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Ruthenium-Catalyzed *meta*-Sulfonation of 2-Phenylpyridines

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Supporting Information Placeholder

ABSTRACT: A selective catalytic *meta*-sulfonation of 2-phenylpyridines was found to occur in the presence of (arene)ruthenium(II) complexes upon reaction with sulfonyl chlorides. The 2-pyridyl group facilitates the formation of a stable Ru-C_{aryl} σ -bond that induces a strong *para* directing effect. Electrophilic aromatic substitution proceeds with the sulfonyl chloride to furnish a sulfone in the *meta* position to the chelating group. This new catalytic process offers access to atypical regioselectivity for reactions involving chelation-assisted cyclometallation.

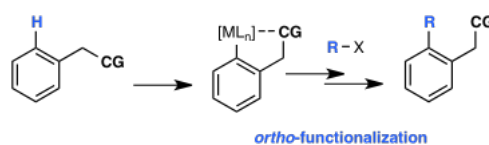
A common approach for the functionalization of aromatic substrates involves the chelation-assisted cleavage of a C–H bond to afford a metallacycle that facilitates subsequent *ortho*-directed C–C or C–X bond forming processes (Scheme 1a).¹ These studies have disclosed a wide-range of directing groups and different coupling partners for new *ortho*-functionalization reactions within this mechanistic setting. Many successful strategies involve Pd-catalyzed *ortho*-coupling reactions with C–H bonds through cyclopalladation of 2-phenylpyridine **1**.² Despite the phenomenal progress in this area, selective catalytic C–H bond activation methods for C–S bond formation remain relatively undeveloped.³ One notable example is the catalytic *ortho*-sulfonation protocol reported by Dong and co-workers.⁴ The use of Pd(CH₃CN)₂Cl₂ as the catalyst in the presence of K₂CO₃ allowed the isolation of *ortho*-sulfone product in good yield (Scheme 1b). From a synthetic perspective the direct introduction of functional groups to an aromatic ring to afford a regioselectivity complementary to the established chelation-assisted cleavage of a C–H bond/*ortho*-functionalization continues to challenge contemporary catalytic methodology.⁵ In this communication we present a study indicating that changing the pre-catalyst from Pd(II) to Ru(II) in the sulfonation of **1** switches the regioselectivity to afford the *meta*-sulfonation products **3a-i** (Scheme 1c, Table 1). The remarkable switch in regioselectivity implies a change in mechanistic pathway and offers new design principles for reactions involving chelation-assisted cyclometallation.

The recent significant achievements of selective catalytic C–H bond activations with Ru(II) species prompted us to explore the catalytic chelation-assisted cyclometallation

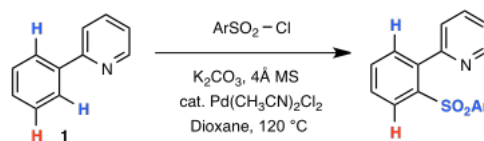
and subsequent sulfonation of 2-phenylpyridine with *p*-toluenesulfonyl chloride **2a** in the presence of six different Ru pre-catalysts (Table 1).⁶

Scheme 1. Chelation-assisted C–H activation

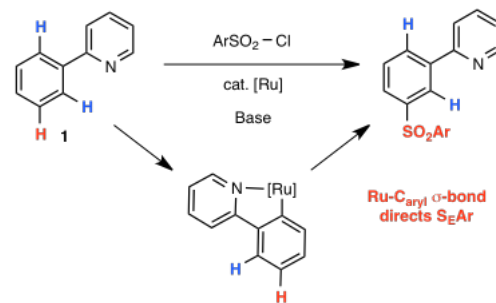
(a) Chelating group (CG) directs formation of a metallacycle



