An Efficient Phosphine-Free Heck Reaction in Water Using Pd(L-Proline)$_2$ as the Catalyst Under Microwave Irradiation

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Abstract: The present report describes an efficient and simple protocol for phosphine-free Heck reactions in water using a Pd(L-proline)$_2$ complex as the catalyst under controlled microwave irradiation conditions. This methodology is versatile and provides excellent yields of products in short reaction times and minimizes costs, operational hazards and environmental pollution.

Key words: Heck reaction, palladium, Pd(L-proline)$_2$, microwave irradiation, phosphine-free

Palladium-catalyzed coupling of alkenes with aryl, benzyl and vinyl halides, a procedure known as the Heck reaction,[1,2] has continued to attract a great deal of attention from the chemical community because of its versatility and the range of products that can be formed.[3] The Heck reaction has found widespread use in the synthesis of natural products, pharmaceuticals, polymers, dendrimers and various conjugated architectures of interest in materials science.[4] Unlike other C–C bond forming reactions that involve a polar addition, the Heck reaction tolerates many sensitive functionalities such as unprotected amino, hydroxy, aldehyde, ketone, carboxy, ester, cyano and nitro groups.[1] A major challenge in this area is the development of new Heck reaction catalysts with higher efficiency and enhanced reactivity. Significant advances have been made to meet these goals, which include the use of phosphorus,[5,6] nitrogen,[7] sulfur[8] and carbene-based ligands.[9,10]

All of these catalyst systems, however, suffer from drawbacks of one kind or another. These include sensitivity towards air and moisture, tedious multi-step syntheses, high costs of the ligands, and the requirement to use various additives.[11] As a result, much attention has been devoted to develop milder and operationally simpler procedures for the Heck reaction. Some important developments include the use of ligand-free palladium catalysts in combination with tetraalkylammonium salts, palladacycles, pincer and supported palladium catalysts, bulky electron-rich phosphines and N-heterocyclic carbene (NHC) complexes of palladium.[12] Reetz et al. have shown that palladium(II) acetate [Pd(OAc)$_2$] in combination with tetrabutylammonium bromide (TBAB) gives rise to nanometric palladium colloids which are the actual catalysts under the so-called Jeffery conditions.[13–15]

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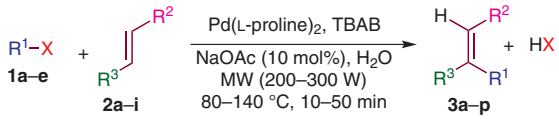
However, despite all these developments on catalyst design, polar aprotic solvents still remain the preferred medium for carrying out Heck reactions. Driven by environmental concerns, much effort has been directed towards using water as the solvent for organic reactions.[16–19] Water offers practical advantages over organic solvents as it is cheap, readily available, nontoxic and nonflammable.

Rapid synthesis using microwave irradiation has attracted a great deal of attention and is characterized by spectacular accelerations in reaction rates, milder conditions, shorter reaction times, higher yields and selectivity, and enhanced product purities.[20–26]

In view of the above, and as a part of our ongoing interest on microwave-assisted organic synthesis (MAOS),[27] we describe herein the first use of the Pd(L-proline)$_2$ complex as an air-stable, efficient and water-soluble catalyst for the controlled microwave-assisted arylation and benzylation of alkenes in the presence of tetrabutylammonium bromide and sodium acetate in water. The procedure does not require phosphorus ligands or toxic organic solvents (Scheme 1).



R^1 = aryl, benzyl
X = Cl, Br, I
R^2 = COOMe, COOEt, CN, COO*n*-Bu, COO*t*-Bu, *n*-Hex, Ph
R^3 = H, Ph
R^2–R^3 = -$(CH_2)_4$-

Scheme 1 Heck reaction between aryl/benzyl halides and various alkenes

The Pd(L-proline)$_2$ complex was prepared in quantitative yield by reacting palladium(II) acetate, L-proline and triethylamine in methanol, at room temperature, under a nitrogen atmosphere. The product was characterized from spectral data.

