

# Catalytic Asymmetric Vinylogous Mannich-type (AVM) Reaction of Nonactivated $\alpha$ -Angelica Lactone

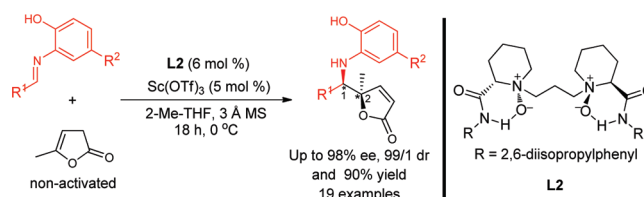
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## ABSTRACT



A direct highly diastereo- and enantioselective asymmetric vinylogous Mannich-type (AVM) reaction of aldimines with nonactivated natural  $\alpha$ -angelica lactone has been successfully developed. It was demonstrated that the nonactivated natural  $\alpha$ -angelica lactone is a useful vinylogous nucleophile to give the chiral  $\delta$ -amino  $\gamma,\gamma$ -disubstituted butenolide carbonyl derivatives. The  $N,N'$ -dioxide L2–Sc<sup>III</sup> complex is efficient toward the obtention of a range of corresponding products with adjacent quaternary and tertiary stereocenters in excellent dr and ee values.

The butenolide unit plays an important role in organic synthesis because of its widespread occurrence in biologically active natural products and pharmaceutically useful molecules.<sup>1</sup> In the past two decades, several kinds of butenolides and analogues, such as simple  $\gamma$ -butenolides<sup>2</sup> and activated silyloxyfurans,<sup>3</sup> have been employed as donors in asymmetric synthesis for accessing such chiral butenolide skeleton derivatives. The natural nonactivated  $\alpha$ -angelica lactone, which is a cheap industrial material,

has attracted some attention as a butenolide variant recently because of its potential in the construction of  $\gamma,\gamma$ -disubstituted butenolides. In 2010, the Chen group reported a highly enantioselective allylic alkylation reaction with  $\beta,\gamma$ -butenolides.<sup>4</sup> Recently, it was successfully applied to the asymmetric Michael addition by the Alexakis group.<sup>5</sup> In addition,  $\alpha$ -angelica lactone also acted as an enol ester for the Mannich-type reaction to afford  $N$ -aryl 5-membered lactam under Sc(OTf)<sub>3</sub> catalysis (Scheme 1, path b, PG = protective group).<sup>6</sup> However, to the best of our knowledge, the direct catalytic asymmetric

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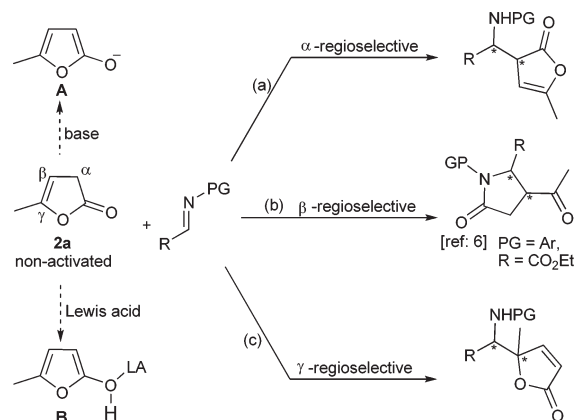
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**Scheme 1.** Proposed Approach of  $\alpha$ -Angelica Lactone with Aldimine



vinylous Mannich-type (AVM) reaction<sup>7–9</sup> of this deconjugated butenolide to afford  $\gamma,\gamma$ -disubstituted butenolides (Scheme 1, path c) has not been achieved. Herein, we describe a  $N,N'$ -dioxide–Sc<sup>III</sup> complex<sup>10</sup> catalyzed direct AVM reaction of  $\alpha$ -angelica lactone to provide the  $\delta$ -amino butenolide blocks bearing adjacent quaternary and tertiary stereocenters.<sup>11,12</sup>

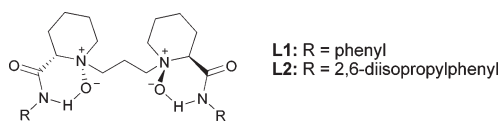
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**Figure 1.** Chiral ligands used in this study.

