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Synthesis of (*R*)-Modafinil via Organocatalyzed and Non-Heme Iron-Catalyzed Sulfoxidation Using H_2O_2 as an Environmentally Benign Oxidant

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Abstract: The first organocatalyzed sulfoxidation reaction towards enantioenriched (*R*)-modafinil (Armodafinil®), a drug against narcolepsy, is reported here. A series of chiral organocatalysts, e.g., different chiral BINOL-phosphates, or a fructose-derived *N*-substituted oxazolidinone ketone (Shi catalyst) were applied for the sulfoxidation reaction with environmentally friendly H_2O_2 as a convenient oxygen transferring agent. Furthermore, the potential of a biomimetic catalytic system consisting of $FeCl_3$ and a dipeptide-based chiral ligand was demonstrated, which constitutes the most successful asymmetric non-heme iron-catalyzed synthesis of (*R*)-modafinil so far.

Keywords: sulfoxidation; (*R*)-modafinil; organocatalysis; non-heme iron catalyst; hydrogen peroxide

1. Introduction

Sulfoxides demonstrate versatile properties and are ubiquitous in bioactive compounds and drugs [1]. Being of medicinal interest, chiral sulfoxides serve as building blocks for the generation of biologically active compounds [2]. With the discovery of their presence in naturally chiral sulfoxide metabolites [3], such as cysteine sulfoxide derivatives, the demand for new synthetic routes was steadily growing, especially since the pioneering work of Kagan and Modena [4–6].

Optically active sulfoxides are important representatives of therapeutically used drugs. There are several examples that playing an important role in medicinal and pharmaceutical chemistry [2], including Esomeprazole [7,8], which acts as proton-pump inhibitor; the selective NK_2 antagonist ZD7944 [9]; and the anti-cancer agent Sulindac® (Figure 1) [10].

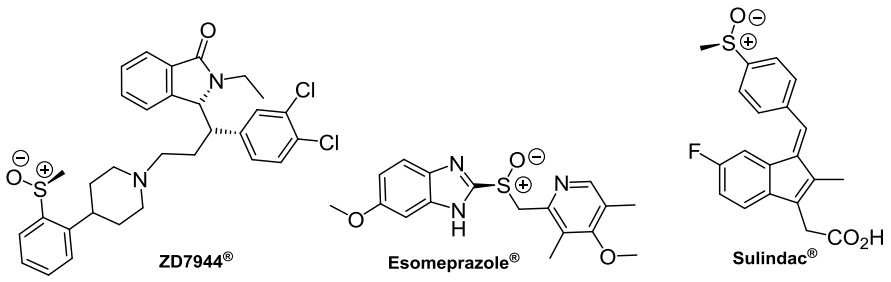


Figure 1. Examples of chiral biologically active sulfoxides.

Modafinil (also known as Provigil® [11], Figure 2), another important sulfoxide, is administered as a drug against narcolepsy [12] with significant advantages compared to dexamphetamine [13] and several other stimulants [14] because of a lower abuse potential [15,16].

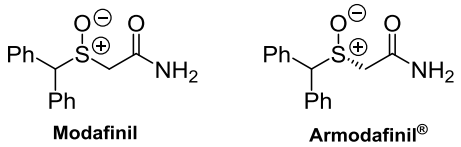


Figure 2. The hippocampal activator in its racemic (modafinil) and optically pure (Armodafinil®) forms.

It is furthermore used for the treatment of depression [17], attention-deficit hyperactivity disorder [18], Parkinson's disease [19], and epilepsy [20]. Moreover, it is a memory-improving and mood-brightening psychostimulant [21].

After the first synthesis was developed in 1979 by Lafon [22], several methods have been envisioned for its racemic generation using hydrogen peroxide as an abundant, environmentally benign oxidant [23–29].

The fact that there is a continued demand for novel synthetic methods to attain modafinil is further demonstrated by a recently published one-pot parallel synthetic approach [29] as well as another strategy, established by Cibulka and co-workers, employing electron-deficient heteroarenium salts for the activation of hydrogen peroxide [30].

The quantitative potency of the two enantiomers of modafinil, however, is indeed influenced by the stereogenic sulfoxide group. (*R*)-modafinil has a longer half-life in the human body compared to (*S*)-modafinil [31], which is metabolized three times faster [32].