In order to optimize the conditions for the Heck reaction a detailed study was undertaken by varying different parameters. Iodobenzene and methyl acrylate were employed as model substrates in water as the reaction medium. The results are presented in Table 1. Initial attempts using 0.5 mol% of Pd(L-proline)$_2$ and a microwave power of 160 W for five minutes at 80 °C or 120 °C resulted in no observable conversion (Table 1, entries 1

and 2). The addition of varying amounts of tetrabutylammonium bromide and changing the temperature did not bring about any change in the reaction profile (Table 1, entries 3–6). However, when the amounts of Pd(L-proline)$_2$ and tetrabutylammonium bromide were increased to 1 mol% and 50 mol%, respectively, a 15% yield of alkene **3a** was obtained (Table 1, entry 7). With the aim of enhancing the product yield further, the concentration of tetrabutylammonium bromide was increased to 100 mol%, and this resulted in an improved 25% yield of the product (Table 1, entry 8).

The effects of varying the microwave power, temperature and time were also studied. Irradiation at 200 W and 80 °C for 10 minutes afforded a 37% yield of alkene **3a** (Table 1, entry 9). Finally, varying the concentration of the base (NaOAc) resulted in the optimum yield of the product (94%, Table 1, entry 16) being obtained. Further variation of the microwave power, temperature, and reaction time did not improve the yield of the product. These results reveal the high activity of the catalytic system used in the present study.

Subsequently, aryl and benzyl halides **1a–e** underwent the Heck reaction with activated and unactivated olefins **2a–i** in a molar ratio of 1:2 using Pd(L-proline)$_2$ (1.0 mol%), tetrabutylammonium bromide (100 mol%) and sodium acetate (10 mol%) in water, using a safe pressure regulation pressurized vial with a 'snap-on' cap. The microwave power, temperature and reaction time were all varied (Table 2). After completion of the reaction, the resulting products **3a–p** were isolated and purified by column chromatography and then characterized based on their physical and spectral data.

Table 1 Optimization of the Model Reaction Conditions under Microwave Irradiation in Water

Entry	Pd(L-Proline)$_2$ (mol%)	TBAB (mol%)	NaOAc (mol%)	Power (W)	Temp (°C)	Time (min)	Yield (%)[a]
1	0.5	0	0	160	80	5	–
2	0.5	0	0	160	120	5	–
3	0.5	50	0	160	80	5	–
4	0.5	50	0	160	120	5	–
5	0.5	100	0	160	80	5	–
6	0.5	100	0	160	120	5	–
7	1	50	0	160	80	5	15
8	1	100	0	160	80	5	25
9	1	100	0	200	80	10	37
10	1	100	0	200	100	10	35
11	1	100	0	300	80	10	36
12	1	100	1	200	80	10	50
13	1	100	3	200	80	10	63
14	1	100	5	200	80	10	72
15	1	100	7	200	80	10	79
16	**1**	**100**	**10**	**200**	**80**	**10**	**94**
17	1	100	10	200	60	10	68
18	1	100	10	300	80	10	92
19	1	100	20	200	80	10	94
20	1	100	10	200	100	10	90
21	1	200	10	200	80	10	91
22	1	100	10	200	80	20	93
23	2	100	10	200	80	10	94

[a] Yield based on iodobenzene.

Table 2 Pd(L-Proline)$_2$-Catalyzed Heck Reaction of Aryl and Benzyl Halides with Alkenes[a] **2a–i**

