Isoquinoline- and piperazinedione-derived α-acylamino peroxide moieties in asymmetric oxidation of sulphides and epoxidation of naphthoquinones

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Abstract

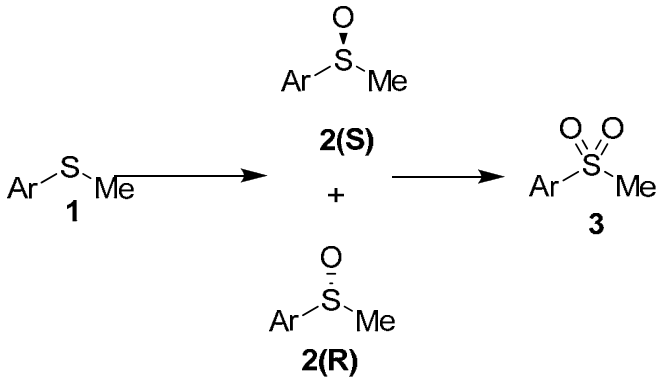
The application of chiral α-acylamino hydroperoxide moieties in asymmetric sulphoxidation and epoxidations was pursued. In order to synthesize new isoquinoline-derived α-acylamino hydroperoxides isoquinolines were treated with (*R*)-menthyl chloroformate and hydrogen peroxide. Instead of the expected hydroperoxides novel bis(2-menthyloxycarbonyl-1,2-dihydroisoquinolin-1-yl) peroxides were obtained as 1:1 epimeric mixtures by a subsequent reaction. 1:1 mixtures of *t*-butyl (2-menthyloxycarbonyl-1,2-dihydroisoquinolin-1-yl) peroxides were formed from *t*-butyl hydroperoxide, isoquinoline and (R)-menthyl chloroformate. For eventual *in situ* preparation of chiral (*R*)-menthyloxycarbonyl-1,2-dihydroisoquinolin-1-yl) hydroperoxides and their application in stereoselective O-transfer reactions, isoquinolines were combined with (*R*)-menthyl chloroformate, hydrogen peroxide and metal alkoxides. These mixtures allowed a stereoselective synthesis of aryl methyl sulphoxides from corresponding sulphides. The stereoselectivity results from a kinetic resolution of racemic sulphoxides formed in the first step wherein the (S)-enantiomer was faster oxidized to the corresponding sulphone. As another type of chiral α-acylamino hydroperoxide moiety piperazinedione hydroperoxide was applied in the transformation of aryl methyl sulphides into sulphoxides. Low enantioselectivities were achieved. The same reagent allowed a high yielding epoxidation of naphthoquinones, but again in modest stereoselectivities.

Keywords: Isoquinolines, asymmetric synthesis, sulphoxides, sulphides, oxidation, hydroperoxides, peroxides

Introduction

Chiral sulphoxides have gained wide interest in asymmetric C-C and C-X bond formation reactions.[1,2] To obtain them in optically active form either resolution of racemic sulphoxides or asymmetric oxidation of sulphides has been used.[3] In the latter strategy, asymmetric oxygen

transfer reagents, such as chiral hydroperoxides can be applied.[4-6] As an alternative, chiral catalysts or chiral reagents in the presence of non-chiral oxidizing reagents (*t*-butyl hydroperoxide, cumene hydroperoxide, oxone or hydrogen peroxide) have been used.[7] Selective oxidations of sulphides **1** to sulphoxides **2** is challenging due to the sensibility to overoxidation to achiral sulphones **3**. When optically active hydroperoxides were used in asymmetric oxidation of sulphides **1** enantioselectivity was achieved mostly in the consecutive step, i. e. by kinetic resolution during the oxidation of the racemic sulphoxides **2(S)** and **2(R)** obtained in the first step. In general, enantioselectivities obtained with chiral hydroperoxides were not satisfactory so far.



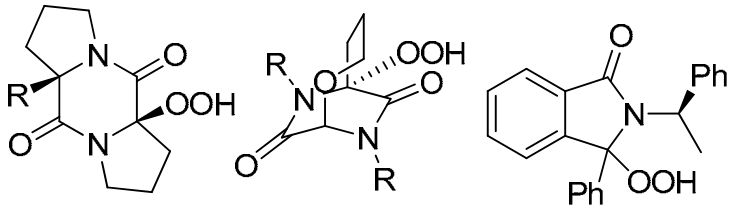
	Ar
1, 2, 3 a	Ph
1, 2, 3 b	4-MeC_6H_4
1, 2, 3 c	4-ClC_6H_4
1, 2, 3 d	4-$NO_2C_6H_4$

Scheme 1. Oxidation of aryl methyl sulphides.

We report here attempts to synthesize new chiral α-*N*-acylamino hydroperoxides derived from isoquinolines, (*R*)-menthyl chloroformate and hydrogen peroxide and the use of the combinations of these reagents in enantioselective oxidation of aryl methyl sulphides **1**.[8] Furthermore the application of a chiral piperazinedione hydroperoxide bearing a chiral *N*-acylamino hydroperoxide moiety in this reaction as well as in the epoxidation of naphthoquinones is included.

α-*N*-Acylamino hydroperoxides have rarely been reported in the literature.[9-21] All of them except the piperazinedione hydroperoxides **4** and **5** and the isoindol-1-one-3-hydroperoxides **6** were racemic. The latter were obtained by Rebek et al. from the corresponding 3-hydroxyisodinol-1-one and hydrogen peroxide under acid conditions and final separation of the resulting epimers **6**. Application of these enantiomers to the epoxidation of *trans*-β-methylstyrene lead to unsatisfactory results (28% yield, 6% ee).[22-24] Very recently, the piperazinedione hydroperoxide **4** reported by U. Schmidt as early as in 1976 [25] was used by

Laschat et al. as enantioselective oxidizing reagent for sulphides, but stereoselectivity could not be achieved.[26] On the other hand, **4** resulted in enantioselective Weiz-Scheffer oxidation of chalcones and cyclic enones, but with modest ee (37% max).[26] α-Aminohydroperoxide structures formed *in situ* from chiral flavine-derived cyclophanes and hydrogen peroxide could be successfully be used in stereoselective sulphoxidation.[21]

