Catalytic Oxidation

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A Biomimetic Iron Catalyst for the Epoxidation of Olefins with Molecular Oxygen at Room Temperature**

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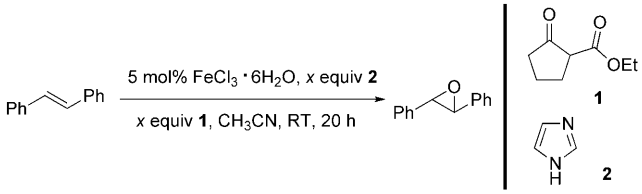
The selective oxidation of organic compounds remains a challenging task fundamentally important to life, the environment, and synthetic chemistry. Requirements for modern oxidation methods include cheap and selective catalysts, high atom efficiency, and environmentally friendly oxidants. In this context, molecular oxygen, especially in form of air, is the most desirable oxidant.[1] However, efficient nonradical transformations using O_2 are scarce, and novel catalysts that can activate O_2 under mild conditions for the direct and selective oxidation of organic substrates are still needed.[2] In this respect iron catalysts are particularly attractive because of the ready availability, low cost, and low toxicity of this metal. Significant progress has been made towards the application of easy-to-use iron catalysis in the last decade.[3] Various methods such as cross-coupling reactions,[4] sulfide oxidations,[5] allylic alkylations and aminations,[6] alcohol oxidations,[7] and Michael additions[8] have been successfully developed. Known iron catalysts for O_2 activation include Gif systems,[9] tris(2-(acetoacetoxy)ethyl methacrylate)iron complexes with aldehydes as co-substrates,[10] macrocyclic iron complexes,[11] and catecholate mimics, which are able to catalyze cleavage of catechols.[12] The main drawbacks of such catalysts are their low selectivity, temperature dependence, and high tendency to react by radical-type autoxidation in the absence of the metal catalyst.[13] In contrast, based on iron-catalyzed oxidations of alcohols or olefins to aldehydes,[14] arenes to quinones,[15] and olefins to epoxides,[16] and the hydroxylation of β-keto esters,[17] we herein report the selective iron-catalyzed oxidation of olefins to epoxides using air as the oxidant. A bio-inspired β-keto ester is employed as a sacrificial co-substrate, and oxygen transfer occurs highly selectively at room temperature. Notably, the mechanism of this type of O_2 activation is similar to that occurring in co-substrate-dependent non-heme iron oxygenases.[18]

While investigating the hydroxylation of β-keto esters under air,[17] we observed the partial epoxidation of *trans*-stilbene in the presence of a combination of iron chloride, imidazole ligands, and ethyl 2-oxocyclohexanecarboxylate. As shown in Table 1, all three components of the catalyst system (Fe/imidazole/β-keto ester) are needed for successful

Table 1: Iron-catalyzed epoxidation of stilbene with air.[a]



Entry	Metal salt	**1** (equiv)	**2** (equiv)	Conv. [%][b]	Yield [%][b]
1[c]	$FeCl_3 \cdot 6H_2O$	0.8	0.2	34	26
2	$FeCl_3 \cdot 6H_2O$	0.8	0.2	45	35
3	$FeCl_3 \cdot 6H_2O$	–	0.5	1	0
4	$FeCl_3 \cdot 6H_2O$	2	–	33	2
5	$FeCl_3 \cdot 6H_2O$	3	1	**93**	**92**
6	$FeCl_3 \cdot 6H_2O$	3	0.5	55	51
7	$FeCl_3 \cdot 6H_2O$	2	1	64	59
8	$FeCl_3 \cdot 6H_2O$	2	0.5	**91**	**81**
9	$FeCl_3 \cdot 6H_2O$	0.5	1	21	16
10	–	2	0.5	1	0
11	$FeCl_2 \cdot 4H_2O$	2	0.5	1	1
12	$NiCl_2 \cdot 4H_2O$	2	0.5	0	0
13	$CoCl_2 \cdot 6H_2O$	2	0.5	1	0
14	$CrCl_3 \cdot H_2O$	2	0.5	3	1
15	$RuCl_3 \cdot 6H_2O$	2	0.5	1	1
16[d]	$CuCl_2 \cdot 2H_2O$	2	0.5	1	0
17	$MnCl_2$	2	0.5	64	28

[a] Reaction conditions: In a 15 mL reaction tube, the metal source (0.025 mmol), **2** (*x* equiv), CH_3CN (10 mL), *trans*-stilbene (0.5 mmol = 1 equiv), and biphenyl (GC internal standard, ca. 20 mg) were added in sequence at room temperature in air. The reaction mixture was stirred and the reaction was initiated by addition of the sacrificial reductant **1** (*x* equiv). [b] Conversion and yield were determined by GC analysis. [c] *tert*-Amyl alcohol was used as solvent. [d] When bulkier imidazole ligands like 1-benzylimidazole were used, low amounts of product were detected (28% yield with 85% selectivity).

