Pd/C-Catalyzed Direct α-Oxygenation of 1,3-Dicarbonyl Compounds Using Molecular Oxygen

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Abstract: A hydroxyl group was readily and directly introduced into the α-position of a variety of β-dicarbonyl compounds by heterogeneous Pd/C-catalyzed oxygenation using molecular oxygen.

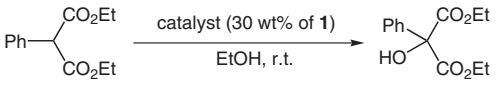
Key words: heterogeneous catalysis, palladium, oxygenation, oxygen, ketones

The direct introduction of a hydroxyl group at the α-position of the carbonyl compounds is a useful technique to construct the α-ketoalcohol functionality, which could be applied as a synthon of a variety of molecules including natural products.[1] A number of methods for such a transformation has been developed using stoichiometric amounts of oxidants such as MoOPH,[2] $Pb(OAc)_4$,[3] *m*-chloroperbenzoic acid,[4] dimethyldioxirane,[5] *N*-sulfonyloxaziridine derivatives,[6] etc. Most of these reagents are ecologically harmful and require the strong base, for example, lithium amide. Then, molecular oxygen has been applied as an environmentally benign oxygen source with chiral phase-transfer catalysts[7] or chiral aza-crown ethers.[8] Oxygenation of α-substituted β-dicarbonyl compounds has also been achieved under oxygen atmosphere with cesium fluoride or cesium carbonate as a base.[9] Recently, molecular oxygen was combined with a catalytic amount of a transition-metal reagent, such as MnO_2,[10] $CoCl_2$,[11] and $CeCl_3$[12] for the hydroxylation of α-substituted β-dicarbonyl compounds, although heterogeneous catalysts were not yet applied.

The use of the carbon-supported transition-metal catalysts, which are easily available, have been investigated for a wide range of reactions, because of their reliable recyclability and easy removal from reaction media.[13] In this paper, we report the α-oxygenation of β-dicarbonyl compounds catalyzed by palladium on carbon (Pd/C).

Stirring diethyl phenylmalonate (**1**) in EtOH at room temperature under an oxygen atmosphere (balloon) in the presence of a catalytic amount of 10% Pd/C (10 wt% of **1**) led to a moderate generation of an α-oxygenated product (**2**) to give a mixture of **1** and **2** in the ratio of 39:61 (entry 1, Table 1).

Table 1 α-Oxygenation of Diethyl Phenylmalonate



1 **2**

Entry	Catalyst	Base (equiv)	Gas	Time (h)	**1/2**[a]
1	10% Pd/C	–	O_2	12	39:61
2	10% Rh/C	–	O_2	12	98:2
3	10% Ru/C	–	O_2	12	98:2
4	10% Ni/C	–	O_2	12	57:43
5	10% Pt/C	–	O_2	12	100:0
6	10% Ir/C	–	O_2	12	92:8
7	10% Au/C	–	O_2	12	90:10
8	Norit	–	O_2	12	88:12
9	10% Pd/C	Et_3N (1.1)	O_2	6	0:100[b]
10	10% Pd/C	Et_3N (0.2)	O_2	12	14:86
11[c]	10% Pd/C	Et_3N (1.1)	Air	12	11:89
12	–	Et_3N (1.1)	O_2	39	100:0
13	10% Pd/C	–	Ar	12	100:0

[a] Determined by ^1H NMR analysis.
[b] Compound **2** was isolated in 98% yield.
[c] The reaction was carried out under the open system.

Replacement of Pd/C with other carbon-supported transition-metal catalysts, such as Rh/C, Ru/C, Ni/C, Pt/C, Ir/C, and Au/C, significantly dropped the yield of **2** (entries 2–7). The use of an activated carbon (Norit) with no metal embedded[14] only slightly produced the conversion (entry 8). On the other hand, the addition of 1.1 equivalents of Et_3N as a weak base to the Pd/C-catalyzed reaction system remarkably enhanced the reaction rate and the hydroxylation was completed within six hours to give **2** in a 98% isolated yield.[15] The reaction was expedited by the addition of even a catalytic amount of Et_3N (entry 10 vs. 1). The use of air instead of oxygen was available but not so efficient for the reaction progress (entry 11). Since the reaction never takes place without 10% Pd/C (entry 12) or oxygen (entry 13), it is obvious that Pd/C is necessary for

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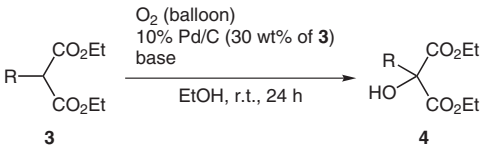
the reaction and molecular oxygen works as the oxygen source.

