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Mixed Picolinate and Quinaldinate Iron(III) Complexes for the Catalytic Oxidation of Alcohols with Hydrogen Peroxide

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A series of Fe mixed picolinate and quinaldinate complexes that catalyze the H_2O_2 oxidation of alcohols are presented. The Fe catalysts are generated in situ by simple mixing of iron acetate with 6-methylpicolinic acid (6-MepicH) and 4-chloropicolinic acid (4-ClpicH); they showed high catalytic activity for H_2O_2 oxidation of 1-phenylethanol to acetophenone. Fe complexes generated in situ as precatalysts were successfully isolated and structurally characterized. Based on the single-crystal X-ray analysis and electrochemical measurements of the Fe complexes, the lability of picolinate and/or quinaldinate ligand and the redox potential of Fe^{III} were found to be important factors for the catalytic reaction.

Introduction

Iron is an ideal transition-metal catalyst because of its abundance, low expense, and low toxicity, and hence, catalysts for a variety of catalytic transformations of organic compounds have been replaced by iron catalysts.[1] In particular, significant attention has been paid to iron in the field of oxidation chemistry owing to its remarkable role as a constituent of enzymes that catalyze extremely mild and selective oxidation reactions.[2] Recently, a variety of iron complexes have been reported as effective oxidation catalysts.[3] Low-valent iron complexes bearing well-designed ligands have been shown to exhibit high catalytic activity for C–H oxidation, olefin epoxidation, dihydroxylation and so on, yet the difficulty of handling these catalysts as well as the necessity of multistep syntheses of ligand/catalyst have hampered their practicality, even though iron itself is a promising transition metal. There is thus need for a simpler iron catalyst to develop truly practical organic transformation processes. In fact, iron-catalyzed oxidation reactions have been investigated for over a century and are known as Fenton[4] and GIF-type oxidation reactions;[5] these reactions are easily realized by the mixing of readily available salts and oxidants. The combination of an iron salt, picolinic acid (picH), and H_2O_2, known as the $GoAgg^{III}$ system, was developed by Barton et al.[6] and Stavropoulos et al.[7] Because of its potential practicality, this system is still being investigated to determine its reaction mechanism, but so far it has only been applied to the oxidation of several alkane substrates. In relation to $GoAgg^{III}$-type complexes, Fe complexes associated with quinaldinic acid (qnH) have also been reported.[8] Although Suzuki et al. observed some interesting behavior of these peroxide species, their application to the catalysis of oxidation reactions has rarely been explored.[8a]

Oxidation of alcohols is one of the most important transformations of organic compounds, and a variety of methodologies have been developed for its catalysis.[9] Recently, a combination of copper salts and organic radicals was found to be an efficient catalyst for oxidation of alcohols by O_2,[10] and some substrates have even been catalytically oxidized by using organic radicals alone, without the need of metal salts.[11] Considering the relatively high cost of organic radical compounds and the toxicity of copper, however, iron complexes with H_2O_2 would be a desirable oxidation catalyst in practical terms, and catalytic systems exhibiting higher activity as well as higher selectivity are still desired.[12]

In general, for transition-metal-based molecular catalysis, the catalysts are optimized by the repeated design and synthesis of suitable ligands for specific transformations. In contrast, in situ generated catalysts comprising more than three compounds can be optimized simply by changing the type, combination, and ratio of the components.[13] Moreover, such catalysts can be easily handled and reproduced, which are advantages for practical application. In our recent communication, iron-catalyzed selective oxidations of styrenes and allylic alcohols under simple and mild reaction conditions by using a small excess amount of H_2O_2 as an oxidant were achieved.[14] Slight modification of the $GoAgg^{III}$ system, namely, the use of a combination of two kinds of picolinic acid as ligands for the iron catalyst, was essential for achieving high reactivity and selectivity. In this study, we further optimized the catalytic performance of Fe catalysts by simply employing a variety of picolinic/quinaldinic acids as ligands (Figure 1), and determined the best catalyst combination for the Fe-catalyzed H_2O_2 oxidation of alcohols. In addition, several mixed-ligand iron complexes

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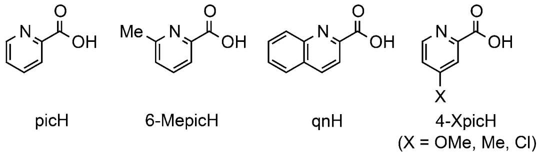


Figure 1. Picolinic acids and quinaldinic acid.

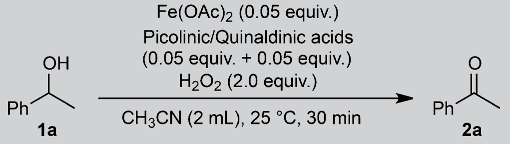
were prepared and characterized to gain insight into the origins of the catalytic activity.

Results and Discussion

Catalytic oxidation of alcohols by in situ-generated iron catalysts

We conducted catalytic H_2O_2 oxidation of 1-phenylethanol **1a** by using $Fe(OAc)_2$ together with various combinations of picolinic/quinaldinic acids (Table 1). Picolinic acid (picH) and some 4-substituted picolinic acids (4-XpicH: X=OMe, Me, and Cl) were combined with two types of sterically hindered ligands (6-MepicH and qnH), as the accommodation of sterically hindered ligands was needed to improve the catalytic performance in our previous study.[14] Catalysis by $Fe(OAc)_2$ with 6-MepicH and picH gave acetophenone **2a** in 71% yield under optimized conditions in this study (entry 1). Some 4-substituted picolinic acids were screened in the place of picH (entries 2–4).

Table 1. Iron-catalyzed oxidation of 1-phenylethanol by various combinations of picolinic/quinaldinic acids.[a]



Entry	Picolinic/Quinaldinic acids		Conversion [%][b]	Yield [%][b]	Selectivity [%][c]
1	6-MepicH	picH	78	71	91
2	6-MepicH	4-OMepicH	74	69	93
3	6-MepicH	4-MepicH	70	63	93
4	6-MepicH	4-ClpicH	85 (94)[d]	81 (93)[d] (91)[e]	95 (99)[d]
5	qnH	picH	46	39	85
6	qnH	4-OMepicH	35	25	71
7	qnH	4-MepicH	39	31	79
8	qnH	4-ClpicH	73	65	89
9[f]	picH	–	57	33	59
10[f]	4-OMepicH	–	13	8	59
11[f]	4-MepicH	–	44	40	91
12[f]	4-ClpicH	–	39	36	93
13[f]	6-MepicH	–	25	20	77
14[f]	qnH	–	9	6	60

[a] CH_3CN solution, 25 °C, dropwise addition of 2.0 equiv. of 35% aq. H_2O_2 over 30 min and further stirring for 5 min, unless otherwise stated. [b] Determined by GC by using biphenyl as an internal standard. Average of two runs. [c] Yield/conversion × 100. [d] 35% H_2O_2 in CH_3CN was used. [e] Yield of isolated product, 10 g scale. [f] 0.10 equiv. of acid were used.

