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

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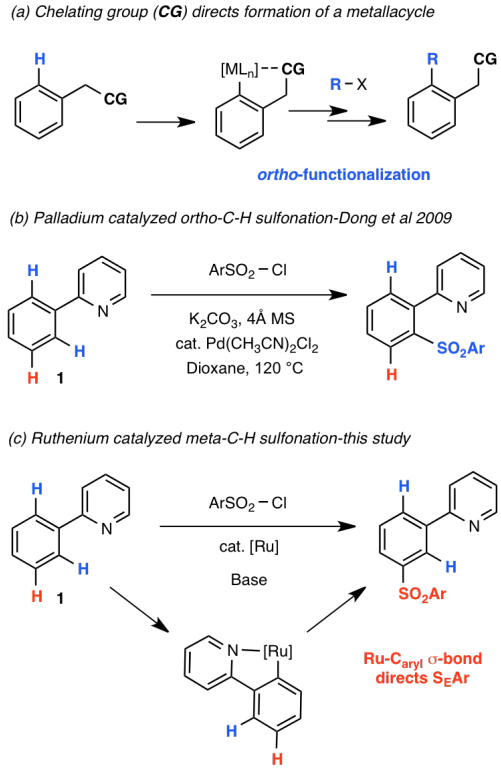
Supporting Information Placeholder

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 $Pd(CH_3CN)_2Cl_2$ as the catalyst in the presence of K_2CO_3 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.

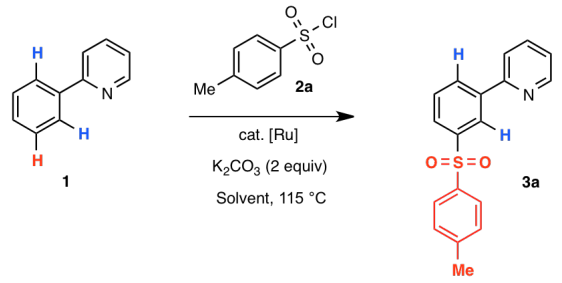
The recent significant achievements of selective catalytic C–H bond activations with Ru(II) species prompted us to explore the catalytic chelation-assisted cyclometallation and subsequent sulfonation of 2-phenylpyridine with *p*-toluenesulfonyl chloride **2a** in the presence of six different Ru pre-catalysts (Table 1).[6]

Scheme 1. Chelation-assisted C-H activation



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 $[Ru(p\text{-cymene})Cl_2]_2$ 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 CH_3CN (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).

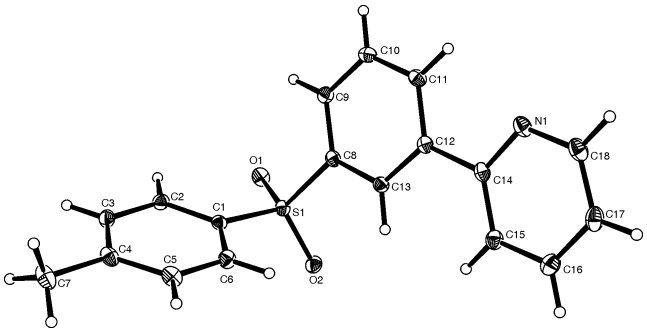
Table 1. Optimization studies for the ruthenium catalyzed *meta*-sulfonation of 2-phenylpyridine.[a]



Entry	[Ru] complex	Solvent	Yield (%)[b]
1	$Ru(PPh_3)_3HCl$	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_3CO_{12}	Dioxane	0
6	$[Ru(p\text{-cymene})Cl_2]_2$	Dioxane	27
7	$[Ru(p\text{-cymene})Cl_2]_2$	EtOAc	24
8	$[Ru(p\text{-cymene})Cl_2]_2$	THF	28
9	$[Ru(p\text{-cymene})Cl_2]_2$	Toluene	5
10	$[Ru(p\text{-cymene})Cl_2]_2$	CH_3CN	62
11	$[Ru(p\text{-cymene})Cl_2]_2$	CH_3CN	80[c]
12	–	CH_3CN	0
13	–	Dioxane	0

