Cyanation of Unactivated Aryl Chlorides and Aryl Mesylates Catalyzed by Palladium and Hemilabile MOP-Type Ligands

Yahui Tu,^a Yi Zhang,^b Sheng Xu,^{*a} Zhaoguo Zhang,^b Xiaomin Xie^{*b}

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Abstract: Palladium-catalyzed cyanation of aryl halides and pseudo halides with potassium hexacyanoferrate is described employing the hemilabile, bulky, and electron-rich MOP-type ligands. When the mixture of *t*-BuOH and H₂O was used as the solvent and K₂CO₃ as the base, the MOP-type ligands showed high efficiency for the palladium-catalyzed cyanation. The effect of ligand structure was studied in detail, and 2-di-*tert*-butylphosphino-2'-isopropoxy-1,1'-binaphthyl was the more effective for the cyanation. The catalyst system allows the cyanation of unactivated aryl chlorides, and even aryl mesylates to occur in good yields. Furthermore, the reactivity of different arylated reagents in the catalytic system was found to be: ArBr > ArCl >> ArOMs > ArOSO₂Im > ArOSO₂NMe₂.

Key words: palladium, monophosphine ligands, cyanation, aryl chlorides, aryl mesylates

Benzonitriles are important building blocks of natural products, pharmaceuticals, agrochemicals, and dyes; moreover, nitriles are versatile intermediates in synthetic organic chemistry which can be easily converted into other functional groups, such as carboxylic acids, amides, amines, ketones, and nitrogen-containing heterocycles.¹ Therefore, the introduction of cyanide groups into aryl compounds is a very important step in the development of a variety of well-known compounds used in pharmacy, complex chemistry, and polymer chemistry.² Among various synthetic methods,^{1,3} the transition-metal-catalyzed cyanation of aryl halides or pseudohalides is the more direct and versatile transformation.⁴ Although nickel,⁵ copper,^{4b} and palladium^{4a} complexes are known to be effective catalysts for this transformation, palladium catalyst systems are more advantageous. In general, palladium catalysts are more tolerant towards functional groups, less sensitive to air and humidity compared to nickel catalytic systems, and can be tuned more easily for activating aryl C-X bonds compared to copper catalysts.^{4a} Hence, a lot of effort has been devoted in developing efficient palladium catalysts for the cyanation.

The main problem of palladium-catalyzed cyanation is the catalyst deactivation by coordination of dissolved cyanide ions in the reaction mixture.⁶ This issue can be circumvented by careful control of the concentration of the dis-

SYNLETT 2014, 25, 2938–2942 Advanced online publication: 21.10.2014 DOI: 10.1055/s-0034-1379483; Art ID: st-2014-w0578-1 © Georg Thieme Verlag Stuttgart · New York solved cyanide ion.⁷ Typically, this was achieved by the use of nonpolar solvents such as toluene or xylene for KCN or NaCN or the use of insoluble cvanide salts $[Zn(CN)_2]$.⁸ Another approach is to slowly release cyanide ions from the transformation of organic compounds silylcyanide,9 (trimethyl acetone cyanohydrin,⁷ Bu₃SnCN¹⁰). In addition, coupling with noncoordinating organic cyanides followed by conversion to the corresponding benzonitriles have also been reported.¹¹ Recently, an attractive improvement was made by Beller's group.¹² Nontoxic, cheap, and easy-to-handle potassium hexacyanoferrate(II) $\{K_4[Fe(CN)_6]\}$ was introduced as a cyanide source in the cyanation reactions. Afterwards, improvement of this protocol was reported continually, such as, development of novel catalyst systems,¹³ application of challenging substrates like aryl chlorides,¹⁴ tosylates,¹⁵ and mesylates.¹⁶

