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Palladium Catalyzed Trifluoromethylthiolation of Chelation Assisted C-H bonds

Arunachalam Kesavan, Manthena Chaitanya and Pazhamalai Anbarasan*[a]

Dedication ((optional))

Abstract: An efficient palladium catalyzed trifluoromethylthiolation of chelation assisted C-H bond have been accomplished employing readily accessible trifluoromethylthiolating reagent. The reaction tolerates various directing groups and functional groups and allows the access to diverse trifluoromethylthiolated arenes in good yield. The plausible mechanism was proposed based on the preliminary mechanistic investigation.

Introduction

Trifluoromethylthiolated arene and heteroarene have gained great attention in the recent past, due to their presence in various therapeutically important molecules as well as their ability to alter the physical, biological and chemical properties of the parent molecule.[1] Representative examples of bioactive molecules containing aryltrifluoromethylthio group is shown in Figure 1. Hence, there has been a significant interest in the synthetic community for the development of elegant strategy for the construction of trifluoromethylthiolated arenes and heteroarenes.[2]

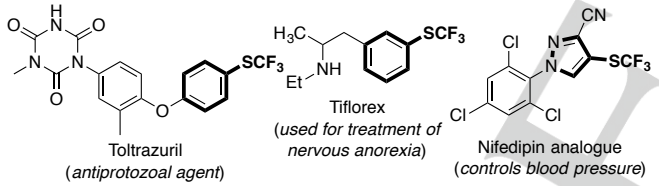
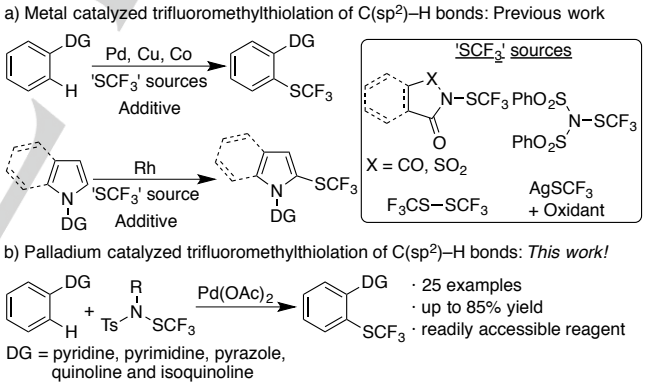


Figure 1. Biologically important trifluoromethylthioaryl moiety containing molecules.

Typically, syntheses of trifluoromethylthiolated arene have been achieved through either formation of S-CF_3 bond[3] or the halogen exchange with the prefunctionalized sulfur-containing molecule[4]. However, these methods are highly limited to specific substrates, due to the harsh reaction conditions. The most viable method that has been practiced in last decade is the direct introduction of 'SCF_3' moiety through C–SCF_3 bond formation. In this context, transition metal catalyzed cross coupling of prefunctionalized aryl electrophiles[5] and nucleophiles[6] with appropriate nucleophilic or electrophilic trifluoromethylthio sources, respectively, have been studied extensively. Surpassing these methods, direct and selective trifluoromethylthiolation of C-H bonds[7] of arenes were also documented employing either electrophilic 'SCF_3' reagent or under oxidative conditions with $AgSCF_3$ (Scheme 1a). For instance, Daugulis and co-workers[8] disclosed the first trifluoromethylthiolation of C-H bond employing substiochimetric amount of copper catalyst and $(CF_3S)_2$. Subsequently, various palladium, cobalt and rhodium catalyzed trifluoromethylthiolation of arenes[9] and indoles[10] were reported employing electrophilic N-SCF_3 reagent. Beside, employing nucleophilic $AgSCF_3$ palladium or cobalt catalyzed trifluoromethylthiolation of C-H bond was also demonstrated under the oxidative conditions.[11] Although most of these methods offer a direct trifluoromethylthiolation of C–H bonds, the major drawback are the use of N-SCF_3 reagents, which are synthesized from relatively unavailable and expensive $AgSCF_3$ in a multistep process and the requirement of additional oxidant. Thus, the development of a general method for the trifluoromethylthiolation of C-H bond employing readily accessible electrophilic reagent is highly warranted.



