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Palladium-Catalyzed Difluoromethylation of Heteroaryl Chlorides, **Bromides and Iodides**

Changhui Lu,[†] Yang Gu,[†] Jiang Wu,[†] Yucheng Gu[‡] and Qilong Shen^{†,*}

A palladium-catalyzed difluoromethylation of a series of heteroaryl chlorides, bromides and iodides under mild conditions was described. A wide range of heteroaryl halides such as pyridyl, pyrimidyl, pyrazyl, funanyl, thienyl, pyazolyl, imidazolyl, thiazolyl, oxazolyl halides were able to be efficiently difluoromethylated, thus providing the medicinal chemists an alternative choice for the preparation of the drug candidates with the difluoromethylated heteroarene unit.

Introduction

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Owing to its increased acidity of the proton in the difluoromethyl group that may interact with the targeting enzyme through hydrogen bonding, the difluoromethyl group (-CF₂H), an analog of the well-recognized trifluoromethyl group (-CF₃) in drug design,¹ is generally considered by the medicinal chemists as a bioisostere of a hydroxyl or a thiol group that will enhance the molecule's binding selectivity.² On the other hand, in general, the heteroaryl moiety is regarded as one of the most common fragments in the majority of marketed drugs. As a logic consequence, difluoromethylated heteroarenes that combines beneficial properties from both units could be conceived as a promising family of pharmacores that are able to modulate the lipophilicity, polarity, and hydrogen bonding capacity of the target molecules, and consequently the physiochemical and pharmacokinetics of the drugs. One of many examples to support such a point of view is provided by the fact that 3-difluoromethylpyrazole⁴ is found to be the common core structural unit in four recently marketed fungicides including Bixafen, Sedaxane, Isopyrazam and Fluxapyroxad (Fig. 1). Thus, methods that can provide an easy access to various difluoromethylated heteroarenes under mild conditions may facilitate the medicinal chemists in their endeavor to hunt new lead compounds for new drug discoverv.⁵

In the past several decades, three different strategies have been reported for the preparation of difluoromethylated



Figure 1. Fungicides with 3-difluoromethylpyrazole core structural unit.

heteroarenes. The first general method to obtain the difluoromethylated heteroarenes involved the use of fluorinated precursors and subsequent cyclocondensation of these building blocks with other coupling partners to give a specific difluoromethylated heteroarene and its derivatives. For example, Leroux successfully synthesized a series of difluoromethylated pyrazoles by 1.3-dipolar cyclo-addition of easily available 1,1,2,2-tetrafluoro-N,N-dimethylethan-1-amine (TFEDMA) with hydrazine in excellent yields.⁶ This strategy is highly efficient for the preparation of one type of difluormethylated heteroarenes. Yet, the availability of versatile difluoromethylated heteroarenes is limited. Alternatively, difluoromethylated heteroarenes may be accessed by direct radical difluoromethylation of heteroarenes with a radical difluoromethylating reagent. For example, in 2012, Baran⁵ reported $Zn(SO_2CF_2H)_2$ (DFMS) is able to difluoromethylate а variety of nitrogen-containing heteroanenes such as pyridines, pyrroles, pyrimidines, quinoxalines, pyrazines, xanthines, purines, quinoline, thiadiazoles, and pyridinones.⁷ These reactions were proposed to process via a radical pathway. Yet, regioselectivity in this method is problematic, which may cause difficulties in

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separation of the resulting isomers. A third strategy for the preparation of difluoromethylated heteroarenes relies on the transition metal-mediated or -catalyzed difluoromethylation of heteroaryl electrophiles such as heteroaryl diazonium salts or halides with an appropriate nucleophilic difluoromethylating reagent.⁸ While several transition metal-mediated/-catalyzed difluoromethylation of aryl halides have been reported to occur with broad scope, efforts for the similar transformation with heteroaryl electrophiles met with only limited success. For example, Prakash and coworkers reported that coppermediated difluoromethylation of 2-iodo-pyridine or 2-iodoquinoline with Bu₃SnCF₂H occurred in moderate to good yields, while similar transformation of more challenging heteroarvl halides such as 3-iodopyridine, or halothiophenes were not described.^{8c} More recently, Vicic and coworkers reported the preparation of a new difluoromethylating reagent $(DMPU)Zn(CF_2H)_2$ that was allowed to couple with iodo- or bromo-substituted pyridine, quinoline, furan or thiophene in good yields in the presence of a nickel catalyst.^{8h} However, high catalyst loading of nickel complex (15 mol%) were required and the turnover number of the catalytic reaction were not high enough. Shortly after, Mikami reported that $(DMPU)Zn(CF_2H)_2$ was able to couple with several activated heteroaryl iodides in the presence of 10 mol% of Cul, while reactions of non-activated heteroaryl iodides or heteroaryl bromides occurred in much less efficiency.^{8f} Later on, Mikami and coworkers developed (TMEDA)Zn(CF₂H)₂ that was allowed to couple with two examples of activated heteroaryl iodides in high years.^{8g} Clearly, new methods that allow to generate a variety of difluoromethylated heteroarenes under mild conditions are still urgently needed.

