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# Chemoselective hydrogen peroxide oxidation of allylic and benzylic alcohols under mild reaction conditions catalyzed by simple iron-picolinate complexes<sup>†</sup>

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Chemoselective oxidation of allylic alcohols to  $\alpha,\beta$ -unsaturated carbonyl compounds proceeded efficiently using hydrogen peroxide with iron-picolinate catalysts. The *in situ* generated [Fe(Me-Pic)<sub>3</sub>] (Me-Pic = 6-methylpicolinate) catalyzed oxidation of the alcohol moiety of primary allylic alcohols while the [Fe(Pic)<sub>3</sub>] (Pic = picolinate) and [Fe(Me-Pic)<sub>2</sub>(Pic)] did not show sufficient catalytic activity.

Chemoselective oxidation reactions are a powerful tool for the functionalization and derivatization of organic compounds and are widely used in both laboratories and industrial settings.1,2 However, environmentally unfriendly reagents such as heavy metal oxidants and organic peroxides with metal catalysts have been used for such selective reactions.3 In order to prevent the formation of undesirable wastes and toxic reagents, the combination of an iron compound plus molecular oxygen or hydrogen peroxide as a terminal oxidant is ideal for such oxidations, since iron compounds are generally very abundant and less toxic, and no waste or only H<sub>2</sub>O would be generated from these oxidants.<sup>4</sup> Iron-catalyzed oxidation reactions have been investigated for over a century and are known as Fenton<sup>5</sup> and Gif-type chemistry.6 In general, these reaction systems show low selectivity and thus their use has been limited.7 The combination of an iron-picolinate complex and hydrogen peroxide, known as the GoAgg<sup>III</sup> system, was explored by Barton et al.8 and realized by Stavropoulos et al.,9 who used it to catalyze the C-H oxidation of alkanes to alcohol or ketone. Because of its potential practicality, the reaction mechanism is still debated, but the low selectivity and narrow substrate generality are



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Chemoselective oxidation of allylic alcohol to  $\alpha,\beta$ -unsaturated carbonyl compounds has long been of interest due to the pharmaceutical applicability of the products.<sup>11</sup> Iron-catalyzed hydrogen peroxide oxidation of allylic alcohols has rarely been reported<sup>12</sup> presumably due to the competitive side reaction leading to epoxide.13,14 Beller et al. demonstrated that the combination of iron salts, base, and picolinic acid bearing a benzimidazole moiety can catalyze the oxidation of benzylic and allylic alcohols.12a Although their catalyst was effective for wide variety of benzylic alcohols, the yield and selectivity for allylic alcohol substrates remained modest. Recently, we found that slight derivatization of the GoAgg<sup>III</sup> system altered it to realize an effective catalyst for selective epoxidation of styrenes.<sup>15</sup> Even though modification of the 6-position of picolinate ligands seems to have little impact on the catalytic activity, we demonstrated that highly active and selective catalytic styrene oxidation proceeded through the use of an iron-mixed picolinate catalyst, where one picolinate (Pic) and two 6-methylpicolinate (Me-Pic) bound to an iron(III) center. Herein we applied this unexpected impact of the 6-methyl group on oxidation activity to another substrate, and found that this system could be adopted for allylic alcohols. In the presented catalyst system, the oxidation reactions proceeded efficiently in a short amount of time under mild conditions even though the experimental operations were simple, and no base and an excess amount of H2O2 were required.



We conducted oxidation of cinnamyl alcohol **1a** by hydrogen peroxide in the presence of  $Fe(OAc)_2$ , PicH, and Me-PicH in various molar ratios (Table 1). Upon treatment of  $Fe(OAc)_2$ 

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: General procedure, procedure for catalytic reaction, spectral data of isolated compounds, Table S1, S2, S3, and Scheme S1. CCDC-1000597 contains the supplementary crystallographic data for complex 3. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra05819d