Scheme 1. Synthesis of trifluoromethylthioarene *via* C–H bond functionalization.

Recently, Billard and co-workers[12] developed a one-step access to various N-SCF_3 reagents from readily available amines, DAST and CF_3TMS, which are also shown to be an excellent electrophilic 'SCF_3' source. Our long standing interest in the synthesis of trifluoromethylthiolated arenes[13] and C-H bond functionalization[14] as well as importance of trifluoromethylthiolated arenes in combination with ready access to N-SCF_3 reagents through Billard protocol prompted us to develop a direct trifluoromethylthiolation of C-H bonds employing readily accessible reagent.[15] Thus, we herein disclose the palladium-catalyzed trifluoromethylthiolation of chelation assisted C-H bonds of arenes (Scheme 1b).

Results and Discussion

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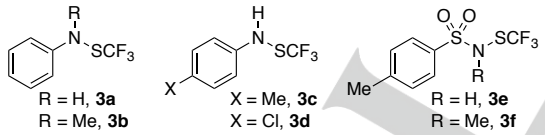
We initiated our studies with synthesis of various N-SCF_3 (**3a**-**3f**) reagents employing the protocol of Billard and co-workers. Next, the synthesized reagents were subjected under the palladium catalyzed trifluoromethylthiolation conditions using 2-phenylpyridine **1a** model substrate. Reaction of **1a** with 1.1 equivalents of N-SCF_3 reagents **3a**-**3d** in the presence of 5 mol% of palladium acetate in trifluoroacetic acid (TFAA) at 120 °C didn't afford the expected product, only decomposition of N-SCF_3 reagents were observed (Table 1, entry 1). Interestingly, employing an more electrophilic trifluoromethylthiolating reagent **3e** under the above conditions, the formation of expected trifluoromethylthiolated product **2a** was observed in 59% yield (Table 1, entry 2).

Table 1. Palladium catalyzed trifluoromethylthiolation of 2-phenylpyridine **1a**: Optimization[a]

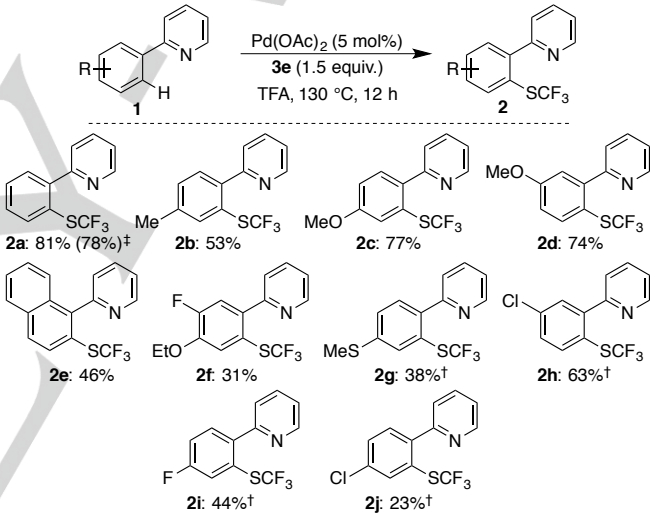
Entry	SCF_3 source	Solvent	Temp (°C)	Yield (%)[b]
1	**3a**-**3d**	TFAA	120	-
2	**3e**	TFAA	120	59
3	**3f**	TFAA	120	93
4	**3f**	TFAA	110	82
5	**3e**	AcOH	120	-
6	**3e**	TfOH	120	-
7	**3e**	DCE/TFAA[c]	120	<5
8	**3e**[d]	TFAA	120	77
9	**3e**[d]	TFAA	130	90 (63)[e]

[a] Reaction conditions: **1a** (1 equiv.), **3a**-**3f** (1.1 equiv.), $Pd(OAc)_2$ (5 mol%), solvent (0.32 M), temp, 12 h. [b] yield is based on ^{19}F NMR using hexafluorobenzene as internal standard. [c] Ratio of solvent is 1:1. [d] 1.5 equiv. of **3e** was used. [e] 2.5 mol% of $Pd(OAc)_2$.



