Pd-Catalyzed Difluoromethylthiolation of Aryl Chlorides, Bromides and Triflates

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A highly efficient Pd-catalyzed difluoromethylthiolation of aryl chlorides, bromides and triflates is described. A variety of aryl halides with common functional groups were difluoromethylthiolated in moderate to excellent yields. Furthermore, several natural, drug and material molecules containing an aryl chloride, bromide, and phenol unit were successfully difluoromethylthiolated, thus providing medicinal chemists a general method for late-stage difluoromethylthiolation of leading compounds.

Keywords Pd-catalyzed, difluoromethylthiolation, late-stage modification

Introduction

It has been well-established that introduction of a fluorine atom or a fluoroalkyl group may significantly improve the drug molecule's pharmacologic properties such as lipophilicity and metabolic stability.[1] As a result, "fluorine scan" has become a routine practice in the optimize the structure of the lead compound.[2] Among many fluoroalkyl groups, difluoromethylthio group (-SCF_2H), represents an under-developed structural motif with great potential. First, the difluoromethylthio group which bears a slightly acidic proton, is generally considered as a lipophilic hydrogen-bonding donor that may improve the molecule's binding selectivity with its hosting enzyme.[3] Secondary, the difluoromethylthio group is less lipophilic, less electron-withdrawing and less stable to strong acid than the analogous trifluoromethylthio group (-SCF_3), thus providing medicinal chemists an opportunity to regulate the drug molecule's metabolic stability.[4] Consequently, there is a urgent recent need for development of efficient methods for the introduction of the difluoromethylthio group into small molecules under mild conditions.

Toward this end, several strategies have been developed to get access to the difluoromethylthiolated compounds. Traditional methods for the preparation of difluoromethylthiolated arenes were typically based on the insertion of an *in situ* generated difluorocarbene into the ArS-H bond, as initially described by Porter *et al.* in 1957, in which HCF_2Cl (F-22) was served as a difluorocarbene precursor.[5a] Since then, a variety of other easily accessible difluorocarbene precursors have been disclosed, such as $FSO_2CF_2CO_2TMS$, $ClCF_2CO_2Na$, $TMSCF_3$, $TMSCF_2Br$, HCF_2OTf, $BrCF_2P(O)(OEt)_2$, $Ph_3P^+CF_2CO_2^-$ and $PhS(O)(NTs)CF_2H$ *etc*.[5] Alternatively, difluoromethylthiolated arenes may be synthesized by reaction of arylthiolate with an electrophilic[6] or a radical[7] difluoromethylating reagent. In addition, difluoromethylthiolated arenes can also be synthesized by difluoromethylation of disulfides via a single-electron-transfer (SET) process.[8] Nevertheless, these methods typically require the preformation of a thiol or its derivative, that may be challenging for structurally complicated molecules, which limits to its widespread applications. Very recently, Goossen discovered that difluoromethylthiolated arenes could be accessed by initial generation of ArSCN from aryl diazonium salts, followed by replacing the cyano group with *in situ* formed [$CuCF_2H$], thus opening a door to new horizon for the preparation of difluoromethylthiolated compounds.[9]

An alternative yet equally attractive approach for the preparation of difluoromethylthiolated arenes is to use a difluoromethylthiolative reagent that can react with various substrates. In this respect, Billard and Besset independently developed two masked electrophilic difluoromethylthiolation reagents.[10] Once the masked difluoromethylthiolated group was introduced, the mask group was removed to generated the desired difluoromethylthiolated compounds. More recently, we have pushed the frontier of this sub-filed one step further by successively inventing the first nucleophilic,[11] the first electrophilic,[12] and the first radical difluoromethylthiolting reagent[13] that allow to direct difluoroemethylthiolate a wide range of substrates under mild conditions.

