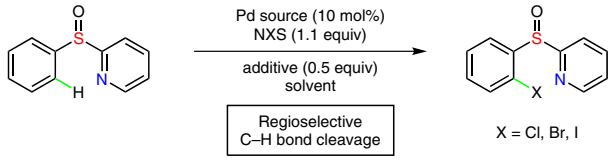
Synlett J.-L. Zhao et al. Letter

Palladium-Catalyzed Highly Regioselective *ortho*-Halogenation of 2-Pyridyl Sulfoxides

Jun-Long Zhao◊
Xiang-Xiang Chen◊
Hu Xie
Jiang-Tao Ren
Xiao-Feng Gou
Meng Sun*

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P. R. of China
sunmeng@nwu.edu.cn

◊ These two authors contributed equally to this work



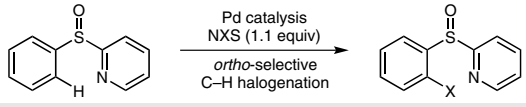
Received: 23.02.2017
Accepted after revision: 26.02.2017
Published online: 16.03.2017
DOI: 10.1055/s-0036-1588756; Art ID: st-2017-w1852-l

Abstract A palladium-catalyzed regioselective *ortho*-halogenation of 2-pyridyl sulfoxides via a C–H activation pathway has been reported. Under the conditions established, this reaction proceeded smoothly and could tolerate a variety of functional groups under mild conditions.

Key words palladium-catalyzed, regioselectivity, halogenation, C–H activation, sulfoxides

Aryl halides have been proved to be important starting materials for constructing complex skeletons in synthetic elaboration, which are able to serve as precursors for the synthesis of organometallic reagents,[1] nucleophilic aromatic substitution,[2] and cross-coupling reactions.[3] Conventional methods of incorporating the halogen group into aromatic rings include electrophilic aromatic substitution[4] and *ortho*-lithiation followed by a halogen quench,[5] which, however, suffer from several notable disadvantages.[6] In recent years, considerable attention has been focused on C–H bond halogenation,[7] which is an atom-economic strategy for rapid building of carbon–halogen atom bonds. For example, in 2004, Sanford[8] reported a palladium-catalyzed halogenation of benzo[*h*]quinolone. Subsequently, the groups of Shi, Yu, Bedford, and Xu illustrated the major importance of these halogenation reactions with the assistance of diverse directing groups.[9] However, although a number of methods have been achieved, application of this strategy to create carbon–halogen bonds for more diverse structures is still highly desirable for expanding the realm of selective C–H functionalization.

Organosulfur compounds have become widely used in natural products, pharmaceuticals, and materials science.[10] Moreover, they also take a privileged position in the fields of reagents, ligands, catalysts, and organic semiconductors.[11,12] Although their importance has attracted considerable attention for the preparation, the exploration of new methodologies for C–H bond functionalization of S-containing compounds is still an extremely attractive,[13,14] but challenging issue (the strong coordination generated by poisoning of transition-metal catalysts[15] and undesirable redox processes). In continuation of our previous work on C–H bond functionalization–halogenation research,[16] herein we report a novel and direct palladium-catalyzed halogenation reaction of 2-pyridyl sulfoxides with commercially available electrophilic halogenating reagents – particularly *N*-bromo-, *N*-chloro-, and *N*-iodosuccinimide (Scheme 1).



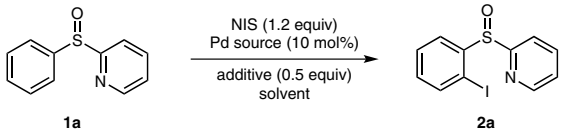
Scheme 1 Palladium-catalyzed *ortho*-halogenation of 2-pyridyl sulfoxides

