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# Catalytic asymmetric hydroxylative dearomatization of 2-naphthols: synthesis of lacinilene derivatives†

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An enantioselective hydroxylative dearomatization of 2-naphthols with oxaziridines has been accomplished using a *N,N'*-dioxide–scandium(III) complex catalyst. Various substituted *ortho*-quinols could be obtained in high yields (up to 99%) and enantioselectivities (up to 95 : 5 er). This methodology could be applied in the synthesis of bioactive lacinilenes in a gram-scale reaction. Based on the experimental investigations and previous work, a possible catalytic model was proposed.

## Introduction

Substituted *ortho*-quinols are essential structural motifs in a number of natural products and pharmaceuticals.<sup>1</sup> For instance, chiral lacinilene derivatives (Fig. 1), a series of phytoalexins isolated from cotton plants, have been utilized for inhibiting the growth of cotton bacterial pathogens, such as *Xanthomonas campestris* or *malvacearum*.<sup>2</sup> Studies have showed that the (*S*)-enantiomer of lacinilene C is more active than the (*R*)-enantiomer.<sup>2c</sup> While these biological activities provide a justification for the development of approaches to the synthesis of enantiomerically enriched lacinilene derivatives, novel catalytic enantioselective methods remain limited.<sup>2b,d</sup>

Optically active lacinilene derivatives in nature were proposed to be produced enzymically from the oxidation of dihydroxycadalenes, thus it is of practical interest to discover a catalytic asymmetric oxidative dearomatization route to the synthesis of these cadinanes.<sup>3</sup> Compared with other successful dearomatization events of phenols or naphthols,<sup>4,5</sup> controlling the chemo-, regio- and enantioselectivity of the asymmetric

hydroxylative dearomatization is more difficult,<sup>6</sup> as there might be serious side reactions in the presence of oxidants including overoxidation of alkene functions, competitive *para*-oxidation and homocoupling.<sup>6c,e</sup> Additionally, the *ortho*-quinol product could undergo an unexpected  $\alpha$ -ketol rearrangement, which enhances the difficulty of controlling the reactivity and selectivity.<sup>6a,7</sup> In this respect, only a few reports related to asymmetric hydroxylative dearomatization of phenols or naphthols have been reported. Asymmetric oxidative dearomatization of phenolate mediated by copper–sparteine–dioxygen complexes followed a [4 + 2] dimerization cascade, giving bicyclo[2.2.2] octenones as the final products.<sup>6a</sup> Several chiral hypervalent organoiodine compounds were developed for the asymmetric hydroxylative dearomatization of phenols and 1-naphthols.<sup>6b–e</sup> Taking these examples into account, we want to engage in discovering new enantioselective strategies for the synthesis of *ortho*-quinol moieties with improved efficiency and selectivity. Here, we present an efficient asymmetric hydroxylative dearomatization of 2-naphthols catalyzed by a chiral *N,N'*-dioxide–scandium(III) complex catalyst.<sup>8</sup> The process could be applied to the synthesis of various 1-hydroxy-1-alkyl-naphthalen-2-one derivatives including lacinilene C methyl ether and lacinilene D, in high to excellent yields and good enantioselectivities under mild reaction conditions (Scheme 1).

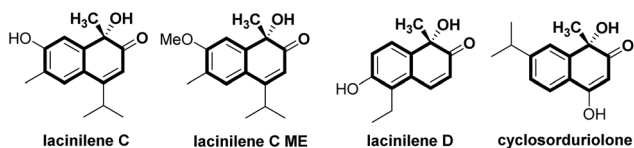


Fig. 1 Representative active lacinilene derivatives bearing *ortho*-quinol structures.

