



Citation for published version:

Saidi, O, Marafie, J, Ledger, AEW, Liu, PM, Mahon, MF, Kociok-Kohn, G, Whittlesey, MK & Frost, CG 2011, 'Ruthenium-catalyzed meta sulfonation of 2-phenylpyridines', *Journal of the American Chemical Society*, vol. 133, no. 48, pp. 19298-19301. <https://doi.org/10.1021/ja208286b>

DOI:

[10.1021/ja208286b](https://doi.org/10.1021/ja208286b)

Publication date:

2011

Document Version

Peer reviewed version

[Link to publication](#)

This document is the Accepted Manuscript version of a Published Work that appeared in final form in *Journal of the American Chemical Society*, copyright © American Chemical Society after peer review and technical editing by the publisher.

To access the final edited and published work see <http://dx.doi.org/10.1021/ja208286b>

University of Bath

Alternative formats

If you require this document in an alternative format, please contact:
openaccess@bath.ac.uk

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

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 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.

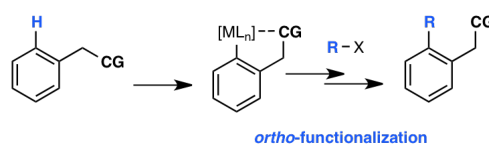
A common approach for the functionalization of aromatic substrates involves the chelation-assisted cleavage of a C-H bond to afford a metallacycle that facilitates subsequent *ortho*-directed C-C or C-X bond forming processes (Scheme 1a).¹ These studies have disclosed a wide-range of directing groups 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

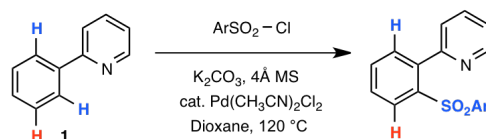
and subsequent sulfonation of 2-phenylpyridine with *p*-toluenesulfonyl chloride **2a** in the presence of six different Ru pre-catalysts (Table 1).⁶

Scheme 1. Chelation-assisted C-H activation

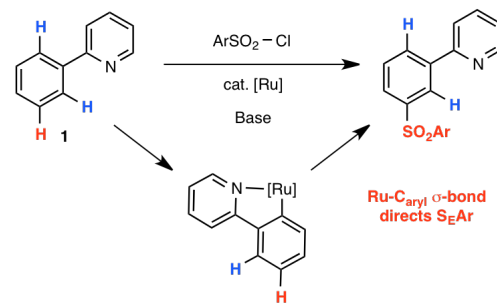
(a) Chelating group (CG) directs formation of a metallacycle



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

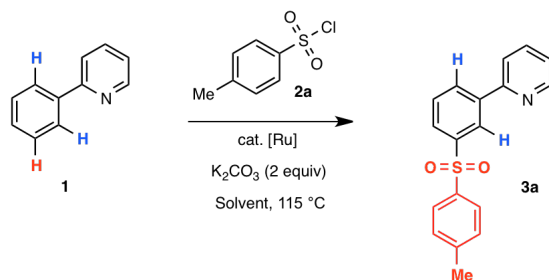


(c) Ruthenium catalyzed *meta*-C-H sulfonation-this study



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).

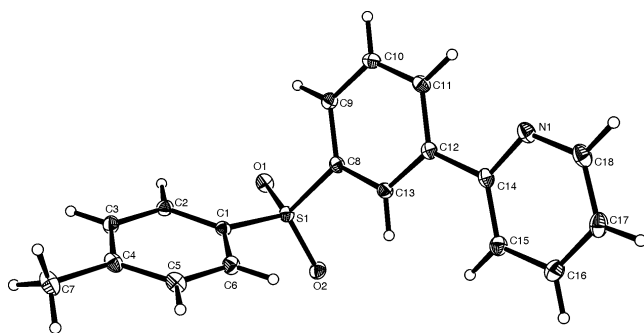
Table 1. Optimization studies for the ruthenium catalyzed *meta*-sulfonation of 2-phenylpyridine.^a



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.

