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An efficient and reusable $PdCl_2$/TBAF system for the Heck reaction under ligand- and solvent-free conditions

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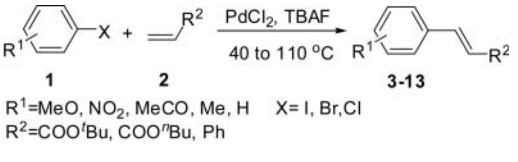
$PdCl_2$ combined with TBAF (n-Bu_4NF) were found to be efficient conditions for the Heck reactions. In the presence of $PdCl_2$ and TBAF, a variety of aryl halides were coupled with alkenes smoothly in moderate to good yields. Moreover, the $PdCl_2$/TBAF system could be recovered and reused several times in the reaction. Note that these reactions are conducted under solvent-free, ligand-free and reusable conditions.

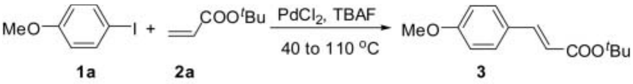
Keywords: $PdCl_2$, TBAF, Heck coupling reaction

Considerable interest in the synthesis of alkenes has been received in the past few years because alkenes are extremely useful intermediates in organic synthesis as well as important units found in a tremendous range of natural products and bioactive molecules. The palladium-catalysed Heck coupling reaction, the coupling reactions between aryl halides and alkenes, is one of the most commonly and straightforward strategies to introduce new substituents into the alkene moiety for the preparation of the new alkenes.[1–29] The Heck reaction is usually conducted under harsh reaction conditions (often at 110–150 °C). Recently, some room temperature Heck reactions have been developed, but the specified ligands were necessary to improve these reactions besides the requirement of harmful organic solvents.[1–4] Although some solvent-free or/and ligand-free Heck procedures have been developed, the promoters, such as phase-transfer catalysts, microwave irradiation, ultrasonic irradiation, electrochemistry and others, were still required.[5–16] Wang and co-workers, for example, have reported a ligand- and solvent-free $Pd(OAc)_2$-catalysed Heck reactions of aryl iodides and aryl bromides with olefins recently, however, the reaction was conducted under the microwave irradiation.[17] Recently, we have reported that TBAF (n-Bu_4NF) was an effective basis for the solvent-free palladium-catalysed Suzuki-Miyaura cross-coupling reactions of aryl halides with arylboronic acids.[18] During this process, Pd nanoparticles.[19–20] were generated *in situ* from $PdCl_2$ with TBAF, which displayed particular efficiency for the Suzuki–Miyaura cross-coupling reaction. As a continuing interest in the coupling reaction, we decided to examine the effect of the $PdCl_2$/TBAF system on the Heck reaction. We found that $PdCl_2$ combined with TBAF displayed highly efficiency for the Heck reaction without the aid of any ligands and solvents under mild conditions (Scheme 1).[21–23] Moreover, the $PdCl_2$ immobilised TBAF system in the Heck reaction process could be recovered and reused several times without loss of catalytic activity.



Scheme 1

Table 1 Palladium-catalysed Heck reaction of 1-iodo-4-methoxybenzene (**1a**) with tert-butyl acrylate (**2a**)[a]



Entry	[Pd]	Base	Recycle no.	Time/h	Isolated Yield/%[b]
1	$PdCl_2$	TBAF		4	96
2	$PdBr_2$	TBAF		10	74
3	PdI_2	TBAF		10	83
4	$Pd(OAc)_2$	TBAF		24	64
5	$PdCl_2(MeCN)_2$	TBAF		4	93
6	$PdCl_2(PPh_3)_2$	TBAF		8	86
7	$PdCl_2/PPh_3$	TBAF		8	81
8	$PdCl_2$	TBAF		4	86
			1	4	81
			2	4	80
9[c]	$PdCl_2$	TBAF		1	95
			1	1	96
			2	1	98
			3	1	100
10[cd]	$PdCl_2$	TBAF		12	100
11[e]	$PdCl_2$	TBAF		24	31
12	$PdCl_2$	KF		8	14
13	$PdCl_2$	Cs_2CO_3		8	16
14	0	TBAF		24	0

[a] Under otherwise indicated, the reaction conditions were as follows: **1a** (0.5 mmol), **2a** (0.75 mmol), [Pd] (3 mol %), base (3 equiv) at 40 °C under argon atmosphere. [b] Isolated yield. [c] At 60 °C. [d] $PdCl_2$ (1 mol%). [e] $PdCl_2$ (0.1 mol%) at 80 °C.

