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Microwave-Promoted Heck Reaction Using $\text{Pd}(\text{OAc})_2$ as Catalyst under Ligand-Free and Solvent-Free Conditions

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Abstract: A rapid and efficient microwave-promoted Heck reaction of aryl iodides and bromides with terminal olefins using a $\text{Pd}(\text{OAc})_2$ (0.05 mol%)/ K_3PO_4 catalytic system under ligand-free and solvent-free conditions is described.

Keywords: aryl halides, Heck reaction, microwave, palladium

Palladium-catalyzed Heck coupling reaction is one of the most powerful tools for carbon–carbon formation in organic synthesis.^[1] The traditional Heck reaction is typically performed with 1–5 mol% of a palladium catalyst along with phosphine ligands in the presence of a suitable base under an inert atmosphere.^[2] However, the palladium complex is always expensive, and the phosphine ligands, especially the electron-rich phosphine ligands, are often toxic and sensitive to water and air. Consequently, several phosphine-free palladium catalytic systems have been developed, which include the heterogeneous palladium catalysts,^[3] nanopalladium catalysts,^[4] sulfur-based palladacycles,^[5] palladium complexes of nitrogen ligands,^[6] and carbene complexes of palladium.^[7] Recently, there has been increasing interest in the use of ligand-free catalyst systems of the Heck reaction.^[8] Yao and coworkers^[9] have shown that $\text{Pd}(\text{OAc})_2$, in combination with K_3PO_4 as the base and DMA as the solvent, was an active catalyst for the ligand-free Heck reaction of aryl bromides, but long reaction times (17–25 h) were required for full conversion. Attempts to reduce the reaction time through enhancing the reaction temperature are seldom effective

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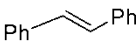
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because of collapse of the catalytic system. On the other hand, microwave-promoted synthesis is an area of increasing research interest as evidenced by a number of papers and reviews appearing in the literature,^[10] and microwave irradiation has also been employed for the Heck reaction.^[11] As a part of our research on microwave chemistry^[12] and the Heck reaction,^[13] we investigated the microwave-promoted Heck reaction of aryl halides using a $\text{Pd}(\text{OAc})_2/\text{K}_3\text{PO}_4$ catalytic system under solvent-free and ligand-free conditions. We herein report the full results of this effort.

Initially, we examined the coupling between bromobenzene and styrene using a $\text{Pd}(\text{OAc})_2/\text{K}_3\text{PO}_4$ system under solvent-free conditions. When 0.1 mol% of $\text{Pd}(\text{OAc})_2$ and 1.4 equiv of K_3PO_4 were employed, irradiation at 300 W of microwave power for 15 min gave *trans*-stilbene in 67% yield (Table 1, entry 1). We then optimized the reaction conditions. As shown in Table 1, the best yield was obtained when 0.05 mol% of $\text{Pd}(\text{OAc})_2$ and 1.4 equiv of K_3PO_4 were used under 300 W for 20–25 min.

With the optimal reaction conditions, we examined a variety of aryl halides and terminal olefins, and the results are summarized in Table 2. Both aryl bromides (Table 2, entries 1–7 and 15–18) and aryl iodides (Table 2, entries 8–11) gave good to excellent yields, whereas aryl chlorides gave poor yields (21–55%) even in the presence of 0.1 mol% of catalyst (Table 2, entries 12–14). The electron-deficient aryl halides (Table 2, entries 1, 4, 15, and 18) are more active than the electron-rich aryl halides (Table 2, entries 3, 11, and 17). Furthermore, 4-methylphenyl halides (Table 2, entries 2 and 9) are more active than their 2-methyl

Table 1. Optimal conditions for $\text{Pd}(\text{OAc})_2$ -catalyzed Heck reaction of bromobenzene and styrene

Ph-Br + 		$\text{Pd}(\text{OAc})_2, \text{K}_3\text{PO}_4$ MW, no solvent				
Entry	Microwave power (W)	$\text{Pd}(\text{OAc})_2$ (mol%)	Time (min)	Yield ^a (%)		
1	200	0.1	15	67		
2	150	0.1	15	55		
3	100	0.1	15	35		
4	250	0.1	15	78		
5	300	0.1	15	93		
6	300	0.1	20	93		
7	300	0.05	15	70		
8	300	0.05	20	85		
9	300	0.05	25	93		
10	300	0.01	25	87		
11	300	0.005	50	80		

^aIsolated yield.

Table 2. Ligand-free Pd(OAc)₂-catalyzed Heck reactions under microwave and solvent-free conditions

Entry	R ₁	X	R ₂	Pd(OAc) ₂ (mol%)	Time (min)	Yield (%) ^a
1	4-COCH ₃	Br	Ph	0.05	20	98
2	4-CH ₃	Br	Ph	0.05	25	90
3	4-OMe	Br	Ph	0.05	25	82
4	2-Me	Br	Ph	0.05	25	75
5	4-Cl	Br	Ph	0.05	25	95
6	4-CN	Br	Ph	0.05	20	98
7	H	Br	Ph	0.05	25	93
8	H	I	Ph	0.05	20	96
9	4-CH ₃	I	Ph	0.05	20	94
10	2-Me	I	Ph	0.05	20	85
11	4-OMe	I	Ph	0.05	20	88
12	H	Cl	Ph	0.1	25	38
13	4-CH ₃	Cl	Ph	0.1	25	21
14	4-COCH ₃	Cl	Ph	0.1	25	55
15	4-CN	Br	CO ₂ Et	0.05	20	95
16	H	Br	CO ₂ Et	0.05	20	90
17	4-CH ₃	Br	CO ₂ Et	0.05	20	86
18	4-COCH ₃	Br	CO ₂ Et	0.05	20	94

^aIsolated yield.

counterparts (Table 2, entries 4 and 10) because of the stereo hindering. The products were isolated as *trans*-isomers in all cases. Compared with Yao's method,^[9] our reaction is rapid and solventfree.

