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# Chiral Fe(II) complex catalyzed enantioselective [1,3] O-to-C rearrangement of alkyl vinyl ethers and synthesis of chromanols and beyond†

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A highly efficient enantioselective [1,3] O-to-C rearrangement of racemic vinyl ethers that operates under mild conditions was developed. This method with chiral ferrous complex catalyst provided an efficient access to a wide range of chromanols with high yields and excellent enantioselectivities. In addition, an important urological drug (*R*)-tolterodine and others were easily obtained after simple transformations.

## Introduction

The [1,3] and [3,3] O-to-C rearrangements are powerful methods widely used in the formation of valuable compounds.<sup>1</sup> Asymmetric catalytic [3,3] O-to-C rearrangement<sup>2</sup> allows stereochemistry to be efficiently relayed through a cyclic transition state, and is more established than its [1,3] counterpart. In comparison, the stereochemistry in [1,3] O-to-C rearrangement is critical, but the development of enantioselective [1,3] O-to-C rearrangement is much slower however.<sup>3</sup> Generally, there are three catalytic activation methods for [1,3]-rearrangement of vinyl ether and its variants. Chiral nucleophilic organocatalysts have been generally used for *O*-carboxyl shift in Steglich-type (Black) rearrangements.<sup>4</sup> Transition metal catalysed reactions have been described but none of these are enantioselective thereof.<sup>5</sup> Thirdly, chiral Brønsted acids and Lewis acids<sup>6</sup> seem to be powerful in asymmetric [1,3] rearrangements of both aryl ethers<sup>7</sup> and vinyl ethers.<sup>8</sup> For instance, Terada and coworkers investigated asymmetric aza-Petasis–Ferrier rearrangement of hemiaminal vinyl ethers using chiral phosphoric acid catalysts (Scheme 1a).<sup>8a</sup> Stereoselective hydroalkoxylation/[1,3]-rearrangement of racemic ynamides through kinetic resolution was accomplished by Ye's group (Scheme 1b).<sup>8b</sup> The stereochemistry of the chiral substrates in the rearrangement could be transferred through zwitterion pairs.<sup>9</sup> This result has also been confirmed in the work related to [1,3]-rearrangement of *Z*-amino enol ethers generated from the insertion of achiral or chiral benzyl alcohols to triazoles (Scheme 1c).<sup>8c</sup> There is no report that describes enantioselective catalysis in [1,3] O-to-C rearrangement of unsubstituted racemic vinyl ethers. To

realize an enantioselective [1,3] O-to-C rearrangement from racemic vinyl alkyl ethers is challenging, and a concerted [1,3] alkyl rearrangement is required to proceed antarafacial which is highly unlikely under thermal conditions.

Substituted chromanols or chromanones are important structural motifs in many natural products and pharmaceuticals.<sup>10</sup> Despite some asymmetric catalytic examples were reported for the construction of chromanols,<sup>11</sup> developing new methods remain highly desirable in order to expand the substrate generality. In recent years, *in situ* generated *o*-quinone



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Scheme 1 Catalytic enantioselective [1,3]-rearrangement of vinyl ethers.



methide has emerged as a popular synthon in chiral acids promoted reactions.<sup>12</sup> We envision that highly enantioselective [1,3] O-to-C arrangement is available from racemic 2-vinyl-oxymethylphenols in the presence of a chiral Lewis acid catalyst (Scheme 1d). In view of the excellent performance of chiral *N,N'*-dioxide-metal complex catalysts in asymmetric catalysis,<sup>13,14</sup> we utilized chiral Lewis acids for the asymmetric [1,3] O-to-C rearrangement of racemic 2-vinyl-oxymethylphenols to synthesize chromanols. In this report, we demonstrate that a readily available chiral iron(III) catalyst achieve extremely high enantioselective rearrangement of racemic vinyl alkyl ethers, and establish that an array of chromanols and the corresponding chromanones could be obtained, one of which is transformed into an important urological drug (*R*)-tolterodine.<sup>15</sup>

