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Catalytic Asymmetric Hydroxylation of Oxindoles by Molecular Oxygen Using a Phase-Transfer Catalyst

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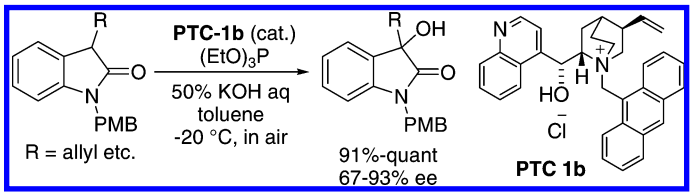
ABSTRACT



The highly enantioselective catalytic hydroxylation of 3-substituted oxindoles was achieved by using a phase-transfer catalyst with molecular oxygen as an oxidant. The product then was converted to an optically active compound 8, which was a synthetic precursor of alkaloid CPC-1.

A number of oxindole alkaloids having a hydroxyl substituent at their C-3 position possess various bioactivities.[1] In the field of medicinal chemistry, chiral 3-substituted-3-hydroxy-2-oxindoles have been targets of synthesis, because they are promising drug candidates.[2] Furthermore, they are used as starting materials and/or intermediates for the synthesis of natural products.[3] The reported methods for the synthesis of chiral 3-substituted-3-hydroxy-2-oxindoles are an asymmetric nucleophilic addition to isatins[4] and asymmetric hydroxylation of 3-substituted-2-oxindoles.[5] In the latter case, a chiral hydroxylation reagent was used, thus a stoichiometric amount of the chiral source was required. Recently, the first catalytic enantioselective hydroxylation of oxindoles with an oxaziridine as an oxidant in the presence of chiral Zn(II) complex was reported.[6] The oxidant resulted in the formation of a benzisothiazole derivative in the reaction mixture, and it seems to be a drawback compared to the hydroxylation with molecular oxygen as an oxidant.[7] The use of O_2 as an oxidant is a paramount process, because it is inexpensive and

(1) (a) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S.; Feng, X.-Z. *Eur. J. Org. Chem.* **2001**, 261. (b) Fréchard, A.; Fabre, N.; Péan, C.; Montaut, S.; Fauvel, M.-T.; Rollin, P.; Fouraste, I. *Tetrahedron Lett.* **2001**, *42*, 9015. (c) Koguchi, Y.; Kohno, J.; Nishino, M.; Takahashi, K.; Okuda, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **2000**, *53*, 105. (d) Codding, P. W.; Lee, T. A.; Richardson, J. F. *J. Med. Chem.* **1984**, *27*, 649.

(2) (a) Tokunaga, T.; Hume, W. E.; Nagamine, J.; Kawamura, T.; Taiji, M.; Nagata, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789. (b) Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, *44*, 4641. (c) Hawawasam, P.; Erway, M.; Moon, S. L.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S;, Gribkoff, V. K.; Meanwell, N. A. *J. Med. Chem.* **2002**, *45*, 1487.

(3) (a) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199. (b) Suárez-Castillo, O. R.; Sánchez-Zavala, M.; Meléndez-Rodríguez, M.; Castelán-Duarte, L. E.; Morales-Ríos, M. S.; Joseph-Nathan, P. *Tetrahedron* **2006**, *62*, 3040. (c) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *62*, 3040.

(4) (a) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353. (b) Toullec, P. Y.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2006**, *8*. 2715. (c) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*. 677. (d) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418.

(5) (a) Hewawasam, P.; Meanwell, N. A.; Gribkoff, V. K.; Dworetzky, S. I.; Biossard, C. G. *Bioorg. Med. Chem. Lett.* **1997**, *7*, **1255**. (b) Hewawasam, P.; Erway, M.; Moon, S. L.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Gribkoff, V. K.; Meanwell, N. A. *J. Med. Chem.* **2002**, *45*, 1487.

(6) Ishimaru, T.; Shibata, N.; Nagi, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488.

(7) There are some examples concerning racemic hydroxylation using molecular oxygen, see: (a) Christoffer, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143. (b) Christoffer, J.; Werner, T.; Frey, W.; Baro, A. *Chem. Eur. J.* **2004**, *10*, 1042. There are three examples concerning the catalytic enantioselective hydroxylation of tetralone and indanone derivatives using molecular oxygen, see: (c) Dehmlow, E. V.; Wagner, S.; Mülller, A. *Tetrahedron* **1999**, *55*, 6335. (d) De Vries, E. F. J.; Ploeg, L.; Colao, M.; Brussee, J.; Van der Gen, A. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1123. (e) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835.

