

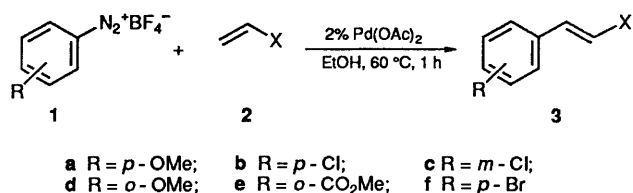
# Heck Reaction of Arenediazonium Salts: a Palladium-catalysed Reaction in an Aqueous Medium

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Heck reaction of arenediazonium salts has been conveniently carried out with 1–2 mol% Pd(OAc)<sub>2</sub> in ethanol. An aqueous one-pot procedure starting with anilines is described.

Palladium-catalysed reactions are a powerful synthetic tool,<sup>1</sup> their applications being widespread, especially where Heck reaction (arylation of olefins)<sup>2</sup> and cross-coupling techniques<sup>3</sup> are now routinely used for convergent assembly of complex molecules.<sup>4</sup> Since, however, for all practical purposes, aromatic components in such reactions remain limited to the aryl halides and triflates, we have attempted to broaden the scope of these reactions, by seeking alternatives to the latter. For the Heck reaction which is our focus here, we have examined acid chlorides (through loss of CO),<sup>5</sup> sulfonyl chlorides (through loss of SO<sub>2</sub>)<sup>6</sup> and the aryl perfluoroalkylsulfonates as possible alternatives.<sup>7</sup> All, however, showed limited reactivity, harsh reaction conditions and side reactions considerably diminishing their general synthetic appeal. While pursuing a general programme on Pd-catalysed reactions of diazonium salts, we reasoned that arenediazonium salts armed with an excellent nucleofuge (N<sub>2</sub>)<sup>8</sup> would be a superior alternative to those mentioned earlier since they would facilitate the rate-determining<sup>9</sup> oxidative addition of PdL<sub>n</sub> and hence allow for Heck reactions under very mild conditions. Moreover, since diazotization is usually carried out in water, Pd-catalysed reactions in aqueous media<sup>10</sup> seemed a possibility. Our preliminary results towards these ends are reported herein.

Previous studies on the Heck reaction of arenediazonium salts show that the reaction is limited to the sole use of [Pd(dba)<sub>2</sub>] as catalyst.<sup>11</sup> We have found an operationally simpler process in which arenediazonium tetrafluoroborates **1a–f**<sup>12</sup> react better with 1–2 mol% of Pd(OAc)<sub>2</sub> in ethanol or methanol as solvent (Scheme 1); other solvents, MeCN or



Scheme 1

DMF, were ineffective. Control experiments show that although Pd(OAc)<sub>2</sub> appears essential it may be replaced by Li<sub>2</sub>PdCl<sub>4</sub>, whereas added Et<sub>3</sub>N, commonly employed in Heck reactions is not required and, in fact, is detrimental to the process; notably, addition of PPh<sub>3</sub> lowered the yields considerably. Table 1 shows the synthetic efficacy of this Heck reaction with yields which are uniformly good to excellent.† The reaction, equally good for *ortho*-, *meta*- and *para*-substituted diazonium salts, failed with nitro-substituted diazonium compounds probably because of their relatively high redox potentials (> 0.6 V)<sup>13</sup> and a preference for homolytic dediazotization. Since activated olefins as well as cyclopentene (entry 9, Table 1) can be used as

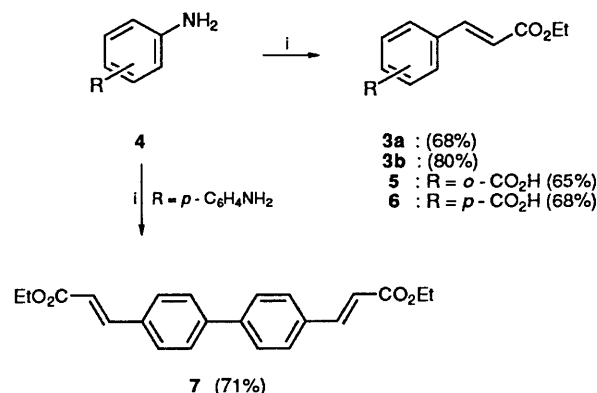
Table 1 Heck reaction of arenediazonium salts **1** (Scheme 1)

Entry	Diazonium salt <b>1</b>	Olefin <sup>a</sup> <b>2</b>	Product <b>3</b>	Yield (%)
1	<b>1a</b>	EA	<b>3a</b> (X = CO <sub>2</sub> Et)	71
2	<b>1b</b>	EA	<b>3b</b> (X = CO <sub>2</sub> Et)	75
3	<b>1c</b>	EA	<b>3c</b> (X = CO <sub>2</sub> Et)	70
4	<b>1d</b>	EA	<b>3d</b> (X = CO <sub>2</sub> Et)	90
5	<b>1e</b>	EA	<b>3e</b> (X = CO <sub>2</sub> Et)	72
6	<b>1f</b>	EA	<b>3f</b> (X = CO <sub>2</sub> Et)	80 <sup>b</sup>
7	<b>1e</b>	AN	<b>3e</b> (X = CN)	80
8	<b>1a</b>	MA	<b>3a</b> (X = CO <sub>2</sub> Me)	57 <sup>c</sup>
9	<b>1b</b>	CP	( <i>p</i> -Chlorophenyl)-cyclopentene <sup>e</sup>	75 <sup>d</sup>

