Biphasic Cyanation of Aryl Halides with Counter Phase Transfer Catalysts

Tamon Okano,* Jitsuo Kiji, and Yoshiharu Toyooka
Department of Materials Science, Faculty of Engineering, Tottori University, Tottori 680

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The cyanation of aryl iodides with NaCN under heptane-water two-phase conditions is efficiently catalyzed by $PdCl_2\{PPh_2(m\text{-}C_6H_4SO_3Na)\}_2$ in the presence of zinc chloride and $NaBH_4$, and gave the corresponding aryl nitriles in high yields. The biphasic cyanation had an advantage in that the aryl nitriles are easily separated from the mixtures of catalyst and reagents.

The catalytic cyanation of aryl halides with alkali metal cyanides in the presence of Pd,[1] Ni[2] and Co[3] complexes is a good method for the synthesis of aryl cyanides, because the conditions are fairly mild compared with those of the stoichiometric substitution with CuCN.[4] However, owing to the insolubility of the cyanide salts in common organic solvents, the cyanation requires special solvents like HMPA,[5] or special reagents such as phase transfer catalysts-cyanide salts,[6] Me_3SiCN,[7] acetone cyanohydrin,[8] zinc cyanide[9] and NaCN impregnated onto alumina.[10] These are the improvements in the cyanide sources, while there have been few studies on the catalyst system. Recently, we reported that Pd complexes chemically modified with crown ethers are catalytically more effective than the mixed system of unmodified Pd catalysts and crown ethers.[11] Another possible way is the application of counter phase transfer catalysts.[12] As these catalysts are water-soluble, the lipophilic products are easily separable from the catalyst and the cyanide sources. Therefore, we investigated the cyanation using water-soluble catalyst, $PdCl_2\{PPh_2(ms)\}_2$ ($ms{=}m\text{-}C_6H_4SO_3Na$), under biphasic conditions.

The cyanation of phenyl iodide with NaCN was efficiently catalyzed by $PdCl_2\{PPh_2(ms)\}_2$ (**1**) under heptane-water two-phase conditions. The reaction was very fast in the presence of $ZnCl_2$ and $NaBH_4$, and gave benzonitrile almost quantitatively.

$$\underset{Org.}{\text{Ph-I}} + \underset{Aq.}{\text{NaCN}} \xrightarrow[NaBH_4,\ ZnCl_2,\ H_2O\ -\ \text{Heptane}]{PdCl_2\{PPh_2(m\text{-}C_6H_4SO_3Na)\}_2} \text{Ph-CN}$$

The solvent effect on the cyanation with the sulfonated phosphine complex was characteristic of the counter phase transfer catalysis.[13] The catalytic activity was somewhat higher in heptane than those in toluene and anisole. Therefore, we considered this cyanation to be a counter phase transfer reaction, in which the hydrophilic Pd complex transports the phenyl iodide from the organic phase into the aqueous phase and catalyzes the reaction with the cyanide source in the aqueous phase.

The cyanation did not proceed in the absence of $ZnCl_2$. This is probably due to deactivation of the water-soluble catalyst by an excess of cyanide anion.[14] The deactivation was prevented by the addition of zinc chloride. The use of zinc chloride more than 0.25 $NaCN/ZnCl_2$ molar ratio had a striking effect, while small amounts of $ZnCl_2$ were inefficient. This fact suggests that tetracyano zincate and/or zinc cyanide are true cyanide sources. In fact, both zinc complexes were efficient for the biphasic cyanation. Some other metal chlorides such as $CdCl_2\cdot 5/2H_2O$, $SnCl_2\cdot 2H_2O$, $CuCl_2\cdot 2H_2O$ and $FeCl_3\cdot 6H_2O$ had no effect, whereas $NiCl_2\cdot 6H_2O$ or $CoCl_2\cdot 6H_2O$ had some effect, but with less satisfactory results than $ZnCl_2$.

Table 1. Effect of $ZnCl_2$ on the biphasic cyanation of PhI with NaCN in the presence of $PdCl_2\{PPh_2(ms)\}_2$[a]

Additive/mmol	MCl_2/NaCN	Organic Phase	Yield/% [b]
$ZnCl_2$ (3)	0.23	Heptane	0
$ZnCl_2$ (3.5)	0.27	Heptane	97 (62)
$ZnCl_2$ (5)	0.38	Heptane	99 (75)
$ZnCl_2$ (5)	0.38	Toluene	97 (69)
$ZnCl_2$ (5)	0.38	Anisole	96 (68)
$ZnCl_2$ (7)	0.54	Heptane	76
$Na_2Zn(CN)_4$[c] (5)		Heptane	52
$Zn(CN)_2$[c] (5)		Heptane	49
$NiCl_2\cdot 6H_2O$ (5)	0.38	Heptane	28
$CoCl_2\cdot 6H_2O$ (5)	0.38	Heptane	17

[a] A mixture of PhI (10 mmol), NaCN (13 mmol), MCl_2, **1** (0.1 mmol), $NaBH_4$ (0.2 mmol), organic solvent (10 cm^3), and water (10 cm^3) was refluxed with vigorous stirring for 1 h. [b] GC using durene as an internal calibrant, and the yields of the reactions for 0.5 h were shown in the parentheses. [c] In the absence of NaCN.

