Organic LETTERS

Letter

pubs.acs.org/OrgLett

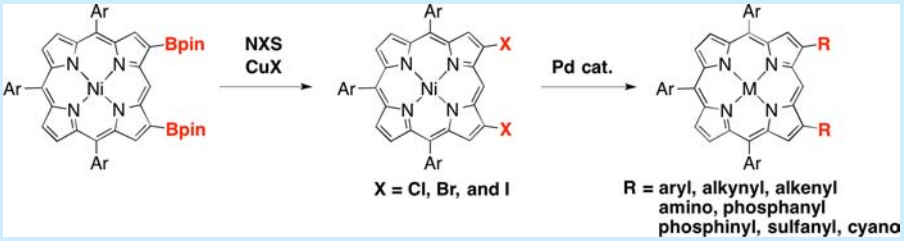
Facile Preparation of β-Haloporphyrins as Useful Precursors of β-Substituted Porphyrins

Keisuke Fujimoto,[†] Hideki Yorimitsu,*[,†,‡] and Atsuhiro Osuka*[,†]

[†]Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan

[‡]ACT-C, Japan Science and Technology Agency, Japan

Supporting Information



ABSTRACT: β-Haloporphyrins were efficiently prepared by halogenation of β-borylporphyrins with *N*-halosuccinimide and copper(I) halide. β-Haloporphyrins are useful precursors to synthesize a wide variety of β-substituted porphyrins through Pd-catalyzed cross-coupling reactions.

Aryl halides are key intermediates in organic synthesis since they undergo a variety of organic reactions, such as cross-coupling reactions, precisely at the halogenated position. It is hence important to introduce a halogen atom into arene with desired regioselectivity. Recently, Cu-mediated or -catalyzed *ipso*-halogenation of arylboronic acids or -boronates emerged as a useful method for regioselective preparation of aryl halides.[1] Notably, Hartwig et al. achieved halogenation of simple arenes at the least sterically hindered position in two steps through Ir-catalyzed regioselective borylation followed by Cu-mediated halogenation.[2] This two-step route is attractive because it offers regioselectivity that is different from the classical electrophilic aromatic substitution (S_EAr) (Figure 1, top).[3]

Porphyrins are an important class of arene, finding a wide range of applications due to their interesting photophysical and electrochemical properties.[4] The S_EAr halogenation of porphyrins usually occurs selectively at their electron-rich *meso* positions (Figure 1, bottom, left).[5] Accordingly, trans-

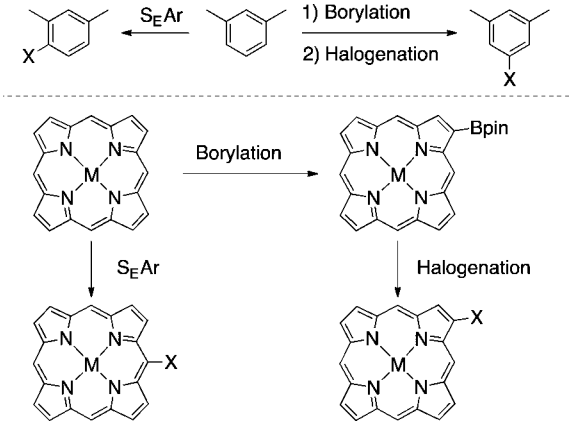
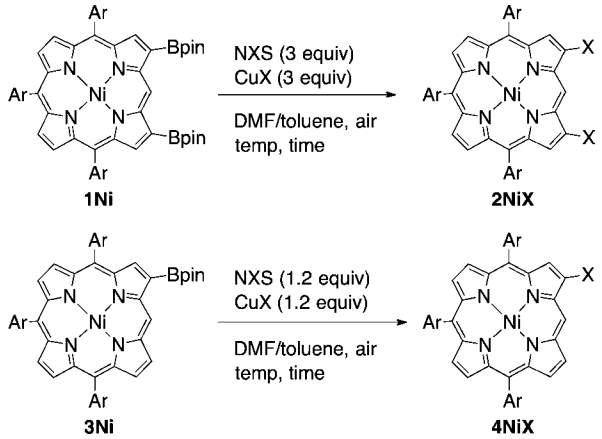


Figure 1. Regioselective halogenation of arenes.

