Remarkable Effects of Metal, Solvent, and Oxidant on Metalloporphyrin-Catalyzed Enantioselective Epoxidation of Olefins

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Three metal complexes of one particular homochiral porphyrin were investigated as catalysts for enantioselective epoxidation of unfunctionalized olefins under various reaction conditions. Much better results were obtained with the iron and ruthenium complexes than with the manganese derivative. The absence of any effect of amines on the iron porphyrin-catalyzed reaction in benzene, as well as the superior results in aromatic as opposed to both more and less polar nonaromatic solvents, suggest that specific association of aromatic molecules to the metalloporphyrin affects its solution structure. Strong evidence for the involvement of active oxidants that are more selective than *trans*-dioxoruthenium(VI) porphyrin is provided by the significant effect of primary oxidants on the ruthenium porphyrin-catalyzed reactions. Preliminary results with the iron complex of an only slightly modified porphyrin under the optimized reaction conditions found in this study resulted in epoxidation of styrene and 4-chlorostyrene to their epoxides with enantiomeric excesses identical to the best ever reported. These results were obtained with an unprecedented large number of catalytic turnovers, requiring only 0.01 mol % of catalyst.

Introduction

Enantioselective epoxidation of olefins by homochiral metal complexes is an important subfield of catalytic asymmetric synthesis, with relevance to organic chemistry, medicine, and industry.[1] Useful levels of asymmetric induction of allylic alcohols—production of the corresponding epoxy alcohols with enantiomeric excesses (ee's) greater than 90%—were first achieved in 1980 by Katsuki and Sharpless,[2] with significant improvements and enlargement of the scope of the reaction over the years.[3] An intrinsic limitation of this system is the essential presence of the hydroxyl group in the organic substrate, required for coordination to the metal center of the catalyst. The ultimate challenge in this field remains enantioselective epoxidation of unfunctionalized olefins, in which chiral recognition is based solely on nonbonding interactions between the prochiral substrate and the homochiral catalyst. The most important early contribution in this respect was provided by Groves and Meyers in 1983,[4] who extended the principles of cytochrome P-450 mimicking synthetic metalloporphyrin catalysts to chiral derivatives. Thus, enantiomerically enriched epoxides were formed in the reaction of simple olefins with mild oxidants in the presence of catalytic amounts of a homochiral iron(III) porphyrin. Major improvements were provided in 1990 by Jacobsen and co-workers,[5] who discovered that replacing the metalloporphyrins by homochiral manganese(III) salen complexes resulted in much higher enantioselectivities. Additional advantages were that cheaper and more available oxidants such as commercial bleach could be used as oxidants, as well as the relatively low price of the catalyst.[6] The easy preparation of a large variety of chiral salen complexes allowed systematic variation of the steric and electronic environment.[7] The major limitation of these catalysts is their quite modest catalytic activity, usually in the range of 80−120 turnovers. Metalloporphyrin catalysts are more promising in this aspect, as extremely large turnover numbers (10^5−10^6) have been achieved with achiral derivatives.[8]

The quite extensive research of metalloporphyrin-catalyzed enantioselective epoxidation of olefins has been concentrated on the superstructures of the iron(III) and manganese(III) catalysts and the role of added pyridine or imidazole ligands.[9] Despite considerable efforts, high ee's—89% and 96% for 2-nitrostyrene and 3,5-dinitrostyrene, respectively, with Naruta's catalyst[10] and 88% for 1,2-dihydronaphthalene with Collman's catalyst (Scheme 1)[11] —are the exception rather than the rule. We have recently prepared a new homochiral porphyrin **1**−H_2 (Scheme 2),[12] whose structural features are based on the catalysts of Naruta and Collman. It contains threitol chiral units as in Collman's porphyrin, which, however, cover both faces of the porphyrin plane as in Naruta's and other catalysts. Utilization of the ruthenium complex of that porphyrin as a catalyst for the epoxidation of styrene—the first example of epoxidation catalysis by any chiral ruthenium porphyrin—revealed promising results.[13] We now report our results for the chloroiron(III), chloromanganese(III), and *trans*-dioxoruthenium(VI) complexes of porphyrin **1**−H_2: **1**−Fe(Cl), **1**−Mn(Cl),

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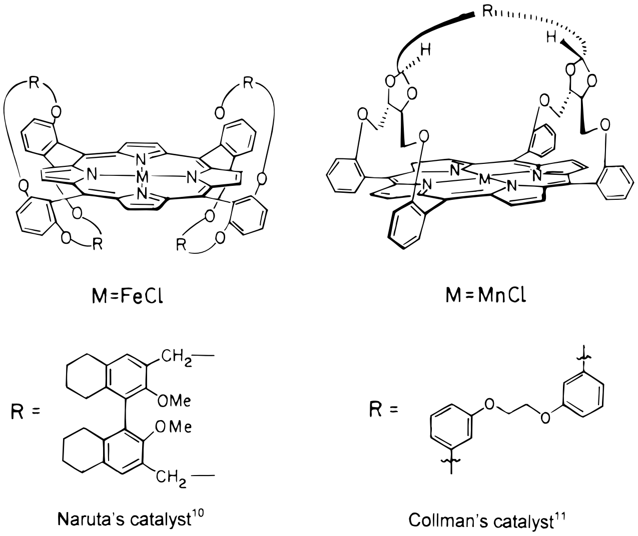
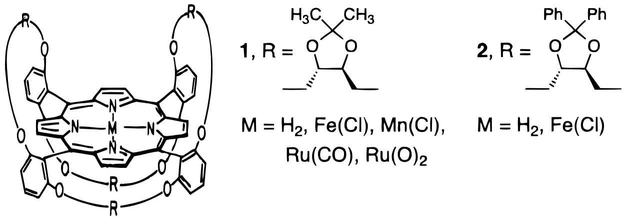
Scheme 1. Structures of the Most Enantioselective Catalysts Utilized by the Groups of Naruta and Collman



Scheme 2. Structures of the Two Homochiral Metalloporphyrins and Their Metal Complexes Utilized in the Current Studies



and **1**−Ru(O)$_2$, respectively (Scheme 2). This paper is dedicated to the elucidation of the effect of metals, primary oxidants, and solvents on the enantioselectivity of epoxidation. The examinations were devoted mostly to styrene, whose enantioselective epoxidation still remains a significant challenge: the highest reported ee of styrene oxide by any metalloporphyrin-based system is 69%; with chiral salen complexes usually only up to 57% ee are obtained.[7] The present results reveal that enantioselectivity is sensitive to the identity of the metal (Ru ≥ Fe ≫ Mn), the solvent (aromatic > chlorinated), and for the ruthenium complex also to the primary oxidant (*N*-oxides > iodosylarenes). Up to 6000 catalytic turnovers were achieved for epoxidation of olefins with the iron complex in aromatic solvents, without a decrease in enantioselectivity. We trust that these and other observations of the current studies will have a significant impact on the enantioselective epoxidation of olefins by metal complexes of other homochiral porphyrins as well. This is demonstrated by preliminary results for a slightly modified iron(III) porphyrin, **2**−Fe(Cl), which catalyzes the epoxidation of styrene to its oxide with 68% ee.