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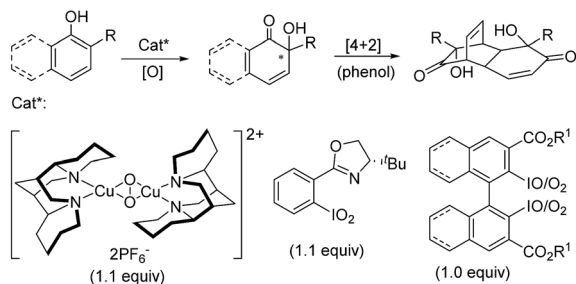
† Electronic supplementary information (ESI) available. CCDC 1536822. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc02809a

## Results and discussion

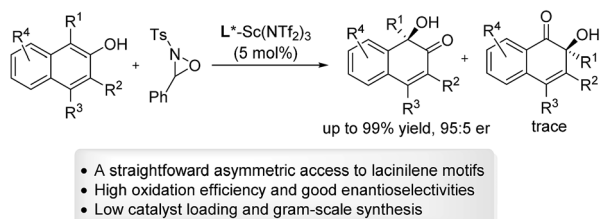
We selected the hydroxylative dearomatization of 1-methylnaphthalen-2-ol **1a** as the model substrate using 3-phenyl-2-tosyl-1,2-oxaziridine **2a** as the oxidant which was proven to be chemoselective as a phase-transfer-catalyst under basic conditions (Table 1).<sup>7a</sup> Initially, the catalytic asymmetric reaction was performed with 10 mol% of chiral *N,N'*-dioxide **L-PiPr<sub>2</sub>-Sc(OTf)<sub>3</sub>** complex in DCM at 30 °C, and the desired product **3a** could be obtained dominantly with 80 : 20 er while the  $\alpha$ -ketol rearrangement byproduct **4a** was isolated in around one-fourth of



**Previous work:** Asymmetric hydroxylative dearomatization of phenols and 1-naphthols

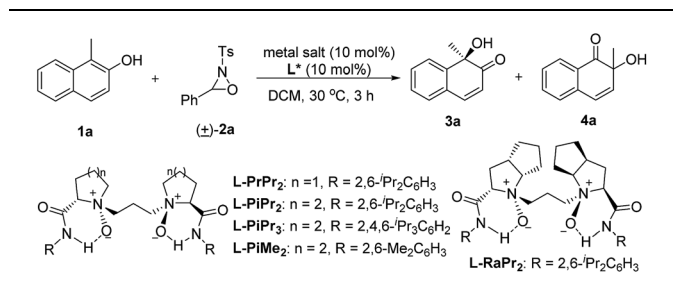


**This work:** Asymmetric hydroxylative dearomatization of 2-naphthols



**Scheme 1** Catalytic asymmetric hydroxylative dearomatization of phenols and naphthols.

**Table 1** Optimization of the reaction conditions<sup>a</sup>



Entry	Metal salt	L*	Yield <sup>b</sup> (%)	Ratio (3a/4a) <sup>c</sup>	er (3a) <sup>c</sup>
1	Sc(OTf) <sub>3</sub>	L-PiPr <sub>2</sub>	96	73 : 27	80 : 20
2	Sc(OTf) <sub>3</sub>	L-PrPr <sub>2</sub>	99	79 : 21	63 : 37
3	Sc(OTf) <sub>3</sub>	L-RaPr <sub>2</sub>	99	75 : 25	53.5 : 46.5
4	Sc(OTf) <sub>3</sub>	L-PiMe <sub>2</sub>	90	>95 : 5	60 : 40
5	Sc(OTf) <sub>3</sub>	L-PiPr <sub>3</sub>	96	89 : 11	73 : 27
6	Sc(NTf <sub>2</sub> ) <sub>3</sub>	L-PiPr <sub>2</sub>	99	>95 : 5	92 : 8
7 <sup>d</sup>	Sc(NTf <sub>2</sub> ) <sub>3</sub>	L-PiPr <sub>2</sub>	99	>95 : 5	95 : 5
8 <sup>e</sup>	Sc(NTf <sub>2</sub> ) <sub>3</sub>	L-PiPr <sub>2</sub>	86	>95 : 5	93.5 : 6.5
9 <sup>d,f</sup>	Sc(NTf <sub>2</sub> ) <sub>3</sub>	L-PiPr <sub>2</sub>	99	>95 : 5	94.5 : 5.5

