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Development of Pd/C-Catalyzed Cyanation of Aryl Halides

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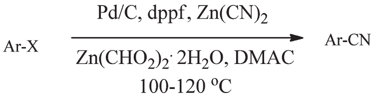


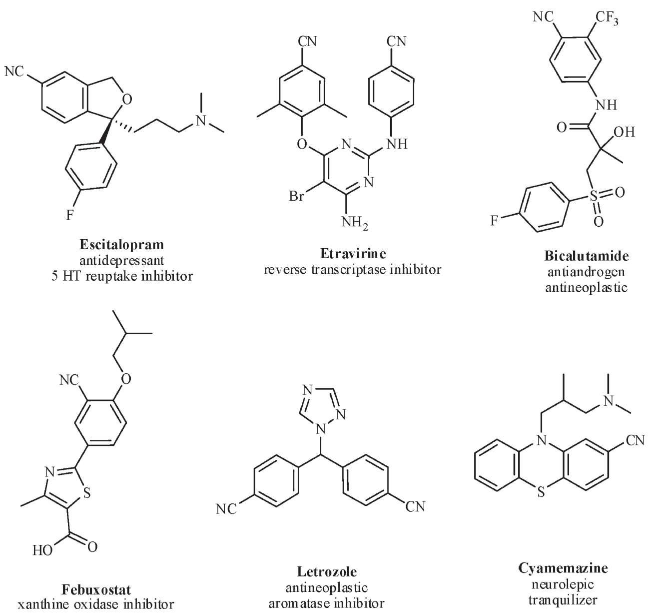
$$\text{Ar-X} \xrightarrow[\text{Zn(CHO}_2)_2\cdot 2\text{H}_2\text{O, DMAC}\ \ 100\text{-}120\ ^\circ\text{C}]{\text{Pd/C, dppf, Zn(CN)}_2} \text{Ar-CN}$$

A practical method for palladium-catalyzed cyanation of aryl halides using Pd/C is described. The new method can be applied to a variety of aryl bromide and active aryl chloride substrates to effect efficient conversions. The process features many advantages over existing cyanation conditions and the practical utility of the process has been demonstrated on scale.

Aromatic nitriles constitute a key component of numerous commercial compounds, including dyes, herbicides, agrochemicals, and natural products.[1] In particular, the motif is present in an increasing number of pharmaceutical products (Scheme 1).[2] The nitrile group is also an important precursor for various functional groups such as amidines, amides, imidoesters, benzamidines, amines, heterocycles, and aldehydes.[3]

The Sandmeyer[4] and Rosemund−Von Braun reactions[5] were reported in early examples in converting aryl halides to aryl cyanides. More recently, the transition metal-catalyzed cyanation has attracted widespread interest.[6−8] One of the major challenges for development of robust cyanation conditions lies in the fact that in the presence of cyanide ions, palladium will interact with the cyanide ions to form unreactive complexes.[9] To circumvent this issue, numerous procedures have been developed to control the level of cyanide in solution. Reagents with weakly ionizable M−CN bonds, such as zinc cyanide[7a,c,d,g,k,m,n,q,r,w] and

SCHEME 1. **Selected Cyano-Substituted Pharmaceutical Products**



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(1) (a) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 819−995. (b) Grundmann, C. In *Houben-Weyl: Methoden der organischen Chemie*, 4th ed.; Falbe, J., Ed.; Georg Thieme: Stuttgart, Germany, 1985; Vol. E5, pp 1313−1527.

(2) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*, 5th ed.; Georg Thieme: Stuttgart, Germany, 2009.

(3) Rappoport, Z. *Chemistry of the Cyano Group*; John Wiley & Sons: London, UK, 1970.

(4) (a) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633. (b) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251. (c) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(5) (a) Mowry, D. T. *Chem. Rev.* **1948**, *42*, 189. (b) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.

(6) For reviews, see: (a) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, UK, 1995; pp 225−226. (b) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513.

