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Catalytic Asymmetric Peroxidation of α,β-Unsaturated Nitroalkenes by a Bifunctional Organic Catalyst

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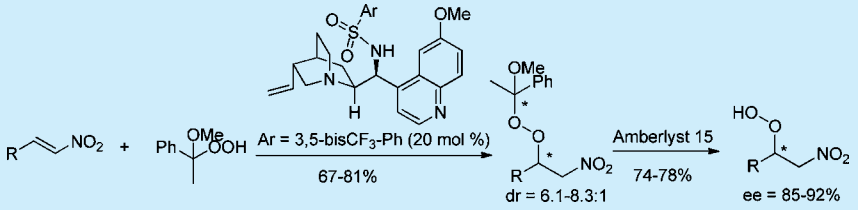
Supporting Information



ABSTRACT: A new enantioselective peroxidation of α,β-unsaturated nitroalkenes was realized with an easily accessible acid−base bifunctional organic catalyst derived from cinchona alkaloids. This reaction provides unprecedented easy access to optically active chiral peroxides, as illustrated by the asymmetric synthesis of β-peroxy nitro compounds.

Numerous peroxy natural products have been isolated, and many of them are identified to be highly potent anticancer, antitumor, and antimalaria compounds.[1] Importantly, the cytotoxicity of the peroxide functionality renders some of them, such as artemisine and yingzhaosu C (Figure 1), the most effective and widely used antimalarial drugs,

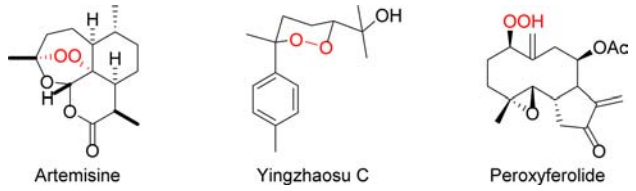


Figure 1. Selected examples of bioactive peroxide natural products.

thereby proving molecules incorporating a peroxide functionality in a proper chiral scaffold could provide compounds of clinical significance.[2] This in turn highlights the urgent need to develop new methods to expand our ability to access chiral peroxides of a broad structural diversity. To our knowledge, the creation of a chiral peroxide motif still relies on the transformation of an optically active precursor designed on an ad hoc basis.[3−7] Thus, enantioselective methods of useful generality for the transformations of prochiral starting materials into optically active peroxides are urgently needed. However, the development of such asymmetric oxidations stands as a challenging problem in asymmetric synthesis.[8]

Recently, our group has reported the first catalytic highly enantioselective peroxidation reaction of α,β-unsaturated ketones via base-iminium catalysis.[8a] To extend our cooperative catalysis approach to the development of highly enantioselective peroxidation reactions of an electron-deficient double bond in conjugation with noncarbonyl functionality, we began to investigate enantioselective peroxidation reactions of α,β-unsaturated nitroalkenes.[9] It is noteworthy that Lattanzi once reported the asymmetric peroxidation of α,β-unsaturated nitroalkenes with TBHP utilizing a proline-derived catalyst.[10] Up to 84% ee was obtained with β-aryl nitroalkenes and TBHP; nevertheless, both the enantioselectivity and yield of the reactions are highly substrate-dependent. In the sole example of a reaction with a simple β-alkyl nitroalkene, the peroxide was reported to be formed in 20% yield and with the ee value undetermined. The enantioselectivity as well as the substrates scope of not only nitroalkenes but also hydroperoxide remained to be significantly improved to render this reaction synthetically applicable for the synthesis of peroxy natural products. Herein, we reported the first highly enantioselective catalytic asymmetric peroxidation of the alkyl nitroalkene to prepare the chiral β-hydroperoxy nitroalkane.

