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Nucleophilic Displacement Catalyzed by Transition Metal. IX.1) $[Pd_2(dba)_3]\cdot CHCl_3$-DPPF Catalyzed Cyanation of Aryl Halides and Aryl Triflates

Kentaro TAKAGI,* Ken SASAKI,† and Yasumasa SAKAKIBARA†
College of Liberal Arts and Science, Okayama University, Tsushima, Okayama 700
†Department of Polymer Science and Engineering, Kyoto Institute of Technology, Kyoto 606

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A catalyst system comprising $[Pd_2(dba)_3]\cdot CHCl_3$ and DPPF was proved to be efficient for the cyanation of aryl iodides and aryl triflates with KCN. The reactivities of aryl substrates decreased in the order ArI>ArOTf>ArBr.

Although a nucleophilic displacement of nonactivated aryl halides with alkali metal cyanides does not take place under conventional conditions, some transition metals like Ni, Pd, and Co induce a reaction through activation of the sp^2 carbon–halogen bonds of the substrates.2) Regarding the Pd catalyst, $Pd(PPh_3)_4$ and Pd(II) salts, such as $Pd(OAc)_2$, are hitherto known to be active for catalytic cyanation.3) The former is one of the most extensively used complexes in a variety of transition metal-catalyzed reactions,4) although its efficiency toward the cyanation is not satisfactory. Several modifications of this method have thus appeared, in which cyanation was accelerated by adding crown ethers as co-catalysts5) or by using Me_3SiCN6) or NaCN impregnated on alumina7) as a cyanide source. Another possible modification, i.e., tuning the reactivity of Pd(0) by controlling the ligating species, has not been explored for this important transformation.8) In this paper we report that an alternation of the ligand from conventional PPh_3 to 1,1′-bis(diphenylphosphino)ferrocene (DPPF) improves the catalytic efficiency of Pd(0) to a great extent, thereby providing a convenient method for the preparation of aryl cyanides from not only aryl

Table 1. Effect of Solvents and/or Ligands for the Pd(0)-Catalyzed Cyanation of Iodobenzenea)

Run	Solvent	Ligand (Molar ratio of Ligand/$[Pd_2(dba)_3]\cdot CHCl_3$)	Time h	Yieldb) %
1	NMP	—	5	40
2	Acetone	—	5	22
3	THF	—	5	8
4	DMFc)	—	5	<1
5	Acetonitrile	—	5	<1
6	Toluene	—	5	<1
7	Methanol	—	5	<1
8	NMP	DPPF (2)	2	96
9	NMP	DPPF (4)	1	98
10	NMP	DPPF (6)	2	98
11	Acetone	DPPF (4)	5	96
12	THF	DPPF (4)	5	34
13	NMP	$P(o\text{-}Tol)_3$d) (8)	5	79
14	NMP	DPPP (4)	5	5
15	NMP	PPh_3 (8)	5	<1
16e)	NMP	PPh_3	5	<1
17	NMP	PBu_3 (8)	5	<1
18	NMP	$P(OPr^i)_3$ (8)	5	<1
19	NMP	PHEN (4)	5	<1
20	NMP	bpy (4)	5	<1
21f)	NMP	DPPF (4)	12	95
22f,g)	NMP	DPPF (4)	2	96
23h)	NMP	DPPF (4)	12	12

a) In the presence of 1 mmol of iodobenzene, 2 mmol of KCN, 0.005 mmol of $[Pd_2(dba)_3]\cdot CHCl_3$, and 0.01—0.04 mmol of ligand in 0.5 cm^3 of the solvent at 60 °C under nitrogen unless otherwise noted. b) Yields were determined by GLC using an internal standard. c) *N,N*-Dimethylformamide. d) Tri-*o*-tolylphosphine. e) $Pd(PPh_3)_4$ was used in the place of $[Pd_2(dba)_3]\cdot CHCl_3$ and ligand. f) This run was carried out at 40 °C. g) This run was carried out by a successive procedure. h) Bromobenzene was used in the place of iodobenzene.