Although palladium-catalyzed cyanation is well-established with aryl iodides,¹⁷ bromides,^{10,13b,18} and triflates;¹⁹ aryl chlorides and aryl mesylates offer potential advantages due to their wider availability and lower cost. However, due to the high bond energy of the aryl C-Cl bond, especially the aryl C–O bond of aryl mesylates,²⁰ only a few successful cyanations of these substrates have been reported. Jin and coworkers reported the first palladium-catalyzed cyanation of aryl chlorides at 150 °C with Zn(CN)₂ as the cyanating source.²¹ The use of bulky and electronrich phosphines as the ligand allowed the palladium-catalyzed cyanation of aryl chlorides to be conducted under milder conditions.^{8d,14a,b,22} However, utilizing potassium ferrocyanide as the cyanide source required harsh reaction conditions (i.e., temperatures ranging from 140–160 °C). Significant advances were reported by the research groups of Huang¹⁵ and Kwong,^{14e,16} who utilized the mixture of organic/aqueous solvent to enable cyanide ion transfer from K₄[Fe(CN)₆] under milder conditions. In these catalytic systems, the effect of the ligand structure was very significant. However, the impact of the structural features of the ligands on the catalytic activity for the cyanation have not been explored in detail.

Compared to the other palladium-catalyzed coupling reactions of the unactive electrophiles (such as Suzuki coupling, Buchwald–Hartwig amination), until now, only a few phosphine ligands have been demonstrated to be efficient for the cyanation with K_4 [Fe(CN)₆]^{14c,16} (Figure 1). The hemilabile MOP-type ligands [2-(dialkyl-phosphi-

^a School of Chemistry and Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. of China

^b School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. of China Fax +86(21)54748925; E-mail: xiaominxie@sjtu.edu.cn

Cyanation of Unactivated Aryl Chlorides 2939

no)-2'-alkoxy-1,l'-binaphthyls] are bulky monodentate phosphines with a binaphthyl skeleton and a tunable alkoxy group at the adjacent position of phosphorus atom.²³ These ligands can coordinate to palladium centers through both the phosphorous and oxygen atoms.²⁴ The coordination of the oxygen is considered to be a hemilabile interaction, and we hypothesized that this additional hemilabile coordination site could stabilize the active palladium center and inhibit cyanide binding that typically leads to catalyst deactivation. Herein, we report the efficiency of the MOP-type ligands in palladium-catalyzed cyanation of 'inert' aryl chlorides and aryl mesylate with potassium ferrocyanide.



Figure 1 Structures of bulky phosphine ligands applied in the palladium-catalyzed cyanation

We initially examined the feasibility of using the MOPtype as the ligands in the palladium-catalyzed cyanation of aryl chloride with potassium ferrocyanide (Table 1). The cyanation of electronically neutral *p-tert*-butyl-chlorobenzene did not occur when Pd(dba)₂ was used as the precatalyst with Cs₂CO₃ and *t*-BuOH (Table 1, entry 1). On the basis that $K_4[Fe(CN)_6]$ was soluble in water and water can promote the dissociation of cyanide ion, the solvent was replaced by a mixture of t-BuOH and water (1:1), however, no coupled product was obtained. Generation of a Pd(0) species in situ by addition of $PhB(OH)_2$ to Pd(OAc)₂ provided the desired 4-(tert-butyl)benzonitrile in 17% yield (Table 1, entry 3).²⁵ The poor catalyst activity of Pd(dba)₂ is likely due to the binding of the electronpoor dibenzylideneacetone (dba) to the palladium center. Replacing the base with other carbonate bases, gratifyingly, increased the cyanation yield significantly. When Na₂CO₃ was used as the base, the coupling product was obtained in 68% yield, and the yield increased to 96% in the case of K_2CO_3 as the base (Table 1, entry 5). However, only trace of aryl nitriles was obtained without the addition of PhB(OH)₂ (Table 1, entry 6). K₃PO₄ and KOAc were inferior in the reaction and provided lower yields of the desired product (Table 1, entries 7 and 8). Reducing the loading of K_2CO_3 led to a decrease of the coupling yield (Table 1, entry 9). When *n*-BuOH or *t*-AmOH was used as the solvent, *tert*-butylbenzene was formed as the major byproduct due to reduction of the aryl chloride (Table 1, entries 10 and 11). In a mixture of acetonitrile and water, the cyanation occurred in a moderate yield of 57% (Table 1, entry 12). However, water–dioxane or toluene– water solvent mixtures were not found to be effective (Table 1, entries 13 and 14). An optimal ratio of *t*-BuOH– water was found to be 1:1 as increasing or decreasing the water amount would decrease the yield (Table 1, entries 16 and 17).

