ORGANIC LETTERS

2007
Vol. 9, No. 9
1711−1714

Mild and General Methods for the Palladium-Catalyzed Cyanation of Aryl and Heteroaryl Chlorides

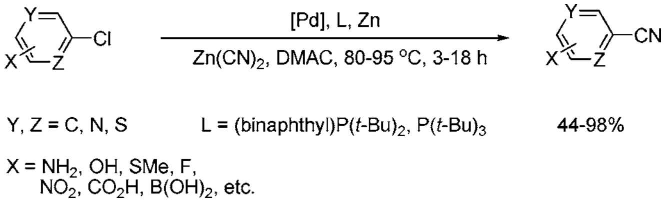
**Adam Littke,*,[†] Maxime Soumeillant,*,[‡] Robert F. Kaltenbach III,[§]
Robert J. Cherney,[§] Christine M. Tarby,[§] and Susanne Kiau[†]**

Process Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, 1 Squibb Drive, P.O. Box 191, New Brunswick, New Jersey 08903-0191, Process Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000, and Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-4000

adam.littke@bms.com; maxime.soumeillant@bms.com

Received February 13, 2007

ABSTRACT



New methods for the palladium-catalyzed cyanation of aryl and heteroaryl chlorides have been developed, featuring sterically demanding, electron-rich phosphines. Highly challenging electron-rich aryl chlorides, in addition to electron-neutral and electron-deficient substrates, as well as nitrogen- and sulfur-containing heteroaryl chlorides can all undergo efficient cyanation under relatively mild conditions using readily available materials. In terms of substrate scope and temperature, these methods compare very favorably with the state-of-the-art cyanations of aryl chlorides.

The palladium-catalyzed cyanation of aryl halides is a common and powerful method to obtain substituted benzonitriles.[1] Recent examples of this transformation in areas as diverse as process chemistry,[2] medicinal chemistry,[3] and ligand synthesis[4] are indicative of the importance of benzonitriles as end products or as synthetic intermediates which can be converted to a multitude of different functional groups.[5]

Aryl chlorides are a desirable class of substrates for palladium-catalyzed coupling reactions due to their lower cost and wider availability than the corresponding aryl bromides or iodides.[6] However, most accounts of palladium-catalyzed cyanations have focused on the use of more reactive aryl iodides and bromides[7] rather than typically reticent aryl chlorides.[8] Some progress in this area has been made. In 2000, Jin and Confalone published the first general method for the palladium-catalyzed cyanation of aryl chlorides based on a Pd/1,1′-bis(diphenylphosphino)ferrocene (dppf) catalyst with Zn as a cocatalyst and $Zn(CN)_2$ as the

---

[†] Process Research and Development New Brunswick.
[‡] Process Research and Development Princeton.
[§] Discovery Chemistry Princeton.
(1) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513−3526.
(2) Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006**, *71*, 4021−4023.
(3) Qiao, J. X.; Cheng, X.; Modi, D. P.; Rossi, K. A.; Luettgen, J. M.; Knabb, R. M.; Jadhav, P. K.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 29−35.
(4) Veauthier, J. M.; Carlson, C. N.; Collis, G. E.; Kiplinger, J. L.; John, K. D. *Synthesis* **2005**, 2683−2686.
(5) Rappoport, Z. *Chemistry of the Cyano Group*; John Wiley & Sons: London, 1970.
(6) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

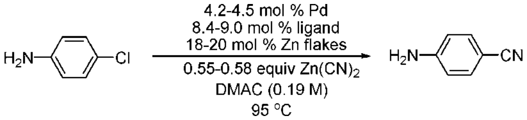
10.1021/ol070372d CCC: $37.00

cyanating agent.[9] Subsequent attempts to engage aryl chlorides have included the use of amine cocatalysts,[10] acetone cyanohydrin,[11] or potassium hexacyanoferrate[12] as the cyanide source, microwaves,[13] or the use of sterically demanding, electron-rich phosphine ligands.[14] Two common themes throughout these methods are (i) the use of very high temperatures, 120−160 °C, and (ii) few successful cyanations of challenging electron-rich aryl chlorides.[15] In addition, the experimental conditions are often difficult to scale (sealed tube, microwaves). Most recently, Beller has demonstrated the successful cyanation of both electron-neutral and electron-rich aryl chlorides using the ligand di(1-adamantyl)-1-butylphosphine; however, this system still requires fairly high thermal activation (140−160 °C).[16]

Herein, we wish to report two new and highly reactive palladium-based catalyst systems for the cyanation of aryl chlorides, including electron-rich aryl chlorides, under relatively mild and operationally simple conditions with reasonable reaction times (80−95 °C, *N*,*N*-dimethylacetamide, 3−18 h). Together, both of these catalyst systems allow the cyanation of a wide variety of aryl and heteroaryl chlorides encompassing varying functionality in good to excellent yields.

