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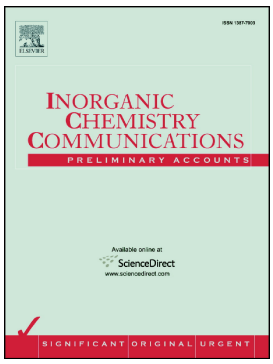

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Kinetics and enantioselectivity of the Baeyer-Villiger oxidation of cyclohexanones by chiral tetrapyridyl oxoiron(IV) complex

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Abstract

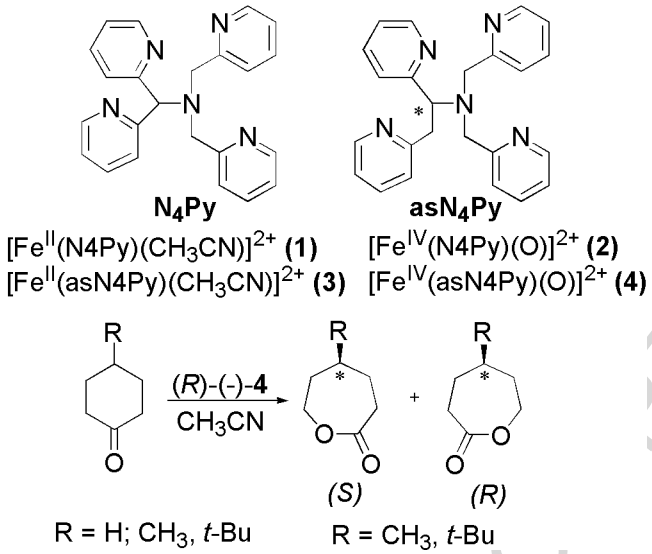
The previously reported oxoiron(IV) complex, $[Fe^{IV}(asN4Py)(O)]^{2+}$ with chiral pentadentate ligand, asN4Py (asN4Py = *N*,*N*-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)ethylamine), is effective for the Baeyer-Villiger oxidation of cyclohexanone derivatives. The reaction is shown to be first order in both cyclohexanone and the oxoiron(IV) species. The second order rate constant is smaller by one order of magnitude than that obtained for the related achiral $[Fe^{IV}(N4Py)(O)]^{2+}$ complex. Oxidation of 4-substituted cyclohexanone derivatives by the chiral oxoiron(IV) complex attains moderate enantioselectivities up to 45% enantiomeric excess (ee).

Keywords: Biomimetics; Baeyer-Villiger oxidation; Iron(IV)-oxo complex; Enantioselectivity, Kinetics

Baeyer-Villiger (B.-V.) oxidation of ketones into esters or lactones by organic peroxyacids as stoichiometric oxidants has a wide range of application, from the synthesis of steroids, antibiotics, pheromones, and herbicides to the synthesis of intermediates for polymerization [1-8]. Since the classical B.-V. reaction lacks of the chemo-, regio-, and enantioselectivity, that are expected for organic synthesis, and the oxidants which are used are hazardous and expensive, these limitations led to the application of biocatalytic processes [9-15]. Baeyer-Villiger monooxygenases (BVMO) are considered highly valuable catalysts for the synthesis of fine chemicals [16-19]. BVMOs can be classified into three groups: Type I BVMOs contain a flavin adenine dinucleotide (FAD) as cofactor and use nicotinamide adenine dinucleotide phosphate (NADPH) as electrons source. Type II BVMOs use flavin mononucleotide (FMN) as flavin cofactor and nicotinamide adenine dinucleotide (NADH) as electron donor. Type III BVMOs are specific cytochrome P450s, which are involved in the synthesis of brassinosteroids, steroidal hormones essential for the growth and development of plants [20,21]. These heme-containing

monooxygenases are supposed to exploit the hydroperoxy heme intermediate ($Fe^{III}OOH$) as a „peracid catalyst". Iron complexes of *meso*-tetraphenylporphyrin, Fe^{III}(TPP)Cl [22,23], and *N*,*N*-bis(2-pyridylmethyl)-*N*-bis(2-pyridyl)methyl-amine $[Fe^{II}(N4Py)(CH_3CN)]^{2+}$ (**1**) [24,25] proved to be efficient catalysts for the aerobic oxidation of cyclohexanone in the presence of various aldehydes as sacrificial reductants, wherein, contrary to the heme-containing monooxygenases, a high-valent iron porphyrin, $[Fe^{V}(TPP)(O)]Cl$ and $[Fe^{IV}(N4Py)(O)]^{2+}$ (**2**) were proposed as key intermediates in the rate-determining oxygen atom transfer step to generate the ε-caprolactone.

