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Versatile Synthesis of *meso*-Aryloxy- and Alkoxy-Substituted Porphyrins via Palladium-Catalyzed C–O Cross-Coupling Reactions

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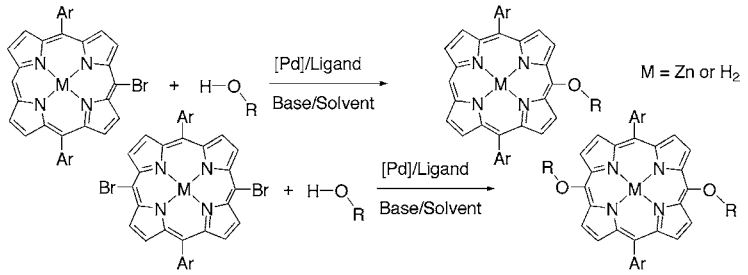
ABSTRACT



***meso*-Aryloxy- and alkoxy-substituted porphyrins were conveniently synthesized by direct reactions of *meso*-halogenated porphyrins with alcohols via palladium-catalyzed C–O cross-coupling reactions. Using a combination of palladium precursor $Pd(OAc)_2$ or $Pd_2(dba)_3$ and phosphine ligand DPEphos or Xantphos allowed both 5-bromo-10,20-diarylporphyrin and 5,15-dibromo-10,20-diarylporphyrin, as well as their zinc complexes, to be effectively coupled with a variety of alcohols to give the corresponding mono- and bis-substituted *meso*-aryloxy/alkoxyporphyrins in moderate to high yields under mild conditions.**

Biologically relevant porphyrins and metalloporphyrins have found a wide range of applications in various fields, including catalysis, materials, and medicine.[1] It has been well documented that the physical, chemical, and biological properties of porphyrins and metalloporphyrins can be fine-tuned or dramatically altered by the use of peripheral substituents having different electronic and steric properties. Significant examples include sterically bulky porphyrins with carbon-based alkyl and aryl groups and electron-deficient porphyrins containing halogen atoms.[2] Additionally, porphyrins and metalloporphyrins that possess directly attached aryloxy and alkoxy groups have been shown to have interesting and different properties.[3−5] However, in marked contrast to the large numbers of synthetic porphyrins with carbon-based peripheral substituents, only a limited number of aryloxy- and alkoxy-substituted porphyrins have been reported.[3−5] In addition to methods based on alkoxypyrroles for β-alkoxyporphyrin synthesis,[4] aryloxy- and alkoxyl-substituted porphyrins have been mainly synthesized through nucleophilic substitution.[5] Considering the multiple steps associated with the synthesis of alkoxypyrroles[4] and the requirement of the

(1) Kadish, K. M.; Smith, K. M.; Guilard, R., Eds. *The Porphyrin Handbook*; Academic Press: San Diego, 2000.

(2) (a) Senge, M. O. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 1, p 239. (b) Jaquinod, L. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, CA, 2000; Vol. 1, p 201.

(3) (a) Kalish, H.; Camp, J. E.; Stepien, M.; Latos-Grazynski, L.; Olmstead, M. M.; Balch, A. L. *Inorg. Chem.* **2002**, *41*, 989. (b) Wojaczynski, J.; Stepien, M.; Latos-Grazynski, L. *Eur. J. Inorg. Chem.* **2002**, 1806. (c) Kalish, H.; Camp, J. E.; Stepien, M.; Latos-Grazynski, L.; Balch, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 11719. (d) Sibilia, S. A.; Czernuszewicz, R. S.; Crossley, M. J.; Spiro, T. G. *Inorg. Chem.* **1997**, *36*, 6450. (e) Wojaczynski, J.; Latos-Grazynski, L.; Hrycyk, W.; Pacholska, E.; Rachlewicz, K.; Szterenberg, L. *Inorg. Chem.* **1996**, *35*, 6861. (f) Binstead, R. A.; Crossley, M. J.; Hush, N. S. *Inorg. Chem.* **1991**, *30*, 1259. (g) Giraudeau, A.; Callot, H. J.; Gross, M. *Inorg. Chem.* **1979**, *18*, 201.

(4) (a) Murashima, T.; Uchihara, Y.; Wakamori, N.; Uno, H.; Ogawa, T.; Ono, N. *Tetrahedron Lett.* **1996**, *37*, 3133. (b) Merz, A.; Schropp, R.; Dotterl, E. *Synthesis* **1995**, 795. (c) Merz, A.; Schropp, R.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 291.

