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An Efficient Epoxidation with Molecular Oxygen Catalyzed by Iron Complex of Multidentate *N*-Heterocyclic Podand Ligand. Additive Effect of 4-Ethoxycarbonyl-3-methyl-2-cyclohexen-1-one

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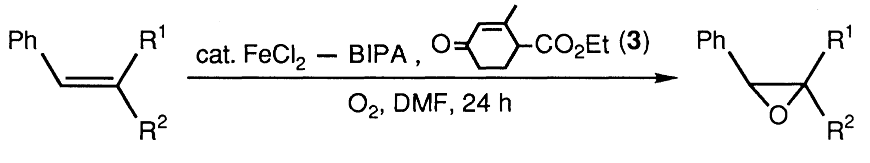
Coexistence of 4-ethoxycarbonyl-3-methyl-2-cyclohexen-1-one facilitated the epoxidation reaction of styrenes with molecular oxygen catalyzed by $FeCl_2$ and the multidentate *N*-heterocyclic podand ligand, *N*,*N*'-bis{2-(4-imidazolyl)ethyl}-2,6-pyridinedicarboxamide.

A variety of oxygenation systems including cytochrome P-450 models have been investigated to achieve an efficient oxygen activation and transfer.1) Imidazoles are proven to serve as an axial *N*-ligand to increase the activity of porphyrin complex catalysts.2) Effect of various additives has been intensely studied to attain the more efficient oxygenation. The rate acceleration is observed in the presence of lipophilic carboxylic acids and lipophilic heterocyclic bases,3) or aldehyde.4) We have also demonstrated that *o*-quinones mediate the Mn(III)TPPCl-catalyzed epoxidation reaction with hydrogen peroxide.5)

Many efforts have been made to address an efficient oxygenation system with molecular oxygen.6) From synthetic viewpoints, such an epoxidation reaction has quite recently been reported to be promoted by addition of excess amounts of cyclic ketones7) or methyl-2-oxocyclopentane carboxylate.8)

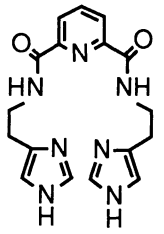
Ligand coordination is envisaged to greatly contribute to smooth electron transfer based on effective interaction with metal center. In a previous paper,9) the complexation of $FeCl_2$ with the flexible multidentate podand ligand, *N*,*N*'-bis{2-(4-imidazolyl)ethyl}-2,6-pyridinedicarboxamide (BIPA), has been revealed to permit the epoxidation reaction with molecular oxygen even in the absence of a co-reductant. An intramolecular coordination interaction of the axial *N*-ligand is considered to participate in forming an efficient catalytic system. These findings prompted us to develop an oxygenation method under milder conditions. This communication describes an additive effect of 4-ethoxycarbonyl-3-methyl-2-cyclohexen-1-one (**3**) in the catalytic epoxidation reaction with molecular oxygen (eq. 1).



(1)

1a : R^1=H, R^2=Ph
b : R^1=H, R^2=Me
c : R^1=Ph, R^2=H

2a : R^1=H, R^2=Ph
b : R^1=H, R^2=Me



BIPA

The presence of **3** in the reaction of *trans*-stilbene (**1a**) with molecular oxygen catalyzed by $FeCl_2$ and BIPA in DMF led to the facile oxidation to *trans*-stilbene oxide (**2a**) under mild conditions.[10] The reaction proceeded even at room temperature under molecular oxygen (1.0×10^3 kPa). Furthermore, **2a** was obtained under an atmospheric pressure of molecular oxygen when the reaction temperature was raised to 50 °C. The results are listed in Table 1. The involvement of BIPA is essential for the efficient epoxidation as reported.[9] The similar effect of **3** was observed in the case of *trans*-β-methylstyrene (**1b**). *cis*-Stilbene (**1c**) showed the lower susceptibility to oxidation under the conditions employed here than **1a** to give only the *trans*-isomer **2a** in a lower yield. This finding suggests that a simple radical mechanism is not operating.

Table 1. Effect of **3** on the epoxidation[a]

1	Ligand	Temp / °C	O_2 / 10^2 kPa	**3**	**2**
R^1 R^2				Molar equiv.[b]	Yield / %[b,c]
H Ph (**1a**)	BIPA	rt	10	10	**2a** 860 (1400)
	—	rt	10	10	0 (0)
	BIPA	rt	10	20	1230 (1470)
	BIPA	rt	10	100	1100 (1740)
	BIPA	50	1	10	990 (270)
	—	50	1	10	trace (0)
	BIPA	50	1	20	2190 (530)
	BIPA	50	1	50	3010 (660)
	BIPA[d]	50	1	50	1140 (300)
	BIPA	50	1	100	1020 (380)
H Me (**1b**)	BIPA	50	1	20	**2b** 1020 (1020)
	—	50	1	20	120 (580)
Ph H (**1c**)	BIPA	rt	10	10	**2a** 420 (420)[e]

a) $FeCl_2$, 0.01 mmol; BIPA, 0.01 mmol; **1**, 1.0 mmol. b) Based on a catalyst. c) Only the *trans*-epoxide was obtained. The number in parenthesis is turnover for the formation of benzaldehyde. d) $FeCl_3$ was used instead of $FeCl_2$. e) The *cis*-epoxide **2c** and the isomerized olefin **1a** were not detected by ^{1}H-NMR.

