

One-Pot Catalytic Synthesis of 2-(1,2-Dihydroxypropyl)phenol Derivatives from 2-Allylphenols in Aqueous Media

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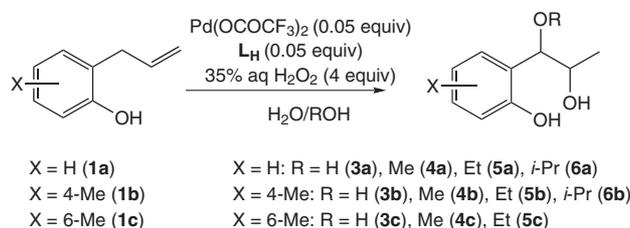
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Abstract: Catalytic amounts of the hydrophilic ligand $[(\text{HOCH}_2\text{CH}_2\text{NHCOCH}_2)_2\text{NCH}_2]_2$ and palladium(II) salts, in the presence of hydrogen peroxide, water and alcohol, allow the direct transformation of 2-allylphenols into 2-(1,2-dihydroxypropyl)phenol derivatives. The mechanism involves sequential isomerisation, epoxidation, and oxirane-opening.

Keywords: alcohols, oxidations, phenols, palladium, epoxidations

Aqueous phase organometallic chemistry has received considerable attention for environmental, economic, and safety reasons.¹ We have recently applied the hydrophilic ligand $[(\text{HOCH}_2\text{CH}_2\text{NHCOCH}_2)_2\text{NCH}_2]_2$ (L_H) in copper-catalyzed allylic oxidations² and palladium-catalyzed allylic substitutions.³ We report here that the association of L_H and palladium(II) salts allows the one-pot oxidation of 2-allylphenols into 2-(1,2-dihydroxypropyl)phenol derivatives, which are potentially physiologically active compounds.⁴

The intramolecular Wacker oxidation of allylphenol (**1a**) is well known,⁵ and we were interested in performing such a reaction with Pd(II)- L_H in aqueous media. Preliminary experiments in aqueous methanol, using a mixture of PdX₂ (X = Cl, OCOF₃) and L_H as the catalyst, and benzoquinone, Cu(II), NaOCl or oxone[®] as oxidizing agents, led, at the best, to traces of oxidized products; the isomerization of **1a** into 2-[(*E*)-prop-1-enyl]phenol (**2a**) being the main reaction with Pd(OCOFCF₃)₂- L_H as catalyst.⁶ However, the use of Pd(OCOFCF₃)₂- L_H with aqueous *t*-BuOOH (70%) afforded 2-(1,2-dihydroxypropyl)phenol (**3a**) and 2-(2-hydroxy-1-methoxypropyl)phenol (**4a**) in 34% yield. Interestingly, 35% aqueous H₂O₂ improved to 92% the yield of **3a** + **4a** (Equation 1, Table 1, run 1).⁷



Equation 1

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Changing Pd(OCOFCF₃)₂ for Pd(OAc)₂, PdCl₂ or a mixture of PdCl₂(MeCN)₂-AgX (X = SO₃CF₃, BF₄) was not beneficial to the process. With EtOH or *i*-PrOH as co-solvent, the expected products **3a**, **5a** and **6a** were obtained in similar yields (runs 2 and 3). MeOH as solvent yielded 75% of **4a** but water present in aqueous H₂O₂ produced 20% of **3a** (run 4). In water, only 50% of **3a** has been obtained (run 5). Oxidation of 2-allyl-4-methylphenol (**1b**) in H₂O–MeOH was less efficient, affording expected products **3b** and **4b** in 9 and 19% yield, respectively (run 6). Such a decrease in the efficiency of the process could be related to the low solubility of the substrate in this aqueous medium. Performing the reaction at room temperature and increasing the amount of alcohol improved the total yield to 59% (run 7). EtOH and *i*-PrOH as co-solvents afforded fair yields (runs 8, 9). 2-Allyl-6-methylphenol (**1c**) was oxidized in water–alcohol mixtures in 45–59% yields (runs 10,11).

A plausible mechanism, depicted in Scheme 1, would involve three successive reactions which could be Pd(II)-mediated: isomerisation of the substrate,⁶ epoxidation of the double bond,^{8,9} and hydrolysis or alcoholysis of the oxirane.¹⁰

In agreement with the above proposals, subjecting **2a** to the conditions used in Table 1 (H₂O–MeOH) led to **3a** and **4a** in 88% yield (Equation 2). Furthermore, the fixation of the methoxy group exclusively at the benzylic position by methanolysis of aryl epoxides under acidic conditions has already been reported.^{10,11} Surprisingly, **3a** and **4a** were also obtained from **2a** in the absence of any palladium catalyst, but with a lower yield (Equation 2).

