

Catalytic Enantioselective Mukaiyama–Michael Reaction of 2-(Trimethylsilyloxy)furan with α' -Phenylsulfonyl Enones

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Abstract: The Mukaiyama–Michael reaction of 2-(trimethylsilyloxy)furan with α' -phenylsulfonyl enones using bis(oxazoline)–copper(II) complexes as chiral catalyst provides the γ -butenolides in high enantio- and diastereoselectivity. This approach is very useful for the enantioselective synthesis of γ -butenolide derivatives under chiral Lewis acid catalysis.

Key words: asymmetric catalysis, Michael additions, Lewis acids, ligands, lactones

The Michael reaction is widely recognized as one of the most important organic reactions for the formation of a new carbon–carbon bond.¹ Among the various Michael reactions, the Mukaiyama reaction involving the Lewis acid catalyzed reaction of a silyl enol ether with an α,β -unsaturated carbonyl derivative has attracted a great deal of attention due to its synthetic usefulness.² The asymmetric version of the Mukaiyama–Michael reactions has been studied by several groups and includes the use of (BINOL)Ti–oxo complex,³ (–)-*trans*- α,α' -(dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) (TADDOL)-derived titanium chloride,^{4a} and bis(oxazoline)–Cu(II) complexes.^{4b,5}

The enantioselective synthesis of γ -butenolide synthons has become synthetically important⁶ because chiral γ -butenolides and their derivatives are common structural subunits in natural products and biologically active compounds,⁷ and chiral building blocks in organic synthesis.⁸ 2-(Trialkylsilyloxy)furans have been widely used for this

purpose with various electrophiles such as carbonyl compounds⁹ and acetals¹⁰ in the presence of a Lewis acid to afford the corresponding 4-substituted butenolides. The Michael reaction of 2-(trialkylsilyloxy)furans provides the butenolides bearing a C4-substituent functionalized at its terminal carbon which allows the further extension of the substituent. Accordingly, this approach is expected to become an efficient tool for the enantioselective synthesis of various butenolide derivatives under chiral Lewis acid catalysis. In fact, several reports on the Michael addition reactions of 2-silyloxyfurans catalyzed by chiral Lewis acids have appeared. Katsuki first examined the Mukaiyama–Michael reaction of 2-(trimethylsilyloxy)furan with oxazolidinone enoates using chiral scandium(III)–BINOL derivatives or a copper(II)–bis(oxazoline) complex as chiral catalysts.¹¹ The former catalyst gave very high *anti/syn* selectivity (>50:1), but only modest enantioselectivity (68% ee), whereas the latter exhibited high enantioselectivity (95% ee), but somewhat low *anti/syn* selectivity of (8.5:1). Desimoni¹² and Suga¹³ also reported the Mukaiyama–Michael reaction of 2-(trimethylsilyloxy)furans using (*E*)-3-crotonyl-1,3-oxazolidin-2-one under chiral Lewis acid catalysis. In addition, it is noteworthy that an asymmetric Michael reaction of 2-silyloxyfurans with α,β -unsaturated aldehydes using an organic catalyst afforded chiral γ -butenolides with high *syn*-selectivity and enantioselectivity.¹⁴

In connection with our continued effort to develop enantioselective conjugate addition reactions using α' -phospho-

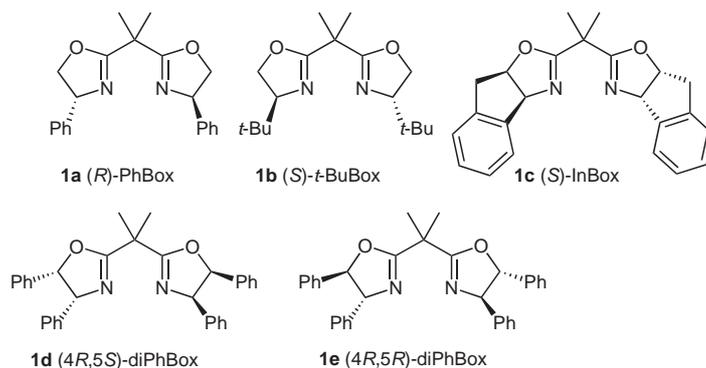
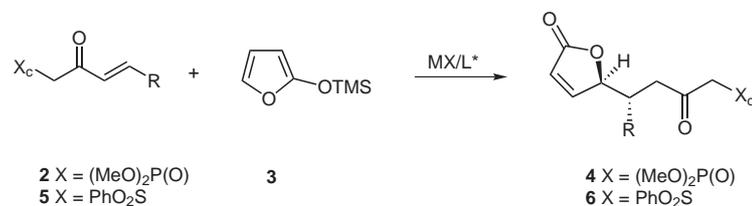
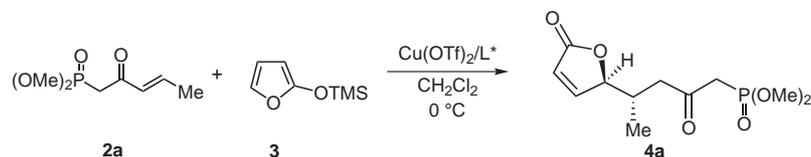


