

Diketopiperazine-derived hydroperoxide for chemoselective oxidations of sulfides and enantioselective Weitz–Scheffer epoxidations

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Abstract

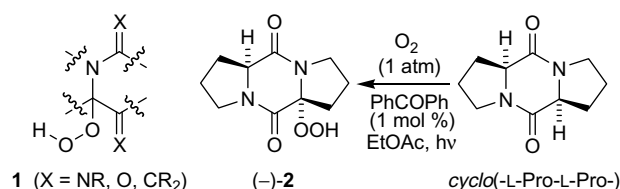
L-Proline-derived hydroperoxide (–)-**2**, which was obtained from the corresponding diketopiperazine by irradiation under oxygen atmosphere, was applied to the oxidation of a variety of sulfides and asymmetric Weitz–Scheffer epoxidations of cyclic and acyclic enones. The sulfoxidation, however, gave only racemic products. In contrast, depending on the base catalyst, enantioselectivities up to 37% were achieved in the epoxidation of chalcone with (–)-**2**.

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The chemo- and stereoselective oxidation of sulfides to the corresponding sulfoxides and the enantioselective Weitz–Scheffer epoxidation of α,β -unsaturated carbonyl compounds constitute two valuable synthetic transformations, which have received enormous interest.^{1,2} Organic hydroperoxides of the general formula **1** (Scheme 1) are known for more than two decades, mostly in the form of flavin derivatives. Their use in the transfer of oxygen to sulfides, amines and other substrates is well established in the literature.³ Most recent results along this direction were reported by Bäckvall⁴ and Murahashi⁵ employing flavins as redox catalysts and hydrogen peroxide as stoichiometric oxidant. Sulfoxidations were performed with excellent chemoselectivities but no enantioselectivity was achieved.

Chiral hydroperoxides, which were obtained via kinetic resolution using peroxidases,^{6,7} Sharpless epoxidation,⁸ separation by column chromatography on a chiral stationary phase⁹ and via diastereomeric perketals,¹⁰ were successfully used in asymmetric oxidations. Rebek was probably



Scheme 1. General formula of organic hydroperoxides **1** and *cis*-configured L-proline-derived hydroperoxide (–)-**2**.¹⁹

the first who studied olefin epoxidations with chiral hydroperoxides.^{11,12} Optically active hydroperoxides have also been employed in sulfoxidations by Wong,¹³ Adam,^{6,14} Hamann¹⁵ and others¹⁶ as well as in asymmetric Weitz–Scheffer epoxidations of enones.^{16d,17} In most cases, the hydroperoxide unit was generated by the oxidation of the corresponding C–H bond with hydrogen peroxide rather than by molecular oxygen. However, the formation of a chiral hydroperoxide under aerobic conditions and its subsequent use in oxidations would be highly desirable. Surprisingly, besides a report by Oda on a Weitz–Scheffer epoxidation under chiral phase transfer conditions with in situ formed 9-hexyl-fluorenone-9-hydroperoxide as achiral oxidant,¹⁸ this issue has never been investigated in detail. Thus, we studied optically active L-proline-derived

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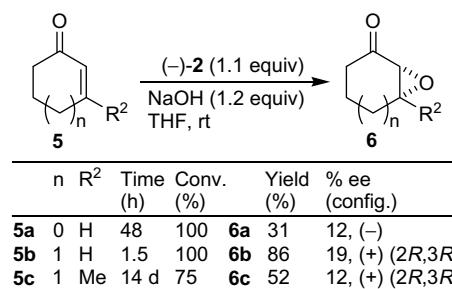
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diketopiperazine hydroperoxide (–)-**2**^{19–23} (Scheme 1), which is accessible by irradiation of precursor *cyclo*-(–L-Pro-L-Pro–) under O₂ atmosphere, as oxygen source in sulfoxidations and Weitz–Scheffer epoxidations.

First, various sulfides **3** were treated with a stoichiometric amount of hydroperoxide (–)-**2** in MeOH at room temperature. Upon complete consumption of starting material **3** (monitored by NMR), the reaction mixture was submitted to aqueous workup and sulfoxides **4** were isolated after chromatography (Table 1).

Dibutylsulfide **3a** reacted rapidly to sulfoxide **4a** in excellent yield of 86% whereas diphenylsulfide **3f** required 5 days for completion (entries 1 and 6). The unsymmetrically substituted sulfides **3b–e** gave sulfoxides **4b–e** in moderate to good yields (entries 2–5). The reactivity of arylmethylsulfides **3g–i** depended on the aryl substituent. Whereas electron-withdrawing substituents such as cyano (**3i**) strongly decreased the reactivity (entry 9), the reaction times were improved for the electron-donating +M substituents: bromo and methoxy (entries 7 and 8). It must be noted that even in the cases of moderate yields, oxidations went with complete chemoselectivities, that is, no trace of the corresponding sulfones was detected. However, despite the use of enantiopure hydroperoxide (–)-**2** no enantioselectivity was observed (separation by HPLC).

In order to assess the reactivity and stereoselectivity of hydroperoxide (–)-**2**, the base-catalyzed Weitz–Scheffer epoxidation was performed with enones **5** (Scheme 2). Cyclopentenone **5a** and cyclohexenone **5b** yielded the corresponding epoxyketones **6a** and **6b** without any problem. The reduced yield of **6a** is due to its high volatility. Steric hindrance at the β-position of the enone moiety significantly decreased the reactivity as shown for 3-methylcyclohexenone **5c** with a reaction time of 14 days.



