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A convenient procedure for palladium catalyzed cyanation using a unique bidentate phosphorus ligand

Rader S. Jensen,[a,b] Anil S. Gajare,[a] Kozo Toyota,[a]
Masaaki Yoshifuji[a,*] and Fumiyuki Ozawa[b]

[a]*Department of Chemistry, Graduate School of Science, Tohoku University, Aoba, Sendai 980-8578, Japan*
[b]*Research Center for Elements Science, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan*

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Abstract—A palladium complex bearing 1,2-diphenyl-3,4-diphosphinidenecyclobutene ligand (DPCB) has been used to facilitate the catalytic cyanation of aryl bromides. A series of substituted benzonitriles was prepared in good to high yields by the treatment of the corresponding aryl bromides with $Zn(CN)_2$ in *N*-methyl-2-pyrrolidone in the presence of 2–4 mol % catalyst at 100 °C for 16 h.

Benzonitriles are frequently encountered in organic chemistry, appearing in a variety of dyes, pharmaceuticals, and agricultural chemicals, among other things. Additionally, the cyano group provides a useful synthetic intermediate, being easily transformed into other functionalities. Indeed, the preparation of benzonitriles has been extensively studied. In addition to traditional methods of preparing substituted benzenes, transition metal-catalyzed cyanation of aryl halides and halide equivalents has been reported.[1–3] The palladium-catalyzed reaction has received particular attention owing to its versatility.[4–9]

Several points can be made concerning the work reported to date. Relatively high temperatures are typically required for bromides and chlorides, although some reactions have been shown to proceed at under 100 °C and in some cases, as low as room temperature. These catalytic systems however, often require highly air- or moisture-sensitive reagents or ligands, or have not yet been demonstrated to be general.[4a,5a,b,6] Furthermore, the reaction of ortho substituted as well as nitro substituted aryl halides tends to proceed in low yields or requires more rigorous conditions than less hindered substrates. A frequently reported problem is the poisoning of palladium catalysts by cyanide. Consequently, methods which have been demonstrated to be useful for a broad range of aryl halides typically require relatively high catalyst loads, although phase transfer conditions[7] as well as the dosed addition of a cyanide source has allowed the use of catalyst loads of less than 1 mol %.[8,9] These reactions however also suffer disadvantages; poor reactivity of bromides in the case of the former, and lack of simplicity in the latter. Beller et al. have reported a system that proceeds in high yields in the presence of 0.1 mol % catalyst, however temperatures over 120 °C are necessary.[10]

It has been pointed out that deactivation occurs through oxidation of palladium(0) and formation of a dicyanopalladium(II) species, which is not easily reduced to a catalytically active palladium(0) complex.[4a] The use of zinc dust has been found to significantly improve catalyst turnover, presumably by maintaining the palladium in a reduced state.[4] It has also been documented that $Zn(CN)_2$ gives better yields than KCN or NaCN as a result of lower concentration of cyanide ion in the catalytic solution.[5]

In these laboratories, considerable effort has been devoted to the chemistry of low-coordinated phosphorus compounds with sp^2-hybridized phosphorus atoms.[11] Particular interest has been focused on the application of 1,2-diphenyl-3,4-bis(2,4,6-tri-*tert*-butylphenylphosphinidene)cyclobutene (DPCB, Eq. 1) to catalysis.[12] This class of compounds bears extremely

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Keywords: Catalytic cyanation; Aryl bromide; Zinc cyanide; Palladium catalyst; Low-coordinated phosphorus ligand.