Much effort has been directed to development of metal-mediated asymmetric B.-V. reaction. In 1994, Bolm et al. [26] and Strucul et. al. [27] reported the first enantiomer-differentiating chiral copper and platinium-catalyzed B.-V. reactions. Since then, various optically active metal complexes including metals, such as Pt [28], Pd [29], Zr [30], Co [31], have been used as catalysts for asymmetric B.-V. reactions. However, noble metals and their compounds are expensive, difficult to obtain and hard to recover that cause limitation in industrial production. Well-characterized and reactive chiral terminal oxo-iron complexes capable of undergoing oxygen-atom transfer reactions in an enantioselective manner are sparse in the literature. Recently, we communicated that the chiral oxoiron(IV) complex, $[Fe^{IV}(asN4Py)(O)]^{2+}$ (**4**) (asN4Py = *N*,*N*-bis(2-pyridylmethyl)-1,2-di(2-pyridyl)ethylamine), generated by the reaction of $[Fe^{II}(asN4Py)(CH_3CN)]^{2+}$ (**3**) with PhIO, can undergo enantioselective sulfoxidation of thioanisole in 84% enantiomeric excess (ee) [32]. As a continuity of our research, we report herein the kinetics of the $[Fe^{IV}(asN4Py)(O)]^{2+}$-mediated stoichiometric oxidation of cyclohaxanone compared to its related oxoiron(IV) derivative, $Fe^{IV}(N4Py)(O)]^{2+}$, and the enantioselectivities towards 4-substituted cyclohexanone derivatives.



Scheme 1

It is well-known that oxoiron(IV) complexes are able to oxidize many organic compounds including various solvents such as toluene and alcohols, but it has been proved that the CH_3CN as solvent is innocent. $[Fe^{IV}(asN4Py)(O)]^{2+}$ (**4**) is one of the most stable oxoiron(IV) species, its half-life ($t_{1/2}$) is ~10 days in acetonitrile (CH_3CN) at room temperature. The oxidation potential of **4**, compared to $Fe^{IV}(N4Py)(O)](ClO_4)_2$ (**2**) has been studied at 25 ˚C in the B.-V. oxidation process with cyclohexanone. Complex **4** was generated by the reaction of **3** with 1.2 equiv. of PhIO (<40 min), and the rate of its rapid decomposition, which coincided with the regeneration of **3** (λ_{max} = 398, 409 nm), and the formation of ε-caprolactone [33], was measured as a function of the concentration of added cyclohexanone (Entry 8 in Table 1, and Fig. 1a). No decay process can be observed in the absence of substrate in CH_3CN under this condition. The yield of ε-caprolactone was almost quantitative (~80%), proving that the UV-vis spectral change corresponds to the OAT process. An isosbestic point was observed at 580 nm, indicating that there were no long-lived intermediates in the conversion of the green species into the Fe^{II} product. The oxoiron(IV) species can be reactivated, and a new stoichiometric cycle can be initiated by the use of additional 1.2 equiv. of PhIO (~75% yield). The rates in the presence of a large excess of cyclohexanone (50-350 equiv.) obeyed pseudo-first order kinetics, with respect to **4**, and the pseudo-first order rate constants increased proportionally with the substrate concentration (Entries

1-5 in Table 1, and Fig. 1b). The linear plot of the reaction rate values (*V*) against the initial concentration of **4** also states that the reaction is first-order with respect to the oxoiron(IV) concentration (Entries 5-8 in Table 1, and Fig. 1c). The above results establish a rate law of -d[**4**]/dt = k_2[**4**][cyclohexanone], and from these linear plotting, the second order rate constant (k_2) was determined to be 2.06×10^{-4} M^{-1} s^{-1} with $\Delta H^{\neq}$ = 87 kJ mol^{-1} and $\Delta S^{\neq}$ = -149 J mol-^{1} K^{-1} at 25 ˚C (Entries 5, 9-11 in Table 1, and Fig. 1d). These results indicate that $[Fe^{IV}(asN4Py)(O)]^{2+}$ (**4**) complex is much less reactive than the $[Fe^{IV}(N4Py)(O)]^{2+}$ (**2**) complex. The second order rate constant is smaller by one order of magnitude, and the activation enthalpy is two times higher, than those obtained for the related achiral $[Fe^{IV}(N4Py)(O)]^{2+}$ complex (1.48×10^{-3} M^{-1} s^{-1}, 41 87 kJ mol^{-1}, Table 2). The large negative activation entropies are typical of associative processes, and indicate that the transition state is better organized than the prior step.

