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Asymmetric vanadium- and iron-catalyzed oxidations: new mild (*R*)-modafinil synthesis and formation of epoxides using aqueous H_2O_2 as a terminal oxidant

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ABSTRACT

The enantioselective oxidation of thioanisole to methyl phenyl sulfoxide and the epoxidation of several alkenes, including terminal ones, have been realized by using new iron(III) complexes, generated in situ from primary amine-derived non-symmetrical Schiff base ligands and aqueous H_2O_2 as environmentally benign oxidant. Further investigations on vanadium catalysis and the application of both catalytic systems in the synthesis of enantiomerically-enriched chiral drug (*R*)-modafinil were undertaken. It was found that the vanadium-based catalytic system ($VO(acac)_2$/ligand **6**), is able to provide (*R*)-modafinil in quantitative yield and acceptable enantiomeric excess within a very short reaction time (15 min).

1. Introduction

The development of environmentally friendly enantioselective oxidation reactions is still an important challenge for chemical research. Thereby, epoxidation of alkenes[1] and sulfoxidation[2] represent two of the most important oxidation reactions in organic synthesis. More and more frequently, chiral epoxides become useful building blocks in natural product synthesis and in the synthesis of biologically active compounds.[3] Chiral sulfoxides are of great interest for organic chemistry and biochemistry since they serve as intermediates in the synthesis of numerous sulfur containing drugs and can also be considered as an independent class of targets suitable for pharmaceutical applications.[4,5] Furthermore, chiral sulfoxides are also used as chiral auxiliaries[6] and organocatalysts[7] (Fig. 1).

Diverse oxygenase- and peroxigenase-enzymes are applied in enantioselective oxidations of olefins[8] and sulfides.[5,9] Analogously to natural models, metal containing enzyme-mimetic oxidation catalysts can be classified into heme and non-heme metal complexes. In the last three decades, biomimetic approaches to oxidation reactions mostly concentrated on synthetic iron–heme complexes and their interactions with oxygen donors such as iodosobenzene, peracids, and hydro-peroxides.[1,2a,10]

While in particular heme containing oxidation catalysts are already well investigated,[1,2a] the application of non-heme iron and/or vanadium complexes as enantioselective oxidation catalysts is less well studied so far.[11–13]

The most prominent chiral ligands for enantioselective vanadium- and iron-catalyzed sulfoxidations, developed by Bolm and co-workers, are presented in Fig. 2.[11]

Chiral sulfoxides, often found in pharmaceutical products, continue to gain attention in the development of new drugs and their analogues.[4,13m,15] For instance, armodafinil (Nuvigil®), which was patented by the pharmaceutical company Cephalon in 2005 and approved by the *food and drug administration* in 2007 (USA), represents an effective drug in the treatment of sleep disorders associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome or shift work sleep disorders.[15,16] Since it has been found

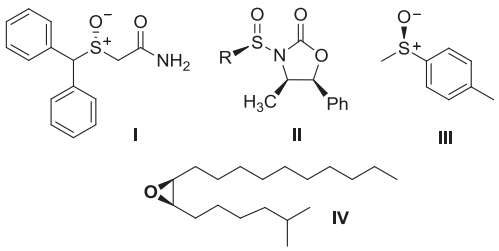

Fig. 1. Selected examples of sulfoxides applied as a drug: (*R*)-modafinil (**I**), a chiral auxiliary (**II**) and an organocatalyst (**III**). Epoxide moiety included in pheromone of gypsy moth (**IV**).

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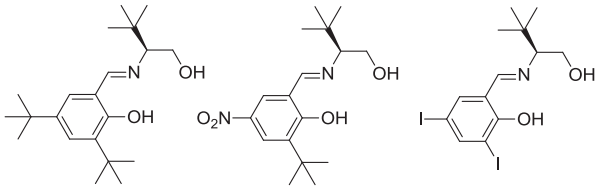


Fig. 2. Bolm's chiral ligands.

that armodafinil (consisting of the pure *R*-enantiomer of modafinil) was more active due to the slower metabolism of the *R*-enantiomer,[17] chemists endeavor to improve or to develop new synthetic routes for the synthesis of this chiral drug.

Several methods such as resolution[18] (e.g., chromatography,[18e] fractional crystallization,[18e,c] separation via diastereomers[18a,b,d]) and the oxidation of prochiral sulfides (using metal catalysts,[16,18e,19] chiral oxaziridines,[19] microbial oxidation[20] or a biocatalytic approach[21]) have been described. In 2007, Guillen and co-workers[19] applied the above-mentioned well-known catalytic systems[11] to the enantioselective synthesis of modafinil. However, only low to moderate yields and low enantioselectivities were achieved in case of the studied iron- and vanadium-catalyzed oxidation: 45%, 12% ee with V-catalyst and 10%, 15% ee with Fe-catalyst using H_2O_2 as an oxidizing agent.[19]

Therefore, there is still a large research potential for vanadium- or iron-based catalysts in enantioselective (*R*)-modafinil synthesis using simple and inexpensive oxidizing agents like H_2O_2. This prompted our present study. Our effort has been directed toward the development of improved vanadium- or iron-based catalytic systems for the synthesis of the enantiomerically-enriched chiral drug (*R*)-modafinil. The potential of the selected iron-catalyst for the epoxidation of unfunctionalized alkenes has also been demonstrated.

2. Results and discussion

2.1. Enantioselective sulfoxidation

2.1.1. Iron(III)-catalyzed oxidation of thioanisole with H_2O_2. Compared with those advancements in metal-catalyzed sulfoxidation reactions achieved with symmetrical Schiff base ligands, much less is known about the sulfoxidation chemistry using non-symmetrical Schiff base ligands. However, transition metals occur in oxygenase- and peroxigenase-enzymes bound to donor atoms of peptide chains, usually in a non-symmetrical environment. Thus, the identification of new non-symmetrical metal catalyst systems, especially *Fe-catalyzed*[11d–f,14] methods, for this important asymmetric reaction remains a challenge.

In particular, metal-catalyzed sulfoxidation using primary amine-derived non-symmetrical Schiff base ligands finds itself just in the early stage.[13h,j,l] Recently, Romanowski and co-workers reported on chiral dioxovanadium(V) primary amine Schiff base complexes for sulfoxidation reactions using cumene hydroperoxide (CHPO)[13h,j] or even hydrogen peroxide[7l] as oxidants and DMSO as solvent yielding the corresponding sulfoxides with 19–39% ee.[13h,7l]

Following our interest in the application of primary amine-based catalysts[22] and taking the aspect of green chemistry into account, we investigated primary amine-derived Schiff bases **2** and **8**–**10** as potential ligands for the *iron*-catalyzed oxidation of thioanisole (chosen for preliminary studies as a well-known model reaction) using *aqueous hydrogen peroxide* as environmentally friendly oxidant.

Our initial work started with the screening of different ligands (Fig. 3): **1** is commercially available and ligands **2**–**8** were

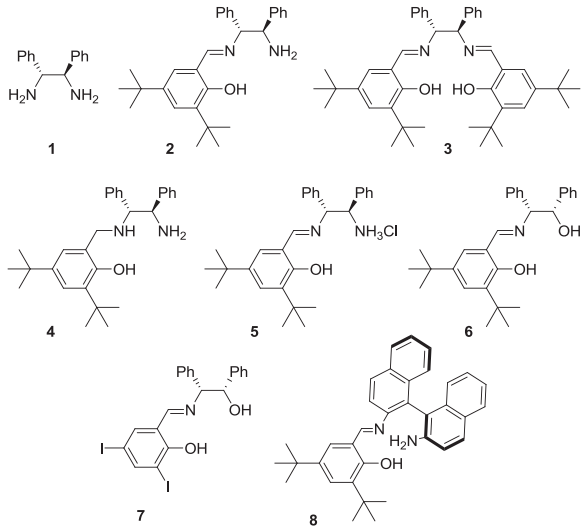
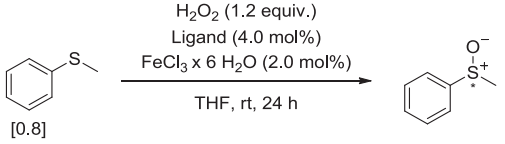


Fig. 3. Designed ligands.

synthesized according to literature known procedures. As depicted in Table 1, the catalytically active species were generated in situ, using inexpensive nontoxic iron(III) chloride hexahydrate and the corresponding ligands (**1**–**8**) in the ratio of 1:2. The oxidation reaction was carried out in THF using a low catalyst loading (4 mol% of ligand, 2 mol% of $FeCl_3 \cdot 6H_2O$) under ambient conditions. First, the investigation of the commercially available chiral diamine **1** furnished the corresponding sulfoxide in 17% yield as a nearly racemic product (3% ee (*S*), entry 1). The introduction of the sterically hindered 3,5-di-*tert*-butylsalicylaldehyde forming Schiff base ligand **2** resulted in a sound enhancement of both yield and enantioselectivity (50% yield, 34% ee, entry 2). In this case, the opposite enantiomer (*R*) was formed. Carrying out the reaction under nitrogen atmosphere resulted in no improvement of yield and enantiomeric excess. To ascertain the importance of the primary amine group, we tested the corresponding salen ligand **3**.

