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Novel Trans-Spanned Palladium Complexes as Efficient Catalysts in Mild and Amine-Free Cyanation of Aryl Bromides under Air

Olga Grossman and Dmitri Gelman*

Department of Organic Chemistry, The Hebrew University of Jerusalem,
Jerusalem 91904, Israel

dgelman@chem.ch.huji.ac.il

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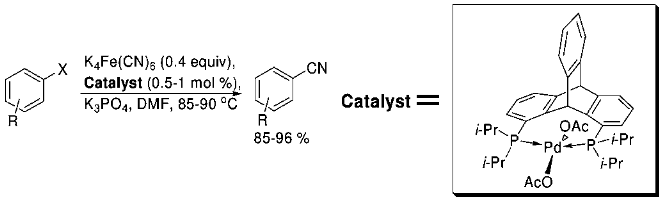
ABSTRACT



The use of a novel trans-spanned palladium complex as an efficient and selective catalyst in the cyanation of aryl halides is described. The suggested reaction conditions are mild, exhibit good scope of substrates, and circumvent the need for an inert atmosphere and amine co-ligands.

Substituted benzonitriles are very common structural motifs in a variety of natural products, pharmaceuticals, dyes, and agrochemicals.[1] In addition, nitriles are valuable precursors in organic synthesis because they can be easily converted into an array of functional groups.[2]

In general, benzonitriles can be prepared via classical reaction of aryl halides with a stoichiometric amount of copper cyanide (Rosenmund-von Braun reaction). However, this method requires very harsh reaction conditions and laborious isolation of products.[3] Since the discovery of transition metal-catalyzed cross-coupling reactions, a great deal of interest has been devoted to the development of a practical catalytic version of this trans-formation.[4] Recently, a number of successful palladium- and nickel-catalyzed protocols were reported disclosing several important factors that govern the overall efficiency of the process. For example, an exposure of a palladium catalyst to high concentrations of cyanide ions significantly inhibits the catalytic cycle, apparently due to the formation of inactive palladium cyanide species which cannot be easily reduced to catalytically active Pd(0) compounds.[5] This problem, namely, the problem of a slow cyanide delivery, can be successfully solved by a careful choice of solvents and cyanide sources. Thus, the use of KCN, CuCN, or Zn(CN)$_2$ in nonpolar solvents such as toluene or xylene was found beneficial in palladium-catalyzed transformations.[6] The recently suggested employment of the masked cyanides such as TMS-CN or acetone cyanohydrin to control the dosage of the inhibiting species appears as an even more elegant overcoming of this drawback.[7]

Further improvements such as the use of TMEDA, DABCO, or MDP as cocatalysts have been introduced. As

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[1] (a) Liu, K. C.; Howe, R. K. *J. Org. Chem.* **1983**, *48*, 4590. (b) Robertson, D. W.; Beedle, E. E.; Swartzendruber, J. K.; Jones, N. D.; Elzey, T. K.; Kauffman, R. F. L.; Wilson, H.; Hayes, J. S. *J. Med. Chem.* **1986**, *29*, 635. (c) Harris, T. M.; Harris, C. M.; Oster, T. A.; Brown, L. E., Jr.; Lee, J. Y. C. *J. Am. Chem. Soc.* **1988**, *110*, 6180. (d) Knight, V. K.; Berman, M. H.; Häggblom, M. M. *Environ. Toxicol. Chem.* **2003**, *22*, 540.

[2] (a) Rappoport, Z. *The Chemistry of the Cyano Group*; Interscience Publishers: London, UK, 1970. (b) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1988.

[3] (a) Ellis, G. A.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. (b) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193.

[4] (a) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513. (b) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.

[5] Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3177.

