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Efficient palladium *n*-heterocyclic carbene catalytic system for the synthesis of cinnamic acid and derivatives in water

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Imidazolium salts (**1a** and **1b**) were synthesized by alkylation of *N*-methyl imidazole with benzyl bromide and isopropyl bromide, respectively. The reaction of the imidazolium salts (**1a** and **1b**) with palladium bromide in 3-methylpyridine afforded the corresponding palladium-*N*-heterocyclic carbene pyridine (Pd-NHC-Py) complexes (**2a** and **2b**) in good yields. The synthesized compounds were characterized using ^{1}H NMR and FT-IR spectroscopic techniques. Elemental compositions of the synthesized compounds were established using C, H, N elemental analyses. The complexes (**2a** and **2b**) were used as catalysts to develop a convenient system for the synthesis of cinnamic acid and derivatives from the coupling reaction of aryl halides with methyl acrylates, acrylic acids, and acrylamides using water as solvent. Various substituted cinnamic acids were obtained in excellent yields (84 – 97%). Moreover, the pre-catalysts were effective in the synthesis of cinnamates. A reaction mechanism based on the formation of active Pd(0) species and the *in-situ* generation of acrylic ions is proposed.

Keywords: Green chemistry; Mizoroki-Heck; imidazolium salts; organometallics; reaction mechanism

INTRODUCTION

For decades, cinnamic acid has been used as a component of scents and flavorings [1]. cinnamates and cinnamides have shown promising anticancer and antituberculosis activities [2, 3]. Classical synthesis of these valuable materials suffers from many limitations, such as a multistep procedure which is associated with side reactions resulting in poor yield of the product; the use of acyl intermediates which are toxic and costly [4]. A mild and straightforward alternative for the synthesis of this important class of compounds is the palladium-catalyzed coupling reaction. Palladium catalysts have been reported to work effectively under mild conditions with a high reaction rate, excellent product yield, high functional group tolerance, and outstanding turnover number [5-9].

In parallel, the Heck reaction is recognized as the most powerful and widely used tool for the preparation of substituted alkenes from organic moieties bearing an appropriate leaving group. It is employed in the synthesis of quite a lot of intermediates for the fine chemical and pharmaceutical industries [6, 8-13].

Until recently, the Heck reaction and most organic transformations employing organometallic catalysts were predominantly carried out in a rigorously dried organic solvent. This is because water is considered the "natural enemy" of organometallic compounds [14]. Nevertheless, the growing concern about environmental safety and protection leads to increased interest in developing a greener alternative to the use of organic solvents. Studies in this area have uncovered cleaner and relatively benign chemical processes that avoid or minimize the use of traditional organic solvents. Among the remarkable discoveries were the solvent-less (neat) reactions [15], reactions in inorganic solvents such as ionic liquids and per-fluorinated liquids [16], reactions in supercritical carbon dioxide [17], and reactions in aqueous media [18].

Water is the most abundant solvent on earth. It is easily accessible, inexpensive, non-flammable, and of course, harmless to the environment and the living system. Without any doubt, water is the natural solvent for biochemical transformations in the living systems because a large number of such reactions occur in this medium. Over the past few decades there has been growing interest in developing organic synthesis in water and tremendous progress has been made. The acceleration of pericyclic reactions in water discovered by Breslow [19, 20], and the "click" reactions [14] are a few examples.

In our continued effort to uncover green, mild and easy protocols for Heck and other coupling reactions [6, 8, 9, 13, 21], we wish to report the synthesis of new palladium *N*-heterocyclic carbene pyridine complexes (Pd-NHC-Py) and a method for their application in the production of cinnamic acids and derivatives in water.

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EXPERIMENTAL

Materials

Starting material for the synthesis of the pre-carbenes and their palladium complexes were purchased from Sigma-Aldrich and used as received. Materials for the coupling reactions were of high purity and were also purchased from Sigma Aldrich. For reactions that require anhydrous conditions, the solvents were distilled and were kept under molecular sieves until when they are required. Distilled-deionized water was used for reactions in water. Purification of the products was carried out by flash column chromatography with silica gel 60 – 120 mesh LOBA Chemie AG (India). Thin-layer chromatography (TLC) analyses were performed on silica gel Merck 60 F_{254} plates.

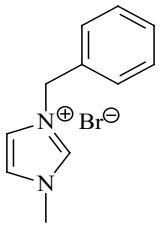
Instrumentation

NMR spectral analyses were carried out at the Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran, Saudi Arabia. The samples were dissolved in $CDCl_3$ solvent and the spectra were recorded using either Bruker 400MHz ultra shield instrument or 500 MHz NMR machine (Joel 1500 model). Chemical shifts (δ) were recorded in ppm using tetramethylsilane (TMS) as reference. Coupling constants (J) were given in Hertz (Hz). ^{1}H NMR signals were labeled as singlet (*s*), doublet (*d*), triplet (*t*), and multiplet (*m*). An Agilent technology FT-IR spectrometer was used for recording the FT-IR spectra of the synthesized compounds in wavenumbers (cm^{-1}). The samples were analyzed neat, either as solids or liquids. Elemental analyses were performed with a Perkin Elmer Series 11 (CHNS/O) Analyzer 2400.

