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Organocatalytic Enantioselective Peroxidation of Ketimines Derived from Isatins

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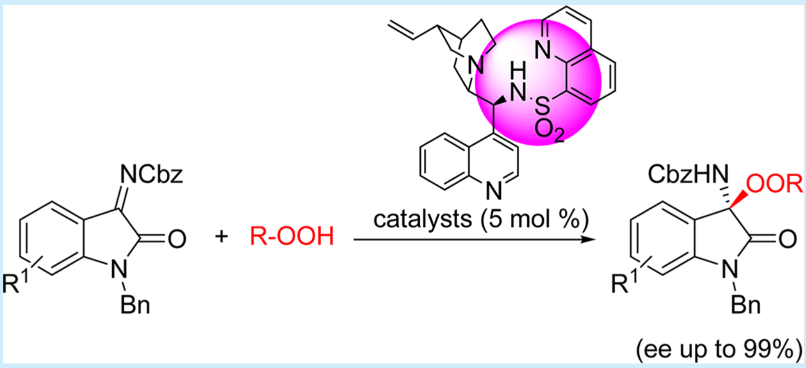
Supporting Information



ABSTRACT: The first catalytic enantioselective addition of hydroperoxides to ketimines derived from isatins has been developed. Excellent yields and enantioselectivities were observed for the reaction of various ketimines with peroxides using a cinchona alkaloid sulfonamide catalyst. Both enantiomers of products could be obtained by using pseudoenantiomeric chiral catalysts. The obtained product can be converted to optically active α-amino hydroperoxide.

Optically active peroxide-containing compounds and their derivatives have been proven to be useful chiral building blocks for the preparation of pharmaceutical targets,[1] such as antimalarial[2] and anticancer drugs.[3] Furthermore, chiral α-amino peroxide moieties can be found in natural products, such as verruculogen[1a] and D-luciferin dioxetanone (Figure 1).[4]

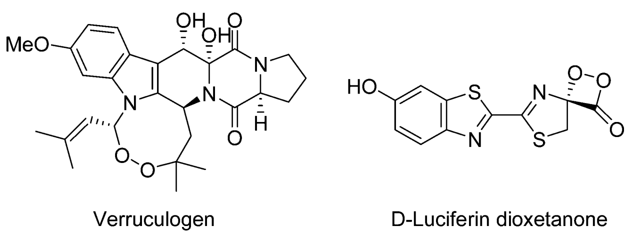


Figure 1. Natural compounds having an α-amino peroxide structure.

Therefore, their synthetic importance has prompted considerable interest to develop the asymmetric synthesis of chiral α-amino peroxides, although catalytic enantioselective synthesis of these compounds remains a considerable challenge.[5]

One of the most efficient methods for the preparation of chiral α-amino peroxides is the enantioselective addition of hydroperoxides to imines.[6] Antilla and co-workers reported the first enantioselective synthesis of chiral α-amino peroxides by the reaction of hydroperoxides with *N*-acylimines derived from aldehydes using chiral phosphoric acids to give chiral α-amino peroxides in excellent yields with high enantioselectivities.[7,8] Although such pioneering studies exist, there are no reports to challenge the difficulty of the enantioselective addition of hydroperoxides to ketimines.[9,10] On the other hand, the reaction of ketimines derived from isatins has attracted much attention, because the reaction affords α-amino peroxides having a 2-oxindole backbone, which is an important structural motif in biologically active compounds.[11] However, only little attention has been paid to the enantioselective addition of heteroatoms to ketimines. We recently reported the first enantioselective reactions of ketimines with some heteroatom nucleophiles, such as phosphites[12] and thiols,[13] and we also developed novel catalysts derived from cinchona alkaloids.[14] Herein, our ongoing interest was extended to the enantioselective addition of hydroperoxides to various ketimines using our original chiral catalysts derived from cinchona alkaloids (Figure 2).

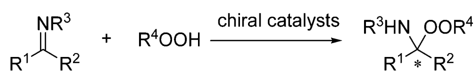


Figure 2. Enantioselective synthesis of α-amino peroxides through the addition of hydroperoxides to ketimines.

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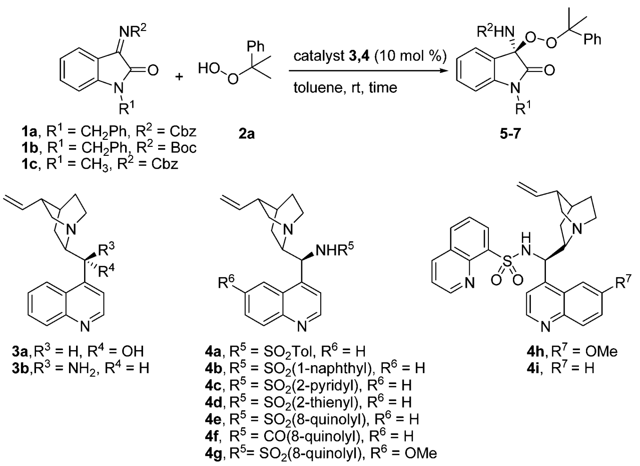
First, we examined the reaction of ketimines derived from isatins **1** with cumene hydroperoxide **2a** in the presence of chiral organocatalysts **3**,**4** derived from various cinchona alkaloids in toluene. The results are shown in Table 1.