During the course of a recent project, it became necessary to develop a robust, practical, and scaleable cyanation of an electron-rich aryl chloride to provide multikilogram quantities of a drug candidate. Using 4-chloroaniline as a model substrate, a variety of palladium sources and commercially available ligands were screened using Zn flakes[17] as a cocatalyst, $Zn(CN)_2$[18] as the cyanating agent, and *N*,*N*-dimethylacetamide (DMAC) as the solvent[19] (Table 1). $Pd(TFA)_2$ (TFA = trifluoroacetate) in combination with the Buchwald biaryl ligand racemic 2-di-*tert*-butylphosphino-1,1′-binaphthyl ((binaphthyl)P(*t*-Bu)$_2$)[20] proved to be by far the best palladium/ligand combination, providing the cyanated product in essentially quantitative yield after 3 h at 95 °C (entry 2). Curiously, $Pd(OAc)_2$ was markedly inferior as the palladium source (entry 1),[21−23] and other Buchwald biaryl ligands S-Phos (2-(dicyclohexylphosphino)-2′,6′-dimethoxy-1,1′-biphenyl; entry 3)[24] and X-Phos (2-(dicyclohexylphosphino)-2′,4′,6′-tri-*iso*-propyl-1,1′-biphenyl; entry 4)[25] proved far less effective. More traditional phosphine ligands such as the aforementioned dppf (entry 5) and PCy_3 (entry 6) also proved quite ineffective, as did the relatively air-stable and crystalline preformed catalyst Pd[P(*t*-Bu)$_3$]$_2$ (entry 7).

Table 1. Effect of Pd Source and Ligand on the Cyanation of 4-Chloroaniline



entry	Pd source	ligand	HPLC solution yield after 3 h
1	$Pd(OAc)_2$	(binaphthyl)P(*t*-Bu)$_2$	<1%
2	$Pd(TFA)_2$	(binaphthyl)P(*t*-Bu)$_2$	99%
3	$Pd(TFA)_2$	S-Phos	3%
4	$Pd(TFA)_2$	X-Phos	12%
5	$Pd(TFA)_2$	dppf (4.2% ligand used)	<1%
6	$Pd(TFA)_2$	PCy_3	<1%
7	Pd[P(*t*-Bu)$_3$]$_2$	none	5%

Other very electron-rich aryl chlorides can be cyanated using $Pd(TFA)_2$/(binaphthyl)P(*t*-Bu)$_2$ such as the ortho-substituted 2-chlorophenol (Table 2, entry 2). *To the best of our knowledge, these are the first examples of successful palladium-catalyzed cyanations of highly challenging 4-chloroaniline and 2-chlorophenol*. Other electron-rich (entry 4) as well as electron-neutral (entry 5) and electron-deficient substrates (entry 7) can also be efficiently cyanated using $Pd(TFA)_2$/(binaphthyl)P(*t*-Bu)$_2$.

Of interest is that an aryl chloride bearing a boronic acid unit may also be cyanated in good yield (entry 11) thus

---

(7) For recent selected articles on palladium-catalyzed cyanation of aryl bromides, see: (a) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441−1444. (b) Marcantonio, K. M.; Frey, L. F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D. J.; Chen, C.-Y. *Org. Lett.* **2004**, *6*, 3723−3725. (c) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508−1510. (d) Hatsuda, M.; Seki, M. *Tetrahedron* **2005**, *61*, 9908−9917. (e) Jensen, R. S.; Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Tetrahedron Lett.* **2005**, *46*, 8645−8647. (f) Li, L.-H.; Pan, Z.-L.; Duan, X.-H.; Liang, Y.-M. *Synlett* **2006**, 2094−2098.

(8) For Ni-mediated cyanation of aryl chlorides, see: Arvela, R.; Leadbeater, N. E. *J. Org. Chem.* **2003**, *68*, 9122−9125 and references therein.

(9) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271−3273.

