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Ruthenium-Catalyzed Meta Sulfonation of 2-Phenylpyridines

Ourida Saidi, Jameel Marafie, Araminta E. W. Ledger, Po Man Liu, Mary F. Mahon, Gabriele Kociok-Köhn, Michael K. Whittlesey, and Christopher G. Frost*

Department of Chemistry, University of Bath, Bath BA2 7AY, U.K.

Supporting Information

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 at the position meta to the chelating group. This new catalytic process offers access to atypical regioselectivity for reactions involving chelation-assisted cyclometalation.

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 the *o*-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 that gives ortho functionalization continues to challenge contemporary catalytic methodology.[5] In this communication, we present a study indicating that changing the precatalyst 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, and Table 2). The remarkable switch in regioselectivity implies a change in mechanistic pathway and offers new design principles for reactions involving chelation-assisted cyclometalation.

The recent significant achievements of selective catalytic C−H bond activations with Ru(II) species prompted us to explore the catalytic chelation-assisted cyclometalation and subsequent sulfonation of **1** with *p*-toluenesulfonyl chloride (**2a**) in the presence of six different Ru precatalysts (Table 1).[6] The initial results were unexpected, as none of the ruthenium complexes gave the ortho product upon spectroscopic analysis of the crude reaction mixture. 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 **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).

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 metalated aromatic ring proceeds with

Scheme 1. Chelation-Assisted C−H Activation

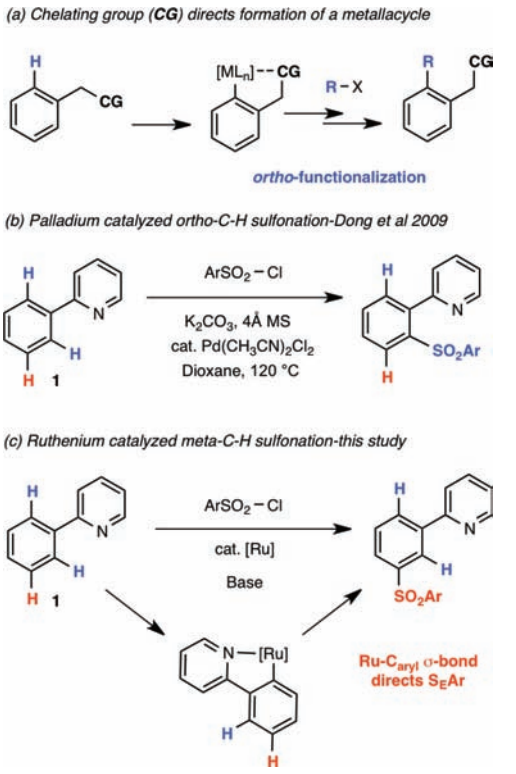

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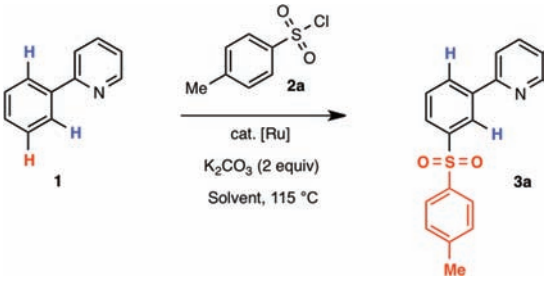
Table 1. Optimization Studies for the Ruthenium-Catalyzed Meta Sulfonation of 2-Phenylpyridine (1)[a]



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: **1** (1.0 mmol), **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 the mass balance being recovered starting material **1**. [c] 5 mol % $[Ru(p\text{-cymene})Cl_2]_2$.

the sulfonyl chloride to furnish a sulfone at the meta position relative to the original chelating group. To test this hypothesis, the cyclometalated Ru complex **4** was prepared by the literature protocol.[10,6r] Treatment of the isolated complex with 3 equiv of **2a** under the standard reaction conditions (Scheme 2) afforded quantitative conversion to **3a**. Demetalation 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 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 2-phenylpyridine **1**-$[D_5]$ showed no evidence of D/H exchange from adventitious water or solvent. Stopping the reaction after 10 h 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) was observed, suggesting that C–H bond cleavage is kinetically significant in the catalytic cycle.