Table 1. Halogenation of 1Ni and 3Ni

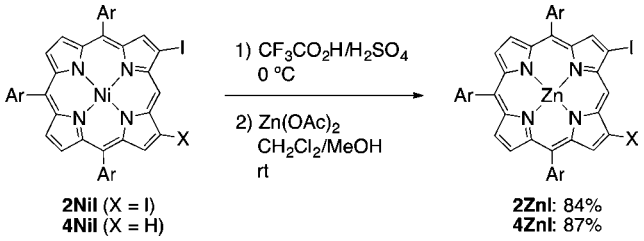


entry	substrate	NXS	CuX	temp (°C)	time (h)	yield (%)
1	**1Ni**	NIS	CuI	80	3	90
2	**1Ni**	NBS	CuBr[a]	110	6	89
3	**1Ni**	NCS	CuCl	110	6	90
4	**3Ni**	NIS	CuI	80	3	90
5	**3Ni**	NBS	CuBr[b]	110	6	72
6	**3Ni**	NCS	CuCl	110	6	78

[a]6 equiv. [b]2.4 equiv.

Received: December 20, 2013
Published: January 28, 2014

Scheme 1. Denickelation and Zincation of 2NiI and 4NiI



2NiI (X = I)
4NiI (X = H)

2ZnI: 84%
4ZnI: 87%

formations of *meso*-haloporphyrins have been extensively investigated and widely applied to the synthesis of *meso*-functionalized porphyrins and multiporphyrinic arrays connected at the *meso* positions.[6] Therefore, it is reasonably expected that β-haloporphyrins are also useful building blocks. However, there are no general and selective approaches to β-haloporphyrins from *meso*-unsubstituted porphyrins.[7]

We have reported facile preparation of β-borylporphyrins by Ir-catalyzed regioselective borylation of *meso*-unsubstituted porphyrins as a unique method for selective functionalization at β-positions over *meso* positions.[8a] Although β-borylporphyrins experienced useful transformations such as Suzuki−Miyaura cross-coupling,[8b] catalytic addition to unsaturated bonds,[8c] and oxidative hydroxylation,[8d] the variety of β-functionalization still remains unexplored. In this paper, we report an efficient route to β-haloporphyrins by Cu-mediated halogenation of β-borylporphyrins (Figure 1, bottom, right) and demonstrate the utility of β-haloporphyrins as new building blocks that complement β-borylporphyrins.

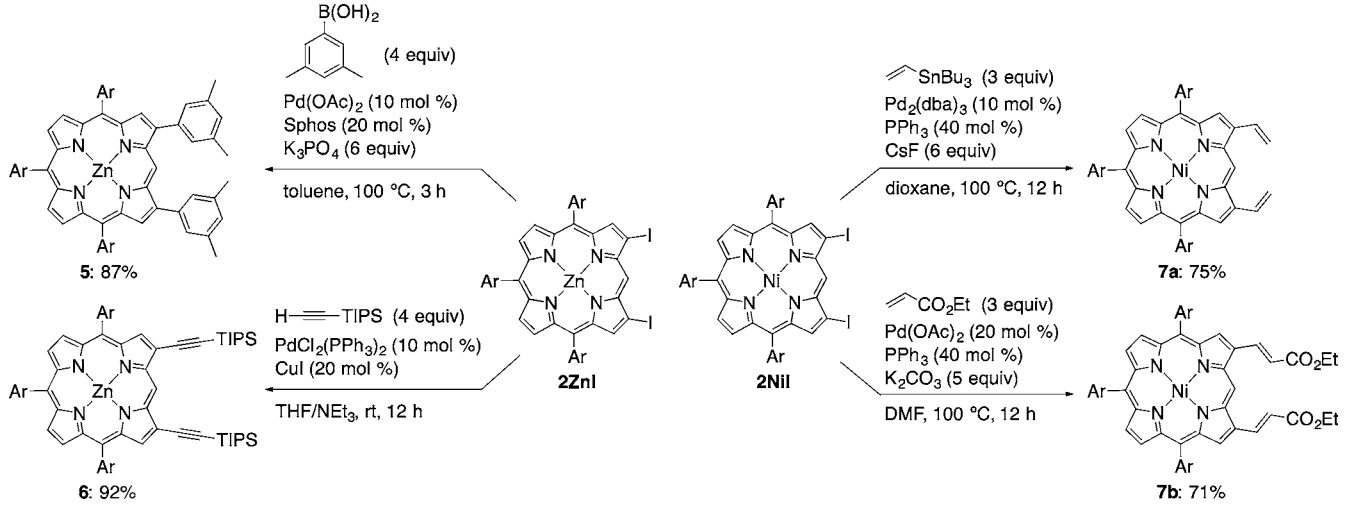
We envisioned that Hynes' halogenation with the aid of *N*-halosuccinimide (NXS) and copper(I) halide (CuX) in acetonitrile in air[1b] would be applicable to β-borylporphyrins. However, β-diborylporphyrin **1Ni** is insoluble in highly polar acetonitrile and did not participate in the halogenation. After extensive screening of reaction conditions, we found that iodination of **1Ni** proceeded efficiently in a 2:1 mixture of *N*,*N*-dimethylformamide (DMF) and toluene to afford β-diiodoporphyrin **2NiI** in 90% yield (Table 1, entry 1, Ar = 3,5-tBu$_2$C$_6$H$_3$ throughout the manuscript). Dibromination and dichlorination also took place under similar conditions at a higher temperature to afford dibromoporphyrin **2NiBr** and dichloroporphyrin **2NiCl** in 89% and 90% yields, respectively (entries 2 and 3). With smaller amounts of NXS and CuX, β-monoborylporphyrin **3Ni** was converted to a series of β-monohaloporphyrins **4NiX** without any significant side reactions although **3Ni** and **4NiX** contain potentially reactive porphyrinic carbons[5d] (entries 4−6).