 Table 1
 Oxidation of cinnamyl alcohol by various catalysts<sup>a</sup>



<sup>a</sup> CH<sub>3</sub>CN solution, 25 °C, dropwise addition of 1.25 eq. of 35% H<sub>2</sub>O<sub>2</sub> aq. for 10 min and further stirring for 5 min, unless otherwise stated.
 <sup>b</sup> Determined by GC using biphenyl as an internal standard. Average of two runs. <sup>c</sup> yield/conversion × 100. <sup>d</sup> FeCl<sub>3</sub>·6H<sub>2</sub>O was used.
 <sup>e</sup> Fe(OAc)<sub>2</sub>(OH) was used. <sup>f</sup> 6-Trifluoromethylpicolinic acid was used.
 <sup>g</sup> 6-Methoxypicolinic acid was used. <sup>h</sup> 2,6-Dicarboxypyridine was used.

(5 mol%) and PicH (15 mol%) to 1a in CH<sub>3</sub>CN solution, cinnamaldehyde 2a was generated in 5% yield (entry 1). Surprisingly, addition of Me-PicH (5 mol%) together with PicH (5 mol%) dramatically enhanced catalytic activity, resulting in full conversion of 1a with 78% yield of 2a (entry 2). Side products of this reaction were determined to be cinnamic acid (11%) and benzaldehyde (7%), which could be produced by overoxidation of cinnamaldehyde and decomposition of the epoxidation product, respectively. The selectivity for 2a was improved when the mixed-ligand system was fully replaced by 15 mol% of Me-PicH, providing 2a in 89% yield with 94% selectivity (entry 4). Addition of a larger amount of Me-PicH increased the yields of 2a but slightly decreased selectivity for 2a (entry 3-5), and therefore the catalyst system was optimized as a combination of  $Fe(OAc)_2$  and Me-PicH in a 1:3 molar ratio. The amounts of the catalyst components could be reduced to 1 mol% of Fe(OAc)<sub>2</sub> and 3 mol% of Me-PicH while maintaining the high yield and selectivity (entry 6). Use of FeCl<sub>3</sub>·6H<sub>2</sub>O instead of Fe(OAc)<sub>2</sub> resulted in lower yield and selectivity (entry 7), but use of  $Fe(OAc)_2(OH)$  maintained the high yield and selectivity, suggesting that the acetate ligand contributed to the catalytic activity. Employment of 6-trifluoromethylpicolinic acid did not show catalytic activity (entry 9), whereas that of 6-methoxypicolinic acid gave 52% yield and 75% selectivity (entry 10). The electron withdrawing effect of the substituent of the ligand might have had a negative effect on the catalytic activity, since a similar phenomenon was observed in the oxidation catalysis of iron-polyamine complexes.16 The finding that a lower yield was obtained via addition of 6-methoxypicolinic acid than via 6-methylpicolinic acid addition could be explained by the steric hindrance of oxidant species (vide infra).

2,6-Dicarboxypyridine, which has been used as a ligand of oxidation catalysis by an iron complex,<sup>14</sup> did not work as a good ligand in this system (entry 11). In order to prove the practical utility of our system, we examined 10 gram scale synthesis of **2a**: a 1.25 eq. of 35% H<sub>2</sub>O<sub>2</sub> aq. was added in a dropwise manner over 30 min to a CH<sub>3</sub>CN solution of **1a** and catalyst. After extraction and distillation, **2a** was isolated as pale yellow oil in 84% yield (eqn (1)).



Next we focused on the scope of the alcohols (Table 2). Lower allylic alcohols such as allyl alcohol and *trans*-crotyl alcohol were converted to the corresponding aldehydes **2b** and **2c** in moderate yields. 3-Methylbutenal **2e** was obtained in 77% yield when 5 mol% of Fe(OAc)<sub>2</sub> and 20 mol% of Me-PicH were used. Linear allylic alcohols were also activated by iron catalyst, affording 2-hexenal **2f** and 2-octenal **2g** in 73% and 71% yields, respectively.