(7) For representative examples of palladium-catalyzed cyanation of aryl halides, see: (a) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. (b) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224. (c) Maligres, P. E. *Tetrahedron Lett.* **1999**, *40*, 8193. (d) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271. (e) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890. (f) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 1828. (g) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441. (h) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837. (i) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388. (j) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576. (k) Stazi, F.; Palmisano, G.; Turconi, M.; Santagostino, M. *Tetrahedron Lett.* **2005**, *46*, 1815. (l) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585. (m) Jensen, R. S.; Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Tetrahedron Lett.* **2005**, *46*, 8645. (n) Hatsuda, M.; Seki, M. *Tetrahedron* **2005**, *61*, 9908. (o) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508. (p) Grossman, O.; Gelman, D. *Org. Lett.* **2006**, *8*, 1189. (q) Pitts, M. R.; McCormack, P.; Whittall, J. *Tetrahedron* **2006**, *62*, 4705. (r) Littke, A.; Soumeillant, M.; Kaltenback, R. F., III; Cherney, R. J.; Tarby, C. M.; Kiau, S. *Org. Lett.* **2007**, *9*, 1711. (s) Schareina, T.; Zapf, A.; Magerlein, W.; Muller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087. (t) Zhu, Y.; Cai, C. *Synth. Commun.* **2007**, *37*, 3359. (u) Ryberg, P. *Org. Process Res. Dev.* **2008**, *12*, 540. (v) Ren, Y.; Liu, Z.; He, S.; Zhao, S.; Wang, J.; Niu, R.; Yin, W. *Org. Process Res. Dev.* **2009**, *13*, 764. (w) Shevlin, M. *Tetrahedron Lett.* **2010**, *51*, 4833.

(8) For representative examples of metal-catalyzed cyanation through C−H functionalization, see: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (c) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. (d) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272.

(9) (a) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (b) Sundermeier, M.; Zapf, A.; Beller., M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (c) Dobbs, K. D.; Marshall, W. J.; Grushin, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 30. (d) Erhardt, S.; Grushin, V. V.; Kilpatrick, A. H.; Macgregor, S. A.; Marshall, W. J.; Roe, D. C. *J. Am. Chem. Soc.* **2008**, *130*, 4828.

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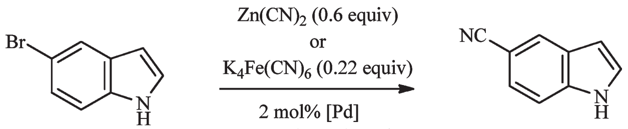
TABLE 1. Identification of the Pd/C-Catalyzed Cyanation Reaction Conditions[a]



3 **4**

entry	conditions	yield[b,c] (%)
1	$Pd(OAc)_2$, $K_4Fe(CN)_6$, Na_2CO_3 (1 equiv), 120 °C	35
2	$Pd(OAc)_2$, dppf (4 mol %), $K_4Fe(CN)_6$, Na_2CO_3 (1 equiv), 120 °C	65
3[d]	$Pd_2(dba)_3$, dppf (4 mol %), $Zn(CN)_2$, wet, 120 °C	66
4	$Pd_2(dba)_3$, dppf (4 mol %), $Zn(CN)_2$, Zn (20 mol %), 120 °C	36
5[e]	Pd/C, PPh_3 (16 mol %), $Zn(CN)_2$, Zn (40 mol %), Br_2 (20 mol %), 120 °C	5
6[e]	Pd/C, dppf (4 mol %), $Zn(CN)_2$, $Zn(CHO_2)_2 \cdot 2H_2O$ (10 mol %), 110 °C	98 (90)

[a]All reactions were run at 1 g scale with 10 min subsurface N_2 sparging. [b]Yield determined by HPLC potency with **4** as the internal standard. [c]Isolated yield is reported in parentheses. [d]DMAC:water = 100:1. [e]10 wt % Pd/C.

potassium ferrocyanide(II),[7i,j,l,o,p,s,v] have been found to be advantageous over the conventional cyanide sources, such as KCN and NaCN. Efforts have also been made to control the cyanide concentration through defined dosing of acetone cyanohydrin,[9a] or through control of addition sequence.[7u,10] In addition, a variety of additives, such as Bu_3SnCl,[7h] diamines,[7f] Zn dust,[7d] $Zn/Zn(OAc)_2$,[7g] $Zn/ZnBr_2$,[7n] and Zn/H_2SO_4,[7w] have been introduced to the system to activate the catalysts. Despite these improvements, the palladium-catalyzed cyanation reaction still often suffers from problems such as a lack of robustness. In addition, many of the conditions reported are not ideal for multikilogram scale preparations. For example, expensive catalysts and high catalyst loadings were often reported. Operating under the acidic conditions also generates cyanide safety concerns. Zinc dust was used in many of the conditions, which requires extra attention to suspend zinc in the reactor and also creates waste treatment liability.

