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Enantioselective arene epoxidation under mild conditions by *Jacobsen* catalyst: The role of protic solvent and co-catalyst in the activation of hydrogen peroxide

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ABSTRACT

The epoxidation of arenes was achieved in high yield and with high enantioselectivity using the system *Jacobsen* catalyst:hydrogen peroxide:co-catalyst, ethanol as reaction solvent at 40 °C. The effect on the catalytic performance of the use of protic (ethanol) and aprotic solvents and of co-catalysts with different acid–base properties was analyzed, as well as, different reaction temperatures, using as substrates indene, 6-cyan-2,2′-dimethylchromene, styrene and α-methylstyrene. The protic solvent showed a positive effect enhancing catalytic performances when compared with the aprotic solvent. For amphoteric co-catalysts (ammonium acetate, 2-methylimidazole and imidazole) it was observed the highest substrate conversions, whereas for basic co-catalysts (1-methylimidazole, 4-methylmorpholine *N*-oxide and pyridine), higher *ee*% and relatively lower C% were observed. Moreover, the reactions at 40 °C showed higher enantiomeric induction than those performed at room or lower temperatures.

The catalytic data are in accordance with a multi-step mechanism for hydrogen peroxide activation by the Mn(*salen*) complex with the formation of two catalytic active intermediates, existing in different extension depending on the reaction conditions: a hydroperoxy intermediate or oxo-metallocomplex. The activating effect of the protic solvent ethanol vs aprotic solvent was explained by the formation of hydrogen bonds between the solvent and the catalytic active intermediates.

1. Introduction

The enantioselective synthesis of chiral arene oxides by *Jacobsen–Katsuki* catalysis [1–4] has opened a vast academic and industrial interest and discussion; [5–8] nevertheless, improved eco-compatible conditions are required and the elucidation of the reaction mechanism still remains an intense field of research [9].

The use of Mn(*salen*) complexes as oxidative catalysts is very attractive [10] due to low cost, easy preparation and handling and high activity, in particular when the *Jacobsen* and *Katsuki* catalysts are considered [11]. They have been applied in association with hydrogen peroxide which is an environmentally clean and a relatively inexpensive oxidant [12–14], both in aqueous and anhydrous forms [15,16]. The major drawback of these catalytic systems is the general use of environmentally unacceptable solvents, such as dichloromethane:methanol [17,18], dichloromethane:water [6], dichloromethane [19], acetone:methanol [20] or dichloromethane:*N,N*'-dimethylformamide [21]; aprotic-low polarity solvents, such as acetonitrile were also used, although often associated with lower catalytic efficiency [22].

The reaction media is a very pertinent issue, since the solvents play a strong impact on cost and safety of the catalytic processes. When applicable, ethanol has been considered a good alternative as *green solvent* [23,24]: *i*) it is appropriate for substances with wide range of polarity; *ii*) it is inexpensive and can be obtained from biomass, *iii*) it is biodegradable and it can be used as a fuel. Water/surfactant or water/ethanol/tamponized media have been reported as eco-compatible reaction solvents, however green oxidants were not used [25,26].

Studies on the alkene epoxidation by Mn(*salen*) complexes have been accompanied by an intense mechanistic debate that involved the effect of catalyst structure and electronic properties [27,28], the oxidant used [29] and reaction conditions (e.g. presence of co-catalyst, solvent and temperature) in the reaction efficiency and enantioselectivity [15,30,31]. Initially, a [Mn(V)-oxo *salen*] species was considered to be the unique active species and the oxygen transfer to the substrate was proposed to proceed through a concerted manner, via a radical intermediate or via a manganaoxetane intermediate [32,33]. The observed differences in the reaction selectivity were associated with the occurrence of each of these pathways in different extent. In the last years,

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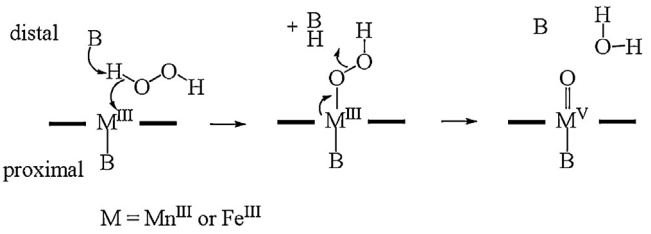

Fig. 1. "*Push and pull*" mechanism: B corresponds to histidine residues on peroxidase active site or to the co-catalyst used in metalloporphyrin catalyzed oxidation reactions.

the mechanistic debate has been directed towards the formation of other active species and, in addition to the oxo-species, a *catalyst–oxidant* adduct species was proposed to be the active intermediate under specific reaction conditions [34–36]. This debate assumes particular relevance when hydrogen peroxide is used as oxidant, since the catalytic activation can take place through multistep pathways, which are very sensitive to the reaction conditions [37,38]. Further interest arises from the analogy with enzymatic pathways described for activation of hydrogen peroxide during catalytic cycles of cytochrome P450 monooxygenases and heme based peroxidases, as well as, their synthetic analogues, the metalloporphyrins [39]. One challenging issue in these mechanistic studies is the short-live character of the catalytic active species formed and consequently the proposed structures have been mainly indirectly inferred [40].

