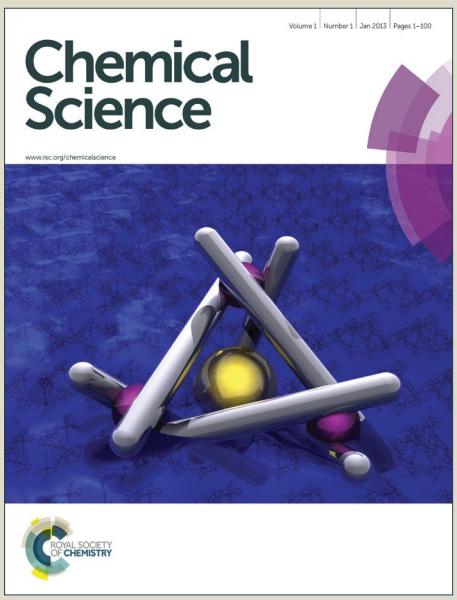
Chemical Science

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Wu, Y. Liu, C. Lu and Q. Shen, *Chem. Sci.*, 2016, DOI: 10.1039/C6SC00082G.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemicalscience

View Article Online
DOI: 10.1039/C6SC00082G

Journal Name

ARTICLE

Palladium-Catalyzed Difluoromethylthiolation of Heteroaryl Bromides, Iodides,Triflates and Aryl Iodides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Jiang Wu, Yafei Liu, Changhui Lu and Qilong Shen*

A palladium-catalyzed difluoromethylthiolation of heteroaryl halides and triflates under mild conditions was described. A vast range of heteroaryl halides such as pyridyl, quinolinyl, benzothiazolyl, thiophenyl, carbazolyl and pyazolyl halides were able to be difluoromethylthiolated efficiently, thus providing the medicinal chemists new tools for their search of new lead compounds for drug discovery. Likewise, aryl iodides were difluoromethylthiolated in high yields under a modified reaction conditions.

Introduction

Heteroarenes are common structural motifs and generally play key roles in pharmaceuticals and agrichemicals, as evidenced by the fact that 640 out of 1086 small molecules approved by the U.S. Food and Drug administration (FDA) are heterocycles.[1] On the other hand, the advantageous impact of the fluorine and fluoroalkyl groups in the field of medicinal and agro-chemistry has also been well-recognized and practised.[2] Very recently, one of the fluoroalkyl groups, difluoromethylthio group (SCF_2H), has attracted increasingly attention.[3] Difluoromethylthio group (Hansch parameter π_R = 0.68)[4] is slightly more lipophilic than the methyl group (π_R = 0.56), but much less lipophilic than its analog trifluoromethylthio group (CF_3S, π_R = 1.44), providing the medicinal chemists the opportunity in fine-tuning the drug molecule's lipophilicity. In addition, the electron-withdrawing nature of the difluoromethylthio group would increase the drug molecule's metabolic stability. Furthermore, the difluoromethylthio group bearing an acidic proton that can act as hydrogen bonding donor to interact with the enzyme could enhance the drug molecule's binding selectivity.[3b] Thus, if the beneficial effects of the difluoromethylthio groups could be combined with the appreciated heteroarene structural motif, a synergistic effect would be achieved that would improve on the drug molecule's overall efficacy.

Despite the potential of the difluoromethylthioheteroarene unit on the drug molecule's properties, its widespread application in medicinal studies remains rather limited due to a lack of efficient synthetic methods. A limited examples for the formation of heteroaryldifluoromethylthioether via difluoromethylation of simple heteroaryl thiolates with a difluorocarbene precursor, a difluoromethyl radical reagent or an electrophilic difluoromethyl reagent have been reported.[5] Nevertheless, various base-sensitive functional groups were not compatible with the strong basic conditions in these reactions. Furthermore, except for some structurally simple heteroarylthiols, few methods are available for the formation of structurally more complicated heteroarylthiols. More recently, we[3e] and Goossen's group[3c-d] independently reported that the heteroaryldifluoromethylthioether could be accessed from heteroaryldiazonium salts under mild conditions. Yet, the explosive nature of the heteroaryldiazonium salts requires extreme care for handling that limits their pratical applications.[6] Alternatively, we recently discovered an electrophilic difluoromethylthiolating reagent-difluoromethyl-thiophthalimide that was able to direct difluoromethylthiolate electron-rich heteroarenes such as indoles, pyrroles, imidazo[1,2-a]pyridine, aminothiazole and isoxazole in the presence of a Lewis acid.[3f] However, no desired difluoromethylthiolated heteroarenes were observed when other less electron-rich or electron-poor heteroarenes such as benzothiophene, benzofuran or pyridine were subjected to the reaction conditions. Thus, new and efficient methods that allow for difluoromethylthiolation of a broad range of common heteroarenes are highly desirable.