An ester, amide, or carboxylic acid moiety close to the sulfide function, however, can adversely affect enantioselectivity [33]. Given that no directing group is available adjacent to the sulfur atom, compared, for instance, to omeprazole [7], most known procedures aim to circumvent an enantioselective oxidation. As an alternative, racemic resolution of diastereomers [34,35], preferential crystallization or chiral chromatography can be applied [36]. Thus, the variety of enantioselective synthetic approaches is limited to a small selection, namely, a microbial sulfoxidation [37], an advanced Kagan method patented by Cephalon [33], and an oxygen-transfer by a chiral oxaziridine in ionic liquid [38].

These methods, however, suffer from the need for hazardous oxidizing agents, expensive solvents, and metal catalysts. Apart from a vanadium-based catalytic system, developed in our group, which was able to provide (*R*)-modafinil in excellent yield and moderate enantiomeric excess within a very short reaction time [39], all other attempts making use of convenient metal complexes generally resulted in a drastically decreased performance of the catalyst [38].

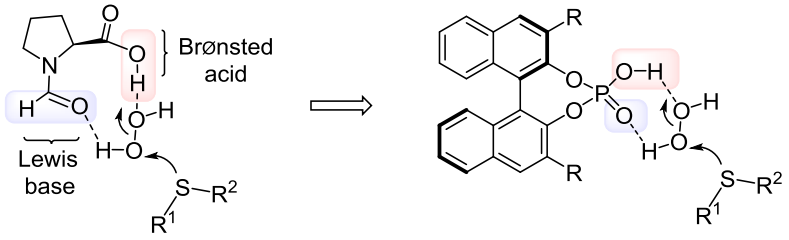
For the pharmaceutical industry it is a permanent issue to free biologically active compounds from metal traces. Thus, the development of a metal-free sulfoxidation process is in high demand.

A class of powerful organocatalysts is represented by Brønsted acid catalysts such as BINOL-derived phosphoric acids, which have already been applied in numerous highly enantioselective transformations [40–49] since the pioneering studies by the groups of Akiyama et al. [50] and Uraguchi and Terada [51].

Wang, Tao and co-workers [52] were the first to develop a sulfoxidation reaction catalyzed by BINOL-phosphates, and List et al. [53,54] impressively demonstrated the potential of a new family of chiral phosphoric acids with results analogous to the best obtained with metal catalysts. Having already shown a very good performance in a patented, efficient, and direct route towards Sulindac® (Figure 1) [53,54], BINOL-derived phosphoric acids have surprisingly never been applied for the enantioselective synthesis of modafinil.

Following our previous successes in applying Lewis base/Brønsted acid catalysts for various organic transformations [55–57], we decided to test BINOL-phosphates (chiral bifunctional

organocatalysts, Scheme 1) and additional catalytic systems. To the best of our knowledge, we present herein the first organocatalyzed synthesis of enantiomerically enriched modafinil via sulfoxidation.



Scheme 1. Proposed Lewis base/Brønsted acid catalysis—BINOL-phosphates as bifunctional organocatalysts in the oxidation of sulfide with hydrogen peroxide as an oxidant.

2. Materials and Methods

Solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial sources were used without further purification. Thin layer chromatography (TLC) chromatography was performed on pre-coated aluminum silica gel ALUGRAM SIL G/UV254 plates (Macherey, Nagel & Co., Düren, Germany). Flash chromatography was performed using silica gel ACROS 60 Å, (particle size 0.035–0.070 mm, Thermofischer ACROS Organics, Janssen-Pharmaceuticalaan 3a, 2440 Geel, Belgium). Proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) spectra were recorded in $CDCl_3$ with Bruker Avance 300 or 400 (Bruker, Billerica, MA, USA). Enantioselectivities were determined by chiral high pressure liquid chromatography (HPLC) analysis in comparison with authentic racemic material.

*2.1. (Methylsulfinyl)Benzene (**1a**):*

The corresponding BINOL-phosphate catalyst (0.048 mmol) was dissolved in CH_2Cl_2 (0.5 mL) at −10 °C. After the addition of the sulfide (0.24 mmol, 29.8 mg) aqueous 30% H_2O_2 (1.2 equiv, 0.29 mmol, 29.4 µL) was added in one portion. The reaction mixture was stirred at room temperature for 24 h. The product was obtained via direct purification by column chromatography (SiO_2, EtOAc/PE 4:1). The enantiomeric excess of the product was determined by chiral HPLC analysis. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.70 (s, 3H), 7.47–7.54 (m, 3H), 7.60–7.64 (m, 2H).

