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PAPER

Highly enantioselective synthesis of γ-substituted butenolides *via* the vinylogous Mukaiyama–Michael reaction catalyzed by a chiral scandium(III)–*N*,*N*′-dioxide complex†

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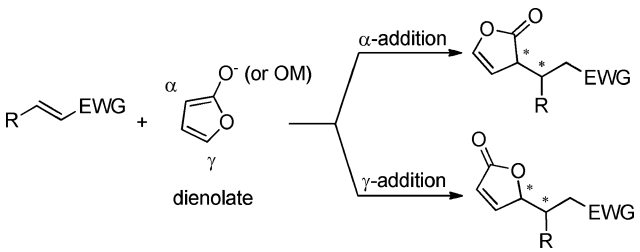
A highly efficient catalytic asymmetric vinylogous Mukaiyama–Michael reaction of the 2-silyloxyfuran with chalcone derivatives, catalyzed by a chiral *N*,*N*′-dioxide–scandium(III) complex, has been accomplished which tolerates a wide range of substrates. The reaction proceeds with complete regioselectivities, excellent diastereoselectivities (up to >99 : 1 dr) and good to excellent enantioselectivities (up to 94% ee) under mild conditions, delivering highly functionalized enantiomerically enriched *anti*-γ-substituted butenolides. The process is air-tolerant and easily manipulated with available reagents. In order to illustrate the synthetic potential of this reaction, the gram-scale synthesis and the elaboration of the butenolides have been explored. On the basis of the experimental results, a possible catalytic cycle and favorable stereorecognition model have been proposed.

Introduction

The butenolide skeleton ranks among one of the most ubiquitous structural motifs found in naturally occurring products and biologically active compounds.[1] Owing to the prevalence of butenolides, much effort has been directed towards exploiting the efficient methodology for its synthesis and transformations.[2] In recent years, the development of enantioselective protocols to access γ-substituted butenolide derivatives by utilizing the concept of vinylogy, which usually involves the carbon–carbon formation with an appropriate electrophile at the γ-position of butenolide to afford the corresponding γ-substituted products, has triggered increasing interest.[3] As a variant of the vinylogous reactions, with the dienolates derived from butenolides,[4–6] the asymmetric vinylogous Michael-type approach is more attractive,[7,8] as it provides highly functionalized chiral γ-substituted butenolides bearing a C4-substituent functionalized at its terminal group that allows the further transformation.

Recently, direct Michael-type versions have been utilized as a convenient strategy for the construction of the chiral butenolides, where the dienolate anion is generated from 2-(5*H*)-furanone by a Lewis acid or base *in situ*.[7] However, this process generally suffers from a regioselective problem that is due to the similar nucleophilicity between the α and γ positions of the dienolate to afford α- or γ- addition products (Scheme 1).[4d,9] Moreover, the utilization of chalcones as Michael acceptors was disclosed in only two reports about the direct Michael addition of 2-(5*H*)-furanones,[7b,7c] in which *syn*-adducts were provided as the major diastereomer with high enantioselectivities, but the reactivity and diastereoselectivity were not well accomplished.



Scheme 1 The regioselective Michael reaction of dienolate to afford α- or γ- addition product. EWG = electron-withdrawing groups.

An efficient alternative approach to circumvent the issues of regioselectivity and reactivity is the use of 2-silyloxyfurans in Lewis acid catalyzed vinylogous Mukaiyama–Michael reactions (VMMR),[8] in which regulating the electronic and steric effects of both the 2-silyloxyfurans and catalyst complex is of paramount importance for high stereoselectivity. Moreover, this methodology has been used in diastereoselective synthesis of important compounds such as (±) mitomycins by Fukuyama and Yang.[10] Nevertheless, the chiral Lewis acid catalyzed enantioselective 2-silyloxyfuran variant with chalcones as the Michael acceptors has never been reported on account of the weak chelating character of chalcones. Thus searching for a suitable and efficient chiral Lewis

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acid catalyst to afford chiral γ-substituted butenolides with well-defined regio-, diastereo- and enantioselectivities is still a high priority.

