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A practical synthesis of highly functionalized aryl nitriles through cyanation of aryl bromides employing heterogeneous Pd/C

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Abstract—An industrially viable cyanation of aryl bromides with $Zn(CN)_2$ was accomplished in the presence of inexpensive and readily accessible Pd/C, Zn dust, $ZnBr_2$, and PPh_3 in DMA to provide functionalized aryl nitriles in moderate to high yields.

Palladium-catalyzed cyanation of aryl halides has recently aroused considerable attention due to the significance in the preparation of valuable compounds such as drugs and natural products.[1] Because of the expanding need for the industrial application, much effort have been devoted to develop a practical cyanation protocol that inexpensively delivers products with prevention of pollution. However, the existing methods[2] employing *homogeneous* Pd catalyst still suffer from at least either one of the following drawbacks:[3] (1) requirement of quite expensive and/or hazardous phosphine ligand or additives, (2) lack of a proper procedure for recovering and/or removing expensive and toxic Pd from the reaction mixture, and (3) poor reproducibility of the reaction. A more efficient and practical cyanation method that fulfills all the criteria on sustainability and economy is, therefore, still in much demand. In a series of our synthetic studies of (+)-biotin,[4] we have reported *heterogeneous* Pd/C-catalyzed Fukuyama reactions, i.e., transformations of thiol esters to aldehydes[4l] or ketones.[4a–e,k] As an extension of the study, reported herein is a novel and highly practical synthesis of aryl nitriles through cyanation of aryl bromides employing inexpensive Pd/C, Zn dust, $ZnBr_2$, and PPh_3.

In our initial study, cyanation of methyl 4-bromobenzoate **1a** was investigated as a typical example. Treatment of **1a** with $Zn(CN)_2$ (0.6 equiv) in the presence of Pd/C[5] (4 mol %), PPh_3 (0.16 equiv) and Zn dust (0.4 equiv) in DMA at 130–150 °C for 20–24 h was found to provide desired aryl nitrile **2a**. However, the reaction often stopped without completion and the yield varied from 31–72% (Table 1, entry 1). The unreliable results may be ascribed to insufficient activation of the surface of the Zn dust and/or unexpected formation of inactive Pd black. Meanwhile, as shown in our previous report[4k] on the Fukuyama coupling reaction of zinc reagents with thiol esters, prior addition of Br_2 to Zn dust, which in situ produces $ZnBr_2$, is very effective not only for activation of Zn dust but also for generation of active alkyl zinc halide (RZnBr) through a shift of the Schlenk equilibrium from R_2Zn to RZnBr (Scheme 1, R = alkyl). We envisioned that the Schlenk-type equilibrium might occur as well on $Zn(CN)_2$ (Scheme 1, R = CN), and much enhanced activity and solubility were expected of CNZnBr rather than $Zn(CN)_2$ because of higher leaving group activity of $ZnBr_2$ as compared with CNZnBr which was liberated on reaction with palladium complex, $ArPdBrL_2$. The well-documented Pd deactivation[2j] by coordination with cyanide ion may be suppressed as well through the gradual formation of soluble CNZnBr from fairly insoluble $Zn(CN)_2$. The reaction was thus conducted with initial addition of Br_2 (0.2 equiv) to the mixture of Zn dust in DMA at 25 °C to activate Zn dust and in situ generate $ZnBr_2$. As expected, with this pre-treatment, the reaction was completed in 3 h at much lower temperature (80 °C) to afford **2a** in 97% yield in highly reproducible manner (Table 1, entry 2).[6] It should be noted that the addition of Zn dust is indispensable for the reaction: elimination of Zn dust

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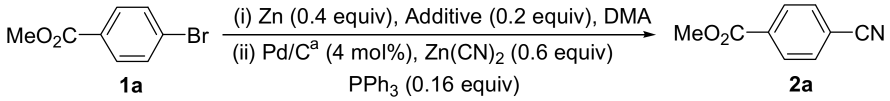
Table 1. Cyanation of methyl 4-bromobenzoate (**1a**) with $Zn(CN)_2$ in the presence of Pd/C, Zn dust, PPh_3, and various additives

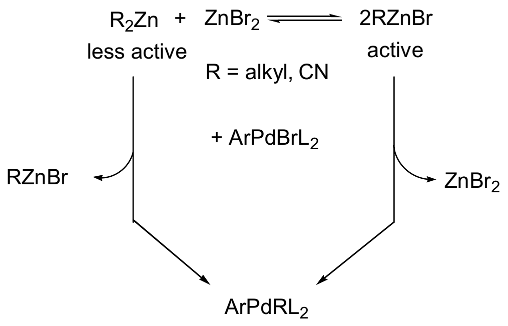


Entry	Additive	Temp. (°C)	Period (h)	Conv.[b] (%)	Assay yield[b] (%)
1	None	130–150	20–24	29–100	31–72
2	Br_2	80	3	100	97
3	I_2	80	4	99	92
4	TMSCl	80	3	100	95
5	$Br(CH_2)_2Br$	80	4	100	90
6	$Zn(OAc)_2$	80	7	73	—[c]

[a] Pd/C was purchased from Degussa Japan Co., Ltd.[5]

[b] Determined by HPLC.