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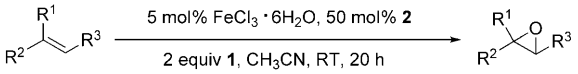
epoxidation (Table 1, entries 3, 4, and 10). Increasing **1** to three equivalents with respect to *trans*-stilbene resulted in 93% conversion with excellent selectivity and 92% yield at room temperature (Table 1, entry 5).

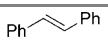
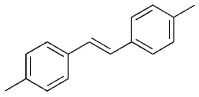
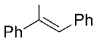
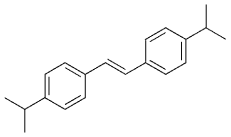
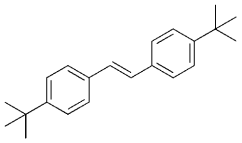
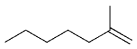
Because Iqbal and co-workers reported the use of Co^{II} complexes for the hydroxylation of methyl 2-oxocyclopentanecarboxylate with concomitant epoxidation of olefins,[19] we also tested different metal chlorides under our conditions (Table 1, entries 11–17). However, no epoxidation was observed in the presence of Ni, Co, Cr, Cu, or Ru chlorides. Only for $MnCl_2$ unselective activity was detected. Apparently the selective epoxidation reaction with air is specific for $FeCl_3 \cdot 6H_2O$, an observation which a priori seems incompatible with a metal-initiated radical autoxidation. The specific nature of the catalyst system was further studied by variation of nine structurally related β-keto esters. However, only in the presence of ethyl 2-oxocyclopentanecarboxylate significant activity (conversion $>30\%$) was observed (Table S2). Next, 14 different amine bases were tested. Although a number of imidazole ligands—except for 2-substituted derivatives—showed activity in the epoxidation reaction, the best results were obtained in the presence of inexpensive imidazole **2** (Table S3).

In Table 2 the general applicability of the room-temperature epoxidation in the presence of air is demonstrated. *trans*-Stilbene derivatives showed high yields and excellent chemoselectivity (Table 2, entries 1 and 6–9); these results are even better than those with the best previously described iron-based systems with hydrogen peroxide as the terminal oxidant.[16] Apart from the desired product, traces of benzaldehyde were detected. Aliphatic olefins were also catalytically epoxidized; however, these reactions generally proceeded in lower yields with selectivities above 65% (Table 2, entries 4, 11, and 13). *cis* Aromatic olefins such as *cis*-stilbene and *cis*-β-methylstyrene (Table 2, entries 2 and 12) were epoxidized to give the corresponding *trans* epoxides. This indicates that the oxygen transfer does not proceed in a concerted manner and a long-lived radical or carbocationic intermediate is apparently created before the second C–O epoxide bond is formed.

To elucidate whether an autoxidation pathway is responsible for this *cis*-to-*trans* stereoscrambling, the oxidation of α-pinene was studied (Table 2, entry 13). It is well known that radical oxidations, which proceed under thermal autoxidation conditions, yield mainly allylic oxidation products with this substrate and only small amounts of the corresponding epoxides.[20] However, with our system minimal amounts (around 2%) of allylic oxidation products were detected (verbenone; 4,6,6-trimethylbicyclo[3.1.1]hept-3-en-2-one) and the main product was α-pinene oxide (44% yield, 66% selectivity). The yields and selectivities exhibited by the present iron system are significantly higher than those of reactions catalyzed by cobalt(II) salen complexes, which operate via free diffusion radicals.[21] Hence, we exclude a metal-initiated radical autoxidation. In agreement with this interpretation, ethylbenzene and tetrahydronaphthalene, which contain weak C–H bonds and are prone to radical pathways,[22] were not oxidized by our system.

