

Palladium-catalyzed cyanation reactions of aryl chlorides

Fuqiang Jin * and Pat N. Confalone

Chemical Process R & D, The DuPont Pharmaceuticals Company, DuPont Experimental Station, Wilmington,
DE 19880-0336, USA

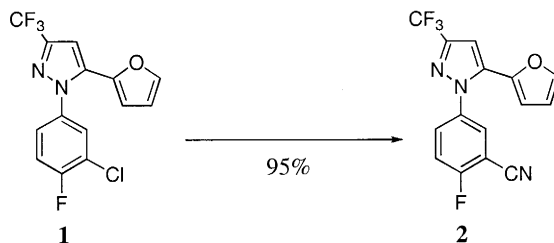
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Abstract

We have discovered an efficient cyanation of aryl chlorides which employs $\text{Pd}_2(\text{dba})_3$, dppf and Zn as the catalyst and $\text{Zn}(\text{CN})_2$ as the cyanide source. Both electron-deficient and electron-rich aryl chlorides are effectively cyanated under these conditions. This discovery represents the first successful palladium-catalyzed cyanation of both electron-deficient and electron-rich aryl chlorides. © 2000 DuPont Pharmaceuticals Company. Published by Elsevier Science Ltd. All rights reserved.

Keywords: aryl chlorides; cyanation; palladium.

Cyanation of aryl halides is a common and useful transformation in organic synthesis.^{1,2} Unfortunately, the use of aryl chlorides, which are the cheapest and most readily available aryl halides, is generally avoided in this reaction due to their low reactivity.^{1,2} For example, much higher temperatures and longer reaction times are required in the classic cyanation reaction, the Rosenmund–von Braun reaction,¹ when a chloride is involved, rendering this methodology impractical. While nickel catalysts have been reported to promote cyanation of aryl chlorides under very mild conditions,^{3,4} the application of this process is rather limited. Palladium complexes have long been considered not to catalyze displacement of Cl^- in ArCl by CN^- , unless the carbon–chlorine bond is strongly activated.⁵ Recently, we desired a conversion of the chloride **1** into the corresponding aryl nitrile derivative **2**. Attempts to cyanate **1** by either the Rosenmund–von Braun reaction or the nickel(0)-mediated cyanation were all unsuccessful. Ultimately, we discovered that the conversion of **1** into **2** can be effectively carried out by a palladium-catalyzed

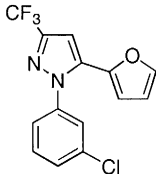
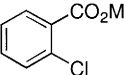
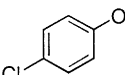
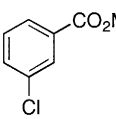
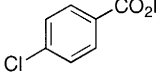
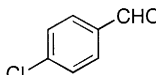
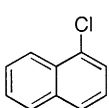


Scheme 1. Conditions: $\text{Zn}(\text{CN})_2$ (0.6 equiv.), $\text{Pd}_2(\text{dba})_3$ (2 mol%), dppf (4 mol%), Zn (12 mol%), DMA, 120°C, 4 h

* Corresponding author. Tel: (302) 695-8666; fax: (302) 695-4632; e-mail: fuqiang.jin@dupontpharma.com (F. Jin)

cyanation. Further study indicated that this palladium-catalyzed cyanation can be widely expanded to a variety of aryl chlorides, not only electron-deficient but also electron-rich aryl chlorides. In this communication, we report our preliminary results.

Table 1
Palladium(0)-catalyzed cyanation of aryl chlorides^a

Ar-Cl 3		$\xrightarrow[\text{cat. Zn, DMA}]{\text{Zn(CN)}_2, \text{ cat. Pd}_2(\text{dba})_3, \text{ cat. dppf}}$			Ar-CN 4
entry	substrate	t (°C)/T (h)	Product	Yield(%) ^b	
1	 3a	150/10	4a	91	
2	 3b	150/12	4b	85	
3	 3c	120/2	4c	93	
4 ^c	 3d	150/4	4d	88	
5	 3e	120/10	4e	91	
6	 3f	120/2	4f	97	
7	 3g	120/0.75	4g	92	
8	 3h	150/2	4h	96	

^a Conditions: 0.6 equiv of Zn(CN)_2 , 2 mol% of $\text{Pd}_2(\text{dba})_3$, 4 mol% of dppf, 12 mol% of Zn unless otherwise stated; ^b Isolated yields; ^c Conditions: 0.6 equiv of Zn(CN)_2 , 4 mol% of $\text{Pd}_2(\text{dba})_3$, 8 mol% of dppf, 24 mol% of Zn