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

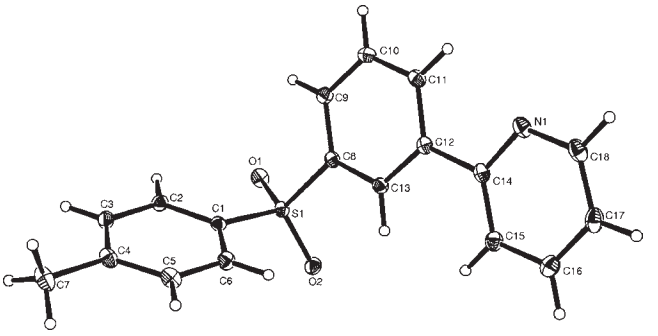
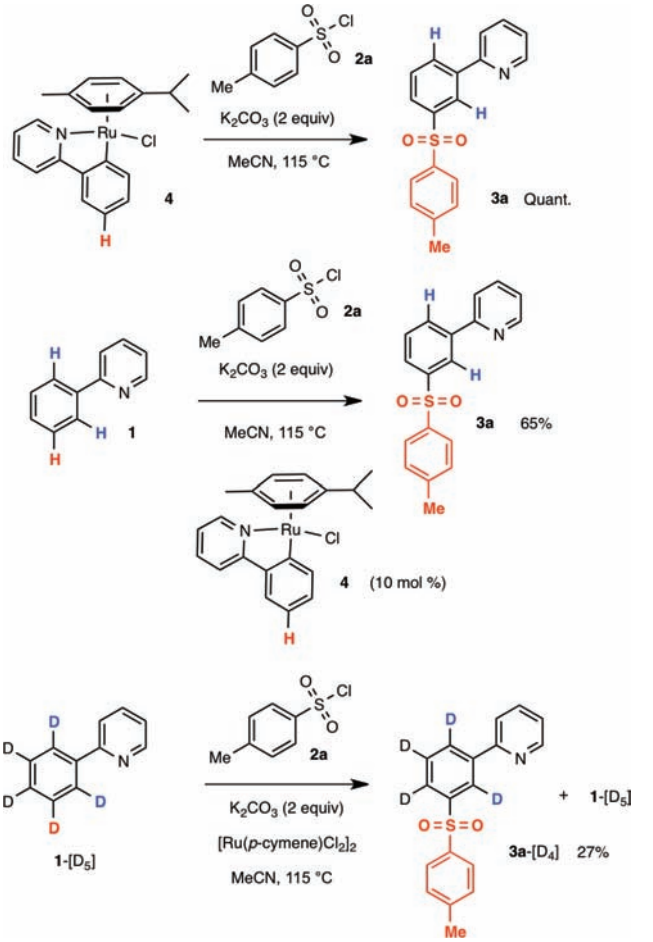


Figure 1. Single-crystal X-ray structure of the novel meta product **3a**. Ellipsoids are represented at 30% probability.

Scheme 2. Catalytic Sulfonation via Chelation-Assisted σ Activation



patterns was tolerated. The use of mesitylenesulfonyl chloride afforded product **3e** in lower yield, presumably because of the increased steric demands of the two *o*-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 resulted in no sulfone product (**10a**) being obtained from the reaction. This substantiates a

