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Water-promoted palladium-catalysed Heck cross-coupling reactions of aryl halides with alkenes in TBAB

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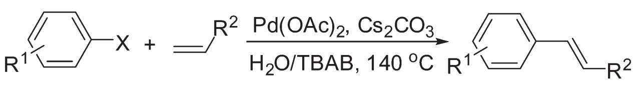
Water was found to promote the ligand-free $Pd(OAc)_2$-catalysed Heck cross-coupling reaction. In the presence of 3 mol% $Pd(OAc)_2$, 2 equiv. of Cs_2CO_3 and 15 mg of water, the coupling of a wide variety of aryl halides with alkenes proceeded smoothly in TBAB (n-Bu_4NBr) in moderate to excellent yield. The $Pd(OAc)_2$/TBAB system could be recovered and reused at least three times without loss of catalytic activity.

Keywords: $Pd(OAc)_2$, H_2O, TBAB, Heck coupling reaction

The palladium-catalysed Heck cross-coupling reaction is a powerful method for the construction of carbon–carbon bonds. The olefins which are formed are useful intermediates for the preparation of a variety of compounds with applications ranging from natural products to other biologically active compounds.[1–22] The most common catalytic system for this reaction is Pd/ligand (usually phosphine ligand) complexes with the aid of organic solvents.[1–3] To address both economic and environmental concerns, a more convenient method is to immobilize the catalyst in a nonvolatile immiscible liquid such as an ionic liquid.[4–7] However, few approaches have reported the combination of TBAB with water for the palladium-catalysed Heck reaction. Recently, TBAB containing about 1.0 wt% of water was found to be highly efficient for the palladium-catalysed Suzuki–Miyaura cross-coupling reaction under ligand-free conditions.[8] Therefore, we decided to examine the co-effect of TBAB/water on the Heck coupling reaction. As expected, the Heck reaction catalysed by $Pd(OAc)_2$ was conducted efficiently in an inexpensive ionic liquid (TBAB) under ligand-free conditions. Notably, the addition of water promoted the reaction, and the $Pd(OAc)_2$/TBAB system could be recovered and reused several times without loss of catalytic activity.



1 **2** **3-12**

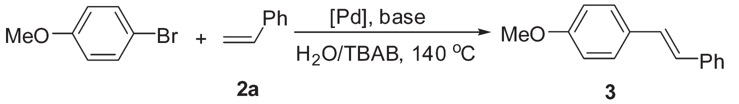
R^1 = MeO, NO_2, MeCO, Me, H X = I, Br, Cl
R^2 = Ph, COO^tBu, COO^nBu

Scheme 1

As shown in Table 1, the Heck cross-couplings between 1-bromo-4-methoxybenzene (**1a**) and styrene (**2a**) was used to define the optimal reaction conditions. Initially the effect of water on the reaction was examined (entries 1–4). It was found that the addition of water had a major influence on the reaction. In the presence of $Pd(OAc)_2$ and Cs_2CO_3, **1a** was treated with **2a** for 12 h to afford the corresponding product **3** in 21% yield using anhydrous TBAB as the medium (entry 1). Excellent results were obtained when 1 wt% of water was added (entry 2). However, further increase in the amount of water reduced the yield (entries 3, 4). For example, the yield was decreased to 62 % when the amount of water was increased to 6 wt% (entry 4). Subsequently, a series of Pd catalysts, such as $Pd(OAc)_2$, $Pd(OAc)_2/PPh_3$, $PdCl_2$, $PdCl_2/PPh_3$, $Pd_2(dba)_3$ and Pd/C were tested in TBAB (containing 1 wt% of water), This screening showed that the best results were obtained using $Pd(OAc)_2$ as the catalyst (entry 2). The addition of PPh_3 had no effect on the reaction (entry 5). A series of bases, such as K_3PO_4, NaOAc, K_2CO_3, Cs_2CO_3 and Et_3N were then evaluated (entries 2 and 10–13), Cs_2CO_3 as the base produced the highest yield (entry 2). Finally, a number of other ionic liquids, such as TBAC (n-Bu_4NCl), TBAI (n-Bu_4NI) and TBAF (n-Bu_4NF) were tested, and they were inferior to TBAB based on the yield and rate (entries 2 and 14–16).