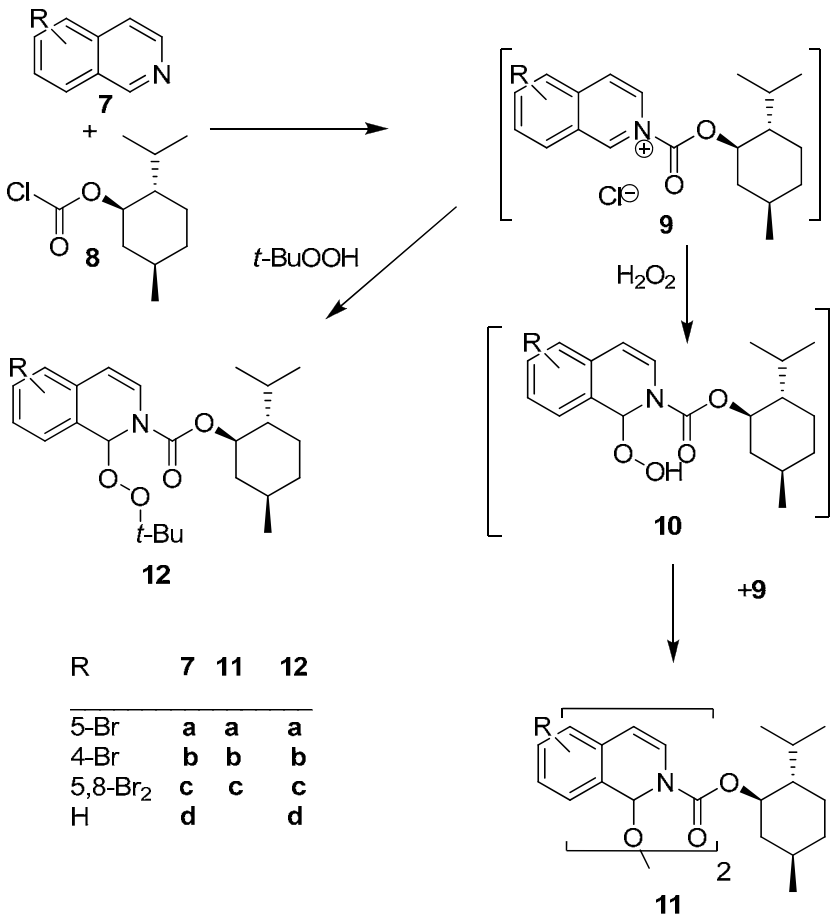


4 (R = H, OOH) **5** **6**

Formulae of known optically active α-aminohydroperoxides.

Results and Discussion

Recently, the reaction of isoquinolines **7** and (*R*)-menthyl chloroformate **8** forming *N*-(*R*)-menthyloxycarbonylisoquinolinium salts **9** was used to attempt stereoselective additions of nucleophiles such as cyanide, organometallics or electron rich heterocycles to position 1 of the isoquinoline.[27-30] However, the original assumption of complete diastereoselective formation of the 1,2-adducts was erroneous, as found out by two independent groups.[28,29] Instead, 1:1 mixtures of epimers were formed. As an alternative to those nucleophiles used before, it would be interesting to investigate how hydrogen peroxide behaves when used in such additions to isoquinolines. Thus we combined isoquinolines **7** with (*R*)-menthyl chloroformate **8** in dichloromethane at -40°C and added a 3 M solution of hydrogen peroxide in diethyl ether after the formation of intermediate *N*-acyliminium salts **9**. Peroxidic products were isolated by quenching with water and column chromatography. All products turned out to be unstable, but NMR-spectra and in part HRMS could be obtained. The latter revealed that the products were not hydroperoxides **10** but peroxides **11** which were formed by a subsequent reaction of the expected **10** with further *N*-acyliminium salt **9**. When *t*-butyl hydroperoxide was used as a nucleophile the expected *t*-butyl peroxides **12** were obtained.

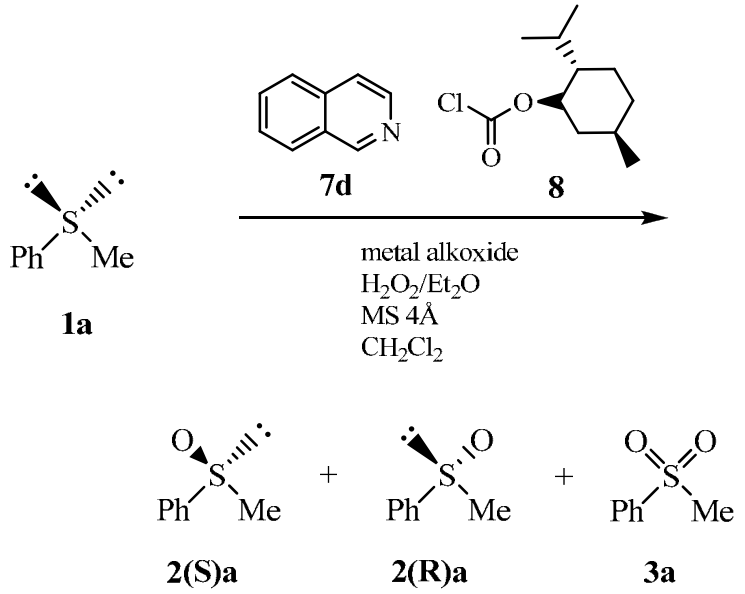


R	7	11	12
5-Br	a	a	a
4-Br	b	b	b
5,8-Br_2	c	c	c
H	d		d

Scheme 2. Formation of chiral isoquinoline-derived peroxides **11**and **12**.

Elucidating the configuration of peroxides **11** and **12** turned out to be difficult. For instance, the H-NMR spectrum of **11d** in $CDCl_3$ at room temperature showed two signals for each proton at position 1, 3 and 4 coalescing at 50°C (see supplementary material). This phenomenon is presumably caused by rotamers derived from hindered rotation around the C-N-bond of the carbamate moiety. Evidence for the formation of diastereomers and rotamers was revealed by the NMR spectra of the *t*-butyl peroxide **12a**. This product is more stable and thus reliable integrations of signals could be obtained. By rising the measuring temperature from 25 °C to 50 °C splitting of the signals of H-8 at about 7.5 ppm into two doublets of J = 3.8 Hz was observed, which is in agreement with the existence of a 1:1 mixture of diastereomers. This fact could also be seen at room temperature when the spectrum was recorded in DMSO-d_6**,** however the compound decomposes relatively fast in this solvent. Attempts to shed light on the configuration of the peroxides **11** and **12** by matrix isolation and vibrational dichroism undertaken by Tarczay et al.[31] were unsuccessful due to the instability of the material and the complexity of the structures.