Compound **2a** was obtained in 81% yield with 95% selectivity when 4-ClpicH was used in combination with 6-MepicH (entry 4). Notably, the catalytic performance of this combination was better than the reported H_2O_2 oxidation of **1a** by an in situ-generated Fe catalyst that required an inorganic base as an additive and a halogenated solvent.[12d] Use of 4-ClpicH also induced better catalytic activity when 6-MepicH was replaced by qnH, although all catalyst combinations gave **2a** in lower yields than that with 6-MepicH (entries 5–8). The reaction conditions were further optimized to give **2a** in 93% yield with 99% selectivity by using a CH_3CN solution of H_2O_2, and **2a** could be isolated in 91% yield by means of a ten-gram-scale reaction (entry 4). For comparison with mixed-ligand combination systems, catalytic reactions using $Fe(OAc)_2$ with single picolinic/quinaldinic acids were also conducted (entries 9–14). Addition of 4-MepicH and 4-ClpicH showed relatively high yields and selectivity for **2a** (entries 11 and 12), but the yields were still lower than by using the mixed-ligand systems.

Observation of catalyst species in solution

To obtain information about the catalyst species in various reaction mixtures, we monitored different catalyst solutions by ESI-MS. The results of the ESI-MS analysis of the catalyst mixtures are indicated in entries 1–8 of Table 1 and are summarized in Figure 2 and Figure S1 in the Supporting Information. Figure 2 displays the ESI-MS results for a 1:1:1 mixture of $Fe(OAc)_2$, 6-MepicH, and 4-XpicH (X=H (a), OMe (b), Me (c), Cl (d)) dissolved in CH_3CN, which was prepared by using the same procedure as for the catalytic reaction. All spectra exhibited distributed peaks assignable to mononuclear Fe^{III} complexes bearing three picolinate ligands. Distributed peaks assignable to dimetallic structures were also observed. The formation of Fe^{III} complexes indicated that the Fe^{II}–picolinate species formed in solution were quickly oxidized to Fe^{III} by air. Among the four catalyst solutions (a)–(d), only the combination of 6-MepicH and 4-ClpicH showed peaks resulting from monometallic species in larger intensity than those of dimetallic species (Figure 2 (d)). In addition, a peak resulting from an Fe^{III} complex bearing 6-Mepic and 4-Clpic in a 2:1 ratio was observed as the largest ($m/z=507$) of the peaks owing to monometallic species. The same trend was observed when 6-MepicH was replaced with quinaldinic acid (Figure S1). A mixture containing $Fe(OAc)_2$, qnH, and 4-ClpicH exhibited relatively intense peaks assignable to a mononuclear mixed-ligand Fe complex (Figure S1 (d)).

Synthesis, structure, and catalytic performance of Fe complexes

It is well-known that Fe ions tend to form a dimer structure bridged by carboxylate ligands, and two Fe ions cooperatively catalyze the oxygenation of organic substrates.[15] According to the ESI-MS analysis, however, the combination of 6-MepicH and 4-ClpicH, which exhibits the best catalytic activity for oxidation of **1a** (Table 1, entry 4), promoted the generation of monometallic Fe^{III} mixed-ligand species in CH_3CN solution, indi-

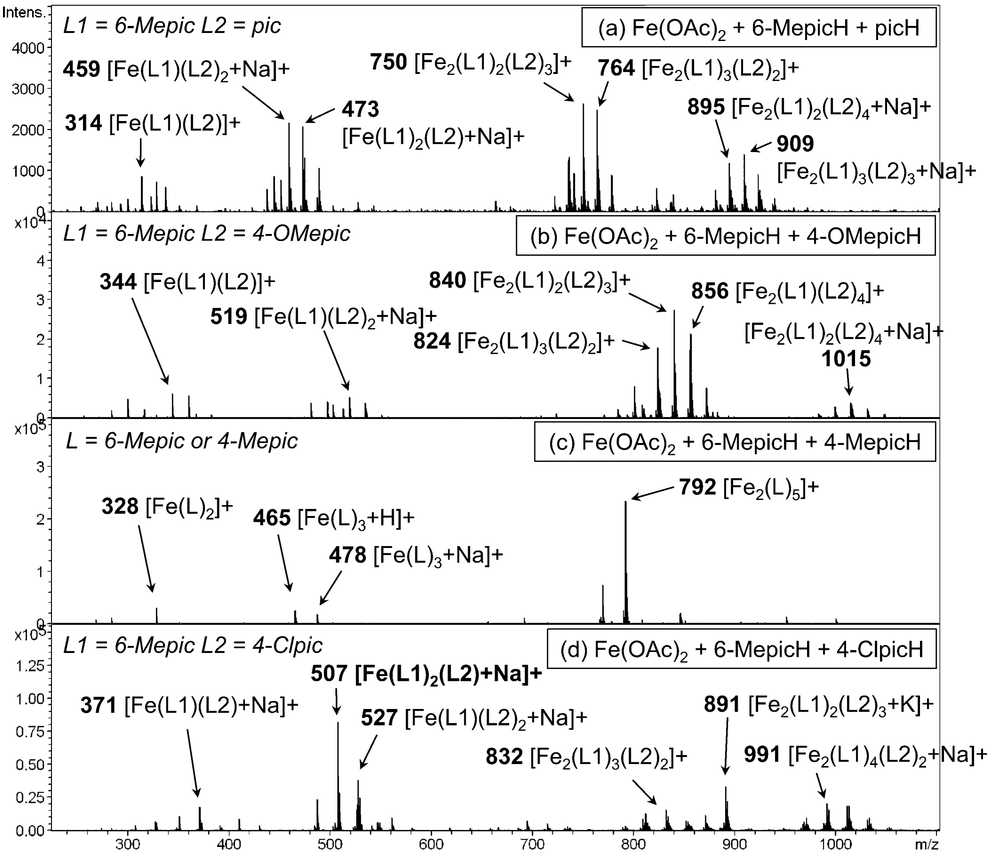
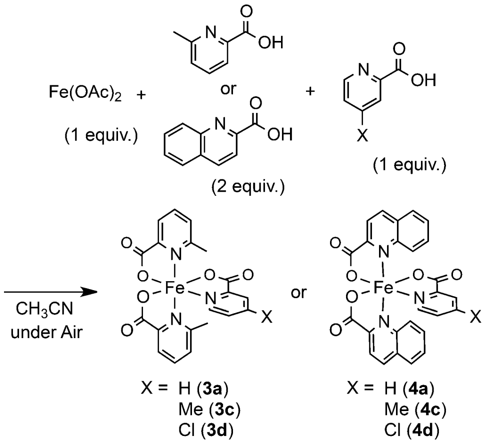


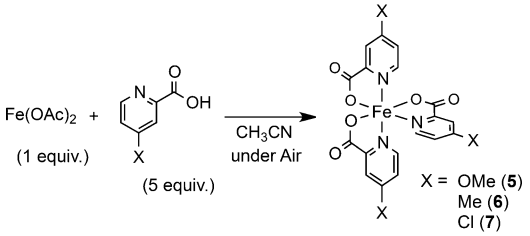
Figure 2. ESI-MS of mixture of $Fe(OAc)_2$, 6-MepicH, and 4-XpicH (X = H (a), OMe (b), Me (c), Cl (d)) in CH_3CN.

