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Nucleophilic Displacement Catalyzed by Transition Metal. I. General Consideration of the Cyanation of Aryl Halides Catalyzed by Palladium(II)

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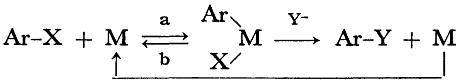
The displacement reaction of various non-activated aryl halides with cyanide ions was investigated in the presence of palladium salts. Various aryl iodides and bromides were converted into the corresponding aryl cyanides in good yields under mild conditions. The addition of certain substances, such as potassium hydroxide and potassium carbonate, enhanced the catalytic activity. Hexamethylphosphoric triamide, in which potassium cyanide was scarcely soluble, was an outstanding solvent for the reaction. The reduced palladium species was supposed to be the active catalyst.

The inertness of aryl halides in the nucleophilic substitution reaction is generally recognized. The reaction with ordinary nucleophiles does not proceed unless the substrates are activated by electron-withdrawing groups.[1] Recently the great affinity of low-valent transition metal complexes for various halides has been reported.[2] Aryl halides, for example, exhibit a remarkable reactivity in oxidative addition to the complexes and sometimes produce isolable adducts in the presence of certain ligands, such as phosphines or isonitriles.[3] This fact suggests that the reversible oxidative addition of an aryl halide to a transition metal, when carried out in the presence of another nucleophile, may produce a product of a displacement reaction.



$$\mathrm{Ar{-}X} + \mathrm{M} \underset{b}{\overset{a}{\rightleftarrows}} \overset{\mathrm{Ar}\diagdown}{\underset{\mathrm{X}\diagup}{\mathrm{M}}} \xrightarrow{\mathrm{Y}^-} \mathrm{Ar{-}Y} + \mathrm{M}$$

a: oxidative addition, b: reductive elimination,
M: transition-metal catalyst, Ar–X: aryl halide,
Y^-: nucleophile

Thus, a net nucleophilic aromatic substitution may take place with the aid of a transition-metal catalyst with otherwise inert substrates. From this point of view, the present authors intended to replace a halogen atom in aryl halide with a cyanide ion and found that palladium (II) salts in *N,N*-dimethylformamide (DMF) did indeed give satisfactory results. When the facile catalytic reaction at a moderate temperature was preliminarily communicated,[4] it was emphasized that the method is more useful for the syntheses of aryl cyanides than the conventional Rosenmund-von Braun reaction.[5] At almost the same time, a catalytic cyanation by a nickel catalyst was also reported.[6] In this paper the results of detailed studies of the reaction conditions will be presented.

Results and Discussion

Outline of the Reaction. Palladium salt, potassium cyanide, and iodobenzene were mixed in an appropriate solvent, and the reaction was carried out under nitrogen, Because of the poor solubility of potassium cyanide, the reaction mixture consisted of a heterogeneous system. The reaction mixture was colorless or pale yellow at the beginning and again at the end of the reaction, whereas it was deep yellow or reddish-brown during the reaction. Sometimes black precipitates appeared, presumably colloidal palladium metal. Benzonitrile, was almost the sole organic product.

$$C_6H_5I + KCN \xrightarrow[\mathrm{Pd(II)}]{} C_6H_5CN + KI$$

Occasionally, small amounts of benzene and biphenyl were detected. Small amounts of water and air stopped the reaction before it reached completion. Under certain conditions, the presence of a co-catalyst such as potassium hydroxide was required to initiate the reaction (*vide infra*).

TABLE 1. Pd(II) CATALYZED CYANATION OF ARYL HALIDES

Run No.	Ar-X	Reaction temp. (°C)	Reaction time (hr)	Ar-X/Pd mole ratio	Other reaction conditions	Yield %
1	C_6H_5–I	100	4.5	100	a)	97.5
2	C_6H_5–I	140	0.2	50	b)	84
3	C_6H_5–I	60	9.0	65	c)	99
4	*p*-CH_3-C_6H_4-I	100	2.0	100	a)	93
5	*o*-CH_3-C_6H_4-I	100	2.0	100	a)	96
6	*m*-Cl-C_6H_4-I	100	5.5	100	a)	70 (*m*-Cl) 21 (*m*-CN)
7	*p*-NH_2-C_6H_4-I	100	10.0	50	a)	0
8	*p*-NO_2-C_6H_4-I	100	10.0	100	a)	70
9	C_6H_5–Br	153	11.5	50	b)	80[f)]
10	C_6H_5–Br	100	0.3	6.5	d)	93
11	C_6H_5–Br	90	2.3	65	c)	94
12	C_6H_5–Cl	90	1.5	65	c)	2
13	C_6H_5–I	140	1.0	50	e)	0