[*] Corresponding author at present address: Department of Chemistry, The University of Alabama, Tuscaloosa, AL 35487-0336, USA. Fax: +1 205 348 9104; e-mail: myoshifuji@bama.ua.edu

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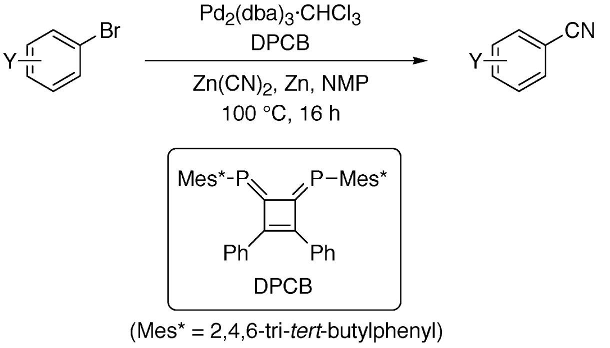
low-lying π* orbitals mainly located around the phosphorus and has a marked tendency to engage in metal-to-phosphorus π-back bonding.[13] This feature could be expected to stabilize low-valent metal species with high electron density and hence to facilitate reduction of transition metal complexes. Therefore, we examined in this study the palladium-catalyzed cyanation of aryl halides using DPCB ligand. It was considered that the unique electronic properties of DPCB would provide a complex more resistant to cyanide poisoning, giving rise to high catalytic performance.



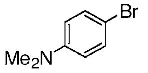
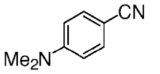
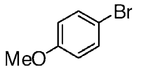
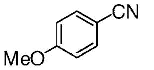
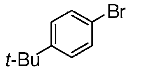
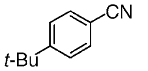
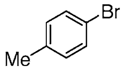
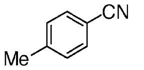
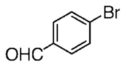
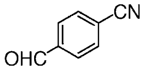
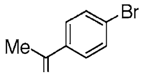
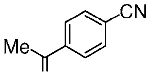
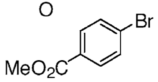
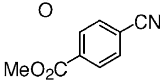
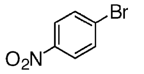
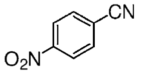
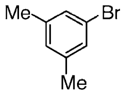
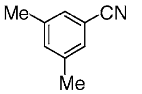
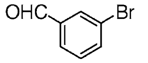
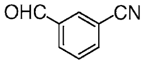
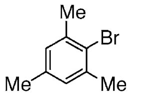
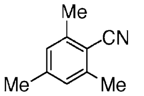
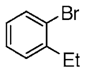
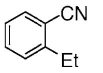
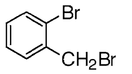
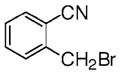
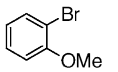
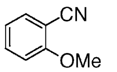
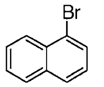
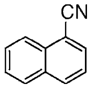
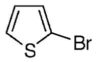
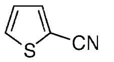
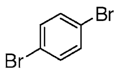
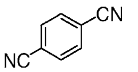
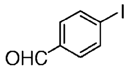
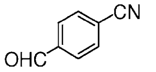
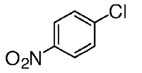
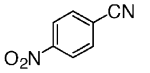
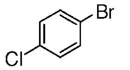
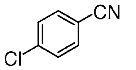
(1)

Preliminary examinations showed that a palladium catalyst generated in situ from $Pd_2(dba)_3·CHCl_3$ and DPCB in DMF successfully converted 4-bromoanisole to 4-methoxybenzonitrile. Accordingly, several solvents and reaction conditions were evaluated in the presence of DPCB (2 mol %), $Pd_2(dba)_3·CHCl_3$ (1 mol %), zinc dust (10 mol %), and $Zn(CN)_2$ (1.1 equiv) at 100 °C, using 4-bromoanisole and 4-bromotoluene as substrates. It was observed that at least 2 mol % of catalyst was required for high conversion (>80%), and the addition of zinc metal was necessary to maintain catalytic activity. As for the solvents, DMF and NMP (*N*-methyl-2-pyrrolidone) gave satisfactory results, however, only when the Pd/DPCB catalyst was generated in a minimum volume of solvent, prior to the addition of substrates.