*Procedure for the synthesis of N, N-dialkylated imidazolium salts (pre-carbenes) (**1a** and **1b**)*

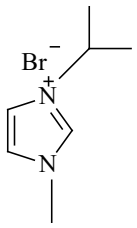
Under nitrogen atmosphere, *N*-methyl imidazole (or its derivative) (12.50 mmol), alkyl bromide (13.00 mmol, 1.54 mL) and THF (10 mL) were measured and transferred into a 25 mL two-necked round-bottom flask. A condenser was attached and the mixture was refluxed with magnetic stirring for 6 h. After completion of the reaction, the mixture was cooled to room temperature to obtain the crude product. The mixture was allowed to settle and the solvent was decanted. The product was washed several times with THF. The isolated product was then subjected to characterization using analytical and spectroscopic techniques [22, 23].

*1-Benzyl-3-methyl imidazolium bromide (**1a**)*



Yellow oil, 77% yield, ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.92 (*s,* 3H, NC*H*$_3$) 5.66 (*s,* 2H, NC*H*$_2$C), 7.00-7.60 (*m*, 7H, Ar-*H*), 10.44 (*s,* 1H, NC*H*N), ^{13}C NMR δ (ppm): (100 MHz, $CDCl_3$) 34.96 (N*C*H$_3$), 53.29 (N*C*H$_2$), 118.73 (*CH*), 124.51 (*CH*), 129.16 (*CH*), 129.21 (*CH*), 129.26 (*CH*), 130.50 (C), 132.98 (*C*HN), 135.65 (N*C*HC), 137.71 (N*C*HN) FT-IR (Neat) (*v cm^{-1})*;1626.77, 1458.68, 1160.44, 2854.91, 724.28. Anal. Calcd.: for $C_{11}H_{13}BrN_2$ C, 52.38; H, 4.76, N, 11.11, Found: C, 52.44; H, 5.02; N, 11.12.

*1-Isopropyl-3-methyl imidazolium bromide (**1b**)*

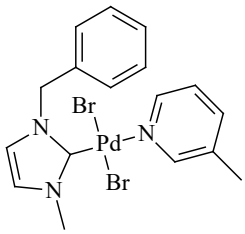


Runny brown oil, 68 % yield, ^{1}H NMR (500MHz, $CDCl_3$) δ (ppm): 1.04 (d, *J* = 6.56 Hz, 6H CH(C*H*$_3$)$_2$), 4.04 (s, 3H NC*H*$_3$), 4.25-4.24 (m, 1H, NC*H*), 7.72 – 7.31 (m, 1H NC*H*Cx2), 10.38 (s, 1H NC*H*N)); ^{13}C NMR δ (ppm): (125 MHz, $CDCl_3$) 19.45 (CH*C*H$_3$), 19.51(CH*C*H$_3$), 35.15 (N*C*H$_3$), 58.83 (N*C*H), 119.63 (C*C*HN), 130.54 (N*C*HC), 137.29 (N*C*HN); FT-IR (Neat) (*v cm^{-1})*; 1629.85, 1462.72, C–N 1167.41, 2959.70, 2933.73, 2869.80. Anal. Calcd. ($C_7H_{13}N_2Br$): C, 40.97; H, 6.34; N, 13.65. Found: C, 41.00; H, 6.51; N 13.69.

*Procedure for the synthesis of Pd-NHC-Py complexes (the pre-catalysts) (**2a** and **2b**)*

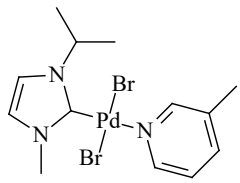
A cleaned and oven-dried 25 mL round-bottom flask, purged with nitrogen gas, was charged with the NHC ligand precursor (**1a** or **1b**; 0.939 mmol), palladium bromide (0.939 mmol, 0.25 g), potassium carbonate (2.00 mmol, 0.28 g) and 5 mL of 3-methylpyridine. The mixture was purged with nitrogen for about 15 min. The reaction flask was covered with a septum and stirred at 90 ^{0}C for 24 h. At the completion of the reaction, the crude product was cooled to room temperature and transferred to an open beaker. The mixture was kept under fume hood until all the pyridine was removed. The product was dissolved in dichloromethane and the solution was passed through a microcolumn packed with silica gel. The eluent was dried to obtain yellow crystals which were further purified by recrystallization from dichloromethane and n-hexane. The crystals were finally washed several times with diethyl ether [22, 23].

