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Short Communication

# 6*H*-Dibenzo[*d*,*f*-[1,3]diazepin-6-ylidene,5,7-dihydro-5,7-diphenylphosphanyl]: A new ligand for palladium-catalyzed Mizoroki–Heck coupling

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ABSTRACT

A novel and conveniently prepared diphosphine ligand 6*H*-Dibenzo[*d*,*f*-[1,3]diazepin-6-ylidene,5,7-dihydro-5,7-diphenylphosphanyl] (DADPP) combined with $[Pd(C_3H_5)Cl]_2$ affords an efficient catalytic system for Mizoroki–Heck cross-coupling of aryl halides with alkenes. The system could give the yield of 95% for 4-chloronitrobenzene with 0.05 mol.% $[Pd(C_3H_5)Cl]_2$. For the bromide-substituted substrates, the highest turnover number (TON) is up to 96,000,000.

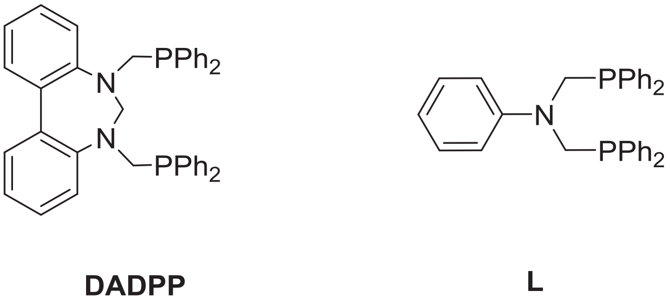
## 1. Introduction

Palladium-catalyzed Mizoroki–Heck coupling is one of the most important tools for constructing C-C bonds in organic synthesis [1–5]. Pd(0) is usually considered as the active species in this transformations. However, the bare Pd(0) is very unstable and easy to aggregate, which leads to the deactivation of Pd(0) species. In order to effectively solve this problem, a high catalyst loading has to be required in the catalysis process [6]. Furthermore, the addition of phosphine ligand is also found to be a useful and reliable method [1,7]. In the past decades, a few multidentate phosphines were used to mediate Heck reaction with an extremely low catalyst loading [8–16]. However, these phosphine ligands did not exhibit good performance toward the chloride-substituted substrates. Moreover, the tedious synthetic routes of multidentate phosphines limit their wide applications. Some diphosphines containing nitrogen atom, which are easily prepared, have also shown good activities in Heck reaction with excellent regioselectivities by chelating to the palladium species. Among them, *N*, *N*-bis(diphenylphosphinomethyl)-amine (**L**) (Scheme 1), seemed to facilitate the coupling of chlorobenzene with alkenes [17]. It has been revealed that the electronic effect of nitrogen atom played a key role [18–20]. Although great progress has been made, to date, extending the lifetime of the Pd(0) active species still remains a challenge. Herein, we developed a simple palladium-catalyzed system for Mizoroki–Heck coupling with a new diphosphine ligand containing two nitrogen atoms, 6*H*-Dibenzo[d,f-[1,3]diazepin-6-ylidene,5,7-dihydro-5,7-diphenyl-phosphanyl] (DADPP) (Scheme 1).

## 2. Experimental

### 2.1. Synthesis of DADPP

A 100-mL three-necked flask equipped with a magnetic bar was charged with $[Ph_2P(CH_2OH)_2]^+Cl^-$ (1.7 g, 4 mmol), 20 mL ethanol, 10 mL triethylamine and 20 mL toluene. 2,2′-Diaminobiphenyl (368 mg, 2 mmol) was dissolved in toluene and added dropwise into the mixture, and then refluxed for 30 h (Scheme 2). At the end of the reaction, removed the solvent and the residue was washed with 2 × 10 mL ethanol and 2 × 10 mL $H_2O$, then the desired product was obtained



**Scheme 1.** Structure of ligands DADPP and **L**.

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*E-mail address:* liruixiang@scu.edu.cn (R. Li).