## Results and discussion

Racemic 2-(phenyl(vinyl)oxy)methylphenol **1a** was selected as the model substrate. Upon investigating routine parameters, we found that a Fe(OTf)<sub>2</sub>/chiral *N,N'*-dioxide **L-PiPr**<sub>2</sub> catalyst can promote the enantioselective [1,3] O-to-C rearrangement, delivering chromanol **2a** in 93% yield and 98% ee (Table 1, entry 1). The use of Sc(OTf)<sub>3</sub> as the metal salt resulted in slightly lower yield and enantioselectivity (entry 2). Whereas, an extremely low yield of the product with moderate enantioselectivity was obtained if Zn(OTf)<sub>2</sub> was used (entry 3). Interestingly, racemic product was observed in poor yield in the presence of Fe(OTf)<sub>3</sub>, instead of Fe(OTf)<sub>2</sub> (entry 4). According to our current research

results,<sup>14</sup> most of the chiral *N,N'*-dioxide-metal complexes, except for lanthanide metal complexes, adopt similar octahedral geometry. We initially proposed that such a sharp contrast in outcomes between Fe(OTf)<sub>3</sub> and Fe(OTf)<sub>2</sub> might raise from the metal cation radii, and Fe(III) has shorter radii than these other metal salts (entry 4 vs. entries 1–3). X-ray single crystal analysis of Fe(OTf)<sub>3</sub>, Fe(OTf)<sub>2</sub> and Sc(OTf)<sub>3</sub> of chiral *N,N'*-dioxides<sup>16</sup> show that the former has a more compact cavity around the metal center, where the distance between the four oxygens of the ligand and metal ion as Fe(III) is shorter than Fe(II) and Sc(III). We probably would have thought that the condensed chiral metal complex might not be beneficial to the coordination of the two oxygen-containing species from the substrate or the intermediates, leading to sharply reduced yield and ee values. However, later we found that when small amount of water was added in connect with the use of Fe(OTf)<sub>3</sub> at 10 mol% catalyst loading, the yield and enantioselectivity dramatically recovered (entry 5 vs. entry 4). The influence of water became inapparent when the catalyst loading of Fe(OTf)<sub>3</sub>/**L-PiPr**<sub>2</sub> was reduced to 1 mol%, and a yield of 63% with 98% ee were still obtained without extra water (entry 6). We rationalized that water might participate in the catalytic cycle, and accelerate the recovery of the metal catalyst. Fe(III) iron has stronger Lewis acidity than Fe(II), and there is closer interaction between Fe(III) and the intermediate species, abating the occurrence of the rearrangement step and its regeneration. The existence of a certain amount of water could overcome the unfavorable issue of Fe(III) catalyst at high catalyst loading. Ferric salts with other

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



Entry	Variation from "standard conditions"	Yield (%)	ee (%)
1	None	93	98
2	Sc(OTf) <sub>3</sub>	86	90
3	Zn(OTf) <sub>2</sub>	13	69
4	Fe(OTf) <sub>3</sub>	19	0
5 <sup>b</sup>	Fe(OTf) <sub>3</sub> + H <sub>2</sub> O	71	99
6	Fe(OTf) <sub>3</sub> in 1 mol% catalyst loading	63	98
7	1 mol% catalyst loading	93	99
8	0.1 mol% catalyst loading	84	98
9	<b>L-RaPr</b> <sub>2</sub>	80	94
10	<b>L-PrPr</b> <sub>2</sub>	80	91
11	<b>L-PiMe</b> <sub>2</sub>	86	96
12	<b>Ph-Box</b>	67	0

<sup>a</sup> "Standard condition": **1a** (0.1 mmol), and **L-PiPr**<sub>2</sub>/Fe(OTf)<sub>2</sub> (1/1, 10 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) at 35 °C for 2 h. Isolated yield of **2a**. Ee was determined by HPLC analysis on a chiral stationary phase. <sup>b</sup> H<sub>2</sub>O (5 μL).



counteranions or HOTf as additive was really no good for the outcomes (see ESI† for details). Finally, an excellent result (93% yield with 99% ee) was achieved if 1 mol% of  $\text{Fe}(\text{OTf})_2/\text{L-PiPr}_2$  catalyst was employed (entry 7), and an even lower loading of  $\text{Fe}(\text{OTf})_2$  and chiral ligand  $\text{L-PiPr}_2$  can be used, without loss in enantioselectivity in the presence of 0.1 mol% of catalyst (entry 8). Other families of  $N,N'$ -dioxide ligands are also acceptable under these conditions, regardless the amino acid backbone and the amide substituents (entries 9–11). The Ph-Box ligand could promote the reaction but gave racemic product (entry 12).