[c] Not determined.



Scheme 1. Equilibrium of zinc reagents and zinc cyanide in the presence of zinc bromide and their reaction with palladised aryl bromides.

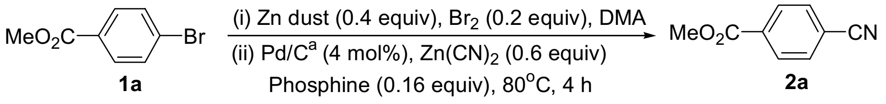
as an additive resulted in no reaction. The presence of Zn dust should be significant not only to reduce the initially oxidic Pd/C[5] (reduction degree: 0–25%) but also to prevent the labile Pd(0) species from oxidation. While the reaction proceeded as well in the presence of other Zn-activating reagents such as I_2, TMSCl or 1,2-dibromoethane which, upon treatment with Zn dust, also generates zinc halides (ZnX_2, X = I, Br or Cl), they furnished somewhat lower yields (Table 1, entries 3–5). Of particular interest is the inferior result (73% yield) obtained by the addition of $Zn(OAc)_2$, a known efficient activator for the cyanation of aryl halides employing homogeneous Pd catalyst (Table 1, entry 6).[2f]

As for the phosphine ligand, dppf participated similarly well in the cyanation (Table 2, entry 2). In contrast, electron-rich bulky ligands such as $P(o\text{-tol})_3$, Cy_3P, and $t\text{-}Bu_3P$ were almost inactive (Table 2 entries 3–5). In considering the cost and the effectiveness, PPh_3 was chosen as the ligand for the cyanation.

The present cyanation tolerates substantial variation in aryl bromides as the substrates (Table 3). Even aryl bromides carrying electron-donating substituents, which gave poor yields through the reported procedure,[7] furnished the corresponding aryl nitriles in good to excellent yields at slightly higher reaction temperature (115–125 °C) (Table 3, entries 3, 4, 6–8). Functional groups such as acetyl, hydroxyl, amino, and sulfide groups were all compatible with the reaction conditions (Table 3, entries 2, 4, and 6–9). To the best of our knowledge, the successful cyanation of sterically congested electron-rich aryl bromides such as 2-*N*,*N*-dimethylaminobromobenzene **1d** and 2-hydroxybromobenzene **1g** represents the first examples hitherto recorded. More inexpensive aryl chloride such as 4′-chlorobenzoate and 4′-chloroacetophenone was not cyanated by the use of the present conditions.

Comparison of the present protocol with those employing homogeneous Pd catalyst was then tested (Table 4). Cyanation of 3-bromo-4-hydroxymorpholinobenzamide **1j** in the presence of $Pd(OAc)_2$ (5 mol %) and PPh_3

Table 2. Screen of the phosphine ligand in the cyanation of methyl 4-bromobenzoate (**1a**)



Entry	Phosphine	Conv[b] (%)	Assay yield[b] (%)
1	PPh_3	100	97
2	dppf[c]	100	88
3	$P(o\text{-tol})_3$	1	—[d]
4	Cy_3P	0	—[d]
5	$t\text{-}Bu_3P$	5	—[d]

[a] Pd/C was purchased from Degussa Japan Co., Ltd.[5]

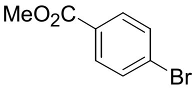
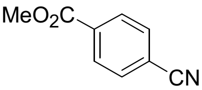
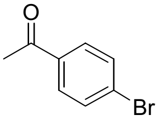
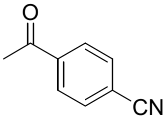
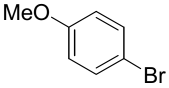
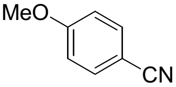
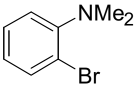
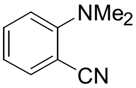
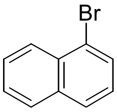
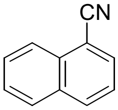
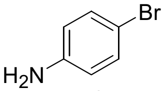
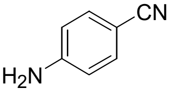
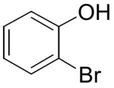
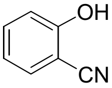
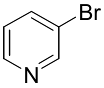
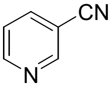
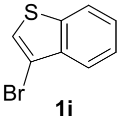
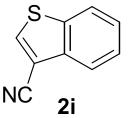
[b] Determined by HPLC.