As listed in Table 1, we initially examined the Heck reaction between 1-iodo-4-methoxybenzene (**1a**) and *tert*-butyl acrylate (**2a**) under ligand- and solvent-free conditions to optimise the reaction conditions. A number of the Pd catalysts, such as $PdCl_2$, $PdBr_2$, PdI_2, $Pd(OAc)_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ and $PdCl_2/PPh_3$ were tested (entries 1–7), The screening results showed that the best results were obtained using $PdCl_2$ as the catalyst. While the commonly used $Pd(OAc)_2$ catalyst in the Heck cross-coupling reaction gave only 64% yield of the target product **3** after 24 h at 40 °C (entry 4), $PdCl_2$ provided a 96% yield of **3** in 4 h without the aid of any ligands (entry 1). Reuse of the $PdCl_2$/TBAF system was subsequently examined at 40 °C. After the initial experimentation, the reaction mixture was extracted with cyclohexane, and the $PdCl_2$/TBAF system were then solidified (evaporated and cooled) and subjected to a second run of the coupling by charging with the same substrates and base (**1a**, **2a** and 1 equiv of TBAF). However, the activity of the system was reduced to some extent in the reused processes (entry 8). Gratifyingly, the reused processes could be preformed successfully providing the identical results in four runs when the temperature was enhanced to 60 °C (entry 9). It was interesting to observe that quantitative yield was still achieved from the reaction of substrate **1a** with **2a** and 1 mol% of Pd at 60 °C after prolonging the reaction time (entry 10). However, only a 31% yield of **3** was isolated in the presence of 0.1 mol% of $PdCl_2$ even at 80 °C (entry 11). Finally, two other inorganic bases, KF and Cs_2CO_3, were evaluated, and they both were found to be ineffective for the reaction (entries 12 and 13). Note that no reaction is observed without Pd catalysts (entry 14).

We subsequently examined the scope and limitations of the protocol based on both aryl halides and alkenes. As shown

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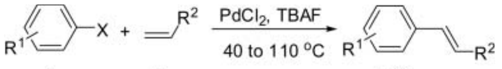
Table 2 PdCl$_2$-Catalysed Heck reaction of aryl halides (**1**) with alkenes (**2**) in the presence of TBAF[a]



1 **2** **3-13**

Entry	Aryl halide	Alkene	Recycle no.	Time/ h	Yield/ %[b]
1	R^1=4-CH$_3$O X=I (**1a**)	R^2=COO^{n}Bu (**2b**)		6	88 (**4**)
2	(**1a**)	R^2=Ph (**2c**)		6	63 (**5**)
3	R^1=4-NO$_2$ X=I (**1b**)	R^2=COO^{t}Bu (**2a**)		3	100 (**6**)
4	(**1b**)	(**2c**)		12	100 (**7**)
5	R^1=4-CH$_3$CO X=I (**1c**)	(**2a**)		3	100 (**8**)
6	R^1=H X=I (**1d**)	(**2a**)	1	3	86 (**9**)
			2	3	84 (**9**)[c]
				4	90 (**9**)[c]
7	R^1=4-Me X=I (**1e**)	(**2a**)		3	100 (**10**)
8	R^1=2-Me X=I (**1f**)	(**2a**)		3	90 (**11**)
9	(1f)	(**2b**)		12	80 (**12**)
10	R^1=4-CH$_3$O X=Br (**1g**)	(**2a**)		18	trace (**3**)
11[c]	(**1g**)	(**2a**)		18	40 (**3**)
12[c]	R^1=4-NO$_2$ X=Br (**1h**)	(**2a**)		9	81 (**6**)
13[c]	R^1=4-CH$_3$CO X=Br (**1i**)	(**2a**)		6	98 (**8**)
14[c]	R^1=H X=Br (**1j**)	(**2a**)		18	77 (**9**)
15[c]	(**1j**)	(**2c**)		18	77 (**13**)
16[c]	R^1=4-Me X=Br(**1k**)	(**2a**)		14	80 (**10**)
17[c]	R^1=2-Me X=Br(**1L**)	(**2a**)		15	65 (**11**)
18[c]	R^1=4-NO$_2$ X=Cl (**1m**)	(**2a**)		15	70 (**6**)
19[c]	R^1=H X=Cl (**1n**)	(**2a**)		24	25 (**9**)

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), PdCl$_2$ (3 mol %) and TBAF·nH$_2$O (3 equiv) at 40 °C under argon atmosphere. [b] Isolated yield. [c] At 110 °C.

in Table 2, the Heck reaction of substrate **1a** with the other alkenes **2b** or **2c**, PdCl$_2$ and TBAF were also conducted smoothly at 40 °C in good yields (entries 1 and 2). Under the same conditions, the other aryl iodides **1b–f** underwent the reaction with alkenes efficiently in good to excellent yields (entries 3–9). We next evaluated the reactions of aryl bromides with alkenes (entries 10–17). Unfortunately, a trace amount of the target product **3** was observed from the reaction of the deactivated bromide **1g** with **2a** at 40 °C (entry 10). Thus, we decided to perform the reaction at a higher reaction temperature, the yield of **3** was enhanced to 40% when the reaction was conducted at 110 °C (entry 11). Subsequently, the Heck reactions of the other bromides **1h–l** were then carried out at 110 °C, and moderate to good yields were obtained (entries 12–17). The activated chloride **1m** also underwent the reaction with **2a** smoothly to give the desired product **6** in a 70% yield under the same conditions (entry 18), but a rather low yield was isolated from the coupling of the less active chloride **1n** (entry 19).