We commenced our exploration by investigating the reaction of 2-pyridyl sulfoxides[17] (**1a**, 1.0 equiv) with NIS (1.1 equiv) in the presence of 10 mol% $Pd(OAc)_2$ in DCE at 100 °C for 20 hours (Table 1, entry 1). Encouraged by this result, different solvents were screened, and chlorobenzene was proved to be best in this transformation (36% yield). It is noteworthy that Brønsted acids are conducive to this transformation, which promoted the electrophilicity of the palladium(II) catalyst[18] and rendering NIS a more effective source of I^+.[19] For example, higher yield could be obtained when TFA was added, while AcOH can also give a comparable yield. Further catalyst screening demonstrated that $Pd(OAc)_2$ was superior to other catalysts and no product was detected in the absence of catalyst. It was found that a noticeable (15%) increase in yield was observed when lowering the temperature, while other parameter changes sup-

pressed the efficiency. Finally, the optimized reaction conditions for the *ortho*-C–H halogenation of 2-pyridyl sulfoxides were determined to be NIS (1.1 equiv) with 10 mol% $Pd(OAc)_2$ as the catalyst, of TFA (0.5 equiv) as additive, and PhCl as solvent, at 80 °C under air for 20 hours.

With the optimized reaction conditions in hand, the scope of the transformation was investigated.[20] The results, summarized in Scheme 2, revealed that the substrates bearing either electron-donating or electron-withdrawing substituents on the 2-pyridyl sulfoxides were smoothly transformed into the corresponding products in acceptable to good yields for most case. For example, good yields were obtained when substrates with a methyl group at the *ortho*, *meta*, or *para* position of the aromatic rings of sulfoxides were involved. Moreover, halogenated substrates (e.g., F, Cl, and Br) executed this chemistry well, producing the desired products in acceptable yields with the possibility of further transformation into other important skeletons. In addition, the strategy was also applicable to 2-(naphthalen-2-ylsulfinyl)pyridine, which highly selectively afforded the corresponding 2-[(3-iodonaphthalen-2-yl)sulfinyl]pyridine in moderate yield.

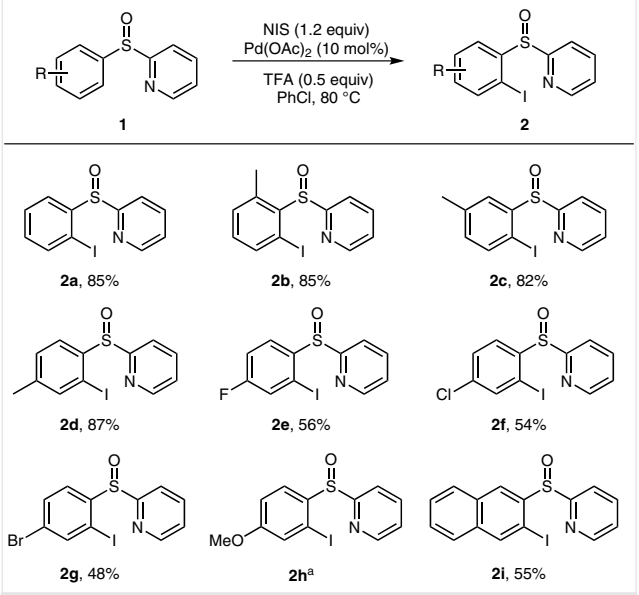
Table 1 Optimization of the Reaction Conditions[a,b]



1a 2a

Entry	Catalyst	Additive	Solvent	Yield (%)
1	$Pd(OAc)_2$		DCE	20
2	$Pd(OAc)_2$		MeCN	trace
3	$Pd(OAc)_2$		DME	23
4	$Pd(OAc)_2$		toluene	5
5	$Pd(OAc)_2$		PhCl	36
6	$Pd(OAc)_2$	AcOH	PhCl	56
7	$Pd(OAc)_2$	TFA	PhCl	60
8	$Pd(OAc)_2$	TfOH	PhCl	15
9	$Pd(OAc)_2$	$MeSO_3H$	PhCl	27
10	$Pd(OAc)_2$	TsOH	PhCl	23
11	$Pd(TFA)_2$	TFA	PhCl	59
12	$PdCl_2$	TFA	PhCl	46
13	$PdCl_2(MeCN)_2$	TFA	PhCl	38
14	$Pd(acac)_2$	TFA	PhCl	47
15[c]	$Pd(OAc)_2$	TFA	PhCl	75
16[d]	$Pd(OAc)_2$	TFA	PhCl	62
17[e]	$Pd(OAc)_2$	TFA	PhCl	33
18[f]	$Pd(OAc)_2$	TFA	PhCl	69

