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Imidazole and Imidazoline Derivatives as *N*-Donor Ligands for Palladium-Catalyzed Mizoroki–Heck Reaction

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Abstract: Imidazole and imidazoline (dihydroimidazole) derivatives can serve as efficient and simple ligands for the palladium-catalyzed Mizoroki–Heck reaction. Among the imidazole and imidazoline derivatives in our investigations, the 2-methylimidazoline-palladium(II) chloride complex exhibited the highest catalytic activity.

Keywords: catalyst design; C−C coupling; ligand effect; Mizoroki–Heck reaction; palladium

Since the first report in 1971, the Mizoroki–Heck reaction has been widely employed in the construction of carbon-carbon bonds.[1] While phosphine and related compounds are often employed as ligands, electron-rich and bulky alkylphosphines, such as P(*t*-Bu)$_3$, have been recently developed as highly effective ligands.[2] Furthermore, because of recent advances in the field of palladacycles,[3] N-heterocyclic carbenes have also been utilized as ligands.[4] Additionally, Mizoroki–Heck reactions involving various catalytic systems such as palladium and activated aryl chlorides [e.g., $(CH_3CN)_2PdCl_2$–PPh_4Cl],[5] $Pd(OAc)_2$ with excess $P(OEt)_3$[6] and heterogeneous Pd/C[7] have also been developed.[8,9] To date, however, the use of imidazole moieties is generally limited to palladium-carbene complexes that possess a carbon-palladium bond.

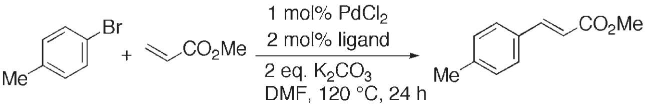
In contrast to phosphine-type ligands, the low toxicity and stability of nitrogen-based ligands, such as pyridine or imidazole derivatives, have attracted the interest of synthetic organic chemists. As examples, Rüther, Cavell, et al. have reported the catalytic behavior of cationic and neutral Pd(II) complexes that feature imidazole-based ligands.[10] Welton et al. have reported on the Suzuki coupling reactions catalyzed by $(CH_3CN)_2PdCl_2$–imidazole and its derivatives.[11]

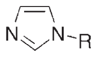
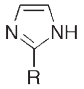
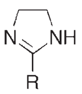
Herein, we report on the palladium-catalyzed Mizoroki–Heck reactions that involve the simple catalytic system of $PdCl_2$–imidazole or $PdCl_2$–imidazoline. Not only are such complexes structurally simple, readily available, and inexpensive, but the imidazole moiety allows for the facile introduction of various substituents into the imidazole framework. Our report also includes the single X-ray crystal structuresof the palladium-complexes, which, to the best of our knowledge, is the first such report.

Initially, we investigated the reaction of 4-bromotoluene with methyl acrylate under the conventional conditions in DMF at 120 °C with K_2CO_3 as a base. The highly reactive $PdCl_2$ [compared to $Pd(OAc)_2$] was chosen as the source of palladium for the reaction. Our results indicated that the ligands are necessary for catalytic activity; in the absence of the imidazole or imidazoline ligands, $PdCl_2$ alone was not effective in catalyzing the reaction (only 9% yield). Various imidazoles and imidazolines, with substituents at the 1- or 2-position (see Table 1), were evaluated as ligands for the reactions, which were run under identical conditions, including the reaction time of 24 h. Among the ligands, 2-methylimidazoline (**1e**) exhibited the highest reactivity (entry 5).

Next, our investigations examined the efficiency of this $PdCl_2$–**1e** catalytic system. Reactions involving various haloarenes and olefins, as listed in Table 2, were carried out in the presence of $PdCl_2$ (1 mol%) and **1e** (2 mol%). Among the haloarenes, the substituted bromobenzenes, which possess either electron-withdrawing groups or electron-donating groups afforded the corresponding Mizoroki–Heck products in high yields. Decreasing the amount of the catalysts ($PdCl_2$, 0.1 mol% and **1e**, 0.2 mol%) did not significantly affect the yield (entry 4). In the case of $PdCl_2$ (0.01 mol%) and **1e** (0.02 mol%), a turnover number (TON) of 2,200 was attained (22% yield). In the cases where styrene was used as an olefin (entries 6–8), the products were obtained as mixtures of *E/Z* isomers, inatios of 97/3–99/1. For the coupling reaction