In previous studies,[11,12] the chiral *N*,*N*′-dioxide–lanthanide complexes have exhibited excellent abilities for the activation of various electrophiles and strong asymmetry-inducing capability for many reactions, especially in bromoamination,[13] the inverse electron-demand aza-Diels–Alder reaction[14] and the Roskamp reaction[15] using *N*,*N*′-dioxide–scandium(III) complexes. In light of these successes, we envisioned that such a catalyst with an electronic and steric tunable chiral environment might be effective for asymmetric VMMR. Herein, we wish to describe our efforts to address the enantioselective synthesis of a series of attractive *anti*-γ-substituted butenolides, where the regio-, diastereo- and enantioselectivities were well accomplished simultaneously using a chiral scandium(III)–*N*,*N*′-dioxide complex.

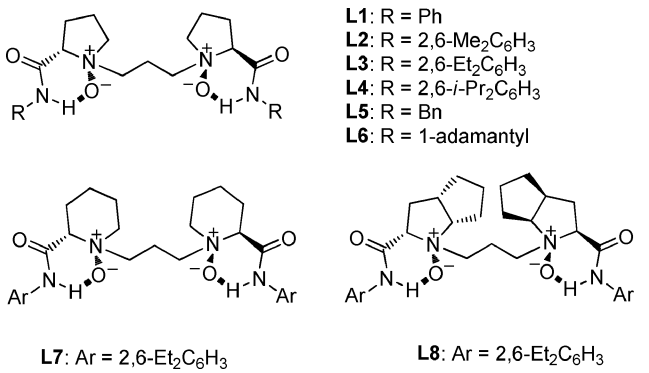


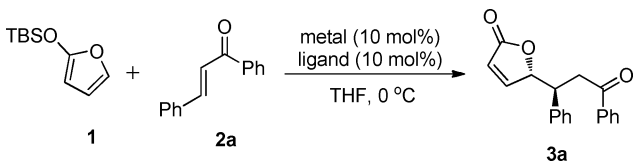
Fig. 1 Ligands employed in this study.

Results and discussion

Initially, chalcone **2a** and 2-(*tert*-butyldimethylsilyloxy)furan (TBSOF) **1** derived from unmodified γ-butenolide were chosen as starting materials for optimizing the conditions. Prompted by the great successes obtained in asymmetric reactions using chiral Ln complexes,[16] our preliminary study began with a systematic screen of Ln complexes in the presence of the *N*,*N*′-dioxide ligand **L1**. As shown in Table 1, the investigation revealed that $Sc(OTf)_3$ (Tf = trifluoromethanesulfonyl) was superior at giving higher yields of the γ-substituted butenolide compared to other representative metals of lanthanides which mainly gave side-products (Table 1, entries 1–4). To obtain the most effective ligand structure, various *N*,*N*′-dioxides were complexed *in situ* with $Sc(OTf)_3$ to catalyze the Mukaiyama–Michael reaction (Fig. 1 and Table 1, entries 5–11). The steric effect of the amide moiety played a crucial role on both the enantioselectivity and the yield. It was shown that ligands with bulky groups at the *ortho* position of the aniline regiospecifically provided the γ-adducts with satisfactory enantioselectivities and excellent yields (Table 1, entry 5–7), meanwhile no side product was detected. Furthermore, when R was replaced by aliphatic amines, such as benzylamine and 1-adamantylamine, no better results were obtained (Table 1, entries 8 and 9). Intensive studies on the amino acid backbone showed that the *N*,*N*′-dioxide **L3**, which was based on L-proline, was superior to both L-pipecolic acid derived *N*,*N*′-dioxide **L7** and L-ramipril derived *N*,*N*′-dioxide **L8** (Table 1, entry 6 *vs*. entries 10 and 11), and afforded the *anti*-γ-substituted butenolide **3a** in 99% yield with >99% dr and up to 82% ee.

To further improve the enantioselectivity of the reaction, solvents of the reaction were intensely investigated and the results are listed in Table 2. They indicated that the reaction solvent played an important role in governing the enantioselectivity of the reaction. Polar and coordinating solvents generally provided the expected product **3a** with higher enantioselectivities than nonpolar solvents did (Table 2, entries 1–6). Compared with THF, ethyl acetate was also found to be a suitable solvent for the reaction to afford **3a** in excellent yield with comparable ee value (up to 81% ee) (Table 2, entry 6 *vs*. 1). Thus further optimization was aimed at fully examining the solvents such as esters and alcohols. The

Table 1 Effects of central metal and ligand on catalytic asymmetric VMMR of TBSOF **1** and chalcone **2a**[a]

