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Graphical Abstract



Highlights

- Arene epoxidation was obtained by *Jacobsen* catalyst using H_2O_2 in ethanol at 40°C
- Use of co-catalyst combined with protic solvent enhanced catalytic efficiency
- Catalytic reactivity is explained by formation of oxo- or hydroperoxy active species
- Role of protic solvent associated with hydrogen bonding with active species
- Best C % was obtained with ammonium acetate and best *ee*% with 1-methylimidazole

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-methylimidazol and imidazol) it was observed the highest substrate conversions, whereas for basic co-catalysts (1-methylimidazol, 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, 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 multi-step 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)porhyrin-OOH]⁻, favored in basic conditions, followed by the heterolysis through the "*push and pull*" mechanism to form a high valent oxo species [Mn(V)porhyrin=O] as shown in Figure 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].

Figure 1

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), Figure 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-methylimidazol, 2-methylimidazol, 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*-butylsalicylidene)-1,2-cyclohexane-diaminomanganese(III) chloride (*Jacobsen* catalyst), ureahydrogen peroxide addition compound (UHP, 98%), hydrogen peroxide solution 30 wt.% in H₂O (H₂O_{2(aq)}), 1-methylimidazol (1-MeIm, 99%), 2-methylimidazol (2-MeIm, 99%) and 4methylmorpholine *N*-oxide (NMO, 97%) were purchased from Aldrich. Pyridine (Py) and ammonium acetate (NH₄AcO, *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 (¹H 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 μ m film thickness) and a chiral column, fused silica Varian Chrompack capillary column CP-Chiralsil-Dex CB (25m × 0.25mm i.d.; 0.25 μ m film thickness). The temperature program was: 70 °C (1 min), 20 °C min⁻¹, 200 °C (5 min); injector temperature, 200 °C; detector temperature, 250 °C. Each aliquot was injected in both columns; the first was used to obtain conversion and selectivity percentages and the second to obtain

ee% values. Substrate conversion (C%) was calculated both by determining the reacted substrate using the internal standard (i.s.) method, C% = { $[A(substrate)/A(i.s.)]_{t=0h}$ – $[A(substrate)/A(i.s.)]_{t=xh}$ × 100 / $[A(substrate)/A(i.s.)]_{t=0h}$ and based on the chromatographic peak areas of substrate and products, C% = $[\Sigma A(products)]$ × 100/ $[A(substrate) + \Sigma A(products)]$; the values obtained by the two procedures always agreed within 10%. The epoxide selectivity (S%) and enantiomeric excess (*ee*%) were calculated as follows: S% = $[A(epoxide)] \times 100/[\Sigma A(products)]$, *ee*% = $[A(major enantiomer) - A(minor enantiomer)] × 100/<math>[\Sigma A(enantiomers)]$, where A stands for chromatographic peak area. The turnover frequency, TOF, was calculated as: TOF = [number of moles of epoxide formed/number moles of catalyst used]/reaction time; the number of moles of epoxide formed was calculated taking into account C% and S% values. Confirmation of the catalytic results obtained by GC-FID was done by analysis of a total reaction mixture by ¹H NMR: the reaction mixture was concentrated, eluted through a small plug of silica, washed with *n*-hexane:ethyl acetate (20%) mixture, evaporated to dryness and finally analyzed by ¹H NMR in CDCl₃.

2.3 Catalytic experiments

Generally, the reactions were performed using 0.3 mmol of substrate; 0.3 mmol of cocatalyst; 0.2 mmol of chlorobenzene (GC internal standard) and *Jacobsen* complex (15 mg, 0.024 mmol) as catalyst; in 4 mL of solvent with continuous stirring at the desired temperature. The oxidant (3 mmol) was added totally at the beginning of the reaction (slowly to prevent gas evolution) or progressively at a rate of 3 mmol h⁻¹. The progress of the reaction was monitored by GC-FID, by removing small samples of the reaction mixture every 15 min. The relative proportions of compounds usually did not change from 30-45 min of reaction time, when oxidant was totally added at the beginning of the reaction or from 120-135 min when oxidant was progressively added to the reaction mixture.

