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Ruthenium-Catalyzed *ortho*/*meta*-Selective Dual C−H Bonds Functionalizations of Arenes

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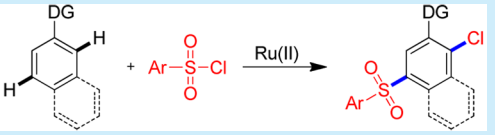
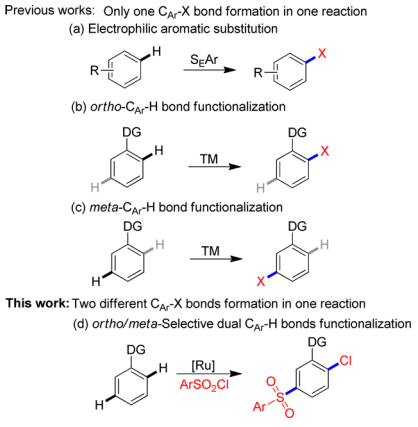
Supporting Information

ABSTRACT: The first example of transition-metal-catalyzed *ortho*/*meta*-selective dual C−H functionalizations of arenes in one reaction is described. In this transformation, *ortho*-C−H chlorination and *meta*-C−H sulfonation of 2-phenoxypyri(mi)dines were achieved simultaneously under catalysis by $[Ru(p\text{-cymene})Cl_2]_2$. The other reactant, namely, an arylsulfonyl chloride, played the role of both a sulfonation and chlorination reagent. More importantly, the arylsulfonyl chloride was also an oxidant in the process. Mechanistic studies indicated that six-membered ruthenacycles were the key intermediate in the reaction.



Aromatic compounds widely exist in pharmaceuticals, natural products, and various functional materials. The direct transformation of aryl C−H bonds to C_{Ar}−X bonds provides a convenient strategy for the synthesis of complex aromatic molecules. Thus, far, there are two major routes to transform aryl C−H bonds to C_{Ar}−X bonds: one is electrophilic aromatic substitution, such as nitration, sulfonation, halogenation and Friedel−Crafts reaction of aromatic compounds (Scheme 1a);[1] the other is transition-metal-catalyzed aryl C−H bond functionalization. Many *ortho*-selective C_{Ar}−H bond functionalization reactions catalyzed by different transition metals have been developed with chelation assistance of directing groups. These reactions have established vigorous group of methods to construct C−X bonds in modern synthetic chemistry (Scheme 1b).[2] More recently, breakthroughs have also been made in the direct transformation of *meta*-C_{Ar}−H bonds to C_{Ar}−X bonds via alternative strategies (Scheme 1c),[3] such as inherent sterics,[4] electronic effects,[5] remote directing groups,[6] norbornene mediation,[7] copper-catalyzed four-membered-ring transition states,[8] and *ortho*/*para*-directing effects of Ru−C_{Ar} σ-bonds.[9]

Scheme 1. Transformation of Aryl C−H Bonds



In all the above C_{Ar}−H functionalization processes, the reactions usually convert one type of C_{Ar}−H bond with controlled selectivity.[10] The selective transformation of dual C_{Ar}−H bonds of different types to different C_{Ar}−X bonds in one reaction remains elusive. Herein, we report the first example of the transition-metal-catalyzed *ortho*/*meta*-selective dual C−H functionalization of arenes. Using $[Ru(p\text{-cymene})Cl_2]_2$ as catalyst, we achieved *ortho*-chlorination and *meta*-sulfonation of 2-phenoxy-pyri(mi)dines with various arylsulfonyl chlorides (Scheme 1d). Removal of the pyri(mi)dine directing groups enabled the facile preparation of 2-chloro-5-(arylsulfonyl)phenol.[11]

Our study began with a typical reaction using 2-phenoxypyridine and *p*-toluenesulfonyl chloride as substrates and $[Ru(p\text{-cymene})Cl_2]_2$ as a catalyst. The dual C_{Ar}−H bond functionalization reaction was examined at 120 °C for 24 h in a sealed tube. As shown in Table 1, the results of the solvent screening showed the desired product (**3aa**) could be obtained in toluene and xylene (Table 1, entries 1 and 2). The major product isolated from the reaction mixture was the dual C_{Ar}−H bond functionalization product, whose structure was confirmed by single-crystal X-ray diffraction (Figure 1). Other solvents, such as acetonitrile, benzene, methanol, 1,4-dioxane, and THF, were not effective (Table 1, entries 3−7). K_2CO_3 was not a suitable base to improve the yield (Table 1, entry 8). Other ruthenium complexes, such as $RuCl_3$ and $Ru(PPh_3)_3Cl_2$,

