## Unique Salt Effect on the High Yield Synthesis of Acid-Labile Terpene Oxides Using Hydrogen Peroxide under Acidic Aqueous Conditions

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Abstract: Acid-labile epoxides such as  $\alpha$ -pinene oxide are (effectively) synthesized in high yield from the epoxidation of terpenes with aqueous H<sub>2</sub>O<sub>2</sub> catalyzed by Na<sub>2</sub>WO<sub>4</sub>, [Me(n-C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>N]HSO<sub>4</sub>, and PhP(O)(OH)<sub>2</sub> in the presence of Na<sub>2</sub>SO<sub>4</sub> as an auxiliary additive under organic solvent-free conditions at ambient temperature. Origin of the salt effect is considered that the addition of a saturated amount of Na<sub>2</sub>SO<sub>4</sub> to aqueous H<sub>2</sub>O<sub>2</sub> strongly inhibited the undesired hydrolysis of the acid-labile epoxide products, despite the highly acidic reaction conditions.

Key words: oxidation, catalysis, epoxides, terpenoids, green chemistry

Epoxides are a versatile class of compounds for the laboratory and industrial manufacturing of a wide variety of useful chemicals.1 While various oxidants are now being used for epoxidation,<sup>2</sup> they often give equimolar amounts of the deoxygenated compounds as waste. Hydrogen peroxide  $(H_2O_2)$  is an ideal oxidant because water is the only side product<sup>3</sup> and the atom efficiency is excellent.<sup>4</sup> Although a number of metal-catalyzed H<sub>2</sub>O<sub>2</sub> epoxidation reactions have been reported thus far,<sup>5,6</sup> the chemical processes using organic solvent and halide compounds should be converted to organic solvent- and halide-free processes from both an industrial perspective, taking costs into account, and an environmental perspective. We have developed various epoxidation reactions of olefins including terminal aliphatic olefins with aqueous H<sub>2</sub>O<sub>2</sub> under organic solvent-free conditions.7 This oxidation process gives the corresponding epoxides in good yield catalyzed by highly active tungsten peroxide species that are effectively formed at 90 °C under acidic conditions.<sup>7b</sup> However, terpene oxides such as  $\alpha$ -pinene oxide were not obtained under these reaction conditions because the generated epoxides easily underwent ring opening, rearrangement, and hydrolysis by acid catalysis or by application of heating.<sup>8</sup> Therefore, to avoid the decomposition of  $\alpha$ pinene oxide under organic solvent-free conditions, the epoxidation of  $\alpha$ -pinene under weak acidic conditions at room temperature was employed.9 It was also revealed that the combination of  $Na_2WO_4$ ,  $[Me(n-C_8H_{17})_3N]HSO_4$ , and  $PhP(O)(OH)_2$  was effective for the epoxidation of  $\alpha$ -pinene at 25 °C. But this process required as much as 0.08 equivalents of catalysts and intractable 60% H<sub>2</sub>O<sub>2</sub> for the reaction to proceed. Based on these results, we have developed another synthetic approach that effectively protects the generated a-pinene oxide from hydrolysis under acidic conditions and under organic solvent-free conditions, maintaining the intrinsic catalyst reactivity at the same time. We here report the effective and convenient tungsten-catalyzed H<sub>2</sub>O<sub>2</sub> epoxidation of terpenes by the simple addition of inorganic salts to give the acid-labile epoxides in good to excellent yields. This process required as much as 0.02 equivalents of tungsten, 0.02 equivalents of phase transfer catalyst, 0.01 equivalents of phenyl phosphonic acid, and commercially available 30%  $H_2O_2$  aqueous solution for the reaction to proceed under organic solvent-free biphasic conditions of substrate (oil phase) and aqueous  $H_2O_2$  (acidic water phase).

Table 1	Effect of Additives on Epoxidation of 1 under Acidic Con-
ditions in	the Presence of Salts <sup>a</sup>



Entry	Salt (equiv)	Conversio	on (%) <sup>b</sup> Yield (%) <sup>b</sup>	Selectivity (	(%)
1	none (0)	55	1	2	
2	NaHCO <sub>3</sub> (0.6)	3	0	0	
3	NaCl (0.6)	20	15	75	
4	NaNO <sub>3</sub> (0.6)	31	0	0	
5	$Na_{2}SO_{4}(0.3)$	89	89	100	
6	Li <sub>2</sub> SO <sub>4</sub> (0.3)	73	40	55	
7	$K_{2}SO_{4}(0.3)$	57	6	11	
8	$(NH_4)_2SO_4(0.3)$	74	44	60	
9	MgSO <sub>4</sub> (0.3)	69	30	43	

<sup>a</sup> Reaction conditions: **1** (1.0 equiv), 30% H<sub>2</sub>O<sub>2</sub> (1.0 equiv), Na<sub>2</sub>WO<sub>4</sub> (0.02 equiv), [Me(n-C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>N]HSO<sub>4</sub> (0.02 equiv), PhP(O)(OH)<sub>2</sub> (0.01 equiv), salt, 25 °C, 1000 rpm, 16 h.