a) $Pd(OAc)_2$ 0.005 mmol, KCN 0.7 mmol, HMPA-(NaOEt incld) 3 ml. b) $Pd(OAc)_2$ 0.04 mmol, KCN(without recrystallization) 4 mmol, DMF 2 ml. c) $Pd(OAc)_2$ 0.015 mmol, KCN 2 mmol, KOH 0.0005 mmol, KI 0.09 mmol, HMPA 1.5 ml. d) $Pd(OAc)_2$ 0.033 mmol, KCN 0.33 mmol, PPh_3 0.066 mmol, $Ca(OH)_2$ 0.03 mmol, DMF 1 ml. e) H_2O 5 μl; other conditions are the same as b. f) Conversion 91%; yield based on consumed bromobenzene.

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The Catalytic Cyanation of Various Aryl Halides. The results from catalytic cyanation with various aryl halides are listed in Table 1.

Aryl iodides, except for amino derivatives (Run 7), produce the corresponding aryl cyanides, in which a cyano group replaces the iodo atom. An *ortho* substituent in aryl iodide does not affect the reaction (Run 5), however, as may be seen in Table 1.

Catalytic cyanation with aryl bromides required more severe conditions than with aryl iodides. That is, a higher temperature (Run 9) or a larger amount of the catalyst and the addition of triphenylphosphine (Run 10) were necessary to complete the reaction. However, the presence of a small amount of potassium iodide promotes the reaction efficiently (Run 11).[7,8]

Chlorobenzene was the least reactive, and even the addition of potassium iodide was scarcelly effective in this case (Run 12). The marked difference in the reactivities of iodo and chloro atoms can also be observed from the experiment cited as Run 6 in Table 1.

The above difference in the reactivities of a series of aryl halides, I>Br>Cl, suggests that the bond dissociation is a crucial step in the catalytic reaction and that the formation of an activated aromatic system, *e.g.*, the π-complex, is not crucial. If such an intermediate should play an important role, the reactivity of aryl halides would decrease in the Cl>Br>I order as in the classical S_NAr reaction with activated aryl halides.[9,10]

The Catalyst System. The catalytic abilities of various palladium (II) salts for the reaction of iodobenzene in hexamethylphosphoric triamide (HMPA) were examined at various temperatures; the results are shown in Table 2. All the palladium salts, except for potassium tetracyanopalladate (II), are effective without the co-operation of any additives. In the presence of a small amount of potassium hydroxide, the reactivity of the catalyst system was greatly enhanced (Table 2). Other active co-catalysts are sodium ethoxide, potassium carbonate, and sodium phenoxide. The palladium complex in the zero oxidation state is also effective as a co-catalyst. The results are shown in Table 3.

Table 2. Activity of various catalyst system (correlation of catalytic activity and reaction temperature)

Catalyst system	Reaction temperature			
	120 °C	100 °C	80 °C	60 °C
$K_2Pd(CN)_4$	C	C	C	C
$Pd(CN)_2$	A	C	C	C
$PdCl_2$	A	B	C	C
$Pd(acac)_2$	A	B	C	C
PdI_2	A	A	B	B
$Pd(OAc)_2$	A	A	B	B
$Pd(OAc)_2$+KOH	A	A	A	A
PdI_2+KOH	A	A	A	A
$Pd(acac)_2$+KOH	A	A	C	C
$Pd(CN)_2$+KOH	A	C	C	C
$K_2Pd(CN)_4$+KOH	C	C	C	C

Reaction condition: C_6H_5I 2 mmol, KCN 4 mmol, HMPA 3 ml, PdX_2 0.03 mmol, KOH (when used) 0.001 mmol.

A represents that the reaction proceeds to completion. B represents that the slower and unpractical reaction takes place or the reaction stops in the middles. C represents that the reaction dose not take place.