During the course of a recent project, we encountered major issues in our attempts to affect consistent conversion of a heteroaryl bromide to a heteroaryl nitrile under a variety of literature conditions. The issues prompted us to look for additional cyanation conditions. Herein, we wish to report a practical and scalable cyanation method using heterogeneous palladium catalyst. This process features many advantages over the existing conditions. Furthermore, the same process could be applied to the synthesis of a broad range of aryl nitriles from aryl bromides and electron-deficient aryl chlorides.

Using 5-bromoindole **3** as a model substrate, we started our cyanation investigation by using 2 mol % of Pd catalyst and $Zn(CN)_2$ or $K_4Fe(CN)_6$ as the cyanide source (Table 1). When **3** was heated with $Pd(OAc)_2$, Na_2CO_3, and $K_4Fe(CN)_6$ under a ligandless condition in DMAC,[7o] significant amounts of starting material, along with major impurities, were observed at the end of the reaction (entry 1). To reduce the rate of potential catalyst aggregation,[7j,o] we attempted the reactions by reducing $Pd(OAc)_2$ loading. However, similar results were observed. The reaction was then conducted in the presence of dppf ligand at 120 °C for 12 h (entry 2).[7i] An incomplete reaction was again observed. Increasing temperature or adjusting catalyst loading had no effect on further conversion. We next turned our attention to using $Zn(CN)_2$ as the cyanide source. Under the treatment of $Pd(dba)_2$, dppf, and $Zn(CN)_2$ in DMAC/water (100:1) at 120 °C,[7c] the reaction stalled when a significant amount of starting material **3** still remained (entry 3). Reducing the catalyst loading to 1 mol % of $Pd(dba)_2$ and 2 mol % of dppf provided a similar amount of starting material at the end of the reaction. When the reaction was conducted under the conditions of $Pd(dba)_2$, dppf, $Zn(CN)_2$, and zinc dust in DMAC (entry 4),[7d] an incomplete reaction was still observed. We then carried out the reaction by using Pd/C, PPh_3, $Zn(CN)_2$, Zn dust, and $ZnBr_2$ (generated from zinc and Br_2) in DMAC at 120 °C (entry 5).[7n,11] However, a minimal amount of product **3** was detected.[12]

From the industrial application perspective, the use of heterogeneous palladium catalysts to facilitate cross-coupling reactions often offers a number of advantages over the homogeneous catalytic conditions.[13,14] We therefore continued our investigation using Pd/C as the catalyst, aiming to develop a simplified cyanation condition with reduced Pd and ligand loading. Under the conditions of Pd/C, dppf, and $Zn(CN)_2$ in DMAC, no cyanation took place. To our delight, when 0.1 equiv of zinc formate dihydrate was added to the reaction mixture, the reaction proceeded smoothly at 105−110 °C to give the desired product with 98% HPLC assay yield (Table 1, entry 6).

The presence of dppf was critical for the success of the reaction. Without the ligand, the product was not formed.[15] Zinc, a common reducing agent used in the palladium-catalyzed cyanation, was not needed under our conditions. Instead, zinc formate dehydrate played a vital role in reactivating the palladium catalyst, presumably via reducing the products of the catalyst poisoning to active Pd(0).[9d,16] Formate had been used in the palladium-catalyzed hydroarylation reactions to convert the corresponding Pd(II) intermediate to Pd(0).[17] One of the potential liabilities of using

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(10) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C. *Org. Lett.* **2004**, *6*, 3723.

(11) Hatsuda, M.; Seki, M. *Tetrahedron Lett.* **2005**, *46*, 1849.

(12) Reactions attempted with higher catalyst loading or using dppf as the ligand also gave little conversion.

(13) Seki, M. *Synthesis* **2006**, 2975.

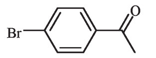
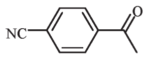
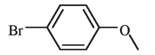
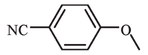
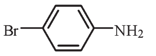
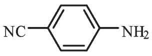
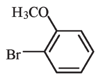
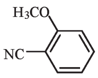
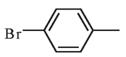
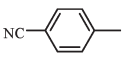
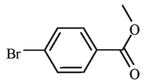
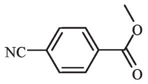
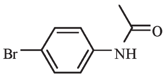
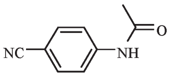
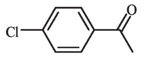
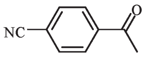
(14) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.

(15) We also examined other ligands, such as PPh_3, $P(o\text{-Tol})_3$, BINAP, and $t\text{-}Bu_3P$. We found dppf to be superior to other ligands in terms of reactivity and general scope.