The epoxide stereoselectivity was determined by ¹H NMR in comparison with published data for (-)-(IR,2S)-1,2-indene oxide [47,48] and (3R,4R)-6-cyan-2,2'-dimethychromene [49] or by comparison of analytic standards for (R)-(+)-styrene oxide.

(*3R*,*4R*)-6-*cyan*-2,2'-*dimethylchromene*: ¹H NMR (400 MHz, CDCl₃, 22°C, TMS): δ=1.45 (s, 6H, H-Me), 3.54 (d, 1H, H-3, *J*=4.2 Hz), 3.91 (d, 1H, H-4, *J*=4.2 Hz), 6.86 (m, 1H, H-8), 7,28 (s, 1H, H-5), 7.52 (d, 1H, H-7, *J*=8.6 Hz).

2.4 Quantification of hydrogen peroxide

The concentration of hydrogen peroxide was quantified using a methodology based on ¹H NMR spectroscopy [50] owing to the linear correlation of $[H_2O_2]$ with the position of the coalescence peak of hydrogen peroxide and water for concentrations in the range 0.1-10 mol dm⁻³ and linear correlation of concentration with peak area for lower concentrations ($10^{-3}-0.1$ mol dm⁻³). Calibration samples were prepared by mixing hydrogen peroxide with the deuterated solvent (CDCl₃:CD₃OD, 1:1), with [2-MeIm] of 0.075 mol dm⁻³ and [H₂O₂] from 0.0-0.75 mol dm⁻³. The coalescence peak of hydrogen peroxide and water shifted from 5.07 to 4.70 ppm. A reaction of indene oxidation was performed in conditions of section 2.3 but using the above mixture of solvents (CDCl₃:CD₃OD, 1:1), 2-MeIm as co-catalyst and the reaction temperature was 40°C and the [H₂O₂] determined at different reaction times, using the CHCl₃ peak as reference.

3. Results and Discussion

The effect of different reaction conditions on catalytic performance was evaluated for indene, CN-chrom, Sty and Me-Sty by analyzing substrate conversion (C%), epoxide selectivity (S%), enantiomeric excess (*ee*%) and TOF. The behavior of ethanol as solvent was compared with other protic (CH₂Cl₂:MeOH) and aprotic (CH₃CN) solvents, the addition form

of hydrogen peroxide, as an aqueous solution $[H_2O_{2(aq)}]$ or as anhydrous urea adduct (UHP), the effect of different co-catalysts and the reaction temperature were also analyzed.

3.1 Effect of solvent, oxidant addition form and reaction temperature

The results of catalytic oxidation of indene under different conditions are presented in Table 1. In the presence of 2-methylimidazole (2-MeIm) as co-catalyst, using hydrogen peroxide in the form of UHP at 40°C, the effect of the solvent CH_2Cl_2 :MeOH (1:1) was compared with EtOH (Table 1, entries 1 and 3). The two catalytic reactions showed similar performance with high C% = 96 and 98% and *ee*% =77%; the epoxide selectivity was also high, 99% and 97%, indicating that epoxide opening pathways have low significance in these conditions. The TOF was 96.5 and 92.7 h⁻¹, respectively. The previous reactions were performed using an excess of 10 molar equivalents of oxidant relatively to the substrate. When the amount of UHP was decreased to 2 molar equivalents, in the same conditions of entry 1, there was a significant decrease in C% and TOF, Table 1, entry 2.

Table 1

On the other hand, in ethanol and using the hydrogen peroxide in the form of aqueous solution (totally added at the beginning of the reaction, entry 4), the C% decreased to 91% with maintenance of *ee*% (78%), but when the aqueous hydrogen peroxide was progressively added to the reaction mixture at a rate of 3 molar equivalents.h⁻¹ (entry 5), the conversion increased again to 96% and *ee*% was kept constant at 77%. The control of H_2O_2 concentration in the reaction mixture was performed by ¹H NMR methodology during a catalytic reaction in conditions of entry 5 [50]. This experiment showed the total consumption of H_2O_2 at the end

of reaction and the occurrence of H_2O_2 decomposition, probably induced by the presence of the catalyst or due to the lower stability of H_2O_2 at the reaction temperature.

