Palladium acetate catalyzed cyanation of aryl halides using Buchwald's 2-(di-*t*-butylphosphino)-1,1'-binaphthyl

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Dedicated to Professor Franklin A. Davis on his 70th birthday

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Abstract

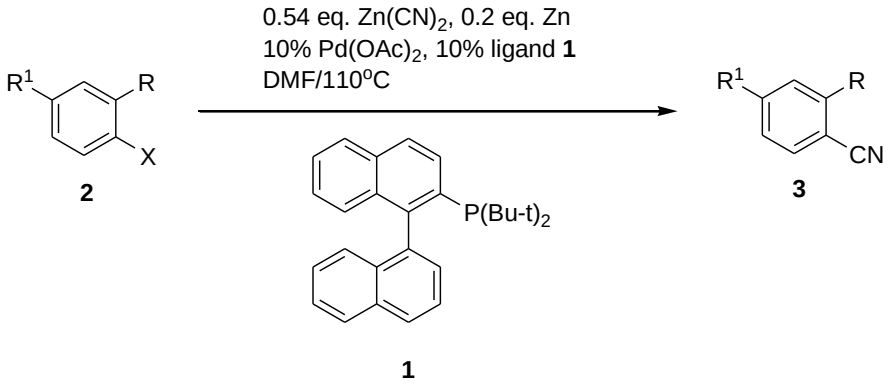
An application of Buchwald's 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1** in palladium acetate catalyzed cyanation of aryl halides was developed. Using this ligand, aryl chlorides substituted with both electron donating or withdrawing groups afforded the desired cyano products in excellent yields. The corresponding aryl bromides gave higher yields within shorter time. Heteroaryl chlorides also reacted under the similar conditions to give the cyano products in excellent yields.

Keywords: Palladium acetate catalyzed, cyanation, aryl halides, Buchwald, 2-(di-*t*-butylphosphino)-1,1'-binaphthyl

Introduction

2-(Di-*t*-butylphosphino)-1,1'-binaphthyl belongs to a class of ligands developed by Buchwald and coworkers for transition metal catalyzed cross coupling reactions. 2-(Di-*t*-butylphosphino)-1,1'-binaphthyl has been found to be an effective ligand in palladium catalyzed C-O and C-N bond formations.[1,2] For example, 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1** has been successfully used in the formation of oxygen heterocycles,[1a] intermolecular[1b,e,f] and intramolecular [1c] synthesis of aryl ethers, amination of aryl sulfonates,[2a] amination of diphenylporphyrins and tetraphenylporphyrins.[2b] In addition, the palladium/2-(di-*t*-butylphosphino)-1,1'-binaphthyl system has found growing application in the synthesis of various chemically and biologically important compounds such as (+)-heliannuol D,[1d] meso-amidoporphyrins[2c] and murrastifoline-A.[2d] In many cases, 2-(di-*t*-butylphosphino)-1,1'-binaphthyl was found to be superior to other related phosphines in these cross coupling reactions.

More recently, an excellent method was published for the cyanation of aryl chlorides using 2-(di-*t*-butylphosphino)-1,1'-binaphthyl and palladium trifluoroacetate as catalyst.[3] This paper promted us to report our findings of using 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1** and palladium acetate for the cyanation of aryl chlorides and bromides **2** to give to benzonitriles **3**.



Scheme 1

Results and Discussion

In our experiments, the palladium acetate catalyzed cyanation of aryl halides **2** was conducted in DMF using 0.1 equiv of $Pd(OAc)_2$ and 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1**, 0.54 equiv of $Zn(CN)_2$ as the cyanide source in addition of 0.2 equiv of zinc dust.[4a] The reaction was run at 110 °C and followed by HPLC. The results are summarized in Table 1.