With optimal reaction conditions in hand, we examined the coupling of a variety of aryl halides **1b–i** with alkenes **2a–c**, and the results are shown in Table 2. We were pleased to observe that aryl bromides **1c–g** bearing either electron-withdrawing or electron-donating groups all worked well with alkenes **2a–c** to give the corresponding products in excellent yields in the presence of 3 mol% of $Pd(OAc)_2$, 2 equiv. of Cs_2CO_3 and 1.5 g of TBAB containing 1 wt% of H_2O (entries

Table 1 Palladium-catalysed Heck reaction of 1-bromo-4-methoxybenzene (**1a**) with styrene (**2a**) in TBAB [a]



2a **3**

Entry	[Pd]	Base	Isolated yield % [b]	Entry	[Pd]	Base	Isolated Yield/ % [b]
1 [c]	$Pd(OAc)_2$	Cs_2CO_3	21	9	Pd/C	Cs_2CO_3	51
2	$Pd(OAc)_2$	Cs_2CO_3	85	10	$Pd(OAc)_2$	K_3PO_4	59
3 [d]	$Pd(OAc)_2$	Cs_2CO_3	75	11	$Pd(OAc)_2$	NaOAc	61
4 [e]	$Pd(OAc)_2$	Cs_2CO_3	62	12	$Pd(OAc)_2$	K_2CO_3	81
5 [f]	$Pd(OAc)_2/PPh_3$	Cs_2CO_3	85	13	$Pd(OAc)_2$	Et_3N	57
6	$PdCl_2$	Cs_2CO_3	76	14 [g]	$Pd(OAc)_2$	Cs_2CO_3	65
7	$PdCl_2/PPh_3$	Cs_2CO_3	77	15 [h]	$Pd(OAc)_2$	Cs_2CO_3	49
8	$Pd_2(dba)_3$	Cs_2CO_3	44	16 [i]	$Pd(OAc)_2$	Cs_2CO_3	53

[a] Under otherwise indicated, the reaction conditions were as follows: **1a** (0.5 mmol), **2a** (0.6 mmol), [Pd] (3 mol %), base (2 equiv.), H_2O (15 mg, 1 wt%) and TBAB (1.5 g) at 140 °C in Ar for 12 h. [b] Isolated yield. [c] no water, [d] water(3 wt%), [e] water(6 wt%), [f] 6 mol % of PPh_3 was added, [g] TBAC instead of TBAB, [h] TBAI instead of TBAB, [i] TBAF instead of TBAB.

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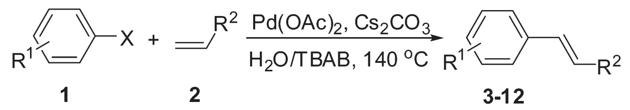
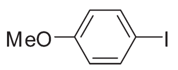
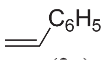
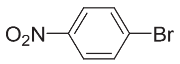
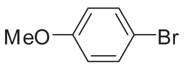
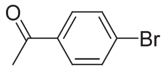
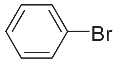
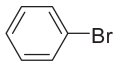
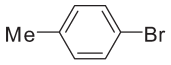
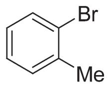
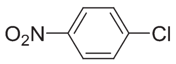
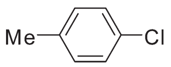
Table 2 $PdCl_2$-catalysed Heck reaction of aryl halides (**1**) with alkenes (**2**) in the presence of TBAB [a]