(16) The reaction did not work when zinc formate was simply replaced with zinc, which suggested additional beneficial effects of zinc formate on the catalyst system. Further investigation is needed to gain additional understanding of the mechanistic effects of zinc formate.

TABLE 2. Pd/C-Catalyzed Cyanation of Aryl Halides[a]

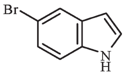
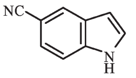
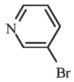
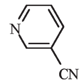
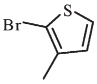
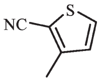
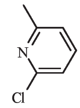
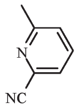
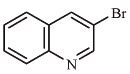
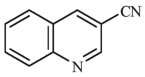
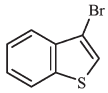
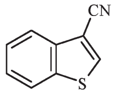
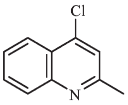
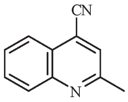
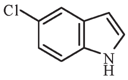
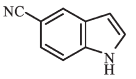
$$\text{Ar-X} \xrightarrow[\text{Zn(CHO}_2)_2\cdot 2\text{H}_2\text{O (0.1 equiv)}, \text{ DMAC, 100-120 }^\circ\text{C}]{\text{Pd/C (2 mol\%), dppf (4 mol\%)}, \text{ Zn(CN)}_2} \text{Ar-CN}$$

entry	ArX	product	temp (°C)	yield[b] (%)
1[c]			100	89 (97)
2			110	87 (96)
3			115	90 (93)
4			110	91 (96)
5			110	95 (98)
6			100	87 (89)
7			110	92 (93)
8			120	70 (79)

[a] Reaction conditions: aryl halide (100 mol %), $Zn(CN)_2$ (60 mol %), Pd/C (2 mol %), dppf (4 mol %), $Zn(CHO_2)_2 \cdot 2H_2O$ (10 mol %), DMAC (0.6 M), 12 h. [b] Isolated yield. HPLC solution yield in parentheses. [c] Pd/C and dppf loadings can be reduced to 0.1 and 0.2 mol %, respectively

TABLE 3. Pd/C-Catalyzed Cyanation of Heteroaryl Halides[a]

$$\text{Ar-X} \xrightarrow[\text{Zn(CHO}_2)_2\cdot 2\text{H}_2\text{O (0.1 equiv)}, \text{ DMAC, 100-120 }^\circ\text{C}]{\text{Pd/C (2 mol\%), dppf (4 mol\%)}, \text{ Zn(CN)}_2} \text{Ar-CN}$$

entry	ArX	product	temp (°C)	yield[b] (%)
1			110	90 (98)
2			100	88 (99)
3			105	85 (90)
4			100	96 (99)
5			100	86 (94)
6			105	82 (90)
7			105	77 (84)
8			120	0

[a] Reaction conditions: aryl halide (100 mol %), $Zn(CN)_2$ (60 mol %), Pd/C (2 mol %), dppf (4 mol %), $Zn(CHO_2)_2 \cdot 2H_2O$ (10 mol %), DMAC (0.6 M), 12 h. [b] Isolated yield. HPLC solution yield in parentheses.

zinc formate in cyanation reactions was the reduction of oxidative addition complex ($ArLnPd^{II}X$)[9c] before transmetalation. Under our reaction conditions, the dehalogenation impurity (indole) was not detected.[18] This suggested that the transmetalation to form the $ArLnPd^{II}CN$ intermediate[9c] was a relatively fast step under the reaction conditions.

This result led to our interest in exploring the scope and limitations of this strategy. The general utility of the heterogeneous Pd/C cyanation procedure for the synthesis of a range of aryl nitriles was explored (Table 2). A variety of aryl bromides were successfully cyanated to give the desired aryl nitriles with excellent yields (entries 1−7). The electron density of the bromide substrates had little effect on the reaction results and full conversion was achieved with electron-deficient, neutral, and electron-rich substrates. The reaction also worked equally well with ortho-substituted aryl bromide (entry 4). In addition, the same conditions could be successfully applied to the cyanation of 4-chloroacetophenone (entry 8).

Although the reactions discussed above were carried out with 2 mol % of Pd/C and 4 mol % of dppf, we also explored the catalyst loading for the cyanation of 4-bromoacetophenone (Table 2, entry 1). The cyanation reaction proceeded efficiently with as little as 0.1 mol % of Pd/C at 100 °C, which corresponded to a catalyst turnover number (TON) approaching 1000.