At this stage it could be presumed that the reaction of isoquinolines **7** with (*R*)-menthyl chloroformate **8** and hydrogen peroxide or *t*-butyl peroxides give rise to new α-*N*-acylamino peroxides **11** and **12**, respectively. However, stereoselectivity could not be achieved, as it was also missing before in analogous reactions with cyanide as nucleophile.[27,29] Thus all these products **11** and **12** were not useful in asymmetric oxidations of sulphides **1**. As a consequence and having in mind the *in situ* formation of α-aminohydroperoxide moieties from flavine-derived cyclophanes and hydrogen peroxide in the stereoselective sulphoxidations,[21] our strategy was turned to the combination of hydrogen peroxide, isoquinolines **7** and (*R*)-menthyl chloroformate **8** and metal compounds as additives (Scheme 3).



Scheme 3. Asymmetric sulphoxidation of methyl phenyl sulphide with H_2O_2.

Since $VO(OiPr)_3$ had turned out to be very useful in oxygen transfer reactions from hydrogen peroxide, [32-34] this compound was applied in the *in situ* procedure according to Scheme 3 giving rise to an enantioselective formation of the sulphoxides **2**. The effect of several parameters on the enantioselectivity was screened (see table in supporting information). Hydrogen peroxide as oxygen donor turned out to be more effective than *t*-butyl peroxide. Lowering the temperature from 0 °C to - 40 °C did not improve the enantioselectivity. Sometimes higher ee were obtained which, however, could not be reproduced. A molar excess of (*R*)-menthyl chloroformate **8** seems to be advantageous.

A time resolved record of the enantiomeric ratio of the reaction of methyl phenyl sulphide **1a** with hydrogen peroxide in the presence of $VO(OiPr)_3$ revealed that an increase of the enantiomeric ratio of **2(R):2(S)** occurred with increasing time reaching 60:40 after 45 min. This indicates a kinetic resolution of primarily formed racemic methyl phenyl sulphoxides **2(R)** and **2(S)**, where the *S*-enantiomer was faster oxidized to the sulphone **3**.

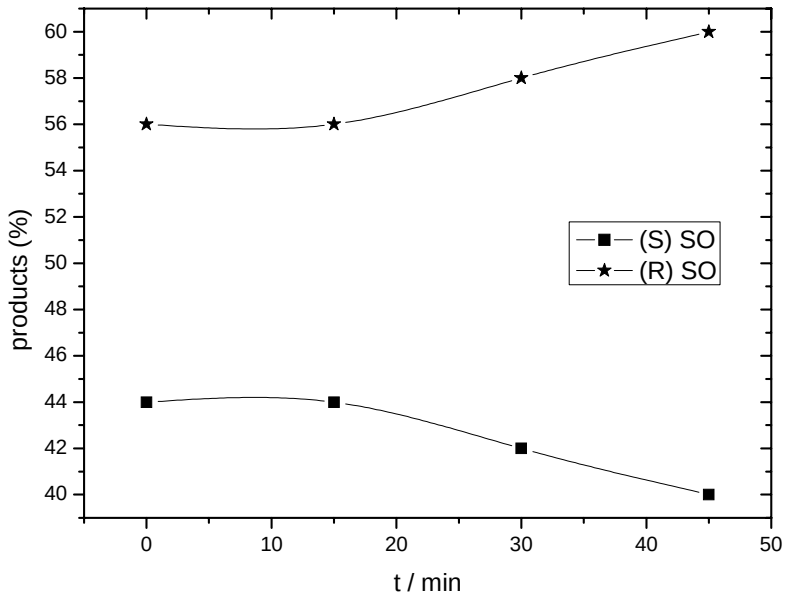


Figure 1. Dependence of enantiomeric ratios on reaction time in the oxidation of methyl phenyl sulphide **1a** with hydrogen peroxide in the presence of isoquinoline **7d, 8** and $VO(OiPr)_3$ on reaction time.

Under slightly changed reaction conditions (mixing of isoquinoline **7** with (*R*)-menthyl chloroformate **8** and addition of $VO(OEt)_3$, PhSMe and H_2O_2, waiting after each addition for 30 min) an ee of 32% was achieved.

In order to prove the assumption of a kinetic resolution being responsible for the stereoselective outcome of this reaction, racemic methyl phenyl sulphoxide **2(R/S)a** was treated with hydrogen peroxide under the same conditions as methyl phenyl sulphide **1a** before. An ee of 36% was obtained thus proving a kinetic resolution. Hence, two oxidation steps are necessary to achieve stereoselective access to sulphoxide **2(R)a** starting from the sulphide **1a**, namely formation of racemic sulphoxide **2(R/S)a** in the first step and further preferential oxidation of the enantiomer **2(S)a** to the sulphone **3a** in a second step. As a consequence, a higher ratio than 1:1 of hydrogen peroxide had to be used for an effective stereoselective synthesis of **2(R)a**. By varying the H_2O_2 ratio (see Table 1) we found an optimum at 1.7 equivalents of this oxidizing reagent.

Table 1. Effect of H_2O_2 ratio on enantiomeric ratios in formation of sulphoxides **2(R)a** and **2(S)a** in oxidation of methyl phenyl sulphide **1a** with hydrogen peroxide in the presence of isoquinoline **7d, 8** and $VO(OiPr)_3$

Equiv. $H_2O_{2\,(eth)}$	**2(R)a/2(S)a**[a]
1.1	52 / 44
1.4	48 / 32
1.7	39 / 0
1.8	35 / 0
2.2	1 / 1

[a] HPLC peak areas obtained by integration, the assignment to the enantiomers **2(R)a** and **2(S)a** is based on the sign of optical rotation and their comparison with reported data.