cating that efficient formation of monometallic Fe^{III} mixed-ligand complexes might be key for higher activity. Therefore, we next attempted the synthesis of mixed picolinate and quinaldinate Fe^{III} complexes. Treatment of two equivalents of 6-MepicH and one equivalent of *para*-substituted picolinic acids with $Fe(OAc)_2$ in CH_3CN under air yielded Fe^{III} mixed-picolinate complexes $[Fe(6\text{-}Mepic)_2(4\text{-}Xpic)]$ (**3a**: X = H, **3b**: X = Me, **3d**: X = Cl) as crystals (Scheme 1). In the same way, Fe^{III} quinaldinate–picolinate complexes $[Fe(qn)_2(4\text{-}Xpic)]$ (**4c**: X = Me, **4d**: X = Cl) were synthesized (Scheme 1). A solution containing 4-OMepicH afforded not crystals but a precipitated powder, which was not consistent with the calculated formula of the corresponding mixed-ligand complexes in the elemental analysis. In addition, the reaction of $Fe(OAc)_2$ with qnH and picH gave two kinds of crystals, one of which was characterized as $[Fe(qn)_2(pic)]$ (**4a**) by X-ray analysis. Crystals of the dinuclear complex $[Fe_2(qn)_4O]$ (**11**) were formed in a solution containing Fe(OAc), qnH, and 4-ClpicH as a minor product (see the Supporting Information). For comparison, homoleptic Fe^{III}–picolinate complexes $[Fe(4\text{-}Xpic)_3]$ (**5**: X = OMe, **6**: X = Me, **7**: X = Cl) were also prepared in CH_3CN solution containing $Fe(OAc)_2$ and an excess amount of the corresponding picolinic acids (Scheme 2). These complexes were characterized by single-crystal X-ray analysis, ESI-MS, and elemental analysis.



Scheme 1. Synthesis of Fe^{III} mixed-picolinate complexes $[Fe(6\text{-}Mepic)_2(4\text{-}Xpic)]$ (**3a**: X = H, **3b**: X = Me, **3d**: X = Cl) and Fe^{III} quinaldinate–picolinate complexes $[Fe(qn)_2(4\text{-}Xpic)]$ (**4c**: X = Me, **4d**: X = Cl).

The molecular structures of complexes **3d**, **4c**, **4d**, and **6** are depicted in Figure 3. In the mixed-ligand complexes **3d**, **4c**, and **4d**, the pyridine moiety of the two sterically hindered ligands coordinate to the Fe center in a *trans* manner, and three N and O atoms are arranged in a meridional form, which are the same structural features as in **3a**.[14a] The Fe–N bond lengths of the Fe^{III}–picolinate complexes are listed in Table 2. The bond length between Fe and N of *para*-substituted picolinic acid (Fe–N1) in **3d** is longer than that of **3a** by approximately 0.06 Å. In addition, the Fe–N1 distance of **4d** is longer than that of **4c** by about 0.02 Å. These observations suggest



Scheme 2. Synthesis of homoleptic Fe^{III}–picolinate complexes [Fe(4-Xpic)$_3$] (**5**: X=OMe, **6**: X=Me, **7**: X=Cl).

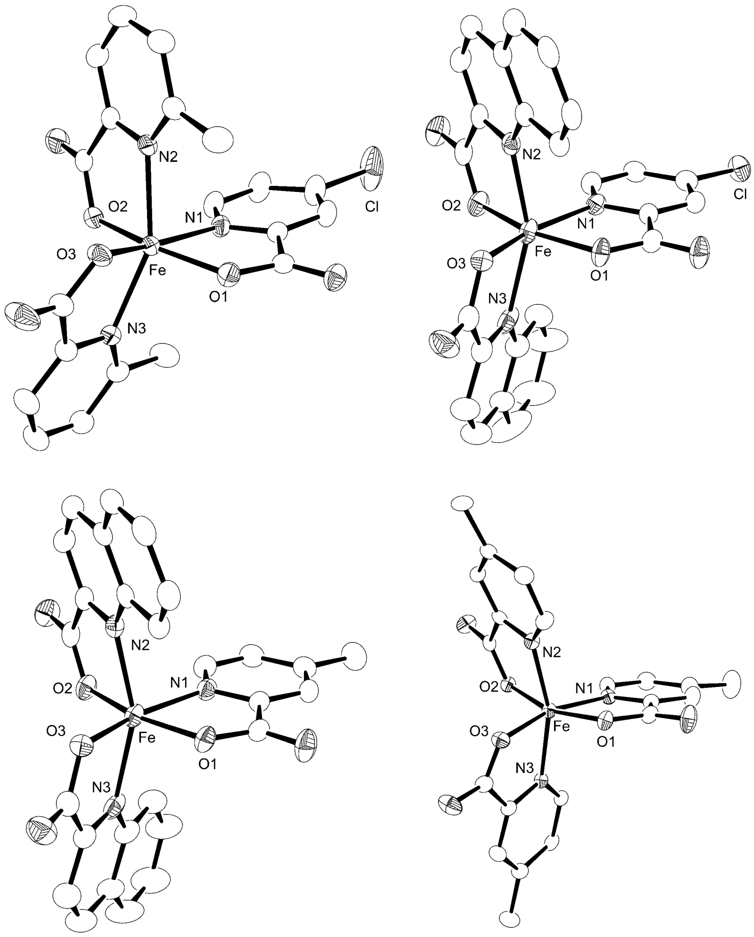


Figure 3. ORTEP plots of **3d** (a), **4d** (b), **4c** (c), and **6** (d). Hydrogen atoms are omitted for clarity.

that the pyridine ring of 4-Clpic coordinates to the Fe center more weakly than the pyridine ring of the other *para*-substituted picolinic acids. The average bond length between the Fe and N of quinaldinate (Fe–N2, Fe–N3) in **4a** and **4d** is longer than that in **3a** and **3d**, indicating that the qn ligand is more sterically hindered than the 6-Mepic ligand. It should be noted that **4a**, **4c**, **4d**, and **11** are the first neutral Fe^{III}–quinaldinate complexes to be structurally characterized. The Fe–N bond lengths in **5**, **6**, and **7** are comparable to those reported for [Fe(pic)$_3$] (**8**)[16a] and [Fe(3-*n*Bupic)$_3$],[16b] but shorter than those of [Fe(6-Mepic)$_3$] (**9**) by 0.06 Å, indicating that the Me group attached to the 6-position of the pyridine ring has a stronger influence on the Fe^{III}–ligand interaction than that attached to the 4-position. The structural features of **11** are similar to those reported for the dinuclear complex [Fe$_2$(6-Mepic)$_4$O] (**10**), except that the former exhibited a longer Fe–N bond and intermolecular stacking structure owing to the π–π interactions of the qn ligands (Figure S3 in the Supporting Information).