10.1021/ol0601038 CCC: $33.50

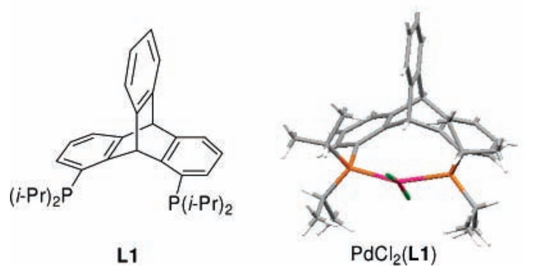


Figure 1. 1,8-Bis(diisopropylphosphino)triptycene.

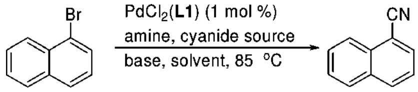
was claimed, the amines serve as co-ligands to allow an additional stabilization of the palladium catalysts.[8]

Finally, the employment of nontoxic cyanide sources such as potassium hexacyanoferrate[9] makes the palladium-catalyzed cyanation of aryl halides an attractive laboratory method.

It is worth noting that despite the diversity of the reported protocols the general reaction conditions remain rather harsh (120−140 °C). As was suggested, the high reaction temperature needed stems from either a slow oxidative addition (due to cyanide interfering)[6−8] or a transmetalation step (when ferrocyanides are used).[9]

Recently, we reported the synthesis and characterization of a new class of strongly bent trans-spanning diphosphine ligands based on the triptycene scaffold that exhibited unique coordination chemistry and promising catalytic activity in cross-coupling reactions (Figure 1 (left)).[10] Inter alia, we found that the palladium geometry in $PdCl_2$(**L1**) (Figure 1 (right)) is strongly distorted from the expected square planar geometry toward a rare butterfly-like environment (P−Pd−P and Cl−Pd−Cl angles are 154.871(17)° and 174.90(2)°, respectively). In principle, this arrangement around the catalytic site might be particularly beneficial in the described transformation. First, we assumed that the unique bent structure of the ligand may provide an effective protection of the transition metal center from the premature contact with inhibiting cyanide ions thus enhancing the reactivity of the catalyst at milder temperatures. One can expect that the effect would be more pronounced if bulky cyanide carriers are employed. Second, the wide bite of the ligand may also assist the reductive elimination[11] of the resulting benzonitrile from the palladium center. Indeed, several theoretical and experimental studies indicate that this step might also be problematic.[12]

Table 1. Initial Optimization Experiments



no.	conditions	GCY,[a,b] %
1	KCN, toluene, TMEDA	8
2	CuCN, DMF, TMEDA	
3	$Zn(CN)_2$, DMF, TMEDA	
4	$K_4Fe(CN)_6$, DMF, K_3PO_4, TMEDA, 85 °C	36 (71)
5	$K_3Fe(CN)_6$, DMF, K_3PO_4, TMEDA, 85 °C	23 (63)
6	$K_4Fe(CN)_6$, DMF, K_3PO_4, no TMEDA, 85 °C	44 (84)
7	$K_4Fe(CN)_6$, DMF, K_3PO_4, no TMEDA, air, 85 °C	41 (81)

[a] GC-based yield after 6 h at 85 °C. [b] Yield in parentheses indicates the GCY after 24 h at 85 °C.

Thus, our initial experiments comprised attempts to accomplish the reaction between 1-bromonaphthalene and different cyanide sources at 85 °C in the presence of 1 mol % of $PdCl_2$(**L1**) (Table 1).

Upon examination of various solvent/base/cyanide combinations we found that the reaction indeed proceeds under mild heating when either $K_4Fe(CN)_6$ or $K_3Fe(CN)_6$ in DMF are used (entries 4 and 5, Table 1). This is especially remarkable because previous reports claimed that the cyanide transfer from $K_4Fe(CN)_6$ is difficult below 120 °C.[9] Interestingly, unlike previously reported procedures, our catalyst does not require the co-assistance of amine ligands (TMEDA, DBU, etc.). In contrast, their effect on the reaction was somewhat deleterious (entry 4 vs entry 6, Table 1).