Palladium-catalyzed cross-coupling reactions[7] represent as one of the most utilized synthetic tools for the formation of carbon-carbon and carbon-heteroatom bonds.[8] In this respect, several palladium-catalyzed coupling of aryl halides with fluoroalkylated nucleophiles for trifluoromethylation, difluoromethylation, monofluoromethylation and trifluoromethylthiolation under significantly different reaction conditions[9] have been developed, while the analogous difluoromethylthiolation has not been reported. One main reason behind the fluoroalkyl group's different behavior is due to the unique properties of fluoroalkyl groups. One subtle change in the structure of fluoroalkyl groups may lead to

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032. E-mail: shenql@sioc.ac.cn

† Electronic Supplementary Information (ESI) available. CCDC 1436785. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x.

View Article Online
DOI: 10.1039/C6SC00082G

dramatic stability and reactivity differences. For instance, $AgSCF_3$ is a stable solid and is known to be a good coupling partner for aryl and heteroaryl iodides and bromides, while its analog $AgSCF_2H$ or other nucleophilic difluoromethylthiolating reagent is an unknown species and many efforts to synthesize it all failed. Since we recently discovered that a bulky *N*-heterocyclic carbene (SIPr) can stabilize $AgSCF_2H$,[3e] we wondered whether this reagent [(SIPr)Ag(SCF_2H)] can be utilized in the palladium-catalyzed difluoromethylthiolation of various heteroaryl halides. Herein, we report the realization of such a new cross-coupling reaction under mild reaction conditions. A vast range of different difluoromethylthiolated hereroarenes could then be accessed, thus providing the medicinal chemists new tools for their search of new lead compounds for drug discovery. In addition, under a modified condition, the difluoromethylthiolation of aryl iodides were also equally achieved.

Results and discussion

One concerning for the palladium-catalyzed difluoromethylthiolation of heteroaryl halides is the reductive-elimination step of the commonly proposed catalytic cycle since it is well-known that reductive-elimination from heteroaryl-palladium complexes proceeded much more difficult than those of aryl-palladium complexes.[10] To probe whether the reductive-elimination from the putative intermediate [L_2Pd(heteroaryl)(SCF_2H)] **3** is problematic, we synthesized Xantphos[11]-ligated complex [(Xantphos)Pd(3-Py)(I)] **1** and studied its reaction with [(SIPr)Ag(SCF_2H)] **2** at various solvent and temperature. To our surprise, reaction of [(Xantphos)Pd(3-Py)(I)] with 1.5 equivalents of [(SIPr)Ag(SCF_2H)] in toluene occurred smoothly at room temperature after 1.0 h to afford the reductive-elimination product 3-difluoromethylthiopyridine as the only product in 73% yield, as determined by ^{19}F NMR spectroscopy of the reaction mixture (Figure 1). These results indicate that reductive-elimination to form heteroaryldifluoromethylthioether is a fast process and would not likely be the turnover limiting step of the possible palladium-catalyzed difluoromethylthiolating reaction.

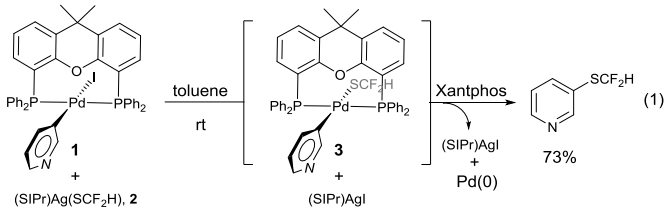
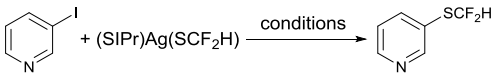


Figure 1 Stoichiometric reaction of complex [(Xantphos)Pd(3-Py)(I)] **1** with [(SIPr)Ag(SCF_2H)] **2** at room temperature.

The observed stoichiometric reaction was successfully translated into the catalytic reaction. Reaction of 3-iodopyridine with reagent **2** in the presence of 10 mol% $Pd(dba)_2$ and 15 mol% Xantphos occurred smoothly after 12 h at 50 °C to give 3-difluoromethylthiopyridine in 72% yield (Scheme 1, entry 1). Reaction using DPEPhos as the ligand

