Transition Metal-free Epoxidation of Alkenes Based on the Existence of (2-hydroxypropyl)-β-CD

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Abstract: A green, efficient epoxidation of alkenes with hydrogen peroxide (H$_2$O$_2$) and sodium bicarbonate (NaHCO$_3$) catalyzed by (2-hydroxypropyl)-β-cyclodextrin (2-hp-β-CD) in aqueous solution has been investigated in detail. A range of alkenes were epoxidized at ambient temperature with high yields.

Keywords: 2-hp-β-cyclodextrin, alkenes, epoxidation, inclusion complex.

1. INTRODUCTION

It is significant for the epoxidation of alkenes because of the production of epoxides, a major industrial organic intermediate and is used as the critical raw materials of drugs, chemicals and food [1, 2]. Lane and Burgess [3] reviewed metal-catalyzed epoxidations of alkenes with hydrogen peroxide, the loss of active metal ingredients and use of toxic organic solvents in some reactions made the process less satisfactory. Thus, metal-free epoxidation of alkenes under mild aqueous conditions with biocatalytic approaches [4-8] are attracting increasing interest, these enzyme catalysts are renewable, non-toxic and biodegradable. Moreover, metal-free asymmetric epoxidations [9-11] have also been developed recently. The increasing focus on the metal-free epoxidation of alkenes promotes further optimization of these methods toward greener processes.

Cyclodextrins, which are cyclic oligosaccharides with hydrophobic cavities, can promote oxidation with excellent selectivity via non-covalent bonding of host–guest complexes [12] as seen in enzymes; and the corresponding reports [13-16] about epoxidation and organic synthesis catalyzed by hp-β-cyclodextrin and its derivatives in water involving the formation of host–guest complexes are increasing. The inclusion rests with the space structures, size, and hydrogen bonds of the guest [17, 18]. It was ever reported that cyclodextrin derivatives could promote the asymmetric epoxidation of alkenes by working as catalyst or the host of the cyclodextrin-substrate complex [19-22]; Chan and coauthors [21] reported a ketoester form the modified cyclodextrin for asymmetric epoxidation of a series of alkenes in 31–40% ee. Rousseau and coauthors [22] investigated four cyclodextrin derivatives as catalysts for space selective epoxidation of a series of alkenes in 0–45% ee with yield of 17–100% in the existence of oxone.

In lots of research fields involving cyclodextrins, we focused on its substrate-selective reactions [23-25]. Surendra [26] reported a novel method about the oxidation of lots of alcohols with NaClO and KBr as oxidants, in comparison with their report, only these alcohols with suitable shape, size and space structures could be oxidized with high yields in our report [23]. It had been shown earlier that substrate-selective oxidation of aldehydes [24] and sulfides [25] were achieved in the same way. In continuation of our efforts, a mild, transition metal-free and substrate-selective approach for the epoxidation of alkenes with H$_2$O$_2$ / NaHCO$_3$ catalyzed by 2-hp-β-cyclodextrin in aqueous solution has been developed.

2. EXPERIMENTAL

The epoxidation was carried out as follows. 30 mL of double-distilled water was heated to 60°C, 2 mmol 2-hp-β-cyclodextrin could be completely dissolved in this water by stirring constantly for about 2 minutes. At this time, 2 mmol styrene was slowly dropped into the solution. Then 25 mmol sodium bicarbonate and 4 × 1 mL of 30% H$_2$O$_2$ was slowly added. The crude product was separated by adding ethyl acetate (60 mL), dried in a vacuum until the solvent was completely removed. Epoxides were all analyzed by GCMS-QP2010.

3. RESULTS AND DISCUSSION

An efficient, selective and transition metal-free epoxidation of alkenes with H$_2$O$_2$ / NaHCO$_3$ as an oxidant catalyzed by 2-hp-β-cyclodextrin was achieved here with water as the only solvent (Scheme 1).

R\[2-hp-β-cyclodextrin] + NaHCO$_3$, 30% H$_2$O$_2$, H$_2$O, 60 °C

Scheme 1. Epoxidation of alkenes catalyzed by (2-hp-β-CD) in aqueous solution.
In order to achieve the optimum epoxidation conditions, styrene as a representative reagent has been investigated at different temperatures; the results are shown in Fig. (I).

Fig. (I) shows that temperature could essentially affect the conversion of styrene and the yield and ratio of the oxidation products (2-phenyloxirane and benzaldehyde). While the reaction temperature was lower than 60°C, the epoxidation rate increased with the increasing temperature, and styrene could be almost completely converted to 2-phenyloxirane without side reactions (curves a, b and c); however, if the reaction temperature was over 60°C, the yield of the desired product 2-phenyloxirane decreased with the increasing temperature, and the by-product such as benzaldehyde could be formed via oxidative cleavage of double bond (curve c). Moreover, elevated temperature promoted decomposition of hydrogen peroxide. Therefore, 60°C was used as the optimum temperature in the later experiments.

During the investigation of biomimetic approaches for styrene with hydrogen peroxide involving 2-hp-β-cyclodextrin in water, it was found that the different amounts of 2-hp-β-cyclodextrin, hydrogen peroxide and sodium bicarbonate could influence the conversion of styrene and the yields of products dramatically, as shown in Table 1 and Table 2.

Table 1. Effect of the different amounts of 2-hp-β-cyclodextrin and H₂O₂ on the epoxidation of styrene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount of hp-β-CD / mmol</th>
<th>Amount of 30% H₂O₂ / mL</th>
<th>Conv. / %</th>
<th>Yield of 2-phenyloxirane / %</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>2</td>
<td>2</td>
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<td>39</td>
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<td>51</td>
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<tr>
<td>7</td>
<td>1</td>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92</td>
<td>71</td>
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</table>

<sup>a</sup>Reaction conditions: styrene (2 mmol), H₂O (30 mL), NaHCO₃ (25 mmol), 60°C, reaction time 2.5 h.