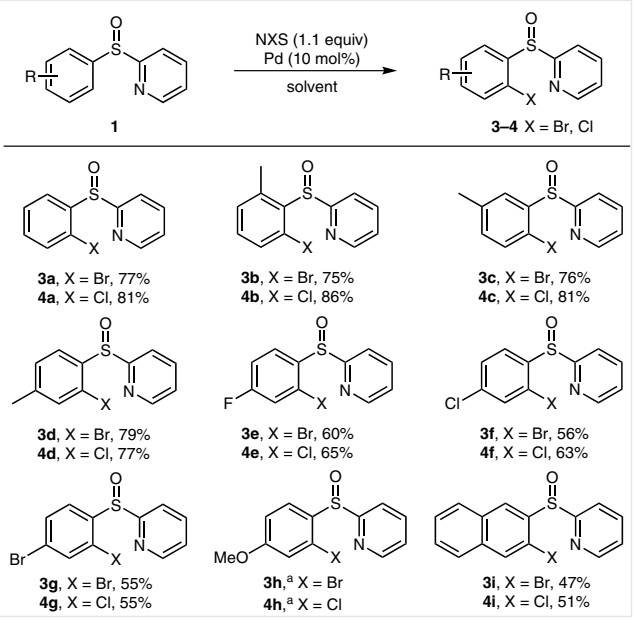
[a] All the reactions were carried out in the presence of 0.2 mmol of **1a**, 0.22 mmol of NBS, and 0.1 mmol of acid (if any) in 1.0 mL of solvents at 100 °C under air condition.
[b] Isolated yield.
[c] At 80 °C.
[d] At 60 °C.
[e] 0.5 mL of PhCl was used.
[f] 2.0 mL of PhCl was used.



Scheme 2 Scope of sulfoxide compounds in *ortho*-iodination reactions. All the reactions were carried out in the presence of 0.2 mmol of **1**, 0.22 mmol of NIS and 0.1 mmol of TFA in 1.0 mL PhCl at 80 °C under air conditions. Isolated yields are given. [a] The product could not be isolated in pure form.

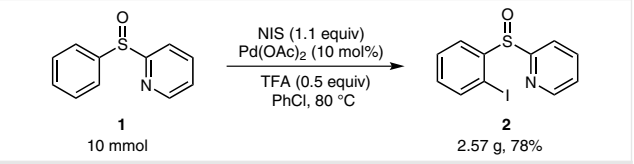
However, there is a notable exception when a methoxy group was included on the aromatic ring, and some unidentified compounds were observed in this process.

Further exploration of this strategy demonstrated that the coupling partner is not restricted to NIS, variation of different halides, such as NBS and NCS, was also found to be compatible with this protocol with a subtle change of reaction parameters (Scheme 3). Reactions of 2-pyridyl sulfoxides bearing electron-donating substituents (*ortho*-, *meta*-, and *para*-methyl) afforded the desired products in good yields, respectively. When the electron-deficient substrates were exposed to the reaction conditions, the corresponding 2-bromo- and 2-chloro-substituted sulfoxides were isolated in moderate yields, which are consistent with iodination procedure.



