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Palladium catalyzed Heck reactions using 2,6-bis(1,2,4-diazaphosphol-1-yl)pyridine as a ligand

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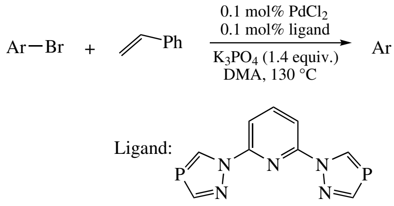
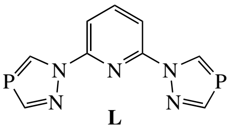
A new catalyst system for the Heck reaction consisting of $PdCl_2$ and 2,6-bis(1,2,4-diazaphosphol-1-yl)pyridine as a ligand is proposed. This system is efficient for the coupling of styrene with aryl bromides (K_3PO_4, DMA, 130 °C) at 0.1 mol% catalyst loading.



Keywords: palladium complexes, coupling, Heck reaction, nitrogen phosphorus heterocycles, 2,6-bis(1,2,4-diazaphosphol-1-yl)pyridine, stilbenes, bromoarenes.

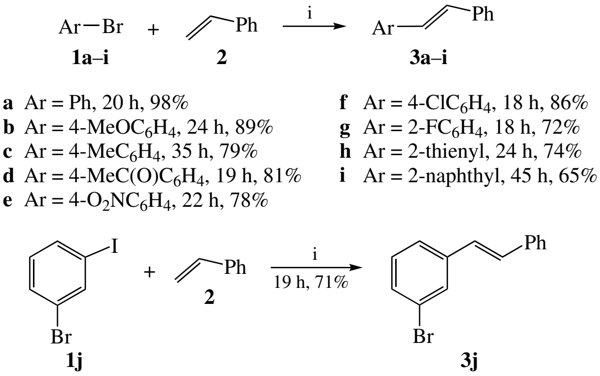
The transition metal catalyzed carbon–carbon bond formation has been recognized as the most powerful tool in the construction of organic compounds. Among them, the Mizoroki–Heck reaction is one of the most important C–C coupling reactions[1–3] employed in the synthesis of natural products and some heterocycles.[4–8] The traditional Heck reaction with aryl iodides normally requires the presence of a phosphine ligand in controlling the reactivity and selectivity.[9,10] The development of more efficient catalyst system to improve the reactivity of less active aryl bromides and in paricular aryl chlorides is of importance. Known catalytic systems include palladium–phosphine complexes,[9,10] phosphine-free palladium catalyst systems,[11,12] the Pd–NHC catalysts or other Pd–N catalyst systems[13,14] as well as Pd^0 catalysts.[15,16] The novel catalyst systems have continued to emerge.[17–19] Although numerous efficient catalyst systems have been established, a literature survey showed that the search for new efficient Heck catalytic systems remains topical. A few years ago, we had synthesized 2,6-bis(1,2,4-diazaphosphol-1-yl)pyridine **L** which formed complexes with the Zn^{2+} or Cu^{2+} cations.[20] In this study, we are pleased to report that this agent can be used as a ligand to form a catalyst system with $PdCl_2$ for catalyzing Heck reaction, and the reaction yields are very high.



L

Our studies began with the cross-coupling of bromobenzene **1a** with styrene **2** to optimize the reaction conditions. Various bases, catalyst types, catalyst loading, solvents and the temperatures were varied. With compound **L** as a ligand, we found that $PdCl_2$ could provide the high yield of the coupling reaction product **3a** (Scheme 1), while $Pd(OAc)_2$ and $Pd(CF_3CO_2)_2$ gave inferior results compared to $PdCl_2$. We examined the influence of catalyst loading and found that the mixture of $PdCl_2$ and **L** (0.1 mol% each) could provide excellent yields of products. Increasing the amount of ligand **L** and $PdCl_2$ has little effect on the product yields, while lowering the amount of ligand and catalyst reduced the yield of **3a**. Using a 0.1 mol% mixture of **L** ligand and $PdCl_2$ as catalytic system in DMF, we tested various bases such as sodium carbonate, sodium acetate, potassium phosphate, triethylamine, pyridine, and potassium diphosphate. Potassium phosphate was found to be the most effecient base while with pyridine none of the product was formed.