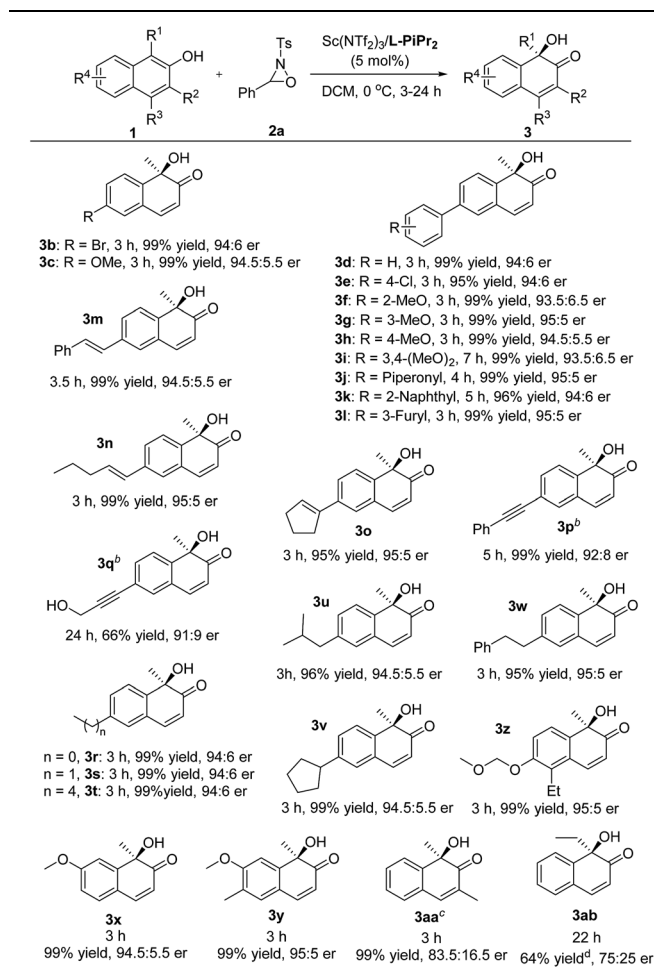
<sup>a</sup> Unless otherwise noted, the reactions were performed with L\*/Sc(m) (1 : 1, 10 mol%), **1a** (0.10 mmol) and **2a** (2.0 equiv.) in DCM (1.0 mL) under N<sub>2</sub> at 30 °C for 3 h. <sup>b</sup> Isolated yield by silica gel chromatography. <sup>c</sup> Determined by chiral HPLC analysis. <sup>d</sup> 5 mol% catalyst loading at 0 °C. <sup>e</sup> 1 mol% catalyst loading at 0 °C for 4 h. <sup>f</sup> **2a** (1.5 equiv.) was used.

a 96% total yield (Table 1, entry 1). The evaluation of the structure of the *N,N'*-dioxides showed that L-PiPr<sub>2</sub> was the optimal ligand in terms of the enantioselectivity albeit ligand L-PiMe<sub>2</sub> and L-PiPr<sub>3</sub> improved the yield of the desired product **3a** (entries 2–5). Fortunately, changing the counterion of the scandium salt from <sup>-</sup>OTf to <sup>-</sup>NTf<sub>2</sub> could suppress the  $\alpha$ -ketol rearrangement, delivering the quinol **3a** in a 99% yield with

92 : 8 er (Table 1, entry 6). Further optimization of the reaction conditions, such as decreasing the temperature and the catalyst loading to 5 mol%, resulted in slightly improved enantioselectivity with maintained efficiency (entry 7). Lowering the catalyst loading to 1 mol% or the amount of the oxidant **2a** decreased either the yield or the selectivity a little (entries 8 and 9). We therefore chose the reaction conditions in Table 1, entry 7 for further studies.

