



# Aerobic cascade oxidation of substituted cyclopentane-1,2-diones using metalloporphyrin catalysts

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## ABSTRACT

A method for the aerobic cascade oxidation of cyclopentane-1,2-diones using metal porphyrins as catalysts, yielding hydroxydiacids **2**, ketoacid **3** and diketoacids **4** which are the intermediates of important biologically active compounds is reported. This method is operationally simple and can be employed under ambient conditions.

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## 1. Introduction

Currently, the development of sustainable chemical processes is one of the major challenges in chemical engineering and applied science. Over the past decades, various transition metal catalysts have been successfully utilized in combination with different oxidizing reagents, such as peroxides, hydroperoxides, peracids and others, to convert alkenes to epoxides or carbonyl compounds.<sup>1–3</sup> However, from both economic and ecological points of view, the use of atmospheric oxygen as a terminal oxidant is more attractive due to its high natural abundance (nearly 20% of air is oxygen) and environmental sustainability. The main limitation for wide application of atmospheric oxygen in oxidation reactions is its relatively low reactivity in ambient conditions and lack of selectivity. Therefore, the selection of a catalyst is vital to carry out aerobic oxidations of different substrates in an efficient manner. Among known catalysts for performing aerobic oxidations of organic compounds,<sup>4,5</sup> synthetic metalloporphyrins, mimics of the oxygen carrier and oxidation catalyst in living organisms, are remarkably efficient and prospective.<sup>6,7</sup> In contrast to natural enzymatic systems, the selectivity of artificial catalysts is governed by the careful choice of a transition metal ion and by modifications in the skeleton of the porphyrin catalyst.<sup>6</sup>

Metalloporphyrin-catalyzed air oxidation has so far been used

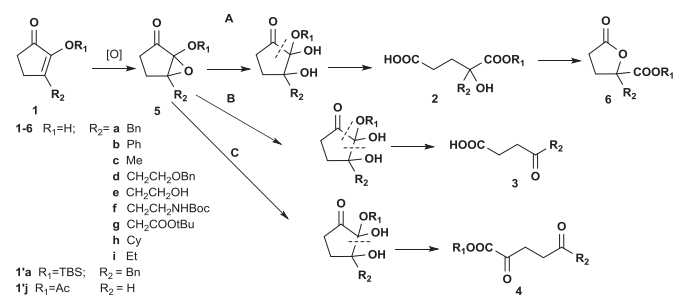
sparsely in organic syntheses to oxidize various compounds and functional groups. For example, it has been used in the oxidation of alkanes,<sup>7–13</sup> alkenes,<sup>7,11,14–16</sup> aromatic hydrocarbons,<sup>7,17,18</sup> steroids,<sup>19,20</sup> and aldehydes.<sup>11,32</sup> The listed examples represent only oxidation reactions, without considering subsequent transformations. However, in the preparation of pharmaceuticals or complex biologically active compounds, as a rule, a multi-step synthesis is necessary. Therefore, the development of catalytic conditions to assist reaction cascades is of importance.

In the present paper we report the first example of a cascade air oxidation of reactive organic molecules. Substituted cyclopentane-1,2-diones (**1**, Scheme 1) have been chosen as substrates because of their multiple functional groups sensitive to oxidation, allowing the formation of oxidation cascades which result in producing hydroxydiacid **2**. Also, the other oxidation products<sup>21–23</sup> of these structures have demonstrated interesting biological activities (e.g. clonamides<sup>22</sup> and dichotomain B.<sup>23</sup>). Hydroxydiacids **2** have also been used as precursors for the synthesis of nucleoside analogues<sup>24</sup> and HIV-1 protease inhibitors.<sup>25</sup> On the other hand, ketoacid **3** is also a viable substrate for the synthesis of  $\gamma$ -lactones,<sup>26</sup> whilst diketoacid **4** is a valuable precursor for the synthesis of heterocycles, including bioactive compounds.<sup>27</sup> Moreover, hydroxydiacid **2** contains an asymmetric center, which may open up additional opportunities for the elaboration of an enantioselective oxidation approach using chiral porphyrin catalysts.<sup>28,29</sup>

We found that enol derivatives **1** can be easily oxidized by air, using a catalytic amount of metalloporphyrin catalyst (1–5 mol%), affording 2-substituted-2-hydroxydiacids **2**, and other ring-cleaved

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Scheme 1. Reaction oxidative cascade of 1.

compounds, such as ketoacids **3** and diketoacids **4**. On the basis of our earlier studies,<sup>30,31</sup> we can suggest a following cascade of occurring aerobic oxidation reactions (Scheme 1): in all cases the first reaction is the epoxidation of the enol double bond (formation of intermediate **5**). The second oxidation reaction that may depend on the oxidizing reagent is a Baeyer-Villiger reaction leading to hydroxydiacid **2** (which easily converse to lactone acid **6**, route A), or the combination of a Bayer-Villiger reaction and diol cleavage resulting in ketoacid **3** (route B), or only a diol cleavage reaction yielding the diketoacid **4** product (route C). The reactions proceed under mild conditions, at ambient temperature and normal air pressure, and the method is operationally simple (see supplementary info).

## 2. Results and discussion

For initial catalyst screening, conventional 3-benzylsubstituted ketoenol (**1a**) was selected as a substrate. The most frequently used transition metal complexes (Mn, Fe, and Co) of octaethylporphyrin (OEP) and tetraphenylporphyrin (TPP) were used as catalysts (Table 1 and Fig. 1).

