

Application of 3-aryl-4(5)-arylimidazoles as efficient ligands in Pd-catalyzed Heck reactions

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Abstract: The Heck coupling of haloarenes with various alkenes was successfully performed in the presence of 0.25 mol% PdCl₂ and 0.5 mol% biphenyl-4-yl-[4(5)-(biphenyl-4-yl)-1*H*-imidazol-2-yl]ketone **2f** as a ligand with Na₂CO₃ as optimal base, in a 1:1 mixture of H₂O/DMF as the reaction solvent at 80 °C for 8 h. Imidazole **2f** was found to be an inexpensive, air-stable, easily available, and efficient ligand in the palladium-catalyzed Heck reactions of aryl iodides (76%–94%), bromides (52%–79%), and chlorides (40%–70%).

Key words: Arylimidazoles, PdCl₂, Heck reaction, aqueous medium

1. Introduction

Imidazoles moieties are broadly found in natural products such as biotin, histidine, histamine, and the pilocarpine alkaloids,^{1,2} and also are present in important synthetic compounds such as losartan, fungicides, herbicides, and therapeutic agents.^{3,4} Furthermore, recently, imidazoles have been found as a skeleton of ionic liquids and efficient ligands in metalloenzymes and metal complexes.⁵ Therefore, there are many reports in the literature on the synthesis of imidazole derivatives.^{6,7}

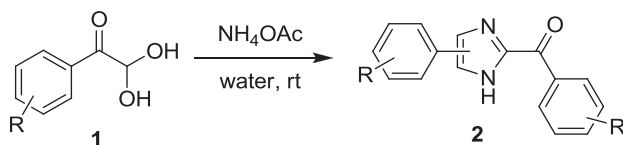
The Mizoroki–Heck reaction,^{8–11} palladium-catalyzed olefination of aryl halides, has become one of the most powerful methods for carbon–carbon bond formation in organic synthesis.^{12–15} Phosphine ligands are commonly used in the Heck reaction but suffer from some disadvantages such as environmental problems, moisture and air sensitivity, high toxicity, and cost of phosphine ligands.^{16–18} Therefore, the development of new phosphine-free catalytic systems for the Heck reaction would be an interesting subject, among which imidazoles play an important role.^{19,20} In continuation of our work on the Heck reaction,^{21,22} recently we have reported the Heck reaction using a Pd(OAc)₂/imidazolium salt catalytic system, which afforded corresponding Heck products in good to excellent yields.²³ The results encouraged us to work on the Heck reaction using easily prepared and air and moisture stable aroylimidazole-based ligands **2**.

2. Results and discussion

Different substituted aroylimidazoles **2** were prepared by reaction of arylglyoxal hydrate **1** with ammonium acetate in water at room temperature as Khalili et al. reported (Scheme),⁷ and then subjected to the Heck

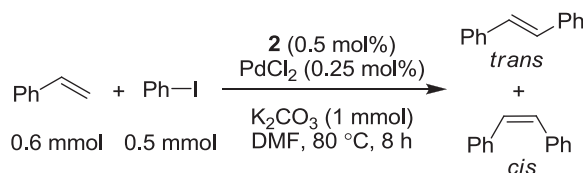
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reaction of styrene with iodobenzene, as a ligand in the presence of PdCl₂ in DMF at 80 °C for 8 h. The results are summarized in Table 1. Electron-donating and electron-withdrawing substituted aroylimidazoles **2** were investigated as ligand in the Heck reaction, and, due to the best results, biphenyl-4-yl-[4(5)-(biphenyl-4-yl)-1*H*-imidazol-2-yl]ketone **2f** (Table 1, entry 6) was selected for further reactions. For investigation of ligand effect on the Heck reaction, we carried out the Heck reaction between styrene and iodobenzene under similar conditions without using any ligand, which afforded the *trans*-stilbene in only 37% yield (Table 1, entry 7).