With both H_2O_2 oxidant forms, when the reaction temperature was lowered from 40°C to room temperature (approximately 20°C) a decrease on *ee*% was observed from 77% to 65-66%, but the C% values were kept at 95-96% (entries 6 and 7).

The oxidation of indene was also performed with a higher quantity of the *Jacobsen* catalyst (from 6.7% to 10% mol, Table 1, entry 8). In this case, the C% was complete (100%), but a decrease of *ee*% to 69% was observed; since the ratio co-catalyst:catalyst was lower, this result evidenced the importance of the molar relation between catalyst and co-catalyst on the observed enantioselectivity and, consequently, the role of the co-catalyst in the catalytic process.

The use of a similar co-catalyst 1-methylimidazole (Table 1, entries from 9 to 14), when the oxidant was $H_2O_{2(aq)}$ totally added at the beginning of the reaction, also led to similar catalytic performance when the solvent was ethanol or a mixture of CH_2Cl_2 :MeOH (entries 9 and 10). However, when the protic solvent ethanol was replaced by the aprotic solvent in the same reaction conditions (entries 11 and 12), a significant decrease in C%, from 85% to 62% and in *ee*%, from 94% and 75%, were observed, indicating the importance of the protic solvent for the catalytic process. With this co-catalyst, the effect of temperature was analyzed by comparing the catalytic performance at 40°C to that at room temperature (20°C) and keeping the other conditions (entries 11 and 13): in this case, a decrease in *ee*% from 94% to 86% was observed, although C% was kept at 85%.

The effects of temperature and protic vs aprotic solvent on the catalytic performance described previously were also tested for the reaction using the co-catalyst ammonium acetate, Table 1 entries from 15 to 20. On going from the oxidation reaction of indene at 40°C to room temperature (entries 15-17), there was a decrease in *ee*% from 89 to 69%, but in both

cases there was a nearly complete substrate conversion of 98-99%; at 0°C, the *ee*% was identical to that observed at r.t. (70%), but the C% slightly decreased to 95%. Furthermore, the change of EtOH to CH₃CN (entries 15 and 19), produced a decrease in C% from 98% to 69% and *ee*% from 89 to 73%.

The catalytic system was also tested in the absence of *Jacobsen* catalyst with ammonium acetate as co-catalyst (entry 20), with no substrate conversion observed.

The oxidation of CN-chrom (2) was screened for the above reaction conditions and, as can be seen in Table 2, it was possible to epoxidize this alkene in ethanol with 100% epoxide selectivity.

Table 2

For this substrate the best catalytic performances were obtained using ammonium acetate or 2-methylimidazole as co-catalysts, in ethanol and hydrogen peroxide as both adduct UHP or aqueous solution; in the latter case, the oxidant was added progressively to the reaction mixture (Table 2 entries 2, 3 and 5). Although very high *ee*% (99%) was observed, the substrate conversions were moderate, C% = 28-35%, due to the deactivation of the double bond by the proximity of the CN group. When $H_2O_{2(aq)}$ was the oxidant (totally added at the beginning of the reaction, entry 1), the substrate conversion was very low, C% =14%, and once more, the reaction at room temperature led to lower *ee*% (86%, Table 2, entry 4). In the presence of pyridine the C% and *ee*% were relatively low (22% and 86%, respectively), but similar catalytic performance for both protic solvents, ethanol and mixture of CH₂Cl₂:MeOH was observed.

3.2 The effect of co-catalyst

The effect of the different co-catalysts in the catalytic oxidation of indene (Table 1) and styrene (Table 3) by adduct UHP in ethanol at 40°C was analyzed: the use of both amphoteric co-catalysts (NH₄AcO, 2-MeIm, Im) and basic co-catalysts (1-MeIm, NMO and Py) led to different C% and *ee*% values that are summarized in Figure 3.

