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Highly Efficient Pd-Catalyzed Coupling of Arenes with Olefins in the Presence of *tert*-Butyl Hydroperoxide as Oxidant

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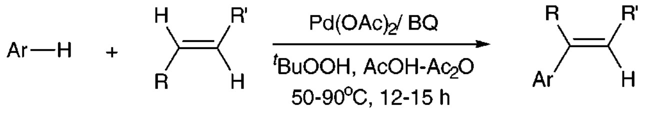
ABSTRACT



ArH : benznoid and non-benzenoid.
R = H, CH_3, Ph. R' = Ph, CO_2Et, COMe, CHO, CO_2H, CN.

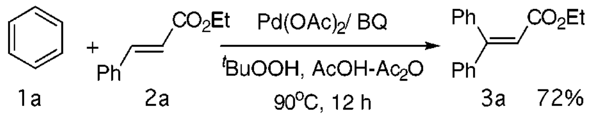
The oxidative coupling of arenes with olefins has been performed efficiently in the presence of catalytic amounts of palladium acetate and benzoquinone (BQ) with *tert*-butyl hydroperoxide as the oxidant in up to 280 turnover numbers (TON). The catalytic system is especially active for the coupling of heterocycles such as furans and indole with activated olefins. The reaction is highly regio- and stereoselective, giving *trans*-olefins predominantly.

The catalytic activation of aromatic C−H bonds leading to the formation of a C−C bond is of considerable interest for chemical and pharmaceutical industries and remains a long-term challenge to chemists.[1] The coupling of arenes with olefins with the cleavage of aromatic C−H bonds in the presence of Pd compounds stoichiometrically or catalytically is one of the earliest such examples.[2] The σ-aryl−Pd(II) complexes formed via electrophilic metalation of aromatic C−H bonds have been isolated as the intermediates.[2f] The reaction is general with regard to arenes which can be benzenoid and nonbenzenoid. The asymmetric version of this reaction catalyzed by chiral Pd complexes has been reported recently.[3]

In the catalytic reactions, in situ regeneration of Pd(II) from Pd(0) is the crucial step for the catalytic cycle. Much effort has been made to find the efficient reoxidation systems to regenerate Pd(II) in situ from Pd(0).[2b−e,4] We have reported several oxidation systems such as $Cu(OAc)_2/O_2$ and AgOAc, and relatively low turnover numbers (TON) were obtained over these systems. It is still desirable for new and efficient catalytic systems from the practical point of view. Here we report an efficient catalytic system which is composed of small amounts of palladium acetate and BQ in the presence of *tert*-butyl hydroperoxide as an inexpensive oxidant. Various arenes and olefins undergo the coupling reaction in high regio- and stereoselectivity with high TON (up to 280, several times higher than ever reported for this reaction[2,4]).

The reaction of benzene (**1a**) with (*2E*)-ethyl cinnamate (**2a**) was used to optimize the reaction conditions and to screen the catalysts (Scheme 1). The reaction gave ethyl 3-phenylcinnamate (**3a**) as the only isolated product.[5] The results are shown in Table 1.

Scheme 1



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[1] (a) Shilov, E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Trost, B. M. *Science* **1991**, 1471. (c) Fujiwara, Y.; Jintoku T.; Takaki, K. *CHEMTECH* **1990**, 636. (d) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403. (f) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616 and references cited therein.

[2] (a) Maritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 1119. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. (c) Asano, R.,; Moritani, I.; Fujiwara, Y.; Teranishi, S. *Chem. Commun.* **1970**, 1293. (d) Fujiwara, Y.; Asano, R.; Moritani, I.; Teranishi, S. J. *J. Org. Chem.* **1976**, *41*, 1681. (e) Fujiwara, Y.; Takaki, K. Taniguchi, Y. *Synlett* **1996**, 591. (f) Fujita, Y.; Hiraki, K.; Kamogawa, Y.; Suenaga, M.; Toggoh, K.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1081.

[3] Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett.* **1999**, 55.

