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PEG-modified *N*-heterocyclic carbene ligands for highly efficient and recyclable Pd-catalyzed Heck reaction in water

Yulan Liu · Yan Wang · Ensheng Long

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Abstract A water-soluble and air-stable $Pd(OAc)_2$/mPEG$_n$MeImI system was found to be a highly efficient and reusable catalyst for the coupling of aryl halides and styrene in neat water using K_2CO_3 as base. After extraction, the catalytic system could be reused several times with only a slight decrease in its activity.

Introduction

The field of *N*-heterocyclic carbenes (NHCs) as ligands in transition metal chemistry remained dormant until Arduengo et al. [1] published initial reports in 1991 that ignited a rapidly growing research field. In this initial report, it was shown that palladium NHC complexes are excellent catalysts for a number of Heck reactions, exemplifying high catalyst activity and a remarkably long catalyst lifetime [2–7]. The combination of metal catalysis and water has led in recent years to the development of a huge number of new and greener synthetic methodologies [8–11]. The most popular strategy for obtaining a water-soluble catalyst is to modify the ligand with a water-soluble functional group, including sulfonate [12, 13], ammonium [14], carboxylate [12], and polyoxyethylene moieties [15]. The water-soluble catalytic system may be easily separated from the water-insoluble organic products by simple purification, leading to the possibility of reuse of the catalyst [16, 17].

More recently, poly(ethylene glycol) (PEG) has been successfully used as an alternative reaction medium [18–21]. Neutral water-soluble ligand substituents such as poly(ethylene glycol) (PEG) are an attractive alternative to ionic substituents. To date, there are only a few examples of PEG-modified NHC ligands used in transition metal-catalyzed organic reactions [22–26].

Zhang and coworkers reported that $Pd(OAc)_2$ in PEG-functionalized imidazolium salts constituted a highly efficient and recyclable catalytic system for the Heck reaction of aryl bromides and activated aryl chlorides in the absence of ligands, but they used them as reaction medium also [27]. In the PEG-supported imidazolium salts, PEG not only remarkably diluted the solvent, but also constituted a bulky imidazolium salt, which possibly results in the active NHC-palladium catalyst in situ.

Herein, we describe the results of our research into the development of $Pd(OAc)_2$/mPEG$_n$MeImI as an efficient and recyclable catalyst for the Heck reaction of aryl bromides and aryl chlorides in water (Scheme 1).

Experimental

General considerations

All chemicals employed in the synthesis were analytical grade, obtained commercially, and used as received without further purification. Solvents were dried with standard methods and freshly distilled prior to use. NMR spectra (^{1}H 400 MHz, ^{13}C 100 MHz) were performed on a Bruker Avance III 400 MHz spectrometer. The NMR studies were carried out in high-quality 5-mm NMR tubes. Signals are

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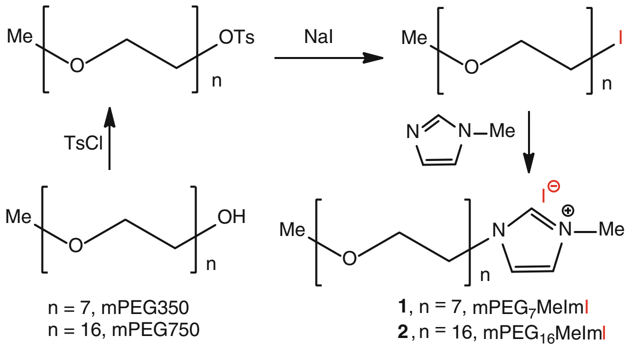
Y. Liu (✉) · Y. Wang · E. Long (✉)
College of Architecture and Environment, Sichuan University,
Chengdu 610207, Peoples Republic of China
e-mail: 625901300@qq.com

E. Long
e-mail: Longes2@163.com



Scheme 1 Synthesis of PEG-functionalized NHC ligands mPEG$_7$MeImI and mPEG$_{16}$MeImI

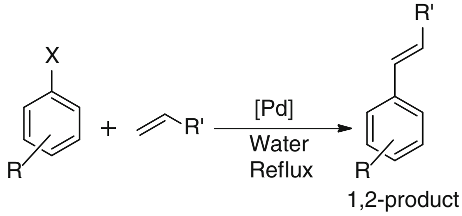
quoted in parts per million as δ downfield from TMS as an internal standard. Coupling constants (J values) are given in Hertz. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet signal. GC–MS analyses were carried out on an Agilent 6,890 GC with 5,973 mass spectral detectors, using an AT.SE-30 column of 50 m length, 0.32 mm diameter, and 0.5 μm film thicknesses. The PEG-modified NHC ligands (mPEG$_n$MeImI, $n = 7$, $n = 16$) were prepared by a modification of the literature method [28].