Attempted halogenation of zinc and freebase porphyrins resulted in moderate to low yields due to undesired metalation of the inner cavity with copper. Instead, denickelation of **2NiI** and **4NiI** with concentrated sulfuric acid in trifluoroacetic acid was successful, leaving the halogen moieties intact (Scheme 1). The denickelation occurred cleanly at 0 °C, and subsequent zincation afforded **2ZnI**[9] and **4ZnI** in 84% and 87% yields, respectively. These results clearly exemplify that a variety of β-haloporphyrin metal complexes should become accessible.

With β-haloporphyrins in hand, we next explored their potentials as synthetic intermediates. We first performed Pd-catalyzed cross-coupling reactions to form carbon−carbon bonds (Scheme 2). The Suzuki−Miyaura coupling reaction of **2ZnI** with arylboronic acid took place smoothly under Pd/Sphos catalysis[10] to afford arylated product **5** in 87% yield. The Sonogashira reaction of **2ZnI** with triisopropylsilylacetylene furnished alkynylated product **6** in 92% yield. Two different approaches have become available for alkenylation of **2NiI**.[11] The Migita−Kosugi−Stille reaction of **2NiI** with tributylvinyltin in the presence of CsF afforded vinylated product **7a** in 75% yield. Alternatively, the Mizoroki−Heck reaction of **2NiI** with ethyl acrylate gave alkenylated product **7b** in 71% yield.[6c]