Furthermore, we found that our catalytic system is perfectly stable to air and the reaction can be performed without rigorous exclusion of oxygen. Only slightly reduced yields were observed when air- and nitrogen-filled reactions were run side by side (entry 6 vs entry 7, Table 1).

Noteworthily, cheap and readily accessible DMF can be used as the solvent to perform the desired reaction: normally, notable decomposition of DMF under the harsh and basic reaction conditions takes place prompting researchers to employ less convenient *N*-methylpyrrolidone (NMP) or *N*,*N*-dimethylacetamide (DMAC) which may complicate the isolation of products.[9c]

Further experiments, which aimed at the discovery of the optimum reaction conditions, revealed that 0.5−1 mol % of

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(6) (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) Okano, T.; Kiji, J.; Toyooka, Y. *Chem. Lett.* **1998**, 425. (c) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193. (d) Sakamoto, T.; Ohsawa, K. *J. Chem.* Soc., *Perkin Trans. 1* **1999**, 2323. (e) Jin, F.; Confalone, P. N. *Tetrahedron Lett*. **2000**, *41*, 3271. (f) Veauthier, J. M.; Carlson, C. N.; Collis, G. E.; Kiplinger, J. L.; John, K. D. *Synthesis* **2005**, 2683.

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(8) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller M. *Eur. J. Org. Chem.* **2003**, *9*, 1828.

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(11) (a) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. (b) Kohara, T.; Yamamoto, T.; Yamamoto, A. *J. Organomet. Chem.* **1980**, *192*, 265. (c) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249. (d) Marcone, J. E.; Moloy, K. G. *J . Am. Chem. Soc.* **1998**, *120*, 8527. (e) Stockland, R. A., Jr.; Levine, A. M.; Giovine, M. T.; Guzei, I. A.; Cannistra, J. C. *Organometallics* **2004**, *23*, 647.

(12) (a) Backvall, J.-E.; Bjorkman, E. E.; Petterson, L.; Siegbahn, P. *J. Am. Chem. Soc.* **1985**, *107*, 7265. (b) Goldberg, K. I.; Yan, J.; Breitung, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 6889. (c) Huang, J.; Haar, C. M.; Nolan, S. P.; Marcone, J. E.; Moloy, K. G. *Organometallics* **1999**, *18*, 297.

the catalyst derived from $Pd(OAc)_2$ and 0.75−1.5 mol % of **L1** can effect the successful transformation of 1-bromonaphthalene into 1-cyanonaphthalene when 0.3 equiv of the nontoxic $K_4Fe(CN)_6$ and 1.5 equiv of K_3PO_4 were used per each equivalent of the aryl halide. Reduction of the starting aryl bromide was the only side reaction (up to 2%).

Since it was previously suggested that $K_4Fe(CN)_6$ can stabilize palladium catalysts under ligand-free conditions,[9b,c] an experiment in the absence of **L1** was carried out to ensure the catalytic effect of $Pd(OAc)_2$/**L1**. Only 26% conversion of the starting material was obtained under the latter reaction conditions in this case.

These results prompted us to study the scope and the possible limitations of the new catalytic systems. The results of this study are tabulated in Table 2.

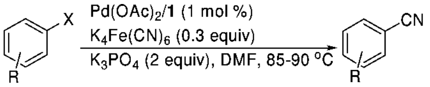
Very efficient transformation of electron deficient (entry 1) and electron neutral (entries 2−8) aryl bromides was observed under mild reaction conditions and air atmosphere. In all these cases, the reaction reached full conversion to the desired cyanoarene after ca. 24 h. Moderately electron-rich heterocycles and polysubstituted aryl bromides exhibited satisfactory reactivity as well (entries 9 and 10, respectively). We also found that 0.5 mol % of the catalyst derived from $Pd(OAc)_2$/**L1** is enough to drive the reaction to completion (entry 6), though slightly higher reaction temperature (90 °C) and a longer reaction time were required. Electron-rich aryl bromides (entry 11) were generally less reactive and led to incomplete reaction under the suggested reaction conditions.