Scheme 1 Optimization of the Palladium-Catalyzed Difluoromethylthiolation of 3-Iodopyridine.[a]



entry	[Pd]	ligand	solvent	temp	yield (%)[b]
1	$Pd(dba)_2$	Xantphos	toluene	50 °C	72
2	$Pd(dba)_2$	DPEPhos	toluene	50 °C	55
3	$Pd(dba)_2$	Josiphos	toluene	50 °C	<2
4	$Pd(dba)_2$	DPPE	toluene	50 °C	<2
5	$Pd(dba)_2$	DPPB	toluene	50 °C	<2
6	$Pd(dba)_2$	DPPF	toluene	50 °C	<2
7	$Pd(dba)_2$	SPhos	toluene	50 °C	-
8	$Pd(dba)_2$	XPhos	toluene	50 °C	-
9	$Pd(dba)_2$	^{t}Bu-BrettPhos	toluene	50 °C	-
10	$Pd(PPh_3)_4$	Xantphos	toluene	50 °C	<2
11	Pd(cinnamyl)Cl_2	Xantphos	toluene	50 °C	51
12	$Pd(dba)_2$	Xantphos	THF	50 °C	71
13	$Pd(dba)_2$	Xantphos	dioxane	50 °C	70
14	$Pd(dba)_2$	Xantphos	toluene	rt	27
15	$Pd(dba)_2$	Xantphos	toluene	80 °C	68
16	$Pd(dba)_2$	Xantphos	toluene	50 °C	84[c]
17	$Pd(dba)_2$	Xantphos	toluene	50 °C	27[d]
18	$Pd(dba)_2$	Xantphos	toluene	50 °C	63[e]
19	$Pd(dba)_2$	Xantphos	toluene	50 °C	42[f]
20	$Pd(dba)_2$	Xantphos	toluene	50 °C	35[g]

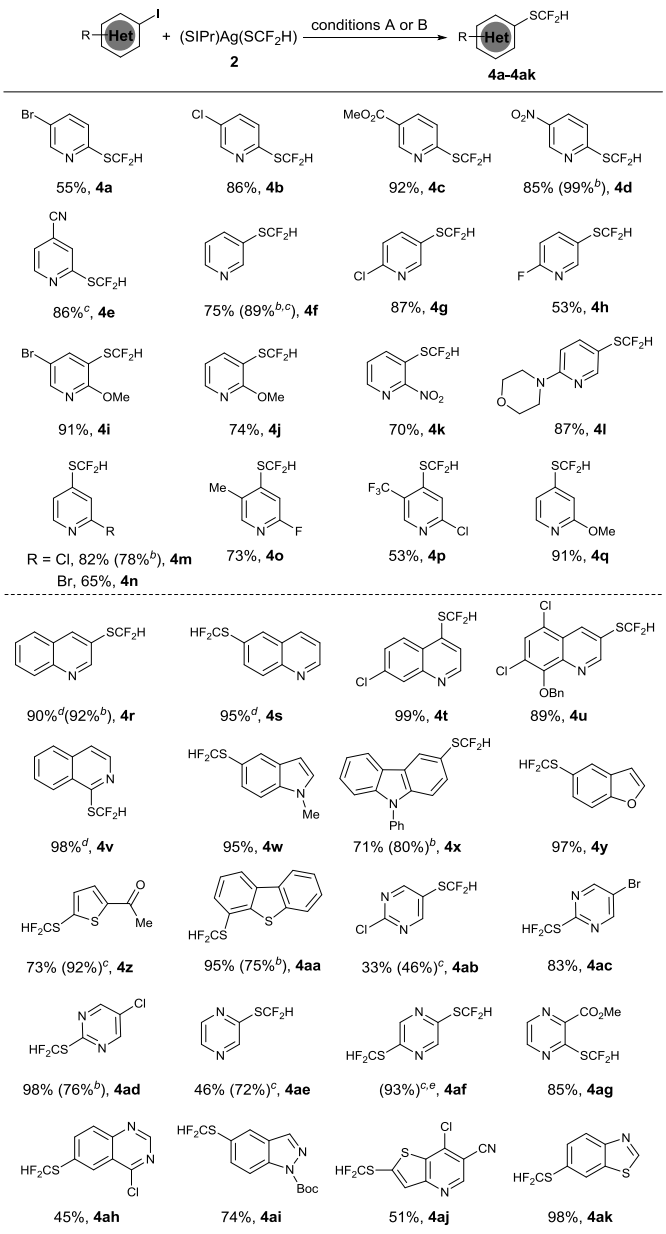
[a] Reaction conditions: 3-iodopyridine (0.05 mmol), (SIPr)Ag(SCF_2H) **2** (0.05 mmol), palladium precursor (10 mol %), ligand (15 mol %) in different solvent (1.0 mL) at 50 °C for 12 h; [b]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with trifluorotoluene as an internal standard; [c]1.2 equiv of (SIPr)Ag(SCF_2H) **2** was used; [d]$Pd(dba)_2$ (10 mol %), Xantphos (10 mol %) were used as the catalyst; [e]$Pd(dba)_2$ (10 mol %), Xantphos (20 mol %) were used as the catalyst; [f]$Pd(dba)_2$ (7.5 mol %), Xantphos (11.3 mol %) were used as the catalyst; [g]$Pd(dba)_2$ (5.0 mol %), Xantphos (7.5 mol %) were used as the catalyst.