In the absence of $NaBH_4$, **1** showed no catalytic activity. A mixture of $Pd_2(dba)_3\cdot CHCl_3$ (dba=1,5-diphenyl-1,4-pentadien-3-one) (**2**) and $PPh_2(ms)$ was active without $NaBH_4$. Therefore, the catalytically active species is probably a zero-valent palladium complex. An excess of zinc powder was also able to serve as a reducing agent for **1**, though zinc powder did not have so immediate effects as $NaBH_4$.

Lipophilic catalysts such as **2**-$P(p\text{-tolyl})_3$ and $Pd(PPh_3)_4$ showed negligible activities for the biphasic cyanation. The addition of normal phase transfer catalysts or surfactants is a common method for improving the reactivity. However, the addition of $n\text{-}Bu_4NBr$ or $n\text{-}C_7H_{15}SO_3Na$ to **2**-$P(p\text{-tolyl})_3$ was ineffective in promoting the cyanation, as the organic phase is highly nonpolar. The catalyst systems of **2**-PPh_2(bc-5) and **2**-PPh_2(ma) were somewhat active, though these phosphines are little soluble in water. As these phosphines possess the function of normal phase-transfer catalyst, the cyanation is probably due to the normal phase-transfer catalysis. The higher activity of these catalysts than the above mixed system is likely attributed to a proximity effect.

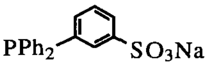
The catalyst system of **2**-PPh_2(mc) was also active for the biphasic cyanation. This phosphine does not have the function of the normal phase-transfer catalyst, while this is water-soluble. Therefore this system probably performs the function of the counter phase-transfer catalyst.

Thus **1** was the best catalyst for the biphasic cyanation, and was applicable to several aryl halides. Aryl iodides having *meta*- or *para*-subusituents were readily cyanated to give the

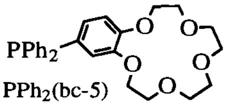
Table 2. Biphasic cyanation of PhI with NaCN in the presence of various phosphine complexes[a]

Catalyst	Additive/mmol	Time/h	Yield/%[b]
$PdCl_2\{PPh_2(ms)\}_2$	none	5	0
$PdCl_2\{PPh_2(ms)\}_2$	$NaBH_4$ (0.4)	1	99
$PdCl_2\{PPh_2(ms)\}_2$	Zn (6)	3	95
$1/2Pd_2(dba)_3\cdot CHCl_3$-$2PPh_2(ms)$	none	5	91
$Pd(PPh_3)_4$	none	5	1
$1/2Pd_2(dba)_3\cdot CHCl_3$-2P(*p*-tolyl)$_3$	none	1	1
	n-Bu_4NBr (1)	1	4
	n-$C_7H_{15}SO_3Na$ (1)	1	1
$1/2Pd_2(dba)_3\cdot CHCl_3$-$2PPh_2$(bc-5)	none	1	8
$1/2Pd_2(dba)_3\cdot CHCl_3$-$2PPh_2(ma)$	none	1	24
$1/2Pd_2(dba)_3\cdot CHCl_3$-$2PPh_2(mc)$	none	1	26

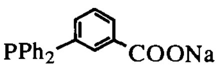
[a]A mixture of PhI (10 mmol), Pd complex (Pd: 0.2 mg atom) and phosphine (0.4 mmol)), NaCN (13 mmol), $ZnCl_2$ (5 mmol), heptane (10 cm^3) and H_2O (10 cm^3) was refluxed. [b]GC yield.