We further tried to apply $Ti(OiPr)_4$ instead of $VO(OEt)_3$ and to use 4-bromoisoquinoline. The latter formed more stable peroxidic structures **11** and **12** (*vide supra*) and thus was expected to perform better than unsubstituted isoquinoline in the 4-component oxidation system according to Scheme 3. As can be seen in Fig. 2, the overoxidation of the sulphoxide **2a** to sulphone **3a** is severe.

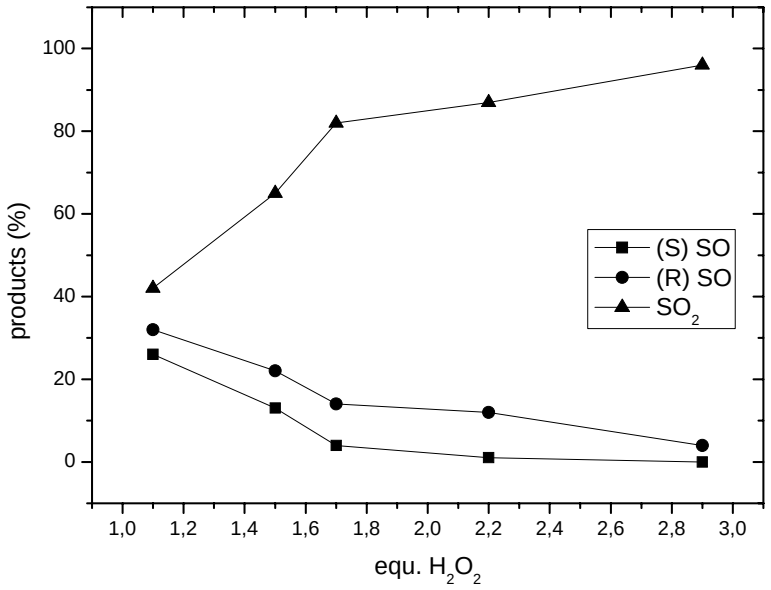


Figure 2. Dependence of enantiomeric ratios on the amount of H_2O_2 used in the oxidation of methyl phenyl sulphide **1a** in the presence of 4-bromoisoquinoline **7b**, **8** and $Ti(OiPr)_4$.

We therefore reduced the reaction time to 10 min, and removed 4-bromoisoquinoline in the work up by 20% hydrochloric acid for effective quenching. As an optimal result we achieved 73% ee at an overoxidation of 49%, when 2.2 equivalents of H_2O_2 were used (see Table 2).

Table 2. Enantioselective oxidation of methyl phenyl sulphide **1a** in the presence of $Ti(OiPr)_4$, H_2O_2, 4-bromoisoquinoline **7b** and (*R*)-menthyl chloroformate **8** at reduced reaction times (10 min)

Equiv. H_2O_2 (eth)	Composition of reaction mixture[a]			
	% Sulphoxide **2(R)a**	% Sulphoxide **2(S)a**	ee (%)	% Sulphone **3a**
1.1	55	31	23	19
2.2	44	7	73	49
3.3	16	0	>99	84
4.5	2	1	-	97

[a] determined by integration of HPLC peaks

The ee could even be further increased to values higher than 99% with 3.3 equivalents of H_2O_2, however overoxidation of 84% occurred. Further variation of reaction conditions revealed that $Ti(OiPr)_4$ is essential as shown by re-isolation of more than 95% of starting material **1** when $Ti(OiPr)_4$ was left out. Slower addition of H_2O_2 over a period of 2 h resulted in low yield while much overoxidation occurred. Increasing the amount of (*R*)-menthyl chloroformate **8** did not show an advantageous effect.

The application of 5-bromoisoquinoline **7a** instead of 4-bromoisoquinoline **7b** in the $Ti(OiPr)_4$-assisted oxidation of methyl phenyl sulphide was possible but gave unsatisfactory results (28% ee with 50% overoxidation). Advantageous effects of adding small amounts of methanol in sulphoxidations of sulphides were reported.[35] But the addition of 1.2 equivalents methanol to our system resulted in unsatisfactory enantioselectivities (2-6% ee) using several ratios of hydrogen peroxide. Surprisingly, an advantageous effect was observed, when the same amount of methanol was added to the oxidizing system with 4-bromoisoquinoline **7b** (17% ee at 54% overoxidation in the absence of methanol versus 23% ee at 69% overoxidation with methanol).

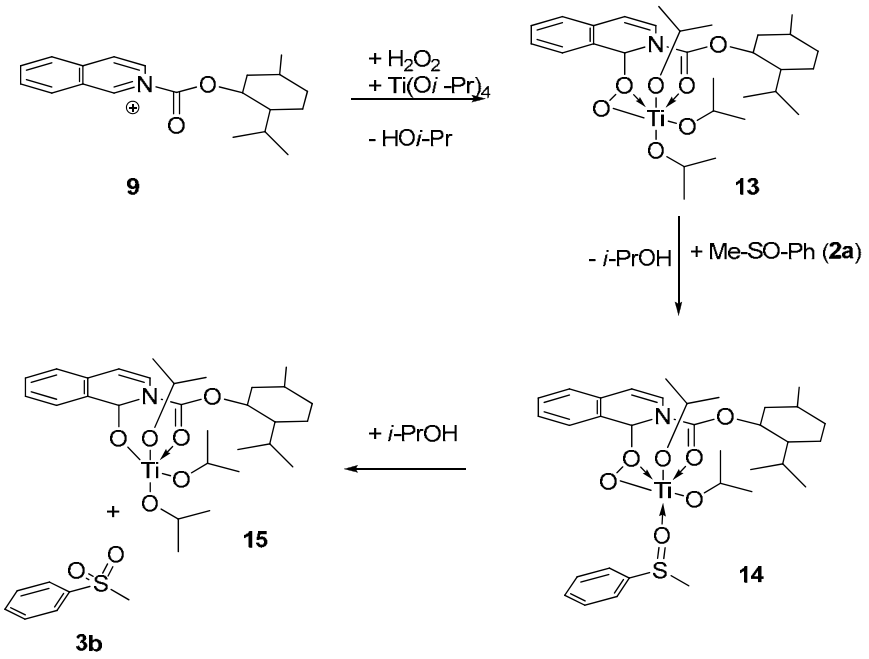
When unsubstituted isoquinoline **7d** was used, a highly chemoselective oxidation of methyl phenyl sulphide **1a** to methyl phenyl sulphoxide **2a** could be achieved with 1.1 equivalents of H_2O_2. However, stereoselectivity was missing as it was also in cases of higher amounts of H_2O_2 where overoxidation occurred. Thus the stereoselectivity increased in the sequence of isoquinoline, 5-bromoisoquinoline and 4-bromoisoquinoline. Obviously, substituents influence the performance of isoquinolines **7** in the oxidation of methyl phenyl sulphide **1a** considerably.

