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Short communication

Pentanidium catalyzed enantioselective hydroperoxidation of 2-oxindole using molecular oxygen

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ABSTRACT

Pentanidium catalyzed enantioselective 3-hydroperoxidation of 2-oxindoles with molecular oxygen has been established. Various 3-hydroperoxy-2-oxindoles were achieved in good *ee* and yield.

Numerous peroxy natural products and metabolites have been isolated, and many of them are found to be highly potent antimalarial, antibacterial, and antitumor compounds (Fig. 1) [1]. Artemisine, as the most widely used antimalarial drug, the peroxy fragment is demonstrated to be essential for the therapeutic action [2]. This in turn stimulate the development of new methods to access chiral peroxy compounds with broad structure diversity. To date, the generation of optically active peroxy compounds dominantly depends on singlet oxygen and peroxy precursors [3], and little study was conducted on the peroxidation of compounds with molecular oxygen [4]. It is known that many carbonyl compounds react rapidly with molecular oxygen under basic conditions to yield α-hydroxy carbonyl products [5], sometimes reductant such as triethyl phosphite was required to reduce the hydroperoxy intermediates. [5f] As the most cheap and abundant green oxidant, molecular oxygen have numerous advantages over other oxidant, such as higher atom efficacy and less byproduct [6]. Therefore, enantioselective methods of useful generality for the incorporation of molecular oxygen into optically active peroxides are urgently needed.

Recently, Nakamura group reported the reaction of hydroperoxides with ketimines derived from isatins (Fig. 2), after deprotection chiral α-amino peroxides were achieved in excellent yield and enantioselectivities [3e]. This is the only known report on the synthesis of 3-hydroperoxy-2-oxindole derivatives. Previously, We had already succeeded in establishing a general and practical synthetic method for the hydroxylation of 2-oxindoles with air using pentanidium as catalyst in the absence of reductant [7]. During our study, noticeable amount of hydroperoxy intermediate was detected in each run so we proposed a two step pathway under air limited condition. The first step generate hydroperoxy intermediate and the second step is the hydroperoxy intermediate got reduced by another molecular of 2-oxindole. To probe the reaction mechanism and verify our proposed reaction pathway, further research was conducted in hope of generate hydroperoxy as the major product by tuning the reaction conditions (Fig. 2).

With our previous established procedure, pentanidium catalyst could be synthesized from commercial available (1*S*, 2*S*)-1,2-diphenylethane-1,2-diamine in few steps [8]. With pentanidium in hand, we began our investigation by employing 2a as the model substrate for hydroperoxidation under phase-transfer catalysis. As we know base have dominate effect on the reaction rate for phase-transfer catalysis, a variety of base were screened first (Table 1). It is encouraging to find this reaction will not proceed under base free condition (Table 1, entry 1), as background reaction will always reduce the *ee* of the final product. Besides, organic base such as triethyl amine cannot promote this reaction (Table 1, entry 2) and inorganic base was tested. Weak inorganic base such CsF and K_2CO_3 are inefficient in promote this reaction, <20% conversion was observed by TLC analysis after 24 h, so the *ee* was not measured (Table 1, entries 3–4). With LiOH as base, 50% conversion was

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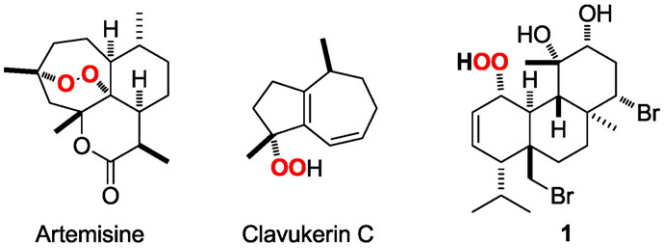


Fig. 1. Selected examples of bioactive peroxy compounds.

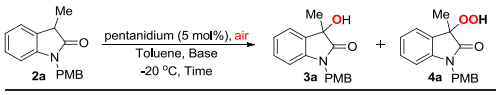
observed after 24 h (Table 1, entry 5), however, no hydroperoxy product 4a was detected. Stronger inorganic base such as NaOH, KOH, RbOH and CsOH favor the generation of hydroperoxy product along with higher *ee* (Table 1, entries 6–10). Conceivably, stronger inorganic base promote the hydroperoxidation of 2a more efficiently than the hydroperoxide 4a reduction step as air is not a limited reagent in this reaction. Therefore, KOH (50%) was considered to be optimal base for further optimization.