*2.2. 1-(Methylsulfinyl)-4-Nitrobenzene (**1b**):*

The corresponding BINOL-phosphate catalyst (0.048 mmol) was dissolved in CH_2Cl_2 (0.5 mL) at −10 °C. The sulfide (0.24 mmol, 40.6 mg) was added, followed by the addition of aqueous 30% H_2O_2 (1.2 equiv, 0.29 mmol, 29.4 µL) in one portion. The reaction mixture was stirred at room temperature for 24 h. The product was directly purified by column chromatography (SiO_2, EtOAc/PE 4:1). The enantiomeric excess of the product was determined by chiral HPLC analysis. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.77 (s, 3H), 7.82 (d, *J* = 8.9 Hz, 2H), 8.38 (d, *J* = 8.9 Hz, 2H).

*2.3. 2-(Benzhydrylsulfinyl)Acetamide (**2**):*

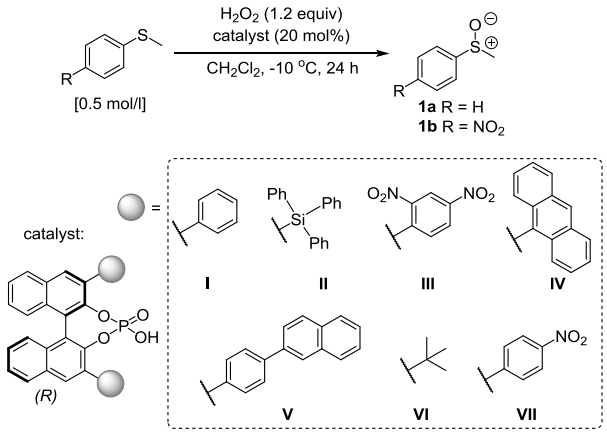
BINOL-phosphate **V** (0.048 mmol, 36 mg) was dissolved in CH_2Cl_2 (0.5 mL) at −10 °C, followed by the addition of aqueous 30% H_2O_2 (1.2 equiv, 0.29 mmol, 29.4 µL) in one portion. Then, the sulfide (0.24 mmol, 61.8 mg) was added to the reaction mixture, which was stirred at −10 °C. The product was directly purified by column chromatography (SiO_2, EtOAc). The isolated enantiomerically enriched *(R)*-modafinil was identified through comparison of ^{1}H-NMR spectra with literature data [38]. The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS, *n*-hexane/*i*-PrOH (60:40), flow 0.9 mL/min, 25 °C, 31 bar). ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.21 (d, *J* = 13.5 Hz, 1H), 3.36 (d, *J* = 13.5 Hz, 1H), 5.34 (s, 1H), 7.32–7.43 (m, 7H), 7.50–7.52 (m, 4H), 7.68 (s, 1H).

3. Results and Discussion

Our initial work started with the screening of different BINOL-phosphates for the sulfoxidation of thioanisole as a model reaction. The required organocatalysts **I**–**VII** for the reaction were prepared by conventional means [58].

Initially, the reaction was performed in dichloromethane using 20 mol % of the organocatalyst at −10 °C within 24 h. In case of BINOL-phosphate **II**, only moderate yield was observed (44% yield, entry 1, Table 1) and the enantiomeric excess was rather low (10% *ee*). A further reduction of the amount of catalyst from 20 mol % to 10 mol % resulted in a decreased yield, but the enantiomeric ratio remained constant (26% yield, 10% *ee*, entry 2, Table 1). Surprisingly, BINOL-phosphate **III** provided the corresponding sulfoxide in high yield (98%) with an enantiomeric excess of 20% (entry 3, Table 1) and we continued to investigate catalyst **I**. To our delight, the enantiomeric excess increased to 36% *ee*, but the yield was lowered to 68% (entry 4, Table 1). In the case of BINOL-phosphate with a more sterically hindered moiety, a complete loss of activity was the consequence (entry 5, Table 1). With catalyst **V**, on the other hand, the product could be isolated with 73% yield and an enantiomeric excess of 30% (entry 6, Table 1). Furthermore, carrying out one reaction without an external catalyst, we could preclude a background reaction (entry 7, Table 1).

Table 1. BINOL-phosphate catalyzed oxidation of thioanisole derivatives.



