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A Hybrid P,N-Ligand Functionalized Imidazolium Salt for Palladium-Catalyzed Heck Reactions in Ionic Liquid Solution

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Abstract A hybrid P,N-donor functionalized imidazolium salt has been synthesized and investigated as a ligand for the palladium catalyzed Heck reaction. Due to the advantageous features of this hybrid P,N-donor like the hemilabile ligation to Pd center, the improved oxidation tolerance and the ionophilicity, the derived palladium catalyst served as an efficient, stable and recyclable system even after seven reuses.

Keywords Heck reactions · Ionic liquids · Imidazolium salts · Hybrid ligands

1 Introduction

The Heck reaction is one of the most important carbon-carbon bond forming methodologies in organic synthesis [1, 2]. In the past decades, the considerable progresses have been made in palladium-catalyzed Heck reactions [1–5]. The development of homogeneous/heterogeneous catalysts led to a variety of different ligand systems, among which phosphine-containing palladacycles [6–9], bulky and electron-rich monodentate phosphine [10], and carbene donors like N-heterocyclic carbenes (NHCs) which are strong σ-donors with negligible π-accepting ability [11–15] are exemplarily attractive owing to the high activities of the derived Pd catalysts. The N-containing ligands recently became preferable in considerations of non-toxicity and insensitivity to oxygen/moisture, but the rapid deactivation of the derived palladium catalysts in the recycling use was still a frustrated problem [16–20].

In contrast to monodentate ligands, bidentate phosphine ligands (P–P) can provide more stable Pd (L–L) complexes suitable for Heck reactions and thereby avoid the use of excess ligands and high loadings of palladium. However catalytic systems based on bidentate phosphine ligands have displayed limited successes due to the low activities [21–24]. In recent years, multidentate ligands that contain significantly different types of hard (N–, or O–) and soft (P–) donor functions have been studied because of their potential application in homogeneous catalysis [25–30]. These ligands possess one weakly coordinating group that can reversibly release during the catalytic cycle providing unsaturation at the metal center. Thus, the less strongly bound moiety of this type of ligand, called hemilabile, is capable of temporarily holding a coordination site on the metal and then being released for the substrate insertion timely [31]. Among the various kinds of hybrid P,N-ligands, those showing pyridyl or imine arms have been widely used to prepare complexes of different transition metals [28–30, 32–34], some of which have been successfully employed in palladium catalyzed coupling reactions [29, 31, 35–37].

Highlighted by the hemilabile nature of bidentate P,N-ligands and the flexible modification of ionic liquids (ILs) by functional groups as well as the recyclable character [38–43], we synthesized a hybrid P,N-ligand functionalized IL, 1-(2-piperid–1-yl-ethyl)-2-diphenylphosphino-3-

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methylimidazolium hexafluorophosphate (**3**), and examined **3** as a desirable ligation for palladium catalyzed Heck reactions.

2 Experimental

2.1 Synthesis

2.1.1 *1-(2-Piperid–1-yl-ethyl)-2-diphenylphosphino-3-methylimidazolium hexafluorophosphate (**3**)*