We began our investigation employing β-phenyl nitroalkene **1A** as the model substrate with cumene hydroperoxide **2a**. A variety of cinchona alkaloid derivatives (Figure 2) were screened for their ability to promote the aforementioned model reaction (Table 1). The 6′-OH cinchona alkaloid

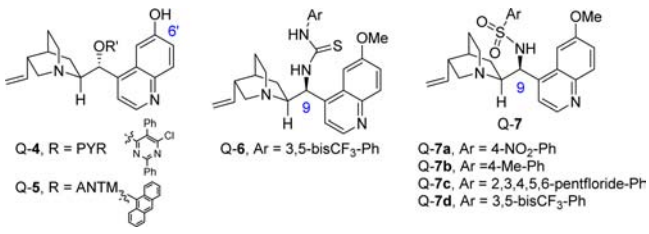


Figure 2. Structures of cinchona alkaloids.

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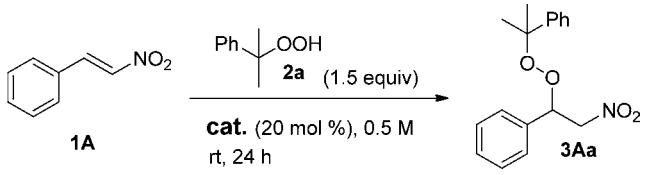
Table 1. Asymmetric Peroxidation Reaction of α,β-Unsaturated Nitroalkene 1A with Cumene Hydroperoxide 2a



entry[a]	cat.	solvent	conv (%)[b]	ee (%)[c]
1	Q-**4**	hexane	33	15
2	Q-**5**	hexane	66	49
3	Q-**6**	hexane	<5	nd
4	Q-**7a**	hexane	49	70
5	Q-**7b**	hexane	50	76
6	Q-**7c**	hexane	41	70
7	Q-**7d**	hexane	57	90
8	Q-**7d**	cyclohexane	60	89
9	Q-**7d**	cyclohexane/toluene = 3:1	47	88
10	Q-**7d**	toluene	29	68
11	Q-**7d**	TBME	<1	nd
12	Q-**7d**	CH_2Cl_2	12	76
13	Q-**7d**	methylcyclohexane	61	91

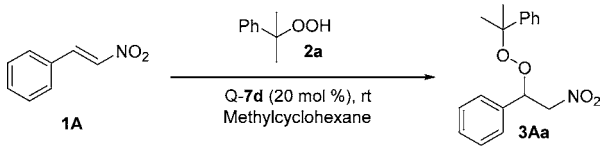
[a]The reaction was run with 0.1 mmol of **1A**. [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis.

afforded good conversion but moderate ee (Table 1, entries 1–2) while Q-**6** just decomposed (Table 1, entry 3). Conceivably, the cumene hydroperoxide might react with thiourea functionality in the Q-**6** catalyst. Our attention was then turned to cinchona alkaloids bearing other hydrogen bond donors at the 9-position; thus, a series of 9-sulfonamide cinchona alkaloids Q-**7** were investigated.[11] To our satisfaction, these 9-sulfonamide catalysts were much better in enantioselectivity (Table 1, entries 4–7). In particular, catalyst Q-**7d** could provide the peroxide with 90% ee and 57% conversion after 24 h (Table 1, entry 7). Solvent screening revealed that methylcyclohexane was the optimal solvent, affording 91% ee and 61% conversion after 24 h (Table 1, entry 13).

The reaction in methylcyclohexane reached 88% conversion with 89% ee after 96 h; however, the isolated yield was only 38% (Table 2, entry 1). Probably, the poor yield might be due to partial decomposition of the nitroalkenes via polymerization, as insoluble byproducts were formed during the reaction. Consequently, a reaction in a reduced concentration of 0.20 M vs 0.50 M (Table 2, entry 2) was attempted to avoid polymerization. However, only 64% conversion was afforded after 96 h with no improvement in isolated yield. Nonetheless, increasing the amount of cumene hydroperoxide from 1.5 to 3.0 equiv improved the isolated yield to 51% (Table 2, entry 3). A further increase of the cumene hydroperoxide led to a yield of 60% although the enantioselectivity decreased noticeably (Table 2, entry 4). Notably, when the reaction was run in a higher substrate concentration (0.33 M) and with 3.0 equiv of cumene hydroperoxide, the chiral peroxide could be produced in 93% ee and 62% yield (Table 2, entry 5).