More specifically, in 2015, we reported that in the of presence of a palladium catalyst generated from a combination $Pd(dba)_2$/Xantphos, nucleophilic difluoro-

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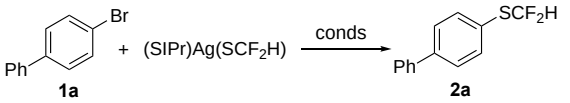
meththiolating reagent [(SIPr)Ag(SCF_2H)] (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene) was able to couple with (hetero)aryl iodides, activated bromides and triflates under mild conditions.[14-15] While activated heteroaryl bromides such as 2-bromopyridine or its derivatives reacted to give the corresponding difluoromethylthiolated pyridine derivatives in acceptable yields, aryl bromides and chlorides using the same catalyst did not react at all.

It is well-known that carbon-bromine bond in aryl bromide is much stronger than carbon-bromine bond in 2-bromopyridine, and the carbon-chloride bond in aryl chloride is more stronger. To activate the strong aryl bromide or chloride bond, a palladium catalyst bearing an electron-rich, sterically bulky alkylphosphine is required.[16] Inspired by these previous observations, we seek to achieve the difluoromethylthiolation of aryl bromides and chlorides by employing a palladium catalyst containing an electron-rich, sterically bulky alkylphosphine ligand. Herein, we report that in the presence of a catalyst generating from a combination of Buchwald' precatalyst with Brettphos, a variety of aryl bromides, chlorides and triflates reacted with (SIPr)Ag(SCF_2H) efficiently to give the corresponding difluoromethylthiolated arenes in high yields. [17]

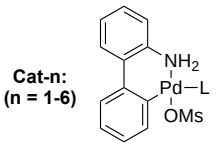
Results and Discussion

Initially, we chose the reaction of 4-bromobiphenyl **1a** with [(SIPr)Ag(SCF_2H)] in the presence of a palladium catalyst as a model reaction to optimize the reaction conditions. Our initial efforts in search of a suitable palladium catalyst by employing a combination of 10 mol% of $Pd(dba)_2$ with 10 mol% of common monodentate phosphine ligands such as XPhos, SPhos and BrettPhos or bidendate ligands such as DPPE, Xantphos and DPEphos, were less successful, giving the corresponding product **2a** in less than 15% yield. Interestingly, when Buchwald's precatalyst **Cat-1** or **Cat-2** that was generated from a palladacycle and BrettPhos or XPhos ligand was used as the catalyst, the yield increased significantly to 79% and 71% yield, respectively, while reaction using Buchwald's precatalyst **Cat-3** bearing RuPhos occurred in much lower yield (Scheme 1, entries 1-3). Likewise, the same type of catalyst containing other bidentate ligands such as DPPF, Xantphos or DPEphos were not efficient at all (Scheme 1, entries 4-6). The yield decreased slightly to 68% when 5.0 mol% of **Cat-1** was used when 1.2 equivalents of [(SIPr)Ag(SCF_2H)] was used (Scheme 1, entry 7). To probe the effect of the solvent, we studied the reaction in different solvents. It turned out that reactions in solvents such as dioxane or DME gave lower yields, while the yield was improved to 73% when THF

Scheme 1. Optimization of the conditions for Pd-catalyzed difluoromethylthiolation of aryl bromide. [a,b]



entry	[Pd]	ligand	solvent	temp	yield (%)[b]
1	**Cat-1**	-	toluene	50 °C	79
2	**Cat-2**	-	toluene	50 °C	71
3	**Cat-3**	-	toluene	50 °C	10
4	**Cat-4**	-	toluene	50 °C	<2
5	**Cat-5**	-	toluene	50 °C	10
6	**Cat-6**	-	toluene	50 °C	<2
7	**Cat-1**	-	toluene	50 °C	68 [c,d]
8	**Cat-1**	-	dioxane	50 °C	54 [c,d]
9	**Cat-1**	-	DME	50 °C	47 [c,d]
10	**Cat-1**	-	THF	50 °C	73 [c,d]
11	**Cat-1**	Brettphos	THF	50 °C	97 [c,d,e]
12	**Cat-1**	Brettphos	THF	rt	70 [c,d,e]
13	**Cat-1**	Brettphos	THF	50 °C	67 [c,d,f]
14	**Cat-1**	Brettphos	THF	50 °C	23 [c,g]