Table 1. Kinetic data for the stoichiometric oxidation of cycklohexanone with $[Fe^{IV}(asN4Py)(O)](ClO_4)_2$ [33].

No.	T (K)	$[Fe^{IV}(O)]^{2+}$ (10^{-3}M)	Cyclohexanone (M)	V (10^{-7} M s^{-1})	k_{obs} (10^{-5} s^{-1})	k_2 (10^{-4} $M^{-1}s^{-1}$)
1	298	2.0	0.1		2.46±0.07	2.46±0.07
2	298	2.0	0.4		7.2±0.2	1.80±0.05
3	298	2.0	0.5		9.5±0.4	1.90±0.08
4	298	2.0	0.6		12.6±0.5	2.10±0.08
5	298	2.0	0.7	2.88	14.4±0.4	2.06±0.06
6	298	1.0	0.7	1.47	14.7±0.5	2.10±0.07
7	298	1.5	0.7	2.07	13.8±0.4	1.97±0.05
8	298	3.0	0.7	4.08	13.6±0.4	1.94±0.05
9	293	2.0	0.7		7.0±0.2	1.00±0.02
10	303	2.0	0.7		23.6±0.7	3.37±0.10
11	308	2.0	0.7		43.6±1.7	6.23±0.24

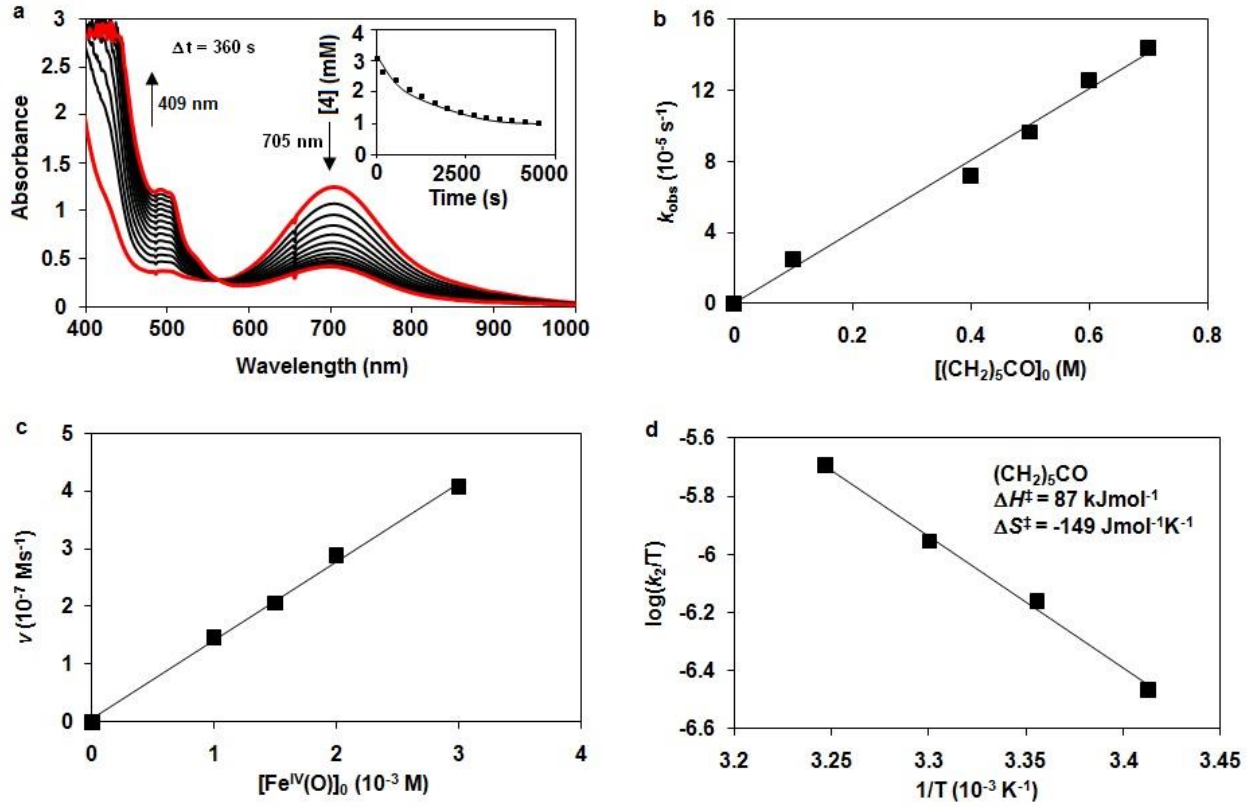


Fig. 1. Reactions of $[Fe^{IV}(asN4Py)(O)]^{2+}$ (**4**) with cyclohexanone in CH_3CN at 298 K. (a) UV-vis spectral change of **4** (3.0 mM) upon addition of 233 equiv. cyclohexanone. Inset shows time course of the decay of **4** monitored at 705 nm (Entry 8 in Table 1). (b) Plot of k_{obs} versus [substrate] for reactions of **4** (2.0 mM) with cyclohexanone (Entries 1-5 in Table 1). (c) Plot of reaction rate (V) versus [**4**] for reactions of **4** with cyclohexanone (Entries 5-8 in Table 1). (d) Eyring plots of log *k*/T versus 1/T for cyclohexanone (Entries 5, 9-11 in Table 1).

Table 2. Comparison of efficiency of $Fe^{IV}(asN4Py)(O)]^{2+}$ and $Fe^{IV}(N4Py)(O)]^{2+}$complexes toward the oxidation of cyclohexanone in acetonitrile at 298 K.

Complex/Substrate	k_2 (M^{-1} s^{-1})	capcolactone (%)	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	Ref.
$[Fe^{IV}(asN4Py)(O)]^{2+}$	2.06×10^{-4}	80	87	-149	this work
$[Fe^{IV}(N4Py)(O)]^{2+}$	1.48×10^{-3}	80	41	-111	[19]

Finally, to get direct evidence for the involvement of the high-valent oxoiron(IV) species in the enantioselective step, the reaction of (*R*)-(-)-**4**$\cdot(ClO_4)_2$ with 4-Me-cyclohexanone and 4-*tert*-butyl-cyclohexanone was investigated at 25˚C in CH_3CN [34], and the enantioselectivities were determined by chiral GC analysis compared to the racemic oxoiron(IV) species (Table 3, and Fig.