Very recently, we developed a cooperative bimetallic Pd/Ag catalyst system that was quite efficient for the catalytic difluoromethylation of various aryl bromides and iodides with TMSCF₂H.⁹ Nevertheless, our efforts to extend this catalyst system for the difluoromethylation of heteroaryl halides only resulted in moderate yields. We realized that to successfully develop efficient methods for the difluoromethylation of heteroaryl halides, we need to overcome two challenging problems: 1) Reductive-elimination from key product-forming intermediate [L₂Pd(heteroaryl)(CF₂H)] is much slower than those from [L₂Pd(aryl)(CF₂H)]; 2) The heteroatom may competingly coordinate to the palladium catalyst and consequently, the phosphino ligand in the catalyst may be replaced by the heteroarene substrates, which may lead to deactivate the catalyst.

In this report, we detailed the development of an effecient palladium-catalyst that overcomes these challegings and is capable of direct difluoromethylation of a vast range of different bromo- or iodo-substituted heteroarenes such as as pyridine, pyrimidine, pyrole, funan, thiophene, quinoline, carbazole, dibenzo[*b*,*d*]thiophene, pyrazine, thiazole, oxazole, pyrazole and activated heteroaryl chlorides. Furthermore, the current method was successfully applied to the synthesis of three examples of difluoromethylated natural product derivatives.

Results and discussion

In order to overcome the challenges associated with the palladium-catalyzed difluoromethylation of heteroarene halides, we began our investigation by preparing the key intermediates and studying their elementary steps in the catalytic cycle. Our choice of Xantphos as the ligand for the putative palladium intermediates was guided by previous observations in stoichiometric or catalytic organometallic chemistry: 1) reductive elimination is accelerated by wide bite angle bisphosphine ligands in many transition-metal-catalyzed C-C bond formation reactions.¹⁰ For example, Grushin reported that reductive-elimination from Xantphos-ligated trifluoromethylated palladium complex [(XantPhos)Pd(Ph)(CF₃)] was much faster than those ligated with other bidendate ligands;¹¹ 2) Xantphos-ligated palladium complex [(Xantphos)Pd(heteroaryl)(X)] (X = halide or amine) is able to resist the ligand replacement by the heteroaryl substrates. For example, Yin and coworkers have reported that palladium complex ligated with Xantphos was able to efficiently catalyze the amination reactions of a broad range of heteroaryl halides even at high temperature.¹² Accordingly, [(Xantphos)Pd(3-Py)(Br)] was prepared by following a known procedure.¹¹ Interestingly, mixing 1/1 ratio of [(Xantphos)Pd(3-Py)(Br)] and [(SIPr)Ag(CF₂H)] (SIPr = 1,3-bis(2,6-diisopropyl phenyl)imidazolin-2-ylidene), а nucleophilic difluoromethylating reagent which was isolated in our laboratory previously, generated the reductive-elimination product 3-difluoromethylpyridine in 50% yield after 1 h at room temperature, as determined by ¹⁹F NMR spectroscopy (Eq. 1). These results clearly suggest that C-CF₂H bond-forming reductive elimination from [(Xantphos)Pd(3-Py)(CF₂H)] is a facile process even at room temperature and likely not the rate-limiting step of the catalytic reaction.



Figure 2 Stoichiometric reaction of complex [(Xantphos)Pd(3-Py)(Br)] 1 with [(SIPr)Ag(CF₂H)] 2 at room temperature.

Having established that reductive elimination from Xantphosligated complex [(Xantphos)Pd(3-Py)(CF₂H)] undergoes smoothly even at room temperature, we then explored the cooperativebimetallic Pd/Ag catalyst system using Xangphos as the ligand for the reaction of 3-((benzyloxy)methyl)-5bromopyridine with TMSCF₂H with NaO^tBu as the base. However, low yield was observed, likely due to the incompatibility of the elementary reactions in two catalytic cycles. Instead, when [(SIPr)Ag(CF₂H)] was used as the nucleophilic difluoromethylation reagent, the formation of the

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 Scheme
 1
 Optimization
 conditions
 for
 Palladium-Catalyzed

