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Asymmetric Catalytic 1,2-Hydroperoxidation of Isatin-Derived Ketimine with Hydrogen Peroxide in the Crowding Environment of PEGs

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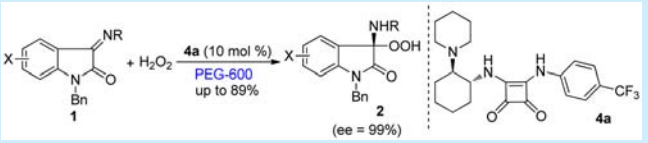
Supporting Information

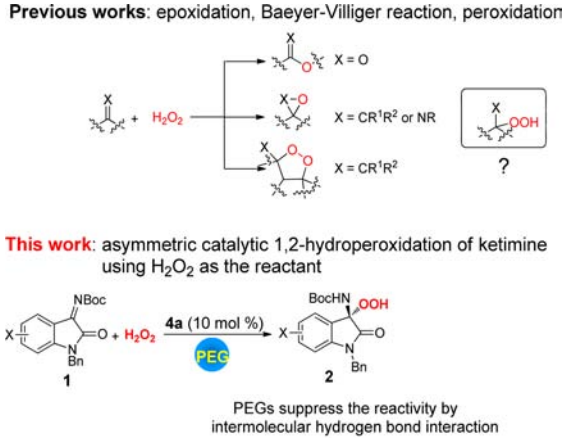
ABSTRACT: The first enantioselective catalytic 1,2-hydroperoxidation has been achieved in the presence of PEG-600 using an acid−base bifunctional chiral squaramide as the organocatalyst, affording a range of enantioenriched α-*N*-substituted hydroperoxides bearing an oxindole moiety with excellent stereoselectivities (up to 99% ee).



The chiral hydroperoxides and peroxides occur as essential structural motifs in a large class of natural products and bioactive unnatural compounds which display antitumor, anticancer, and antiparasite activities.[1] Moreover, many hydroperoxides have been used in asymmetric oxidations mimicking biological oxidant hydroperoxyflavin, an α-*N*-substituted hydroperoxide.[2] As a result, the development of methods for the synthesis of structurally distinct classes of chiral peroxides and hydroperoxides has become a attractive sustainable field in synthetic and medicinal chemistry.[3] Since the first successful formations of chiral peroxides (ROOR′) were reported by the Deng group[4] and List group[5] independently in 2008, significant progress has been achieved in developing asymmetric catalytic methodologies for this purpose.[6] In contrast, the synthesis of chiral hydroperoxides (ROOH) has captured much less attention. Current approaches for the enantioselective synthesis of hydroperoxides were mainly based on the stoichiometric use of chiral starting materials[7a−c] or via optical resolution of racemic hydroperoxides.[7d−f] To the best of our knowledge, to date there is still no approach available for direct catalytic synthesis of chiral hydroperoxide.[8]

We envisioned that enantioenriched hydroperoxide could be accessed directly via nucleophilic addition to the C═N double bond using H_2O_2 as the donor in the presence of an appropriate chiral organocatalyst. In the past, several organocatalytic systems for efficient asymmetric epoxidation,[9] Baeyer−Villiger reactions,[10] peroxidation,[5,6d] and other oxidations[11] have been successfully developed by using H_2O_2 as the terminal oxidant, thanks to the pioneering works of Jørgenson, Miller, List, Ding, Ooi, Arai, and co-workers (Scheme 1). Nevertheless, none of these processes has involved the isolation of hydroperoxide. One of the major difficulties may be attributed to the inherent high reactivity of the relevant hydroperoxides, which can readily undergo subsequent intra- or intermolecular reactions to form more stable epoxides,[9] peroxides,[5] etc. It thus became our goal to exploit new strategies for the development of asymmetric hydroperoxidation.

Scheme 1. Organocatalytic Additions to Double Bonds Using Hydrogen Peroxide as Nucleophile



Polyethylene glycols (PEGs), polyethers with monomeric structure, are widely used as crowding reagents in the structural study of biological macromolecules such as proteins, nucleic acids, etc.[12] As acceptors, PEGs can bring about strong hydrogen-bonding (HB) interactions with biological molecules, which play key roles in such research systems. Inspired by the utilization of PEG in biology and recent advances in supramolecular catalysis,[13] we targeted the asymmetric synthesis of hydroperoxides and found that an intermolecular HB crowding environment generated between the PEG-600 and −OOH group can suppress the reactivity of hydroperoxides. This strategy allowed us to develop the first organocatalyzed asymmetric 1,2-hydroperoxidation of isatin-derived ketimines **1** using H_2O_2 as nucleophile (Scheme 1) to afford a variety of α-*N*-substituted oxindole-3-hydroperoxides with excellent ee (up to 99%).