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<sup>&</sup>lt;sup>b</sup> Determined by GC analysis with decane as an internal standard.

<sup>&</sup>lt;sup>c</sup> Yield/conversion (%).

We examined the  $H_2O_2$  epoxidation of  $\alpha$ -pinene (1), as shown in Table 1. The reaction was conducted with 30%  $H_2O_2$  (1.0 equiv to 1),  $Na_2WO_4$  (0.02 equiv), [Me(n-C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>N]HSO<sub>4</sub> (0.02 equiv), and PhP(O)(OH)<sub>2</sub> (0.01 equiv) at 25 °C for 16 hours with vigorous stirring. As shown in Table 1 (entry 1), the epoxidation reaction in the absence of any additional salts proceeded moderately, but the produced epoxide 2 decomposed under the acidic conditions (55% conversion of 1 and 1% yield of 2). The addition of 0.6 equivalents NaHCO<sub>3</sub> to the aqueous phase created an alkaline solution (pH 9.0), and as a result the  $H_2O_2$  epoxidation did not proceed (Table 1, entry 2). The addition of 0.6 equivalents NaCl to the epoxidation reaction afforded only 20% conversion of 1 and 15% yield of **2** (Table 1, entry 3). The addition of 0.6 equivalents NaNO<sub>3</sub> did not give 2 at all (Table 1, entry 4). One of the reasons for the low conversion of 1 (Table 1, entries 1–4), is that the formation of sobrerol (3) by the hydrolysis of 2 might be chelated with tungstate metal at the 1,2-diol moiety of **3**,<sup>10</sup> which would prohibit any possibility of the epoxidation proceeding. It is noteworthy that Na<sub>2</sub>WO<sub>4</sub>,  $[Me(n-C_8H_{17})_3N]HSO_4$ , and  $PhP(O)(OH)_2$  catalyzed the  $H_2O_2$  epoxidation of 1 with 0.3 equivalents  $Na_2SO_4$  as divalent neutral salts, which displayed excellent efficiency despite the acidic conditions (pH 2.0) and produced 2 in 89% yield and 100% selectivity (Table 1, entry 5). The catalytic  $H_2O_2$  epoxidation of 1 with sulfates of other cation species such as Li<sup>+</sup>, NH<sub>4</sub><sup>+</sup>, and Mg<sup>2+</sup> proceeded moderately to give 40%, 44%, and 30% yields of 2 with selectivity of 55%, 60%, and 43%, respectively (each 0.3 equiv, Table 1, entries 6, 8, and 9). In contrast, the reaction in the presence of 0.3 equivalents  $K_2SO_4$  afforded 2 in only 6% yield (Table 1, entry 7).

Table 2 Effect of  $Na_2SO_4$  on the Hydrolysis of 2 in the Presence of  $30\%~H_2O_2^{a}$ 



Entry	$Na_2SO_4$ (eq	uiv) Decomposit	ion of $2  (\%)^{\mathrm{b}}$ Yield of $3  (\%)^{\mathrm{b}}$
1	0	100	62
2	0.1	59	22
3	0.2	11	11
4	0.3	5	5
5	0.4	4	4

 $^a$  Reaction conditions: 2 (1.0 equiv), 30%  $\rm H_2O_2$  (1.0 equiv),  $\rm Na_2SO_4,$  25 °C, 1000 rpm, 16 h.

<sup>b</sup> Determined by GC analysis with decane as an internal standard.

To clarify the effect of the addition of salt on  $H_2O_2$  epoxidation, we produced a simple hydrolysis reaction of **2** with aqueous 30%  $H_2O_2$  (1.0 equiv to **2**) in the presence of Na<sub>2</sub>SO<sub>4</sub> (0.3 equiv) without any other catalysts at 25 °C for 16 hours (Table 2). As a result, the hydrolysis of **2** was observed in only 5% yield with the addition of 0.3 equivalents Na<sub>2</sub>SO<sub>4</sub> to a stirred biphasic mixture of **2** with 30% H<sub>2</sub>O<sub>2</sub> (Table 2, entry 4). On the other hand, the hydrolysis of **2** occurred completely in the absence of Na<sub>2</sub>SO<sub>4</sub>, and the hydrolysis of **2** to give **3** was observed in 62% yield (Table 2, entry 1).<sup>8</sup> The amount of the added salts is also crucial to effectively protect the generated epoxides from hydrolysis. Table 2 shows the results of the investigation regarding the relationship between the conversion of **2** and the amount of Na<sub>2</sub>SO<sub>4</sub> in the biphasic reaction. The

Table 3 $H_2O_2$  Epoxidation of Terpenes with Acidic Conditions inthe Presence or Absence of Na2SO4<sup>a</sup>



<sup>a</sup> Reaction conditions: terpenes (1.0 equiv), 30%  $H_2O_2$  (1.0 equiv),  $Na_2WO_4$  (0.02 equiv),  $[Me(n-C_8H_{17})_3N]HSO_4$  (0.02 equiv),  $PhP(O)(OH)_2$  (0.01 equiv),  $Na_2SO_4$  (0.3 equiv), 25 °C, 1000 rpm, 16 h.