Table 3. Oxidation of methyl phenyl sulphide **1a** with isoquinoline **7d**, H_2O_2, (R)-menthyl chloroformate **8** and Ti(OiPr)4.

Equiv. H_2O_2 (eth)	Composition of reaction mixture [a] (%) Sulphoxide **2(R)a**	(%) Sulphoxide **2(S)a**	ee (%)	(%) Sulphone **3a**
1.1	44	42	2	14
1.5	40	38	3	22
1.8	34	32	3	34
2.2	28	27	2	45
2.6	25	24	2	51
2.9	22	19	7	59

[a] determined by integration of HPLC peaks

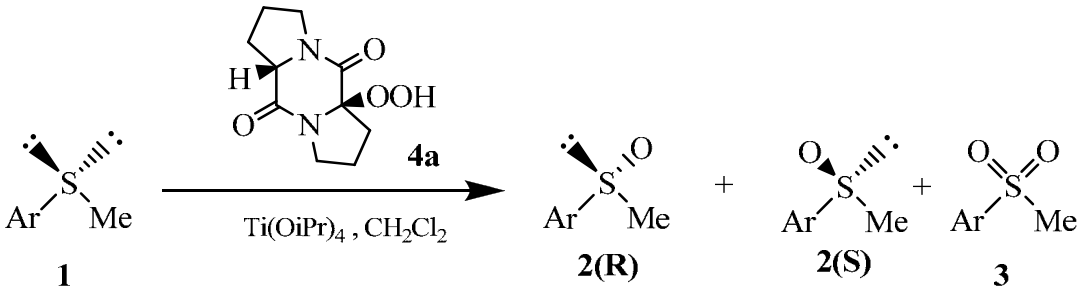
The phenomenon of stereoselective oxygen transfer by our 4-component system to sulphoxides **2a** could be explained in several ways.[36-39] Adopting a proposal made by Adam et al. a Ti-complex **13**, could be assumed formed from **9**, hydrogen peroxide and $Ti(OiPr)_4$. **13** binds the sulphoxide via the O-atom (transition state **14**) and transfers oxygen from the peroxide moiety affording the sulphone **3a** and the complex **15**.[40] The transition state of the (*S*)-enantiomer must be lower in energy to lead to the observed kinetic resolution.



Scheme 4. Mechanistic proposal for the transformation of methyl phenyl sulphoxide **2a** into methyl phenyl sulphone **3a** during the kinetic resolution. The transformation of **14** into **3b** is faster for the (S)-enantiomer of **2a**.

We further thought there might be an opportunity to regenerate the Ti-complex **13** from **15** via *N*-acyliminium salt **9** and further hydrogen peroxide while water is eliminated. Thus we checked if the oxidation system of isoquinolines **7**, (*R*)-menthyl chloroformate **8**, $Ti(OiPr)_4$ can act in catalytic quantities when molecular sieve was added to trap the water, which would be formed by the transformation of **15** into **13**. Two equivalents of hydrogen peroxide, *t*-butyl hydroperoxide or oxone were used as oxygen-donor with or without additional bases, such as DABCO or sodium bicarbonate in the presence of molecular sieve. However, all attempts resulted in unsatisfactory enantioselectivities. Thus the system according to Scheme 3 could not be used in a catalytic fashion.

Independently of the investigations of Laschat et al. who failed to achieve enantioselectivity in sulphoxidation reactions we also sought to apply the piperazinedione hydroperoxide **4a** as potential stereoselective oxygen-transfer reagent.[26] Unlike Laschat et al. we added $Ti(OiPr)_4$ and succeeded in enantioselective transformations of aryl methyl sulphides into aryl methyl sulphoxides **2**. Wide variations of reaction conditions (see supporting information) lead to a maximal ee of 33% while 17% of sulphone **3** was isolated as overoxidation product. Remarkably, two equivalents of the piperazinedione hydroperoxide **4a** were necessary for an enantioselective reaction although only one equivalent was consumed. The application of just one equivalent of **4a** led to a lower extent of overoxidation while the sulphoxides were formed in similar yields, however almost racemic. Treatment of racemic methyl phenyl sulphoxide **2a** under the same conditions did not give any ee´s of **2a** but an almost complete transformation into the sulphone **3** under the same conditions.



Scheme 5. Enantioselective sulphoxidation of aryl methyl sulphides **1** with piperazinedione hydroperoxide **4a**.

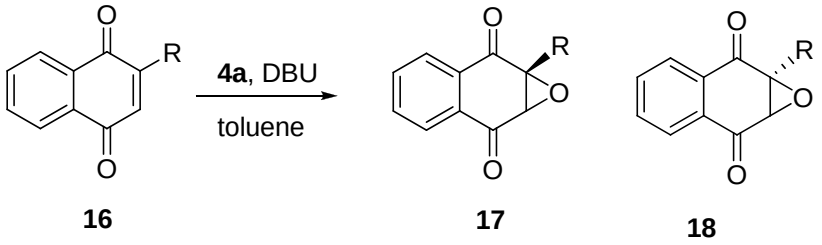
Table 4. Oxidation of aryl methyl sulphides **1** with piperazinedione hydroperoxide **4a**