Table 1
Screening of ligands **1**–**8**



Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	**1**	17	3 (*S*)
2	**2**	50	34 (*R*)
3[c]	**2**	51	36 (*R*)
4	**3**	36	*rac*
5	**4**	48	6 (*R*)
6	**5**	49	21 (*R*)
7	**6**	68	6 (*R*)
8	**7**	72	7 (*R*)
9	**8**	74	*rac*
10[d]	**2**	9	*rac*
11	—	78	*rac*
12[d]	—	13	n.d.

[a] Yield of isolated product.
[b] ee was determined by HPLC (OD, hexane/*i*-PrOH (93:7), flow 1.0 mL/min).
[c] Reaction was carried out under N_2-atmosphere.
[d] Reaction was carried out without iron salt.

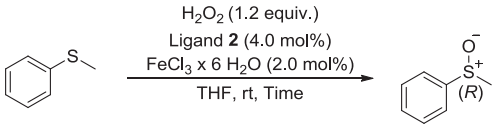
The yield decreased to 36% and a racemic sulfoxide was obtained (entry 4). The yield remained almost constant when reduced ligand **4** was used for this model reaction, but the enantiomeric excess

decreased to 6% (entry 5 vs entry 2). Next, we studied ligand **5** in which the primary amino function is protected as a hydrochloride salt. The desired product was isolated in 49% yield and with 21% ee (entry 6).

It is assumed that ligand **5** releases hydrochloric acid during the complex formation (or the oxidation process) through which the free amino group is partly recovered. Additionally, we synthesized the known Schiff base ligands **6** and **7** containing a hydroxy instead of a primary amino group and verified their efficiency in our catalytic system. In both cases the yield could be increased (68%, entry 7 and 72%, entry 8), but the enantiomeric excess decreased significantly (6% ee, entry 7 and 7% ee, entry 8). The use of ligand **8**, containing a binaphthyl moiety as a chiral building block, resulted in a good yield of the methyl phenyl sulfoxide (74%, entry 9), but no enantioselectivity was observed.

We tried to further improve the current reaction conditions by reducing the reaction time from 24 h to 5 h (Table 2). To our delight, we observed no loss of both yield and enantioselectivity (Table 2, entry 2 vs entry 1). Moreover, we changed the way of adding the hydrogen peroxide to the reaction mixture by using a syringe pump instead of the addition in one portion. The enantioselectivity increased to 43%, while the yield remained constant (Table 2, 52%, entry 3). Additional efforts to achieve better yields and enantioselectivities remained unsuccessful (Table 2, entries 4–9). A further reduction of reaction time (3 h, 1 h) resulted in a reduction of both yield and enantioselectivity (Table 2, entries 10 and 11).

Table 2
Optimization of reaction conditions with selected ligand **2**



Entry	H_2O_2 (equiv)	Concn (mol/L)	Time (h)	Yield[a] (%)	ee[b] (%)
1	1.2	0.8	24	50	34
2	1.2	0.8	5	52	31
3[c]	1.2	0.8	5	52	43
4[c,d]	1.2	0.8	5	48	44
5[c,e]	1.2	0.8	5	52	32
6[c]	1.2	1.2	5	39	49
7[c]	2.0	0.8	5	56	35
8[c,f]	1.2	0.8	5	28	24
9[c,g]	1.2	0.8	5	31	24
10[c]	1.2	0.8	3	46	39
11[c]	1.2	0.8	1	41	36

[a] Yield of isolated product.
[b] ee was determined by HPLC (OD, hexane/*i*-PrOH (93:7), flow 1.0 mL/min).
[c] H_2O_2 was added via a syringe pump.
[d] Ligand **2** contaminated with 3% of bis-imine **3**.
[e] Reaction was carried out in CH_3CN.
[f] Reaction was carried out at 0 °C.
[g] Sulfide was added by a syringe pump simultaneously.

For this reason we modified the structure of primary amine-based ligand **2** and introduced sterically more hindered salicylaldehyde derivatives, which are shown in Fig. 4 (ligands **9** and **10**).

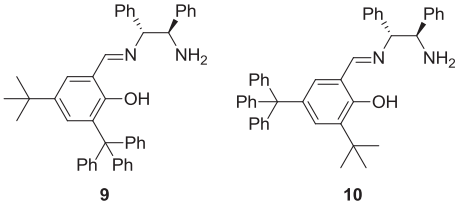
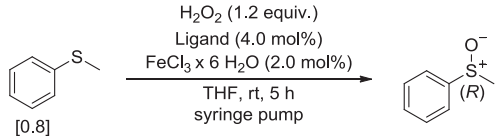


Fig. 4. New sterically hindered ligands **9** and **10**.

The application of ligand **9** for the oxidation of thioanisole under selected reaction conditions resulted in 65% yield (Table 3, entry 2), but the enantioselectivity decreased to 36% ee (Table 3, entry 2). The best result was obtained when the reaction was performed using ligand **10**, containing a trityl group in position-5 instead of position-3 of the salicylaldehyde. Both yield and enantiomeric excess were moderate (66% yield, 53% ee, Table 3, entry 3). The yield could be slightly increased to 69% when 1.7 equiv of hydrogen peroxide was added within 7 h, whereas the enantioselectivity of the product remained nearly constant (54% ee, Table 3, entry 4).

Table 3
Application of ligands **9** and **10** to the oxidation of thioanisole



Entry	Ligand	Yield[a] (%)	ee[b] (%)
1	**2**	52	43
2	**9**	65	36
3	**10**	66	53
4[c]	**10**	69	54

[a] Yield of isolated product.
[b] ee was determined by HPLC (OD, hexane/*i*-PrOH (93:7), flow 1.0 mL/min).
[c] Reaction was carried out within 7 h; after 5 h and after 6 h further addition of 10 μL H_2O_2 (overall addition of H_2O_2 was 1.7 equiv).

Additionally, we aimed to investigate whether the use of the isolated complexes in contrast to those formed in situ had any influence on the model reaction. We prepared complexes **11**–**13**, using 2 equiv of the corresponding ligands **2**, **9** or **10** and 1 equiv of iron(III) chloride hexahydrate in THF. The complex formation was carried out within 2 h under ambient conditions. No further purification was necessary due to only one characteristic peak *m*/*z*=910.48 $[M-Cl]^+$ in ESI-MS, except for the free ligand at *m*/*z*=429.28 $[M+H]^+$ (e.g., complex **11**, Fig. 5). While the actual structures of the catalysts in the reaction medium, as well as the exact role of the primary amine group are unclear yet, we postulate structures of all complexes as depicted in Scheme 1. The simulated isotopic pattern of postulated mononuclear complexes (coordination of two tridentate Schiff base ligands to iron(III)) is identical with the measured ones, obtained for all synthesized complexes (**11**–**13**). Further, we assume that the primary amine group may promote the release of a Cl^- anion from the iron center. Detailed investigations (e.g., crystallization) are currently ongoing in our laboratory.