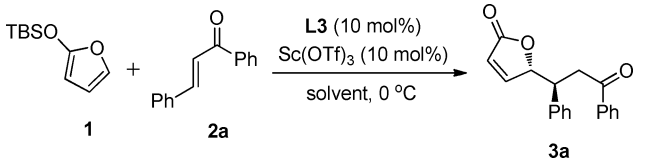


1 **2a** **3a**

Entry	Ligand	Metal	Time (h)	Yield (%)[b]	Dr[c]	Ee (%)[d]
1	**L1**	$Sc(OTf)_3$	12	35	> 99 : 1	11
2	**L1**	$Y(OTf)_3$	12	*trace*[e]	—	—
3	**L1**	$La(OTf)_2$	12	*trace*[e]	—	—
4	**L1**	$Yb(OTf)_3$	12	*trace*[e]	—	—
5	**L2**	$Sc(OTf)_3$	3	96	> 99 : 1	77
6	**L3**	$Sc(OTf)_3$	3	99	> 99 : 1	82
7	**L4**	$Sc(OTf)_3$	12	99	> 99 : 1	80
8	**L5**	$Sc(OTf)_3$	12	37[e]	> 99 : 1	12
9	**L6**	$Sc(OTf)_3$	12	99	95 : 5	4
10	**L7**	$Sc(OTf)_3$	3	99	> 99 : 1	72
11	**L8**	$Sc(OTf)_3$	12	99	> 99 : 1	59

[a] Unless otherwise noted, reactions were carried out with *N*,*N*′-dioxide (10 mol%), $Sc(OTf)_3$ (10 mol%), **1** (0.25 mmol), **2a** (0.1 mmol) in THF (0.3 mL) at 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis and ^1H NMR spectroscopy. [d] The ee value of the major diastereomer is given, determined by HPLC using chiral OD–H column. [e] Side products were detected.

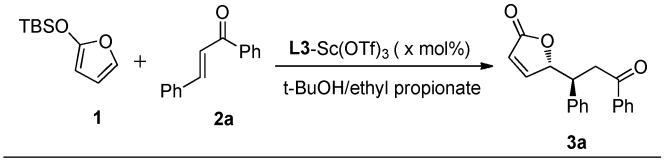
Table 2 Screening of the solvents in catalytic asymmetric VMMR of TBSOF **1** and chalcone **2a**[a,b]



Entry	Solvent	Time (h)	Yield (%)[c]	Ee (%)[d]
1	THF	3	99	82
2	toluene	12	86	75
3	CH_2Cl_2	3	99	67
4	$CHCl_3$	3	99	75
5	Et_2O	3	99	56
6	ethyl acetate	3	99	81
7	propyl acetate	3	99	81
8	ethyl propionate	3	99	86
9	ethyl benzoate	12	93	86
10	EtOH	<2	99	70
11	*i*-PrOH	<2	99	84
12[e]	*t*-BuOH	15 min	99	85
13[f]	*t*-BuOH/THF	3	99	87
14[f]	*t*-BuOH/ethyl propionate	3	99	88

[a] Unless otherwise noted, reactions were carried out with *N*,*N*′-dioxide **L3** (10 mol%), $Sc(OTf)_3$ (10 mol%), **1** (0.25 mmol), **2a** (0.1 mmol) in indicated solvent (0.3 mL) at 0 °C. [b] The *anti*-product was obtained as the major diastereomer and the *anti* : *syn* ratio was up to >99 : 1, which was determined by HPLC analysis and ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The ee value of the major diastereomer was given, determined by HPLC using chiral OD–H column. [e] The reaction temperature was 30 °C. [f] The volume ratio was 1 : 1.

Table 3 Effects of temperature and catalyst loading on catalytic asymmetric VMMR of TBSOF **1** and chalcone **2a**[a,b]



Entry	Catalyst loading (*x* mol%)	*T* (°C)	Time (h)	Yield (%)[c]	Ee (%)[d]
1	10	0	3	99	88
2	5	0	3	99	90
3	2	0	18	trace	89
4	1	0	18	n.r.[e]	—
5	5	−20	18	99	89
6	5	*rt*	< 3	99	84