Replacing **3e** with the relatively electrophilic[16] methylated derivative **3f** afforded the product **2a** in 93% yield (Table 1, entry 3). Decreasing the reaction temperature with **3f** also slightly decrease the yield (82%) of **2a** (Table 1, entry 4). Since the synthesis of reagent **3f** requires the addition step, best conditions were optimized with reagent **3e**. Thus, changing the reaction medium to acetic acid, triflic acid or the 1:1 mixture of 1,2-dichloroethane (DCE) and trifluoroacetic acid with reagent **3e** gave either no reaction or only detectable amount of product (Table 1, entries 5-7). Interestingly, increase in yield (77%) was observed with 1.5 equivalents of **3e** in TFAA at 120 °C (Table 1, entry 8). The best result (90%) was achieved at 130 °C with 1.5 equivalents of **3e** and 5 mol% of palladium acetate in TFAA. Decreasing the catalyst loading to 2.5 mol% also decrease the yield of **2a** (Table 1, entry 9). Thus, the optimized conditions for the trifluoromethylthiolation of C-H is 1.5 equivalents of **3e** or 1.1 equivalents of **3f** in the presence of 5 mol% of $Pd(OAc)_2$ in TFAA at 130 or 120 °C.

Having identified the suitable conditions for the trifluoromethylthiolation of chelation assisted C-H bonds, scope and limitation of the developed method was investigated. Keeping pyridine as directing group various substituted 2-arylpyridines were subjected under the optimized conditions (Scheme 2). Electron donating alkyl and alkoxy substituted aryl derivatives furnished the corresponding trifluoromethylthiolated product (**2a**-**2d**) in good yield. Sterically congested 2,3-benzofused 2-arylprydine gave the product **2e** in 46% yield. Additional coordination containing methylaryl thioether afforded the product **2g** in 38% yield with **3f** as trifluoromethylthiolating reagent. In addition, relative electron withdrawing, halo substituted trifluoromethylthio arenes (**2f**, **2h**-**2j**) were also achieved in moderate to good yield *via* C-H bond functionalization.



Scheme 2. Palladium catalyzed trifluoromethylthiolation of 2-arylpyridines **1** with **3e**/**3f**: Scope and limitation. † Reaction was performed with 1.1 equiv. of **3f** at 120 °C. ‡ Yield of gram scale reaction.

Next, compatibility of various directing group under the present trifluoromethylthiolation conditions were examined. Simple 4-methylpyridine efficiently directed the trifluoromethylthiolation of C-H bond and led to the product **2l** in 77% yield (Scheme 3). Sterically hindered 3-methyl and 6-methoxy substituted pyridine derivatives also afforded the product **2k** and **2m** in excellent yield. Similarly, 5-fluoropyridine derivative also furnished the corresponding product **2n** in 42% yield. In place of pyridine, isoquinoline and quinoline showed high compatibility as directing group and let the formation of **2o** and **2p** in 66 and 65% yield, respectively. However, pyrimidine, which has additional coordination site gave the corresponding product (**2q**) in relatively lower yield. Trifluoromethylthiolation of benzo[*h*]quinoline under the present conditions gave the product **2r** in 63% yield. The formation of trifluoromethylthiolated product was unambiguously confirmed by X-ray analysis, which also

