Green C-C Coupling Reactions

Toward Waste-Free Production of Heck Products with a Catalytic Palladium System under Oxygen**

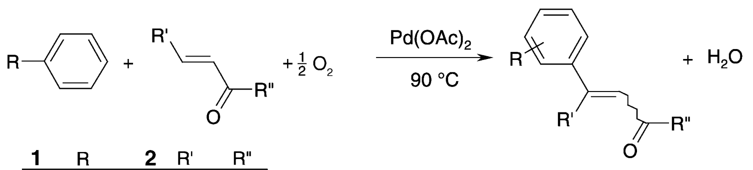
*Mieke Dams, Dirk E. De Vos, Sofie Celen, and Pierre A. Jacobs**

The sp^2–sp^2 coupling of an aromatic ring with an alkene is one of the key transformations catalyzed by Pd. This reaction was pioneered by Heck and Mizoroki and has undergone a lot of progress since that time, but it still suffers from one major drawback, namely the production of salt waste.[1] Indeed, the use of halogenated aromatic compounds requires the use of stoichiometric amounts of base for Pd^0 regeneration, which leads to the formation of large quantities of halide salt by-products, especially in large-scale processes. To circumvent these problems, aromatic carboxylic acid anhydrides and esters have been used by de Vries and co-workers[2] and Gooßen et al.,[3] respectively, as sources of the aryl component in the $PdCl_2$-catalyzed sp^2–sp^2 coupling. When benzoic anhydride is used as the arylating reagent, the benzoic acid produced as a side product can be recycled to the anhydride by dehydration;[2] when an activated *p*-nitrophenyl ester is used, the nitrophenol produced can be esterified to give the starting ester by reaction with the appropriate carboxylic acid.[3] Although CO and H_2O are the only by-products, these reactions still have the disadvantages that they require high temperatures (160 °C), two separate steps, and a minimum concentration of alkali-metal halides for moderate catalyst activity (maximum TON (total turnover number = moles of coupling product per mole of Pd) of 400–150).

Herein we propose a 100% carbon-efficient and halide-free alternative for the synthesis of Heck-coupling products, which involves the direct Pd-catalyzed coupling of arenes with olefins (Scheme 1). Pd^0 intermediates can be reoxidized to active Pd^{II} species under an appropriate pressure of O_2. As no reactive substituents are required on the arene, water is the only by-product. The reactions can be performed under mild conditions, for example at 90 °C and under O_2 (0.8 MPa), have a high turnover frequency, and do not require a solvent or a halide promoter.

Only a few methods exist for the transition-metal-catalyzed reaction of an arene with an olefin through direct C–H bond activation.[4] These include the chelation-assisted alkylation of aromatic ketones mediated by Ru or Rh,[5–6] the hydroarylation of alkenes or alkynes with Ir or Pd,[7–8] and the arylation of an olefin with Rh,[9] Ru,[10] or Pd.[8c,11] This last type of catalytic coupling reaction requires an oxidant.[10,11] As dioxygen is the cheapest available oxidant, we attempted in an initial experiment to couple toluene (**1b**) with ethyl *trans*-cinnamate (**2b**) in the presence of $Pd(OAc)_2$ (1 mol%) and $Mn(OAc)_3$ (4 mol%) under O_2 at 90 °C in neat toluene. Surprisingly, the arylation product **3e** was obtained in 91% yield, together with the diarylated product ethyl 3-phenyl-2,3-ditolyl-propenoate (1.7%).[12] By contrast, when the reaction was carried out under the classical conditions for such Pd-catalyzed coupling reactions, namely in a mixture of acetic acid and acetic anhydride, **3e** was obtained in only 2.5% yield, along with an equimolar amount of the by-product benzyl acetate, formed by the acetoxylation of toluene.[13,14] Thus, in acetic acid only low reactivity and a selectivity of 50% were observed, whereas under solvent-free conditions the reaction proceeded to high conversion with high selectivity.