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Table 1. Optimization of Reaction Conditions of Pd-Catalyzed Coupling of Benzene with (2*E*)-Ethyl Cinnamate[a]

entry	catalyst (mol %)	oxidant	yield[b] (%)	TON
1	Pd(OAc)$_2$ (1)	AgOAc	51	51
2	Pd(OAc)$_2$ (1)	AgO$_2$CPh	53	53
3	Pd(OAc)$_2$ (1)/BQ (5)	MnO$_2$	46	46
4	Pd(OAc)$_2$ (1)/BQ (5)	30% H$_2$O$_2$	35	35
5	Pd(OAc)$_2$ (1)	^{t}BuOOH	60	60
6	Pd(OAc)$_2$ (1)/BQ (5)	^{t}BuOOH	71	71
7	Pd(OAc)$_2$ (1)/BQ (5)[c]	^{t}BuOOH	76	76
8	Pd(OAc)$_2$ (1)/BQ (10)[c]	^{t}BuOOH	81[e]	81
9	Pd(OAc)$_2$ (0.5)/BQ(5)[c,d]	^{t}BuOOH	70	140
10	Pd(OAc)$_2$ (0.2)/BQ(3)[c,d]	^{t}BuOOH	56	280
11	Pd(OAc)$_2$ (1)/Cu(OAc)2(5)[c]	^{t}BuOOH	25	25
12	Pd(PPh$_3$)$_4$ (1)/BQ (15)[c]	^{t}BuOOH	43	43

[a] A similar procedure is used[5] unless otherwise indicated. The quantity of the catalyst is based on ethyl cinnamate. [b] GC yield based on ethyl cinnamate. [c] Acetic anhydride (1 mL) was added. [d] Ethyl cinnamate (30 mmol), ^{t}BuOOH (60 mmol), benzene (150 mmol), AcOH (30 mL), and Ac$_2$O (7 mL) were employed, 90 °C, 15 h. [e] 72% isolated yield.

The results in Table 1 indicate that ^{t}BuOOH is the most powerful of the tested oxidants which include AgOAc, AgOOCPh, MnO$_2$, and H$_2$O$_2$ (entries 1−5). Addition of BQ to the catalytic system enhanced the reaction considerably, and the yields increased with increasing quantity of BQ (entries 5−8). BQ is believed to stabilize the Pd(0) species by the in situ formation of Pd(0)−BQ complexes to prevent the Pd(0) species from aggregation to Pd black and subsequently BQ to oxidize Pd(0) to Pd(II).[6] The yields were also improved by addition of acetic anhydride (entries 6−8), presumably because it removed water from the peroxide and facilitated the formation of *tert*-butyl peracetate.[7c] The quantity of Pd(OAc)$_2$ can be reduced to a very small amount in this catalytic system (entry 10 in Table 1), and the highest TON (280) was obtained. Cu(OAc)$_2$ quickly decomposed the peroxide and is apparently unsuitable as a cocatalyst in this system (entry 11 in Table 1). Pd(II)/BQ/peroxides as an efficient and environmentally clean system also has been used in other reactions such as oxidative acetoxylation of olefins.[7]

Various arenes and olefins undergo the coupling reactions using the Pd(OAc)$_2$/BQ/^{t}BuOOH system, and the results are shown in Table 2. All the reactions of arenes with the olefins bearing an electron-withdrawing group at the α-carbon selectively gave β-aryl *trans*-olefins ($J_{\mathrm{H-H}} > 15$ Hz). The yields of the products ranged from low to good yields, depending on the reactivity of the corresponding arenes and olefins.