Figure 1



Scheme 1

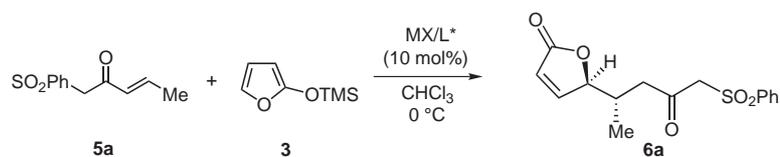
Table 1 Screening of the Chiral Catalysts with **2a**^a

Entry	L*	Time (h)	Yield (%)	ee (%) ^b	<i>anti/syn</i> (%) ^c
1	1a	0.2	92	82	97:3
2	1b	7	85	-1	99:1
3	1c	0.2	88	84	94:6

^a All reactions were carried out on a 0.1-mmol scale.

^b Enantiomeric excess was determined by chiral HPLC.

^c The *anti/syn* ratio was determined by ¹H NMR.

Table 2 Screening of the Chiral Catalysts with **5a**^a

Entry	MX	L*	Time (h)	Yield (%)	ee (%) ^b	<i>anti/syn</i> (%) ^c
1	Cu(OTf) ₂	1a	2	99	98	98:2
2	Zn(OTf) ₂	1a	18	99	88	99:1
3	Mg(OTf) ₂	1a	72	31	8	94:6
4	Sc(OTf) ₃	1a	72	35	10	96:4
5	Yb(OTf) ₃	1a	72	39	-2	93:7
6	Cu(OTf) ₂	1b	2	18	-3	n.d. ^d
7	Cu(OTf) ₂	1c	2	95	64	97:3
8	Cu(OTf) ₂	1d	2	95	99	>99:1
9	Cu(OTf) ₂	1e	2	18	18	83:17

^a All reactions were carried out on a 0.1-mmol scale.

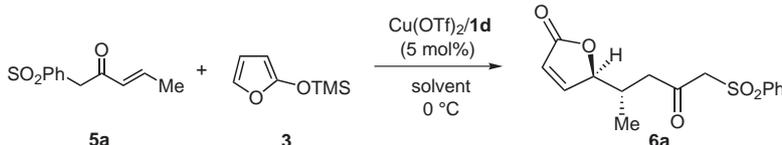
^b Enantiomeric excess was determined by chiral HPLC.

^c The *anti/syn* ratio was determined by ¹H NMR.

^d The ratio was not determined.

the reaction was carried out with several chiral bis(oxazoline) (Box) ligands (Figure 1) using copper(II) triflate (20 mol%) in dichloromethane. As shown in Table 1, the reaction was highly stereospecific and gave almost exclusively the *anti* product. Good results were obtained with (*R*)-PhBox (**1a**) and (*S*)-InBox (**1c**) in terms of chemical

yield and enantioselectivity (Scheme 1). However, (*S*)-*t*-BuBox (**1b**) slowed down the reaction significantly and almost no enantiomeric excess was obtained. Further improvements using α' -phosphoric enone were not successful. We next turned our attention to α' -phenylsulfonyl

Table 3 Effect of Solvent in Mukaiyama–Michael Reaction of 2-(Trimethylsilyloxy)furan **3** with α' -Phenylsulfonyl Enone **5a**^a


Entry	Solvent	Time (h)	Yield (%)	ee (%) ^b	<i>anti/syn</i> (%) ^c
1	CH ₂ Cl ₂	2	80	94	91:9
2	CHCl ₃	2	90	99	>99:1
3	THF	72	8	80	90:10
4	toluene	72	14	62	94:6

^a All reactions were carried out on a 0.1-mmol scale.

^b Enantiomeric excess was determined by chiral HPLC.

^c The *anti/syn* ratio was determined by ¹H NMR.