Results

Preparation of the Catalysts. The active oxidants in metalloporphyrin-catalyzed epoxidations are high-valent oxometal species,[14] in which the oxygen atom that is transferred to the substrate is located above one of the porphyrin's faces. Enantioselective recognition is based on nonbonding interactions of the substrate with the chiral moieties during its approach to the oxometal bond. Thus, it is necessary to assure that the oxometal bond is formed inside the cavity created by the chiral units. This prerequisite was achieved in monofaced iron and manganese porphyrins such as Collman's porphyrin by applying bulky amines or phenoxides that coordinate to the metal at the opposite and less sterically hindered face. But since for ruthenium porphyrins the active form of the catalyst has a *trans*-dioxoruthenium(VI) structure,[15] both faces of the porphyrin plane must be identical. For that purpose, we have prepared the new homochiral porphyrin **1**−H_2, in which both faces are the same. As discussed in our earlier paper,[12] the etherfication of 5,10,15,20-tetrakis(2,6-dihydroxyphenyl)porphyrin with the commercially available (*S*,*S*)-(−)-1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol proceeded in high yields. Purification was also very easy since only one of the two possible isomers was formed. The three required metal complexes—**1**−Fe(Cl), **1**−Mn(Cl), and **1**−Ru(O)$_2$ in Scheme 2—were prepared by reaction of **1**−H_2 with $FeCl_2$, $MnCl_2$, and $Ru_3(CO)_{12}$, respectively, by standard methods[16] with surprising ease and high yields, probably because of the very large deviation from planarity of the free base.[12] In addition, the acquired X-ray crystal structures of both **1**−H_2 and its ruthenium(II) carbonyl complex **1**−Ru(CO) reveal the chiral cavities around the center of the porphyrin.[12,13] Although variations of the porphyrin's superstructure were not part of the main research program, we have prepared one additional porphyrin and its iron(III) complex **2**−Fe(Cl) by similar synthetic routes. In these derivatives, the 1,3-dioxolane rings carry 2,2-diphenyl substituents instead of the 2,2-dimethyl groups in **1**−H_2 (Scheme 2).

Table 1. Enantiomeric Excesses (ee) and Chemical Yields in Epoxidation of Styrene by Iodosylbenzene in the Indicated Solvents, Catalyzed by 1−Fe(Cl), 1−Mn(Cl), and 1−Ru(CO)[a]

	solvent	
catalyst	CH_2Cl_2 % ee (% yield)	benzene % ee (% yield)
1−Mn(Cl)	6 (38)	10 (77)
1−Fe(Cl)	13 (46)	44 (65)
1−Ru(CO)	5 (12)	42 (47)

[a] 25 °C, 0.5 M styrene, styrene:iodosylbenzene:catalyst = 1000:100:1, chemical yields relative to iodobenzene.

Epoxidations: Metal and Solvent Effects. The enantioselective epoxidation of styrene by iodosylbenzene in the presence of catalytic amounts of the three metal complexes **1**−Fe(Cl), **1**−Mn(Cl), and **1**−Ru(CO) were first compared in the most commonly used solvent, CH_2Cl_2 (Scheme 3). The results, which are summarized in Table 1, show that in CH_2Cl_2 the enantiomeric excesses (ee's) of styrene oxide were very low for all complexes and that both the chemical yields and the ee's decreased in the order of Fe > Mn > Ru. Higher chemical yields were obtained in benzene for all three complexes, accompanied by significantly larger ee's for the **1**−Fe(Cl)- and **1**−Ru(CO)-catalyzed reactions, but not for that of **1**−Mn(Cl): the solvent change from CH_2Cl_2 to benzene induced changes in the ee's from 13% to 44% for **1**−Fe(Cl) and from 5% to 42% for **1**−Ru(CO). The **1**−Fe(Cl)-catalyzed

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Scheme 3. Catalytic Enantioselective Epoxidation of Styrene Derivatives

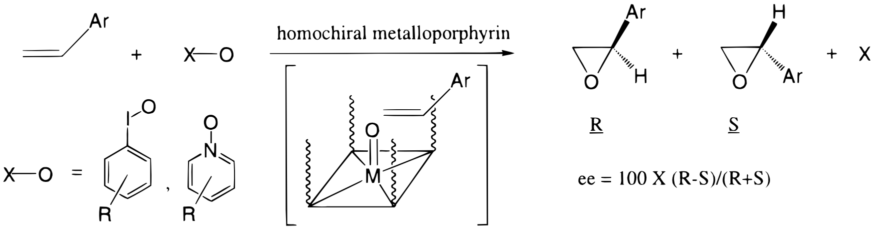


Table 2. Enantiomeric Excesses (ee) and Chemical Yields in 1−Fe(Cl)-Catalyzed Epoxidation of Styrene by Iodosylbenzene in Various Solvents[a]

	solvent				
	CH_3CN	CH_2Cl_2	benzene	toluene	CCl_4
E_T[b]	46.0	41.1	34.5	33.9	32.5
% ee	10	13	44	44	36
% yield	46	46	65	54	78

[a] Same reaction conditions as in Table 1. [b] Solvent polarizability parameter.[26]

reaction was further examined in a variety of solvents (Table 2). It is clear that in the aromatic solvents benzene and toluene the ee's (44% ee) are higher than in both the more polar acetonitrile (10% ee) and CH_2Cl_2 (13% ee) and the less polar CCl_4 (36% ee). Similarly, for the **2**−Fe(Cl)-catalyzed epoxidation of styrene, while the ee was 59% in benzene, only 31% and 38% ee were obtained in CH_2Cl_2 and heptane, respectively.