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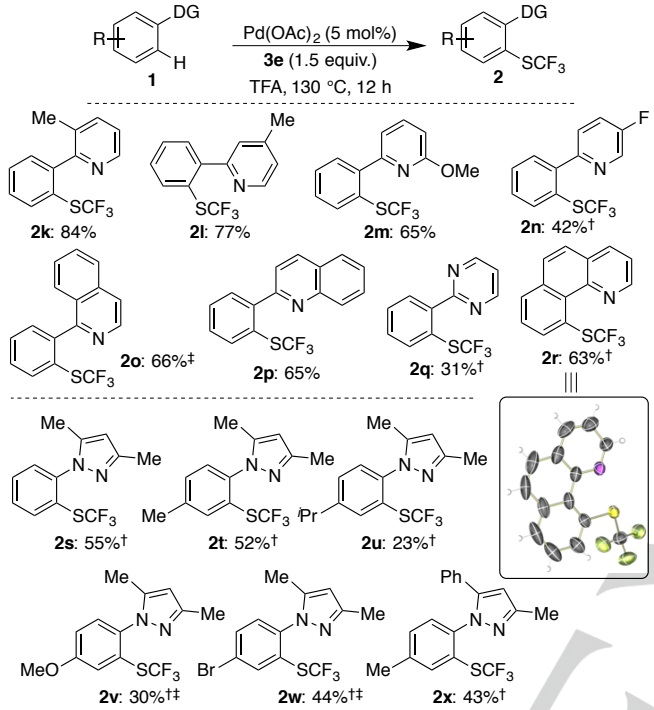
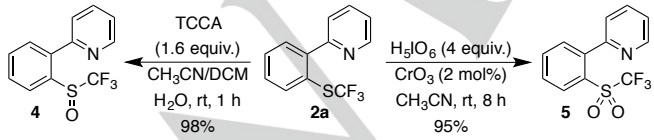
matches with the literature report[9a] (Scheme 3). Interestingly, the developed method was successfully extended to the selective *ortho*-trifluoromethylthiolation of *N*-arylpyrazoles employing **3f** as trifluoromethylthiolating reagent. Thus, using 3,5-dimethylpyrazole as directing group, trifluoromethylated arenes **2s**-**2w** were achieved in moderate to good yield. Bulky 3-methyl-5-phenyl also successfully directed trifluoromethylation to furnish **2t** in 43% yield.



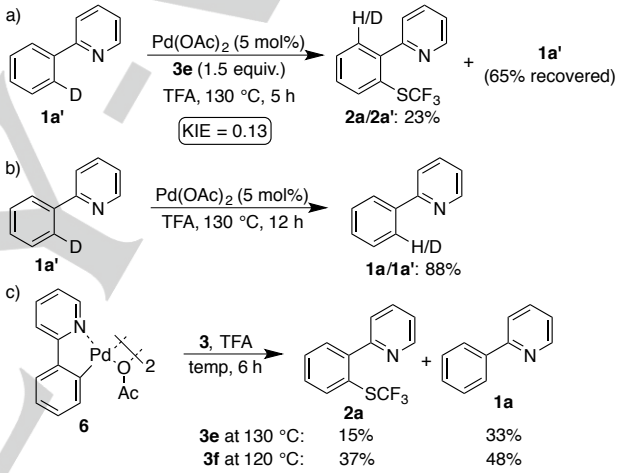
Scheme 3. Palladium catalyzed trifluoromethylthiolation: Scope and limitation of directing group. Reaction of all the pyrazole derivatives were performed with 10 mol% of $Pd(OAc)_2$. † Reaction was performed 1.1 equiv. of **3f** at 120 °C. ‡ ^1H NMR yield.

Synthetic utility of the present transformation was demonstrated through oxidative conversion to sulfoxide **4** and sulfone **5**, which are shown to have unique physiochemical properties. Oxidation of **2a** with trichloroisocyanuric acid and water at room temperature furnished the sulfoxide **4** in 98% yield. On the other hand, using strong oxidation conditions, H_5IO_6 and catalytic amount of CrO_3, complete oxidation of **2a** to sulfone **3** was observed in 95% yield.



Scheme 4. Synthetic applications.