As can be seen from the Table 1, cyanation of 2-acetamido phenyl chloride **2a** using 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1** in DMF at 110 °C for 1h gave the desired 2-acetamido benzonitrile **3a** in 90% conversion (Table 1, entry 1). Heating the reaction mixture for an additional hour improved the conversion to 97% and the product was isolated in 90% after usual work-up and silica gel chromatographic purification (Table 1, entry 2). With this initial success, we tried various other phenyl chlorides and bromides substituted with different electron donating and electron withdrawing groups (Table 1, entries 3 to 11). Under the same reaction conditions, all the desired benzonitrile products were obtained. A number of general observations were made in our palladium catalyzed cyanation of aryl halides using 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1**. Firstly, aryl chlorides with electron donating group on the phenyl ring tend to be less reactive than those with electron withdrawing groups (Table 1, compare entry 1-8). Secondly, the yield for the less active aryl chlorides could be improved by simply heating the reaction mixture for longer time (Table 1, compare entry 1 vs. 2 and entry 3 vs. 4). Thirdly, the reaction rate and yield enhancement could be more readily achieved by using the corresponding bromo instead of chloro substrates, which is consistent with the observation made for other phosphine ligands reported for such a transformation.[4b] For example, use of 4-methyl phenyl

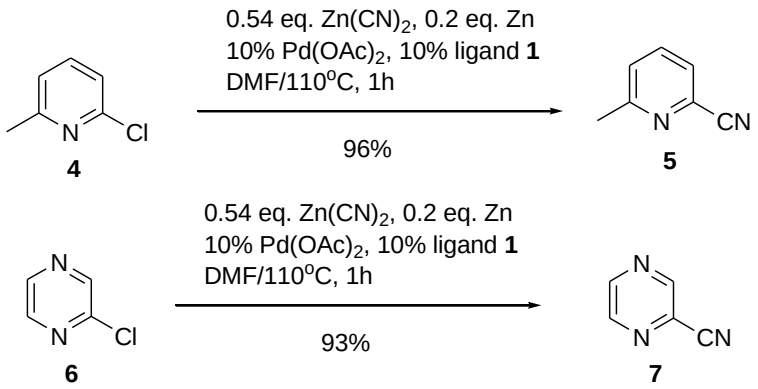
bromide instead of 4-methyl phenyl chloride in the reaction improved the conversion from 44% to 97% in one hour (Table 1, compare entry 3 vs. 10). A similar trend was observed for other substrates such as **2a**/**2g** and **2c**/**2i**.

Table 1. Palladium acetate catalyzed cyanation of aryl halides **2** using 2-(di-*t*-butylphosphino)-1,1'-binaphthyl (**1**) in DMF at 110 °C

Entry	Substrate (**2**)	X	R	R^1	Reaction Time (h)	Product (**3**)	Yield (%)[a]
1	**a**	Cl	NHAc	H	1h	**a**	90
2	**a**	Cl	NHAc	H	2h	**a**	97 (90)
3	**b**	Cl	H	Me	1h	**b**	44
4	**b**	Cl	H	Me	7h	**b**	94 (85)
5	**c**	Cl	H	SMe	1h	**c**	42
6	**d**	Cl	H	CF_3	1h	**d**	99 (91)
7	**e**	Cl	H	MeCO	1h	**e**	97 (90)
8	**f**	Cl	H	NO_2	1h	**f**	90 (80)
9	**g**	Br	NHAc	H	1h	**a**	98 (93)
10	**h**	Br	H	Me	1h	**b**	97 (93)
11	**i**	Br	H	SMe	1h	**c**	96 (90)

[a]Yields in ( ) are isolation yields.

Next, we tried the palladium acetate catalyzed cyanation using 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1** on heteroaryl chlorides. Thus, treatment of 2-chloro-6-methylpyridine **4** under the same conditions described above afforded 2-cyano-6-methylpyridine **5** in 96% yield. It should be pointed out that cyanation of **4** using KCN was reported previously.[5] The reaction was carried out at 170-180°C for 10hr and the desired product **5** was obtained in 39% yield.[5] Cyanation of chloropyrazine **6** using 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1** as ligand under the new reaction conditions gave 2-cyanopyrazine **7** in 93%.



Scheme 2

Conclusions

In summary, an application of Buchwald's 2-(di-*t*-butylphosphino)-1,1'-binaphthyl **1** in palladium acetate catalyzed cyanation of aryl halides was developed. Using this ligand, aryl chlorides substituted with both electron donating or withdrawing groups afforded the desired cyano products in excellent yields. The corresponding aryl bromides gave higher yields within shorter time. Heteroaryl chlorides also reacted under the similar conditions to give the cyano products in excellent yields. The application of this method to the synthesis of our biologically active compounds will be reported in due course.

