions for the trifluoromethylthiolation of 2-phenylpyridine.[a]



Entry	Oxidant	Ligand (20 mol%)	Additive	Solvent	Yield [%]
1	$PhI(OAc)_2$	–	–	DME	0
2	NBS	–	–	DME	0
3	**F1**	–	–	DME	trace
4	**F2**	–	–	DME	7
5	**F3**	–	–	DME	trace
6	**F4**	–	–	DME	4
7	**NFSI**	–	–	DME	5
8	Selectfluor	–	–	DME	32
9	Selectfluor	pyridine	–	DME	trace
10	Selectfluor	BQ	–	DME	24
11	Selectfluor	bpy	–	DME	0
12	Selectfluor	Ph_3P	–	DME	trace
13	Selectfluor	–	Et_3PhNI (2 equiv.)	DME	0
14	Selectfluor	–	$(n\text{Bu})_4NBr$ (2 equiv.)	DME	0
15	Selectfluor	–	HOAc[b]	DME	85
16	Selectfluor	–	TFA[b]	DME	0
17	Selectfluor	–	HOAc (5 equiv.)	toluene	20
18	Selectfluor	–	HOAc (5 equiv.)	THF	27
19	Selectfluor	–	HOAc (5 equiv.)	DMF	0
20[c]	Selectfluor	–	HOAc (5 equiv.)	DME	90
21[d]	Selectfluor	–	HOAc (5 equiv.)	DME	0

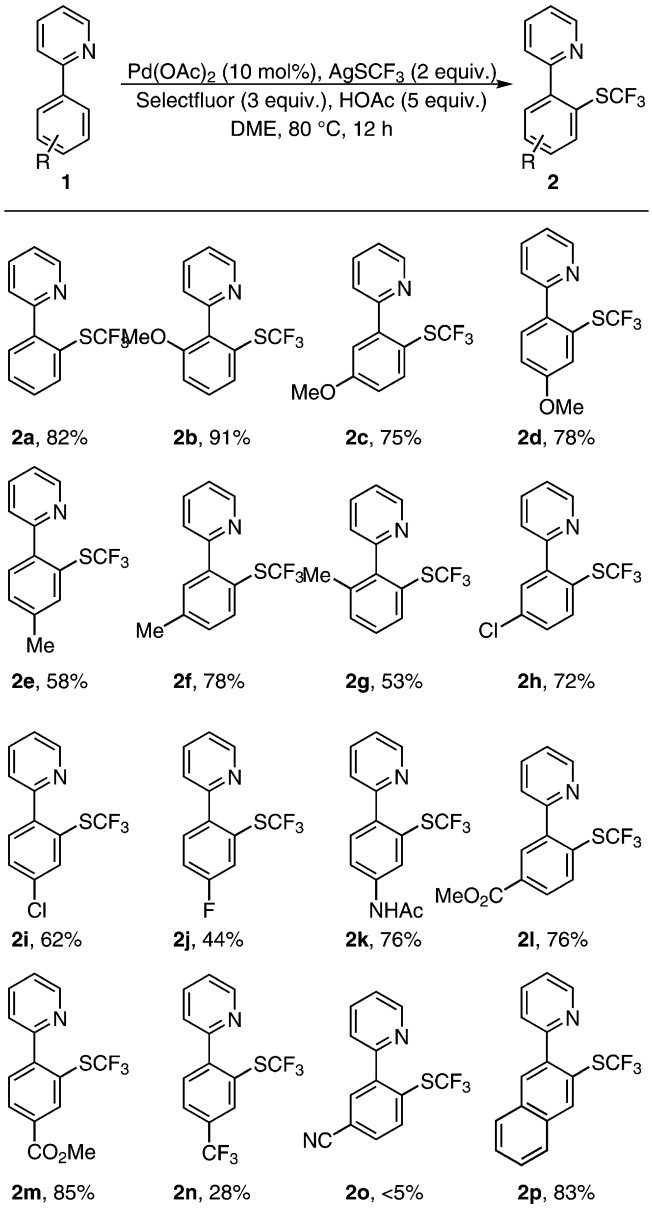
[a] **1a** (0.06 mmol), $Pd(OAc)_2$ (0.006 mmol), $AgSCF_3$ (0.12 mmol), oxidant (0.18 mmol), additive (0.30 mmol) were heated in a solvent (1 mL) at 60 °C for 12 h; yield was determined by GC using biphenyl as the internal standard.
[b] 0.2 mL HOAc or TFA.
[c] 80 °C for 12 h.
[d] Without $Pd(OAc)_2$

silver, which interfered with the ligand exchange. The reaction indeed did not proceed in acetonitrile. The reaction of 2-(naphthalen-2-yl)pyridine led to β-trifluoromethylthiolated product **2p** in 83% yield.

The scope of the directing groups was also examined. Substituted pyridines were generally good DGs for this transformation (Table 3, **3a**, **3b**, **3d**, **3f**). *ortho*-Methylpyridine afforded a low yield of the product **3c**, due to an unfavorable steric repulsion upon coordinating to palladium. *para*-Cyanopyridine was also a poor DG (Table 3, **3e**). Most nitrogen-containing heteroaromatics were good DGs for this trifluoromethylthiolation reaction. Pyrimidine was equally competent as pyridines (Table 3, **3g**). Quinoline fused to the arene was also effective (Table 3, **3h**). The pyrazole-substituted benzene gave 71% of product **3i**. No reaction was observed when dimethyldihydrooxazole was used as the DG, due to steric reasons. An attempt to functionalize an sp^3 C–H bond using quinoline as the DG gave a very low yield (**3p**, <5%). Other common non-heterocyclic DGs, such as NHAc, N(Me)NO, CONHO-*t*-Bu, N=NPh failed to yield any of the desired SCF_3 products. Considering that pyridine is a static directing group and cannot be readily removed or transformed, efforts were made to identify a DG with better synthetic utility. Preliminary studies revealed that 8-aminoquinoline (QA) was also an effective DG for the *ortho*-trifluoromethylthiolation reaction (Table 3, **3q–s**).