generated the corresponding product in 55% yield, while reactions using other bidentate ligands such as DPPE, DPPB, DPPF occurred in less than 2% yields (Scheme 1, entries 2-6). Interestingly, electron-rich, monodentate alkyl phosphines such as BrettPhos or XPhos that can be used efficiently in the palladium-catalyzed trifluoromethylthiolation were not effective at all[9d] (Scheme 1, entries 7-9). We then further studied the effect of solvent and the temperature. It turned out that the reaction in other solvents such as THF or dioxane gave comparable yields (Scheme 1, entries 10-11). The reaction conducted at room temperature occurred in much lower conversion (Scheme 1, entries 14-15). Further studies indicated that the ratio of the palladium to ligand is very important for the reaction. Using a combination of 10 mol% $Pd(dba)_2$ and 10 mol% Xantphos as the catalyst was much less effective while reaction with 10 mol% $Pd(dba)_2$ and 20 mol% Xantphos occurred in slightly lower yield (Scheme 1, entries 17-18). Finally, reactions in lower catalyst loading resulted in 35-42% yields (Scheme 1, entries 19-20).

The reaction conditions optimized for difluoromethylthiolation of 3-iodopyridine turned out to be rather effective for difluoromethylthiolation of a variety of heteroaryl iodides, as summarized in Scheme 2. In general, pyridyl iodides bearing the halogen in the 2, 3, or 4-position with electron-donating or withdrawing groups underwent

View Article Online
DOI: 10.1039/C6SC00080C

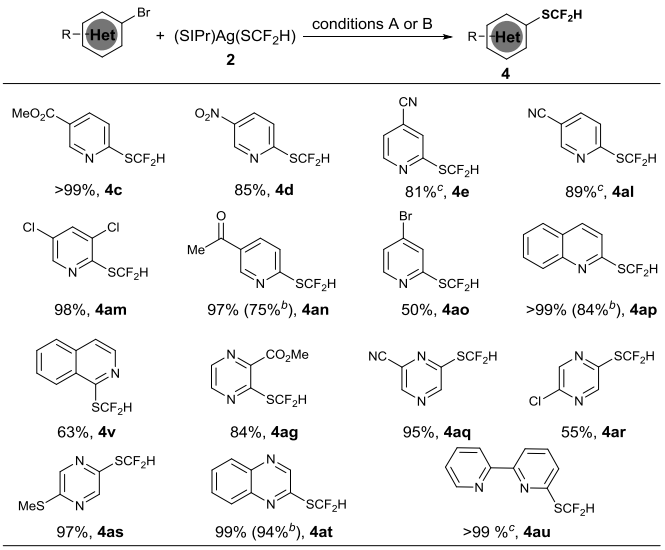
Scheme 2 Scope of the Palladium-Catalyzed Difluoromethylthiolation of Heteroaryl Iodides.[a]



[a]Reaction conditions A: heteroaryl iodine (0.5 mmol), (SIPr)Ag(SCF_2H) **2** (0.6 mmol), Pd(dba)$_2$ (10 mol %), Xantphos (15 mol %) in toluene (2.5 mL) at 50 °C for 12 h; Isolated yields; [b]Reaction conditions B: heteroaryl iodine (0.5 mmol), (SIPr)Ag(SCF_2H) 2 (0.6 mmol), (XantPhos)Pd(3-py)(Br) (5.0 mol %), XantPhos (2.5 mol %) in toluene (5.0 mL) at 50 °C for 6 h; Isolated yields; [c]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with trifluorotoluene as an internal standard; [d]Pd(dba)$_2$ (10 mol%), DPEPhos (10 mol%) were used; [e]2-Bromo-5-iodopyrazine and 2.4 equiv of (SIPr)Ag(SCF_2H) **2** were used.