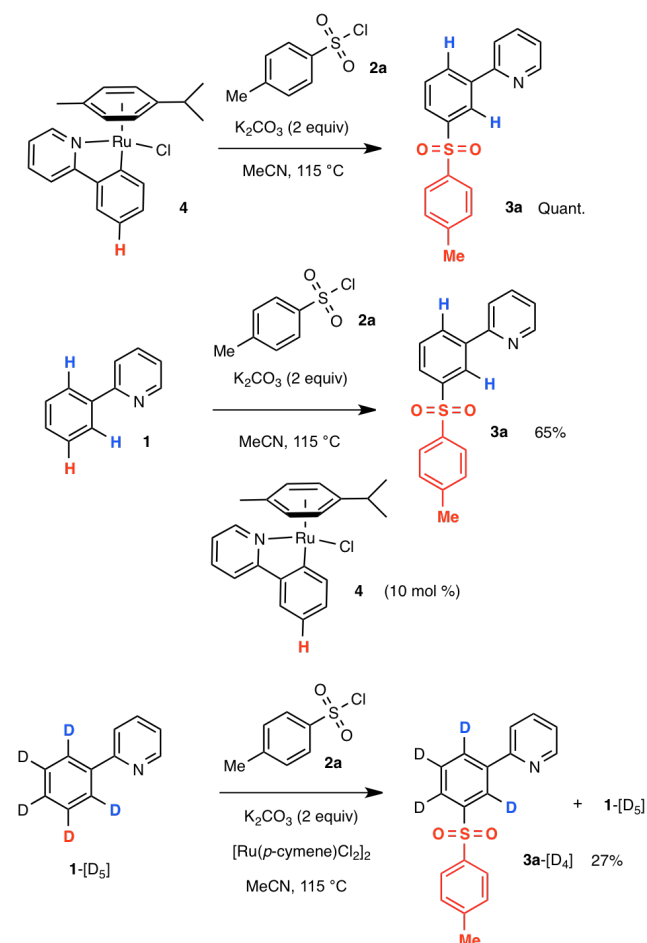
Figure 1. Single crystal X-ray structure of novel *meta*-product 3a. Ellipsoids are represented at 30% probability.



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

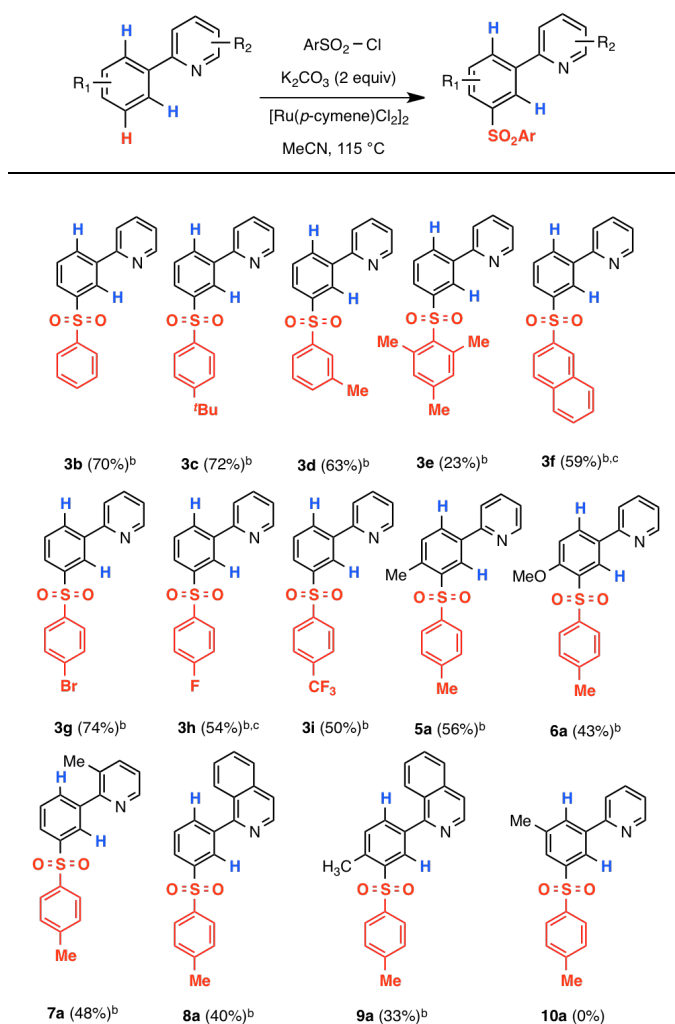
para directing effect.⁹ Substitution of the metallated aromatic ring proceeds with the sulfonyl chloride to furnish a sulfone in the *meta* position relative to the original chelating group. To test this hypothesis the cyclometallated Ru-complex **4** was prepared by the literature protocol.^{10,6r} 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

