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Triethanolamine as an Efficient and Reusable Base, Ligand and Reaction Medium for Phosphane-Free Palladium-Catalyzed Heck Reactions

Hong Ji Li[a] and Lei Wang*[a,b]

Keywords: Heck reaction / Palladium / Phosphane-free catalysis / Triethanolamine / Catalysis

Triethanolamine was found to be an efficient and reusable base, ligand and reaction medium for phosphane-free palladium-catalyzed Heck reactions. The olefination of iodo- and bromoarenes generated the corresponding products in good to excellent yields in the presence of catalytic amounts of palladium acetate in triethanolamine without any additive. Moderate yields of the desired products were obtained with activated chloroarenes. In addition, triethanolamine could be recovered and recycled for five consecutive trials without significant loss of its reactivity.

Introduction

The palladium-catalyzed coupling of olefins with aryl or vinyl halides, known as the Heck reaction, is one of the most important, reliable and general reactions for carbon–carbon bond formation in organic synthesis.[1] This powerful reaction can lead to the construction of an sp^2–sp^2 C–C bond at an unfunctionalized olefinic carbon atom in a single transformation using a wide variety of aryl and vinyl halide substrates. It may be used for the synthesis of multifunctional derivatives,[2] including bioactive compounds, natural products,[3] pharmaceuticals and high-performance materials.[4] Palladium compounds, usually complexes with phosphane ligands, are very often used as catalyst precursors in Heck reactions. Phosphanes act as stabilizers of in situ formed soluble Pd^0 complexes, which are generally considered the catalytically active forms.[5] On the other hand, phosphane-free catalysts have received great interest recently as a less complicated, environmentally friendly alternative to phosphane-containing systems.[6] Significant advances have been made in the past few years in developing such catalysts. These include the use of nitrogen-[7] and sulfur-based palladacycles,[8] N,S-based carbenes[9] and N-heterocyclic carbenes (NHC) as ligands in palladium-catalyzed Heck reactions.[10] However, all of these catalyst systems suffer from drawbacks of one kind or another, such as the high sensitivity of ligands towards air and moisture, a tedious multistep synthesis, and hence high cost of the ligands, and the use of various additives. It would still be desirable to develop more robust, simple and cost-effective non-phosphane ligands for use in palladium-catalyzed Heck reactions.

It is well known that chiral amino alcohols, such as natural amino alcohols, carbohydrate- and camphor-derived amino alcohols and ferrocenyl amino alcohols, have been widely used as ligands (*O*,*N*-ligands) in, for example, the asymmetric alkynylation of aldehydes,[11] the asymmetric addition of diethylzinc to aldehydes and imines,[12] the asymmetric ruthenium-catalyzed transfer hydrogenation of ketones,[13] the enantioselective trimethylsilylcyanation of aldehydes[14] and in enantioselective Henry reactions.[15] Furthermore, Buchwald and co-workers have disclosed that *trans*-1,2-diaminocyclohexane serves as an excellent ligand (*N*,*N*-ligand) in the copper-catalyzed amidation of aryl halides and in the *N*-arylation of N-heterocycles (C–N bond coupling)[16] and ethylene glycol as a ligand (*O*,*O*-ligand) in the copper-catalyzed amination of aryl iodides (C–N bond coupling)[17] in 2001 and 2002, respectively. Most recently, Gonzalez-Bobes and Fu discovered that amino alcohols such as prolinol and *trans*-2-aminocyclohexanol are effective ligands (*O*,*N*-ligands) in the nickel-catalyzed Suzuki reactions of unactivated alkyl halides, including secondary alkyl chlorides, with arylboronic acids (C–C bond coupling).[18] However, triethanolamine exhibited lower activity in the Heck reaction of chlorobenzene with styrene in water using catalytic palladium on carbon.[19]

Herein we report on triethanolamine, a cheap and commercially available organic compound, as an efficient and recyclable base, ligand (*O*,*N*-ligand) and reaction medium in palladium-catalyzed Heck reactions (C–C bond coupling). The olefination reactions of iodo- and bromoarenes with olefins generated the corresponding cross-coupling products in good to excellent yields under phosphane-free reaction conditions. For activated chloroarenes, moderate

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[a] Department of Chemistry, Huaibei Coal Teachers College,
Huaibei, Anhui 235000, P. R. China
Fax: +86-561-3090-518
E-mail: leiwang@hbcnc.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
Shanghai 200032, P. R. China