difluoromethylthiolation in high yields (Scheme 2, **4a**-**q**). For example, reaction of 2-chloro-5-iodopyridine with [(SIPr)Ag(SCF_2H)] **2** occurred after 12 h at 50 °C to give 2-chloro-5-difluoromethylthiopyridine in 87% yield (**4g**), while the same reaction with 4-iodo-2-methoxypyridine occurred in 91% yield (**4q**). Not only pyridyl iodides, but also reactions of iodine-substituted quinoline, isoquinoline, indole, carbazole, benzofuran, thiophene, or dibenzothiophene occurred in good to excellent yields (Scheme 1, **4r**-**4aa**). In addition, iodo-substituted heteroarenes with two hetero-atoms such as pyrimidine, pyrazine, quinazoline, indazole, thieno[3,2-b]pyridine, benzothiazole all can be difluoromethylthiolated in high yields (Scheme 1, **4ab**-**ak**). Interestingly, in most cases, when a heteroarene containing both an iodo group and another halogen such as fluoride, chloride or bromide was subjected to the reaction conditions, the iodo group was preferentially difluoromethylthiolated (Scheme 2, **4a**-**b**, **4g**-**i**, **4m**-**p**, **4t**-**u**, **4ab**-**ad**, **4ah**, **4aj**). However, the bisdifluoromethylthiolated pyrazine was obtained as the only product when 2-bromo-5-iodopyrazine was used (**4af**). Notably, a variety of functional groups other than halogens such as nitro, cyano, ester, enolizable ketone or protected phenolic hydroxyl group were compatible with the reaction conditions (Scheme 2, **4c**-**e**, **4k**-**l**, **4u**, **4z**, **4ag**, **4aj**). These compounds are of great interesting since they allow further functional group transformation or derivatization. Interestingly, the isolated complex [(Xantphos)Pd(3-py)(Br)] could also served as the catalyst for the same transformation. In these cases, the catalyst loading could be decreased to 5.0 mol% (Scheme 2, **4d**, **4f**, **4m**, **4r**, **4x**, **4aa** and **4ad**).

Scheme 3 Scope of the Palladium-Catalyzed Difluoromethylthiolation of Heteroaryl Bromides.[a]



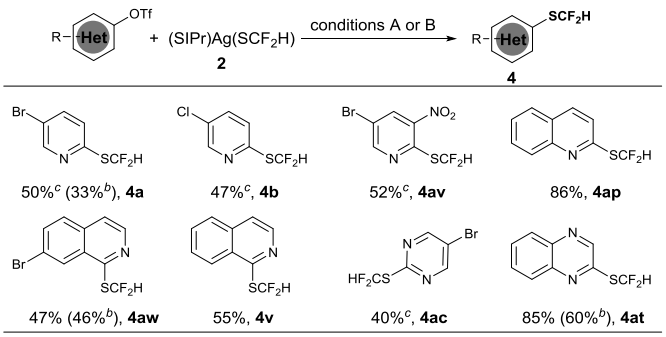
[a]Reaction conditions A: heteroaryl bromides (0.5 mmol), (SIPr)Ag(SCF_2H) **2** (0.6 mmol), Pd(dba)$_2$ (10 mol %), Xantphos (15 mol %) in toluene (2.5 mL) at 50 °C for 6 h; Isolated yields; [b]Reaction conditions B: heteroaryl bromides (0.5 mmol), (SIPr)Ag(SCF_2H) **2** (0.6 mmol), (XantPhos)Pd(3-py)(Br) (5.0 mol %), XantPhos (2.5 mol %) in toluene (5.0 mL) at 50 °C for 6 h; Isolated yields; [c]Yields were determined by ^{19}F NMR spectroscopy using trifluorotoluene as the internal standard.

Since we observed that heteroaryl bromide can also be difluoromethylthiolated in the case of **4af**, we studied the reaction of heteroaryl bromides with [(SIPr)Ag(SCF_2H)] **2** in detail, as summarized in Scheme 3. Reactions of various activated heteroaryl bromides could be difluoromethylthiolated in high yields, while reactions of the electron-rich heteroaryl bromides occurred in less than 5%

conversion. Heteroaryl bromides bearing two bromo groups at different positions reacted preferentially at the activated carbon-bromide bond. For example, reaction of 2,4-dibromopyridine gave 4-bromo-2-difluoromethylthiopyridine exclusively in 50% yield (Scheme 3, **4ao**). Nevertheless, various heteroaryl bromides such as bromo- pyridine, quinoline, isoquinoline, pyrazine, and bipyridine were successfully difluoromethylthiolated in good to excellent yields. Likewise, when isolated palladium complex [(Xantphos)Pd(3-py)(Br)] (5.0 mol%) was used as the catalyst, the reactions also occurred in comparable yields, as demonstrated in the cases of **4an**, **4ap**, **4at** in Scheme 3.

