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Chiral *N,N′*-dioxide–iron(III)-catalyzed asymmetric sulfoxidation with hydrogen peroxide

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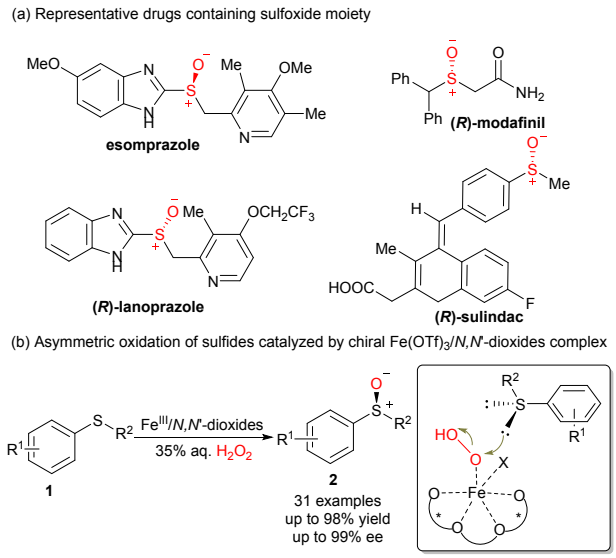
A highly enantioselective sulfoxidation of various sulfides has been achieved by a *N,N′*-dioxide–iron(III) complex with 35% aq. H_2O_2 as the oxidant. The utility of current method was demonstrated by asymmetric gram-scale synthesis of drug molecule (*R*)-modafinil. Moreover, a possible working mode was provided to elucidate the chiral induction.

Optically active sulfoxides are highly important molecules because of their wide application in asymmetric synthesis[1,2] and frequent existence in many pharmaceuticals (Scheme 1a).[3] Over the past several decades, the synthesis of chiral sulfoxides has attracted considerable interest and various methods have been developed.[4] Among all strategies established so far, catalytic asymmetric sulfoxidation of prochiral sulfides by metal-based catalysts is one of the most attractive and generalized routes for the preparation of enantioenriched chiral sulfoxides. Since the pioneered works by Kagan[5a-b] and Modena,[6] a huge spurt of progress has been made in this research area, and various Lewis acid salts in combination with chiral diols, Schiff bases, and salen-type ligands have been employed to promote the reaction in the presence of different oxidants, supplying numerous functionalized chiral sulfoxide compounds.[4] Remarkably, the demand of efficient and green catalytic systems for enantioselective oxidation of sulfides is continuously growing in line with toughening economic and environmental constraints. In this context, nontoxic and inexpensive iron complexes[7] have been developed successfully by the group of Bolm[8a-c] and others,[8d-f] using environmentally benign H_2O_2[9] as a terminal oxidant. Despite of these significant achievements, there still leaves room for further improvement in terms of chiral ligands, catalytic efficiency and substrate scope.

Inspired by our previous works on the asymmetric oxidation of α,β-unsaturated carbonyl compounds[10a,b] as well as our recent reports on enantioselective rearrangements[10c,d] involving sulfide derivatives, we envisioned that *N,N′*-dioxide–metal complex[11] developed by our group was potential to be an efficient catalyst for exerting the oxidation of unsymmetric sulfides. As depicted in Scheme 1b, with H_2O_2 as the oxidant, *N,N′*-dioxide–metal–OOH complex could be formed in-situ, which subsequently works as the possible active specie to oxidize the prochiral sulfides to chiral sulfoxides by discriminating the heterotopic lone pairs on sulfur. Herein, we wish to disclose our effort along this line. Chiral *N,N′*-dioxide–iron(III) complex[12] was found to be efficient as the catalyst to mediate the proposed sulfoxidation reaction with H_2O_2 as the terminal oxidant. Under the optimal conditions, an array of aryl alkyl sulfides and dialkyl sulfides converted to the corresponding chiral sulfoxides in moderate to good yield with high enantioselectivity. The utility of the current method was



Scheme 1. Representative drugs bearing sulfoxide unit and our method for the asymmetric synthesis of chiral sulfoxides.