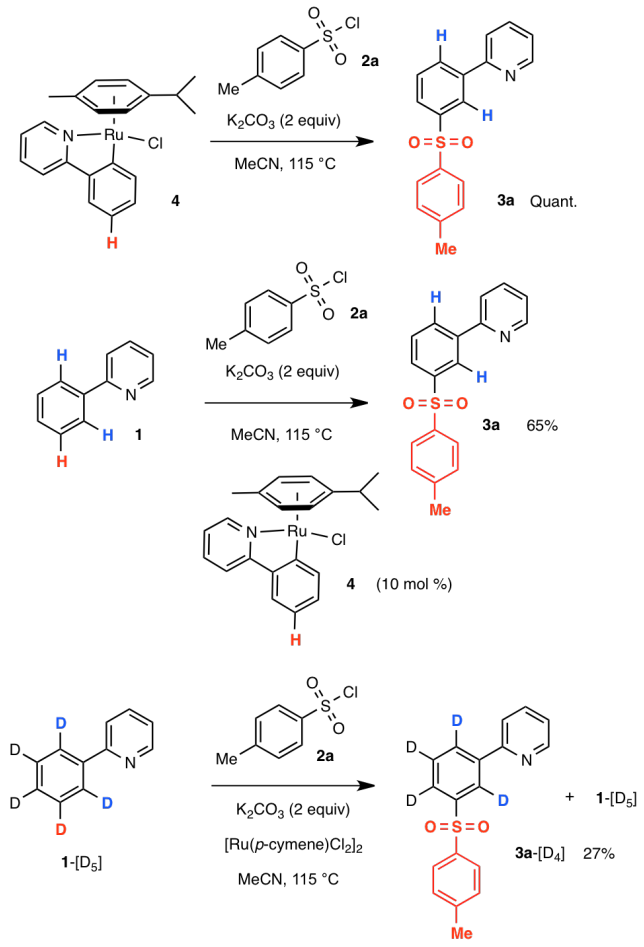
[a] Unless otherwise noted, the reaction conditions were as follows: 2-phenylpyridine **1** (1.0 mmol), *p*-toluenesulfonylchloride **2a** (3.0 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %), K_2CO_3 (2 equiv), solvent (3 mL), 115 °C, 15 h. [b] Isolated yields with mass balance being recovered starting material **1**. [c] 5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$.

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



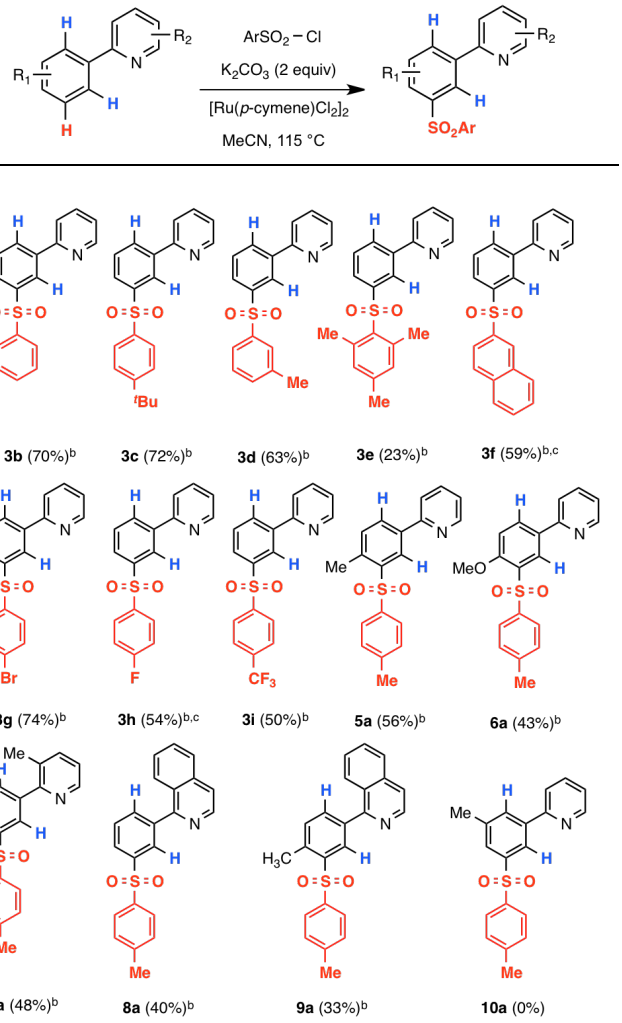
To account for the switch in regioselectivity from Pd to Ru, we hypothesized that the chelating group facilitates the formation of a stable Ru-C_{aryl} σ-bond that induces a strong *para* directing effect.[9] Substitution of the metallated aromatic ring proceeds with the sulfonyl chloride to furnish 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**-[D_4] in 27% yield along with unreacted **1**-[D_5].[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]