In N_2 atmosphere, the solution of **1** (13.56 g, 40 mmol) in 60 mL dry CH_2Cl_2 (refluxed in CaH_2 and distilled freshly before use) was cooled down to −70 °C, in which 15 mL BuLi (2.9 M, in petroleum ether, 44 mmol) was added dropwise. After stirring the mixed solution for 1 h, chlorodiphenylphosphine (PPh_2Cl, 8.82 g, 35 mmol) was added dropwise. The resultant mixture was stirred at −70 °C for 3 h, and then the reaction temperature simultaneously increased from −70 °C to ambient after overnight. After quenching excess n-LiBu with deionized water, the obtained mixture was removed of solvent in vacuo. The left residue was recrystallized with CH_2Cl_2/EtOH to yield a white solid as the product **3** (Yield, 86 mol%). Mp 138–139 °C. IR (KBr disc): 3165 (w), 2932 (s), 2854 (s), 1565 (w), 1479 (s), 1429 (s), 1374 (m), 1227 (m), 1122 (m), 840 (s). ^1H NMR (500 MHz, $CDCl_3$, ppm): δ_H 7.7 (singlet, H, $NC(H)C(H)N^+$), 7.5 (singlet, H, $NC(H)C(H)N^+$), 7.4 (quint, 6H, $J = 2$ Hz, $CH_3NCP(Ph_2)N^+$), 7.3 (quint, 4H, $J = 4$ Hz, $CH_3NCP(Ph_2)N^+$), 4.4 (triplet, 2H, $J = 4$ Hz, N^+CH_2), 3.4 (singlet, 3H, NCH_3), 2.5 (triplet, 2H, $J = 6$ Hz, $N^+CH_2CH_2$), 2.2 (singlet, 4H, piperidyl, CH_2NCH_2),1.3 (triplet, 6H, $J = 4$ Hz, piperidyl, $CH_2CH_2CH_2$), ^{31}P NMR ($CDCl_3$, ppm): δ_P −28.1 (singlet, $-PPh_2$),−143.7 (septet, $J = 12$ Hz, PF_6^-). ESI-MS:M^+/z 378, M^-/z 145.

2.2 General Procedures for the Heck Reaction and Recycling of the Catalyst

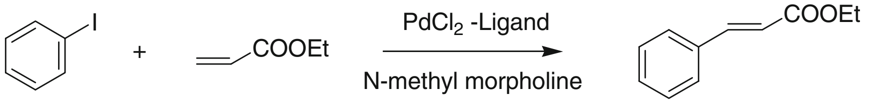
In a typical example, a solution of iodobenzene (5 mmol) with ethyl acrylate (6.0 mmol) in $[Bmim]PF_6$ (2 mL) was mixed with the ionic ligand **3** (0.025 mmol), *N*-methyl morpholine (7.5 mmol), and $PdCl_2$ (0.025 mmol). The mixture sealed in the glass vials reacted at 110 °C for 2 h on an Advantage Series^{TM} 2410 Personal Screening Synthesizer (Argonaut Technologies Inc). On completion, the reaction mixture was extracted with diethyl ether (2.5 mL × 4). The ether fractions were combined, and then analyzed by GC to determine the conversions (1-dodecane as internal standard) and the selectivities (normalization method). The structures of obtained products were further confirmed by GC-Mass. The remaining IL phase composed by $PdCl_2$, ligand **3** and the formed salt of *N*-methyl morpholine HI was dried in vacuo at room temperature and then used directly without further treatment for the next run. Due to the stoichiometric consumption of the base, the *N*-methyl morpholine (7.5 mmol) was added additionally per pass.

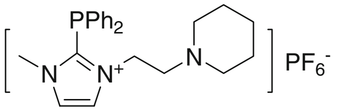
All manipulations were conducted in air.

3 Results and Discussion

To evaluate the activity of the catalyst formed in situ from ligand **3** and $PdCl_2$ in Heck reaction, the coupling reaction of iodobenzene with ethyl acrylate has been chosen as a model reaction. Two other structurally similar ligands, N-containing ligand of 1-(2-piperid-1-yl-ethyl)-3-methylimidazolium hexafluorophosphate (**1**) [17(a)] and P-containing ligand of 1-n-butyl-2-diphenylphosphino-3-methylimidazolium hexafluorophosphate (**2**) [17(b)] were also synthesized and used as comparisons in the study of the Heck reaction. Investigations into the bases (triethylamine, tri-n-butylamine, *N*-methyl morpholine, *N*-methyl piperidine, K_2CO_3) indicated that the reaction rate was significantly enhanced by using *N*-methyl morpholine as a base. Under the optimal reaction conditions (0.5 mol% $PdCl_2$, 1.2 equiv. of ethyl acrylate, 1.5 equiv. of *N*-methyl morpholine, temperature 110 °C, reaction time 2 h), the coupling product was obtained in good yield (95%) by using **3** as the ligand and $[Bmim]PF_6$ as the solvent (Table 1, entry 1). In consideration of the same benchmark of the coordinating sites in ligand **1**, **2**, and **3**, the ligand/Pd molar ratio of 2 for ligand **1** and **2** was investigated in entries 3, 5, 9 and 11 of Table 1, respectively. It can be seen that the molar ratio of ligand to $PdCl_2$ influenced the reaction rate and the catalyst stability greatly. In $[Bmim]PF_6$, the activity of $PdCl_2$-**3** was better than the corresponding **2** and slightly worse than **1** (Entries 1 vs. 2–5). The presence of the excess soft ligand of **2** led to the dramatically decreased reaction rate (Entry 3), due to the stable Pd(II) complex formed against further reduction to Pd(0) active species [21–27]. In contrast, the excess of hard ligand of **1** showed no difference in the catalytic performance of $PdCl_2$ (Entries 4, 5), due to the weak ligation to Pd center which resulted in reversibly ligand release. Possibly, the base of *N*-methyl morpholine in large excess equally could act as a N-containing ligand which might counteract the role of ligand **1**. However the result in Entry 6 revealed that the contribution of ligand **1** to the activity of the derived Pd catalyst could not be replaced by *N*-methyl morpholine, probably owing to the potential formation of six-member N-heterocyclic carbene palladium complex via a bidentate chelation of the N-donor and the carbene-donor