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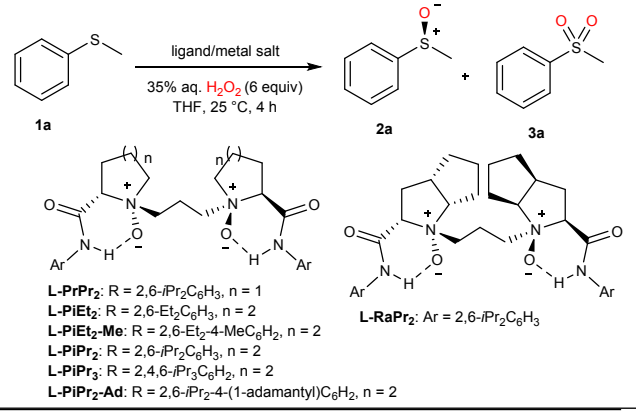
Table 1. Optimization of the reaction conditions[a]



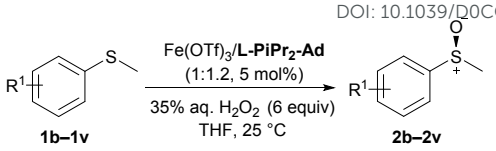
Entry	Ligand	Metal salt	Yield (%)[b]	ee (%)[c]
1	**L-PiPr$_2$**	Fe(OTf)$_3$	52	63
2	**L-PiPr$_2$**	Fe(ClO$_4$)$_3$·H$_2$O	42	10
3	**L-PiPr$_2$**	Fe(acac)$_3$	32	0
4	**L-PrPr$_2$**	Fe(OTf)$_3$	30	7
5	**L-RaPr$_2$**	Fe(OTf)$_3$	27	53
6	**L-PiEt$_2$**	Fe(OTf)$_3$	55	56
7	**L-PiPr$_3$**	Fe(OTf)$_3$	61	87
8	**L-PiPr$_2$-Ad**	Fe(OTf)$_3$	70	93
9[d]	**L-PiPr$_2$-Ad**	Fe(OTf)$_3$	70	98
10[e]	**L-PrPr$_2$**	Fe(OTf)$_3$	80	98

[a] The reactions were performed with **1a** (0.1 mmol), 35% aq. H_2O_2 (0.6 mmol), and ligand/metal salt (1:1, 10 mol%) in THF (1.0 mL) at 25 °C for 4 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Metal salt/ligand (1:1.2, 10 mol%). [e] Metal salt/ligand (1:1.2, 5 mol%) in THF (0.2 M).

demonstrated by the asymmetric gram-scale synthesis of drug molecule (*R*)-modafinil.

Initially, phenyl methyl sulfide (**1a**) was chosen as the model substrate to optimize the reaction conditions. Various metal salts were screened by coordinating with **L-PiPr$_2$** in THF at 25 °C (For details, See ESI, Page 2). To our delight, promising results (52% yield with 63% ee) were obtained by using **L-PiPr$_2$**/Fe(OTf)$_3$ complex as the catalyst (Table 1, entry 1). Further examination of Fe(III) with different counteranions, for instance, ClO_4^- and acac, was carried out, however, no better results were afforded (Table 1, entries 2 and 3).[13] Next, the investigation of the chiral backbone of the *N*,*N*′-dioxide ligands showed that *S*-pipecolic acid derived **L-PiPr$_2$** was superior to *L*-proline-derived **L-PrPr$_2$** and *L*-ramipril-derived **L-RaPr$_2$** in term of enantioselectivity and reactivity (Table 1, entry 1 *vs.* entries 4 and 5). Varying the amide moiety of the *N*,*N*′-dioxide ligands indicated that with the increase of steric hindrance of the amide unit, the enantioselectivity of the reaction increased gradually (Table 1, entries 6-8). *N*,*N*′-Dioxide with 2,6-*i*Pr$_2$-4-(1-adamantyl)C$_6$H$_2$ group afforded the corresponding sulfoxide **2a** with 70% yield and 93% ee. Subsequent investigation of the ratio of metal salt with ligand exhibited that a slight excess of ligand was benefit to the chiral control (Table 1, entry 12, 70% yield, 98% ee).[14] Other parameters including solvent, temperature were screened as well, but no better results were provided (for further details, see ESI, Page 3-5). A higher yield (80%) with maintained enantioselectivity was delivered when the catalyst