We attempted the catalytic oxidation of **1a** by using 35% aq. H_2O_2 in CH_3CN solution with isolated Fe complexes as the catalyst. Fe complexes bearing two 6-Mepic ligands (**3a**, **3c**, and **3d**) showed slightly lower catalytic activity than the corresponding in situ-generated catalysts. Compound **2a** was obtained in 56–65% yield with 85–86% selectivity (Table 3, entries 1–3), and catalysis using the qn-based complexes **4c** and **4d** gave **2a** in comparable yields (**4c**: 33%, **4d**: 64%) as the catalysts generated in situ (Table 3, entries 4 and 5). Interestingly, there was a correlation between the average Fe–N bond length and catalytic performance: Fe complexes in which the average Fe–N bond length is longer exhibited better yields and selectivity for the product, except for **4c** and **9** (Figure 4a). For **9**, the steric hindrance of the ligands and the lower redox potential of the Fe ion diminished the catalytic activity (see below). This tendency suggested that the lability of ligands is key for the selective oxidation. Stavropoulous et al. reported the reaction of **8** with H_2O_2 yielded Fe^{II} species along with decomposition of H_2O_2.[16a] Such side reactions, including free radical generation, might diminish the selectivity of the catalytic reaction. To clar-

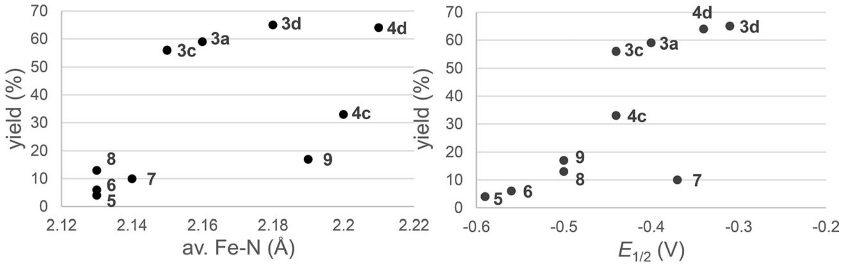
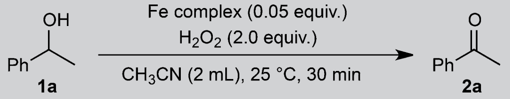


Figure 4. Plots of the yields of catalytic oxidation of **1a** by isolated Fe^{III} complexes against their average Fe–N bond lengths as determined by X-ray analysis (a) and $E_{1/2}$ values determined by CV analysis (b).

Table 2. Selected bond lengths of Fe–picolinate complexes.

Complex	Fe–N1	Fe–N2	Fe–N3	av. Fe–N	Ref.
3a	2.154(3)	2.166(2)	2.150(2)	2.16	[14a]
3c	2.155(3)	2.143(4)	2.166(3)	2.15	this work
3d	2.2170(16)	2.1783(17)	2.1436(16)	2.18	this work
4a	2.146(4)	2.179(5)	2.166(6)	2.16	this work
4c	2.197(4)	2.170(3)	2.238(3)	2.20	this work
4d	2.220(4)	2.167(4)	2.235(4)	2.21	this work
5	2.156(3)	2.105(3)	2.121(3)	2.13	this work
6	2.138(3)	2.105(3)	2.142(3)	2.13	this work
7	2.137(2)	2.1274(17)	2.1410(17)	2.14	this work
Fe(pic)$_3$ (**8**)	2.150(5)	2.126(4)	2.128(4)	2.13	[16a]
Fe(6-Mepic)$_3$ (**9**)	2.1561(17)	2.1670(16)	2.2459(16)	2.19	[14b]
[Fe(6-Me pic)$_2$]$_2$O (**10**)	2.1428(13)	–	–	–	[14a]
[Fe(qn)$_2$]$_2$O (**11**)	2.157(4)	–	–	–	this work

Table 3. Catalytic oxidation of 1-phenylethanol by isolated Fe complexes.[a]



Entry	Fe complex	Conversion[b] [%]	Yield[b] [%]	Selectivity[c] [%]
1	[Fe(6-Mepic)$_2$(pic)] (**3a**)	69	59	85
2	[Fe(6-Mepic)$_2$(4-Mepic)] (**3c**)	66	56	85
3	[Fe(6-Mepic)$_2$(4-Clpic)] (**3d**)	76 (67)[d]	65 (63)[d]	86 (95)[d]
4	[Fe(qn)$_2$(4-Mepic)] (**4c**)	39	33	85
5	[Fe(qn)$_2$(4-Clpic)] (**4d**)	76	64	84
6	[Fe(4-OMepic)$_3$] (**5**)	24	4	17
7	[Fe(4-Mepic)$_3$] (**6**)	8	6	75
8	[Fe(4-Clpic)$_3$] (**7**)	14	10	71
9	[Fe(pic)$_3$] (**8**)	24	13	54
10	[Fe(6-Mepic)$_3$] (**9**)	22	17	74

[a] CH_3CN solution, 25 °C, dropwise addition of 2.0 equiv. of 35% aq. H_2O_2 over 30 min and further stirring for 5 min, unless otherwise stated. [b] Determined by GC by using biphenyl as an internal standard. Average of two runs. [c] Yield/conversion × 100. [d] 0.10 equiv. of CH_3COOH was added.

ify the effect of liberated acetic acid under the in situ-generation conditions, we carried out a catalytic reaction by using **3d** as the catalyst in the presence of 0.10 equivalents of acetic acid. Compound **2a** was obtained in 63% yield with higher selectivity (95%) than catalysis without acetic acid (86%) and, accordingly, acetic acid might promote ligand exchange reactions (Table 3, entry 3). The difference in yields between catalytic reactions with isolated catalysts and in situ-generated catalysts was attributed to the presence of an extra amount (0.05 equiv.) of the sterically hindered ligand. In fact, the catalytic reaction of **1a** under the in situ-generation conditions when using Fe(OAc)$_2$ (0.05 equiv.), 6-MepicH (0.10 equiv.), and 4-ClpicH (0.05 equiv.) gave **2a** in 64% yield with 89% selectivity. From the viewpoint of practical catalysis, the better catalytic performance of the in situ-generated catalysts rather than isolated Fe complexes is considered as one of the advantages of this easy-to-handle catalyst system.

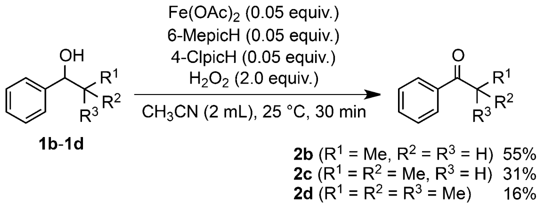
Magnetic and electrochemical properties of Fe complexes

Table 4. μ_{eff} and $E_{1/2}$ values for the Fe complexes.

Entry	Fe complex	μ_{eff}[a] [μ_B]	$E_{1/2}$ (Fe^{III}/Fe^{II})[b] [V]
1	[Fe(6-Mepic)$_2$(pic)] (**3a**)	5.5	−0.40
2	[Fe(6-Mepic)$_2$(4-Mepic)] (**3c**)	5.6	−0.44
3	[Fe(6-Mepic)$_2$(4-Clpic)] (**3d**)	5.4	−0.31
4	[Fe(qui)$_2$(4-Mepic)] (**4c**)	3.9	−0.44
5	[Fe(qui)$_2$(4-Clpic)] (**4d**)	4.5	−0.34
6	[Fe(4-OMepic)$_3$] (**5**)	5.2	−0.59
7	[Fe(4-Mepic)$_3$] (**6**)	5.7	−0.56
8	[Fe(4-Clpic)$_3$] (**7**)	6.0	−0.37
9	[Fe(pic)$_3$] (**8**)	6.3	−0.50
10	[Fe(6-Mepic)$_3$] (**9**)	3.8	−0.50

[a] Determined by the Evans' method in CD_3CN solution. [b] Determined by CV measured in CH_3CN (1 mM) with nBu$_4$NBF$_4$ (0.1 M) as a supporting electrolyte. Conditions: rt; scan rate 100 mV s^{-1}; AgNO$_3$/Ag in CH_3CN reference electrode; glassy carbon working electrode; Pt wire counter electrode. $E_{1/2}$ values are referenced to $E_{1/2}$(FcH$^+$/FcH) measured under the same conditions.