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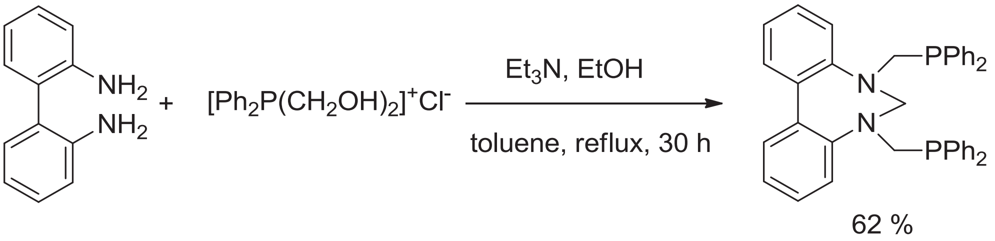


**Scheme 2.** Synthesis of DADPP.

as a white solid (720 mg, 62% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.44–6.96 (m, 28H), 4.70 (s, 2H), 3.71 (t, $J = 6.2$ Hz, 4H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$): δ 148.27, 137.77, 133.05, 128.32, 123.64, 120.52, 81.85, 77.48 and 53.95 ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): δ −26.23 ppm. HRMS (ESI) *m*/*z*: calc for $[C_{39}H_{34}N_2P_2\ Na]^+$: 615.2089; found: 615.2090.

### *2.2. General procedure for the Heck coupling*

$Na_2CO_3$ (212 mg, 2 mmol), 4-chloronitrobenzene (1 mmol) and styrene (1.5 mmol) were added successively into a dried Schlenk tube under nitrogen. Then the DMA (0.1 mL) solution of DADPP (0.002 mmol) and $[Pd(C_3H_5)Cl]_2$ (0.0005 mmol), which was reacted at 100 °C for 10 min prior to use, was added into the mixture. The reaction was performed at 130 °C. At the end of reaction, the mixture solution was extracted with ethyl acetate (3 × 5 mL). Combined organic phase was washed with brine (3 × 5 mL) and dried over $MgSO_4$. The dried solution was filtered and purified with silica gel chromatography (petroleum ether 60–90 °C) to give a corresponding product.

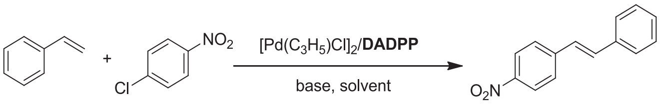
## 3. Results and discussion

To evaluate the catalytic reactivity of $[Pd(C_3H_5)Cl]_2$/DADPP system, the coupling of 4-chloronitrobenzene with styrene was used as a model reaction to explore the optimum conditions. According to the well-established mechanism [21–23], bases are crucial for the regeneration of the Pd active species. The effect of NaOAc, $NaHCO_3$, $Na_2CO_3$, $K_3PO_4$ and NaOH on the reaction was investigated in DMA (Table 1). Desired product was almost not observed when NaOAc or $NaHCO_3$ was used as the base (Table 1, entries 1–2). $K_3PO_4$ obviously promoted the reaction, but a low conversion of 36% was obtained (Table 1, entry 4). Gratifyingly, the highest conversion of 100% was obtained in the presence of $Na_2CO_3$ (Table 1, entry 3). Furthermore, after screening various solvents (Table 1, entries 3, 6–9), DMA was found to be an optimum solvent in this reaction system.

Subsequently, we devoted much effort to screen palladium species. It was found that other palladium precursors such as $PdCl_2$, $Pd(dba)_2$ and $Pd(COD)Cl_2$ also could give the relatively satisfying results except $Pd(OAc)_2$ (Table 2, entries 1, 3–5 and 7). However, when the molar ratio of substrate to catalyst (S/C) was increased to 5,000, the obvious difference of the catalytic results was shown with the different palladium precursors (Table 2, entries 2, 6 and 8). Among them, $[Pd(C_3H_5)Cl]_2$ gave the best result in 87% yield with a TON of 4,350 (Table 2, entries 1). Thus, $[Pd(C_3H_5)Cl]_2$ was chosen as the catalyst precursor in the following experiments. Compared with other well-known simple ligands, such as dppe, dppb, P-Phos and Bisbi, the bidentate phosphine ligand **L**, DADPP was favourable for accelerating the reaction (Table 2, entries 10–14). A low yield of 6% was obtained in the absence of ligand DADPP (Table 2, entry 9). Based on these optimization studies (Tables 1 and 2), further reactions were performed at 130 °C under nitrogen using $[Pd(C_3H_5)Cl]_2$/DADPP, $Na_2CO_3$ in DMA.