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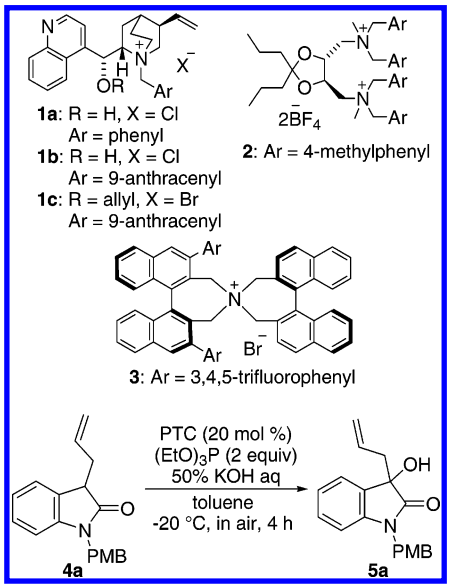
environmentally benign. In the course of our investigation of the synthesis of chiral 3,3-disubstituted oxindoles,[8] we have found that 3-substituted oxindoles react with molecular oxygen in the presence of a base to give the corresponding 3-hydroxy derivatives quantitatively. The result prompted us to investigate an asymmetric version of the hydroxylation reaction using chiral phase-transfer catalyst (CPTC). In this paper, we describe these results.

In the initial study, CPTCs were screened for the reaction of 3-allyl-2-oxindole **4a** with molecular oxygen. Although the reaction with solid KOH proceeded without catalyst in toluene to give 3-allyl-3-hydroxy-2-oxindole **5a**, no product was obtained when the reaction was run in toluene/50% KOH aq solution. Thus the screening of CPTC was carried out in the two-phase system (Table 1), and it was found that

Table 1. Catalyst Screening for the Asymmetric Hydroxylation Reaction

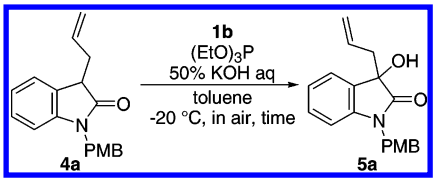


entry	PTC	yield (%)	ee (%)
1	**1a**	96	49
2	**1b**	86	83
3	**1c**	quant	20
4	**2**	88	22
5	**3**	93	38

spirobinaphthyl quaternary ammonium salt[9] **3** and tartrate-derived bis-ammonium salt[10] **2** gave high chemical yields, but low enantioselectivities. When cinchonidine derived CPTC **1a**[11] or **1b**[12] was used, high chemical yields and moderate to good enantioselectivities were obtained. When the hydroxyl group of **1b** was converted to allyl ether,[13] the ee of the reaction lowered.

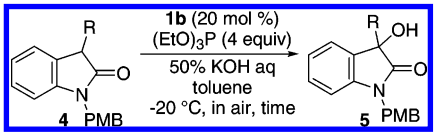
Using the selected catalyst **1b**, we next carried out the optimization of the solvent (Table 2). While ethereal

Table 2. Optimization of the Conditions for the Asymmetric Hydroxylation of **4a**[14]



entry	catalyst (mol %)	$(EtO)_3P$ (equiv)	solvent	time (h)	yield (%)	ee (%)
1	20	0	toluene	4	71	56
2	20	2	toluene	4	86	83
3	20	2	xylene	4	74	73
4	20	2	mesitylene	4	89	50
5	20	2	Et_2O	4	51	3
6	20	2	iPr_2O	4	0	
7	20	2	MeO*t*-Bu	4	78	4
8	20	4	toluene	2.5	98	85
9	20	10	toluene	2.5	97	85
10	10	4	toluene	7.5	85	80
11	5	4	toluene	12	93	74
12	1	4	toluene	72	16	31