Entry	Product	BINOL-Phosphate	Yield, [a] %	*ee*, % (*S*)
1	**1a**	**II**	44	10 [b]
2	**1a**	**II** [d]	26	10 [b]
3	**1a**	**III**	98	20 [b]
4	**1a**	**I**	68	36 [b]
5	**1a**	**IV**	Traces	n.d.
6	**1a**	**V**	73	30 [b]
7	**1a**	**–**	Traces	n.d.
8	**1b**	**VI**	11	33 [c]
9	**1b**	**VI** [e]	14	59 [c]
10	**1b**	**VII**	Traces	18 [c]

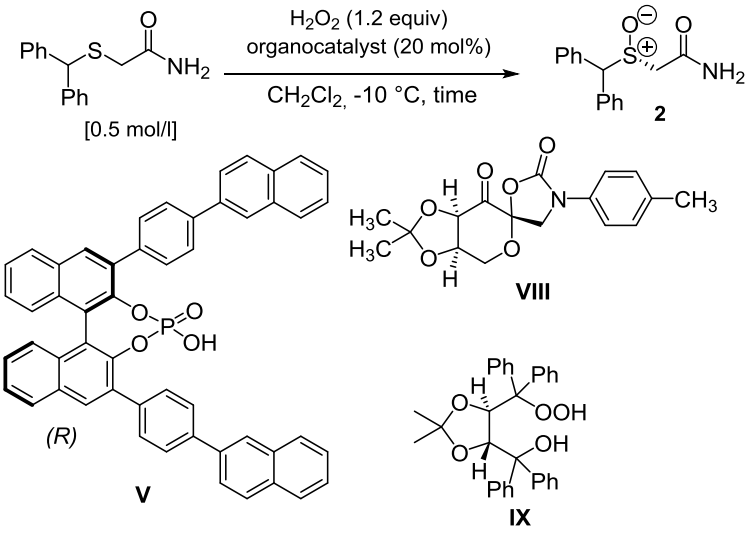
[a] Yield of isolated product; [b] determined by HPLC (OD, *n*-hexanes/*i*PrOH (93:7), flow 1.0 mL/min); [c] determined by HPLC (IA, *n*-hexanes/*i*PrOH (90:10), flow 1.0 mL/min); [d] 10 mol % catalyst loading; [e] c (educt) = 0.8 mol/l; H_2O_2 = 0.27 equiv. For details of the reaction procedures and product characterizations, see Supplementary Information.

We investigated the oxidation of a thioanisole derivative bearing a nitro moiety in 4-position (entries 8–11, Table 1). We applied BINOL-phosphate **VI,** and found that the product could be isolated with a low yield of 11% and a moderate enantiomeric excess of 33% (entry 8, Table 1). Carrying out the reaction with a lower amount of hydrogen peroxide (0.27 equivalent) under otherwise identical conditions, the isolated product had a significantly higher enantiomeric excess of 59% (entry 9, Table 1).

With catalyst **VII**, bearing an electron withdrawing substituent on the phenyl moiety in para position, the desired product was generated only in traces (entry 10, Table 1).

Subsequently, we studied the sulfoxidation of the prochiral sulfide in the presence of 20 mol % of BINOL-phosphate **V**, which had previously performed best. The reaction proceeded at −10 °C, in CH_2Cl_2 as a solvent (Table 2). Initially, we applied the optimized reaction conditions, and the product could be isolated after 24 h in quantitative yield with an enantiomeric excess of 10% (entry 1, Table 2) In order to examine the temperature effect on the reaction, we carried out the sulfoxidation at 0 °C. The product was obtained quantitatively but with a slightly lower *ee* value of 7% (entry 2, Table 2). A shorter reaction time of 12 h resulted in a lower yield of 61%, and no enantioselectivity could be detected (entry 3, Table 2). A higher initial concentration of the sulfide had a positive influence on the stereoselectivity of the oxidation. Thus, following the previous trend concerning the oxidation of thioanisole (entry 9, Table 1), we observed this supporting effect on the reaction outcome for modafinil as well. Due to an accelerated reaction, the desired compound could be isolated in quantitative yield already after 12 h and the *ee* value slightly increased to 13% (entry 4, Table 2).

Table 2. Organocatalytic synthesis of modafinil.