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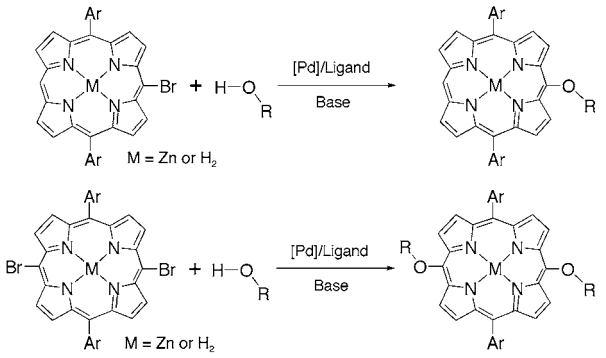
Scheme 1. Palladium-Catalyzed Etherification Reactions of *meso*-Monobromo- and *meso*-Dibromoporphyrins



presence of electron-withdrawing groups in the nucleophilic substitution reactions,[5] it is desirable to develop alternative methods for the synthesis of aryloxy- and alkoxyl-substituted porphyrins, which allows further study of this class of porphyrins.

The palladium-catalyzed reactions of aryl halides with soft, nonorganometallic nucleophiles have been emerging as powerful tools for the formation of carbon−heteroatom bonds, especially C−N and C−O bonds.[6] Applying palladium-catalyzed amination to halogenated porphyrin precursors,[7] we[8] and others[9] have recently developed general and efficient methods for the synthesis of arylamino- and alkylamino-substituted porphyrins. Extending the synthetic strategy with palladium-catalyzed etherification,[6] we report herein a convenient new approach for the versatile synthesis of *meso*-aryloxy- and alkoxyl-substituted porphyrins from corresponding bromoporphyrin precursors (Scheme 1). The

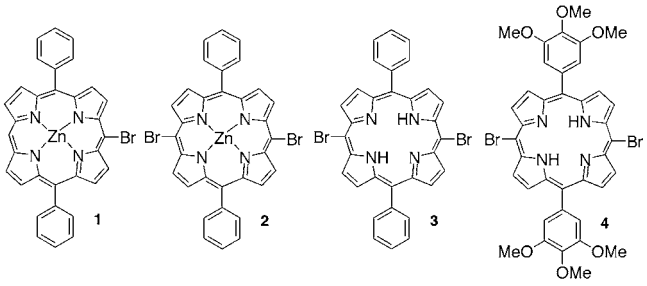


Figure 1. Structures of *meso*-bromoporphyrins.

synthesis can be performed under mild conditions with a wide range of alcohols, leading to a family of novel porphyrins with oxo functionalities directly attached at the *meso*-positions in moderate to high yields.

meso-Bromoporphyrins **1**−**4** (Figure 1), which were straightforwardly prepared in gram scale via selective bromination of 5,15-diaryporphyrins,[7,8] were adopted as representative halogenated porphyrin precursors for palladium-catalyzed etheration reactions. At an early stage of the investigation, a variety of different catalytic conditions were screened for the reaction of monobromoporphyrin zinc complex **1** with phenol. Although Buchwald's biphenyl-based electron-rich bulky monophosphine ligands enjoy the broadest reported substrate scope of palladium-catalyzed etheration,[10,11] the use of these ligands for the C−O coupling reactions of bromoporphyrins resulted in low yields of the desired products. Our results, however, indicated that simple bidentate phosphine ligands such as DPEphos and Xantphos (Figure 2) worked best for the transformation (Scheme 1).

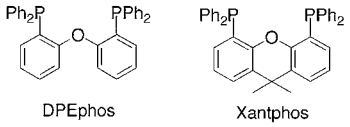


Figure 2. Structures of bidentate phosphine ligands.

Although somewhat surprising,[12,13] this was in line with our recent results on aminoporphyrin synthesis via palladium-catalyzed amination.[8] Both $Pd_2(dba)_3$ and $Pd(OAc)_2$ were

(5) (a) Crossley, M. J.; King, L. G.; Simpson, J. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3087. (b) Crossley, M. L.; King, L. G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1251. (d) Hombrecher, H. K.; Gherdan, V. M.; Ohm, S. *Tetrahedron* **1993**, *49*, 8569. (d) Crossley, M. J.; King, L. G.; Pyke, S. M. *Tetrahedron* **1987**, *43*, 4569. (e) Gong, L.-C.; Dolphin, D. *Can. J. Chem.* **1985**, *63*, 406. (f) Catalano, M. M.; Crossley, M. J.; King, L. G. *J. Chem. Soc., Chem. Commun.* **1984**, 1537. (g) Arnold, D. P.; Johnson, A. W.; Mahendran, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 366. (h) Evans, B.; Smith, K. M. *Tetrahedron* **1977**, *33*, 629. (i) Barnett, G. H.; Evans, B.; Smith, K. M. *Tetrahedron* **1975**, *31*, 2711.

