

A chiral iron-sexipyridine complex as a catalyst for alkene epoxidation with hydrogen peroxide†

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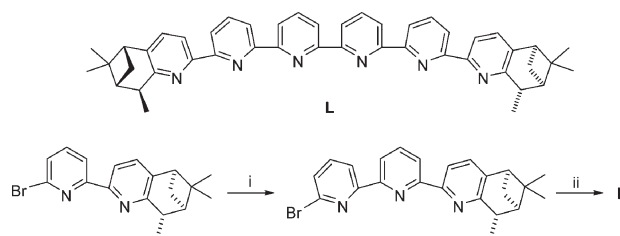
A chiral iron-sexipyridine complex–hydrogen peroxide mixture is a highly efficient catalytic system for styrene epoxidation with excellent reactivity (3 min, 95% yield) and chemoselectivity (98%).

Iron complexes have been extensively studied as models for non-heme iron oxygenases¹ and as catalysts for oxidation of organic substrates.² Among the commonly used terminal oxidants,³ hydrogen peroxide has received much attention because it is environmentally friendly and biologically important.⁴ Hence the development of iron-based catalysts that utilize hydrogen peroxide as the terminal oxidant is a very active research area.⁵

Since iron catalysts bearing 2,2′-bipyridine, 1,10-phenanthroline and their derivatives have been demonstrated to be active oxidation catalysts,^{3,6} we are interested in investigating iron complexes of oligopyridines. Herein, we report the synthesis of a novel chiral sexipyridine ligand **L** and the use of its iron complex as an active catalyst for alkene epoxidation using H₂O₂ as the terminal oxidant.

Ligand **L** was readily prepared by a Ni-catalyzed homocoupling reaction of a bromo-substituted terpyridine, which was obtained from Pd-catalyzed Suzuki-coupling of 6-bromo-2-pyridineboronic acid with a bromo-substituted bipyridine (Scheme 1).[‡] Reaction of FeCl₂ with **L** in a molar ratio of 2 : 1 afforded the binuclear species [Fe₂O(L)Cl₄], which was isolated as a deep red air stable solid (85% yield) and was characterized by elemental analysis and ESI-MS. The ESI mass spectrum of [Fe₂O(L)Cl₄] exhibits a parent peak at *m/z* 879 of formula [Fe₂O(L)Cl₂]⁺ and there is excellent agreement between the experimental and calculated iron isotopic mass distributions for each peak (Fig. 1).

The proposed structure of the [Fe₂O(L)Cl₄] complex is shown in Fig. 2. The molar conductivity of [Fe₂O(L)Cl₄] in CH₃CN is 95 Ω⁻¹ cm² mol⁻¹, which is below the range 120–160 Ω⁻¹ cm² mol⁻¹ for 1 : 1 electrolytes in CH₃CN. This suggests that the compound is neutral in the solid state but substantial chloride dissociation occurs in CH₃CN to give [Fe₂O(L)Cl₃(CH₃CN)]⁺. The UV-vis spectrum (in CH₂Cl₂) shows a strong absorption band at 358 nm (ε = 11 000 M⁻¹ cm⁻¹) and a shoulder at 510 nm (ε = 450 M⁻¹ cm⁻¹),[†] which are characteristic for diiron(III) (μ-oxo) complexes.^{7,8} An isotope exchange experiment of [Fe₂O(L)Cl₄] with H₂¹⁸O, carried out by mixing a 1 : 1 ratio of H₂¹⁸O and CH₃CN at ambient



Scheme 1 (i) Pd(PPh₃)₄, 6-bromo-2-pyridineboronic acid, Na₂CO₃, toluene–MeOH–H₂O, 40%; (ii) hydrated NiCl₂, PPh₃, Zn, DMF, 25%.