Table 3	
Figure 3	

For indene oxidation (Figure 3, a), all the amphoteric co-catalysts, NH₄AcO, 2-MeIm and Im, led to high C% values in the range 97-98% and *ee*% decreased in the order: NH₄AcO > 2-MeIm > Im, from 89% to 70%. The *ee*% for the reaction in the presence of 2-MeIm and Im compare with *ee*% values of the reaction performed without co-catalyst, but all the C% values are significantly higher than that obtained for the reaction performed in the absence of co-catalyst.

For the basic co-catalysts, 1-MeIm and Py, the C% values are lower (85% and 74%, respectively) than those of reactions in the presence of amphoteric co-catalysts. The former is approximately of the same magnitude as that of the reaction in the absence of co-catalyst, but the latter shows a negative effect relatively to the absence of co-catalyst. Furthermore, the reaction in the presence of 1-MeIm showed the highest *ee*% value observed (94%), whereas for Py *ee*% = 84%, which is of the same magnitude as that of the reaction in the absence of co-catalyst.

In order to test the use of a higher amount of co-catalyst in the catalytic reaction, NH_4AcO and 1-MeIm were chosen as representatives of the amphoteric and basic co-catalysts, respectively. Indene oxidation was performed doubling the molar quantity of 1-MeIm (Table 1, entry 14) or NH_4AcO (Table 1, entry 18), but keeping the other reaction

conditions. No significant variation of the catalytic performance of the catalyst was observed since the C% and *ee*% values were of the same magnitude as those described previously.

The oxidation of styrene (**3**) was also studied in ethanol by the catalytic system *Jacobsen*:H₂O₂ (Table 3). Styrene is less reactive relatively to indene and due to the terminal position of the double bond the epoxidation reaction is also less selective for styrene epoxide (S% values in the range of 91-94%), since low amounts of benzaldehyde were formed. The effect of co-catalysts for styrene oxidation (Table 3 and Figure 3, b) showed the same reactivity pattern that was typically observed as for indene (Figure 3, a). Although the C% and *ee*% values are lower relatively to indene, similarly, the highest C% values are observed for amphoteric catalysts: NH₄AcO (68%), 2-MeIm (66%) and Im (56%) and the *ee*% values follow the order NH₄AcO (66%) > 2-MeIm (58%) > Im (54%). The basic co-catalyst 1-MeIm, when compared to the previous ones, led to lower C% (51%), but the highest *ee*% value observed for this substrate (72%); NMO gave the second highest *ee*% (66%) and a higher conversion relatively to 1-MeIm (62%). As previously, the use of pyridine resulted almost usefulness, since its presence in the reaction medium did not enhance the catalytic performance relatively to the reaction in the absence of co-catalyst (Table 3, entry 7).

Finally, higher catalytic efficiency was observed for the epoxidation of α -methylstyrene by the system *Jacobsen* catalyst: H₂O₂: UHP: ethanol: 40°C (Table 3) when compared to styrene (79% substrate conversion, 96% epoxide selectivity and 98% *ee*, due to the higher activation and steric hindrance of the double bond.

3.3 Mechanistic considerations

The present results showed the pronounced effect of the solvent (protic/aprotic), the cocatalyst properties and the reaction temperature, in the activity and selectivity of the *Jacobsen* catalyst in arene epoxidation by hydrogen peroxide and they are in accordance with a multi-

step mechanism for the activation of hydrogen peroxide, where the extension of the different pathways are highly sensitive to the reaction conditions [37,38].

In agreement with what was already described for the activation of H_2O_2 by other metal complexes, namely metalloporphyrins and by peroxidase, [51,52] the activation of H_2O_2 by Mn(salen) based complexes can be similarly described through a stepwise reaction, as schematically represented in Figure 4. Upon addition of hydrogen peroxide to the catalyst (I), the peroxyl group is activated through formation of a [Mn(III)salen-H_2O_2] adduct (Figure 5, II), which by deprotonation leads to a hydroperoxy intermediate, [Mn(III)salen-OOH]⁻ (III). Then, the hydroperoxy intermediate (III) can undergo protonation and dehydration, generating the oxo-species [Mn(V)salen=O] (IV). The hydroperoxy species can be able to epoxidize olefins through a concerted mechanism, as observed for the epoxidation by peracids, namely *m*-CPBA, since the electrophilicity of the distal peroxidic oxygen is enhanced, due to metal bond activation. On the other hand, the activity of the oxo-species was found to be high and independent of the oxidant used and was considered to be the intermediate mainly responsible for the high enantioselectivity of *Jacobsen* catalyst relatively to other systems, as a consequence of the high proximity of the active oxygen to the non-planar and hindered *salen* ligand [53,54].