Entry	Starting material	Additives	Equiv.[b)]	Temp °C	Composition of reaction mixture [a]				
					1 %	**2(R)** %	**2(S)** %	ee %	**3** %
1	PhSMe	$Ti(OiPr)_4$	1:1:1	RT	32	34	32	3	2
2	PhSMe	$Ti(OiPr)_4$	1:1:1	0	33	34	31	5	3
3	PhSMe	$Ti(OiPr)_4$	2:2:1	-20	19	33	35	3	10
4	PhSMe	$Ti(OiPr)_4$	2:1:1	-30	9	49	28	27	14
5	PhSMe	$Ti(OiPr)_4$ MS 4 Å, 4d	2:1:1	-30	0	5	3	25	91
6	PhSMe	$Ti(OiPr)_4$	2:1:1	-78	96	2	2	0	0
7	rac PhSOMe	$Ti(OiPr)_4$	2:1:1	-30	0	4	4	0	91
8	PhSMe	without	1:0:1	-30	93	4	3	14	0
9	PhSMe	$VO(acac)_2$	2:1:1	-30	100	0	0	0	0
10	PhSMe	$MoO_2(acac)_2$	2:1:1	-30	0	41	45	5	14
11	4-MePhSMe	$Ti(OiPr)_4$	2:1:1	-30	0	36	18	33	17
12	4-ClPhSMel	$Ti(OiPr)_4$	2:1:1	-30	12	35	35	0	17
13	4-NO_2PhSMe	$Ti(OiPr)_4$	2:1:1	-30	20	29	26	5	26

[a] determined by integration of HPLC peaks

[b] piperazinedione hydroperoxide **4a** : $Ti(OiPr)_4$: methyl phenyl sulphide **1**

While the 4-component oxygen transfer system consisting of isoquinolines **7**, (*R*)-menthyl chloroformate, $Ti(OiPr)_4$ and hydrogen peroxide successfully used in the stereoselective synthesis of sulphoxides **2** turned out to fail in epoxidation reactions the piperazinedione hydroperoxide, **4a** could successfully be employed in certain epoxidations. Laschat et al. used **4a** in a Weitz-Scheffer epoxidation of cyclic enones and chalcones and could achieve full conversion with a maximal ee of 37 %. Our investigations with 2-alkylnaphthoquinones as another interesting target revealed that **4a** can also epoxidize 2-alkylnaphthoquinones **16** in the presence of DBU in excellent yields, but with unsatisfactory enantioselectivities. Extensive variation of temperatures and reaction times (see Table 5) led to 14 % ee at best. If the reaction temperature was lowered too much the reaction stopped. Other bases such as KOH or LiH gave worse results. Thus the piperazinedione hydroperoxide **4a** performed less satisfactory in the epoxidation of 2-alkylnaphthoquinones than known cases using sugar-derived hydroperoxides.[41-43]



16 **17** **18**

Scheme 6. Attempted enantioselective epoxidation of naphthoquinones **16** with **4a**.

Table 5. Epoxidation of naphthoquinones **16** with piperazinedione hydroperoxide **4a**

Entry	R	Conditions	Unreacted **16** (%)	**17**)[a] (%)	**18** (%)	ee (%)
1	Me	rt, 14 h	0	51	49	2
2	Me	0 °C, 5 h	11	46	43	4
3	Me	0 °C, 5h + rt 14 h	1	50	49	1
4	Me	-20 °C, 5 h	39	33	28	8
5	Me	-20 °C, 5 h + rt, 14 h	1	51	48	3
9	Me	-25 °C, 3 d	2	53	45	8
7	Me	-30 °C, 6 d	4	55	41	14
6	Me	-50 °C, 30 min + -30 °C, 3 d	3	53	44	10
8	Me	-78 °C, 6 d	74	14	12	8
9	Me	-40 °C, MeCN, KOH	> 99	0	0	0
10	Ph_2CH	-30 °C, 9 d	56	21	23	5
11	*t*-Bu	-30 °C	> 95	2	3	[b]
16	t-Bu	-78 °C	> 99	0	0	0
17	t-Bu	-30 °C, 7 d	> 99	0	0	0
18	t-Bu	-30 °C, 21 d	80	8	12	20

[a] assignment of configuration for R = Me by comparison with literature data.[44,45] [b] not determined

Conclusions

Novel isoquinoline-derived peroxides could be synthesized from isoquinolines, (*R*)-menthyl chloroformate and ethereal hydrogen peroxide or t-butylhydroperoxide. This synthesis lacks stereoselectivity, i. e. 1:1 epimeric mixtures were obtained. The same components were used in an *in situ* method in the presence of $Ti(OiPr)_4$ or other metal compounds for a novel stereoselective oxidation of methyl phenyl sulphide. As a best result 73% ee with 49%

overoxidation to the sulphone was achieved. This is a much better result as obtained with isolated chiral *N*-acylamino hydroperoxides so far. Unlike other findings reported in the literature, the application of optically active piperazinedione hydroperoxide **4a** gave also a stereoselective access to aryl methyl sulphoxides, but in a less efficient way than in the first method. **4a** is an effective epoxidizing reagent for 2-alkylnaphthoquinones, however in unsatisfactory stereoselectivities.

Experimental Section

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with a Bruker AC 300 in $CDCl_3$ with TMS as internal standard. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. Bromoisoquinolines **4a-c** and the substituted 2-methylnaphthoquinones **16** were synthesized according to literature procedures.[44,46-50] All the other materials were purchased from commercial suppliers.

General procedure for the synthesis of peroxides 11 and 12

(-)-(*R*)-Menthyl chloroformate (105 mg, 0.48 mmol) was added to a solution of an isoquinoline **4** (0.48 mmol) in dry dichloromethane (15 mL) at -40°C under argon. After 60 min while the solution turned slightly yellow, it was cooled to -78°C and a 3 M solution of *t*-butyl hydroperoxide (0.16 mL, 0.48 mmol) or 3 M ethereal hydrogen peroxide (0.16 mL, 0.48 mmol) was added by a syringe. The mixture was kept at this temperature for 60 min and was then quenched by pouring into water (30 mL). The organic phase was separated and the aqueous layer extracted with dichloromethane (20 mL). The combined organic phases were dried (Na_2SO_4) and the solvent stripped off under vacuum. The remainder was purified by column chromatography (80 g of silica, cyclohexane/AcOEt 7:3). R_f of the products around 0.9.

