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Cu(II)-catalyzed enantioselective oxygen atom transfer from oxaziridine to oxindole derivatives with chiral phenanthroline

Yuki Naganawa,* Tomotaka Aoyama and Hisao Nishiyama*

In the presence of Cu(II) complex of axially chiral, N,N,O-tridentate phenanthroline ligand (S)-2, asymmetric oxygen atom transfer of oxindole derivatives (3) using Davis’ oxaziridine (4) underwent to give the corresponding 3-aryl-3-hydroxy-2-oxindole derivatives (1) with excellent enantioselectivity (up to 96% ee). The X-ray crystallographic analysis of isolated Cu(II) complex disclosed its N,N,O-tridentate coordination, which is critical to realize effective catalytic activity.

Introduction

Optically active 3-aryl-3-hydroxy-2-oxindole derivatives (1) have been exploited as biologically active pharmaceutical compounds.1 For example, SM-130686 (A) is a highly potent and orally nonpeptidic growth hormone secretagogue reported by Nagata.2a,b Another example is a compound B which has been evaluated as a calcium-dependent, large conductance potassium (maxi K) channel opener with neuroprotective properties.2c Each of enantiomers of these compounds represents different biological activities.2 However, the large scale preparation of these drugs basically relies on the resolution of racemic products, and hence the challenge of developing new protocols for these scaffolds has been attracted attention in the field of asymmetric synthesis (Scheme 1).3

![Fig. 1 Drugs containing 3-aryl-3-hydroxy-2-oxindole structure](image)

For example, a transition metal-catalyzed enantioselective addition of arylmetallic reagents to isatin derivatives have been explored to provide the corresponding 3-aryl-3-hydroxy-2-oxindoles (1) (Scheme 1a).4 To avoid using expensive transition metal catalysts and arylmetallic reagents, enantioselective Friedel-Crafts reactions are also developed, but limited to the use of highly electron-rich arenes such as indoles.5 The second protocol though C-C bond formation, giving 3-aryl-3-hydroxy-2-oxindole derivatives (1), is an asymmetric intramolecular arylation of α-ketoamide derivatives (Scheme 1b).4b,c Although this transformation is recognized as an alternative methodology of asymmetric addition to isatins, highly functionalized starting materials are required. Both of two strategies involve enantioselective C-C forming processes through nucleophilic addition to carbonyl compounds.

Meanwhile, the different synthetic approach to this end is asymmetric nucleophilic attack of 3-aryl-2-oxindole to electrophilic oxygen atom through a C-O bond formation in the presence of appropriate catalysts (Scheme 1c).3 For example, a representative oxygen source is a benzoyl peroxide (BzOOBz). Antilla reported an enantioselective benzyloxylolation of 3-aryloxindoles catalyzed by chiral calcium salt.7a However, the removal of redundant group with harsh reactants (i.e. TFA and DIBAL-H)b was necessary to obtain protecting group-free oxindole.

On the other hand, a direct C-H oxidation of 3-aryl-2-oxindoles is the most simple and straightforward synthesis of 3-aryl-3-hydroxy-2-oxindole (1). Site-selective C-H oxidations with generality and operational ease are considerable issues, and a number of investigations have revealed appropriate combinations of substrate and catalysts.8 The asymmetric formal C-H oxidation of 3-aryl-2-oxindoles had been conducted with the corresponding enolate and chiral N-sulfonyloxaziridine developed by Davis (Davis’ oxaziridine).9 To avoid the use of an equimolar amount of chiral auxiliaries, enantioselective oxygen transfer from racemic oxaziridine under the influence of chiral catalysts have been investigated.10-12 In this vein, Shibata and Toru reported the pioneering research on zinc-catalyzed enantioselective oxygen transfer to oxindole derivatives using racemic oxaziridine as the terminal oxidant and a chiral DBFOX ligand (Scheme 1d).11a
Despite this achievement in 2006, however, there has been little further investigation of transition-metal-catalyzed enantioselective C-H oxidation of 3-substituted-2-oxindoles. In addition, the detailed discussion about the origin of asymmetric induction has been rarely examined. Conceptually novel chiral ligands have often had a significant impact in changing synthetic protocols. During the course of our studies on the challenge of developing new chiral ligands based on 1,10-phenanthroline (phen), discovered an unprecedented copper complex is an effective catalyst for the enantioselective oxygen transfer from oxaziridine to 3-aryl-2-oxindoles, and herein report the results and discuss the mechanistic insight of this transformation.