Heteroaryl phenols are common in naturally occurring organic molecules and the corresponding triflic esters are valuable coupling partners for transition metal-catalyzed cross-coupling reactions.[12] Having establishing a general and excellent protocol for the formation of heteroaryldifluoromethylthioether, we next tried to extend this method to the easily available heteroaryl triflates. Yet, less than 10% conversion was observed when 5-bromo-2-pyridyl triflates was subjected to the standard conditions for heteroaryl bromides and iodides. After a quick screening of the reaction conditions, we found that the addition of 2.0 equivalents of NaBr dramatically improved the yields of the reaction. It is likely that the bromide anion could stabilize [(XantPhos)Pd(heteroaryl)(OTf)] by forming stable palladium intermediate [(XantPhos)Pd(heteroaryl)(Br)](OTf). Under these conditions, a variety of heteroaryl triflates could be successfully converted into their corresponding difluoromethylthiolated compounds in moderate to good yields, as summarized in Scheme 4.

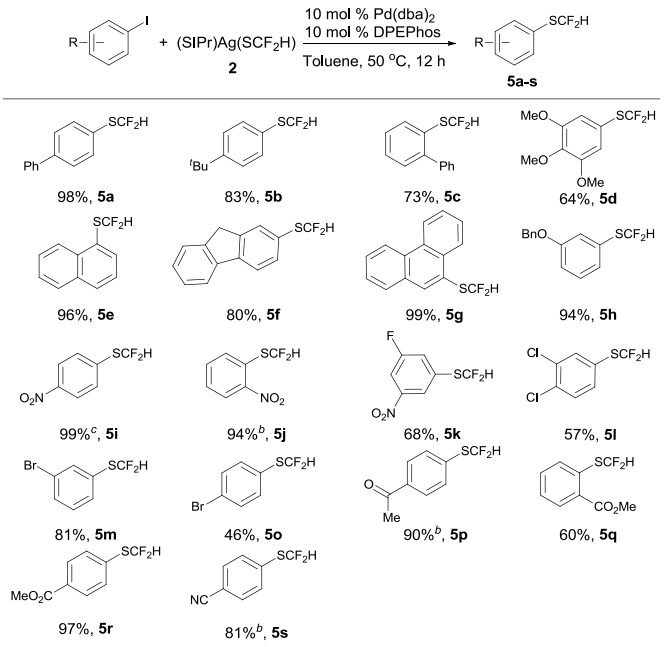
Scheme 4 Scope of the Palladium-Catalyzed Difluoromethylthiolation of Heteroaryl Triflates.[a]



[a]Reaction conditions A: heteroaryl triflates (0.5 mmol), (SIPr)Ag(SCF_2H) **2** (0.6 mmol), $Pd(dba)_2$ (10 mol %), Xantphos (15 mol %) and NaBr (2.0 equiv) in toluene (2.5 mL) at 50 °C for 6 h; Isolated yields; [b] Reaction conditions B: heteroaryl triflates (0.5 mmol), (SIPr)Ag(SCF_2H) **2** (0.6 mmol), (XantPhos)Pd(3-py)(Br) (6.0 mol %), XantPhos (3.0 mol %) and NaBr (2.0 equiv) in toluene (5.0 mL) at 50 °C for 6 h; Isolated yields; [c]$Pd(dba)_2$ (20 mol%), XantPhos (30 mol%) was used.

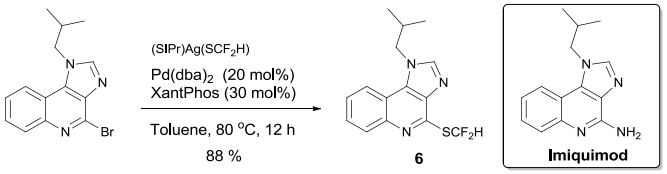
Encouraged by the broad scope of the palladium-catalyzed difluoromethylthiolation of heteroaryl substrates, we would like to further extend this protocol to difluoromethylthiolation of aryl iodides. However, only moderate yields were observed when a combination of $Pd(dba)_2$/Xantphos was used as the catalyst. Instead, high yields were obtained when DPEPhos was used the ligand, as summarized in Scheme 5. In the presence of 10 mol% $Pd(dba)_2$ and 10 mol% DPEPhos, a variety of aryl iodides were able to difluoromethylthiolated in excellent yields. The catalyst loading can be decreased to 5-7.5 mol% when activated aryl iodides with electron-withdrawing groups were subjected to the reaction conditions (Schmeme 5, **5i**, **5j**, **5p**, **5s**) . Noteworthily, common functional groups such as halides, ester, ketone, nitro and cyano group were compatible (Scheme 5, **5i-s**). Nevertheless, reactions of aryl bromides occurred in low yields under current reaction conditions and further optimization of the conditions are needed.