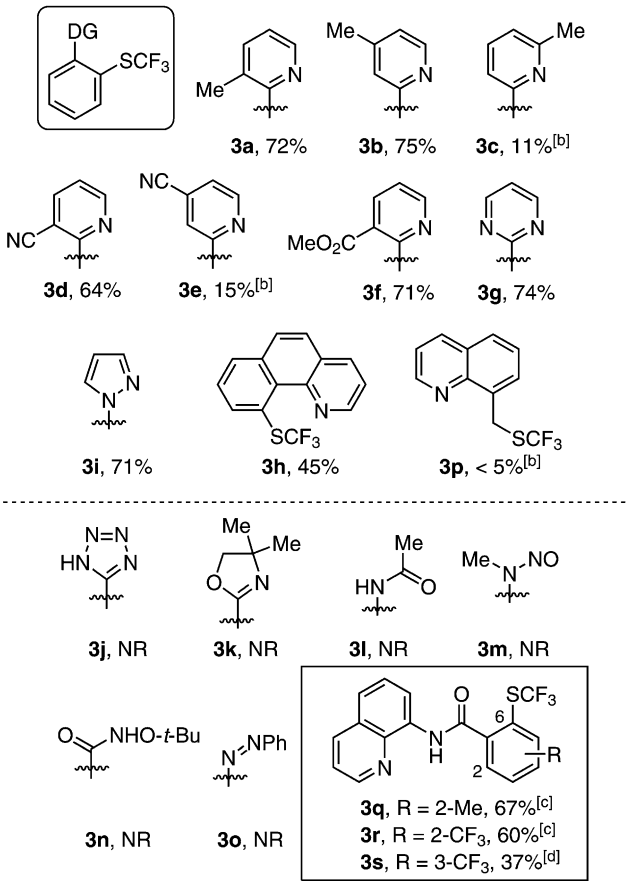
A positive primary KIE ($k_H/k_D = 2.7$) was observed for both intermolecular and intramolecular KIE experiments (Scheme 2). The convergence of both KIE values suggests that the C–H palladation step is not reversible. Separate H/D scrambling experiments

Table 2. Substrate scope for arenes.[a].



[a] *Reaction conditions:* **1** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), $AgSCF_3$ (0.4 mmol, 2 equiv.), Selectfluor (0.6 mmol, 3 equiv.) and HOAc (1 mmol, 5 equiv.) in DME (2 mL) at 80 °C for 12 h; isolated yields.

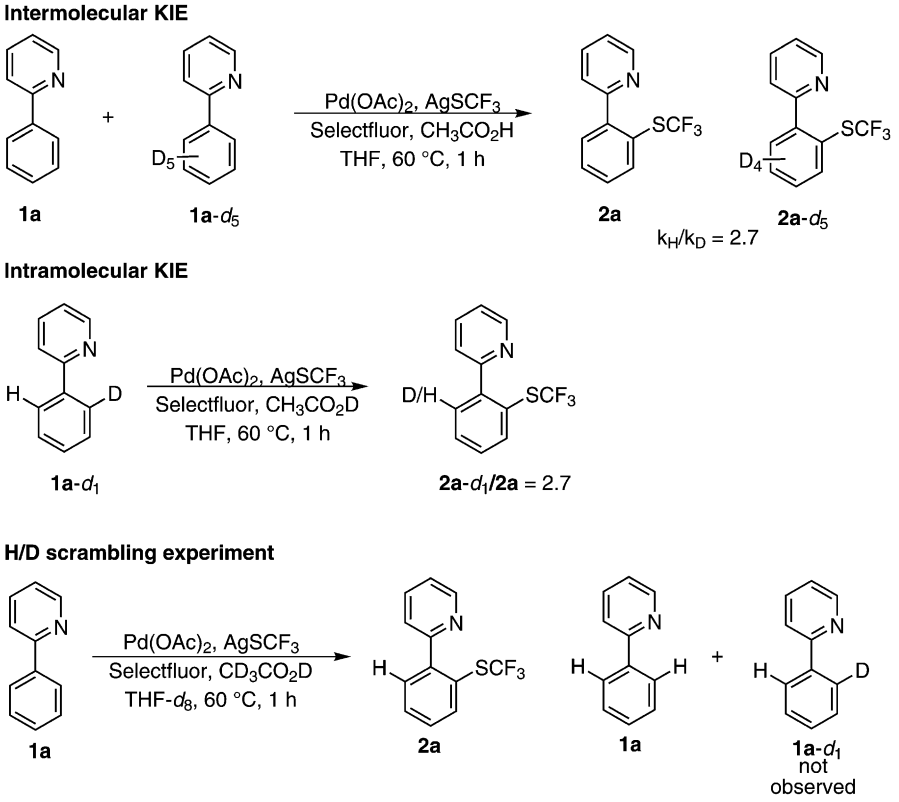
Table 3. Scope of the directing groups.[a]