**Table 1.** Optimization of the Reaction Conditions<sup>a</sup>

entry	L/metal ratio	MS (3 Å)	yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>c</sup> (%)
1	<b>L1</b> /Cu(OTf) <sub>2</sub> 1/1	none	NR		
2	<b>L1</b> /Mg(OTf) <sub>2</sub> 1/1	none	NR		
3	<b>L1</b> /Ni(acac) <sub>2</sub> 1/1	none	NR		
4	<b>L1</b> /In(OTf) <sub>3</sub> 1/1	none	NR		
5	<b>L1</b> /Sc(OTf) <sub>3</sub> 1/1	none	22	85/15	68
6 <sup>d</sup>	<b>L1</b> /Y(OTf) <sub>3</sub> 1/1	none	13	90/10	23
7 <sup>d</sup>	<b>L1</b> /La(OTf) <sub>3</sub> 1/1	none	19	85/15	20
8	<b>L2</b> /Sc(OTf) <sub>3</sub> 1/1	none	43	93/7	90
9	<b>L2</b> /Sc(OTf) <sub>3</sub> 1/1	30 mg	68	91/9	82
10 <sup>e</sup>	<b>L2</b> /Sc(OTf) <sub>3</sub> 1.2/1	30 mg	74	95/5	94
11 <sup>e,f</sup>	<b>L2</b> /Sc(OTf) <sub>3</sub> 1.2/1	30 mg	81	95/5	95

<sup>a</sup> Unless otherwise noted, the reactions were performed with **1a** (0.10 mmol), metal (0.005 mmol), and  $N,N'$ -dioxide under nitrogen in THF (0.5 mL) at 30 °C for 15 min, and then **2a** (0.12 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 18 h. <sup>b</sup> Isolated yield, NR = no reaction. <sup>c</sup> Determined by chiral HPLC analysis (Chiralcel IC). <sup>d</sup> Reaction was performed at 30 °C. <sup>e</sup> 2-Me-THF as solvent. <sup>f</sup> Using 0.3 mmol of **1a**, adding **2a** two times and preparing catalyst beforehand.

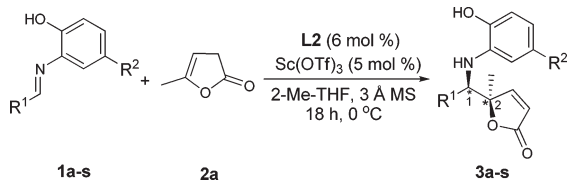
In the previous studies using  $\alpha$ -angelica lactone as vinylous nucleophile,<sup>4</sup> chiral amine catalysts were used that might aid in the  $\alpha$ -deprotonation to form activated enolate (Scheme 1, A). We envisioned that this donor could also be activated through in situ generated O-bond metal enolate in the presence of Lewis acids (Scheme 1, B). The model reaction was initiated with  $\alpha$ -angelica lactone **2a** and  $N$ -aryldimine **1a**. Various Lewis acids coordinated with chiral  $N,N'$ -dioxide ligand **L1** (Figure 1) were surveyed (Table 1, entries 1–5), and only Sc(OTf)<sub>3</sub> could afford the  $\gamma$ -regioselective product **3a** in 22% yield with moderate dr and ee values at 0 °C (Table 1, entry 5). At higher temperature (30 °C), other lanthanide metals could perform the reaction with worse yields and ee values (Table 1, entries 6 and 7). Comparatively, the conjugated furanone **2b** (Scheme 2) failed to undergo the AVM reaction, and no product was observed under **L1**–Sc(OTf)<sub>3</sub> catalysis. All of these implied that the approach of  $\alpha$ -enolization would be responsible for the occurrence of nucleophilic addition.