Preliminary deuterium labeling and stoichiometric study were performed to understand the possible mechanism of the present trifluoromethylthiolation. Reaction of mono-deuteriated 2-phenylpyridine **1a'** under the optimized conditions with **3e** for 5 h afforded the mixture of **2a** and **2a'** in 23% yield and the 65% of **1a'** recovered (Scheme 5a). Kinetic isotopic effect observed for this reaction is 0.13, which suggests that the initial metallation through C-H bond functionalization is reversible and not the rate-determining step. This is further supported by the reaction of **1a'** in the absence of **3e** under the optimized conditions with palladium acetate, where significant amount of loss of deuterium was observed. Subsequently, the stable palladacycle **6** was synthesized and stoichiometric reaction was performed under the optimized conditions. Thus, the trifluoromethylthiolation of palladacycle **6** with **3e** in TFAA at 130 °C furnished the product **2a** in 15% yield along protodemetallation to **1a** in 33% yield. On the other hand, more reactive trifluoromethylthiolating reagent **3f** at 120 °C gave the product **2a** in 37% yield. These observations revealed that 1) palladacycle **6** like intermediate might be formed in the catalytic cycle, 2) the reductive elimination to product **2** is possibly the slow and rate determining step and 3) also support the reversible metallation and protodemetallation.



Scheme 5. Mechanistic investigation.

Based on the preliminary mechanistic investigation and literature precedence, the plausible mechanism for the present trifluoromethylthiolation of arene C-H bond was postulated. Palladium acetate in the presence of trifluoroacetic acid would generate activated palladium species **A**, which on reaction with arene **1** would furnish palladacycle **B** *via* chelation assisted electrophilic metallation of arene C-H bond. Oxidative addition of trifluoromethylthiolating reagent **3** to palladacycle **B** would afford the Pd-intermediate **C**. Formation of product **2** from intermediate **C** could be rationalized through reductive elimination and the generation of palladium species **D**. Ligand exchange with TFAA would complete the catalytic cycle and regenerate the active palladium species **A** for the next cycle.

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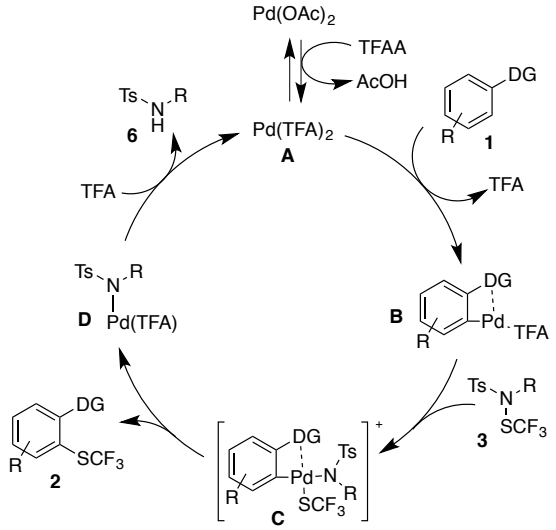

Scheme 6. Plausible mechanism.

Conclusions

In summary, we have developed an efficient palladium catalyzed trifluoromethylthiolation of chelation assisted C-H bond of arenes. The reaction utilizes the readily accessible trifluoromethylthiolating reagent and various directing group like pyridine, pyrimidine, pyrazole, quinoline and isoquinoline. This also allows the synthesis of various trifluoromethylthiolated arenes in good to excellent yield. Synthetic application was demonstrated through ready conversion to sulfoxide and sulfone. Furthermore, preliminary mechanistic investigation was performed to understand the in-sight of the reaction mechanism.

Acknowledgements

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Keywords: trifluoromethylthiolation • C-H bond functionalization • palladium • N-SCF3 reagent • arylpyridine

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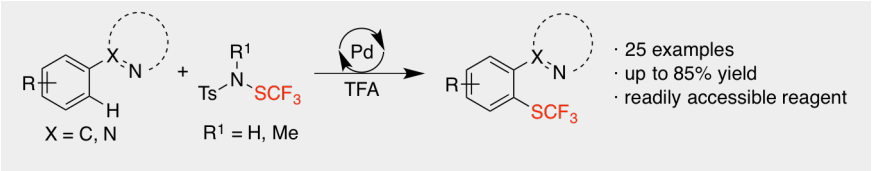

Trifluoromethylthiolation*

*Arunachalam Kesavan, Manthena Chaitanya and Pazhamalai Anbarasan**

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Palladium Catalyzed Trifluoromethylthiolation of Chelation Assisted C-H bonds

Palladium catalyzed trifluoromethylthiolation of chelation assisted C-H bond have been accomplished employing readily accessible electrophilic trifluoromethylthiolating reagent.

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