Selective Aerobic Oxidation of Allylic Alcohols to Carbonyl Compounds Using Catalytic $Pd(OAc)_2$: High Intramolecular Selectivity

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Abstract: Allylic alcohols were selectively oxidized into aldehydes or ketones using a $Pd(OAc)_2$–Et_3N–O_2 system. Diols with one allylic function were selectively oxidized, with one of the hydroxyl groups remaining untouched.

Key words: palladium, oxidation, allylic alcohols, selectivity, intramolecular, oxygen

The oxidation of alcohols into aldehydes or ketones is one of the most important reactions in organic synthesis. Many systems, catalytic or not,[1,2] have been described, using metal or metal-free[3] conditions. Several oxidants or co-oxidants have been used[4–6] but for ecological reasons, oxygen was chosen more often.[7,8] Among the different metals employed to perform the reaction,[9–11] palladium[6,12] was the most widely used. Thus, many results have been published with the Pd/O_2 system, and among them, we found the procedure described by Sigman and coworkers[13] of special interest: a catalytic amount of $Pd(OAc)_2$ in presence of Et_3N and 3 Å molecular sieves (MS 3A) under an atmospheric pressure of oxygen allowed the oxidation of a large variety of alcohols at room temperature. We thus examined each parameter in detail and found that in the absence of molecular sieves and at 45 °C both activity and selectivity of the catalytic system were modified (Figure 1).

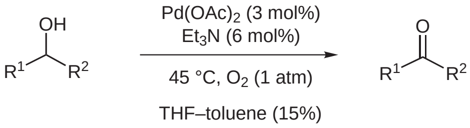

Figure 1 Catalytic aerobic oxidation of alcohols

Thus allylic alcohols were oxidized more rapidly than nonallylic ones (entries 3 and 4 vs. entries 1 and 2). A comparison with Sigman's results showed very significant differences in the case of cinnamic alcohol (entry 6). Even with forced conditions (5 mol% Pd instead of 3 mol% and 300 mol% Et_3N instead of 6 mol%) the authors could not reach more than 39% isolated yields whereas we isolated 77% of the desired aldehyde, the only differences being the absence of MS 3A and the heating at 45 °C. To explain the poor activity of their system with linear allylic alcohols, Sigman et al. proposed the ability of the α,β-unsaturated carbonyl product to act as a ligand of Pd(0), thus inhibiting the reaction. In our case, we think that this type of chelation has to occur between the starting alcohol and the catalyst to explain the allylic/nonallylic selectivity. Nevertheless, in the case of geraniol (Table 1, entry 7) our results (25% conversion) were quite similar to those that Sigman reported (33% conversion) probably because the substrate was chelated too strongly to palladium, due to its additional double bound. For products bearing an ester function close to the hydroxyl group (β-hydroxy ester) (Table 1, entry 8) the same explanation could be proposed to explain the low conversion (<10%) due to chelation by the carbonyl group. It is nevertheless noteworthy that our system tolerated the benzyl protecting group (Table 1, entry 9). Benzylic alcohols were also easily oxidized (Table 1, entries 10 and 11) and especially *o*-methoxy-1-phenyl ethanol, unreactive under Sigman's conditions, oxidized into product **11**. In our case, as soon as the allylic or benzylic substrate was added, the reaction mixture turned black, whereas the solution remained orange with nonallylic alcohols. In Sigman's case,[13] the solution was orange, irrespective of the alcohol. This indicates two different mechanisms. Stahl et al.[15] have studied the influence of molecular sieves in the case of quiet similar systems: the $Pd(OAc)_2$–pyridine–O_2 system reported by Uemura et al.[16] and the $Pd(OAc)_2$–DMSO–O_2 system reported by Larock et al.[17] They claimed that the MS 3A increased the catalyst stability by providing an heterogeneous surface that hinders the bulk aggregation of palladium metal. We have no evidence for or against this proposal but we assume that our catalytic system might be different than theirs because of the absence of molecular sieves.

We thus performed competitive experiments to test the level of chemoselectivity of our system.