**Scheme 1.** Representative synthetic strategies leading to optically active 3-aryl-3-hydroxy-2-oxindole derivatives (1).

**Results and discussion**

**Fig 2.** Chiral N,N,O-tridentate phenanthroline ligand (S)-2

Table 1. Optimization of enantioselective oxygen transfer.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Solvent</th>
<th>% Yield</th>
<th>% ee&lt;sup&gt;*&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>88</td>
<td>10 (R)</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>42</td>
<td>rac</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>86</td>
<td>14 (R)</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>26</td>
<td>15 (R)</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>91</td>
<td>65 (R)</td>
</tr>
<tr>
<td>6</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>53</td>
<td>rac</td>
</tr>
<tr>
<td>7</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>90 (R)</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>18</td>
<td>69 (R)</td>
</tr>
<tr>
<td>9</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>45</td>
<td>76 (R)</td>
</tr>
<tr>
<td>10</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>CPME</td>
<td>98 (R)</td>
</tr>
<tr>
<td>11</td>
<td>2a</td>
<td>CH₂Cl₂</td>
<td>Et₂O</td>
<td>&gt;99 (R)</td>
</tr>
<tr>
<td>12</td>
<td>2b</td>
<td>CH₂Cl₂</td>
<td>Et₂O</td>
<td>73 (R)</td>
</tr>
<tr>
<td>13</td>
<td>2c</td>
<td>CH₂Cl₂</td>
<td>Et₂O</td>
<td>85 (R)</td>
</tr>
<tr>
<td>14</td>
<td>2d</td>
<td>CH₂Cl₂</td>
<td>Et₂O</td>
<td>63 (R)</td>
</tr>
<tr>
<td>15</td>
<td>2e</td>
<td>CH₂Cl₂</td>
<td>Et₂O</td>
<td>31 (S)</td>
</tr>
<tr>
<td>16</td>
<td>2f</td>
<td>CH₂Cl₂</td>
<td>Et₂O</td>
<td>80 (S)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed on a 0.1 mmol scale. 3a (0.1 mmol), 4 (0.12 mmol), (S)-2 (5.5 mol%), metal (5 mol%). The chiral catalyst was prepared in situ by mixing (S)-2 and metal for 60 min at rt. Yield of the isolated product after column chromatography. The ee value was determined by HPLC using a chiral stationary phase.

To deal with this issue, we employed original chiral phen ligands (S)-2, which enables N,N,O-tridentate coordination through the phen moiety and an additional phenolic hydroxyl group (Fig. 2).<sup>13</sup> First, optimization of enantioselective oxygen atom transfer from racemic Davis' oxaziridine (4) to N-Boc-3-phenyl-2-oxindole (3a) in the presence of (S)-2a (5.5 mol%) and various metals (5 mol%) was carried out, and the results are summarized in Table 1. On the basis of Shibata and Toru's report, we conducted the initial reaction using Zn(OAc)₂ in CH₂Cl₂ at room temperature (entry 1). The reaction proceeded smoothly to give the corresponding 3-hydroxy-3-phenyl-2-oxindole 1a in good yield, albeit with very low enantioselectivity. Since the use of other zinc salts did not improve the selectivity (entry 2), we next moved to the screening of several transition metal catalysts (entries 3-5). Cu(OAc)₂·H₂O proved the best catalyst, providing moderate enantioselectivity (65% ee), although no enantioinduction was observed in the case of other copper salts such as Cu(OTf)₂ (entry 6). Eventually, we found that the choice of solvent had a significant impact on enantioselectivity, and the reaction performed in Et₂O resulted in a much improved yield and ee (entries 7-11). We employed several (S)-2 ligands bearing different substituents on the phenyl ring to improve the ee (entries 12-16). The best result was observed in the reaction using (S)-2c, which contains a 3,5-xylyl group (entry 13). The
presence of aromatic rings on the naphthyl group is essential to achieve good enantioselectivity, because the reaction using (S)-2f, which contains no aromatic ring at this position, resulted in a dramatic decrease in ee, with inversion of stereochemistry (entry 16). The absolute configuration of the product 1a should be R, according to the literature. 

