Palladium-Catalyzed Oxidative Cross-Coupling of 2-Phenylphenols with Alkenes

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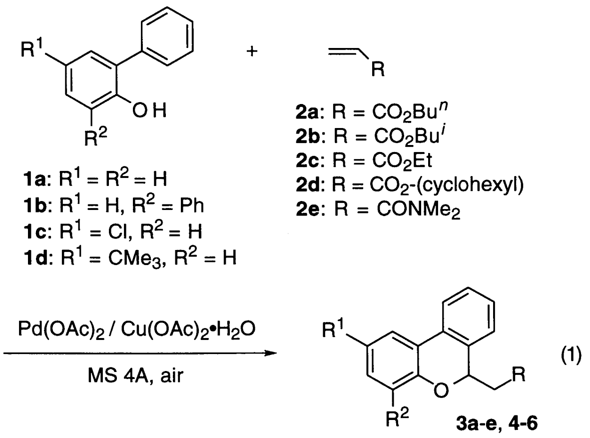
2-Phenylphenols react with alkenes such as acrylate esters in the presence of a palladium-copper catalyst system under air to give the corresponding 6-substituted 6*H*-dibenzo[*b,d*]pyran derivatives.

Considerable attention has been so far devoted to development of orthopalladation of aromatic compounds attached by suitable substituents containing heteroatoms such as N, P, S, and O.[1,2] Since the σ-arylpalladium species formed by this manner can undergo insertion and substitution reactions, the sequence of these reactions is recognized to be a powerful tool for the regiospecific functionalization of the aromatic rings. However, it is generally considered to be difficult to make the reactions catalytic.[2] Meanwhile, in the context of our study of palladium-catalyzed reactions employing phenolic substrates,[3] we observed that the coupling reactions of salicylaldehyde and 2-phenylphenol with aryl iodides could proceed in the presence of a palladium catalyst and a base to give the corresponding 2-aroylphenols and 2-(2'-arylphenyl)phenols, respectively, which appear to involve the regioselective cleavage of the aldehyde and aromatic C-H bonds.[3c] In these reactions, each phenolic function seems to act as a good anchor at the key palladation step. We now report our new findings that 2-phenylphenol and its derivatives can effectively undergo oxidative coupling with alkenes by using a palladium-copper catalyst system under air (Eq. 1). This is, to our knowledge, the first example that palladium- and functional group-assisted oxidative coupling of an aromatic C-H bond with alkenes is made catalytic with synthetically reasonable efficiency.[4,5]



When a mixture of 2-phenylphenol (**1a**) (1 mmol) and butyl acrylate (**2a**) (1 mmol) was stirred in the presence of $Pd(OAc)_2$ (0.05 mmol), $Cu(OAc)_2{\bullet}H_2O$ (0.05 mmol), and molecular sieves (MS 4A) (400 mg) in DMF (5 cm^3) under *diluted* air (N_2:air = 5:1, 1 atm) at 100 °C for 26 h, *n*-butyl 6*H*-dibenzo[*b,d*]pyran-6-acetate (**3a**) was formed in a yield of 69% (Entry 1 in Table 1).[6] The structure of **3a** was unambiguously determined by its 2D-NMR spectra (C,H-COSY and COLOC) and NOE experiments. Under *non-diluted* air (1 atm), the yield of **3a** was considerably low (43%). An increase in the reaction temperature to 120 °C remarkably enhanced the reaction rate, while a further elevation to 140 °C somewhat reduced the product yield (Entries 2 and 3). Addition of MS 4A appeared to be essential for the reaction to proceed effectively (Entry 4 *versus* 2). The ratio of $Pd(OAc)_2/Cu(OAc)_2$ also affected the reaction (Entries 2, 5, and 6); a maximum yield of **3a** was obtained at a ratio of 1.

Table 1. Oxidative Coupling of 2-Phenylphenol (**1a**) with *n*-Butyl Acrylate (**2a**)[a]

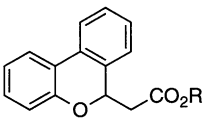
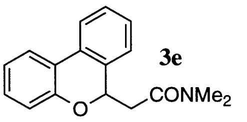
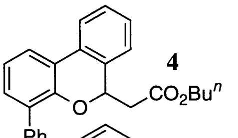
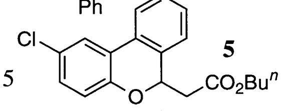
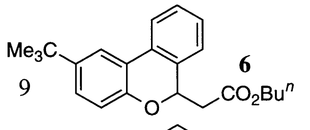
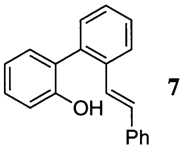
Entry	$Cu(OAc)_2{\bullet}H_2O$ / mmol	Temp / °C	Time / h	Yield of **3a** / %[b]
1	0.05	100	26	69
2	0.05	120	9	67
3	0.05	140	5	52
4[c]	0.05	120	9	17
5	0.1	120	9	43
6	0.025	120	9	19

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), MS 4A (400 mg), in DMF (5 cm^3) under N_2-air (5:1, total 900 cm^3). [b] GLC yield based on amount of **1a** used. [c] Without MS 4A.