This first experiment showed convincingly that O_2 can be used for Pd^0 reoxidation instead of, for example, *t*BuOOH, which has been recognized until now as the most effective oxidant for a Fujiwara coupling reaction.[15] Just as observed for oxidative phenol carbonylation[16] or the Wacker olefin oxidation,[17] the electron transfer from Pd^0 to O_2 may be accelerated by cocatalysts. Over 15 transition-metal salts were screened in the reaction of anisole (**1c**) with ethyl *trans*-cinnamate (**2b**). Acetate complexes appear to be more effective than acetylacetonate complexes. Nearly full conversion of the cinnamate occurred in the presence of Co^{II}, Fe^{II}, Mn^{II}, and Mn^{III} acetates, of which the Mn^{II} and Mn^{III} acetates gave the best results (see Table 1, entries 1–3). Remarkably, the reaction reached completion even in the absence of a cocatalyst (Table 1, entry 4), and the same was



1	R
a	H
b	Me
c	OMe

2	R'	R''
a	H	OBu
b	Ph	OEt
c	Ph	Me

3	R	R'	R''
a	H	H	OBu
b	H	Ph	OEt
c	H	Ph	Me
d	Me	H	OBu
e	Me	Ph	OEt
f	Me	Ph	Me
g	OMe	H	OBu
h	OMe	Ph	OEt
i	OMe	Ph	Me

Scheme 1. Pd-catalyzed oxidative coupling of an arene with an olefin under O_2.

---

[*] Prof. P. A. Jacobs, M. Dams, Prof. D. E. De Vos, S. Celen
Centre for Surface Chemistry and Catalysis, K. U. Leuven
Kasteelpark Arenberg 23, 3001 Leuven (Belgium)
Fax: (+32) 16-321-998
E-mail: pierre.jacobs@agr.kuleuven.ac.be

[**] This work was supported by the Belgian Federal Government within the framework of an IAP program for supramolecular catalysis. M.D. is a research assistant of FWO (Belgium).

DOI: 10.1002/ange.200351524

Table 1: Optimization of the coupling of anisole (**1c**) with ethyl *trans*-cinnamate (**2b**).[a]

Entry	Additive (mmol)	t_1 [h]	Conv. [%][b]	t_2 [h]	Conv. [%][c]	TON	Max. TOF [h^{-1}]
1	$Mn(acac)_2$ (0.06)			22	0.9	0.9	0.2
2	$Co(OAc)_2 \cdot 4H_2O$ (0.06)	[d]		22	83	87	3.7
3	$Mn(OAc)_3 \cdot 2H_2O$ (0.06)	[e]		22	99	100	7.6
4	-	[d]		22	94	96	4.3
5	$Mn(OAc)_3 \cdot 2H_2O$ (0.12)	5	17	25	97	99	4.4
6[f]	$Mn(OAc)_3 \cdot 2H_2O$ (0.12)	4	11	26	92	93	3.5
7[g]	$Mn(OAc)_3 \cdot 2H_2O$ (0.12)	3.5	6	20	71	73	3.6
8	PhCOOH (0.6)	6.2	83	25	98	97	13.4
9	4-*i*Pr-C_6H_4COOH (0.6)	8.5	27	25	49	50	3.3
10	3-Cl-C_6H_4COOH (0.6)	6	40	24	50	51	8.9
11[h]	PhCOOH (0.18)	6.6	27	23	96	174	7.5
12[i]	PhCOOH (0.18)	8	66	24	90	**762**	**73**

[a] Reaction conditions, unless otherwise indicated: **1c** (4 mL, 37 mmol), **2b** (3 mmol), 90 °C, O_2 (0.8 MPa), and $Pd(OAc)_2$ (1 mol% with respect to **2b**). [b] Conversion of **2b** after t_1. [c] Conversion of **2b** after t_2. [d] Induction period: 2.5 h. [e] Induction period: <1 h. [f] O_2: 0.4 MPa. [g] O_2: 1.6 MPa. [h] $Pd(OAc)_2$: 0.55 mol%. [i] $Pd(OAc)_2$: 0.12 mol%, 110 °C.

observed for arylations of butyl acrylate and ethyl cinnamate with benzene or toluene. In the absence of a cocatalyst there is an induction period, but not when hydrated $Mn(OAc)_3$ is present (Figure 1). This induction period can also be eliminated by the addition of water (0.6 mmol; Figure 1). All these elements indicate that the metal salts do not necessarily intervene in a rate-determining Pd^0 reoxidation; rather, both water and the hydrated acetate salts appear to facilitate the formation of a suitable catalytically active Pd^{II} species in the initial phase of the reaction.