 Table 1
 Optimization of Reaction Conditions for Coupling of *p-tert*-Butyl-Chlorobenzene (1a) with Potassium Ferrocyanide^a

<i>t</i> -Bu	-	<i>t</i> -Bu
+ $K_4[Fe(CN)_6] \cdot 3H_2O$	Pd (2 mol%), L1 (8 mol%)	
	base, solvent, 100 °C, 6 h	
CI		CN

1a				2a	
Entry	Pd Source	Base	Solvent	Conv. (%) ^b	Yield (%) ^b
1	Pd(dba) ₂	Cs ₂ CO ₃	<i>t</i> -BuOH	_	_
2	Pd(dba) ₂	Cs_2CO_3	<i>t</i> -BuOH–H ₂ O	18	trace
3°	Pd(OAc) ₂	Cs_2CO_3	<i>t</i> -BuOH–H ₂ O	25	17
4 ^c	Pd(OAc) ₂	Na ₂ CO ₃	<i>t</i> -BuOH–H ₂ O	75	68
5°	Pd(OAc) ₂	K ₂ CO ₃	<i>t</i> -BuOH–H ₂ O	99	96
6	Pd(OAc) ₂	K ₂ CO ₃	<i>t</i> -BuOH–H ₂ O	trace	trace
7°	Pd(OAc) ₂	K_3PO_4	<i>t</i> -BuOH–H ₂ O	23	16
8°	Pd(OAc) ₂	KOAc	<i>t</i> -BuOH–H ₂ O	8	trace
9 ^{c,d}	Pd(OAc) ₂	K ₂ CO ₃	<i>t</i> -BuOH–H ₂ O	86	83
10°	Pd(OAc) ₂	K ₂ CO ₃	<i>n</i> -BuOH–H ₂ O	99	27
11°	Pd(OAc) ₂	K ₂ CO ₃	<i>t</i> -AmOH–H ₂ O	76	34
12 ^c	Pd(OAc) ₂	K_2CO_3	MeCN-H ₂ O	65	57
13°	Pd(OAc) ₂	K ₂ CO ₃	dioxane-H ₂ O	10	3
14°	Pd(OAc) ₂	K ₂ CO ₃	toluene-H ₂ O	10	trace
15°	Pd(OAc) ₂	K ₂ CO ₃	H ₂ O	33	11
16°	Pd(OAc) ₂	K ₂ CO ₃	t-BuOH–H ₂ O (2:1)	97	74
17°	Pd(OAc) ₂	K ₂ CO ₃	t-BuOH–H ₂ O (1:2)	94	81

^a Reaction conditions: aryl chloride (1.0 mmol), K₄[Fe(CN)₆]·3H₂O (0.5 equiv), precatalyst (2 mol%), L1 (8 mol%), base (1.0 equiv), solvent (4.0 mL).

^b Conversion and yields determined by GC analysis of the crude reaction mixture.

^c Additive: PhB(OH)₂ (5 mol%).

^d K₂CO₃ (0.25 equiv).

Next, the structural influence of ligands on the catalytic activity for the cyanation was studied (Scheme 1). Compared to X-Phos, the series of 2-dialkyl phosphino-2'alkoxyl-1,1'-binaphthyl ligands all showed higher catalytic activity for the palladium-catalyzed cyanation of electronically neutral aryl chlorides. Among this type of ligands, both the substituents on the phosphorus atom and oxygen atom affected the catalytic activity. Overall, increasing the steric profile of the dialkylphosphino group or alkoxy group led to higher catalyst activity. Ligands L1 and L4 with an *iso*-propoxy group showed high efficiency for the cyanation. The conversion of aryl chloride increased to 99%, while the yield of the cyanation increased further to 96% when the steric hindrance of substituents on the phosphorus was increased. Under these reaction conditions, DavePhos with a dimethylamino group at the adjacent position of phosphorus atom showed higher activity than that of XPhos. This can be attributed to the additional coordination of the hemilabile amino group. The high catalytic activity of the bulky MOP-type ligands may be attributed to both the bulky nature of the ligands which facilitates the reductive elimination and the hemilabile co-



conv.: 99%; yield: 96% conv.: 66%; yield: 57% conv.: 45%; yield:40% ^a conv.: 99%; yield: 93%