Scheme. Synthesized aroylimidazole ligands **2a-f**.

Table 1. The effect of ligands **2a-f** on the Heck reaction.



Entry	Ligand 2 ; R	Yield %		<i>Trans/cis</i> ^a
		GC	Isolated	
1	2a ; H	75	65	91/9
2	2b ; 4-NO ₂	73	62	94/6
3	2c ; 3-MeO	82	69	94/6
4	2d ; 4-MeO	85	73	94/6
5	2e ; 3,4-(MeO) ₂	86	78	93/7
6	2f ; 4-Ph	97	85	91/9
7	None	37	-	> 99/1

^aDetermined by GC.

Different solvents were used in the Heck reaction of 0.6 mmol styrene with 0.5 mmol iodobenzene in the presence of 0.5 mol% ligand **2f**, 0.25 mol% of PdCl₂, and 1 mmol K₂CO₃. The reactions were carried out at 80 °C for 8 h. The results are summarized in Table 2, which shows that EtOH, EtOH/water (50/50: v/v), *t*-BuOH, *t*-BuOH/water (50/50: v/v), and toluene (entries 6–10) afforded stilbene in very low yield. When DMSO or DMSO/water was used as reaction medium, stilbene was obtained in 66% or 80% yield, respectively, with low selectivity (*trans/cis* = 50/50–60/40). Reaction in DMF afforded the product in 80% isolated yield with a *trans/cis* ratio of 94/6. When the reaction was conducted in DMF/water (50/50: v/v), stilbene was isolated in 88% yield, with a 91/9 ratio of *trans/cis*. Interestingly, in water (entry 5), *cis*-stilbene was the major product. Due to high yield and selectivity and environmental acceptability, the 50/50 (v/v) mixture of DMF/water was selected as the best reaction solvent for the Heck reaction.

As illustrated in Table 3, also, different bases were examined in the Heck reaction between 0.6 mmol styrene and 0.5 mmol iodobenzene in the presence of 0.25 mol% PdCl₂ and 0.5 mol% ligand **2f** in DMF/water (50/50: v/v) at 80 °C. In the case of Na₃PO₄, the reaction did not occur after 8 h. However, NaOAc and Et₃N afforded the product with excellent *trans*-selectivity, but the yields were very low, in both cases. When

Na_2CO_3 and K_2CO_3 were used, stilbene was obtained in 92% and 88% yields with 94/6 and 91/9 *trans/cis* selectivity, respectively. Therefore, Na_2CO_3 was selected as the optimum base for further Heck reactions.

Table 2. The effect of solvent on the Heck reaction.^a

Entry	Solvent	Yield %		<i>Trans/cis</i> ^b
		GC	Isolated	
1	DMF	97	80	94/6
2	DMSO	79	66	60/40
3	DMF/water (50/50: v/v)	100	88	91/9
4	DMSO/water (50/50: v/v)	99	80	50/50
5	water	52	20	17/83
6	EtOH	NR ^c	NR ^c	–
7	<i>t</i> -BuOH	–	11	–
8	EtOH/water (50/50: v/v)	–	10	–
9	<i>t</i> -BuOH/water (50/50: v/v)	NR ^c	NR ^c	–
10	Toluene	NR ^c	NR ^c	–

^a Reaction conditions: Styrene (0.6 mmol), iodobenzene (0.5 mmol), PdCl_2 (0.25 mol%), Ligand **2f** (0.5 mol%), K_2CO_3 (1 mmol), 80 °C, 8 h. ^b Determined by GC. ^c No reaction.