iodides, but also aryl triflates:[9]

$$ArX + KCN \xrightarrow[X=I\ or\ OTf]{\text{"Pd(0)-DPPF"}} ArCN + KX$$

Results and Discussion

Cyanation of Aryl Iodides. At the beginning, the reaction of iodobenzene with KCN was studied using tris(dibenzylideneacetone)dipalladium(0)-chloroform (1/1) ([$Pd_2(dba)_3$]·$CHCl_3$; dba=dibenzylideneacetone), a commercially available, air-stable zerovalent palladium possessing substitution-labile ligands,[10] as a catalyst precursor to investigate the effect of ligands and solvents on the progress of the Pd(0)-catalyzed cyanation (Table 1). Even in the absence of supporting ligands, the catalytic reaction took place in 1-methyl-2-pyrrolidinone (NMP), acetone, and tetrahydrofuran (THF), but stopped before it reached completion. Although such additives as PPh_3, PBu_3, 1,3-bis(diphenylphosphino)propane (DPPP), triisopropyl phosphite ($P(OPr^i)_3$), 1,10-phenanthroline (PHEN), and 2,2′-bipyridyl (bpy) lowered the catalytic activity of Pd(0), DPPF raised it reversely.[11] Thus, a clean reaction of iodobenzene with KCN proceeded in NMP or acetone at 60 °C by the catalysis of [$Pd_2(dba)_3$]·$CHCl_3$ and DPPF to afford benzonitrile in excellent yield. The present catalyst system is far more reactive than the conventional $Pd(PPh_3)_4$, as exemplified by Runs 9, 15, and 16. The same reaction took place at a lower temperature of 40 °C, as well. In the presence of this catalyst system, a variety of aryl iodides readily underwent cyanation with KCN: substituents like alkyl, alkoxy, acyl, alkoxycarbonyl, and chloro and one attached on the ortho position to iodo-leaving group did not interfere with the progress of cyanation (Table 2). Bromobenzene, however, was ascertained to be far less reactive than aryl iodides for cyanation. It is to be noted that the manner of operation influences the progress of the reaction to a great extent. That is, a simple procedure (see Experimental) required prolonged heating to complete the reaction, compared with a successive procedure: [$Pd_2(dba)_3$]·$CHCl_3$, DPPF, and a solvent were mixed at room temperature before the substrate and KCN were added successively; entire mixture was then heated to the cited temperature (Tables 1 and 3).[12] For the sake of convenience, however, the former procedure was adopted for all runs, except otherwise noted.

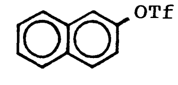
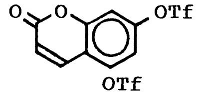
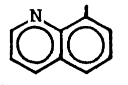
Table 2. Cyanation of Aryl Iodides[a]

Run	$R-C_6H_4-I$ R	Time h	Yield[b] %
24	*p*-$COCH_3$	2	94
25	*p*-Cl	2	93
26	*p*-CH_3	4	94
27[c]	*p*-OCH_3	1	92
28	*m*-CO_2CH_3	2	96
29	*o*-CO_2CH_3	8	93
30	*o*-CH_3	4	87

a) In the presence of 1 mmol of aryl iodide, 2 mmol of KCN, 0.005 mmol of [$Pd_2(dba)_3$]·$CHCl_3$, and 0.02 mmol of DPPF in 0.5 cm^3 of NMP at 60 °C under nitrogen. b) Isolated yield. c) This run was carried out at 80 °C.