(6) (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (c) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (e) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (f) Hartwig, J. F. *Synlett* **1997**, 329. (g) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(7) For selective examples that applied Suzuki and Stille cross-coupling reactions for porphyrin synthesis, see: (a) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 2513. (b) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Org. Chem.* **1993**, *58*, 5983. (c) Hyslop, A. G.; Kellett, M. A.; Iovine, P. M.; Therien, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 12676. (d) Liu, C.-J.; Yu, W.-Y.; Peng, S.-M.; Mak, T. C. W.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1998**, 1805. (e) Shi, X.; Amin, R.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 1650. (f) Shanmugathasan, S.; Johnson, C. K.; Edwards, C.; Matthews, E. K.; Dolphin, D.; Boyle, R. W. *J. Porphyrins Phthalocyanines* **2000**, *4*, 228. (g) Iovine, P. M.; Kellett, M. A.; Redmore, N. P.; Therien, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 8717. (h) Deng, Y.; Chang, C. K.; Nocera, D. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1066. (i) Chng, L. L.; Chang, C. J.; Nocera, D. G. *J. Org. Chem.* **2003**, *68*, 4075.

(8) (a) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432. (b) Gao, G.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 6215.

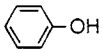
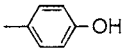
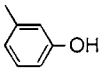
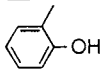
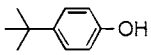
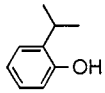
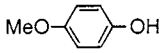
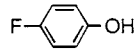
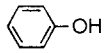
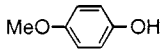
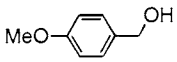
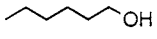
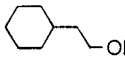
(9) Khan, M. M.; Ali, H.; van Lier, J. E. *Tetrahedron Lett.* **2001**, *42*, 1615. Note that no yields were reported in this paper.

(10) (a) Torraca, K. E.; Huang, X.-H.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(11) For a ferrocene-based electron-rich bulky monophosphine system that showed good substrate scope of palladium-catalyzed etherification, see (a) Shelby, Q.; Kataoka, N.; Mann, G.; Hatwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224.

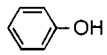
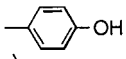
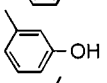
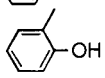
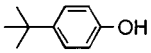
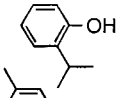
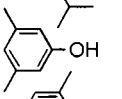
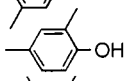
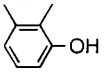
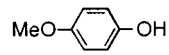
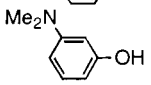
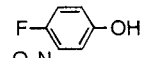
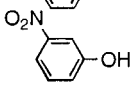
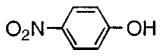
(12) To the best of our knowledge, the simple bidentate DPEphos and Xantphos have not be demonstrated to effect palladium-catalyzed C−O cross-coupling reactions.

Table 1. Palladium-Catalyzed C−O Cross-Coupling of *meso*-Bromoporphyrin Zinc Complexes with Alcohols[a]

entry	BrPor[b]	alcohol	temp (°C)	time (h)[c]	yield (%)[d]
1[e]	1		100	23	80
2[e]	1		100	16	65
3	1		100	16	78
4	1		100	16	89
5[e]	1		100	18	73
6[e]	1		100	17	72
7[e]	1		100	17	93
8[e]	1		100	17	78
9	2		80	5	44
10	2		100	18	68
11[f]	2		80	5	44
12	2		100	25	54
13[f]	2		100	23	51
14	2		100	48	50

[a] Reactions were carried out in toluene under N_2 with 1.0 equiv of bromoporphyrin, 2.0−4.0 equiv of alcohol, 5 mol % $Pd_2(dba)_3$, and 10 mol % DPEphos in the presence of 2.0 equiv of Cs_2CO_3 per Br. Concentration: 0.01 mmol of bromoporphyrin/mL of toluene. [b] Structures of bromoporphyrins are shown in Figure 1. [c] Reaction times have not been optimized. [d] Yields represent isolated yields of >95% purity as determined by ^1H NMR. [e] $Pd(OAc)_2$ was used instead. [f] Xantphos was used instead.