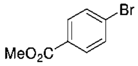
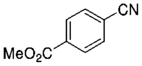
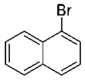
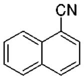
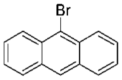
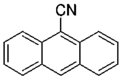
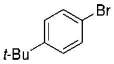
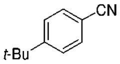
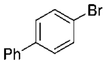
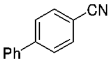
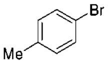
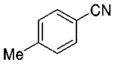
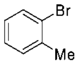
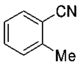
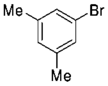
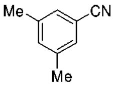
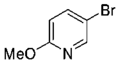
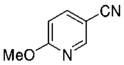
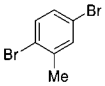
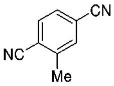
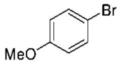
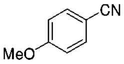
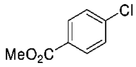
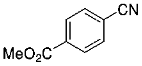
Remarkably, our catalyst was quite insensitive to the steric hindrance of substrates and very good to excellent yields of ortho-substituted benzonitriles were obtained with 2-bromotoluene, 1-bromonaphthalene, and 9-bromoanthracene (entries 2, 3, and 7).

Inspired by these results, we attempted to extend the suggested method to less reactive but less costly aryl chlorides.[8,13] Unfortunately, the reactivity of our catalyst was insufficient to drive the reaction to completion even under higher reaction temperature and prolonged reaction time (entry 12, Table 2).

To conclude, we demonstrated that 1,8-bis(diisopropylphosphino)triptycene (**L1**) is an efficient ligand for the mild palladium-catalyzed cyanation of aryl bromides. In addition, a simple and efficient protocol for the above-mentioned reaction has been developed that circumvents the use of amine co-ligands, nitrogen atmosphere, and troublesome solvents. Finally, the strong dependence of the reaction efficiency on the steric properties of the ligand was observed. The most important ramification of this finding is that the steric properties of the ligand can lead to enhanced protection against premature contact between a catalyst and an inhibiting reagent, and consequently, to more effective catalysis. Therefore, steric factors should not be neglected when more efficient catalysts for this and related transformation are sought.

Table 2. $Pd(OAc)_2$/L1-Catalyzed Cyanation of Aryl Halides under Air



Nº	Ar-X	product	conversion %[c]	isol. yield,%[d]
1[a]			>99	96
2[a]			>99	98
3[b]			>99	84
4[a]			>99	94
5[a]			>99	93
6[a]			>99(>98)[e]	96(91)[e]
7[a]			>99	88
8[a]			>99	91
9[b]			>99	81
10[b]			>99	95
11			71	69[f]
12			34[g]	21[f]

[a] Reaction conditions: 1 equiv of aryl bromide (1 mmol), 0.3 equiv of $K_4Fe(CN)_6$, 2 equiv of K_3PO_4, 1 mol % of $Pd(OAc)_2$, 1.5 mol % of **L1**, 3 mL of DMF, 85 °C, 24 h. [b] Reaction temperature of 90 °C was required to reach full conversion. [c] GC-based conversion. [d] Isolated yield of at least 95% pure material (average of two runs). [e] Conversion obtained with 0.5 mol % of the catalyst after 36 h at 90 °C. [f] GC yield is reported. [g] Full conversion was not reached even after 48 h (120 °C).

In-depth studies on the ligand influence on this transformation, as well as attempts to activate industrially favorable aryl chlorides, are underway.

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Supporting Information Available: General procedure and spectral data for the compounds listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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