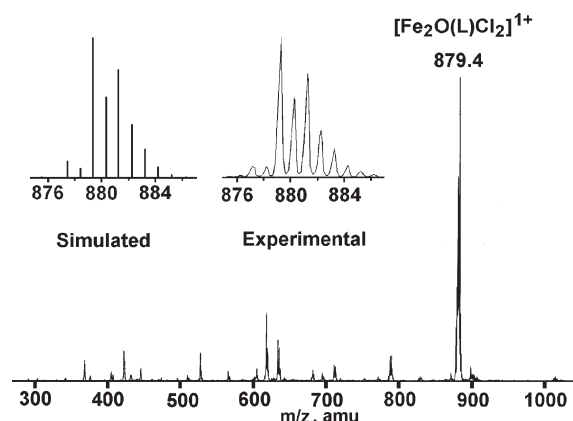


Fig. 1 ESI-MS spectrum of [Fe₂O(L)Cl₄] in CH₂Cl₂. The insets show experimental and simulated isotopic distribution patterns of [Fe₂O(L)Cl₂]⁺.

temperature, showed 75% incorporation of ¹⁸O within the starting complex after 45 min, also suggesting the presence of a μ-oxo species. Although attempts to obtain single crystals suitable for X-ray crystallography were unsuccessful, preliminary MM2 modeling studies suggest that the single-stranded helical structure for [Fe₂O(L)Cl₄] is feasible.

The CD spectrum of [Fe₂O(L)Cl₄] (2.5 × 10⁻⁵ M) shows medium to strong absorptions (Cotton effect) at 270–420 nm (Fig. 3), suggesting a helical nature for the complex. Although

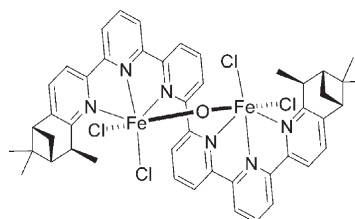


Fig. 2 Proposed structure of [Fe₂O(L)Cl₄].

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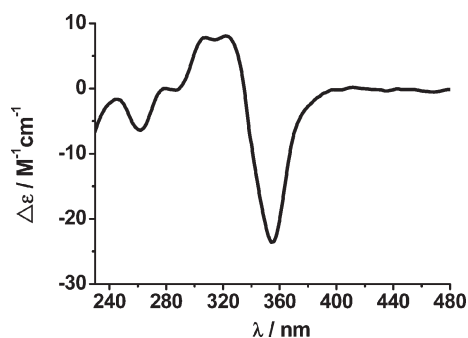


Fig. 3 CD spectrum of $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$ in CH_2Cl_2 .

a double helical complex is formed between $\text{Fe}(\text{II})$ and achiral sexipyridine,⁹ in this case the ESI-MS result is more consistent with a single helical structure for $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$. A single helical complex of Zn^{2+} having a μ -oxo and a dimethyl quinquenylidene ligand has been reported previously.¹⁰

The efficiency of the iron-sexipyridine complex as a catalyst for the epoxidation of styrene with H_2O_2 was investigated using the conditions reported by Jacobsen *et al.*,^{5e} *i.e.* in CH_3CN in the presence of $\text{CH}_3\text{CO}_2\text{H}$. Complex $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$ afforded, within 3 min at room temperature, 76% conversion and 79% selectivity of styrene oxide, with 12% benzaldehyde and 9% phenylacetaldehyde as side products (Table 1, entry 1). The absence of acetic acid resulted in slightly lower yields and selectivity for the epoxide (Table 1, entry 2); this effect was also observed in other iron catalytic systems.^{5e,11} Remarkably, at 0 °C, the catalytic oxidation reached 100% conversion in 3 min with 98% epoxide selectivity (Table 1, entry 3). However, further decrease in temperature to between -10 to -40 °C did not lead to an increase in conversion and selectivity. The epoxidation was ineffective when CH_2Cl_2 was used instead of CH_3CN . No epoxide was formed when peracetic acid was used as the terminal oxidant indicating the *in situ* formation of peracetic acid from H_2O_2 and acetic acid is not responsible for the oxidation and implying a different role of acetic acid. Use of benzoic acid (yield: 91%; selectivity: 88%), propionic acid (yield: 84%; selectivity: 87%) or potassium acetate (yield: 75%; selectivity: 84%) showed generally good results, but not as good as acetic acid. Thus, the best conditions are 2 mol% catalyst, 1.5 equiv. of H_2O_2 , 10 equiv. of acetic acid in CH_3CN at 0 °C; under these conditions complete conversion of styrene to styrene oxide with 98% selectivity occurs within 3 min.