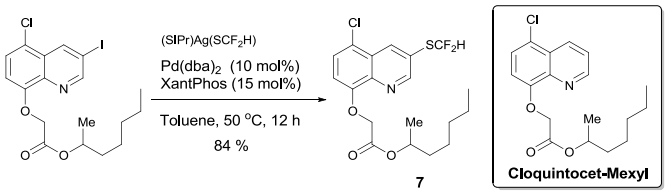
Scheme 5. Scope of the Palladium-Catalyzed Difluoromethylthiolation of Aryl Iodidess.[a]



[a]Reaction conditions: aryl iodides (0.5 mmol), (SIPr)Ag(SCF_2H) **2** (0.6 mmol), $Pd(dba)_2$ (10 mol %), DPEPhos (10 mol %) in toluene (2.5 mL) at 50 °C for 12 h; Isolated yields; [b] $Pd(dba)_2$ (7.5 mol%), DPEPhos (7.5 mol%) was used; [c] $Pd(dba)_2$ (5.0 mol%), DPEPhos (5.0 mol%) was used.

To demonstrate the applicability of this difluoromethylthiolating protocol, we studied the difluoromethylthiolation of two medicinally important compounds. Compound **6**, a difluoromethylthiolated analog of Imiquimod,[13] a medicine that acts as an immune response modifier to treat genital warts, was generated in 88% yield. Likewise, compound **7**, a difluoromethylthiolated derivative of herbicide safener Cloquintocet-mexyl,[14] was formed in 84% yield under standard reaction conditions.





Conclusions

In summary, we have developed the first palladium-catalyzed direct difluoromethylthiolation of heteroaryl bromides, iodides, triflates and aryl iodides. The reactions were conducted under mild reaction conditions and many common functional groups were tolerant. Thus, the current method provides an alternative and attractive strategy for the preparation of the difluoromethylthiolated heteroarenes. In detailed mechanistic studies including isolation of the difluoromethylthiolated palladium intermediate, investigation of the reaction kinetics and expansion the reaction scope to other common aryl halides/triflates are undergoing currently in our laboratory.

Acknowledgements

The authors thank the financial support from National Basic Research Program of China (2012CB821600), National Natural Science Foundation of China (21372247/21572258/21421002) and SIOC.

Notes and references

1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257-10274.

2 a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.,* 2008, **37**, 320-330; b) W. K. Hagmann, *J. Med. Chem.,* 2008, **51**, 4359-4369; c) N. A. Meanwell, *J. Med. Chem.,* 2011, **54**, 2529-2591; d) J. Wang, M. Sánchez-Roselló, J. Aceña, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.,* 2014, **114**, 2432-2506; e) D. T. Wong, K. W. Perry and F. P. Bymaster, *Nat. Rev. Drug Discovery,* 2005, **4**, 764-774; f) K. L. Kirk, *Org. Process Res. Dev.,* 2008, **12**, 305-321; f) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731-764.

3 a) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.,* 2005, **105**, 827-856; b) B. Manteau, S. Pazenok, J.-P. Vors and F. R. Leroux, *J. Fluorine Chem.,* 2010, **131**, 140-158; c) B. Bayamagnai, C. Matheis, K. Jouvin and L. J. Gooßen, *Angew. Chem. Int. Ed.,* 2015, **54**, 5753-5756; d) K. Jouvin, C. Matheis and L. J. Gooßen, *Chem. Eur. J.,* 2015, **21**, 14324-14327; e) J. Wu, Y. Gu, X.-B. Leng and Q. Shen, *Angew. Chem. Int. Ed.,* 2015, **54**, 7648-7652; f) D.-H. Zhu, Y. Gu, L. Lu and Q. Shen, *J. Am. Chem. Soc.,* 2015, **137**, 10547-10553.

4 a) T. Fujita, J. Iwasa and C. Hansch, *J. Am. Chem. Soc.,* 1964, **86**, 5175-5180; b) I. Rico and C. Wakselman, *Tetrahedron Lett.,* 1981, **22**, 323-326.

5 a) P. Deprez and J.-P. Vevert, *J. Fluorine Chem.,* 1996, **80**, 159-162; b) W. Zhang, J.-M. Zhu and J.-B. Hu, *Tetrahedron Lett.,* 2008, **49**, 5006-5008; c) W. Zhang, F. Wang and J. Hu, *Org. Lett.,* 2009, **11**, 2109-2112; d) G. K. Surya Prakash, Z. Zhang, F. Wang, C.-F. Ni and G. A. Olah, *J. Fluorine Chem.,* 2011, **132**, 792-798; e) F. Wang, W.-Z. Huang and J.-B. Hu, *Chin. J. Chem.,* 2011, **29**, 2717-2721; f) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collin, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.,* 2012, **134**, 1494-1497; g) L.-C. Li, F. Wang, C.-F. Ni and J.-B. Hu, *Angew. Chem. Int. Ed.,* 2013, **52**, 12390-12394; h) V. P. Mehta and M. F. Greaney, *Org. Lett.,* 2013, **15**, 5036-5039; i) K. Fuchibe, M. Bando, R. Takayama and J. Ichikawa, *J. Fluorine Chem.,* 2015, **171**, 133-138.