<sup>b</sup> Determined by GC analysis with decane or biphenyl as an internal standard.

<sup>c</sup> The reaction was run in the absence of Na<sub>2</sub>SO<sub>4</sub>.

amount of Na<sub>2</sub>SO<sub>4</sub> increased from 0 to 0.4 equivalents, and the decomposition rate of **2** decreased from 100% to 4% (Table 2, entries 1 and 5). These results suggest that the addition of Na<sub>2</sub>SO<sub>4</sub> clearly enhanced the inhibition of the hydrolysis of **2**. But in comparing entries 4 and 5 (Table 2), the addition of more than 0.3 equivalents Na<sub>2</sub>SO<sub>4</sub> seems less effective because the aqueous  $H_2O_2$ solution was saturated by the addition of 0.3 equivalents Na<sub>2</sub>SO<sub>4</sub>. The results clearly showed that the addition of a saturated amount of Na<sub>2</sub>SO<sub>4</sub> effectively inhibited the hydrolysis of **2** in the  $H_2O_2$  epoxidation reaction conditions at room temperature without deactivation of the tungsten peroxide species.

This epoxidation reaction using Na<sub>2</sub>SO<sub>4</sub> as an additive in the biphasic conditions can be adopted for various other terpenes to generate the corresponding terpene oxides. These results are summarized in Table 3. A reaction with a bicyclic monoterpene, 3-carene, which is known to undergo an acid-catalyzed rearrangement upon treatment with peracid,<sup>11</sup> also provided an excellent yield of the corresponding epoxides under the acidic conditions (90%, Table 3, entry 3). The reaction with  $\alpha$ -terpineol and terpinen-4-ol, having a hydroxy group that causes intramolecular addition reactions in its product under acidic conditions,<sup>12</sup> also gave the corresponding epoxides in good to high yield (67% and 82%, respectively, Table 3, entries 5 and 7). On the other hand, a reaction with isopulegol gave the corresponding epoxides in excellent yield (97%, Table 3, entry 9). The epoxidation of limonene, which has two alkene moieties in the molecule, also successfully produced the corresponding monoepoxides in high yield (89%, Table 3, entry 11). Meanwhile, it should be noted that the addition of a catalytic amount of  $Na_2SO_4$ for H<sub>2</sub>O<sub>2</sub> epoxidation of limonene has been already reported,<sup>13</sup> while the reaction required an organic solvent and the yield was lower than that in the present study. Epoxidation of carvone, which has a carbonyl group and two alkenes (cyclic alkene and exomethylene), also gave two types of monoepoxides in a total 50% yield with a specific rate. Carvone 7,8-oxide was obtained in 41% yield, and carvone 1,6-oxide was formed in 9% yield (Table 3, entry 13). These tungsten-catalyzed  $H_2O_2$  epoxidation reactions were also performed in the absence of Na<sub>2</sub>SO<sub>4</sub>, and several terpenes provided the corresponding terpene oxides in similar yields in comparison with adding Na<sub>2</sub>SO<sub>4</sub> (Table 3, entries 4, 12, and 14). However, the epoxidation reactions that included a hydroxy group in the absence of  $Na_2SO_4$  have lower yields (Table 3, entries 6, 8, and 10).

Under the biphasic conditions of benzene (oil phase) and aqueous solution (water phase), the solubility of benzene to the water phase was effectively reduced by  $Na_2SO_4$ .<sup>14</sup> The greater ability of sulfate anion  $SO_4^{2-}$  and sodium cation  $Na^+$  compared with other anions and cations, respectively, to decrease protein solubility in aqueous solution is known as the Hofmeister effect.<sup>15</sup> Among the neutral salts containing monovalent cations such as  $Na^+$ ,  $Li^+$ ,  $K^+$ , and

 $\rm NH_4^+$  with sulfate anion  $\rm SO_4^{2-}$ ,  $\rm Na^+$  is the most effective salt for the salting-out process under biphasic conditions.<sup>16</sup> However, the findings regarding hydrolysis inhibition in the biphasic epoxidation reaction cannot simply explain the reactivity due to the interaction between the substrate **2** and cations as well as the catalyst species and anions.

In summary, we have demonstrated the effective and selective salt effect on the high yield synthesis of acid-labile epoxides using  $H_2O_2$  with the  $Na_2WO_4$ , [Me(n- $C_8H_{17}$ )\_3N]HSO\_4, and PhP(O)(OH)\_2 catalysts under not only organic solvent-free but also acidic aqueous biphasic conditions. The simple addition of a saturated amount of  $Na_2SO_4$  strongly promotes the production of  $\alpha$ -pinene oxide due to the suppression of hydrolysis without deactivation of the catalytic  $H_2O_2$  epoxidation system. We consider the present synthetic improvement by the salt addition will be quite promising for the practical preparation of a variety of acid-labile epoxides using  $H_2O_2$ .

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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