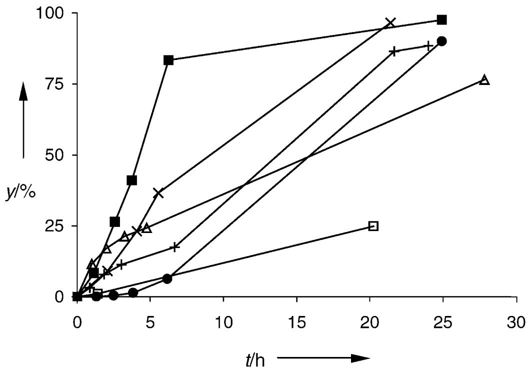


Figure 1. The conversion y of **2b** as a function of time: a) no additive (●); b) $Mn(OAc)_3 \cdot 2H_2O$ (2 mol%; ×); c) water (0.6 mmol; +); d) benzoic acid (0.6 mmol; ■), e) trifluoroacetic acid (0.6 mmol; △); f) hexanoic acid (0.6 mmol; □). Other reaction conditions: **1c** (4 mL, 37 mmol), **2b** (3 mmol), $Pd(OAc)_2$ (1 mol% with respect to **2b**), O_2 (0.8 MPa), 90 °C.

Earlier work on aromatic C–H activation suggests that Pd can break the C–H bond by electrophilic aromatic substitution to form an arene–Pd^{II} complex. As high reactivity has been ascribed to highly electrophilic Pd^{II} species such as $Pd(OOCCF_3)^+$,[8c] over 20 different acids were tested as additives in the $Pd(OAc)_2$-catalyzed coupling of ethyl *trans*-cinnamate (**2b**) with neat anisole (**1c**). The effect of the acids largely depends on their structure, substitution pattern, and solubility. Excellent results were obtained with benzoic acid (Table 1, entry 8), and to a lesser extent with *p*- and *o*-toluic acid. These acids eliminate the induction period and the conversion of the cinnamate proceeds about four times faster than in the absence of an additive (Figure 1). ^1H NMR spectroscopic experiments in [D_6]benzene indicated that under these conditions the acetate ligands are displaced and a Pd–benzoate species is formed.[18] Neither electron-donating nor electron-withdrawing groups on the benzoic acid improve the catalyst efficiency (Table 1, entries 9 and 10). With some aliphatic acids, such as acetic, trifluoroacetic, and hexanoic acids, the reaction does not reach completion, in contrast with the acid-free reaction (Figure 1). The unique accelerating effect of benzoic acid on the Pd catalysis appears to be generally true for these coupling reactions, for example, for those of anisole (**1c**) and toluene (**1b**) with butyl acrylate (**2a**), ethyl *trans*-cinnamate (**2b**), and *trans*-4-phenyl-3-buten-2-one (**2c**) (Table 2). In all these reactions, high rates were observed without an induction period.

Several reaction parameters, such as O_2 pressure, reaction volume, and concentration of benzoic acid were optimized for the Pd-catalyzed coupling of anisole with ethyl *trans*-cinnamate. For 4 mL of anisole, 0.8 MPa of O_2 appears to be optimal. When the pressure is too high, lower catalytic activity is observed (Table 1, entries 5–7). A sixfold excess of PhCOOH with respect to Pd^{2+} is sufficient to promote high reaction rates. Under these conditions, the Pd concentration could be reduced to 0.12 mol% at 110 °C (Table 1, entries 11 and 12) with complete conversion to ethyl 3-anisyl-3-phenylpropenoate (**3h**) maintained, which corresponds to a total turnover number (TON) of 762. The maximum turnover frequency (TOF = moles of coupling product per mole of $Pd(OAc)_2$ per hour) was 73 h^{-1}. To our knowledge, these are the highest TON and TOF values described for such oxidative coupling reactions.[19]