As expected, under the commonly applied palladium-catalyzed cyanation conditions for aryl iodides and aryl bromides,^{6,7} e.g. using $\text{Pd(PPh}_3)_4$ as catalyst and an alkaline metal cyanide such as KCN as cyanide source in a suitable solvent such as CH_3CN or DMF at 60–80°C, cyanation of **1** did not proceed, even at a higher temperature. When the catalyst was replaced with $\text{Pd}_2(\text{dba})_3$ and dppf [1,1'-bis(diphenylphosphino)ferrocene], which is commonly used as a ligand to enhance the reactivity of a palladium complex,⁸ we noticed a modest conversion (40%) at 120°C in *N,N*-dimethylacetamide (DMA), suggesting the occurrence of an oxidative addition of the palladium complex to the carbon–chlorine bond

in **1**. Realizing the incomplete conversion was probably caused by CN^- -induced catalyst deactivation, we improved the conversion to 100% by use of $\text{Zn}(\text{CN})_2$ ⁹ as the cyanide source and addition of a catalytic amount of Zn powder.¹⁰ Thus, when treated with $\text{Zn}(\text{CN})_2$ in the presence of $\text{Pd}_2(\text{dba})_3$ (2 mol%), dppf (4 mol%) and Zn (12 mol%) in DMA at 120°C, **1** was transformed to **2** completely within 4 h in a yield of 95% (Scheme 1).

As the successful example of palladium-catalyzed cyanation of non-activated aryl chlorides, we were extremely interested in the generality of this cyanation reaction. In the cases of **3a** (Table 1), which does not have a fluorine substitute *ortho* to the chlorine atom and **3b**, which lacks the pyrazole ring, under related conditions (150°C), both **3a** and **3b** demonstrate a reasonable reactivity towards cyanation. Thus, **3a** was transformed to the corresponding nitrile (**4a**) in a yield of 91% on treatment with $\text{Zn}(\text{CN})_2$ and catalytic amounts of $\text{Pd}_2(\text{dba})_3$, dppf and Zn in DMA at 150°C after 10 h, while **4b** was generated in a yield of 85% after 12 h from **3b**.

As can be seen from Table 1, both electron-deficient and electron-rich aryl chlorides are cyanated in high yields.¹¹ As a general trend, electron-deficient aryl chlorides are more reactive than electron-rich chlorides. For example, a complete conversion is reached within 2 h at 120°C for methyl 2-chlorobenzoate (**3c**). However, 4-chloroanisole (**3d**) requires a higher temperature (150°C), higher catalyst load, and longer reaction time.

In conclusion, we have discovered a palladium-catalysed cyanation which is suitable for both electron-deficient and electron-rich aryl chlorides. This cyanation offers practical improvement to the Rosenmund–von Braun reaction. Further study on the scope and limitation of this cyanation reaction of aryl chlorides is underway and will be reported in due course.

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11. Typical experimental procedure: **1** (1.0 g, 3.0 mmol), $\text{Pd}_2(\text{dba})_3$ (55 mg, 2 mol%), dppf (66 mg, 4 mol%), Zn powder (23 mg, 12 mol%) and $\text{Zn}(\text{CN})_2$ (210 mg, 1.8 mmol) were placed in a flask which was flushed with N_2 . DMA (6 ml) was added via syringe. The resulting mixture was heated at 120°C under N_2 with vigorous agitation until TLC showed the disappearance of **1** (~4 h). The mixture was cooled to room temperature, diluted with ethyl acetate (50 ml), and then washed with 2 N NH_4OH solution and brine. After drying over Na_2SO_4 , the ethyl acetate solution was concentrated by rotary evaporation. The residue was chromatographed on silica gel using a mixed solvent of ethyl acetate and hexane (1:2) to afford 1-(3'-cyano-4'-fluorophenyl)-3-trifluoromethyl-5-(2'-furanyl)pyrazole (**2**) as a white solid (920 mg, 95% yield): mp 111–113°C (hexane); ^1H NMR δ 7.70 (m, 2H), 7.44 (m, 1H), 7.31 (t, $J=8.2$ Hz, 1H), 6.89 (s, 1H), 6.46 (m, 1H), 6.32 (d, $J=3.6$ Hz, 1H); ^{19}F NMR δ –60.0 (s, 3F), –105.3 (m, 1F); MS ($\text{NH}_3\text{-Cl}$) m/z 322 (100, M^++1). Anal. calcd for $\text{C}_{15}\text{H}_7\text{F}_4\text{N}_3\text{O}$: C, 56.09; H, 2.206; N, 13.08. Found: C, 55.96; H, 2.49; N, 12.90.