Table 1 Optimization of the reaction conditions

Entry	Precat (mol %)	T (K)	Base	Yield (%)[a]
1	Pd(OAc)$_2$, 1.0	373	K_2CO_3	36
2	Pd/**1** = 1:5, 1.0	373	K_2CO_3	77
3	Pd/**2** = 1:5, 1.0	373	K_2CO_3	97
4	Pd/**2** = 1:5, 1.0	373	NaOH	72
5	Pd/**2** = 1:5, 1.0	373	*t*-BuONa	68
6	Pd/**2** = 1:5, 1.0	373	Na_2CO_3	50
7	Pd/**2** = 1:5, 1.0	373	LiCl	21
8	Pd/**2** = 1:5, 1.0	373	Et_3N	46
9	Pd/**2** = 1:5, 1.0	373	Cs_2CO_3	85
10	Pd/**2** = 1:5, 1.0	373	KOH	70
11	Pd/**2** = 1:5, 1.0	373	K_3PO_4	82
12	Pd/**2** = 1:1, 1.0	373	K_2CO_3	66
13	Pd/**2** = 1:2, 1.0	373	K_2CO_3	78
14	Pd/**2** = 1:3, 1.0	373	K_2CO_3	82
15	Pd/**2** = 1:4, 1.0	373	K_2CO_3	88
16	Pd/**2** = 1:5, 1.0	298	K_2CO_3	Trace
17	Pd/**2** = 1:5, 1.0	413	K_2CO_3	98
18	Pd/**2** = 1:5, 0.05	413	K_2CO_3	90
19	Pd/**2** = 1:5, 0.5	373	K_2CO_3	96
20	Pd/**2** = 1:5, 0.1	373	K_2CO_3	78
21	Pd/**2** = 1:5, 0.01	373	K_2CO_3	48
22	Pd/**2** = 1:5, 1.0	373	NaOAc	30
23	Pd/**2** = 1:5, 1.0	373	None	Trace

Reaction conditions: 4-bromotoluene (0.5 mmol), styrene (0.75 mmol), catalyst Pd(OAc)$_2$/mPEG$_n$MeImI, base (1.0 mmol), water (3.0 mL), 3 h

[a] Measured by GC–MS



Scheme 2 Heck cross-coupling reaction of aryl halides and styrene

Typical procedure for the Heck cross-coupling of aryl halides with styrene

The appropriate amounts of mPEG$_n$MeImI, base, and metal precursor were added to the required water (3.0 mL). The mixture was stirred for 5 min; then, the aryl halide (0.5 mmol) and styrene (0.75 mmol) were added, and the mixture was vigorously stirred in a sealed tube at 373 K. The course of the reaction was monitored by GC–MS analysis, and yields were calculated against the aryl halides. On completion of the reaction, the aqueous solution wass mixed with Et_2O (3.0 mL), followed by extraction with Et_2O (3 × 3.0 mL). The organic fraction was dried over anhydrous $MgSO_4$ and then filtered, and the solvent was evaporated. Further purification of the product was achieved by flash chromatography on a silica gel column. Products were characterized by NMR-spectroscopy, which was consistent with the literature data.

1. (*E*)-4-Methoxystilbene[19] (Table 3, entries 1, 6, and 12)
2. (*E*)-4-Methylstilbene[20] (Table 3, entries 2 and 4)
3. (*E*)-Stilbene[27] (Table 3, entries 3, 8, and 11)
4. (*E*)-2-Methylstilbene[1] (Table 3, entry 5)
5. (*E*)-4-Nitrostilbene[1] (Table 3, entries 7 and 10)
6. (*E*)-4-Acetylstilbene[28] (Table 3, entry 9)

Table 2 Reusability of the catalyst in the Heck reaction

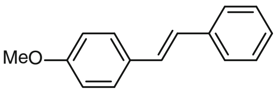
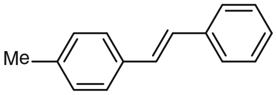
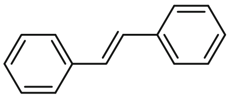
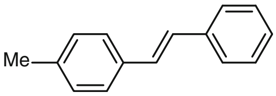
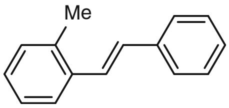
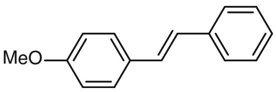
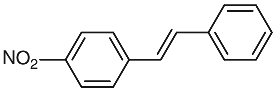
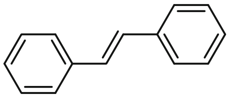
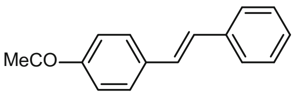
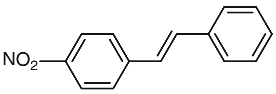
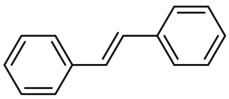
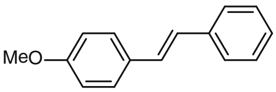
Run	Conversion[a]	Yield (%)[b]
1	99	96
2	97	94
3	96	93
4	92	90
5	91	88

Reaction conditions: 4-bromotoluene (0.5 mmol), styrene (0.75 mmol), catalyst (Pd(OAc)$_2$:**2** = 1:5, 0.5 mol %), K_2CO_3 (1.0 mmol), water (3.0 mL), 373 K, 3 h