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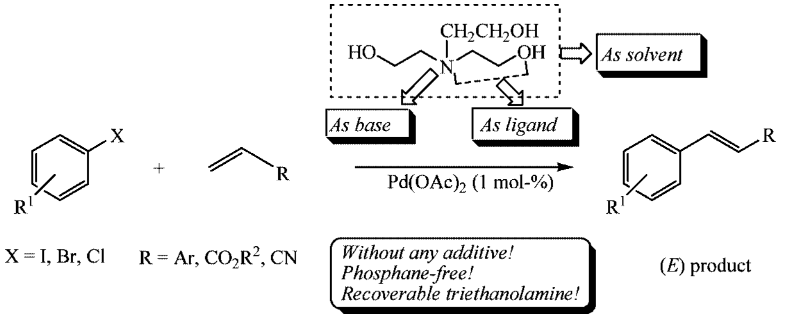


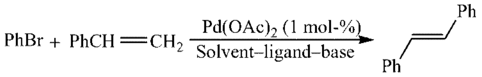
Scheme 1.

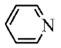
yields of the desired products were obtained. Moreover, triethanolamine could be recovered and recycled for five consecutive trials without significant loss of its reactivity (Scheme 1).

Results and Discussion

Although phosphorus ligands stabilize palladium and influence its reactivity, the simplest and cheapest palladium catalysts are of course phosphane-free systems, specifically when used in low loading. Such an experimental protocol would constitute a significant advancement, especially if generally applicable. In our initial screening experiments, our goal was to perform palladium-catalyzed Heck reactions in the absence of phosphorus ligands. When we searched for a cross-coupling protocol for the reaction between bromobenzene and styrene, we observed that no cross-coupling products were isolated when the reactions were carried out in *n*-butylamine, piperidine, morpholine, triethylamine, pyridine or ethylenediamine (Table 1, Entries 1–6) in the absence of any phosphorus ligand. To our delight, 58 and 64% yields of products were obtained when the reactions were conducted in a triethylamine/ethylene glycol (1:1, v/v) or triethylamine/glycerol mixture (1:1, v/v), respectively (Table 1, Entries 10 and 11), which indicates that hydroxy groups in polyhydric alcohols can promote phosphane-free palladium-catalyzed Heck reactions. Encouraged by these results, we continued to improve the yield by optimizing the reaction conditions. When monoethanolamine, diethanolamine or triethanolamine, which contain hydroxy and amine groups within a molecular unit, was used instead of a triethylamine/ethylene glycol or triethylamine/glycerol mixture as reaction medium, excellent yields of products were isolated for the Heck olefination of bromobenzene and styrene (Table 1, Entries 12–14). Among them, triethanolamine was found to be superior to monoethanolamine and diethanolamine. However, no reaction occurred when the reaction was performed in a triethylamine/methanol (1:1, v/v), triethylamine/ethanol (1:1, v/v) or *n*-propanol/triethylamine mixture (1:1, v/v) (Table 1, Entries 7–9). In addition, no Heck olefination product was isolated when the reaction was carried out in ethylene glycol or glycerol without triethylamine being added to the reaction system (Table 1, Entries 15 and 16).

Table 1. Effect of solvent, ligand and base on the Heck reaction.[a]



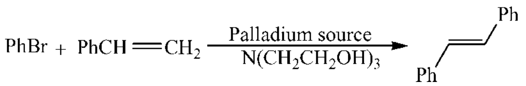
Entry	Solvent–ligand–base (v/v)	Temp. [°C]	Yield [%][b]
1	n-$C_4H_9NH_2$	78	N.R.[c]
2		106	N.R.[c]
3		130	N.R.[c]
4	$(C_2H_5)_3N$	90	N.R.[c]
5		115	N.R.[c]
6	$NH_2CH_2CH_2NH_2$	118	N.R.[c]
7	$CH_3OH/(C_2H_5)_3N$ (1:1)	68	N.R.[c]
8	$C_2H_5OH/(C_2H_5)_3N$ (1:1)	78	N.R.[c]
9	$CH_3CH_2CH_2OH/(C_2H_5)_3N$ (1:1)	85	N.R.[c]
10	$HOCH_2CH(OH)CH_2OH/(C_2H_5)_3N$ (1:1)	100	58
11	$HOCH_2CH_2OH/(C_2H_5)_3N$ (1:1)	100	64
12	$HOCH_2CH_2NH_2$	100	92
13	$(HOCH_2CH_2)_2NH$	100	90
14	$(HOCH_2CH_2)_3N$	100	99
15	$HOCH_2CH(OH)CH_2OH$	100	N.R.[c]
16	$HOCH_2CH_2OH$	100	N.R.[c]

[a] Styrene (104 mg, 1.00 mmol), bromobenzene (157 mg, 1.00 mmol) and [Pd(OAc)$_2$] (2.3 mg, 0.01 mmol) in the solvent (2.0 mL) and at the temperature indicated in Table 1 for 10 h. [b] Isolated yields. [c] n.r. = no reaction.