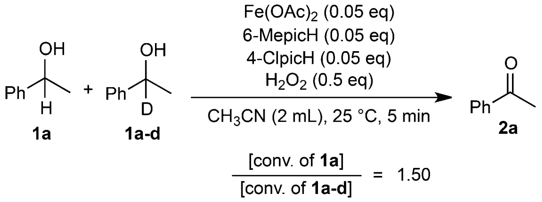
The magnetic susceptibility of the isolated Fe complexes was determined by the Evans' NMR method in CD_3CN solution. The μ_{eff} values of Fe complexes bearing 6-Mepic ligand **3a**, **3c**, and **3d** were determined to be 5.5, 5.6, and 5.4 μ_B (Table 4), respectively, indicating the high-spin nature of the Fe^{III} species. Notably, these values were lower than that of [Fe(pic)$_3$] **8** (6.3 μ_B). Costas et al. reported Fe^{II} complexes showing catalytic activity for H_2O_2 oxidation; their μ_{eff} values were much more highly dependent on the type of 2-substituent of the pyridine ring than on the type of 4-substituent.[16] The more sterically hindered quinaldinate complexes **4c**, **4d** and [Fe(6-Mepic)$_3$] (**9**) exhibited lower μ_{eff} values (3.9, 4.5, and 3.8 μ_B, respectively). Based on the μ_{eff} values of each of these complexes, the spin nature of the Fe^{III} complex did not play a considerable role in the catalytic reaction (Figure S5 in the Supporting Information). In contrast, the $E_{1/2}$ (Fe^{III}/Fe^{II}) value of the Fe complexes was correlated with the catalytic reaction yield. The previously reported electrochemical measurement of Fe complexes in CH_3CN solution revealed a chemically reversible redox wave assignable to Fe^{III}/Fe^{II}.[18] Among the Fe complexes with a 6-Mepic ligand, **3d** showed the highest potential, −0.31 V, which was consistent with the electron-withdrawing nature of the Cl atom at the 4-position of the picolinate ligand. In same way, the cyclic voltammogram (CV) of the quinaldinate complex containing 4-Clpic (**4d**) showed a higher redox potential (−0.34 V) than that containing 4-Mepic (**4c**; −0.44 V). Interestingly, the Fe complexes displaying higher redox potential showed higher reaction yields in the catalytic reaction among the mixed-ligand Fe complexes (Figure 4b). This correlation suggested that the nonselective oxidation through a Fenton mechanism, which would normally occur more frequently with a Fe complex with a higher redox potential,[12e] was efficiently inhibited owing to the lability of the ligands. Moreover, the reduction of high-valent Fe species might be the key step rather than the formation of high-valent Fe species during catalysis. The $E_{1/2}$ values of homoleptic Fe complexes (**5**–**9**) were determined to be −0.59, −0.56, −0.37 −0.50, and −0.50 V, respectively. Unlike in the series of mixed-ligand complexes, there was no correlation between the redox potential and reaction yield in complexes **5**–**8**, which was probably due to the nonlabile nature of the ligands, which inhibited the generation of catalytically active Fe species. For the most sterically hindered complex **9**, the lower redox potential might have caused a lower catalytic activity even though the ligand exchange reaction proceeded efficiently. To examine whether steric hindrance around the Fe center has a negative effect on catalytic activity, the catalytic oxidations of 1-phenyl-1-propanol (**1 b**), 1-phenyl-2-methyl-1-propanol (**1 c**), and 1-phenyl-2,2-dimethyl-1-propanol (**1 d**) were conducted (Scheme 3). The yields of the corresponding ketones decreased in the order of substrate bulkiness (**2 b**: 55 %; **2 c**: 31 %; **2 d**: 16 %). In addition, **9** exhibited higher catalytic activity for oxidation of primary alcohols than **3 a** in a previous study.[14b] Taken together, these facts indicated that the lower catalytic activity of **9** compared with the mixed-ligand complexes was attributable to steric bulkiness around the Fe center, as well as to the stable nature of the higher oxidation state.



Scheme 3. Catalytic oxidations of 1-phenyl-1-propanol (**1 b**), 1-phenyl-2-methyl-1-propanol (**1 c**), and 1-phenyl-2,2-dimethyl-1-propanol (**1 d**).

Mechanistic studies

To identify the rate-determining step of the catalytic cycle, we carried out a competitive H_2O_2 oxidation reaction by using a 1:1 mixture of **1 a** and **1 a-D** as substrate (Scheme 4). The ratio of conversion between **1 a** and **1 a-D** was determined to be 1.50 under catalytic conditions, suggesting the possibility that C–H bond cleavage was the rate-determining step.



Scheme 4. Competitive H_2O_2 oxidation reaction by using a 1:1 mixture of **1 a** and **1 a-D** as substrate.

For further investigation of the C–H bond cleavage step in this catalysis, a Hammett plot was studied by using *para*-substituted 1-phenylethanols as substrates. The initial relative rates for the four types of substituents (OMe, Me, Cl, and CF_3) were plotted against their $\sigma+$ values. A first-order equation with $\rho = -0.75$ as the reaction constant was obtained (Figure 5). This ρ value was intermediate between that for the typical alcohol oxidation through a hydrogen atom transfer mechanism and that for the typical alcohol oxidation through a hydride transfer mechanism.[12e] Considering that the oxidation of cyclobutanol generated no ring-opened product, but cyclobutanone exclusively in a previous study,[14b] it seems reasonable to conclude that C–H bond cleavage through hydride transfer took place rather than H atom transfer.

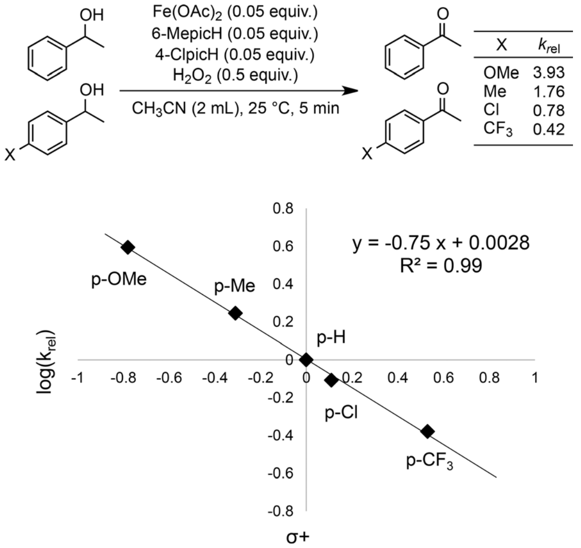
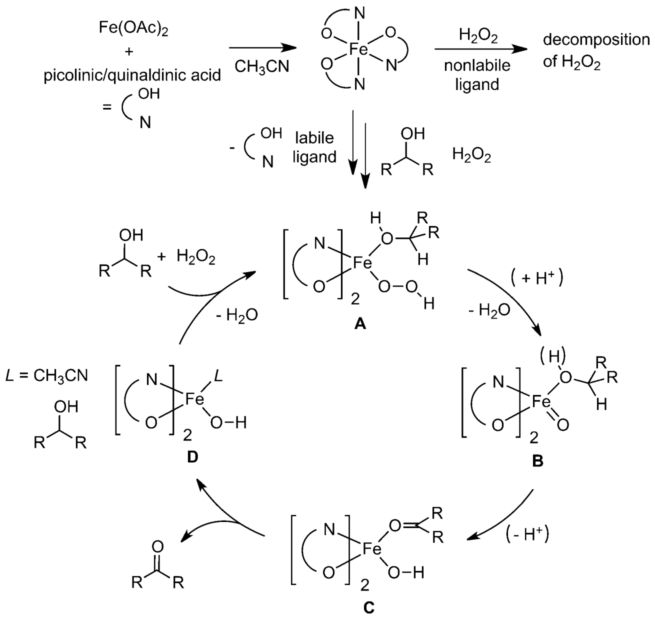


Figure 5. Hammett plot for H_2O_2 oxidation of *para*-substituted 1-phenylethanol by iron catalysis.

