

## A Simple, Iron-Catalyzed, Pyridine-Assisted Hydrogen Peroxide Epoxidation System

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**A simple and inexpensive system comprised of H<sub>2</sub>O<sub>2</sub>-pyridine-FeCl<sub>3</sub>·6H<sub>2</sub>O for the catalysis of olefin epoxidation was established. Intriguingly, the reactivity of this system greatly depends on the amounts of pyridine. Various substrates, including aromatic and aliphatic olefins, were epoxidized by this simple system in moderate to excellent yields.**

**Key words** hydrogen peroxide; iron(III) chloride; olefin epoxidation; pyridine; acceleration

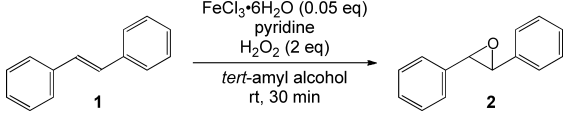
Epoxides are highly desirable building blocks for the formation of fine chemicals, which are used in the production of pharmaceuticals, agricultural chemicals, industrial products or synthetic intermediates.<sup>1–3</sup> Peracids are often used as oxidants. In particular, *m*-chloroperbenzoic acid (*m*-CPBA) has received considerable interest for use in the epoxidation of olefins to obtain the corresponding epoxides.<sup>4–6</sup> However, because of the cost, toxicity, and by-products of *m*-CPBA, a more cost-effective, harmless and clean oxidant is needed. Consequently, hydrogen peroxide has been extensively investigated as an alternative oxidant. Because hydrogen peroxide is safe and inexpensive, possesses a high oxygen content, and generates water as the only by-product, it is a viable candidate for use in epoxidation reactions.<sup>7–10</sup>

Metal-catalyzed epoxidations with hydrogen peroxide results in outstanding yields.<sup>11–13</sup> Nevertheless, although the superior metal catalysts like Re<sup>14</sup> or Pt<sup>15,16</sup> have excellent reactivity, the disadvantages of these metals cannot be ignored—namely, their high cost and quantitative insufficiency. Thus, our research focus has been on iron salts, which are relatively inexpensive compared with other transition metals, due to their natural abundance. Furthermore, iron salts have little risk to human health and are commercially available.<sup>17–21</sup>

Beller and co-workers performed epoxidation of olefins in a reaction system comprised of FeCl<sub>3</sub>·6H<sub>2</sub>O and H<sub>2</sub>O<sub>2</sub>, employing dipicolinic acid and an amine to activate the reaction. This method afforded the corresponding epoxides in good to excellent yields.<sup>22–26</sup> Recently, they also reported a simpler system that uses imidazole derivatives, rather than dipicolinic acid and amines,<sup>27,28</sup> as ligands. However, the reactivity of this system was moderate, and the ligands which resulted in relatively high yields had to be synthesized *ad hoc* before use because of commercial inavailability. Moreover its versatility regarding the use of different olefin substrates was limited.<sup>27,28</sup>

We performed a more economical and practical H<sub>2</sub>O<sub>2</sub>-oxidized epoxidation of *trans*-stilbene **1** with a catalytic iron salt and a different ligand. This simple, FeCl<sub>3</sub>·6H<sub>2</sub>O and pyridine

Table 1. Effects of Pyridine Loading on Epoxidation of *trans*-Stilbene<sup>a)</sup>



Entry	Pyridine (eq)	Yield <sup>b)</sup>	Recov. <sup>c)</sup> (%)
1	0.1	20	78
2	0.25	40	52
3	0.5	69	26
4	1	82	12
5	2	90	6
6 <sup>d)</sup>	2	96	0
7 <sup>e)</sup>	2	94	3
8	3	93	2
9	4	94	2

a) Reaction conditions: FeCl<sub>3</sub>·6H<sub>2</sub>O (5 mol%), H<sub>2</sub>O<sub>2</sub> (2 eq), *tert*-amyl alcohol (10 ml), *trans*-stilbene (0.5 mmol). b) Isolated yields. c) Recovery yields of *trans*-stilbene. d) 10 mol% of FeCl<sub>3</sub>·6H<sub>2</sub>O was used. e) 3 eq of hydrogen peroxide were used.