Jacobs et al. have reported the phenol-mediated epoxidation of alkenes by H₂O₂ without metal catalyst. They proposed that intermolecular hydrogen bonding between phenol and H₂O₂ activates this latter for oxygen-atom transfer.¹² Therefore, we suspect an activation by the phenolic OH in the metal-free process leading to 2-(3-methyloxiran-2-yl)phenols; their high instability¹³ would lead to a spontaneous ring opening. However, the strong acceleration of the palladium catalyzed reaction of **2a** (Equation 2) indicates some participation of Pd(OCOFCF₃)₂- L_H in the process.

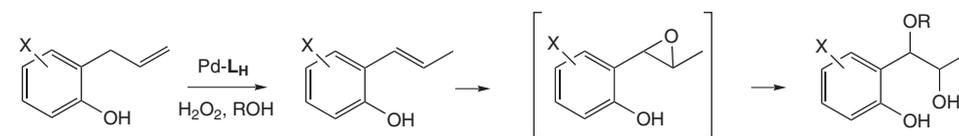
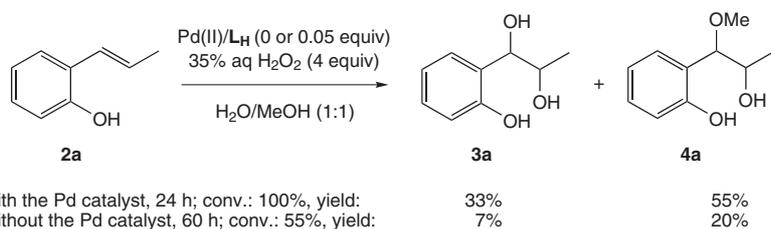
In conclusion, the association Pd(OCOFCF₃)₂- L_H in aqueous media catalyses the oxidation with H₂O₂ of 2-allylphenols to 2-(1,2-dihydroxypropyl)phenol derivatives. This process occurs via a cascade reaction involving the

Table 1 Oxidation of 2-Allylphenols^a

Run	Substrate	Temp (°C)	Time (h)	Solvent (ratio)	Products (%) ^b
1	1a	50	24	H ₂ O–MeOH (1:1)	3a (35), 4a (47)
2	1a	50	24	H ₂ O–EtOH (1:1)	3a (43), 5a (38)
3	1a	50	24	H ₂ O– <i>i</i> -PrOH (1:1)	3a (38), 6a (38)
4	1a	50	24	MeOH	3a (20), 4a (75)
5	1a	50	24	H ₂ O	4a (50)
6	1b	50	24	H ₂ O–MeOH (1:1)	3b (9), 4b (19)
7	1b	r.t.	72	H ₂ O–MeOH (1:2)	3b (18), 4b (41)
8	1b	r.t.	72	H ₂ O–EtOH (1:2)	3b (21), 5b (31)
9	1b	r.t.	72	H ₂ O– <i>i</i> -PrOH (1:2)	3b (20), 6b (24)
10	1c	r.t.	72	H ₂ O–MeOH (1:2)	3c (15), 4c (30)
11	1c	r.t.	72	H ₂ O–EtOH (1:2)	3c (18), 5c (41)

^a Experimental conditions are those depicted in Equation 1 (see also the experimental part).

^b Isolated yields.

**Scheme 1****Equation 2**

isomerisation of the C=C bond, followed by the epoxidation and the opening of the resulting oxirane.

¹H and ¹³C NMR spectral data were recorded on a Bruker AC 250 spectrometer at 250 MHz and 67.5 MHz, respectively, in CDCl₃ using TMS as internal standard. FTIR spectra were recorded on an Avatar 320 FT-IR instrument as KBr pellets or films. Column chromatography was performed on silica gel (70–230 mesh). All solvents and reagents were from commercial sources and were used as received. **L_H** was synthesized as previously described.² Mass spectra using electrospray ionization were performed with a Q-TOF micro from Micromass. Petroleum ether refers to the fraction with boiling point (40–60 °C).