Table 2 summarizes the results for the reaction of **1a** with alkenes **2b**-**f** and substituted 2-phenylphenols **1b**-**d** with **2a**. When acrylate esters **2b**-**d** and amide **2e** were used in place of **2a**, the corresponding 6*H*-dibenzo[*b,d*]pyrans **3b**-**e** were produced in fair to good yields, as was **3a**. The reactions of **1b**-**d** with **2a** also gave dibenzopyrans **4**-**6**. It is worth noting that 6*H*-dibenzo[*b,d*]pyran-6-acetate derivatives are known to exhibit hypolipidemic activity.[7] From the reaction of **1a** with styrene (**2f**) was obtained compound **7** which was not the expected dibenzopyran compound, but had an acyclic stilbene structure.[6]

The observed regioselectivity, exclusive substitution at the 2'-position of **1**, may be attributed to the coordination ability of its phenolic oxygen to Pd(II) species, which seems to play an important role in the initial C-H bond cleavage of **2**, *i. e.* cyclopalladation, even under the nearly neutral conditions employed.[3d,f] After the palladation, coupling with **2** may occur to give the corresponding alkenylated products such as **7** accompanied by formation of Pd(0) species and the subsequent Michael-type cyclization affords **3**-**6**. The role of $Cu(OAc)_2$ may be reoxidation of Pd(0) species formed in the oxidative coupling, as has been generally considered to be involved in Wacker-type reactions.[8] In the present case, H_2O should be generated in the reoxidation process. It seems to be effectively removed by MS 4A, so that the reaction proceeds smoothly.

Table 2. Oxidative Coupling of 2-Phenylphenols **1** with Alkenes **2**[a]

1	**2**	Temp / °C	Time / h	Product	Yield / %[b]
1a	**2b**	120	5	 R = Bu^i **3b**	79 (54)
1a	**2c**[c]	100	9	R = Et **3c**	80 (56)
1a	**2d**	120	5	R = cyclohexyl **3d**	72 (55)
1a[d]	**2e**	100	8	 **3e**	48 (44)[e]
1b	**2a**	100	7	 **4**	52 (35)
1c	**2a**	120	5	 **5**	27
1d	**2a**	120	9	 **6**	60 (46)
1a	**2f**[c,f]	80	5	 **7**	68 (53)

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), MS 4A (400 mg) in DMF (5 cm^3) under N_2-air (5:1, 900 cm^3). [b] GLC yield based on amount of **1** used. Value in parentheses indicates yield after purification. [c] **2** (3 mmol) was used. [d] **1** (1.5 mmol) was used. [e] Yield based on amount of **2** used. [f] **2f**: styrene.

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References and Notes

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5 Recently, the relevant chelation-controlled coupling reactions of aromatic compounds with alkenes *via* cleavage of aromatic C-H bonds by using ruthenium[a,b] and rhodium[c] catalysts have been successfully developed: a) F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, and S. Murai, *Bull. Chem. Soc. Jpn.*, **68**, 62 (1995); b) N. Chatani, Y. Ie, F. Kakiuchi, and S. Murai, *J. Org. Chem.*, **62**, 2604 (1997); c) Y.-G. Lim, J.-B. Kang, and Y. H. Kim, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2201, and references therein.

6 Typical experimental procedure: In a 100 cm^3 two-necked flask with a reflux condenser, a balloon, and a rubber cup were placed $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $Cu(OAc)_2 \cdot H_2O$ (10.0 mg, 0.05 mmol), and MS 4A (400 mg). After the apparatus was evacuated by pumping, nitrogen (750 cm^3) was introduced. Then, **1a** (170 mg, 1 mmol), **2a** (128 mg, 1 mmol), 1-methylnaphthalene (*ca.* 100 mg) as an internal standard, DMF (5 cm^3), and air (150 cm^3) were injected into the flask, and the resulting mixture was stirred at 120 °C for 9 h. After cooling, the reaction mixture was extracted with diethyl ether, and dried over sodium sulfate. GLC and GLC-MS analyses of the mixture confirmed formation of **3a** (198 mg, 67%). Product **3a** (151 mg, 51%) was also isolated by column chromatography on silica gel using hexane-ethyl acetate (99.5:0.5, v/v) as eluent. **3a**: Oil; *Anal.* Found: C, 76.60; H, 6.93%. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80%. ^1H NMR (400 MHz, $CDCl_3$) δ = 0.93 (3H, t, J = 7.3 Hz), 1.32-1.42 (2H, m), 1.58-1.65 (2H, m), 2.68 (1H, dd, J = 4.9, 15.1 Hz), 2.94 (1H, dd, J = 8.8, 15.1 Hz), 4.10-4.17 (2H, m), 5.71 (1H, dd, J = 4.9, 8.8 Hz), 6.96 (1H, dd, J = 1.0, 7.8 Hz), 7.06 (1H, t, J = 7.3 Hz), 7.17 (1H, d, J = 7.3 Hz), 7.23 (1H, dd, J = 1.5, 7.8 Hz), 7.29 (1H, dt, J = 1.0, 7.3 Hz), 7.39 (1H, dt, J = 1.5, 7.8 Hz), 7.72-7.75 (2H, m). HRMS m/z (M^+) Found: 296.1430. Calcd for $C_{19}H_{20}O_3$: 296.1412. Products **3b-e** and **4-6** were also obtained as oils which showed similar ^1H NMR spectra to that of **3a**. **7**: Oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.86 (1H, s), 6.93 (1H, d, J = 16.1 Hz), 6.99-7.03 (2H, m), 7.10 (1H, d, J = 16.1 Hz), 7.16-7.35 (8H, m), 7.38 (1H, dt, J = 1.5, 7.8 Hz), 7.45 (1H, dt, J = 1.5, 7.8 Hz), 7.84 (1H, dd, J = 1.0, 7.8 Hz). HRMS m/z (M^+) Found: 272.1212. Calcd for $C_{20}H_{16}O$: 272.1201.

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8 It can not be, however, excluded the possibility of participation of an alternative mechanism where the formal oxidation state of Pd(II) remains constant during the reaction, which has been proposed for the Wacker-type oxidative cyclization of 2-allylphenols: T. Hosokawa and S.-I. Murahashi, *Acc. Chem. Res.*, **23**, 49 (1990).