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Experimental Section

General. Proton and 13-carbon magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a JEOL Eclipse 500 spectrometer and are reported in *ppm* using TMS as internal standard. Melting points are uncorrected. HPLC and LCMS analyses were conducted using a Shimadzu SCL-10A liquid chromatograph and a SPD uv-vis detector at 220 or 254 nm with the MS detection performed with either a Micromass Platform LC spectrometer or a Waters Micromass ZQ spectrometer. All flash column chromatography was performed on EM Science silica gel 60 (particle size of 40 – 60 μm). All reagents were purchased from commercial sources and used without further purification unless otherwise noted.

Preparation of *N*-(2-cyanophenyl)acetamide, 3a. Typical procedure

To a mixture of N-(2-chlorophenyl)acetamide (169 mg, 1 mmol), zinc cyanide (63 mg, 0.54 mmol), zinc (13 mg, 0.2 mmol), 1,1'-binaphthyl-2-yldi-tert-butylphosphine (40 mg, 0.1 mmol) in DMF (3 ml) was added palladium acetate (22 mg, 0.1 mmol). The reaction was heated rapidly to 110 °C and stirred vigorously under N_2 for 1h before the mixture was cooled to room temperature. The mixture was diluted with ethyl acetate (30 ml), washed with 2 N NH_4OH solution (25 ml) and brine (20 ml). The organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue was refluxed in toluene (6 ml) for 5 min and then cooled to room temperature. The precipitate was collected by filtration to give product as a white solid (145 mg, 90% yield). mp 132-134 °C, lit.[9] 133-134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J*= 8.2 Hz, 1H), 7.62 (s, 1H), 7.58 (t, *J*= 8.2 Hz, 2H), 7.15 (t, *J*= 7.7 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 68.52, 140.80, 134.18, 132.20, 124.11, 121.30, 116.40, 101.95, 24.71; *m/z* [M+1] 161.14.

Preparation of 4-acetobenzonitrile, 3e. Typical procedure

To a mixture of 4'-chloroacetophenone (155 mg, 1 mmol), zinc cyanide (63 mg, 0.54 mmol), zinc (13 mg, 0.2 mmol), 1,1'-binaphthyl-2-yldi-tert-butylphosphine (40 mg, 0.1 mmol) in DMF (3 ml) was added palladium acetate (22 mg, 0.1 mmol). The reaction was stirred under N_2 and heated rapidly to 110 °C for 1h. The mixture was cooled to room temperature, diluted with ethyl acetate (30 ml), washed with 2 N NH_4OH solution (25 ml) and brine (2 x 20 ml). The organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography on silica gel with ethyl acetate/hexane to provide the desired product as a white solid (130 mg, 90% yield). mp 56-57 °C, lit.[6] 57-58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.76 (dd, *J*= 1.6, 5.0 Hz, 2H), 2.62 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 196.20, 140.00, 132.49, 128.66, 117.84, 116.47, 26.65; *m/z* [M+1] 146.19.

6-Methylpicolinonitrile, 5. Following the experimental procedure described above using 2-chloro-6-methylpyridine **4**, 6-methylpicolinonitrile **5** was obtained in 96% yield as a solid after purification by flash column chromatography on silica gel with ethyl acetate/hexane. mp 70-72 °C, lit.[7] 71.5-72 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, *J*= 7.7 Hz, 1H), 7.46 (d, *J*= 7.7 Hz, 1H), 7.32 (d, *J*= 8.2 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 160.65, 136.98, 133.21, 126.76, 125.59, 117.32, 24.28.

2-Cyanopyrazine, 7. Following the experimental procedure described above using chloropyrazine **6**, 2-cyanopyrazine **7** was obtained in 93% yield as an oil after purification by flash column chromatography on silica gel with ethyl acetate/hexane. The spectroscopic data were consistent with those reported in the literature.[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.72 (d, *J*= 2.8 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 147.96, 147.17, 145,19, 130.52, 115.01.

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