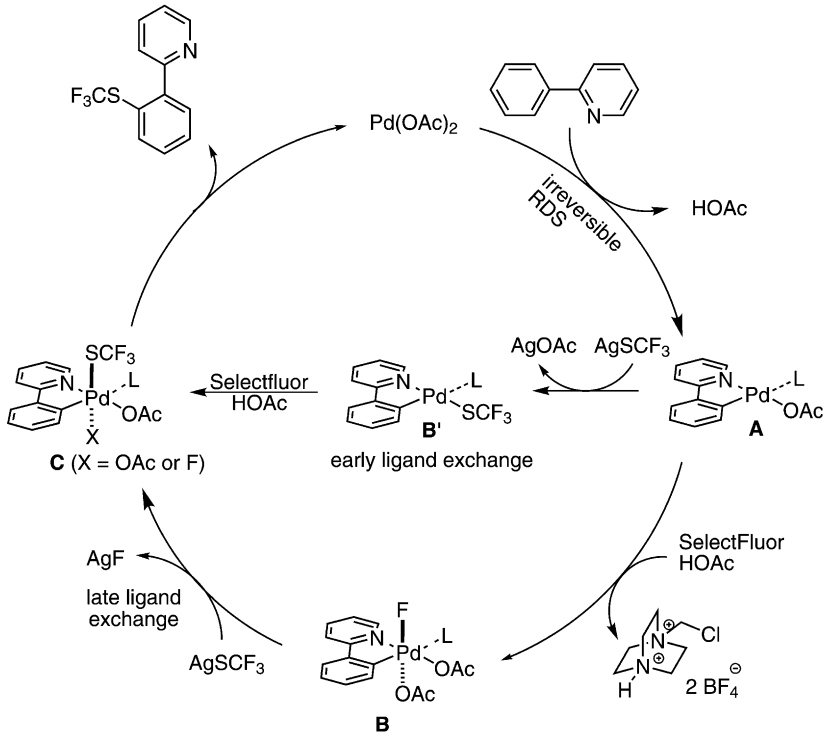
[a] 0.2-mmol scale following the standard conditions (Table 2); isolated yields.
[b] Yield was determined by GC using biphenyl as the internal standard.
[c] A 1:1 mixture of HOAc/DME at 70 °C for 1 h.
[d] 20 equiv. of $Cl_2CHCOOH$ were used in lieu of HOAc.

were carried out and no H/D scrambling was observed using either H-substrate in D-solvent or D-substrate in H-solvent (see the Supporting Information, Scheme S1). This observation is inline with a recent report by Yu and co-workers, where *ortho*-deuteration of 2-phenylpyridine was problematic.[16] These results suggest that the irreversible C–H palladation step is the rate-determining step, not the ligand exchange step, the oxidation, or the reductive elimination step. This observation is also consistent with our previous designs to ensure a fast ligand exchange step prior to the competing Ar–OAc reductive elimination.

Control experiments were carried out to gain a deeper mechanistic understanding of the ligand exchange step. The trifluoromethylthiolation reaction was inhibited by $(n\text{-Bu})_4NCl$ or $(n\text{-Bu})_4Br$ (see the Supporting Information, Table S2), suggesting that Ag might play an important role for the ligand exchange. A comparable conversion of **2a** was obtained (83% yield) when 2 equiv. NaOAc was introduced. No Ar–OAc product was observed in this experiment, suggesting that the ligand exchange step is not affected by the concentration of OAc. In sharp contrast, very low conversion was observed when $(n\text{-Bu})_4NF$ or CsF was added. Presumably, the high concentration of F inhibits the F/SCF_3 exchange. When $PhI(OAc)_2$ was used under otherwise identical conditions, the major product was the corresponding Ar–OAc, suggesting



Scheme 2. Isotope experiments.



Scheme 3. Proposed mechanism for palladium-catalyzed trifluoromethylthiolation.

that an Ar–$Pd(OAc)_3$ species was produced with this oxidant and the correpsonding OAc/SCF_3 exchange was slow. All these data suggested a synergistic effect by the Ag cation that facilitates the SCF_3 exchange with fluoride. Based on these data, we propose the following mechanism (Scheme 3): upon the irreversi-

ble cyclopalladation, the resulting Pd(II)(phpy)(OAc) **A** was readily oxidized to Pd(IV)(Phpy)F(OAc)$_2$ **B** by Selectfluor in the presence of HOAc.[17] Silver is believed to assist the "F$^-$" displacement by SCF_3 anion to generate Pd(IV)(Phpy)SCF_3(OAc)$_2$ **C**,[18] which undergoes reductive elimination to yield the desired SCF_3 product. Alternatively, the ligand exchange could occur before the oxidation, where the "OAc$^-$/SCF_3^-" exchange takes place to give Pd(II)(phpy)SCF_3 **B′**. Subsequent oxidation and reductive elimination complete the catalytic cycle. Further in-depth studies are currently underway to differentiate these two reaction pathways. The role of HOAc is intriguing.[19] Sanford and co-workers observed an Ar–Cl coupling product for a Pd(IV)-(phpy)$_2$Cl$_2$ species in HOAc, while other solvents favored the dimerization of phpy.[19a] In addition, the introduction of HOAc might also facilitate the oxidation of Pd(II) to Pd(IV) by Selectfluor, supported by Sanford's observation that the oxidation of dimeric Pd(II)(phpy)(OAc) by Togni's reagent was accelerated by HOAc.[19b,c]

Conclusions

In summary, we have developed a simple protocol for the synthesis of *ortho*-SCF_3-substituted arenes using palladium and $AgSCF_3$. HOAc was found to be crucial to suppress the oxidative dimerization of the substrate. The reaction is proposed to go through a Pd(II)/Pd(IV) cycle. Facile F to SCF_3 ligand exchange ensured a smooth overall trifluoromethylthiolation reaction. Excellent selectivity for the coupling of C–S bond was accomplished over the formation of C–O, C–F and C–C bonds. We believe that this strategy will have broad applications for the development of novel *ortho*-functionalization reactions using an "innocent" oxidant and a nucleophilic reagent.

