# Chiral Lewis Acid Promoted Asymmetric Michael Addition Reaction of 2-(Trimethylsilyloxy)furans

Hiroshi Kitajima and Tsutomu Katsuki*

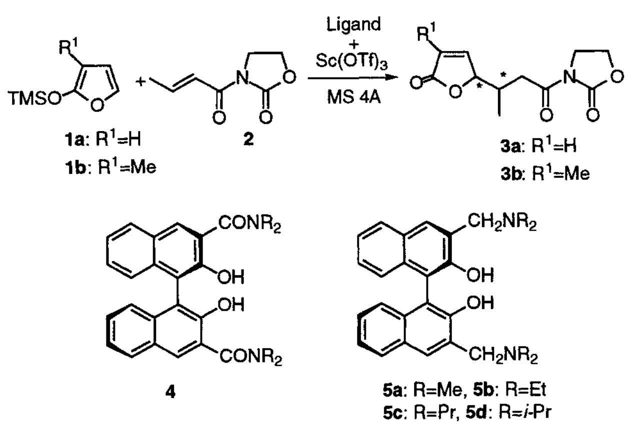
Department of Chemistry, Faculty of Science, Kyushu University 33, Hakozaki, Higashi-ku, Fukuoka 812-81, Japan

Fax +81 92 642 2607

*Received 18 February 1997*

**Abstract**: Lewis acid promoted Michael addition of 2-(trimethylsilyloxy)furan to 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one (**2**) was examined. A 1:1 complex prepared from scandium triflate and 3,3'-bis(diethylaminomethyl)-1,1'-bi-2-naphthol **5b** *in situ* showed excellent *anti*-selectivity and moderate enantioselectivity, while Cu(II)-bis(oxazolines) complex exhibited excellent enantioselectivity and moderate to good *anti*-selectivity.

Optically active butenolides are important class of compounds since they not only constitute subunits of naturally occurring compounds[1] but also serve as the precursors for the synthesis of densely substituted chiral γ–lactone compounds.[2] 2-(Trialkylsilyloxy)furans are nucleophiles and react with various electrophiles such as ketones,[3] aldehydes,[3a,4] acetals,[3a,5] nitron,[6] and enone[7] in the presence of Lewis acid to afford the corresponding γ–substituted butenolides. Although some of these reactions have used chiral electrophiles as substrates,[8] no enantioselective version has been reported. Fukuyama *et al.* have already reported that the Michael reaction of simple trimethylsilyloxyfuran and chalcones proceeds with modest diastereoselectivity,[7a] while the reaction of 2-ethylthio-5-(trimethylsilyloxy)furan proceeds with high diastereoselectivity.[7b,c] Since this type of reaction is useful for organic synthesis, we studied on the stereochemistry of the reaction of 2-(trimethylsilyloxy)furans (**1**) with 3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one (**2**).



**Scheme 1**

We first examined the reaction of **1a** with **2** in the presence of various Lewis acid catalysts. Among the catalysts examined, metal triflates such as $Sc(OTf)_3$[9] and $Cu(OTf)_2$ showed high diastereoselectivity (*anti*:*syn* = >50:1), though chemical yield of **3a** was only modest (36% and 38%, respectively).[10] Recently, Kobayashi and co-workers have demonstrated that $Sc(OTf)_3$ or $Yb(OTf)_3$ modified by (*R*)-1,1-bi-2-naphthol [(*R*)-BINOL] and tertiary amine is an effective catalyst for asymmetric Diels-Alder reaction.[11] Therefore, we next examined the reaction of **1a** and **2** using a combination of $Sc(OTf)_3$, (*R*)-BINOL, and $Et_3N$ as a catalyst but the chemical yield and enantiomeric excess of the desired product were only modest (35%, 12% ee).[10] On the other hand, we have reported that optically active *N,N,N',N'*-tetraalkyl-BINOL-3,3'-dicarboxamides (**4**) are efficient chiral auxiliaries for asymmetric Simmons-Smith cyclopropanation of allylic alcohols[12] and for enantioselective diethylzinc addition to aldehydes.[12b,13] Thus, we examined the reaction using the complex of $Sc(OTf)_3$ and **4** as a catalyst and found that the reaction proceeded smoothly, though enantioselectivity was poor (18% ee). Encouraged by this result and Kobayashi's report,[11] we synthesized the BINOL derivatives **5** bearing a tertiary aminomethyl group at 3,3'-carbons,[14] expecting that the conformation of the aminomethyl group would be fixed by intramolecular hydrogen-bond formation upon its coordination to $Sc(OTf)_3$ and examined the reaction of **1** and **2**.