The activation of hydrogen peroxide by metallocomplexes generally requires the presence of a co-catalyst in order to obtain efficient reactions and sometimes to enhance the enantioselectivity [15,21,41]. Different classes of compounds have been used as reaction co-catalysts such as pyridines, imidazoles, *N*-oxides or carboxylates and in metalloporphyrin catalysis their role has been considered to be similar to that of proximal and distal histidine residues during the heterolytic O—O bond cleavage by peroxidase, which act through the so called "*push and pull*" mechanism [42]. In a similar way, the activation of hydrogen peroxide catalyzed by manganese porphyrins was proposed to occur through the initial formation of a hydroperoxy intermediate [Mn(III)porphyrin-OOH]$^-$, favored in basic conditions, followed by the heterolysis through the "*push and pull*" mechanism to form a high valent oxo species [Mn(V)porphyrin=O] as shown in Fig. 1. The axial ligands provide electron density to the O—O bond through the metal center, the "*push*", while the co-catalyst mediates the proton delivery to the terminal oxygen creating a better leaving group, the "*pull*" [43,44].

Pertinent mechanistic studies on metalloporphyrin catalysis showed that when the dehydration step is unfavorable, a metallo-hydroperoxy species can also be a plausible electrophilic oxidant in the alkene epoxidation catalytic cycle, under specific conditions. Rebelo et al. [44] showed that efficient alkene epoxidation by a metallo-hydroperoxy species can occur when a protic solvent and a highly electron withdrawing metalloporphyrin were used in the absence of co-catalyst. In the enzymatic context, it was also shown the involvement of a proton network during activation of peroxo intermediates [42].

In the present work, the epoxidation of four olefins with synthetic interest: indene (**1**) [45], 6-cyan-2,2′-dimethylchromene (**2**) [46], styrene (**3**) and α-methylstyrene (**4**), Fig. 2, was performed using hydrogen peroxide as oxidant and ethanol as the solvent, in the presence of the *Jacobsen* catalyst. We intend to investigate the effect, on the catalytic performance, of co-catalysts with different acid-base properties (1-methylimidazole, 2-methylimidazole, 4-methylmorpholine *N*-oxide, pyridine and ammonium acetate), oxidant addition form and reaction temperature, as well as, to evaluate the effect of protic vs aprotic solvent and other solvent combinations already used as reaction medium. With these, we endeavor to contribute to the elucidation of the epoxidation reaction mechanism when hydrogen peroxide is used as the oxidant in the presence of *Jacobsen* catalyst.

2. Experimental

2.1. Materials and reagents

The indene (98%), 2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (6-cyan-2,2′-dimethylchromene, CN-Chrom, 97%), styrene (Sty > 99%), (*R*)-(+)-styrene oxide (98%), α-methylstyrene (Me-Sty, 99%), chlorobenzene (99,5%) (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butyl-salicylidene)-1,2-cyclohexane-diaminomanganese(III) chloride (*Jacobsen* catalyst), urea-hydrogen peroxide addition compound (UHP, 98%), hydrogen peroxide solution 30 wt.% in H_2O ($H_2O_{2(aq)}$), 1-methylimidazole (1-MeIm, 99%), 2-methylimidazole (2-MeIm, 99%) and 4-methylmorpholine *N*-oxide (NMO, 97%) were purchased from Aldrich. Pyridine (Py) and ammonium acetate (NH_4AcO, *p.a.* grade) were obtained from Merck. Methanol (*p.a.*) was supplied by Fisher Chemical, dichloromethane and acetonitrile by Romil (HPLC grade) and absolute ethanol (analytical grade) from Panreac.

2.2. Analytical methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra of compounds and total reaction mixtures were recorded using a Brucker Advance III spectrometer at a frequency of 400 MHz and 22 °C, at Centro de Materiais da Universidade do Porto (CEMUP), Porto, Portugal.

Analysis by gas chromatography with flame ionization detector (GC-FID) were performed with a Varian CP-3380 gas chromatograph equipped with a FID detector using helium as carrier gas, a fused silica Varian Chrompack capillary column CP-Sil 8 CB Low Bleed/MS (30 m × 0.25 mm i.d.; 0.25 μm film thickness) and a chiral column, fused silica Varian Chrompack capillary column CP-Chiralsil-Dex CB (25 m × 0.25 mm i.d.; 0.25 μm film thickness). The temperature program was: 70 °C (1 min), 20 °C min^{-1}, 200 °C (5 min); injector temperature,

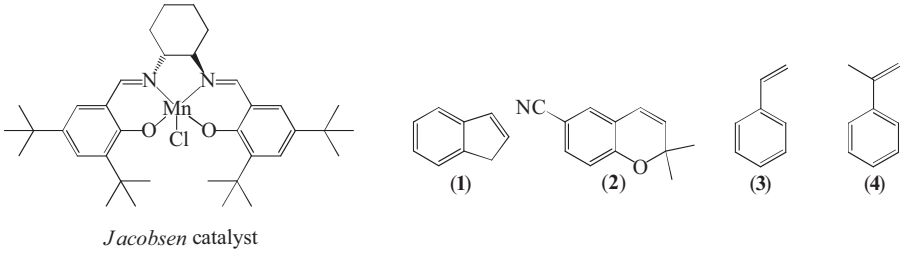

Fig. 2. *Jacobsen* catalyst and benzylic olefins used in this work: indene (**1**), 6-cyan-2,2′-dimethylchromene (CN-chrom) (**2**), styrene (**3**) and α-methylstyrene (**4**).