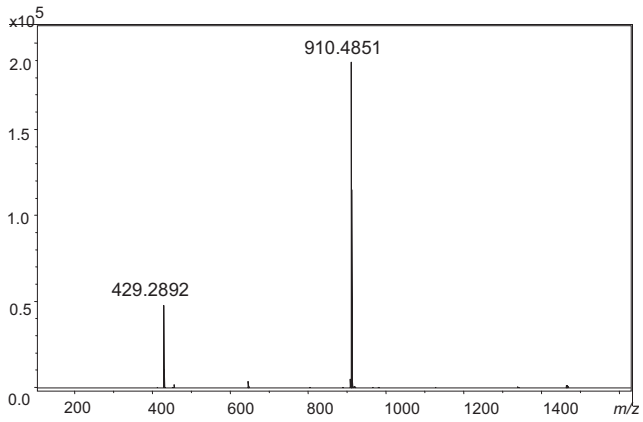
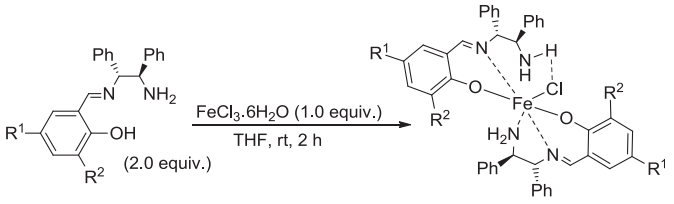


Fig. 5. Selected ESI-MS spectrum for complex **11**.

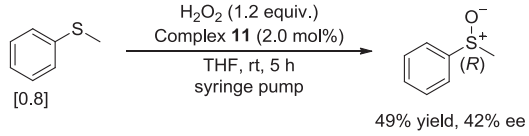


2 $R^1 = R^2 = t$Bu
9 $R^1 = t$Bu; R^2 = trityl
10 R^1 = trityl; $R^2 = t$Bu

11: ESI-MS: *m/z* = 910.48 $[M\text{-}Cl]^+$
12: ESI-MS: *m/z* = 1282.57 $[M\text{-}Cl]^+$
13: ESI-MS: *m/z* = 1282.57 $[M\text{-}Cl]^+$

Scheme 1. Syntheses of new iron(III) complexes.

We proved the activity of complex **11** for the oxidation of thioanisole and obtained comparable results to those in which the complex formation was carried out in situ (Scheme 2 vs Table 3, entry 1). The methyl phenyl sulfoxide was produced in 49% yield and 42% ee (Scheme 2).



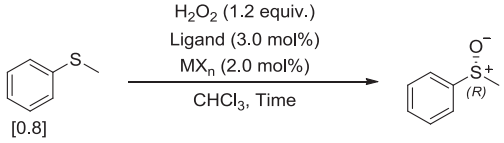
Scheme 2. Application of isolated complex **11** for the oxidation of thioanisole.

2.1.2. Vanadium-catalyzed oxidation of thioanisole with H_2O_2. Since vanadium was found in active centers of non-heme enzymes (e.g., vanadiumbromoperoxidase[9b,23]), great efforts have been devoted to the development of analogous models, which might be able to mimic their biological activity.[13l,n,24]

According to our results obtained in the iron-catalyzed oxidation of thioanisole with primary amine-based ligand **2**, we investigated $VO(acac)_2$ as potential metal source. In general, chlorinated solvents are known as well suitable solvents for the vanadium-catalyzed oxidation of sulfides to sulfoxides.[13c,d,g] Hence, we applied ligand **2** with $VO(acac)_2$ for the model reaction using similar reaction conditions as mentioned before, but $CHCl_3$ instead of THF as solvent.

After 48 h, methyl phenyl sulfoxide was isolated in high yields (79%), but unfortunately only low enantioselectivity (9% ee) could be observed (Table 4, entry 1). Due to the knowledge that Schiff base ligands derived from aminoalcohols are powerful ligands in the vanadium-catalyzed sulfoxidation,[25] we investigated Schiff base ligand **6** under identical conditions. Moderate yield and enantioselectivity were achieved for the corresponding sulfoxide (67% yield, 43% ee, Table 4, entry 2). A further reduction of the reaction time, to 24 h, resulted in a higher yield (79%) and a comparable enantioselectivity (45% ee) (Table 4, entry 3). Moreover, the effect of a sequence altering of the single component addition was examined. Thus, H_2O_2 was added first to a stirred solution of Schiff base ligand **6** and $VO(acac)_2$ in chloroform, subsequently followed by the addition of the substrate thioanisole. Interestingly, the yield of the sulfoxide remained almost constant (81%), but the enantioselectivity dropped to 34% ee (Table 4, entry 4). Additional investigations prompted us to the assumption that primary amine-based ligand **2** is more reliable for the iron-catalyzed oxidation of methyl phenyl sulfoxide conducted in tetrahydrofuran, whereas ligand **6** delivered more convenient results in the vanadium-catalyzed oxidation using chloroform as solvent (Table 1, entry 2 vs Table 4, entry 3).

Table 4
Further investigations of ligand **2** and **6** in the oxidation of thioanisole with H_2O_2



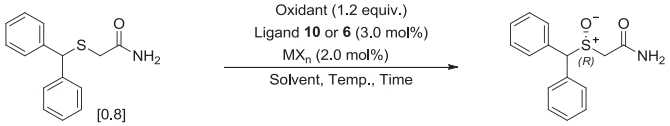
Entry	Ligand	MX_n	Time (h)	Yield[a] (%)	ee[b] (%)
1	**2**	$VO(acac)_2$	48	79	9
2	**6**	$VO(acac)_2$	48	67	43
3	**6**	$VO(acac)_2$	24	79	45
4[c]	**6**	$VO(acac)_2$	24	81	34
5	**2**	$FeCl_3 \cdot 6H_2O$	48	20	33
6	**6**	$FeCl_3 \cdot 6H_2O$	48	8	28

[a] Yield of isolated product.
[b] ee was determined by HPLC (OD, hexane/*i*-PrOH (93:7), flow 1.0 mL/min).
[c] Sequence of the addition of single components was changed: ligand and metal were stirred for 1 h, then H_2O_2 followed by thioanisole were added (vs general procedure in Experimental section).

2.1.3. Application of the catalytic systems for the synthesis of (R)-modafinil. Next, our effort has been directed toward the application of the above shown iron- and vanadium-based catalytic systems for the synthesis of enantiomerically-enriched (*R*)-modafinil.

Regarding the iron-catalyzed oxidation using primary amine-based ligand **10** as potential chiral source in the synthesis of (*R*)-modafinil, unsatisfying results were obtained (45%, *rac*, Table 5, entry 1) even though this catalytic system has proven to be quite active for the oxidation of thioanisole. We next replaced $FeCl_3 \cdot 6H_2O$ by $VO(acac)_2$ and investigated ligand **10** in chloroform as solvent. High yields (89%) could be achieved for (*R*)-modafinil, but again a low enantioselectivity (9% ee) (Table 5, entry 2). Based on these results, primary amine-based ligands seemed not to be suitable for the synthesis of (*R*)-modafinil under the current reaction conditions. Thus, we verified Schiff base ligand **6**, derived from the aminoalcohol (1*S*,2*R*)-2-amino-1,2-diphenylethanol with the metal source $VO(acac)_2$ in chloroform as solvent. Surprisingly, after 24 h (*R*)-modafinil could be isolated in high yields (92%) with an enantiomeric excess of 33% (Table 5, entry 3). By carrying out the reaction at 0 °C, the yield of (*R*)-modafinil could be increased to 99% but the enantioselectivity dropped to 22% (Table 5, entry 4). A further reduction of the reaction time to only 15 min resulted in excellent yields (>99%) without any loss of enantioselectivity (32% ee) under ambient conditions (Table 5, entry 6 vs entries 3 and 5).

Table 5
Application of selected ligands **10** and **6** to the synthesis of enantiomerically-enriched (*R*)-modafinil



Entry	Ligand	MX_n	Oxidant	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1[c]	**10**	$FeCl_3 \cdot 6H_2O$	H_2O_2	THF	rt	24	45	*rac*
2	**10**	$VO(acac)_2$	H_2O_2	$CHCl_3$	rt	24	89	9 (*R*)
3	**6**	$VO(acac)_2$	H_2O_2	$CHCl_3$	rt	24	92	33 (*R*)
4	**6**	$VO(acac)_2$	H_2O_2	$CHCl_3$	0	24	>99	22 (*R*)
5	**6**	$VO(acac)_2$	H_2O_2	$CHCl_3$	rt	3.5	93	35 (*R*)
6	**6**	$VO(acac)_2$	H_2O_2	$CHCl_3$	rt	0.25	>99	32 (*R*)
7	**6**	$VO(acac)_2$	PhIO	$CHCl_3$	rt	24	Traces	n.d.