Under the conditions of selected base using 0.1 mol% ligand **L**–$PdCl_2$ catalytic system, a range of solvents was screened including DMF, DMA, NMP, 1,4-dioxane and acetonitrile. The reaction proceeded in all tested polar aprotic solvents, however the yields were much lower in less polar solvents such as 1,4-dioxane and acetonitrile while in DMA, the highest yield of product **3a** was achieved. The temperature test showed that 130 °C was optimal, its raising to 140 °C led to a slight decrease in yield of the products whereas lowering to 110 °C caused significant drop in the yield. In the absence of ligand **L** and with maintaining other parameters, the yield of *E*-stilbene **3a** was only 18%.



a Ar = Ph, 20 h, 98%
b Ar = 4-$MeOC_6H_4$, 24 h, 89%
c Ar = 4-MeC_6H_4, 35 h, 79%
d Ar = 4-$MeC(O)C_6H_4$, 19 h, 81%
e Ar = 4-$O_2NC_6H_4$, 22 h, 78%
f Ar = 4-ClC_6H_4, 18 h, 86%
g Ar = 2-FC_6H_4, 18 h, 72%
h Ar = 2-thienyl, 24 h, 74%
i Ar = 2-naphthyl, 45 h, 65%

Scheme 1 *Reagents and conditions*: i, $PdCl_2$ (0.1 mol%), ligand **L** (0.1 mol%), K_3PO_4 (1.4 equiv.), DMA, 130 °C, 18–45 h.

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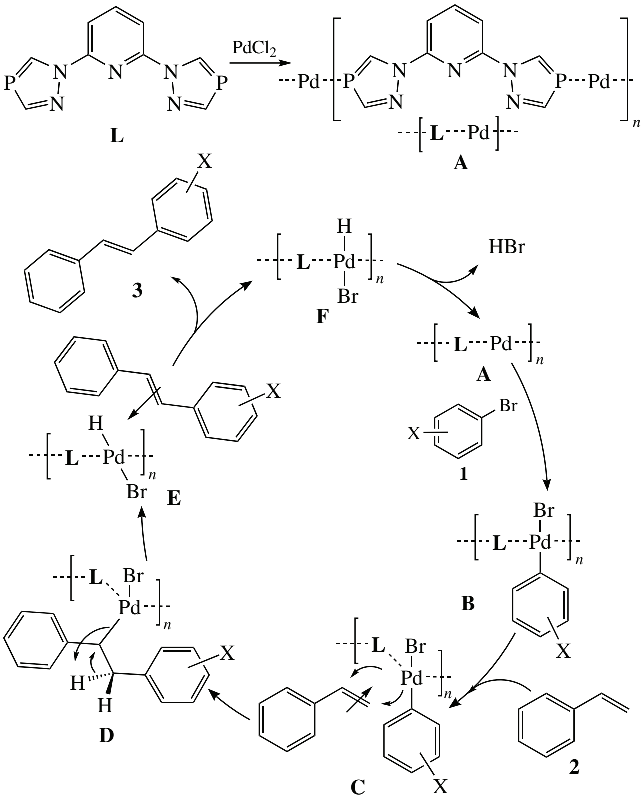
With optimized conditions in hand, we examined the coupling reaction of several other representative aryl bromides **1b–j** with olefin **2** to explore the reaction scope and limitation (see Scheme 1).[†] Aryl bromides **1b–e** with an electron-donating or electron-withdrawing group reacted smoothly to afford the corresponding coupling products **3b–e**. Under the same conditions without ligand **L**, 4-methoxybromobenzene **1b** on coupling with styrene **2** gave only 15% of 4-methoxystilbene **3b**. A comparison of the results obtained for **3b–e** indicates that the electrical property of substituent groups is an important factor: the reaction times providing good yields for substrates **1d**,**e** with electron-withdrawing groups were noticeably shorter. 4-Bromochlorobenzene **1f** containing different halogen atoms reacted exclusively at the Br atom to form 4-chlorostilbene **3f** exclusively. This phenomenon is similar to the results of the palladium catalyzed reaction with carbamoylsilane that we have studied previously.[21] Substrate **1j** containing both iodo and bromo substituents reacted only at the iodo terminus to give 3-bromostilbene **3j** in 71% yield. We were pleased to find that deactivated 2-bromothiophene **1h** reacted with styrene **2** smoothly to provide a good yield of product **3h**. 2-Bromonaphthalene **1i** also coupled with styrene to afford product **3i** in reasonable yield. The reaction of styrene with less active chlorobenzene did not occur while with iodobenzene it proceeded smoothly even at 100 °C (*cf.* case with 3-bromoiodobenzene **1j**). It should be noted that our procedure turned unsuitable for acrylic olefins, only their resinification and some homocoupling of bromoarenes were observed.