Effect of Amines. In many cases, inclusion of amine ligands in the reaction mixtures was found to have a large positive effect on both the chemical yields and the enantioselectivities.[9] For the present cases, no enhanced enantioselectivity was found for the **1**−Mn(Cl)-catalyzed reactions in both CH_2Cl_2 and benzene solutions or for the **1**−Fe(Cl)-catalyzed reactions in benzene (Table 3). The very low yields in the presence of unsubstituted imidazole are reasonably accounted for by bis-coordination to the metal. For the **1**−Fe(Cl)-catalyzed reactions in CH_2Cl_2 (Table 3), almost all pyridine ligands had a positive effect on the enantioselectivity, most pronounced for pyridine, 2,4-dimethylpyridine, and quinoline. Still, the 36% ee for **1**−Fe(Cl) in the presence of 2,4-dimethylpyridine in CH_2Cl_2 is lower than the 44% ee for the same catalyst in benzene without added amine. Finally, no enhanced enantioselectivities were found in CH_2Cl_2 with the imidazole ligands, and the chemical yields were much lower than without ligand.

Temperature Effect. The effect of temperature on the chemical yields and the enantioselectivity of the epoxidation of styrene was examined for the reactions catalyzed by both **1**−Fe(Cl) and **2**−Fe(Cl) in toluene. The results presented in Figure 1 show that in both cases the highest ee's—57 and 68%, respectively—were obtained at −20 °C. Fortunately, at this temperature the chemical yields were still quite reasonable, 47% and 59%, respectively. The same temperature effect—increased enantioselectivity with only slightly lower chemical yields—was also displayed by other olefins, as shown in Table 5 for **2**−Fe(Cl) catalysis at 23 °C and −20 °C. It must be emphasized that ee's of 68% and 70% for epoxidation of styrene and 4-chlorostyrene, respectively, are practically identical to the best ever reported results (69% and 70% ee, respectively) by metalloporphyrin catalysis.[11] In addition, these results were obtained with an extremely low concentration of catalyst, 0.01 mol % .

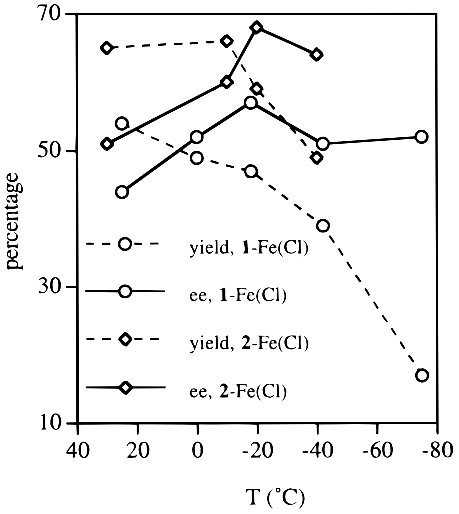


Figure 1. Effect of temperature on the chemical yields and enantiomeric excesses (ee) in **1**−Fe(Cl)- and **2**−Fe(Cl)-catalyzed epoxidation of styrene by iodosylbenzene.

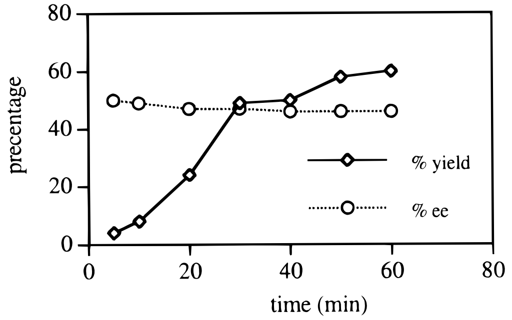
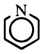
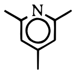
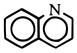
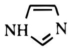
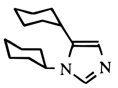
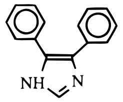


Figure 2. Time-dependent changes in chemical yields and enantiomeric excesses (ee) in **1**−Fe(Cl)-catalyzed epoxidation of styrene by iodosylbenzene at 20 °C.

Catalytic Turnovers. As already mentioned in the introduction, the main advantage of metalloporphyrin-based systems relative to salen complexes is the much higher turnover numbers obtainable with the former catalysts. In many cases, however, the enantioselectivity decreases with time due to chemical modification of the catalyst. This aspect was studied with catalyst **1**−Fe(Cl). Results are shown in Figure 2 for the reaction of styrene with iodosylbenzene in benzene at 23 °C in the presence of 0.01 mol % of **1**−Fe(Cl). While the chemical yield increased with time, the ee remained constant at 48 ± 2%. Furthermore, the final yield of 60% corresponds to 6000 turnovers, which to our knowledge is the highest ever reported number for enantioselective epoxidation of olefins. In addition, the 50% yield after 30 min corresponds to 167 turnovers/min. Thus, reduction of the catalyst's concentration from 1.0 to 0.1 and even 0.01 mol % had practically no effect on either the chemical yields (64, 67, and 60%, respectively) or the ee's (44, 42, and 46%, respectively).

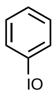
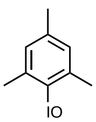
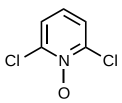
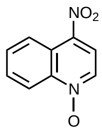
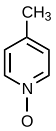
Effect of Oxidant. Similar ee's were obtained for epoxidation of styrene under **1**−Fe(Cl) catalysis with two

Table 3. Effect of Amine Ligands on the Enantiomeric Excesses (ee) and Chemical Yields in Epoxidation of Styrene by Iodosylbenzene, Catalyzed by 1−Fe(Cl) and 1−Mn(Cl) in CH_2Cl_2 and Benzene[a]

Catalyst/Solvent	1-Fe(Cl)/CH_2Cl_2	1-Fe(Cl)/benzene	1-Mn(Cl)/CH_2Cl_2	1-Mn(Cl)/benzene
Ligand	% ee (% yield)	% ee (% yield)	% ee (% yield)	% ee (% yield)
none	13 (46)	44 (65)	6 (38)	10 (77)
	35 (41)	44 (52)	--	--
	23 (46)^b	44 (62)	--	11 (73)
	34 (28)^c	44 (54)	7 (40)	--
	11 (5)	0 (5)	8 (17)^d	14 (3)
	16 (20)	49 (53)	2 (51)	15 (47)
	13 (1)	46 (6)	5 (17)	11 (22)

[a] 0.5 M styrene, styrene:iodosylbenzene:amine:catalyst = 1000:100:250:1, chemical yields relative to iodobenzene. [b] The ee's with 2-methyl-, 2,3-dimethyl-, 2,4-dimethyl-, and 2,6-dimethylpyridine were 20, 18, 36, and 25% ee, respectively. [c] The ee's with 6-, 7-, and 8-methylquinoline were 18, 14, and 12%, respectively. [d] 6% ee and 20% chemical yield with 1-methylimidazole.