<sup>a</sup> EA = ethyl acrylate, AN = acrylonitrile, MA = methyl acrylate, CP = cyclopentene. <sup>b</sup> At 25 °C for 7 h. <sup>c</sup> 2% Li<sub>2</sub>PdCl<sub>4</sub> used. <sup>d</sup> At 25 °C for 1 h. <sup>e</sup> 1:1.5 Mixture of 1- and 3-isomers.

the olefinic partner, the present reaction is clearly differentiated from the classical Meerwin arylation.<sup>14</sup> Most notably, the reaction displays a high degree of chemoselectivity as evident from the superior reactivity of the diazonium nucleofuge over the chloride (entries 2, 3 and 9) and even the bromide (entry 6), the latter feature promising much broader synthetic scopes in terms of differential coupling.

The above success with alcohols as solvents led us to consider water as a solvent for this reaction. In this, a two-step (diazotization and Heck reaction) 'one-pot' reaction starting directly with anilines seemed possible with, as a bonus, avoidance of the prior isolation of the sensitive ArN<sub>2</sub><sup>+</sup>BF<sub>4</sub><sup>-</sup> salts. Although a one-pot Heck reaction from anilines by way of *in situ* diazotization with Bu'ONO in MeCN is known,<sup>15</sup> our aqueous version involving an air-stable Pd<sup>II</sup> catalyst has many operational advantages. Thus, diazotization<sup>12</sup> of anilines **4** (NaNO<sub>2</sub>/42% HBF<sub>4</sub> at 0 °C) followed by addition of ethyl acrylate–2% Pd(OAc)<sub>2</sub> and warming on a water-bath for 1 h indeed gave the desired cinnamate esters **3a, b, 5** and **6**



Scheme 2 Reagents and conditions: i, NaNO<sub>2</sub>, 42% HBF<sub>4</sub>, 0 °C, 1 h, then CH<sub>2</sub>=CHCO<sub>2</sub>Et, 2% Pd(OAc)<sub>2</sub>, 50–60 °C, 1 h

† All products displayed spectral properties (IR, NMR) consistent with the assigned structures.

(Scheme 2) in yields comparable to those involving isolated diazonium tetrafluoroborates (*cf.* Table 1). Successful Heck reaction of anthranilic acid (to give **5**) by way of this one-pot process is important since not only is the corresponding diazonium salt unstable but the Heck reaction of *o*-bromobenzoic acid usually gives low product yields. Benzidine **4** ( $R = p\text{-C}_6\text{H}_4\text{NH}_2$ ) underwent bis-coupling with 2 equiv. of ethyl acrylate by way of this aqueous one-pot process to produce the symmetrical *p*-biphenylene derivative **7** in good yield. However, it was noted that this aqueous Heck process fails if diazotization is conducted in dil. HCl instead of aqueous  $\text{HBF}_4$ .

In summary, anilines as their diazonium tetrafluoroborates, either isolated or *in situ*, can be induced to take part in a high-yielding Heck reaction. In terms of reactivity, the arenediazonium salts are much superior to the conventionally used aryl bromides as shown by intramolecular competition experiment (entry 6, Table 1). Comparison of the one-pot Heck reaction on anthranilic acid with *o*-bromobenzoic acid also corroborates this notion.

### Experimental

**Typical One-pot Heck Reaction with Anilines.**—A solution of  $\text{NaNO}_2$  (0.57 g, 8.26 mmol) in water (3  $\text{cm}^3$ ) was added dropwise to an ice-cold mixture of *p*-anisidine (1.0 g, 8.13 mmol) in 42%  $\text{HBF}_4$  (3.3  $\text{cm}^3$ , 20.62 mmol). Stirring was continued for 1 h at 0 °C after which methanol (0.5  $\text{cm}^3$ ), ethyl acrylate (1.11 g, 1.5  $\text{cm}^3$ , 11.13 mmol) and  $\text{Pd}(\text{OAc})_2$  (35 mg, 0.15 mmol) were added to the mixture which was then heated on a water-bath for 1 h. The mixture was then extracted with diethyl ether, and the extract washed with saturated aqueous  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated. Chromatography of the residue over silica gel (10% EtOAc in light petroleum) gave **3a** as a colourless oil (1.13 g, 68%);  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  1700, 1630, 1600 and 1500;  $\delta(\text{CDCl}_3)$  1.33 (3 H, t, *J* 7), 3.84 (3 H, s), 4.26 (2 H, q, *J* 7), 6.25 (1 H, d, *J* 16), 6.90 (2 H, d, *J* 8), 7.50 (2 H, d, *J* 8) and 7.65 (1 H, d, *J* 16).

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