(10) (a) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707−6710. (b) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem.−Eur. J.* **2003**, *9*, 1828−1836.

(11) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661−1664.

(12) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576−4583.

(13) Pitts, M. R.; McCormack, P.; Whittall, J. *Tetrahedron* **2006**, 62, 4705−4708.

(14) Chobanian, H. R.; Fors, B. P.; Lin, L. S. *Tetrahedron Lett.* **2006**, *47*, 3303−3305.

(15) For an alternative method to synthesize electron-rich benzonitriles from electron-rich aryl chlorides using irradiation, see: Dichiarante, V.; Fagnoni, M.; Albini, A. *Chem. Commun.* **2005**, 3001−3003.

(16) Schareina, T.; Zapf, A.; Magerlein, W.; Muller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087−1090.

(17) The type of zinc used (flakes vs dust) was largely irrelevant on small-scale reactions; however, we found it was essential to use fine zinc particles on larger scales to enable a homogeneous dispersion throughout the reaction medium under mechanical overhead stirring conditions.

(18) Other cyanide sources were found to be inferior: *t*-BuSi(Me)$_2$CN, $SiMe_3CN$, acetone cyanohydrin, CuCN, NaCN, $K_4Fe(CN)_6$.

(19) DMAC was found to be superior to DMF and NMP.

(20) Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907−12908.

(21) For cyanations of less electron-rich substrates, we have found $Pd(OAc)_2$ to be as efficient as $Pd(TFA)_2$.

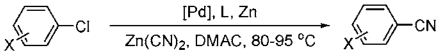
(22) We speculate that the greater efficacy of $Pd(TFA)_2$ may be due to a more rapid reduction of the Pd(II) precatalyst to the Pd(0) active species. Successful cyanations are often characterized by a deep purple color, and this deep purple color consistently develops at a lower temperature when using $Pd(TFA)_2$ as the Pd source.

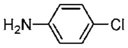
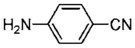
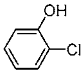
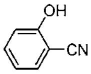
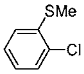
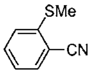
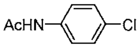
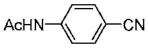
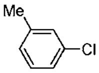
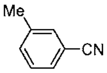
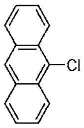
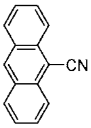
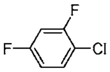
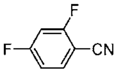
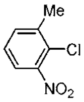
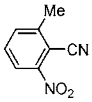
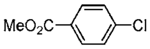
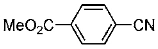
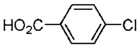
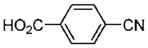
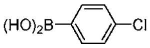
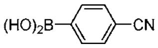
(23) Amatore and Jutand have demonstrated that the rate of formation of anionic Pd(0) complexes is more rapid for $Pd(TFA)_2$ than $Pd(OAc)_2$ and that $[Pd(PPh_3)_2TFA]^-$ is slightly more reactive than $[Pd(PPh_3)_2OAc]^-$ toward oxidative addition with phenyl iodide in DMF at 25 °C: Amatore, C.; Jutand, A.; Lemaitre, F.; Ricard, J. L.; Kozuch, S.; Shaik, S. *J. Organomet. Chem.* **2004**, *689*, 3728−3734.

(24) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876.

(25) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655.

Table 2. Cyanation of Aryl Chlorides[a]



entry	ArCl	catalyst[b]	product	yield[c]
1		A		93% (98%)
2		A		88% (90%)
3		B		56% (68%)
4		A		92% (98%)
5		A		83% (87%)
6		B		98% (98%)
7		A		73% (86%)
8		B		85% (93%)
9		B		86% (99%)
10		B		84% (97%)
11		A		74% (89%)

[a] Reaction conditions: aryl chloride (100 mol %), Zn(CN)$_2$ (55−58 mol %), catalyst, Zn flakes (18−20 mol %), DMAC (17 mL/g of ArCl), 80−95 °C, 3−14 h. [b]Catalyst A = Pd(TFA)$_2$ (4.2−4.4 mol %), (binaphthyl)P(*t*-Bu)$_2$ (8.4−8.8 mol %). Catalyst B = Pd[P(*t*-Bu)$_3$]$_2$ (4.2−4.4 mol %). [c]Isolated yield. HPLC solution yield in parentheses.

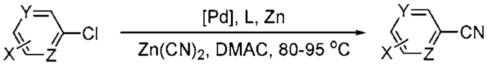
allowing a potential cyanation−Suzuki cross-coupling sequence.