Table 4. Enantiomeric Excesses (ee) and Chemical Yields in 1−$Ru(O)_2$-Catalyzed Epoxidation of Styrene by Various Oxidants in Benzene[a]

oxidant	none					
% ee	35^b	42	29	50^c	49	54
% yield	21	47^d	6	20	3^e	0.4^f

[a] 25 °C, 2 h, 0.165 M styrene, styrene:oxidant:catalyst = 330:330:1. Yields determined by GC integration against external standard, unless otherwise noted. [b] Stoichiometric epoxidation, 1.45 μmol of 1−$Ru(O)_2$ and 9 μmol of styrene-d_8 in 1 mL of benzene-d_6. [c] 57% ee and 15% chemical yield at 15 °C. [d] Determined by GC integration against iodobenzene. [e] The low yields are probably due to the insolubility of this oxide. [f] The low yields are due to inhibition by the produced amine.[34]

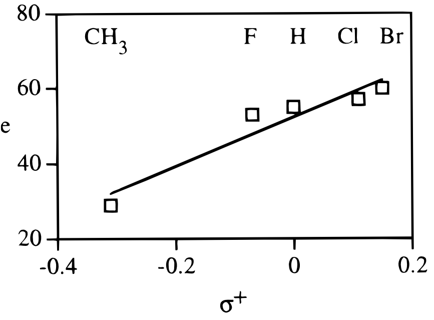
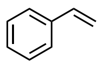
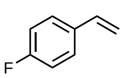
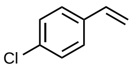
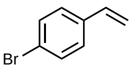
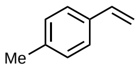
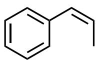
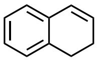


Figure 3. Hammett plot of the enantiomeric excesses (ee) in 1−$Ru(O)_2$-catalyzed epoxidation of *para*-substituted styrenes (substituents are indicated) by 2,6-dichloropyridine *N*-oxide.

oxidants, iodosylbenzene and iodosylmesitylene. This is in contrast with the results for epoxidation of styrene by iodosylbenzene, iodosylmesitylene, and three different aromatic *N*-oxides in the presence of catalytic amounts of **1**−$Ru(O)_2$ in benzene, which are presented in Table 4. The large difference between iodosylbenzene and iodosylmesitylene, the significantly higher ee's obtained with all *N*-oxides, and the small differences between them clearly indicate that **1**−$Ru(O)_2$ is not the sole reactive intermediate in these systems. This is also emphasized by the stoichiometric epoxidation of styrene by **1**−$Ru(O)_2$, which produced styrene oxide with only 35% ee.

Effect of Substrates and LFER Relationships. Although the emphasis of the present studies was placed on styrene, several substituted derivatives were also investigated. The results for catalysis by **1**−Fe(Cl) and **2**−Fe(Cl), which are summarized in Table 5, clearly show that larger enantioselectivities are obtained for the less reactive, electron-poor olefins, in accord with studies of other research groups.[9−11] The low enantioselectivities obtained for the more reactive *cis*-β-methylstyrene and 1,2-dihydronaphthalene probably also fall into this category. The enantioselectivities of epoxidation of the ring-substituted styrenes was also examined for the **1**−$Ru(O)_2$-catalyzed reaction with 2,6-dichloropyridine *N*-oxide and iodosylbenzene. These very different results are shown as Hammett plots in Figures 3 and 4, respectively. While in the reactions with 2,6-dichloropyridine *N*-oxide a linear plot was obtained, the Hammett plot describing the reactions with iodosylbenzene is clearly curved.

Table 5. Enantiomeric Excesses (ee) and Chemical Yields in Epoxidation of Aromatic Olefins, Catalyzed by 1−Fe(Cl), 2−Fe(Cl), and 1−Ru(O)$_2$

catalyst	**1**−Fe(Cl)	**2**−Fe(Cl)	**2**−Fe(Cl)	**1**−Ru(CO)	**1**−Ru(O)$_2$
T	25 °C	23 °C	−20 °C	25 °C	25 °C
substrate	ee (yield)[a]	ee (yield)[a]	ee (yield)[b]	ee (yield)[c]	ee (yield)[d]
	44 (76)	59 (75)	**68** (59)	48 (39)	54 (29)
	56 (68)	65 (70)	**73** (64)	51 (39)	53 (9)
	53 (55)	63 (56)	**70** (26)	45 (15)	57 (2)
	51 (79)	55 (10)	33 (24)	41 (22)	60 (2)
	31 (73)	37 (56)	53 (43)	20 (41)	29 (9)
	32 (99)[e]	45 (99)[e]	60 (55)[e]		36 (12)
	3 (60)	11 (16)	30 (39)		23 (6)

[a] Reaction conditions: 0.5 M styrene/benzene, styrene:iodosylbenzene:catalyst = 100 000:10 000:1 for 3 h. Chemical yields are reported relative to consumption of iodosylbenzene. [b] In toluene, under otherwise identical reaction conditions. [c] Styrene:iodosylbenzene:catalyst = 1000:100:1, under otherwise identical reaction conditions. [d] Reaction conditions: 330 μmol of styrene, 330 μmol of 2,6-dichloropyridine *N*-oxide, and 1 μmol of catalyst in 2 mL of *m*-xylene for 5 h. Chemical yields are reported relative to an external standard. [e] The ee and yields refers to the *cis*-epoxide (the enantiomers of the *trans*-epoxide could not be separated). The ratio of *cis*-epoxide/(*trans*-epoxide + benzyl methyl ketone) were 99, 1.3, and 0.3 at 25, −20, and −40 °C, respectively.