(b) Palladium catalyzed *ortho*-C–H sulfonation-Dong et al 2009

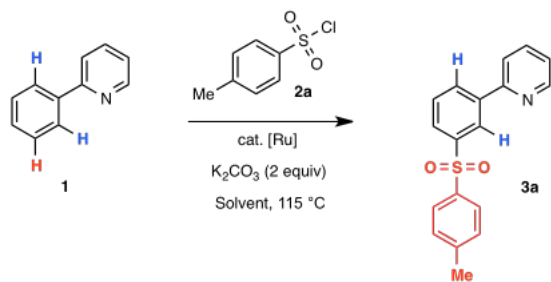


(c) Ruthenium catalyzed *meta*-C–H sulfonation-this study



The initial results were unexpected, as none of the ruthenium complexes gave the *ortho*-product upon spectroscopic analysis of the crude reaction mixtures. Although the conversions were low, the major product isolated from the reaction mixture in all cases was the *meta*-sulfonation product **3a**, the structure of which was unequivocally confirmed by single crystal X-ray diffraction (Figure 1).⁷ In each case the isolated yield reflected the conversion of 2-phenylpyridine **1**. As [Ru(*p*-cymene)Cl₂]₂ showed the highest level of catalytic activity (Table 1, entries 1-6) attempts were made to increase the isolated yield. After extensive screening, an improved process was realized by simply switching the solvent to CH₃CN (Table 1, entries 6-11).⁸ Control experiments showed that no coupling between **1** and **2a** took place in the absence of ruthenium (entries 12 and 13).

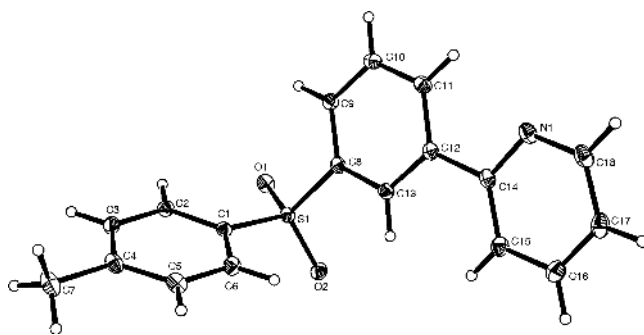
Table 1. Optimization studies for the ruthenium catalyzed *meta*-sulfonation of 2-phenylpyridine.^a



Entry	[Ru] complex	Solvent	Yield (%) ^b
1	Ru(PPh ₃) ₃ HCl	Dioxane	25
2	Ru(dppf)(PPh ₃)HCl	Dioxane	7
3	Ru(xantphos)(PPh ₃)HCl	Dioxane	trace
4	Ru(PPh ₃) ₃ (CO)H ₂	Dioxane	8
5	Ru ₃ CO ₁₂	Dioxane	0
6	[Ru(<i>p</i> -cymene)Cl ₂] ₂	Dioxane	27
7	[Ru(<i>p</i> -cymene)Cl ₂] ₂	EtOAc	24
8	[Ru(<i>p</i> -cymene)Cl ₂] ₂	THF	28
9	[Ru(<i>p</i> -cymene)Cl ₂] ₂	Toluene	5
10	[Ru(<i>p</i> -cymene)Cl ₂] ₂	CH ₃ CN	62
11	[Ru(<i>p</i> -cymene)Cl ₂] ₂	CH ₃ CN	80 ^c
12	-	CH ₃ CN	0
13	-	Dioxane	0

^a Unless otherwise noted, the reaction conditions were as follows: 2-phenylpyridine **1** (1.0 mmol), *p*-toluenesulfonylchloride **2a** (3.0 mmol), [Ru(*p*-cymene)Cl₂]₂ (2.5 mol %), K₂CO₃ (2 equiv), solvent (3 mL), 115 °C, 15 h. ^b Isolated yields with mass balance being recovered starting material **1**. ^c 5 mol% of [Ru(*p*-cymene)Cl₂]₂.