Table 2. Optimization of enantioselective oxygen transfer.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>85%</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>75%</td>
<td>96%</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>87%</td>
<td>93%</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>63%</td>
<td>94%</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>87%</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>85%</td>
<td>95%</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>76%</td>
<td>95%</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>86%</td>
<td>95%</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>73%</td>
<td>98%</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)$_2$·H$_2$O (5 mol%), oxaziridine (1.2 eq)</td>
<td>71%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Reactions were performed on a 0.1 mmol scale. 3 (0.1 mmol), 4 (0.12 mmol), (S)-2c (5.5 mol%), Cu(OAc)$_2$·H$_2$O (5 mol%). The chiral catalyst was prepared in situ by mixing (S)-2c and Cu(OAc)$_2$·H$_2$O for 60 min at 25 °C. 

Applying the optimized conditions, we examined the scope of N-Boc-3-substituted-2-oxindole derivatives 3 (Table 2) for Cu(II)-catalyzed Davis oxidation. In order to examine the para-substituent effect of a phenyl ring at the C-3 carbon, we used 3b-e, containing methyl, methoxy, trifluoromethyl and fluoro group, respectively. Regardless of the electronic factor of each substituent, the desired 3-aryl-3-hydroxy-2-oxindole derivatives 1b-e were uniformly obtained with excellent enantioselectivity (93-96% ee). In contrast, the introduction of a substituent at the ortho-position tended to diminish the enantioselectivity slightly. For example, oxidation of N-Boc-3-(o-tolyl)oxindole (2f) provided the corresponding product (R)-1f in 87% yield and with 80% ee. Also, hydroxylation of 3g, bearing a large 1-naphthyl ring, furnished the corresponding products 1g with moderate ee. For substrates with a bulky or electron-withdrawing aromatic ring such as 3d and 3g, the higher reaction temperature (40 °C) was necessary to achieve satisfactory yields, probably due to the weaker nucleophilicity of the Cu(II) enolate. Next, in order to examine the substituent effect on the oxindole core, we conducted reactions of oxindoles 3h-j, with methyl, methoxy and fluoro groups at the C-5 position, respectively. These substrates were converted to the corresponding 3-aryl-3-hydroxy-2-oxindole derivatives 1h-j with excellent enantioselectivity (94-96% ee). Finally, we carried out hydroxylation of N-Boc-3-aryl-2-oxindoles 3k-m, which have various substituents at both the C-2 carbon of the phenyl ring and the C-5 carbon of oxindole. Enantioinduction of the optically active products 1k-m was well controlled in every case (95-96% ee).

Fig 3. Plausible roles of Cu(II) catalyst.

Encouraged by this result, we attempted to understand the mechanistic aspects of Cu(II)-catalyzed enantioselective oxygen transfer reaction. We assume that the role of Cu(II) is basically a Lewis acid catalyst. However, there are two possibilities as shown in Fig 3: (a) activation of oxaziridine or (b) activation of oxindole. Both of them have been proposed in the literature. For example, Yoon et al. have developed several novel transformations utilizing oxaziridines with alkenes catalysed by Cu(II) salts and therein explained that Cu(II) catalyst coordinates and activates oxaziridine (Fig 3. (a)). In addition, the possible reaction mechanism contains Cu(II) and Cu(III) redox cycle. On the other hand, some of previous reports on enantioselective α-hydroxylation of β-ketocarbonyl compounds with oxaziridine describe Lewis acid-catalyzed activation of nucleophiles to accelerate the generation of metal enolates (Fig 3. (b)).
Considering the activation of Davis’ oxaziridines 4, we conducted Yoon’s asymmetric aminohydroxylation reaction of styrene with our Cu(II) catalyst; however, no reaction was observed (Scheme 2).