Based on these experiments, the catalytic cycle is shown in Scheme 5. First, as indicated by ESI-MS analysis, a mixed-ligand Fe^{III} species was generated as the major component from the catalyst mixture containing $Fe(OAc)_2$ and two carboxylic acids in CH_3CN. Subsequent additions of alcohol and H_2O_2 led to the formation of the catalytically active species through a ligand exchange reaction. In this step, the decomposition of H_2O_2 by an outer-sphere redox reaction with the Fe^{III} complex was not favored, because the picolinate ligands were sufficiently labile for replacement. From Fe–hydroperoxo species **A**, a high-valent Fe–oxo species **B** formed through the abstraction of H^+ of the free carboxylic acid or coordinated alcohol to liberate H_2O.[19] Reaction of the O ligand in species **B** with the C–H bond of alcohol, which was the rate-determining step based on the $E_{1/2}$ value of the Fe complexes and the isotope experiment, gave the reduced Fe species **C** bearing the product ketone. Finally, the product and OH ligand on the Fe center were replaced in species **C** and **D** by the substrate and H_2O_2 to regenerate active species **A**.



Scheme 5. Plausible catalytic cycle.

Conclusion

In this report, we developed a simple iron catalyst for H_2O_2 oxidation of alcohols. Self-assembly of $Fe(OAc)_2$ and two types of picolinic/quinaldinic acid generated efficient catalyst precursors for the H_2O_2 oxidation reaction. The best catalyst was determined to be $Fe(OAc)_2$ with 6-MepicH and 4-ClpicH, and was obtained simply by changing the combination of picolinic/quinaldinic acids. In addition, the origin of the efficient catalytic activity by this optimal catalyst combination was explored in detail by studying the Fe complexes. Several mixed picolinate/quinaldinate Fe^{III} complexes were successfully isolated and structurally characterized, and their magnetic and electrochemical properties were revealed. The catalytic activity of isolated Fe complexes for the oxidation of 1-phenylethanol by H_2O_2 was shown to be dependent on the Fe–N bond length and the redox properties of the individual Fe complexes. According to these observations, the role of the two types of ligand in the improved catalytic oxidation was described as follows: (1) 6-MepicH enhanced the lability of the ligand of the coordinatively saturated Fe^{III} center to generate Fe–oxidant species and it avoided unselective side reactions resulting from the decomposition of H_2O_2; (2) 4-ClpicH enhanced the activity of the high-valent Fe-based oxidant species, resulting in faster C–H bond cleavage in a rate-determining step. In addition, the lower activity of the Fe catalyst with only sterically hindered ligands was attributed to both the electronic and steric effect. This contribution implies that controlling the lability of ligands is key[20] along with electronic and steric control when coordinatively saturated Fe^{III} species, which are easily handled and potentially practical, are employed as the catalyst.

Experimental Section

General procedure

^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with JEOL 400 MHz NMR spectrometers. All spectra were recorded at 25±1 °C. Chemical shifts (δ) are in parts per million relative to residual $CHCl_3$ at 7.26 ppm for ^1H and at 77.0 ppm for ^{13}C unless otherwise noted. Gas chromatographic (GC) analyses were performed with a Shimadzu GC-2014 using a TC-WAX column (0.25 mm × 30 m, GL Sciences Inc.). All samples were analyzed and quantified by using biphenyl as an internal standard. Melting points were measured with a Yanaco MP-500 V Macro Melting Point Apparatus. Elemental analyses were measured with a Thermo Fisher Scientific Inc. Flash2000 instrument. ESI-Mass spectra were measured with a Bruker mocrOTOF spectrometer. In the X-ray crystallographic analyses, data were collected with a Bruker APEX-II CCD diffractometer using graphite-monochromated MoK_α radiation. The structures were solved by direct methods (SIR92,[21] SHELXS-97[22]) and refined by full-matrix least-squares techniques on F^2 (SHELXL-97).[22] The ORTEP-3 program was used to draw the molecule.[23] $[Fe(6\text{-Mepic})_2(pic)]$(**3 a**),[14a] $[Fe(pic)_3]$(**8**),[16a] and $[Fe(6\text{-Mepic})_3]$(**9**)[14b] were prepared according to literature procedures. 35 % H_2O_2 in CH_3CN was prepared by dilution of 87 % aq. H_2O_2 with CH_3CN. Other chemicals were purchased from chemical suppliers. The oxidation reactions of alcohols on the small scale were performed by using a ChemiStation (Tokyo Rika Inc.) equipped with thermostated apparatus.

Typical procedure for the oxidation reaction

$Fe(OAc)_2$ (9.5 mg, 0.055 mmol), PicH (7.7 mg, 0.063 mmol), and 6-MePicH (7.9 mg, 0.057 mmol) were suspended in CH_3CN (2.0 mL). The mixture was warmed to 50 °C with gentle stirring until almost all the $Fe(OAc)_2$ was dissolved (ca. 5 min), then the solution was filtered with a membrane filter (pour size: 0.20 μm). Alcohol (1.0 mmol) was dissolved in the filtrate. Aqueous H_2O_2 (35%, 0.18 mL, 2 mmol) was added dropwise to the solution by using a syringe pump for 30 min at 25 °C. CH_3CN (6 mL) was then added to the resulting mixture along with a measured amount of biphenyl (as an internal standard for GC analysis). The conversion of substrate and the yield of carbonyl compounds were determined by GC analysis. Products were identified by comparison with the GC retention time of authentic samples. The same reaction was performed twice for each set of reaction conditions.

Oxidation of 1-phenylethanol 2 a (10 g scale)

$Fe(OAc)_2$ (0.87 g, 5.0 mmol), 4-ClPicH (0.79 g, 5.0 mmol), and 6-MePicH (0.69 g, 5.0 mmol) were suspended in CH_3CN (0.20 L). The mixture was warmed to 50 °C with gentle stirring until almost all of iron acetate was dissolved (ca. 5 min), then the solution was filtered with a membrane filter (pour size: 0.20 μm). 1-Phenylethanol **2 a** (12 g, 0.10 mol) was dissolved in the filtrate. A CH_3CN solution of 35 % H_2O_2 (18 mL, 0.20 mol) was added to the solution dropwise with a dropping funnel for 60 min at 25 °C, and the reaction solution was stirred for a further 5 min at 25 °C. Saturated sodium thiosulfate solution (20 mL) was added to the resulting solution, and the mixture was stirred for another 5 min at 25 °C. The organic layer was separated, and CH_3CN was removed by rotary evaporator, giving 11 g of acetophenone (91 % yield).