*Dibromido(1-benzyl-3-methyl-imidazol-2-ylidene)3-methylpyridinepalladium(II) (**2a**)*



Yellow crystals, 81% yield, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (*s,* 3H, NC*H*$_3$), 4.14 (*s,* 3H, Ar-C*H*$_3$), 6.90 (*s,* 2H, NC*H*$_2$C), 7.21-7.57 (*m*, 9H, Ar-*H*), 8.82 (*t,* J = 6.4 Hz, 2H, NC*H*C*2), FT-IR (Neat) (*ν cm^{-1})*; C-H SP^3 2851.73, C=C aromatic 1406.71, NHC-Pd 2344.85; Anal. Calcd. for $C_{17}H_{20}Br_2N_3Pd$: C, 38.38; H, 3.58; N, 7.90. Found: C, 38.64; H, 3.56; N, 7.67.

*Dibromido[(1-isopropyl-3-methylimidazole-2-ylidene)(3-methylpyridine)palladium (II)] (**2b**)*



Yellow crystals, 62 % yield, ^{1}H NMR (500MHz, $CDCl_3$) *δ* (ppm): 1.061-1.043 (d, 6H CHC*H*$_3$), 2.371 (s, 3H Py-C*H*$_3$), 4.200-4.112 (t, 3H NC*H*$_3$), 4.579-4.511 (t, 1H NC*H*), 7.571-7.237 (m, 4H, Ar-*H*), 8.837 (s, 2H NC*H*C) FT-IR (Neat) (*ν cm^{-1})*; C=C aromatic 1424.51, C=C aromatic 1462.50, NHC–Pd 2344.80, C–H aliphatic 2955.63, C–H aliphatic 2925.59, CH_3 stretching 2858.66. Anal. Calcd. for ($C_{13}H_{19}N_3PdBr_2$): C (32.28), H (3.93), N (8.69). Found: C (32.00), H (4.32), N (8.51).

Procedure for the Mizoroki-Heck cross-coupling reaction

A modification of a published procedure was used [11]. Pd-NHC-Py complex (**2a** or **2b**; 0.005 mmol), aryl halide (1.0 mmol), alkene (1.5 mmol), base (2.0 mmol) and solvent (4.0 mL) were introduced into a 25 mL round-bottom flask. A condenser was attached and the mixture was stirred at the required temperature for the required time. Progress of the reaction was monitored using TLC until no free aryl halide was observed. The reaction was stopped and cooled down to room temperature. In the case of the reaction involving water as solvent, the crude product was acidified using 5 mL of 1M HCl prior to the extraction. The product was then extracted three times with 10 mL of ethyl acetate. The combined ethyl acetate extracts were dried with anhydrous magnesium sulfate. The solvent was removed in a rotary evaporator to afford the corresponding internal alkenes. The alkene was then analyzed with TLC before further purification. The characterization data of the product were found to agree with the reported literature [6, 21].

*(E)-Cinnamic acid (**5a**)*

White solid, 96 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.78 (d, *J* = 15.9 Hz, 1H, CH), 7.65 – 7.45 (m, 2H, CH arom.), 7.40 – 7.37 (m, 3H, CH arom), 6.44 (d, *J* = 15.9 Hz, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 172.3 , 147.03, 134.01, 130.72, 128.94, 128.35, 117.28; GC-MS m/z 148 (M^+).

*(E)-Methyl cinnamate (**5h**)*

White solid, 89% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.68 (d, *J* = 15.9 Hz, 1H, CH), 7.51 – 7.49 (m, 2H, CH arom.), 7.38 – 7.35 (m, 3H, CH arom), 6.43 (d, *J* = 16.2 Hz, 1H, CH), 3.79 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 167.4 , 144.8, 134.4, 130.3, 129.5, 129.1, 128.9, 117.8, 51.7; GC-MS m/z 162 (M^+).

*(E)-Methyl 3-(4-methoxyphenyl)acrylate (**5i**)*

White solid, 76 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.63 (d, *J* = 15.9 Hz, 1H, CH), 7.44 (d, *J* = 5.8 Hz, 2H, CH arom), 6.87 (d, *J* = 5.8 Hz, 2H, CH arom), 6.29 (d, *J* = 15.9 Hz, 1H, CH), 3.79 (s, 3H, CH_3), 3.77 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 167.6, 161.2, 144.3, 129.6, 126.9, 115.1, 114.1, 55.1, 51.4; GC-MS m/z 192 (M^+).

(E)-Methyl 3-(4-aminophenyl)acrylate (5j)

Yellow solid; 70 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (d, *J* = 15.8 Hz, 1H, CH), 7.32 (d, *J* = 5.8 Hz, 2H, CH arom), 6.60 (d, *J* = 8.6 Hz, 2H, CH arom), 6.19 (d, *J* = 15.8 Hz, 1H, CH), 3.98 (s, 2H, NH_2), 3.76 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 168.0 (C), 148.9, 145.2, 129.7, 124.3, 114.6 (CH), 113.0 (CH), 51.2 (CH_3); GC-MS m/z 197 (M^+).

