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Imidazolium Ionic Liquid-supported Diol: An Efficient and Recyclable Phosphine-free Ligand for Palladium Catalyzed Heck Reaction

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Abstract A new imidazolium IL-supported diol has been synthesized and used as a phosphine-free ligand for palladium catalyzed Heck reaction, which was proved to be a convenient and economical system due to its efficiency, non-toxicity and recyclability.

Keywords Ionic liquid · Diol · Phosphine-free ligand · Heck reaction

1 Introduction

The Heck reaction, which is one of the most important methods for C–C bond formation in preparative organic chemistry, has received increasing attention in the past decade [1]. Typical procedures for the Heck coupling are using a palladium catalyst with a ligand [2]. Much work has focused on utilizing phosphine-based ligands, as they tend to be more active and stable [3]. However, P-containing ligands have limited applications, mainly because they are highly toxic and air/moisture sensitive. More recently, many coupling reactions have been carried out in homogeneous solutions with phosphine-free catalytic systems, such as nitrogen- [4] and sulfur-based palladacycles [5], *N,S*-based carbenes [6], *N*-heterocyclic carbenes (NHC) [7], amino alcohols (*N,O*-ligands) [8] and ethylene glycol (*O,O*-ligands) [9]. Nevertheless, the major disadvantage of homogeneous catalysts was difficult separation from the reaction product, which resulted in economical and environmental problems. Therefore, in view of practical uses, the development of solid-supported palladium complexes is of importance to avoid these limitations [10]. For instance, several inorganic or organic supports (including Wang resin [11], Merrifield resin [12], polystyrene [13], and silica [14]) Pd catalysts have been reported in recent years. However, the technique of heterogeneous palladium-catalyzed Heck reaction has drawbacks of requirements for the large amount of catalyst and longer reaction time due to solid-liquid interface.

Since ionic liquids (ILs) came into the spotlight during the last decade, many vigorous and consistent efforts have paved the way for alternative and new synthetic strategies in the realm of synthetic organic chemistry, because of their unique characters such as reasonable thermal and chemical stability, negligible vapor pressure, and ease of recyclability [15]. In this field, it has been recognized that the IL-supported reagents combine the advantages of homogeneous and heterogeneous reagents in reactions [16]. Herein, for the first time we reported on an imidazolium IL-supported diol, (2,2-bis-(1-(1-methyl imidazolium)-methylpropane-1,3-diol hexafluorophosphate, **1**) as a kind of ligand with multiple coordinating sites from readily available starting materials (Scheme 1), and demonstrated its utility as an efficient and recyclable phosphine-free ligand for palladium-catalyzed Heck reaction.

2 Results and Discussion

The IL-supported diol **1** was synthesized according to the method in Scheme 1, which was identified by ^{1}H NMR, ^{13}C NMR, FT-IR, MS (ESI), and elemental analysis.

Initially, the influences of a variety of bases (K_2CO_3, Na_2CO_3, $NaHCO_3$, NEt_3, pyridine), solvents (CH_3CN,

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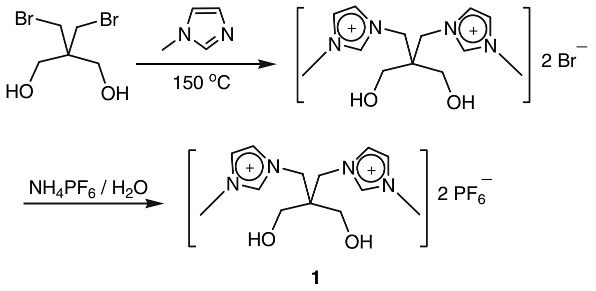


Scheme 1

DMF, NMP, DMSO), ratio of **1** to $PdCl_2$ catalyst, ratio of the substrates (ethyl acrylate : PhI), and temperature were examined with iodobenzene and ethyl acrylate as the substrates. After optimization of the reaction conditions, the satisfactory result (conversion 100% and selectivity 98%) was obtained when the reaction was carried out in DMF using K_2CO_3 as a base at 130 °C, only with 0.05 mol % of $PdCl_2$ as well as 0.1 mol% of **1** (Table 1, Entry 2). With the decrease of $PdCl_2$ concentration to 0.01 mol%, the same conversion still achieved by extending reaction time from 1 h to 2 h, implying the high efficiency of this catalytic system with TON of 10^4 (Table 1, Entry 3).

The scope of the Heck reaction was investigated with a wide array of substrates with different electronic and steric effects. As shown in Table 1, all aryl iodides were rapidly converted to the corresponding products with excellent conversions (100%) and selectivities (95–100%), regardless of the electro-rich/deficient nature of the substituents (Table 1, Entries 4–19). The chain length of terminal acrylates had no obvious impacts on conversions of the substrates and selectivities of the cross coupling products. As to the activation of aryl bromides, the satisfactory conversions were obtained in cases of bromobenzene, *p*-bromonitrobenzene and *p*-bromoanisole applied (Table 1, Entries 20–22). Unfortunately, as to the activation of chlorobenzne, the relatively poor activity was given out (Table 1, Entry 23).