Since these co-catalysts have been widely used to reduce transition-metal ions of a higher valence to their corresponding lower-valent ones,[11] the above results seem to suggest the importance of zero-valent palladium. The inertness of cyanide salts ($Pd(CN)_2$, $K_2Pd(CN)_4$) and the solvent effect (*vide infra*) support this idea: since cyanide ion possesses a positive value as the oxidation potential of the next reaction, palladium cyanides may be hard to reduce, and the reduction of palladium cyanides can be achieved only at higher temperatures.[12]

$$Pd + 4X^- = PdX_4^{2-} + 2e^-$$
$$E^0(V) = -0.18\,(X{=}I),\ +0.4\,(X{=}CN)^{13)}$$

Table 3. Effect of various co-catalysts

Run No.	$Pd(OAc)_2$ mmol	Co-catalyst (mmol)	Reaction temp. °C	Reaction time hr	Aryl halide (mmol)	KCN mmol	HMPA ml	Conversion %
14	0.015	—	70	1	C_6H_5I (1)	2	1.5	>1
15	0.015	KOH (0.15)	70	4.5	C_6H_5I (1)	2	1.5	100
16	0.015	K_2CO_3 (0.09)	70	7.5	C_6H_5I (1)	2	1.5	100
17	0.015	NaOPh (0.015)	70	4	C_6H_5I (1)	2	1.5	100
18	0.0065	NaOEt (0.0013)	100	0.5	C_6H_5I (0.33)	1	7.5	100
19	0.015	NaOAc (0.15)	60	2	C_6H_5I (1)	2	1.5	0
20	0.015	Na_2HPO_4 (0.15)	70	1.5	C_6H_5I (1)	2	1.5	0
21	0.015	KOH (0.0005)	60	12	C_6H_5I (1)	2	1.5	100
22	0.015	KOH (0.0005)	90	13	C_6H_5Br (1)	2	1.5	25
11	0.015	KOH (0.0005) KI (0.09)	90	2.3	C_6H_5Br (1)	2	1.5	100
23	0.01	$Pd(PPh_3)_4$ (0.001)	60	0.5	C_6H_5I (0.5)	1.3	1	18.5
24	0.01	PPh_3 (0.006)	60	0.5	C_6H_5I (0.5)	1.3	1	2.9
25[a]	—	$Pd(PPh_3)_4$ (0.01)	70	0.8	C_6H_5I (0.5)	0.7	1	<1

a) Recently $Pd(PPh_3)_4$ catalysed cyanation of aryl iodides in tetrahydrofuran was reported; A. Sekiya and N. Ishikawa, *Chem. Lett.*, **1975**, 278.

In fact, palladium acetate is spontaneously reduced to palladium metal on standing in HMPA at room temperature under nitrogen, whereas palladium cyanide resists the reduction.[14]

Solvent Effect. The catalytic cyanation of iodobenzene was examined in various solvents. The results are shown in Table 4. It is apparent that the solvent affects the catalytic reaction in a striking manner.

TABLE 4. SOLVENT EFFECT

Run No.	Solvent	Reaction temp. °C	Other condition	Conversion %
	DMSO, sulfolane, acetic acid,[a] 1-butanol,[a] diethylene glycol diethyl ether, acetonitrile,[a,b] propionitrile[a,b]	140	A	0
	DMF, PC, DMAc, NMP, TMU, HMPA	140	A	100
	DMF, PC, DMAc, NMP	90	A	0
26	HMPA	90	A	100
27	TMU	90	A	50
28	DMF	120	A	98
29	DMF	100	B	>1
30	DMF	100	C	80
31	DMF	100	D	100

a) reflux, b) convesion$<5\%$

Reaction condition A: $Pd(OAc)_2$ 0.015 mmol, KCN 2 mmol, KOH 0.0005 mmol, C_6H_5I 1 mmol, Solvent 1 ml. Reaction condition B: $Pd(OAc)_2$ 0.033 mmol, KCN 0.5 mmol, C_6H_5I 0.2 mmol, DMF 1 ml. Reaction condition C: $Pd(OAc)_2$ 0.033 mmol, KCN 0.33 mmol, C_6H_5I 0.2 mmol, DMF 1 ml. Reaction condition D: $Pd(OAc)_2$ 0.033 mmol, KCN 0.33 mmol, $Ca(OH)_2$ 0.1 mmol, C_6H_5I 0.2 mmol, DMF 1 ml.

In such protic solvents as acetic acid and 1-butanol, the reaction did not occur under the conditions examined. Some dipolar aprotic solvents, such as acetonitrile, propionitrile, sulfolane, dimethyl sulfoxide (DMSO), and diethylene glycol dimethyl ether, also gave unfavorable results, while DMF, *N*,*N*-dimethylacetamide (DMAc), HMPA, tetramethylurea (TMU), propylene carbonate (PC), and *N*-methylpyrrolidone (NMP) gave satisfactory results. The favorable dipolar aprotic solvents may be further classified into two groups. The more favorable ones include HMPA and TMU, while the others consist of DMF, DMAc, PC, and NMP. That is, the catalytic reaction takes place at lower temperatures in solvents of the former group than in those of the latter (Runs 26, 27).