Although the present reaction using 10% Pd/C and O_2 was applied to the α-oxygenation of diethyl benzylmalonate (**3a**), no reaction took place with or without 1.1 equivalents of Et_3N (entries 1 and 2, Table 2).

Table 2 α-Oxygenation of α-Substituted Diethyl Malonates



Entry	R	Base (equiv)	Isolated yield (%)
1	Bn (**3a**)	–	0[a]
2	Bn (**3a**)	Et_3N (1.1)	0[b]
3	Bn (**3a**)	EtONa (0.15)	94
4[c]	Bn (**3a**)	EtONa (0.15)	0[d]
5	Et (**3b**)	EtONa (0.15)	84

[a] Compound **3a** was quantitatively recovered.
[b] No reaction took place; 94% of **3a** was recovered.
[c] The reaction was carried out in the absence of 10% Pd/C.
[d] No reaction took place; 87% of **3a** was recovered.

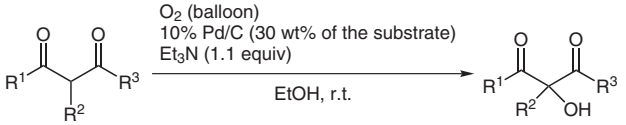
Instead, the use of EtONa as a stronger base significantly improved the reactivity, and the oxygenated product **4a** was obtained even with a catalytic amount (0.15 equiv) of EtONa in 94% yield (entry 3). Furthermore, Pd/C was found to be essential for the reaction (entry 4). The α-oxygenation of diethyl ethylmalonate (**3b**) was also achieved using 0.15 equivalents of EtONa (entry 5).

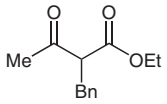
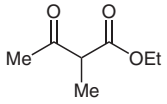
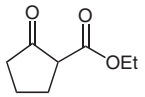
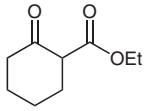
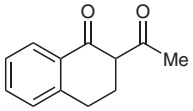
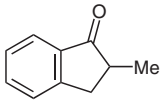
The α-oxygenation of a variety of 1,3-dicarbonyl compounds was then investigated (Table 3).

Both acyclic and cyclic α-substituted-β-ketoesters were smoothly oxygenated at the α-position to give the corresponding secondary alcohols in good yields (entries 1–4, Table 3). 2-Acetyl-tetralone as a 1,3-diketone (entry 5) could also be applied to the reaction. It is noteworthy that a hydroxyl group was successively introduced to the α-position of 2-methylindanone, which is a monocarbonyl compound, under such mild conditions (entry 6).

We next investigated the Pd/C-catalyzed oxygenation of the biomolecular uridine derivatives, which has a malonate moiety at the 5-position. This reaction easily proceeded without base, regardless of the protection at the N1-position (Scheme 1).

Table 3 α-Oxygenation of Various β-Dicarbonyl Compounds

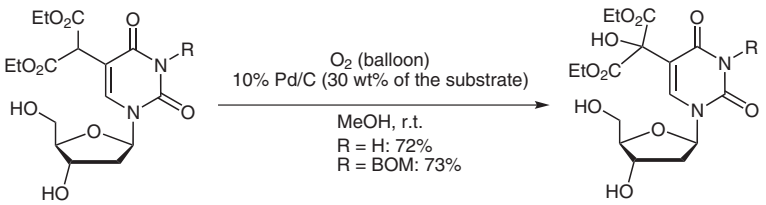


Entry	Substrate	Time (h)	Yield (%)[a]
1		16	76
2		24	56
3		3.5	86
4		36	61
5		24	57
6		38	88

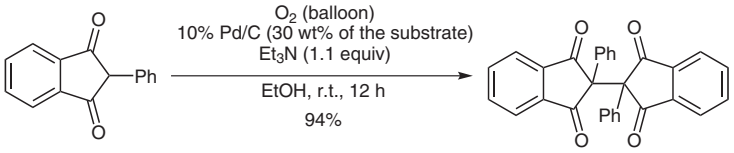
[a] Isolated yield.

When 2-phenyl-1,3-indanedione was employed as the substrate, the homocoupling reaction preferably took place rather than the desired oxygenation to give a dimer in 94% yield (Scheme 2), suggesting the existence of a radical intermediate at the 2-position.[16,17] Interestingly, the oxygenation reaction of 1,3-dicarbonyl compounds bearing no substituent at the 2-position, such as diethyl malonate, never proceeded. It is rational to consider that the present α-oxygenation reaction is mediated by the radical intermediate since a radical on the tertiary carbon is more stable than a radical on the secondary carbon, as generated on the 2-unsubstituted 1,3-dicarbonyl compounds.