[a] Yield of isolated product.
[b] ee was determined by HPLC (AS, hexane/*i*-PrOH (60:40), flow 0.9 mL/min).
[c] Ligand **10** of 4.0 mol % was used.

Notably, using iodosobenzene (PhIO) as an oxidizing agent, no oxidation product was observed even after 24 h reaction time. Thus, to our delight, we could establish a remarkably improved vanadium-catalyzed system to obtain enantiomerically-enriched (*R*)-modafinil in >99% yields within a very short reaction time (15 min) and at room temperature using hydrogen peroxide as simple, inexpensive, and environmentally benign oxidant.

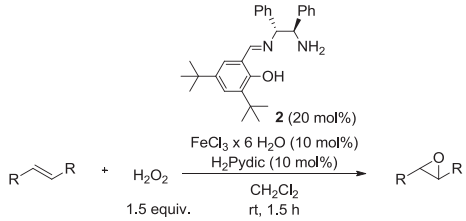
2.2. Enantioselective epoxidation

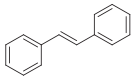
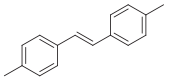
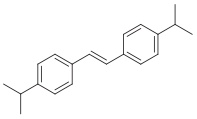
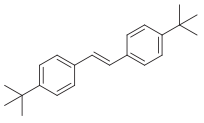
Despite the potential of chiral epoxides as highly useful intermediates and precursors for the synthesis of different biologically active compounds and natural products,[3,26] effective synthetic methods (among them organocatalytic and transition metal procedures), in particular, *Fe-catalyzed methods*, for the preparation of the chiral epoxides, are limited.[12] Notably, iron is ubiquitous and also one of the most versatile transition metals known. Thus, our particular focus lies on the development of environmentally friendly non-heme iron-catalyzed epoxidation of alkenes using H_2O_2 as oxidation agent.

We, therefore, investigated the potential of the selected Fe-catalytic system—primary amine-derived Schiff base ligand **2** (as used for the sulfide oxidation) in combination with iron(III) chloride hexahydrate—for the epoxidation of alkenes. Under the conditions shown in Table 6, *trans*-stilbene oxide was yielded in 84% with an enantiomeric excess of 19% (Table 6, entry 1). Further application of this catalytic system to the *trans*-stilbene derivative with methyl groups in *para*-position, a yield of 70% and an enantioselectivity of 9% (Table 6, entry 2) were obtained. Next we replaced the groups in *para*-position with the more bulky *iso*-propyl (Table 6, entry 3) and *tert*-butyl (Table 6, entry 4) residues, which resulted in decreased yields of 61% and 50% and enantioselectivities of 5% and 24%.

In particular, the epoxidation of terminal alkenes is still a challenging subject in the field of oxidation chemistry.[12b,c,d] Thus we also carried out the epoxidation of styrene furnishing the corresponding styrene oxide in 44% conversion and 21% ee (Table 6, entry 5). Changing the substrate to *trans*-β-methyl styrene resulted in a conversion of 47% with a slightly increased enantiomeric excess of 30% (Table 6, entry 6).

Table 6
Application of the primary amine-based ligand **2** to the enantioselective epoxidation of different alkenes



Entry	Substrate	Yield (%)	ee (%)
1[d,g]		84[a]	19[b]
2[e,g]		70[a]	9[b]
3[f,g]		61[a]	5[b]
4[e,g]		50[a]	24[b]
5[f,g]		44[c]	21[c]
6[f,g]		47[c]	30[c]

[a] Yield of isolated product.
[b] ee was determined by HPLC (IA-column).
[c] Conversion and ee were determined by GC analysis (Hydrodex β-TBDAc).
[d] Impurities of **2** with bis-imine **3** were: 3%.
[e] Impurities of **2** with bis-imine **3** were: 6%.
[f] Impurities of **2** with bis-imine **3** were: 9%.
[g] Addition of H_2O_2 in one portion.

3. Conclusion

Although the iron-catalyzed oxidation of thioanisole is well documented,[11d–f,14] we demonstrate here the first examples of primary amine-derived non-symmetrical Fe-catalysts for the enantioselective sulfoxidation under mild conditions and with H_2O_2 as oxidant. Moderate yields (up to 69%) and reasonable enantiomeric excesses (up to 54% ee) could be achieved when the reaction was carried out in THF using a syringe pump within 5 or 7 h. It turned out that the primary amino function, as well as the unsymmetric environment of the ligand played an important role in order to observe enantioselectivity in this new catalytic system.

We also showed the application of the selected primary amine-based ligand **2** in the iron-catalyzed epoxidation of different alkenes. In case of *trans*-stilbene and derivatives, yields of up to 84% and ee values of up to 30% were obtained.

Our further studies on enantioselective oxidation of thioanisole and of a modafinil precursor using $VO(acac)_2$/ligand **6** as a catalytic system provided us with an interesting observation. Intriguingly, while well-known vanadium–Schiff base complexes[11a–c,13c,g] are successful catalysts for the thioanisole oxidation, their application as chiral catalysts for (*R*)-modafinil synthesis provides disappointingly low yields and enantioselectivities (e.g., 45%, 12% ee, after 16 h reaction time).[19] In stark contrast, we found that the vanadium-based catalytic system ($VO(acac)_2$/ligand **6**), which performs moderately with thioanisole (79–81% yields and 34–45% ee after 24 h), is able to provide (*R*)-modafinil in excellent yield of >99% and acceptable enantiomeric excess of 32% within a very short reaction time (15 min).

The presented results are laying the basis for further successful design of new highly active and enantioselective non-heme vanadium catalysts for (*R*)-modafinil synthesis and non-heme iron catalysts for enantioselective epoxidation of olefins using H_2O_2 as environmentally friendly oxidation agent.

4. Experimental

4.1. General information

Chemicals were used as received from common commercial sources. All solvents were distilled before use and all reactions were carried out under nitrogen atmosphere if not mentioned otherwise. NMR spectra were recorded on Jeol (400 MHz) or Bruker Avance (300 MHz or 400 MHz). NMR spectra were referenced to the residual solvent signal (^{1}H: $CDCl_3$, 7.24 ppm; ^{13}C: $CDCl_3$, 77.0 ppm)

and recorded at ambient probe temperature. IR spectra were recorded as thin films on a Varian IR-660 spectrometer. Mass spectra (MALDI-TOF) were recorded on a Shimadzu Biotech Axima Confidence spectrometer. High mass accuracy ESI spectra were recorded on an ultra-high-resolution ESI-Time-Of-Flight MS, a Bruker Daltoniks (Bremen, Germany) maXis. Spectra were obtained in positive-ion mode, with the capillary held at 4000 V. The drying gas flow rate was 7.0 L/min at 240 °C. The nebulizer gas was at a pressure of 30.5 psi/2 bar. The *m*/*z* range was detected from 100 to 2000. A calibration tune mix (Agilent Technologies) was sprayed immediately prior to analysis to ensure a high mass accuracy to assist in the identification of peaks. The flow rate of the solutions was 300 μL/h. HPLC spectra were recorded at 25 °C with an Agilent Technologies 1200 Series HPLC. TLC chromatography was performed on precoated aluminum silica gel SIL G/UV254 plates (Marcherey, Nagel & Co.). Flash column chromatography was performed using silica gel 60M (Macherey-Nagel). Syringe pump: KD Scientific, Model 100 Series. Gas chromatography (GC) was carried out on a Thermo Instrument Trace GC Ultra (Hydrodex β-TBDAc, 25 m×0.25 mm ID (Macherey-Nagel)).