Figure 4

The effect of the reaction solvent, CH_3CN (aprotic solvent) vs EtOH (protic solvent), observed during the catalytic epoxidation of indene is highlighted in Figure 5, either in the absence of co-catalyst or in the presence of 1-MeIm or NH_4AcO , co-catalysts with basic and amphoteric character, respectively.

Figure 5

In the absence of co-catalyst (Figure 5, a and d), the epoxidation performance was significantly enhanced when the reaction was carried out in EtOH compared to CH_3CN : the C% was 82% vs 39% and the asymmetric induction was 75% vs 51%. This result can be related with the possibility of hydrogen bond formation between the protic solvent and the active oxidizing intermediates, exemplified by intermediate (**V**) in Figure 4, in analogy with what was proposed for H_2O_2 activation by metalloporphyrins and heme peroxidase [44]. This new adduct will have improved electrophilicity on the distal oxygen of the peroxyl bond and consequently high reactivity towards epoxidation; concomitantly, the rigidity imposed by the three dimensional hydrogen bond network in the ethanol-hydroperoxy adduct may lead to the observed improvement of *ee*% values.

In the presence of the co-catalysts, the epoxidation performance was further enhanced: 1-MeIm led to the highest *ee*% and NH₄AcO to the highest C%. This tendency can be also noticed for the other co-catalysts (Figure 3), where the different reactivity pattern is ascribed to co-catalysts with amphoteric or basic characters. For both indene and styrene epoxidation, the amphoteric co-catalysts (NH₄AcO, 2-MeIm and Im) always led to the highest substrate conversions, whereas basic co-catalysts (1-MeIm, NMO and pyridine), produced relatively higher *ee*% and relatively lower C%. These results can be explained by the preferential formation of oxo-species with amphoteric co-catalysts, in accordance with their highest capability to induce the dehydration step through protonation of the peroxyl bond in intermediate (**III**) to afford (**IV**), as shown in Figure 4 (*pull* effect). Besides the effect of the acid-base properties of the co-catalyst in the *Jacobsen* catalyst performance, discussed above, they also act as axial ligands and consequently their electronic properties can influence differently the reactivity of the metal centre in the intermediates (**III**) and (**IV**), thus

originating a variety of *ee*% and C% values for each group of co-catalysts (amphoteric vs basic).

Previous reports on Mn(*salen*) epoxidation showed that low temperatures tend to induce higher *ee*% in comparison with reactions performed at room temperature.[9] However, an efficient epoxidation of 2-styrylchromones and analogues using *Jacobsen* catalyst and hydrogen peroxide at 40°C was reported [55,56]. In this present work, we observed higher enantiomeric induction at 40°C compared to room temperature. The improvements in *ee*% with temperature reaction were higher for amphoteric co-catalysts (for 2-MeIm and NH₄AcO the improvements were 17% and 20%, respectively) than for basic co-catalysts (for 1-MeIm the improvement was 8%). These can be related with the highest extension of the dehydration reaction and concomitant formation of the oxo-species during the catalytic cycle, in the case of amphoteric co-catalysts.

4. Concluding remarks

The enantioselective epoxidation of mono- and bicyclic arenes using the system *Jacobsen* catalyst: co-catalyst: hydrogen peroxide was achieved using a mild synthetic route comprising ethanol as reaction solvent at 40°C. High catalytic performances (very high substrate conversions and enantiomeric inductions) were obtained, both using the hydrogen peroxide-urea adduct and aqueous hydrogen peroxide added progressively to the reaction mixture combined with co-catalysts with amphoteric and basic properties. Typically, better catalytic performances were observed for the protic solvent compared with the aprotic solvent CH₃CN and the amphoteric co-catalysts (NH₄AcO, 2-MeIm and Im) always led to the highest substrate conversions, whereas the basic co-catalysts (1-MeIm, NMO and pyridine), led to relatively higher *ee*% and relatively lower C%. Furthermore, the reactions at 40°C showed higher enantiomeric induction than those performed at room or lower temperature.