2). Oxidation of 4-substituted-cyclohexanone derivatives by the chiral oxoiron(IV) complex attains moderate enantioselectivities up to 39% enantiomeric excess (ee) at 25˚C (Table 3). Significantly better value can be observed at lower temperature, namely 45% *ee* for 4-Me-cyclohexanone at 5˚C compared to that observed at 25˚C (*ee* 30%).

In the present work, we carried out B.V. oxidation reactions with spectroscopically well characterized chiral mononuclear nonheme iron(IV) complex. The reactivity of chiral and achiral nonheme oxoiron complexes has been briefly compared as well. To the best of our knowledge, this study provides the first details of enantioselective 4-substituted-cyclohexanone oxidations with oxoiron(IV) complexes generated in situ, which bear nonheme chiral ligand. Our results demonstrate that the iron(IV)-oxo complex with a chiral moiety can significantly affect the enantiomeric selectivity, therefore the oxidation must be bound to the metal-based oxidant. In conclusion, we have reported the first example of a chiral nonheme iron(IV)-oxo intermediate that is capable of the stereoselective B.-V. reaction of cyclohexanone derivatives, suggesting that iron(II) compexes with chiral ligands may serve as a good candidates for an efficient and selective catalyst for the B.-V. reactions.

Table 3. Stoichiometric 4-*tert*-butyl-cyclohexanone oxidations by racemic and (*R*)-(-)-Fe^{IV}(asN4Py)(O)]$^{2+}$ complexes, [**4**]$_0$ = 5.90 × 10^{-3} M, [substrate]$_0$ = 2.06 × 10^{-1} M. [33]

no.	oxidant	substrate	ee (%)	yield (%)[a]	T (K)
1	(R,S)-(+/-)-**4**	4-*tert*-butyl-cyclohexanone	0	50	298
2	(R)-(-)-**4**	4-*tert*-butyl-cyclohexanone	39 (*R*)	48	298
3	(R)-(-)-**4**	4-methyl-cyclohexanone	30 (*R*)	54	298
4	(R)-(-)-**4**	4-methyl-cyclohexanone	45 (*R*)	25	278

[a]Based on [**4**]; IS = PhBr.