Table 2. Epoxidation of styrene at the different amount of NaHCO₃.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount of NaHCO₃ / mmol</th>
<th>Conv. / %</th>
<th>Yield of 2-phenyloxirane / %</th>
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<tr>
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<td>0</td>
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<td>59</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>35</td>
<td>82</td>
<td>65</td>
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<sup>a</sup>Reaction conditions: 2-hp-β-cyclodextrin (2 mmol), styrene (2 mmol), H₂O (30 mL), 4 mL of 30% H₂O₂ (1 mL at the start, then 1 mL every 0.5 h), 60°C, reaction time 2.5 h.
entry 3), and the yield of the desired product 2-phenyloxirane increased from 47% to 88%. It should be also noticed the amount of 2-hp-β-cyclodextrin was sensitive. When the amount of 2-hp-β-cyclodextrin was less than 2 mmol, 2 mmol styrene could not be completely oxidized at 60°C, and the yield of 2-phenyloxirane was also much lower (entries 5-7).

Sodium bicarbonate was used to produce peroxy acids instantly from hydrogen peroxide in the classical bicarbonate-activated peroxide route [27, 28]. The peroxy acid generated was then utilized directly for the epoxidation of styrene. Table 2 (entries 1-4) shows that NaHCO₃ additive is crucial and styrene could not be oxidized at all without sodium bicarbonate (entry 1). The amount of sodium bicarbonate affected the oxidation greatly, rise in the amount of sodium bicarbonate strongly increased the conversion of styrene (2 mmol) from 0 to 99% and the yield of 2-phenyloxirane from 0 to 88% (entries 1 and 3). However, when the amount of sodium bicarbonate was higher than 25 mmol, both the conversion of styrene and the yield of 2-phenyloxirane were significantly reduced (entry 4).

Therefore, 2 mmol of 2-hp-β-cyclodextrin, 4 mL of 30% H₂O₂ (1 mL at the start, then 1 mL every 0.5 h), 25 mmol sodium bicarbonate and 60°C were determined as the optimum reaction condition for epoxidation of alkenes (2 mmol).

For the further application of the method, the epoxidation of several alkenes has been investigated under the above experimental conditions. The results of the epoxidation of these alkenes are shown as in Table 3.

It is well-known that cyclodextrins and substrates may form inclusion complex in aqueous solution [14, 15]. The inclusion rests with the space structures, size, and hydrogen bonds between cyclodextrin and guest. This interaction may activate the substrate and enhance the solubility of the substrate in aqueous solution [24]. In the present research, the space configuration of guest molecules is crucial for

**Table 3. Epoxidation of various alkenes by H₂O₂ in the presence of 2-hp-β-cyclodextrin**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time/h</th>
<th>Conv./%</th>
<th>Yield/%</th>
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</tbody>
</table>

*Reaction conditions: substrate (2 mmol), 2-hp-β-cyclodextrin (2 mmol), H₂O (30 mL), NaHCO₃ (25 mmol), 4 mL of 30% H₂O₂ (1 mL at the start, then 1 mL every 0.5 h), 60°C.*
smooth epoxidation. As shown in Table 2, some aromatic alkenes (entries 1–2) and cyclohexenes (entries 3–5) could be oxidized to the corresponding epoxides catalyzed by 2-hp-β-cyclodextrin in water with excellent yields, however, some other aromatic alkenes or cyclohexenes (entries 6–7) could not be oxidized to the corresponding epoxides in the same reaction conditions, indicating that the epoxidation of alkenes was a substrate-selective reaction in the existence of 2-hp-β-cyclodextrin in aqueous solution, and those alkenes with larger molecular size were hardly oxidized by hydrogen peroxide because the complexation of the alkenes and 2-hp-β-cyclodextrin were hardly formed due to the larger steric effect (entries 6–7). This could be further supported by the fact that reaction rate of the epoxidation of D-limonene (entry 5) was much lower than cyclohexene (entry 3) or 1-methylecyclohex-1-ene (entry 4) for the existence of –(CH₂CH=CH₂) group.

1-octene and 2-octene could not be oxidized by H₂O₂ / NaHCO₃ in 2-hp-β-cyclodextrin aqueous solution, no products were detected within 6 hours (entries 8–9). The result is similar to oxidation of 2-octanol and 1-octanol [23] or the reaction of 2-heptyl-1, 3-dioxolane [29] in water, where the inclusion composed of substrate with long chain alkyl groups and β-cyclodextrin were difficultly formed, the epoxidation of 1-octene and 2-octene was also hardly achieved.

Based on the above research, it could be concluded that the formation of the complexation of alkenes and 2-hp-β-cyclodextrin was crucial to the epoxidation of the alkenes in water. The oxidation might follow the pathway in Fig. (2). Firstly, 2-hp-β-cyclodextrin and styrene could form host-guest inclusion in aqueous solution. At this time, the anion HCO³⁻ produced from hydrogen peroxide attacked the styrene in water. Since the C=C bond of styrene was weakened because of the existence of the 2-hp-β-cyclodextrin, the conversion of styrene would be accelerated.

**CONCLUSION**

In conclusion, a green, efficient, selective and biomimetic epoxidation of alkenes with H₂O₂ / NaHCO₃ as oxidant in water has been developed. The 2-hp-β-cyclodextrin could be easily recycled by adding some organic solvents like acetone, methanol and ethyl acetate [23].

**CONFLICT OF INTEREST**

The authors confirm that this article content has no conflict of interest.

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**REFERENCES**