4.2. Synthesis of the ligands

*4.2.1. 2-((E)-(((1R,2R)-2-Amino-1,2-diphenylethyl)imino)methyl)-4,6-di-tert-butylphenol (**2**).*[27] To a solution of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (500.0 mg, 2.35 mmol, 1.01 equiv) in anhydrous DCM (8 mL) with molecular sieve 3 Å (5.3 g), a solution of 3,5-di-*tert*-butylsalicylaldehyde (546.5 mg, 2.33 mmol, 1.0 equiv) in DCM (10 mL) was added dropwise over a period of 30 min. After the reaction mixture was stirred for 3 h at room temperature, the solution was concentrated (at 30 °C) and quickly purified by flash column chromatography (SiO_2, PE/EtOAc 7:3) to afford the desired product in 37% yield (367.3 mg) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.27 (s, 9H), 1.46 (s, 9H), 1.64 (br s, 2H), 4.29 (d, *J*=7.8 Hz, 1H), 4.40 (d, *J*=7.8 Hz, 1H), 7.06 (d, *J*=2.4 Hz, 1H), 7.11–7.20 (m, 10H), 7.38 (d, *J*=2.4 Hz, 1H), 8.45 (s, 1H), 13.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.4, 31.4, 34.0, 34.9, 62.1, 82.2, 117.8, 126.4, 127.2, 127.3, 127.4, 127.7, 127.8, 128.1, 128.2, 136.6, 140.3, 140.6, 141.8, 158.0, 167.2.

*4.2.2. 6,6′-((1E,1′E)-(((1R,2R)-1,2-Diphenylethane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-di-tert-butylphenol) (**3**).*[27] The desired product was isolated in a yield of 34% as a byproduct of compound **2**. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.21 (s, 9H), 1.41 (s, 9H), 4.72 (s, 2H), 6.98 (d, *J*=2.4 Hz, 2H), 7.16–7.19 (m, 10H), 7.30 (d, *J*=2.4 Hz, 2H), 8.40 (s, 2H), 13.6 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.4, 31.4, 34.0, 34.9, 80.0, 117.8, 126.3, 127.1, 127.3, 127.9, 128.2, 136.3, 139.7, 139.9, 157.9, 167.2. Maldi-TOF: *m*/*z*=645 $[M+H]^+$.

*4.2.3. 2-((((1R,2R)-2-Amino-1,2-diphenylethyl)amino)methyl)-4,6-di-tert-butylphenol (**4**).*[28] Compound **2** (200.0 mg, 0.46 mmol, 1.0 equiv) was dissolved in anhydrous methanol (5 mL) followed by the addition of $NaBH_4$ (70.8 mg, 1.87 mmol, 4.0 equiv) in portions. The reaction mixture was stirred overnight at room temperature. Water (10 mL) was added and the product was extracted with dichloromethane (3×2 mL). The combined organic phases were dried over $MgSO_4$. After evaporation the product was obtained in 76% yield (154.0 mg) as a white solid without further purifications. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (s, 9H), 1.39 (s, 9H), 3.53–3.62 (m, 1H), 3.74–3.80 (m, 2H), 4.04–4.14 (m, 1H), 6.61–6.68 (m, 1H), 6.91–7.28 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.6, 31.6, 34.0, 34.8, 51.3, 61.0, 68.9, 122.5, 122.9, 123.4, 127.0, 127.3, 127.5, 127.9, 128.3, 128.4, 135.9, 139.5, 140.5, 142.9, 154.5.

*4.2.4. 2-((E)-(((1R,2R)-2-Amino-1,2-diphenylethyl)imino)methyl)-4,6-di-tert-butylphenol·hydrochloride (**5**).*[29] (1*R*,2*R*)-1,2-Di-phenylethylenediaminemonohydrochloride (350.0 mg, 1.40 mmol, 1.0 equiv) was dissolved in anhydrous methanol (9 mL) and anhydrous ethanol (9 mL). After the addition of 3,5-di-*tert*-butylsalicylaldehyde (329.7 mg, 1.40 mmol, 1.0 equiv), the reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated to approximately 1 mL and the solid was filtered and washed with ethanol. The filtrate was concentrated and the resulting precipitate was washed with diethylether to remove unreacted aldehyde. The product was obtained in 87% yield as a white solid (568.6 mg). ^{1}H NMR (300 MHz, MeOH-d_4): δ=1.30 (s, 9H), 1.46 (s, 9H), 4.87 (d, overlapping with water signal, 1H), 4.92 (d, *J*=9.9 Hz, 1H), 7.16–7.27 (m, 6H), 7.32 (s, 5H), 7.45 (d, *J*=2.4 Hz, 1H), 8.71 (s, 1H). Maldi-TOF: *m*/*z*=429 $[M-Cl]^+$.

*4.2.5. 2,4-Di-tert-butyl-6-((E)-(((1R,2S)-2-hydroxy-1,2-diphenylethyl)imino)methyl)phenol (**6**).*[30] To a solution of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (400.0 mg, 1.87 mmol, 1.0 equiv) in anhydrous methanol (10 mL) and Na_2SO_4 (1.0 g, 4.0 equiv) a solution of 3,5-di-*tert*-butylsalicylaldehyde (438.2 mg, 1.87 mmol, 1.0 equiv) in methanol (2 mL) was added dropwise. After the reaction mixture was stirred for 3 d at room temperature, the solution was concentrated and purified by flash column chromatography (SiO_2, PE/EtOAc 3:1) to afford the desired product in 87% yield (699.0 mg) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (s, 9H), 1.47 (s, 9H), 2.08 (d, *J*=3.0 Hz, 1H), 4.54 (d, *J*=6.8 Hz, 1H), 5.10 (dd, *J*=3.0 Hz, *J*=6.8 Hz, 1H), 6.96 (d, *J*=2.4 Hz, 1H), 7.26–7.40 (m, 12H), 8.17 (s, 1H), 13.43 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.3, 31.3, 33.9, 34.9, 78.3, 80.0, 117.8, 126.3, 127.2, 127.9, 127.9, 128.1, 128.1, 128.7, 136.6, 139.6, 140.1, 140.2, 157.9, 167.1. Maldi-TOF: *m*/*z*=431 $[M+H]^+$.

*4.2.6. 2-((E)-(((1R,2S)-2-Hydroxy-1,2-diphenylethyl)imino)methyl)-4,6-diiodophenol (**7**).*[31] To a solution of (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (200.0 mg, 0.94 mmol, 1.0 equiv) in anhydrous methanol (3 mL) and $MgSO_4$ (564.4 mg, 5.0 equiv) a solution of 3,5-diiodosalicylaldehyde (350.6 mg, 0.94 mmol, 1.0 equiv) in methanol (14 mL) was added dropwise. After the reaction mixture was stirred for 3 d at room temperature, $MgSO_4$ was filtered off, and the solution was concentrated and purified by flash column chromatography (SiO_2, PE/EtOAc 3:1) to afford the desired product in 56% yield (300.0 mg) as an orange foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.04 (br s, 1H), 4.48 (d, *J*=7.3 Hz, 1H), 5.00 (d, *J*=7.3 Hz, 1H), 7.19–7.39 (m, 11H), 7.77 (s, 1H), 7.98 (d, *J*=2.0 Hz, 1H), 14.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 78.0, 79.3, 79.7, 87.3, 119.8, 127.0, 127.9, 128.3, 128.4, 128.9, 138.4, 139.7, 139.9, 148.7, 160.4, 163.6. FAB: *m*/*z*=570 $[M+H]^+$.