[a] Measured by GC–MS

[b] Isolated yield

Table 3 Heck reactions of aryl halides and styrene

Entry	Aryl halide	Product	Time (h)/temp (K)	Yield (%)[a]
1	*p*-$MeOC_6H_4I$		1 h/373 K	97
2	*p*-MeC_6H_4I		1 h/373 K	98
3	C_6H_5I		1 h/373 K	95
4	*p*-MeC_6H_4Br		3 h/373 K	96
5	*o*-MeC_6H_4Br		3 h/373 K	92
6	*p*-$MeOC_6H_4Br$		3 h/373 K	94
7	*p*-$NO_2C_6H_4Br$		3 h/373 K	97
8	C_6H_5Br		3 h/373 K	93
9	*p*-$CH_3COC_6H_4Cl$		6 h/373 K	90[c]
10	*p*-$NO_2C_6H_4$ Cl		6 h/373 K	91[c]
11	C_6H_5Cl		24 h/393 K	52[c]
12	*p*-$MeOC_6H_4Cl$		24 h/393 K	38[c]

Reaction conditions: aryl halides (0.5 mmol), styrene (0.75 mmol), catalyst ($Pd(OAc)_2$:**2** = 1:5, 0. 5 mol %), K_2CO_3 (1.0 mmol), water (3.0 mL), 373 K

[a] Measured by GC–MS

[b] Catalyst 1.0 mol %

Results and discussion

The Heck reaction was carried out in water by the reaction of 4-bromotoluene with styrene in the presence of various bases (Table 1, entries 2–11). We found that K_2CO_3 gave the best results for this reaction, and other bases such as Na_2CO_3, LiCl, and triethylamine (Et_3N) were not suitable (Table 1, entries 6–8) (Scheme 2).

The catalyst formed with mPEG$_{16}$MeImI appears to be more efficient than the one with mPEG$_7$MeImI because of their different PEG chain lengths (Table 1, entries 1 and 2). Several Pd/ligand mole ratios were also examined (Table 1, entries 3, 12–15), and Pd/mPEG$_{16}$MeImI = 1:5 was selected as the optimal reaction condition. Since this imidazoline salt can play a dual role both as reaction medium and also through the PEG group that it bears, as a potential complexing agent in the Heck reactions [28].

The reaction temperature is one of the important factors to control the reaction process [29]. In consequence, an optimum of the reaction temperature in the Heck reactions might be observed (Table 1, entries 3, 16, and 17), and 373 K was selected as the optimal reaction temperature. Various catalyst concentrations were also tested (Table 1, entries 19–21), and 1.0 mol % gave the best result.

The dual property (both as reaction medium and complexing agent) offers the potential for recycling of the imidazoline salt together with its corresponding catalytic Pd complex, which should thus eliminate wastage both of the ligand and also of the Pd compound [28]. The reusability of the catalytic system was tested in the Heck reaction of styrene and 4-bromotoluene using K_2CO_3 as the base in the presence of 0.5 mol % $Pd(OAc)_2$/mPEG$_{16}$MeImI (mole ratio = 1:5) at 373 K for 3 h. The remaining mixture of PEG-modified NHC ligand and its corresponding Pd complex was washed with water to remove the water-soluble impurities and could be reused for five runs in the reaction between 4-bromotoluene and styrene with only a small decrease in activity, giving *trans* products (Table 2). The *trans* products to were confirmed by ^{1}H NMR analysis.

Furthermore, under the optimized reaction conditions (K_2CO_3 as base, water as solvent at 373 K), a range of aryl halides were coupled with styrene with 0.5 mol % of catalyst $Pd(OAc)_2$/**2** (1:5), and the results are summarized in Table 3.

Iodobenzene could react with styrene to furnish the product in a 95 % yield (Entry 3), and aryl iodides, 4-methoxy-iodobenzene, and 4-methyl-iodobenzene were able to be coupled efficiently under this system, the corresponding products being obtained at yields of 97 and 98 % (entries 1 and 2). As for the coupling of aryl bromides, we found that almost all aryl bromides could couple with styrene to afford the corresponding Heck coupling products in yields between 93 and 97 %.

In the case of cheaper aryl chlorides, the in situ generated palladium complex coupled with the styrene under the same reaction conditions; however, 1 mol % of catalyst was required (entries 9–12). When an electron-rich aryl chloride, such as 4-methoxy-chlorobenzene was coupled with styrene, the corresponding product was afforded but in low yield (entry 11). We found that only activated aryl chlorides could couple with styrene to afford the corresponding Heck coupling products in good yields (entries 9 and 10).

Conclusion

In summary, the in situ-generated $Pd(OAc)_2$/**2** (1:5) complex represents an efficient and reusable catalyst system for the Heck coupling reactions of aryl iodides, bromides, and activated aryl chlorides in water. However, $Pd(OAc)_2$/**2** was not a good catalyst for the Heck reaction of unactivated aryl chlorides in our system. The reusability of PEG-modified NHCs ligands with Pd can also be regarded as offering strong practical advantages for Heck reactions. Further studies of its applicability in other C–C bond forming reactions are currently under investigation.

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