Although the Pd/PhCOOH catalyst gives rise to selectivities of over 95% in these coupling reactions, several regioisomers are formed under the solvent-free conditions with anisole and toluene (Table 2).[20] The Pd catalyst attacks all aromatic C–H bonds, with attack at the *para* position of anisole favored over the *ortho* and, to a greater extent, *meta* positions. On the other hand, when toluene is used as the arylating agent, more of the *meta* isomer is formed than the *ortho* isomer. Such data suggest that the first step in the catalytic cycle may not correspond to a classical electrophilic aromatic substitution, as such reactions heavily favor *ortho* and *para* substitution.[21]

As the reaction mixture contains a 12–15-fold excess of the arene, the olefin can be arylated once, twice, or possibly even three times. The selectivity for these multiply arylated

Table 2: Influence of the cocatalyst $Mn(OAc)_3 \cdot 2H_2O$ and the additive benzoic acid on the induction period and the catalyst activity in the oxidative coupling of arenes and olefins.[a]

Entry	**1**	**2**	Additive	t_1 [h]	Conv. [%][b]	t_2 [h]	Conv. [%][c]	Sel. [%][d]	*o*/*m*/*p*[e]
1	**c**	**b**	–	6	10	22.5	94	100:0	38:14:48
2	**c**	**b**	$Mn(OAc)_3$ (2 mol%)	3.5	18	21.5	99	86:14	37:16:47
3	**c**	**b**	PhCOOH (0.6 mmol)	6.2	83	25	98	100:0	32:15:53
4	**c**	**a**	–	6.5	12	25.2	75	100:0:0	45:55[f]
5	**c**	**a**	$Mn(OAc)_3$ (2 mol%)	5.5	26	22.7	93	25:75:0	44:56[f]
6	**c**	**a**	PhCOOH (0.6 mmol)	8.2	74	30	96	91:9:0	43:57[f]
7	**c**	**c**	–	8	6	96	14	100:0	34:13:53
8	**c**	**c**	$Mn(OAc)_3$ (2 mol%)	25	31	168	87	100:0	35:12:53
9	**c**	**c**	PhCOOH (0.6 mmol)	8.2	25	120	99	100:0	33:17:50
10	**b**	**b**	PhCOOH (0.6 mmol)	4.5	12	21.5	89	85:15	30:40:30
11	**b**	**a**	PhCOOH (0.6 mmol)	7.5	76	24.5	96	15:85:0[g]	24:36:40
12	**b**	**c**	PhCOOH (0.6 mmol)	7.5	14	118	97	n.d.[h]	n.d.[h]
13	**a**	**b**	$Mn(OAc)_3$ (4 mol%)	90	97			95:5	–
14	**a**	**a**	–	24	56			99:1:0	–
15	**a**	**a**	–	47	**98**			**89**:11:0	–
16	**a**	**a**	–	76	**97**			37:**63**:0	–
17	**a**	**a**	–	165	**98**			7:18:**75**	–
18	**a**	**c**	$Mn(OAc)_3$ (4 mol%)	77	99			100:0	–

[a] Reaction conditions: arene (4 mL, 37–45 mmol), olefin (3 mmol), $Pd(OAc)_2$ (1 mol%), O_2 (0.8 Mpa), 90°C. All organic products were isolated and characterized by GC–MS, as well as ^1H and ^{13}C NMR spectroscopy. [b] Conversion of the olefin after t_1. [c] Conversion of the olefin after t_2. [d] Selectivity for the 1:1 arene–olefin, 2:1 arene–olefin, and possibly 3:1 arene–olefin adducts after t_2. [e] Selectivity for the *ortho*, *meta*, and *para* adduct after t_2. [f] The *ortho* and *meta* isomers could not be separated by GC. [g] After 7.5 h the selectivity for the monoarylated product was 90%. [h] Not determined.

olefins can be tuned. By stopping the reaction at appropriate times, one may obtain a high yield of the mono-, di-, or even triarylated product. The clean consecutive coupling process is illustrated in Table 2 (entries 14–17) for the reaction of benzene with butyl acrylate. Similar double or triple couplings are feasible with, for example, anisole and toluene.