(E)-Methyl 3-(4-acetylphenyl)acrylate (5k)

White solid; 95 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.90 (d, *J* = 6.5 Hz, 2H, CH arom), 7.65 (d, *J* = 16.0 Hz, 1H, CH), 7.55 (d, *J* = 6.6 Hz, 2H, CH arom), 6.47 (d, *J* = 16.0 Hz, 1H, CH), 3.77 (s, 3H, CH_3), 2.57 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 197.0 (C), 166.7 (C), 143.2 (CH), 138.6 (C), 138.0 (C), 128.7 (CH), 128.1 (CH), 120.2 (CH), 51.2(CH_3), 26.7 (CH_3); GC-MS m/z 205 (M+1).

(E)-Methyl 3-(4-nitrophenyl)acrylate (5l)

Yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.23 (d, *J* = 8.8 Hz, 2H, CH arom), 7.69-7.62 (m, 3H), 6.52 (d, *J* = 16.1 Hz, 1H, CH), 3.80 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 166.5 (C), 148.6, 141.7, 140.3, 128.5, 124.0, 122.0, 52.0 (CH_3); GC-MS m/z 207 (M^+).

RESULTS AND DISCUSSION

*Synthesis of imidazolium bromides (**1a** and **1b**)*

The pre-carbenes (imidazolium bromides **1a** and **1b**) were prepared in good yields by the direct alkylation of the 1-methyl imidazole with benzyl bromide (Scheme 1). Formation of the imidazolium bromides was confirmed by the appearance of downfield singlet peaks at 10.44 ppm (**1a**) and 10.38 ppm (**1b**) in the proton NMR spectra, which were assigned to the acidic *C-2* protons of the imidazole rings [13, 23-25]. These peaks would not be observed in the spectrum of 1-methyl imidazole. Furthermore, the benzylic protons in **1a** were observed as a single peak (δ = 5.66 ppm) whereas the isopropyl 1H in **1b** was observed as multiplet (δ = 4.25 - 4.24 ppm) in their respective proton NMR spectrum. This indicates successful alkylation of 1-methyl imidazole. All the remaining signals observed in the 1H and 13C NMR spectra of both **1a** and **1b,** as well as the functional groups identified from their respective FT-IR spectra were in total agreement with the proposed structures.

*Synthesis of Pd(II)-NHC-Py complexes (**2a** and **2b**) (pre-catalysts)*

The dibromido palladium(II) pyridine (Pd-NHC-Py) complexes (**2a** and **2b**) were isolated as yellow solids, in good yields. In the proton NMR spectra of both complexes **2a** and **2b**, the signals due to the acidic C-2 protons observed at 10.44 and 10.38 ppm in the spectrum of the pre-carbenes (**1a** and **1b**), have completely disappeared, indicating the palladation of the NHC-precursors and therefore, successful formation of the complexes. Moreover, signals due to neighboring protons were observed to shift as a result of the complexes' formation. The proposed structures were further confirmed from the FT-IR spectral data and the elemental analyses results and were supported by the relevant literature [13, 23, 24, 26].

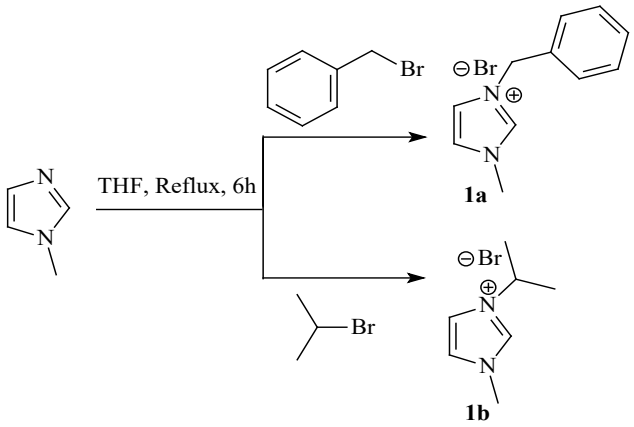
*Evaluation of the catalytic activities of the Pd-NHC-Py complexes (**2a** and **2b**) in the synthesis of cinnamic acids and derivatives. Optimization of reaction conditions*

The cross-coupling reaction of aryl halides with olefins catalyzed using palladium (0) or palladium (II) compounds, known as the Mizoroki-Heck reaction, is a well-established and widely used protocol for the regioselective synthesis of internal alkenes under mild reaction conditions [6, 8, 9, 13]. The new Pd-NHC-Py complexes were used to develop a mild and friendly method for Mizoroki-Heck coupling reactions of alkenes and aryl halides. Several aryl halides including iodides (**3a - c**) and bromides (**3d - f**) were coupled with acrylates, acrylic acids, and acrylamides.