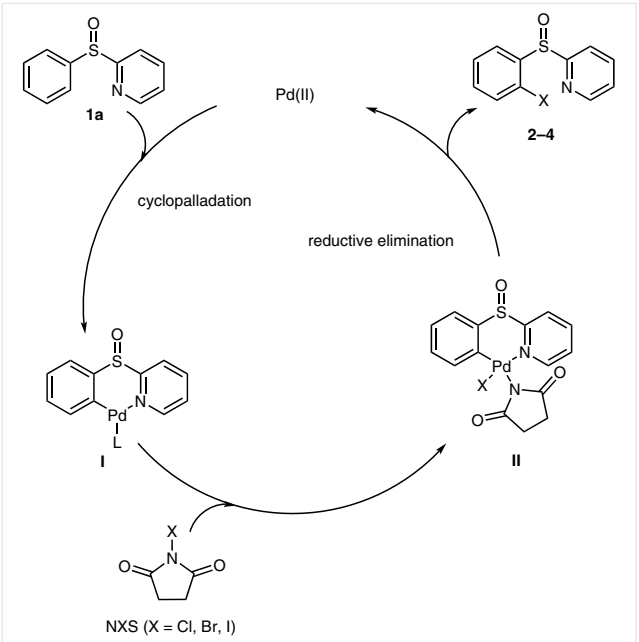
Scheme 3 Scope of sulfoxide compounds in *ortho*-bromination/chlorination reactions. Bromination reactions were carried out in the presence of 0.2 mmol of **1**, 0.22 mmol of NBS, and 10 mol% of $Pd(acac)_2$ in 1.0 mL PhCl at 80 °C under air conditions. Chlorination reactions were carried out in the presence of 0.2 mmol of **1**, 0.22 mmol of NCS, and 0.1 mmol of PivOH in 1.0 mL DCE at 100 °C under air conditions. Isolated yields are given. [a] The products could not be isolated in pure form.

Aiming to further expand the scope of the reaction, we examined this protocol on gram scale under the established conditions, which is usually a key restraining factor in the use of transition-metal-catalyzed C–H functionalization strategies in organic synthesis. 2-[(2-Iodophenyl)sulfinyl]pyridine was achieved in moderate yield (2.57 g, 78%) but good regioselectivity, which demonstrates the possibility to use this transformation in general organic synthesis (Scheme 4).



Scheme 4 Scale-up of the iodination reaction

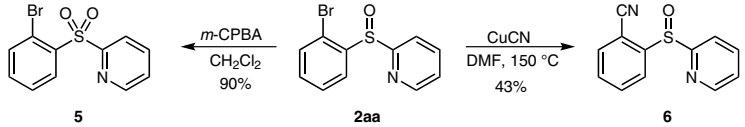
Although the exact mechanism of this reaction is not clear, a proposed pathway is depicted in Scheme 5.[16] Firstly, the Pd(II) catalyst reacted with 2-pyridyl sulfoxide to form a five-membered palladacycle intermediate **I** with the assistance of N atom, which is generally considered to be a better coordinating atom than O. Then, the palladacycle intermediate **I** was oxidized to Pd(IV) complex **II**[21] with NXS. Finally, reductive elimination from intermediate **II** generated the *ortho*-halogenated sulfoxides and released active Pd(II) to continue the catalytic cycle.



Scheme 5 Proposed reaction mechanism

To demonstrate the synthetic usefulness of this method, derivatization of **2aa** has been carried out (Scheme 6). The widely used *m*-CPBA can oxidize the sulfoxide to the corresponding sulfone in good yield. In addition, treatment of **2aa** with CuCN led to cyano-substituted sulfoxide and the desired product was isolated in 43% yield.[16b]

In summary, we have realized the palladium-catalyzed regioselective *ortho*-halogenation of 2-pyridyl sulfoxides with various NXS. This protocol proceeded smoothly in moderate to good yields, and the potential for gram-scale functionalization has been demonstrated. Moreover, the established efficient method can provide a useful strategy for the synthesis of S-containing compounds, overcoming the



Scheme 6 Representative transformations of the iodination sulfoxides

challenging issues mentioned above. Further investigation on the application of this chemistry and other functionalization of sulfoxides are ongoing in our laboratory.

Acknowledgment

We are grateful to China Postdoctoral Science Foundation (2016M590967), Shaanxi Provincial Science and Technology Development Funds (2016JQ2022), National Found for Fostering Talents of Basic Science (NFFTBS-J1103311, J1210057), and the National Natural Science Foundation of China (21402071) for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588756.