The formation of **2a** is dependent on the amount of **3** as shown in Figure 1. When the reaction was carried out under an atmospheric pressure of molecular oxygen, the epoxidation yield was raised by the increase of **3**, but lowered by addition of more than 70 molar equiv. of **3**.

It remains obscure why **3** facilitates the epoxidation reaction, but there must exist an electrical interaction between the iron species and **3**. The peak at 530 nm in the UV-VIS spectra attributable to the iron complex with BIPA in DMF disappeared on the addition of **3** (5 molar equiv.) as shown Figure 2. Such an interaction is assumed to enhance one of the catalytic cycle steps. On the contrary, the epoxidation reaction was disturbed by excess amounts of **3** to prevent **1** from coordination. Use of dimethyl maleate or 2-cyclohexen-1-one instead of

3 resulted in no epoxidation, indicating that the role of **3** is not simply based on the characteristic of an electron-deficient olefin.

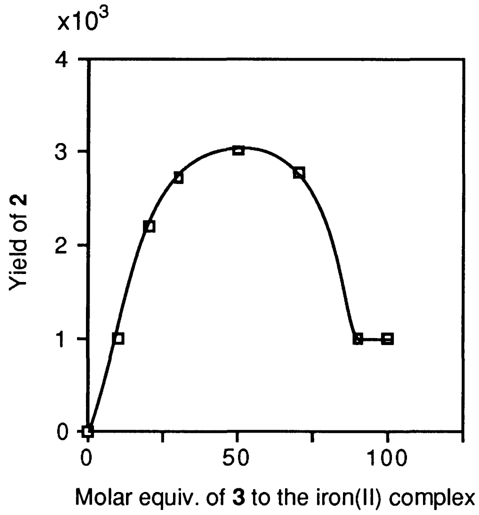


Fig. 1. Effect of **3** on the epoxidation at 50 °C under an atmospheric pressure of molecular oxygen.

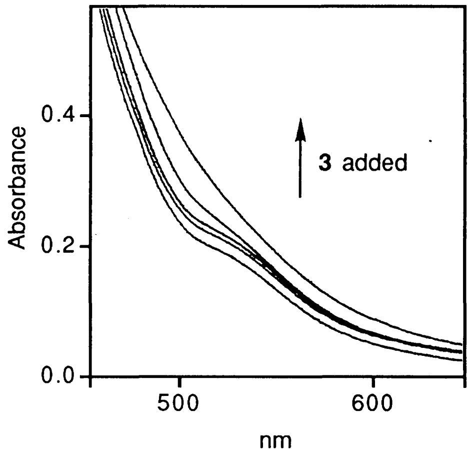


Fig. 2. UV - VIS spectra of $FeCl_2$ – BIPA with **3**. [$FeCl_2$ – BIPA] = 1.0x10^{-3} M; [**3**] = 0, 1.0, 2.0, 3.0, 5.0x10^{-3} M; solv. DMF; under nitrogen.

Another possibility to be checked is that **3** serves as an electron donor. If so, $FeCl_3$ could be used as a catalyst with equal ease. The serious decrease in the yield of **2a** was, however, observed with $FeCl_3$-BIPA. The dehydrogenation product, 4-ethoxycarbonyl-3-methylphenol, was not detected in the reaction mixture, suggesting that the contribution of **3** only as an electron donor is not always reasonable. 2-Cyclohexen-1-one was not oxidized to phenol under the similar conditions without formation of **2** (*vide supra*). Since **3** is found to be oxidized to 4-ethoxycarbonyl-4-hydroxy-3-methyl-2-cyclohexen-1-one with molecular oxygen,[11)] molecular oxygen is assumed to be activated in the presence of **3** to afford a peroxide at the α-position of the ethoxycarbonyl group. Although almost half amounts of **3** or 2-cyclohexen-1-one (50 molar equiv. were used in each case) were only recovered, a small amount of the oxygenated alcohol was observed as a sole detectable product by GLC and ^{1}H-NMR.

These findings imply that only one of the interaction and paths mentioned above is not necessarily the case operating here. It is not deniable that these roles are considered to cooperate each other to construct a real catalytic oxygenation system.

Although the mechanism on the additive effect of **3** has to wait for further studies, the iron(II) complex with the multidentate *N*-heterocyclic podand ligand forms an efficient catalyst for epoxidation in cooperation with the cyclohexenone **3**. Further investigation is now in progress.

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10) A typical experimental procedure is as follows. To a mixture of *trans*-stilbene (**1a,** 1.0 mmol) and BIPA (0.01 mmol) was added $FeCl_2$ (0.01 mmol) in DMF (0.8 mL), and then the resulting mixture was stirred under nitrogen at room temperature for 24 h. After the reaction vessel was substituted with molecular oxygen, the mixture was stirred under an atmospheric pressure of molecular oxygen at 50 °C for 24 h. The mixture was diluted with ether (30 mL), washed with 1.5 M HCl solution and brine, dried over $MgSO_4$, and concentrated. The formation of *trans*-stilbene oxide (**2a**) was detected by ^{1}H-NMR.

11) T. Hirao and I. Ikeda, unpublished result. Treatment of 4-ethoxycarbonyl-3-methyl-2-cyclohexen-1-one with a catalytic amount of polyaniline as a synthetic metal catalyst12) under an atmospheric pressure of molecular oxygen resulted in hydroxylation to 4-ethoxycarbonyl-4-hydroxy-3-methyl-2-cyclohexen-1-one.

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