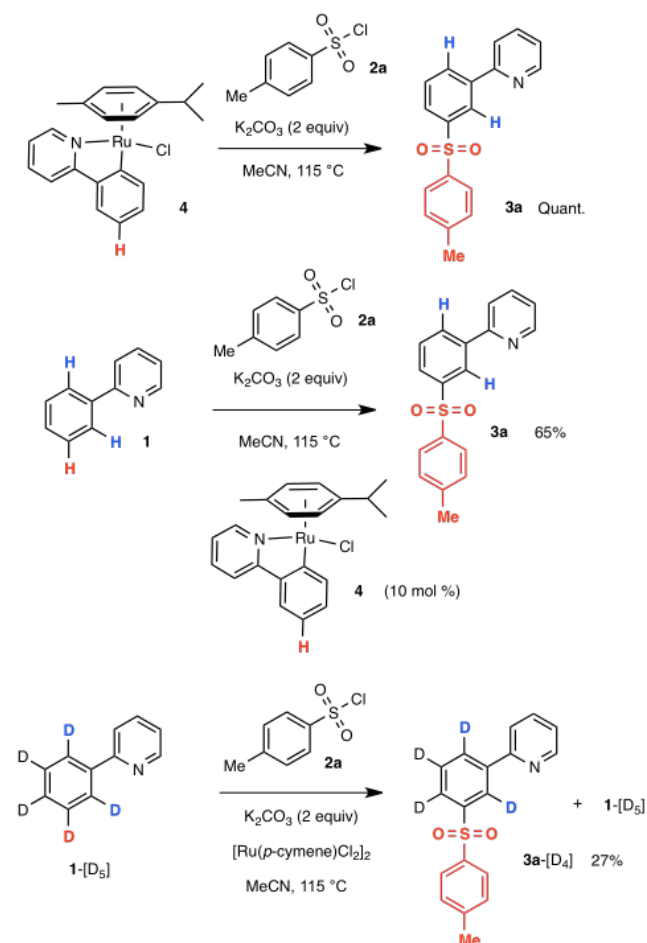
Figure 1. Single crystal X-ray structure of novel *meta*-product 3a. Ellipsoids are represented at 30% probability.



To account for the switch in regioselectivity from Pd to Ru, we hypothesized that the chelating group facilitates the formation of a stable Ru-C_{aryl} σ-bond that induces a strong

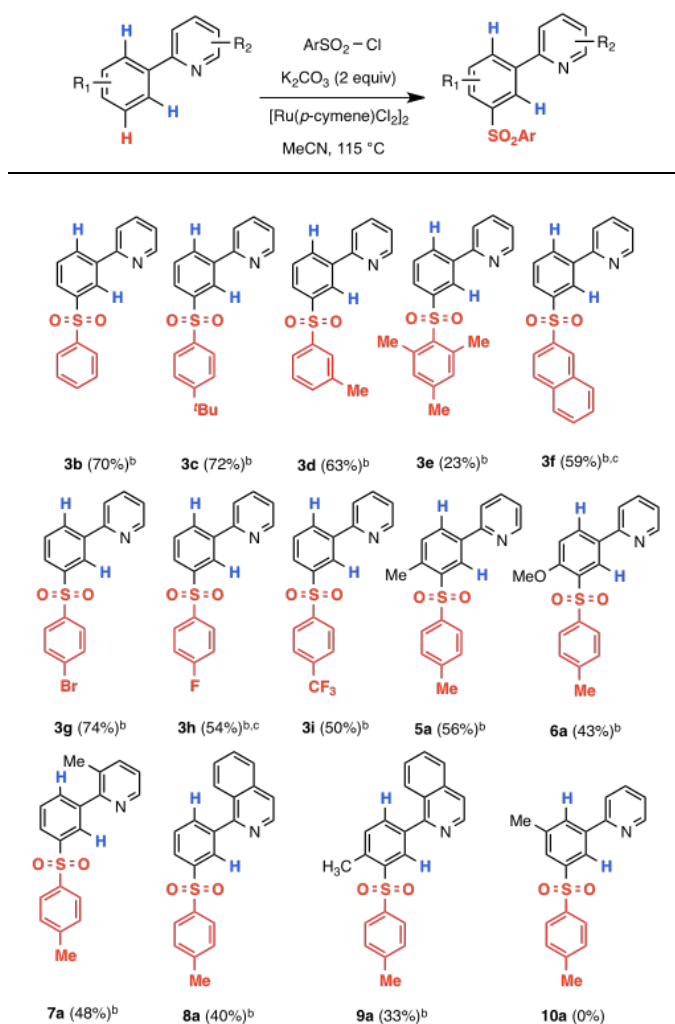
para directing effect.⁹ Substitution of the metallated aromatic ring proceeds with the sulfonyl chloride to furnish a sulfone in the *meta* position relative to the original chelating group. To test this hypothesis the cyclometallated Ru-complex **4** was prepared by the literature protocol.^{10,6r} Treatment of the isolated complex with 3 equiv of *p*-toluenesulfonyl chloride **2a** under the standard reaction conditions (Scheme 2) afforded quantitative conversion to **3a**. De-metallation under the reaction conditions would be necessary for catalyst turnover and indeed, when **1** was reacted with 3 equiv of **2a** in the presence of a catalytic amount of **4** (10 mol%), the *meta*-sulfonation product **3a** was isolated in 65% yield indicating the likely involvement of Ru-C_{aryl} σ-bond complexes in the catalytic cycle.¹¹ Although the σ-activation of aromatics has been studied for a range of stoichiometric processes such as electrophilic halogenation, acylation and nitration to the best of our knowledge this is the first example of a catalytic σ-activation process.¹² Preliminary experiments with isotopically labeled starting material showed no evidence of a D/H exchange from adventitious water or solvent. Stopping the reaction after 10 hours afforded the *meta*-sulfonation product **3a**-[D₄] in 27% yield along with unreacted **1**-[D₅].¹³ A kinetic isotope effect (*K*_H/*K*_D = 3.0) is observed suggesting that C-H bond cleavage is kinetically significant in the catalytic cycle.

