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Short Communication

Heck coupling reaction catalyzed by $[(C_3H_5)PdCl]_2$-*N*,*N*,*N*′,*N*′-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine

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ABSTRACT

Pd-*N*,*N*,*N*′,*N*′-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine was used for Heck coupling reaction and showed a good activity. When the molar ratio of substrate to palladium was 1000, the yield of the coupling product was up to 99% for activated aryl bromides and 58% for aryl chloride. ^{31}P NMR *in situ* indicated that the good activity of this system results from the active palladium species stabilized effectively by this tetraphosphine.

1. Introduction

Construction of carbon–carbon bonding between aryl halide and alkene catalyzed by palladium is one of the most important methods in synthetic chemistry [1–3]. In the past decades, many natural products, key intermediates, pharmaceuticals and others useful compounds are successfully synthesized in the different kinds of palladium catalytic systems. This cross-coupling reaction was originally developed by Mozoriki and Heck in the presence of $Pd(OAc)_2$ [4,5]. While PPh_3 was added, the selectivity and yield of the coupling product were obviously improved [6]. Consequently, a great number of triaryl phosphines were used in this reaction. For example, a yield of 95% was observed with PhBr as a substrate in the presence of *o*-Tol_3P [7,8]. It was also found that the palladium complexes with bulky and strong electron-donating trialkylphosphines are favorable to C–C coupling between aryl halide and styrene [9,10]. In spite of this, the catalyst loading is generally over 1% because monophosphines could not efficiently stabilize Pd species under the reaction conditions. However, a diphosphine generally shows better coordination ability to stabilize active Pd species in catalytic cycle due to its chelating effect. Even if the catalytic activity of stable Pd-diphosphine systems is lower [2,11–15], their long lifetime causes a higher TON [2,3]. Based on these findings, the design and synthesis of polydentate phosphine and its application in Heck reaction are promoted. The typical tetraphosphine, which was derived from ferrocene, gave a TON of 65,000 for the coupling reaction of 4-bromoanisole with styrene [16,17]. The most successful tetraphosphine Tedicyp, reported by M. Santelli [18], gave a high TON of 210,000,000 in Heck coupling reaction of acrylate with aryl bromide [3,19–23].

However, the difficulties in synthesis of the mentioned tetraphosphines and their inefficiency in the coupling reaction of aryl chloride limit their applications. Interestingly, a bidentate phosphine containing nitrogen, *N*,*N*-*bis*(diphenylphosphinomethyl)amine, could facilitate Heck reaction and gave a good yield with PhCl as substrate [11,24,25]. This result encourages us to study on tetraphosphines containing nitrogen for Heck coupling. Herein, we originally use a tetraphosphine *N*,*N*,*N*′,*N*′-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine to investigate the Heck coupling reaction of aryl halide with styrene. It is found that the reaction proceeds smoothly with aryl chloride and gives medium conversion in the condition of low catalyst loading of 0.1 mol%.

2. Experimental

2.1. General

All chemicals were purchased from commercial suppliers. Except for some liquid reagents being sensitive to light and moisture that were redistilled, there is no further treatment. $[PdCl(C_3H_5)]_2$ [26] and *N*,*N*,*N*′,*N*′-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine [27]

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were prepared with the reported methods. ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on Bruker AV II-400 MHz.

2.2. General procedure of Heck coupling reaction

NaOH (160 mg, 4 mmol) or K_2CO_3 (4 mmol), PhBr (211 µL, 2 mmol) and styrene (461 µL, 4 mmol) were added successively into a dried Schlenk tube with a magnetic bar. Then DMA (2 mL) and DMF solution of tetraphosphine-$[PdCl(C_3H_5)]_2$ (1 mL, 0.02 mmol), which was formed at 120 °C for 30 min, were added into it, respectively. The solution was stirred at 120 °C for 30 h. At the end of reaction, the solution was cooled to room temperature and water (4 mL) was added into it. The mixture solution was extracted with ethyl acetate (3 × 5 mL) and organic layer was dried over $MgSO_4$. The dried solution was filtered and purified with silica gel chromatography (petroleum ether) to give a corresponding product with an isolation yield of 94% (340 mg) or GC yield of 97%.