Table 1 The Heck reaction of iodobenzene with ethyl acrylate





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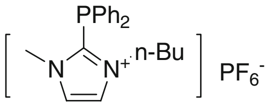

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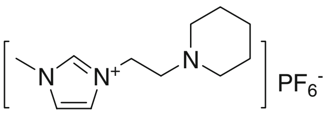


1

Entry	Ligand	Solvent	Conversion (%)[a]	Selectivity (%)[b]
1	**3** (0.025 mmol)	[Bmim]PF_6	96	99
2	**2** (0.025 mmol)	[Bmim]PF_6	88	99
3	**2** (0.050 mmol)	[Bmim]PF_6	18	100
4	**1** (0.025 mmol)	[Bmim]PF_6	97	100
5	**1** (0.050 mmol)	[Bmim]PF_6	98	100
6	–	[Bmim]PF_6	93	99
7	**3** (0.025 mmol)	DMF	90	99
8	**2** (0.025 mmol)	DMF	72	100
9	**2** (0.050 mmol)	DMF	10	99
10[c]	**1** (0.025 mmol)	DMF	90	99
11[c]	**1** (0.050 mmol)	DMF	92	99
12[c]	–	DMF	90	99

$PdCl_2$, 0.025 mmol; phenyl iodide, 5 mmol; ethyl acrylate, 6.0 mmol; *N*-methyl morpholine 7.5 mmol; reaction time 2 h; solvent 2 mL; reaction temperature, 110 °C

[a] Of iodobenzene

[b] To *E*-ethyl cinnamate

[c] Pd black precipitated largely

Table 2 The recycling uses of the catalysts formed in situ from the investigated ligands and $PdCl_2$ for Heck reaction

Runs	Cat.: $PdCl_2$-**3** (**3**/$PdCl_2$ = 1[a])		Cat.: $PdCl_2$-**2** (**2**/$PdCl_2$ = 1[a])		Cat.: $PdCl_2$-**1** (**1**/$PdCl_2$ = 1[a])	
	Conv. (%)[b]	Sel. (%)[c]	Conv. (%)[b]	Sel. (%)[c]	Conv. (%)[b]	Sel. (%)[c]
1	96	99	88	100	97	100
2	98	99	89	99	91	100
3	98	99	84	99	83[d]	99
4	99	100	86	100	76[d]	99
5	99	100	81	99	61[d]	99
6	98	99	87	98	49[d]	99
7	98	100	84	99	46[d]	100

$PdCl_2$, 0.025 mmol; phenyl iodide, 5 mmol; ethyl acrylate, 6.0 mmol; *N*-methyl morpholine 7.5 mmol, which was added per cycle; reaction time 2 h; [Bmim]PF_6 2 mL; reaction temperature, 110 °C