Table 2. Substrate scope of aromatic group in sulfides[a]



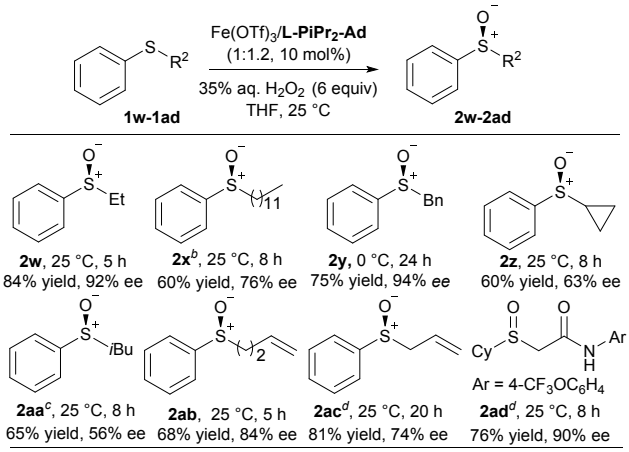
Entry	R^1	T(°C)	t (h)	Yield(%)[b]	ee (%)[c]
1	2-F	25	4	91 (**2b**)	87
2[b]	2-Cl	25	4	98 (**2c**)	84
3	2-Br	25	4	98 (**2d**)	84
4	3-Cl	25	4	90 (**2e**)	99
5[c]	3-Br	25	4	92 (**2f**)	99
6	4-F	25	4	70 (**2g**)	98
7[c]	4-Cl	25	4	81 (**2h**)	98
8[b]	4-Br	25	6	79 (**2i**)	99
9	4-Me	0	12	97 (**2j**)	99
10	4-OMe	0	12	96 (**2k**)	99
11	4-OH	25	12	90 (**2l**)	83
12	4-OSi(*i*Pr)$_3$	35	14	61 (**2m**)	89
13	4-OBn	35	8	86 (**2n**)	96
14	4-NH$_2$	25	15	90 (**2o**)	72
15	4-NHBoc	0	4	92 (**2p**)	92
16[b]	4-NO$_2$	35	20	66 (**2q**)	96
17	4-CO$_2$Me	35	18	80 (**2r**)	98
18	4-COMe	35	20	60 (**2s**)	99
19	2-naphthyl	35	22	76 (**2t**)	90
20	2-indolyl	–40	18	88 (**2u**)	90
21	5-MeO-1*H*-benzo[*d*]imidazolyl	35	48	32 (**2v**)	99

[a] The reactions were performed with Fe(OTf)$_3$/**L-PiPr$_2$-Ad** (1:1.2, 5 mol%), **1** (0.1 mmol) and 35% aq. H_2O_2 (0.6 mmol) in THF (0.5 mL). [b] Fe(OTf)$_3$/**L-PiPr$_2$-Ad** (1:1.2, 10 mol%). [c] Fe(OTf)$_3$/**L-PiPr$_2$-Ad** (1:1.2, 2.5 mol%).

loading was decreased to 5 mol% and reaction concentration was increased to 0.2 M. Therefore, our optimal reaction conditions were established as Fe(OTf)$_3$/**L-PiPr$_2$-Ad** (1:1.2, 5 mol%), sulfide and six equivalents of 35% aq. H_2O_2 in THF (0.2 M) at 25 °C for 4 h. It should be noted that a small amount of sulfone **3a** was generated through over-oxidation in the current system, which partly contributed to the obtained high enantioselectivity via kinetic resolution process (for further details, see ESI, Page 12). The absolute configuration of product **2a** was assigned to be (*S*) by comparing with the optical rotation value reported in the literature.[8c]

With the optimized reaction conditions in hand, the substrate scope of sulfides was then evaluated. As illustrated in Table 2, various methyl substituted sulfides bearing different aromatic groups reacted with aqueous hydrogen peroxide smoothly, providing the respective enantioenriched sulfoxides in moderate to good yield (60-98%) with high enantioselectivity (72-99%). Generally, the position of substituents exhibited a significant effect on the chiral control of the reaction. *Meta*- and *para*-substituted sulfides (**1e** and **1f**, **1g**-**1k**) gave higher enantioselectivity than *orthro*-substituted ones (**1b**-**1d**). Although the electronic nature of substituents on the Ar moiety has limited influence on the enantioselectivity, over-oxidation was usually heavier for electron-rich sulfides (**1j** and **1k**) than electron-deficient ones (**1g**, **1h** and **1i**). This issue could be partly solved by lowering the reaction temperature. At 0 °C, the