Good yields were obtained from the reaction of equimolar furan (**1h**), methyl furan (**1g**), benzofuran (**1i**), or indole (**1j**) with methyl/ethyl acrylate (**2k**/**2f**) or vinyl methyl ketone (**2g**) using the Pd(OAc)$_2$/BQ/^{t}BuOOH system (entries 15−17 and 20−26 in Table 2). A high TON (260) can be obtained also from the reaction of **1g** with **2f** in the presence of a small amount of Pd(OAc)$_2$ (0.2 mol %, entry 16 in Table 2). Dicoupling products (two olefins with one arene) such as diethyl (2*E*,2′*E*)-3,3′-(2,5-furandiyl)bispropenoate (**3s**) or (2*E*,2′*E*)-dimethyl 3,3′-(2,3-benzofurandiyl)bispropenoate (**3u**)[8] were found as the minor products together with monocoupling products (2*E*)-ethyl 3-(2-furanyl)propenoate (**3r**) or (2*E*)-methyl 3-(2-benzofuranyl)propenoate (**3t**) in the reactions of **1h** with **2f**, or **1i** with **2k**, respectively (entries 21 and 23). When 2 equiv of olefins **2f** or **2k** with ^{t}BuOOH were employed, dicoupling products **3s** or **3u** were isolated as the major products (entries 22 and 24), respectively. The reaction of either toluene (**1b**) or anisole (**1c**) with **2f** gave a mixture of *p*-, *o*-, and *m*-substituted isomers **3i** or **3j**, respectively (entries 11 and 12), however favoring *p*-substitution. The reaction of naphthalene (**1f**) with **2f** gave a mixture of (2*E*)-ethyl α- and β-naphthyl propenoates (**3l**) (entry 14) in a 5/1 ratio of α-/β-substitution. The reactivity of arenes follows the order furans > indole > naphthalene > anisole > toluene, benzene. All these indicate that the reaction is of the electrophilic nature to arenes used in the present catalytic system. The formation of the σ-aryl−Pd(II) complexes via electrophilic metalation of aromatic C−H bonds is the rate-determining step.[2]

For olefins, the reaction of active olefins such as (2*E*)-ethyl cinnamate (**2a**) and (2*E*)-4-phenyl 3-buten-2-one (**2b**) with benzene gave good yields of coupling products **3a** and **3b**, respectively (entries 1 and 2 in Table 2). The olefins bearing a nitrile or carboxyl substituent (**2c**, **2l**, and **2d**) somehow exhibited low reactivity (entries 3, 18, and 4), possibly because of strong coordination of these groups to palladium, which blocks the coordination of olefins to Pd. The reaction of the olefins having an aldehyde substituent (**2e** or **2m**) gave low to fair yields of coupling products (entries 5 and 19), the main reason being that the aldehydes are easily oxidized to carboxylic acid. The reactivity of

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(4) (a) Shue, R. S. *Chem. Commun.* **1971**, 1510. (b) Tsuji, J.; Nagashima, H. *Tetrahedron* **1984**, 2699.

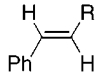
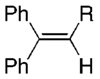
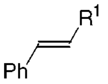
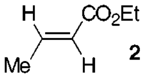
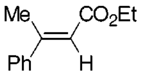
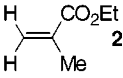
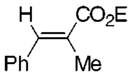
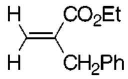
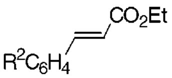
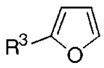
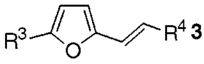
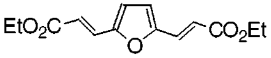
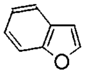
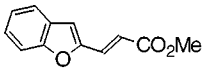
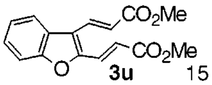
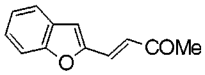
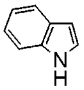
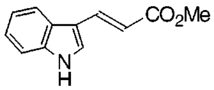
(5) **Typical experimental procedure** (entry 8 in Table 1): (2*E*)-ethyl cinnamate (0.54 g, 3 mmol), benzene (1.2 g, 15 mmol), Pd(OAc)$_2$ (6.7 mg, 0.03 mmol), benzoquinone (32 mg, 0.3 mmol), 3 mL of acetic acid, and 1 mL of acetic anhydride were mixed in a 25 mL reaction tube equipped with a magnetic stirrer, and the tube was sealed with a rubber septum. The reaction mixture was heated to 90 °C (oil bath), and 80% ^{t}BuOOH (0.4 g, 3.9 mmol) was injected within 1 h. The reaction mixture was kept at the same temperature for another 11 h. The reaction was monitored by GC (with diethyl 1,4-benzenedicarboxylate as internal standard) and TLC analysis of the reaction mixture. After the usual workup of the reaction mixture, column chromatography with hexane/ethyl acetate (10/1) as eluent gave ethyl 3-phenyl cinnamate in 72% yield. Its structure was confirmed by ^{1}H and ^{13}C NMR.

