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Lewis Acid-Catalyzed Enantioselective Hydroxylation Reactions of Oxindoles and β-Keto Esters Using DBFOX Ligand

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3-Hydroxy-2-oxindoles are key structural functionalities throughout natural products and drug candidates.[1,2] Chiral 3-aryl-3-hydroxy-2-oxindoles[2] are particularly promising molecules in the field of medicinal chemistry represented by SM-130686.[2b] Probably the most direct approach to enantioselective synthesis of 3-aryl-3-hydroxy-2-oxindoles is through both asymmetric nucleophilic arylation of isatins[3] and enantioselective electrophilic hydroxylation of 3-aryl-2-oxindoles.[2a,c] Although several examples of the catalytic asymmetric preparation of 3-aryl or alkyl-3-hydroxy-2-oxindoles have been reported,[3a−e] the asymmetric synthesis of these compounds by way of direct catalytic asymmetric hydroxylation reaction of oxindoles is rare. One report detailed the application of Davis' chiral oxaziridine[4] as asymmetric hydroxylating reagent for stoichiometric approach to the synthesis of chiral 3-aryl-3-hydroxy-2-oxindoles;[2a,c] however, to the best of our knowledge, there is no catalytic enantioselective hydroxylation of oxindoles dealing with asymmetric catalysis. Recently, our group has demonstrated the DBFOX−Ni(II)-catalyzed enantioselective fluorination and chlorination of β-keto esters as well as oxindoles.[5a] As a part of our ongoing research program directed to the development of new methodology leading to biologically active indole compounds,[5] we herein describe the first example of catalytic enantioselective hydroxylation reaction of 2-oxindoles **1** using the DBFOX−Zn(II) catalyst with oxaziridine **3** as oxidant. The extension of the method to the Ni(II)-catalyzed enantioselective hydroxylation reaction of β-keto esters **4** using DBFOX ligand is also described (Figure 1).

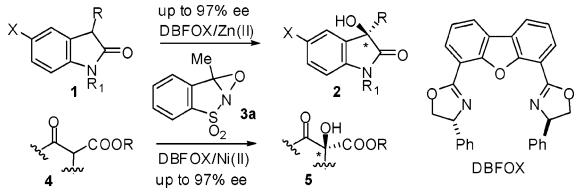
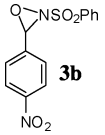


Figure 1. Lewis acid-catalyzed enantioselective hydroxylations of oxindoles and β-keto esters using DBFOX with oxaziridine.

Our studies on the DBFOX-catalyzed enantioselective hydroxylation of oxindoles **1** are summarized in Table 1. We first attempted the reaction of *N*-Boc-3-phenyl-2-oxindole **1a**[5a,6] using racemic oxaziridine **3b**[4] [3-(4-nitrophenyl)-2-(phenylsulfonyl)-1,2-oxaziridine, 4-NO_2-C_6H_4-CH(O)N-Ph] under the previously reported conditions for enantioselective fluorination/chlorination of oxindoles,[5a] $Ni(OAc)_2$·$4H_2O$ in CH_2Cl_2. The 3-hydroxy-3-phenyl-2-oxindole **2a** was obtained in 97% yield, but the enantioselectivity was only 11% (run 1). Optimization of the Lewis acid and solvent revealed that both chemical yield and enantioselectivity were largely dependent on this combination. When the reaction was performed in the presence of $Ni(SbF_6)_2$ in CH_2Cl_2, the hydroxylation proceeded in 68% yield with 65% ee (run 5). While $Zn(SbF_6)_2$ in EtOH