 Difluoromethylation of 3-((benzyloxy)methyl)-5-bromopyridine.^{a,b}

BnO	$ \begin{array}{c} $	[Pd]/Ligand Toluene 80 °C, 6 h	CF ₂ H N 4a
entry	[Pd]	ligand	yield (%) ^b
1	Pd(dba) ₂	Xantphos	60
2	Pd(dba) ₂	DPEPhos	80
3	Pd(dba) ₂	DPPF	57
4	Pd(dba) ₂	BINAP	62
5	Pd(dba) ₂	DPPE	<2
6	Pd(dba) ₂	BrettPhos	17
7	Pd(PPh ₃) ₄	DPEPhos	76
8	Pd(OAc) ₂	DPEPhos	58
9	PdCl ₂	DPEPhos	33
10	[Pd(cinnamyl)(Cl)] ₂	DPEPhos	63
11	Pd(dba) ₂	DPEPhos	90 <i>°</i>
12	Pd(dba) ₂	DPEPhos	50 ^d

^{*a*} Reaction condition: **3a** (27.7 mg, 0.1 mmol), (SIPr)Ag(CF₂H) **2** (55 mg, 0.1 mmol), [Pd] (5 mol %) and ligand (10 mol %) in 1.0 mL toluene for 6 h under Ar

atmosphere; ^bYields were determined by ¹⁹F NMR analysis of the crude reaction mixture with trifluorotoluene as an internal standard; ^c1.3 equiv of (SIPr)Ag(CF₂H) was used; ^d[Pd] (2.0 mol %) and DPEPhos (4.0 mol %).

desired product was observed in 60% yield after 6 h at 80 °C when a combination of 5.0 mol% Pd(dba)₂ and 10.0 mol% Xantphos was used as the catalyst (Scheme 1, entry 1). The yield was improved to 80% when another bidentate bisphosphino ligand with a wide bite angle DPEPhos was used as the ligand (Scheme 1, entry 2). In contrast, catalyst generated from ligands with smaller bite angle ligand such as DPPF, BINAP, DPPE were less effective, forming the desired product in 65%, 17% and less than 2%, respectively (Scheme 1, entries 3-5). Likewise, catalyst derived from sterically hindered, electron-rich, mono-dentate phosphine Brettphos was also less effective (Scheme 1, entry 6). Next, we studied the effect of the different palladium precursors on the palladiumcatalyzed difluoromethylation of the heteroaryl bromide. It turned out that reactions occurred in lower yields when catalysts derived from Pd(PPh₃)₄, Pd(OAc)₂, PdCl₂ or [Pd(cinnamyl)(Cl)]₂ were used (Scheme 1, entries 7-10). Finally, the yield of the desired product was further improved to 90% when 1.3 equivalents of [(SIPr)Ag(CF₂H)] was used (Scheme 1, entry 11), while efforts to decrease the catalyst loading were ineffective. Lower yield (50%) was observed when 2.0 mol % Pd(dba)₂/4.0 mol % DPEPhos was used as the catalyst (Scheme 1, entry 12).

With the above optimized reaction conditions in hand, we first studied the difluoromethylation of an array of heteroaryl bromides to investigate the generality and scope of the reaction. As summarized in Scheme 2, a wide range of electron-deficient bromo-substituted nitrogen containing heteroarenes such as pyridine (**3a-k**), pyrimidine (**3I-o**), pyrazine (**3p-q**), quinoline (**3r-t**), isoquinoline (**3u-w**), 1*H*-pyrrolo[2,3-*b*]pyridine (**3x**), quinoxaline (**3y**), imidazo[1.2-*a*)pyrazine (**3z**), pyrido[2,3-b]pyrazine (**3aa**) underwent difluoromethylation smoothly

 $\label{eq:scheme2} \begin{array}{l} \mbox{Scheme 2. Scope of the Palladium-Catalyzed Diffuoromethylation of Heteroaryl Bromides.} \end{array}$

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^aReaction conditions: heteroaryl bromide (0.5 mmol), (SIPr)Ag(CF₂H) **2** (0.65 mmol), Pd(dba)₂ (5.0 mol%), DPEPhos (10 mol%) in 2.0 mL toluene at 80 °C for 6-12 h under an argon atmosphere; ^bIsolated yields; ^cPd(dba)₂ (10 mol%) and DPEPhos (20 mol%) are used; ^dReactions conducted with Pd(dba)₂ (10 mol%) and DPEPhos (20 mol%) for 24 h.

under mild conditions to afford corresponding difluoromethylated heteroarenes **4a-4aa** in high yields. Remarkably, these reaction conditions can also be applied to electron-rich bromo-substituted heteroarenes that are typically more challenging stubstrates due to slow oxidative addition/reductive-elimination, although reactions of these bromo-heteroarenes were slower (24 h) and required higher