Experimental Section

General Information

Commercial reagent grade DME was used without further purification. The reactions were carried out in air. All reagents were purchased and used without further purification unless specified otherwise. Solvents for chromatography were technical grade and distilled prior to use. Flash chromatography was performed using 200–300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed using Huanghai silica gel plates with HSGF 254. Qingdao Haiyang Chemical HG/T2354-92 silica gel was used for silica gel flash chromatography. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or appropriate stains. ^{1}H NMR data were recorded on Bruker nuclear magnetic resonance spectrometers (300, 400 or 500 MHz) unless otherwise specified. Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of chloroform (^{1}H 7.26 ppm or ^{13}C 77.16 ppm). Multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); and coupling constants (J) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded on Bruker spectrometers (75, 101 or 126 MHz) with total proton decoupling. Data for ^{13}C NMR are reported in terms of chemical shift. ^{19}F NMR chemical shifts are reported as values (ppm). GC yields were determined using a Shimadzu GC-2014AF spectrometer, using biphenyl as the internal standard. HR-MS (ESI) analysis was performed by The Analytical Instrumentation Center at Peking University, Shenzhen Graduate School and (HR-MS) data were reported with ion mass/charge (m/z) ratios as values in atomic mass units.

General Procedure for the Synthesis of 2a–2p, 3a, 3b, 3d, 3f–i, 3q–s

An oven-dried test tube equipped with a magnetic stirring bar was charged with **1** (0.2 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol, 0.1 equiv.), $AgSCF_3$ (83 mg, 0.4 mmol, 2 equiv.), Selectfluor (212.6 mg, 0.6 mmol, 3 equiv.), 2 mL DME and HOAc (60 mg, 1.0 mmol, 5 equiv.). The reaction mixture was stirred at 80 °C for 12 h. After completion, the reaction was diluted with ethyl acetate, washed by saturated $NaHCO_3$, brine and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography (eluent: petroleum ether/ethyl acetate = 50:1 to 10:1) afforded the desired trifluoromethylthiolation product **2**.

2-{2-[(Trifluoromethyl)thio]phenyl}pyridine (2a): yield: 41.8 mg (82%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.79 (td, J = 7.7, 1.8 Hz, 1H), 7.61 (dd, J = 7.6, 1.6 Hz, 1H), 7.57–7.50 (m, 2H), 7.47 (td, J = 7.6, 1.7 Hz, 1H), 7.32 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.72, 148.93, 145.23, 136.23, 135.86, 130.71, 130.14, 129.64 (q, J = 307 Hz), 129.17, 124.21, 124.15, 122.44; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.76; HR-MS: m/z = 256.0405 $[M+H]^+$, calculated for $[C_{12}H_9F_3NS]^+$: 256.0408.

2-[2-Methoxy-6-(trifluoromethylthio)phenyl]pyridine (2b): yield: 51.9 mg (91%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (dd, J = 4.9, 0.6 Hz, 1H), 7.76 (td, J = 7.7, 1.8 Hz, 1H), 7.43 (dd, J = 6.8, 4.1 Hz, 2H), 7.36 (d, J = 7.8 Hz, 1H), 7.31–7.24 (m, 1H), 7.08 (dd, J = 6.4, 3.0 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.82, 155.20, 149.12, 135.89, 135.19, 129.88, 129.63 (q, J = 307 Hz), 127.96, 126.10, 125.89, 122.51, 113.12, 56.13; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.69; HR-MS: m/z = 286.0508 $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NOS]^+$: 286.0513.

2-{5-Methoxy-2-{[(trifluoromethyl)thio]phenyl}pyridine (2c): yield: 42.8 mg (75%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74–8.67 (m, 1H), 7.78 (td, J = 7.7, 1.8 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.32 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 7.13 (d, J = 2.9 Hz, 1H), 7.00 (dd, J = 8.7, 2.9 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.47, 157.83, 149.09, 148.02, 139.15, 136.03, 129.53 (q, J = 307 Hz), 124.56, 122.52, 116.14, 115.30, 113.78, 55.58; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −43.04; HR-

MS: $m/z = 286.0507$ $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NOS]^+$: 286.0513.

2-{4-Methoxy-2-[(trifluoromethyl)thio]phenyl]pyridine (2d): yield: 44.5 mg (78%); white solid; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.70$ (ddd, $J = 4.9$, 1.7, 0.9 Hz, 1H), 7.78 (td, $J = 7.7$, 1.8 Hz, 1H), 7.57 (d, $J = 8.6$ Hz, 1H), 7.52 (dt, $J = 7.9$, 1.0 Hz, 1H), 7.37 (d, $J = 2.0$ Hz, 1H), 7.28 (ddd, $J = 7.4$, 4.9, 1.1 Hz, 1H), 7.08 (dd, $J = 8.6$, 2.6 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 159.74$, 157.46, 148.80, 137.49, 136.09, 131.59, 129.70 (q, $J = 306$ Hz), 125.40, 123.95, 121.97, 120.35, 115.93, 55.58; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.58$; HR-MS: $m/z = 286.0509$ $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NOS]^+$: 286.0513.

2-{4-Methyl-2-[(trifluoromethyl)thio]phenyl}pyridine (2e): yield: 31.2 mg (58%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.73$–8.66 (m, 1H), 7.77 (td, $J = 7.7$, 1.8 Hz, 1H), 7.64 (s, 1H), 7.50 (d, $J = 7.9$ Hz, 2H), 7.34 (dd, $J = 7.8$, 0.9 Hz, 1H), 7.29 (ddd, $J = 7.8$, 5.0, 1.1 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 157.76$, 148.89, 142.47, 139.34, 136.35, 136.12, 131.01, 130.57, 129.70 (q, $J = 306$ Hz), 124.17, 123.74, 122.22, 21.07; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.74$; HR-MS: $m/z = 270.0561$ $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NS]^+$: 270.0564.