Synthesis of [Fe(6-Mepic)$_2$(4-Mepic)] (3c)

Fe(OAc)$_2$ (87 mg, 0.50 mmol), 6-MepicH (0.14 g, 1.0 mmol), and 4-MepicH (69 mg, 0.50 mmol) were suspended in MeCN (25 mL). The mixture was warmed to 50 °C with gentle stirring until almost all of the iron acetate was dissolved (ca. 15 min). The solution was then filtered, and concentrated to ca. 1 mL under reduced pressure. Diffusion of Et$_2$O into the residue at 5 °C yielded [Fe(6-MePic)$_2$(4-MePic)] (**3c**, 0.11 g, 0.20 mmol, 49 % yield) as pale-yellow crystals, which were collected by filtration and washed with CH_3CN (2 mL). M.p.: 197–203 °C (decomp.); ESI-MS (CH_3CN, positive): $m/z=465$ ($M+H^+$), 487 ($M+Na^+$), 503 ($M+K^+$); elemental analysis calcd (%) for $C_{21}H_{18}FeN_3O_6$: C 54.33; H 3.91; N 9.05; found: C 53.95; H 3.85; N 8.83.

Synthesis of [Fe(6-Mepic)$_2$(4-Clpic)] (3d)

Complex **3d** was synthesized by a similar procedure as **3c** but by using 4-ClpicH instead of 4-MepicH. Complex **3d** was obtained as pale-yellow crystals (16 % yield). M.p.: 195–198 °C (decomp.); ESI-MS (CH_3CN, positive): $m/z=507$ ($M+Na^+$), 523 ($M+K^+$); elemental analysis calcd (%) for $C_{20}H_{15}FeClN_3O_6$: C 49.57; H 3.12; N 8.67; found: C 49.27; H 3.13; N 8.59.

Synthesis of [Fe(qn)$_2$(4-MePic)] (4c)

Complex **4c** was synthesized by a similar procedure as **3c** but by using qnH and 4-MepicH instead of 6-MepicH and 4-MepicH, respectively. Complex **4c** was obtained as red crystals (56 % yield). M.p.: 218–225 °C (decomp.); ESI-MS (CH_3CN, positive): $m/z=523$ ($M+H^+$), 559 ($M+Na^+$); elemental analysis calcd (%) for $C_{27}H_{18}FeN_3O_6$: C 60.47; H 3.38; N 7.84; found: C 60.21; H 3.38; N 8.16.

Synthesis of [Fe(qn)$_2$(4-Clpic)] (4d)

Complex **4d** was synthesized by a similar procedure as **3c** but by using qnH and 4-ClpicH instead of 6-MepicH and 4-MepicH, respectively. Complex **4d** was obtained as deep-orange crystals (6 % yield). M.p.: 216–219 °C (decomp.); ESI-MS (CH_3CN, positive): $m/z=579$ ($M+Na^+$), 595 ($M+K^+$); elemental analysis calcd (%) for $C_{26}H_{15}ClFeN_3O_6$: C 56.09; H 2.72; N 7.55; found: C 55.32; H 2.55; N 7.86.

Synthesis of [Fe(4-OMepic)$_3$] (5)

Fe(OAc)$_2$ (91 mg, 0.52 mmol) and 4-OMepicH (0.38 g, 2.5 mmol) were suspended in MeCN (25 mL). The mixture was warmed to 50 °C with gentle stirring until almost all of the iron acetate was dissolved (ca. 5 min). The solution was then filtered, and allowed to stand at room temperature. After several days, [Fe(4-OMePic)$_3$] (**5**) was formed as greenish-yellow crystals, which were collected by filtration and washed with CH_3CN (2 mL) to give 72 mg, 0.14 mmol, 27 % yield. M.p.: 221–226 °C (decomp.); ESI-MS (CH_3CN, positive): $m/z=513$ ($M+H^+$), 535 ($M+Na^+$), 551 ($M+K^+$); elemental analysis calcd (%) for $C_{21}H_{18}FeN_3O_9$: C 49.24; H 3.54; N 8.20; found: C 49.13; H 3.71; N 8.38.

Synthesis of [Fe(4-Mepic)$_3$] (6)

Complex **6** was synthesized by the same procedure as **5** but by using 4-MepicH instead of 4-OMepicH. Complex **6** was obtained as greenish-yellow crystals (14 % yield). M.p.: 215–220 °C (decomp.); ESI-MS (CH_3CN, positive): $m/z=465$ ($M+H^+$), 487 ($M+Na^+$), 487 ($M+K^+$); elemental analysis calcd (%) for $C_{21}H_{18}FeN_3O_6\cdot(CH_3CN)$: C 54.67; H 4.19; N 11.05; found: C 54.32; H 4.11; N 10.66.

Synthesis of [Fe(4-Clpic)$_3$] (7)

Complex **7** was synthesized by the same procedure as **5** but by using 4-ClpicH instead of 4-OMepicH. Complex **7** was obtained as greenish-yellow crystals (15 % yield). M.p.: 197–199 °C (decomp.); ESI-MS (CH_3CN, positive): $m/z=525$ ($M+H^+$), 547 ($M+Na^+$), 565 ($M+K^+$); elemental analysis calcd (%) for $C_{18}H_9FeN_3O_6$: C 41.14; H 1.73; N 8.00; found: C 41.17; H 1.46; N 8.34.

Catalytic oxidation by Fe complexes

Compound **1a** (1.0 mmol) was added to a test tube containing the Fe complex (0.050 mmol) in CH_3CN (2.0 mL). Aqueous H_2O_2 (35 %, 0.18 mL, 2.0 mmol) was added dropwise to the mixture by using a syringe pump for 30 min at 25 °C. CH_3CN (6 mL) was then added to the resulting mixture along with a measured amount of biphenyl (as an internal standard for GC analysis). The conversion of substrate and the yield of carbonyl compounds were determined by GC analysis. Products were identified by comparison with the GC retention times of authentic samples. The same reaction was performed twice for each set of reaction conditions.

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Keywords: catalysis · hydrogen peroxide · iron · oxidation · practical synthesis

[1] a) S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317; *Angew. Chem.* **2008**, *120*, 3363; b) C.-L. L. Sun, B.-J. J. Li, Z.-J. J. Shi, *Chem. Rev.* **2011**, *111*, 1293; c) A. Correa, O. Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; d) G. Bauer, K. Kirchner, *Angew. Chem. Int. Ed.* **2011**, *50*, 5798; *Angew. Chem.* **2011**, *123*, 5918.

[2] A. C. Mayer, C. Bolm in *Iron Catalysis in Organic Chemistry* (Ed.: B. Plietker), Wiley-VCH, Weinheim, **2008**, pp. 73–123.

[3] Recent examples of iron-based oxidation catalysts: a) A. Gonzalez-de-Castro, J. Xiao, *J. Am. Chem. Soc.* **2015**, *137*, 8206; b) O. Cussó, X. Ribas, J. Lloret-Fillol, M. Costas, *Angew. Chem. Int. Ed.* **2015**, *54*, 2729; *Angew. Chem.* **2015**, *127*, 2767; c) Y. Hitomi, K. Arakawa, T. Funabiki, M. Kodera, *Angew. Chem. Int. Ed.* **2012**, *51*, 3448; *Angew. Chem.* **2012**, *124*, 3504; d) M. S. Chen, M. C. White, *Science* **2010**, *327*, 566.

