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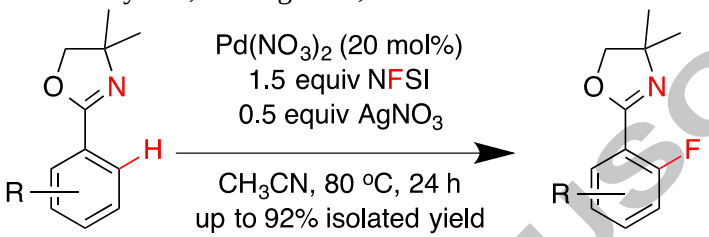

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Palladium-catalyzed electrophilic C–H fluorination of arenes using oxazoline as a removable directing group

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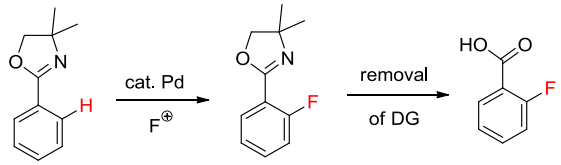
ABSTRACT

Dimethyloxazoline was rationally designed to act as a removable *ortho*-directing group (DG) for the palladium-catalyzed C–H electrophilic fluorination of arenes. Using NFSI as the fluorinating agent, and Pd(II), Ag(I) catalytic system, electrophilic C(sp^2–H) *ortho*-fluorination took place on a variety of aryl substrates to afford the corresponding mono- and di-fluorinated products.

The introduction of fluorine has been widely used in medicinal chemistry, to boost potency, increase membrane permeability, modulate p*K*a, and block metabolic sites on potential drug molecules.[1] In addition, ^{18}F-Labeled compounds are indispensable as radionuclides in radiotracers for positron emission tomography (PET). These unique properties make the introduction of fluorine to bioactive molecules intriguing. The construction of C–F bonds is very challenging,[2] particularly in a selective late-stage manner. However, recently there have been advances in *ortho*-directed palladium-catalyzed electrophilic fluorination of arenes via C–H activation.[2] In 2006 Sanford used 8-methylquinolines and phenyl-pyridines to accomplish this transformation in acceptable yields and under microwave conditions.[3] The Xu group has also shown that a wide variety of *N*-heterocyclic DGs such as quinoxaline, pyrazole and benzo[*d*]oxazole can promote selective mono-*ortho*-fluorination using trifluoroacetic acid as an additive.[4] A more expansive investigation into the electrophilic fluorination of aryls using benzo[*d*]oxazole and pyrazole as DGs has also been established.[5,6] Experimental studies of the electrophilic fluorination of arylpyrazoles has shown evidence of an alternative mechanism to the standard Pd(II)/Pd(IV) process, suggesting a possible oxidative addition of N-fluorobenzenesulfonimide (NFSI) to Pd(II).[6]

Despite these recent advances in *ortho*-directed palladium-catalyzed *electrophilic* fluorination via C–H activation many of the initial DGs were heteroaryls thus not easily removable thus limiting their synthetic utility. A set of removable non-heteroaryl DGs have since been developed. The Xu group was able to demonstrate that O-methyloxime as a DG for *ortho*-fluorination of arenes at moderate temperatures.[7] They also demonstrated the selective *ortho*-mono-fluorination of 2-phenoxylpyridines via a six-membered cyclopalladation step. Yu has reported the fluorination of arenes using the –C(O)NHC$_6$F$_4$CF$_3$ amide-DG and was able to achieve selective mono-fluorination by increasing the acidity of the benzamide DG.[8] Other benzamides such as oxalyl amide and triflamides have also been shown to be suitable DGs for selective mono *ortho*-fluorination.[9] These DGs are labile and their removal makes the aryls amenable for further synthetic transformations but most of the benzamides suffer from their large size and poor atom economy.

We have developed *ortho*-directed palladium-catalyzed electrophilic fluorination using dimethyl oxazoline as DG. The oxazoline is an N-heterocycle which can be employed for *ortho*-C–H activation and is also labile and be unmasked to the carbocylic acid (Scheme 1). Aryloxazolines have been shown to be suitable DGs for C–C bond formation via C–H activation[10] and aryl-oxazolines have been fluorinated via *ortho*-metalation using magnesate bases and by lithiation.[11,12] Thus the development of a palladium catalyzed oxazoline ortho-directed electrophilic fluorination takes advantage of the heterocyclic moiety to direct fluorination for late stage synthesis and can be hydrolyzed for other synthetic transformations.