Furthermore, we focused on the experimental outcome that Davis’ oxaziridine 4 used for the present reaction is a racemic form, and the use of just 1.2 equivalents of this oxidant is enough to realize sufficient enantioselectivity. To gain more insight, we attempted kinetic resolution using 2 equivalents of 3; however, the ee of the recovered Davis’ oxaziridine 3 was, interestingly, almost racemic (Scheme 3). This result indicated that the reaction rates of the oxidants (S)-4 and (R)-4 were almost comparable, and hence enantioinduction is predominantly achieved by effective chiral environment surrounding prochiral Cu(II) enolate. Also, the interaction of Cu(II) catalyst toward oxaziridine might be less feasible.

Table 3. The relationship between ee of (S)-2a and ee of the product (R)-1a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ee of (S)-2a</th>
<th>% yield</th>
<th>Ee of (R)-1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>45</td>
<td>54 (R)</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>37</td>
<td>70 (R)</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>60</td>
<td>89 (R)</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>77</td>
<td>92 (R)</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>85</td>
<td>93 (R)</td>
</tr>
</tbody>
</table>

* Reactions were performed on a 0.1 mmol scale. 3a (0.1 mmol), 4 (0.12 mmol), (S)-2a (5.5 mol%), metal (5 mol%). The chiral catalyst was prepared in situ by mixing (S)-2a and metal for 60 min at rt. All data are the average of two experiments.

We next examined the non-linear effect of the reaction (Table 3). Interestingly, the ee of the product was higher than one of the ligand in the reaction with ligands being of low enantiopurity. Although the reason of this positive non-linear effect is still unclear at the moment, one plausible explanation is that the complexation of Cu(OAc) and lower ee ligands (entries 1-2) provides Cu(II) complexes which has no or low catalytic activities. The lower yields in entries 1-2 also implies the formation of other off-cycle Cu(II) complexes.

Based on the absolute configuration, a proposed explanation of asymmetric induction is illustrated in Fig 4. The initial step is thought to be exchange of the acetate ligand on copper with an enolate of the oxindole derivative 3. We assume that the role of the Boc group on the nitrogen atom is not only as a protecting group but also as a chelating group, enabling bidentate coordination of the oxindole enolate 3 with the Cu(II) center. (S)-2 shows C₁ symmetry, and the two orientations of these chelate coordination of the Cu(II) enolate are distinguished as I-1 and I-2. We hypothesized that the favored intermediate is I-1 due to steric repulsion between the bulky Boc group and the aromatic ring on the naphthyl group in I-2. In addition, the naphthyl ring blocks the si-face of the Cu(II) enolate and nucleophilic attack to the oxidant 4 occurs from the re-face to furnish (R)-1a as the major product. This consideration may explain why (S)-2f, which contains no aromatic ring, is ineffective as a ligand (Table 1, entry 16).

Fig 4. Possible explanation of asymmetric induction.

The reaction using a control ligand (S)-5, in which the hydroxyl group of (S)-2a is protected with a methyl group, did not proceed at all (Scheme 4). This result suggests that the N,N,O-tridentate property of (S)-2 plays a crucial role not only for asymmetric induction but also for acquiring reactivity.
Scheme 4. Control experiment to demonstrate the importance of the N,N,O-tridentate property of the ligand.

As another control experiment, we performed the reaction of N-methyl-3-phenyl-2-oxindole 6, however, no reaction was observed (Scheme 5). Probably, the exchange of acetate ligand on Cu(II) to 6 is too sluggish, whereas the exchange between acetate ligand and easily-enolize bidentate substrate 3 is entropically favoured and smoothly undergoes. Therefore, an N-Boc group plays an important role not only for the protection of free nitrogen but also for gaining efficiency in terms of reactivity and enantioselectivity.

Scheme 5. Reaction of N-methyl-3-phenyl-2-oxindole 6.