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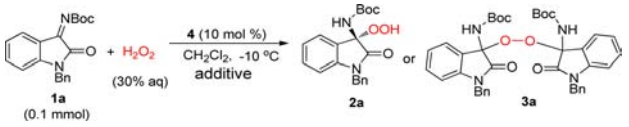
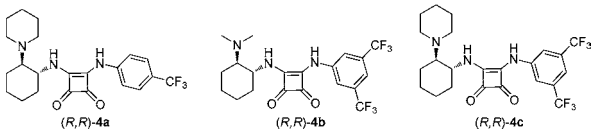
For the asymmetric hydroperoxidation using H_2O_2 as the oxidant, isatin-derived ketimine **1a** was examined as the electrophile with regard to its high reactivity and the structural relevance of this type of compounds in bioactivity studies.[14] At the outset of this investigation, organic base catalysis, as our ongoing interest,[15] was tested in the model reaction. We speculated that base catalysts with HB donors[16] might be plausible catalysts for hydroperoxidation via electrophilic activation of the ketimine with HB interaction and nucleophilic activation of H_2O_2 with tertiary amine. However, the dimeric peroxide **3a** was isolated in high yield (81%) (Table 1, entry 1)

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	additive	2/3[b]	2 or 3, yield[c] (%)	ee[d] (%)
1	**4a**	no	1:20	**3a**, 81	ND
2	**4a**	ether[e]	1:8	**3a**, 60	ND
3	**4a**	THF[e]	6:1	**2a**, 68	77
4[h]	**4a**	1,4-dioxane	1:1	ND	ND
5[i]	**4a**	1,4-dioxane	2:1	ND	ND
6[j]	**4a**	1,4-dioxane	6:1	73/**2a**	84
7	**4a**	PEG-600	2:1	ND	ND
8	**4a**	PEG-600	6:1	ND	ND
9	**4a**	PEG-600	10:1	**2a**, 80	95
10	**4a**	PEG-200	ND	**2a**, 51	80
11	**4a**	PEG-300	ND	**2a**, 69	76
12	**4a**	PEG-400	ND	**2a**, 74	73
13	**4a**	PEG-800	ND	**2a**, 60	94
14	**4a**	PEG-1000	ND	**2a**, 70	67
15	**4b**	PEG-600	7:1	**2a**, 59	64
16[f]	**4c**	PEG-600	10:1	**2a**, 15	90
17[g]	**4a**	PEG-600	ND	**2a**, 61	95

[a]Unless otherwise indicated, all reactions were carried out on a 0.1 mmol scale with 2.5 equiv of H_2O_2, the corresponding PEG (200 mg), and 10 mol % of (*R*,*R*)-**4** in CH_2Cl_2 (0.5 mL) for 2 h. PEG = polyethylene glycol. ND: not determined. [b]The ratio of **2a** and **3a** was determined by crude ^{1}H NMR analysis. [c]Isolated yield based on **1a** purified by silica gel column chromatography. [d]Determined by HPLC analysis using a Daicel AD-H column. [e]As solvent, 0.5 mL, respectively. [f]The reaction is very sluggish. [g]2 mol % of catalyst, reaction time: 24 h. [h]50 μL of 1,4-dioxane. [i]100 μL of 1,4-dioxane. [j]200 μL of 1,4-dioxane.