We next explored the substrate scope of 2-naphthols (Table 2). The introduction of bromo or methoxy groups at the C6-position of 2-naphthols had no obvious effect on the result. The 6-aryl substituted 2-naphthol derivatives **1d–1l** tethering various electron-donating and electron-withdrawing substituents could undergo the transformations smoothly, providing the products **3d–3l** in 95–99% yield and 93.5 : 6.5–95 : 5 er. It was noteworthy that 6-alkenyl and alkynyl substituted substrates **1m–1q** were compatible with the reaction conditions, and no aminohydroxylation of the unsaturated carbon–carbon bond occurred, giving the hydroxylative dearomatization products **3m–3q** in good to excellent yields and enantioselectivities.<sup>9</sup>

**Table 2** Substrate scope for 2-naphthols<sup>a</sup>



<sup>a</sup> Reaction conditions: the same as entry 7 in Table 1. <sup>b</sup> 10 mol% catalyst loading. <sup>c</sup> L-PiEt<sub>2</sub>-Sc(OTf)<sub>3</sub> (1 : 1, 5 mol%). <sup>d</sup> Total yield of **3ab** and **4ab**, **3ab/4ab** = 87 : 13.



Additionally, 6-alkyl substituted 2-naphthols **3r–3w** bearing methyl, ethyl, and butyl groups were well tolerated, accomplishing the asymmetric hydroxylative reaction with the outcomes of 95–99% yield and 94 : 6–95 : 5 er. The installation of substituents to the 5- and 7-positions did not influence the reaction efficiency (**3x–3z**). The MOM-protected substrate **1z** could deliver the desired product **3z** with good results without any deprotection process occurring under the reaction conditions. However, the increase of steric hindrance at the *ortho*-position of 2-naphthol was harmful as a consequence (**3aa** and **3ab**).

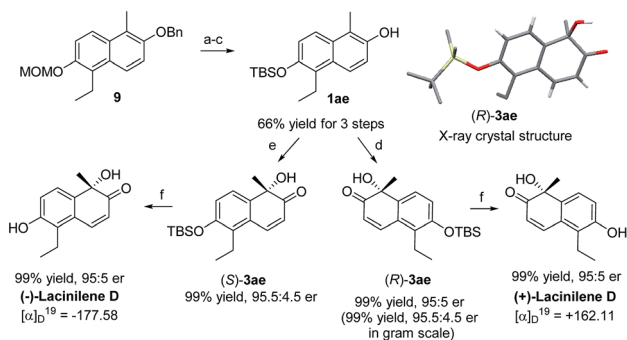
To show the synthetic utility of the current catalyst system, asymmetric synthesis of bioactive lacinilenes was carried out (Scheme 2). Initially, the direct deprotection of the product **3z** under acidic conditions formed the optically active lacinilene D, but an aromatization side product 1-ethyl-5-methylnaphthalene-2,6-diol was obtained.<sup>24,10</sup> It was anticipated that the TBS protecting group could be easily removed under neutral conditions, which might avoid the occurrence of the aromatization process. As expected, the TBS-substituted 2-naphthol **1ae** could be easily synthesized from **9** in 66% yield after 3 steps, which was further enantioselectively oxidized into the product **3ae** in quantitative yield and 95 : 5 er, even when it was performed at the gram scale. The absolute configuration of **3ae** from **L-PiPr<sub>2</sub>-Sc(NTf<sub>2</sub>)<sub>3</sub>** complex catalysis was determined to be (*R*) by X-ray crystal diffraction analysis.<sup>11</sup> For the benefit of the further differential biological activity study on