[c] 0.08 equiv of phosphine was employed.

[d] Not determined.

Table 3. Cyanation of various aryl bromides **1a–i** to aryl nitriles **2a–i**[a]

$$\text{Ar-Br} + \text{Zn(CN)}_2 \xrightarrow[\text{DMA}]{\text{Pd/C}^{\text{b}},\text{Zn dust},\text{Br}_2,\text{PPh}_3} \text{Ar-CN}$$

Entry	Substrate **1a–i**	Product **2a–i**	Temp. (°C)	Period (h)	Assay yield[c] (%)
1[d]	 **1a**	 **2a**	80	3	97
2[d]	 **1b**	 **2b**	80	5	82
3[d]	 **1c**	 **2c**	115	8	89
4[d]	 **1d**	 **2d**	115	8	93
5[d]	 **1e**	 **2e**	115	2	92
6[e]	 **1f**	 **2f**	125	4	65
7[e]	 **1g**	 **2g**	125	4	60
8[d]	 **1h**	 **2h**	80	5	75
9[d]	 **1i**	 **2i**	115	8	89

[a] The compounds **2a–i** obtained have been fully characterized by IR, NMR and Mass spectra.

[b] Pd/C was purchased from Degussa Japan Co., Ltd.[5]

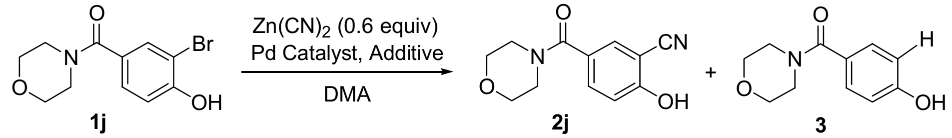
[c] Determined by HPLC.

[d] Pd/C (4 mol %), PPh_3 (0.16 equiv), Zn dust (0.4 equiv), Br_2 (0.2 equiv), $Zn(CN)_2$ (0.6 equiv).

[e] Pd/C (8 mol %), PPh_3 (0.32 equiv), Zn dust (1.2 equiv), Br_2 (0.4 equiv), $Zn(CN)_2$ (0.5 equiv).

(20 mol %) required much higher temperature (150 °C) and yielded an undesirable result (82% conversion) accompanied by considerable amount of reduction byproduct **3** [**2j**/4-hydroxymorpholinobenzamide (**3**) = 75/25] (Table 4, entry 2). Addition of $ZnBr_2$, which was in situ generated from Zn dust and Br_2, to the system involving $Pd(OAc)_2$ and PPh_3 considerably improved the reaction to provide **2j** in a higher yield (87%), though it is poorer than that employing Pd/C (Table 4, entry 3 vs 1). The present process using Pd/C

Table 4. Comparison of the present cyanation employing Pd/C with those catalyzed by homogeneous Pd catalysts[a]



Entry	Pd Catalyst (mol %)	Additive (equiv)	Temp. (°C)	Period (h)	Conv.[b] (%)	Assay yield[b] (%)	2j:3[b]
1	Pd/C[c] (4)	PPh_3 (0.16), Zn (0.6), Br_2 (0.2)	115	4	100	91	98/2
2	$Pd(OAc)_2$ (5)	PPh_3 (0.2), Zn (0.56)	150	2	82	—[d]	75/25
3	$Pd(OAc)_2$ (4)	PPh_3 (0.16), Zn (0.6), Br_2 (0.2)	115	3	100	87	98/2

[a] The compound **2j** obtained has been fully characterized by IR, NMR, and Mass spectra.

[b] Determined by HPLC.

[c] Pd/C was purchased from Degussa Japan Co., Ltd.[5]

[d] Not determined.

in conjunction with the addition of Zn dust, $ZnBr_2$, and PPh_3 thus appears to be superior to the protocols employing homogeneous Pd catalysts.