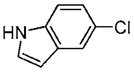
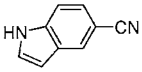
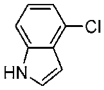
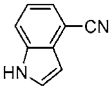
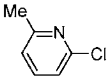
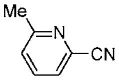
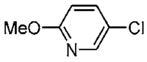
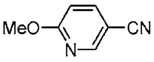
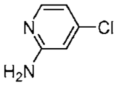
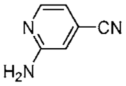
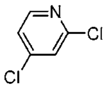
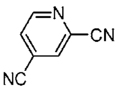
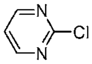
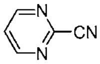
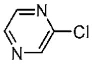
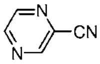
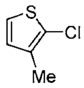
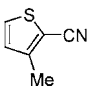
Using 4′-chloroacetanilide (entry 4) as a model substrate, we briefly investigated lowering the catalyst loadings. In this particular case, the catalyst loading could be decreased to 1.9 mol % of Pd(TFA)$_2$, 3.7 mol % of (binaphthyl)P(*t*-Bu)$_2$, and 8.3 mol % of Zn to still furnish a 92% isolated yield of 4′-cyanoacetanilide after 2 h at 95 °C.

However, certain substrates do not perform well using this catalyst system; in particular, we have found sulfur-containing substrates are more efficiently cyanated using Pd[P(*t*-Bu)$_3$]$_2$.[26] Although a modest 68% solution yield is obtained for the cyanation of 2-chlorothioanisole (entry 3), only 16% of 2-cyanothioanisole is obtained with Pd(TFA)$_2$/(binaphthyl)P(*t*-Bu)$_2$. In addition, for the highly hindered 3-nitro-2-chlorotoluene, Pd[P(*t*-Bu)$_3$]$_2$ also proved to be the superior catalyst (entry 8).[27] Other nonactivated (entry 6) and activated substrates (entries 9 and 10) undergo facile cyanation using Pd[P(*t*-Bu)$_3$]$_2$; it is noteworthy that free carboxylic acids are well tolerated.

Given the importance of heterocycles in the pharmaceutical industry, we chose to pay special attention to cyanations of heteroaryl chlorides, in particular, nitrogen-containing heterocycles. Cyanations of such substrates can be nontrivial owing to the ability for nitrogen to bind to, and potentially deactivate, palladium-based catalysts.[26b,c] Gratifyingly, we have found that Pd(TFA)$_2$/(binaphthyl)P(*t*-Bu)$_2$ is a very general and efficient catalyst for cyanations of nitrogen-containing heterocycles (Table 3). Although cyanation of 5-chloroindole results in only 44% yield of 5-cyanoindole,[28] 89% yield is obtained with the 4-isomer (entry 2). 2-, 3-, and 4-chloropyridines all undergo smooth reaction (entries

Table 3. Cyanation of Heteroaryl Chlorides[a]



entry	HetArCl	product	yield[b]
1			44% (49%)
2			89% (93%)
3			97% (99%)
4			94% (97%)
5			89% (91%)
6			68% (71%)[c]
7			87% (94%)
8			73% (89%)
9			86% (99%)[d]

[a] Reaction conditions: heteroaryl chloride (100 mol %), Zn(CN)$_2$ (55−58 mol %), Pd(TFA)$_2$ (4.2−4.4 mol %), (binaphthyl)P(*t*-Bu)$_2$ (8.4−8.8 mol %), Zn flakes (18−20 mol %), DMAC (17 mL/g of ArCl), 80−95 °C, 3−18 h. [b]Isolated yield. HPLC solution yield in parentheses. [c]114 mol % of Zn(CN)$_2$ used. [d]Pd[P(*t*-Bu)$_3$]$_2$ (4.2−4.4 mol %) used as catalyst.

---

(26) For examples of Pd/P(*t*-Bu)$_3$-catalyzed cyanations of aryl bromides and iodides, see: (a) Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rakhit, S.; Maddaford, S. *Synlett* **2003**, 2237−2239. (b) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837−2840. (c) Stazi, F.; Palmisano, G.; Turconi, M.; Santagostino, M. *Tetrahedron Lett.* **2005**, *46*, 1815−1818.