Table 1. Optimization Studies for Enantioselective Hydroxylation of 3-Phenyl-2-oxindole **1a** to 3-Hydroxy-3-phenyl-2-oxindole **2a**[a]

run	oxidant **3**	Lewis acid	solvent	yield (%)	ee (%)
1	 **3b**	$Ni(OAc)_2$·$4H_2O$	CH_2Cl_2	97	11
2	**3b**	$Zn(ClO_4)_2$	CH_2Cl_2	41	2
3	**3b**	$Zn(SbF_6)_2$	CH_2Cl_2	57	74
4	**3b**	$Mg(SbF_6)_2$	CH_2Cl_2	78	16
5	**3b**	$Ni(SbF_6)_2$	CH_2Cl_2	68	65
6	**3b**	$AgSbF_6$	CH_2Cl_2	65	2
7	**3b**	$Zn(SbF_6)_2$	toluene	59	13
8	**3b**	$Zn(SbF_6)_2$	ether	62	25
9	**3b**	$Zn(SbF_6)_2$	EtOH	37	85
10	**3b**	$Zn(OAc)_2$	CH_2Cl_2	81	39
11	**3a**	$Zn(SbF_6)_2$	EtOH	54	12
12	**3a**	$Zn(OAc)_2$	CH_2Cl_2	82	93

[a] **1a** (1.0 equiv), oxaziridine **3** (1.2 equiv), DBFOX (11 mol %), and Lewis acid (10 mol %) were reacted in solvent in the presence of MS4A at rt for 1−2 h. Enantioselectivity was determined by chiral HPLC analysis.

conditions gave good ee of 85%, the conversion was rather low (37%, run 9). On further optimization of the reaction conditions, we found that the racemic oxaziridine **3a**[4] was much more effective than **3b** for the enantioselective hydroxylation in the presence of $Zn(OAc)_2$ in CH_2Cl_2 (run 12). Thus, the use of oxaziridine **3a** (1.2 equiv), DBFOX (11 mol %), and $Zn(OAc)_2$ (10 mol %) in the presence of 4 Å molecular sieves (MS4A) in CH_2Cl_2 at room temperature became the standard conditions for our catalytic enantioselective hydroxylation reaction of oxindoles **2**.

The scope of the hydroxylation reaction of a series of 3-aryl-2-oxindoles **1** was investigated; we found that the DBFOX/$Zn(OAc)_2$ catalyst exhibits excellent enantioselectivity in the level of >90% ee with high yields (90−97% ee, Table 2, entries 1−8). It is interesting to note that the method is effective not only for the synthesis of chiral 3-aryl-3-hydroxy-2-oxindoles **2a**−**h** but also for chiral 3-alkyl-3-hydroxy-2-oxindoles **2i**−**m** (entries 9−13, 83−86% ee). More than 83% ee of products was observed for 3-alkyl-3-hydroxy-2-oxindoles in high yields independent of the substituents at C-3, except the case of 3-perfluorophenyl-2-oxindole **2n** (entry 14). The absolute configuration of **2a** was determined by comparing the optical rotation of the NH derivative of **2a** with that of the known 3-hydroxy-3-phenyl-2-oxindole, and the stereochemistry of other oxindoles **2** was tentatively assumed by analogy (see the Supporting Information, SI, for details). Very recently, an excellent but different procedure for chiral 3-aryl-3-hydroxy-2-oxindoles using rhodium-catalyzed asymmetric addition of arylboronic acids

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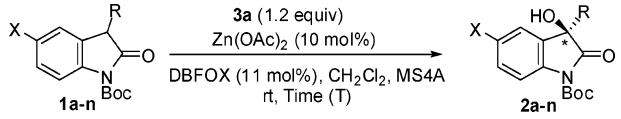
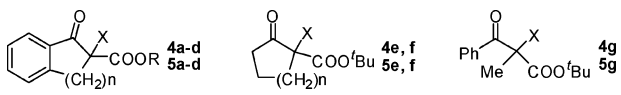
Table 2. Enantioselective Hydroxylation of 3-Aryl- and 3-Alkyl-2-oxindoles **1a**−**n**[a]