Due to the prevalence of heterocycles in pharmaceutical products, we are particularly interested in evaluating the cyanation of heteroaryl halides. Cyanation of nitrogen-containing heterocycles can often be challenging due to the ability of nitrogen to potentially deactivate the catalyst.[19]

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(17) (a) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4329. (b) Ruchirawat, S.; Namsa-aid, A. *Tetrahedron Lett.* **2001**, *42*, 1359. (c) Kulagowski, J. J.; Curtis, N. R.; Swain, C. J.; Williams, B. J. *Org. Lett.* **2001**, *3*, 667. (d) Mitchell, D.; Yu, H. *Curr. Opin. Discovery Dev.* **2003**, *6*, 876.

(18) A detection limit of 0.1% was applied.

(19) Expensive ligands and higher catalyst loading are often needed for nitrogen-containing heterocycles, see refs 7k, 7r, and 7u.

To our delight, various heteroaryl halides participated efficiently under our cyanation conditions (Table 3). 3-Bromopyridine (entry 2), 3-bromo-4-methylthiophene (entry 3), 3-bromoquinoline (entry 5), and 3-bromothianaphthene (entry 6) could all be cyanated with Pd/C and dppf to give complete conversions. 2-Chloro-6-methylpyridine (entry 4) also underwent smooth reaction to afford the desired 2-cyano-6-methylpyridine with 96% isolated yield. 4-Chloroquinaldine could also be cyanated at 105 ^{o}C under the same conditions (entry 7). Inspired by these results, we attempted our cyanation conditions with less reactive 5-chloroindole. Unfortunately, the reactivity was not sufficient to drive the reaction and only starting material was recovered (entry 8).

In summary, we have developed a general condition for the synthesis of aryl nitriles utilizing easily available Pd/C as the palladium source. The condition could be applied to a variety of aryl bromide and active aryl chloride substrates to effect efficient conversions. More importantly, the process features many advantages over the existing cyanation conditions, such as avoiding the use of zinc metal, less Pd contamination in product, and use of easily available and inexpensive catalyst and ligand. The practical utility of this process has been consistently demonstrated on the scale-up of a challenging heteroaryl bromide substrate to afford the desired nitrile with over 87% yield after crystallization. We believe the method will find wide use by allowing a practical access to a variety of aromatic nitriles on scale. Studies are underway to establish the overall kinetics and to obtain true mechanistic understanding of the reaction.

Experimental Section

Representative Procedure (Preparation of 4). To a round-bottomed flask were added 5-bromo-1*H*-indole (**3**) (1.0 g, 5.1 mmol), zinc cyanide (0.36 g; 3.1 mmol; 0.6 equiv) (**Caution**: highly toxic), 10 wt % Pd/C[20] (108 mg; 0.10 mmol; 2 mol %), 1,1′-bis(diphenylphosphino)ferrocene (dppf) (111 mg; 0.20 mmol; 4 mol %), and DMAC (8.5 mL). The resulting slurry was sparged with subsurface nitrogen for 10 min, and zinc formate dihydrate (79 mg; 0.51 mmol; 10 mol %) was added to the reaction mixture. The reaction mixture was again sparged with subsurface nitrogen for 10 min and was heated under nitrogen to 110 °C. Reaction conversion was monitored by HPLC. Upon completion, the reaction mixture was cooled to rt and diluted with 10 mL of EtOAc. The resulting slurry was filtered and the cake was rinsed with EtOAc (2 mL). The product was isolated by washing the filtrate with water (2 × 10 mL) and 5% NH_4OH (1 × 10 mL). The organic layer was dried with Na_2SO_4. The volatile was removed in vacuo to give a residue, which was further purified by silica gel chromatography (EtOAc/heptanes) to provide **4** as a white solid (653 mg; 4.6 mmol; 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.81 (1 H, bs), 8.02 (1 H, s), 7.28−7.51 (3 H, m), 6.65 (1 H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 137.60, 127.70, 126.63, 126.60, 124.84, 120.99, 112.13, 103.40, 102.67. HRMS (ES+) exact mass calcd for $C_9H_6N_2$ 141.0047, found, 141.0457.

Acknowledgment. We thank Johnson Matthey for investigating the effects of different types of Pd/C on a related substrate.

Supporting Information Available: Experimental details and spectral data for all entries in Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] Reproducible results were obtained with all lots of Pd/C tested. Most of the reactions were run with 10 wt % Pd/C purchased from Aldrich (wet, Degussa type E101 NE/W).