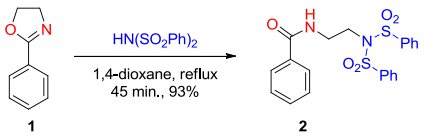


Scheme 1. Oxazoline directed C–H bond fluorination and hydrolysis

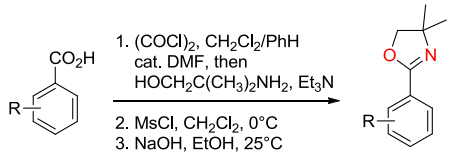
We began our investigation into fluorination using 4,4-dimethyl-2-phenyl-2-oxazoline because we have previously shown that ring opening occurred on 2-phenyl-oxazoline, **1**, when N-fluorobenzenesulfonimide (NFSI) was used as the electrophilic fluorine source and produced the corresponding sulfonimides, **2**, as the predominate product[13] (Scheme 2). The dimethyl substituents add steric bulk to the oxazline in order to hinder the ring opening reaction and promote fluorination.

The 4,4-dimethyl oxazoline derivatives were prepared using standard procedures (Scheme 3). The corresponding benzoic acid

was converted to the acyl chloride using oxalyl chloride and catalytic DMF, followed by formation of the amide using 2-amino-2-methyl-1-propanol. The corresponding alcohol was then mesylated and then cyclized using NaOH in ethanol in high yield.



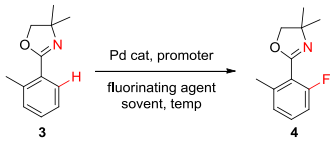
Scheme 2. Sulfonamidation via nucleophilic ring-opening of 2-oxazolines with acidic sulfonimides



Scheme 3. Procedures for formation of substituted aryl oxazolines

With the oxazoline in hand we began treating our model substrate **3** with several fluorinating agents (**A**, **B**, **C**, **D**, **E**, and **F)** that have previously been shown to be successful (Table 1). DMF was initially used as the solvent for the fluorination reactions because this polar solvent was shown to retard the ring opening of phenyl oxazolines.[13] $Pd(OAc)_2$ catalyst and TFA as an additive was the catalytic system was first used based on Xu's positive results. NFSI (**A**) and Selectfluor (**B**) afforded the fluorinated product **4** in 28% and 13%, respectively (Entries 1–2). The four 1-fluoropyridinium-based fluorinating agents including $[PyF]BF_4$ (**C**), $[Cl_2PyF]OTf$ (**D**), complex **E**, and $[Me_2PyF]BF_4$ (**F**) all failed to produce more than a trace amount of the desired product (entries 3–6). NFSI was selected as the fluorinating agent of choice and it was determined that five equivalents of TFA was needed to promote the fluorination reaction (See SI). A selection of Pd(II) and Pd(0) catalysts were screened (entry 8–12). Pd(0) catalysts gave low conversion to the fluorinated product (entry 8 and 11). Surprisingly $Pd(TFA)_2$ did not give a significant boost in conversion (entry 7). This is in contrast to previously known reports which show that using TFA along with $Pd(TFA)_2$ leads to higher yields of fluorinated product.[4] $Pd(NO_3)_2$ gave the best conversion to **4** (entry 12). As a result of this catalyst giving superior conversion, a series of nitrates were screened as promoters but the use of KNO_3 and $Ca(NO_3)_2$ completely halted the reaction (entry 13–14). $AgNO_3$ gave the best conversion of all the screened nitrates (entry 15). Other silver salts were screened however none of them showed any effectiveness at promoting the reaction (entry 16–17). No trace of fluorinated product was detected when no additive was used. It appears that that the silver nitrate salt is unique in its ability to promote fluorination. Solvents that have promoted other fluorination reactions were then screened. Trifluorotoluene, 1,2-dichloroethane, ethyl acetate, and dioxane all gave no reaction. Nitromethane was able to give conversion to desired product **4** but acetonitrile gave the full conversion to the fluorinated product. It was also concluded that when using acetonitrile as the solvent only 50 mol% of $AgNO_3$ was needed to give full conversion to the desired product. Using the optimized reaction conditions (Table 2) ,the scope of the reaction was then explored. Electron rich oxazolines showed moderate to good yields of fluorinated products. The fluorination of 2-*o*-tolyl substrate **4a** and 2-*o*-methoxyl substrate **4b**, gave moderate yields of fluorinated product. When the electron rich 4-*p*-methoxyl **4i** was fluorinated the 2,6-difluorination product **5i** was the major product with trace amounts of the monofluorinated observed by GCMS. Surprisingly 4-*p*-methyl **4h** was only able to be fluorinated once despite increasing the amount of fluorinating agent used to 5 equivalents and increasing reaction time. Electron deficient oxazolines were not able to be fluorinated as readily as electron-rich oxazolines. The un-substituted oxazoline **4f** gave