entry	1	R	X	*T* (h)	2	yield (%)	ee (%)
1	**1a**	Ph	H	6	**2a**	82	93
2	**1b**	*p*-Tol	H	15	**2b**	84	94
3	**1c**	*p*-F−C_6H_4	H	15	**2c**	77	91
4	**1d**	*p*-Tol	Me	13	**2d**	76	93
5	**1e**	Ph	Me	2	**2e**	91	90
6	**1f**	*p*-F−C_6H_4	Me	1	**2f**	92	90
7	**1g**	Ph	MeO	3	**2g**	95	97
8	**1h**	*p*-F−C_6H_4	MeO	1	**2h**	88	91
9	**1i**	Me	H	19	**2i**	68[b]	84[b]
10	**1j**	*i*-Pr	H	48	**2j**	43(83)[c]	83
11	**1k**	*p*- Br−$C_6H_4CH_2$	H	14	**2k**	97	86
12	**1l**	*p*-Cl−$C_6H_4CH_2$	H	19	**2l**	91	86
13	**1m**	*p*-MeO−$C_6H_4CH_2$	H	28	**2m**	90	85
14	**1n**	C_6F_5	H	3	**2n**	60	36

[a] Enantioselectivity was determined by chiral HPLC analysis. The reaction was carried out for several hours to overnight. See Supporting Information for details. [b] After removal of Boc group. [c] Based on recovered starting material.

Table 3. Enantioselective Hydroxylation of β-Keto Esters **4** with **3a** (Ad = 1-adamantyl)[a]



entry	substrate **4** (X = H)	time (h)	product **5** (X = OH)	yield (%)	ee (%)
1	**4a**: $n = 1$, R = ^{t}Bu	2	**5a**	96	97
2	**4b**: $n = 1$, R = Ad	0.5	**5b**	85	96
3[b]	**4b**: $n = 1$, R = Ad	0.5	**5b**	81[b]	91[b]
4	**4c**: $n = 2$, R = ^{t}Bu	7	**5c**	84	94
5	**4d**: $n = 2$, R = Ad	18	**5d**	97	96
6	**4e**: $n = 1$	1	**5e**	82	97
7	**4f**: $n = 2$	18	**5f**	83	95
8[c]	**4g**	50	**5g**	27(55)[d]	93

[a] **4** (1.0 equiv), **3a** (1.2 equiv), DBFOX (11 mol %), and $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %) were reacted in CH_2Cl_2 in the presence of MS4A at rt. [b] Oxaziridine **3b** was used instead of **3a**. [c] The reaction was carried out at 40 °C. [d] Based on recovered starting material.

to isatins was reported,[3a] and our method was slightly more enantioselective than the reported procedure.

To demonstrate the further synthetic utility of this DBFOX-catalyzed hydroxylation system, we tested other substrates, β-keto esters. The α-hydroxy-β-dicarbonyl functional unit is an important structural motif found in many bioactive molecules.[7] Examples include the antibacterial kjellmanianone[7a] and tetracycline antibiotic doxycycline.[7b]A few successful examples of catalytic enantioselective α-hydroxylation of β-keto esters[8−10] have appeared; however, the scope of the reaction is not broad. After optimization of the reaction conditions, solvent, Lewis acid, and oxidant (see SI for details), the combination of oxaziridine **3a**, DBFOX, and $Ni(ClO_4)_2 \cdot 6H_2O$ in the presence of MS4A in CH_2Cl_2 afforded the best results in both chemical yield and enantioselectivity. The results are shown in Table 3, and excellent enantioselectivities, 93−97% ee, were obtained. In most cases, our hydroxylation was more enantioselective than the reported procedures for the catalytic asymmetric hydroxylation of β-keto esters.[8,9] The absolute stereochemistry of **5** was tentatively determined to be *S*, as shown in Figure 1 (see the SI).

In conclusion, we have described the first catalytic enantioselective hydroxylation reaction of both 3-aryl- and 3-alkyl-2-oxindoles using the DBFOX−Zn(II) complex, leading to pharmaceutically important chiral 3-aryl-3-hydroxy-2-oxindoles. The structure of oxaziridine **3** was found to play an important role to increase the enantioselectivity. The methodology has been applied to the highly enantioselective hydroxylation[11] of β-keto esters using the DBFOX−Ni(II) complex.

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

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