Scheme 1 The effect of the structure of ligands on the palladium-catalyzed coupling of *p-tert*-butyl-chlorobenzene (1a) with potassium ferrocyanide. *Reagents and conditions*: aryl chloride (1.0 mmol), K_4 [Fe(CN)₆]·3H₂O (0.5 equiv), Pd(OAc)₂ (2 mol%), ligand (8 mol%), PhB(OH)₂ (5 mol%), K_2 CO₃ (1.0 equiv), *t*-BuOH–H₂O (1:1) (4.0 mL). Conversion and yields determined by GC analysis of the crude reaction mixture. ^a Pd(OAc)₂ (2 mol%), L1 (6 mol%). ^b Pd(OAc)₂ (2 mol%), L1 (4 mol%).

ordination of the oxygen atom with palladium, which stabilizes the active palladium center and increases the electron density to facilitate the oxidative addition of aryl chloride. Di-*tert*-butyl {2'-isopropoxy-[1,1'-binaphthalen]-2-yl}phosphane (L1) provided the highest conversions and yields (Scheme 1). Decreasing the loading of the ligands led to slightly reduced yields of the desired cyanation product. Therefore, the optimized conditions of the palladium-catalyzed cyanation were identified as: Pd(OAc)₂ (2 mol%), L1 (8 mol%), PhB(OH)₂ (5 mol%), K₃PO₄ (1.0 equiv) as the base, and the mixture of *t*-BuOH and H₂O (1:1) as the solvent at 100 °C.

Under the optimized reaction conditions, we explored the reactivity of different kinds of arylation reagents in the catalytic system (Scheme 2). The comparative rate studies showed that aryl bromides and aryl chloride have very high reactivity in the Pd/MOP catalyst system. The conversion of 4-tert-butylbromobenzene (2a) and corresponding chloride reached 99% and 92% in one hour, respectively, while the conversion rate of the phenol derivatives were slower. This is in accordance to the higher aryl C-O bond strength relative to aryl C-X bonds. The results revealed that the oxidative addition of the aryl C-X or C-O bond may be the rate-determining step during the catalytic cycle. Gratifyingly, the unactive aryl mesylate was also transformed into the aryl nitrile in good yield (83%) after 16 hours, and in the case of the sulfamates, more inert electrophiles, the catalytic system also showed some catalytic activity. Aryl imidazolesulfonates which show high reactivity in palladium-catalyzed Suzuki-Miyaura couplings reactions,²⁶ showed moderate selectivity to give the product in 73% yield after 24 hours.

The scope of the palladium-catalyzed cyanation of aryl chlorides was then explored, and the results are given in



Scheme 2 The reactivity of different kinds of arylation reagents in the Pd/MOP catalytic system

Scheme 3.²⁷ The unactivated aryl chlorides were coupled to give the aromatic nitriles in good yields. The products of benzonitrile (2b) and 2-naphthonitrile (2c) were isolated in 78% and 83% yields, respectively. Furthermore, the electron-rich aryl chlorides were also reacted in high yields. 3,4-(Methylenedioxy)chlorobenzene (1e) and N-Boc-4-chloroaniline (1f) afforded the coupling products in 81% and 80%, respectively. Even the unprotected 4-chloroaniline (1g) was cyanated to obtain the desired aryl nitriles in 50% yield, and no amination product, diarylamine, was detected. Reaction of *o*-tolylchloride (1h) provided a diminished yield of 53% which is likely due to the steric hindrance near the C-Cl bond. Moreover, the catalytic system tolerated heterocyclic substrates. Reaction of 3-chloropyridine (1j) proceeded smoothly to give the desired product in 76% yield. The cyanation of 6-chloroquinoline (1k) was also successful and afforded the product in 62% yield.



Scheme 3 Palladium-catalyzed the cyanation of aryl chlorides. *Reagents and conditions*: aryl chloride (1.0 mmol), K_4 [Fe(CN)₆]·3H₂O (0.5 equiv), Pd(OAc)₂ (2 mol%), L1 (8 mol%), PhB(OH)₂ (5 mol%), K_3PO_4 (1.0 equiv), *t*-BuOH–H₂O (1:1, 4.0 mL), 100 °C, isolated yield. ^a Pd(OAc) (4 mol%) was used.