Further optimization of the reaction conditions was then aimed at exploring the efficiency of  $\text{Sc}(\text{OTf})_3$  with other  $N,N'$ -dioxide ligands (for details: see the Supporting Information). Fortunately, when the ligand **L2** containing bulkier isopropyl groups at the *ortho* position of aniline was employed, good diastereo- and enantioselectivity (93:7 dr and 90% ee) with 43% yield were achieved (Table 1, entry 8). The addition of 3 Å molecular sieves (MS) as additive benefited the yield while the enantiomeric excess had an obvious decrease (Table 1, entry 9). To our delight, changing the ratio of the ligand **L2** to  $\text{Sc}(\text{OTf})_3$  to 1.2/1, meanwhile using 2-Me-THF as the solvent, could greatly improve the enantiomeric excess to 94% (Table 1, entry 10). Increasing the amount of aldimine **1a** and adding  $\alpha$ -angelica lactone **2a** two times could further enhance the yield to 81% with the dr and ee maintained. In addition, the catalyst could be prepared beforehand and did not affect the results at all (Table 1, entry 11; for details, see the Supporting Information). This operation made the procedure more convenient. In these cases, no  $\alpha$ - or  $\beta$ -regioselective byproduct was observed (Scheme 1).

Under the optimal conditions (Table 1, entry 11), various aldimines **1**<sup>13</sup> were evaluated, affording the  $\gamma,\gamma$ -disubstituted butenolide derivatives in excellent diastereo- and enantioselectivities (up to 99/1 dr and 98% ee). As shown in Table 2, the electronic effects of the phenol protective group of imines were investigated. The introduction of an electron-donating methyl group to  $N$ -arylimine decreased the enantioselectivity slightly with good yield, while electron-withdrawing chloric group gave the corresponding adduct with higher diastereo- and enantioselectivity in moderate yield (Table 2, entries 1–3). The enantioselectivity of the reaction was sensitive to the electronic property rather than to the steric hindrance of substituents on the phenyl ring of aromatic aldimines. The substrates with electron-withdrawing substituents gave higher ee values than those with electron-donating ones (Table 2, entries 12–15 vs 4–9). Generally, the desired  $\gamma$ -methyl- $\gamma$ -phenylmethanamino butenolides **3** were isolated in excellent diastereomeric and good enantiomeric excesses with moderate to good yields (Table 2, entries 4–15). Moreover, fused ring and heteroaromatic aldimines were also tolerable, affording the desired products with 93% to 97% ee (Table 2, entries 16–19). In addition, the absolute configuration of **3s** was determined to be 1*S*,2*R* by X-ray analysis.<sup>14</sup> Notably, by treatment of 1.0 mmol of  $\alpha$ -angelica lactone **2a** under the optimal reaction conditions,  $\gamma,\gamma$ -disubstituted butenolide **3a** was produced smoothly in 71% yield with 94% ee (Table 2, entry 20).

To have a better insight into the mechanism of this process, several control experiments were performed. Using conjugated furanone **2b** and **2c** as donors, no products were observed (Scheme 2, eqs 1 and 2) under