With the optimal reaction conditions in hand, we explored the scope of the halide substrates for Heck coupling. As expected, for low-cost and less-active aryl chlorides, this catalytic system gave low yields in the presence of 0.1 mol.% Pd. However, when the Pd loading was increased to 0.2 mol.%, 2-chloronitrobenzene, 4-chlorobenzonitrile and 2-chlorobenzonitrile could afford the corresponding coupling products **2**–**4** in moderate yields of 71%, 52% and 48%, respectively (Table 3, entries 2–4). However, for 4-chlorobenzaldehyde, only a moderate yield of 60% was achieved even if increasing Pd loading to 1 mol.% (Table 3, entry 5). The low reactivity was usually attributed to the reluctance of the aryl-chloride bond to oxidative addition to Pd(0) [1]. Under the optimized reaction conditions, good to excellent

**Table 1**
Effect of bases and solvents on Heck reaction of 4-chloronitrobenzene with styrene[a]



| Entry | Base | Solvent | S/C | Yield (%) |
|---|---|---|---|---|
| 1 | NaOAc | DMA | 1,000 | – |
| 2 | $NaHCO_3$ | DMA | 1,000 | – |
| 3 | $Na_2CO_3$ | DMA | 1,000 | 100 |
| 4 | $K_3PO_4$ | DMA | 1,000 | 36 |
| 5 | NaOH | DMA | 1,000 | 20 |
| 6 | $Na_2CO_3$ | *n-butanol* | 1,000 | –[b] |
| 7 | $Na_2CO_3$ | NMP | 1,000 | 36[c] |
| 8 | $Na_2CO_3$ | EtOH | 1,000 | –[b] |
| 9 | $Na_2CO_3$ | DMF | 1,000 | 45 |

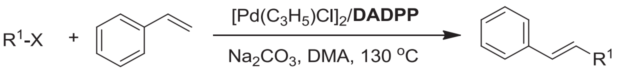
[a] Reaction condition: 4-chloronitrobenzene 1 mmol, styrene 1.5 mmol, catalyst $[Pd(C_3H_5)Cl]_2$/DADPP = 1/4, [Pd] 0.1 mol.%, base 2.0 mmol, solvent 3 mL, 130 °C, 20 h and GC yield.
[b] 70 °C.
[c] 110 °C.

**Table 2**
Effect of palladium precursors and ligands on the Heck coupling reaction[a].

| Entry | Pd | Ligand | S/C | Yield (%) |
|---|---|---|---|---|
| 1 | $[Pd(C_3H_5)Cl]_2$ | DADPP | 1,000 | 94[b] |
| 2 | | | 5,000 | 87 |
| 3 | $PdCl_2$ | DADPP | 1,000 | 78 |
| 4 | $Pd(OAc)_2$ | DADPP | 1,000 | 24 |
| 5 | $Pd(dba)_2$ | DADPP | 1,000 | 93 |
| 6 | | | 5,000 | 53 |
| 7 | $Pd(COD)Cl_2$ | DADPP | 1,000 | 82 |
| 8 | | | 5,000 | 21 |
| 9 | $[Pd(C_3H_5)Cl]_2$ | none | 1,000 | 6[c] |
| 10 | $[Pd(C_3H_5)Cl]_2$ | P-Phos | 1,000 | 85 |
| 11 | $[Pd(C_3H_5)Cl]_2$ | Bisbi | 1,000 | 77 |
| 12 | $[Pd(C_3H_5)Cl]_2$ | dppe | 1,000 | 71 |
| 13 | $[Pd(C_3H_5)Cl]_2$ | dppb | 1,000 | 80 |
| 14 | $[Pd(C_3H_5)Cl]_2$ | **L** | 1,000 | 6 |

[a] Reaction condition: 4-chloronitrobenzene 1 mmol, styrene 1.5 mmol, $Na_2CO_3$ 2.0 mmol, DMA 3 mL, catalyst $[Pd(C_3H_5)Cl]_2$/DADPP = 1/4, 130 °C, 20 h, GC yield, 2,2′,6,6′-Tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine (P-Phos), 2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl (Bisbi) and 1,4-bis(diphenylphosphino)-butane (dppb).
[b] 2 h.
[c] No ligand.