*4.2.7. (E)-2-(((2′-Amino-[1,1′-binaphthalen]-2-yl)imino)methyl)-4,6-di-tert-butylphenol (**8**).*[31] To a solution of *R*-(+)-2,2`-diamino-1,1-binaphthalene (200.0 mg, 0.70 mmol, 1.0 equiv) in anhydrous methanol (4 mL)/toluene (4 mL) and $MgSO_4$ (423.3 mg, 5.0 equiv) a solution of 3,5-di-*tert*-butylsalicylaldehyde (164.8 mg, 0.70 mmol, 1.0 equiv) in DCM (4 mL) was added dropwise. After the reaction mixture was stirred for 3 d at room temperature, $MgSO_4$ was filtered off, and the solution was concentrated and purified by flash column chromatography (SiO_2, PE/EtOAc/Et_3N 8:2:0.1) to afford the desired product in 26% yield (91.6 mg) as an orange foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.23 (s, 9H), 1.24 (s, 9H), 3.60 (s, 2H), 6.88–6.91 (m, 1H), 7.02 (d, *J*=2.4 Hz, 1H), 7.08–7.19 (m, 3H), 7.27 (d, *J*=2.4 Hz, 1H), 7.30–7.35 (m, 1H), 7.43–7.49 (m, 2H), 7.63 (d, *J*=8.8 Hz, 1H), 7.73–7.78 (m, 2H), 7.94 (d, *J*=8.1 Hz, 1H), 8.03 (d, *J*=8.6 Hz, 1H), 8.64 (s, 1H), 12.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.1, 31.4, 34.0, 34.9, 114.2, 117.8, 118.1, 118.1, 122.0, 123.9, 125.9, 126.3, 126.4, 126.4, 127.1, 127.6, 127.9, 128.1, 128.3, 129.2, 129.7, 132.6, 133.3, 133.9, 136.7, 139.8, 141.7, 144.3, 158.3, 162.7. Maldi-TOF: *m*/*z*=502 $[M+H]^+$.

*4.2.8. 2-((E)-(((1R,2R)-2-Amino-1,2-diphenylethyl)imino)methyl)-4-(tert-butyl)-6-tritylphenol (**9**).* To a solution of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (150.5 mg, 0.71 mmol, 1.02 equiv) in

anhydrous DCM (8 mL) and molecular sieve 3 Å (1.7 g) a solution of 5-(*tert*-butyl)-2-hydroxy-3-tritylbenzaldehyde[32] (293.9 mg, 0.69 mmol, 1.0 equiv) in DCM (7 mL) was added dropwise over a period of 10 min. After the reaction mixture was stirred for 3 h at room temperature, the solution was concentrated at 30 °C and quickly purified by flash column chromatography (SiO_2, PE/EtOAc 7:3, then 1:1) to afford the desired product in 42% yield (185.0 mg) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.11 (s, 9H), 1.85 (br s, 2H), 4.21 (s, 2H), 6.94–7.21 (m, 26H), 7.29 (d, J=2.4 Hz, 1H), 8.34 (s, 1H), 13.10 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=31.2, 34.0, 62.0, 63.4, 82.0, 118.1, 125.5, 127.0, 127.1, 127.2, 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 131.0, 132.0, 134.0, 140.0, 140.3, 141.6, 145.5, 157.5, 166.7. ESI-MS: calcd for [$C_{44}H_{42}N_2O$+H^+] m/z=615.3369. Found: m/z=615.3381. Anal. Calcd for $C_{44}H_{42}N_2O$: C, 85.96; H, 6.89; N, 4.56. Found: C, 85.22; H, 6.99; N, 4.39.

*4.2.9. 2-((E)-(((1R,2R)-2-Amino-1,2-diphenylethyl)imino)methyl)-6-(tert-butyl)-4-tritylphenol (**10**).* To a solution of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (200.0 mg, 0.94 mmol, 1.02 equiv) in anhydrous DCM (10 mL) and molecular sieve 3 Å (2.2 g) a solution of 3-(*tert*-butyl)-2-hydroxy-5-trityl-benzaldehyde[32] (396.4 mg, 0.94 mmol, 1.0 equiv) in DCM (10 mL) was added dropwise over a period of 30 min. After the reaction mixture was stirred for 3 h at room temperature, the solution was concentrated at 30 °C and quickly purified by flash column chromatography (SiO_2, PE/EtOAc 7:3) to afford the desired product in 37% yield (214.0 mg) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26 (s, 9H), 1.95 (br s, 2H), 4.19 (d, J=8.2 Hz, 1H), 4.37 (d, J=8.2 Hz, 1H), 6.89 (d, J=2.4 Hz, 1H), 7.04–7.23 (m, 26H), 8.27 (s, 1H), 13.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.3, 34.9, 62.1, 64.3, 117.3, 125.9, 127.3, 127.4, 127.6, 128.0, 128.1, 131.0, 131.9, 133.8, 136.0, 136.1, 146.8, 158.4. ESI-MS: calcd for [$C_{44}H_{42}N_2O$+H^+] m/z=615.3369. Found: m/z=615.3368. Anal. Calcd for $C_{44}H_{42}N_2O$: C, 85.96; H, 6.89; N, 4.56. Found: C, 86.40; H, 7.14; N, 4.41.

4.3. Synthesis of new iron(III) complexes 11–13

4.3.1. General procedure. $FeCl_3 \cdot 6H_2O$ (1.0 equiv, 0.30 mmol) was added to a solution of Schiff base ligands **2**, **9** or **10** (2.0 equiv, 0.60 mmol) in THF (14 mL). The reaction mixture was stirred for 2 h at room temperature under air after which the solvent was removed completely furnishing the corresponding complexes **11**, **12** or **13**.

*4.3.1.1. Complex **11**.* ESI-MS: calcd for [$C_{58}H_{70}FeN_4O_2$−Cl]$^+$ m/z=910.4844. Found: m/z=910.4851; IR (thin film): 3061, 3031, 2950, 2902, 2864, 2340, 2359, 1759, 1725, 1600, 1250, 1170, 772, 697 cm^{-1}.

*4.3.1.2. Complex **12**.* ESI-MS: calcd for [$C_{88}H_{82}FeN_4O_2$−Cl]$^+$ m/z=1282.5785. Found: m/z=1282.5789; IR (thin film): 3054, 3027, 2957, 2864, 2359, 2340, 1768, 1719, 1599, 1442, 1257, 1163, 1030, 747, 697 cm^{-1}.

*4.3.1.3. Complex **13**.* ESI-MS: calcd for [$C_{88}H_{82}FeN_4O_2$−Cl]$^+$ m/z=1282.5785. Found: m/z=1282.576; IR (thin film): 3055, 3028, 2953, 2866, 2359, 2339, 1768, 1721, 1598, 1441, 1163, 1032, 750, 698 cm^{-1}.

4.4. Iron-catalyzed oxidation of thioanisole

4.4.1. General procedure—addition of H_2O_2 in one portion. $FeCl_3 \cdot 6H_2O$ (2 mol %) and one corresponding ligand **1**–**10** (4 mol %) were dissolved in THF (0.5 mL). The solution, which turned immediately dark violet, was stirred for 30 min. Thioanisole (47.6 μL, 0.40 mmol) was added, followed by the addition of aqueous H_2O_2 (30%, 1.2 equiv). The reaction mixture was stirred at room temperature for 24 h. The product was directly purified by column chromatography on silica gel (EtOAc/PE 4:1). The isolated methyl phenyl sulfoxide was identified through comparison of ^{1}H NMR spectra with literature data (see Refs. 11e and 14a). The enantiomeric excess of the product was determined by chiral HPLC analysis (Macherey-Nagel OD, flow 1.0 mL/min, Hex/*i*-PrOH 93:7, 25 °C, 30–32 bar).

4.4.2. General procedure—slow addition of H_2O_2 via syringe pump. $FeCl_3 \cdot 6H_2O$ (2 mol %) and corresponding ligands **2, 9, 10** (4 mol %) were dissolved in THF (500 μL). The solution turned immediately dark violet and was stirred for 30 min. Thioanisole (50.0 mg, 47.6 μL, 0.40 mmol) was added, followed by the dropwise addition of aqueous H_2O_2 (30%, 1.2 equiv) via syringe pump over a period of 5 h. The product was directly purified by column chromatography on silica gel (EtOAc/PE 4:1).

4.5. Vanadium-catalyzed oxidation of thioanisole

4.5.1. General procedure. $VO(acac)_2$ (2 mol %) and ligand **6** (3 mol %) were dissolved in $CHCl_3$ (500 μL). The solution turned slightly green-brown after stirring for 60 min. Thioanisole (50.0 mg, 47.6 μL, 0.40 mmol) was added, followed by the addition of aqueous H_2O_2 (30%, 1.2 equiv) in one portion. The reaction mixture was stirred at room temperature for 24 h. The product was directly purified by column chromatography on silica gel (EtOAc/PE 4:1).