Cyanation of Aryl Triflates. The catalytic cyanation of phenolic oxygen was examined next. There has hitherto been no convenient way to convert the hydroxyl group into a cyano group, mainly because of a difficult nucleophilic displacement at the sp^2 carbon atoms.[14] In view of the facts that 1) aryl triflates are prepared readily from phenols[15] and 2) their carbon-oxygen bonds are cleaved by transition metals to form the oxidative adducts,[16] the application of our Pd(0)-catalyzed cyanation to aryl triflates looks promising as an approach to this problem. Recently, a reaction of vinyl triflates with LiCN was attempted in the presence of catalytic amounts of $Pd(PPh_3)_4$ and 12-crown-4.[17] As shown in Table 3, with the aid of the catalyst system comprising [$Pd_2(dba)_3$]·$CHCl_3$ and DPPF, aryl triflates readily underwent a reaction with KCN to afford the corresponding aryl cyanides in good yields:

Table 3. Cyanation of Aryl Triflates[a]

Run	Aryl Triflate $R-C_6H_4-OTf$ R	Time h	Yield[b] %
31	H	8	(94)
32[c]	H	30	(96)
33[c,d]	H	8	(93)
34	*p*-$COCH_3$	3	92
35	*p*-Cl	3	(94)
36	*p*-CH_3	25	87
37	*p*-CN	2	95
38	*p*-CO_2CH_3	3	94
39	*p*-NO_2	2	90
40	*p*-C_6H_5	8	92
41	*p*-OCH_3	25	(45)[e]
42	*p*-$NHCOCH_3$	25	(35)[f]
43		4	91
44		2	98
45		2	95

a) In the presence of 1 mmol of aryl triflate, 2 mmol of KCN, 0.02 mmol of [$Pd_2(dba)_3$]·$CHCl_3$, and 0.08 mmol of DPPF in 0.5 cm^3 of NMP at 60 °C under nitrogen. b) Isolated yield. Yield in parentheses were determined by GLC. c) This run was carried out using 0.005 mmol of [$Pd_2(dba)_3$]·$CHCl_3$ and 0.02 mmol of DPPF. d) This run was carried out by a successive procedure. e) The conversion was 50%. f) The conversion was 48%.

alkyl, aryl, chloro, acyl, alkoxycarbonyl, cyano, or nitro substituent but also 2-naphthyl, 2-oxo-2*H*-benzopyran-7-yl, or 8-quinolyl did not interfere with the progress of cyanation. Electron-donating groups, like alkoxyl and acylamino, however, retarded the reaction, so that the catalytic reaction did not reach completion, even after long heating.

The order of reactivity of aryl substrates in the present Pd(0)-catalyzed cyanation is ArI>ArOTf>ArBr>ArCl. For the closely related Pd(0)-catalyzed cross-coupling with organostannanes, however, a different order (ArI>ArBr>ArOTf>ArCl) had been reported.[18]

At present, the reason why the DPPF-ligand works so well is not clear. Recent papers describe the efficiency of chelation with diphosphorus ligands in the Pd(0)-catalyzed carbonylation of aryl halides.[19] In our case, the cyanide anion, although absolutely neccesary as a reagent, has an inhibitory action on the catalyst; it is capable of binding to Pd(0) too strongly to render the catalyst inactive.[2,3,8,13] Therefore, ligands which can appropriately protect the palladium center from an attack of the free cyanide anion might be desirable.

In conclusion, a catalyst system comprising $[Pd_2(dba)_3]\cdot CHCl_3$ and DPPF was found to be effective for the cyanation of various aryl iodides and aryl triflates with KCN. The facile procedure adopted, owing to the stability of the catalyst precursor and the convenience of the batch method, also makes this catalytic reaction attractive as a new synthetic method of aryl cyanides.

Experimental

$[Pd_2(dba)_3]\cdot CHCl_3$ was utilized as obtained from Kanto Chemical Co. KCN was recrystallized from water and dried under reduced pressure (at ca. 300 °C) prior to use. The solvents were distilled and dried over Molecular Sieves. Aryl triflates were prepared according to a procedure described in the literature.[15] The other materials were commercial products and were used without further purification. A Hitachi 160 gas chromatograph was used for the GLC analysis. The ^{1}H NMR spectra were obtained on a JEOL FX90A spectrometer, using Me_4Si as the internal standard. The IR spectra were recorded on a Hitachi 260-10 spectrometer.