2-[5-Methyl-2-(trifluoromethylthio)phenyl]pyridine (2f): yield: 41.9 mg (78%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.75$–8.66 (m, 1H), 7.77 (td, $J = 7.7$, 1.8 Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 1H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.43 (d, $J = 1.5$ Hz, 1H), 7.32–7.25 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 157.89$, 149.01, 145.61, 141.01, 136.61, 136.05, 131.62, 130.03, 129.62 (q, $J = 308$ Hz), 124.40, 122.36, 120.22, 21.25; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -42.23$; HR-MS: $m/z = 270.0557$ $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NS]^+$: 270.0564.

2-[2-Methyl-6-(trifluoromethylthio)phenyl]pyridine (2g): yield: 28.5 mg (53%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.74$–8.68 (m, 1H), 7.79 (td, $J = 7.7$, 1.8 Hz, 1H), 7.66 (d, $J = 7.5$ Hz, 1H), 7.42–7.30 (m, 3H), 7.28 (d, $J = 7.1$ Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 157.98$, 149.36, 146.06, 138.10, 136.15, 134.39, 132.67, 129.44 (q, $J = 308$ Hz), 128.81, 124.82, 123.91, 122.38, 20.59; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -42.02$; HR-MS: $m/z = 270.0556$ $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NS]^+$: 270.0564.

2-[5-Chloro-2-(trifluoromethylthio)phenyl]pyridine (2h): yield: 41.6 mg (72%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (ddd, $J = 4.9$, 1.6, 0.9 Hz, 1H), 7.81 (td, $J = 7.7$, 1.8 Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 2.4$ Hz, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 7.44 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.34 (ddd, $J = 7.6$, 4.9, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 156.43$, 149.13, 146.68, 137.14, 136.64, 136.43, 130.84, 129.34 (q, $J = 308$ Hz), 129.31, 124.12, 122.91, 122.60; ^{19}F NMR (376 MHz, $CDCl_3$): δ −41.86; HR-MS: $m/z = 290.0013$ $[M+H]^+$, calculated for $[C_{12}H_8ClF_3NS]^+$: 290.0018.

2-{4-Chloro-2-[(trifluoromethyl)thio]phenyl}pyridine (2i): yield: 35.8 mg (62%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.70$ (d, $J = 4.4$ Hz, 1H), 7.86–7.76 (m, 2H), 7.59–7.47 (m, 3H), 7.36–7.29 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 156.55$, 149.00, 143.06, 136.46, 134.87, 134.63, 131.62, 130.12, 129.36 (q, $J = 308$ Hz), 126.24, 123.94, 122.72; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.50$; HR-MS: $m/z = 290.0010$ $[M+H]^+$, calculated for $[C_{12}H_8ClF_3NS]^+$: 290.0018.

2-[4-Fluoro-2-(trifluoromethylthio)phenyl]pyridine (2j): yield: 24.1 mg (44%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.73$–8.64 (m, 1H), 7.80 (td, $J = 7.7$, 1.8 Hz, 1H), 7.58 (ddd, $J = 11.1$, 8.7, 4.0 Hz, 2H), 7.51 (d, $J = 7.9$ Hz, 1H), 7.32 (ddd, $J = 7.6$, 4.9, 1.0 Hz, 1H), 7.26–7.19 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 162.28$ (d, $J = 250$ Hz), 156.78, 149.01, 140.76, 136.60, 132.11 (d, $J = 8$ Hz), 129.54 (q, $J = 308$ Hz), 126.78 (d, $J = 8$ Hz), 123.99, 122.69, 121.60 (d, $J = 22$ Hz), 117.10 (d, $J = 22$ Hz); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.55$, −111.40; HR-MS: $m/z = 274.0310$ $[M+H]^+$, calculated for $[C_{12}H_8F_4NS]^+$: 274.0314.

***N*-[4-(Pyridin-2-yl)-3-(trifluoromethylthio)phenyl]acetamide (2k):** yield: 47.4 mg (76%); pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.68$ (d, $J = 4.3$ Hz, 1H), 8.25 (s, 1H), 7.83 (s, 1H), 7.81–7.70 (m, 2H), 7.50 (dd, $J = 8.1$, 3.0 Hz, 2H), 7.31 (ddd, $J = 7.5$, 4.9, 0.9 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 169.03$, 157.37, 148.86, 140.51, 138.98, 136.62, 131.27, 129.64 (q, $J = 308$ Hz), 126.43, 124.80, 124.41, 122.59, 121.70, 24.57; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.61$; HR-MS: $m/z = 313.0619$ $[M+H]^+$, calculated for $[C_{14}H_{12}F_3N_2OS]^+$: 313.0622.

Methyl 3-(pyridin-2-yl)-4-(trifluoromethylthio)benzoate (2l): yield: 47.6 mg (76%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.71$ (ddd, $J = 4.9$, 1.6, 0.9 Hz, 1H), 8.27 (d, $J = 1.9$ Hz, 1H), 8.09 (dd, $J = 8.3$, 2.0 Hz, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.83 (td, $J = 7.7$, 1.8 Hz, 1H), 7.62 (dd, $J = 7.9$, 0.9 Hz, 1H), 7.34 (ddd, $J = 7.6$, 4.9, 1.1 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.08$, 156.66, 148.85, 143.50, 136.85, 133.52, 133.50, 131.28, 130.89, 129.86, 129.52 (q, $J = 308$ Hz), 123.70, 122.96, 52.58; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.06$; HR-MS: $m/z = 314.0459$ $[M+H]^+$, calculated for $[C_{14}H_{11}F_3NO_2S]^+$: 314.0463.