Table 3. The effect of bases on the Heck reaction.^a

Entry	Base	Yield %		<i>Trans/cis</i> ^b
		GC	Isolated	
1	K_2CO_3	98	88	91/9
2	Na_2CO_3	100	92	94/6
3	NaOAc	21	16	100/0
4	Et_3N	13	10	100/0
5	Na_3PO_4	NR ^c		–

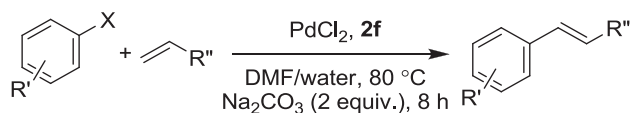
^a Reaction condition: styrene (0.6 mmol), iodobenzene (0.5 mmol), PdCl_2 (0.25 mol%), ligand **2f** (0.5 mol%), DMF/water (50/50: v/v; 2 mL), 80 °C, 8 h. ^b Determined by GC. ^c No reaction.

To broaden the catalytic applicability of the ligand **2f**, we subsequently examined Heck coupling reactions of arylhalides with various olefins (Table 4). The results indicated that the combination of PdCl_2 and **2f** was efficient for the Heck coupling reaction of a series of alkenes and aryl halides (Table 4). The reaction of aryl iodides and bromides with olefins occurred easily and the desired products were obtained in good yields (Table 4, entries 1–12). As expected, the catalytic activity depended on the halide, while electron-withdrawing groups on the aryl ring increased the reaction rate and this general trend was observed for both aryl bromides and chlorides. However, the Heck coupling of chlorobenzene was difficult to achieve under the same reaction conditions and low amounts of coupling product were observed (Table 4, entries 13–19). In general, coupling of aryl iodides and bromides with olefins was found to give products in good to excellent yields (52%–97%). The reduced yields of chlorobenzenes are mostly a consequence of the nonreactive nature of these substrates.

It is clear that ligands with coordination to palladium during the catalytic process of the Heck reaction could improve the stability of palladium complexes and therefore the catalytic activity induced by ligands is indeed better than under ligandless conditions.²⁴ To study the coordination of ligand **2f** to palladium and complex formation during the catalytic process, IR and the electronic spectra of ligand and complex

PdCl_2 /ligand **2f** were recorded. The C=O stretching frequencies for the ligand occur at 1619 cm^{-1} and for the complex it is expected to appear at lower frequencies (1602 cm^{-1}) when compared to the ligand. This shift by at least 17 cm^{-1} to a lower frequency compared to that of the free ligand indicates a decrease in the bond order due to the coordinate bond of the palladium with the oxygen lone pair of ligand. Moreover, the signal appearing at 3274 cm^{-1} , due to the imidazole NH group, disappears in the spectra of the complex, demonstrating that the coordination of ligand was performed. The coordinating modes of the ligand **2f** were confirmed by comparing the electronic spectra of ligand and complex in DMSO solution (Figure). It was found that, in complex, the band at 360 nm of ligand slightly shifted to longer wavelength along with decreases in its intensity. Conversely, the new band at $\lambda_{\text{max}} = 465\text{ nm}$ was observed in complex. On the basis of spectral results, one could assume the formation of new species of type Pd-ligand **2f** as a catalytic complex involved in the reaction.

Table 4. Heck reaction between aryl halides and olefins. ^a



Entry	X	R'	R''	Yield % ^b
1	I	H	Ph	85
2	I	H	CO ₂ ⁿ Bu	84
3	I	H	CO ₂ Me	76
4	I	H	CO ₂ Et	80
5	I	H	COMe	94
6	Br	4-MeCO	Ph	63
7	Br	4-MeCO	CO ₂ ⁿ Bu	57
8	Br	4-MeCO	CO ₂ Et	64
9	Br	4-MeCO	CO ₂ Me	52
10	Br	4-MeCO	COMe	75
11	Br	H	CO ₂ ⁿ Bu	79 ^c
12	Br	H	Ph	58 ^c
13	Cl	4-MeCO	Ph	45
14	Cl	4-MeCO	CO ₂ ⁿ Bu	40
15	Cl	4-MeCO	CO ₂ Et	55
16	Cl	4-MeCO	CO ₂ Me	40
17	Cl	4-MeCO	COMe	70
18	Cl	H	Ph	50 ^c
19	Cl	H	CO ₂ ⁿ Bu	40 ^c

^a Reaction conditions: 0.5 mmol of aryl halide, 0.6 mmol of olefins, 1 mmol of Na_2CO_3 , 0.25 mol% PdCl_2 , 0.5 mol% **2f**, $80\text{ }^\circ\text{C}$, 2 mL (1:1) mixture of H_2O /DMF as solvent. ^b Isolated yield. ^c 24 h.