Phenol derivatives are complementary to aryl halides as electrophiles in the transition-metal-catalyzed coupling reactions, because phenols are easily available, and the oxygen atom on the aromatic ring can be used to introduce additional substituents via a number of pathways which would enrich the coupling substrates.²⁰ Among the phenol derivatives, aryl mesylates are cheaper and more stable than aryl triflates, so they are highly favorable as the substrates of cyanation. Encouraged by the reactivity of different electrophiles (Scheme 2), the cyanation of aryl mesylates was explored with our catalytic system. When

the bath temperature was increased to 120 °C, electronically neutral and electron-rich aryl mesylates were cyanated in good yield (Scheme 4).²⁷ The coupling reaction of *p*-methoxyphenyl (**5d**) or *p*-(*N*-Boc)aminophenylmethanesulfonate (**5f**) afforded the products in 85% and 78%, respectively. Similar to the reactivity of aryl chlorides, an increase in the steric hindrance of the substrate led to a decrease in yield. The cyanation of *o*-methylphenylmethanesulfonate (**5h**) generated the product in 53% yield. However, the cyanation of the electron-deficient aryl mesylates **5l–n** occurred in moderate yield, and was accompanied by the formation of the corresponding phenols due to competitive hydrolysis.



Scheme 4 Palladium-catalyzed cyanation of aryl mesylates. *Reagents and conditions*: aryl chloride (1.0 mmol), K_4 [Fe(CN)₆]·3H₂O (0.5 equiv), Pd(OAc)₂ (2 mol%), L1 (8 mol%), PhB(OH)₂ (5 mol%), K_3PO_4 (1.0 equiv), *t*-BuOH–H₂O (1:1, 4.0 mL), 120 °C, isolated yield. ^a Pd(OAc) (3 mol%) was used.

In summary, the hemilabile and bulky MOP-type ligands were found to be efficient ligands for the palladium-catalyzed cyanation of unactivated aryl chlorides and aryl mesylates with the nontoxic $K_4[Fe(CN)_6] \cdot 3H_2O$ as the cyanide source. The steric profile and the presence of a hemilabile coordination contribute to the effectiveness of these ligands. 2-Di-*tert*-butylphosphino-2'-isopropoxy-1,1'-binaphthyl (L1) exhibited the highest efficiency for the cyanation of both aryl chlorides and aryl mesylates. The mild catalytic system tolerated electron-donating substituents, such as free amino groups and heterocyclic groups. In the catalytic system, the reactivity of different arylated reagents was also obtained: ArBr > ArCl >> ArOMs > ArOSO_2Im > ArOSO_2NMe_2.

LETTER

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(27) General Procedures for the Cyanation of Aryl Chlorides and Mesylates An oven-dried Schlenk tube was evacuated and backfilled with nitrogen. The Schlenk tube was charged with Pd(OAc)₂ (4.5 mg, 0.02 mmol), L1 (36.5 mg, 0.08 mmol), PhB(OH)₂ (6.1 mg, 0.05 mmol), and t-BuOH (2 mL), and the mixture was stirred for half hour at 50 °C. After cooling to r.t., aryl chloride or mesylates (1.00 mmol), K₄[Fe(CN)₆]·3H₂O (211.2 mg, 0.50 mmol), K₂CO₃ (138.2 mg, 1.00 mmol), and H₂O (2 mL) were added. The septum was replaced with an inside reflux condenser, and then the Schlenk tube was placed in an oil bath preheated to 100 °C (120 °C for aryl mesylates) with stirring for 6 h (24 h for aryl mesylates). Then the reaction mixture was allowed to cool to r.t., extracted with CH2Cl2, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel.

4-(*tert*-Butyl)benzonitrile (2a)

The crude material was purified by column chromatography on silica gel (eluting with PE–EtOAc, 20:1) to give the compound as yellow oil (127.4 mg, 80%). ¹H NMR (400 MHz, CDCl₃): δ = 7.61–7.57 (m, 2 H), 7.50–7.46 (m, 2 H), 1.33 (s, 9 H). ¹³C NMR (100 MHz, CDCl₃): δ = 156.4, 131.7, 126.0, 118.9, 109.1, 35.1, 30.8. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.