3. Results and discussion

3.1. Coupling reaction of aryl halide with styrene

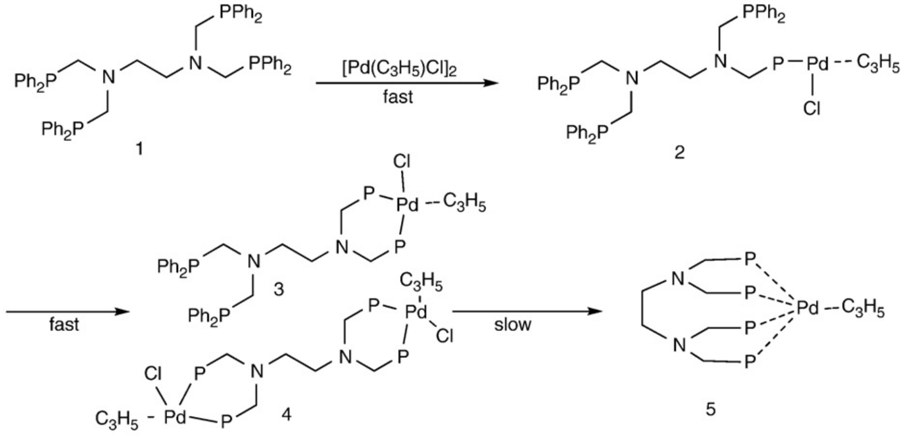
To evaluate the catalytic activity of Pd-tetraphosphine (**1**, Scheme 1) in Heck coupling reaction, we investigated first the reaction of styrene with PhI in the presence of 1 mol% tetraphosphine (**1**)-$[PdCl(C_3H_5)]_2$ and a good yield was obtained at 100 °C (Table 1, entry 1). Then, we increased the ratio of styrene to PhI to 2 *equiv*., and a yield of 90% was achieved with slight loss in (*E*)-isomer selectivity (Table 1, entry 2). In order to improve the conversion of the coupling reaction, reaction temperature was increased to 120 °C, and a complete conversion of PhI was observed whether tetraphosphine (**1**) existed or not (Table 1, entries 3 and 4). When reaction time was shortened to 4 h, palladium–phosphine system gave a higher yield than phosphine-free system (Table 1, entries 5 and 6). It is well known that ArI was an active substrate for Heck reaction due to weak C–I bond. So phenyl bromide was used as a substrate and 71% conversion was obtained at 120 °C for 30 h (Table 1, entries 7–9). It is noteworthy that the yield of the coupling reaction increased gradually with the extension of reaction time. Obviously, the catalyst did not deactivate during this long period and showed a good stability. After reaction temperature was further increased to 140 °C, at which Heck coupling is generally performed, the activity of the catalyst system was obviously improved and a conversion of 65% was obtained in 10 h (Table 1, entry 10). When $[PdCl(C_3H_5)]_2$ was replaced with the conventional catalytic precursor $PdCl_2$ and $Pd(OAc)_2$, the lower conversions were given under the same reaction conditions (Table 1, entries 11 and 13). If the molar ratio of ligand to metal increased to 4 with $PdCl_2$ as a precursor, its activity was still lower. So $[PdCl(C_3H_5)]_2$ was chosen as the catalyst precursor in the following research. A similar result, in which 1:1 (molar ratio) of tetraphosphine to Pd gave the best conversion of Heck coupling, was reported by Semeril et al. [28]. Interestingly, after the ratio of substrate to catalyst was increased to 1000, the conversion only decreased a little under a similar reaction condition (Table 1, entry 14).

Table 1
Heck coupling in different conditions.[a]

Entry	Substrate	Substrate/catalyst	Time (h)	Yield (%)	(*E*)-Sel (%)
1[b,c]	PhI	100	20	84	90
2[b]	PhI	100	20	90	88
3	PhI	100	20	>99 (86)	89
4[d]	PhI	100	20	>99 (99)	90
5	PhI	100	4	95	88
6[d]	PhI	100	4	84	89
7	PhBr	100	16	58	92
8	PhBr	100	24	65	92
9	PhBr	100	30	71	90
10[e]	PhBr	100	10	65	91
11	PhBr	100 (M = $PdCl_2$)	30	58	92
12	PhBr	100 (L/M = 4)	30	54	92
13	PhBr	100 (M = $Pd(OAc)_2$)	30	41	95
14	PhBr	1000	30	60	92

[a] Reaction condition: ArX 2 mmol, styrene 4 mmol, K_2CO_3 4 mmol, **1**/$[PdCl(C_3H_5)]_2$ = 2/1, DMF as solvent (3 mL), yield analyzed by GC, temperature 120 °C, yields in parentheses correspond to isolated yield.
[b] Temperature 100 °C.
[c] Styrene 1.1 equivalent.
[d] Phosphine free.
[e] Temperature 140 °C.