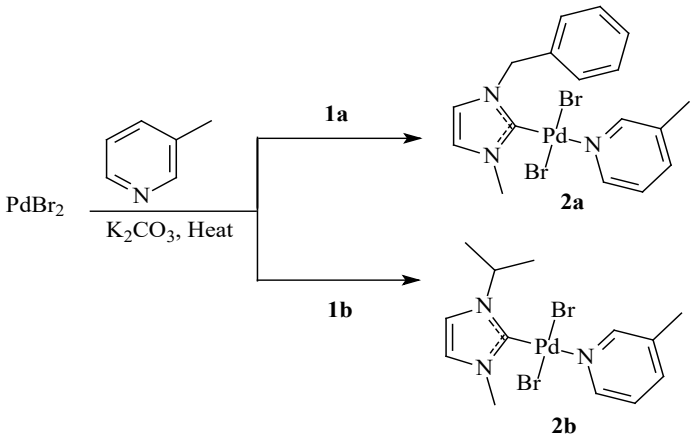
In order to find suitable experimental conditions, bromobenzene (**3d**) and methyl acrylate were selected as model substrates (Table 1). The catalytic activities of the Pd-NHC-Py complexes (**2a** and **2b**) were studied alongside commercially available palladium (II) salts. Initially, the reaction was carried out for 6 h using DMF as a solvent and KOH as a base. The conversion of the bromobenzene (**3d**) to the corresponding methyl cinnamate was poor (**5a**; 38%) (Table 1, entry 1). However, upon changing the solvent system to DMF/H_2O (3:1 v/v) the yield of the product was improved to 78 % (Table 1, entry 2) with subsequent hydrolysis of the ester to the corresponding salt of the carboxylic acid. Moreover, the cinnamic acid (**5h**) was obtained in 95% yield upon changing the solvent DMF/H_2O (1:1 v/v) (Table 1, entry 3). Interestingly, the yield remained excellent (96%) when the reaction was carried in neat water (Table 1, entry 4) thus, water was chosen as the optimum solvent. We went further and studied the effect of temperature on the reaction. Amazingly, the high yield was maintained when the temperature was reduced to 100 ^oC (Table 1, entry 5). As expected, the yield of the cinnamic acid (**5h**) isolated was found to decrease with a decrease in the reaction temperature up to 22 % at room temperature (Table 1, entries 6 - 8) therefore, 100^oC was adopted as optimum. The effect of time on the reaction was then studied and the yield of the product was found to decrease with a decrease in reaction time (Table 1, entries 9, 10). We further studied the effect of a base on the reaction. As expected, no product was obtained in the absence of base (Table 1, entry 13) [7, 21] however, a similar yield was obtained with K_2CO_3 as a base (Table 1, entry 11).

*Mizoroki-Heck coupling reactions of alkenes with aryl halides using Pd-NHC-Py (**2a**) as catalyst. Synthesis of cinnamic acids*

Complex (**2a**) was further tried in a substrate scope study using the optimized reaction conditions [**2a** (1.0 mol%), KOH (2.0 mmol), water (4.0 mL), 100^oC]. Aryl halides (nonactivated, deactivated, and activated, **3a – 3j**) were reacted with methyl acrylate (**4a**), acrylic acid (**4b**) methyl methacrylate (**4c**), and acrylamide (**4d**) to afford smoothly the corresponding cinnamic acid derivatives (**5a – 5g**) in moderate to excellent isolated yields.

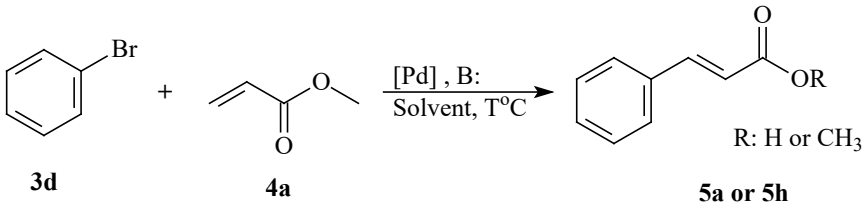


Scheme 1. Synthesis of 1,3-dialkylatedimidazolium bromides (NHC ligand precursors, **1a** and **1b**).



Scheme 2. Synthesis of NHC-pyridine palladium(II) bromides (**2a** and **2b**).

Table 1. Optimization of reaction conditions for the Mizoroki-Heck reaction of aryl halides with alkenes.