[4] a) S. Rachmilovich-Calis, A. Masarwa, D. Meyerstein, R. van Eldik, *Chem. Eur. J.* **2009**, *15*, 8303; b) D. T. Sawyer, A. Sbkowiak, T. Matsushita, *Acc. Chem. Res.* **1996**, *29*, 409.

[5] D. H. R. Barton, *Tetrahedron* **1998**, *54*, 5805.

[6] G. Balavoine, D. H. R. Barton, J. Boivin, A. Gref, *Tetrahedron Lett.* **1990**, *31*, 659.

[7] P. Stavropoulos, R. Celenligil-Cetin, A. E. Tapper, *Acc. Chem. Res.* **2001**, *34*, 745.

[8] a) T. Tsugawa, H. Furutachi, M. Marunaka, T. Endo, K. Hashimoto, S. Fujinami, S. Akine, Y. Sakata, S. Nagatomo, T. Tosha, T. Nomura, T. Kitagawa, T. Ogura, M. Suzuki, *Chem. Lett.* **2015**, *44*, 330; b) D. Houghton, N. Gydesen, N. Arulsamy, M. Mehn, *Inorg. Chem.* **2010**, *49*, 879; c) H. Furutachi, K. Hashimoto, S. Nagatomo, T. Endo, S. Fujinami, Y. Watanabe, T. Kitagawa, M. Suzuki, *J. Am. Chem. Soc.* **2005**, *127*, 4550; d) S. Jain, A. Slawin, D. Woollins, P. Bhattacharyya, *Eur. J. Inorg. Chem.* **2005**, 721; e) D. Dobrzyń-

ska, L. Jerzykiewicz, M. Duczmal, *Polyhedron* **2005**, *24*, 407; f) K. Hashimoto, S. Nagatomo, S. Fujinami, H. Furutachi, S. Ogo, M. Suzuki, A. Uehara, Y. Maeda, Y. Watanabe, T. Kitagawa, *Angew. Chem. Int. Ed.* **2002**, *41*, 1202; *Angew. Chem.* **2002**, *114*, 1250; g) N. Okabe, T. Makino, *Acta Crystallogr. Sect. C* **1998**, *54*, 1279; h) A. G. Högberg, K. Madan, C. Moberg, B. Sjöberg, M. Weber, M. Muhammed, *Polyhedron* **1985**, *4*, 971.

[9] L. W. C. E. Arends, R. A. Sheldon in *Modern Oxidation Methods, 2nd ed.* (Ed.: J.-E. Bäckvall), Wiley-VCH, Weinheim, **2010**, 147–185.

[10] B. Ryland, S. Stahl, *Angew. Chem. Int. Ed.* **2014**, *53*, 8824; *Angew. Chem.* **2014**, *126*, 8968.

[11] M. Shibuya, Y. Osada, Y. Sasano, M. Tomizawa, Y. Iwabuchi, *J. Am. Chem. Soc.* **2011**, *133*, 6497.

[12] a) M. Lenze, E. B. Bauer, *Chem. Commun.* **2013**, *49*, 5889; b) H. Hosseini-Monfared, C. Näther, H. Winkler, C. Janiak, *Inorg. Chim. Acta* **2012**, *391*, 75; c) B. Biswas, A. Al-Hunaiti, M. T. Räisänen, S. Ansalone, M. Leskelä, T. Repo, Y.-T. Chen, H.-L. Tsai, A. D. Naik, A. P. Railliet, Y. Garcia, R. Ghosh, N. Kole, *Eur. J. Inorg. Chem.* **2012**, 4479; d) B. Join, K. Möller, C. Ziebart, K. Schröder, D. Gördes, K. Thurow, A. Spannenberg, K. Junge, M. Beller, *Adv. Synth. Catal.* **2011**, *353*, 3023; e) F. Shi, M. K. Tse, Z. Li, M. Beller, *Chem. Eur. J.* **2008**, *14*, 8793.

[13] a) K. Mikami, S. Matsukawa, T. Volk, M. Terada, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2768; *Angew. Chem.* **1997**, *109*, 2936; b) F. Yang, D. Zhao, J. Lan, P. Xi, L. Yang, S. Xiang, J. You, *Angew. Chem. Int. Ed.* **2008**, *47*, 5646; *Angew. Chem.* **2008**, *120*, 5728; c) B. Breit, *Angew. Chem. Int. Ed.* **2005**, *44*, 6816; *Angew. Chem.* **2005**, *117*, 6976.

[14] a) T. Chishiro, Y. Kon, T. Nakashima, M. Goto, K. Sato, *Adv. Synth. Catal.* **2014**, *356*, 623; b) S. Tanaka, Y. Kon, T. Nakashima, K. Sato, *RSC Adv.* **2014**, *4*, 37674.

[15] a) E. Y. Tshuva, S. J. Lippard, *Chem. Rev.* **2004**, *104*, 987; b) S. V. Kryatov, E. V. Rybak-Akimova, S. Schindler, *Chem. Rev.* **2005**, *105*, 2175.

[16] a) S. Kiani, A. Tapper, R. J. Staples, P. Stavropoulos, *J. Am. Chem. Soc.* **2000**, *122*, 7503; b) N. Okabe, Y. Muranishi, Y. Wada, *Acta Crystallogr. Sect. C* **2002**, *58*, m511.

[17] I. Prat, A. Company, T. Corona, T. Parella, X. Ribas, M. Costas, *Inorg. Chem.* **2013**, *52*, 9229.

[18] S. Richert, P. Tsang, D. Sawyer, *Inorg. Chem.* **1989**, *28*, 2471.

[19] a) R. Mas-Ballesté, L. Que, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 15964; b) O. Y. Lyakin, K. P. Bryliakov, E. P. Talsi, *Inorg. Chem.* **2011**, *50*, 5526; c) A. Ansari, A. Kaushik, G. Rajaraman, *J. Am. Chem. Soc.* **2013**, *135*, 4235.

[20] G. Olivo, M. Nardi, D. Vidal, A. Barbieri, A. Lapi, L. Gómez, O. Lanzalunga, M. Costas, S. Di Stefano, *Inorg. Chem.* **2015**, *54*, 10141.

[21] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.

[22] M. Sheldrick, *Programs for Crystal Structure Analysis (Release97–2)*; University of Göttingen, Göttingen, Germany, **1997**.

[23] L. J. J. Farrugia, *Appl. Crystallogr.* **1997**, *30*, 565.

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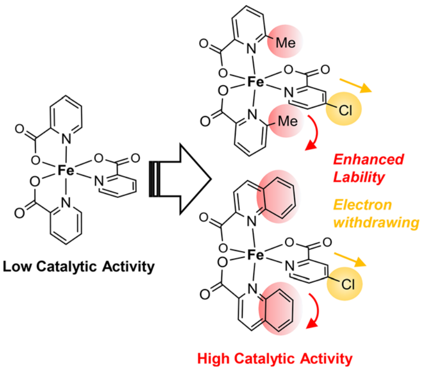
■■–■■

Mixed Picolinate and Quinaldinate Iron(III) Complexes for the Catalytic Oxidation of Alcohols with Hydrogen Peroxide



Mixing ligands: Mixed picolinate and quinaldinate iron(III) complexes show high catalytic activity for the H_2O_2 oxidation of alcohols. The suitable combination of sterically hindered and electronegative ligands enabled the efficient generation of catalytically active species from the coordinatively saturated iron(III) ion, which has been less investigated as a catalyst owing to low activity in spite of its potentially high practicality.