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Novel biomimetic iron-catalysts for environmentally benign epoxidations of olefins

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Abstract—A new selective and easily manageable epoxidation method is presented using an inexpensive and efficient $FeCl_3 \cdot 6H_2O$ and imidazole derivatives as catalysts. Aqueous hydrogen peroxide as an environmentally benign oxidant is utilized. This novel Fe/imidazole system gives moderate to excellent yields toward aromatic mono-, di-, and tri-substituted olefins.

Epoxides play an important role in industry as intermediates for the production of fine chemicals as well as pharmaceuticals. With respect to environmental and economical considerations, the applied oxidant determines to a significant extent the value of the system.[1] Thus, the combination of hydrogen peroxide with a non-toxic and inexpensive metal source constitutes an ideal system for epoxidation reactions, especially in liquid phase processes in industry.[2,3] Among the various metals iron is the most abundant metal in nature and is indispensable in nearly all organisms.[4] Many biological systems such as hemoglobin, myoglobin, cytochrome oxygenases, and non-heme oxygenases are iron containing enzymes or co-enzymes.[5,6]

Due to its low cost and biological relevance there is an increasing interest to use iron complexes as catalysts for a wide range of reactions.[7] In this respect, recently we developed iron catalysts for C–C-coupling reactions,[8] transfer hydrogenations[9] as well as epoxidations.[10,11] Based on the latter work, we report here a novel biomimetic $FeCl_3$/imidazole-system for epoxidations of olefins using aqueous hydrogen peroxide as the oxidant.[12]

Imidazole derivates play a fundamental role as ligands or base in enzymes.[13] For instance, the imidazole part of histidine often acts as a ligand in metalloenzymes, for example, hemoglobin.[14] With regard to epoxidations it is noteworthy that 1-sulfonylated imidazoles and hydrogen peroxide are known as powerful oxidant in stoichiometric amount for the reactions.[15] Besides, imidazoles and pyrazoles are widely employed as additives in epoxidation systems, such as iron[16] and manganese[17] porphyrins, manganese salen complexes,[18] methyltrioxorhenium,[19] and manganese schiff bases.[20]

Recently, we demonstrated that a combination of $FeCl_3 \cdot 6H_2O$, pyridine-2,6-dicarboxylic acid (H_2pydic) and an organic base like pyrrolidine catalyzes the epoxidation of *trans*-stilbene with 30% H_2O_2 to *trans*-stilbene oxide in high yield within 1 h.[11] Key to the success of this reaction is the use of pyridine-2,6-dicarboxylic acid as ligand. By studying the effect of the organic base in more detail, we found that a combination of $FeCl_3 \cdot 6H_2O$ with simple imidazole *without any* pyridine-2,6-dicarboxylic acid gave also *trans*-stilbene oxide in 38% yield with 90% selectivity (Table 1, entry 1).[21] Further investigations showed that the activity and selectivity of the catalytic system can be improved by varying the imidazole ligands (Table 1).

The influence of the substitution pattern of the imidazole ligands reveals some interesting aspects. Substitution

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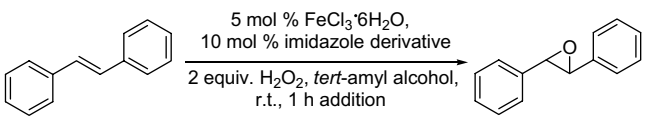
Table 1. Reactivity of different imidazole derivatives



Entry	Imidazole derivative	Conv.[a,b] (%)	Yield[b] (%)	Selectivity[c] (%)
1		43	38	90
2		47	39	83
3		**83**	**80**	**97**
4		69	69	100
5		40	39	99
6		5	4	90
7		39	36	93
8		5	5	87

[a] Reaction conditions: in a 25 mL Schlenk tube, $FeCl_3{\cdot}6H_2O$ (0.025 mmol), imidazole derivative (0.05 mmol), *tert*-amyl alcohol (9 mL), *trans*-stilbene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added in sequence at rt in air. To this mixture, a solution of 30% H_2O_2 (115 μL, 1.0 mmol) in *tert*-amyl alcohol (885 μL) was added over a period of 1 h at rt by a syringe pump.
[b] Conversion and yield were determined by GC analysis.
[c] Selectivity refers to the ratio of yield to conversion in percentage.

at the 2-position of the imidazole gave inferior results (Table 1, entries 1, 2, 6, and 8). Furthermore, N-substitution of the 5-bromoimidazole led to a higher yield and conversion (Table 1, entries 4 and 7). In addition, 5-halo-*N*-methylimidazoles enhanced the yield significantly. In fact 5-chloro-1-methylimidazole (Table 1, entry 3) gave the best result (80% yield; 97% selectivity). It is noteworthy that 5-chloro-1-methylimidazole (5-Cl-1-MeIm) is a near-optimal imidazole activity enhancing additive with balanced steric and electronic factors in an iron–porphyrin system.[16]

Next, we tried to find out more about the mechanism of this novel epoxidation catalyst. One of the possibilities for the effectiveness of these imidazole ligands might be the participation of a carbene type ligand in the reaction system due to their outstanding σ-donor strength.[22]

However, replacement of the imidazole derivative with 1,3-dimesityl-2,3-dihydro-1*H*-imidazol-2-ide gave no conversion at all. Besides, in the presence of the radical trap TEMPO (2,2,6,6-tetramethyl-piperidine-1-oxyl; 1.5 equiv), the reaction showed insignificant conversion and yield. This suggests the participation of a radical in the catalytic cycle in this epoxidation system. Control experiments indicated that all the components are essential for the activity and selectivity. Indeed, in the presence of 10 mol % of 5-Cl-1-MeIm without $FeCl_3{\cdot}6H_2O$ no product formation is observed. On the other hand 5 mol % of $FeCl_3{\cdot}6H_2O$ without 5-Cl-1-MeIm gave only 5% yield. These results exclude the possibility of organocatalysis.