Due to the great effect of base on Heck reaction, the effect of $NaHCO_3$, K_3PO_4, K_2CO_3, NEt_3, NaOH, KOH, DMAP (*N*,*N*-dimethylamimopyridine) and NaO^tBu (Table 2) were investigated. As a result, the highest conversion was given with NaOH. Although a complete conversion of PhBr was observed with KOH, the signal of desired product was almost not detected on GC signal. Probably, the strong basicity of KOH caused the serious side reactions. Similarly, when some activated substrates, such as 4-bromo-phenylacetone and 4-$CF_3C_6H_4Br$ were used, the existence of NaOH was disfavorable to the formation of desired products and a weak base K_2CO_3 could effectively promote the formation of the desired products (Table 3, entries 2 and 3). It is well known that DMF is a good solvent for Heck reaction, but DMF will decompose in the presence of NaOH at 120 °C. Considering the difference of polarity and chemical properties between DMA and DMF, we used a mixed solvent (2 mL DMA and 1 mL DMF) for the coupling reaction of PhBr. To our delight, a yield of 97% was achieved (Table 3, entry 4).



Scheme 1. Possible formation process of catalyst.

Table 2
Effect of different bases on the Heck coupling reaction.[a]

Entry	Base	Conv. (%)	Sel. (%)
1	$NaHCO_3$	41	93
2	NaO^tBu	60	92
3	K_2CO_3	60	92
4	NEt_3	15	90
5	DMAP	38	91
6	NaOH	93 (89)	93
7	K_3PO_4	53	93
8	KOH	>99	–

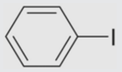
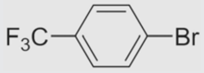
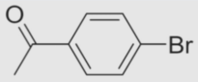
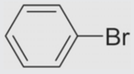
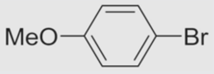
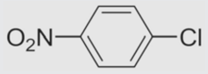
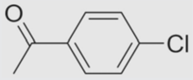
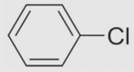
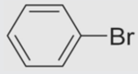
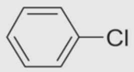
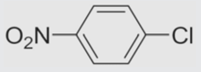
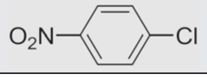
[a] Reaction condition: PhBr 2 mmol, styrene 4 mmol, base 4 mmol, **1**/$[PdCl(C_3H_5)]_2=2/1$, DMF as solvent (3 mL), substrate/catalyst = 1000, temperature 120 °C, time 30 h, conversion analyzed by GC.

So the optimum conditions were the reaction temperature of 120 °C, molar ratio 1000 of substrate to the catalyst, a mixture of DMA and DMF as solvent and NaOH as a base (except for some activated substrates). The catalytic performance of this system for a series of aryl halides were tested at these conditions. The coupling reaction of PhI and aryl bromide bearing 4-acetyl, 4-trifloromethyl and 4-methoxy substituent showed an excellent yield (Table 3, entries 1–5). For the aromatic chloride substrate, which is the most difficult to occur the coupling reaction, this system gave a good yield of 58% for an activated ArCl (Table 3, entry 6). Furthermore, we investigated the Heck coupling of aromatic chloride substrates with acrylate (Table 3, entries 10–12). When ethyl acrylate and the inactivated chlorobenzene were used as the starting materials, a yield of 35% was given (Table 3, entry 10). If ethyl acrylate reacted with the activated substrate 4-nitrochlorobenzene, the yield was up to 96% (Table 3, entry 11). In addition, the reaction of a bulky butyl acrylate with 4-nitrochlorobenzene also gave a satisfying yield of 69% (Table 3, entry 12). To the best of our knowledge, this is the best result in the Heck coupling of aryl chloride in the presence of 0.1 mol% catalyst at 120 °C [3,16] as the reported best yield of the Heck coupling reaction between 4-nitrochlorobenzene and butyl acrylate was only 32% with Pd-Tedicyp of 0.2 mol% at the higher temperature of 130 °C [18]. Although some bulky alkylphosphines and palladacyles [29,30] could catalyze this coupling efficiently, a high reaction temperature and catalyst loading are required. Similarly, Keles et al. [24,25] reported that Heck reaction of PhCl with acrylate was carried out in the presence of 3 mol% Pd to give 70% conversion, but the conversion was not more than 90% to PhBr with 3.3% catalyst loading. Obviously, this tetraphosphine (**1**) showed a higher activity than diphosphine *N,N-bis*(diphenylphosphinomethyl)amine.