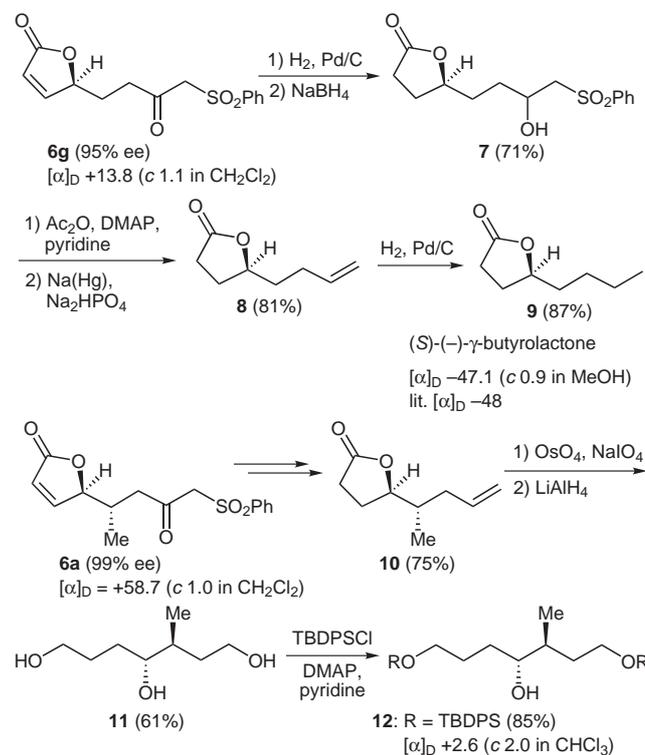
enone. Previously, Kanemasa utilized the α' -phenylsulfonyl enone **5** in asymmetric Diels–Alder reactions.¹⁶

To study the enantiomeric efficiency of the α' -phenylsulfonyl enone, the reaction was carried out with enone **5a** and 2-(trimethylsilyloxy)furan **3** in the presence of several chiral Box ligand–metal complexes (10 mol%) in chloroform at 0 °C and the experimental results are summarized in Table 2. From experimental results obtained in this study, several features are noteworthy. First, the α' -phenylsulfonyl enone exhibited higher enantioselectivity than the α' -phosphoric enone (98% ee vs 82% ee; entry 1). Second, (4*R*,5*S*)-diPhBox (**1d**)¹⁷ and copper(II) complex gave a slightly better result in terms of enantioselectivity and *anti* selectivity than **1a** (entry 8). Third, **1a** and Zn(OTf)₂ complex was also effective but slowed down the reaction significantly (entry 2). Finally, other metal–ligand complexes derived from Mg(OTf)₂, Sc(OTf)₃, and Yb(OTf)₃ were ineffective, yielding very low ee along with slightly lower *anti/syn* selectivities (entries 3–5).

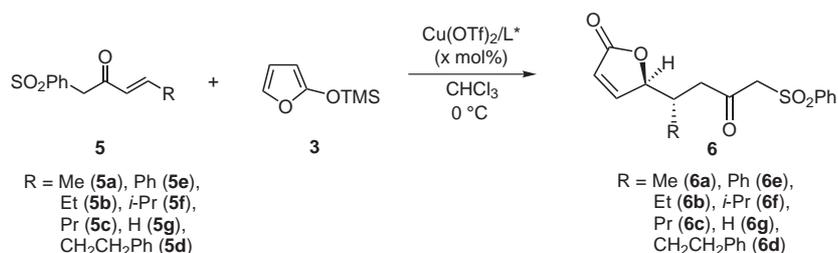
We also studied the solvent effect using 5 mol% of **1d**–Cu(OTf)₂ complex (Table 3). Chloroform gave the best result in terms of chemical yield, enantio- and diastereoselectivity. However, tetrahydrofuran and toluene slowed the reaction down drastically and reduced the ee significantly (entries 3 and 4). To test the catalytic ability of **1d**–Cu(OTf)₂ complex, when we reduced the amount of the catalyst from 10 mol% to 3 mol%, the reaction was slowed down and required five hours for completion without a significant loss of the ee (98% ee) and the same *anti/syn* selectivity. Thus, the remaining reactions were carried out with several α' -phenylsulfonyl enones **5** and **3** using 5 mol% and 10 mol% **1d**–Cu(OTf)₂ complex in chloroform at 0 °C.

Table 4 summarizes the experimental results and illustrates the scope and the efficiency of the present method. The use of 5 mol% of **1a**–Cu(OTf)₂ complex slowed down the reaction significantly and also reduced the *anti/syn* ratio to some extent. Although the similar phenomena were observed with **1d**, **1a** was more noticeable than **1d**.