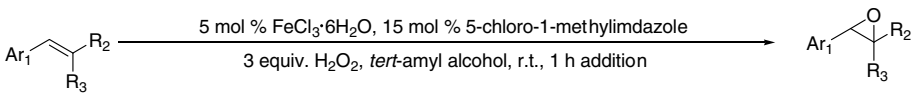
Further optimization showed that a higher yield (84% yield and 99% selectivity) can be reached when 3 equiv of 30% hydrogen peroxide is used.[23] The yield was maintained with a slight drop of selectivity when 4 equiv of hydrogen peroxide was added. Applying a higher amount of the ligand 5-Cl-1-MeIm gave slightly better results. Hence, with 15 mol % of 5-Cl-1-MeIm and 5 mol % $FeCl_3{\cdot}6H_2O$, the product yield reached 86% with 97% selectivity. No further significant improvement is observed with higher ligand loading.

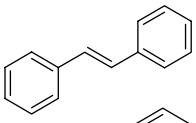
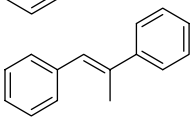
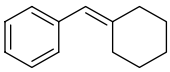
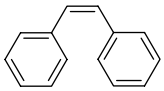
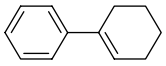
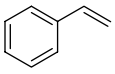
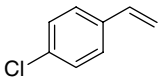
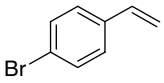
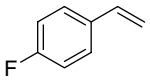
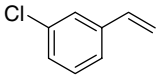
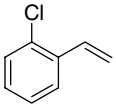
Next, various olefins were applied to the reaction under the optimized reaction conditions (3 equiv H_2O_2, 5 mol % $FeCl_3{\cdot}6H_2O$, and 15 mol % 5-Cl-1-MeIm) (Table 2).

In the presence of Fe/imidazole catalyst mono-, di-, and tri-substituted olefins can be epoxidized in moderate to excellent yield with high selectivity (Table 2). Compared with our previously reported first generation iron catalyst, this reaction system improved both the yield and selectivity especially for trisubstituted olefins.[11] For example, epoxidation of (cyclohexylidenemethyl)-benzene gave 25% yield with 64% selectivity in the new protocol (Table 2, entry 3) while the old system gave only 11% yield with 39% selectivity. Furthermore, all halogen-substituted styrenes gave improved selectivity compared to the first generation catalysts (up to 91%).

In conclusion, we have developed a novel, biomimetic and easily manageable epoxidation reaction. For the first time it is possible to perform epoxidations with hydrogen peroxide in the presence of simple Fe/imidazole catalysts. Compared to our previous catalyst system the newly developed iron catalyst does not need any pyridine-2,6-dicarboxylic acid and gave improved yield and selectivity for more difficult tri-substituted olefins and styrenes.[24] Efforts to examine the reaction mechanism and to realize an asymmetric version of this reaction are going on in our group.

Table 2. Scope and limitations of the reaction[25]



Entry	Substrates	Conv.[a,b] (%)	Yield[b] (%)	Selectivity[c] (%)
1		92	87	94
2		46	41	88
3		39	25	64
4		34	24[d]	71
5		52	36	68
6		74	70	95
7		90	79	88
8		91	82	90
9		73	62	86
10		74	67	91
11		55	46	84

[a] Reaction conditions: in a 25 mL Schlenk tube, $FeCl_3·6H_2O$ (0.025 mmol), 5-chloro-1-methylimidazole (0.075 mmol), *tert*-amyl alcohol (9 mL), *trans*-stilbene (0.5 mmol) and dodecane (GC internal standard, 100 μL) were added in sequence at rt in air. To this mixture, a solution of 30% H_2O_2 (170 μL, 1.5 mmol) in *tert*-amyl alcohol (830 μL) was added over a period of 1 h at rt by a syringe pump.

[b] Conversion and yield were determined by GC analysis.

[c] Selectivity refers to the ratio of yield to conversion in percentage.

[d] Additionally 3% *trans*-stilbene oxid and *trans*-stilbene were observed.

Acknowledgments

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Mr. I. Zenz, Dr. Feng Shi and Dr. B. Spilker (LIKAT) are acknowledged for their valuable support in the laboratory.

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23. Aqueous H_2O_2 (30%) from Merck was used as received. The peroxide content varied from 33% to 40% as determined by titration.
24. Side-products are rearrangement products of the corresponding epoxide.
25. Most of the substrates and epoxides for GC–FID calibration are commercially available. The others were synthesized according to literature methods and determined by NMR and GC–MS. In addition, authentic samples of the commercial products were analyzed by GC–MS and GC–FID.