Table 1. Mizoroki–Heck reaction catalyzed by $PdCl_2$ and a nitrogenous ligand system.[a]

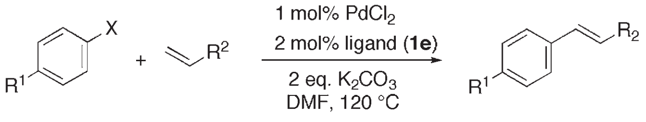


entry	ligand		% yield[b]
1		R = H (**1a**)	62
2		R = Me (**1b**)	45
3		R = Me (**1c**)	47
4		R = *i*-Pr (**1d**)	74
5		R = Me (**1e**)	79
6		R = *i*-Pr (**1f**)	67
7		R = Ph (**1g**)	70
8	none		9

[a] All reactions were carried out in DMF at 120 °C for 24 h using 1 mol% of $PdCl_2$ and 2 mol% of the nitrogen-based ligand.

[b] Isolated yield by silica gel column chromatography.

Table 2. Mizoroki–Heck reactions between 4-substituted haloarenes and olefins.[a]



Entry	X	R^1	R^2	Time [h]	Yield [%][b]
1	Br	Me	CO_2Me	24	79
2	Br	Me	CO_2-*t*-Bu	3	77
3	Br	COMe	CO_2-*t*-Bu	1	99
4[c]	Br	COMe	CO_2-*t*-Bu	7	95
5	Br	OMe	CO_2-*t*-Bu	3	80
6	Br	OMe	Ph	3	91(98/2)[d]
7	Br	Me	Ph	8	94 (99/1)[d]
8	Br	COMe	Ph	3	98 (97/3)[d]
9	Cl	CHO	CO_2-*t*-Bu	24	18
10[e]	Cl	CHO	CO_2-*t*-Bu	24	85

[a] All reactions between halobenzene (2 mmol) and olefin (2 mmol) were carried out in DMF at 120 °C.

[b] Isolated yields determined using silica gel column chromatography.

[c] $PdCl_2$ (0.1 mol%) was used.

[d] *E/Z* ratio shown in parentheses.

[e] *n*-Bu_4NBr (2 equivs.) was added.

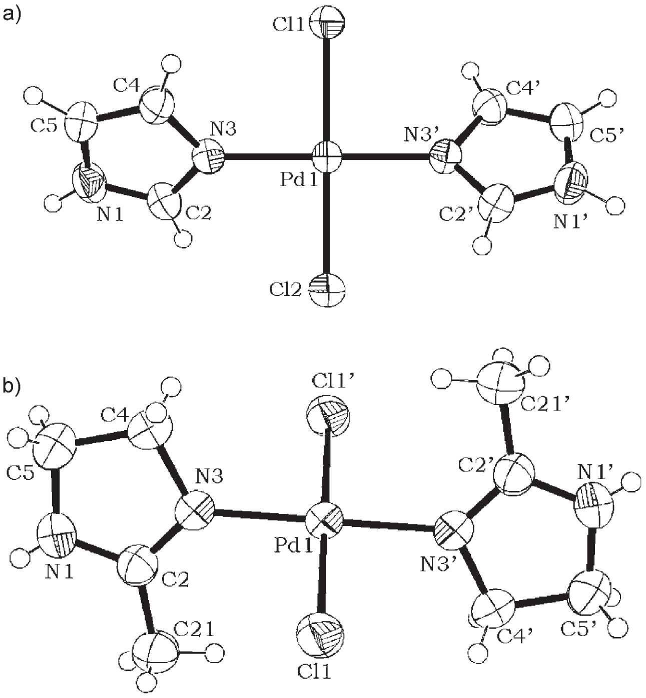
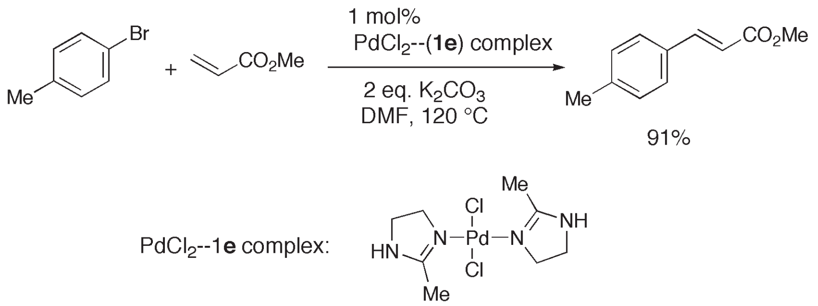