In the catalytic Pd/O_2 system described above, the reactivity of the aromatic compounds decreases in the following order: anisole > toluene > benzene > acetophenone and chlorobenzene. Thus, the activation of an aromatic C–H bond by Pd is facilitated by electron-donating groups. The trends are less clear for the olefinic component. Unsaturated esters such as acrylates and cinnamates react smoothly. Steric hindrance may explain the sometimes lower reactivity of ethyl *trans*-cinnamate in comparison with butyl acrylate. The unsaturated ketone *trans*-4-phenyl-3-buten-2-one also undergoes complete conversion, but only when a metal cocatalyst or benzoic acid is used (Table 2, entries 7–9, 12, and 18). Furthermore, simple olefins such as styrene and 1-octene can also be oxidatively coupled to arenes. In these reactions styrene is more reactive than 1-octene.

To gain deeper mechanistic insight, oxidative couplings of ethyl *trans*-cinnamate were performed with toluene and $[D_8]$toluene under the conditions described in Table 2, and the kinetic isotope effect (KIE) was determined. The rates considered are derived from the maximal slopes on the conversion curve, that is, after the induction time. With only 1 mol% of $Pd(OAc)_2$, the v_H/v_D ratio was 2.6. When benzoic acid was added, the v_H/v_D ratio decreased to 2.1. This indicates that C–H activation by Pd^{II} is a slow step in the catalytic cycle rather than Pd^0 regeneration, at least in the oxidative coupling of toluene with ethyl *trans*-cinnamate under oxygen. The accelerating effect of benzoic acid, together with the relative reactivity of several arenes as described earlier, suggest the reaction may occur through an electrophilic attack on the aromatic compound, which was also the first step in the mechanism originally proposed by Fujiwara.[11f] The rather high fraction of *meta* products formed in some cases indicates that the Pd species might not be of a purely electrophilic nature. Besides the catalytically active Pd^{II} species, the catalytic cycle probably also involves a Pd^0 intermediate. Indeed, under standard conditions (see Table 2), in the presence of PhCOOH (0.18 mmol), bromobenzene does not only undergo oxidative coupling with ethyl cinnamate, but a stoichiometric amount (with respect to the catalyst: 0.03 mmol) of the Heck product is also formed, probably through oxidative addition of the C–Br bond to Pd^0.

In conclusion, we have presented a 100% carbon-efficient, halide- and solvent-free system for the oxidative arylation of olefins, with water as the only by-product. No organic oxidants or electron-transfer mediators are required, the Pd/benzoic acid catalyst appears to be infinitely stable, and both the TON and the TOF are far higher than those observed previously in similar reactions. This work therefore presents a significant step toward waste-free Heck reactions.

Received: March 31, 2003 [Z51524]

Keywords: C–C coupling · green chemistry · homogeneous catalysis · oxygen · palladium

---

[1] a) R. F. Heck, *Acc. Chem. Res.* **1979**, *12*, 146; b) A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379; c) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2; d) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; e) A. Biffis, M. Zecca, M. Basato, *J. Mol. Catal. A* **2001**, *173*, 249.

[2] M. S. Stephan, A. J. J. M. Teunissen, G. K. M. Verzijl, J. G. de Vries, *Angew. Chem.* **1998**, *110*, 688; *Angew. Chem. Int. Ed.* **1998**, *37*, 662.

[3] L. J. Gooßen, J. Paetzold, *Angew. Chem.* **2002**, *114*, 1285; *Angew. Chem. Int. Ed.* **2002**, *41*, 1237.

[4] V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731.

[5] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.

[6] Y. G. Lim, J. S. Han, S. S. Yang, J. H. Chun, *Tetrahedron Lett.* **2001**, *42*, 4853.

[7] T. Matsumoto, D. J. Taube, R. A. Periana, H. Taube, H. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 7414.