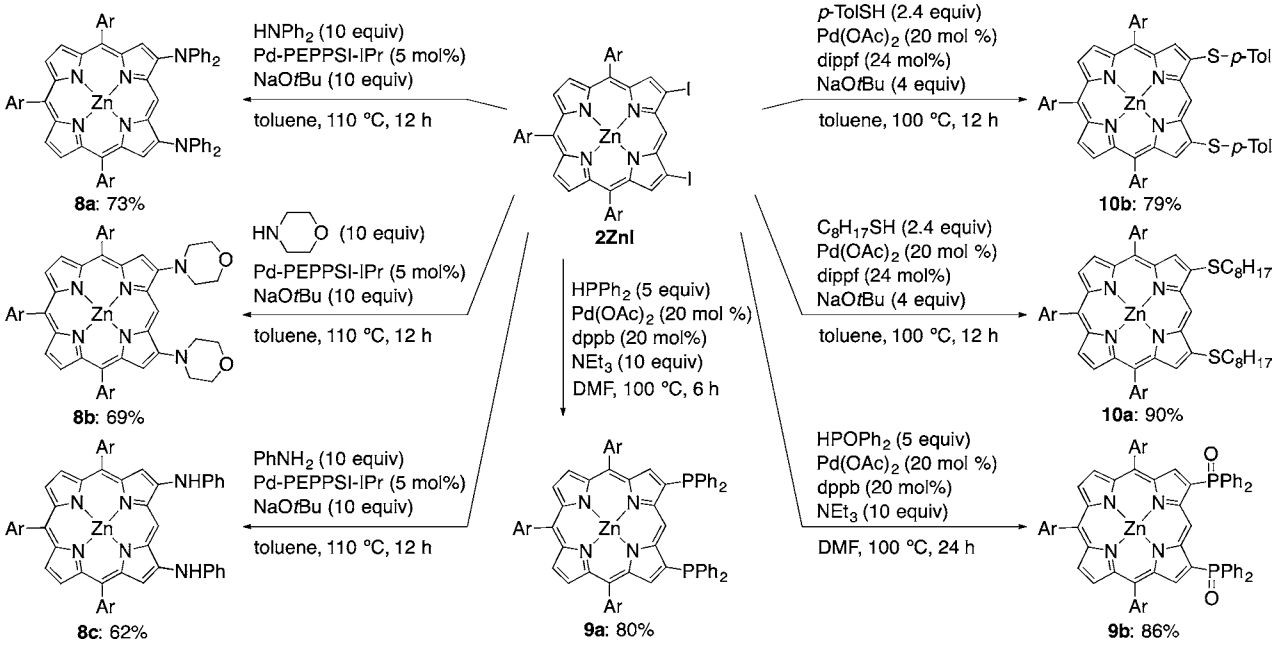
Promoted by the successful carbon−carbon bond formation, we next investigated Pd-catalyzed carbon−heteroatom bond formation (Scheme 3). Buchwald−Hartwig amination of **2ZnI** with diphenylamine, morphorine, and aniline proceeded with the aid of the Pd-PEPPSI-IPr catalyst[12] and NaOtBu,[13] providing **8a**,[9] **8b**, and **8c**, respectively, in good yields. Phosphanylation with diphenylphosphine and phosphinylation with diphenylphosphine oxide also took place smoothly under the conditions that we applied to porphyrinyl triflate.[14] Highly efficient carbon−sulfur bond formation was accomplished by means of 1,1′-bis(diisopropylphosphino)ferrocene, dippf, as a rigid bidentate phosphine ligand that inhibits catalyst poisoning,[15] affording β-disulfanylporphyrins **10a** and **10b** in 90% and 79% yields, respectively.

Scheme 2. Pd-Catalyzed Carbon−Carbon Bond Formation Reactions of 2ZnI and 2NiI

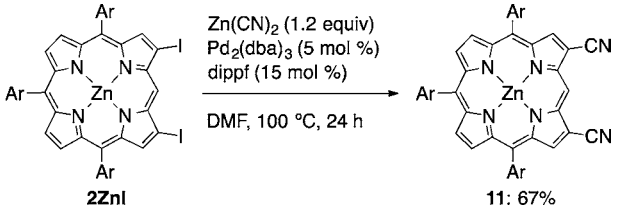


dx.doi.org/10.1021/ol4037049 | *Org. Lett.* 2014, 16, 972−975

Scheme 3. Pd-Catalyzed Carbon–Heteroatom Bond Formation Reactions of 2ZnI



Scheme 4. Pd-Catalyzed Cyanation of 2ZnI



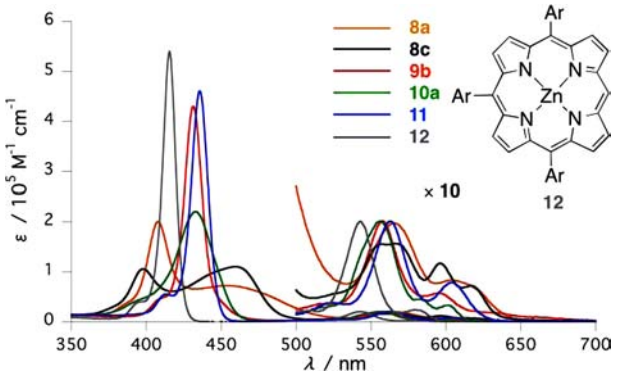


Figure 2. UV/vis absorption spectra of **8a**, **8c**, **9b**, **10a**, **11**, and **12** in CH_2Cl_2.

We finally attempted cyanation of **2ZnI** (Scheme 4).[16] Pd-catalyzed cyanation of aryl halides is known to be deteriorated due to facile formation of inactive anionic cyanopalladates.[17] To overcome this difficulty, the Pd-catalyzed cyanation of **2ZnI** was achieved with $Zn(CN)_2$ as a slow cyanide supplier and dippf as a phosphine ligand to obtain *β*-dicyanoporphyrin **11**[9] in 67% yield.