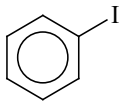
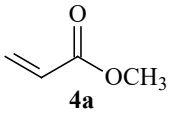
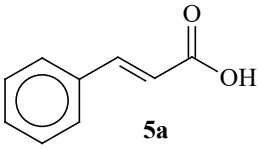
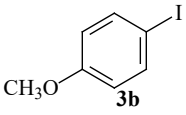
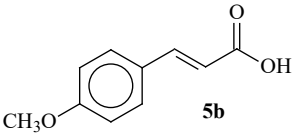
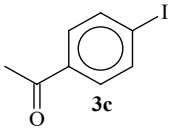
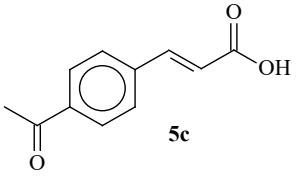
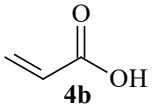
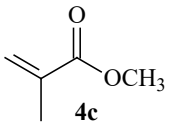
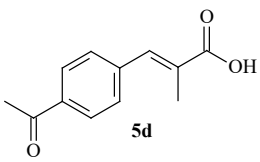


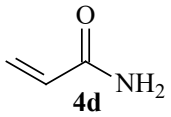
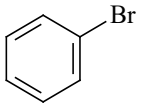
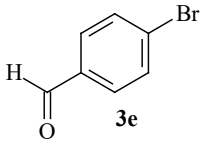
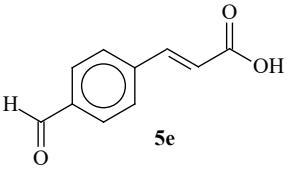
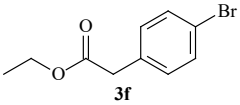
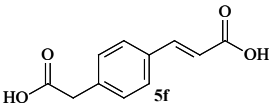
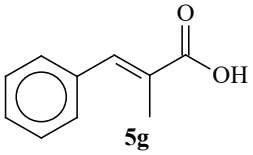
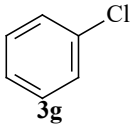
S/N	Catalyst	Solvent (4 mL)	Base	Temp. (^{0}C)	Time (h)	Yield (%)[b]
1	2a	DMF	KOH	120	6	38
2	2a	DMF/Water (3:1)	KOH	120	6	78
3	2a	DMF/Water (1:1)	KOH	120	6	95
4	2a	Water	KOH	120	6	96
5	2a	Water	KOH	100	6	95
6	2a	Water	KOH	80	6	62
7	2a	Water	KOH	60	6	59

8	2a	Water	KOH	Rt	6	22
9	2a	Water	KOH	100	4	80
10	2a	Water	KOH	100	2	69
11	2a	Water	K_2CO_3	100	6	90
12	2a	Water	Et_3N	100	6	22
13	2a	Water	-	100	6	00
14	-	Water	KOH	100	6	00
15	2b	Water	KOH	100	6	90
16	$PdBr_2$	Water	KOH	100	6	60
17	$PdCl_2(PPh_3)_2$	Water	KOH	100	6	69
18	$Pd(OAc)_2$	Water	KOH	100	6	59

[a] Reaction conditions: aryl halide (1.0 mmol), alkene (1.5 mmol), base (2.0 mmol), solvent (4.0 mL), catalyst loading (0.005 mmol). [b] Isolated yield.

Table 2. Mizoroki-Heck coupling reactions of alkenes with aryl halides using complex (**2a**) in water.

Entry	Aryl halide	Alkene	Coupling Product	Time (h)	Yield (%)[b]
1	 **3a**	 **4a**	 **5a**	1.5	96
2	 **3b**	**4a**	 **5b**	1.5	97
3	 **3c**	**4a**	 **5c**	1.5	96
4	**3a**	 **4b**	**5a**	1.5	94
4	**3c**	 **4c**	 **5d**	1.5	84

7	**3a**	 **4d**	**5a**	1.5	96
8	 **3d**	**4a**	**5a**	3	92
9	 **3e**	**4a**	 **5e**	3	94
10	 **3f**	**4a**	 **5f**	3	95
11	**3d**	**4c**	 **5g**	3	90
12	**3f**	**4d**	**5f**	6	92
13	 **3g**	**4a**	-	12	00
14	**3g**	**4b**	-	12	00
15	**3g**	**4d**	-	12	00

[a] Reaction conditions: *Pd-NHC-Py* **(2a)** (0.0100 mmol), aryl halide (1.00 mmol), alkene (1.50 mmol), KOH (2.00 mmol), H_2O (4 mL), 100 °C. [b] Isolated yield.

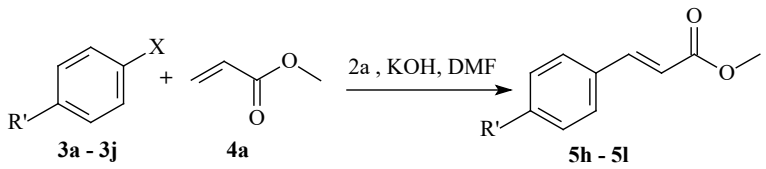
Various functional groups on the aryl halides were well tolerated during the reaction, however, both the ester and the amide functional groups on the alkene were hydrolyzed during the reaction to the corresponding potassium salts of the carboxylic acids. The corresponding cinnamic acids were obtained upon acidification with 1 M HCl. Aryl iodides (**3a - 3c**) were found to be most reactive and were converted quantitatively to the corresponding cinnamic acids (Table 2, entries 1-7) within an hour and a half. To our satisfaction, aryl bromides (**3d – 3f**) cooperated well in the reaction though they required longer time relative to their iodo-counterparts (Table 2, entries 8 - 12). Aryl chloride (**3g**) (Table 2, entries 13-15) on the other hand, was found to be unreactive even for a longer reaction time of 12 h. The results were in agreement with the literature [27].