To improve the practicability of the reaction, the integrity of ligand **L** after oxidation was examined. We were able to recover 88% of the ligand by treating the reaction mixture with aqueous Na_2EDTA (EDTA = ethylenediaminetetraacetic acid). Thus, regeneration of the catalyst is possible by simply adding 2 equiv. of FeCl_2 to a CH_3CN solution. Successive epoxidations carried out with this process gave albeit 10% lower yield in each cycle, but maintained very high selectivity for epoxide (90–95%).

To explore the substrate scope of this epoxidation reaction, different terminal alkenes and 1,2-disubstituted alkenes were examined (Table 2). A wide range of terminal alkenes proved to be excellent substrates for epoxidation with $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$ (53–100% conversion in 3 min). Electron-rich substrates such as 4-methoxystyrene and 4-methylstyrene were efficiently epoxidized with TON of up to 83 (Table 2, entries 2 and 3). Good

Table 1 Epoxidations catalyzed by $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]^a$

Entry	Time/min	Temperature/°C	Conversion (%) ^b	Selectivity (%) ^b
1	3	Rt	76	79
2 ^c	3	Rt	70	72
3	3	0	100	98
4	3	-10	75	64
5	3	-20	64	68
6	3	-30	40	66
7	3	-40	24	68

^a Reaction conditions: olefin (0.14 mmol, 0.22 M in CH_3CN), $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$ (2.0 mol%), acetic acid (10 equiv. to catalyst), H_2O_2 (aqueous 35 wt%, 0.21 mmol, 1.5 M in CH_3CN). ^b Determined by GC-FID. ^c No acetic acid added.

Table 2 Asymmetric epoxidations catalyzed by $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]^a$

Entry	Alkene	Conversion (%) ^b	Selectivity (%) ^b	Yield (%) ^b	% ee ^c
1		100	98	95	43 (R)
2 ^e		100	100	100	15 (R)
3 ^e		100	100	100	30 (R)
4		95	95	90	42 (R) ^d
5		94	85	80	17 (R) ^d
6		56	57	52	—
7		94	90	96	37 (1R,2S)
8		62	100	100	40 (1S,2R) ^d
9		53	55	50	31 (1R,2S) ^d
10 ^f		78	75	95	ND

^a Reaction conditions: alkene (0.14 mmol, 0.22 M in CH_3CN), $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$ (2.0 mol%), $\text{CH}_3\text{CO}_2\text{H}$ (10 equiv. to catalyst), H_2O_2 (aqueous 35 wt%, 0.21 mmol, 1.5 M in CH_3CN), 0 °C, 3 min. ^b Determined by GC-FID. ^c Determined by GC with a Cyclodex-B chiral column or HPLC with a Daicel Chiralcel OD column. ^d The absolute configuration was determined by comparing the order of elution with that of a sample with known configuration. ^e Use 1.2 mol%. ^f No diepoxide product was detected.

yields of epoxides were also obtained from electron-deficient styrenes (Table 2, entry 4). On the other hand, the catalytic oxidation is greatly affected by steric effects, which presumably is due to the bulkiness of the iron catalyst. For example, α -methylstyrene gave lower epoxide yield and selectivity than styrene (Table 2, entry 5), and replacing the α -methyl group by a phenyl group leads to even lower yield (52%) and selectivity (57%) (Table 2, entry 6). Similarly, β -substituted styrenes gave lower yields than styrene (Table 2, entries 7–9). Apart from aromatic alkenes, cyclooctadiene was also efficiently epoxidized (Table 2, entry 10). On the other hand, aliphatic alkenes such as 1-heptene were unreactive. All epoxide products were stable under the acidic conditions used and no acid-catalyzed ring opening of the epoxides formed was observed.