[a] Unless otherwise noted, reactions were carried out with *N*,*N*′-dioxide **L3** (10 mol%), $Sc(OTf)_3$ (10 mol%), **1** (0.25 mmol), **2a** (0.1 mmol) in *t*-BuOH/ethyl propionate (0.3 mL, 1 : 1) at 0 °C. [b] The *anti*-product was obtained as the major diastereomer and the *anti*: *syn* ratio was up to >99 : 1, which was determined by HPLC analysis and ^{1}H NMR spectroscopy. [c] Isolated yield. [d] The ee value of the major diastereomer was given, determined by HPLC using chiral OD–H column. [e] No reaction.

investigation of esters revealed that the γ-substituted butenolide **3a** was isolated with better enantioselectivity and reactivity by utilizing ethyl propionate as a solvent and up to 86% ee was achieved (Table 2, entry 8 *vs.* 6–9). On the other hand, alcohols benefited the activity greatly and complete transformation was achieved within 2 h (Table 2, entries 10–12). In particular, in the case of *t*-BuOH **3a** was obtained with comparable ee value in only 15 min at 30 °C (Table 2, entry 12). In order to observe the performance of *t*-BuOH at lower temperature, the strategy of adding a cosolvent was adopted. To our delight, a mixture of ethyl propionate and *t*-BuOH (1 : 1) provided the adduct with best results (>99% yield, >99 : 1 dr and 88% ee) (Table 2, entry 13 *vs.* 14).

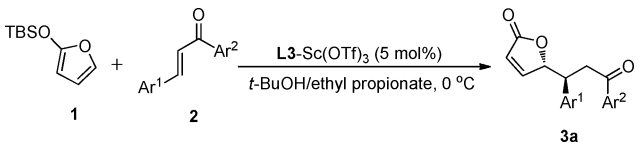
Subsequently, the effects of the catalyst loading and reaction temperature were examined and the results are presented in Table 3. Reducing the loading from 10 mol% to 5 mol% caused a slight increase in the enantioselectivity without deterioration of reactivity, affording the adduct **3a** with 90% ee, >99 : 1 dr and 99% yield in 3 h (Table 3, entry 2 *vs.* 1). However, when using 2 mol% catalyst, only trace amounts of product was obtained with maintained enantioselectivity in 18 h (Table 3, entry 3). Further reducing the loading of the catalyst to 1 mol% resulted in no product (Table 3, entry 4). Then the reaction temperature was evaluated. It revealed that the reaction rate decreased dramatically at −20 °C, whereas increasing the temperature to rt led to a slight decrease in the enantioselectivity (Table 3, entries 5–6). Extensive screening showed that the optimal conditions were as follows: 5 mol% **L3**–$Sc(OTf)_3$ complex (1 : 1), 0.2 mmol TBSOF **1** and 0.1 mmol chalcone in 0.3 mL *t*-BuOH/ethyl propionate (1 : 1) at 0 °C. It should be noted that the process was air and moisture tolerant.

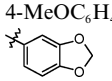
With the optimized conditions in hand, the substrate scope of the VMMR was explored.[17] A series of functionalized chalcones **2** was investigated, and the corresponding enantioenriched γ-substituted butenolides **3** were obtained in excellent yields with complete regioselectivities and excellent stereoselectivities. The results of significant structural variations in chalcone derivatives are collected in Table 4. It is notable that this catalyst system exhibited a remarkably broad substrate scope under exclusive diastereocontrol without any side product from α-addition.

Regardless of the electronic properties or steric hindrance of the substituent at the β-phenyl group of the chalcones, excellent enantioselectivities were observed (Table 4, entries 1–17). To our delight, the catalyst was also applicable to heterocyclic systems, which delivered the adducts with excellent ee values of 92% and 90%, respectively (Table 4, entries 18–19). Chalcone derivatives containing an electron-donating group functionalized on a benzoyl moiety reacted smoothly with TBSOF **1** to give the expected products **3t–3w** in good enantioselectivities (Table 4, entries 20–23). Furthermore, exploring the effect of the substituents on both aromatic rings Ar^1 and Ar^2 revealed chalcones such as **2x–2aa** were also suitable substrates for this reaction (Table 4, entries 24–27). Particularly, with electron-withdrawing groups on the β-phenyl moiety and electron-donating groups on the benzoyl moiety, the variations proceeded in excellent ee values with a longer reaction time.