Entry	Aryl halide	Alkene	Recycle no	Time/h	Yield/%[b]
1	 **(1b)**	 **(2a)**		4	90 (**3**)
2	**(1b)**	 **(2b)**	1 2	4 4 4	96 (**4**) 97 (**4**) 100 (**4**)
3	**(1b)**	 **(2c)**		4	95 (**5**)
4	 **(1c)**	**(2a)**		8	84 (**6**)
5	**(1c)**	**(2b)**		8	88 (**7**)
6	 **(1a)**	**(2b)**		10	87 (**4**)
7	 **(1d)**	**(2b)**		8	86 (**8**)
8	 **(1e)**	**(2a)**		10	78 (**9**)
9	 **(1e)**	**(2b)**		10	77 (**10**)
10	 **(1f)**	**(2b)**		10	82 (**11**)
11	 **(1g)**	**(2b)**		12	79 (**12**)
12	 **(1h)**	**(2a)**		18	51 (**6**)
13	 **(1i)**	**(2b)**		24	22 (**11**)

[a] Reaction conditions: **1** (0.5 mmol), **3** (0.6 mmol), $Pd(OAc)_2$ (3 mol %), Cs_2CO_3 (2 equiv.), H_2O (15 mg, 1 wt%) and TBAB (1.5 g) at 140 °C in Ar. [b] Isolated yield.

4–11). Under the same conditions, aryl iodides **1b** underwent the Heck coupling with alkenes **2a–c** efficiently in excellent yields (entries 1–3). In the coupling of aryl chlorides **1h–i**, the activated chloride **1h** also underwent the reaction with **2a** smoothly to give the desired product in 51 % yield under the same conditions (entry 12), but a rather low yield was isolated from the coupling of the less active chloride **1i** (entry 13). To our delight, the $Pd(OAc)_2$/TBAB system could be recovered and reused at least three times in the couplings of aryl halides with alkenes to give desired results without any loss of activity. For example, the $Pd(OAc)_2$/TBAB system among the Heck reaction of 1-iodo-4- methoxybenzene (**1b**) with tert-butyl acrylate (**2b**) could be recovered and reused three times to afford the target product (entry 2).

In summary, we have demonstrated that $Pd(OAc)_2$ combined with TBAB (containing about 1 wt% of water) was highly active for the Heck cross-couplings of aryl halides with alkenes under ligand-free conditions. The addition of water was found to promote the reactions in TBAB. A variety of aryl halides including the deactivated chlorides underwent the palladium cross-coupling to afford the corresponding products in moderate to excellent yields. It is worth noting that the $Pd(OAc)_2$/TBAB system could be recovered and reused three times without loss of catalytic activity.

Experimental

NMR spectroscopy was performed on an INOVA-400 (Varian) or a Bruker-300 spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) or 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR). TMS (tetramethylsilane) was used an internal standard and $CDCl_3$ was used as the solvent.

Experimental procedure for the palladium-catalysed Heck coupling reaction.

A mixture of aryl halide **1** (0.50 mmol), alkene **2** (0.60 mmol), $Pd(OAc)_2$ (3 mol%), Cs_2CO_3 (2 equiv.) and H_2O (15 mg) in TBAB (1.5 g) was stirred under Ar at 140 °C for the indicated time until the consumption of the starting material was complete as monitored by TLC. After the reaction was finished, the mixture was extracted with diethyl ether and the solvent evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired coupled product **3–12**.

Experimental procedure for the reusable palladium-catalysed Heck cross-coupling reaction

A mixture of **1** (0.50 mmol), **2** (0.60 mmol), $Pd(OAc)_2$ (3 mol%), Cs_2CO_3 (2 equiv.) and H_2O (15 mg) in TBAB (1.5 g) was stirred under Ar at 140 °C for the desired time until the consumption of the starting material was complete as judged by TLC. After the reaction was finished, the product was extracted by cyclohexane (5 mL × 7), the mixture of $Pd(OAc)_2$ and TBAB was solidified (evaporated under vacuum, then cooled) and subjected to a second run of the reaction by the addition of with the same substrates (**1**, **2** and Cs_2CO_3). The combined extracts were evaporated, and then purified by flash column chromatography to afford the desired coupled product **3**.