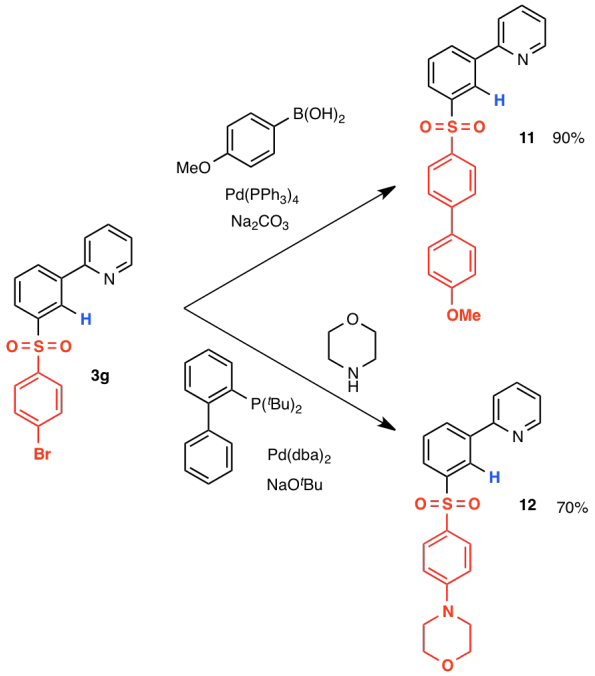


[a] The reaction conditions were as follows: 2-phenylpyridine **1** (1.0 mmol), arylsulfonylchloride (3.0 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), K_2CO_3 (2 equiv), CH_3CN (3 mL), 115 °C, 15 h. [b] Isolated yields with mass balance being recovered starting material **1**. [c] X-ray structure obtained. 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 a 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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(7) Crystal data for **3a (**CCDC 838883**)**: $C_{18}H_{15}NO_2S$, M = 309.37, monoclinic, a = 12.0800(2), b = 6.5760(1), c = 19.2930(4) Å, β = 104.500(1)°, U = 1483.78(5) Å^3, T = 150(2) K, space group $P2_1/a$, Z = 4, 24599 reflections measured, 3390 independent reflections (R_{int} = 0.0457). The final $R1$ and $wR(F^2)$ values were 0.0391 and 0.0941, respectively ($I > 2\sigma(I)$). Comparative values (all data) were 0.0506 and 0.1002.

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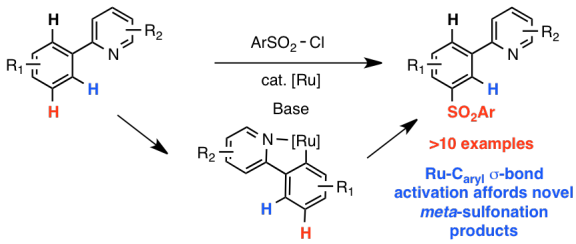
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R2
N
R1
H
H
ArSO2 - Cl
cat. [Ru]
Base
N – [Ru]
R2
R1
H
H
H
R2
N
R1
H
SO2Ar
>10 examples
Ru-Caryl σ-bond
activation affords novel
meta-sulfonation
products