The effect of the palladium source on the Heck reaction was also examined. Among the palladium sources tested, [Pd(OAc)$_2$] and $PdCl_2$ proved to be the best choice. [Pd(CH$_3$CN)$_2$]Cl$_2$ and palladium on activated carbon were inferior and led to slower reactions. Palladium powder (micron), [Pd$_2$(dba)$_3$] and [Pd(PPh$_3$)$_2$]Cl$_2$ were found to be inactive towards the Heck reaction in triethanolamine. [Pd(OAc)$_2$] was chosen as the palladium source in further investigations because of its high efficiency (Table 2).

During the course of our further optimization of the reaction conditions, when using 1 mol-% of palladium acetate in triethanolamine, the reactions were generally completed in a matter of hours, but the time, as expected, was inversely proportional to the temperature. A reaction temperature of 100 °C was found to be optimal. Thus, the optimal reaction conditions for this Heck reaction are [Pd(OAc)$_2$] (1 mol-%) in triethanolamine at 100 °C for 10 h in the absence of any additive.

Table 2. Effect of palladium source on the Heck reaction.[a]

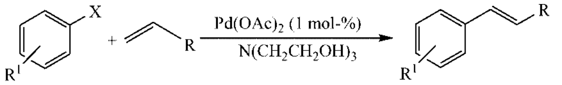


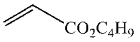
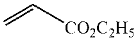
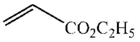
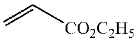
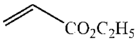
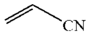
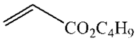
Entry	Palladium source (amount)	Yield [%][b]
1	palladium powder (micron, 1 mol-%)	n.r.[c]
2	$[Pd_2(dba)_3]$ (1 mol-%)	n.r.[c]
3	$[Pd(PPh_3)_2]Cl_2$ (1 mol-%)	trace
4	$[Pd(CH_3CN)_2]Cl_2$ (1 mol-%)	75
5	Pd on activated carbon (1 mol-%)	50
6	$PdCl_2$ (1 mol-%)	98
7	$[Pd(OAc)_2]$ (1 mol-%)	99

[a] Styrene (104 mg, 1.00 mmol), bromobenzene (157 mg, 1.00 mmol), palladium source (0.01 mmol) and triethanolamine (2.0 mL) at 100 °C for 10 h. [b] Isolated yields. [c] n.r. = no reaction.

To examine the versatility of this procedure, the Heck reactions of styrene with iodoarenes containing electron-rich, electron-poor or electron-neutral substituents were investigated. The results are listed in Table 3. It shows that the conversions, regioselectivities [>99% (*E*) products] and yields were satisfactory under the present reaction conditions (Table 3, Entries 1–3). For bromobenzene and activated bromoarenes, excellent yields of cross-coupling products were isolated under the standard reaction conditions (Table 3, Entries 4–7). On the other hand, unactivated bromoarenes, such as *p*-, *m*-, and *o*-bromotoluene as well as *p*-bromoanisole, also reacted with styrene to generate the corresponding cross-coupling products in good yields (Table 3, Entries 8–11). Olefination of the haloarene was also tolerant of *ortho* substitution in the aryl bromide and led to a good yield (Table 3, Entry 10). The scope of this catalytic system with other vinyl substrates, such as ethyl acrylate, butyl acrylate and acrylonitrile, was also examined and good to excellent results were obtained for iodo- and bromoarenes including deactivated ones under identical conditions (Table 3, Entries 12–17). As expected, moderate yields of the desired products were obtained with activated chloroarenes (Table 3, Entries 18 and 19).

Table 3. Palladium-catalyzed Heck reactions in triethanolamine.[a]