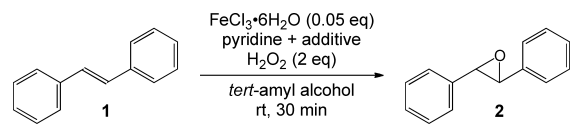
combinative system catalyzed the reaction in excellent yield within only 30 min. In addition, this system was suitable for other substrates, such as aromatic and aliphatic olefins, both of which displayed good reactivity and excellent mass balance.

At the onset of this work, a model catalytic epoxidation of *trans*-stilbene **1** was conducted in *tert*-amyl alcohol<sup>29</sup> at room temperature in the presence of pyridine (Table 1). Use of 10 mol% resulted in only 20% yield of epoxide **2** (entry 1), and extending the reaction time did not improve the product yield. Surprisingly, the epoxidation was improved at higher pyridine concentrations (entries 1–5),<sup>27,28</sup> and use of 50 mol% of pyridine resulted in a good product yield of 69% (entry 3). To our delight, use of 2 eq of pyridine increased the yield to 90% (entry 5). Such a phenomenon was not reported previously in the protocols of transition metal-catalyzed epoxidation, including dipicolinic acid and amine or imidazole derivative systems. It indicates that pyridine acts as different way from dipicolinic acid or imidazole derivatives, leading to a different mechanism in FeCl<sub>3</sub>-catalyzed hydrogen peroxide epoxidation. Further increases in the pyridine equivalent did not affect the product yield obviously (entries 8, 9). As expected, increasing the amount of iron catalyst improved the yield (entry 6), and *vice versa*.<sup>30</sup> In the absence of FeCl<sub>3</sub>·6H<sub>2</sub>O, no reaction was observed when using 2 eq of pyridine, suggesting that the FeCl<sub>3</sub>·6H<sub>2</sub>O plays an indispensable role in this epoxidation system. It should be noted that the mass balance of this reaction system was *ca.* 96%, which indicates minimal side reactions of the epoxide product.

To elucidate the effects of pyridine on the ability to coordinate to iron species, activation following addition of pyridine to the FeCl<sub>3</sub>-aromatic amine-assisted epoxidation system was investigated (Table 2).

Imidazole and its derivatives, which are good ligands, are commonly employed in transition metal-catalyzed epoxidation.<sup>31,32</sup> However, when we performed our model epoxidation reaction with imidazole **3** instead of pyridine, the yields were unsatisfactory and tended to decrease with increasing amounts of imidazole (entries 1–4). Intriguingly, when an excess amount of pyridine was added to the imidazole-FeCl<sub>3</sub>

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Table 2. Effects of the Combination of Additive and Pyridine on the Epoxidation of *trans*-Stilbene<sup>a)</sup>


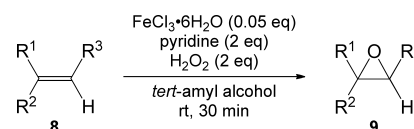
Entry	Additive	Pyridine : Additive (mol% : mol%)	Yield <sup>b)</sup> (%)
1	Imidazole (3)	0 : 5	16
2	3	0 : 10	24
3	3	0 : 30	15
4	3	0 : 100	6
5	3	190 : 10	55
6	3	195 : 5	78
7 <sup>c)</sup>	<i>N</i> -Methylimidazole (4)	0 : 10	18
8	4	0 : 200	6
9	4	195 : 5	61
10	2,6-Lutidine (5)	0 : 60	0
11	5	170 : 30	62
12	5	195 : 5	74
13	2,2'-Bipyridyl (6)	190 : 10	0
14	Phenanthroline (7)	195 : 5	0

a) Reaction conditions: see Table 1. b) Isolated yields. c) See ref. 28.

complex, the catalytic activity was dramatically restored, giving the epoxides in good yields (entries 5, 6). Similar phenomena were also observed for the *N*-methylimidazole (4) and 2,6-lutidine (5)–FeCl<sub>3</sub> complexes (entries 7–9, 10–12). By contrast, 2,2'-bipyridyl (6) and phenanthroline (7)–FeCl<sub>3</sub> complexes did not facilitate the epoxidation reaction, and pyridine did not reactivate the reaction (entries 13, 14). One possible explanation for these results is the strong coordination of 2,2'-bipyridyl and phenanthroline to iron species. From Table 2, we assume that pyridine competes with imidazole, *N*-methylimidazole or 2,6-lutidine for coordination to the iron(III) to form the Fe(III)-pyridine catalyst, which has greater activity than either the Fe(III)-(*N*-methyl)imidazole or Fe(III)-2,6-lutidine complex. By contrast, 2,2'-bipyridyl and phenanthroline coordinated tightly to the iron(III), resulting in inactive complexes.