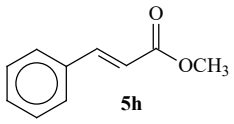
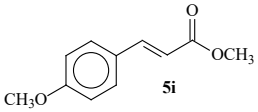
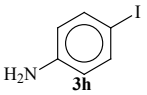
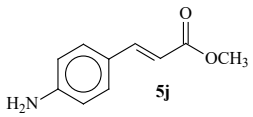
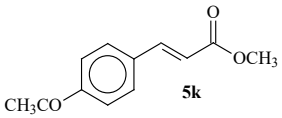
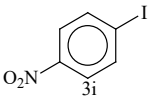
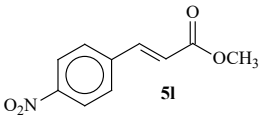
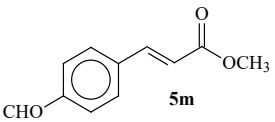
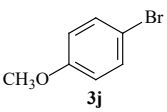
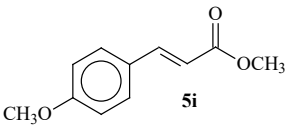
*Mizoroki-Heck coupling reactions of alkenes with aryl halides using Pd-NHC-Py (**2a**) as catalyst. Synthesis of cinnamates*

In addition to their use in the production of drugs, cinnamates are common raw materials for the cosmetic and perfumery industries [28, 29] A direct route to this important class of compounds is the palladium-catalyzed Mizoroki-Heck coupling reaction. Owing to the outstanding catalytic activity and selectivity displayed by the Pd-NHC-Py complexes in the synthesis of cinnamic acid derivatives, we envisaged that the new system can be adopted in the synthesis of cinnamates. However, as observed during the optimization reactions (Table 1), hydrolysis of the ester can easily be avoided by adopting anhydrous solvents such as anhydrous dimethylformamide. In fact, complex **2a** efficiently catalyzed the reaction of aryl iodides (**3a - 3c**, **3h**,

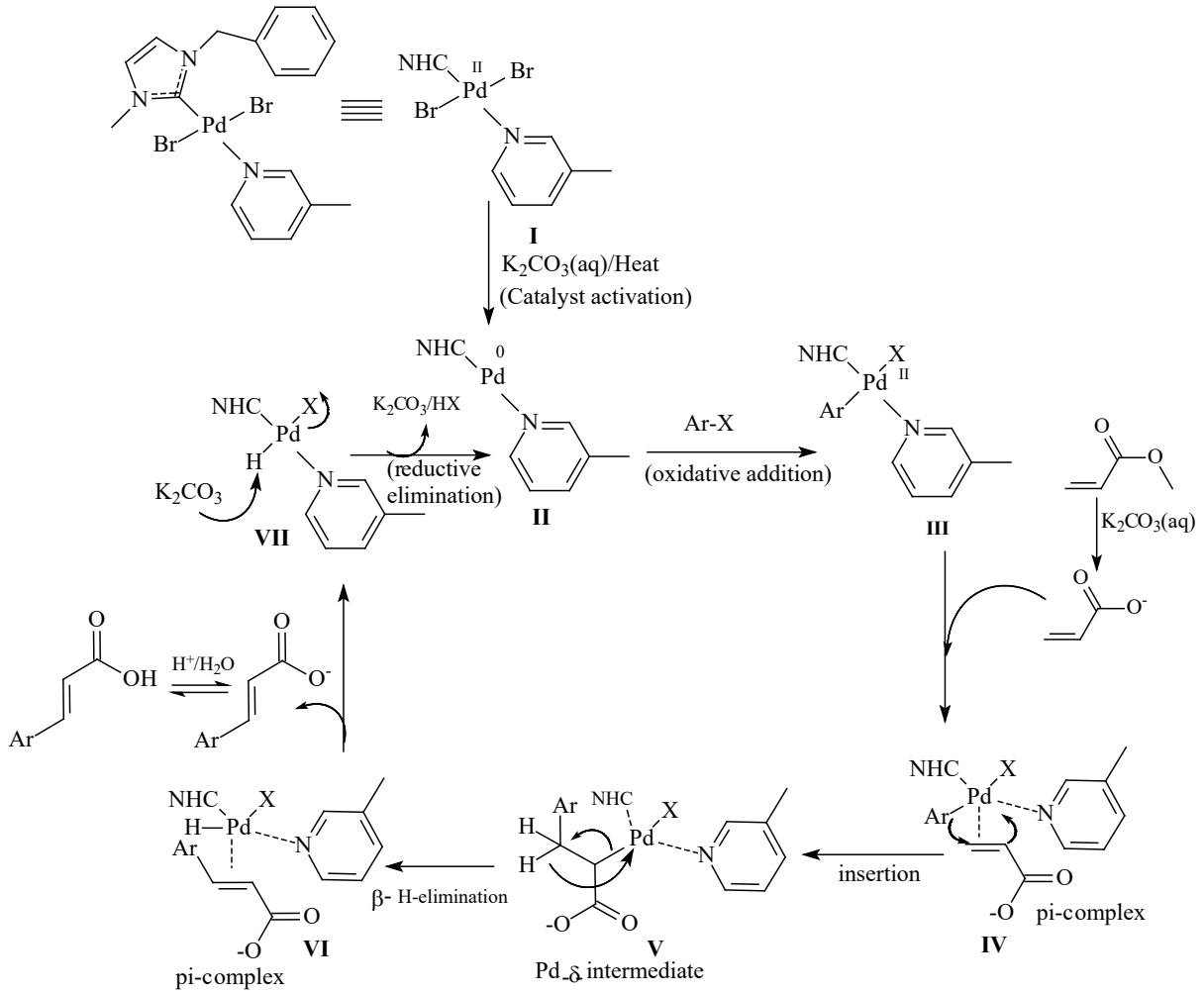
and **3i**) and aryl bromides (**3d**, **3e,** and **3j**) with methyl acrylate (**4a**) in dried DMF, resulting in the corresponding cinnamate esters (**5h** – **5l**). We are delighted to report that all the activated and deactivated aryl iodides (Table 3, entries 1 - 5) and bromides (Table 3, entries 6 - 8) coupled with the methyl acrylate to afford the corresponding methyl cinnamate in good to excellent yields. It is worth mentioning that the aryl bromides required higher temperatures and longer reaction times to afford a reasonable yield of the ester. This is not surprising due to the higher reactivity of the aryl iodides compared to the bromides.

