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Pentanidium–Catalyzed Enantioselective α-Hydroxylation of Oxindoles Using Molecular Oxygen

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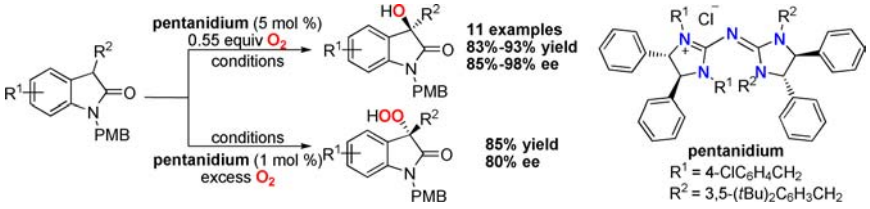
ABSTRACT



Pentanidium-catalyzed α-hydroxylation of 3-substituted-2-oxindoles using molecular oxygen has been developed with good yields and enantioselectivities. This reaction does not require an additional reductant such as triethyl phosphite, which was typically added to reduce the peroxide intermediate. The reaction was demonstrated to consist of two-steps: an enantioselective formation of hydroperoxide oxindole and a kinetic resolution of the hydroperoxide oxindole via reduction with enolates generated from the oxindoles.

Molecular oxygen can be obtained at almost no cost and as a reagent, produces no environmentally hazardous byproduct and is thus considered by many to be the ideal oxidant. In the past few decades, several transition metal-catalyzed oxidations of organic substrates with molecular oxygen have been developed.[1] The insertion of hydroxy groups, particularly to the α-position of functional groups is an important transformation,[2] as many compounds of biological importance and synthetic interest consist of oxygenated carbon skeletons. It is known that many carbonyl compounds react rapidly with molecular oxygen under basic conditions.[3]

Phase-transfer catalysis has the advantages of having simple experimental procedures and mild reaction conditions.[4] It was demonstrated that α-hydroxylation of achiral ketones can be achieved with molecular oxygen as oxidant in the presence of *Cinchona* alkaloid-derived phase-transfer catalysts.[5] α-Hydroxy ketones with moderate

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enantioselectivities were obtained, and triethyl phosphite was added to reduce the peroxide intermediate. Optically active crown ethers were also shown to be effective as phase transfer catalysts for α-hydroxylation of cyclic ketones with molecular oxygen.[6]

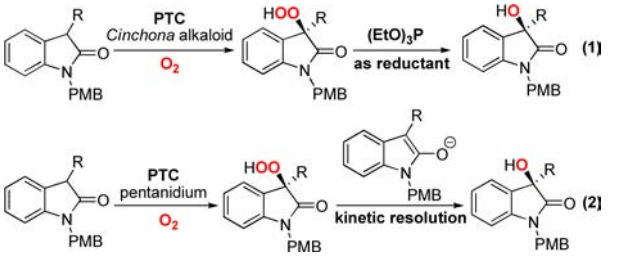

Figure 1. Enantioselective α-hydroxylation of 3-substituted-2-oxindoles (1) with $(EtO)_3P$ as reductant (known),[9b] (2) without reductant (this work).

3-Substituted-3-hydroxy-2-oxindole is the core structure of a number of several natural products with a broad spectrum of biological activities, and it is the focus of a number of medicinal chemistry programs.[7] The 3-hydroxy position greatly affects the biological activities and developing an efficient method to obtain enantiopure 3-hydroxy-2-oxindoles is critical for further investigations of these compounds.[8] Shibata, Toru and co-workers demonstrated the enantioselective α-oxidation of 3-substituted-2-oxindole using DBFOX-Zn(II) catalyst and oxaziridine as oxidant.[9a] Subsequently, Itoh and co-workers investigated the reaction under phase transfer condition using molecular oxygen in the presence of *Cinchona* alkaloid-derived catalyst (Figure 1, eq 1).[9b] Moderate to good enantioselectivities were observed. More recently, Barbas and co-workers utilized a dimeric quinidine to catalyze the aminooxygenation of 3-substituted-2-oxindole with nitrosobenzene as an approach toward chiral 3-hydroxy-2-oxindoles.[9c]

