

# Transition metal-free and substrate-selective oxidation of alcohols using water as an only solvent in the presence of $\beta$ -cyclodextrin

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**Abstract**—A facile, substrate-selective and transition metal-free oxidation of benzylic and allylic alcohols catalyzed by  $\beta$ -cyclodextrin with NaOCl oxidant using water as an only solvent was developed.

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Green oxidation of alcohols under mild condition is gathering much attention in synthetic organic chemistry.<sup>1</sup> A recent review was published by Mallat and Baiker of alcohol oxidations with molecular oxygen on solid catalysis.<sup>2</sup> Although solid catalysts acting in the liquid phase under mild conditions have been developed and applied in various alcohols oxidation, a major challenge in liquid-phase oxidation of alcohols with solid catalysts is to prevent leaching of the active species and to improve the activity of these heterogeneous catalysts. Therefore, more environmentally-friendly transition metal-free oxidation of alcohols was of great interest.

Liang and coauthors<sup>3</sup> reported a transition metal-free catalyst system for aerobic alcohol oxidations. Although molecular oxygen was used as a terminal oxidant, other additives such as Br<sub>2</sub>, NaNO<sub>2</sub> and nitroxyl radicals TEMPO (2,2,6,6-tetramethyl-piperidyl-1-oxyl) were necessary to fulfil the coupling of multiple redox reactions, and the usage of CH<sub>2</sub>Cl<sub>2</sub> as solvent and high reaction temperature made this process extremely complex. Surendra and coauthors<sup>4</sup> also reported the oxidation of alcohols with *o*-iodoxybenzoic acid (IBX) catalyzed by  $\beta$ -cyclodextrin in a water/acetone mixture. The use of organic solvent acetone and oxidant *o*-iodoxybenzoic acid made this process a little less benign. They<sup>5</sup> have also reported another  $\beta$ -cyclodextrin-mediated oxidation of some alcohols using a special oxidant, that is,

*N*-bromosuccinimide (NBS), which commonly is a brominating agent.

On the basis of green principle, here a facile, substrate-selective and transition metal-free oxidation of alcohols catalyzed by  $\beta$ -cyclodextrin has been developed with cheap oxidant using solely water as the solvent. In comparison with alcohols oxidation using *o*-iodoxybenzoic acid oxidant in a water/acetone mixture and using *N*-bromosuccinimide in water, the present catalyst system presents substrate-selective performance towards alcohols oxidation and the reaction could occur entirely in water. Moreover, NaOCl is much cheaper than *o*-iodoxybenzoic acid or *N*-bromosuccinimide. Furthermore, the supramolecular catalysis mechanism of  $\beta$ -cyclodextrin under the unique host–guest relation was preliminarily explored. A significant advantage of this approach is that alcohols oxidation can be accomplished in a homogeneous system, and  $\beta$ -cyclodextrin can be recovered by the addition of organic solvents such as ethyl acetate or acetone after the reaction.

$\beta$ -Cyclodextrin (1 mmol) was dissolved in 25 mL of deionized water at 50 °C and to this was added 1 mmol of substrate while stirring. Then 5 mL of 10% NaOCl was slowly added. When the reaction was finished, the mixture was extracted by ethyl acetate (2 × 30 mL) and dried over anhydrous sodium sulfate. Then ethyl acetate was removed in vacuum. The crude product was analyzed by GC (Shimadzu GC-14C) or GC–MS (Shimadzu GCMS-QP2010) and compared with authentic samples.

Transition metal-free and substrate-selective  $\beta$ -cyclodextrin-catalyzed oxidation of alcohols was achieved here

**Keywords:** Transition metal-free oxidation; Substrate-selective oxidation;  $\beta$ -Cyclodextrin.

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using NaOCl as an oxidant with water as the only solvent (Scheme 1). These reactions do not need any other additives.

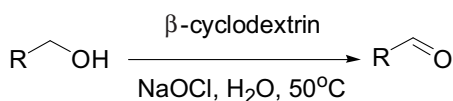
Firstly, various oxidants such as molecular oxygen, air, hydrogen peroxide and NaOCl were subject to benzyl alcohol oxidation, and the result is shown in Table 1.

It could be concluded that neither weak oxidants such as O<sub>2</sub> or air nor moderate oxidant such as H<sub>2</sub>O<sub>2</sub> could be used as effective oxidants towards benzyl alcohol with  $\beta$ -cyclodextrin (entries 2–4). The addition of strong oxidant NaClO significantly prompted the oxidation, and complete conversion from benzyl alcohol to benzaldehyde could be achieved within 1 h without the formation of by-products such as benzoic acid (entry 5). The existence of  $\beta$ -cyclodextrin is crucial because nearly no product was formed without the addition of  $\beta$ -cyclodextrin. It should be noted that  $\beta$ -cyclodextrin is stable under the present reaction system. Although seven primary hydroxyls and fourteen secondary hydroxyls exist in  $\beta$ -cyclodextrin, the recovered  $\beta$ -cyclodextrin gave identical IR spectra to the fresh one after one reaction. The fact that the recovered  $\beta$ -cyclodextrin could be reused under the same reaction condition, which will be discussed later, also supported that  $\beta$ -cyclodextrin was unchanged.