With the optimal reaction conditions established, the reaction scope with respect to the nitroalkenes was investigated. The aromatic nitroalkenes bearing both the *meta*- and *para*-substituted groups could be transformed into the corresponding peroxide in good yield and enantioselectivity (Table 3, entries 2–5). Furthermore, substituents of

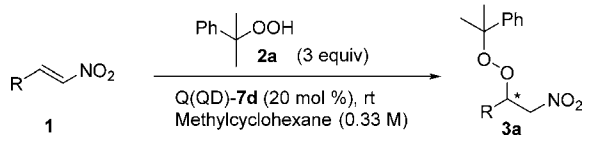
Table 2. Optimization of Asymmetric Peroxidation between β-Nitrostyrene 1A and Cumene Hydroperoxide 2a



entry[a]	2a equiv	concn (M)	time (h)	conv (%)[b]	ee (%)[c]	yield (%)
1	1.5	0.50	96	88	89	38
2	1.5	0.20	96	64	92	37
3	3.0	0.20	88	77	92	51
4	5.0	0.20	120	78	84	60
5	3.0	0.33	80	86	93	62

[a]The reaction was run with 0.2 mmol of **1A**. [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis

Table 3. Substrate Scope of α,β-Unsaturated Nitroalkenes 1 with Cumene Hydroperoxide 2a



entry[a]	1	R	time (h)	yield (%)	ee (%)[d]
1	**1A**	Ph	80	62	93[e]
2	**1B**	4-Me-Ph	120	51	88
3	**1C**	3-Me-Ph	96	58	90
4[b]	**1D**	4-Br-Ph	96	43	91
5[b]	**1E**	3-Br-Ph	120	43	87
6[b,f]	**1F**	4-Cl-Ph	96(120)	52(45)	94(83)
7[b,f]	**1G**	4-F-Ph	120(144)	63(50)	88(83)
8[b]	**1H**	4-OMe-Ph	120	65	92
9[c]	**1I**	n-C_4H_9	120	59	83
10[c]	**1J**	n-C_7H_{15}	120	61	90
11[c]	**1K**	$PhCH_2CH_2$	88	67	84
12[c]	**1L**	i-C_4H_9	100	55	86

[a]Unless noted, all the reactions were carried out with 0.2 mmol of nitroalkene **1**. [b]The reactions were run with 0.6 mL of methylcyclohexane and 0.2 mL of dichloromethane. [c]The reactions were run at 0 °C with 1.5 equiv of **2a** and 0.4 mL of methylcyclohexane. [d]It is determined by the HPLC analysis. [e]Absolute configuration was determined to be *R*; for details, see Supporting Information. [f]Results in parentheses were obtained with QD-**7d**.

either an electron-withdrawing or electron-donating nature on the aromatic ring were tolerated (Table 3, entries 2–8). For nitroalkenes of low solubility in methylcyclohexane, the combined solvent system methylcyclohexane/CH_2Cl_2 = 3:1 proved to be optimal because additional dichloromethane assisted in dissolving the solid nitroalkenes (Table 3, entries 4–8). Importantly a variety of aliphatic nitroalkenes were found to undergo peroxidation in good yields and enantioselectivity at 0 °C (Table 3, entries 9–12).

To render this asymmetric peroxidation reaction more synthetically applicable for the synthesis of peroxy natural product, we investigated the peroxidation of α-alkoxyl