Table 1. Enantioselective Addition of Cumene Hydroperoxide 2a to Ketimines 1a−c Derived from Isatins Using Various Chiral Organocatalysts 3,4[a]



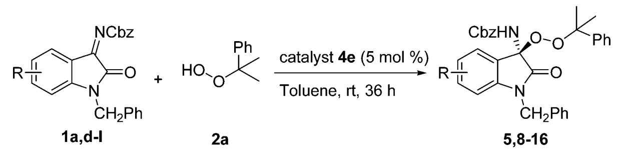
run	1	cat.	product	time (h)	yield (%)[b]	ee (%)
1	**1a**	**3a**	**5**	12	94	12
2	**1a**	**3b**	**5**	48	75	67
3	**1a**	**4a**	**5**	36	96	88
4	**1b**	**4a**	**6**	48	48	67
5	**1c**	**4a**	**7**	48	94	79
6	**1a**	**4b**	**5**	36	74	88
7	**1a**	**4c**	**5**	12	91	36
8	**1a**	**4d**	**5**	36	91	60
9	**1a**	**4e**	**5**	12	90	97
10	**1a**	**4f**	**5**	36	11	0
11	**1a**	**4g**	**5**	12	99	97
12	**1a**	**4h**	**5**	36	94	85[c]
13	**1a**	**4i**	**5**	36	99	67[c]
14[d]	**1a**	**4e**	**5**	60	98	96
15[e]	**1a**	**4e**	**5**	72	90	91
16[f]	**1a**	**4e**	**5**	36	99	97

[a]Reaction condition: ketimine **1** (0.03 mmol), **2a** (3.0 equiv), **3**,**4** (10 mol %), and toluene (0.06 M) were used. [b]Isolated yield. [c]Opposite enantiomer was obtained. [d]**4e** (2 mol %) was used. [e]**4e** (1 mol %) and **2a** (5.0 equiv) were used. [f]The reaction was carried out in an open flask using 5 mol % of **4e**.

Although the reaction of *N*-Cbz-*N*′-benzyl isatinimine **1a** with **2a** using cinchonidine **3a** or 9-amino-9-deoxy-*epi*-cinchonidine **3b** afforded product **5** in high yield with low or moderate enantioselectivity (Table 1, entries 1 and 2), the reaction using *N*-tosylated 9-amino-9-deoxy-*epi*-cinchonidine **4a** gave **5** in high yield with good enantioselectivity (Table 1, entry 3). In order to improve the reactivity and enantioselectivity, we attempted the reaction of various substituted ketimines with **2a**. However, the reaction of ketimines derived from *N*-Boc-*N*′-benzyl isatin **1b** or *N*-Cbz-*N*′-methyl isatin **1c** gave products **6**,**7** with lower enantioselectivity than that from the reaction using **1a** (Table 1, entries 4 and 5). We next investigated the effect of the catalyst structure on stereoselectivity. The reaction using various *N*-substituted 9-amino-9-deoxy-*epi*-cinchonidines **4b−f** having 1-naphthalenesulfonyl, 2-pyridinesulfonyl, 2-thiophensulfonyl, 8-quinolinesulfonyl, and 8-quinolinecarbonyl groups afforded product **5**. The best enantioselectivity and reactivity were obtained in the reaction using **4e** having an 8-quinolinesulfonyl group (Table 1, entries 6−10). We also examined the reaction using 8-quinolinesulfonylated catalysts **4g−i**, prepared from quinine, quinidine, and cinchonine (Table 1, entries 11−13). The reaction using **4g** also afforded product **5** with excellent enantioselectivity (Table 1, entry 11).[15] The reaction using **4h** and **4i** afforded product **5** with good enantioselectivity having an opposite stereochemistry than that using **4e** (Table 1, entries 12−13). The catalyst loading of **4e** was successfully reduced to 1 mol %, although the reactivity and enantioselectivity were gradually reduced (Table 1, entries 14 and 15). The reaction could be carried out in an open flask to give product **5** in high yield with high enantioselectivity (Table 1, entry 16).

The scope and limitations of the addition of **2a** to various ketimines **1a**,**d−l** using 5 mol % of **4e** were investigated. The results are summarized in Table 2. The reaction of imines **1d**,**e** bearing an electron-donating methyl or methoxy group gave the corresponding products **8**,**9** in high yield with high enantioselectivity (Table 2, entries 2 and 3). Electron-deficient imines **1f−l** having fluoro, chloro, or bromo groups were tolerable in these reaction conditions, giving products **10−16** with high enantioselectivity (Table 2, entries 4−10). Chemical yield was excellent in most cases.[16] To our knowledge, this is the first example of the enantioselective synthesis of α-amino peroxides from a reaction with ketimines.[9f]

Table 2. Enantioselective Addition of Cumene Hydroperoxide 2a to Various Ketimines 1a,d−m Using 4e



entry	1	R	product	yield (%)	ee (%)
1	**1a**	H	**5**	99	97
2	**1d**	5-Me	**8**	99	97
3	**1e**	5-MeO	**9**	95	96
4	**1f**	5-F	**10**	90	97
5	**1g**	5-Cl	**11**	99	96
6	**1h**	5-Br	**12**	90	97
7	**1i**	5-NO_2	**13**	81	95
8	**1j**	6-Cl	**14**	97	96
9	**1k**	6-Br	**15**	90	97
10	**1l**	7-F	**16**	87	96

The reaction of ketimines **1a** with other hydroperoxides **2b** and **2c**[17] using **4e** also gave products **17**,**18** in high yield with high enantioselectivity (Scheme 1).