The absolute configuration of the adduct **3j** was determined to be (1*S*, 2*S*) by a single crystal X-ray structural analysis (Fig. 2).[18] Different from the previous reports about 2-(5*H*)-furanones,[7b,7c] the major adduct of vinylogous Mukaiyama–Michael variant catalyzed by the chiral *N*,*N*′-dioxide–Sc(III) complex is *anti*. In addition, for some solid products, enantiopure samples (up to >99% ee) were obtained upon a single recrystallization. Undoubtedly, the good substrate generality combined with the

Table 4 Substrate scope of catalytic asymmetric VMMR of TBSOF **1** and chalcone **2** under the optimal conditions[a,b]



Entry	Ar^1	Ar^2	Time (h)	Yield (%)[c]	Ee (%)[d]
1	Ph	Ph	3	99 (**3a**)	90 (>99)[e]
2	4-MeC_6H_4	Ph	3	99 (**3b**)	87 (93)[e]
3	3-MeC_6H_4	Ph	3	97 (**3c**)	90
4	2-MeC_6H_4	Ph	2.5	99 (**3d**)	90
5	4-$MeOC_6H_4$	Ph	6	98 (**3e**)	90
6	3-$MeOC_6H_4$	Ph	3	99 (**3f**)	91
7	4-FC_6H_4	Ph	3	98 (**3g**)	90 (>99)[e]
8	4-ClC_6H_4	Ph	3	92 (**3h**)	90 (>99)[e]
9	3-ClC_6H_4	Ph	8	95 (**3i**)	92
10	3,4-$Cl_2C_6H_3$	Ph	48	99 (**3j**)	92 (>99)[e]
11	4-BrC_6H_4	Ph	15	99 (**3k**)	91 (>99)[e]
12	3-BrC_6H_4	Ph	8	96 (**3l**)	92
13	4-CNC_6H_4	Ph	18	99 (**3m**)	92 (>99)[e]
14	3-$CF_3C_6H_4$	Ph	5	98 (**3n**)	94 (>99)[e]
15		Ph	18	99 (**3o**)	91
16	3-$PhOC_6H_4$	Ph	3	99 (**3p**)	91
17	4-PhC_6H_4	Ph	24	94 (**3q**)	91 (>99)[e]
18	2-thienyl	Ph	3	99 (**3r**)	92 (>99)[e]
19	3-thienyl	Ph	16	99 (**3s**)	90
20	Ph	4-MeC_6H_4	3	99 (**3t**)	88 (>99)[e]
21	Ph	3-MeC_6H_4	5	96 (**3u**)	84 (93)[e]
22	Ph	4-$MeOC_6H_4$	24	99 (**3v**)	83 (>99)[e]
23	Ph		36	99 (**3w**)	83
24	4-$MeOC_6H_4$	4-$MeOC_6H_4$	36	92 (**3x**)	82
25	4-BrC_6H_4	4-MeC_6H_4	18	92 (**3y**)	88
26	3-BrC_6H_4	4-MeC_6H_4	18	99 (**3z**)	91
27	3-$CF_3C_6H_4$	4-MeC_6H_4	48	99 (**3aa**)	89

[a] Unless otherwise noted, reactions were carried out with *N*,*N*′-dioxide **L3** (5 mol%), $Sc(OTf)_3$ (5 mol%), **1** (0.25 mmol), **2** (0.1 mmol) in *t*-BuOH/ethyl propionate (0.3 mL, 1 : 1) at 0 °C. [b] The *anti*-product was obtained as the major diastereomer and *anti* : *syn* ratio was up to >99 : 1, which was determined by HPLC analysis and ^1H NMR spectroscopy. [c] Isolated yield. [d] The ee value of the major diastereomer was given, determined by HPLC using commercial chiral columns. [e] After a single recrystallization in ethyl acetate/petroleum ether.

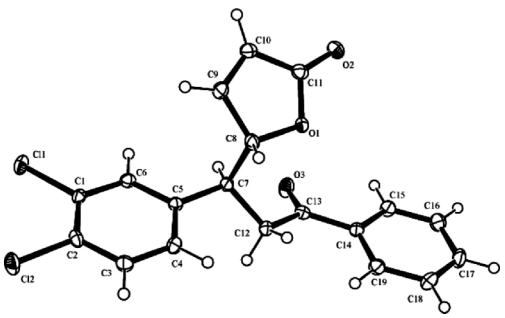
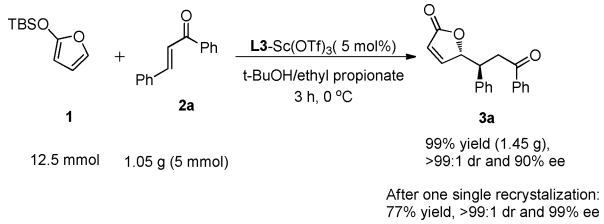


Fig. 2 X-ray structure of product **3j**.

