A Convenient and Efficient Palladium-Catalyzed System for Cross-Coupling of Aryl Bromides with Active Methylene Compounds

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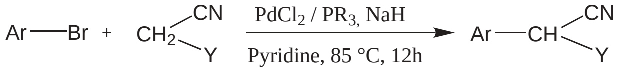
Abstract: A simply catalytic system containing palladium-phosphine complex, generated in situ from $PdCl_2$/*tert*-phosphino ligand in pyridine, has been systematically studied in the cross-coupling of bromobenzene with malononitrile or ethyl cyanoacetate anion. The effect of molar ratio of phosphine ligand to $PdCl_2$ on the activity of the coupling was also discussed. It is found that the catalytic system has highly catalytic activity to produce aryl malononitriles and cyanoacetates in considerable yields (67–90%) when the substituted aryl bromides were used as substrates.

Key word: palladium catalysis, cross-coupling, arylmalononitrile, arylcyanoacetate, aryl bromide

Transition metal-catalyzed cross coupling reaction is a key tool of carbon-carbon bond formation in organic synthesis.[1] Since the 1980s', metal-mediated synthesis of α-arylmalononitriles and α-aryl-β-cyanoacetates has attracted a lot of interests due to their use as important intermediates in the preparation of organic compounds like bioactive materials,[2] heterocyclic compounds,[3] and organic conducting materials.[4] After Suzuki et al.[5] reported the cross-coupling of aryl iodides with malononitrile or cyanoacetate anion by using copper(I) iodide as catalyst, several successful preparations of arylmalononitriles and arylcyanoacetates by the catalytic cross-coupling of aryl halides using $PdCl_2(PPh_3)_2$,[6] $Pd(PPh_3)_4$,[7] Cu(I) salts[8] and $PdCl_2(PPh_3)_2$/dppe[9] as catalysts have been reported in satisfactory yield. Cristau et al. also reported the arylation of aryl halides with malononitrile catalyzed by 10–20 mol% of nickel(0) complexes in good yields.[10] Generally, the amounts of the metal catalysts used in the reactions are 4 mol% or more, and sometimes in order to smoothly perform the process, some special solvents, such as HMPA, DMSO and DME are employed.

A noteworthy advance in the palladium-catalyzed arylation of cyanoesters and malonates was made by Hartwig et al. by using sterically hindered trialkyl- and ferrocenyldialkylphosphine ligands.[11] Recently we have reported that the N-heterocyclic carbene palladium complexes could effectively promote the arylation of aryl halides with malononitrile anion in excellent yields.[12]



1 **2**, Y = CN
3, Y = CO_2Et
2 a–g
3 a–g

Scheme 1

Now we herein report the palladium-catalyzed C-C bond coupling of aryl bromides with active methylene compounds using a simple catalytic system[13] of Pd(II) chloride and tertiary phosphine ligand in pyridine. Our initial experiments were carried out starting from the coupling of bromobenzene with malononitrile as a model[14] by directly using catalytic amounts of $PdCl_2$ (1 mmol%) and triphenylphosphine ligand (TPP, 3 mol%) (Scheme 1). Phenylmalononitrile, the reaction product, was obtained in satisfactory yield in the presence of sodium hydride at 85 °C (Table 1, entries 5 and 6). Obviously, without the presence of $PdCl_2$ and phosphine ligand, the target product was not detected (Table 1, entries 1–3). In addition, when the amount of $PdCl_2$ was increased by two times, the yield was not enhanced evidently (Table 1, entry 6, 89% yield). But when its amount was cut down to 0.5 mol%, the yield was sharply decreased to 45% (Table 1, entry 4). When employing tetrahydrofuran instead of pyridine as solvent, it only afforded 24% yield (Table 1, entry 7). Obviously, pyridine as solvent possibly plays an important role in promoting the formation of the catalytic species.

The effect of the molar ratio of phosphine ligand to metal palladium (II) on activity of the coupling was also investigated. As seen in Table 1 (entries 8–13), with the increase of the amounts of triphenylphosphine ligand from 1 mol% to 3 mol%, the yields of catalytic reactions ascended from 65% to 88% (entries 8–10). While the ratio was up to 10 equivalent, the excess ligand led to the decrease in the yields of the coupling product to a certain extent (entry 13). Therefore, the best ratio of phosphine ligand to $PdCl_2$ is 3:1.

To explore the effect of phosphine ligands on the activity, a series of tertiary phosphine ligands including some chelating ligands were used in the coupling. The experimental results demonstrated that other *tert*-phosphine ligands, like tri-2-methoxyphenyl phosphine (TMPP), bis(diphenylphosphino) methane(dppm), bis(1,2-diphenylphosphino) ethane (dppe), bis(1,3-diphenylphosphino) propane (dppp), bis(1,4-diphenylphosphino) butane (dppb) and bis(diphenylphosphino) ferrocene (dppf),

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Table 1 Effect of Molar Ratio of Ligand TPP to $PdCl_2$ and *tert*-Phosphino Ligands on Cross-Coupling of Bromobenzene with Malononitrile Anion[a]