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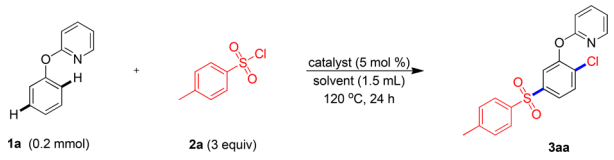
Table 1. Ru(II)-Catalyzed Dual C_{Ar}−H Functionalization[a]



entry	catalyst	solvent	yield (%)[b]
1	**$[Ru(p\text{-cymene})Cl_2]_2$**	**xylene**	**83**
2	$[Ru(p\text{-cymene})Cl_2]_2$	toluene	73
3	$[Ru(p\text{-cymene})Cl_2]_2$	acetonitrile	trace
4	$[Ru(p\text{-cymene})Cl_2]_2$	benzene	0
5	$[Ru(p\text{-cymene})Cl_2]_2$	methanol	0
6	$[Ru(p\text{-cymene})Cl_2]_2$	1,4-dioxane	0
7	$[Ru(p\text{-cymene})Cl_2]_2$	THF	0
8	$[Ru(p\text{-cymene})Cl_2]_2$	xylene	82[c]
9	$RuCl_3$	xylene	trace
10	$Ru(PPh_3)_3Cl_2$	xylene	trace
11	$Ru_3(CO)_{12}$	xylene	0
12	$Pd(OAc)_2$	xylene	0
13	–	xylene	0

[a]The reaction conditions were as follows: **1a** (0.2 mmol), **2a** (0.6 mmol, 3 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), solvent (1.5 mL), 120 °C, 24 h. [b]Isolated yields based on recovered starting material. [c]K_2CO_3 (2 equiv) was added

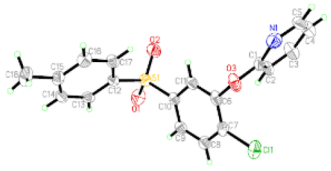


Figure 1. Single-crystal X-ray structure of product **3aa**.

exhibited poorer catalytic activities (Table 1, entries 9 and 10). When $Ru_3(CO)_{12}$ or $Pd(OAc)_2$ was used as a catalyst or when no catalyst was added, no desired product was observed (Table 1, entries 11, 12, and 13).

With the optimized conditions in hand, the scope of the substrates was examined. As summarized in Figure 2, 2-phenoxypyridines bearing a methyl group at different positions of the phenyl ring were employed as coupling partners with *p*-toluenesulfonyl chloride. The methyl group at the *ortho* or *para* position of the 2-pyridyloxy directing group did not impede the reaction (**3ba** and **3ca**). Only trace desired product was obtained for substrates bearing a methyl group at the *meta* position, which presumably resulted from the obvious steric hindrance. Significant electronic effects of the phenyl substituents were observed in the process. Electron-donating substituents (CH_3O−) were favorable for the reaction (**3da**). In contrast, electron-withdrawing groups deactivated the reaction. No desired product was obtained when 2-(4-nitrophenoxy)pyridine was used as a substrate. It is worth noting that 2-(naphthalen-2-yloxy)pyridine was also a suitable substrate, and the desired product was obtained in a moderate yield under the optimized conditions (**3ea**). The methyl-substituted 2-pyridyloxy groups and 2-pyrimidyloxy group were also efficient directing groups in the dual C_{Ar}−H bond functionalization process (**3fa**, **3ga**, and **3ha**).

Moreover, the scope of the arylsulfonyl chlorides was surveyed under the same conditions as summarized in Figure 3. According to results, alkyl (**3ac** and **3ad**), aryl (**3ae**),

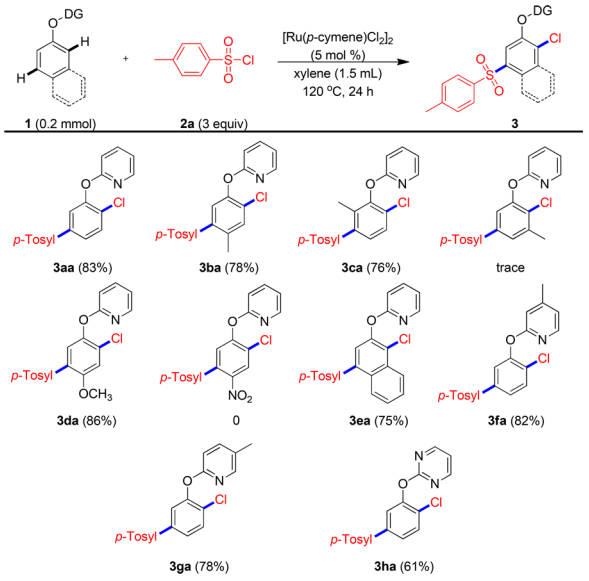


Figure 2. Scope of 2-aryloxypyri(mi)dine. **1** (0.2 mmol), **2a** (0.6 mmol, 3 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), xylene (1.5 mL), 120 °C, 24 h. Isolated yields based on recovered starting material.