General Procedure for Cyanation. Preparation of *p*-Chlorobenzonitrile: To the dry KCN (139 mg, 2.0 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (5.2 mg, 0.005 mmol), DPPF (11.1 mg, 0.02 mmol), *p*-chloroiodobenzene (238 mg, 1.0 mmol), and NMP (0.5 cm^3) were added, evacuated, flushed with nitrogen, and kept at 60 °C with stirring for 2 h. The resulting mixture was chromatographed on a silica-gel column using hexane-ethyl acetate as an eluent, affording 129 mg of *p*-chlorobenzonitrile (93%). Mp 90—91 °C (lit,[20] 90 °C); IR 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.3—7.5 (m, 4H).

***p*-Cyanoacetophenone:** Mp 56.5—57 °C (lit,[21] 60—61 °C); IR 1680, 2210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.7 (s, 3H), 7.8 (d, *J*=8.0 Hz, 2H), 8.1 (d, *J*=8.0 Hz, 2H).

***p*-Cyanotoluene:** Mp 25. 5—27.5 °C (lit,[22] 27—28 °C); IR 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.4 (s, 3H), 7.3 (d, *J*=8.0 Hz, 2H), 7.5 (d, *J*=8.0 Hz, 2H).

***p*-Cyanoanisole:** Mp 56—56.5 °C (lit,[23] 59 °C); IR 1020, 1260, 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.8 (s, 3H), 7.0 (d, *J*=9.0 Hz, 2H), 7.6 (d, *J*=9.0 Hz, 2H).

Methyl *m*-Cyanobenzoate: Mp 58.5—59 °C (lit,[24] 65 °C); IR 1290, 1720, 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.0 (s, 3H), 7.4—7.9 (m, 2H), 8.2—8.4 (m, 2H).

Methyl *o*-Cyanobenzoate: Mp 48.5—49 °C (lit,[25] 50—51 °C); IR 1270, 1720, 2210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.0 (s, 3H), 7.6—7.8 (m, 3H), 8.1—8.2 (m, 1H).

***o*-Cyanotoluene:** IR 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.5 (s, 3H), 7.2—7.6 (m, 4H).

1,4-Dicyanobenzene: Mp 221—222 °C (lit,[26] 221—222.5 °C); IR 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.8 (s, 4H).

Methyl *p*-Cyanobenzoate: Mp 67—68 °C (lit,[27] 62 °C); IR 1280, 1745, 2235 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.0 (s, 3H), 7.8 (d, *J*=8.7 Hz, 2H), 8.2 (d, *J*=8.6 Hz, 2H).

***p*-Cyanonitrobenzene:** Mp 147—149 °C (lit,[26] 148—149 °C); IR 1350, 1530, 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.9 (d, *J*=8.8 Hz, 2H), 8.4 (d, *J*=8.8 Hz, 2H).

1,1′-Biphenyl-4-carbonitrile: Mp 87.5—88 °C (lit,[28] 86—86.5 °C); IR 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.4—7.8 (m, 9H).

2-Cyanonaphthalene: Mp 67.5—68 °C (lit,[29] 65—66 °C); IR 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.6—7.7 (m, 3H), 7.9—8.0 (m, 3H), 8.25 (s, 1H).

7-Cyanocoumarin: Mp 229—230 °C; IR 1620, 1730, 2240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=6.6 (d, *J*=9.6 Hz, 1H), 7.6 (m, 3H), 7.7 (d, *J*=9.7 Hz, 1H); Calcd for $C_{10}H_5NO_2$: C, 70.18; H, 2.94; N, 8.18%. Found: C, 70.09; H, 3.00; N, 8.10%.

8-Cyanoquinoline: Mp 83—83.5 °C (lit,[30] 82—83.5 °C); IR 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=7.5—7.7 (m, 2H), 8.0—8.4 (m, 3H), 9.1—9.2 (m, 1H).

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