<sup>*a*</sup> CH<sub>3</sub>CN solution, 25 °C, dropwise addition of 1.25 eq. of 35% H<sub>2</sub>O<sub>2</sub> aq. for 10 min and further stirring for 5 min, unless otherwise stated. <sup>*b*</sup> Yields were determined by GC using biphenyl as an internal standard. Average of two runs. Selec. = yield/conversion  $\times$  100. <sup>*c*</sup> 20 mol% of Me-PicH was used. <sup>*d*</sup> Isolated yield. <sup>*e*</sup> 5 mol% of Fe(OAc)<sub>2</sub>, PicH and Me-PicH were used.

Methacrolein 2d and 2-methyl-3-phenylbutenal 2h were generated in slightly lower yields (44% and 70%) than those of 2b (71%) and 2a (91%), indicating that the methyl substituent at the β-position of alcohol inhibited activation of the alcohol moiety. Even though geraniol has another alkene group at the remote position, citral 2i was obtained in 60% yield with 76% selectivity. In contrast to the catalyst system reported by Beller and co-workers,<sup>12a</sup> the catalytic activity for benzyl alcohol was moderate. For the oxidation of secondary allylic alcohols, the optimized system used for 1a was not suitable for  $\alpha$ -phenylcinnamyl alcohol 1k. Thus, we performed the optimization again and determined that a mixture of Fe(OAc)<sub>2</sub>, PicH, and Me-PicH in a 1:1:1 molar ratio was a good system for secondary allylic alcohols (Table S1<sup>†</sup>). Chalcone 2k, 1-buten-3-on 2l, 3octen-2-on 2m, and 2-cyclohexen-1-one 2n were obtained in high yields with high selectivity by using this catalyst system. Here again, catalytic activity for the benzylic alcohol was moderate, giving acetophenone 20 in 64% yield.

In order to obtain information about the reaction mechanism, we isolated an iron complex that formed in the catalyst solution. Reaction of Fe(OAc)<sub>2</sub> with an excess amount of Me-PicH gave a homoleptic complex  $[Fe(Me-pic)_3]$  (3) as yellow crystals. Single crystal X-ray structure analysis revealed that complex 3 holds three Me-Pic ligands in an N,O-chelating manner, and each donor atom is arranged in a meridional form, which is basically the same structural feature seen in [Fe(Me-Pic)<sub>2</sub>(Pic)] (4)<sup>15</sup> and [Fe(Pic)<sub>3</sub>] (5) (Fig. 1).<sup>17</sup> In complex 3, the distance between the iron atom and the nitrogen atom of the coordinated pyridine ring located at the cis-position to the other two pyridine rings are longer than the other Fe-N bond distances in 3 by 0.1 Å, and longer than all Fe–N bond distances in 4 and 5. This elongation of the Fe-N bond distance was attributed to steric repulsion of the Me moiety rather than transinfluence and indicates that one of the Me-Pic ligands in 3 is labile for ligand substitution.

Complex **3** (5 mol%) was employed as a pre-catalyst for the oxidation of **1a**, giving **2a** in 90% yield with 92% selectivity, and thus oxidant species were thought to be generated *via* complex **3** in catalyst solution (Table S2†). In addition, we performed the

oxidation of alcohols in the presence of radical trapping reagents-duroquinone, 2,6-di-*tert*-butyl-4-methylphenol or *tert*-butylphenylnitrone-to examine whether the reaction proceeds through a free radical mechanism. However, inconsistent results were obtained among the three reagents in reactions using **1a** or **1k** as substrate, probably due to the association of these reagents with iron complexes (Table S3†). Thus, we next tested the oxidation of cyclobutanol **1p** under our optimized condition for secondary alcohols. An *in situ* generated high valent iron-oxo species has been reported to oxidize **1p** to cyclobutanone **2p** without formation of a ring-opened product, confirming that the reaction underwent through a 2-electrons pathway.<sup>18</sup> Upon treatment of the iron catalyst with **1p**, **2p** was produced with 95% selectivity (Scheme S1†).

