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Ruthenium-catalyzed *meta*-C_{Ar}–H bond difluoroalkylation of 2-phenoxypyridines

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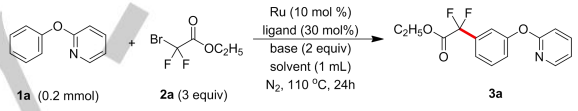
Abstract: A ruthenium-catalyzed *meta*-selective C_{Ar}–H bond difluoroalkylation of 2-phenoxypyridine using 2-bromo-2,2-difluoroacetate has been developed. Mechanistic studies indicated that this difluoroalkylation might involve a radical process. Furthermore, a new method is reported for the synthesis of 2-(*meta*-difluoroalkylphenoxy)pyridine derivatives, which are present in many pharmaceuticals and other functional compounds.

2-Phenoxypyridine derivatives are common in various pharmaceuticals, agrochemicals, and bioactive natural compounds.[1] Modifications and functionalizations of common 2-phenoxypyridine are convenient methods for preparing its derivatives.[2] Electrophilic aromatic substitution is a traditional and effective route to introducing substituents onto an aromatic ring. The site selectivities of reactions on aromatic rings are determined by substituents. For phenol derivatives, electrophilic aromatic substitution mainly affords *ortho*/*para*-modified product because the pyridoxy group acts as an *ortho*/*para* director.[3] With the increase in transition-metal-catalyzed C–H bond functionalizations reported in recent years, 2-phenoxypyridine derivatives have been prepared via transition-metal-catalyzed C_{Ar}–H functionalizations. However, these methods have been mainly limited to *ortho*-C_{Ar}–H bond functionalizations. Recently, with the help of the strong *ortho*/*para*-directing character of Ru–C_{Ar} σ-bonds, we have achieved *meta*-C–H alkylation and sulfonylation of 2-phenoxypyridine.[4]

The introduction of fluorine into organic molecules uniquely affects their chemical, biological, and physical properties, such as metabolic stability, lipophilicity, mimic effect, and bioavailability.[5] In particular, the difluoromethylene group (CF_2), which can be employed as a bioisostere for oxygen atoms and lipophilic hydrogen bond donor, has unique applications in biologically active molecules.[6] In this study, based on the *ortho*/*para*-directing character of Ru–C_{Ar} σ-bonds and ruthenium-catalyzed *meta*-C_{Ar}–H functionalization,[7] we have developed a ruthenium-catalyzed *meta*-selective C_{Ar}–H bond difluoroalkylation of 2-phenoxypyridine using 2-bromo-2,2-difluoroacetate.

Table 1. Optimization of reaction conditions for *meta*-C_{Ar}–H difluoroalkylation of 2-phenoxypyridine.