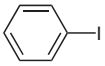
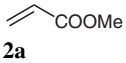
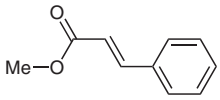
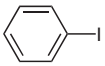
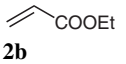
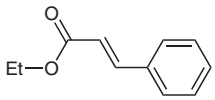
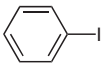
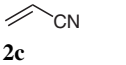
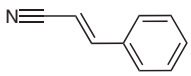
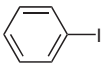
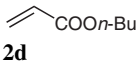
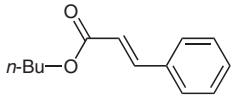
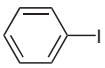
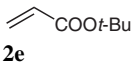
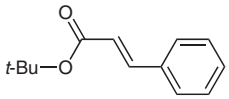
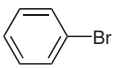
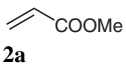
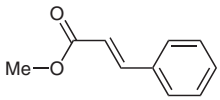
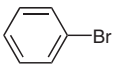
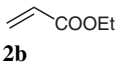
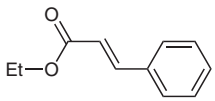
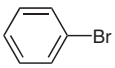
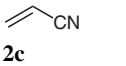
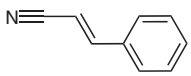
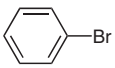
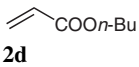
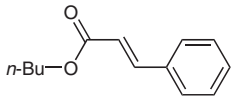
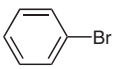
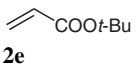
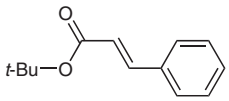
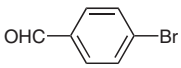
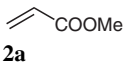
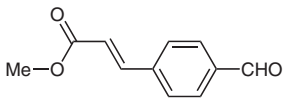
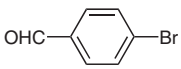
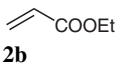
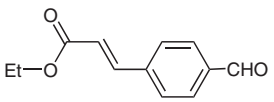
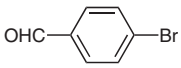
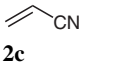
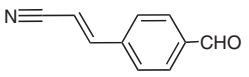
Entry	R^1–X	R^2, R^3	Power (W)	Temp (°C)	Time (min)	Product	Yield (%)[b]
1	 **1a**	 **2a**	200	80	10	 **3a**	94
2	 **1a**	 **2b**	200	110	20	 **3b**	90
3	 **1a**	 **2c**	200	110	25	 **3c**	92
4	 **1a**	 **2d**	200	120	20	 **3d**	91
5	 **1a**	 **2e**	300	125	25	 **3e**	89
6	 **1b**	 **2a**	300	135	35	 **3a**	87
7	 **1b**	 **2b**	300	140	50	 **3b**	83
8	 **1b**	 **2c**	300	135	30	 **3c**	85
9	 **1b**	 **2d**	300	135	35	 **3d**	86
10	 **1b**	 **2e**	300	140	40	 **3e**	85
11	 **1c**	 **2a**	300	130	20	 **3f**	88
12	 **1c**	 **2b**	300	130	35	 **3g**	87
13	 **1c**	 **2c**	300	130	30	 **3h**	85

Table 2 Pd(L-Proline)$_2$-Catalyzed Heck Reaction of Aryl and Benzyl Halides with Alkenes[a] **2a–i** (continued)