In the presence of an allylic alcohol, 2-octanol was poorly oxidized (only 11%) whereas under the same conditions 70% of 2-octanol were converted into the corresponding ketone when oxidized alone (Table 2, entry 1 compared to Table 1, entry 2). An allylic alcohol was also more preferentially oxidized than a benzylic one (Table 2, entry 2). But the most spectacular results were obtained with diols bearing both an allylic function and a nonallylic one. In these substrates, we found that without molecular sieves, the allylic alcohol was selectively oxidized whereas the

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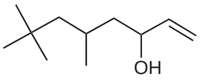
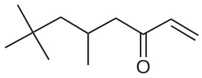
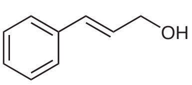
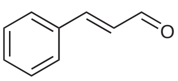
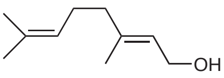
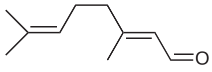
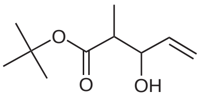
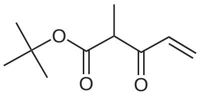
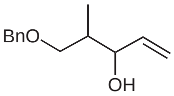
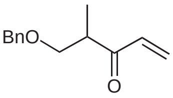
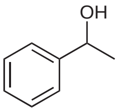
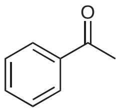
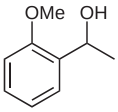
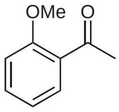
Table 1 Different Alcohols Oxidized by the $Pd(OAc)_2$–Et_3N–O_2 System[14]

Entry	Substrate	Product	Conversion[a] (%)[b]
1	1-octanol	1-octanal **1**	56
2	2-octanol	2-octanone **2**	70
3	1-octen-3-ol	1-octen-3-one **3**	100 (95)
4	2-octen-1-ol	2-octen-1-al **4**	80
5		 **5**	100 (85)
6		 **6**	86 (77)
7		 *E*/*Z* = 89:11 **7**	25
8		 **8**	<10
9		 **9**	100 (95)[c]
10		 **10**	100 (95)
11		 **11**	68 (45)

[a] Estimated by ^1H NMR after 20 h of reaction. It is noteworthy that when the conversion was not complete after 20 h, Pd black precipitated and there was no more evolution of the reaction.

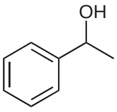
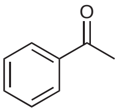
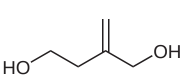
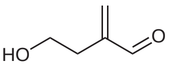
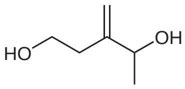
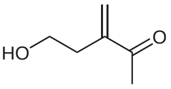
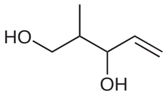
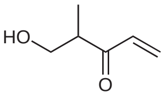
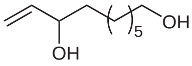
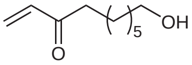
[b] Isolated yield.

[c] $Pd(OAc)_2$ (2 × 3 mol%) and Et_3N (2 × 6 mol%) were used.

nonallylic function remained untouched (Table 2, entries 3–6). No trace of dicarbonyl compounds was detected. This high level of chemoselectivity (allylic alcohol vs. nonallylic one) is noticeable as it avoids the use of protecting groups.

Among the published methods, only very few allowed the selective oxidation of allylic alcohols in the presence of nonallylic alcohols. The most known procedure very commonly proposed in organic synthesis uses MnO_2. Chromium(VI) reagents associated with amine ligands were also described[18] for the same purpose. In both cases, a large excess of reagents was necessary (10 equiv or more). We thus propose here a very selective method for allylic alcohols,[19] even in the presence of other alcohols, which is catalytic, generates water as the only by-product and is very easy to handle. Investigations into the reasons for the observed selectivity are in progress in our laboratory, as aerobic oxidation chemistry remains a subject of critical importance in the course of studies on green methods for organic transformations.

Table 2 Chemoselective Oxidation of Allylic Alcohols

Entry	Substrate	Product	Conversion[a] (%)[b]
1	2-octanol + 1-octen-3-ol	2-octanone **2** + 1-octen-3-one **3**	**2** (11%) + **3** (100%)
2	1-octen-3-ol + 	1-octen-3-one **3** +  **10**	**3** (100%) + **10** (55%)
3		 **12**	100 (80)[c]
4		 **13**	100 (95)[d]
5		 **14**	100 (94)
6		 **15**	80 (77)[e]

[a] Estimated by ^{1}H NMR after 20 h of reaction. It noteworthy that when the conversion was not complete after 20 h, Pd black precipitated and there was no more evolution of the reaction.

[b] Isolated yield.

[c] Conditions: r.t., 8 h.

[d] Pd(OAc)$_2$ (2 × 3 mol%) and Et$_3$N (2 × 6 mol%) were used.

[e] Conditions: r.t., 40 h.