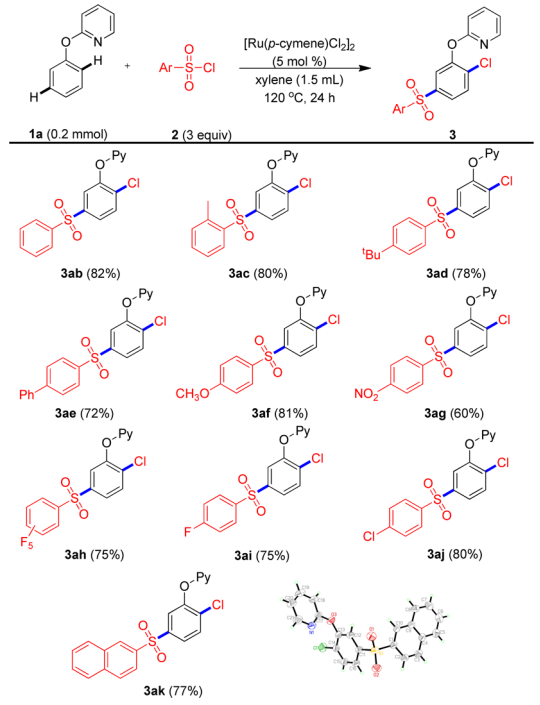


Figure 3. Scope of the arylsulfonyl chlorides. **1a** (0.2 mmol), **2** (0.6 mmol, 3 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), xylene (1.5 mL), 120 °C, 24 h. Isolated yields based on recovered starting material.

electron-donating (−OCH_3, **3af**), and strong electron-withdrawing (−NO_2, **3ag**) functional groups and halogens (**3ah**, **3ai**, and **3aj**) were well tolerated in the transformation. Naphthalene-2-sulfonyl chloride was also a good coupling partner, and the structure of the desired product was confirmed by single-crystal X-ray diffraction (**3ak**).

It is important to note that the 2-pyridyl group can be readily be removed to deliver 2-chloro-5-tosylphenol.[10] Therefore, the new Ru-catalyzed reaction provides a fast-track strategy for the synthesis of 2-chloro-5-(arylsulfonyl)phenols (Scheme 2).

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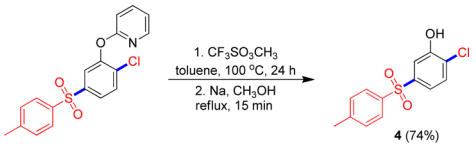
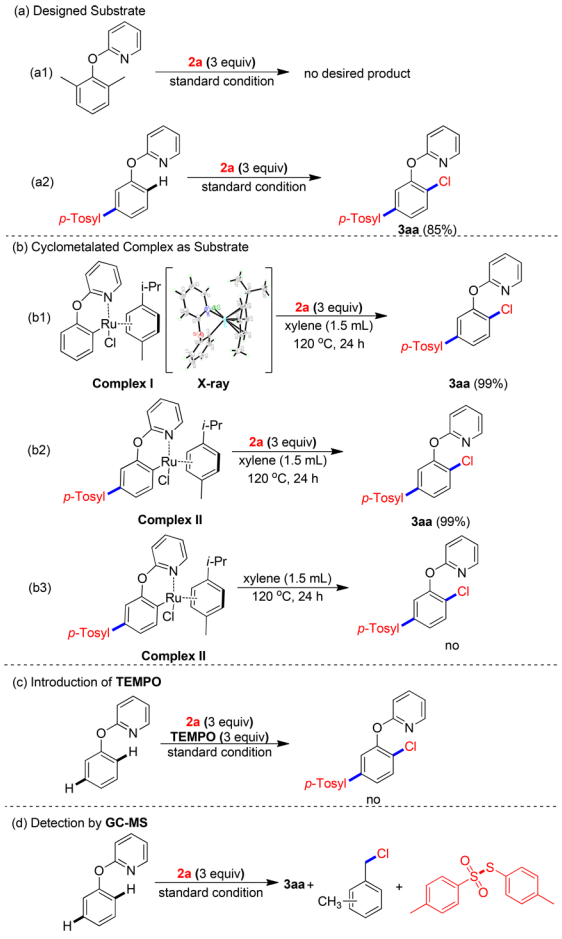
Scheme 2. Removal of the Directing Group



To gain insights into the reaction pathway, a series of additional experiments were performed as shown in Scheme 3.