3.2. Possible Pd–P species in this system

Recently, it was proposed that P–Pd bond in η^4**-**palladium complexes bearing tetraphosphine was weak [16,17]. For tetraphosphine (**1**), the reported single crystal structure of its η^2-Pd complex showed that the P–Pd bond was strong and no interaction between N atoms of tetraphosphine (**1**) and Pd was observed [31,32]. We considered that the formation of η^2-Pd complex was easy and η^4-Pd complex was difficult due to its linear structure. In order to illustrate this question in detail and obtain some useful information of the active species, ^{31}P NMR signals of the mixture of phosphine (**1**) and $[Pd(C_3H_5)Cl]_2$ in $CDCl_3$ at different time intervals were recorded at room temperature (Fig. 1). It was found that new ^{31}P NMR signals (**A**, **B**, and **E**) appeared very quickly, and signal intensity of **A** at 2.9 ppm, **B** at 2.7 ppm, **E** at −28.2 ppm and **F** at −28.4 ppm gradually decreased with the extension of time, while some new signals appeared at −15.7 ppm (**C**) and −10.7 ppm (**D**) 20 h later. Santalli reported that tetraphosphine Tedicyp reacted with palladium precursor to form η^4-palladium complex in 20 min or less as all P atoms in Tedicyp were in *cis* position [3,17]. Although tetraphosphine **1** was difficult to form η^4 complex for a short time due to its linear backbone, the formation of complexes **2** and **3** (Scheme 1) was fast undoubtedly. We had prepared η^2 complex, and it showed a singlet at 2.9 ppm on ^{31}P NMR spectra. So it was reasonable to assign that the signal **A** was from η^2-Pd complex. Moreover, when **B**, **E** and **F** signals disappeared, the **A** signal still existed. This result also proved the good stability of η^2-Pd complex. According to the change of **B** and **E** signal intensities on ^{31}P NMR spectra, we speculated that **B** and **E** signals should come from η^1-Pd complex (**2**) because the coordination of phosphorus atom with Pd did not obviously affect the chemical shifts of other phosphorus atoms which were far from the coordinated phosphorus atom. As stated previously [16,17], η^4-phosphine–Pd complex was always in rapid equilibrium of dissociation and association, which would result in broadened signals on ^{31}P NMR spectra. Also, Hierso et al. [17] disclosed that the ^{31}P NMR signal of η^4-tetraphosphine (derived from ferrocene)–

Table 3
Heck coupling of different aryl halides.[a]

Entry	Substrate	Yield (%)[b]
1		90 (>99)
2[c]		89 (>99)
3[c]		85
4		94 (97)
5		83 (89)
6		58
7		43
8[d]		(3)
9[d]		(39)
10[e]		35
11[e]		96
12[f]		69

[a] Reaction condition: ArX 2 mmol, styrene 3 mmol, NaOH 3 mmol, **1**/$[PdCl(C_3H_5)]_2=2/1$, DMF:DMA = 1:2 as solvent (3 mL), substrate/catalyst = 1000, temperature 120 °C, time 30 h.

[b] Isolated yield. Yields in parentheses correspond to GC yield. All GC yield's (*E*)-isomer selectivity is more than 90%.

[c] K_2CO_3 as base.

[d] S/C: 100 (entry 8); 10000 (entry 9).

[e] $NaHCO_3$ as base, ethyl acrylate as olefin, time 20 h.

[f] $NaHCO_3$ as base, butyl acrylate as olefin, time 20 h.