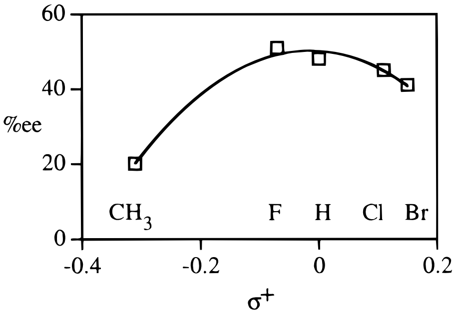


Figure 4. Hammett plot of the enantiomeric excesses (ee) in **1**−Ru(O)$_2$-catalyzed epoxidation of *para*-substituted styrenes (substituents are indicated) by iodosylbenzene.

Discussion

In principle, three variables are of primary importance in enantioselective epoxidation of unfunctionalized olefins by homochiral metal complexes: the chiral environment created by the superstructure of the catalyst, the steric and/or electronic effect of the olefin, and the identity of the metal. Traditionally, the research in this field has focused on the first two factors,[7,9] while much less is known about the effect of the metal. To our knowledge, in no previous case was the same porphyrin studied with more than two different metals,[17,18] and homochiral ruthenium porphyrins were not reported as epoxidation catalysts prior to our recent contribution.[13] Since it is well known that for metalloporphyrin catalysts the reactivity is Mn > Fe >> Ru,[19] it may be anticipated that enantioselectivity will increase in the opposite order. Indeed, for Groves and Viski's porphyrin,[18] the iron(III) complex was more enantioselective than the manganese(III) derivative. Also, in series of nonporphyrinic metal complexes, better results were obtained with ruthenium than with manganese derivatives.[20] Accordingly, the main initiative of the present studies was to compare the enantioselectivity of epoxidation catalysis by the three most important metal complexes—iron, manganese, and ruthenium—of one particular porphyrin, **1**−H$_2$.

The results for the **1**−Fe(Cl)- and **1**−Mn(Cl)-catalyzed epoxidation of styrene were significantly different: higher ee's were obtained for **1**−Fe(Cl) under all reaction conditions, the solvent effect (benzene vs CH$_2$Cl$_2$, Table 1) was much larger for **1**−Fe(Cl), and the effect of amines on the enantioselectivity was different for the two catalysts (Table 3). All these results are readily understandable, considering known phenomena in iron(III) and manganese(III) porphyrin chemistry:[14,19,21] (a) Formation of the most reactive intermediate in iron(III) porphyrin-catalyzed reactions does not rely on amine coordination,[22] but oxomanganese(V) porphyrins are the main active oxidant only in the presence of *trans*-coordinated amines, while in their absence oxomanganese(IV) porphyrin intermediates are dominant.[23] (b) The equilibrium constants for coordination of amines to iron(III) porphyrins are much larger than for manganese(III) porphyrins.[24] (c) Imidazole binds to iron(III) porphyrins more strongly than pyridine by 3 orders of magnitude.[25] (d) The equilibrium constants for coordination of imidazoles and pyridines to iron(III) porphyrins are smaller in benzene than in CH$_2$Cl$_2$ by about 3 orders of magnitude.[25] Thus, the reduced

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(17) Maillard, P.; Guerquin-Kern, J. L.; Momenteau, M. *Tetrahedron Lett.* **1991**, *32*, 4901.

(18) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628.

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(22) Gross, Z.; Nimri, S. *Inorg. Chem.* **1994**, *33*, 1731. Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1986**, *108*, 507.

(23) Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1988**, *110*, 8628.

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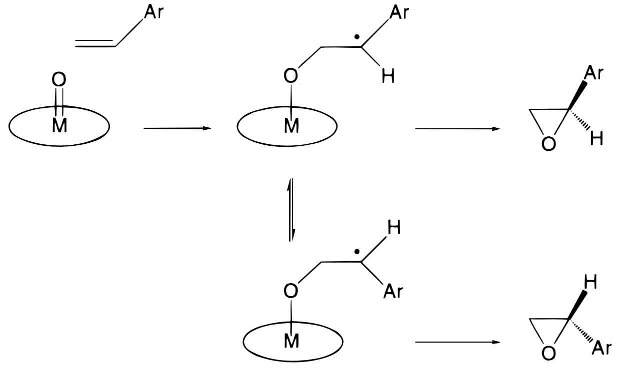
Scheme 4. Plausible Mechanism for Racemization through a Long-Lived Radical Intermediate in Epoxidation Catalysis by Homochiral Metalloporphyrins



chemical yields for the **1**–Fe(Cl)-catalyzed reactions with all imidazole ligands in CH_2Cl_2 and with unsubstituted imidazole in benzene are probably due to formation of bis-ligated iron(III). The enhancement of the ee's by most pyridine ligands suggests catalysis by amine-coordinated oxoiron(IV) porphyrin cation radical in CH_2Cl_2. On the other hand, the absence of a real effect of amine ligands on the **1**–Mn(Cl)-catalyzed reactions is consistent with the small "aminophilicity" of manganese porphyrins. Furthermore, it also suggests that oxygen atom transfer from oxidized catalyst to substrate occurs via an oxomanganese(IV) porphyrin intermediate.[23] As 2 equiv of Mn(IV) is required for oxidation of styrene to its oxide, the reaction must proceed stepwise, most probably with a relatively long-lived benzylic radical intermediate (Scheme 4).[26] Since for terminal olefins rotation around the C–phenyl bond necessarily leads to racemization, the low ee's (2–15%) for epoxidation of styrene under **1**–Mn(Cl) catalysis are reasonable. Interestingly, for a monofaced version of the same catalyst,[11] which due to its available coordination site can form a *trans*-amine–oxomanganese(V) porphyrin intermediate, the enantioselectivity is significantly larger. Finally, a similar explanation is proposed for the optimum enantioselectivity observed at −20 °C in the reactions catalyzed by **1**–Fe(Cl) and **2**–Fe(Cl) (Figure 1). The anticipated increased differentiation between the *re* and *si* approaches of styrene to the oxometal center at lower temperatures—enhancing the enantioselectivity—is probably compensated for by an increased lifetime of the racemization-causing radical intermediate. Support for this proposal is provided by the epoxidation results of *cis*-β-methylstyrene, in which the identity of the major product changes from the *cis*-epoxide at high temperature to the *trans*-epoxide at temperatures lower than −20 °C.