each enantiomer of the chiral lacinilenes,<sup>2c</sup> (*S*)-lacinilene D was synthesized using an *ent*-**L-PiPr<sub>2</sub>-Sc(NTf<sub>2</sub>)<sub>3</sub>** complex with a comparable result of 99% yield and 95 : 5 er. Next, the synthesis of optically active lacinilene C methyl ether was explored. The synthetic route began from 1,2-dihydronaphthalene **12**, which could be easily accessed from 2-methoxytoluene through a four-step protocol.<sup>2d</sup> Subsequent two-step oxidation could afford the 2-naphthol derivative **1y** in 49% yield, which underwent hydroxylative dearomatization catalyzed by 0.1 mol% of the **Sc(NTf<sub>2</sub>)<sub>3</sub>/rac-L-PiPr<sub>2</sub>** complex to produce racemic lacinilene **3y** in 90% yield.<sup>2d</sup> After trimethylsilylation and copper catalyzed 1,4-addition/aromatization, 2-naphthol **1af** could be attained in 45% yield after two steps. By treatment with oxaziridine **2a** in the presence of **Sc(OTf)<sub>3</sub>/L-RaPr<sub>2</sub>**, chiral lacinilene C methyl ether could be obtained in quantitative yield and 83 : 17 er, which could further transform to lacinilene C according to the literature.<sup>2b</sup>

To elucidate the stereochemical course of the oxidation process, some control experiments were conducted (Scheme 3). The optically pure oxaziridine (*S*)-**2a** reacted with 2-naphthol **1a** in the presence of the **Sc(NTf<sub>2</sub>)<sub>3</sub>/L-PiPr<sub>2</sub>** complex, affording the (*R*)-quinol **3a** in 49% yield and 95.5 : 4.5 er with the recovered oxaziridine (*S*)-**2a** in 45% yield.<sup>12d</sup> Using *ent*-**L-PiPr<sub>2</sub>** as the ligand, (*S*)-quinol **3a** was obtained in 46% yield and 90 : 10 er with the recovered oxaziridine (*S*)-**2a** in 52% yield. This indicates that the chiral matched and mis-matched effect between chiral ligand and chiral oxaziridine was not obvious in this case compared to previous reports,<sup>12</sup> and there might be negligible interaction between the chiral catalyst and oxaziridine.

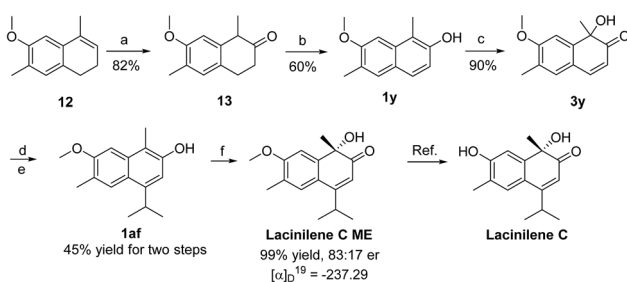
To probe into the interaction between the catalysts and 2-naphthol, <sup>1</sup>H NMR analysis of the mixture of components was carried out (see ESI† for details). The chemical shift of 1-methyl 2-naphthol **1a** remained nearly unchanged after **Sc(NTf<sub>2</sub>)<sub>3</sub>** was added. There was an obvious high-field shift for most signals of **1a** after mixing with the **Sc(NTf<sub>2</sub>)<sub>3</sub>/L-PiPr<sub>2</sub>** catalyst. This indicates that the chiral catalyst makes the 2-naphthol reactive for hydroxylative reactions. Based on these results and our previous study on the chiral *N,N'*-dioxide–metal complex catalysts,<sup>8,13</sup> we suggested an enantioselective catalytic model as shown in Fig. 2. The ligand **L-PiPr<sub>2</sub>** binds to the scandium(III) center *via* four oxygens to form a polycyclic octahedral metal complex catalyst. The 2-naphthol coordinates to the metal center at one of the vacant sites, with its *Re*-face shielded by one amide unit of the ligand. Therefore, **2a** preferably attacked the  $\alpha$ -position of 2-naphthol from the *Si*-face to generate the corresponding *R*-configured product **3ae** and imine byproduct. If a substituent was introduced into the C3 or C4 positions of 2-naphthol, the steric hindrance discrimination between the two sides of the