In summary, we have demonstrated that microwave irradiation could efficiently promote the Heck reaction using a Pd(OAc)₂/K₃PO₄ catalytic system. A few notable advantages of this procedure are (1) that Pd(OAc)₂ was used as catalyst without utilizing expensive ligands and/or requiring the presence of various additives, (2) reasonably good yields, (3) fast reaction times (20–25 min), and (4) avoidance of toxic solvents.

EXPERIMENTAL

General Procedure for the Heck Reaction

Aryl halides (1 mmol), olefin (1.2 mmol), K₃PO₄ (1.4 mmol, 0.298 g), and Pd(OAc)₂ (1.67 × 10^{−4} mmol/g, 3 g, 0.0005 mmol) absorbed on neutral

alumina were mixed thoroughly. Subsequently the mixture was placed inside the cavity of the microwave reactor and irradiated at 300 W power for 25 min. After the reaction mixture was cooled to room temperature, the solid was extracted with ethyl acetate, and the solvent was evaporated in a vacuum. The residue was purified by flash-column chromatography on silica gel using ethyl acetate/hexane (1:20).

Data

(E)-1-(4-Styryl-phenyl)-ethanone (Table 2, entry 1): ^1H NMR (500 MHz, CDCl_3): δ 7.96 (d, 2H, $J = 8.3$ Hz), 7.60 (d, 2H, $J = 8.2$ Hz), 7.55 (d, 2H, $J = 7.6$ Hz), 7.40 (t, 2H, $J = 7.5$ Hz), 7.30 (m, 1H), 7.23 (d, 1H, $J = 16.3$ Hz), 7.13 (d, 1H, $J = 16.3$ Hz), 2.62 (s, 3H). MS (EI): m/z (%) 222 (66) [M^+], 207 (100), 178 (66), 152 (15), 89 (20), 76 (16), 43 (43).

(E)-1-Methyl-4-styryl-benzene (Table 2, entry 2): ^1H NMR (500 MHz, CDCl_3): δ 7.51 (d, 2H, $J = 7.6$ Hz), 7.42 (d, 2H, $J = 8.0$ Hz), 7.37 (t, 2H, $J = 7.6$ Hz), 7.25 (m, 1H), 7.18 (d, 2H, $J = 7.6$ Hz), 7.08 (d, 2H, $J = 2.0$ Hz), 2.38 (s, 3H). MS (EI): m/z (%) 180 (100) [M^+], 179 (68), 178 (38), 165 (34), 102 (8), 76 (11), 51 (17).

(E)-Methoxy-4-styryl-benzene (Table 2, entry 3): ^1H NMR (500 MHz, CDCl_3): δ 7.50 (q, 4H, $J = 8.2$ Hz), 7.36 (t, 2H, $J = 7.6$ Hz), 7.26 (d, 1H, $J = 7.3$ Hz), 7.07 (d, 1H, $J = 16.3$ Hz), 6.98 (d, 1H, $J = 16.3$ Hz), 6.90 (d, 2H, $J = 8.7$ Hz), 3.83 (s, 3H). MS (EI): m/z (%) 210 (100) [M^+], 195 (22), 179 (14), 167 (33), 165 (37), 152 (27), 89 (15), 63 (15), 51 (12).

(E)-1-Methyl-2-styryl-benzene (Table 2, entry 4): ^1H NMR (500 MHz, CDCl_3): δ 7.60 (d, 1H, $J = 7.3$ Hz), 7.53 (d, 2H, $J = 7.6$ Hz), 7.37–7.43 (m, 3H), 7.23–7.33 (m, 4H), 7.05 (d, 1H, $J = 16.2$ Hz), 2.48 (s, 3H). MS (EI): m/z (%) 194 (100) [M^+], 195 (22), 179 (14), 167 (33), 165 (37), 152 (27), 89 (15), 63 (15), 51 (12).

(E)-1-Chloro-4-styryl-benzene (Table 2, entry 5): ^1H NMR (500 MHz, CDCl_3): δ 7.50 (d, 2H, $J = 7.5$ Hz), 7.44 (d, 2H, $J = 8.5$ Hz), 7.37 (t, 2H, $J = 7.5$ Hz), 7.32 (d, 2H, $J = 8.5$ Hz), 7.28 (m, 1H), 7.06 (d, 2H, $J = 4.3$ Hz). MS (EI): m/z (%) 214 (70) [M^+], 216 (23) [$\text{M} + 2^+$], 179 (90), 178 (100), 152 (20), 89 (25), 76 (10).

(E)-1-Cyano-4-styryl-benzene (Table 2, entry 6): ^1H NMR (500 MHz, CDCl_3): δ 7.63 (d, 2H, $J = 8.3$ Hz), 7.59 (d, 2H, $J = 8.4$ Hz), 7.53 (d, 2H, $J = 7.5$ Hz), 7.39 (t, 2H, $J = 7.5$ Hz), 7.33 (d, 1H, $J = 7.3$ Hz), 7.22 (d, 1H, $J = 16.3$ Hz), 7.09 (d, 1H, $J = 16.3$ Hz). MS (EI): m/z (%) 205 (100) [M^+], 190 (28), 177 (7), 165 (6).

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