The presence and absence of a pyridine–ligand effect on the enantioselectivity of the **1**–Fe(Cl)-catalyzed epoxidation reactions in CH_2Cl_2 and benzene, respectively, suggest that these amines do not coordinate to the catalyst in benzene. This was confirmed by adding the same concentration of pyridine to CH_2Cl_2 and benzene solutions of **1**–Fe(Cl). Indeed, the UV–vis spectrum of the CH_2Cl_2 solution changed upon addition of pyridine, while the benzene solution was unaffected. Still, the 44% ee in benzene without addition of amines relative to the best result in CH_2Cl_2—36% ee in the presence of 2,4-lutidine—was surprising. This pronounced solvent effect, which was also apparent in the **1**–Ru(O)$_2$-catalyzed epoxidation of styrene (5% ee in CH_2Cl_2 vs 42% in benzene, Table 1), called for special attention.

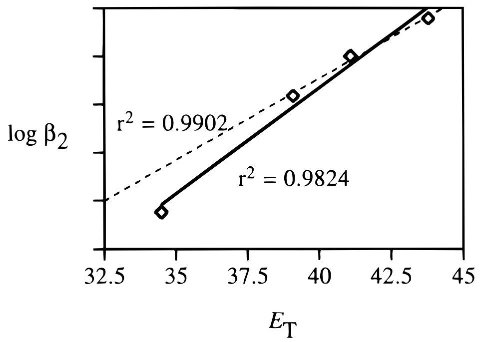


Figure 5. Plot of log β_2, the equilibrium constant for bis-coordination of *N*-methylimidazole to (tpp)Fe(Cl) in DMF, CH_2Cl_2, $CHCl_3$, and benzene vs the polarizability parameter E_T of the solvents. The solid line describes the best linear fit through all points, while the broken line is generated by ignoring the data point for benzene. The data are taken from Walker *et al.*[25]

First, we have reexamined the correlation found by Walker *et al.*[25] between a polarizability parameter of the solvents (E_T)[27] and the equilibrium constant for coordination of *N*-methylimidazole to (tpp)Fe(Cl).[28] The results of their study with DMF, $CHCl_3$, CH_2Cl_2, and benzene are shown in Figure 5 with two linear fit lines, the full line taking into account all four solvents and the broken line only three points, ignoring the result for benzene. The negative deviation of the point for benzene from the broken line might suggest that the low equilibrium constant in benzene is due not only to its low polarity. This proposal was checked by comparing the coordination of *N*-methylimidazole (CH_3-imid) to (tmp)Fe(Cl) in CCl_4 and benzene solutions. Considering the lower E_T value of CCl_4 (32.5) relative to that of benzene (34.5), a lower equilibrium constant would be expected in the former solvent if only solvent polarizability is important. But, as shown in Figure 6, coordination is much stronger in CCl_4. Thus, the bis-imidazole complex $[(tmp)Fe(CH_3\text{-imid})_2]^+$ is fully formed at 0.6 M *N*-methylimidazole in CCl_4, but not in benzene (2.5 M is required).[29] These data clearly indicate specific interactions of benzene with the iron(III) porphyrin. Further evidence comes from the crystal structures of aromatic solvates of iron and manganese porphyrins, as well as from solution characteristics of a ruthenium porphyrin. Thus, a comparison of the X-ray structures of the isoelectronic (tpp)Mn·(toluene)$_2$ and $[(tpp)Fe\cdot(p\text{-xylene})_2]^+$ complexes clearly shows that in the iron complex the aromatic molecules have a much stronger and more specific association (with both the porphyrin π-system and the metal d orbitals).[30,31] The interaction of benzene with ruthenium porphyrins

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[26] For evidence for the proposed radical intermediate in catalysis by achiral metalloporphyrins, see: (a) Groves, J. T.; Gross, Z.; Stern, M. *Inorg. Chem.* **1994**, *33*, 5065. (b) Gross, Z.; Nimri, S. *J. Am. Chem. Soc.* **1995**, *117*, 8021. (c) Gross, Z. *J. Biol. Inorg. Chem.* **1996**, *1*, 368.

[27] Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 29.

[28] (a) It was recently shown (Nesset, M. J. M.; Shokhirev, N. V.; Enemark, P. D.; Jacobson, S. E.; Walker, F. A. *Inorg. Chem.* **1996**, *35*, 5188) that, in contrast to common belief, the equilibrium constants for binding of substituted pyridines and imidazoles (including 2-methylimidazole) to sterically hindered iron(III) porphyrins such as (tmp)-Fe(ClO_4) is actually very large. This justifies the utilization of the sterically hindered amines included in this study. (b) Abbreviations: tpp, 5,10,15,20-tetraphenylporphyrin dianion; tmp, 5,10,15,20-tetramesitylporphyrin dianion.

[29] The equilibrium constant for bis-coordination (β_2) of *N*-methylimidazole to (tmp)Fe(Cl) in CCl_4 was determined as 17.4 M^{-1}, but no reliable equilibrium constant could be measured in benzene because of the very large amount of *N*-methylimidazole (2.5 M) required for full formation of the bis-adduct.

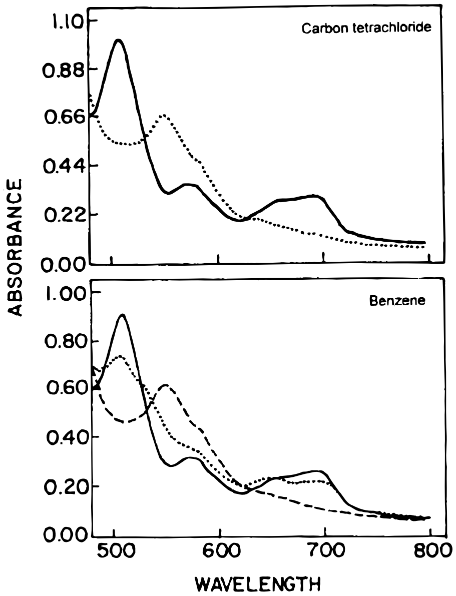

Figure 6. UV−vis spectra of identical concentrations of (tmp)-Fe(Cl) in CCl_4 and benzene solutions: without base (—), with 0.6 M CH_3-imid (• • •), and with 2.5 M CH_3-imid (- - -).

is so strong that it persists even in solution, as was disclosed from the ^{1}H NMR spectrum of (tmp)Ru^{II} in benzene-d_6.[32] Most important, the relative strength of interaction of aromatic molecules with the metalloporphyrins in the order of Ru > Fe > Mn parallels the effect of increased enantioselectivity in changing the solvent from CH_2Cl_2 to benzene (Table 1). Accordingly, we propose that the strong association of benzene and the other aromatic solvents with the **1**−Fe(Cl) and **1**−Ru(O)$_2$ catalysts affects the solution structure of the chiral cavity. This can explain the 44% ee in benzene relative to 36% ee in CCl_4 for **1**−Fe(Cl) and the 59% vs 38% ee for **2**−Fe(Cl)-catalyzed epoxidation of styrene in benzene and heptane, respectively.