With the optimized conditions in hand, we next explored the substrate scope (Table 2). The [1,3] rearrangement reaction can

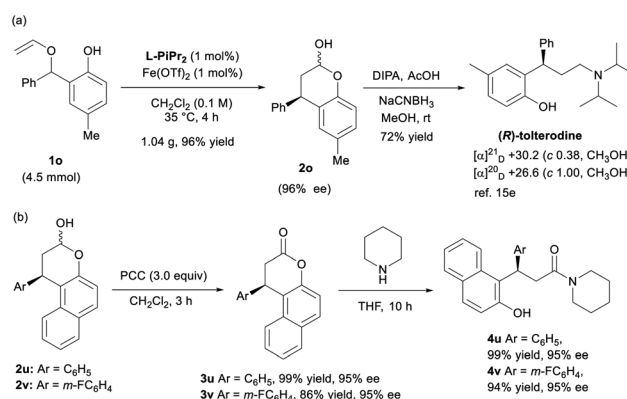
Table 2 Substrate scope of the reaction<sup>a</sup>



<sup>a</sup> Unless otherwise stated, all reactions were performed with **1** (0.2 mmol) and  $\text{L-PiPr}_2/\text{Fe}(\text{OTf})_2$  (1/1, 1 mol%) in  $\text{CH}_2\text{Cl}_2$  (0.1 M) at 35 °C. Isolated yield of the product **2**. Ee was determined by HPLC analysis based on the related derivative **3**. <sup>b</sup>  $\text{L-PiPr}_2/\text{Fe}(\text{OTf})_2$  (5 mol%). <sup>c</sup>  $\text{L-PiPr}_2/\text{Sc}(\text{OTf})_3$  (5 mol%). <sup>d</sup>  $\text{L-PiPr}_2/\text{Fe}(\text{OTf})_2$  (0.1 mol%). <sup>e</sup>  $\text{L-RaPr}_2/\text{Fe}(\text{OTf})_2$  (10 mol%) in  $\text{CH}_2\text{ClCH}_2\text{Cl}$ . <sup>f</sup>  $\text{L-RaPr}_2/\text{Fe}(\text{OTf})_2$  (10 mol%) in  $\text{CHCl}_3$ .

perform smoothly no matter what electron-donating or electron-withdrawing substituents at *meta*- or *para*-position of the aryl group, delivering the corresponding products **2c–2g** in good yields (76–94% yield) and excellent ee values (96–99% ee). The *ortho*-methyl aryl group substituted chromanol **2b** was obtained in 70% yield and 97% ee. Moreover, alkyl substituted 2-vinyloxymethylphenols were also tolerated, affording the desired products **2h–2k** in 77–92% yields and 88–99% ee. In addition, the effects of the substituent  $\text{R}^2$  at the phenol unit were investigated. Either electron-withdrawing or electron-donating substituents at *para*-position of the hydroxyl group of phenol provided the corresponding products **2o–2s** in excellent yields (94–99% yield) and enantioselectivities (98–99% ee). It was noteworthy that the catalyst loading in the reaction of the substrate **1q** containing a *para*-fluoro-substituent can decrease to 0.1 mol%. Substituent at *meta*-position to the hydroxyl group was also tolerable (**2n**). Nevertheless, the effect of steric hindrance around the hydroxyl group of phenol unit was obvious (**2l**, **2m**, and **2t**). In these cases, good yield and enantioselectivity were available at higher catalyst loading (5 mol%) or employing  $\text{Sc}(\text{OTf})_3$  as the metal precursor. Grati-fyingly, naphthyl substituted substrates were proved to be suitable substrates in the reaction, giving the corresponding products **2u** and **2v** in fair yield and excellent enantioselectivities with 10 mol% of  $\text{L-RaPr}_2/\text{Fe}(\text{OTf})_2$  catalyst, albeit in moderate yields.