Generally, better ee *anti/syn* selectivities were realized with the use of more bis(oxazoline)–copper(II) catalyst. When the reaction was carried out with 10 mol% of **1d**–Cu(OTf)₂ complex, the best ee (>97% ee) and *anti/syn* selectivity (99:1) were obtained. In the case of sterically bulky **5f** (entries 23 and 24), the reaction was incomplete using 10 mol% of **1d**–Cu(OTf)₂ complex and required 20 mol% of **1d**–Cu(OTf)₂ complex for completion along with a slightly lower *anti/syn* selectivity and enantioselectivity.

**Scheme 2** Conversion of **6g** and **6a** into **9** and **12**, respectively

To establish the absolute configuration and to demonstrate the utility of the present approach, butenolide ad-

Table 4 Mukaiyama–Michael Reaction of **3** with α' -Phenylsulfonyl Enones **5** Using Cu(II)–Bis(oxazoline) Complexes^{a,18}

Entry	L*	R	x (mol%)	Time (h)	Yield (%)	ee (%) ^b	<i>anti/syn</i> (%) ^c
1	1a	H (5g)	10	2	85 (6g)	91	–
2	1a	Me (5a)	10	2	99 (6a)	98	98:2
3	1a	Me (5a)	5	72	82 (6a)	82	91:9
4	1a	Et (5b)	10	8	80 (6b)	99	>99:1
5	1a	Et (5b)	5	96	17 (6b)	95	92:8
6	1a	Pr (5c)	10	3	99 (6c)	99	83:17
7	1a	Pr (5c)	5	96	16 (6c)	65	69:31
8	1a	CH ₂ CH ₂ Ph(5d)	10	3	92 (6d)	>99	95:5
9	1a	CH ₂ CH ₂ Ph(5d)	5	96	45 (6d)	69	91:9
10	1a	Ph (5e)	10	3	95 (6e)	97	>99:1
11	1a	Ph (5e)	5	96	72 (6e)	96	64:35
12	1d	H (5g)	5	2	91 (6g)	95	–
13	1d	Me (5a)	10	2	95 (6a)	99	>99:1
14	1d	Me (5a)	5	2	90 (6a)	99	>99:1
15	1d	Et (5b)	10	72	79 (6b)	99	98:2
16	1d	Et (5b)	5	96	71 (6b)	99	>99:1
17	1d	Pr (5c)	10	18	92 (6c)	98	>99:1
18	1d	Pr (5c)	5	96	72 (6c)	99	>99:1
19	1d	CH ₂ CH ₂ Ph(5d)	10	24	88 (6d)	97	>99:1
20	1d	CH ₂ CH ₂ Ph(5d)	5	96	85 (6d)	97	95:5
21	1d	Ph (5e)	10	2	>99 (6e)	99	>99:1
22	1d	Ph (5e)	5	12	>99 (6e)	99	75:25
23	1d	<i>i</i> -Pr (5f)	20	96	75 (6f)	97	97:3
24	1d	<i>i</i> -Pr (5f)	10	96	28 (6f)	97	95:5

^a All reactions were carried out on a 0.1-mmol scale.

^b Enantiomeric excess was determined by chiral HPLC.

^c The *anti/syn* ratio was determined by ¹H NMR.

duct **6g** was converted to the natural product, (*S*)-(-)- γ -butyrolactone **9** by routine operations (Scheme 2). Hydrogenation and reduction of the keto group afforded **7** in 71% yield. Acetylation of **7** followed by desulfonation provided **8** in 81% yield, which was further reduced to the previously known product **9**. Compared with the optical

rotation value of **9** and the previously known compound, the absolute configuration was assigned as *S*.¹⁹ Furthermore, **6a** was similarly converted into **10** by routine operations. Treatment of **10** with osmium tetroxide and sodium periodate in aqueous THF followed by reduction with lithium aluminum hydride afforded **11**, which was

further converted into **12** (Scheme 2). According to the optical rotation value of **12**, it was an enantiomer of the previously known product $\{[\alpha]_D -2.5 (c = 2.2 \text{ in } \text{CHCl}_3)\}$.^{11b} Thus, the configuration of (+)-*anti*-**6a** was proven to be *S,S*.