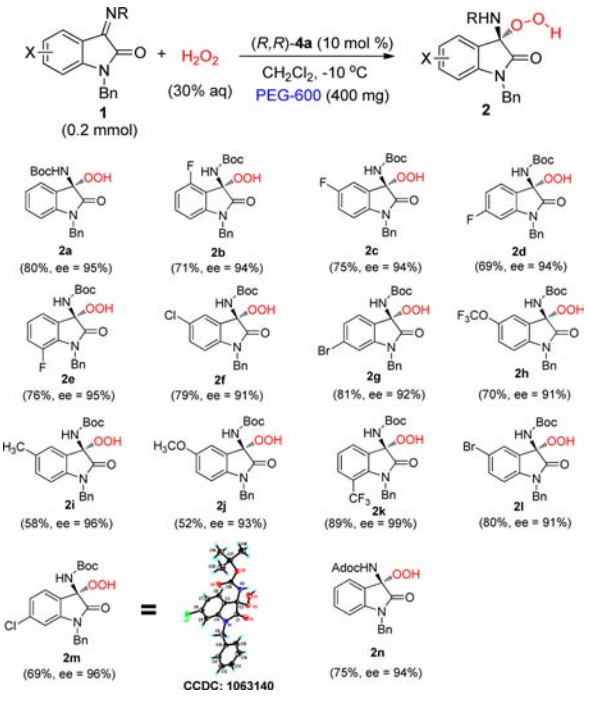


with squaramide bifunctional organocatalyst **4a**,[17] probably due to the good nucleophilicity of hydroperoxide **2a**. We envisioned that nucleophilicity of hydroperoxide may be depressed to some extent through weak HB interaction with an appropriate acceptor. Such a HB acceptor can inhibit the further deprotonation of hydroperoxide, thus allowing for effective trapping and isolation of the generally reactive hydroperoxide. To verify this idea, several additives and solvents bearing HB acceptor groups were tested to reduce the dimer formation (Table 1, entries 2–9). We were glad to find that these additives and solvents could promote the generation of hydroperoxide **2a** as major product. Moreover, we also found that the ratios of **2a** were enhanced significantly with increasing amounts of additives (Table 1, entries 4–9). These results suggested that crowding HB can indeed suppress the dimerization and enhance the proportion of hydroperoxide **2a**. Our persistence was finally rewarded when the same reaction was carried out in the presence of PEG-600. We were pleased to find that the reaction proceeded smoothly at −10 °C to give the hydroperoxide **2a** as the major product in 80% yield and 95% ee after 2 h (Table 1, entry 9). Interestingly, the use of PEGs with different molecular weights as additives led to different enantioselective control for the 1,2-hydroperoxidations (Table 1, entries 9–14). Only PEG-600 and -800 could afford hydroperoxide **2a** with excellent enantioselectivities. These results indicated that PEGs with appropriate degrees of polymerization could provide favorable microenvironments for this catalytic reaction. Further screening of squaramide catalysts **4a–c** proved that **4a** was the optimal catalyst in terms of isolated yield and enantioselectivity (Table 1, entry 9 versus entries 15 and 16). To further explore the efficiency of this catalytic system, the model reaction was carried out with a reduced catalyst loading (2 mol %), affording **2a** with the enantioselectivity as high as 95% after prolonged reaction time to 24 h (Table 1, entry 17).

With the optimized reaction conditions in hand (Table 1, entry 9), we examined the substrate scope of this hydroperoxidation reaction. A wide range of isatin-derived ketimines with different substitution patterns were found to be viable substrates for this reaction, affording the corresponding hydroperoxides **2a–n** in excellent enantioselectivities (91–99% ee) (Scheme 2).

Notably, the reaction system tolerates a variety of functional groups on the aryl ring, including F, Cl, Br, OCF_3, CF_3, CH_3, and OMe substituents **2b–m**. On the other hand, the electronic nature of the substituents on the aryl ring of the ketimines exhibited a significant influence on the product

Scheme 2. Substrate Scope



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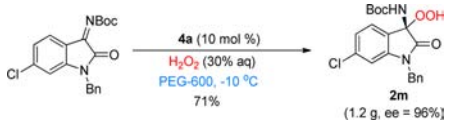
yields. In general, electron-withdrawing groups furnished the hydroperoxide products **2b–h,k–m** in higher yields than those with electron-donating substituents **2i,j**, albeit with similarly high ee values. Changing the substituent on the nitrogen in the imino group from the Boc group to the 1-adamantyloxycarbonyl group (Adoc) also showed high enantioselectivity (**2n**, ee = 94%).[18] The absolute configuration of **2m** was unambiguously established as *S* on the basis of the X-ray crystallographic analysis, and those of others were assigned by analogy.

