

Benzimidazolylidene Carbene Ligated Palladium Catalysis of the Heck Reaction in Aqueous Media

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A highly effective, easy to handle and environmentally benign process for a palladium mediated Heck reaction was developed. The in situ prepared 3-component system, Pd(OAc)₂ / 1,3-dialkylbenzimidazolium chlorides (LHX = **1a-g**) and Cs₂CO₃, catalyzes quantitatively the Heck coupling of aryl bromides under mild conditions in aqueous media.

Key Words: Heck coupling, palladium, benzimidazolin-2-ylidene, benzimidazolium, *N*-heterocyclic carbene.

Introduction

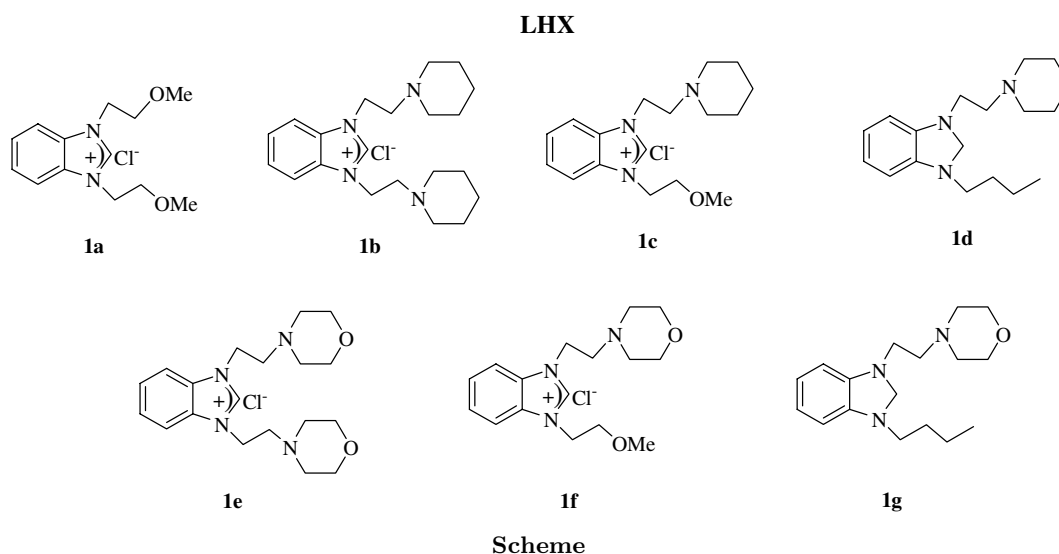
The palladium-catalyzed coupling of olefins with aryl or vinyl halides, known as the Heck reaction, is one of the most important, reliable, and general reactions for carbon-carbon bond formation in organic synthesis.¹⁻³ This powerful reaction can lead to the construction of an sp²-sp² C-C bond at an unfunctionalized olefinic carbon in a single transformation employing a wide variety of aryl and vinyl halide substrates. It may be used for the synthesis of multifunctional derivatives,^{4,5} including bioactive compounds,⁵ natural products,⁶ pharmaceuticals, and high performance materials.⁷ Traditionally, triarylphosphine palladium complexes and aryl iodide are employed for Heck reactions and the experiments are carried out under inert atmosphere to minimize the deleterious effect of oxygen in the air. Recently, great progress has been made in the field of Heck catalysis. Modified phosphine ligands, such as sterically demanding tri-*t*-butylphosphine and phosphine containing palladacycles and their analogues, have shown especially high coupling activities for a variety of substrates.⁸⁻¹¹ Apart from phosphine related ligands, new types of non-phosphine ligands such as heterocyclic carbene, imine, and amine palladacycles have emerged as an alternative for palladium catalyzed Heck reactions.¹²⁻¹⁴ Recently, nucleophilic *N*-heterocyclic carbenes (NHCs),¹⁵ with stronger σ -donor properties than bulky tertiary phosphines,¹⁶ have emerged as a new family of ligands. In contrast to metal phosphine complexes, the metal-NHC complexes appear to be extraordinarily stable towards heat, air, and moisture due to the high dissociation energies of the metal-carbon bond.¹⁷