Finally, we attempted to isolate the active Cu(II) complex. Complex (S)-7 was prepared by a reaction between Cu(OAc)$_2$·H$_2$O and (S)-2a in a mixed solvent of CH$_2$Cl$_2$ and MeOH (Scheme 6). The solvent was removed and recrystallization in acetone gave an air-stable crystal suitable for X-ray crystallographic analysis, in which the N,N,O-tridentate structure was confirmed (Fig 5).


Fig 5. ORTEP diagram of (S)-7. Thermal ellipsoids are shown at the 50% probability level. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): O(1)-Cu(1) 1.860(5), O(2)-Cu(1) 1.974(5), N(1)-Cu(1) 1.967(6), N(2)-Cu(1) 1.979(6), O(1)-Cu(1)-N(2) 171.3(2), O(1)-Cu(1)-N(1) 91.9(2), N(1)-Cu(1)-N(2) 83.8(2).

To determine whether (S)-7 is actually a catalyst, a reaction was carried out using isolated (S)-7 (Scheme 7). Although a slightly poorer result was obtained (50% yield, 89% ee), we found that the addition of a catalytic amount of AcOH improved the yield and ee to the level of the reaction using the in-situ prepared Cu(II) complex (80% yield, 94% ee). This result suggests that AcOH, generated from Cu(OAc)$_2$·H$_2$O and (S)-2a, acts as a promoter in this oxidation reaction catalysed by an in-situ generated catalyst probably because of the activation of electrophiles. This kind of acceleration effect by Brønsted acids has been reported in the literature.

Scheme 7. Effect of AcOH as an additive in the reaction with the isolated Cu(II) complex (S)-7.

Conclusions

In summary, we demonstrated Cu(II)-catalyzed enantioselective direct hydroxylation of 3-aryl-2-oxindole derivatives 3 with racemic Davis’ oxaziridine 4. To our knowledge, this is the first example of highly enantioselective Cu(II)-catalyzed oxygen transfer reaction using Davis oxaziridine as the terminal oxidant. The original phenanthroline ligand (S)-2 adopts N,N,O-tridentate coordination with Cu(OAc)$_2$·H$_2$O, as confirmed by X-ray crystallographic analysis. Based on several experimental evidences, we proposed the mechanistic details of this enantioselective oxygen transfer reaction; The chiral environment of (S)-2 plays an important role for the discrimination of prochiral face of Cu(II) enolate.
Further studies on the application of this chiral ligand (S)-2 with other electrophiles and nucleophiles are continuing in our laboratory in order to demonstrate the broad synthetic utility. This research was partly supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (Nos. 15H03808, 15K21063).

**Experimental Section**

**General procedure for enantioselective oxygen transfer from oxaziridine (4) to oxindoles (2).**

To a mixture of (S)-1c (3.0 mg, 5.5 µmol) and Cu(OAc)₂·H₂O (1.0 mg, 5.0 µmol) in schlenk tube under Ar atmosphere, dry diethyl ether (1 mL) were added at 25 °C. After stirring for 1 h at 25 °C, oxindole 2 (0.1 mmol) was added portion-wise to the mixture. After stirring another 5 min, Davis’ oxaziridine 3 (33.0 mg, 0.12 mmol) was added portion-wise to the mixture and stirred for 24 h at the same temperature. The catalyst was removed by passing through short column chromatography on silica gel (eluting hexane/EtOAc) and the solvent was evaporated. The residue was purified by column chromatography (eluting hexane/EtOAc) to give the desired product (R)-4.

(R)-N-t-Butoxycarbonyl-3-hydroxy-3-phenyl-2-oxindole (4a).

1H NMR (300 MHz, CDCl₃): δ (ppm) = 7.94 (d, J = 7.8 Hz, 1H), 7.17-7.43 (m, 7H), 3.37 (s, 1H), 1.64 (s, 9H). The detailed spectral data has been reported in the literature. The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 1.0 mL/min, retention time; 31.0 min (R) and 28.3 min (S)). [e.r. = 96.0%/e.e. = 96.0%]

(R)-N-t-Butoxycarbonyl-3-hydroxy-3-(4-methylphenyl)-2-oxindole (4b).