**Table 3**
Heck coupling of aryl halides with styrene catalyzed by $[Pd(C_3H_5)Cl]_2$/DADPP[a]



$R^1$= Aryl or Heteroaryl
X= Br, Cl

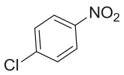
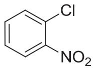
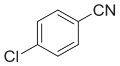
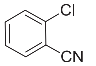
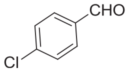
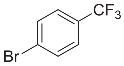
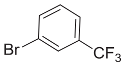
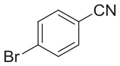
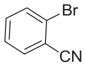
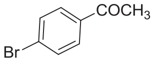
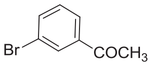
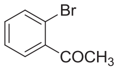
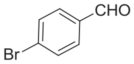
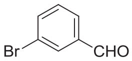
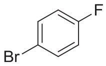
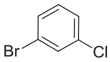
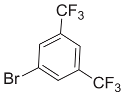
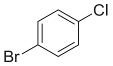
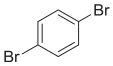
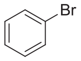
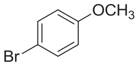
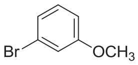
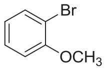
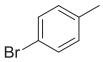
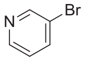
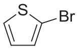
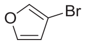
| Entry | ArX | S/C | T (h) | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | 1,000 | 2 | **1** | 94 |
| 2 |  | 500 | 24 | **2** | 71 |
| 3 |  | 500 | 24 | **3** | 52 |
| 4 |  | 500 | 24 | **4** | 48 |
| 5 |  | 100 | 24 | **5** | 60 |
| 6 |  | 10,000<br>100,000 | 24<br>48 | **6** | 95<br>81[b] |
| 7 |  | 10,000 | 24 | **7** | 83 |
| 8 |  | 10,000<br>1,000,000<br>10,000,000<br>10,000,000 | 24<br>72<br>96<br>120 | **3** | 80 [b]<br>91 [b]<br>60 [b]<br>63 [b] |
| 9 |  | 1,000 | 24 | **4** | 21 |
| 10 |  | 100,000 | 48 | **8** | 95 |
| 11 |  | 10,000 | 24 | **9** | 90 |
| 12 |  | 1,000 | 24 | **10** | 69 |
| 13 |  | 10,000<br>100,000 | 24<br>48 | **5** | 89<br>95[b] |
| 14 |  | 10,000 | 24 | **11** | 88 |
| 15 |  | 10,000 | 24 | **12** | 85 |
| 16 |  | 10,000 | 24 | **13** | 78 |
| 17 |  | 10,000 | 24 | **14** | 61 |
| 18 |  | 10,000 | 24 | **15** | 91 |
| 19 |  | 10,000 | 48 | **16** | 96[c] |
| 20 |  | 500 | 24 | **17** | 74 |
| 21 |  | 1,000 | 24 | **18** | 78 |
| 22 |  | 500 | 24 | **19** | 82 |
| 23 |  | 500 | 24 | – | 10[b] |
| 24 |  | 500 | 24 | **20** | 78 |

**Table 3** *(continued)*

| Entry | ArX | S/C | T (h) | Product | Yield (%) |
|---|---|---|---|---|---|
| |  | | | | |
| 25 |  | 5,000 | 24 | **21** | 95 |
| 26 |  | 2,000 | 24 | **22** | 87 |
| 27 |  | 2,000 | 24 | **23** | 91 |

[a]Reaction condition: catalyst $[Pd(C_3H_5)Cl]_2$/DADPP = 1/4, aryl bromides 1 mmol, styrene 1.5 mmol, $Na_2CO_3$ 2 mmol, DMA 3 mL, 130 °C, under nitrogen and isolated yields.
[b]GC yield.
[c]Styrene 3.0 mmol.