For the practical application of a catalyst, the separation from reaction product and reusability of the catalyst are very important factors. To demonstrate this issue, the recycling experiments were conducted over $PdCl_2$-**1** for coupling reaction of iodobenzene and ethyl acrylate. In order to justify the recyclability of $PdCl_2$-**1** catalytic system, the conversion of first run should be less than 100% so that all subsequent runs can be benchmarked. Therefore the reaction time was shortened to 40 min during the recycling runs. On completion monitored by TLC and GC, the reaction mixture was cooled to room temperature and then treated with water. The resulting mixture was extracted with ether to give the product. The aqueous phase containing $PdCl_2$-**1** was concentrated to remove DMF as well as water and reused directly for next run without further purification. The results in Table 2 showed that the catalytic activity maintained very well even after ten cycles without any Pd precipitation. The leaching of Pd in the extracted organic phases was below the detection limit of ICP (<0.1 μg/g), indicating that the palladium complex was locked efficiently by ligand **1** because of favorable coordination. It was conjectured that the ligand **1** could behave as *O,O*-ligand as well as *N,O*-ligand dually by forming six-member ring intermediates [8, 9]. On the other hand, the imidazolium skeleton of **1** could participate the formation of N-heterocyclic Pd-carbenes (NHC-Pd) [6, 7]. Such more available coordination modes prevented $PdCl_2$ from possible dissociation, which resulted in thermally and oxdatively stable catalyst.

Compared to the conventional *O,O*-ligand (ethylene glycol), *N,O*-ligand (triethanolamine), or NHC-Pd catalyst, the main advantages of the developed ligand **1** were more available coordinating sites to $PdCl_2$, and the ionic nature giving rise to the recyclability of the palladium catalyst and the facilitated workup for product/catalyst separation.

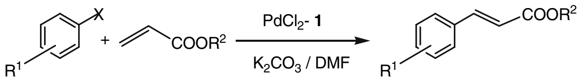
3 Conclusion

We have developed a novel phosphine-free IL-supported ligand **1** for Pd-catalyzed Heck reaction, with the advantages of homogeneous system and simple workup for separation of product as well as recyclability of catalyst. The coupling reactions of aryl iodides or aryl bromides with terminal acrylates using catalyst $PdCl_2$-**1** afforded the desired products in high conversions and selectivities. Moreover, assisted by the ligand **1** with more available coordinating sites, the palladium catalyst showed good stability and could be reused at least ten runs without the activity loss and the obvious Pd leaching. The specific coordination modes of the ligand **1** with palladium complex will be investigated in our further studies.

4 Experimental

N-methyl imidazole was dried with 5 Å molecular sieve overnight and purified by distillation before use. All the other solvents and chemicals were reagent grade purchased commercially and used without prior treatment. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-500 (500 MHz) instrument with DMSO-d_6 as solvent. MS (ESI) was detected by Agilent 1100LC/MSDVL spectrometer. IR spectra were recorded on a Nicolet Nexus 670 FT-IR spectrometer (KBr tablet). Elemental analysis data was recorded on a vario EL III instrument. GC-MS analyses

Table 1 Heck reactions of haloarenes with acrylates[a]



Entry	R^1	R^2	X	Time (h)	Conversion (%)[d]	Selectivity (%)[d]
1[b]	H	C_2H_5	I	4	99	97
2	H	C_2H_5	I	1	100	98
3[c]	H	C_2H_5	I	2	100	99
4	*p*-OCH_3	CH_3	I	1	100	98
5	*o*-OCH_3	CH_3	I	1	100	100
6	*p*-CH_3	CH_3	I	1	100	98
7	*o*-CH_3	CH_3	I	1	100	99
8	*p*-NO_2	CH_3	I	2	100	99
9	*p*-NO_2	C_2H_5	I	1	100	100
10	*o*-CF_3	C_2H_5	I	1	100	100
11	*p*-CH_3	C_2H_5	I	1	100	99
12	*p*-OCH_3	C_2H_5	I	1	100	98
13	*o*-OCH_3	C_2H_5	I	1	100	100
14	*m*-CH_3	C_2H_5	I	1	100	100
15	*o*-CH_3	C_2H_5	I	1	100	100
16	*p*-OCH_3	*n*-C_4H_9	I	1	100	99
17	*m*-CH_3	*n*-C_4H_9	I	1	100	95
18	*p*-CH_3	*n*-C_4H_9	I	1	100	99
19	*o*-CF_3	*n*-C_4H_9	I	2	100	97
20[e]	H	CH_3	Br	48	85	98
21[e]	*p*-NO_2	CH_3	Br	20	100	98
22[e]	*p*-OCH_3	CH_3	Br	48	83	96
23[e]	*p*-NO_2	CH_3	Cl	48	31	95

[a] $PdCl_2$ 0.05 mol%, IL-supported diol **1** 0.01 mmol, haloarene 10 mmol, ethyl acrylate 20 mmol, K_2CO_3 10 mmol, DMF 5 mL