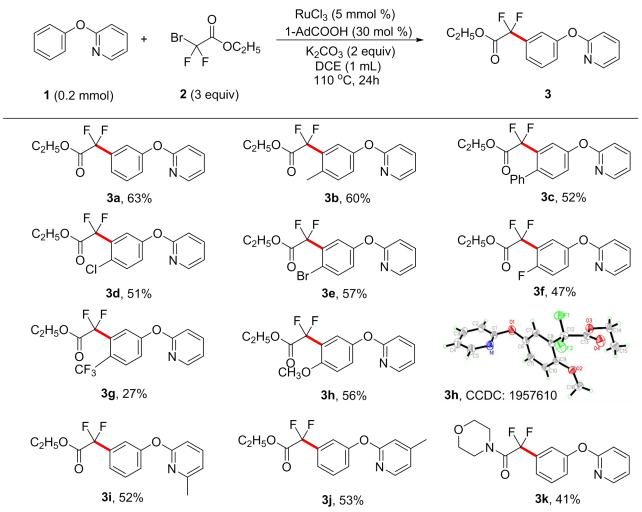
1a (0.2 mmol) **2a** (3 equiv) **3a**

Entry	Catalyst	Base	Ligand	Solvent	Yield (%)
1	$RuCl_3$	K_2CO_3	—	DCE	10
2	$RuCl_3$	K_2CO_3	1-AdCOOH	DCE	63
3	$RuCl_3$	K_2CO_3	^{t}BuCOOH	DCE	45
4	$RuCl_3$	K_2CO_3	MesCOOH	DCE	35
5	$RuCl_3$	K_2CO_3	Ac-Val-OH	DCE	22
6	$RuCl_3$	K_2CO_3	1-AdCOOH	1,4-dioxane	30
7	$RuCl_3$	K_2CO_3	1-AdCOOH	toluene	15
8	$RuCl_3$	K_2CO_3	1-AdCOOH	acetonitrile	0
9	$RuCl_3$	K_2CO_3	1-AdCOOH	DMF	0
10	$RuCl_3$	KOAc	1-AdCOOH	DCE	10
11	$RuCl_3$	Cs_2CO_3	1-AdCOOH	DCE	0
12	$RuCl_3$	Na_2CO_3	1-AdCOOH	DCE	42
13	$Ru_3(CO)_{12}$	K_2CO_3	1-AdCOOH	DCE	28
14	$Ru(PPh_3)_3Cl_2$	K_2CO_3	1-AdCOOH	DCE	13
15	$[Ru(p\text{-cymene})Cl_2]_2$	K_2CO_3	1-AdCOOH	DCE	0
16	$Pd(OAc)_2$	K_2CO_3	1-AdCOOH	DCE	0

To explore the possibility of a ruthenium(III)-catalyzed *meta*-C_{Ar}–H bond difluoroalkylation of phenol derivatives, readily available 2-phenoxypyridine (**1a**) and ethyl 2-bromo-2,2-difluoroacetate (**2a**) were selected as representative substrates to screen reaction conditions. The reaction was conducted at 110 °C for 24 h in a sealed Schlenk tube under a N_2 atmosphere, as shown in Table 1. Pleasingly, when $RuCl_3$ was employed as catalyst, K_2CO_3 as base and DCE as solvent, the desired product was obtained in 10% yield (entry **1**). When carboxylic acids, which are often used to promote Ru-catalyzed organic reactions, were added to the system, the conversion improved greatly (entries **2**–**5**). In particular, when 1-AdCOOH was used as an additive, the desired product was obtained in a 63% isolated yield (entry **2**). Solvent also played a vital role in this reaction. A small amount of the desired product was also obtained when 1,4-dioxane and toluene were employed as solvent (entries **6** and **7**). However, acetonitrile and DMF were ineffective reaction solvents (entries **8** and **9**). Base screening indicated that K_2CO_3 was highly efficient in the system, while KOAc, Cs_2CO_3, and Na_2CO_3 resulted in poor or no reactivity (entries **10**–**12**). Using

$Ru_3(CO)_{12}$ and $Ru(PPh_3)_3Cl_2$ as catalysts afforded the desired product in low yields (entries **13**–**15**). When $[Ru(p\text{-cymene})Cl_2]_2$ and $Pd(OAc)_2$ were employed as catalysts, the reaction did not proceed (entries **16** and **17**).

Scheme 1. Scope and generality of the Ru-catalyzed *meta*-C_{Ar}–H difluoroalkylation of 2-phenoxypyridine.

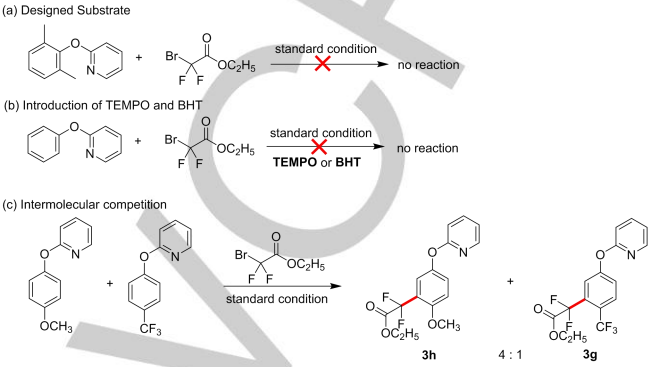


[a] Reaction Conditions: **1** (0.2 mmol), **2** (0.6 mmol), $RuCl_3$ (5 mol %), 1-AdCOOH (30 mmol %), K_2CO_3 (0.4 mmol), DCE (1 mL), 110 °C, 24 h. Isolated yield.

Under the optimized conditions, the scope and generality of this Ru-catalyzed *meta*-C_{Ar}–H difluoroalkylation were examined using various 2-phenoxypyridine substrates and difluoroalkylation reagents, as shown in Scheme 1. Initially, several 2-phenoxypyridines bearing various substituents on the phenyl ring were used as substrates. 2-Phenoxypyridines bearing alkyl and aryl groups on the benzene ring were suitable substrates for this transformation, affording the desired products in moderate yields (**3b** and **3c**). Halogen substituents were also compatible with this transformation (**3d**–**3f**), providing the opportunity for further transformations to afford highly functionalized derivatives. These results indicated that electronic properties dramatically affected the reaction efficiency. Although the desired products were obtained using substrates bearing both electron-donating (–OCH_3, **3h,** CCDC: 1957610) and electron-withdrawing (–CF_3, **3g**) substituents, electron-withdrawing substituents (-CF_3) were unfavorable for the *meta*-C_{Ar}–H difluoroalkylation. Methyl-substituted 2-pyridyloxy groups were also efficient directing groups in this transformation (**3i** and **3j**), while 2-bromo-2,2-difluoroacetamide was a good difluoroalkylation reagent (**3k**).