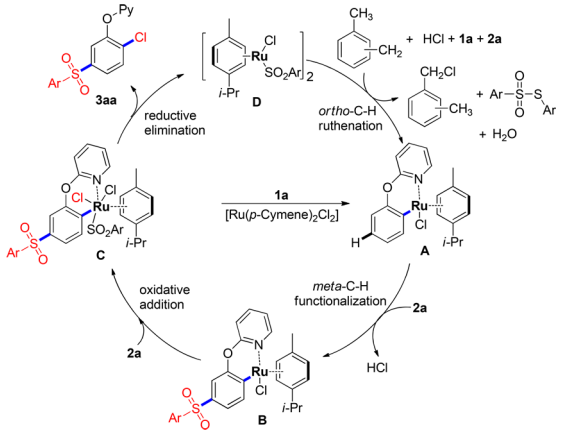
Scheme 3. Preliminary Mechanistic Studies



First, the designed compounds were selected as substrates (a). When using 2-(2,6-dimethylphenoxy)pyridine bearing two methyl groups to block the two *ortho* positions of the phenyl ring, the desired product was not obtained under the standard conditions (a1), supporting the necessity of *ortho*-C_{Ar}–H metalation in the reaction process. The desired product was also given when employing 2-(3-tosylphenoxy)pyridine bearing a sulfonyl group in the *meta* position. These results indicate that sulfonyl and chlorine groups can be introduced into arene ring in turn. Second, six-membered ruthenacycle complexes I and II were separately preprepared by mixing 2-phenoxypyridine and 2-(3-tosylphenoxy)pyridine with $[Ru(p\text{-cymene})Cl_2]_2$ in MeOH at 80 °C for 48 h. It was found that the preprepared complexes I and II reacted separately with 3 equiv of p-toluenesulfonyl chloride to give the desired products in nearly quantitative yields (b1 and b2). These findings indicated that both preformed complexes I and II might be key active intermediates in the dual C_{Ar}–H bond functionalization reaction. Furthermore, when complex II in xylene was heated at 120 °C for 24 h without *p*-toluenesulfonyl chloride, the desired product was not obtained (b3). This result shows that the oxidative addition of complex II with p-toluenesulfonyl chloride is essential, and the catalytic process involves a Ru(II)/Ru(IV) cycle, not a Ru(II)/Ru(0) cycle. Third, when the radical scavenger TEMPO was added into the model reaction, no desired product was found in the system (c). This indicates that the reaction involves a radical process, which is consistent with the mechanism proposed for the ruthenium-catalyzed *meta*-sulfonation reaction of arenes.[9h] Fourth, the reaction mixture was investigated by GC-MS.[12] In addition to the desired product, 1-(chloromethyl)-methylbenzene and *S*-*p*-tolyl-4-methylbenzenesulfonothioate were observed in the reaction system (d). This result indicates that the arylsulfonyl chloride not only was a dual sulfonation and chlorination reagent but also was an oxidant in the reaction. The observation of 1-(chloromethyl)-methylbenzene further confirmed that the dual C_{Ar}–H bond functionalization reaction involved a radical process.

On the basis of the above experimental observations and related literature,[9,13] a plausible catalytic cycle was proposed to rationalize the ruthenium-catalyzed *ortho*/*meta*-selective dual C_{Ar}–H bond functionalization. As shown in Scheme 4, the key

Scheme 4. Proposed Catalytic Cycle



six-membered ruthenacycle **A** was initially formed from 2-phenoxypyridine and $[Ru(p\text{-cymene})Cl_2]_2$ via an *ortho*-C_{Ar}–H ruthenation process with chelation assistance from the directing group. Then, the arylsulfonyl chloride attacked the *para* position of the Ru–C_{Ar} σ-bond through the strong directing effect of the Ru–C_{Ar} σ-bond to provide the Ru(II) species **B**. Furthermore, oxidative addition of the arylsulfonyl chloride on species **B** gave the active Ru(IV) complex **C**, which underwent reductive elimination to release the final product 2-(2-chloro-5-(arylsulfonyl)phenoxy)-pyridine and Ru(II) species **D**. Finally, C–H bond ruthenation of 2-phenoxypyridine with species D restarted the catalytic cycle and gave the byproducts S-aryl arylsulfonothioate and xylene chloride.

In conclusion, we described the discovery of a ruthenium(II)-catalyzed *ortho*-chlorination/*meta*-sulfonation dual C_{Ar}–H bond functionalization of 2-aryloxypyri(mi)dine arenes with arylsulfonyl chlorides. This reaction provided a fast-track strategy for synthesis of 2-chloro-5-(arylsulfonyl)phenols after the removal of the directing group. Novel six-membered ruthenacycle complexes were identified as the key active

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intermediate in the reaction. Further studies to expand the application of the ruthenium complexes in the dual C_{Ar}–H bond functionalization reaction are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02439.

Experimental procedures, characterization data, NMR spectra of products, and crystal structure (PDF)

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Notes

The authors declare no competing financial interest.

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