[b] Ethyl acrylate 15 mmol

[c] $PdCl_2$ 0.01 mol%, iodoarene 50 mmol, ethyl acrylate 100 mmol, K_2CO_3 50 mmol, DMF 25 mL

[d] Determined by GC. The trace of biphenyl as byproduct was confirmed by GC-MS

[e] $PdCl_2$ 0.1 mol%, IL-supported diol **1** 0.02 mmol

were recorded on an Agilent 6890 instrument equipped with Agilent 5973 mass selective detector. GC analyses were performed on SHIMADZU-14B equipped with HP-1 capillary column (30 m × 0.25 mm × 0.25 μm). The concentration of palladium in the extracted organic phase was detected by ICP (inductive coupled plasma emission spectrometer, IRIS Intrepid II XSP), according to the standard sample with the lowest concentration of 0.1 μg/g.

4.1 Synthesis of IL-supported Ligand of 2,2-bis-(1-(1-methyl imidazolium)-methyl-propane-1,3-diol hexafluorophosphate (1)

A mixture of 1-methylimidazole (2.05 g, 25 mmol) and 2,2-bis-(bromomethyl)- propane-1,3-diol (2.60 g, 10 mmol) was stirred vigorously at 150 °C for 8 h. After cooling to room temperature, the crude product was washed with acetonitrile. The resulting solid collected by filtration was treated with water (20 mL) as well as NH_4PF_6 (3.26 g, 20 mmol) and the reaction mixture was stirred at room temperature for 1 h. After filtration, the white solid was washed with ethanol and dried in *vacuo* to give the desired product (4.67 g, 84%). FT-IR (KBr disc): 3604, 3165, 3122, 2977, 2913, 1588, 1577, 1448, 1425, 1301, 1173, 1014, 846 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ_H 3.10 (d, J = 4 Hz, 4H, OH-CH_2), 3.90 (s, 6H, CH_3), 4.25 (s, 4H, N-CH_2), 5.25 (t, J_1 = 5 Hz, J_2 = 4 Hz, 2H, O*H*), 7.70 (s, 2H, NC*H*), 7.80 (s, 2H, NC*H*), 9.15 (s, 2H, N (*H*) CN). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): δ_C 137.80, 123.75, 123.41, 58.51, 48.68, 45.37, 35.85. MS (ESI) *m/z*: 554.7 $(M-H)^-$,

Table 2 Recycling uses of $PdCl_2$-1 catalytic system in Heck reaction[a]

Recycling Times	Time (min)	Conversion (%)[b]	Selectivity (%)[b]
1	40	96	98
2	40	94	97
3	40	96	98
4	40	95	98
5	40	95	97
6	40	94	98
7	40	94	98
8	40	95	96
9	40	93	97
10	40	93	97

[a] $PdCl_2$ 0.005 mmol (0.05 mol%), IL-supported ligand **1** 0.01 mmol, iodobenzene 10 mmol, ethyl acrylate 20 mmol, K_2CO_3 10 mmol (additionally added per pass), DMF 5 mL (additionally added per pass)

[b] Determined by GC. The trace of biphenyl as byproduct was confirmed by GC-MS

290.2 ($([PF_6]_2)^{2-}$). Anal. calcd. for $C_{13}H_{22}N_4O_2P_2F_{12}$: C, 28.07; H, 3.99; N, 10.07, found: C, 28.01; H, 3.98; N, 10.02.

4.2 General Procedures for Heck Reaction of Lodoarenes with Acrylates

In a typical experiment, a solution of iodobenzene (2.04 g, 10 mmol) and ethyl acrylate (2.00 g, 20 mmol) in DMF (5 mL) was treated with K_2CO_3 (1.38 g, 10 mmol), $PdCl_2$ (0.0009 g, 0.05 mol%), as well as ligang **1** (0.0056 g, 0.1 mol%). The resulting mixture was heated at 130 °C for 1 h. Upon completion, the reaction mixture was treated with water and extracted with diethyl ether (10 mL × 3). The combined organic phase were dried with Na_2SO_4 and concentrated in *vacuo* to give the product as yellow oil (0.86 g, separated yield 98%). MS (GC/MS) *m/z*: 176 (M^+), 147, 131,103, 77, 51. ^1H NMR (500 MHz, DMSO-d_6): δ_H 1.25 (t, $J_1 = 7$ Hz, $J_2 = 8$ Hz, 3H, CH_3), 4.20 (m, 2H, CH_2), 6.40 (d, $J = 16$ Hz, 1H, C*H*), 7.35–7.50 (m, 5H, ArH), 8.65 (d, $J = 16$ Hz, 1H, C*H*). The remaining aqueous phase composed of $PdCl_2$ catalyst, ligand **1** and the formed salt of KI was concentrated to remove water in *vacuo*. The resultant residues were used directly without further treatment for next run through treated with iodobenzene (2.04 g, 10 mmol), ethyl acrylate (2.00 g, 20 mmol), DMF (5 mL) and K_2CO_3 again.

All manipulations were conducted in air.

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