The observed effects of solvent, co-catalyst and reaction temperature were explained by a multi-step mechanism for activation of hydrogen peroxide with the formation of different active species, Mn(III)*salen* hydroperoxy- and oxo- intermediates, depending on the reaction conditions. The positive effect of protic solvent on the reaction performance was explained by the establishment of hydrogen bonding between the protic solvent and the active oxidizing intermediates enhancing both the electrophilicity and steric hindrance.

The development of heterogeneous catalysts by immobilization of chiral Mn(III)*salen* complexes onto solid inorganic supports and their catalytic performance in these optimized conditions are currently being studied [57]: these will add the advantages of using mild reaction conditions and the inherent advantages of easy separation and recycling of the catalyst.

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Table 1. Catalytic data for the oxidation of indene (1) in the presence of *Jacobsen* catalyst with hydrogen peroxide and UHP in different reaction conditions.



	Reaction Conditions ^a				Catalytic results (%)		s (%)	$\mathrm{TOF}^{\mathrm{f}}$	
Entry	Solvent	Oxidant ^b	Co-cat	T(°C)	Other	C ^c	\mathbf{S}^{d}	ee ^e	(h^{-1})
1	CH ₂ Cl ₂ :MeOH ^g	UHP	2-MeIm	40°C		98	99	77	96.5
2	CH ₂ Cl ₂ :MeOH ^g	$\mathrm{UHP}_{\mathrm{2eq}}^{\mathrm{h}}$	2-MeIm	40°C		37	99	78	36.4
3	EtOH	UHP	2-MeIm	40°C		96	97	77	92.7
4	EtOH	$H_2O_{2(aq)}$	2-MeIm	40°C		91	97	78	87.8
5	EtOH	H ₂ O _{2(aq) prog}	2-MeIm	40°C		96	97	77	92.7
6	EtOH	UHP	2-MeIm	r.t.		96	98	66	93.6
7	EtOH	$H_2O_{2(aq) prog}$	2-MeIm	r.t.		95	99	65	93.6
8	EtOH	$H_2O_{2(aq) prog}$	2-MeIm	40°C	Cat. 10%	100	94	69	62.7
9	CH ₂ Cl ₂ :MeOH ^g	$H_2O_{2(aq)}$	1-MeIm	40°C		75	97	93	72.4
10	EtOH	$H_2O_{2(aq)}$	1-MeIm	40°C		77	96	90	73.6
11	EtOH	UHP	1-MeIm	40°C		85	97	94	82.0
12	CH ₃ CN	UHP	1-MeIm	40°C		62	96	75	59.2
13	EtOH	UHP	1-MeIm	r.t.		85	97	86	82.0
14	EtOH	UHP	1-MeIm	40°C	+1-MeIm	84	96	94	80.2
15	EtOH	UHP	NH ₄ AcO	40°C		98	96	89	93.6
16	EtOH	UHP	NH ₄ AcO	r.t.		99	96	69	94.6
17	EtOH	UHP	NH ₄ AcO	0°C		95	96	70	90.7
18	EtOH	UHP	NH ₄ AcO	40°C	+NH ₄ AcO	100	91	89	90.5
19	CH ₃ CN	UHP	NH ₄ AcO	40°C		69	98	73	67.3
20	EtOH	UHP	NH ₄ AcO	40°C	no cat.	0	-	-	-
21	EtOH	UHP	Im	40°C		97	97	70	93.6
22	EtOH	UHP	Ру	40°C		74	96	84	70.7
23	EtOH	UHP		40°C		82	87	75	71.0
24	CH ₃ CN	UHP	-	40°C		39	95	51	36.9

^aReaction conditions unless otherwise said: substrate (0.3 mmol), chlorobenzene - GC internal standard (0.2 mmol), cocatalyst (0.3 mmol), Jacobsen catalyst at 6.7 molar %, hydrogen peroxide (3 mmol), solvent (4 mL), results after 30 min of reaction time. ^bThe hydrogen peroxide was added in two forms: anhydrous adduct with urea (UHP) or 30% aqueous solution [H₂O₂(aq)], the addition was performed totally at the beginning or progressively (prog) at a rate of 3 mmol h⁻¹, in this last case the catalytic results are reported after 1h of reaction time; ^cConversion; ^dEpoxide selectivity; ^cEnantiomeric excess;^fTurnover frequency; ^gmixture (1:1); ^hreaction in the same conditions as in a) but using 2 molar equivalents of oxidant.