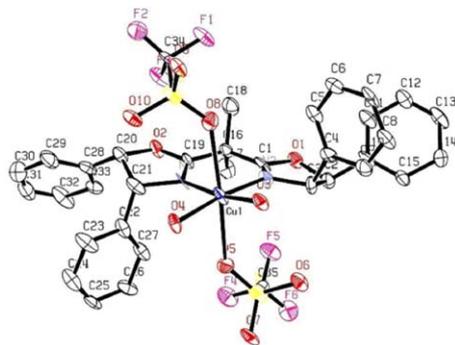


Figure 2 X-ray crystallography of [(4*R*,5*S*)-diPhBox]Cu(OTf)₂(H₂O)₂

The structure of [(4*R*,5*S*)-diPhBox]Cu(OTf)₂(H₂O)₂ was determined by X-ray crystallography (Figure 1). This complex shows the octahedral geometry, the counter ions weakly coordinate to the apical site and two H₂O's are located in equatorial site. Based on X-ray crystallographic information and the observed enantioselectivity in this study, a tentative model would have the *s-trans* enone template in a distorted square planar geometry. The *s-trans* conformation would be attributed to a π - π stabilization of the transition state as shown in Figure 2.²⁰

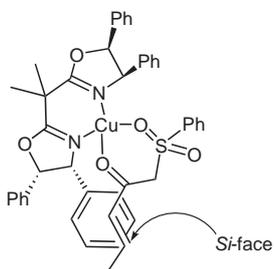


Figure 3 The expected model of the substrate–catalyst complex

In summary, we have shown that the α' -phenylsulfonyl enone templates are highly efficient for the catalytic enantioselective Mukaiyama–Michael reactions. Using **1d**–Cu(OTf)₂ complex, the Mukaiyama–Michael reaction of 2-(trimethylsilyloxy)furan with α' -phenylsulfonyl enones affords γ -butenolides in high enantioselectivities up to 99% ee and high *anti/syn* selectivities (up to 99:1).

Acknowledgment

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(18) **Typical Procedure for the Mukaiyama–Michael****Reaction of 2-(Trimethylsilyloxy)furan (3) with α' -**

Phenylsulfonyl Enone 5a: To the flask of freshly prepared [(4*R*,5*S*)-diPhBox]Cu(OTf)₂ (5 mol%) in CHCl₃ (1 mL) was added a solution of α' -phenylsulfonyl enone **5a** (0.11 mmol, 25 mg) in CHCl₃ (1 mL). After being stirred at r.t. for 0.5 h, the reaction mixture was cooled to 0 °C, and the solution of **3** (0.22 mmol, 35 mg) in CHCl₃ (1 mL) was added to the reaction mixture. The reaction was maintained at the desired temperature until a complete consumption of the α' -phenylsulfonyl enone **5a** as monitored by TLC. After completion of the reaction, the reaction was quenched with sat. aq NaHCO₃ solution, extracted with CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **6a** as an oil in 99% yield (34 mg). Spectroscopic data for **6a**: ¹H NMR (400 MHz, CDCl₃): δ = 1.01 (d, *J* = 6.9 Hz, 3 H), 2.41 (m, 1 H), 2.60 (dd, *J* = 18.8, 7.2 Hz, 1 H), 2.84 (dd, *J* = 18.8, 5.3 Hz, 1 H), 4.14 (dd, *J* = 21.4, 13.3 Hz, 2 H), 4.90 (dd, *J* = 6.1, 3.2 Hz, 1 H), 6.08 (dd, *J* = 5.8, 1.9 Hz, 1 H), 7.43 (d, *J* = 5.9 Hz, 1 H), 7.56 (t, *J* = 8.0 Hz, 2 H), 7.67 (t, *J* = 7.7 Hz, 1 H), 7.84 (d, *J* = 7.4 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 16.02, 31.88, 46.12, 66.86, 85.73, 122.26, 128.05, 129.34, 134.32, 138.60, 154.66, 172.39, 196.34. IR (KBr): 3700, 3139, 3022, 2953,

2360, 1731, 1612, 1566, 1490, 1432, 1353, 1223, 1116, 1060, 1005, 946, 870, 783, 720, 669 cm⁻¹. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₅H₁₇O₅S: 309.0798; found: 309.0791. Product ratio was determined by HPLC analysis (Chiralcel OD-H, 30%

i-PrOH–hexane, 0.6 mL/min, λ = 254 nm); *S,S*-isomer (major): *t*_R = 42.4 min and *R,R*-isomer (minor): *t*_R = 53.7 min; [α]_D²⁵ +58.7° (*c* = 1.0 in CH₂Cl₂).

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