Table 3. Catalytic Asymmetric Phase-Tranfer Hydroxylation of **4**



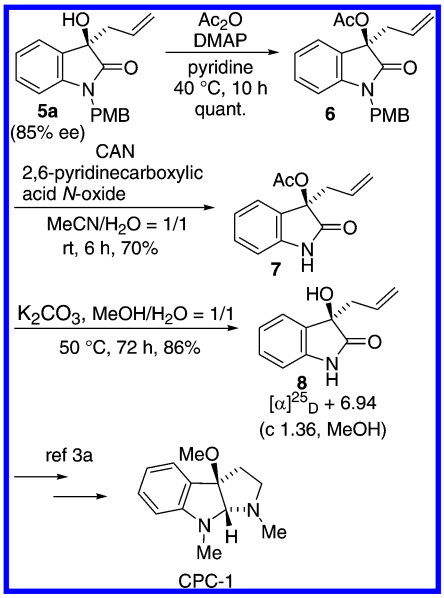
entry	R	product	time (h)	yield (%)	ee (%)
1	$CH_2CH{=}CH_2$	**5a**	2.5	98	85
2	CH_2Ph	**5b**	2.5	95	86
3	$CH_2C{\equiv}CH$	**5c**	24	92	93
4	$CH_2CH_2CH_3$	**5d**	6.0	97	67
5	$CH_2(CH_2)_4CH_3$	**5e**	48	quant	92
6	$CH_2CH{=}C(CH_3)_2$	**5f**	2.5	91	84
7	CH_2Ph(4-OMe)	**5g**	48	97	91
8	$CH_2(CH_2)_2CO_2Et$	**5h**	75	quant	82

solvents gave low enantioselectivities, aromatic hydrocarbon afforded good enantioselectivity, and toluene was found to

(8) Nagata, K.; Sano, D.; Itoh, T. *Synlett* **2007**, 547.
(9) (a) Ooi, T.; Takeuch, M.; Kameda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (b) Ooi, T.; Kameda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.
(10) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539.
(11) Dolling, U.-H.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.
(12) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.
(13) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
(14) We also carried out the hydroxylation reaction toward other substrates, which have a benzyl or Boc protecting group, under the same condition as that of entry 8 in Table 2. But the reaction of the oxindole having a benzyl protecting group resulted in 49% yield and 61% ee. In the case of the oxindole having a Boc protecting group, corresponding hydroxylated product was not obtained probably due to the instability of the product under the conditions.

give the best result (entries 2−7). On further optimization of reaction conditions, it was found that using 4 equiv of

Scheme 1. Transformation of **5** into **8**



triethyl phosphite gave the highest yield. The absolute configuration of **5** was confirmed to be *R* by chemical correlation with 3-allyl-3-hydroxy-indolin-2-one (**8**) (Scheme 1). Acetylation of the hydroxyl group of **5** followed by CAN oxidation in the presence of 2,6-pyridinecarboxylic acid *N*-oxide gave compound **7**. Then hydrolysis of **7** gave 3-allyl-3-hydroxyindolin-2-one (**8**), which was reported to be a synthetic precursor of alkaloid CPC-1.[3a] Absolute configuration of **8** at the 3-position was determined to be *R* by comparing the specific rotation of **8** with the reported one (for (*S*)-**8**[3a], $[\alpha]^{26}_{D}$ −10 (*c* 1.3, MeOH)).

We then investigated the asymmetric hydroxylation using 2-oxindoles having various substituents at the 3-position (Table 3). It was found that alkyl-, alkenyl-, and alkynyl-substituted oxindoles were hydroxylated in high yields and with high enantioselectivities.[15] Even in the presence of the ester group, enantioselective hydroxylation was performed in high yield without hydrolysis (entry 8).

In conclusion, we have shown that the catalytic enantioselective hydroxylation reaction of 3-substituted-2-oxindoles with molecular oxygen was established, and high enantioselectivity was achieved using cinchonidine-derived CPTC. The reaction is operationally simple and environmentally benign in that an organocatalyst from a natural source and molecular oxygen are used. 3-Hydroxy-2-oxindoles obtained in the present reaction are thought to be useful intermediates to synthesize the natural products which have bioactivities. Application of the present method for the synthesis of natural and bioactive compounds is under investigation.

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Supporting Information Available: Experimental procedures and full spectroscopic date for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The present reaction is thought to proceed via radical intermediate. The detailed mechanism, which involves an asymmetric process, however, is not cleared and the mechanistic consideration is now under investigation.