Then, the effect of solvent parameter on the product distribution and *ee* was screened and summarized in Table 2. The solvent was found to have significant effect on the product distribution and *ee*. Non-polar solvent such toluene, mesitylene and ether give lower ratio of hydroperoxy 4a but higher *ee* (Table 2, entries 1–3), while polar solvent such as THF, anisole and fluorobenzene give higher ratio of hydroperoxy 4a but lower *ee* (Table 2, entries 4–6). When isopropanol was applied as solvent, hydroperoxy 4a was obtained as dominant product but in almost racemic form, so toluene was considered to be optimal solvent for further optimization.

Finally, the effect of reaction temperature and oxygen parameter was screened and summarized in Table 3. With the decrease of temperature, the ratio of hydroperoxy 4a increased steadily along with the enantioselectivity (Table 3, entries 1–4) and becomes the major product when the temperature reached −60 °C. When oxygen balloon was used instead of air, the ratio of hydroperoxy 4a increased from 55% to 68%, and further increased to 87% when solvent mixture was used under oxygen balloon condition (Table 3, entries 5–7). Moreover, the catalyst loading could be reduced to 1 mol% in maintaining the product ratio and enantioselectivity (Table 3, entry 8), albeit longer reaction time. The absolute configuration of 4a was designated as *R* by comparing with an example in the literature after reduction to 3a.

With the optimized reaction condition on hand, the hydroperoxylation could be applied to a variety of 3-substituted-2-oxindoles to give 3-hydroperoxy-2-oxindoles (Table 4). Studies showed that introduction of various substituents onto the phenyl group of oxindoles has little affect on *ee* and product ratio (Table 4, entries 1–3). While the substituent at C3-position of 2 have significant effect on *ee* and product ratio (Table 4, entries 4–6). Moreover, lower ratio of 4 always resulting lower *ee* of 4. These results suggest that *R*-4 was preferentially reduced to *R*-3 leading to 4 with lower yield along with lower *ee*, which indicates kinetic resolution may involved in the second step.

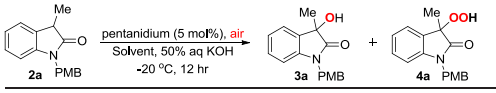
Table 1
Optimizing conditions for pentanidium-catalyzed α-hydroperoxidation of 3-methyl-2-oxindole 2a.



Entry	Base	Time/h	Conv. (%)[a,b]	4a *ee* (%)[c]	Ratio 3a:4a[c]
1	\	24	<5	\	\
2	Et_3N	24	<5	\	\
3	CsF	24	<5	\	\
4	K_2CO_3	24	<20	\	\
5	$LiOH·H_2O$	24	50	\	>95:5
6	NaOH (50%)	6	100	30	85:15
7	RbOH (50%)	5	100	39	76:24
8	CsOH (50%)	2	100	45	71:29
9	KOH solid	2	100	56	65:35
10	KOH (50%)	2	100	60	67:33

[a] Reactions were run on a 0.05 mmol scale with 5 mol% PTC in 3 ml solvent, air.
[b] Conversion determined by TLC.
[c] Determined by HPLC analysis.

Table 2
Optimizing conditions for pentanidium-catalyzed α-hydroperoxidation of 3-methyl-2-oxindole 2a.



Entry[a]	Solvent	Conv. (%)[b]	4a *ee*(%)[c]	Ratio 3a:4a[c]
1	Toluene	100	60	67:33
2	Et_2O	100	57	68:32
3	Mesitylene	100	58	73:27
4	THF	100	50	57:43
5	Anisole	100	42	43:57
6	PhF	100	38	31:69
7	IPA	80	5	12:88

[a] Run on a 0.05 mmol scale with 5 mol% PTC in 3 ml solvent, air.
[b] Conversion determined by TLC.
[c] Determined by HPLC analysis.

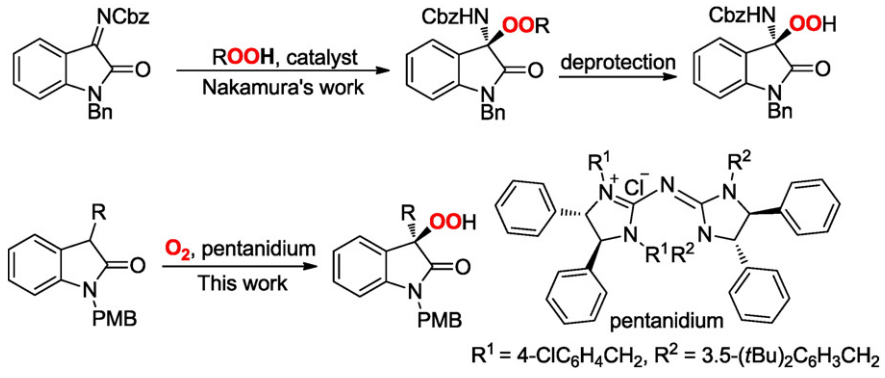
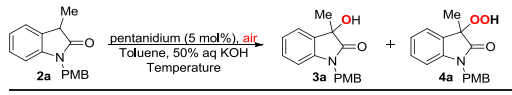


Fig. 2. Enantioselective synthesis of 3-hydroperoxy-2-oxindole derivatives.