Figure 2 shows the UV/vis absorption spectra of a series of *β*-disubstituted porphyrins. Diphosphinylporphyrin **9b**, disulfanylporphyrin **10a**, and dicyanoporphyrin **11** display red-shifted Soret and Q bands by ca. 20 nm compared to the corresponding *β*-unsubstituted porphyrin **12** due to electronic perturbations by the *β*-substituents. Aminoporphyrins **8a** and **8c** exhibit a broad and split Soret-like band around 450 nm that is similar to those of known *β*-arylamino-substituted porphyrins.[18] The larger substituent effect in **8c**, compared to **8a**, implies the sterically less hindered nature of the anilino group to cause more effective interaction between the porphyrin chromophore and the amino groups.

In summary, we have established an efficient method to synthesize *β*-haloporphyrins through Cu-mediated halogenation of the corresponding *β*-borylporphyrins. The resulting *β*-haloporphyrins are useful precursors of a series of *β*-substituted porphyrins through Pd-catalyzed reactions. Further applications of *β*-haloporphyrins to the construction of novel *π*-conjugate systems and multiporphyrinic arrays are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, complete characterizations (NMR, HRMS, UV/vis, fluorescence), and X-ray crystallographic data for **2ZnI**, **8a**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yori@kuchem.kyoto-u.ac.jp.
*E-mail: osuka@kuchem.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid from MEXT (Nos.: 24106721 “Reaction Integration” and 25107002 “Science of Atomic Layers”) and from JSPS (Nos.: 25220802 (Scientific Research (S)), 24685007 (Young Scientists (A)), 23655037 (Exploratory Research)).

REFERENCES

(1) (a) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 547. (b) Wu, H.; Hynes, J., Jr. *Org. Lett.* **2010**, *12*, 1192. (c) Zhang, G.; Lv, G.; Li, L.; Chen, F.; Cheng, J. *Tetrahedron Lett.* **2011**, *52*, 1993. (d) Yang, H.; Jiang, L. M.; Wang, J.; Fu, H. *Chem.—Eur. J.* **2011**, *17*, 5652. (e) Niu, L.; Yang, H.; Yang, D.; Fu, H. *Adv. Synth. Catal.* **2012**, *354*, 2211. (f) Ren, Y.-L.; Tian, X.-Z.; Dong, C.; Zhao, S.; Wang, J.; Yan, M.; Qi, X.; Liu, G. *Catal. Commun.* **2013**, *32*, 15.

(2) (a) Merphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434. (b) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864. (c) Partridge, B. M.; Hartwig, J. F. *Org. Lett.* **2013**, *15*, 140. (d) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552.

(3) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.

(4) (a) *Handbook of Porphyrin Science*, Vols. *1*–*10*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific Publishing: Singapore, 2010. (b) *Handbook of Porphyrin Science*, Vols. *11*–*15*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific Publishing: Singapore, 2011. (c) *Handbook of Porphyrin Science*, Vols. *16*–*25*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific Publishing: Singapore, 2012.

(5) (a) Odobel, F.; Suzenet, F.; Blart, E.; Quintard, J.-P. *Org. Lett.* **2000**, *2*, 131. (b) Senge, R. O.; Richter, J. *J. Porphyrins Phthalocyanines* **2004**, *8*, 934. (c) Jin, L.-M.; Chen, L.; Yin, J.-J.; Zhou, J.-M.; Guo, C.-C.; Chen, Q.-Y. *J. Org. Chem.* **2006**, *71*, 527. (d) Chumakov, D. E.; Khoroshutin, A. V.; Anisimov, A. V.; Kobrakov, K. L. *Chem. Heterocycl. Compd.* **2009**, *45*, 259.