4.6. General procedure for the synthesis of (*R*)-modafinil—vanadium catalysis

4.6.1. General procedure. $VO(acac)_2$ (2 mol %) and ligand **6** or **10** (3 mol %) were dissolved in $CHCl_3$ (145 μL). The solution turned slightly green-brown after stirring for 60 min. 2-(Benzhydrylthio) acetamide (30 mg, 0.12 mmol) was added, followed by the addition of aqueous H_2O_2 (30%, 1.2 equiv) in one portion. The reaction mixture was stirred at room temperature for a certain time (see Table 5, entries 2–7). The product was directly purified by column chromatography on silica gel (EtOAc). The isolated enantiomerically-enriched (*R*)-modafinil was identified through comparison of ^{1}H NMR spectra with literature data (see Ref. 19). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS, flow 0.9 mL/min, Hex/*i*-PrOH 60:40, 25 °C, 31 bar).

4.7. Epoxidation of alkenes

4.7.1. General procedure for the oxidation of trans-stilbene and derivatives. $FeCl_3 \cdot 6H_2O$ (0.017 mmol), H_2Pydic (0.017 mmol), and ligand **2** (0.033 mmol) were dissolved in dichloromethane (1.6 mL). The mixture was stirred for 1 h at room temperature after which the addition of the substrate (0.167 mmol) and H_2O_2 (30%, 0.250 mmol) followed. The reaction mixture was stirred for additional 1.5 h at room temperature. The reaction was quenched with Na_2SO_3. The product was directly purified by column chromatography on silica gel. The product was obtained as a colorless solid. The enantiomeric excess was determined by chiral HPLC analysis.

4.7.1.1. trans-Stilbene oxide. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.42–7.32 (m, 10H), 3.87 (s, 2H). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak IB, flow 1.0 mL/min, Hex/*i*-PrOH 92:8, 25 °C, $t_{R(R)}$=4.80 min, $t_{R(S)}$=6.52 min).

4.7.1.2. 2,3-Di-p-tolyloxirane. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.22–7.16 (m, 8H), 3.81 (s, 2H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.1, 134.2, 129.2, 125.4, 62.8, 21.2; MS (MALDI) m/z:

224 (5%, M^+), 210 (10), 195 (55). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak IA, flow 1.0 mL/min, Hex/*i*-PrOH 98:2, 25 °C, t_{R1}=6.58 min, t_{R2}=10.92 min).

4.7.1.3. 2,3-Bis(4-iso-propylphenyl)oxirane. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.26–7.21 (m, 8H), 3.82 (s, 2H), 2.95–2.85 (m, 2H), 1.24 (d, J=6.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.1, 134.6, 126.6, 125.5, 62.7, 33.9, 24.0. The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak IA, flow 1.0 mL/min, Hex/*i*-PrOH 98:2, 25 °C, t_{R1}=6.47 min, t_{R2}=9.94 min).

4.7.1.4. 2,3-Bis(4-(tert-butyl)phenyl)oxirane. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40 (d, J=8.3 Hz, 4H), 7.27 (d, J=8.3 Hz, 4H), 3.85 (s, 2H), 1.32 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.3, 134.3, 125.5, 125.2, 62.7, 34.6, 31.3; MS (EI) m/z: 308 (5%, M^+), 293 (10), 279 (90). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak IA, flow 1.0 mL/min, Hex/*i*-PrOH 98:2, 25 °C, t_{R1}=5.78 min, t_{R2}=6.30 min).

4.7.2. General procedure for the oxidation of styrol-derivatives. $FeCl_3 \cdot 6H_2O$ (0.017 mmol), H_2Pydic (0.017 mmol), and ligand **2** (0.033 mmol) were dissolved in dichloromethane (1.6 mL). The mixture was stirred for 1 h at room temperature after which the addition of styrol or the derivative (0.166 mmol) and H_2O_2 (30%, 0.250 mmol) followed. The reaction mixture was stirred for additional 1.5 h at room temperature. The conversion of the products was determined by GC analysis with the internal standard undecan (24.0 μL, 0.118 mmol). A sample of 100 μL was taken out of the reaction mixture, filtered (SiO_2-plug, 1 cm) and washed with diethylether (2.50 mL). The enantiomeric excess was determined by GC analysis.

4.7.2.1. 2-Methyl-3-phenyloxirane. The enantiomeric excess of the product was determined by chiral GC analysis (Hydrodex β-TBDAC-column, 25 m, ID 0.25 mm, 120 °C, carrier gas: N_2, flow: 2.0 mL/min, FID: 200 °C, split: 60 mL/min; t_{R1}=7.26 min, t_{R2}=7.65 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7.24 (m, 5H), 3.56 (d, J=1.9 Hz, 1H), 3.05–3.00 (m, 1H), 1.44 (d, J=5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.7, 128.4, 128.0, 125.5, 59.5, 59.0, 17.9; MS (MALDI) *m*/*z*: 133 (80%, $[M-1]^+$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.052.