Based on the above results and the previously proposed mechanism, we deduced that several roles of TBAF may play in the reaction:[3–4,18] (i) conversion of PdCl$_2$ to Pd nanoparticles; (ii) activation of the active Pd(0) nanoparticles species; (iii) stabilisation of the low coordination Pd(0) nanoparticles species; (iv) as a basis to improve the reaction; (v) phase-transfer catalyst for the substrate/catalysis/base/product phases; and (vi) as medium (TBAF·nH$_2$O is ropy liquid) to improve the reaction.

In summary, a simple and reusable PdCl$_2$/TBAF system has been developed for the Heck coupling reactions under solvent- and ligand-free conditions. Based on the present results, several interesting features are apparent: (1) PdCl$_2$ combined with TABF showed highly efficiency for the Heck coupling reactions. (2) The present protocol is mild, efficient, highly inexpensive and general. (3) The PdCl$_2$ immobilised TBAF system could be recovered and reused several times without loss of any activity. (4) Importantly, these reactions were conducted under solvent- and ligand-free conditions.

Experimental

NMR spectroscopy was performed on an INOVA-400 (Varian) or a Bruck-300 (Bruck) 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.

Typical experimental procedure for the palladium-catalysed Heck coupling reaction

A mixture of aryl halide **1** (0.5 mmol), alkene **2** (0.75 mmol), PdCl$_2$ (3 mol %), and TBAF·nH$_2$O (3 equiv) was stirred in a Schlenk tube at the indicated temperature (40 to 110 °C) for the indicated time until complete consumption of starting material as monitored by TLC. After the reaction was finished, ethyl acetate was poured into the mixture, then washed with brine, extracted with diethyl ether, dried by anhydrous Na$_2$SO$_4$ and evaporated under vacuum. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired coupled product **3–13**.

Typical experimental procedure for the reusable palladium-catalysed Heck cross-coupling reaction

A mixture of aryl halide **1** (0.5 mmol), alkene **2** (0.75 mmol), PdCl$_2$ (3 mol %), and TBAF·nH$_2$O (3 equiv) was stirred in a Schlenk tube at the indicated temperature (40–60 °C) for the indicated time until complete consumption of starting material as monitored by TLC. After the reaction was finished, the product was extracted by cyclhexane (1m × 8). The extraction was then evaporated under vacuum to give the residue, which was purified by flash column chromatography (hexane–ethyl acetate) to afford the desired coupled product. After initial experimentation, the residue (the PdCl$_2$/TBAF system) was then solidified (evaporated *in vacuo* and cooled) and subjected to a second run of the Heck reaction by charging with the same substrates (aryl halide, alkene and 1 equiv of TBAF).

tert-Butyl (E)-3-(4-methoxyphenyl)acrylate (**3**)[24–27]: 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 (**4**)[24,26–27]: 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)-1-(4-Methoxystyryl)benzene (**5**)[24–25]: White solid. m.p. 131–134 °C (Lit.[24] 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), 7.02 (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-nitrophenyl)acrylate (**6**)[27]: Pale-yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.23 (d, J = 8.8 Hz, 2H), 7.67–7.58 (m, 3H), 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.

(E)-2-(4-Nitrophenyl)styrene (**7**)[24,28–29]: Pale-yellow solid, m.p. 86–88 °C (lit.[24] 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), 7.43–7.11 (m, 5H); ^{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-acetylphenyl)acrylate (**8**)[24]: 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.

tert-Butyl (E)-cinnamate (**9**)[26]: 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 (**10**)[24–27]: 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 (**11**)[24–27]: 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.

n-Butyl (*E*)*-3-(2-methylphenyl)acrylate* (**12**)[24–27]: Colourless liquid. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.97 (d, *J* = 15.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.28–7.24 (m, 1H0, 7.19 (t, *J* = 7.6, 1H), 6.36 (d, *J* = 16.4, 1H), 4.21 (t, *J* = 6.8 Hz, 2H), 2.43 (s, 3H), 1.71–1.67 (m, 2H), 1.47–1.41 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 167.1, 142.2, 137.5, 133.4, 130.7, 129.9, 126.3 (2C), 119.2, 64.4, 30.7, 19.7, 19.2, 13.7.

(*E*)*-1,2-Diphenylethene* (**13**)[27–28]: White solid. m.p. 122–125 °C (lit.[27] 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.

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