Previously, we disclosed a new class of phase transfer catalysts, pentanidiums, and showed that it can catalyze the enantioselective Michael reactions of *tert*-butyl glycinate-benzophenone Schiff base with high enantioselectivities and low catalyst loading.[10] In this communication, we wish to report that α-hydroxylation of 3-substituted-2-oxindoles can be efficiently conducted using pentanidium as catalyst with high enantioselectivities. Molecular oxygen was used as the oxidant, and contrary to all previous reports, no reductant such as triethyl phosphite was required (Figure 1, eq 2).

Figure 2. Various chiral pentanidiums.

The oxidation of 3-methyl-2-oxindole **2a** with air in the presence of 5 mol % pentanidium **1a** was initially conducted with 2 equiv of triethyl phosphite as the reductant. The solvent used was toluene with 50% aq KOH (v/v = 10:1) and at a reaction temperature of −20 °C. The reaction proceeded smoothly to afford 3-hydroxy-2-oxindole **3a** with 52% yield and 56% ee in 12 h (Table 1, entry 1).[11] We found that in the absence of triethyl phosphite, the reaction also proceeded well. We were pleasantly surprised when we found that the ee of **3a** was increased to 67%. However, significant amount of hydroperoxide oxindole **4a** was detected as a side product (**3a**/**4a** = 70:30, entry 2). Next, we tried to determine if the steric and electronic properties of pentanidiums **1** (Figure 2) would alter the product ratio and enantioselectivities. The use of more bulky and electron-deficient benzylic groups on pentanidiums **1** improved the enantioselectivities (entries 3−5); pentanidium **1d** afforded **3a** with 92% ee (entry 5).[11] Further optimization of the reaction conditions were carried out by examining different solvents with **1d** as catalyst (entries 6−7); toluene was identified as the ideal solvent.[11] Lower reaction temperature (−60 °C) improved the ee to 97% without loss of reaction rate, but the ratio of **3a**/**4a** was decreased to 43:57 (entry 9). We observed that the amount of molecular oxygen affects the ratio of **3a**/**4a**. When the amount of air was restricted to 0.55 equiv of O_2, the ratio of **3a**/**4a** was enhanced to 91:9, and ee of **3a** was slightly decreased to 95% (entry 10). The hydroperoxide oxindole **4a** could be isolated and determined to have an ee of 36% ee (entry 10). When a slightly lesser amount of O_2 was used (0.4 equiv), the ratio of **3a**/**4a** was even better, but the enantioselectivity suffered slightly (82% ee, **3a**/**4a** >95:5, entry 11). The absolute configuration of **3a** was designated as *R* by comparing with an example in the literature, and the absolute configuration of **4a** was determined to be *S* via reduction.[11]

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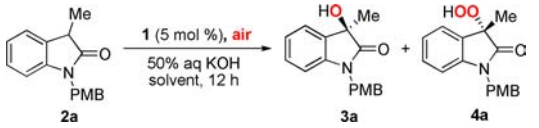
(11) See the Supporting Information for details.

Table 1. Optimizing Conditions for Pentanidium-Catalyzed α-Hydroxylation of 3-Methyl-2-oxindole **2a**[a]



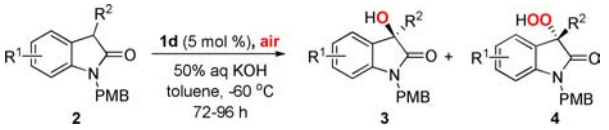
entry	1	solvent	temp (°C)	ee of **3a** (%)[b]	ratio of **3a**/**4a**[b]
1	**1a**	toluene	−20	56[c]	>95:5
2	**1a**	toluene	−20	67	70:30
3	**1b**	toluene	−20	78	69:31
4	**1c**	toluene	−20	86	72:28
5	**1d**	toluene	−20	92	71:29
6	**1d**	THF	−20	38	51:49
7	**1d**	ether	−20	87	66:34
8	**1d**	toluene	−40	93	62:38
9	**1d**	toluene	−60	97	43:57
10[d,e,f]	**1d**	toluene	−60	95	91:9
11[e,g]	**1d**	toluene	−60	82	>95:5