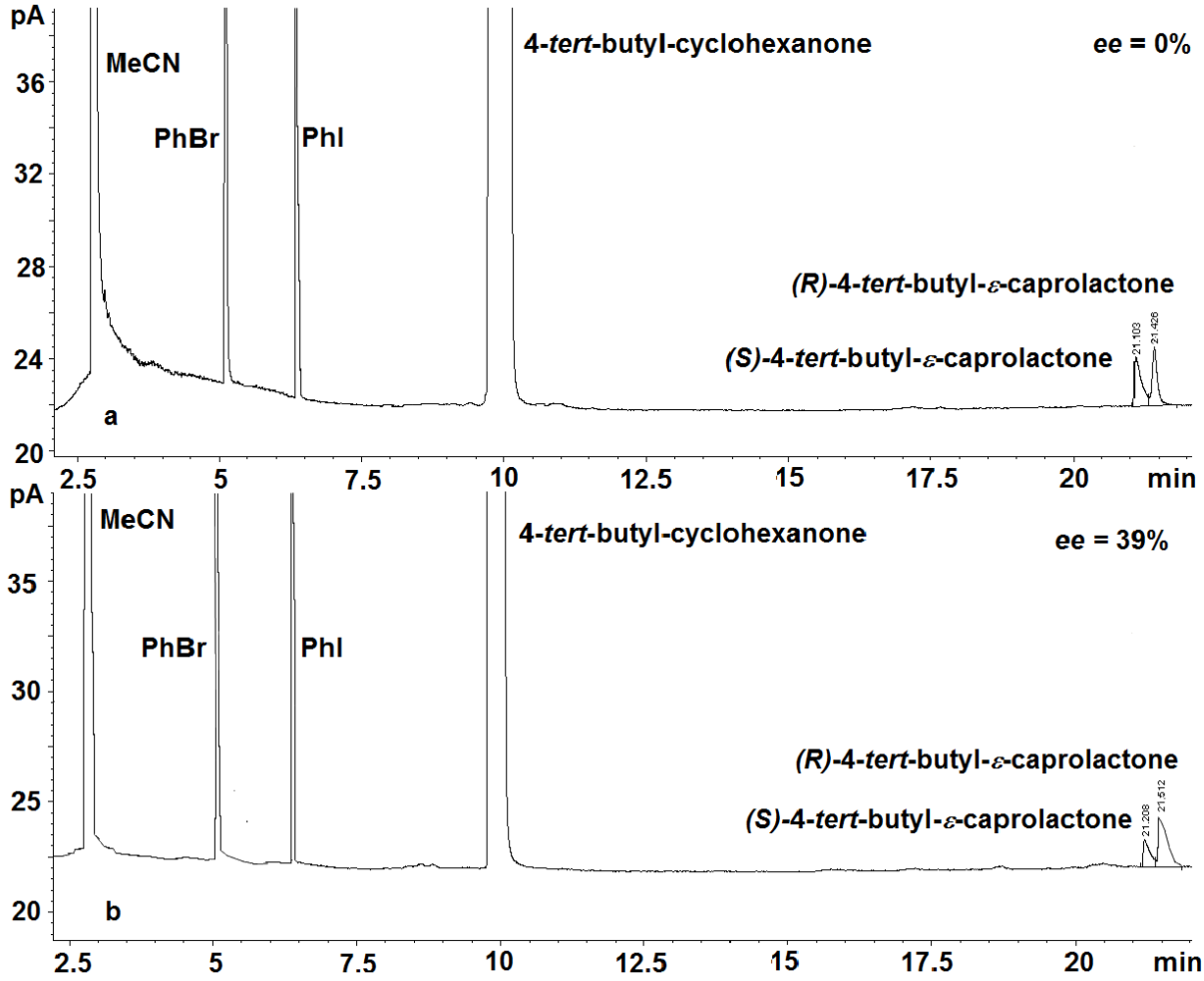


Fig. 2. The GC chromatogram of the reaction of racemic **4** and 4-*tert*-butyl-cyclohexanone (**a**); and (*R*)-(-)-**4** and 4-*tert*-butyl-cyclohexanone (**b**) in MeCN at 298 K. $[(R)\text{-}(-)\text{-}\mathbf{4}]_0 = 5.90 \times 10^{-3}$ M, $[\text{PhIO}]_0 = 1.18 \times 10^{-2}$ M, $[4\text{-}tert\text{-butyl-cyclohexanone}]_0 = 2.06 \times 10^{1}$ M.