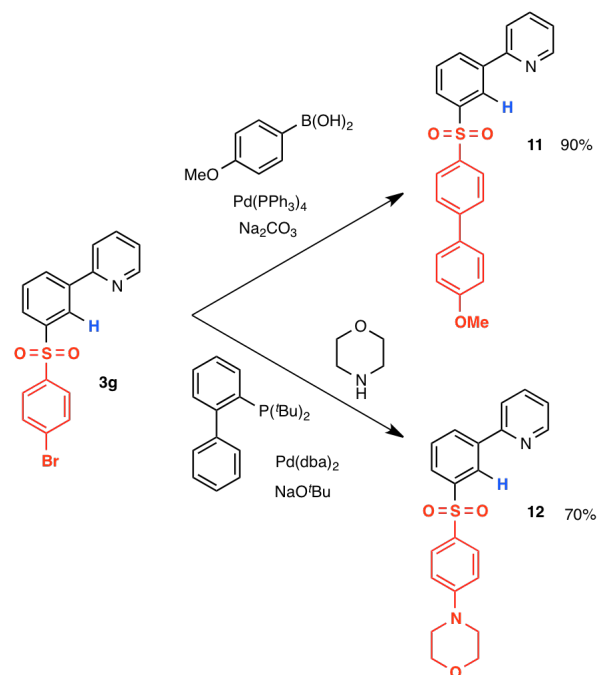


^a The reaction conditions were as follows: 2-phenylpyridine **1** (1.0 mmol), arylsulfonylchloride (3.0 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol %), K₂CO₃ (2 equiv), CH₃CN (3 mL), 115 °C, 15 h. ^b Isolated yields with mass balance being recovered starting material **1**. ^c X-ray structure obtained. See Supporting 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>.

AUTHOR INFORMATION

Corresponding Author

c.g.frost@bath.ac.uk

ACKNOWLEDGMENT

We are grateful to the University of Bath, EPSRC and GlaxoSmithKline for funding. We acknowledge the valuable assistance of Dr Matthew Jones (GC-MS), Dr Anneke Lubben (Mass Spectrometry) and Dr John Lowe (NMR).

REFERENCES

(1) For selected reviews, see: (a) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403–424. (b) Miura, M.; Nomura, M. *Current Topics in Chemistry*; Springer-Verlag: Berlin, 2002; Vol. 129, pp 212–241.