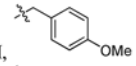
[a] Unless otherwise noted, the reaction was carried out with 0.05 mmol **2a**, 0.3 mL of 50% aq KOH and 0.0025 mmol catalyst **1** in 3.0 mL of solvent, and the conversions of all reactions were determined as 100% by ^{1}H NMR analysis. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Yield = 52%, 12 h, 2 equiv of $(EtO)_3P$. [d] 0.55 equiv of O_2 (2.9 mL air, calculated at 25 °C, 1 atm, 21% v/v of O_2 in air) was used, introduced to reaction via a syringe. [e] Reaction time was 3 days. [f] The ee of **4a** is 36%. [g] 0.4 equiv of O_2 (2.1 mL of air) was used, and 83% conversion was observed.

With the optimized reaction condition on hand, the α-hydroxylation could be extended to a variety of 3-substituted-2-oxindoles to give 3-hydroxyl-2-oxindoles **3b**−**k** in 85−98% ee and 83−93% yield (Table 2). Studies showed that the introduction of various substituents onto the phenyl group of oxindoles did not affect the ee (Table 2, entries 1−3). When the substitutent at C3-position of **2** was an *n*-butyl group, the ee was slightly decreased to 85% (entry 4). It was also found that benzyl, allyl and alkynyl-substituted oxindoles were hydroxylated in high yields and with excellent enantioselectivities (entries 5−10). In all reactions, the ratios of **3**/**4** were satisfactory, and the side product **4** could be readily removed by chromatography.[11]

We found that, from the optimization studies, the amount of hydroperoxide oxindoles obtained was related to amount of molecular oxygen in the reaction. When 3-methyl-2-oxindole **2a** was oxidized using an O_2 balloon instead of air, hydroperoxide oxindole **4a** could be obtained in high yield and good enantioselectivity (85% yield, 80% ee, eq 3). A mixture of toluene and THF was helpful to increase the yield of **4a**; it was observed that polar solvent promoted the formation of the hydroperoxide oxindole. It is interesting to note that the absolute configuration of **4a** obtained in this experiment is *R*, opposite to that when **4a** was obtained as a minor product and air was used as the oxidant (Table 1, entry 10). Therefore, we proposed that the α-hydroxylation should be a two-step reaction (Figure 3). First, 3-substituted-2-oxindoles **2** react with O_2 in an enantioselective fashion to give the hydroperoxide oxindoles **4**,

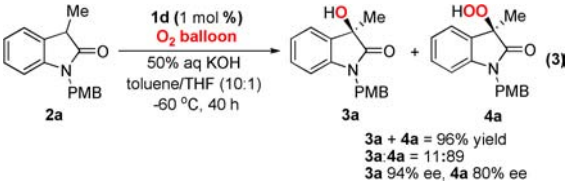
Table 2. Pentanidium-Catalyzed α-Hydroxylation of 3-Substituted-2-Oxindoles **2** with Molecular Oxygen[a]



entry	R^1, R^2	3	yield (%)[b]	ee (%)[c]	ratio of **3**/**4**[c]
1	5-F, Me	**3b**	84	86	90:10
2	5-OMe, Me	**3c**	88	98	91:9
3	5-Me, Me	**3d**	86	96	92:8
4	H, *n*Bu	**3e**	84	85	90:10
5	H, CH_2Ph	**3f**	92	92	97:3
6	H, 	**3g**	93	92	97:3
7	H, 	**3h**	92	97	96:4
8	H, $CH_2CH{=}CH_2$	**3i**	85	91	92:8
9	5-OMe, $CH_2CH{=}CH_2$	**3j**	89	93	94:6
10	H, $CH_2C{\equiv}CH$	**3k**	83	94	94:6

[a] Unless otherwise noted, the reaction was carried out with 0.05 mmol **2**, 0.3 mL of 50% aq KOH and 0.0025 mmol catalyst **1d** in 3.0 mL of toluene. [b] Isolated yields of **3**. [c] Enantiomeric excesses of **3** determined by HPLC analysis on a chiral stationary phase.

which configuration is controlled by pentanidium **1**. The hydroperoxide oxindoles **4** are subsequently reduced by the enolates of 3-substituted-2-oxindoles, generated in situ under the basic reaction condition. This kinetic resolution step further improved the enantiopurity of the hydroxyloxindole obtained.