Based on these results and similar catalytic systems using iron compounds, we tentatively postulated that oxidation of proceeded via high-valent iron-oxo species alcohols (Scheme 1).18a,19 Substitution reaction of one of the Me-Pic ligands in complex 3 gave the iron-peroxo complex [Fe(Me-Pic)<sub>2</sub>(Me-PicH)(OOH)] (6),<sup>20</sup> which was then transformed into  $[Fe=O(Me-Pic)_3]$  (7) with generation of water.<sup>21</sup> In this stage, iron-oxo species 7 could react with allylic alcohols 1 in two or more pathways: one was the attack of alkene moieties on the oxo ligand of 7 to give epoxide, and another was the reaction with hydrogen attached to the α-carbon of alcohol with an oxo ligand leading to  $\alpha,\beta$ -unsaturated carbonyl compounds. Because of the steric hindrance of the two methyl groups of picolinate ligands, reaction with the hydrogen atom of primary alcohols might proceed prior to attack of the alkene part, affording  $\alpha,\beta$ -unsaturated aldehydes 2 in good selectivity. In contrast, iron-oxo species generated from the mixed picolinate complex 4 could be approached by an alkene moiety and product compounds because of the reduced bulkiness around the iron-oxo moiety, and thus the selectivity of the product was decreased. In the case of secondary allylic alcohol, however, the hydrogen atom on the tertiary carbon atom did not approach the oxo ligand owing to the steric hindrance of two ortho-methyl groups attached to picolinate ligands. Thus, use of the mixed picolinate system resulted in better yield and selectivity for secondary allylic alcohols.



Fig. 1 Molecular structure of complex 3. Hydrogen atoms were omitted for clarity. Selected bond distances (Å) and angles (°): Fe-N1 2.1561(17), Fe-N2 2.1670(16), Fe-N3 2.2459(16), Fe-O1 1.9431(14), Fe-O2 1.9641(13), Fe-O3 1.9666(14).



Scheme 1 Possible competitive reaction of high-valent iron-oxo species with alkene and alcohol moiety of allylic alcohols.



With two types of iron-picolinate catalysts in hand, the selective oxidation reactions of diol substrates were examined. 1-Phenyl-1,2ethanediol 8 was converted to  $\beta$ -hydroxyacetophenone 9 in 40% vield with 91% selectivity by catalyst B, although catalyst A showed low catalytic activity as well as selectivity for 9 (Scheme 2). In contrast, catalyst A displayed high selectivity for oxidation of 4-(1hydroxy-1-phenylmethyl)benzylalcohol 10, giving 4-(1-hydroxy-1phenylmethyl)benzaldehyde 11 in 77% yield with 91% selectivity. Secondary alcohol selective oxidations of 8 using environmentally benign methods have been achieved by W-Zn<sup>22</sup> and Fe<sup>12c,23</sup> catalysts with hydrogen peroxide, while Cu catalysts with oxygen were required for primary alcohol selective oxidation of a regioisomer of 10.11c In our catalyst system, both of these diol substrates were oxidized with high selectivity by a combination of hydrogen peroxide and iron-picolinate, in which a suitable ligand system could be easily tuned by changing the ratio of picolinic acids.

#### Conclusions

In summary, we achieved chemoselective oxidation of allylic alcohols to  $\alpha,\beta$ -unsaturated carbonyl compounds by a combination of hydrogen peroxide and iron-picolinate complexes, which was a modified GoAgg<sup>III</sup> system by addition of Me-PicH in a suitable ratio instead of pyridine and PicH. The catalyst prepared by simple mixing of Fe(OAc)<sub>2</sub> with Me-PicH or PicH and Me-PicH efficiently converted allylic alcohols to  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds with good selectivity. Although investigation of the reaction mechanism is still underway, steric hindrance of the two picolinate ligands around the high-valent iron-oxo species might affect the selectivity of reaction pathways. In our system, a metal-based oxidant suitable for a substrate could be tuned simply by changing the kind or ratio of commercially available picolinic acids. Because the preparation of sterically and/or electronically tuned ligands could be avoided, this system should be a good candidate for a practical ironbased chemoselective oxidation catalyst.

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