In the present studies, the effects of different oxidants were checked for the **1**−Fe(Cl)- and **1**−Ru(O)$_2$-catalyzed epoxidations for the following reason. The concept of oxometal porphyrins as the oxygen-atom-transfer intermediates implies that the identity of the primary oxidant must have no effect on the chemical yields, shape, or enantioselectivity. This is especially true for iron porphyrins, for which the oxoiron(IV) porphyrin radical intermediate is known to be a much more potent oxidant than all other high valent complexes.[33] As mentioned earlier, the situation is more complex for catalysis by manganese(III) porphyrins because of the potential involvement of both oxomanganese(V) and oxomanganese(IV) intermediates.[22] Finally, *trans*-dioxoruthenium(VI) derivatives are the best characterized epoxidizing intermediates in the catalytic cycle of ruthenium porphyrins.[15] But, Hirobe *et al.* have recently demonstrated that more reactive intermediates must be formed in the combination of either (carbonyl)ruthenium(II) or dioxoruthenium(VI) porphyrins with aromatic *N*-oxides.[34] In an even more recent investigation of that system, Groves *et al.* have provided evidence for involvement of oxoruthenium(V) under these conditions.[35]

The almost identical results obtained for **1**−Fe(Cl)-catalyzed epoxidation of styrene with either iodosylbenzene or iodosylmesitylene indicate that the reaction proceeds through only one common intermediate. On the contrary, the different ee's obtained in the reactions of styrene with different oxidants in the presence of catalytic amounts of **1**−Ru(O)$_2$ (Table 4) clearly demonstrate that the *trans*-dioxoruthenium(VI) porphyrin is not the only oxygen-atom-transfer intermediate. Actually, the stoichiometric oxidation of styrene by **1**−Ru(O)$_2$ with only 35% ee reveals that epoxidation by the other not yet characterized intermediates is more enantioselective (49−57% ee for reactions with the pyridine *N*-oxides). Another demonstration of the differences in the reactions with iodosylbenzene and *N*-oxides is shown in Figures 3 and 4. While construction of a Hammett plot for the ee's in **1**−Ru(O)$_2$-catalyzed epoxidation of ring-substituted styrenes by 2,6-dichloropyridine *N*-oxide vs the σ^+ values[36] of the substituents yields a reasonable straight line; for the corresponding reactions with iodosylbenzene a curved line is obtained. These data indicate that the reaction mechanisms of these two reactions are significantly different, due to the involvement of different oxygen-atom-transfer intermediates.

The last point of interest is the catalytic activity of the homochiral iron porphyrin complexes. Most asymmetric epoxidations of styrene and similar substrates deal with less than 100 catalytic turnovers (we are aware of only three exceptions, with 2800 (20% ee),[37] 1800 (52% ee),[38] and 485 (58% ee)[10] turnovers).[7] Moreover, in many cases, the enantioselectivity changes during the process. For example, while 78% ee are obtained in Collman's manganese porphyrin-catalyzed epoxidation of *cis*-β-methylstyrene after 89 turnovers, as the process continues the ee gradually decreases down to 57% ee after 1000 turnovers.[11] Such phenomena are usually ascribed to irreversible chemical modification of the catalyst's superstructure.[9] In the present case, the ee remained practically constant even at a large turnover number, with both the **1**−Fe(Cl) and **2**−Fe(Cl) catalysts. For **2**-Fe(Cl) catalyzed epoxidation of styrene by iodosylbenzene, 68% ee were obtained after 800 turnovers at −20 °C and 59% ee after 6000 turnovers at room temperature. To our knowledge, this is the largest ever reported turnover number for enantioselective epoxidation of unfunctionalized olefins. In addition, the 68% ee for epoxidation of styrene and 70% ee for 4-chlorostyrene are practically identical to the highest ever reported values for these olefins—69% and 70% ee with 86 and and 83 turnovers, respectively, by the most advanced Collman's porphyrin.[11] Finally, the enantioselectivity is also significantly higher than that obtained with homochiral salen catalysts,[7] with the exception of 86% ee for epoxidation of styrene by a combination of *m*-CPBA and *N*-methylmorpholine *N*-oxide at −78 °C with 22 turnovers.[39]

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Summary and Conclusions

Several variables that affect the enantioselective epoxidation of unfunctionalized olefins by metalloporphyrin catalysis were investigated in the present studies. Of the three metal complexes of one particular porphyrin, much better results were obtained with iron and ruthenium than with manganese. The poor ee's obtained with the manganese catalyst, even in the presence of amines, suggest oxomanganese(IV) rather than oxomanganese(V) as the oxygen-transfer intermediate. For the ruthenium and iron catalysts, the superior enantioselectivity in aromatic compared to both more and less polar nonaromatic solvents suggest that specific association of aromatic molecules to the metalloporphyrin affects its solution structure. Strong evidence for the involvement of active oxidants that are more selective than *trans*-dioxoruthenium(VI) porphyrin is provided by the significant effect of primary oxidants on the ruthenium porphyrin-catalyzed reactions. Although variations of the porphyrin's superstructure were not the major research goal of the present studies, seemingly remote structural changes had major effects. Preliminary results with the iron complex of the modified porphyrin under the optimized reaction conditions found in this study resulted in epoxidation of styrene derivatives to their epoxides with enantiomeric excesses identical to the best ever reported, together with an unprecedented large catalytic turnover number. The high yield condensation of the porphyrin precursor with the chiral moieties, which are readily available by simple modification of tartaric acid, together with the selective formation of only one isomer, ensures that a large number of similar complexes can be prepared. Optimization of the catalytic process, which already has the advantage of mild and simple working conditions and high catalytic efficiency, with a large number of similar porphyrin complexes is currently under investigation.