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With their phosphine mimic¹⁸ ligating, NHCs have attracted the attention of several research groups.^{19,20} Various NHC ligands have been synthesized within a short period of time, and some of them have been successfully used for a variety of palladium catalyzed transformations.^{21–29} Although NHC-palladium complexes used for Heck reactions were claimed to be air and moisture stable, only a few examples carried out under air were reported previously.³⁰ Most reactions catalyzed by NHC-palladium complexes are conducted under an inert atmosphere. Therefore, easy to handle while highly efficient catalytic processes that are stable towards oxidants and moisture variations are still being sought. The use of water as a solvent for chemical reactions clearly has both economical and environmental advantages because it is inexpensive, abundant, nontoxic, nonflammable, and readily separable from organic compounds.³¹ There have been a number of reports of the palladium-mediated Heck reaction being performed using water as solvent.^{32–36}

We have previously reported the use of an in situ formed imidazolidin-2-ylidene, tetrahydropyrimidin-2-ylidene, and tetrahydrodiazepin-2-ylidenepalladium(II) systems that exhibit high activity for various coupling reactions of aryl bromides and aryl chlorides.^{37–39} In order to obtain more stable, efficient, and active systems, we have also investigated benzo-annelated derivatives.^{40,41} Recently our group reported that novel complexes of rhodium(I) 1,3-dialkylimidazolidin-2-ylidenes gave secondary alcohols in good yields by the addition of phenylboronic acid to aldehydes.⁴²

In this article, we report air and water stable, more efficient palladium catalysts by employing a series of benzimidazolium salts (LHX), **1a–g** (Scheme), containing nitrogen and oxygen atoms and we report here in situ Pd-carbene based catalytic systems for Heck reactions in aqueous media.



Experimental

All reactions for the preparation of **1a–g** were carried out under argon in flame-dried glassware using standard Schlenk-type flasks. Flash chromatography: Merck silica gel 60 (230–400 mesh) eluent ethylacetate/hexane (1:5). The 1,3-dialkylbenzimidazolium salts (**1a–g**) were prepared according to known methods.^{43–45} All reagents were purchased from Aldrich. All ¹H- and ¹³C-NMR were performed in CDCl₃. ¹H-NMR and ¹³C-NMR spectra were recorded using a Varian As 400 Merkur spectrometer operating at 400 MHz (¹H)

and 100 MHz (^{13}C). Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) in Hz. Infrared spectra were recorded as KBr pellets in the range 400-4000 cm^{-1} on an ATI UNICAM 1000 spectrometer. Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus and are uncorrected. Elemental analyses were performed by TÜBİTAK (Ankara, Turkey) Microlab.

General Procedure for the Heck Coupling reaction

$\text{Pd}(\text{OAc})_2$ (1.0 mmol %), 1,3-dialkylbenzimidazolium salts **1** (2 mmol %), aryl bromide (1.0 mmol), styrene (1.5 mmol), Cs_2CO_3 (2 mmol), and water (3 mL)-DMF (3 mL) were added to a small Schlenk tube and the mixture was heated at 80 °C for 4 h. At the conclusion of the reaction, the mixture was cooled, extracted with ethylacetate/hexane (1:5), filtered through a pad of silica gel with copious washings, concentrated, and purified by flash chromatography on silica gel. Purity of the compounds was checked by NMR and GC; yields are based on arylbromide.

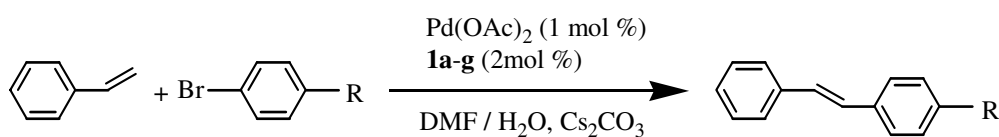
Results and Discussion

1,3-Dialkylbenzimidazolium salts (**1a-g**) are conventional NHC precursors. The functionalized benzimidazolium **1** was synthesized by consecutive alkylation of 1-alkylbenzimidazole with functionalized alkyl halides (Scheme). The 1,3-dialkylbenzimidazolium salts (**1a-g**) were obtained in almost quantitative yield by quarternization of 1-alkylbenzimidazole (1 and 3) in DMF with alkyl halides according to known procedures.⁴³⁻⁴⁵ The salts are air and moisture stable both in the solid state and in solution.