Methyl 4-(pyridin-2-yl)-3-(trifluoromethylthio)benzoate (2m): yield: 53.2 mg (85%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.72$ (ddd, $J = 4.9$, 1.6, 0.9 Hz, 1H), 8.50 (s, 1H), 8.18 (dd, $J = 8.0$, 1.7 Hz, 1H), 7.82 (td, $J = 7.7$, 1.8 Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 7.9$ Hz, 1H), 7.35 (ddd, $J = 7.6$, 4.9, 1.0 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 165.70$, 156.71, 149.09, 148.86, 136.67, 136.45, 131.01, 130.97, 130.80, 129.41 (q, $J = 308$ Hz), 125.11, 124.10, 122.98, 52.57; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.62$; HR-MS: $m/z = 314.0455$ $[M+H]^+$, calculated for $[C_{14}H_{11}F_3NO_2S]^+$: 314.0463.

2-{4-(Trifluoromethyl)-2-[(trifluoromethyl)thio]phenyl}-pyridine (2n): yield: 18.1 mg (28%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.74$ (ddd, $J = 4.9$, 1.6, 0.9 Hz, 1H), 8.09 (s, 1H), 7.85 (td, $J = 7.7$, 1.8 Hz, 1H), 7.82–7.72 (m, 2H), 7.56 (dt, $J = 7.9$, 0.9 Hz, 1H), 7.38 (ddd, $J = 7.6$, 4.9, 1.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 156.43$, 149.28, 148.09, 136.72, 132.18, 131.58 (q, $J = 34$ Hz), 131.24, 129.4 (q, $J = 308$ Hz), 126.86 (q, $J = 4$ Hz), 126.10 (q, $J = 2$ Hz), 123.46 (q, $J = 271$ Hz), 123.26, 122.10; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -41.53$, −62.81; HR-MS: $m/z = 324.0275$ $[M+H]^+$, calculated for $[C_{13}H_8F_6NS]^+$: 324.0282.

2-[3-(Trifluoromethylthio)naphthalen-2-yl]pyridine (2p): yield: 50.6 mg (83%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.75$ (dd, $J = 4.8$, 0.7 Hz, 1H), 8.39 (s, 1H), 8.07 (s, 1H), 7.92 (dd, $J = 9.4$, 5.4 Hz, 2H), 7.83 (td, $J = 7.7$, 1.8 Hz, 1H), 7.66–7.56 (m, 3H), 7.34 (ddd, $J = 7.6$, 4.9, 1.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 157.91$, 148.96, 141.27, 136.88, 136.33, 133.50, 133.04, 130.14, 129.70 (q, $J = 308$ Hz), 128.13, 128.04, 127.94, 127.43, 124.34, 122.36, 121.55; ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -42.06$; HR-MS:

m/z = 306.0556, $[M+H]^+$, calculated for $[C_{16}H_{11}F_3NS]^+$: 306.0564.

3-Methyl-2-{2-[(trifluoromethyl)thio]phenyl}pyridine (3a): yield: 38.7 mg (72%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.3 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.25 (dd, *J* = 7.7, 4.9 Hz, 1H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.51, 146.46, 145.88, 138.03, 136.63, 131.60, 130.38, 130.23, 129.58 (q, *J* = 308 Hz), 129.01, 124.19, 122.88, 18.99; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.50; HR-MS: *m/z* = 270.0561 $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NS]^+$: 270.0564.

4-Methyl-2-{2-[(trifluoromethyl)thio]phenyl}pyridine (3b): yield: 40.4 mg (75%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 5.0 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.51 (td, *J* = 7.5, 1.3 Hz, 1H), 7.45 (td, *J* = 7.6, 1.7 Hz, 1H), 7.34 (s, 1H), 7.17–7.11 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.57, 148.64, 147.46, 145.22, 135.49, 130.59, 129.94, 129.68 (q, *J* = 308 Hz), 129.05, 124.94, 124.41, 123.46, 21.18; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.68; HR-MS: *m/z* = 270.0560 $[M+H]^+$, calculated for $[C_{13}H_{11}F_3NS]^+$: 270.0564.

2-[2-(Trifluoromethylthio)phenyl]nicotinonitrile (3d): yield: 35.8 mg (64%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.10 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.69–7.54 (m, 3H), 7.47 (dd, *J* = 7.9, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.77, 152.12, 143.31, 140.56, 137.88, 131.20, 130.87, 130.77, 129.38 (q, *J* = 307 Hz), 123.91, 122.50, 116.47, 110.37; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −42.17; HR-MS: *m/z* = 281.0352 $[M+H]^+$, calculated for $[C_{13}H_8F_3N_2S]^+$: 281.0360.

Methyl 2-[2-(trifluoromethylthio)phenyl]nicotinate (3f): yield: 44.4 mg (71%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.36 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51–7.40 (m, 3H), 3.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.20, 158.64, 151.81, 146.66, 138.37, 136.87, 130.65, 130.18, 129.40 (q, *J* = 307 Hz), 129.20, 126.56, 123.35, 122.70, 52.44; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.88; HR-MS: *m/z* = 314.0460 $[M+H]^+$, calculated for $[C_{14}H_{11}F_3NO_2S]^+$: 314.0463.

2-{2-[(Trifluoromethyl)thio]phenyl}pyrimidine (3g): yield: 37.9 mg (74%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 4.9 Hz, 2H), 8.13–8.02 (m, 1H), 7.88–7.79 (m, 1H), 7.56–7.46 (m, 2H), 7.28 (dd, *J* = 10.0, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.92, 156.68, 140.95, 133.03, 131.13, 130.33, 129.74 (q, *J* = 307 Hz), 128.96, 126.65, 119.19; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.40; HR-MS: *m/z* = 257.0356 $[M+H]^+$, calculated for $[C_{11}H_8F_3N_2S]^+$: 257.0360.