Bis(2-(1*R*)-menthyloxycarbonyl-5-bromo-1,2-dihydroisoquinoline) peroxide (11a). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 - 2.40 (m, 18H, menthyl), 4.76 (m, 1H, CHO), 6.35 (d, 1H, *J* = 8.0 Hz, CH_{ar}), 6.70 (m, 1H), 7.16 (m, 2H, CH_{ar}), 7.44 (m, 1H), 7.62 (dd, 1H, *J* = 1.0Hz, *J* = 8.0 Hz, CH_{ar}), 7.74 (d, 1H, *J* = 7.6 Hz, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (CH_3), 29.6 ($\underline{C}H(CH_3)$), 21.9 (CH_3), 23.2 (CH_2), 26.3 (2 x $\underline{C}H(CH_3)$), 31.5 (CH_3), 33.6 (CH_2), 41.0 (CH_2), 46.7 (CH), 81.3 (CHO), 84.0 (CHOO), 106.4 (C_{ar}), 109.9 (C_{ar}), 120.3 (C_{ar}), 124.9 (CHN), 127.2 (C_{ar}), 129.1 (C_{ar}), 131.8 (C_{ar}), 133.9 (C_{ar}), 153.4 (CO) ppm. HRMS (+ESI) $C_{40}H_{50}Br_2N_2NaO_6$ calc. 835.1933, found 835.1953.

Bis(2-(1*R*)-menthyloxycarbonyl-4-bromo-1,2-dihydroisoquinoline) peroxide (11b). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.19 - 2.43 (m, 18H, menthyl), 4.77 (m, 1H, CHO), 6.75 (m, 1H, CHOO), 7.09 - 7.81 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (CH_3), 20.6 (C*H*(CH3)), 21.9 (CH_3), 23.4 (CH_2), 26.3 (2 x CH(CH_3)), 31.4 (CH_3), 34.2 (CH_2), 40.2 (CH_2), 46.9 (CH), 81.4 (CHO), 84.0 (CHOO), 106.0 (C_{ar}), 110.0 (C_{ar}), 124.9 (C_{ar}), 125.0 (CHN), 127.6 (C_{ar}), 129.5 (C_{ar}), 130.4 (C_{ar}), 131.2 (C_{ar}), 152.4 (CO) ppm.

Bis(2-(1*R*)-menthyloxycarbonyl-5,8-dibromo-1,2-dihydroisoquinoline) peroxide. (11c). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 - 2.40 (m, 18H, menthyl), 4.76 (m, 1H, CHO), 6.42 (m, 1H, CH_{ar}), 7.01 (s br, 1H, CHOO), 7.28 (m, 1H, CH_{ar}), 7.37 (m, 1H, CH_{ar}), 7.48 (m, 1H, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (CH_3), 20.6 (*C*H(CH_3)), 21.9 (CH_3), 23.4 (CH_3), 26.3 (2 x (CH(*C*H_3)), 31.5 (CH_3), 33.8 (CH_2), 40.1 (CH_2), 46.8 (CH), 81.2 (CHO), 84.0 (CHOO), 106.3 (C_{ar}), 119.4 (C_{ar}), 126.6 (C_{ar}), 127.2 (C_{ar}), 131.2 (C_{ar}), 131.4 (C_{ar}), 134.5 (C_{ar}), 134.9 (C_{ar}), 150.0 (CO) ppm. HRMS (+EI) $C_{20}H_{25}Br_2NO_4$ calc 501.0150, found 501.0150.

Bis(2-(1*R*)-menthyloxycarbonyl-1,2-dihydroisoquinoline) peroxide (11d). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.18 – 2.19 (m, 18 H, menthyl), 4.69 (m, 1 H, CHO, menthyl), 5.91 (d, 1 H, *J* = 7.8, C*H*CHN), 6.91 (d, 1 H, *J* = 7.8, CHC*H*N), 7.05 – 7.35 (m, 4 H, CH_{ar}), 7.47(m, 1 H, HCOO) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 16.5 (CH_3), 20.6 (*C*H(CH_3)$_2$), 21.9 (2 CH_3), 23.4 (CH_2) 26.3 (*C*HCH_3), 31.4 (CH), 34.2 (CH_2), 41.1 (CH_2), 47.0 (CH), 77.2 (CHO), 81.3 (CHOO), 107.7 (*C*HCHN), 123.3 (CH*C*HN), 124.8 (CH_{ar}), 126.3 (CH_{ar}), 126.5 (C_{ar}), 126.7 (CH_{ar}), 129.6 (CH_{ar}), 132.1 (C_{ar}), 153.6 (CO) ppm. HRMS (FAB) $C_{20}H_{27}NO_4$: calc 345.1940, found 345.1950 fragment.

1-*tert*-Butylperoxy-2-(1*R*)-menthyloxycarbonyl-5-bromo-1,2-dihydroisoquinoline (12a). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 - 2.40 (m, 18H, menthyl), 1.19 (s, 9H, C(CH_3)$_3$), 4.76 (dt, 1H, *J* = 4.5 Hz, *J* = 11.0 Hz), CHO), 6.41 (m, 1H, CH_{ar}), 6.91 (m, 1H,CHOO), 7.14 (t, 1H, *J* = 7.8 Hz), 7.26 (m, 1H, CH_{ar}), 7.38 (m, 1H, CH_{ar}), 7.62 (dd, 1H, *J* = 1.1 Hz, *J* = 8.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (CH_3), 20.6 (*C*H(CH_3)), 21.9 (CH_3), 23.4 (CH_2), 26.3 (5 x CH(*C*H_3)), 31.5 (CH_3), 33.8 (CH_2), 40.1 (CH_2), 46.9 (CH), 81.0 (CHO), 83.5 (O*C*(CH_3)), 84.0 (CHOO), 106.4 (C_{ar}), 109.9 (C_{ar}), 120.3 (C_{ar}), 125.5 (CHN), 127.2 (C_{ar}), 128.1 (C_{ar}), 131.4 (C_{ar}), 133.6 (C_{ar}), 150.6 (CO) ppm. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.60 - 2.40 (m, 18H, menthyl), 1.19 (s, 9H, C(CH_3)$_3$), 4.76 (dt, 1H, *J* = 4.5 Hz, *J* = 11.0 Hz), CHO), 6.30 (s br, 1H, CH_{ar}), 6.88 (m, 1H, CHOO), 7.24 (dt, 1H, *J* = 1.3Hz, *J* = 7.8Hz, CH_{ar}), 7.25 (m br, 1H, CH_{ar}), 7.58 (d, 1H, *J* = 7.5Hz), 7.70 (dd, 1H, *J* = 2.8Hz, *J* = 8.0Hz, CH_{ar}) ppm. HRMS (+ESI) $C_{24}H_{34}BrNNaO_4$ calc 502.1569, found 502.1565.