Table 2: Scope and limitations in the epoxidation of olefins with oxygen.[a]



Entry	Substrate	Conv. [%][b]	Yield [%][b]	Sel. [%][c]
1		91	81	89
2		28	27[d]	97
3		73	50	69
4		48	35	72
5		78	63	81
6		89	69	78
7		93	82	88
8		89	(81)	91
9		99	96 (84)	97
10		57	30	52
11		32	24	75
12		40	37[d]	94
13		66	44	66

[a] Reaction conditions: In a 15 mL reaction tube, $FeCl_3 \cdot 6H_2O$ (0.025 mmol), imidazole **2** (0.25 mmol), CH_3CN (10 mL), substrate (0.5 mmol) and biphenyl (GC internal standard, ca. 20 mg) were added in sequence at room temperature in air. The reaction mixture was stirred for 20 h and the reaction was initiated by addition of the sacrificial reductant **1** (1 mmol) by syringe. [b] Conversion and yield were determined by GC analysis; yields of isolated products are given in brackets. [c] Selectivity refers to the ratio of yield to conversion in percentage; [d] The corresponding *cis*-stilbene and *cis*-methyl styrene oxide could not be observed; instead *trans*-stilbene oxide and *trans*-methyl oxide were detected.

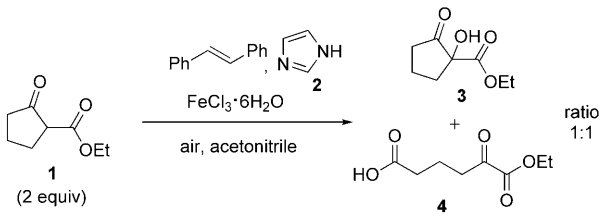
Interestingly, the catalyst system is not deactivated after the reaction. Indeed, after a reaction time of 20 hours, complete reactivation of the iron catalyst was observed upon addition of another charge of *trans*-stilbene (0.5 mmol) and 2 equiv of keto ester **1**. Noteworthy, the excellent chemoselectivity remained.

To obtain more insight into the molecular nature of the catalyst, mass spectroscopic measurements were carried out. The ESI mass spectrum of a freshly prepared reaction mixture (5 mol% $FeCl_3 \cdot 6H_2O$/2 equiv **1**/0.5 equiv imidazol/1 equiv

trans-stilbene) under an air atmosphere in acetonitrile showed in positive-ion mode a series of cluster ions at *m*/*z* 366.0760, 434.1137, and 522.1554, which are assigned to $[Fe^{III}(\mathbf{1}-H)_2]^+$, $[Fe^{III}(\mathbf{1}-H)_2(\mathbf{2})]^+$ and $[Fe^{III}(\mathbf{1}-H)_3]+H^+$, respectively. In addition, when the experiment is performed in negative-ion mode, a cluster ion assigned to $[FeCl_4]^-$ is also observed at *m*/*z* 197.8. $[FeCl_4]^-$ has been reported as a kind of inactive iron-sink complex for Michael additions.[8b,23] Along this line, addition of 5 mol% HCl, NaCl, or Bu_4NCl to our reaction system led to a distinct decrease of activity and product yield (Table S4 in the Supporting Information). Therefore, we conclude that inactive $[FeCl_4]^-$ complexes reduce the iron pool for the formation of active species in our reaction.

Next, the catalytic activity of well-defined isolated complexes was investigated. When *trans*-$[FeCl_2(\mathbf{2})_4]Cl$[16a] was applied under reaction conditions, only poor reactivity was observed (<5% conversion), demonstrating that this complex is not an active precatalyst. Unfortunately, all efforts to prepare $[Fe(\mathbf{1})_3]$ failed. Nevertheless, a related catalytically active complex [Fe(2-acetylcyclopentanone)$_3$] could be prepared and structurally characterized by X-ray diffraction (Figure S1). In accordance with the required balance of imidazole and keto ester **1** (1:3 to 1:4, see Table 1), the latter complex was studied in the presence of additional 2-acetylcyclopentanone (Table S5), but only poor activity was observed. Based on these results, and the ESI-MS analysis, we propose that the active species corresponds to $[Fe^{III}(\mathbf{1}-H)_2]^+$, and $[Fe^{III}(\mathbf{1}-H)_2(\mathbf{2})]^+$, and the latter appears as the most likely catalyst candidate because of the requirement of imidazole ligands under the catalytic conditions.