10-[(Trifluoromethyl)thio]benzoquinoline (3h): yield: 25.1 mg (45%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.04 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.83 (t, *J* = 8.9 Hz, 2H), 7.75–7.65 (m, 2H), 7.57 (dd, *J* = 8.0, 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.01, 145.74, 135.35, 135.01, 130.13 (q, *J* = 312 Hz), 129.75, 128.35, 128.03, 127.87, 127.05, 126.53, 125.72, 125.53 (d, *J* = 3 Hz), 121.49; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −43.22; HR-MS: *m/z* = 280.0406 $[M+H]^+$, calculated for $[C_{14}H_9F_3NS]^+$: 280.0408.

1-{2-[(Trifluoromethyl)thio]phenyl}pyrazole (3i): yield: 34.6 mg (71%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.8 Hz, 1H), 7.80–7.73 (m, 2H), 7.62–7.52 (m, 2H), 7.50–7.42 (m, 1H), 6.49 (t, *J* = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.62, 141.20, 137.02, 131.61, 131.23, 129.28 (q, *J* = 308 Hz), 129.12, 127.48, 121.43, 107.22; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.83; HR-MS: *m/z* = 245.0355 $[M+H]^+$, calculated for $[C_{10}H_8F_3N_2S]^+$: 245.0360.

2-Methyl-*N*-(quinolin-8-yl)-6-[(trifluoromethyl)thio]benzamide (3q): yield: 48.5 mg (67%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$); δ = 10.03 (s, 1H), 9.00 (dd, *J* = 7.1, 1.8 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.67–7.57 (m, 3H), 7.47–7.40 (m, 3H), 2.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.10, 148.39, 143.95, 138.53, 136.77, 136.35, 134.88, 134.10, 133.23, 129.85, 129.34 (q, *J* = 307 Hz), 128.03, 127.37, 122.37, 121.77, 121.34, 117.01, 19.67; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.90; HR-MS: *m/z* = 363.0774 $[M+H]^+$, calculated for $[C_{18}H_{14}F_3N_2OS]^+$: 363.0779.

***N*-(Quinolin-8-yl)-2-(trifluoromethyl)-6-[(trifluoromethyl)thio]benzamide (3r):** yield: 49.9 mg (60%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1H), 8.93 (dd, *J* = 5.9, 3.1 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.69 (td, *J* = 8.0, 0.6 Hz, 1H), 7.66–7.59 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.92, 148.44, 141.60, 140.79, 138.44, 136.33, 133.86, 130.28, 129.29, 128.95 (q, *J* = 307 Hz), 128.94 (m), 127.99, 127.35, 124.62, 122.98 (q, *J* = 273 Hz), 122.68, 121.81, 117.13; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −41.50, −59.31; HR-MS: *m/z* = 417.0491 $[M+H]^+$, calculated for $[C_{18}H_{11}F_6N_2OS]^+$: 417.0496.

***N*-(Quinolin-8-yl)-5-(trifluoromethyl)-2-[(trifluoromethyl)thio]benzamide (3s):** yield: 30.8 mg (37%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.48 (s, 1H), 8.89 (t, *J* = 4.5 Hz, 1H), 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.10 (d, *J* = 1.4 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.82 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.63 (d, *J* = 4.2 Hz, 2H), 7.50 (dd, *J* = 8.3, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.13, 148.58, 140.79, 138.55, 136.47, 135.12, 133.85, 132.06 (d, *J* = 34 Hz), 129.82, 129.2 (q, *J* = 308 Hz), 128.00, 127.73 (m), 127.33, 125.32 (m), 123.2 (q, *J* = 272 Hz) 122.77, 121.94, 117.09; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −40.87, −62.98; HR-MS: *m/z* = 417.0491 $[M+H]^+$, calculated for $[C_{18}H_{11}F_6N_2OS]^+$: 417.0496.

Acknowledgements

This work was financially supported by grants from the National Natural Science Foundation of China (21372013), the Shenzhen Peacock Program (KQTD201103) and the Shenzhen innovation funds (CXZZ20130517152257071). Y. H. thanks the MOE for the Program for New Century Excellent Talents in University. The Shenzhen municipal development and reform commission is acknowledged for their public service platform program.

References

[1] a) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827; b) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880.

[2] C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207.

[3] a) N. N. Yarovenko, A. S. Vasileva, *J. Gen. Chem. USSR (Engl. Transl.)* **1958**, *28*, 2537; b) E. Nodiff, A. S. Lipschutz, P. N. Craig, M. Gordon, *J. Org. Chem.* **1960**, *25*, 60; c) A. E. Feiring, *J. Org. Chem.* **1979**, *44*, 2907.

[4] For selected examples, see: a) T. Billard, G. Blond, B. R. Langlois, *Tetrahedron Lett.* **1997**, *38*, 65; b) G. Blond, T. Billard, B. R. Langlois, *Tetrahedron Lett.* **2001**, *42*, 2473; c) S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848; d) C. Pooput, M. Médebielle, W. R. Dolbier Jr, *Org. Lett.* **2004**, *6*, 301; e) J. Russell, N. Roques, *Tetrahedron* **1998**, *54*, 13771; f) T. Billard, N. Roques, B. R. Langlois, *J. Org. Chem.* **1999**, *64*, 3813; g) V. N. Boiko, G. M. Shchupak, N. V. Kirij, *Ukr. Khim. Zh.* **2001**, *67*, 51; h) C. Pooput, J. W. R. Dolbier, M. Médebielle, *J. Org. Chem.* **2006**, *71*, 3564; i) I. Kieltsch, P. Eisenberger, A. Togni, *Angew. Chem.* **2007**, *119*, 768; *Angew. Chem. Int. Ed.* **2007**, *46*, 754; j) A. Harsányi, E. Dorkó, A. Csapó, T. Bakó, C. Peltz, J. Rábai, *J. Fluorine Chem.* **2011**, *132*, 1241.