In summary, we have developed a heterogeneous Pd/C-catalyzed α-oxygenation of 1,3-dicarbonyl compounds using molecular oxygen as the oxygen source. The present



Scheme 1 Application to the oxygenation of uridine derivatives



Scheme 2 Oxidative homocoupling of 2-phenyl-1,3-indanedione

reaction efficiently proceeds in the presence of a stoichiometric amount of Et_3N or a catalytic amount of EtONa under ambient pressure and temperature.

General Procedure for the α-Oxygenation of 1,3-Dicarbonyl Compounds

To a test tube with a stir bar were added the 1,3-dicarbonyl compound (0.250 mmol), EtOH (1 mL), 10% Pd/C (30% of the substrate weight), and Et_3N (38.3 μL, 0.275 mmol). The system was sealed with a septum and the air inside was replaced with O_2 (balloon) by five vacuum and oxygen cycles. The mixture was stirred at r.t. for 12 h and passed through a 0.45 μm membrane filter (Millipore, Millex®–LH). The filter was washed with EtOH (3 × 10 mL) and the combined filtrates were concentrated in vacuo. The residue was purified by flash column chromatography on SiO_2 (hexane–EtOAc) to give the α-oxygenated product.

Diethyl 2-Hydroxy-2-phenylmalonate[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (2 H, dd, *J* = 8.0, 1.7 Hz), 7.39–7.26 (3 H, m), 4.38 (1 H, s), 4.38 (1 H, s), 4.29 (4 H, m), 1.28 (6 H, t, *J* = 7.0 Hz). MS (EI): *m/z* (%) = 252 (1) [M$^+$], 179 (29), 105 (100). HRMS (EI): *m/z* calcd for $C_{13}H_{16}O_5$ [M$^+$]: 252.09977; found: 252.10066.

Diethyl 2-Benzyl-2-hydroxymalonate[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.24 (5 H, m), 4.24 (4 H, q, *J* = 7.3 Hz), 3.73 (1 H, s), 3.35 (2 H, s), 1.28 (6 H, t, *J* = 7.3 Hz). MS (EI): *m/z* (%) = 266 (1) [M$^+$], 248 (36), 91 (100). HRMS (EI): *m/z* calcd for $C_{14}H_{18}O_5$ [M$^+$]: 266.11542; found: 266.11645.

Diethyl 2-Ethyl-2-hydroxymalonate[19]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (4 H, q, *J* = 7.1 Hz), 3.75 (1 H, s), 2.06 (2 H, q, *J* = 7.3 Hz), 1.29 (6 H, t, *J* = 7.1 Hz), 0.91 (3 H, t, *J* = 7.3 Hz). No molecular ion peak was observed, see ref. 17.

Ethyl α-Acetyl-α-hydroxy-benzenepropanoate[12b]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.21 (5 H, m), 4.22 (2 H, q, *J* = 7.3 Hz), 4.07 (1 H, s), 3.41 (1 H, d, *J* = 14.4 Hz), 3.18 (1 H, d, *J* = 14.4 Hz), 2.27 (3 H, s), 1.27 (3 H, t, *J* = 7.3 Hz). MS (EI): *m/z* (%) = 236 (2) [M$^+$], 194 (92), 91 (100). HRMS (EI): *m/z* calcd for $C_{13}H_{16}O_4$ [M$^+$]: 236.10486; found: 236.10425.

Ethyl 2-Hydroxy-2-methylacetoacetate[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (2 H, q, *J* = 7.1 Hz), 4.17 (1 H, s), 2.28 (3 H, s), 1.59 (3 H, s), 1.30 (3 H, t, *J* = 7.1 Hz). No molecular ion peak was observed.

Ethyl 1-Hydroxy-2-oxo-1-cyclopentanecarboxylate[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19 (2 H, q, *J* = 7.3 Hz), 3.71 (1 H, s), 2.45–2.36 (3 H, m), 2.10–1.99 (3 H, m), 1.22 (3 H, t, *J* = 7.3 Hz). MS (EI): *m/z* (%) = 172 (17) [M$^+$], 145 (30), 99 (100). HRMS (EI): *m/z* calcd for $C_8H_{12}O_4$ [M$^+$]: 172.07356; found: 172.07421.