3. Experimental section

All the reactions were carried out under air. Chemicals and solvents were purchased from the Fluka and Merck Chemical companies and used without purification. The reaction products of the Heck reaction were determined and analyzed by a HP Agilent 6890 gas chromatograph equipped with a HP-5 capillary column (phenyl methyl siloxane $30\text{ m} \times 320\text{ }\mu\text{m} \times 0.25\text{ }\mu\text{m}$) and a flame-ionization detector. All products were isolated by short column chromatography on silica gel 60 (0.063–0.20 mesh ASTM) using hexane/ethyl acetate as eluent.

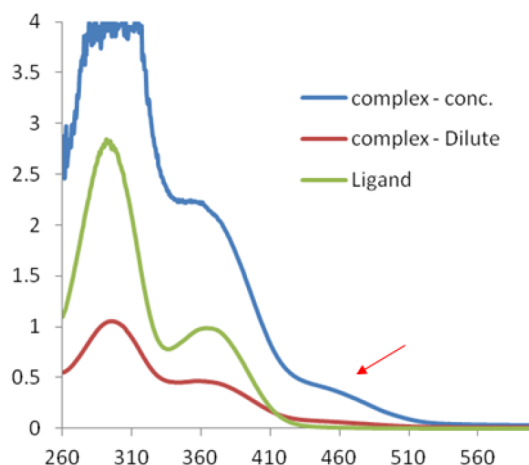


Figure. UV-Vis spectra of ligand **2f** and complex.

In order to show the merit and efficiency of the present catalytic complex, the Heck coupling reaction between iodobenzene and styrene under the same reaction conditions was studied. It was found that complex promoted the Heck coupling reaction, giving excellent conversion (100%) and high selectivity (93%) to *trans*-stilbene.

3.1. Synthesis of ligands **2**

To a mixture of an arylglyoxal hydrate (1 mmol) in water (5 mL) was added NH_4OAc (5 mmol) at room temperature and stirred at the same temperature for 1 h. Then the reaction mixture was solidified and the obtained solid was filtrated, washed with water (3–15 mL), and the crude product was purified by crystallization from ethanol.⁷

3.2. Synthesis of PdCl_2 -ligands **2f** complex

A mixture of ligand **2f** (0.07 mmol) and PdCl_2 (0.035 mmol) in 4 mL of DMF/water (1/1; v/v) was heated at 100 °C for 1.5 h. Then the obtained solid was filtered and washed with water.

3.3. General procedure for the Heck reactions

All Heck reactions were carried out under air. A mixture of aryl halide (0.5 mmol), olefins (0.6 mmol), Na_2CO_3 (1 mmol), PdCl_2 (0.25 mol%), and ligand **2f** (0.5 mol%) in a 1/1 (v/v) mixture of H_2O /DMF (2 mL) was allowed to react in a sealed tube at 80 °C. The reaction mixtures were added to brine (15 mL) and extracted 3 times with diethyl ether (3×15 mL). The combined organic phase was analyzed by GC. The further purification of the product was achieved by flash column chromatography on silica gel using hexane/ethyl acetate (5:1).

In summary, we have developed an efficient phosphine-free Heck reaction using aroylimidazoles as ligand in aqueous DMF. Easy preparation of aroylimidazoles ligands and high yields of the Heck products with high *trans*-selectivity using a cheap and available base (Na_2CO_3) are some advantageous of it.

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