**Table 2.** Substrate Scope for the Direct AVM Reaction<sup>a</sup>



entry	R <sup>1</sup>	R <sup>2</sup>	yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>c</sup> (%)
1	Ph	H	<b>3a</b> : 81	95/5	95
2	Ph	Me	<b>3b</b> : 82	93/7	90
3	Ph	Cl	<b>3c</b> : 67	96/4	97
4	2-MeC <sub>6</sub> H <sub>4</sub>	H	<b>3d</b> : 78	99/1	93
5	3-MeC <sub>6</sub> H <sub>4</sub>	H	<b>3e</b> : 77	95/5	92
6	4-MeC <sub>6</sub> H <sub>4</sub>	H	<b>3f</b> : 83	95/5	92
7	3-MeOC <sub>6</sub> H <sub>4</sub>	H	<b>3g</b> : 77	95/5	90
8	4-MeOC <sub>6</sub> H <sub>4</sub>	H	<b>3h</b> : 82	96/4	94
9	2,3-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	<b>3i</b> : 90	97/3	90
10	4-PhC <sub>6</sub> H <sub>4</sub>	H	<b>3j</b> : 75	95/5	94
11	3-PhOC <sub>6</sub> H <sub>4</sub>	H	<b>3k</b> : 82	95/5	91
12	4-FC <sub>6</sub> H <sub>4</sub>	H	<b>3l</b> : 76	96/4	98
13	4-ClC <sub>6</sub> H <sub>4</sub>	H	<b>3m</b> : 74	96/4	96
14	2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	<b>3n</b> : 71	99/1	95
15	4-BrC <sub>6</sub> H <sub>4</sub>	H	<b>3o</b> : 58	96/4	97
16	1-naphthyl	H	<b>3p</b> : 75	97/3	95
17	2-naphthyl	H	<b>3q</b> : 83	95/5	93
18	2-furyl	H	<b>3r</b> : 62	86/14	95
19	2-thienyl	H	<b>3s</b> : 82	96/4	97 <sup>d</sup>
20 <sup>e</sup>	Ph	H	<b>3a</b> : 71	94/6	94

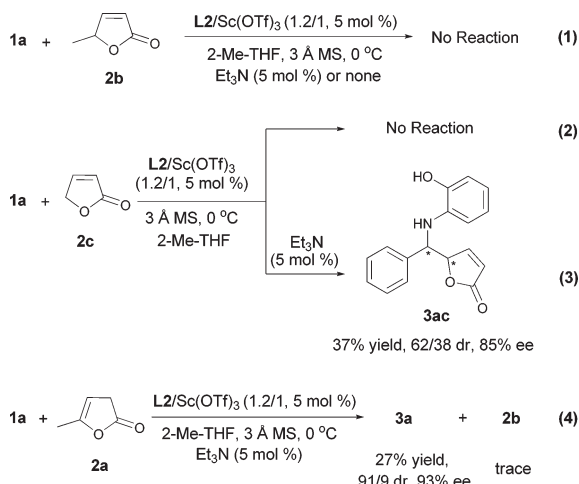
<sup>a</sup> Unless otherwise noted, the reactions were performed with **1** (0.30 mmol), 36.4 mg of chiral catalyst:  $N,N'$ -dioxide (3.9 mg, 0.006 mmol), metal (2.5 mg, 0.005 mmol), 30 mg of 3 Å molecular sieves (MS), **2a** (0.05 mmol) in a dry reaction tube, then 2-Me-THF (0.5 mL) was added at 0 °C. After the reaction mixture was stirred for 6 h at 0 °C, the remaining **2a** (0.05 mmol) was added, and then the reaction mixture was stirred at 0 °C for an additional 12 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by HPLC analysis. <sup>d</sup> The absolute configuration was determined to be 1*S*,2*R* by X-ray analysis. <sup>e</sup> 1.0 mmol substrate was used.

the optimal reaction conditions, which suggested that the  $\alpha$ -enolization of unconjugated  $\alpha$ -angelica lactone **2a** was easier than  $\gamma$ -enolization of conjugated furanones. Moreover, in the presence of triethylamine as additive, the AVM product **3ac** from simple  $\gamma$ -butenolide **2c** was isolated in 37% yield with 62/38 dr and 85% ee (Scheme 2, eq 3), which demonstrated that  $\gamma$ -deprotonation of **2c** could be promoted by amine base. On the other hand, the electron-donating property and steric hindrance of methyl group of 5-methylfuranone **2b** might impede the  $\gamma$ -deprotonation and result in no product (Scheme 2, eq 1). It indicates that  $\alpha$ -angelica lactone would be a good candidate as a vinylogous nucleophile compared with the related furanone. In contrast to the chiral amine promoted nucleophilic addition of  $\beta,\gamma$ -butenolides in previous study,<sup>4</sup> the addition of amine reduced the yield to 27% with the dr and ee value basically maintained in this scandium complex catalyzed AVM reaction (Scheme 2, eq 4). The generation of only a trace amount of inert 5-methylfuranone **2b** from  $\alpha$ -angelica lactone **2a** accelerated by  $\text{Et}_3\text{N}$  would not be the main

(13) Only trace amounts of products were obtained from aliphatic imines. See the Supporting Information for details.