Entry	Ligand (mol%)	$PdCl_2$ (mol%)	Yield[b] (%)
1	None (0)	1	0
2	None (0)	0	0
3	TPP (3)	0	0
4	TPP (1.5)	0.5	45
5	TPP (3)	1	88
6	TPP (6)	2	89
7[c]	TPP (3)	1	24
8	TPP (1)	1	65
9	TPP (2)	1	80
10	TPP (3)	1	88
11	TPP (4)	1	86
12	TPP (6)	1	80
13	TPP (10)	1	70
14	TMPP (3)	1	87
15	dppm (3)	1	85
16	dppe (3)	1	87
17	dppp (3)	1	88
18	dppb (3)	1	90
19	dppf (3)	1	86

[a] All reactions were performed in pyridine at 85 °C for 10–12 h; PhBr:$CH_2(CN)_2$:NaH = 1:1.25:2.7.
[b] Isolated yields were based on ArBr after separation of preparative TLC using silica gel.
[c] Reacted in THF.

have similar excellent activity to that of triphenylphosphine (TPP) for the coupling under the mentioned reaction conditions (Table 1, entries 14–19). It indicates that a broad spectrum of *tert*-phosphino-ligands could be applied to this kind of catalytic coupling.

On the basis of the above results, we have tried to extend the application field of the $PdCl_2$–PPh_3 catalysis system to the preparation of substituted arylmalononitriles and arylcyanoacetates. As seen from Table 2, a series of substituted aryl bromides could smoothly proceed the catalytic coupling with a malononitrile anion or an ethyl cyanoacetate anion in high efficiency, and the corresponding coupling products of aryl substituted malononitriles or ethyl cyanoacetates were obtained in good yields of 67–88% (Table 2, entries 1–14).

Table 2 The Reaction of Aryl Bromide with Malononitrile and Ethyl Cyanoacetate Anion[a]

Entry	Ar	Product	Yield[b] (%)
1	C_6H_5	**2a** (Y = CN)	88
2	C_6H_5	**3a** (Y = CO_2Et)	84
3	2-$CH_3C_6H_4$	**2b** (Y = CN)	73
4	2-$CH_3C_6H_4$	**3b** (Y = CO_2Et)	77
5	4-$CH_3C_6H_4$	**2c** (Y = CN)	80
6	4-$CH_3C_6H_4$	**3c** (Y = CO_2Et)	85
7	2- $CH_3OC_6H_4$	**2d** (Y = CN)	75
8	2- $CH_3OC_6H_4$	**3d** (Y = CO_2Et)	73
9	4-$CH_3OC_6H_4$	**2e** (Y = CN)	72
10	4-$CH_3OC_6H_4$	**3e** (Y = CO_2Et)	75
11	4-F-C_6H_4	**2f** (Y = CN)	73
12	4-F-C_6H_4	**3f** (Y = CO_2Et)	85
13	1-Napthelyl	**2g** (Y = CN)	82
14	1-Napthelyl	**3g** (Y = CO_2Et)	67

[a] Reaction conditions: ArBr:$CH_2(CN)Y$:NaH:$PdCl_2$:PPh_3 = 2:2.5:5.4:2%:6%; Pyridine (6 mL), 85 °C for 10–12 hours;
[b] Isolated yields were based on ArBr after separation of preparative TLC using silica gel.

Briefly, we herein provide a convenient and effective procedure of preparing α-aryl-malononitriles and α-aryl-β-cyanoacetates by the arylation of aryl bromides with a α-difunctionalized anion using a convenient and efficient catalytic system of $PdCl_2$–PAr_3. The reaction, simple and inexpensive, works effectively with low moles of metal palladium(II) and mild reaction conditions in good yields. In addition, there is no need to prepare the palladium complex prior to use.

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(13) **Preparation of the catalyst in pyridine**: Triphenylphosphine (0.06 mmol) and palladium chloride (0.02 mmol) were mixed in a predried Schlenk tube under dry argon. Then 1 mL of dry pyridine was added and the mixture was stirred at 60 °C for 15 min.

(14) **General procedure for the cross-coupling of aryl bromides with active methylene compounds**: Under an Ar atmosphere to a predried Schlenk tube with 5 mL of dry pyridine was added a mixture of NaH (5.4 mmol) and malononitrile or ethyl cyanoacetate (2.5 mmol), respectively. Following the catalyst ($PdCl_2$/Ligand)[13] prepared as described above was injected, and the mixture was stirred at ambient temperature for 5min. After addition of an aryl bromide (2 mmol), the mixture was heated at 85 °C for an appropriate time (10–12 h). The progress of the reaction was monitored by TLC. After removal of the solvent by distillation in vacuum, the residue was neutralized with diluted hydrochloric acid (10 mL), and the product was extracted with 15 mL × 3 diethylether, washed with 2 × 10 mL of brine, dried over Na_2SO_4, filtered and concentrated. The residue from the ether extract was purified by TLC (silica gel GF254, 20 × 20 cm) using a developing solution of petroleum ether (60–90 °C)/ethyl acetate (6:1 for arylmolononitriles or 10:1 for aryl ethyl cyanoacetates), and the fractions containing the products were collected and extracted with CH_2Cl_2. The products were obtained after evaporation of the extract. The arylmolononitriles were further purified by recrystallization [petroleum ether (60–90 °C)/CH_2Cl_2, 6:1]. The products of coupling were identified by means of ^{1}H NMR and mp, which are in agreement with literature data.[5–11]