#### Concise synthesis of (–)-lacinilene D and (+)-lacinilene D



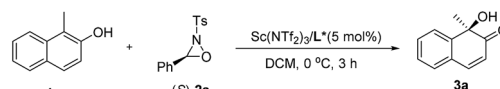
Reaction Condition: a) HCl, MeOH; b) TBSCl, imidazole, DMF; c) 10 % Pd/C, H<sub>2</sub> (balloon), EtOH; d) **Sc(NTf<sub>2</sub>)<sub>3</sub>/L-PiPr<sub>2</sub>** (5 mol%), **2a**, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; e) **Sc(NTf<sub>2</sub>)<sub>3</sub>/ent-L-PiPr<sub>2</sub>** (5 mol%), **2a**, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; f) TBAF, THF.

#### Concise synthesis of chiral lacinilene C methyl ether



Reaction condition: a) *m*-CPBA, TsOH·H<sub>2</sub>O, TFE/DCM; b) Ce(SO<sub>4</sub>)<sub>2</sub>·4H<sub>2</sub>O, O<sub>2</sub> (balloon), <sup>t</sup>BuOH; c) **Sc(NTf<sub>2</sub>)<sub>3</sub>/rac-L-PiPr<sub>2</sub>** (0.1 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 35 °C; d) TMSCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>; e) CuCN, iPrMgCl, BF<sub>3</sub>·Et<sub>2</sub>O, THF/Et<sub>2</sub>O; f) **Sc(OTf)<sub>3</sub>/L-RaPr<sub>2</sub>** (5 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C.

Scheme 2 Concise synthesis of chiral lacinilene C methyl ether, (–)-lacinilene D and (+)-lacinilene D.



L\*: **L-PiPr<sub>2</sub>**, (*R*)-**3a**, 49% yield, 95.5:4.5 er, recovered (*S*)-**2a**: 45% yield  
L\*: *ent*-**L-PiPr<sub>2</sub>**, (*S*)-**3a**, 46% yield, 90:10 er, recovered (*S*)-**2a**: 52% yield

Footnote: Yield was calculated for **2a**

Scheme 3 Control experiments.



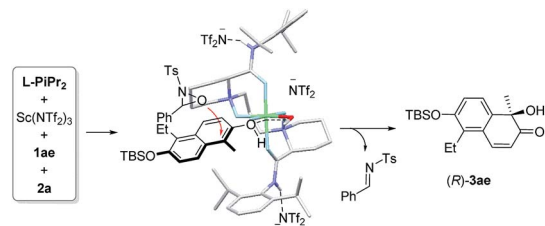


Fig. 2 Proposed enantioselective catalytic model.

hydroxyl group decreases, thus it is difficult to control the face-selection. As a result, the enantioselectivity for the generation of product **3aa** and lacinilene C methyl ether is lower than that for the others.

## Conclusions

In summary, we have described a highly chemo- and enantioselective hydroxylative dearomatization of 2-naphthol derivatives with oxaziridine catalyzed by a chiral  $N,N'$ -dioxide-Sc(NTf<sub>2</sub>)<sub>3</sub> complex catalyst. The desired substituted *ortho*-quinols with one quaternary carbon stereogenic center were afforded with high enantioselectivities and reactivity (up to 99% yield and 95 : 5 er). The  $\alpha$ -ketol rearrangement byproducts were efficiently suppressed. This new procedure has been successfully applied to the catalytic asymmetric synthesis of the phytoalexins lacinilenes. The application of the  $N,N'$ -dioxide/metal catalyst system in the synthesis of other bioactive molecules will be explored.

## Acknowledgements

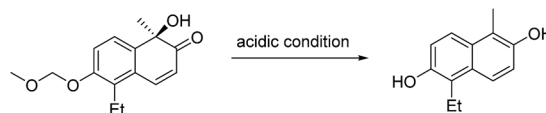
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see ref. 2d for details.

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