General Procedure

To a stirred solution of Pd(OCOCF₃)₂ (24.9 mg, 0.075 mmol) and ligand **L_H** (34.8 mg, 0.075 mmol) in H₂O (1 mL), was added the allylphenol (1.5 mmol), H₂O₂ (35% in H₂O, 0.51 mL, 6 mmol) and the alcohol (1 or 2 mL). After stirring at 50 °C for 24 h or at r.t. for 72

h, Et₂O (3 × 5 mL) was added. The organic layer was separated and dried (MgSO₄). After evaporation of the solvent under vacuum, products were isolated from chromatography column (petroleum ether–EtOAc, 70:30) as yellow pastes.

2-(1,2-Dihydroxypropyl)phenol (**3a**)

IR: 3326, 1590, 1490, 1456, 1242, 1021 cm⁻¹.

¹H NMR: δ = 1.11 (d, *J* = 6.0 Hz, 3 H), 4.08 (quint, *J* = 6.5 Hz, 1 H), 4.58 (d, *J* = 8.0 Hz, 1 H), 6.82–7.27 (4 H).

¹³C NMR: δ = 19.1, 70.2, 80.3, 117.2, 119.7, 123.9, 128.9, 129.4, 131.5.

HRMS: *m/z* calcd for C₉H₁₂O₃Na: 191.0684; found: 191.0681.

2-(2-Hydroxy-1-methoxypropyl)phenol (**4a**)

IR: 3336, 1606, 1458, 1240, 1100 cm⁻¹.

¹H NMR: δ = 1.05 (d, *J* = 6.3 Hz, 3 H), 3.44 (s, 3 H), 4.03–4.15 (2 H), 6.84–7.27 (4 H).

^{13}C NMR: δ = 18.5, 57.7, 69.3, 90.4, 117.0, 117.3, 119.9, 129.7, 129.9, 155.4.

HRMS: m/z calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3\text{Na}$: 205.0841; found: 205.0839.

2-(1-Ethoxy-2-hydroxypropyl)phenol (5a)

IR: 3346, 1586, 1489, 1456, 1240, 1079 cm^{-1} .

^1H NMR: δ = 1.05 (d, J = 6.1 Hz, 3 H), 1.26–1.31 (3 H), 2.90–3.75 (2 H), 4.03 (quint, J = 6.8 Hz, 1 H), 4.13 (d, J = 8.1 Hz, 1 H), 6.83–7.26 (4 H).

^{13}C NMR: δ = 15.2, 18.6, 66.0, 69.2, 89.1, 117.2, 119.9, 121.9, 129.8, 129.9, 155.8.

HRMS: m/z calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3\text{Na}$: 219.0997; found: 219.1000.

2-(2-Hydroxy-1-isopropoxypropyl)phenol (6a)

IR: 3353, 1587, 1488, 1456, 1239 cm^{-1} .

^1H NMR: δ = 1.04 (d, J = 6.3 Hz, 3 H), 1.17–1.26 (6 H), 3.77 (sept, J = 6.1 Hz, 1 H), 4.00 (quint, J = 6.3 Hz, 1 H), 4.20 (d, J = 8.2 Hz, 1 H), 6.81–7.25 (4 H).

^{13}C NMR: δ = 18.7, 21.5, 23.3, 69.3, 71.8, 86.9, 117.5, 120.1, 122.7, 129.9, 130.0, 156.2.

HRMS: m/z calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3\text{Na}$: 233.1154; found: 233.1146.

2-(1,2-Dihydroxypropyl)-4-methylphenol (3b)

IR: 3352, 1615, 1504, 1254, 1029 cm^{-1} .

^1H NMR: δ = 1.11 (d, J = 6.2 Hz, 3 H), 2.28 (s, 3 H), 4.08 (quint, J = 7.0 Hz, 1 H), 4.58 (d, J = 7.8 Hz, 1 H), 6.82–7.27 (3 H).

^{13}C NMR: δ = 19.1, 20.3, 70.1, 80.2, 116.9, 123.5, 128.9, 129.1, 129.8, 153.0.

HRMS: m/z calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3\text{Na}$: 205.0841; found: 205.0840.

2-(2-Hydroxy-1-methoxypropyl)-4-methylphenol (4b)

IR: 3444, 1615, 1507, 1449, 1264, 1090 cm^{-1} .

^1H NMR: δ = 1.06 (d, J = 5.7 Hz, 3 H), 2.26 (s, 3 H), 3.41 (s, 3 H), 4.03–4.13 (2 H), 6.76 (d, J = 8.2 Hz, 1 H), 6.82 (s, 1 H), 7.01 (d, J = 8.2 Hz, 1 H).