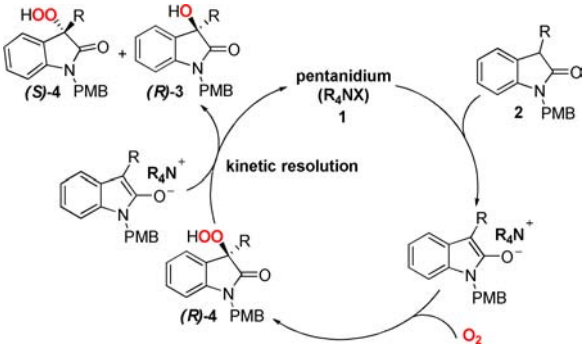
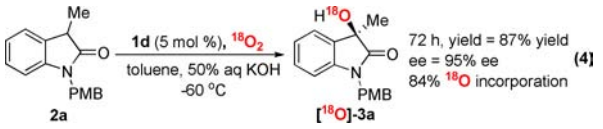


Figure 3. Proposed reaction pathway.

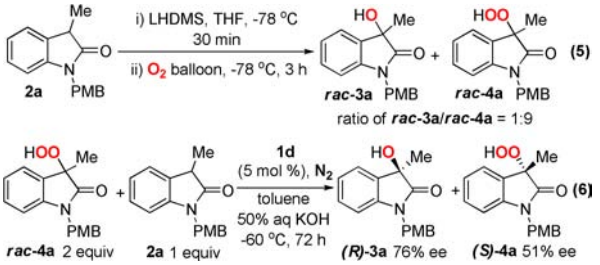
A simple isotope labeling experiment was conducted with $^{18}O_2$ (eq 4) to verify the role of molecular oxygen as

oxidant.[12] It was observed that [^{18}O]-**3a** was obtained with 84% level of ^{18}O incorporation, as determined by mass spectroscopy.



Under strongly basic condition and at low temperature, racemic hydroperoxide oxindole **4a** can be obtained as a major product by treating **2a** under O_2 atmosphere (eq 5). Pure ***rac*-4a** can be obtained through recrystallization. In order to elucidate the second step of the α-hydroxylation, we utilized 5 mol % of pentanidium **1d** as catalyst and 2 equiv of ***rac*-4a** as oxidant. In the absence of air, 3-methyl-2-oxindole **2a** can be hydroxylated to **(*R*)-3a** with 76% ee, and the remained hydroperoxide oxindole was determined to be **(*S*)-4a** with 51% ee (eq 6).[11] The selectivity factor S (or K_{rel}) was determined to be 5 on the basis of this result.[11,13] This result demonstrated that the pentanidium catalyst has a bias for selecting **(*R*)-4a** (match case) and used it to form **(*R*)-3a** preferentially.

In summary, a highly enantioselective reductant-free α-hydroxylation of 3-substituted-2-oxindoles using molecular oxygen has been developed using pentanidium as the chiral phase-transfer catalyst. Several 3-hydroxyl-2-oxindoles with excellent enantioselectivities (85%−98% ee) were obtained. This reaction was demonstrated to be a two-step reaction: an enantioselective formation of hydroperoxide oxindole followed by kinetic resolution of the hydroperoxide oxindole. We are currently using this protocol to prepare enantiopure biologically active 3-hydroxyl-2-oxindoles. Further mechanistic studies will be carried out, and results will be reported in due course.



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Supporting Information Available. General information, typical experimental procedures, characterization and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.

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