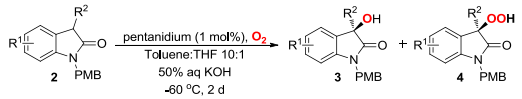
Table 3
Optimizing conditions for pentanidium-catalyzed α-hydroperoxidation of 3-methyl-2-oxindole 2a.



Entry[a]	Temp °C	Time	Conv. (%)[b]	4a *ee*(%)[c]	Ratio 3a:4a[c]
1	rt	5 min	100	NA	>95:5
2	0	30 min	100	NA	>9:1
3	−20	2 h	100	60	67:33
4	−40	6 h	100	67	60:40
5	−60	12 h	100	75	45:55
6[d]	−60	12 h	100	79	32:68
7[e]	−60	12 h	100	81	13:87
8[def]	−60	48 h	100	80	11:89

[a] Reactions were run on a 0.05 mmol scale with 5 mol% PTC in 3 ml solvent, air.
[b] Conversion determined by TLC.
[c] Determined by HPLC analysis.
[d] O_2 balloon was used instead of air.
[e] Toluene:THF 10:1 was used as solvent.
[f] 1 mol% PTC was used.

Table 4
Pentanidium-catalyzed α-hydroperoxidation of 3-substituted-2-oxindoles 2 with molecular oxygen.



Entry[a]	R^1, R^2	Yield(%)[b]	3, 4 *ee* (%)[c,d]	Ratio 3:4[c]
1, 4a	H, Me	96	94, 80	11:89
2, 4b	5-F, Me	94	83, 72	10:90
3, 4c	5-OMe, Me	96	95, 83	17:83
4, 4d	H, propagyl	95	88, 66	49:51
5, 4e	H, Allyl	92	92, 56	41:59
6, 4f	H, Bn	93	92, 47	67:33

[a] Reactions were run on a 0.05 mmol scale with 1 mol% PTC in 3 ml toluene and 0.3 ml THF with a O_2 balloon.
[b] Yield was calculated based on mixture of 3 and 4 after a quick filtration to remove PTC.
[c] Determined by HPLC analysis.
[d] The absolute configuration of 4a was determined to be *R* after reduction and compare optical rotation with literature.

To probe the reaction mechanism, racemic hydroperoxy oxindole 4a was synthesized as major product under strongly basic condition at low temperature by treating 2a under O_2 atmosphere (Fig. 3). Pure *rac*-4a can be obtained after single recrystallization. We utilized 2 equiv of *rac*-4a as oxidant and 5 mol% of pentanidium as catalyst. Under nitrogen atmosphere, 3-methyl-2-oxindole 2a can be converted into (*R*)-3a with 76% *ee*, and the remaining hydroperoxy oxindole was determined to be (*S*)-4a with 51% *ee* (Fig. 3). The selectivity factor S (or K_{rel}) was determined to be 5 on the basis of this result [9]. This result demonstrated that the pentanidium catalyst preferentially consume (*R*)-4a to form (*R*)-3a, and that is why lower ratio of 4a always resulting lower *ee* 4a.

In summary, an enantioselective α-hydroperoxidation of 2-oxindoles with molecular oxygen has been established using pentanidium as the chiral phase-transfer catalyst. Several 3-hydroperoxy-2-oxindoles with good enantioselectivities (47%–83% *ee*) were obtained. Partial lower yield and *ee* of hydroperoxide is due to pentanidium catalyzed selective (*R*)-4a consumption.

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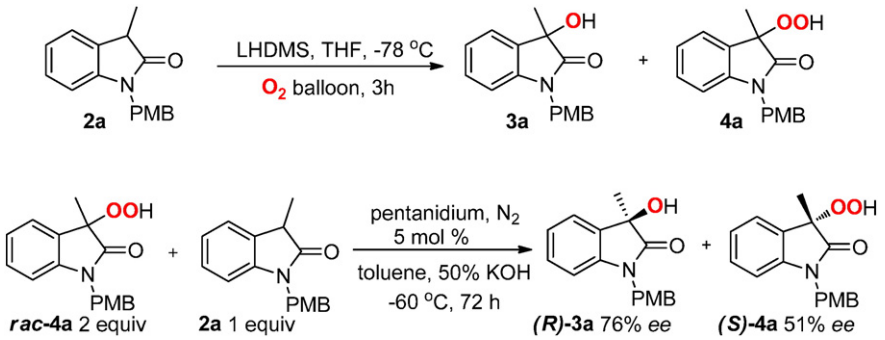

Fig. 3. Mechanistic study for the oxidation of 2-oxindole.