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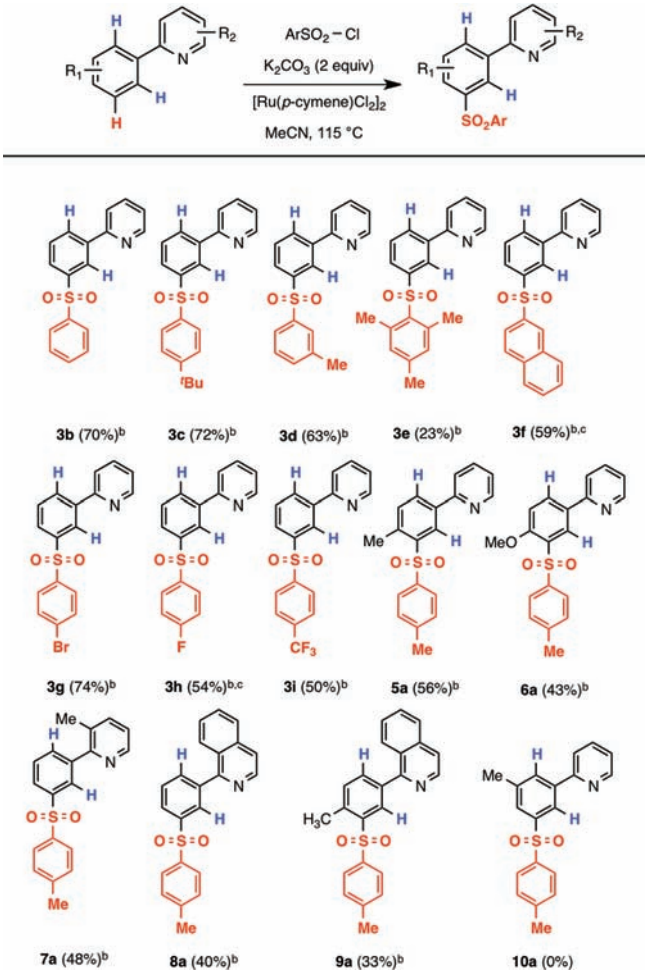
Table 2. Scope of Ruthenium-Catalyzed Meta Sulfonation[a]



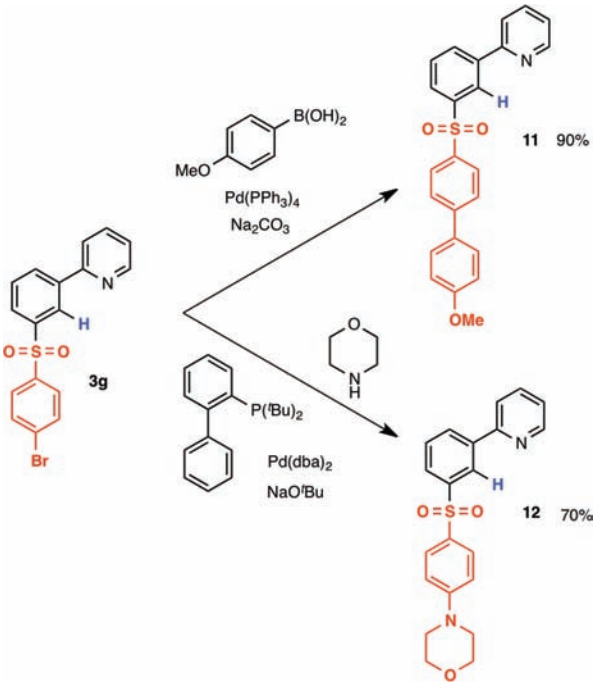
[a] The reaction conditions were as follows: **1** (1.0 mmol), arylsulfonyl chloride (3.0 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), K_2CO_3 (2 equiv), CH_3CN (3 mL), 115 °C, 15 h. [b] Isolated yields, with the mass balance being recovered starting material **1**. [c] The X-ray structure was obtained (see the Supporting Information for details).

chelation-assisted σ-activation pathway, as the cyclometalation presumably 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]

The incorporation of a bromo substituent in the product (**3g**) allowed for further synthetic modification utilizing Pd(0)-catalyzed Suzuki−Miyaura cross-coupling and Buchwald−Hartwig amination reactions (Scheme 3).[14,15] The exemplar reactions proceeded 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 cyclometalation. Further work to establish the synthetic scope of catalytic

Scheme 3. Palladium-Catalyzed Cross-Coupling



chelation-assisted σ activation and additional mechanistic studies are in progress.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization data for all new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
c.g.frost@bath.ac.uk

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■ REFERENCES

(1) For selected reviews, see: (a) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403. (b) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (d) Kakiuchi, F.; Chatani, N. *Top. Organomet. Chem.* **2004**, *11*, 45. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (f) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (h) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (i) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (j) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (k) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (l) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (m) Colby, D. A.; Bergman, R. G.;

Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (n) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (o) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (p) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1314. (q) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (r) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (s) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976.