Table 2. Palladium-Catalyzed C−O Cross-Coupling of Free-Base *meso*-Bromoporphyrins with Aromatic Alcohols[a]

entry	BrPor[b]	alcohol	temp (°C)	time (h)[c]	yield (%)[d]
1[e]	3		80	4	66
2	3		100	24	69
3[f]	3		100	23	61
4[g]	3		100	48	59
5	3		100	48	45
6	3		100	25	50
7	3		100	21	58
8	3		100	21	62
9	3		100	21	54
10[f]	3		80	16	78
11[f]	3		80	18	44
12[e]	3		80	4	55
13	4		100	40	45
14	4		100	24	56

[a] Reactions were carried out in toluene under N_2 with 1.0 equiv of bromoporphyrin, 2.0−4.0 equiv of alcohol, 5 mol % $Pd_2(dba)_3$, and 10 mol % DPEphos in the presence of 2.0 equiv of Cs_2CO_3 per Br. Concentration: 0.01 mmol of bromoporphyrin/mL of toluene. [b] Structures of bromoporphyrins are shown in Figure 1. [c] Reaction times have not been optimized. [d] Yields represent isolated yields of >95% purity as determined by ^1H NMR. [e] $Pd(OAc)_2$ was used instead. [f] Xantphos was used instead. [g] K_3PO_4 was used instead.

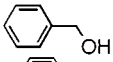
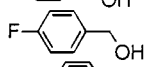
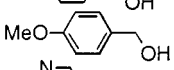
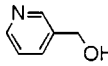
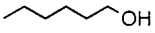
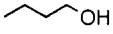
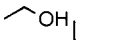
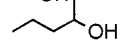
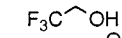
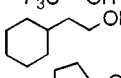
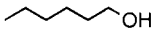
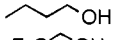
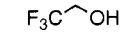
suitable palladium precursors for the reaction. The use of toluene resulted in superior results in comparison with other solvents such as THF. Among several common bases, the selection of Cs_2CO_3 as a mild base appears to be essential for the success of the process. An elevated temperature seems to be necessary for effective transformation, as low conversions were observed at low temperature. On the basis of these preliminary outcomes, succeeding reactions were generally conducted in toluene at 80 or 100 °C under a nitrogen atmosphere with 2.0−4.0 equiv of alcohol with use of 5 mol % palladium precursor in combination with phosphine ligand (L/Pd = 2) in the presence of 2.0 equiv of Cs_2CO_3 per bromide.

Under the general reaction conditions, zinc complexes of both *meso*-monobrominated and *meso*-dibrominated 10,20-diphenylporphyrins **1** and **2**, respectively, can be effectively coupled with a variety of different alcohols. As summarized in Table 1, phenol (entry 1) and 4-*tert*-butylphenol (entry 5), as well as three cresol isomers (entries 2−4), were successfully reacted with **1** to give the desired *meso*-monoaryloxyporphyrins in high yields. Besides *o*-cresol (entry 4), even more sterically hindered 2-isopropylphenol could be transformed in good yield (entry 6). Electron-rich and -poor phenol derivatives such as 4-methoxyphenol (entry 7) and 4-fluorophenol (entry 8) were also efficiently coupled with **1**. Zinc complexes of *meso*-diaryloxyporphyrins can be directly obtained in good yields via double etheration of **2** with phenol derivatives, as demonstrated with phenol (entry 9) and 4-methoxyphenol (entry 10). The double etheration can also be extended to aliphatic alcohols, including benzyl (entry 11), linear primary (entry 12), cyclic primary (entry 13), and cyclic secondary (entry 14) alcohols. The 50% yield of double etheration (~71% per step) with cyclopentanol (entry 14) is close to the best yield reported with this difficult secondary alcohol.[14]

(13) For a bidentate a Tol-BINAP-based system that catalyzed C−O couplings of active substrates, see: Palucki, M.; Wolfe, J. P.; Buchwlad, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395.