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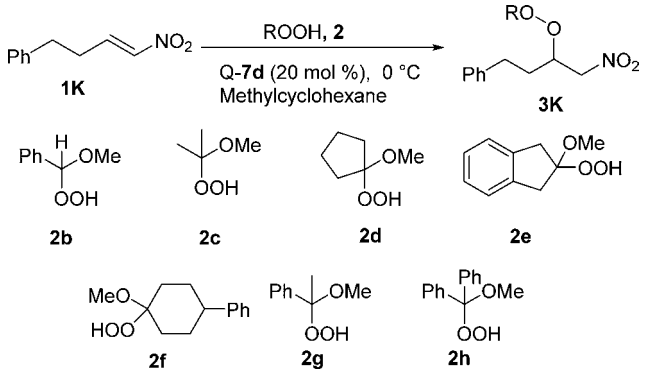
hydroperoxides with nitroalkene **1K**, as peroxide **3K** could be readily converted to the corresponding β-hydroperoxy nitroalkane by treating with acid. A variety of α-alkoxyl hydroperoxides were synthesized according to literature reports.[12] We first found that the secondary hydroperoxide **2b** readily decomposed (Table 4, entry 1). Tertiary α-alkoxyl

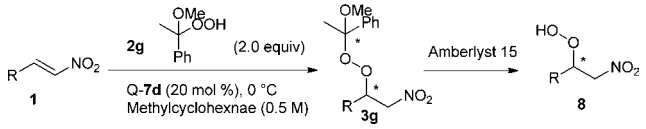
Table 4. Asymmetric Peroxidation of Nitroalkenes with α-Alkoxyl Hydroperoxide



entry[a]	2	2 (equiv)	time (h)	conv (%)[b]	ee (%)[c]
1	**2b**	1.2	24	0	nd
2	**2c**	1.2	48	50	60
3	**2d**	1.2	72	60	51
4	**2e**	1.2	24	<5	nd
5	**2f**	1.2	24	<5	nd
6[d]	**2g**	2.0	144	>95	89
7	**2h**	1.2	24	0	nd

[a]All the reactions were carried out with 0.1 mmol of nitroalkene. [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis. [d]6.5:1 dr was observed, and ee was determined after hydrolysis to the hydroperoxide.

Table 5. Substrate Scope of Nitroalkene 1 with α-Alkoxyl Hydroperoxide 2g



entry[a]	1, R	time (h)	3g (dr)[b]	3g, yield (%)	8, ee (%)[c]	8, yield (%)
1	**K**, homobenzyl	144	6.5:1	80	89	77[d]
2	**M**, *n*-propyl	144	6.8:1	81	90	74
3	**I**, *n*-butyl	144	6.2:1	67	90	75
4	**J**, *n*-heptyl	140	8.3:1	74	85	77
5	**L**, isobutyl	148	6.1:1	68	92	78

[a]All the reactions were carried out with 0.2 mmol of nitroalkene **1**. [b]Determined by ^{1}H NMR analysis. [c]Determined by HPLC analysis. [d]Absolute configuration was determined as *S*; see Supporting Information for details.

hydroperoxides such as **2c** and **2d** afforded the peroxide adduct with moderate conversion and ee. Interestingly, the reaction is sensitive to the bulk of the peroxide as reactions with bulky α-alkoxyl hydroperoxides such as **2e** and **2f** failed to occur (Table 4, entries 4–5). On the other hand, peroxide **2g** was shown to be a suitable reagent giving us >95% conversion and 89% ee (Table 4, entry 6). No reaction was observed with the bulkier peroxide **2h** (Table 4, entry 7).

With the hydroperoxide **2g**, the substrate scope with respect to nitroalkenes **1** was investigated. A variety of aliphatic nitroalkenes underwent peroxidation in good yield and excellent enantioselectivity. Significantly, the addition product **3g** could be efficiently transformed to the β-hydroperoxy nitroalkane **8** with good yield (Table 5). Interestingly, the peroxidation also took place in 6.1 to 8.3:1 dr, indicating the peroxidation proceeded not only in high enantioselectivity in terms of recognizing the enantio topic face of the nitroalkenes, but also in resolution of the hydroperoxide **2g** with a significant level of selectivity.

In summary, we have developed the first catalytic highly enantioselective peroxidation of both aromatic and aliphatic nitroalkenes utilizing the easily accessible reagents and catalysts. Utilizing the hydroperoxide **2g**, the first asymmetric synthesis of chiral β-hydroperoxy nitroalkane was successfully developed.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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