Various experiments were also conducted to investigate the mechanism of this Ru(III)-catalyzed *meta*-C_{Ar}–H bond difluoroalkylation, as shown in Scheme 2. First, difluoroalkylation did not proceed when 2-(2,6-dimethylphenoxy)pyridine bearing two methyl groups was used as a reactant to block the two *ortho*-positions on the phenyl ring, which suggests that *ortho*-C_{Ar}–H metalation was indispensable in the *meta*-difluoroalkylation process (Scheme **2a**). Next, the model reaction was inhibited when radical trapping agent 2,2,6,6-tetramethylpiperidin-1-yl)oxyl or butylated hydroxytoluene was added to the system, which suggests that this process might involve a single-electron transfer mechanism (Scheme **2b**). Finally, a competitive difluoroalkylation between 2-(4-methoxyphenyl)pyridine, bearing an electron-donating group,

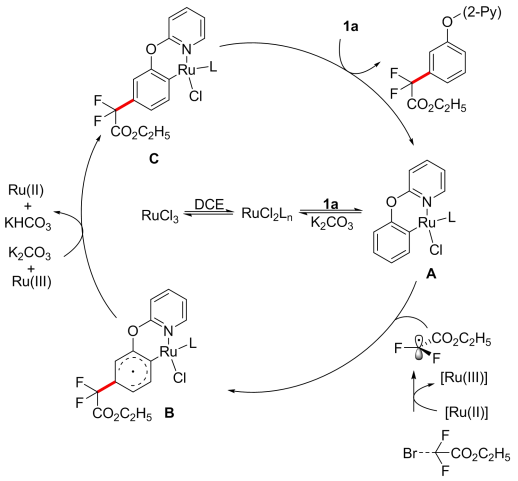
Scheme 2. Preliminary mechanistic studies.



and 2-(4-(trifluoromethyl)phenyl)pyridine, bearing an electron-withdrawing group, was conducted to study the impact of substrate electronic properties on the transformation. The result indicated that electron-rich substrates were better suited to this reaction than electron-deficient substrates, supporting the classification of Ru(III)-catalyzed difluoroalkylation as a base-assisted electrophilic C-H activation process (Scheme **2c**).[8]

Accoding to the experimental observations and previous studies on Ru-catalyzed *meta*-selective C_{Ar}–H bond functionalizations,[7] a plausible catalytic mechanism was proposed for this difluoroalkylation reaction. As shown in Scheme 3, the C_{Ar}–H functionalization is usually initiated by divalent ruthenium. Divalent $RuCl_2L_n$ is obtained from $RuCl_3$ via a strange redox process. Combination of $RuCl_2L_n$ with 2-phenoxypyridine initially provides six-membered ruthenacycle species **A** via nitrogen-assisted *ortho*-C_{Ar}–H bond metalation. Next, assisted by the *ortho*/*para*-directing effect of the C_{Ar}–Ru σ-bond, the difluoromethyl radical attacks at the *meta*-position of the 2-pyridoxyl group to give active species **B**. Meanwhile, a difluoromethyl radical forms via ruthenium-mediated single-

Scheme 3. Proposed catalytic mechanism.



electron transfer. Aided by ruthenium(III) and K_2CO_3, species **B** is deprotonated to give more stable intermediate **C**. Finally, ligand exchange of intermediate **C** with 2-phenoxypyridine gives the final difluoroalkylation product and regenerates the active ruthenium catalyst species for further cycling.

In conclusion, we have developed ruthenium-catalyzed *meta*-selective C–H bond difluoroalkylation of 2-phenoxypyridines. This development offers a new strategy for the preparation of 2-(meta-difluoroalkylphenoxy)pyridine derivatives. Further studies to expand the substrate scope and apply this difluoroalkylation method to chemical synthesis are underway.

Acknowledgements

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Keywords: Ruthenium • C-H activation • *meta*-C_{Ar}–H • Difluoroalkylation • Phenoxypyridine

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Difluoroalkylation

A ruthenium-catalyzed *meta*-selective C_{Ar}–H bond difluoroalkylation of 2-phenoxypyridine using 2-bromo-2,2-difluoroacetate has been developed, which provide a new method to synthesize 2-(*meta*-difluoroalkylphenoxy)pyridine derivatives, which are present in many pharmaceuticals and other functional compounds.