Table 3. Substrate scope of methyl group[a]

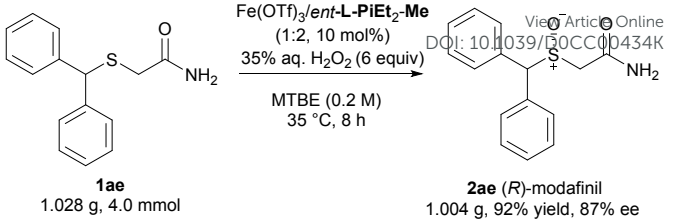


[a] The reactions were performed with Fe(OTf)$_3$/**L-PiPr$_2$-Ad** (1:1.2, 10 mol%), **1** (0.1 mmol) and 35% aq. H_2O_2 (0.6 mmol) in THF (0.5 mL). [b] **L-PiPr$_3$** was used instead of **L-PiPr$_2$-Ad**. [c] **L-PiPr$_2$** was used instead of **L-PiPr$_2$-Ad**. [d] Fe(OTf)$_3$/**L-PiPr$_2$-Ad** (1:1.2, 5 mol%).

reaction of electron-rich sulfide **1j** or **1k** performed well, delivering the desired products **2j** and **2k** with good yield and high ee value (**2j**, 97% yield, 99% ee; **2k**, 96% yield, 99% ee). For *meta*-bromo or *para*-chloro substituted sulfides **1f** and **1h**, the catalyst loading could be reduced to 2.5 mol% with equally good results (**2f**, 92% yield, 99% ee; **2h**, 81% yield, 98% ee). It should be noted that many types of functionalized sulfides including NH_2, NHBoc, OH, BnO, OSi(*i*Pr)$_3$, CO_2Me and CH_3CO groups were compatible in this transformation, good results were afforded (**2l**-**2s**). In general, the substrates with protected hydroxyl or amino group yielded the product with higher enantioselectivity than the ones with hydroxyl or amino group. 2-naphthyl substituted sulfide **1t** was suitable in current system, giving the expected product **2t** in 76% yield with 90% ee. The reaction of sulfides bearing hetero-aromatic ring, such as indole or 1H-benzo[*d*]imidazole moiety, took place well, delivering the expected products **2u** and **2v** in high enantioselectivity (90% ee and 99% ee, respectively).

Further investigation was conducted for phenyl sulfides with different alkyl substituents. Changing the methyl group to ethyl or benzyl group, the corresponding products were obtained in high yield with excellent ee value (Table 3, 92% and 94 % ee for **2w** and **2y**). Long chain alkyl substituted substrate (**1x**) as well as the the substrates with sterically bulky cyclopropyl (**1z**) or *i*Bu (**1aa**) substituent resulted in decreased reactivity (60-65% yield) and enantioselectivity (56-76% ee). Under slightly modified conditions, alkene substituted sulfoxides (**2ab** and **2ac**) were generated in decent yield with reasonable ee value. Furthermore, the Fe(III)-H_2O_2-based system was capable of promoting asymmetric sulfoxidation of alkyl alkyl substituted sulfides, yielding the desired product **2ad** with good results.

The practical synthetic relevance of current method was demonstrated by enantioselective synthesis of biologically active sulfoxide (*R*)-modafinil **2ae** (Scheme 2), which is used for the treatment of sleep disorders. As shown in Scheme 2, the oxidation of sulfide **1ae** with H_2O_2 occurred smoothly in the

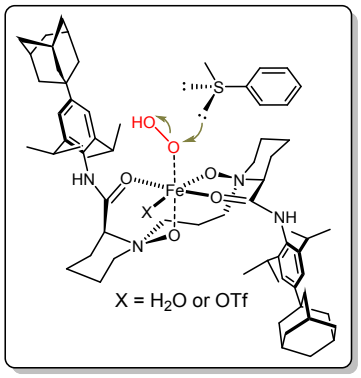


Scheme 2. Gram-scale synthesis of (*R*)-modafinil.

presence of Fe(OTf)$_3$-*ent*-**L-PiEt$_2$-Me** (1:2, 10 mol%) in methyl tert-butyl ether (MTBE) at 35 °C for 8 h, and the corresponding sulfoxide **2ae** was yielded in 94% yield with high enantioselectivity (87% ee). Remarkably, the gram-scale up of the reactions (4 mmol scale) allows readily preparation of large quantities of (*R*)-modafinil (1.004g, 92% yield, 87% ee).