1-*tert*-Butylperoxy-2-(1*R*)-menthyloxycarbonyl-4-bromo-1,2-dihydroisoquinoline (12b). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 - 2.40 (m, 18H, menthyl), 1.19 (s, 9H, C(CH_3)$_3$), 4.68 (m, 1H, CHO), 6.41 - 6.98 (m, 1H, CHOO), 7.35 - 7.65 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 16.3 (CH_3), 20.6 (*C*H(CH_3)), 21.9 (CH_3), 23.4 (CH_2), 26.3 (5 x CH(*C*H_3)), 31.4 (CH_3), 34.2 (CH_2), 40.2 (CH_2), 47.0 (CH), 81.1 (CHO), 83.7 (O*C*(CH_3)), 84.0 (CHOO), 106.4 (C_{ar}), 109.9 (C_{ar}), 124.9 (C_{ar}), 125.8 (CHN), 127.9 (C_{ar}), 128.4 (C_{ar}), 130.1 (C_{ar}), 130.1 (C_{ar}), 152.4 (CO) ppm. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.60 - 2.40 (m, 18H, menthyl), 4.68 (m, 1H, CHO), 6.41 - 6.98 (m, 1H, CHOO), 7.35 - 7.65 (m, 5H) ppm.

1-*tert*-Butylperoxy-2-(1*R*)-menthyloxycarbonyl-5,8-dibromo-1,2-dihydroisoquinoline (12c). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.60 - 2.40 (m, 18H, menthyl), 1.19 (s, 9H, C(CH_3)$_3$) , 4.76 (dt, 1H, *J* = 4.5 Hz, *J* = 11.0 Hz), CHO), 6.39 (m, 1H, CH_{ar}), 7.24 (s br, 2H, CH_{ar} / CHOO), 7.33 (d, 1H, *J* = 8.5Hz, CH_{ar}), 7.47 (d, 1H, *J* = 8.5Hz, CH_{ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3 (CH_3), 20.6 (*C*H(CH_3)), 21.9 (CH_3), 23.4 (CH_3), 26.3 (5 x CH(*C*H_3)), 31.5 (CH_3), 33.8 (CH_2),

40.1 (CH_2), 46.8 (CH), 81.2 (CHO), 82.6 ($C(CH_3)_3$), 84.0 (CHOO), 106.3 (C_{ar}), 119.4 (C_{ar}), 126.6 (C_{ar}), 127.2 (C_{ar}), 131.2 (C_{ar}), 131.4 (C_{ar}), 134.5 (C_{ar}), 134.9 (C_{ar}), 150.0 (CO) ppm.

1-*tert*-Butylperoxy-2-(1*R*)-menthyloxycarbonyl-1,2-dihydroisoquinoline (12d). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.58 – 2.29 (m, 18 H, menthyl), 1.11 (s, 9 H, *tert*-butyl), 4.70 (m, 1 H, CHO, menthyl), 5.91 (d, 1 H, *J* = 7.5, C*H*CHN), 7.13 (d, 1 H, *J* = 7.5, CHC*H*N), 7.07 – 7.39 (m, 4 H, CH_{ar}), 6.95 (m, 1 H, HCOO) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 16.2 (CH_3), 20.5 ($CH(CH_3)_2$), 21.9 (2 CH_3), 23.4 (CH_2) 26.3 ($CHCH_3$), 31.4 (CH), 34.2 (CH_2), 41.2 (CH_2), 47.2 (CH), 76.8 (CHO), 80.8 (CCH_3), 83.7 (CHOO), 107.7 (*C*HCHN), 124.8 (CH*C*HN), 126.4 (CH_{ar}), 126.7 (CH_{ar}), 128.5 (C_{ar}), 129.6 (CH_{ar}), 131.6 (CH_{ar}), 132.0 (C_{ar}), 153.5 (CO) ppm. HRMS (+ESI) $C_{24}H_{35}NO_4{}^{23}Na$: calc 424.2464, found 424.2461.

Oxidation of aryl methyl sulphides by hydrogen peroxide in the presence of isoquinolines, (*R*)-menthyl chloroformate and metal compounds (Tables 1, 2, 3)

Molecular sieve 4 Å (150 mg) (*R*)-menthyl chloroformate **8** (87 mg, 0.4 mmol) and the metal compound (e.g. $Ti(OiPr)_4$) (0.4 mmol) were added to a solution of the isoquinoline **7** (0.4 mmol) in dry dichloromethane at 0 °C under argon. After 30 min the aryl methyl sulphide **1** (0.4 mmol) were added. After 30 min stirring 3 M ethereal hydrogen peroxide (preferably 0.8 mmol, 2.2 equivalents, see Tables 2) was added. After 60 or 10 min (see Tables 1, 2) the mixture was poured into water (40 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was stripped off under vacuum. The remaining oil was investigated by analytical chiral HPLC.

Oxygen transfer to aryl methyl sulphides 1 and naphthoquinones 16 by the piperazinedione hydroperoxide 4a (Tables 4, 5)

$Ti(OiPr)_4$ (0,01 mL, 0.04 mmol) and sulphide **1** or DBU (0.006 mL, 0.04 mmol) and the 2-methylnaphthoquinone **16** (0.04 mmol) were added to a solution of the piperazinedione hydroperoxide **4a** (0.08 mmol respectively 0.04 mmol) in dry dichloromethane under argon at the reported temperature (see Tables 4, 5). The mixture was kept at this temperature overnight and was then poured into water (30 mL) containing a few drops of concentrated aqueous Na_2SO_3. The mixture was extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was stripped off. The remaining oil was investigated by chiral HPLC (see also supporting information).

Supporting Information Available

NMR-spectra of selected peroxides **12**, Table with results of oxidation of methyl phenyl sulphide in the presence of $VO(OiPr)_3$, parameters of analyses or reaction mixtures.

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