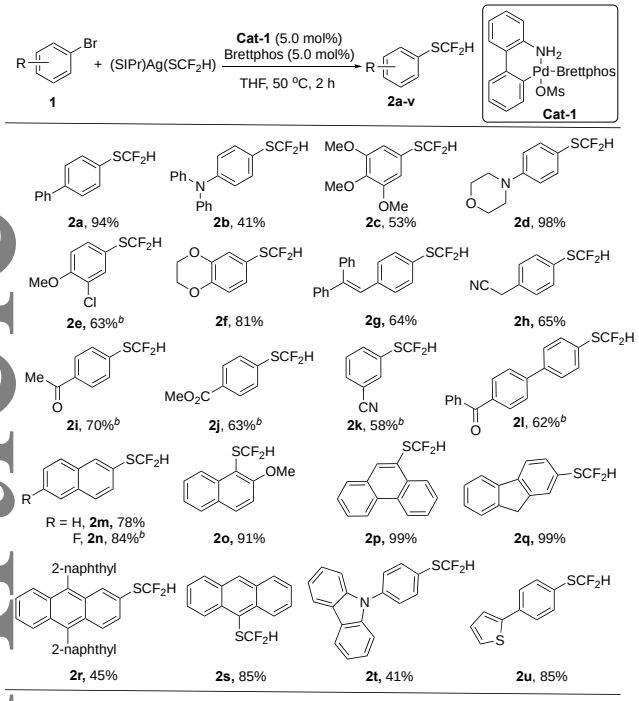
Ligand
L1: BrettPhos
L2: XPhos
L3: RuPhos
L4: DPPF
L5: Xantphos
L6: DPEphos

[a]Reaction condition: **1a** (11.6 mg, 0.0500 mmol), (SIPr)Ag(SCF_2H) (29 mg, 0.050 mmol), [Pd] (10.0 mol%) and ligand (20.0 mol%) in toluene (1.0 mL) for 2 h under an argon atmosphere; [b]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with trifluorotoluene as an internal standard; [c]1.2 equiv of (SIPr)Ag(SCF_2H) was used; [d][Pd] (5.0 mol%) was used; [e]Brettphos (5.0 mol%) was added; [f]Brettphos (3.0 mol%) was added; [g][Pd] (3.0 mol%) and Brettphos (3.0 mol%) was added.

was used as the solvent (Scheme 1, entries 8-10). Notable, the yield was further increased to 97% when additional 5.0 mol % of BrettPhos was added (Scheme 1, entry 11). The same reaction conducted at room temperature occurred in lower yield (70%) (Scheme 1, entry 12). When the amount of the additional BrettPhos was decreased to 3.0 mol%, the yield of the product **2a** also decreased (Scheme 1, entry 13). Likewise, the yield decreased dramactically to 23% when 3.0 mol% of **Cat-1** and 3.0 mol% BrettPhos was used (Scheme 1, entry 14).