The advantage of dipolar aprotic solvents in organic reactions has generally been attributed to the stabilization of transition states by its high polarizability and to the formation of so-called naked anions by strong solvation to counter cations.[15] However, the solvent effect here observed could not be interpreted by the general concept alone. The difference in the concentrations of potassium cyanide in these solvents must be taken into account, because the present reaction system is heterogeneous. The solubilities of potassium cyanide in DMSO, DMF, or HMPA, as representatives of the three distinct groups mentioned above, were determined. The results suggest that the most favorable solvent is the one which dissolves potassium cyanide with most difficulty. This conclusion is supported by the fact that sodium cyanide could not be used in place of potassium cyanide as a source of cyanide ions, not even in HMPA: the former is more soluble in HMPA than the latter, which may mean that the cyanide anion itself inhibits the reaction, probably by forming an inert palladium-cyanide bond (*cf.* the discussion of the catalyst system above).[16]

Thus, the ratio of the concentrations of palladium to that of cyanide ions must be kept large for facile catalytic reactions. For example, the catalytic reaction took place at 60 °C in HMPA, whereas it did not occur below 120 °C in DMF (Runs 21, 28), into which potassium cyanide dissolves relatively well, with the same concentration of the catalyst. However, when the amount of the catalyst was increased greatly, the reaction in DMF took place at 100 °C (Runs 29—31).

Experimental

Materials. The palladium acetate,[17] potassium tetracyanopalladate,[18] palladium acetylacetonate,[19] tetrakis(triphenylphosphine)palladium,[20] and substituted iodobenzene[21] were prepared following the literature. The other materials were commercial products.

General Procedure and Analysis. All the reactions were performed in a test tube equipped with a magnetic stirrer and a three-way trap under a nitrogen stream following the procedures described in the previous section. Analytical glc were performed on a Hitachi Perkin-Elmer F 6D gas chromatograph: 35% silicon DC 200 on celite 545, 2 m for the analysis of iodobenzene, *p*-iodotoluene, *o*-iodotoluene, *m*-chloroiodobenzene, bromobenzene, and chlorobenzene at 140 °C (0.8 kg/cm^2 of a nitrogen carrier) and 20% silicon DC 200 on celite 545, 1 m for the analysis of *p*-iodoaniline and *p*-nitroiodobenzene at 160 °C (0.7 kg/cm^2 of a nitrogen carrier). The yields were determined by using internal standards.

A Typical Example of the Catalytic Reactions. Reaction of *p*-iodotoluene: To a mixture of 45.5 mg (0.7 mmol) of KCN (recrystallized from water), 109 mg (0.5 mmol) of *p*-iodotoluene, and 1.1 mg (0.005 mmol) of $Pd(OAc)_2$, a 3 ml portion of HMPA (NaOEt was dissolved) was added. The reaction system was then flushed with nitrogen under stirring and kept at 100 °C. After stirring for 2 hr, aqueous sodium chloride (5 ml) and benzonitrile (50 mg, internal standard) were added to the reaction mixture. The organic products were extracted with ether (5 ml), washed with aqueous sodium chloride (5 ml), and dried over sodium sulfate. The glc analysis showed the formation of 54 mg (0.47 mmol) of *p*-tolunitrile (yield, 93%).

Reaction of Bromobenzene with Potassium Iodide. A suspension of 200 mg (1.2 mmol) of KI, 78 mg (0.5 mmol) of bromobenzene, 3.4 mg (0.015 mmol) of $Pd(OAc)_2$, 6.7 mg (0.1 mmol) of NaOEt, and 1.5 ml of HMPA was heated at 100 °C for 4 hr under a nitrogen. Analysis showed the complete absence of iodobenzene in the solution.

Solubilities of Potassium Cyanide in HMPA, DMF, and DMSO. After a suspension of potassium cyanide in a solvent had been stirred overnight at room temperature under a nitrogen, the potassium metal in the solution was determined with an atomic absorption spectrophotometer (Nippon Jarrell Ash, Type AA-I). One liter of HMPA, DMF, or DMSO dissolved about 0.1, 10, or 200 mmol of KCN respectively. (The solvents used contained, respectively, 10^{-4}, 10^{-5}, and 10^{-4} g of water per 1 ml of the solvent.)

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