(2) For representative reviews, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949.

(3) Beletskaya, I.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.

(4) (a) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466. (b) Zhao, X.; Dong, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 932.

(5) For selected examples, see: (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305. (b) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434. (c) Do, H.-Q.; Kassif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (d) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (e) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (f) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458. (g) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463. (h) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864.

(6) For selected examples of ruthenium-catalyzed C−H bond activation/functionalization, see: (a) Murai, S.; Kakiuchi, F.; Sekini, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098. (c) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (d) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (e) Cheng, K.; Zhang, Y.; Zhao, J.; Xie, C. *Synlett* **2008**, 1325. (f) Cheng, F.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (g) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887. (h) Pozgan, F.; Dixneuf, P. H. *Adv. Synth. Catal.* **2009**, *351*, 1737. (i) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871. (j) Kochi, T.; Urano, S.; Seki, H.; Mizushima, E.; Sato, M.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 2792. (k) Guo, X.; Deng, G.; Li, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 2071. (l) Arockiam, P.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629. (m) Luo, N.; Yu, Z. *Chem.—Eur. J.* **2010**, *16*, 787. (n) Prades, A.; Poyatos, M.; Peris, E. *Adv. Synth. Catal.* **2010**, *352*, 1155. (o) Li, H.; Wei, W.; Xu, Y.; Zhang, C.; Wan, X. *Chem. Commun.* **2011**, *47*, 1497. (p) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706. (q) Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J. F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 1436. (r) Ferrer Flegeau, E.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161. (s) Kochi, T.; Tazawa, A.; Honda, K.; Kakiuchi, F. *Chem. Lett.* **2011**, *40*, 1018. (t) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875.

(7) Crystal data for **3a** (CCDC 838883): $C_{18}H_{15}NO_2S$, M = 309.37 g/mol; monoclinic; a = 12.0800(2) Å, b = 6.5760(1) Å, c = 19.2930(4) Å, β = 104.500(1)°; V = 1483.78(5) Å^3; T = 150(2) K; space group $P2_1/a$; Z = 4; 24 599 reflns measured, 3390 independent reflns (R_{int} = 0.0457). The final R_1 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.

(8) Adding phosphine ligands (e.g., PPh_3, XantPhos, DPPF), employing alternative bases (e.g., KOAc, Et_3N), or changing the reaction temperature resulted in lower yields of the meta-sulfonation product.

(9) (a) Clark, G. R.; Headford, C. E. L.; Roper, W. R.; Wright, L. J.; Yap, V. P. D. *Inorg. Chim. Acta* **1994**, *220*, 261. (b) Clark, A. M.; Rickard, C. E. F.; Roper, W. R.; Wright, L. J. *Organometallics* **1999**, *18*, 2813.

(10) Boutadla, Y.; Al-Duaij, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics* **2009**, *28*, 433.

(11) To rule out simple Lewis acid activation of the sulfonyl chloride, we carried out a number of control reactions based on literature precedent. See: (a) Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Synlett* **2001**, 830. (b) Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Synlett* **2002**, 1928.

(12) Gagliardo, M.; Snelders, D. J. M.; Chase, P. A.; Klein Gebbink, R. J. M.; van Klink, G. P. M.; van Koten, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8558.

(13) When 2-phenylpyridine was treated with $[Ru(p\text{-cymene})Cl_2]_2$ and K_2CO_3 (2 equiv) in MeOH-$[D_4]$, no H/D exchange was observed. However, previous studies have shown the reversibility of ruthenium-catalyzed C−H bond cleavage. See: (a) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409. (b) Reference 6(n). (c) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032.

(14) For selected reviews of Suzuki−Miyaura coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (d) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013.

(15) For selected reviews of Buchwald−Hartwig amination, see: (a) Hartwig, J. F. *Nature* **2008**, *455*, 314. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (c) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.