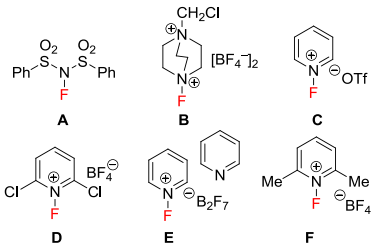
Table 1. Optimization of palladium-catalyzed fluorination of aryl 4,4-dimethyloxazoline **3**



Entry	Pd cat.	F^+ source	promoter	solvent	Yield (**3**:**4**)[a]
1[b]	$Pd(OAc)_2$	**A**	TFA	DMF	72:28
2[b]	$Pd(OAc)_2$	**B**	TFA	DMF	87:13
3[b]	$Pd(OAc)_2$	**C**	TFA	DMF	NR
4[b]	$Pd(OAc)_2$	**D**	TFA	DMF	NR
5[b]	$Pd(OAc)_2$	**E**	TFA	DMF	NR
6[b]	$Pd(OAc)_2$	**F**	TFA	DMF	NR
7[b]	$Pd(TFA)_2$	**A**	TFA	DMF	71:29
8[b]	$Pd(dba)_2$	**A**	TFA	DMF	90:10
9[b]	$PdCl_2$	**A**	TFA	DMF	NR
10[b]	$Pd(OTf)_2$	**A**	TFA	DMF	82:18
11[b]	$Pd(PPh_3)_4$	**A**	TFA	DMF	66:34
12[b]	$Pd(NO_3)_2$	**A**	TFA	DMF	60:40
13[c]	$Pd(NO_3)_2$	**A**	KNO_3	DMF	92:8
14[c]	$Pd(NO_3)_2$	**A**	$Ca(NO_3)_2$	DMF	89:11
15[c]	$Pd(NO_3)_2$	**A**	$AgNO_3$	DMF	51:49
16[c]	$Pd(NO_3)_2$	**A**	AgTFA	DMF	100:0
17[c]	$Pd(NO_3)_2$	**A**	AgOAc	DMF	93:7
18[d]	$Pd(NO_3)_2$	**A**	$AgNO_3$	Dioxane	NR
19[d]	$Pd(NO_3)_2$	**A**	$AgNO_3$	DCE	NR
20[d]	$Pd(NO_3)_2$	**A**	$AgNO_3$	$PhCF_3$	NR
21[d]	$Pd(NO_3)_2$	**A**	$AgNO_3$	CH_3NO_2	73:27
22[d]	$Pd(NO_3)_2$	**A**	$AgNO_3$	EtOAc	NR
23[e]	$Pd(NO_3)_2$	**A**	$AgNO_3$	CH_3CN	0:100

Reaction conditions: Pd (20 mol %) aryloxazoline (0.1 mmol), NFSI (0.15 mmol), solvent (1 mL). [a]GCMS conversions using dodecane as an internal standard. [b]TFA (0.5 mmol) 150 °C. [c]Nitrate (0.5mmol) 150 °C. [d]$AgNO_3$ (0.5mmol) 100 °C. [e]$AgNO_3$ (50 mol%) 80 °C.