To shed more light on the reaction mechanism, we studied the products that arose from the conversion of the sacrificial reductant **1** during the epoxidation reaction. Interestingly, both the hydroxylated keto ester **3** and the ring-opened product **4** are formed (Scheme 1). Alcohol **3** is formed by two-electron oxidation of the keto ester.[17] In contrast, the

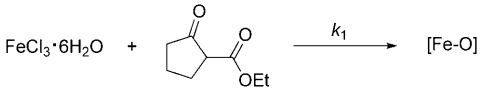


Scheme 1. Main products resulting from the oxidation of keto ester **1**.

formation of the carboxylic acid **4** formally corresponds to a dioxygenase type of reaction, where two oxygen atoms are inserted into the β-keto ester, in a formal four-electron oxidation. Indeed, the latter reaction bears strong resemblance to that mediated by acetylacetone dioxygenase (Dke1), an iron-dependent enzyme that cleaves various diketones and β-keto esters.[25]

Next, time-dependent oxidations of *trans*-stilbene, styrene, and 1-octene were studied. The consumption of **1** in the absence of substrate was also analyzed. No induction periods were observed in any of the reactions studied, and the conversion of **1** after 24 h was independent of the nature of the substrate (within experimental error). For the initial stages of the reaction (conversion of **1** <50%), **1** was consumed at similar reaction rates for all three substrates (Table 3, Figure S2). This strongly suggests that a common reaction intermediate is formed regardless of the substrate. Furthermore, the formation of *trans*-stilbene epoxide occurred at the same rate as the consumption of **1** (Figure 1).

Table 3: Rate constants for the pseudo-first-order oxidation reaction of **1** as a function of the olefinic substrate.



Substrate	k_1 [10^{-5} s^{-1}]	R^2
trans-stilbene	2.88 ± 0.13	0.986
styrene	3.27 ± 0.13	0.989
1-octene	2.75 ± 0.11	0.990
–	1.83 ± 0.09	0.983

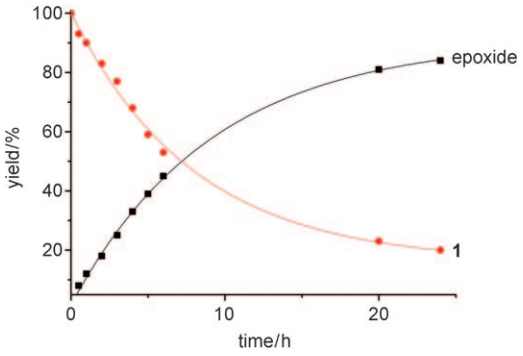


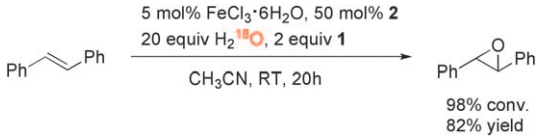
Figure 1. Consumption of **1** compared to the yield of *trans*-stilbene oxide with a single-exponential fit $y=a-bc^{k_1}$.

A more detailed analysis showed that the ratio of **3** to *trans*-stilbene epoxide is constant over the course of the reaction (Figure S3). Additional NMR experiments after filtration of the crude mixture showed a ratio of about 1:1 for the formed epoxide and **3**. In addition, a 50–60% yield of **4** was recorded (with respect to stilbene). This proves the role of **1** as a sacrificial reductant and shows that the conversion of **1** is closely connected with the selective formation of *trans*-stilbene epoxide (Figure 1).

Similar results are observed for styrene as substrate. *trans*-Stilbene and styrene react at comparable rates, but in the latter case the reaction proceeded with lower chemoselectivity towards the epoxide. Investigations in the ratio of products **3** and **4**, which arise from two- and four-electron oxidations of the co-substrate, respectively, could be used to estimate the relative rates of these two reactions. GC analysis showed that the ratio **4**/**3** is substrate independent and decreased during the reaction time. Apparently, the different oxidations of **1** are parallel pathways.