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catalyst loading (10 mol% Pd(dba)₂ and 20 mol% DPEPhos) to occur to full conversion. Nevertheless, good to excellent yields for the formation of a variety of difluoromethylated electronrich heteroarenes including thiophene (4ab-ad). benzothiophene (4ae-4af, 4ak), furan (4ag), dibenzo[b,d]furan (4ah), benzofuran (4ai-aj), indole (4an), benzo[d]oxazole (4al), benzo[d]thiazole (4am), indazole (4ao) and carbazole (4ap) were achieved. Notably, bromo-substituted heteroarenes with functional groups such esters, cyano, protected aldehyde, enolizable ketone, thioether, or Boc-protected amino group, all underwent smooth difluoromethylation, illustrating the good functional compatibility of the current method. Furthermore, the reaction is scalable. The reaction of 1.0 g of 1-(5-bromothiophen-2-yl)ethanone with [(SIPr)Ag(CF₂H)] 2 formed 0.50 g of the corresponding product 4ab in 57% yield under the standard conditions (Scheme 2, 4ab).

Scheme 3. Scope of the Palladium-Catalyzed Difluoromethylation of Heteroaryl chlorides. a



^oReaction conditions: heteroaryl chlorides (0.5 mmol), (SIPr)Ag(CF₂H) **2** (0.65 mmol), Pd(dba)₂ (5 mol %), DPEPhos (10 mol %) in toluene (2.5 mL) at 80 ^oC for 18 h; Isolated yields.^b

In general, carbon-iodine bonds in heteroarenes are weaker than those of carbon-bromide bonds and the Pd-catalyzed cross-coupling reactions are easier. In fact, reactions of a few heteroaryl iodides with [(SIPr)Ag(CF₂H)] **2** in the presence of 5.0 mol% or Pd(dba)₂/10.0 mol% of DPEPhos occurred smoothly after 18 h at 80 °C to give the corresponding difluoromethylated heteroarenes in good to excellent yields (Scheme 3, **5a-d**). For example, reaction of 4-iodo-1-(4methoxyphenyl)-1*H*-pyrazole with [(SIPr)Ag(CF₂H)] **2** generated the corresponding 4-difluoromethyl-1-(4-methoxyphenyl)-1*H*pyrazole **5d** in 60% yield, while efforts to convert its analog 3iodo-1-(4-methoxyphenyl)-1*H*-pyrazole resulted in low yield (Scheme 3, **5d**). On the other hand, carbon-chloride bonds in heteroarenes are stronger than those of carbon-bromide bonds and the Pd-catalyzed cross-coupling reactions are much more difficult. Nevertheless, it was found that activatived heteroaryl chlorides in which the chlorine atom is at the ortho position of the heteroatom in the heteroarene coupled with [(SIPr)Ag(CF₂H)] 2 under the optimized conditions to give the corresponding difluoromethylated heteroarenes in high yields (Scheme 3, 5d-o). When the carbon-chloride bond is at the meta- or para-position of the heteroatom in the heteroarene, the formation of the difluoromethyled heteroarene was not observed. For example, reaction of ethyl 4,6-dichloronicotinate with [(SIPr)Ag(CF₂H)] 2 generated exclusively ethyl 4-chloro-6difluoromethylnicotinate in 75% yield (Scheme 3, 5g). The 4difluoromethylated isomer was not observed. Control experiments in the absence of the palladium catalyst did not form the corresponding difluoromethylated product. To the best of our knowledge, this represents the first difluoromethylation reaction of heteroaryl chloride by any transition metal catalyst.

To demonstrate the applicability of this difuoromethylating protocol, we applied this method to the difuoromethylation of three medicinally important compounds. Compound **6a**, a difuoromethylthiolated analog of Imiquimod,¹³ a medication that acts as an immune response modifier to treat genital warts, was generated in an 93% yield. Likewise, compound **6b**, a difluoromethylated derivative of herbicide safener Cloquintocet-mexyl,¹⁴ was formed in 58% yield under standard reaction conditions Furthermore, a difluoromethylated derivative of the Vitamin E, was prepared from its bromosubstituted precursor in an 92% yield under standard reaction conditions (Figure 3).



Figure 3. Preparation of difluoromethylated derivatives of drug compounds.

Conclusions

In summary, we have developed a palladium-catalyzed direct difluoromethylation of heteroaryl chlorides, bromides, and iodides. The reaction was conducted under mild reaction conditions and many common functional groups were tolerated. Thus, the current method represents the first general method for the site-specific incorporation of the difluoromethyl into heteroarenes. Currently, expansion of the reaction scope to aryl chlorides and unactivated heteroaryl chlorides are undergoing in our laboratory.

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