Entry	Catalyst	Time, h	Yield, [a] %	*ee*, [b] % (*R*)
1	**V**	24	>99	10
2	**V** [c]	24	>99	7
3	**V**	12	61	*rac*
4 [d]	**V**	12	>99	13
5	**VIII**	24	38	26
6	**IX** [e]	96	66	16

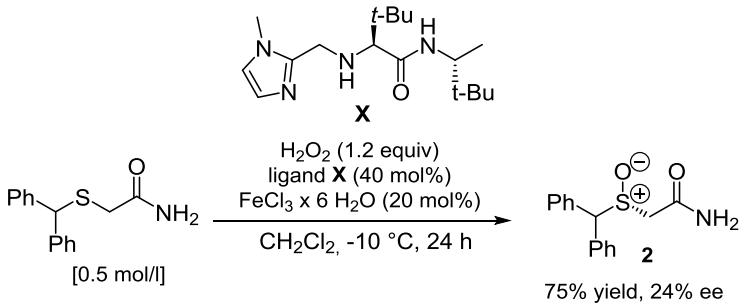
[a] Yield of isolated product; [b] determined by chiral HPLC (AS, *n*-hexanes/*i*PrOH (60:40), flow 0.9 mL/min, 25 °C, 31 bar); [c] T = 0 °C; [d] c (sulfide) = 0.8 mol/l; [e] without H_2O_2, 1.5 equiv of **IX**, T = −30 °C > room temperature (RT), tetrahydrofuran (THF). For details of the reaction procedures and product characterizations, see Supplementary Information.

The Shi's *N*-substituted oxazolidinone ketone **VIII** belongs to the attractive class of fructose-derived asymmetric organocatalysts, generally employed for the epoxidation of unfunctionalized terminal alkenes [59,60]. Having successfully applied it to the one-pot, two-step synthesis of β-adrenergic blockers via epoxidation as a key enantioselective step [60], we decided to evaluate its activity for the sulfoxidation reaction as well. Modafinil was generated with a yield of 38% and an enantioselectivity of 26% *ee* (entry 5, Table 2).

In order to minimize the number of reactants, we next intended to combine the oxidizing agent and the chiral source. Therefore, we applied the synthesized chiral hydroperoxide TADOOH **IX**, which

is generally known for its high efficiency for sulfoxidation reactions [61]. A striking feature of this method is that no further external catalyst is needed. With an amount of 1.5 equivalent of the oxidant in tetrahydrofuran (THF), the product was generated in 66% yield with an enantioselectivity of 16% (entry 6, Table 2).

Following our previous interest in the application of the non-heme iron-catalyzed sulfoxidation reaction, which exhibited high activity in the oxidation of the thioanisol but, up to now, showed unsatisfactory results for the modafinil precursor [39], we decided to investigate a dipeptide-based chiral ligand as an alternative chiral source (Scheme 2).



Scheme 2. Application of a dipeptide-based ligand **X** to the biomimetic iron-catalyzed synthesis of *(R)*-modafinil.

Under these conditions, modafinil could be isolated in good yield of 75% and with an *ee* value of 24%. This represents the most successful asymmetric non-heme iron-catalyzed synthesis of (*R*)-modafinil so far.

4. Conclusions

We report here the first organocatalytic synthesis of enantiomerically enriched *(R)*-modafinil (Armodafinil®), accomplished with the chiral bifunctional BINOL-phosphate **V**, a fructose-derived N-substituted oxazolidinone ketone **VIII,** or the chiral peroxide TADOOH **IX**, respectively. The desired compound could be obtained via sulfoxidation using H_2O_2 with excellent yield up to >99% and *ee* values up to 23%. This protocol includes all the advantages of metal-free asymmetric organocatalysis.

We additionally showed the successful application of a dipeptide-based ligand in the biomimetic non-heme iron-catalyzed sulfoxidation towards enantiomerically enriched *(R)*-modafinil, which could be isolated in good yield of 75% with an enantioselectivity of 24% *ee*. The sulfoxidation reported here makes use of mild reaction conditions using aqueous hydrogen peroxide as an environmentally friendly oxidant.

Supplementary Materials: The following are available online at www.mdpi.com/2073-8994/9/6/88/s1: Experimental Procedures, Analytical and Spectroscopic Data of Products.

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Author Contributions: Felix E. Held conducted the sulfoxidation reactions. Kerstin A. Stingl contributed to the catalyst screening of the model reaction. Svetlana B. Tsogoeva conceived and directed the research, supervised the synthetic experiments. The manuscript was written through contribution of all authors.

Conflicts of Interest: The authors declare no conflict of interest.

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