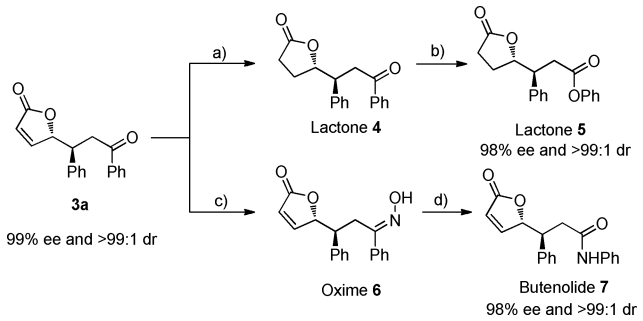


Scheme 2 Gram-scale version of catalytic asymmetric VMMR of TBSOF **1** and chalcone **2a**.

simplicity of the experimental procedure for the reaction made it very attractive from a synthetic point of view.

The mild reaction conditions, the inexpensive starting materials and the catalyst for this vinylogous Mukaiyama–Michael reaction offered a practical use of the present approach, so a gram-scale synthesis of the chiral γ-substituted butenolide was performed under the optimized conditions. As shown in Scheme 2, upon treatment of 5 mmol of chalcone **2a**, the vinylogous Michael product **3a** was produced in 99% yield without any loss of stereoselectivity. After a single recrystallization, only one single isomer of **3a** (up to 99% ee and >99 : 1 dr) was obtained in 77% yield.

The VMMR products **3** were versatile building blocks, as they allowed for further elaboration at the terminal carbon of the butenolide side chain. Compound **3a** served as a model to straightforwardly illustrate this synthetic potential. As shown in



Scheme 3 Elaboration of a vinylogous Michael adduct. Reagents and conditions: a) 20% Pd/C, 1 atm H_2, MeOH, rt, 12 h, 95% yield; b) *m*-CPBA, KH_2PO_4, $CH_2Cl\,CH_2Cl$, 60 °C, 5 h, 65% yield; c) $NH_2OH{\cdot}HCl$, pyridine, EtOH, 5 h, 90% yield; d) PCl_5, toluene, 3 h, 70% yield.

Scheme 3, the Michael adduct **3a** was readily converted to γ-lactone **4** in 95% yield after reduction of the olefinic double bond of the butenolide moiety. Baeyer–Villiger oxidation of **4** proceeded with *m*-CPBA to afford lactone **5** in 65% yield with >99 : 1 dr and up to 98% ee. In addition, considering that the butenolide moiety was also synthetically useful, the product **3a** could be easily transformed into oxime **6** by treatment with $NH_2OH{\cdot}HCl$. Beckmann rearrangement of **6** afforded butenolide **7** bearing an amide group on the side chain in 70% yield with >99 : 1 dr and 98% ee.

To gain insight into the reaction mechanism, the relationship between the enantiomeric excess of the product **3a** and *N*,*N*′-dioxide **L3** complex showed that the ee correlated linearly to each other (Fig. 3).[19] This suggested that dimeric species of **L3**–$Sc(OTf)_3$ complex did not participate in this reaction and all the events occurred in a monomeric species of **L3**–$Sc(OTf)_3$ complex. Moreover, on the HRMS spectrum of the sample only one MS peak at 907.2258 assigned to the monomeric scandium species $[\mathbf{L3}\text{–}Sc(OTf)_2]^+$ (HR-ESIMS: *m*/*z* calcd: 907.2259) was obtained and no oligomeric species of **L3**–$Sc(OTf)_3$ complex was detected.