[5] For reviews on recent development of direct introduction of the SCF_3, see: a) T. Billard, A. Tlili, *Angew. Chem.* **2013**, *125*, 6952; *Angew. Chem. Int. Ed.* **2013**, *52*, 6818; b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; c) F. Tougoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2415.

[6] a) F. Baert, J. Colomb, T. Billard, *Angew. Chem.* **2012**, *124*, 10528; *Angew. Chem. Int. Ed.* **2012**, *51*, 10382; b) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312; c) C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183; d) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem.* **2012**, *124*, 2542; *Angew. Chem. Int. Ed.* **2012**, *51*, 2492; e) C.-P. Zhang, D. A. Vicic, *Chem. Asian J.* **2012**, *7*, 1756; f) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem.* **2013**, *125*, 1588; *Angew. Chem. Int. Ed.* **2013**, *52*, 1548; g) M. Rueping, N. Tolstoluzhsky, P. Nikolaienko, *Chem. Eur. J.* **2013**, *19*, 14043; h) X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem.* **2013**, *125*, 3541; *Angew. Chem. Int. Ed.* **2013**, *52*, 3457.

[7] a) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160; b) Y. Yang, X. Jiang, F.-L. Qing, *J. Org. Chem.* **2012**, *77*, 7538; c) J. Sheng, S. Li, J. Wu, *Chem. Commun.* **2004**, *50*, 578.

[8] G. Mann, D. Baranano, J. F. Hartwig, A. L. Rheingold, I. A. Guzei, *J. Am. Chem. Soc.* **1998**, *120*, 9205.

[9] For reviews on high-valent Pd chemistry, see: a) K. Muñiz, *Angew. Chem.* **2009**, *121*, 9576; *Angew. Chem. Int. Ed.* **2009**, *48*, 9412; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177.

[10] a) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237; b) C. Xu, Q. Shen, *Org. Lett.* **2014**, *16*, 2046.

[11] For examples of Ar–F formation *via* Pd(IV), see: a) K. L. Hull, W. Q. Anani, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134; b) X. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520; c) K. S. L. Chan, M. Wasa, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 9247; *Angew. Chem. Int. Ed.* **2011**, *50*, 9081.

[12] For examples of Ar–CF_3 formation *via* Pd(IV), see: a) X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648; b) X.-G. Zhang, H.-X. Dai, M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 11948; c) L.-S. Zhang, K. Chen, G. Chen, B.-J. Li, S. Luo, Q.-Y. Guo, J.-B. Wei, Z.-J. Shi, *Org. Lett.* **2013**, *15*, 10; d) M. Miura, C.-G. Feng, S. Ma, J.-Q. Yu, *Org. Lett.* **2013**, *15*, 5258.

[13] For examples of C–C bond formation using ligand exchange strategy, see: a) T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 16354; b) X. Mu, T. Wu, H.-Y. Wang, Y.-L. Guo, G. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 878; c) X. Mu, S. Chen, X. Zhen, G. Liu, *Chem. Eur. J.* **2011**, *17*, 6039; d) K. B. McMurtrey, J. M. Racowski, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4094.

[14] a) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047; b) H. Kawai, Y. Kobayashi, S. Oi, Y. Inoue, *Chem. Commun.* **2008**, 1464; c) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488; d) A. J. Hickman, M. S. Sanford, *ACS Catal.* **2011**, *1*, 170; e) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864; f) J. M. Racowski, N. D. Ball, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 18022; g) N. A. B. Juwaini, J. K. P. Ng, J. Seayad, *ACS Catal.* **2012**, *2*, 1787; h) A. Maleckis, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2013**, *135*, 6618.

[15] For the strategy of early ligand exchange then oxidation and selective reductive elimination, see: K. M. Engle, T.-S. Mei, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 1514; *Angew. Chem. Int. Ed.* **2011**, *50*, 1478.

[16] S. Michel, G. Villa, P. S. Thuy-Boun, A. Homs, J.-Q. Yu, *Angew. Chem.* **2014**, *126*, 753; *Angew. Chem. Int. Ed.* **2013**, *53*, 734.

[17] Pd(II) species are readily oxidized to Pd(III) or Pd(IV) by Selectfluor under mild conditions, see: a) T. Furuya, H. M. Kaiser, T. Ritter, *Angew. Chem.* **2008**, *120*, 6082; *Angew. Chem. Int. Ed.* **2008**, *47*, 5993; b) T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2008**, *130*, 10060; c) T. Furuya, D. Benitez, E. Tkatchouk, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 3793; d) A. R. Mazzotti, M. G. Campbell, P. Tang, J. M. Murphy, T. Ritter, *J. Am. Chem. Soc.* **2013**, *135*, 14012; e) G. Shan, X. Yang, L. Ma, Y. Rao, *Angew. Chem.* **2012**, *124*, 13247; *Angew. Chem. Int. Ed.* **2012**, *51*, 13070.

[18] A. Maleckis, M. S. Sanford, *Organometallics* **2011**, *30*, 6617.

[19] For a study of the HOAc effect, see: a) S. R. Whitfield, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 15142; b) Y. Ye, D. B. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 14682; c) D. C. Powers, E. Lee, A. Ariafard, M. S. Sanford, B. Y. Yates, A. J. Canty, T. Ritter, *J. Am. Chem. Soc.* **2012**, *134*, 12002.