[8] a) C. Jia, W. Lu, J. Oyamada, T. Kitamura, K. Matsuda, M. Irie, Y. Fujiwara, *J. Am. Chem. Soc.* **2000**, *122*, 7252; b) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura, Y. Fujiwara, *Science* **2000**, *287*, 1992; c) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633.

[9] K. Sasaki, T. Sakakura, Y. Tokunaga, K. Wada, M. Tanaka, *Chem. Lett.* **1988**, 685.

[10] H. Weissman, X. Song, D. Milstein, *J. Am. Chem. Soc.* **2001**, *123*, 337.

[11] a) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166; b) R. Asano, I. Moritani, Y. Fujiwara, S. Teranishi, *J. Chem. Soc. Chem. Commun.* **1970**, 1293; c) R. S. Shue, *J. Chem. Soc. Chem. Commun.* **1971**, 1510; d) R. S. Shue, *J. Catal.* **1972**, *26*, 112; e) J. Tsuji, H. Nagashima, *Tetrahedron* **1984**, *40*, 2699; f) C. Jia, W. Lu, T. Kitamura, Y. Fujiwara, *Org. Lett.* **1999**, *1*, 2097; g) T. Yokota, M. Tani, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2003**, *125*, 1476.

[12] Reaction conditions: toluene/ethyl *trans*-cinnamate = 12.5:1, neat, 90 h; ratio of isomers of **3e**: *o*/*m*/*p* = 29:41:30.

[13] Reaction conditions: toluene/ethyl *trans*-cinnamate = 5:1, HOAc (3 mL), Ac$_2$O (1 mL), 70 h; ratio of isomers of **3e**: *o*/*m*/*p* = 25:36:39.

[14] E. Benazzi, C. J. Cameron, H. Mimoun, *J. Mol. Catal.* **1991**, *69*, 299.

[15] For the oxidative coupling of ethyl cinnamate (30 mmol) with benzene (150 mmol), catalyzed by Pd(OAc)$_2$ (0.06 mmol) and benzoquinone (0.9 mmol) in the presence of *t*BuOOH (60 mmol), in HOAc/Ac$_2$O (30 mL/7 mL) at 90 °C, Fujiwara obtained ethyl 3-phenylcinnamate in 56 % yield in 15 h with a TON value of 280.[11f]

[16] A. Vavasori, L. Toniolo, *J. Mol. Catal. A* **1999**, *139*, 109; b) A. Vavasori, L. Toniolo, *J. Mol. Catal. A* **1999**, *149*, 321; c) A. Vavasori, L. Toniolo, *J. Mol. Catal. A* **2000**, *151*, 37.

[17] J. W. Francis, P. M. Henry, *J. Mol. Catal. A* **1995**, *99*, 77.

[18] When Pd(OAc)$_2$ (0.01 mmol) and benzoic acid (0.20 mmol) were heated to 90 °C in [D$_6$]benzene (1 mL), complete exchange of the acetate and benzoate ligands was observed by ^{1}H NMR spectroscopy (300 MHz); new peaks were observed at δ = 7.95 ppm (d; *o*-Ar-H, Pd(OBz)$_2$) and at δ = 6.71 ppm (m; *m*- and *p*-Ar-H, Pd(OBz)$_2$).

[19] When the oxidative coupling of benzene (30 mmol) with ethyl acrylate (1.5 mmol) was performed in propionic acid (5 mL) at 90 °C, catalyzed by a mixture of Pd(OAc)$_2$ (0.1 mmol), $H_7PMo_8V_4O_{40}$ (0.02 mmol), acetylacetone (0.1 mmol), and NaOAc (0.08 mmol) under O$_2$ (1 atm), Ishii and co-workers obtained a TON value of 12.6 within 3 h.[11g]

[20] The *ortho, meta*, and *para* isomers of **3d**–**3i** were prepared by Heck reactions of the corresponding iodotoluenes and iodoanisoles.

[21] See, for example: R. M. Roberts, *Friedel–Crafts Alkylation Chemistry: A Century of Discovery*, Marcel Dekker, New York, **1984**.