Acknowledgements

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[33] [Fe^{II} (asN_4Py)(CH_3CN)](ClO_4)$_2$ (**3**) complex (2.0×10^{-3} M) was dissolved in acetonitrile (1.5 mL), and then iodosobenzene (2.4×10^{-3} M) was added to the solution. The mixture was stirred for 40 minutes then the excess of iodosobenzene was removed by filtration. Substrate (0.1 – 0.7 M) was added to the solution and the reaction was monitored with UV-vis spectrophotometer (Agilent 8453 diode-array spectrophotometer) at 705 nm (ε = 400 M^{-1} cm^{-1}) (Table 1). Product analysis of the resulting solution was performed by GC and GC/MS (Shimadzu QP2010SE equipped with a secondary electron multiplier detector with conversion dynode and a 30 m HP-5MS column): Product: ε-caprolactone (80%); *m/z* (%) 114 (M^+; 12.6); 84 (24.1); 70 (15.3); 56 (39.6); 55 (100); 42 (99.8); 41 (49.6); 39 (23.5).

[34] (*R*)-(-)-Fe^{II}(asN4Py) complex (5.90×10^{-3} M) was dissolved in acetonitrile (1.0 mL), then iodosylbenzene (1.18×10^{-2} M) was added to the solution. The mixture was stirred for 50 minutes then the excess iodosylbenzene was removed by filtration. 4-*tert*-butyl-cyclohexanone (4-methyl-cyclohexanone) (2.06×10^{1} M) was added to the solution and the mixture was stirred at 25°C for 5 hours. The products were identified by GC (Agilent 6850 gas chromatograph equipped with a flame ionization detector), and the yield of 4-*tert*-butyl-ε-caprolactone (4-methyl-ε-caprolactone) were calculated based on the amount of iron(IV)-oxo using bromobenzene as an internal standard in the reactions. Enantiomeric excess was determined with GC analysis on chiral CHIRASIL-L-VAL column: ([R] - [S]) / ([R] + [S]). 4-*tert*-butyl-ε- caprolaktone: *m/z* (%) 170 (M^+; 4.1); 114 (69.2); 86 (79.6); 83 (12.7); 69 (12.5); 68 (16.8); 57 (100); 56 (12.1); 55 (75.8); 54 (12.8); 43 (9.5); 42 (6.8);

41 (46.8); 39 (14.0); 4-methyl-ε-caprolactone: m/z (%) 128 (M^+ , 8.1); 98 (13.2); 70 (9.5); 69 (51.3); 57 (6); 56 (100); 55 (51.4); 43 (11.3); 42 (20.7); 41 (41.4); 39 (14.4).

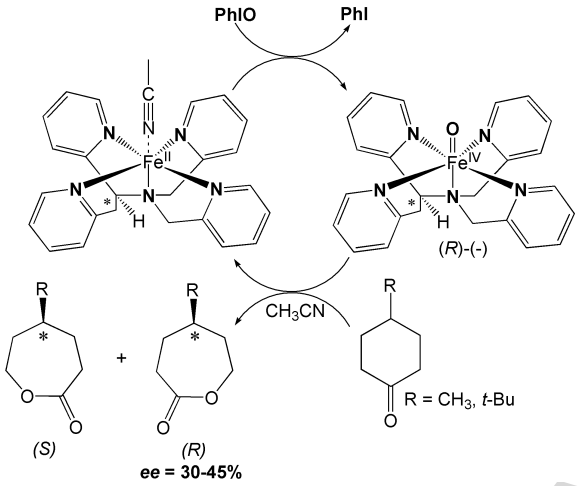
List of Schemes and Figures

Graphical abstract

Kinetics and enantioselectivity of the Baeyer-Villiger oxidation of cyclohexanones by chiral tetrapyridyl oxoiron(IV) complex

Ramona Turcas, Dóra Lakk-Bogáth, Gábor Speier, József Kaizer*

The reactivity of oxoiron(IV) complex, $[Fe^{IV}(asN4Py)(O)]^{2+}$ with chiral pentadentate ligand, has been investigated in the Baeyer-Villiger oxidation of cyclohexanone derivatives.



Highlights

- Reactivity of chiral oxoiron(IV) complex towards cyclohexanone
- Reaction kinetics with UV-Vis spectroscopy
- Enantioselective Baeyer-Villiger reactions