On the basis of the smooth oxidation of benzyl alcohol with NaOCl, different reaction conditions including the amount of NaOCl, the amount of  $\beta$ -cyclodextrin and reaction temperature were investigated. As a result, 1 mmol of  $\beta$ -cyclodextrin, 5 mL of NaOCl (10%) and 50 °C were chosen as a suitable reaction condition for oxidation of alcohols.

In view of the efficient oxidation of benzyl alcohol, the oxidation for various other alcohols was investigated and the results are shown in Table 2.

It is known that  $\beta$ -cyclodextrin and substrates can form host–guest complex. This complexation depends on the size, shape and hydrophobicity of the guest molecule. In the present research, benzylic primary alcohols



Scheme 1.

Table 1. Benzyl alcohol oxidation by various oxidants<sup>a</sup>

| Entry          | Oxidant                                  | Conv. (%) | Yield (%) |
|----------------|--|-----------|-----------|
| 1              | Ar                                       | <1        | <1        |
| 2              | O <sub>2</sub>                           | 3         | 3         |
| 3              | Air                                      | 3         | 3         |
| 4              | 30% H <sub>2</sub> O <sub>2</sub> (5 mL) | 6         | 6         |
| 5              | 10% NaClO (5 mL)                         | >99       | >99       |
| 6 <sup>b</sup> | 10% NaClO (5 mL)                         | 3         | 3         |

<sup>a</sup> Reaction conditions:  $\beta$ -cyclodextrin (1 mmol), benzyl alcohol (1 mmol), H<sub>2</sub>O (25 mL), 1 h, 50 °C.

<sup>b</sup> Blank experiment, without addition of  $\beta$ -cyclodextrin.

underwent smooth oxidation (entries 2–4). Commonly, the existence of electron donating group such as –OCH<sub>3</sub> group favours alcohols oxidation,<sup>6,7</sup> however the existence of –OCH<sub>3</sub> group lowered the reaction rate, indicating that the space configuration of guest molecules is more important for smooth conversion than the influence from electron effect in the present catalytic system (entry 3). This could be further supported by the fact that the heteroaromatic primary alcohol such as 2-pyridinemethanol could be converted to the corresponding aldehyde with the similar reaction rate as benzyl alcohol oxidation (entry 4). The length between benzene ring and –OH group could significantly influence the oxidation rate, since cinnamyl alcohol reacted for 4 h till the completion of conversion (entry 1).

The existence of other groups on the carbon bonded to the –OH group could make the oxidation hardly occur. For example, the oxidation of benzylic secondary alcohols could be completely retarded (entries 5–6), further indicating the importance of space configuration. As for the substrate 2-adamantanol, Liu and coauthors<sup>8</sup> reported that 2-adamantanol afforded very stable complex with complex stability constant of 13,900, indicating that L-Trp- $\beta$ -cyclodextrin could recognize the minor difference in substitution pattern. The formation of a hydrogen bond with the cyclodextrin's secondary hydroxyls is more favourable for the adamantanol's hydroxyl group at the 2-position. This result presents that host–guest complex between  $\beta$ -cyclodextrin and 2-adamantanol possesses a more rigid structure, making the hydroxyl group in 2-adamantanol hardly to be activated and converted. This might account for the lack of oxidation for 2-adamantanol (entry 7). The oxidation of 2-octanol and 1-octanol for 24 h hardly gave any products, with starting material recovered (entries 8–9). This result is comparable to the deprotection of 2-heptyl-1,3-dioxolane catalyzed by  $\beta$ -cyclodextrin, where the complexation between long chain aliphatic alcohol and  $\beta$ -cyclodextrin might be hardly formed.<sup>9</sup>

Unlike the aromatic primary alcohols or other secondary alcohols, cyclohexanol exhibited some reactivity towards the oxidation (entry 10). The bulk of the cyclohexyl group, with chair and boat conformations occupying more space than an aromatic group, might explain the low reactivity towards oxidation. The other possible reason should attribute to the inactive hydroxyl group in virtue of the absence of electron cloud conjugation.