1H NMR (300 MHz, CDCl₃): δ (ppm) = 7.96 (d, J = 7.8 Hz, 1H), 7.18-7.43 (m, 7H), 3.37 (s, 1H), 1.64 (s, 9H). The detailed spectral data has been reported in the literature. The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 0.5 mL/min, retention time; 15.1 min (R) and 28.3 min (S)). [e.r. = 96.0%/e.e. = 96.0%]

(R)-N-t-Butoxycarbonyl-3-hydroxy-3-(4-fluorophenyl)-2-oxindole (4c).

IR (KBr): 3865, 3803, 3751, 3446, 3059, 2980, 2931, 1730, 1608, 1480, 1292, 1149, 1036 cm⁻¹; 1H NMR (300 MHz, CDCl₃): δ (ppm) = 7.90-7.95 (m, 2H), 7.22-7.42 (m, 4H), 7.05-7.16 (m, 3H), 3.18 (s, 1H), 1.88 (s, 3H), 1.67 (s, 9H); 13C NMR (75 MHz, CDCl₃): δ (ppm) = 175.0, 148.6, 143.3, 139.4, 130.5, 129.8, 129.1, 128.4, 125.9, 125.6, 124.7, 115.2, 84.8, 77.3, 28.2, 19.8; [α]D = +86.5 (c = 0.97, CHCl₃); HRMS (FAB) Calcld for C₂₀H₁₄FNO₃ ([M+H⁺]⁺) 340.1549. Found 340.1560. The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 0.5 mL/min, retention time; 31.0 min (R) and 103.6 min (S)). [e.r. = 90.0/10.0][e.e. = 80.0%]

(R)-N-t-Butoxycarbonyl-3-hydroxy-3-(1-naphtyl)-2-oxindole (4d).

IR (KBr): 3846, 3803, 3751, 3446, 3059, 2980, 2931, 1730, 1608, 1480, 1292, 1149, 1036 cm⁻¹; 1H NMR (300 MHz, CDCl₃): δ (ppm) = 7.86 (d, J = 7.8 Hz, 1H), 7.22-7.42 (m, 4H), 7.05-7.16 (m, 3H), 3.18 (s, 1H), 1.88 (s, 3H), 1.67 (s, 9H); 13C NMR (75 MHz, CDCl₃): δ (ppm) = 175.0, 148.8, 139.9, 137.3, 134.3, 131.4, 130.1, 128.7, 128.4, 125.9, 125.6, 124.7, 115.2, 84.8, 77.3, 28.2, 19.8; [α]D = +86.5 (c = 0.97, CHCl₃); HRMS (FAB) Calcld for C₂₀H₁₄FNO₃ ([M+H⁺]⁺) 340.1549. Found 340.1560. The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 0.5 mL/min, retention time; 31.0 min (R) and 103.6 min (S)). [e.r. = 90.0/10.0][e.e. = 80.0%]
determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 0.8 mL/min, retention time; 18.6 min (R) and 32.0 min (S)). [e.r. = 97.8/2.2][e.e. = 95.6%]

(R)-N-t-Butoxycarbonyl-3-hydroxy-5-methoxy-3-phenyl-2-oxindole (4i).
1H NMR (300 MHz, CDCl3): δ (ppm) = 7.86 (d, J = 9.0 Hz, 1H), 7.26-7.36 (m, 5H), 6.93 (dd, J = 9.0 Hz, 2.4 Hz, 1H), 6.85 (d, 2.7 Hz, 1H), 3.77 (s, 3H), 3.31 (br, 1H), 1.63 (s, 9H); [α]D = +31.6 (c = 1.0, CHCl3). The detailed spectral data has been reported in the literature.10 The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 0.8 mL/min, retention time; 30.0 min (R) and 54.0 min (S)). [e.e. = 96.9/3.1][e.e. = 93.8%]