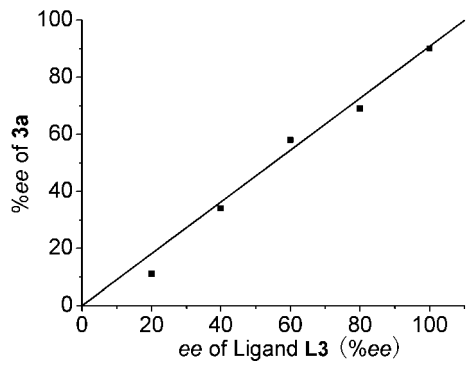
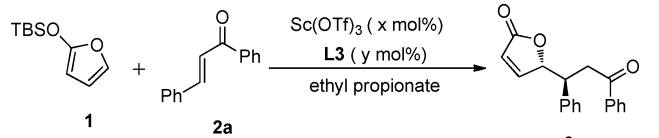


Fig. 3 Nonlinear effects observed in the **L3**–$Sc(OTf)_3$-catalyzed VMMR of TBSOF **1** and chalcone **2a**.

Control experiments (Table 5) and HRMS analysis (see supporting information †) were carried out to investigate the coordination states of the reactants. Initially, only trace amounts of product **3a** were obtained without $Sc(OTf)_3$ and *N*,*N*′-dioxide **L3** with poor diastereoselectivity (4 : 1 dr) (Table 5, entry 1). In contrast, 5 mol% $Sc(OTf)_3$ as Lewis acid was effective enough to complete the reaction and provided **3a** with 19 : 1 dr in 99% yield (Table 5, entry 2). The distinct consequence of the diastereoselectivity

Table 5 Control experiments for mechanistic studies of catalytic asymmetric VMMR of TBSOF **1** and chalcone **2a**[a]



1 2a 3a

Entry	$Sc(OTf)_3$ (*x* mol%)	**L3** (*y* mol%)	Yield (%)[b]	Dr[c]	Ee (%)[d]
1[e]	none	none	trace	4 : 1	0
2	5	none	99	19 : 1	0
3	none	5	n.r.[g]	—	—
4[f]	5	5	99	>99 : 1	86

[a] Unless otherwise noted, reactions were carried out with *N*,*N*′-dioxide **L3**, $Sc(OTf)_3$, **1** (0.25 mmol), **2a** (0.1 mmol) in ethyl propionate (0.3 mL) at 0 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC analysis and ^1H NMR spectroscopy. [d] The ee value of the major *anti*-diastereomer is given, determined by HPLC using chiral OD–H column. [e] The reaction time was 12 h. [f] The reaction time was 5 h. [g] No reaction.

revealed that both of the substrates were securely fixed at a specific location by the chelation of $Sc(OTf)_3$, which has been mentioned in previous studies.[5e,6o,7a] The coordination of the two reactants to the central metal was confirmed directly by the HRMS experiment. On the spectrum of the sample an acquired ion at *m*/*z* 1115.4252 (HR-ESIMS: *m*/*z* calcd for $[(\mathbf{L3}\text{–}Sc(OTf)_2)+\mathbf{2a}]^+$: 1115.3147) was revealed, which corresponded to the species of **L3**–Sc(III) complex coordinating with one molecule chalcone **2a**. And characteristic signal of $[(\mathbf{L3}\text{–}Sc^{III})+\mathbf{2a}+\mathbf{1}-2H^+]^+$ (HR-ESIMS: *m*/*z* calcd: 1013.5026) at *m*/*z* 1013.5045 were observed. These results suggested that the central metal conducted the two substrates into the highly organized chiral environment in sequence by a manner of dual control.

Based on the X-ray structure of *N*,*N*′-dioxide–scandium complex[12f] and the experimental results, as well as the absolute configuration of the product, a concerted stereorecognition model was proposed (Fig. 4). The favourable *anti*-diastereoselectivity was rationalized through the Newman projection. To avoid steric repulsion between the TBS group and the phenyl group, the nucleophilic addition proceeded *via* projection **II** preferentially to afford *anti*-product. A possible stereorecognition model is given in Fig. 4 to explain the enantioselectivity. In this model, the *N*-oxide and amide oxygen atoms of **L3** coordinated to scandium in a tetradentate manner to form two six-membered chelate rings, and the chalcone was attached to scandium at the favourable equatorial position. The *Re* face of the chalcone was shielded

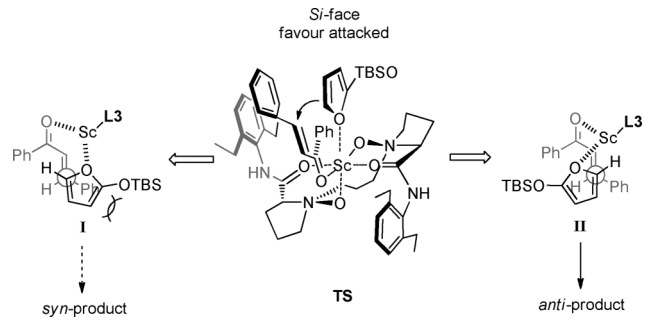


Fig. 4 Stereorecognition models for catalytic VMMR.

by the neighboring 2,6-diethylphenyl group of the ligand, and the nucleophile, TBSOF **1**, attacked from the *Si* face to give the (*S*,*S*)-product.