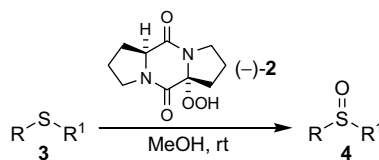
Scheme 2. Weitz–Scheffer epoxidation of cyclic enones **5** by hydroperoxide **2**. Yields refer to isolated yields, ee values were determined by HPLC on a chiral phase Chiracel OD-H. The configuration of the major enantiomer of **6b** was derived from the comparison of optical rotation with the literature data,^{16d,24} that of **6c** was assigned by analogy.

Unfortunately, only poor enantioselectivities up to 19% ee were obtained.

Recently, Adam reported the important influence of the base catalyst on the enantioselectivity in Weitz–Scheffer epoxidations.^{17b,c} We therefore studied the epoxidation of 4-phenylbut-3-en-2-one (**7a**) and chalcone **7b** by hydroperoxide **2** in the presence of various bases (Table 2).²⁵

In most cases, conversions and yields for **7b** are better than those for **7a**. The most surprising outcome, however, was the different reactivity of enones **7a** and **7b** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entries 3, 8, 9). Whereas 4-phenylbutenone **7a** and hydroperoxide (–)-**2** did not give any trace of the desired product **8a**, epoxide **8b** was isolated in excellent yields with the highest enantioselectivities of 35–37% ee. From the results in Table 2 it is obvious that chalcone **7b** displays a much higher reactivity than 4-phenylbutenone **7a**. Again, the absolute configuration of products **8a,b** (entries 4 and 10) was

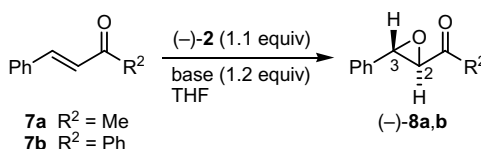
Table 1
Oxidation of sulfides **3** to the corresponding sulfoxides **4** using hydroperoxide **2**



Entry	Sulfide	R	R ¹	Oxidant 2 (equiv)	Time	Sulfoxide	Yield (%)
1	3a	Bu	Bu	1.1	1.5 h	4a	86
2	3b	Ph	Me	1.0	24 h	4b	67
3	3c	Ph		1.1	24 h	4c	44
4	3d	Ph		1.0	19 h	4d	78
5	3e	Ph		1.0	24 h	4e	39 ^a
6	3f	Ph	Ph	1.0	5 d	4f	86
7	3g	4-BrC ₆ H ₄	Me	1.1	72 h	4g	84
8	3h	4-MeOC ₆ H ₄	Me	1.1	20 h	4h	41
9	3i	4-CNC ₆ H ₄	Me	1.1	9 d	4i	15

^a 20% of sulfide **3e** was recovered.

Table 2

Epoxidation of enones **7** with hydroperoxide **2** in the presence of various bases

Entry	Enone	Base	<i>T</i> (°C)	Time	Conv. (%)	Product	Yield ^a (%)	% ee ^b
1	7a	KOtBu	−20 ^c	7 h	66	8a	33	18
2	7a	LiOH	0	24 h	93	8a	62	24
3	7a	DBU	0	7 d	0 ^d	8a	—	—
4	7a	KOH	0	24 h	72	8a	48	11 ^e
5	7a	<i>n</i> BuLi	−20	5 h	60	8a	57	18
6	7b	KOtBu	0	42 h	77	8b	53	11
7	7b	LiOH ^f	0	44 h	100	8b	87	22
8	7b	DBU	0	6 d	95	8b	84	37
9	7b	DBU	25	6 d	100	8b	95	35
10	7b	KOH	0	8 h	100	8b	98	2 ^e
11	7b	<i>n</i> BuLi	−20	8 h	100	8b	98	26

^a Yields refer to isolated yields.^b Enantioselectivities of **8a** were detected by GC on a chiral stationary phase Bondex un- α , those of **8b** by HPLC on a chiral phase Chiracel OD-H.^c Low temperature to achieve higher enantioselectivity.^d Complete reisolation of **7a**.^e Configuration of (−)-**8a** and (−)-**8b** was assigned by comparison of optical rotation with the literature data^{16d,26} to be (2*R*,3*S*).^f 2.5 equiv.

assigned by comparison of optical rotation with the literature data.^{16d,26} According to Adam's findings,^{17b} the (2*R*,3*S*)-configuration of the major enantiomer of epoxyketone **8a** and **8b** indicates that hydroperoxide (−)-**2** preferentially attacks the *Re* face of enones **7a,b**.

In conclusion, enantiomerically pure diketopiperazine hydroperoxide (−)-**2** could be successfully used for chemoselective sulfoxidations and enantioselective Weitz–Scheffer epoxidations under mild conditions. The formation of hydroperoxide **2** under oxygen atmosphere is particularly important, thus avoiding the use of hydrogen peroxide. However, further efforts are necessary to achieve enantioselectivity in sulfoxidations as well, to improve the chirality transfer in Weitz–Scheffer epoxidations and to develop a catalytic version of this process. Work along these lines are currently under way in our laboratories.

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