References and Notes

(1) (a) *Handbook of Grignard Reagents*; Silverman, G. S.; Rakita, P. E., Eds.; Dekker: New York, **1996**. (b) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 275.

(2) Crampton, M. R.; Knipe, A. J. *Organic Reaction Mechanism*; Wiley: New York, **2007**.

(3) (a) Diederich, F.; Stang, P. J. *Metal Catalyzed Cross Coupling Reactions*; Wiley-VCH: Weinheim, **1998**. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, **2004**. (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (f) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (g) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, *12*, 1253. (h) Yin, L. X.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (i) McGlacken, G. P.; Fairlamb, I. J. S. *Eur. J. Org. Chem.* **2009**, 4011.

(4) (a) De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, **1976**, Chap. 5. (b) Merkushev, E. B. *Synthesis* **1988**, 923. (c) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley: New York, **1990**.

(5) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(6) (a) Evans, P. A.; Brandt, T. A. *J. Org. Chem.* **1997**, *62*, 5321. (b) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083. (c) Tamhankar, B. V.; Desai, U. V.; Mane, R. B.; Wadgaonkar, P. P.; Bedekar, A. V. *Synth. Commun.* **2001**, *31*, 2021. (d) Lee, K.; Cho, H. K.; Song, C. *Bull. Korean Chem. Soc.* **2002**, *23*, 773. (e) Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 4085. (f) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003**, *32*, 932. (g) Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* **2003**, *44*, 8781. (h) Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501. (i) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770. (j) Iskra, J.; Stavber, S.; Zupan, M. *Synthesis* **2004**, 1869. (k) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, 461. (l) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 2837.

(7) For selected reviews, see: (a) *Activation and Functionalization of C-H Bond, ACS Symposium Series 885*; Goldberg, K. I.; Goldman, A. S., Eds.; American Chemical Society: Washington DC, **2004**. (b) Dyker, G. *Handbook of C-H Transformations: Applications in Organic Synthesis*; Wiley-VCH: Weinheim, **2005**. (c) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (d) Yu, J.-Q.; Shi, Z.-J. *C-H Activation* 2010.

(8) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (c) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (d) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (e) Whitfield, S. R.; Sanford, M. S. *Organometallics* **2008**, *27*, 1683.

(9) (a) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112. (c) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452. (d) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 5215. (e) Bedford, R. B.; Engelhart, J. U.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Dalton Trans.* **2010**, *39*, 10464. (f) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 5524. (g) Song, B.; Zheng, X.; Mo, J.; Xu, B. *Adv. Synth. Catal.* **2010**, *352*, 329.

(10) For selected reviews, see: (a) Fedorak, P. M. *Microbial Metabolism of Organosulfur Compounds in Petroleum, ACS Symposium Series 429*; Orr, W. L.; White, C. M., Eds.; American Chemical Society: Washington DC, **1990**, 93. (b) Moriarty, R. M.; Naithani, R.; Surve, B. *Mini-Rev. Med. Chem.* **2007**, *7*, 827. (c) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. (d) Hiroi, K.; Sone, T. *Curr. Org. Synth.* **2008**, *5*, 305. (e) Kielbasinski, P. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186*, 1104.

(11) (a) *Comprehensive Organic Functional Groups Transformations*; Vol. 4; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W.; Kirby, C. W., Eds.; Pergamon Press: Cambridge, **1994**, 958–960. (b) Andersen, K. K. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S.; Rappaport, Z.; Stirling, C. J. M., Eds.; John Wiley and Sons: New York, **1998**, 56–94. (c) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T.; Bolm, C., Eds.; Wiley-VCH: Weinheim, **2008**.

(12) Melkonyan, F. S.; Zhao, W.; Drees, M.; Eastham, N. D.; Leonardi, M. J.; Butler, M. R.; Chen, Z.; Yu, X.; Chang, R. P. H.; Ratner, M. A.; Facchetti, A. F.; Marks, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 6944.