We next examined the removal of an alkyl group on peroxide in **18**. Treatment of **18** with Amberlyst 15E as an acidic resin in CH_2Cl_2 afforded α-amino hydroperoxide **19** in high yield (Scheme 2).

In order to improve synthetic efficiency, we next examined the one-pot synthesis of α-amino peroxides through the aza-Wittig reaction and hydroperoxide addition reaction (Scheme 3). Although Ph_3PO remained in the reaction mixture, the hydroperoxide addition reaction afforded product **5** in high yield with high enantioselectivity.

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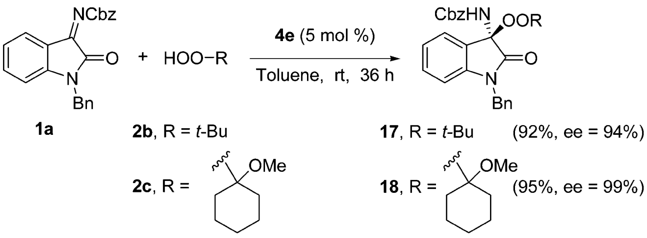
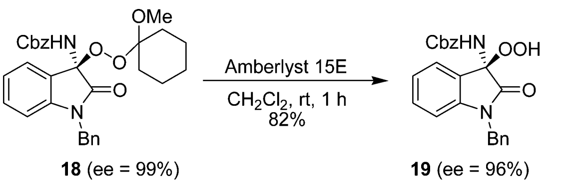
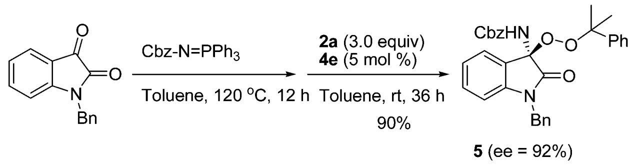
Scheme 1. Enantioselective Addition of Hydroperoxides 2b,c with 1a



Scheme 2. Transformation of 18 to α-Amino Hydroperoxide 19



Scheme 3. One-Pot Synthesis of α-Amino Peroxide



The assumed transition state for the reaction of hydroperoxide **2a** to ketimine **1a** using a chiral sulfonamide catalyst **4e** is proposed in Figure 3. Catalyst **4e** could efficiently enhance

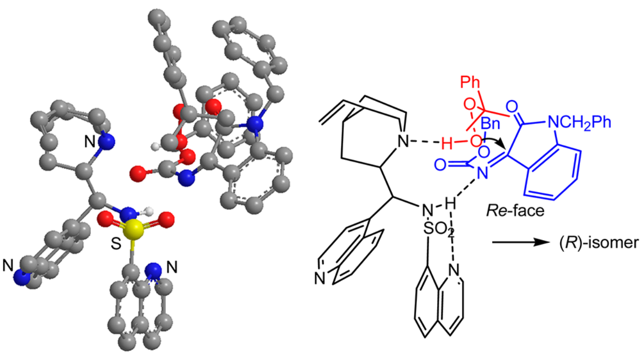


Figure 3. Proposed transition state for the reaction of *N*-Cbz-*N*′-benzyl isatinimine **1a** with cumene hydroperoxide **2a** using **4e**.

the nucleophilicity of hydroperoxide and activate ketimine **1a** through hydrogen bonding interactions with quinolinesulfonamide, which also enables intramolecular hydrogen bonding. The reaction of hydroperoxide with ketimine in the coordination sphere of the chiral catalyst **4e** gives a product with high enantioselectivity.

In conclusion, we developed the asymmetric addition of hydroperoxide to ketimines derived from isatins using our original chiral catalysts. This approach would not only be the first example of catalytic enantioselective formation of α-amino peroxides from the reaction of ketimines but also provide direct access to both enantiomers of optically active α-amino peroxides with satisfactory yield and enantioselectivity. The reaction of a broad range of ketimines derived from isatins afforded products with high enantioselectivity. Further studies focusing on the scope of the asymmetric reaction using novel organocatalysts are currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and experimental procedures for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00805.

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Notes

The authors declare no competing financial interest.

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(15) The absolute configuration of compound **5** was determined by analogy of the CD spectrum of thiol derivatives. See also Supporting Information.

(16) We also examined the enantioselective reaction of Cbz-ketimines derived from α-ketoesters and acetophenone. However, the reaction did not proceed.

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