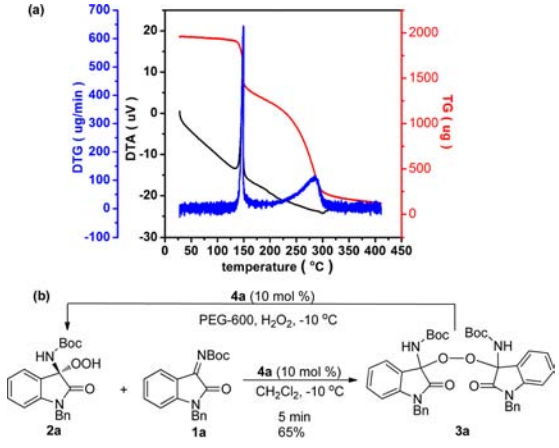
To explore the practicality of the current methodology, a gram-scale synthesis of **2m** was carried out under optimized conditions with catalyst **4a**. The corresponding product **2m** was obtained with 71% yield and 96% ee (Scheme 3). Furthermore, HRMS analysis revealed that **4a** was not oxidized by H_2O_2 or **2** and could be recovered in 73% yield.

Scheme 3. Gram-Scale Synthesis



In the studies of the reactions between H_2O_2 and ketimines **1**, we found that *α-N*-substituted peroxide **3**, the dimeric products, are unstable and decomposed quickly during NMR measurements or HPLC analysis. In contrast, *α-N*-substituted hydroperoxides **2** exhibit good stabilities (Scheme 4a). We

Scheme 4. (a) Thermal Stability of Hydroperoxide 2m; (b) Control Experiments



reasoned that the stability of hydroperoxides **2** might result from intramolecular hydrogen bonding between the −OOH moiety and the oxindolyl carbonyl. ^{1}H NMR spectra of *tert*-butyl hydroperoxide exhibited that the chemical shift of the −OOH moiety is around 7.4 ppm. In comparison, the ^{1}H NMR signal of the −OOH moiety in **2m** is around 10.0 ppm. Upon addition of CD_3OD ($CD_3OD/CDCl_3$, 1:20), H/D exchange of the −OOH proton in **2m** (15 min, 59%) was much slower than that in *tert*-butyl hydroperoxide (2 min, 100%) under the same conditions. These results are consistent with the existence of intramolecular hydrogen bonding in the structure of **2**. Moreover, upon addition of CD_3OD, **2m** in deuterated $CDCl_3$/PEG-600 shows a much slower rate of H/D exchange (15 min, 32%) than **2m** in $CDCl_3$, which suggests that there may exist some intermolecular hydrogen-bonding interactions between PEG and **2m**.[19]

Control experiments were conducted to investigate the generation of dimer **3** (Scheme 4b). Using CH_2Cl_2 as the solvent, hydroperoxide **2a** reacted with ketimine **1a** via catalysis of **4a** to afford the dimer **3a** with 65% yield in just 5 min. In contrast, there was no further reaction between the dimer **3a** and aqueous H_2O_2 in the presence of **4a** and PEG-600. These results demonstrate that dimer **3** is very likely formed via the intermediacy of hydroperoxides **2**.[20]

In summary, the first acid–base bifunctional organocatalyzed asymmetric 1,2-hydroperoxidation has been developed, thus providing a direct and highly efficient approach for the synthesis of enantioenriched *α-N*-substituted hydroperoxide bearing an oxindole motif. In all cases, excellent enantioselectivities (91–99% ee) were achieved. Mechanistic studies revealed that the crowding intermolecular HB between the additive (PEG-600) and −OOH group plays an important role in the control of the chemoselectivity. This strategy offers a potential opportunity for the discovery of biomimetic asymmetric oxidation systems. Further work will be devoted to the development of new hydroperoxidations and biomimetic asymmetric oxidation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00032.

Experimental procedures, characterization of products, NMR spectra, HPLC traces, and X-ray data for **2m** (PDF)

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Notes

The authors declare no competing financial interest.

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(18) When *N*-Me-isatin-derived ketimine was used as substrate, the desired product and corresponding dimer **3** formed an inseparable mixture that could not be purified by column chromatography. The NMR yield is about 65%.

(19) The NMR analysis revealed the existence of interaction between catalyst **4a** and PEGs. For details, See S-Figure 2 in the Supporting Information.

(20) Control experiments were performed for further demonstration of the role of the PEG on chemoselectivity. For details, see S-Scheme 4 in the Supporting Information.

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