References and notes

1. (a) *Methods of Organic Chemistry (Houben Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart/New York, NY, 1995; vol. E21e; (b) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, NY, 2000, Chapter 6B.
2. (a) Kagan, H. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, NY, 2000, Chapter 6C; (b) Kagan, H. B. Asymmetric Synthesis of Chiral Sulfoxides In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008, Chapter 1; (c) For recent review on organocatalytic sulfoxidation reactions, see: Stingl, K. A.; Tsogoeva, S. B. *Tetrahedron: Asymmetry* **2010**, *21*, 1055–1074.
3. Lindberg, P.; Brandstrom, A.; Wallmark, B.; Mattson, H.; Rikner, L.; Hoffman, K.-J. *Med. Res. Rev.* **1990**, *10*, 1–54.
4. Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19–31.
5. Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3706.
6. (a) Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977–5985; (b) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760.
7. Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610–6611.
8. For enzymatic enantioselective epoxidation, see: (a) de Vries, E. J.; Janssen, D. B. *Curr. Opin. Biotechnol.* **2003**, *14*, 414–420; (b) Archelas, A.; Furstoss, R. *Top. Curr. Chem.* **1999**, *200*, 160–191; (c) de Bont, J. A. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1331–1340.
9. For enzymatic enantioselective sulfoxidation, see: (a) Mata, E. G. *Phosphorus Sulfur Relat. Elem.* **1996**, *117*, 231–286; (b) Andersson, M.; Willetts, A.; Allenmark, S. *J. Org. Chem.* **1997**, *62*, 8455–8458; (c) Boyd, D. R.; Sharma, N. D.; Haughey, S. A.; Kennedy, M. A.; McMurray, B. T.; Sheldrake, G. N.; Allen, C. C. R.; Dalton, H.; Sproule, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1929–1933.
10. (a) Collman, J. P.; Brauman, J. I.; Meunier, B.; Raybuck, S. A.; Kodadek, T. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3245–3248; (b) Que, L.; Ho, R. Y. N. *Chem. Rev.* **1996**, *96*, 2607–2624; (c) McLain, J. L.; Lee, J. J.; Groves, T. In *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Meunier, B., Ed.; Imperial College Press: London, 2000; pp 91–169.
11. (a) Bolm, C.; Bienewald, F. *Angew. Chem.* **1995**, *107*, 2883–2885; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640–2642; (b) Bolm, C.; Schlingloff, G.; Bienewald, F. *J. Mol. Catal., A* **1997**, *117*, 347–350; (c) Bolm, C.; Bienewald, F. *Synlett* **1998**, 1327–1328; (d) Legros, J.; Bolm, C. *Angew. Chem.* **2003**, *115*, 5645–5647; *Angew. Chem., Int. Ed.* **2003**, *42*, 5487–5489; (e) Legros, J.; Bolm, C. *Angew. Chem.* **2004**, *116*, 4321–4324; *Angew. Chem., Int. Ed.* **2004**, *43*, 4225–4228; (f) Legros, J.; Bolm, C. *Chem.—Eur. J.* **2005**, *11*, 1086–1092.
12. For examples of iron-catalyzed enantioselective epoxidation, see: (a) Francis, M. B.; Jacobsen, E. N. *Angew. Chem.* **1999**, *111*, 987–991; (b) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; und Beller, M. *Angew. Chem.* **2007**, *119*, 7431–7435; (c) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; und Beller, M. *Chem.—Eur. J.* **2008**, *14*, 7687–7698; (d) Yeung, H.-L.; Sham, K.-C.; Tsang, C.-S.; Lau, T. C.; Kwong, H. L. *Chem. Commun.* **2008**, 3801–3803.
13. Selected examples for metal-catalyzed enantioselective sulfoxidation: (a) Green, S. D.; Monti, C.; Jackson, R. F. W.; Anson, M. S.; Mcdonald, S. J. F. *Chem. Commun.* **2001**, 2594–2595; (b) Ohta, C.; Shimizu, H.; Kondo, A.; Katsuki, T. *Synlett* **2002**, 161–163; (c) Pelotier, B.; Anson, M. S.; Campbell, I. B.; McDonald, S. J. F.; Priem, G.; Jackson, R. F. W. *Synlett* **2002**, 1055–1060; (d) Blum, S. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 150–155; (e) Zeng, Q.; Wang, H.; Wang, T.; Cai, Y.; Weng, W.; Zhao, Y. *Adv. Synth. Catal.* **2005**, *347*, 1933–1936; (f) Jeong, Y.-C.; Huang, Y. D.; Choi, S.; Ahn, K.-H. *Tetrahedron: Asymmetry* **2005**, *16*, 3497–3501; (g) Drago, C.; Caggiano, L.; Jackson, R. F. W. *Angew. Chem.* **2005**, *117*, 7387–7389; (h) Kwiatkowski, E.; Romanowski, G.; Nowicki, W.; Kwiatkowski, M.; Suwinska, K. *Polyhedron* **2007**, *26*, 2559–2568; (i) Hsieh, S.-H.; Kuo, Y.-P.; Gau, H.-M. *Dalton Trans.* **2007**, 97–106; (j) Romanowski, G.; Kwiatkowski, E.; Nowicki, W.; Kwiatkowski, M.; Lis, T. *Polyhedron* **2008**, *27*, 1601–1609; (k) Koneva, E. A.; Volcho, K. P.; Korchagina, D. V.; Komarova, N. I.; Kochnev, A. I.; Salakhutdinov, N. F.; Tolstikov, A. G. *Russ. Chem. Bull., Int. Ed.* **2008**, *57*, 108–117; (l) Romanowski, G.; Wera, M. *Polyhedron* **2010**, *29*, 2747–2754; (m) Wojaczynska, E.; Wojaczynski, J. *Chem. Rev.* **2010**, *110*, 4303–4356; (n) O'Mahony, G. E.; Kelly, P.; Lawrence, S. E.; Maguire, A. R. *Arkivoc* **2011**, *i*, 1–110; (o) Wu, Y.; Mao, F.; Meng, F.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 1707–1712.
14. For selected examples of iron-catalyzed sulfide oxidation with H_2O_2 as terminal oxidant, see: (a) Duboc-Toia, C.; Ménage, S.; Ho, R. Y. N.; Que, L., Jr.; Lambeaux, C.; Fontecave, M. *Inorg. Chem.* **1999**, *38*, 1261–1268; (b) Mekmouche, Y.; Hummel, H.; Ho, R. Y. N.; Que, L., Jr.; Schünemann, V.; Thomas, F.; Trautwein, A. X.; Lebrun, C.; Gorgy, K.; Leprêtre, J.-C.; Collomb, M.-N.; Deronzier, A.; Fontecave, M.; Ménage, S. *Chem.—Eur. J.* **2002**, *8*, 1196–1204; (c) Gosiewska, S.; Lutz, M.; Spek, A. L.; Klein Gebbink, R. J. M. *Inorg. Chim. Acta* **2007**, *360*, 405–417; (d) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 8940–8941; (e) Egami, H.; Katsuki, T. *Synlett* **2008**, 1543–1546; (f) Jayaseeli, A. M. I.; Rajagopal, S. *J. Mol. Catal., A: Chem.* **2009**, *309*, 103–110.
15. Liu, KK.-C.; Sakya, S. M.; O'Donnell, C. J.; Flick, A. C.; Li, J. *Bioorg. Med. Chem.* **2011**, *19*, 1136–1154.
16. Rebiere, F.; Duret, G.; Prat, L. W.O. Patent 028428, 2005; *Chem. Abstr.* 2005.
17. Wong, Y. N.; King, S. P.; Simcoe, D.; Gorman, S.; Laughton, W.; McCormick, G. C.; Grebow, P. *J. Clin. Pharmacol.* **1999**, *39*, 281–288.
18. (a) Lafon, L. U.S. Patent 4,927,855, 1990; *Chem. Abstr.* **1990**, *112*, 35457; (b) Osorio-Lozada, A.; Prisinzano, T.; Olivo, H. F. *Tetrahedron: Asymmetry* **2004**, *15*, 3811–3815; (c) Prisinzano, T.; Podobinski, J.; Tidgewell, K.; Luoa, M.; Swenson, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1053–1058; (d) Moshkovits-Kaptsan, R.; Braude, V.; Chen, K. W.O. Patent 103221 A2, 2007; *Chem. Abstr.* **2007**, *147*, 365263; (e) Hauck, W.; Adam, P.; Bobier, C.; Landmesser, N. *Chirality* **2008**, *20*, 896–899; (f) Rao, R. N.; Ramachandra, B.; Santhakumar, K. *Chirality* **2012**, *24*, 339–344; (g) Wang, W.; Xiang, S.; Zhou, X.; Ji, Y.; Xiang, B. *Molecules* **2012**, *17*, 303–314.
19. Ternois, J.; Guillen, F.; Plaquevent, J.-C.; Coquerel, G. *Tetrahedron: Asymmetry* **2007**, *18*, 2959–2964.
20. (a) Olivo, H. F.; Osorio-Lozada, A.; Peeples, T. L. *Tetrahedron: Asymmetry* **2005**, *16*, 3507–3511; (b) Olivio, H. F.; Osorio-Lozada, A. V. U.S. Patent 0026,507 A1, 2007; *Chem. Abstr.* **2007**, *146*, 183125.
21. Nigel-Etinger, I.; Mahammed, A.; Gross, Z. *Catal. Sci. Technol.* **2011**, *1*, 578–581.
22. (a) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451–1453; (b) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826–832; (c) Wei, S.;

Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catal. Today* **2007**, *121*, 151–157; (d) Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6624–6628.
23. (a) Vilter, H. *Phytochemistry* **1984**, *23*, 1387–1390; (b) Ten Brink, H. B.; Tuynman, A.; Dekker, H. L.; Hemrika, W.; Izumi, Y.; Oshiro, T.; Schoemaker, H. E.; Wever, R. *Inorg. Chem.* **1998**, *37*, 6780–6784; (c) Ten Brink, H. B.; Holland, H. L.; Schoemaker, H. E.; van Lingen, H.; Wever, R. *Tetrahedron: Asymmetry* **1999**, *10*, 4563–4572; (d) ten Brink, H. B.; Schoemaker, H. E.; Wever, R. *Eur. J. Biochem.* **2001**, *268*, 132–138.
24. Ligtenbarg, A. G. J.; Hage, R.; Feringa, B. L. *Coord. Chem. Rev.* **2003**, *237*, 89–101.
25. Bolm, C. *Coord. Chem. Rev.* **2003**, *237*, 245–256.
26. Weiß, K. M.; Tsogoeva, S. B. *Chem. Rec.* **2011**, *11*, 18–39.
27. Nielsen, M.; Gothelf, K. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2440–2444.
28. Balsells, J.; Carroll, P. J.; Walsh, P. J. *Inorg. Chem.* **2001**, *40*, 5568–5574.
29. Campbell, E. J.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 1221–1225.
30. Jiang, Y.; Zhou, X.; Hu, W.; Wu, L.; Mi, A. *Tetrahedron: Asymmetry* **1995**, *6*, 405–408.
31. Zhou, X.-G.; Huang, J.-S.; Ko, P.-H.; Cheung, K.-K.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1999**, 3303–3309.
32. Kochnev, A. I.; Oleynik, I. I.; Oleynik, I. V.; Ivanchev, S. S.; Tolstikov, G. A. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 1125–1129.