(6) (a) Aratani, N.; Osuka, A. *Org. Lett.* **2001**, *3*, 4213. (b) Chen, Y.; Zhang, P. *J. Org. Chem.* **2003**, *68*, 4432. (c) Locos, O. B.; Arnord, D. P. *Org. Biomol. Chem.* **2006**, *4*, 902. (d) Esdaile, L. J.; Senge, M. O.; Arnold, D. P. *Chem. Commun.* **2006**, 4192. (e) Sahoo, A. K.; Mori, S.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7972. (f) Matano, Y.; Matsumoto, K.; Terasaka, Y.; Hotta, H.; Araki, Y.; Ito, O.; Shiro, M.; Sasamori, T.; Tokitoh, N.; Imahori, H. *Chem.—Eur. J.* **2007**, *13*, 891. (g) Matano, Y.; Shinokura, T.; Matsumoto, K.; Imahori, H.; Nakano, H. *Chem.—Asian J.* **2007**, *2*, 1417. (h) Liu, C.; Shen, D.-M.; Chen, Q.-Y. *J. Org. Chem.* **2007**, *72*, 2732. (i) Atefi, F.; Arnold, D. P. *J. Porphyrins Phthalocyanines* **2008**, *12*, 801. (j) Nakamura, Y.; Jang, S. Y.; Tanaka, T.; Aratani, N.; Lim, J. M.; Kim, K. S.; Kim, D.; Osuka, A. *Chem.—Eur. J.* **2008**, *14*, 8279. (k) Maretina, I. A. *Russ. J. Gen. Chem.* **2009**, *79*, 1544. (l) Tokuji, S.; Yurino, T.; Aratani, N.; Shinokubo, H.; Osuka, A. *Chem.—Eur. J.* **2009**, *15*, 12208. (m) Beletskaya, I. P. Tyurin, V. S.; Uglov, A.; Stern, C.; Guilard, R. In *Handbook of Porphyrin Science*, Vol. *23*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; World Scientific Publishing: Singapore, 2012; Chapter 108.

(7) Selected examples of *β*-halogenation of fully *meso*-substituted porphyrins: (a) Zhang, C.; Suslick, K. S. *J. Porphyrins Phthalocyanines* **2005**, *9*, 659. (b) Cunha, A. C.; Gomes, A. T. P. C.; Ferreira, V. F.; de Souza, M. C. B. V.; Neves, M. G. P. M. S.; Tome, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *Synthesis* **2012**, 510. (c) Bhyrappa, P.; Velkannan, V.; Karunanithi, K.; Varghese, B.; Harikrishna. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 995. Also see ref 5d.

(8) (a) Hata, H.; Shinokubo, H.; Osuka, A. *J. Am. Chem. Soc.* **2005**, *127*, 8264. (b) Yamaguchi, S.; Katoh, T.; Shinokubo, H.; Osuka, A. *J. Am. Chem. Soc.* **2007**, *129*, 6392. (c) Baba, H.; Chen, J. P.; Shinokubo, H.; Osuka, A. *Chem.—Eur. J.* **2008**, *14*, 4256. (d) Hisaki, I.; Hiroto, S.; Kim, K. S.; Noh, S. B.; Kim, D.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5125.

(9) The structures of **2ZnI**, **8a**, and **11** were confirmed by X-ray crystallographic analysis (Figures S63–65 in the Supporting Information).

(10) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(11) Diiodoporphyrins **2NiI** and **2ZnI** generally exhibited similar reactivities in the palladium-catalyzed reactions shown in this paper.

(12) Pd-PEPPSI-IPr denotes (1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene)(3-chloropyridine)palladium(II) dichloride. Valente, C.; Calimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314. PEPPSI is an abbreviation of Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation.

(13) Suzuki, Y.; Fukui, N.; Murakami, K.; Yorimitsu, H.; Osuka, A. *Asian J. Org. Chem.* **2013**, *2*, 1066.

(14) (a) Gilbertson, S. R.; Starker, G. W. *J. Org. Chem.* **1996**, *61*, 2922. (b) Fujimoto, K.; Yoneda, T.; Yorimitsu, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 1127.

(15) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397.

(16) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193.

(17) (a) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem.—Eur. J.* **2006**, *12*, 7782. (b) Erhardt, S.; Grushin, V. V.; Kilpatrick, A. H.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2008**, *130*, 4828.

(18) (a) Gao, G.-Y.; Ruppel, J. V.; Allen, D. B.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2007**, *72*, 9060. (b) Pereira, A. M. V. M; Alonso, C. M. A.; Neves, M. G. P. M. S.; Tomé, A. C.; Cavaleiro, J. A. S. *J. Org. Chem.* **2008**, *73*, 7353. (c) Tsurumaki, E.; Osuka, A. *Chem.—Asian J.* **2013**, *8*, 3042.