- (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834. (d) Kakiuchi, F.; Chatani, N. In *Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer-Verlag: Berlin, 2004; Wang, 11, pp 45–79. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770. (f) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, 1253–1264. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (h) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (i) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (j) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (k) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (l) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1139. (m) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (n) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.-Eur. J.* **2010**, *16*, 2654–2672. (o) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (p) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1314–1345. (q) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761. (r) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (s) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991.
- (2) For representative reviews, see: (a) Chen, X.; Engle, K. M.; Wang D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (b) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949–957.
- (3) Beletskaya, I.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596–1636.
- (4) (a) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466–3467. (b) Zhao, X.; Dong, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 932–934.
- (5) For selected examples, see: (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, Jr., R. E.; Smith III, M. R. *Science* **2002**, *295*, 305–308. (b) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434–15435. (c) Do, H.-Q.; Kassif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185–15192. (d) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593–1597. (e) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074. (f) Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 458–462. (g) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463–466. (h) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864–13867.
- (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*, 529–531. (b) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098–6099. (c) Ozdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157. (d) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278–6282. (e) Cheng, K.; Zhang, Y.; Zhao, J.; Xie, C. *Synlett* **2008**, 1325–1330. (f) Cheng, F.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309–5312. (g) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887–7895. (h) Pozgan, F.; Dixneuf, P. H. *Adv. Synth. Catal.* **2009**, *351*, 1737–1743. (i) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871–1875. (j) Kochi, T.; Urano, S.; Seki, H.; Mizushima, E.; Sato, M.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 2792–2793. (k) Guo, X.; Deng, G.; Li, C.-J. *Adv. Synth. Catal.* **2009**, *351*, 2071–2074. (l) Arockiam, P.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629–6632. (m) Luo, N.; Yu, Z. *Chem.—Eur. J.* **2010**, *16*, 787–791. (n) Prades, A.; Poyatos, M.; Peris, E. *Adv. Synth. Catal.* **2010**, *352*, 1155–1162. (o) Li, H.; Wei, W.; Xu, Y.; Zhang, C.; Wan, X. *Chem. Commun.* **2011**, *47*, 1497–1499. (p) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706–708. (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*, 1436–1439. (r) Ferrer Flegeau, E.; Bruneau, C.; Dixneuf, P. H.; Jutand A. *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170. (s) Kochi, T.; Tazawa, A.; Honda, K.; Kakiuchi, F. *Chem. Lett.* **2011**, *40*, 1018–1020. (t) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877.
- (7) Crystal data for **3a** (CCDC 838883): C₁₈H₁₅N₂O₂S, 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) Å³, *T* = 150(2) K, space group *P*2₁/*a*, *Z* = 4, 24599 reflections measured, 3390 independent reflections (*R*_{int} = 0.0457). The final *R*1 and *wR*(*F*²) values were 0.0391 and 0.0941, respectively (*I* > 2σ(*I*)). Comparative values (all data) were 0.0506 and 0.1002.
- (8) The addition of phosphine ligands (e.g. PPh₃, XantPhos, DPPF), employing alternative bases (e.g. KOAc, Et₃N) or changing 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*, 261–272. (b) Clark, A. M.; Rickard, C. E. F.; Roper, W. R.; Wright, L. J. *Organometallics* **1999**, *18*, 2813–2820.
- (10) Boutadla, Y.; Al-Duaij, O.; Davies, D. L.; Griffith, G. A.; Singh, K. *Organometallics*, **2009**, *28*, 433–440.
- (11) To rule out simple Lewis acid activation of the sulfonyl chloride, we carried out a number of control reactions based on literature precedent: (a) Frost, C. G.; Hartley J. P.; Whittle, A. J. *Synlett* **2001**, 830–832. (b) Frost, C. G.; Hartley J. P.; Whittle, A. J. *Synlett* **2002**, 1928–1930.
- (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*, 8558–8573.
- (13) When 2-phenylpyridine was treated with [Ru(*p*-cymene)Cl₂]₂ and K₂CO₃ (2 equiv) in MeOH-[D₄] no H/D exchange was observed. However, previous studies have shown the reversibility of ruthenium-catalyzed C-H bond cleavage: (a) Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Lett.* **2008**, *10*, 3409–3412. (b) Prades, A.; Poyatos, M.; Peris, E. *Adv. Synth. Catal.* **2010**, *352*, 1155–1162. (c) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035.
- (14) For selected reviews of Suzuki-Miyaura coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473. (d) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013–2030.
- (15) For selected reviews of Buchwald-Hartwig amination, see: (a) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (c) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.