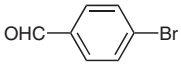
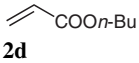
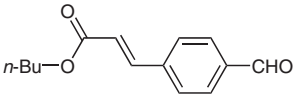
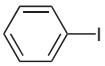
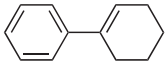
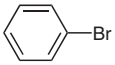
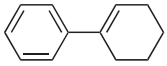
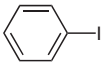
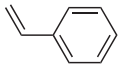
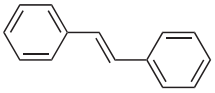
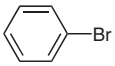
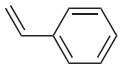
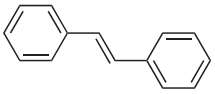
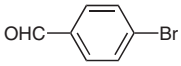
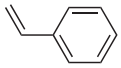
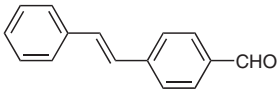
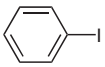
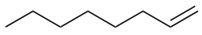
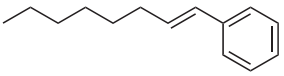
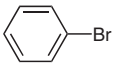
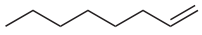
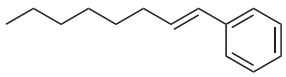
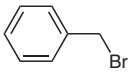
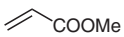
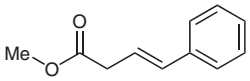
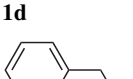
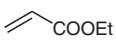
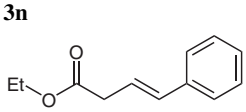
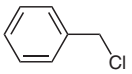
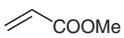
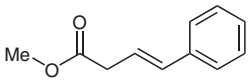
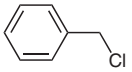
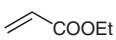
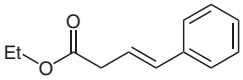
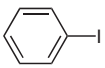
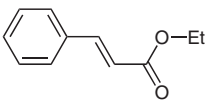
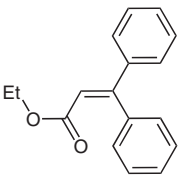
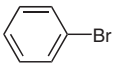
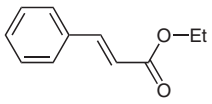
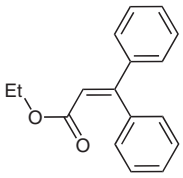
Entry	R^1–X	R^2 / R^3	Power (W)	Temp (°C)	Time (min)	Product	Yield (%)[b]
14	 **1c**	 **2d**	300	125	20	 **3i**	86
15	 **1a**	 **2f**	300	135	25	 **3j**	79[c]
16	 **1b**	 **2f**	300	135	25	 **3j**	77[c]
17	 **1a**	 **2g**	300	135	20	 **3k**	90
18	 **1b**	 **2g**	300	135	25	 **3k**	85[c]
19	 **1c**	 **2g**	300	135	25	 **3l**	87
20	 **1a**	 **2h**	300	140	15	 **3m**	86
21	 **1b**	 **2h**	300	140	25	 **3m**	83
22	 **1d**	 **2a**	300	135	20	 **3n**	80[c]
23	 **1d**	 **2b**	300	135	20	 **3o**	84[c]
24	 **1e**	 **2a**	300	135	30	 **3n**	78[c]
25	 **1e**	 **2b**	300	135	30	 **3o**	81[c]
26	 **1a**	 **2i**	200	130	20	 **3p**	86

Table 2 Pd(L-Proline)$_2$-Catalyzed Heck Reaction of Aryl and Benzyl Halides with Alkenes[a] **2a–i** (continued)

Entry	R^1–X		Power (W)	Temp (°C)	Time (min)	Product	Yield (%)[b]
27	 **1b**	 **2i**	200	130	25	 **3p**	84

[a] Aryl/benzyl halide **1** (1 mmol), alkene **2** (2 mmol), Pd(L-proline)$_2$ (0.01 mmol), TBAB (1 mmol), NaOAc (0.1 mmol).
[b] Isolated yield after column chromatography based on aryl/benzyl halide **1**.
[c] Reaction conducted with 0.3 mmol of base.
[d] Yield corresponds to *E*-isomers only.

In conclusion, we have demonstrated a novel application of the Pd(L-proline)$_2$ complex as an air-stable and water-soluble catalyst for efficient phosphine-free Heck reactions under controlled microwave irradiation in water. This simple method offers advantages in terms of product yield, versatility, low catalyst concentration and minimization of environmental pollution.

All chemicals were obtained from Aldrich, USA, and E. Merck, Germany and were purified prior to use. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in ppm relative to TMS as the internal standard. Microwave irradiation was carried out using a CEM Discover Bench Mate single-mode microwave synthesis system in a safe pressure regulation 10 mL pressurized vial with a 'snap-on' cap. Thin-layer chromatography (TLC) was performed using silica gel 60 [Kieselguhr F_{254} precoated on aluminium sheets (thickness 0.2 mm)], commercially available from Merck. The visualization of spots on TLC plates was effected by UV illumination or exposure to iodine. Column chromatography was performed using commercial (Merck) column chromatography grade silica gel (60–120 mesh) using mixtures of EtOAc and hexane as eluting agent.