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(14) **Typical Procedure**: Pd(OAc)$_2$ (0.015 mmol, 3 mol%) and Et$_3$N (0.03 mmol, 6 mol%) were dissolved in THF–toluene (15%; 1.7 mL). Then the substrate (0.5 mmol) was added and the reaction mixture was heated to 45 °C under 1 atm of O$_2$ (balloon) for 20 h. The reaction was monitored by TLC. In the case of total conversion, the product was obtained in its pure form after evaporation of the solvents, precipitation of Pd in Et$_2$O and filtration on celite. In other cases, it was purified by chromatography on silica.

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(19) All the products have been fully characterized by ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) and the analyses are in agreement with published data. Data that were not found in the literature are as follows: Product **5**: ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.83$ (s, 9 H), 0.87 (d, $J = 6.6$ Hz, 3 H), 1.10 (dd, $J = 6.4$, 14.0 Hz, 1 H), 1.17 (dd, $J = 4.0$, 14.0 Hz, 1 H), 2.06

(m, 1 H), 2.35 (dd, *J* = 7.9, 15.5 Hz, 1 H), 2.47 (dd, *J* = 5.8, 15.5 Hz, 1 H), 5.73 (d, *J* = 10.3 Hz, 1 H), 6.12 (d, *J* = 17.5 Hz, 1 H), 6.28 (dd, *J* = 10.3, 17.5 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 23.1, 26.4, 30.3, 31.4 (C$_q$), 49.6, 51.2, 128.1, 137.3, 201.0 (C$_q$). Product **9**: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.13 (d, *J* = 7.0 Hz, 3 H), 3.19 (m, 1 H), 3.48 (m, 1 H), 3.70 (m, 1 H), 4.49 (d, *J* = 3.2 Hz, 2 H), 5.80 (dd, *J* = 1.1, 10.3 Hz, 1 H), 6.28 (dd, *J* = 1.1, 17.5 Hz, 1 H), 6.46 (dd, *J* = 10.6, 17.5 Hz, 1 H), 7.31 (m, 5 H). Product **12**: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.50 (td, *J* = 1.0, 5.3 Hz, 2 H), 3.18 (m, 1 H, OH), 3.69 (td, *J* = 1.0, 5.3 Hz, 1 H), 6.09 (s, 1 H), 6.38 (s, 1 H), 9.53 (s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 31.8, 60.9, 136.6, 147.1 (C$_q$), 195.3 (C$_q$). IR (neat): 3394, 2932, 1686, 1437, 1267, 1043, 950, 736 cm^{-1}. Product **13**: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.33 (s, 3 H), 2.49 (t, *J* = 6.1 Hz, 2 H), 3.65 (t, *J* = 6.1 Hz, 2 H), 5.89 (s, 1 H), 6.08 (s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 26.0, 34.7, 62.0, 128.0, 146.4, 200.9 (C$_q$). IR (neat): 3399, 2932, 1675, 1627, 1369, 1184, 1128, 1050, 948, 735 cm^{-1}. Product **14**: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.08 (d, *J* = 7.2 Hz, 3 H), 3.01 (m, 2 H), 3.62 (dd, *J* = 4.5, 11.1 Hz, 1 H), 3.72 (dd, *J* = 7.2, 11.1 Hz, 1 H), 5.78 (dd, *J* = 1.3, 10.1 Hz, 1 H), 6.24 (dd, *J* = 1.3, 17.5 Hz, 1 H), 6.39 (dd, *J* = 10.1, 17.5 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.8, 45.6, 64.4, 129.3, 135.4, 204.3 (C$_q$). IR (neat): 3402, 2973, 2880, 1677, 1611, 1458, 1405, 1238, 1193, 1025, 977, 735 cm^{-1}. Product **15**: ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.31 (m, 6 H), 1.57 (m, 4 H), 1.80 (m, 1 H), 2.55 (t, *J* = 7.3 Hz, 2 H), 3.60 (t, *J* = 6.6 Hz, 2 H), 5.79 (dd, *J* = 1.3, 10.3 Hz, 1 H), 6.18 (dd, *J* = 1.3, 17.5 Hz, 1 H), 6.35 (dd, *J* = 10.3, 17.5 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 24.2, 25.8, 29.5, 33.0, 39.9, 63.2, 128.3, 136.9, 201.5 (C$_q$). IR (neat): 3391, 2930, 2857, 1681, 1615, 1463, 1403, 1268, 1075, 736 cm^{-1}.