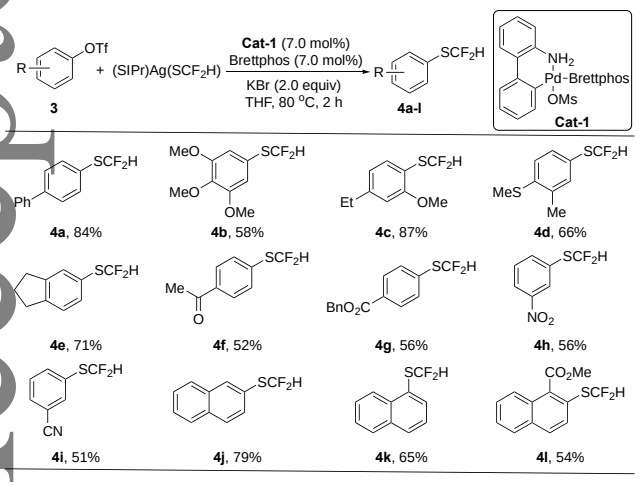
Under the conditions of entry 11 in Scheme 1, we next studied the generality of the reactions toward other aryl bromides. As shown in Scheme 2, the optimized conditions were quite effective for a variety of aryl bromide with different substituted groups. In general, reactions of aryl bromides with electron-donating substituents occurred faster and more efficiently than those with electron-withdrawing groups. For example, reactions of aryl bromides with *para*-ketone, ester or *meta*-cyano group required to increase the catalyst to 7.0 mol% to occur in full conversions (Scheme 2, **2i-l**). Polycyclic aromatic bromides, and aryl bromides with carbazole or thiophene moiety as well, can also be difluoromethylthiolated in good to excellent yields. (Scheme 2, **2m-2v**). It is

Scheme 2. Scope of Pd-catalyzed difluoromethylthiolation of aryl bromide. [a]



[a]Reaction conditions: aryl bromides (0.5 mmol), (SIPr)Ag(SCF_2H) (0.6 mmol), **Cat-1** (5.0 mol %), BrettPhos (5.0 mol %) in THF (10.0 mL) at 50 °C for 2 h; isolated yields; [b]**Cat-1** (7.0 mol %), BrettPhos (7.0 mol %) was used.

Scheme 3. Scope of Pd-catalyzed difluoromethylthiolation of aryl triflates.[a]

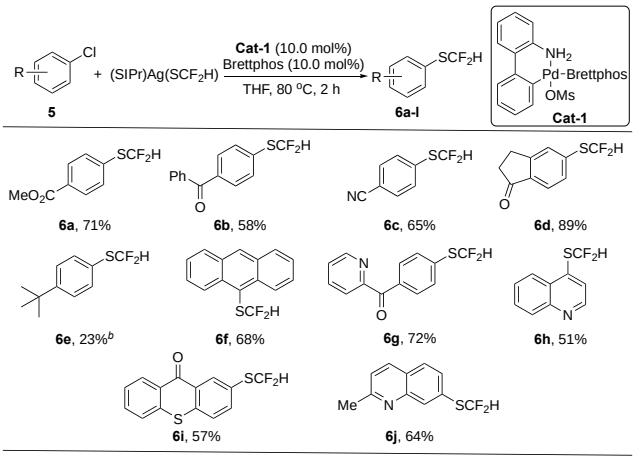


[a]Reaction conditions: aryl triflates **3** (0.5 mmol), (SIPr)Ag(SCF_2H) (0.6 mmol), **Cat-1** (7.0 mol %), BrettPhos (7.0 mol %) and KBr (2.0 equiv) in THF (10.0 mL) at 80 °C for 2 h; isolated yields.

noteworthy that common functional groups such as chloride (**2e**), alkene (**2g**), enolizable ketone (**2i**), ester (**2j**), and cyano group (**2h** and 2**k**) were compatible.

Phenol is a common structure in natural products or drugs, and the corresponding triflates are valuable coupling partners for transition metal-catalyzed cross coupling reactions.[18] After a quick screen of the reaction

Scheme 4. Scope of Pd-catalyzed difluoromethylthiolation of aryl chlorides.[a]