Conclusions

We have developed a highly efficient catalytic asymmetric vinylogous Mukaiyama–Michael reaction of 2-silyloxyfuran with chalcone derivatives using a chiral *N*,*N*′-dioxide–scandium complex. This contribution provides a practical synthetic strategy for the formation of highly functionalized chiral γ-substituted butenolides with broad substrate scope. In the presence of 5 mol% *N*,*N*′-dioxide–Sc(III) complex, complete regioselectivities, exclusive diastereoselectivities and good to excellent enantioselectivities (up to 94% ee) have been achieved under mild conditions. The synthetic potential of this methodology was also demonstrated by the excellent results obtained on a gram scale. And the elaboration of the product has also been explored to illustrate the synthetic versatility of γ-substituted butenolides. Moreover, the pathway is air-tolerant and easily manipulated, and reagents are readily available. On the basis of the experimental results, a possible catalytic cycle and favorable stereorecognition model have been proposed to probe the reaction mechanism and explain the origin of the asymmetric induction. Application of *N*,*N*′-dioxide–metal complexes to other reactions involving 2-silyloxyfurans as nucleophiles is ongoing in our laboratory.

Experimental section

General methods and materials

^{1}H NMR spectra were recorded on commercial instruments (400 MHz or 600 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra are reported as follows: chemical shift (δ (ppm)), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR spectra were collected on commercial instruments (100 MHz or 150 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). The enantiomeric excess was determined by HPLC analysis on commercial chiral columns. Optical rotations were measured on a commercial polarimeter and reported as follows: $[\alpha]_D^T$ (c = g/100 mL, solvent). HR-ESIMS spectra were recorded using a commercial apparatus and methanol or acetonitrile was used to dissolve the sample. Unless otherwise indicated, reagents obtained from commercial sources were used without further purification. Solvents were dried and distilled prior to use according to the standard methods. The *N*,*N*′-dioxide ligands were prepared according to previous reports.[12b,12c] TBSOF **1**, 2-(*tert*-butyldimethylsilyloxy)furan, was prepared according to reported procedures[4a,20] and immediately used due to its instability.

Typical experimental procedure for catalytic VMMR

N,*N*′-Dioxide **L3** (0.005 mmol, 2.9 mg), $Sc(OTf)_3$ (0.005 mmol, 2.5 mg), chalcone **2a** (0.1 mmol, 20.8 mg), *t*-BuOH (0.15 mL) and ethyl propionate (0.15 mL) were stirred in a dry reaction tube under air at 30 °C for 0.5 h. Subsequently, TBSOF **1** (0.25 mmol, 60 μL) was added at 0 °C. The reaction was stirred at 0 °C and monitored by TLC. After complete consumption of the starting material **2a**, the mixture was direct purified by column chromatography on silica gel (ethyl acetate/petroleum ether 1 : 5 to 1 : 3) to afford the white solid **3a** in 99% yield, as a mixture of diastereomers (90% ee, >99 : 1 dr; >99% ee was obtained after a single recrystallization in ethyl acetate/petroleum ether). The ee and diastereoselectivity were determined by HPLC analysis [Chiralpak OD–H, 80 : 20 *n*-hexane/*i*PrOH, 1.0 mL min^{-1}; t_r (major) = 16.495 min, t_r (minor) = 18.822 min] and ^{1}H NMR spectroscopy. M.p. 99–102 °C. $[\alpha]_D^{25}$ –75.5 (*c* 0.58 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 7.5, 2H), 7.55 (t, *J* = 7.4, 1H), 7.43 (t, *J* = 7.7, 2H), 7.36–7.25 (m, 6H), 5.27 (dd, *J* = 7.3, 1.4, 1H), 3.70 (td, *J* = 7.7, 5.0, 1H), 3.58 (dd, *J* = 17.7, 5.0, 1H), 3.48 (dd, *J* = 17.7, 8.2, 1H) ppm.

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