Experimental Section

Physical Methods. The ^{1}H NMR spectra were recorded on a Brucker AM 200, operating at 200 MHz. Chemical shifts are reported in ppm relative to residual hydrogens in the deuterated solvents: 7.20, 7.24, and 5.32 ppm for benzene, chloroform, and dichloromethane, respectively. An HP 8452A diode array spectrophotometer was used to record the electronic spectra. Gas chromatographic analysis was performed on a HP-5890 GC with a J&W chiral cyclodex-B capillary column and FID detector, linked to the HP Chem-Station (HP-3365). The ee's were reproducible within ±2% for multiple experiments.

Materials. Dichloromethane (Lab-Scan, HPLC grade) was dried by distillation over CaH_2. Benzene (RDH, thiophene free) was further purified by repeated washing with concentrated H_2SO_4 until the aqueous layer was colorless, followed by washing with water and aqueous NaOH. The benzene was dried by $CaCl_2$ and distilled over CaH_2. DMF (Merck, GC grade) was dried by distillation over CaH_2 at reduced pressure. The deuterated solvents C_6D_6, $CDCl_3$, and CD_2Cl_2 (Aldrich products) were used as received. The olefins were purchased from Aldrich (*cis*-β-methylstyrene from K&K, ICN Biomedicals) and filtered through a plug of basic alumina prior to their use to remove stabilizers. (*R*)-(+)-styrene oxide, which was purchased from Aldrich, was utilized for determination of (*R*)-(+)-styrene oxide as the major enantiomer in all reactions. The other epoxides were obtained from the corresponding olefins by standard *m*-CPBA oxidations. All epoxides, except *trans*-β-methylstyrene oxide, were resolved on the J&W chiral cyclodex-B capillary column, but the absolute configuration of the major enantiomer in the reactions of the substituted styrenes (Table 5) was not determined.

Preparation of Catalysts. The preparation of porphyrin **1**−H$_2$, its ruthenium complexes **1**−Ru(CO) and **1**−Ru(O)$_2$, and the X-ray crystal structures of the first two derivatives were described previously.[12,13] The porphyrin **2**−H$_2$ and its iron complex **2**−Fe(Cl) were obtained by procedures similar to that of porphyrin **1**−H$_2$ and its iron complex. The exact procedures will be published separately in a forthcoming publication. Preparation of the iron(III) and manganese(III) porphyrins from **1**−H$_2$ was achieved by the following procedures.

Homochiral Chloroiron(III) Porphyrin 1−Fe(Cl). Porphyrin **1**−H$_2$ (30 mg, 24 μmol) was dissolved in DMF (4 mL) containing 2,6-lutidine (24 μL) and heated to reflux under Ar. A solution of anhydrous $FeCl_2$ (13 mg, 0.1 mmol) in DMF (4 mL) was added in one portion, and heating was continued for 2 h. The cooled reaction mixture was diluted with CH_2Cl_2, washed with 5% HCl (twice) and water, and dried by solid NaCl. After evaporation of the solvent, one fast-moving fraction was obtained by column chromatography on basic alumina (EtOAc/CH_2Cl_2, 3:2). Final purification by recrystallization from $CHCl_3$/heptane resulted in the dark pink solid product (20 mg, 62%): FAB MS *m/z*: 1300.5 ([M − H]$^+$, 100); $R_f = 0.32$ (alumina, CH_2Cl_2/EtOAc 2:3); UV−vis (CH_2Cl_2, λ_{max}, nm) 444 (Soret), 368; ^{1}H NMR ($CDCl_3$) δ 76.4 (s, *pyrrole*-H).

Homochiral Chloromanganese(III) Porphyrin 1−Mn(Cl). Porphyrin **1**−H$_2$ (15 mg, 12 μmol) was dissolved in DMF (15 mL) containing three drops of 2,6-lutidine, and $MnBr_2$ (52 mg, 0.24 mmol) was added in one portion. The reaction mixture was heated overnight at 100 °C, during which time the changes in the UV−vis spectrum from $\lambda_{max} = 440$ to $\lambda_{max} = 486$ nm were complete. The cold reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with brine (2 × 30 mL), and dried with solid NaCl. After evaporation of the solvent, column chromatography on basic alumina was used to separate traces of free base (CH_2Cl_2/EtOAc/Et_3N 50:49:1) from the manganese porphyrin (MeOH/EtOAc 1:1). Final purification by recrystallization from $CHCl_3$/heptane resulted in the green solid product (14.6 mg, 90%): FAB MS *m/z* 1299.7 ([M − H]$^+$, 100); $R_f = 0.42$ (alumina, MeOH/EtOAc 1:1); UV−vis (benzene, λ_{max}, nm) 384, 412, 494 (Soret), 606, 648.

Catalytic Oxidation Procedures. a. With Iodosylbenzene. The reactions were performed at 25 °C by adding 100 μmol of iodosylbenzene in one portion to well-stirred 1 mL solutions of 1 mmol of olefin and 1 μmol of catalyst. Reactions were stopped after 1 h by freezing the reaction mixture using liquid N_2. The reaction products were separated from the catalyst and any unreacted iodosylbenzene by bulb-to-bulb vacuum distillation prior to gas chromatographic analysis. Both the chemical yields—reported relative to the reduced oxidant, iodobenzene—and the ee's were determined by GC, using a Cyclodex-B capillary column. For determination of the effect of catalyst concentration (1.0, 0.1, and 0.01 mol %) on the process, stock solutions of **1**−Fe(Cl) were utilized under otherwise identical reaction conditions. The reaction with 0.01 mol % catalyst was also examined in two additional ways. The results in Figure 2 were obtained by removing aliquots from the reaction mixture at different time intervals, followed by freezing, bulb-to-bulb vacuum distillation, and gas chromatographic analysis. The yields in these reactions are reported relative to nitrobenzene, present as internal standard in the reaction mixtures. For even more reliable turnover numbers, the epoxidation reactions of styrene by iodosylbenzene in the presence of 0.01 mol % **1**−Fe(Cl) and **2**−Fe(Cl) were performed in toluene-d_8 with nitrobenzene (50 μmol, 5.15 μL) as internal standard. The chemical yields were determined by ^{1}H NMR without any workup procedure, while the ee's were determined after the usual workup procedure.

b. With Pyridine *N*-Oxides. The reactions were performed at 25 °C by adding 330 μmol of the appropriate pyridine *N*-oxide in one portion to well-stirred 2 mL benzene solutions of 330 μmol of olefin and 1 μmol of catalyst, followed by the same workup procedure. The chemical yields are reported relative to iodobenzene, added after the workup procedure.

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