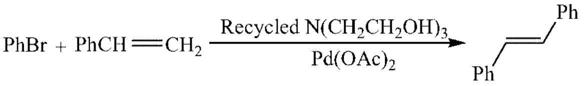


Entry	Organic halide	Olefin	Yield [%][b]
1	C_6H_5I	$C_6H_5CH{=}CH_2$	98[c]
2	p-$CH_3OC_6H_4I$	$C_6H_5CH{=}CH_2$	99[c]
3	p-$CH_3COC_6H_4I$	$C_6H_5CH{=}CH_2$	99[c]
4	C_6H_5Br	$C_6H_5CH{=}CH_2$	99
5	p-$CH_3COC_6H_4Br$	$C_6H_5CH{=}CH_2$	99
6	p-CNC_6H_4Br	$C_6H_5CH{=}CH_2$	95
7	p-$C_2H_5O_2CC_6H_4Br$	$C_6H_5CH{=}CH_2$	92
8	p-$CH_3C_6H_4Br$	$C_6H_5CH{=}CH_2$	89
9	m-$CH_3C_6H_4Br$	$C_6H_5CH{=}CH_2$	81
10	o-$CH_3C_6H_4Br$	$C_6H_5CH{=}CH_2$	76
11	p-$CH_3OC_6H_4Br$	$C_6H_5CH{=}CH_2$	80
12	C_6H_5I	 $CO_2C_4H_9$	97
13	p-$CH_3OC_6H_4I$	 $CO_2C_2H_5$	96
14	p-$NO_2C_6H_4Br$	 $CO_2C_2H_5$	90
15	C_6H_5Br	 $CO_2C_2H_5$	94
16	p-$CH_3OC_6H_4Br$	 $CO_2C_2H_5$	86
17	C_6H_5Br	 CN	91
18	p-$NO_2C_6H_4Cl$	 $CO_2C_4H_9$	62
19	p-CNC_6H_4Cl	$C_6H_5CH{=}CH_2$	58

[a] Olefin (1.00 mmol), organic halide (1.00 mmol) and $[Pd(OAc)_2]$ (2.3 mg, 0.01 mmol), in triethanolamine (2.0 mL) at 100 °C for 10 h. [b] Isolated yields. [c] $[Pd(OAc)_2]$ (1.1 mg, 0.005 mmol) was used.

To investigate the recyclability of triethanolamine, a more practical method was applied to the reaction between bromobenzene and styrene under the present reaction conditions. When bromobenzene was treated with styrene with a catalyst loading of 1 mol-% of palladium acetate in triethanolamine at 100 °C for 10 h, the desired coupling product was obtained in 99% isolated yield. After extraction of the product from the reaction mixture using diethyl ether, the triethanolamine was recovered and fresh starting materials and palladium catalyst were added to the reaction mixture. The reactions still proceeded well and no unreacted substrates were detected at the end of the reaction. Triethanolamine was recycled five times with no loss of its activity (Table 4).

Table 4. Successive trials of the Heck reaction using recovered triethanolamine.[a]



Trial	Yield [%][b]	Trial	Yield [%][b]
1	99	4	94
2	96	5	93
3	95	6	90

[a] Styrene (104 mg, 1.00 mmol), bromobenzene (157 mg, 1.00 mmol), $[Pd(OAc)_2]$ (2.3 mg, 0.01 mmol) and triethanolamine (2.0 mL) at 100 °C for 10 h. [b] Isolated yield.

Conclusions

We have presented herein an efficient and economic catalyst system for Heck reactions using triethanolamine as the solvent, ligand and base and palladium acetate as the catalyst under phosphane-free reaction conditions. The olefination reactions of iodo- and bromoarenes with olefins generated the corresponding coupling products in good to excellent yields under these reaction conditions. Moreover, triethanolamine could be recovered and recycled for five consecutive trials without significant loss in activity.

Experimental Section

General Remarks: Melting points were recorded with a WRS-2 melting point apparatus and are uncorrected. All ^1H NMR spectra were recorded at 400 or 300 MHz with Bruker NMR spectrometers. Chemical shifts are given as δ values in ppm and are referenced to tetramethylsilane (TMS) as the internal standard. IR spectra were obtained by using a Nicolet NEXUS 470 spectrophotometer. Products were purified by flash chromatography on 230–400 mesh silica gel (SiO_2).

General Heck Olefination Procedure: Under nitrogen, an oven-dried, two-necked round-bottom flask containing a stirring bar was charged with an organic halide (1.00 mmol), olefin (1.00 mmol), [$Pd(OAc)_2$] (2.3 mg, 0.01 mmol) and triethanolamine (2.0 mL). The mixture was heated and stirred at 100 °C for 10 h. After cooling to room temperature, diethyl ether (2 × 3.0 mL) was added to extract the product. The combined organic layers were washed with water and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was finally purified by flash chromatography on silica gel to give the desired product.

Recyclability of Triethanolamine: After carrying out the reaction, the mixture was extracted with diethyl ether [note: the solubility of triethanolamine in diethyl ether is 1.6% at 25 °C]. After neutralization of the ammonium salt formed during the reaction with potassium carbonate, triethanolamine was separated and washed successively with Et_2O (3.0 mL) and hexane (3.0 mL) in order to remove adsorbed organic substrates. After drying in an oven, it can be reused directly without further purification.

Supporting Information (see footnote on the first page of this article): Selected characterization data for Heck reaction products.

Acknowledgments

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