[a] Molar ratio

[b] Of iodobenzene

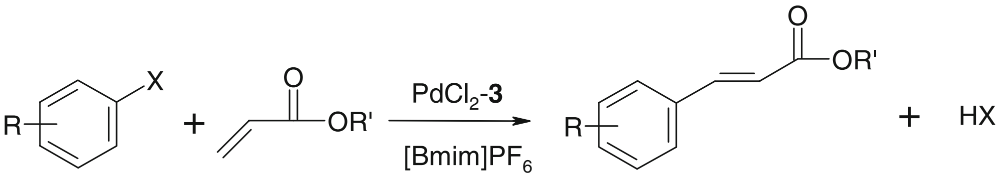
[c] To *E*-ethyl cinnamate

[d] Pd black precipitated

in ligand **1**. In the organic solvent of DMF, the stability of the fresh $PdCl_2$ catalyst only could be guaranteed by the P-containing ligands **3** and **2** (Entries 6–8). The excess of ligand **2** indeed stabilized the Pd catalyst against deactivation, but exhibiting the poor activity similarly (Entries 3 vs. 9). The N-containing ligand **1** or excess *N*-methyl morpholine unexceptionally led to the Pd black precipitation (Entries 10–12). Notably, the advantage to use $[Bmim]PF_6$ as a solvent was to ensure a complete dissolution of both the ionic ligand and $PdCl_2$ complex to perform a homogeneous reaction. On the other hand, $[Bmim]PF_6$ could offer nucleophilic N-heterocyclic carbene site, which was regarded to play the role of stabilizing Pd (0) species with no formation of Pd black by forming N-heterocyclic carbene palladium complex (NHC) in situ [44, 45].

The recycling uses of $PdCl_2$ mediated by **1**, **2**, and **3** in $[Bmim]PF_6$ were examined in Table 2, respectively. With the involvement of the hybrid P,N-ligand of **3**, $PdCl_2$ exhibited the very good activity and stability even after 7 runs without any precipitation of Pd black. The cumulative ammonium salts (*N*-methyl morpholine HI) showed no degraded impacted on the activity of $PdCl_2$-**3**. In each run, the pure product of ethyl cinnamate was directly obtained in >96% yield by extracting with diethyl ether and concentrating under vacuum. The ICP (inductive coupled plasma

Table 3 Heck reactions with different substrates catalyzed by $PdCl_2$-**3** in $[Bmim]PF_6$



Entry	R	R′	X	Conversion[a] (%)	Selectivity[b] (%)
1	H	$-CH_2CH_3$	I	99	100
2	*p*-Me	$-CH_2CH_3$	I	100	100
3	*m*-Me	$-CH_2CH_3$	I	99	100
4	*o*-Me	$-CH_2CH_3$	I	91	100
5	*p*-OMe	$-CH_2CH_3$	I	100	100
6	*m*-OMe	$-CH_2CH_3$	I	100	100
7	*o*-OMe	$-CH_2CH_3$	I	83	100
8	*p*-NO_2	$-CH_2CH_3$	I	100	100
9	*m*-NO_2	$-CH_2CH_3$	I	100	100
10	*o*-NO_2	$-CH_2CH_3$	I	66	100
11	*p*-CF_3	$-CH_2CH_3$	I	98	100
12	*m*-CF_3	$-CH_2CH_3$	I	91	100
13	*o*-CF_3	$-CH_2CH_3$	I	67	100
14[c]	*p*-NO_2	$-CH_3$	Br	100 (15 h[d])	100
15[c]	*m*-NO_2	$-CH_3$	Br	97 (15 h[d])	99
16[c]	*o*-NO_2	$-CH_3$	Br	88 (15 h[d])	99
17[c]	*m*-CF_3	$-CH_3$	Br	79 (15 h[d])	100
18[c]	H	$-CH_3$	Br	49 (15 h[d])	100
19[c]	*p*-CH_2CN	$-CH_3$	Br	62 (25 h[d])	100
20[c]	*p*-OMe	$-CH_3$	Br	44 (25 h[d])	100
21[c]	*p*-Me	$-CH_3$	Br	45 (25 h[d])	100