Table 3. Mizoroki-Heck coupling reactions of methyl acrylate with aryl halides using **2a** as catalyst under anhydrous conditions.



Entry	Aryl halide	Alkene	Cinnamate obtained	Yield (%)[b]
	3a	**4a**	 **5h**	89
2	**3b**	**4a**	 **5i**	76
3	 **3h**	**4a**	 **5j**	70
4	3c	**4a**	 **5k**	95
5	 3i	**4a**	 **5l**	92
6[c]	**3d**	**4a**	**h**	74
7[c]	**3e**	**4a**	 **5m**	81
8[c]	 **3j**	**4a**	 **5i**	66

[a] Reaction conditions: **(2a)** (0.0100 mmol), aryl halide (1.00 mmol), methylacrylate (1.50 mmol), KOH (2.00 mmol), DMF (4 mL), 12h, 100ºC. [b] Isolated yield. [c] 110ºC



Scheme 3. Plausible mechanism for the Pd-NHC-Py catalyzed Mizoroki-Heck cross-coupling reaction.

The mechanism of the Mizoroki-Heck cross-coupling is proposed based on established methods. The pre-catalyst Pd(II)-(S_1)(Py)Br_2 (**I**) is activated through base-promoted reductive elimination of the bromo ligands to generate active Pd(0)-(S1)(Py) catalyst (**II**). This step is followed by oxidative addition of the aryl halide to the activated palladium (0) species to form a palladium (II) intermediate $ArPdS_1PyX$ (**III**). The alkene then coordinates to the intermediate (**III**) to form a π complex (**IV**). At this stage, there is insertion of the alkene into the Ar-Pd bond to yield a palladium-sigma intermediate (**V**), then beta hydride elimination to produce another π complex (**VI**). Release of the cross-coupled product followed by reductive elimination regenerates the active palladium catalyst (**II**).

The higher catalytic activity realized using the Pd-NHC-Py system compared to the palladium/phosphine systems could be attributed to the following: contrary to the phosphine ligands, NHCs are known to be stronger sigma donors and form more stable transition metal complexes than the phosphine-based analogues [22, 30]. Furthermore, both the pre-catalyst Pd(II)-(S_1)(Py)Br_2 (**I**) and the proposed active species Pd(0)-(S_1)(Py) (**II**) are more stable compared with the phosphines and other commercially available palladium precursors and catalysts (Table 1). In the proposed new systems, both the oxidative addition and substitution steps are likely to be enhanced by the more electron-rich species Pd(0)-(S_1)(Py) (**II**). Moreover, the inductive and mesomeric effects of the benzyl substituent resulted in a more electron-rich palladium centre leading to a catalyst of higher activity.

CONCLUSION

Imidazolium salts and their corresponding palladium-pyridine complexes (Pd-NHC-Py) were successfully synthesized and characterized. The synthesis of cinnamic acids and cinnamates was achieved under mild reaction conditions using the synthesized pre-catalysts. Various cinnamic acids derivatives and cinnamates were obtained in good to excellent yields. A reaction mechanism was proposed based on the formation of an active palladium (0) species.

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