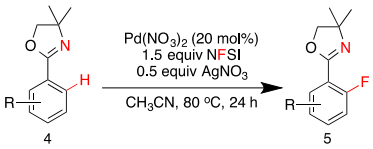
electrophilic fluorinating agents

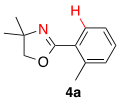
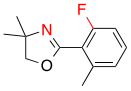
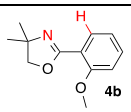
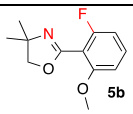
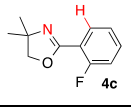
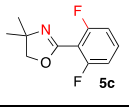
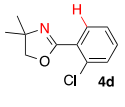
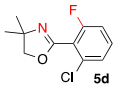
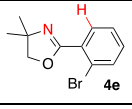
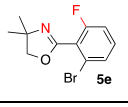
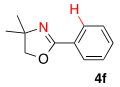
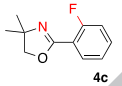
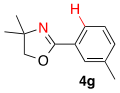
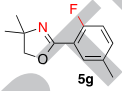
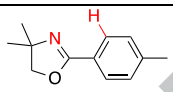
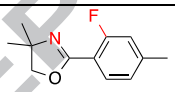
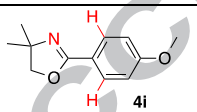
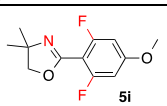
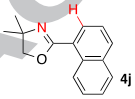
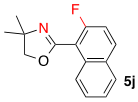
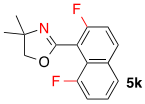
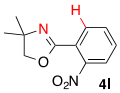
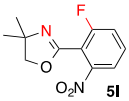
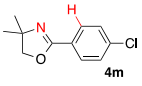
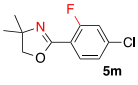


the monofluorinated product **4c** in 46% yield, and the difluoro-product, 5%. Similar results were observed when the reaction was carried out in nitromethane. This experimental result is in contrast with other fluorination reactions which show nitromethane promotes fluorination and even promotes derivative **4c** gave only 19% isolated yield of the desired difluoro-product **5c**. The extremely deactivated 2-*o*-nitro-oxazoline **4k**, was completely unable to be fluorinated and 4-*p*-chloro substituted aryloxazoline **4l**, showed only 13% GCMS conversion to the mono fluorinated product **5l**, and no difluoro-product was observed. The stark lack of reactivity observed for the

fluorination of electron-deficient aryloxazolines compared to difluorination reactions.[4] The fluorination of 2-*o*-fluoro- electron-rich oxazolines has precedent in the literature.[4]

Table 2. Palladium-catalyzed fluorination of aryl 4,4-dimethyloxazolines substituted arenes

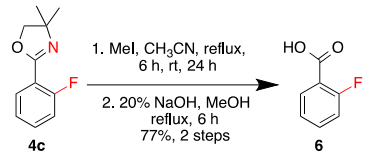


Entry	Substrate	Product	Yield
1	 4a	 5a	100[b] (65)
2	 4b	 5b	97[b] (42)
3	 4c	 5c	27[b] (19)
4	 4d	 5d	63[b] (68)
5	 4e	 5e	47[b] (37)
6	 4f	 4c	46[b] (48)
7	 4g	 5g	19[b] (12)
8	 4h	 5h	17[bc] (23)
9	 4i	 5i	100[bc] (92)
9	 4j	 5j	91[b] (88)
		 5k	7[b]
10	 4l	 5l	0[b]
11	 4m	 5m	13[b]

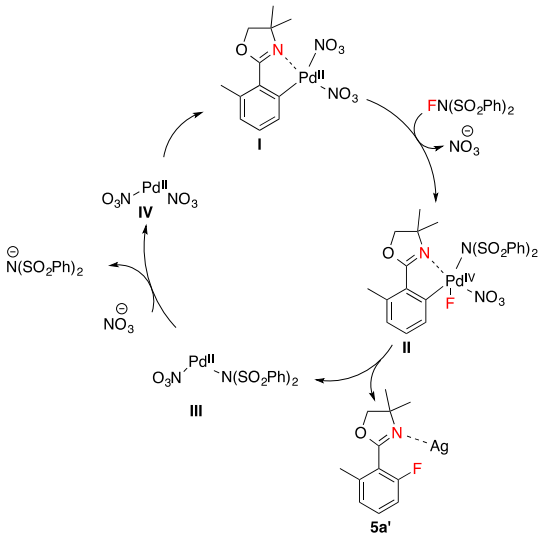
[a]Reaction conditions: Substrate **4** (0.5 mmol), NFSI (1.5 equiv), $Pd(NO_3)_2$ (20 mol%), $AgNO_3$ (50 mol%) in MeCN at 80 °C for 24 h. [b]GCMS conversion using dodecane as internal standard. Percent of isolated yields in parenthesis. [c]2.5 equivalents NFSI