(6) The formation of Pd(0)−BQ complexes and acid-induced transformation of the Pd(0)−BQ complexes to Pd(II) have been reported. Grennberg, H.; Gogoll, A.; Backvall, J. E. *Organometallics* **1993**, *12*, 1790.

(7) (a) Jia, C.; Mimoun, H.; Mueller, P. *J. Mol. Catal., A Chem.* **1995**, *101*, 127−136; European Patent 685450, 1995. (b) Akermark, B.; Larsson, E. M.; Oslob, J. D. *J. Org. Chem.* **1994**, *59*, 5729. (c) Strukul, G., Ed. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer Academic Publishers: Dordrecht, 1992.

(8) (2*E*,2′*E*)-Dimethyl 3,3′-(2,3-benzofurandiyl)bispropenoate (**3u**) was isolated as yellow crystals: mp 119.5−220.6 °C (recrystallized from hexane/EtOAc 5/1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.85 (s, 3H, CH$_3$O), 3.86 (s, 3H, CH$_3$O), 6.65 (d, $J = 15.9$ Hz, 1H, vinyl), 6.70 (d, $J = 15.3$ Hz, 1H, vinyl), 7.35 (td, $J = 1.5$, 8.4 Hz, 1H, aryl), 7.45 (td, $J = 1.5$, 8.1 Hz, 1H, aryl), 7.52 (d, $J = 8.4$ Hz, 1H, aryl), 7.82 (d, $J = 15.3$ Hz, 1H, vinyl), 7.85 (d, $J = 8.1$ Hz, 1H, aryl), 7.95 (d, $J = 15.9$ Hz, 1H, vinyl). ^{13}C NMR (75 MHz, CDCl$_3$) δ 51.90, 52.04, 111.83, 119.13, 120.39, 120.85, 121.58, 124.23, 125.75, 127.39, 127.77, 133.68, 152.81, 155.22, 166.66, 167.06. IR (KBr, cm^{-1}): 1720 (C═O), 1737 (C═O). Anal. Calcd for C$_{16}$H$_{14}$O$_5$: C, 67.13; H, 4.93. Found: C, 66.96; H, 4.90.

Table 2. Pd(OAc)$_2$-Catalyzed Oxidative Coupling of Arenes with Olefins

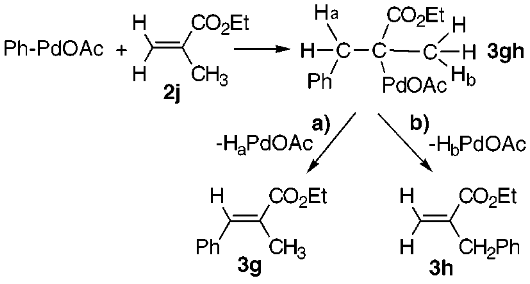
Entry	Arene	Olefin	Method [c]	Product and	Yield (%) [a]
1	Benzene **1a**	 **2a** R = CO_2Et	A	 **3a** R = CO_2Et	72
2	**1a**	**2b** R =COMe	A	**3b** R = COMe	74
3	**1a**	**2c** R = CN	B	**3c** R = CN	15
4	**1a**	**2d** R = CO_2H	B	**3d** R = CO_2H	(25)
5	**1a**	**2e** R = CHO	B	**3e** R = CHO 36; **3d** + **2d**	10 + 40[b]
6	**1a**	CH_2=CHR^1 **2f** R^1 = CO_2Et	B	 **2a**	(31)
7	**1a**	**2g** R^1= COMe	B	**2b**	(26)
8	**1a**	**2h** R^1= Ph	G	Stilbene (*tans-* / *cis-* = 5) **3e**	(25)
9	**1a**	 **2i**	B	 **3f**	18
10	**1a**	 **2j**	B	 **3g**  **3h**	12+12[b]
11	Toluene **1b**	**2f**	B	 **3i** R^2 = Me (*p / o / m =3 /1 /1*)	(24)[b]
12	Anisole **1c**	**2f**	C	**3j** R^2 = OMe (*P / o / m = 6 / 1 /1*)	(48)[b]
13	1,4-Dimethoxy benzene **1d**	**2f**	C	**3k** R^2 = 2, 5-dimethoxy	36
14	Naphthalene **1f**	**2f**	B	*trans*-Ethyl 3-naphthyl 2-propenoate **3l** (α / β = 5)	(41)[b]
15	 R^3 = Me **1g**	**2f**	D	 **3m** R^3 =Me R^4 = CO_2Et	75
16	**1g**	**2f**	E	**3m**	52 (TON: 260)
17	**1g**	**2g**	D	**3n** R^3 = Me, R^4 = COMe	73
18	**1g**	CH_2=CHR^5 **2l** R^5 = CN	D	**3o** R^3 = Me, R^4 = CN	23
19	**1g**	**2m** R^5 = CHO	D	**3p** R^3 = Me, R^4 = CHO	20
20	**1h** R^3 = H	**2g**	D	**3q** R^3 = H, R^4 = COMe	72
21	**1h**	**2f**	D	**3r** R^3 = H, R^4 = CO_2Et  **3s**	56 10
22	**1h**	**2f**	F	**3r** 15 **3s**	42
23	 **1i**	CH_2=$CHCO_2Me$ **2k**	D	 **3t** 56  **3u**	15
24	**1i**	**2k**	F	**3t** 12 **3u**	37
25	**1i**	**2g**	D	 **3v**	63
26	 **1j**	**2k**	D	 **3w**	52