yields of coupled products were obtained for a wide range of aryl bromides with styrene (Table 3). As expected, aryl halides with electron-withdrawing substituents in para positions reacted smoothly, and aryl halides with electron-donating substituents were less reactive. For example, even with 0.00001 mol.% palladium, 4-bromobenzonitrile could give a yield of 60% after 96 h (Table 3, entry 8), which is much higher than the best value reported in the literature (35,500) [24–27]. The electron-poor 4-bromobenzaldehyde was almost completely converted into the desired product at a palladium loading of 0.001 mol.% for 48 h (Table 3, entry 13). The results demonstrated that the catalyst did not deactivate during the long period and showed a good stability. It is noteworthy that the coupling took place on both sites of 1,4-dibromobenzene with styrene (Table 3, entry 19). Using 2-bromobenzonitrile and 2-bromoanisole as the substrates, low conversions (21% and 10%) were observed due to steric hindrance (Table 3, entries 9 and 23). For electronic factor or poison of heteroatom to Pd active species, Heck coupling of heteroaryl halides generally proceeds slowly and requires high catalyst loadings [28]. However, in our system, 2-bromothiophene and 3-bromofuran still gave the TONs of 1,740 and 1,820, respectively (Table 3, entries 26–27). In addition, a higher TON of 4,750 was obtained for 3-bromopyridine (Table 3, entry 25).

Inspiringly, the coupling of aryl bromides bearing electron-withdrawing groups with activated terminal olefin *n*-butyl acrylate could be performed at the very low catalyst loadings (Table 4). For example, 4-bromobenzotrifluoride and 4-bromoacetophenone underwent the Heck coupling with *n*-butyl acrylate to afford the desired products in 85% and 84%, respectively (Table 4, entries 3 and 4). The maximum TON of 96,000,000 was achieved for 4-bromobenzaldehyde (Table 4, entry 5), which can take an advantage over the TON value achieved by Tedicyp in 72 h for the same substrate (210,000) [20].

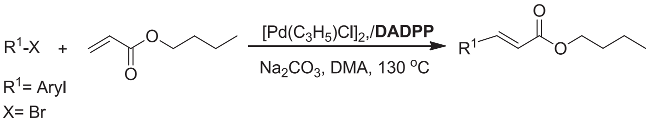
## 4. Conclusions

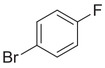
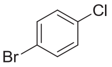
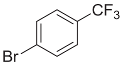
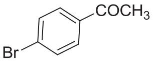
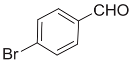
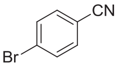
In summary, we have developed a highly efficient Pd-catalyzed Mizoroki–Heck coupling reaction of aryl halides using a new diphosphine DADPP as ligand, which was easily synthesized from readily available materials. The protocol features wide substrate scope and high functionality tolerance. A variety of aryl halides, even some heteroaryl halides, can smoothly react with olefins to afford the corresponding products. Importantly, current catalytic system has a predominant activity for electron deficient alkenes as long as the amount of $[Pd(C_3H_5)Cl]_2$ is in the low range of 0.005–0.0000 005 mol.%.

## Acknowledgments

This project was supported by the National Natural Science Foundation of China (grant no. 21202104).

**Table 4**
Heck coupling of aryl bromides with *n*-butyl acrylate catalyzed by $[Pd(C_3H_5)Cl]_2$/DADPP[a]



| Entry | ArX | S/C | T (h) | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 |  | 100,000<br>1,000,000<br>100,000,000 | 24<br>44<br>120 | **24** | 96<br>$43^b$<br>$25^b$ |
| 2 |  | 1,000,000<br>10,000,000<br>100,000,000 | 44<br>72<br>120 | **25** | 89<br>$90^b$<br>$82^b$ |
| 3 |  | 1,000,000<br>10,000,000<br>100,000,000 | 44<br>72<br>120 | **26** | 96<br>$83^b$<br>$85^b$ |
| 4 |  | 1,000,000<br>10,000,000<br>100,000,000 | 44<br>72<br>120 | **27** | 98<br>$87^b$<br>$84^b$ |
| 5 |  | 1,000,000<br>10,000,000<br>100,000,000 | 44<br>72<br>120 | **28** | 98<br>$93^b$<br>$96^b$ |
| 6 |  | 1,000,000<br>10,000,000<br>100,000,000 | 44<br>72<br>120 | **29** | 98<br>$97^b$<br>$78^b$ |

[a]Reaction condition: catalyst $[Pd(C_3H_5)Cl]_2$/DADPP = 1/4, butyl acrylate 1 mmol, styrene 1.5 mmol, $Na_2CO_3$ 2 mmol, DMA 3 mL, 130 °C, under nitrogen and isolated yields.
[b]GC yield.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2014.07.031.

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