3−5), and both chlorides can undergo cyanation in 2,4-dichloropyridine (entry 6); thus far, our attempts to monocyanate a variety of dichloropyridine substrates selectively have been unsuccessful.[29] Heterocycles with more than one nitrogen atom are also excellent substrates (entries 7 and 8). Chlorothiophenes, which often give poor yields when using other Pd-based catalysts,[30] including $Pd(TFA)_2$/(binaphthyl)P-(*t*-Bu)$_2$,[31] are best cyanated with $Pd[P(t\text{-Bu})_3]_2$ (entry 9).[32]

In conclusion, we have demonstrated the most general and mild methods for palladium-catalyzed cyanations of aryl and heteroaryl chlorides reported to date. $Pd(TFA)_2$/(binaphthyl)P(*t*-Bu)$_2$ is uniquely effective for promoting cyanations of nitrogen-containing heterocycles and typically unreactive electron-rich aryl chlorides, whereas the preformed catalyst $Pd[P(t\text{-Bu})_3]_2$ is sufficient for less challenging electron-neutral and electron-deficient aryl chlorides as well as sulfur-containing substrates. Functional groups such as anilines, phenols, esters, nitro groups, amides, and carboxylic and boronic acids are all tolerated. Future efforts will focus on further enhancing the substrate scope[33] and continuing efforts to reduce Pd, ligand, and Zn loadings to improve turnover numbers. Given the commercial availability and ease of handling of all the components, we believe that these methods should find wide use in organic synthesis.

Acknowledgment. The authors wish to thank Drs. Frederic Buono (BMS Process, New Brunswick), Rulin Zhao, and Ms. Bei Wang (BMS Discovery, Princeton) for helpful discussions and Drs. Rajendra Deshpande, David Kronenthal (BMS Process, New Brunswick), and Robert Discordia (BMS Process, Princeton) for review of the paper.

Supporting Information Available: Experimental procedures, reaction times, temperatures, 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.

OL070372D

---

(27) <10% yield of 2-cyano-3-nitrotoluene is observed with $Pd(TFA)_2$/(binaphthyl)P(*t*-Bu)$_2$.

(28) As for all the nonquantitative reactions reported herein, the remainder of the mass balance was predominantly unreacted 5-chloroindole as in this example.

(29) For example, attempted monocyanation of both 2,4- and 2,5-dichloropyridine yields a mixture of starting material, monocyanated pyridine (at the 2-position), and dicyanated pyridine.

(30) For example, see: Erker, T.; Nemec, S. *Synthesis* **2004**, 23−25.

(31) $Pd(TFA)_2$/(binaphthyl)P(*t*-Bu)$_2$ gives only a 32% yield of 2-cyano-3-methylthiophene for the cyanation of 2-chloro-3-methylthiophene.

(32) These palladium-catalyzed cyanations are sensitive to oxygen; however, glovebox techniques and rigorously purified reagents and catalysts are not required. Sample illustrative procedure (Table 2, entry 1): palladium-(II)trifluoroacetate ($Pd(TFA)_2$) (9.6 mg, 0.0289 mmol, 4.3 mol %), zinc flakes, 1.1 μm thick −325 mesh (8.3 mg, 0.127 mmol, 19 mol %), racemic 2-di-*tert*-butylphosphino-1,1′-binaphthyl (23.5 mg, 0.059 mmol, 8.8 mol %), 4-choroaniline (85.4 mg, 0.669 mmol, 100 mol %), and $Zn(CN)_2$ (43.9 mg, 0.374 mmol, 56 mol %) were charged successively to a 25 × 90 mm glass test tube equipped with a magnetic stir bar and a Teflon screw-cap. The test tube was evacuated and back-filled with nitrogen. DMAC (anhydrous, 99.8%, 3.6 mL) was added via syringe, and the resulting reaction mixture was stirred at room temperature for 20 min while performing 3 evacuation−nitrogen refill cycles. The reaction mixture was then heated to 95 °C over 45 min and held at that temperature for 14 h. The reaction mixture was then cooled to room temperature, diluted with acetonitrile, and filtered through a 45 μm HPLC syringe filter, and the supernatant was analyzed by HPLC. HPLC analysis indicated a solution yield of 97.8% of 4-aminobenzonitrile. For workup procedures used to obtain isolated yields, please refer to the Supporting Information.

(33) Certain substrates such as 4-chlorostyrene and 2-chloro-*m*-xylene do not perform well under these cyanation conditions using either catalyst system.