Table 2. Catalytic data for the oxidation of chromene (2) in the presence of Jacobsen catalyst with

hydrogen peroxide and UHP in different reaction conditions.



	Reaction Conditions ^a				Catalyt	ic result		
Entry	Solvent	Oxidant ^b	Co-cat	T(°C)	C ^c	\mathbf{S}^{d}	ee ^e	TOF $(h^{-1})^{f}$
1	EtOH	$H_2O_{2(aq)}$	2-MeIm	40°C	14	100	99	13.9
2	EtOH	$H_2O_{2(aq) prog}$	2-MeIm	40°C	30	100	99	29.9
3	EtOH	UHP	2-MeIm	40°C	28	100	99	27.9
4	EtOH	UHP	2-MeIm	r.t.	23	100	95	22.9
5	EtOH	UHP	NH ₄ AcO	40°C	35	100	99	34.8
6	EtOH	UHP	Ру	40°C	22	100	86	21.9
7	CH ₂ Cl ₂ :MeOH ^g	UHP	Ру	40°C	23	100	84	22.9

^aReaction conditions unless otherwise said: substrate (0.3 mmol), chlorobenzene - GC internal standard (0.2mmol), cocatalyst (0.3 mmol), Jacobsen catalyst at 6.7 molar %, hydrogen peroxide (3 mmol), solvent (4 mL), results after 30 min of reaction time. ^bThe hydrogen peroxide was added in two forms: anhydrous aduct with urea (UHP) or 30% aqueous solution $[H_2O_2(aq)]$, the addition was performed totally at the beginning or progressively (prog) at a rate of 3 mmol h⁻¹, in this last case the catalytic results are reported after 1h of reaction time; ^cconversion; ^dEpoxide selectivity; ^cEnantiomeric excess; ^fTurnover frequency; ^gmixture (1:1).

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			Catalytic results					
Entry	Substrate	Co-cat	C (%) ^b	S (%) ^c	$ee~(\%)^{d}$	TOF $(h^{-1})^{e}$		
1		NH ₄ AcO	68	91	66	61.6		
2		2-MeIm	66	94	58	61.7		
3		Im	56	_f	54	-		
4		1-MeIm	51	93	72	47.2		
5		Ру	43	93	47	39.8		
6	·	NMO	62	92	66	56.8		
7		-	42	91	48	38.0		
8		2-MeIm	79	96	98	75.5		

Table 3. Catalytic data for the oxidation of styrene (3) and α -methylstyrene (4) by *Jacobsen* catalyst with UHP in ethanol.^a

^aReaction conditions: substrate (0.3 mmol), chlorobenzene - GC internal standard (0.2 mmol), co-catalyst (0.3 mmol), *Jacobsen* catalyst at 6.7 molar %, hydrogen peroxide (UHP, 3 mmol), ethanol (4 mL), results after 1h of reaction time; ^bconversion; ^cEpoxide selectivity; ^dEnantiomeric excess; ^cTurnover frequency; ^fNot determined.

Captions to Figures

- Figure 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.
- Figure 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).
- Figure 3. Effect of the co-catalyst on substrate conversion and enantioselectivity of epoxidation of a) indene (1); b) styrene (3).
- **Figure 4.** Mechanism proposal for arene epoxidation by hydrogen peroxide/UHP in the presence of *Jacobsen* catalyst
- Figure 5. Comparison of catalytic efficiency and enantioselectivity for indene epoxidation in protic/aprotic solvents in the presence and absence co-catalyst.

Figure 1



Figure 2



Figure 3



Figure 4