The origin of the oxygen in the products was studied by means of isotopic-labeling experiments under an inert

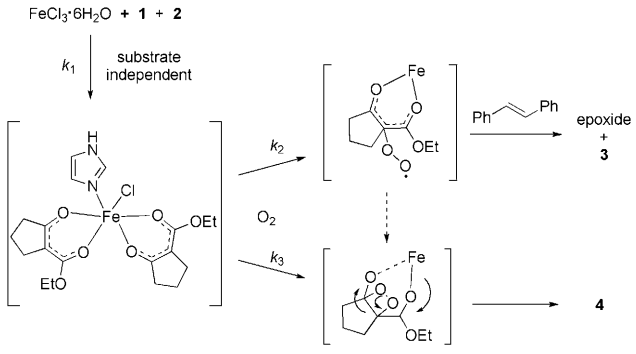
atmosphere of argon with *trans*-stilbene. As expected, no reaction is observed under these conditions. Afterwards labeling experiments were carried out in the presence of oxygen and $H_2{}^{18}O$. When 20 equiv $H_2{}^{18}O$ (with respect to *trans*-stilbene) was added, labeled oxygen was not incorporated into the product and there was insignificant influence on the yield and conversion (Scheme 2).



Scheme 2. Labeling studies with $H_2{}^{18}O$.

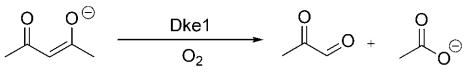
On the other hand, while *trans*-stilbene oxide did not show any incorporation of labeled oxygen, small amounts of benzaldehyde (< 5%), which is formed as cleavage product, displayed incorporation of the labeled oxygen (roughly 5–10%). ^{18}O incorporation (approximately 30%) from water was also observed in the carboxylic acid **4** but not in the hydroxylated product **3**. Since oxygen exchange between water and α-keto acids is known,[24] we added labeled water after the reaction was complete (20 h) and then stirred the reaction mixture for an additional 16 h. Indeed incorporation of comparable amounts of ^{18}O-labeled oxygen into benzaldehyde and **4** was observed together with traces of ^{18}O-labeled **3** (< 5%). Therefore, we conclude that the incorporation of ^{18}O atoms in benzaldehyde and carboxylic acid **4** occurred after the oxidation event. Clearly, the oxygen atoms incorporated into the epoxide and **3** or in **4** are derived from O_2.

Based on all these investigations our proposed mechanism is shown in Scheme 3. Despite the inherent difficulty of analyzing complex reaction mixtures, the results of the ESI-MS experiments in combination with catalytic experiments suggest an active $[Fe^{III}(\mathbf{1}\text{-}H)_2(\mathbf{2})]^+$ catalyst species. The hydroxylation of **1** and the epoxidation reaction are closely connected, and the rate of conversion of **1** is independent of the nature of the olefinic substrate. These observations provide convincing evidence that **1** acts as a co-substrate, strictly required for selective O_2 activation, generating the active species that epoxidize the olefin.



Scheme 3. Proposed mechanistic pathways during the reaction.

Notably, related Fe complexes play an important role in the O_2 activation of acetylacetone dioxygenase (Dke1), an iron-dependent enzyme that cleaves various diketones and β-keto esters (Scheme 4).[25] For this enzyme it is known that 2,4-pentadione participates in the O_2 activation by forming an organic peroxide species; however, there is an ongoing debate on whether the formation of this intermediate takes place through a concerted step[26] or via an iron(III) superoxido complex.[27]



Scheme 4. Cleavage of 2,4-pentadione into methylglyoxal and acetate by the enzyme Dke1.

Based on these precedents, we envision an iron superoxide as the active species in our system. Subsequent radical-type addition to the olefin leads to an intermediate susceptible to epimerization. Finally, the second C–O bond forms and the O–O bond is cleaved to form the corresponding epoxide and **3**. Alternatively, along a parallel reaction path, an oxetane species is formed that gives **4** as the main product. Stilbenes are unique substrates because there is an excellent correlation between two-electron oxidation of the co-substrate and formation of the epoxide. This epoxidation constitutes a unique example of co-substrate-assisted activation of O_2 in a monooxygenase type of reaction.

In conclusion, we have developed a novel and practical synthetic method for the epoxidation of olefins with air as the oxidant and with fair to excellent chemoselectivities under very mild conditions. Notably, the catalyst can be easily reactivated. Mechanistic investigations point out substantial differences to known radical-based autoxidation paths. The oxygenase-like co-substrate-assisted activation of O_2 generates the active iron species responsible for the epoxidation. The present methodology exploits a highly challenging four-electron reduction of the O_2 molecule, and by doing so it differs from the most commonly used peroxides ($2e^-$ reduced versions of O_2). Thus, it constitutes a unique biomimetic catalyst system and opens up attractive alternatives for bio-inspired catalysis.

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Keywords: β-keto esters · epoxidation · imidazole · iron · oxygen

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