6 a) D. S. Wulfmann, in The Chemistry of Diazonium and Diazo Groups, Part 1, S. Patai, Ed.; Wiley, New York, 1978; b) B. J. Deadman, S. g. Collins and A. R. Maguire, *Chem. Eur. J.,* 2015, **21**, 2298-2308; c) N. Oger, E. L. Grogmec and F.-X. Felpin, *Org. Chem. Front.,* 2015, **2**, 590-614.

7 a) A. Milnar, Ed., *Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Development*, Wiley-VCH, Weinheim, 2013; b) A. de Meijere, F. Diederich, Eds. *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 2010.

8 Selected examples for Pd-catalyzed functionalization of heteroaryl halides: a) X. Wu, C. Lei, G. Yue and J. Zhou *Angew. Chem. Int. Ed.,* 2015, **54**, 9601-9605; b) X. Wu, J. See, K. Xu, H. Hirao, J. Roger, J.-C. Hierso and J. Zhou, *Angew. Chem. Int. Ed.,* 2014, **53**, 13573-13577; c) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.,* 2009, **48**, 9792-9826; d) P. Xi, F. yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.,* 2010, **132**, 1822-1824; e) D. Mandal, A. D. Yamaguchi and K. Itami, *J. Am. Chem. Soc.,* 2010, **132**, 1822-1824; f) D. Zhao, J. You and C. Hu, *Chem. Eur. J.* 2011, **17**, 5466-5492; g) M. W. Hooper, M. Utsunomiya and J. F. Hartwig, *J. Org. Chem.,* 2003, **68**, 2861-2873; h) J. Yin, M. Zhao, M. A. Huffman and J. M. Mcnamara, *Org. Lett.,* 2002, **4**, 3481-3484.

9 a) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Z. hang, D. A. Watson and S. L. Buchwald, *Science,* 2010, **328**, 1679-1681; b) Y. Gu, X.-B. Leng and Q. Shen, *Nat. Commun.,* 2014, **5**, 5405, doi: 10.1038/ncomms6405; c) S. Ge, W. Chaładaj and J. F. Hartwig, *J. Am. Chem. Soc.,* 2014, **136**, 4149-4152; d) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem. Int. Ed.,* 2011, **50**, 7312-7314; e) G.-Y. Yin, I. Kalvet and F. Schoenebeck, *Angew. Chem. Int. Ed.,* 2015, **54**, 6809-6813; f) J.-Y. Hu, B. Gao, L.-C. Li, C.-F. Ni and J.-B. Hu, *Org. Lett.,* 2015, **17**, 3086-3089.

10 a) M. W. Hooper and J. F. Hartwig, *Organometallics,* 2003, **22**, 3394-3403; b) Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.,* 2007, **129**, 7734-7735.

11 Xantphos was chosen initialy as the ligand for the Pd-catalyzed difluoromethylthiolation of 3-iodopyridine because reductive-elimination from Xantphos-ligated trifluoromethylated palladium complex [(XantPhos)Pd(Ph)(CF_3)] was much faster than those ligated with other bidendate ligands: V. V. Grushin and W. J. Marshall, *J. Am. Chem. Soc.,* 2006, **128**, 4632-4641.

12 P. J. Stang, M. Hanack and L. R. Subramanian, *Synthesis*, 1982, 85-126; b) W. J. Scott and J. E. MuMurry, *Acc. Chem. Res.* 1988, **21**, 47-54; c) K. Ritter, *Synthesis*, 1992, 735-727.

13 M. van Seters, M. van Beurden, F. J. ten Kate. I. Beckmann, P. C. Ewing, M. J. Eijkemans, M. J. Meijer, N. K. Aaronson, A. Kleinjan, C. Heijmans-Antonissen, F. J. Zijistra, M. P. Burger and T. J. Helmerhorst, *The New England J. Med.,* 2008, **358**, 1465.

14 J. Amrein, J. Rufener and M. Quadranti, *Br. Crop Prot. Conf.-Weeds*, 1989, **1**, 71.

15 CCDC 1436785 contains the supplementary crystallographic data for complex [(Xantphos)Pd(3-Py)(Br)] reported in this communication. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or pm application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44-1223/336-033; email: deposit@ccdc.cam.ac.uk].