It has been found that the in situ formation of the ligand by deprotonation of the benzimidazolium bromides led to significantly better results than use of the preformed carbene.⁴⁶⁻⁵⁰ The Heck reaction⁵¹ has been shown to be very useful for the preparation of disubstituted olefins in particular. The rate of the coupling is dependent on a variety of parameters such as temperature, solvent, base, and catalyst loading. Generally, Heck reactions conducted with tertiary phosphine⁵² or NHC^{53,54} complexes required high temperatures (above 120 °C) and polar solvents. For the choice of base, we tested Cs_2CO_3 , K_2CO_3 , *t*-BuOK, and K_3PO_4 . Finally, we found that use of 1% mol $\text{Pd}(\text{OAc})_2$, 2% mol **1**, 2 equiv. Cs_2CO_3 in DMF/ H_2O (1:1) at 80 °C led to the best conversion within 4 h. We initially tested the catalytic activity of $\text{Pd}(\text{OAc})_2$ /**1a-g** for the coupling of *p*-bromoacetophenone with styrene (Table, entries 1-7). In addition, the reactions were performed in air and without degassing the water and DMF prior to use.

The control experiment indicated that the coupling reaction did not occur in the absence of **1a**. Under the determined reaction conditions, a wide range of aryl bromides bearing electron-donating or electron-withdrawing groups can react with styrene, affording the coupled products in good to excellent yields. As expected, electron-deficient bromides were beneficial for the conversions.

Under those conditions, *p*-bromoacetophenone, *p*-bromobenzaldehyde, bromobenzene, and *p*-bromoanisole react very cleanly with styrene in good yields (Table, entries 1, 8, 15, and 22). However, chloroarenes basically do not react under standard conditions, and yields are less than 6%. It is evident that the NHC precursors that contain electron donating methoxyethyl substituent (**1a, c**) are the most effective of the salts examined. The coordinating ability of the alkoxy group may be an important contributor to the increase in reactivity, as has been demonstrated by previous examples.⁵⁵

Table. The Heck coupling reaction of aryl bromides with styrene.

Entry	R	LHX	Yield ^{a,b,c,d} (%)
1	COCH ₃	1a	98
2	COCH ₃	1b	93
3	COCH ₃	1c	95
4	COCH ₃	1d	91
5	COCH ₃	1e	85
6	COCH ₃	1f	87
7	COCH ₃	1g	80
8	CHO	1a	93
9	CHO	1b	83
10	CHO	1c	94
11	CHO	1d	76
12	CHO	1e	79
13	CHO	1f	79
14	CHO	1g	72
15	H	1a	91
16	H	1b	89
17	H	1c	90
18	H	1d	87
19	H	1e	73
20	H	1f	75
21	H	1g	69
22	CH ₃ O	1a	89
23	CH ₃ O	1b	78
24	CH ₃ O	1c	85
25	CH ₃ O	1d	79
26	CH ₃ O	1e	75
27	CH ₃ O	1f	80
28	CH ₃ O	1g	73

^a Reaction conditions: 1.0 mmol R-C₆H₄Br-*p*, 1.5 mmol styrene, 2 mmol Cs₂CO₃, 1 mmol % Pd(OAc)₂, 2 mmol % **1**, water (3 mL)-DMF (3 mL), ^b purity of compounds is checked by NMR and yields are based on arylhalide. ^c All reactions were monitored by GC, ^d temperature 80 °C, 4 h.

Conclusion

The 1,3-dialkylbenzimidazol-2-ylidene ligand palladium catalyst system reported herein represents an easy to handle, robust, and high yielding procedure for Heck couplings.

A convenient and highly user friendly method for Heck coupling reaction is present, which employs a catalyst formed in situ from Pd(OAc)₂, the readily accessibly and fully air stable benzimidazolium salts. This ligand family allows highly efficient coupling reactions of electron-rich as well as electron-poor aryl bromides with styrene under mild conditions. This concept for making catalysts in situ opens the way for the discovery of many new catalysts via the interaction of commercially available metal complexes and suitable electron

releasing ligands. Further study is underway to optimize the reactivity of these *N*-heterocyclic carbene precursors for C-C and C-N, C-O coupling with Pd(OAc)₂, and transition metal complexes of Ru, Pd, and Rh to explore their catalytic activity.

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