(13) S-Containing compounds in directed C–H activations: (a) Garcia-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511. (b) Xu, R.; Wan, J.-P.; Mao, H.; Pan, Y. *J. Am. Chem. Soc.* **2010**, *132*, 15531. (c) Garcia-Rubia, A.; Urones, B.; Arrayas, R. G.; Carretero, J. C. *Chem. Eur. J.* **2010**, *16*, 9676. (d) Tsui, G. C.; Lautens, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8938. (e) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330.

(14) Sulfoxide in directed C–H activations: (a) Twao, M.; Iihama, T.; Mahalanabis, K. K.; Perrier, H.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 24. (b) Quesnelle, C.; Iihama, T.; Aubert, T.; Terrier, H.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2625. (c) Richter, H.; Beckendorf, S.; Mancheno, G. *Adv. Synth. Catal.* **2011**, *353*, 295. (d) Romero-Revilla, J. A.; Garcia-Rubia, A.; Arrayas, R. G.; Fernandez-Ibanez, M. A.; Carretero, J. C. *J. Org. Chem.* **2011**, *76*, 9525. (e) Yu, M.; Liang, Z.; Wang, Y.; Zhang, Y. *J. Org. Chem.* **2011**, *76*, 4987. (f) Garcia-Rubia, A.; Fernandez-Ibanez, M. A.; Arrayas, R. G.; Carretero, J. C. *Chem. Eur. J.* **2011**, *17*, 3567. (g) Zhang, X.; Yu, M.; Yao, J.; Zhang, Y. *Synlett* **2012**, *23*, 463.

(15) (a) *Catalyst Poisoning*; Hegedus, L. L.; McCabe, R. W., Eds.; Marcel Dekker: New York, **1984**, For the suppression of metal-catalyst deactivation with sulfur species by addition of P ligands, see for example:. (b) Beletskaya, I. P.; Ananikov, V. P.

Eur. J. Org. Chem. **2007**, 3431. (c) Ananikov, V. P.; Gayduk, K. A.; Orlov, N. V.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y. *Chem. Eur. J.* **2010**, *16*, 2063.

(16) (a) Sun, M.; Chen, X.; Zhang, L.; Sun, W.; Wang, Z.; Guo, P.; Li, Y.-M.; Yang, X.-J. *Org. Biomol. Chem.* **2016**, *14*, 323. (b) Sun, M.; Wang, Z.; Wang, J.; Guo, P.; Chen, X.; Li, Y.-M. *Org. Biomol. Chem.* **2016**, *14*, 10585.

(17) Phenyl sulfoxide did not afford the corresponding product.

(18) For a review, see: Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.

(19) Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504.

(20) **General Procedure for the *ortho*-Iodination of 2-Pyridyl Sulfoxides with NIS**

A mixture of 2-pyridyl sulfoxides (40.6 mg, 0.2 mmol, 1.0 equiv), NIS (49.5 mg, 0.22 mmol, 1.1 equiv), TFA (11.4 mg, 0.1 mmol, 0.5 equiv), and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %) in PhCl (1 mL) was stirred under air at 80 °C for 20 h. The reaction mixture was cooled to r.t., then the volatiles were removed under reduced pressure. The contents were subjected to flash chromatography to give the corresponding product (60.0 mg, 85%) as pale yellow solid. The purified material was dried under an oil-pump vacuum.

2-[(2-Iodophenyl)sulfinyl]pyridine (2a)

Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (dd, *J* = 0.8, 4.0 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.87 (dd, *J* = 2.0, 8.0 Hz, 1 H), 7.85–7.83 (m, 1 H), 7.80 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.52 (dt, *J* = 1.2, 8.0 Hz, 1 H), 7.36–7.33 (m, 1 H), 7.17 (dt, *J* = 1.6, 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.81, 150.09, 147.09, 139.59, 137.95, 132.67, 129.21, 127.34, 125.14, 120.49, 94.66. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{11}H_8INOSNa^+$: 351.9296; found: 351.9272.

(21) For a review on organopalladium(IV) chemistry, see: Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712.