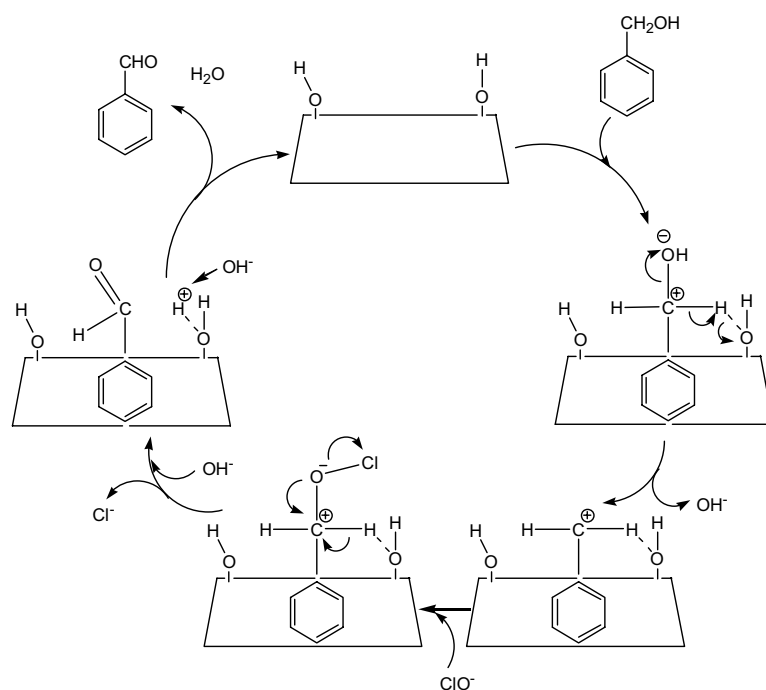
The formation of aldehydes might occur through S<sub>N</sub>1 mechanism. Firstly, a  $\beta$ -cyclodextrin inclusion complex between  $\beta$ -cyclodextrin and substrate was formed in situ,<sup>10</sup> followed by the formation of carbonium ion. This carbonium ion was then attacked by ClO<sup>–</sup> anion on carbon atom. Further elimination of HCl gave the corresponding aldehydes (Fig. 1).

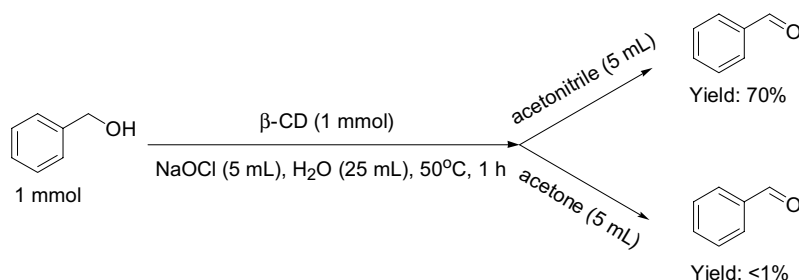
It should be noted that the existence of hydrogen bond derived from H<sub>2</sub>O influenced benzyl alcohol oxidation dramatically. The influence of other organic solvents was given as in Scheme 2.

**Table 2.** Oxidation of various alcohols<sup>a</sup>

| Entry | Substrate | Product | Time (h) | Conv. (%) | Yield (%) |
|-------|-----------|---------|----------|-----------|-----------|
| 1     |           |         | 4        | >99       | >99       |
| 2     |           |         | 1        | >99       | >99       |
| 3     |           |         | 2        | >99       | >99       |
| 4     |           |         | 1        | >99       | >99       |
| 5     |           |         | 5        | Trace     | Trace     |
| 6     |           |         | 24       | 0         | 0         |
| 7     |           |         | 24       | 0         | 0         |
| 8     |           |         | 24       | Trace     | Trace     |
| 9     |           |         | 24       | Trace     | Trace     |
| 10    |           |         | 5        | 30        | 30        |

<sup>a</sup> Reaction conditions:  $\beta$ -cyclodextrin (1 mmol), substrate (1 mmol), H<sub>2</sub>O (25 mL), 50 °C.

**Figure 1.** A plausible reaction mechanism.



Scheme 2.

To the present reaction system, the addition of organic solvents such as acetone or acetonitrile gave the different reaction rate for benzyl alcohol oxidations. The fact that the usage of acetone has a greater impact on the reaction rate than acetonitrile does on the benzyl alcohol oxidation indicates the importance of hydrogen bond. The strong hydrogen bond between acetone and water prevented the formation of the benzyl alcohol,  $\text{ClO}^-$  and  $\text{H}_2\text{O}$  complex due to the weak hydrogen bond between benzyl alcohol and  $\text{H}_2\text{O}$ .

The  $\beta$ -cyclodextrin could be easily recycled simply by the addition of acetone, followed by the separation with centrifugation; however, the amount of acetone added is crucial for good recovery. When the volume ratio of acetone to water reached 2:1, 95%  $\beta$ -cyclodextrin could be recovered. The recycled  $\beta$ -cyclodextrin was reused for three times with no loss of activity or selectivity.

In conclusion, we have developed a facile, substrate-selective and transition metal-free oxidation of alcohols catalyzed by  $\beta$ -cyclodextrin with cheap NaOCl oxidant using water as the only solvent. Since  $\beta$ -cyclodextrin is widely used as food additive and benzaldehyde is widely used as essence and spice, this process would provide a new method for the synthesis of benzaldehyde aiming for essence and spice, if using NaOCl for food processing is adopted.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2005.01.178](https://doi.org/10.1016/j.tetlet.2005.01.178).

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