With respect to the synthetic utility of this new method, an enantioselective synthesis of (*R*)-tolterodine, an urological drug, has been started in the case of a gram-scale rearrangement of **1o** in the presence of 1 mol% of  $\text{Fe}(\text{OTf})_2/\text{L-PiPr}_2$ , and the carbon-carbon formation proceeded well in 96% yield and 96% ee (Scheme 2a). Subsequently, chroman-2-ol **2o** underwent reductive amination in the presence of diisopropylamine and sodium cyanoborohydride to furnish (*R*)-tolterodine in 72% yield. Its absolute configuration was determined to be *R* by comparing the optical rotation with the literature value.<sup>15e</sup> Thus, the stereochemistry of the product **2o** and **3o** was assigned as (*R*)-isomers. The configuration of other products was assigned by comparing with the CD spectrum of the compound **3o**. Furthermore, the chromanols **2u** and **2v** were oxidized with PCC



Scheme 2 (a) Scale-up synthesis of **2o** and concise synthesis of (*R*)-tolterodine; (b) further transformation of chromanols **2u** and **2v**.



to the corresponding chromanones **3u** and **3v** in excellent yields and enantioselectivities. The chromanone **3u** was reported to exhibit activity as an inhibitor of Sir2.<sup>17</sup> Subsequently, ring-opened amination reaction of chromanones **3u** and **3v** using piperidine yields ROR- $\gamma$ -modulator analogs **4u** and **4v** with good results (Scheme 2b).<sup>18</sup>

As the second most abundant metal on earth, iron salts are popular Lewis acids and metal complexes catalysts.<sup>19</sup> In most cases, ferric salt was used instead of ferrous salt because the former is classified hard acid according to Pearson's HSAB principle. We conducted HRMS spectra to probe into the difference of the two iron species toward water (see ESI† for details). The signals in response to the complexes of iron salt, chiral ligand and water showed that higher peaks was found from the system of Fe(OTf)<sub>2</sub> than Fe(OTf)<sub>3</sub>. It might indicate that the ferrous catalyst is a slightly sensitive to moisture than the corresponding ferric catalyst. Trace amount of water might be brought from the catalysts and other reaction components into the reaction system.

Based on the stereo-outcome of the chiral catalysts and our previous work,<sup>16d</sup> a possible catalytic model was proposed (Scheme 3). At first, the *N,N'*-dioxide **L-PiPr**<sub>2</sub> and the two oxygen atoms of **1o** coordinated to the Fe(II) center, which undergoes the heterolytic cleavage of alkyl C–O bond to generate enolate anion and *o*-quinone methide cation, depreciating the formal stereo-arrangement. The activation of protonated *o*-quinone methide further increases its electrophilicity, so the efficiency of the chiral catalyst is extremely high. Reoordination of the enolate and *o*-quinone methide to the chiral Lewis acid center occurs, followed by bond recombination through 1,4-conjugate addition/cyclization cascade reaction to afford chromanol with the new stereogenic center. As shown in the working mode, the *Si*-face of *o*-quinone methide cation was shielded by the bulky 2,6-diisopropylphenyl group of **L-PiPr**<sub>2</sub>, thus enolate anion would prefer to attack from the *Re*-face of *o*-quinone methide to generate (*R*)-intermediate. Next, the trace amount of

water in the catalytic system assists the formation of acetal, affording the chiral chromanol product **2o** and regenerating the chiral catalyst. Additionally, the chiral ligand was found to reduce the generation of 2-methyl-4*H*-benzo[*d*][1,3]dioxine byproduct (see ESI† for details).

## Conclusions

In summary, we have successfully developed a highly efficient [1,3] O-to-C rearrangement of racemic vinyl alkyl ethers using a chiral *N,N'*-dioxide/Fe(OTf)<sub>2</sub> complex. Various important chiral chromanols were obtained with high yields and excellent enantioselectivities (up to 99% yield and 99% ee). The catalyst loading is as low as 0.1–5.0 mol% in most cases. Moreover, this methodology has been applied in the highly efficient synthesis of an important urological drug (*R*)-tolterodine. Further investigations on other type of rearrangements are currently underway.

## Conflicts of interest

There are no conflicts to declare.

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Scheme 3 Proposed catalytic cycle.



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