(R)-N-t-Butoxycarbonyl-3-hydroxy-5-fluoro-3-phenyl-2-oxindole (4j).
IR (KBr): 3429, 2927, 1789, 1732, 1610, 1485, 1371, 1341, 1297, 1252, 1149, 1108, 1034, cm⁻¹; 1H NMR (300 MHz, CDCl3): δ (ppm) = 7.94 (dd, J = 4.8 Hz, 9.0 Hz, 1H), 7.33 (m, 5H), 7.01-7.13 (m, 2H), 3.35 (s, 1H), 1.64 (s, 9H); 13C NMR (75 MHz, CDCl3): δ (ppm) = 175.2, 159.9 (d, J = 243 Hz), 148.6, 139.0, 135.2 (d, J = 2.3 Hz), 131.6 (d, J = 1.0 Hz), 128.6, 125.9, 125.1, 116.8 (d, J = 4.0 Hz), 116.6 (d, J = 19.4 Hz), 112.3 (d, J = 2.4 Hz), 85.1, 77.6 (d, J = 1.7 Hz), 28.2; [α]D = +69.6 (c = 0.71, CHCl3). HRMS (FAB) Calcd for C19H18FNO3 [(M+Na)+] 366.1118. Found 366.1122. The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 0.8 mL/min, retention time; 14.5 min (R) and 25.5 min (S)). [e.e. = 97.3/2.7][e.e. = 94.6%]

(R)-N-t-Butoxycarbonyl-3-hydroxy-5-methyl-3-(4-methylphenyl)-2-oxindole (4k).
1H NMR (300 MHz, CDCl3): δ (ppm) = 7.80 (d, J = 8.4 Hz, 1H), 7.12-7.23 (m, 6H), 3.25 (s, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 1.63 (s, 9H). The detailed spectral data has been reported in the literature.11 The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 1.0 mL/min, retention time; 16.5 min (R) and 27.0 min (S)). [e.e. = 97.3/2.7][e.e. = 94.6%]

(R)-N-t-Butoxycarbonyl-3-hydroxy-5-methoxy-3-(4-methylphenyl)-2-oxindole (4l).
1H NMR (300 MHz, CDCl3): δ (ppm) = 7.86 (d, J = 9.0 Hz, 1H), 7.23-7.26 (m, 2H), 7.70 (d, J = 8.4 Hz, 2H), 6.92 (dd, J = 2.7 Hz, 8.7 Hz 1H), 6.86 (d, J = 2.7 Hz 1H), 3.77 (s, 3H), 3.18 (s, 1H), 2.33 (s, 3H), 1.63 (s, 9H); 13C NMR (75 MHz, CDCl3): δ (ppm) = 175.6, 157.0, 148.8, 138.2, 136.5, 132.6, 131.1, 129.1, 125.2, 116.3, 115.4, 110.1, 84.5, 77.8, 55.7, 28.2, 21.3; [α]D = -1.0 (c = 1.0, CHCl3); HRMS (FAB) Calcd for C21H23NOS ([M+Na]+) 392.1474. Found 392.1479. The enantiomeric purity of the product was determined by HPLC analysis (Daicel CHIRALCEL AD-H, hexane/iPrOH = 95/5, flow rate = 1.0 mL/min, retention time; 27.2 min (R) and 50.7 min (S)). [e.e. = 97.9/2.1][e.e. = 95.8%]

Notes and references
3 (a) A. Kumar and S. S. Chimmi, RSC Advances, 2012, 2, 9748.
We carried out the study on a deuterium incorporation of N-methyl-3-phenyl-2-oxindole 6 with D$_2$O (30 eq) in the presence of in-situ generated Cu catalyst (5 mol%) for 24 h at rt. The conversion of incorporation of deuterium was ca. 90% in $^1$H NMR analysis. This result suggests that enolization of 6 actually occurs, however, the following C-O bond formation cannot undergo.

18 Crystallographic data was obtained for (S)-7 and had been deposited with the Cambridge Crystallographic Data Centre. CCDC-1405289 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


21 The reactions using other oxidants such as H$_2$O$_2$, TBHP, CHP and iodosobenzene did not provide the desired products.