The nature of the active intermediate involved in the oxidation has been probed by intermolecular competition reactions. A competitive reaction of 4-methoxystyrene and styrene showed a 9 : 1 preference for the former substrate. A Hammett plot with good linearity, correlated to σ^+ with $\rho = -1.04$, was observed, indicating the electrophilic nature of the active oxidant. Similar observations have been reported with other diiron (μ -oxo) catalysts.^{3f,12} The retention in stereochemistry of the epoxide products of *cis*- β -methylstyrene and *trans*- β -methylstyrene supports a non-radical oxidation process. It is noteworthy that non-heme iron system, $[\text{Fe}_2(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)(\text{mep})]$ (mep = *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)ethane-1,2-diamine), reported by Jacobsen and co-workers,^{5e} is so far the most efficient catalyst for epoxidation of aliphatic alkenes using H_2O_2 as the terminal oxidant. The results obtained here show that the rate of epoxidation using $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$ is comparable to that of $[\text{Fe}_2(\mu\text{-O})(\mu\text{-CH}_3\text{CO}_2)(\text{mep})]$. Since $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]$ is good for aromatic substrates, this catalyst is complementary to the Jacobsen catalyst.

A good to high level of enantioselectivities has been achieved in the asymmetric epoxidation with H_2O_2 as terminal oxidant.¹³ However, only a few non-heme iron- H_2O_2 systems are able to catalyze asymmetric epoxidation, and in general they give low enantioselectivities (around 20% ee). The highest enantioselectivity (82%, for a *trans*-stilbene substrate) was recently reported by Beller *et al.*^{5f} A high ee was also observed in Fe-catalyzed asymmetric sulfur oxidation using H_2O_2 .^{5h} In our studies, although the ees of the epoxides are modest, (15 to 43%), the ee for epoxidation of β -methylstyrene (37%) is comparable to that obtained using Beller's catalyst (28%).

In summary, a new class of iron catalyst based on sexipyridines for epoxidation using H_2O_2 has been explored. The diiron system shows excellent reactivity and selectivity towards terminal and 1,2-disubstituted aromatic alkenes. Further modification of the ligand to achieve better enantioselectivities and understanding of the nature of the active intermediates are under active investigation in our laboratory.

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Notes and references

† L: ¹H NMR (300 MHz, CDCl₃): δ 0.71 (s, 6H), 1.37 (d, 2H), 1.46 (s, 6H), 1.53 (d, 6H), 2.21–2.23 (m, 2H), 2.60–2.64 (m, 2H), 2.85–2.96 (m, 2H), 3.38 (m, 2H), 7.37–7.40 (d, 2H, $J = 7.8$ Hz), 7.97–8.07 (m, 4H), 8.34 (d, 2H,

$J = 8.1$ Hz), 8.54 (d, 2H, $J = 7.8$ Hz), 8.66–8.74 (m, 6H); ESI-MS m/z : 681 (M + H)⁺. $\text{Fe}_2\text{O}(\text{L})\text{Cl}_4$: ¹H NMR spectrum showed paramagnetic in nature. IR (KBr) ν_{max} (cm⁻¹): 540 (m), 831 (m), 1096 (s), 1564 (s), 2922 (s); ESI-MS m/z : 879 $[\text{Fe}_2\text{O}(\text{L})\text{Cl}_4]^+$; anal. calcd for C₄₆H₄₄N₈Fe₂OCl₄: C, 50.98; H, 4.56; N, 7.34. Found: C, 50.64; H, 4.44; N, 7.38%.

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