Scheme 2. Catalytic sulfonation via chelation-assisted σ-activation



We next explored the scope of the ruthenium-catalyzed *meta* sulfonation (Table 2). Variation of the sulfonyl chloride afforded a useful range of products in good isolated yields (**3b-d** and **3f-i**). A range of functionality and substitution patterns was tolerated. The use of mesitylenesulfonyl chloride afforded product **3e** in lower yield, presumably due to the increased steric demands of the two *ortho*-methyl substituents. Notably, the reaction proceeded with substituents on the aromatic ring (**5a** and **6a**), the chelating pyridine ring (**7a** and **8a**) or both rings (**9a**). Interestingly, the blocking of one of the *meta* positions on the substrate results in no sulfone product (**10a**) being obtained from the reaction. This substantiates a chelation-assisted σ -activation pathway as presumably the cyclometallation proceeds *via* the least hindered C-H bond resulting in a complex where the methyl substituent is *para* to the activating Ru-C_{aryl} σ -bond. With this site blocked no reaction can take place.^{9b}

Table 2. Scope of ruthenium-catalyzed *meta* sulfonation^a

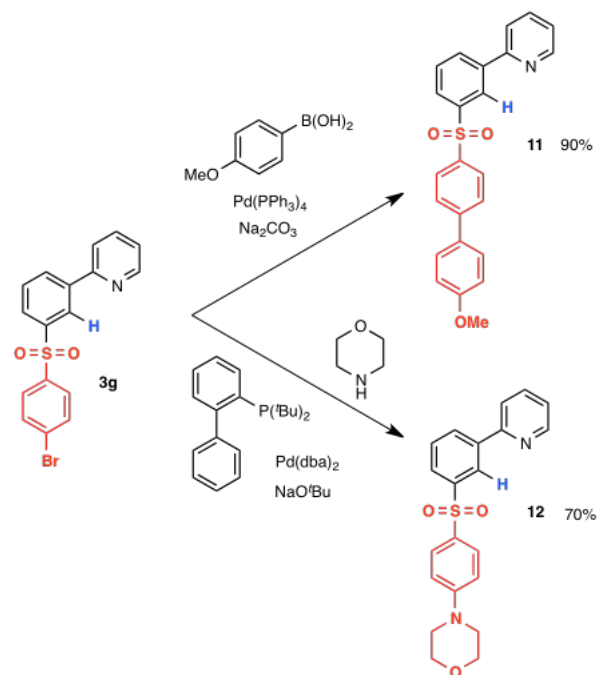


^a The reaction conditions were as follows: 2-phenylpyridine **1** (1.0 mmol), arylsulfonylchloride (3.0 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (5 mol %), K_2CO_3 (2 equiv), CH_3CN (3 mL), 115 °C, 15 h. ^b Isolated yields with mass balance being recovered starting material **1**. ^c X-ray structure obtained. See Supporting Information for details.

The incorporation of a bromo substituent in the product (**3g**) allows for further synthetic modification utilizing Pd(0)-catalyzed Suzuki-Miyaura cross-coupling and Buchwald-Hartwig amination reactions (Scheme 3).^{14,15} The exemplar reactions proceed in good isolated yield offering the capability to access a broader range of functional molecules in just two steps.

In summary, we have developed a ruthenium-catalyzed sulfonation of 2-phenylpyridines that affords the *meta*-product. The remarkable switch in regioselectivity implies a change in mechanistic pathway and offers new design principles for reactions involving chelation-assisted cyclometallation. Further work to establish the synthetic scope of catalytic chelation-assisted σ -activation along with additional mechanistic studies is in progress.

Scheme 3. Palladium-catalyzed cross-coupling



ASSOCIATED CONTENT

Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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