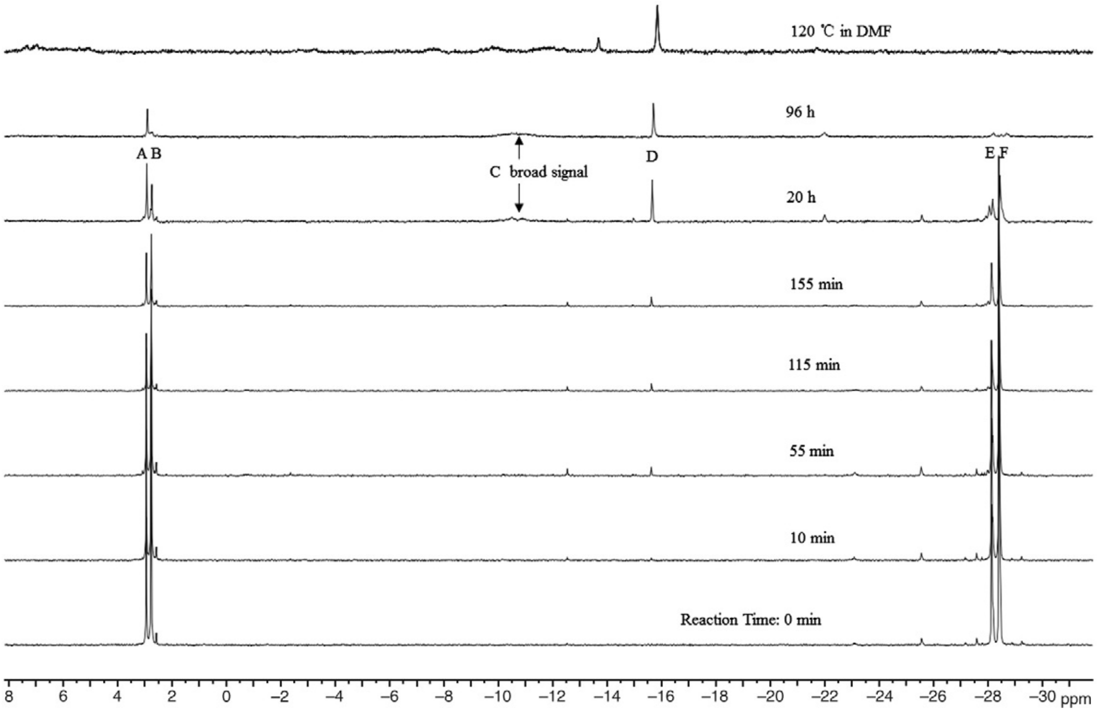


Fig. 1. ^{31}P NMR spectra of $[(C_3H_5)PdCl]_2$-*N,N,N′,N′*-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine *in situ*.

Pd appeared at 8.9 and 3.5 ppm, respectively, and η^2-P–Pd complex showed two signals at 39.2 and 41.7 ppm. So it is reasonable to attribute the signals **C** and **D** on ^{31}P NMR to be η^4-palladium complex (**5**). This complex (**5**) could be formed in 20 h at room temperature and its concentration increased with the extension of time. Until 96 h later, η^4-palladium complex (**5**) was completely formed. Furthermore, the catalyst, which was prepared *in situ* in 120 °C in DMF for 20 min, presented two feature signals at −16.3 ppm and −10.5 ppm (broadened peak) and all signals of η^1 and η^2 complexes disappeared. The result proved that η^4 complex could be quickly formed in reaction conditions. Based on the varieties of these signals and possible coordination reactions, the reaction process of tetraphosphine (**1**) with $[Pd(C_3H_5)Cl]_2$ was concluded in Scheme 1. It is noteworthy that the complete formation of P–Pd complex **5** spends about 100 h at room temperature, but the Pd complex of tetraphosphine derived from ferrocene has been dissociated in 107 h [17]. Why can the existence of N atom in ligand **1** cause the much better stability of Pd-tetraphosphine complex in Heck coupling reaction? To date, we are not clear and our research is progressing.

Furthermore, we investigated Heck reaction of PhBr with styrene in the presence of the η^2 complex (**4**) and a yield of 80% was given. After the formation temperature of the catalyst *in situ* was increased to 120 °C, the catalyst showed a better activity. Because the stable 18-electron structure of Pd–P complex (**3, 4**) was very difficult to be transformed into complex **5** at room temperature, NMR signal of **A** could be maintained after 96 h (Fig. 1). However, ^{31}P NMR of the catalyst, which was prepared *in situ* in the temperature of 120 °C for 20 min, demonstrated that η^4-palladium complex was fast formed in the reaction condition. In other words, the complexes **2**, **3** and **4** were completely converted into η^4-palladium complex for a short time and they were not the active ingredient, and the really active species for Heck reaction was η^4-palladium complex (**5**).

4. Conclusion

In summary, we used an easily synthesized tetraphosphine (**1**) to develop a new system for Heck coupling. This system could give a good to perfect conversion of aryl bromide in a low ratio of catalyst to substrate. Moreover, the coupling reaction between arylchloride and styrene proceeded smoothly with medium yield in a low catalyst loading. ^{31}P NMR *in situ* indicated that tetraphosphine (**1**) could enhance the stability of the formed Pd complex.

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