[a] Isolated yield (GC yield in parentheses) based on the olefin. [b] A mixture of isomers. [c] Method A: same as the typical procedure.[5] Method B:similar to A but 0.09 mmol of Pd(OAc)$_2$ was used. Method C: similar to B but 0.2 mL of CF_3COOH was added. Method D: both olefin and arene (3 mmol), ^{t}BuOOH (3.9 mmol), Pd(OAc)$_2$ (0.015 mmol), BQ (0.15 mmol), HOAc (3 mL), Ac_2O (1 mL), 50 °C, 12 h. Method E: double all the reactants and solvent in D, and 0.012 mmol of Pd(OAc)$_2$ was added. Method F: double the olefin and ^{t}BuOOH in D. Method G: similar to A but AgO_2CPh (3.9 mmol) was used instead of ^{t}BuOOH.

olefins is in the order PhCH═CHCO$_2$Et, PhCH═CHCOMe > CH$_2$═CHCO$_2$Et > CH$_3$CH═CHCO$_2$Et > CH$_2$═CHCN.

The coupling of **1a** with **2j** gave a mixture of **3g** and **3h** (entry 10 and Scheme 2), which could result from two possible ways of palladium β-hydride elimination (route **a** and **b** in Scheme 2) from arylpalladation intermediate **3gh**. This sheds some light on the possible mechanism of this reaction, which is considered to be essentially similar to our previously proposed one.[2e] The σ-aryl−Pd(II) complexes from electrophilic substitution of arenes undergo *syn*-addition to olefins, which is followed by β-hydride elimination to give aryl alkenes and Pd−H or Pd(0) species. The in situ formation of BQ−Pd(0) or BQ−PdH complexes leads to subsequent transformation of these species to Pd(II) and at same time produces hydroquinone, which is oxidized back to BQ by either ^{t}BuOOH or ^{t}BuOOAc. Also it is possible that Pd−H or Pd(0) species could be reoxidized to Pd(II) directly by ^{t}BuOOH or ^{t}BuOOAc.[7,9]

Scheme 2



In summary, a highly efficient catalytic system has been developed for the oxidative coupling of simple arenes with olefins. The reaction utilizes readily available starting materials, is conducted under mild conditions, and should find wide application in organic synthesis.

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(9) (a) Mimoun, H.; Charpertier, R.; Mitscher, A.; Weiss, R. *J. Am. Chem. Soc*. **1980**, *102*, 1047. (b) Roussel, M.; Mimoun, H. *J. Org. Chem*. **1980**, *45*, 5387.