$PdCl_2$ 0.025 mmol (0.5%), **3** 0.025 mmol, $[Bmim]PF_6$ 2 mL, aryl halide 5 mmol, ethyl/methyl acrylate 6.0 mmol, *N*-methyl morpholine 7.5 mmol, reaction temperature 110 °C, reaction time 2 h

[a] Of aryl halide

[b] To *E*-cross-coupling product. The structure of the coupling product was further confirmed by GC-MS

[c] Reaction temperature 130 °C

[d] Reaction time was indicated in the parenthesis

emission spectrometer) analysis indicated that the leaching of Pd into organic phase was below the detection limit (<0.1 μg/g). When the P-containing ligand of **2** was applied, the relatively low activity but good stability was observed. When the N-containing ligand of **1** was applied, the palladium catalyst deactivated gradually during the recycling use accompanying with the obvious precipitation of Pd black, though its fresh activity was even better than the corresponding $PdCl_2$-**3**. It was implicated that the hybrid P,N-ligand **3** with bidentate chelation to metal center exhibited many advantageous characteristics, including the good protection ability against deactivation of the Pd catalyst like P-containing ligand **2** [10, 21–27], the improved activity arising from the random release from metal center like N-containing ligand **1**, and the practical recyclability like the IL compound. As a bidentate ligand, **3** with a hemilabile ligation to metal center could offer a necessary unsaturation site for the substrate at N-coordinating site and simultaneously hold the Pd atom by the P-ligand arm [31]. On the other hand, among many reported hybrid P,N-ligands, those showing direct bonding of a N-heterocycle to the phosphorous center, such as 2-pyridyldiphenylphosphine [46–50] or 2-pyrimidylediphenylphosphine [51–53], inevitably increases the electron density at the phosphorous center, which is less tolerant against oxidation, and consequently unfavorable to the stability of palladium catalysts. In ligand **3**, the bonding of the phosphine moiety to 2C position of imidazolium, which is endowed with strong electron-withdrawing nature as a quaternary ammonium group, results in the decreased electron density at the phosphorous center, leading to the improved oxidation tolerance of itself and the consequently favorable stability of the palladium catalyst as shown in Table 2. Hence, the ligand **3** with hydrophobicity (PF_6^- as the counter anion) and the improved oxidation tolerance could be handled in open air, which facilitated the purification and separation workup greatly.

As shown in Table 3, $PdCl_2$-**3** in $[Bmim]PF_6$ could catalyze Heck reactions with a wide array of substrates with different electronic and steric effects. It was indicated that, due to the high reactivity of the aryl iodides, the cross-coupling products were all obtained in high yields (66–100%) under mild conditions (110 °C, 2 h) without obvious discrimination of the electronic nature of the substituents. The steric effect could only be observed when the *o*-substituting group involved (Entries 4, 7, 10). As for the aryl bromides with relatively low reactivity, the activated substrates with electron-withdrawing character, such as (*p,m,o*)-bromonitrobenzene and *p*-bromotrifluoromethylbenzene, coupled with methyl acrylate in the good yields (79–100%) as the reaction time extended to 15 h and the reaction temperature raised to 130 °C (Entries 14–17). The highly deactivated substrates (*p*-bromoanisole, *p*-bromotoluene) coupled in moderate yields at much longer reaction time (Entries 20, 21). Attempts had been made to use the electro-deficient aryl chlorides like *p*-chloronitrobenzene to perform the Heck reaction. However, no desired coupled product was obtained.

4 Conclusions

The developed hybrid N,P-bidentate ligand **3**, endowed with ionophilicity as an imidazolium-based IL and the hemlabile ligation to Pd center, proved to be dramatically beneficial to the activities, stability and recyclability of the derived Pd catalyst in the Heck reaction of iodobenzene with ethyl acrylate. Meditated by the similar structured IL of $[Bmim]PF_6$ as the solvent, $PdCl_2$-**3** system could successfully catalyze the Heck reactions available for an array of substrates including sterically hindered and electron-rich aryl iodides and aryl bromides. This study shows that the hybrid N,P-bidentate ligand incorporated into an IL with multiple ligations to the palladium complex represents a very promising class of ligands for Heck reactions.

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