Having optimized the reaction conditions, we proceeded to investigate the scope and limitations of different olefin substrates using 5 mol% of FeCl<sub>3</sub>·6H<sub>2</sub>O, 2 eq of pyridine and 2 eq of H<sub>2</sub>O<sub>2</sub>. Table 3 summarizes the results of the pyridine–FeCl<sub>3</sub>-catalyzed epoxidation of various olefin substrates. Thus, the intrinsically inefficient substrate *cis*-stilbene **10** gave the corresponding epoxide in 28% yield (entry 2),<sup>33,34</sup> whereas 49% yield was achieved when 20 mol% of FeCl<sub>3</sub>·6H<sub>2</sub>O was used (entry 3).<sup>35</sup> Cinnamyl acetate oxide was produced in 56% yield from **11** (entry 4) in the absence of side reactions. Cinnamyl alcohol **12** gave a moderate yield of 44%, showing that our simple and mild pyridine system results in chemoselective epoxidation in the presence of hydroxy groups (entry 5). 1-Phenylcyclohexene **13** and *trans*-β-methylstyrene **14** were epoxidized in 50% and 58% yield, respectively (entries 6, 7). The chemical yield obtained for 1-phenylcyclohexene were much higher than the previously reported values.<sup>22</sup> An aliphatic olefin, 4-phenyl-1-butene **15**, also gave a good yield (entry 8).

In conclusion, we established a simple epoxidation system comprised of the catalytic FeCl<sub>3</sub>–pyridine complex and H<sub>2</sub>O<sub>2</sub>,

Table 3. Pyridine–FeCl<sub>3</sub>-Catalyzed Epoxidation of Different Olefin Substrates<sup>a)</sup>


Entry	Substrate	Conv. (%)	Yield <sup>b)</sup> (%)
1	<b>1</b>	94	90
2	<b>10</b>	36	28
3 <sup>c)</sup>	<b>10</b>	64	49
4	<b>11</b>	56	56
5	<b>12</b>	63	44
6	<b>13</b>	75	50
7 <sup>d)</sup>	<b>14</b>	83	58
8 <sup>d)</sup>	<b>15</b>	91	70

a) Reaction conditions: see Table 1. b) Isolated yields. c) 20 mol% of FeCl<sub>3</sub>·6H<sub>2</sub>O was used. d) Calculated from <sup>1</sup>H-NMR after distillation of solvent.

which is economically and environmentally friendly and convenient in operation at room temperature and under open-air. This simple system is applicable to aromatic and aliphatic olefins for the production of the corresponding epoxides in good to excellent yields. Although some of the substrates resulted in moderate yields, the unconverted starting material could be recovered and recycled in subsequent reactions. The reactivity of inherently inactive substrates was improved by increasing the loading of the FeCl<sub>3</sub>·6H<sub>2</sub>O catalyst. Intriguingly, the catalytic activity of Fe(III)-pyridine was highly dependent on the number of pyridine equivalents added to the reaction system. Further studies are in progress.

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- 29) The same reaction shown in entry 5, Table 1, was also tried in ethanol, THF, MeCN and *t*-BuOH/CH<sub>2</sub>Cl<sub>2</sub> (7/3) in place of *t*-amyl alcohol to give the corresponding epoxide in 0%, 12%, 15% and 91% yields, respectively. Considering the chemical yields and the simplicity of reaction system, we chose *t*-amyl alcohol as a standard solvent.
- 30) 54% yield was achieved with 2.5 mol% of FeCl<sub>3</sub>·6H<sub>2</sub>O.
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- 35) 52% yield was achieved when the same reaction was performed for 3 h.