The oxidation of **1a** without presence of catalyst proceeds, as expected, considerably slower (81% of unreacted substrate), without any selectivity (Table 1, No. 1). In reactions with the catalysts, it was found that formation of different products **2a**, **3a** or **4a** was highly dependent on the central metal ion of the porphyrin complex. In the case of the Mn complexes **cat1** and **cat4** (Table 1, No. 2, 5 and 6) mostly diacid **2a** and ketoacid **3a** were formed, while diketoacid **4a** was not observed (route A and route B). However, with Co (**cat3** and **cat6**) and with Fe porphyrin complexes (**cat2** and **cat5**) the reaction yielded mostly diketoacid **4a** and ketoacid **3a** (route C and double oxidation according to route B; Table 1, No. 3, 4, 7 and 8). The yield of hydroxydiacid **2a** was up to 55% in the best case with Mn catalyst (Table 1, No. 6), for ketoacid **3a** the highest yield was 67% (Table 1, No. 2) and for **4a** 48% (Table 1, No. 8).

**Table 1**  
Oxidation of 3-benzyl-cyclopentane-1,2-dione **1** (enol form) with air using different porphyrin metal complexes as a catalyst.

No	Catalyst	Loading mol%	Unreacted 1a,%	Products,%		
				2a	3a	4a
1	-	—	81	10	9	—
2	<b>cat1</b>	5	—	33	67	—
3	<b>cat2</b>	5	30	—	30	40
4	<b>cat3</b>	5	49	—	18	33
5	<b>cat4</b>	5	—	54	46	—
6	<b>cat4</b>	1	3	55	42	—
7	<b>cat5</b>	5	31	—	37	32
8	<b>cat6</b>	5	20	8	24	48

Reaction conditions: CDCl<sub>3</sub>; rt; 5 mol% catalyst; 24 h. Product composition determined by <sup>1</sup>H NMR.

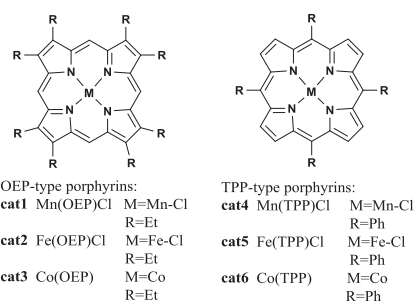


Fig. 1. Used TPP- and OEP-type metalloporphyrin metal complexes.

The substrate was completely consumed in the case of Mn catalysts (**cat1** and **cat4**; Table 1, No. 2 and 5). However, in the case of Fe catalysts (**cat2** and **cat5**) and with Co catalysts **cat3** and **cat6**, a certain amount of substrate remained unreacted (from 20 to 49%; Table 1, No. 3, 4, 7 and 8). From Mn catalysts Mn (TPP)Cl **cat4** was more efficient, affording a considerably higher yield of the target product hydroxyl diacid **2a** than **cat1**; (55% vs 33%; Table 1, No. 2 and 6). It was also found that **cat4** was efficient even with 1 mol% of catalyst (Table 1, No. 6). However, with preliminary results Mn catalysts had poor chemoselectivity: pathways A and B formed an almost equimolecular mixture of compounds **2** and **3** (55–42% in the best case). To follow the formation of **2a** and **3a**, the kinetics of these compounds were monitored by <sup>1</sup>H NMR. The obtained curves clearly indicate that hydroxydiacid **2a** and ketoacid **3a** form in parallel reactions (Fig. 2).

An effort was made to affect the relative rates of these reactions by using different solvents and **cat4** because of its highest selectivity towards formation of diacid **2**. The results are presented in Table 2.

With the initial chlorinated solvents both transformations were fast but not selective (Table 2, No. 1 and 2). Benzene did not give any improvement in selectivity (Table 2, No. 3). From the investigated solvents the best selectivity for **2** was obtained by using toluene, with a 75/16 ratio of **2a** to **3a** (Table 2, No. 4). The selectivity was very sensitive to temperature—both lowering and increasing of temperature decreased the selectivity towards **2** (Table 2, No. 4–8).

The use of ether solvent (THF) and alcohol (MeOH) completely hindered the reaction (Table 2, No. 9 and 10, respectively), while in dimethylcarbonate (DMC) only the formation of 31% of ketoacid **3** was observed (Table 2, No. 11).

Previously it has been shown that external ligands are able to accelerate porphyrin-catalyzed oxidation reactions.<sup>33,34</sup> However, in our case the addition of pyridine (10 mol%) or a basic and widely used organocatalyst, squaramide<sup>35</sup> (10 mol%), to the porphyrin

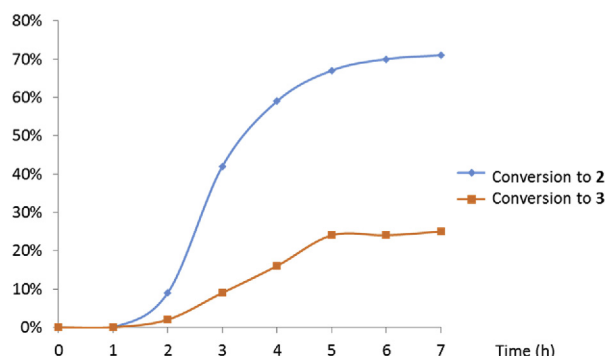


Fig. 2. Reaction monitoring results.

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