(E)-1-(4-Methoxystyryl)benzene (**3**):[18,19] White solid. m.p. 131–134 °C (lit.[18] 132 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49–7.44 (m, 4H), 7.34 (t, J = 8.0 Hz, 2H), 7.24–7.23 (m, 1H), 7.03, 6.99 (dd, J = 16.8 Hz, 16.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0, 137.7, 130.2, 128.6, 128.2, 127.7, 127.2, 126.6, 126.2, 114.1, 55.3.

tert-Butyl (E)-3-(4-methoxyphenyl)acrylate (**4**):[18–21] Colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.55 (d, J = 15.9 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 9.0, 2H), 6.24 (d, J=15.9, 1H), 3.83 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.1, 143.2, 129.5, 127.4, 118.2, 117.7, 114.2, 80.2, 55.3, 28.2.

Butyl (E)-3-(4-methoxyphenyl)acrylate (**5**):[18,20,21] Colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (d, J = 16.0 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.31 (d, J = 16.0 Hz, 1H), 4.20 (d, J = 6.6 Hz, 2H), 3.83 (s, 3H), 1.73–1.64 (m, 2H), 1.50–1.37 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 161.3, 144.2, 129.6, 127.2, 115.7, 114.2, 64.2, 55.3, 30.8, 19.2, 13.7.

(E)-2-(4-Nitrophenyl)styrene (**6**):[18,22] Pale-yellow solid, m.p. 86–88 °C (lit.[18] 88 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.43–7.33 (m, 3H), 7.27 (d, J = 16.2 Hz, 1H), 7.14 (d, J = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.8, 143.8, 136.2, 133.3, 128.9, 128.8, 127.0, 126.8, 126.3, 124.1.

tert-Butyl (E) 3-(4-nitrophenyl)acrylate (**7**):[21] Pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 16.0 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 1.55 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.2, 148.3, 140.9, 140.6, 128.5, 124.5, 124.1, 81.3, 28.1.

tert-Butyl (E)-3-(4-acetylphenyl)acrylate (**8**):[18] Colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (d, J = 8.4 Hz, 2H), 7.63–7.58 (m, 3H), 6.46 (d, J = 15.8 Hz, 1H), 2.61 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.3, 165.7, 141.9, 139.0, 137.8, 128.8, 128.0, 122.8, 80.9, 28.1, 26.6.

(E)-1,2-Diphenylethene (**9**):[21–23] White solid. m.p. 122–125 °C (lit.[21] 124 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (d, J = 8.4 Hz, 4H), 7.35 (t, J = 7.2 Hz, 4H), 7.27 (t, J = 6.3 Hz, 2H), 7.11 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.3, 128.7, 127.6, 126.5.

tert-Butyl (E)-cinnamate (**10**):[20,23] Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J = 16.4 Hz, 1H), 7.52–7.50 (m, 2H), 7.38–7.36 (m, 3H), 6.37 (d, J = 16.0 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 143.6, 134.6, 130.0, 128.8, 127.9, 120.1, 80.5, 28.2.

tert-Butyl (E)-3-(4-methylphenyl)acrylate (**11**):[18–21] Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, J = 16.0 Hz, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.18 (t, J = 8.0, 2H), 6.33 (d, J = 16.0 Hz, 1H), 2.37 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 143.4, 140.1, 131.6, 129.4, 127.8, 118.8, 80.2 28.0, 21.3.

tert-Butyl (E)-3-(2-methylphenyl)acrylate (**12**):[18–21] Colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J = 16.0 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.26 (t, J = 8.4, 1H), 7.20 (t, J = 7.6, 2H), 6.30 (d, J = 16.0 Hz, 1H), 2.43 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 141.0, 137.3, 133.3, 130.5, 129.6, 126.1 (2C), 120.8, 80.3, 28.0, 19.6.

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