Ethyl 1-Hydroxy-2-oxo-1-cyclohexanecarboxylate[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 (1 H, s), 4.25 (2 H, q, *J* = 7.2 Hz), 2.70–2.53 (3 H, m), 2.04 (1 H, m), 1.88–1.79 (2 H, m), 1.77–1.63 (3 H, m), 1.30 (3 H, t, *J* = 7.2 Hz). MS (EI): *m/z* (%) = 186 (50) [M$^+$], 142 (60), 85 (100). HRMS (EI): *m/z* calcd for $C_9H_{14}O_4$ [M$^+$]: 186.08921; found: 186.08839.

2-Acetyl-3,4-dihydro-2-hydroxy-1-naphthalene[21]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (1 H, d, *J* = 7.7 Hz), 7.46 (1 H, dd, *J* = 7.7, 7.4 Hz), 7.27 (1 H, dd, *J* = 7.4, 7.1 Hz), 7.18 (1 H, d, *J* = 7.1 Hz), 4.53 (1 H, s), 3.06–3.03 (2 H, m), 2.53 (1 H, m), 2.20 (3 H, s), 2.12 (1 H, m). MS–FAB (Gly): *m/z* (%) = 205 (3) [M$^+$ + H]. HRMS–FAB: *m/z* calcd for $C_{12}H_{13}O_3$ [M$^+$ + H]: 205.08648; found: 205.08740.

2-Hydroxy-2-methyl-1-indanone[22]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (1 H, d, *J* = 7.6 Hz), 7.63 (1 H, d, *J* = 7.6 Hz), 7.43 (1 H, d, *J* = 7.6 Hz), 7.39 (1 H, t, *J* = 7.6 Hz), 3.28 (1 H, d, *J* = 16.7 Hz), 3.22 (1 H, d, *J* = 16.7 Hz), 3.21 (1 H, s), 1.45 (3 H, s). MS (EI): *m/z* (%) = 162 (100) [M$^+$], 120 (68), 91 (55). HRMS (EI): *m/z* calcd for $C_{10}H_{10}O_2$ [M$^+$]: 162.06808; found: 162.06755.

5-(1,1-Diethoxycarbonyl-1-hydroxymethyl)-2′-deoxyuridine

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.47 (1 H, s), 7.79 (1 H, s), 6.64 (1 H, br s), 6.18 (1 H, m), 5.25 (1 H, d, *J* = 4.1 Hz), 4.91 (1 H, t, *J* = 5.1 Hz), 4.17–4.06 (5 H, m), 3.79 (1 H, m), 3.54–3.48 (2 H, m), 2.03 (1 H, m), 1.97 (1 H, m), 1.15 (6 H, t, *J* = 7.2 Hz). MS–FAB (NBA): *m/z* (%) = 403 (8) [M$^+$], 176 (6), 154 (100). HRMS–FAB (NBA): *m/z* calcd for $C_{16}H_{23}N_2O_{10}$ [M$^+$]: 403.13523; found: 403.13589.

3-Benzyloxymethyl-5-(1,1-diethoxycarbonyl-1-hydroxymethyl)-2′-deoxyuridine

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (1 H, s), 7.30 (5 H, m), 6.76 (1 H, s), 6.20 (1 H, m), 5.31 (1 H, s), 5.28 (1 H, d, *J* = 4.1 Hz), 4.94 (1 H, t, *J* = 5.1 Hz), 4.56 (2 H, s), 4.21 (1 H, m), 4.14 (4 H, q, *J* = 7.2 Hz), 3.82 (1 H, m), 3.53 (2 H, m), 2.17 (1 H, m), 2.03 (1 H, m), 1.15 (6 H, t, *J* = 7.2 Hz). MS–FAB (NBA): *m/z* (%) = 523 (6) [M$^+$], 154 (100). HRMS–FAB (NBA): *m/z* calcd for $C_{24}H_{31}N_2O_{11}$ [M$^+$]: 523.19283; found: 523.19109.

2,2′-Diphenyl-[2,2′-biindane]-1,1′,3,3′-tetrone[23]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.88 (4 H, dd, *J* = 5.7, 3.0 Hz), 7.73 (4 H, dd, *J* = 5.7, 3.0 Hz), 7.33 (2 H, t, *J* = 7.6 Hz), 7.25 (4 H, t, *J* = 7.6 Hz), 7.19 (4 H, d, *J* = 7.6 Hz). MS (EI): *m/z* (%) = 442 (45) [M$^+$], 221 (100). HRMS (EI): *m/z* calcd for $C_{30}H_{18}O_4$ [M$^+$]: 442.12051; found: 442.12028.

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