As we found previously,[8] the use of a zinc ion as an "inorganic protective group" for the central −NH units of porphyrins turned out to be unnecessary. As shown in Tables 2 and 3, free base dibromoporphyrins **3** and **4** (Figure 1) can be doubly etherated with both aromatic and aliphatic alcohols. For example, 5,15-dibromo-10,20-diphenylporphyrin **3** could be effectively cross-coupled with phenol (Table 2, entry 1) and its derivatives having various alkyl substituents at different positions (Table 2, entries 2−9), including sterically hindered ortho-substituted examples (Table 2, entries 4, 6, 8, and 9). Both electron-rich and -poor phenol derivatives were also suitable coupling partners (Table 2, entries 10−12). Furthermore, a wide variety of aliphatic alcohols were successfully coupled with **3** (Table 3). In addition to benzyl alcohol, its derivatives and heterocyclic substrates (Table 3, entries 1−4), examples include various primary alcohols having different chain lengths (Table 3, entries 5−7), a cyclic moiety (Table 3, entry 10), and a trifluoromethyl group (Table 3, entry 9). As in the case of the zinc complex **2** (Table 1, entry 14), free base **3** could also be coupled with the challenging secondary alcohol,[14] cyclopentanol, giving the desired product in 62% double etheration yield (~79% yield per step). When the electron-rich 5,10-dibromo-10,20-bis-(trimethoxyphenyl)porphyrin **4** was used instead of **3**, better yields were observed for several primary aliphatic alcohols (Table 3, entries 12−14). It was also found that electron-deficient 3- and 4-nitrophenols, which failed to react with **3**, could be successfully coupled with **4** (Table 2, entries 13 and 14).

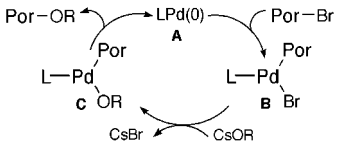
Table 3. Palladium-Catalyzed C−O Cross-Coupling of Free Base *meso*-Bromoporphyrins with Aliphatic Alcohols[a]

entry	BrPor[b]	alcohol	temp (°C)	time (h)[c]	yield (%)[d]
1	**3**		80	18	40
2[e]	**3**		80	20	48
3[e]	**3**		80	4	41
4[e]	**3**		80	17	62
5[e]	**3**		80	17	51
6[e]	**3**		100	39	66
7	**3**		100	47	50
8[e]	**3**		100	39	30
9	**3**		100	48	33
10[e]	**3**		80	17	63
11	**3**		80	48	62
12	**4**		100	40	81
13[e]	**4**		100	47	80
14	**4**		100	24	54

[a] Reactions were carried out in toluene under N_2 with 1.0 equiv of bromoporphyrin, 2.0−4.0 equiv of alcohol, 5 mol % $Pd_2(dba)_3$, and 10 mol % DPEphos in the presence of 2.0 equiv of Cs_2CO_3 per Br. Concentration: 0.01 mmol of bromoporphyrin/mL of toluene. [b] Structures of bromoporphyrins are shown in Figure 1. [c] Reaction times have not been optimized. [d] Yields represent isolated yields of >95% purity as determined by ^{1}H NMR. [e] Xantphos was used instead.

These reactions are assumed to proceed via a mechanism similar to that which was proposed for palladium-catalyzed C−O cross-coupling of simple aromatic halides.[15] As shown in Scheme 2, oxidation addition of Pd(0) active species **A** with bromoporphyrin to provide porphyrin Pd(II) bromide **B**, which undergoes transmetalation with cesium alcoholate to form porphyrin Pd(II) alcoholate **C**. Reductive elimination of intermediate **C** results in the formation of the desired product and the regeneration of the active species **A**, which continues the catalytic cycle. The fact that the catalytic reactions proceeded well even for secondary alcohols using simple nonelectron-rich and nonbulky bidentate DPEphos and Xantphos suggests that the porphyrin units play possible roles in the catalytic cycle, including preventing intermediate **C** from undergoing β-hydride elimination.

Scheme 2. Proposed Catalytic Cycle



In summary, a facile and versatile synthesis of aryloxy- and alkoxy-substituted porphyrins from the halogenated precursors via palladium-catalyzed C−O cross-coupling has been developed. In view of the accessibility of large numbers of different alcohols, this methodology will permit quick entrance to a family of novel porphyrins with *meso*-oxo functionalities, the properties of which should be able to be fine-tuned or dramatically altered through the judicious use of various alcohols. These new aryloxy- and alkoxy-substituted porphyrins could find applications in areas such as catalysis, materials, and medicine.

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Supporting Information Available: Analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

(15) (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224.