Figure 1. X-ray structures of the $PdCl_2$–**1a** complex (*above*) and the $PdCl_2$–**1e** complex (*below*).

between an unreactive aryl chloride and *tert*-butyl acrylate (entry 9), the $PdCl_2$–**1e** catalyst system was improved by the addition of two equivalents of *n*-Bu_4NBr (TBAB), so-called Jeffery conditions,[12] (entry 10). Except for that of entry 9, the reaction times in Table 2 depended on the substrates and the reactants – the reactions were terminated when the haroarenes were completely consumed. For the reactions that proceeded smoothly, the formation of Pd black (precipitate) was not observed.

The $PdCl_2$–**1e** complex was prepared by modifying the reported procedures for $PdCl_2$–**1a**.[13,14] The coordination between one Pd atom and two molecules of **1e** was confirmed by structural analysis of $PdCl_2$–**1a** and $PdCl_2$–**1e** complexes using X-ray crystallography (Figure 1; depository numbers: CCDC 279171 and 289173, respectively) and ^1H NMR spectroscopy (see Supporting information). It is worthy of note that these palladium complexes are stable under ambient atmosphere, and are soluble in DMF, DMA, and DMSO, but only slightly soluble in acetonitrile.

Additional investigations were carried out for the Mizoroki–Heck coupling between 4-bromotoluene and methyl acrylate in the presence of $PdCl_2$–**1e** complex (Scheme 1). Using the palladium complex that was generated *in situ* (1 mol%), the product was obtained with a yield of 79%. In contrast, the use of the isolated $PdCl_2$–**1e** complex (1 mol%), as described above, increased the yield to 91%. Presumably, the *in situ* catalyst may consist of some unreacted $PdCl_2$ resulting in lower yield. Even the presence of 0.01 mol% of the isolated $PdCl_2$–**1e** complex gave the product in 70% yield (TON = 7,000). Among the compatible solvents for the $PdCl_2$–**1e** complex, DMF resulted in the highest reactivity and was thus chosen as the preferred solvent for the reactions.



Scheme 1. Mizoroki-Heck reactions between 4-bromotoluene and methyl acrylate in the presence of $PdCl_2$–**1e** complex.

In summary, a simple catalytic system involving palladium-imidazole or -imidazoline was developed for the Mizoroki–Heck reaction. Because the reaction using only $PdCl_2$ afforded the coupling product with a yield of merely 9%, it was evident that the presence of imidazole or imidazoline ligands significantly improves the effectiveness of the catalyst. The X-ray structural analysis of the complex reveals that Pd atom is coordinated to two imidazole or imidazoline molecules *via* their nitrogen atoms. In the case of the unreactive chlorobenzene reaction, the yield was improved under Jeffery (n-Bu_4NBr) conditions. A high TON (up to 7,000) was achieved in the reaction of 4-acetylbromobenzene with *tert*-butyl acrylate using isolated $PdCl_2$–**1e** complex. Further investigations towards other coupling reactions using our catalytic system are currently in progress.

Experimental Section

General Procedure for Mizoroki–Heck Reaction

A mixture of $PdCl_2$ (3.55 mg, 0.01 mmol), imidazole-based ligand (0.02 mmol) and K_2CO_3 (2 equivs.) in DMF (10.0 mL) was stirred at 50 °C for 1 h. To this mixture was added 4-bromotoluene (2 mmol) and olefin (2 or 4 mmol), then it was then stirred at 120 °C. After allowing the reaction mixture to cool to room temperature, the precipitates were removed by filtration, and the products were extracted with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to afford the crude product, which was purified by silica gel column chromatography to give the coupling products.

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