Based on our experimental results and the mechanism of Heck reaction reported previously,[22–24] a reasonable catalytic mechanism may be proposed (Scheme 2). Initially, the activated Pd^0 species were generated by reducing PdCl$_2$ with ligands and they could be stabilized through the ligands. The bdppy ligand could form a long-chain polymeric complex **A**. During the reaction process, the active Pd^0 complex **A** is inserted into aryl bromide **1** *via* oxidative addition with aryl bromide, and σ-aryl-Pd^{II} complex **B** is formed. Then the palladium atom and olefin **2** form a π-complex **C**, and after that the coordinated olefin is *cis* inserted into the Pd–C bond to result in intermediate **D**. When intermediate **D** undergoes rotational isomerization into a *transoid* conformer with low torsional tension, an intramolecular β-hydride elimination takes place to give an intermediate π-complex **E** of Pd coordination with the coupling olefin product. After a dissociation of intermediate **E**, the coupling product, olefin **3**, is released with the formation of palladium complex **F**. Under basic conditions, HBr can be removed from palladium complex **F**, and the catalyst **A** can be regenerated.



Scheme 2 A plausible mechanism of the catalyzed coupling reaction.

To conclude, a new catalyst system has been developed for the Heck reaction, in which a complex of PdCl$_2$ and 2,6-bis(1,2,4-diazaphosphol-1-yl)pyridine ligand serves as an effective catalyst for the coupling reaction between styrene and aryl bromides. Using this catalyst system, the reaction tolerates aryl bromides bearing a wide variety of functional groups, heteroaryl halides and polycyclic aryl halides, to afford the coupling products in good to excellent yields. We believe that this catalyst system will be a useful contribution in the utilization of the Heck reaction.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.017.

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[†] *General procedure for the coupling reaction of aryl halides and olefins.* A Schlenk tube equipped with a Teflon vacuum cock and micro stirring bar was charged with aryl bromide (1.0 mmol), styrene (1.2 mmol), K$_3$PO$_4$ (1.4 mmol) and DMA (1 ml). After mixing the components, ligand **L** (0.01 mmol) and PdCl$_2$ (0.01 mmol) were added. The mixture was stirred at 130 °C until aryl bromide **1** was consumed completely (TLC control). The reaction mixture was cooled to room temperature, poured into water (25 ml), and extracted with ethyl acetate. The combined organic phase was washed with brine, dried with Na$_2$SO$_4$, and evaporated. The crude material was purified by column chromatography (eluent: light petroleum and ethyl acetate mixtures).

For more details and characterization of products **3a**–**j**, see Online Supplementary Materials.

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