^{13}C NMR: δ = 18.7, 20.7, 57.9, 69.7, 90.3, 117.0, 121.5, 129.3, 130.4, 130.5, 153.4.

HRMS: m/z calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3\text{Na}$: 219.0997; found: 219.0997.

2-(1-Ethoxy-2-hydroxypropyl)-4-methylphenol (5b)

IR: 3361, 1615, 1504, 1452, 1257, 1077 cm^{-1} .

^1H NMR: δ = 1.05 (d, J = 5.7 Hz, 3 H), 1.24–1.30 (3 H), 2.25 (s, 3 H), 3.47–3.72 (2 H), 3.99–4.09 (2 H), 6.75 (d, J = 8.2 Hz, 1 H), 6.78 (s, 1 H), 7.01 (d, J = 8.1 Hz, 1 H).

^{13}C NMR: δ = 15.4, 18.8, 20.8, 66.1, 69.4, 89.3, 117.2, 121.7, 129.3, 130.4, 130.5, 153.4.

HRMS: m/z calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3\text{Na}$: 233.1154; found: 233.1160.

2-(2-Hydroxy-1-isopropoxypropyl)-4-methylphenol (6b)

IR: 3356, 1615, 1502, 1456, 1261, 1046 cm^{-1} .

^1H NMR: δ = 1.05 (d, J = 6.2 Hz, 3 H), 1.18–1.25 (6 H), 2.25 (s, 3 H), 3.75 (sept, J = 6.0 Hz, 1 H), 4.00 (quint, J = 6.4 Hz, 1 H), 4.15 (d, J = 8.0 Hz, 1 H), 6.76 (d, J = 7.7 Hz, 1 H), 6.78 (s, 1 H), 7.00 (d, J = 8.1 Hz, 1 H).

^{13}C NMR: δ = 18.7, 20.7, 21.4, 23.3, 69.3, 71.7, 86.7, 117.2, 122.3, 129.2, 130.2, 130.4, 153.8.

HRMS: m/z calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{Na}$: 247.1310; found: 247.1315.

2-(1,2-Dihydroxypropyl)-6-methylphenol (3c)

IR: 3356, 1596, 1471, 1222, 1028 cm^{-1} .

^1H NMR: δ = 1.12 (d, J = 6.3 Hz, 3 H), 2.23 (s, 3 H), 4.07 (quint, J = 6.3 Hz, 1 H), 4.48 (d, J = 8.1 Hz, 1 H), 6.74 (t, J = 7.5 Hz, 1 H), 6.83 (d, J = 7.6 Hz, 1 H), 7.07 (d, J = 7.3 Hz, 1 H).

^{13}C NMR: δ = 16.1, 19.9, 70.4, 81.5, 119.6, 121.9, 126.9, 128.1, 131.1, 154.0.

HRMS: m/z calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3\text{Na}$: 205.0841; found: 205.0847.

2-(2-Hydroxy-1-methoxypropyl)-6-methylphenol (4c)

IR: 3373, 1596, 1471, 1232, 1084 cm^{-1} .

^1H NMR: δ = 1.04 (d, J = 5.8 Hz, 3 H), 2.23 (s, 3 H), 3.45 (s, 3 H), 3.99–4.14 (2 H), 6.79 (t, J = 7.6 Hz, 1 H), 6.85 (d, J = 7.5 Hz, 1 H), 7.09 (d, J = 7.1 Hz, 1 H).

^{13}C NMR: δ = 16.0, 18.7, 58.1, 69.4, 91.4, 119.7, 120.7, 126.2, 128.0, 131.1, 153.9.

HRMS: m/z calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3\text{Na}$: 219.0997; found: 219.1002.

2-(1-Ethoxy-2-hydroxypropyl)-6-methylphenol (5c)

IR: 3358, 1596, 1470, 1235, 1074 cm^{-1} .

^1H NMR: δ = 1.03 (d, J = 5.9 Hz, 3 H), 1.21–1.31 (3 H), 2.21 (s, 3 H), 3.48–3.73 (2 H), 3.97–4.24 (2 H), 6.78 (t, J = 7.3 Hz, 1 H), 6.84 (d, J = 7.6 Hz, 1 H), 7.08 (d, J = 6.1 Hz, 1 H).

^{13}C NMR: δ = 15.4, 16.0, 18.8, 66.1, 69.3, 89.6, 119.6, 121.1, 126.2, 127.8, 131.2, 154.1.

HRMS: m/z calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3\text{Na}$: 233.1154; found: 233.1161.

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