The differences in the reactivity of electron-rich and electron-deficient oxazolines could be presumably attributed to the basicity of the nitrogen on the oxazoline. The 4,4-dimethyl-2-phenyl-2-oxazoline **4h** has a p*K*a of 4.4[14] and the substituent effect on the aryl can either increase or decrease the basicity of the nitrogen. Electron-rich substituted aryls increase the basicity of the oxazolines and increases its ability to facilitate the fluorination reaction whereas electron-poor aryls have the opposite effect. Other effects of substituted aryl oxazolines were also investigated. *ortho*-Chloro- and *ortho*-bromo derivatives **4d** and **4e** were tolerated in the reaction and gave good to moderate yields respectively. The fluorination of 3-*m*-tolyl **4g** was low yielding and gave predominantly the less sterically hindered product **5g**. The naphthalene derivative **4j** gave impressive yield of the monofluorinated product **5j** at the 2-position, 88% and 7% conversion to the 2,8-difluorinated product **5k**. However increasing the amount of NFSI to 5 equivalents and prolonged reaction time did not increase the amount of difluorinated product **5k. 5k** is an interesting product because it represents a C–H activation at the 8 position of the naphthalene resulting in a 6-membered palladacyclic intermediate which then undergoes fluorination.

The oxazoline was converted to the corresponding acid using a 2-step sequence.[15] Treatment of **6a** with methyl iodide followed by basic hydrolysis using NaOH afforded 2-fluorobenzoic acid **8** in 77% in 2 steps (Scheme 4).



Scheme 4. Removal of the DG.



Scheme 5. Proposed Mechanism

Mechanistic insight for palladium-catalyzed electrophilic C–H fluorination has been forwarded by many investigators.[4,6] Based on the experimental results and compared to the results other groups have reported a plausible mechanism is proposed based on *Hierso's* catalytic cycle, which has been supported by experimental, and mass spectrometric analysis.[6] As shown in Scheme 4, *C–H activation* of substrate **4a** by $Pd(NO_3)_2$ assembles Pd(II) complex **I**. *Oxidative addition* of NFSI to **II** which undergoes *reductive elimination* to deliver fluorinated product **5a**. Based on the experimental results during the optimization we propose that the Ag(I) assists in liberating the palladium from the oxazline, giving complex **5a'**. This interaction between silver and phenyl oxazolines has precedent in the literature.[16,17] Similarly the proton from the trifluoroacetic acid could have the same effect as the silver. This proposed interaction could be why in the absence of an additive no reaction

occurs. Complex **III** undergoes ligand exchange with nitrate to regenerate the catalyst, complex **IV**.

In summary we have reported an *ortho*-directed palladium-catalyzed electrophilic fluorination reaction using oxazoline as a removable DG. The aryl substituents can efficiently promote the fluorination reaction and the reaction conditions are tolerant to chloro- and bromo-substituents. The reaction conditions can be used for late stage fluorination and the dimethyloxazoline DG may be hydrolyzed to give the corresponding acid. While the scope of substrates for this removable DG is narrower in comparison to O-methyloxime[7] and the $-C(O)NHC_6F_4CF_3$ amide[9] DGs, we have demonstrated that dimethyloxazoline is a viable alternative as a removable directing in palladium-catalyzed electrophilic fluorination.

Supplementary Material

Supplementary material will be inserted here,

References and notes

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Highlights

For the first time, the old directing group dimethyloxazoline, which was used to direct *ortho*-lithiation has now been applied in palladium-catalyzed C-H fluorination. The removable directing group may be unmasked readily via hydrolysis.