(14) CCDC 815001 (**3s**) 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](http://www.ccdc.cam.ac.uk/data_request/cif).

## Scheme 2. Comparison Experiments



cause for the loss of reactivity. It should be considered that the introduction of amine to the system would probably restrain the catalytic recycle, which overestimated its role in accelerating the  $\alpha$ -enolization of  $\alpha$ -angelica lactone.

The relationship between the ee value of ligand **L2** and the product **3a** showed poor nonlinear effects<sup>15</sup> (see the Supporting Information), suggesting that minor oligomeric aggregates might exist in the reaction system. According to our previous study on the X-ray crystal structure of  $N,N'$ -dioxide- $Sc^{III}$ <sup>16</sup> and the oxygen-affinity property of scandium,<sup>17</sup> a catalytic cycle is proposed in Figure 2. It suggested that the use of **L2** and  $Sc(OTf)_3$  in the direct AVM reaction is likely to generate a hexacoordinate  $Sc(OTf)_3$ -derived intermediate, in which not only the oxygens of  $N$ -oxide but also carbonyl oxygens coordinated with  $Sc(III)$  in a tetradentate manner. First, aldimines **1**<sup>18</sup> and the four oxygen atoms of the ligand **L2** were coordinated to the  $Sc(III)$  center, giving the intermediate **T1**. After  $\alpha$ -angelica lactone **2a** was added, chiral scandium intermediate **T2** containing ligand,  $\alpha$ -enolized **2a**, and imine was generated, in which the attack of 5-methylfuran-2-ol to the *Si* face of the aldimine provided the access to

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(18) The hydroxyl group on the imines **1** was crucial in the catalysis. No corresponding products were observed with imines derived from aniline or 2-methoxyaniline. See the Supporting Information for details.

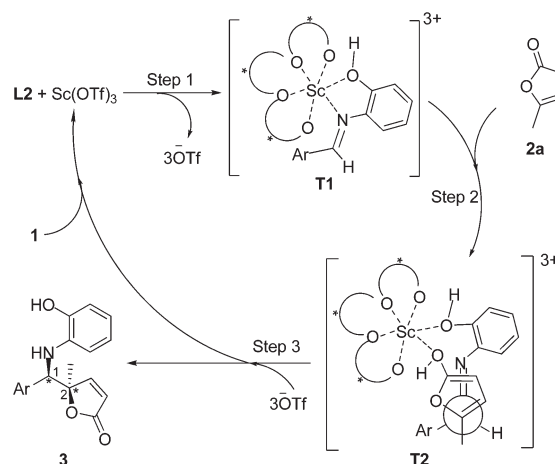


Figure 2. Proposed catalytic cycle.

1*R*,2*R*-configured  $\gamma,\gamma$ -disubstituted butenolides. The negative effect of  $Et_3N$  in the comparison experiments (Scheme 2) could be rationalized that the interaction between the phenol group of aldimine and the base weakened the coordination of the substrate. The existence of base was also unfavorable for the final protonation step. The competition coordination between imines and  $\alpha$ -angelica lactone was responsible for the improved yield by partial feeding of  $\alpha$ -angelica lactone.

In summary, we have successfully developed a direct highly diastereo- and enantioselective asymmetric vinylogous Mannich-type (AVM) reaction of aldimines with  $\alpha$ -angelica lactone. Nonactivated natural  $\alpha$ -angelica lactone was demonstrated to be a useful vinylogous nucleophile to afford the chiral  $\delta$ -amino  $\gamma,\gamma$ -disubstituted butenolide carbonyl derivatives. The  $N,N'$ -dioxide **L2**- $Sc(OTf)_3$  complex is efficient for affording a range of the corresponding products with adjacent quaternary and tertiary stereocenters in excellent dr and ee values. Further mechanistic studies of this catalytic system are still in progress.

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**Supporting Information Available.** Experimental procedures and spectral and analytical data for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.