Elucidation of the precise mechanism of the present cyanation needs further investigation. Nonetheless, the use of the heterogeneous Pd/C catalyst has an advantage in that Pd metal is embedded and finely dispersed on the charcoal matrix at least in the initial stage of the reaction,[8] which may assure the formation of monomeric or dimeric Pd–phosphine complex without aggregating to inactive Pd black.[9] The recovery of Pd was conducted in the reaction of **1a** to **2a** by initial oxidation of PPh_3.[10] Air bubbling of the reaction mixture at 60 °C followed by simple filtration at 25 °C led to virtually complete recovery of Pd (99% yield). Although the recovered catalyst was not reused as such, it could be employed in the subsequent cyanation without any problems after subjecting to usual recovery process involving combustion.

In conclusion, a practical cyanation of aryl bromides employing heterogeneous Pd/C was worked out by the use of inexpensive Zn dust, $ZnBr_2$ (in situ generated from Zn dust and Br_2) and PPh_3. The present process is featured by ease of operation, high recovery of Pd, use of inexpensive phosphine ligand (PPh_3) and additives (Zn dust and $ZnBr_2$), and high reproducibility, which would permit a highly sustainable and robust access to multifunctional aryl nitriles, compounds of great pharmaceutical significance.

Acknowledgements

The authors wish to thank Degussa Japan Co., Ltd. for disclosing the chemical properties of the Pd/C catalyst.

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2. For recently developed Pd-catalyzed cyanation of aryl halides, see: (a) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224–8228; (b) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193–8195; (c) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271–3273; (d) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 1828–1836; (e) Sundermerier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661–1664; (f) Chidambaram, R. *Tetrahedron Lett.* **2004**, *45*, 1441–1444; (g) Yang, C.; Williams, J. M. *Org. Lett.* **2004**, *6*, 2837–2840; (h) 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; (i) Shareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389; (j) For a review, see: Sundermerier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513–3526.
3. The reported cyanation procedures need expensive and/or hazardous Pd catalyst, ligand and/or additive: Anderson approach:[2a] $Pd(PPh_3)_4$, CuI; Maligres approach:[2b] $Pd_2(dba)_3$, dppf; Jin approach:[2c] $Pd_2(dba)_3$, dppf; Beller approach:[2d] dpppe, TMEDA; Beller approach:[2e] dpppe, TMSCN; Chidambaram approach:[2f] $Pd_2(dba)_3$, dppf; Yang approach:[2g] $Pd_2(dba)_3$, Bu_3SnCl; $t\text{-}Bu_3P$; Marcantonio approach:[2h] $P(o\text{-tol})_3$; Beller approach:[2i] dppf.
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5. Pd/C catalyst employed in this study was purchased from Degussa Japan Co., Ltd. and has the following chemical properties: impregnation depth, 200–500 nm (thick shell); reduction degree, 0–25%; Pd dispersion, 28%; water content, less than 3 wt %. The catalyst is commercially available at Degussa Japan Co., Ltd.
6. General procedure for the Pd-catalyzed cyanation: A reaction vessel was charged with zinc dust (52 mg, 0.8 mmol) and DMA (5.7 mL). The vessel was then briefly

evacuated and backfilled with N_2 five times. Then, Br_2 (20 μL, 0.4 mmol) was dropwise added at 25 °C and the mixture was stirred at 25 °C for 0.5 h. To the mixture were successively added $Zn(CN)_2$ (141 mg, 1.2 mmol), PPh_3 (85 mg, 0.32 mmol), Pd/C[5] (Pd: 5 wt %, 170 mg, 0.08 mmol) and aryl bromide (2 mmol) at 25 °C. The vessel was briefly evacuated and backfilled with N_2 five times. The mixture was stirred at 80–125 °C for 3–15 h. After completion of the reaction, the suspension was cooled down to room temperature, diluted with AcOEt (15 mL), and filtered. The filtrate was concentrated, and the residue was purified by silica gel column chromatography or recrystallization to provide the desired product.

7. The conversion from **1f** to **2f** by the use of Chidambaram approach [$Pd_2(dba)_3$, dppf, 90 °C, 24 h][2f] has been reported to be 20%.
8. The leaching of Pd from Pd/C was measured at the end of the reaction of **1a** to **2a** by X-ray fluorescence analysis of the filtered solution, and 30% of the initially added Pd was found to dissolve from the charcoal matrix to the solution phase.
9. For the side reaction (precipitation to Pd black) in the Suzuki coupling, see: *Chem. Eng. News* **2004**, Sep. 6, 49–58.
10. In contrast, the recovery of Pd in the Heck reaction employing Pd/C was conducted by reducing the Pd(II) species, see: Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J.; Köhler, K. *J. Mol. Cat. A* **2002**, *182–183*, 499–509.