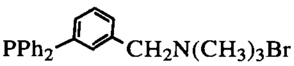
$PPh_2(ms)$



PPh_2(bc-5)



$PPh_2(mc)$



$PPh_2(ma)$

Table 3. Biphasic cyanation of various aryl halides

Substrate	Time/h	Yield/% of Nitrile[a]	
p-Iodoanisole	7	98	
p-Chloroiodobenzene	5	90	
p-Bromoiodobenzene	3	82[b]	
p-Iodoacetophenone	1	97	(91)[c]
Ethyl *p*-iodobenzoate	3	94	
m-Chloroiodobenzene	3	98	
m-Trifluoromethyliodobenzene	3	98	(93)[c]
o-Iodoanisole	24	78	
o-Bromoiodobenzene	24	73	
1-Iodonaphthalene	7	97	(89)[c]
Bromobenzene	5	8	
p-Bromobenzonitrile	7	88	
p-Bromoacetophenone	10	95	
2-Pentene-3-yl trifulate[d]	5	81[e]	

A Mixture of aryl halide (10 mmol), NaCN (13 mmol), $ZnCl_2$ (5 mmol), **1** (0.1 mmol), $NaBH_4$ (0.2 mmol), heptane (10 cm^3), and H_2O (10 cm^3) was refluxed with vigorous stirring. [a]GC yield. [b]*p*-Terephthalonitrile (13%) was detected. [c]Isolated yield. [d]Z:E ratio = 75:25. [e]Z:E ratio = 65:35.

corresponding nitriles in excellent yields. The *ortho*-analouges, however, were less reactive than the *meta*- and *para*-analogues. Though phenyl bromide and chloride were not cyanated under these conditions, aryl bromides having electron-withdrawing substituents gave the nitriles in good yields. Interestingly, 2-pentene-3-yl trifulate was also cyanated in a considerable yield. In all reactions, the cyanated products were easily isolated by a simple layer separation.

In conclusion, the sulfonated phosphine complex is a counter phase transfer catalyst, which is able to perform the double function of inverse phase transfer catalyst and metal catalyst concertedly. The catalyst system has the advantages of easy separation of the product and of high efficiency in inexpensive solvents.

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References and Notes

1 Y. Andersson and B. Langestrom, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1395; K. Takagi, K. Sasaki, and Y. Sakakibara, *Bull. Chem. Soc. Jpn.*, **64**, 1118 (1991); A. Sekiya and N. Ishikawa, *Chem. Lett.*, **1975**, 277.

2 V. V. Grushin and H. Alper, *Chem Rev.*, **94**, 1047 (1994); Y. Sakakibara, F. Okuda, A. Shimobayashi, K. Kirino, M. Sakai, N. Uchino, and K. Takagi, *Bull. Chem. Soc. Jpn.*, **61**, 1985 (1988).

3 T. Funabiki, H. Nakamura, and S. Yoshida, *J. Organomet. Chem.*, **243**, 95 (1983).

4 G. P. Ellis and T. M. Romney-Alexander, *Chem Rev.*, **87**, 779 (1987).

5 Y. Sakakibara, Y. Ido, K. Sasaki, M. Sakai, and N. Uchino, *Bull. Chem. Soc. Jpn.*, **66**, 2776 (1993); K. Takagi, T. Okamoto, Y. Sakakibara, A. Ohno, S. Oka, and N. Hayama, *Bull. Chem. Soc. Jpn.*, **48**, 3298 (1975).

6 E. Piers and F. F. Fleming, *Can. J. Chem.*, **71**, 1867 (1993); N. Sato and M. Suzuki, *J. Heterocyclic Chem.*, **24**, 1371 (1987); M. Prochazka and M. Siroky, *Coll. Czech. Chem. Commun.*, **48**, 1765 (1983); L. Cassar, M. Foa', F. Montanari, and G. P. Marinelli, *J. Organomet. Chem.*, **173**, 335 (1979); A. Jonczyk, M. Ludwikow, and M. Makosza, *Angew. Chem. Int. Ed. Engl.* **17**, 62 (1978); K. Yamamura and S. Murahashi, *Tetrahedron Lett.* **1977**, 4429.

7 N. Chatani and T. Hanafusa, *J. Org. Chem.*, **51**, 4714 (1986).

8 L. Cassar, S. Ferrara, and M. Foa', *Adv. Chem. Ser.*, **132**, 252 (1974).

9 D. M. Tschaen, R. Desmond, A. O. King, M. C. Fortin, B. Pipik, S. King, and T. R. Verhoeven, *Syn. Commun.*, **24**, 887 (1994).

10 J. R. Dalton and S. L. Regen, *J. Org. Chem.*, **44**, 4443 (1979).

11 T. Okano, M. Iwahara, and J. Kiji, *Synlett*, **1998**, in press.

12 T. Okano, Y. Moriyama, H. Konishi, and J. Kiji, *Chem Lett.*, **1986**, 1463.

13 T. Okano, T. Hayashi, and J. Kiji, *Bull. Chem. Soc. Jpn.*, **67**, 2339 (1994); T. Okano, J. Kiji, and T. Doi, *Chem. Lett.*, **1998**, 5.

14 L. Cassar, *Ann. N. Y. Acad. Sci.*, **333**, 208 (1980); (b) P. J. Peerce-Landers and R. J. Jasinski, *J. Electrochem. Soc.*, **130**, 1862 (1983).