A typical procedure is as follows. A 5 mL screw-cap vial with a magnetic stirring bar was charged with DPCB (15 mg, 0.02 mmol), $Pd_2(dba)_3·CHCl_3$ (10 mg, 0.01 mmol), zinc dust (7 mg, 0.1 mmol), and 0.1 mL of NMP. The reaction vial was then briefly flushed with a gentle stream of argon, capped, and stirred for 10 min. 4-Bromoanisole (187 mg, 1 mmol) was added, and the purple mixture was stirred for another 10 min. Finally, $Zn(CN)_2$ (62 mg, 0.55 mmol) was added, and the vial was heated on an oil bath at 100 °C. After 16 h, the mixture was allowed to cool, diluted with about 30 mL of Et_2O, washed with water followed by brine, dried over Na_2SO_4, and concentrated under reduced pressure. Conversion of the bromide was 90% as confirmed by ^1H NMR. 4-Methoxybenzonitrile as the product was isolated by flash chromatography on silica gel using hexane/EtOAc as mobile phase (113 mg, 85%) (see Table 1, entry 2).

The present catalyst exhibited a wide functional-group tolerance (Table 1). Phenyl bromides having a variety of *p*- and *m*-substituents, except for the NMe_2 group (entry 1), were converted to the corresponding benzo-

Table 1. Palladium-catalyzed cyanation of aryl halides with $Zn(CN)_2$ using DPCB ligand[a]

Entry	Substrate	Product	Yield (%)[b]
1			41
2			85 (90)
3			94
4			76 (94)
5			74 (96)
6			68 (94)
7			88 (90)
8			92 (98)
9			76
10			61
11			83 (90)
12			50 (65)
13			60
14			68 (80)
15			64 (68)
16			14
17			85[c]
18			80 (85)
19			15
20			35

[a] All reactions were run at 100 °C for 16 h on a 1 mmol scale using a Pd/DPCB catalyst, prepared in situ from $Pd_2(dba)_3·CHCl_3$ (0.01 mmol) and DPCB (0.02 mmol) in NMP (0.1 mL) at room temperature.

[b] The numbers given in parentheses are conversion of aryl halides confirmed by ^1H NMR analysis.

[c] The reaction was performed using 4 mol % of Pd/DPCB catalyst.

nitriles in good to high yields (entries 2–10). The high reactivity of sterically congested 2,4,6-trimethylphenyl bromide was of particular interest, giving the cyanation product in 83% yield (entry 11). Similarly, *o*-substituted phenyl bromides were converted to the corresponding nitriles in good yields (entries 12–14). The excellent conversion of 1-bromo-4-nitrobenzene was particularly gratifying (entry 8). In comparison, identical reaction conditions employing PPh_3 or dppf as ligand as opposed to DPCB provided 45% and 46% conversion of the nitro-arene, respectively. 2-Bromonaphthalene was sufficiently reactive (entry 15), but the reactivity of 2-bromothiophene was poor (entry 16). 1,4-Dibromobenzene was converted to 1,4-dicyanobenzene in 85% yield (entry 17). The reaction of phenyl iodide with a formyl group was also successful (entry 18). On the other hand, aryl chlorides were unreactive under these conditions, except for 1-chloro-4-nitrobenzene, which was converted to the corresponding nitrile in 15% yield (entry 19). Consequently, 1-bromo-4-chlorobenzene reacted only at the bromide position to give 4-chlorobenzonitrile in 35% yield (entry 20). An attempt to convert 4-fluorotoluene to the corresponding nitrile was unsuccessful, giving a complex mixture containing neither the starting material nor the desired product.

In summary, DPCB proved to be an effective ligand for palladium-catalyzed cyanation of aryl bromides. The ligand is stable toward air and moisture, and is conveniently stored and handled under ambient conditions. Furthermore, the catalytic reaction does not require the rigorous exclusion of oxygen or water, and all reagents and solvents can be used as commercially supplied. Although there are some limitations, it does provide a convenient and general access to benzonitriles from aryl bromides.

Acknowledgements

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