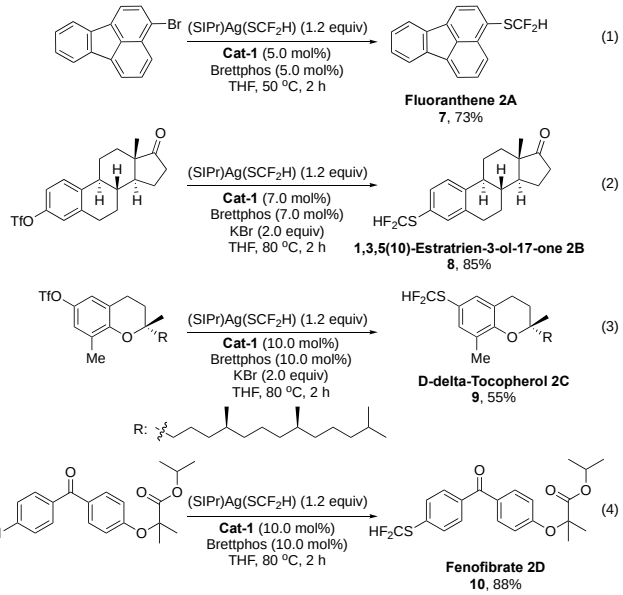
[a]Reaction conditions: aryl chloride 5 (0.5 mmol), (SIPr)Ag(SCF_2H) (0.6 mmol), **Cat-1** (10.0 mol %), BrettPhos (10.0 mol %) in THF (10.0 mL) at 80 °C for 2 h; [b] Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with trifluorotoluene as an internal standard.

conditions, it was found that aryl triflates can also be difluoromethylthiolated in moderate to good yields when 2.0 equivalent KBr was added and the reaction temperature was increased to 80 °C. As summarized in Scheme 3, a variety of aryl triflates were difluoromethylthiolated. Again, common functional groups such as thioether (**4d**), ketone (**4f**), ester (**4g**), nitro (**4h**), and cyano group (**4i**) were tolerant.

Aryl chlorides are the most cheap, abundant and easily available coupling partners.[19] Because of C-Cl bond of aryl chloride is stronger than C-Br bond of aryl bromide, it was found that we need increased the amount of **Cat-1** and additional BrettPhos to 10.0 mol% to enable the reaction to full conversion. Under these conditions, aryl chlorides bearing with electron-withdrawing groups such as ester (**6a**), ketone (**6b**, **6d**, **6g**, **6l**), cyano (**6c**) or electron-poor heteroaryl chloride (**6h** and **6j**) could be difluoromethylthiolated in moderate to good yields, as summarized in Scheme 4. Nevertheless, the reactions of aryl chlorides with electron-donating groups occurred in low yield and will be the subject of future study (Scheme 4, **6e**).

To demonstrate the applicability of this difluoromethylthiolating protocol, we studied the difluoromethylthiolation of some natural, medicinally important compounds and material molecules. Fluoranthene, a fluorescer for metal defect detection, can been difluoromethylthiolated in 73% yield (Scheme 5, Eq. 1). Likewise, a difluoromethylthiolated natural product oestrone and tocopherol was generated in moderate yield *Scheme 5, Eqs 2-3. Furthermore, a difluoromethylthiolated Fenofibrate, a medication that treats with hyperlipemia, was formed in an 88% yield under standard reaction conditions (Scheme 5, Eq. 4).

Scheme 5. Preparation of the difluoromethylthiolated natural, medicinally important compounds and material molecule.



Conclusions

In summary, we developed a palladium-catalyzed direct difluoromethylthiolation of aryl bromides, chlorides and triflates with (SIPr)Ag(SCF_2H) by employing a combination of Buchwald's precatalyst **Cat-1** and BrettPhos as the catalyst. The mild conditions, good functional group compatiblility, and the ease in applications in the difluoromethylthioation of a few natural, pharmaceutical and material molecules make the current a powerful tool for the medicinal chemists in the late stage modification of drug compounds. Efforts to elucidation of the reaction mechanism and expand the scope of the reaction toward aryl chlorides with electron-rich is currently undergoing in our lab.

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Entry for the Table of Contents

Page No.

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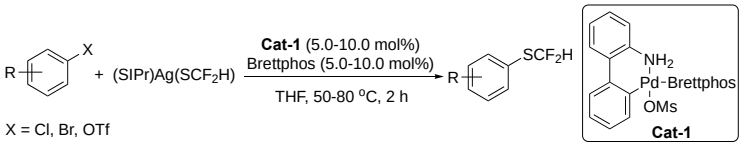

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