According to the previous reports,[15] two possible intermeidates, either a peroxo Fe^{III}-OOH or high valent iron–oxido, were postulated to be the catalytically active species. To gain direct evidence for the mechanism, a series of mechanistic experiments were performed. Firstly, EPR spectrum of **L-PiPr$_2$-Ad**-Fe(OTf)$_3$ (1:1.2) with 20-100 equivalents of 35% aq. H_2O_2 was recorded at 120 K (see ESI, Page 7), it was indicated that only a high spin Fe^{III} specie (g = 4.4) was detected.[16] Meanwhile after addition of $H_2{}^{18}O$ even in large excess, the only reaction product detected by HRMS was PhS(^{16}O)Me (see ESI, Page 9, for details).[17] UV-Vis absorption spectrum showed that the addition of H_2O_2 did not lead to new peaks along with decay of the 284 nm absorption in UV-Vis absorption spectrum of **L-PiPr$_2$-Ad**-Fe(OTf)$_3$ (1:1.2) in THF at room temperature (see ESI, Page 8),.[18] The above results tempted us to conclude that the high spin Fe^{III}-OOH compound was probably to be the real key active specie in present system.[15b,c,19]

Based on the X-ray crystal structure of **L-PiPr$_2$-Ad**/Fe(OTf)$_3$ complex[20] and the configuration of product **2a** as well as above experimental results, a possible transition state model was proposed as depicted in Scheme 3. The tetradentate **L-PiPr$_2$-Ad**, and OOH^- coordinate with Fe(III) in an octahedral fashion. Due to the steric repulsion between the aryl groups in the sulfide with the neighboring 2,6-diisopropyl-4-(1-adamantyl)phenyl group of the ligand, discrimination of the heterotopic lone pairs is available and *S*-configured sulfoxide was formed preferably.



Scheme 3. Proposed working model.

Conclusions

In summary, we have developed an efficient chiral *N*,*N*′-dioxide/Fe(OTf)$_3$ complex catalytic system for the asymmetric sulfoxidation of a series of alkyl aryl sulfides. The corresponding sulfoxides were obtained in moderate to high yield (60-98%) and ee value (56-99%), and the reaction is suitable for the asymmetric synthesis of bioactive drug (*R*)-modafinil.[21] Further exploration of the reaction mechanism is currently underway.

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Conflicts of interest

There are no conflicts to declare.

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19 Molecular ion peak of [**L-PiPr$_2$-Ad**/Fe-OOH/OTf$^-$/CH$_3$OH] was found in the spectrum of HRMS, See ESI page 10 for details.

20 CCDC 1975799 [**L-PiPr$_2$-Ad**/Fe(OTf)$_3$ complex].

21 As suggested by one reviewer, a detailed comparison of current method with other iron-based catalyst system was provided in ESI, Page 28.

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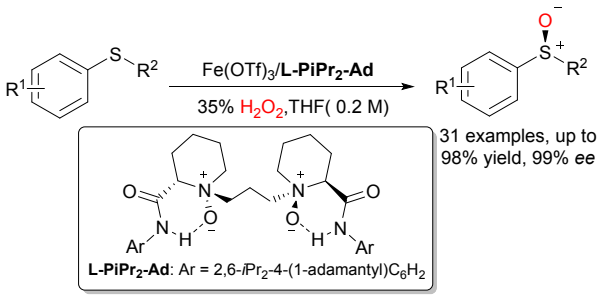

Gram-scale synthesis of drug molecule (*R*)-modafinil was accomplished by chiral *N*,*N*-dioxide–iron(III) complex catalyzed asymmetric sulfoxidation.