Pd(L-Proline)$_2$

Et_3N (0.6 mL, 600 μL) was added to a vigorously stirred soln of L-proline (4.34 mmol, 499 mg) in MeOH (10 mL). After 30 min, $Pd(OAc)_2$ (2.17 mmol, 487 mg) was added and the mixture was stirred under an N_2 atm for 5 h at r.t. After the reaction was complete, the precipitated complex was filtered, washed with MeOH (2 × 2 mL) and dried to afford Pd(L-proline)$_2$ in quantitative yield.

IR (KBr): 3447, 3075, 2934, 2862, 2510, 1624, 1442, 1351, 1311, 1213, 1082, 929, 863, 777, 649, 545 cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 1.61 (br s, 2 H), 1.75–2.01 (br m, 4 H), 2.09–2.12 (br m, 2 H), 3.03 (br s, 4 H), 3.70–3.88 (br m, 2 H).

^{13}C NMR (75 MHz, D_2O): δ = 25.6, 25.8, 30.4, 30.8, 52.1, 53.7, 64.5, 65.9, 187.5, 189.1.

Microwave-Assisted Heck Reaction; General Procedure

A mixture of aryl/benzyl halide **1** (1 mmol), alkene **2** (2 mmol), Pd(L-proline)$_2$ complex (0.01 mmol, 3 mg, 1 mol%), TBAB (1 mmol, 322 mg, 100 mol%) and NaOAc (0.1 mmol, 8 mg, 10 mol%) was placed in a safe pressure regulation 10 mL pressurized vial containing H_2O (1 mL). The vial was sealed with a 'snap-on' cap and irradiated in a single-mode CEM microwave reactor at 200–300 W and 80–140 °C for 10–50 min. After the reaction was complete (TLC monitoring), the mixture was allowed to cool to r.t. and then extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, filtered and the solvent removed under vacuum. The residue was purified by column chromatography to afford the pure product.

Butyl (2*E*)-3-Phenylprop-2-enoate (3d)[28]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3 H), 1.40–1.50 (m, 2 H), 1.67–1.74 (m, 2 H), 4.21 (t, *J* = 6.6 Hz, 2 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 7.37–7.40 (m, 3 H), 7.51–7.54 (m, 2 H), 7.68 (d, *J* = 16.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 19.2, 30.8, 64.4, 118.3, 128.0, 128.8, 130.2, 134.5, 144.5, 167.0.

Cyclohex-1-enylbenzene (3j)[29]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.71 (m, 2 H), 1.76–1.82 (m, 2 H), 2.22–2.23 (m, 2 H), 2.44–2.47 (m, 2 H), 6.14 (br s, 1 H), 7.21–7.42 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 23.0, 26.0, 27.3, 124.7, 124.8, 126.6, 128.2, 136.6, 142.7.

4-[(*E*)-2-Phenylethenyl]benzaldehyde (3l)[30]

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.26–7.50 (m, 5 H), 7.65 (d, *J* = 7.3 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 7.91 (d, *J* = 8.3 Hz, 2 H), 10.01 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 126.9, 127.2, 128.7, 130.0, 131.9, 135.0, 136.5, 142.9, 192.3.

(1*E*)-Oct-1-enylbenzene (3m)[31]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.0 Hz, 3 H), 1.20–1.37 (m, 8 H), 2.15–2.24 (m, 2 H), 6.23 (dt, *J* = 16.0, 6.6 Hz, 1 H), 6.40 (d, *J* = 16.0 Hz, 1 H), 7.21–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.7, 28.8, 29.4, 31.8, 33.0, 125.9, 126.8, 128.0, 128.5, 128.9, 129.7, 131.2.

Methyl (3*E*)-4-Phenylbut-3-enoate (3n)[32]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.24 (dd, *J* = 7.0, 1.4 Hz, 2 H), 3.71 (s, 3 H), 6.30 (dt, *J* = 16.0, 7.2 Hz, 1 H), 6.48 (dt, *J* = 16.0, 1.3 Hz, 1 H), 7.02–7.46 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.1, 51.7, 121.5, 126.3, 127.4, 128.5, 133.5, 136.6, 172.0.

Acknowledgment

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