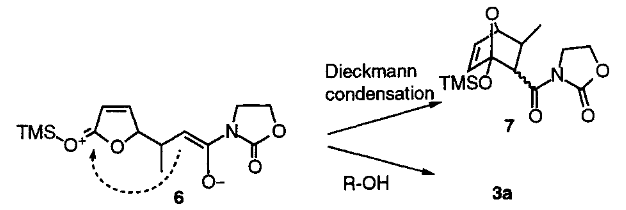
**Table 1.** Michael addition of 2-(trimethylsilyloxy)furans using chiral scandium complex.

| entry[a] | substrate | ligand | additive | solvent | yield[b] (%) | *anti*:*syn*[c] | ee[d] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | **5b** | none | $CH_2Cl_2$ | 44 | >50:1 | 73 |
| 2 | **1a** | **5b** | *i*-PrOH | $CH_2Cl_2$ | 78 | >50:1 | 49 |
| 3 | **1a** | **5b** | HFIP | $CH_2Cl_2$ | 80 | >50:1 | 65 |
| 4[e] | **1a** | **5b** | HFIP | $CH_2Cl_2$ | 86 | >50:1 | 68 |
| 5 | **1a** | **5b** | HFIP | toluene | 80 | >50:1 | 57 |
| 6 | **1a** | **5b** | HFIP | Ph-Cl | 87 | >50:1 | 56 |
| 7 | **1b** | **5b** | HFIP | $CH_2Cl_2$ | 94 | >50:1[f] | 56 |

a) All reactions were carried out at 0 °C in the presence of 5 mol% of $Sc(OTf)_3$ and 6 mol % of **5**, unless otherwise mentioned.
b) The yield refers to the total yield of *syn* and *anti* isomers.
c) Estimated by $^1$H-NMR (270 MHz) analysis.
d) Determined by HPLC using optically active column: (Daicel Chiralpak AD; hexane:*i*-PrOH = 2:1).
e) Ten mol% of $Sc(OTf)_3$ and 12 mol% of **5b** were used.
f) Relative configuration was tentatively assigned by analogy with the reaction of **1a**.

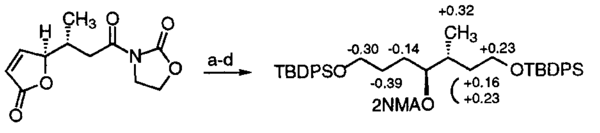
Table 1 summarizes the results obtained. The reaction with **5b** as a chiral source in dichloromethane proceeded with excellent diastereoselectivity and good enantioselectivity, but the chemical yield was moderate (entry 1). Other chiral sources **5a**, **5c**, and **5d** were less effective in terms of enantioselectivity. The major side product of these reactions was a Diels-Alder type adduct **7** which was probably produced by Dieckmann condensation of the intermediary enolate **6** (Scheme 2). To avoid this undesired side reaction, we carried out the reaction in the presence of 1 equiv. of isopropyl alcohol which would accelerate the quenching of the enolate. These modified reaction conditions increased the yield of **3a** but decreased enantioselectivity to some extent (entry 2). Although the reason for the decrease of enantioselectivity was unclear, we assumed that the added alcohol coordinated to scandium ion and changed its coordination atmosphere. Thus, we examined hexafluoroisopropanol (HFIP) as an additive, which is more acidic and has poor coordinating ability. As expected, the reaction proceeded with high chemical yield and a similar level of stereoselectivity as compared with the reaction without additive (entries 3 and 4). We also examined the effect of solvent (entries 3, 5, and 6). However, the reaction in dichloromethane showed the highest enantioselectivity. The reaction of **1b** and **2** under the same reaction conditions also proceeded with high diastereo- and moderate enantioselectivity.

Recrystallization of **3a** from ethyl acetate-hexane gave optically pure single crystals, X-ray analysis[15] confirmed the relative configuration of



**Scheme 2**

**3a**, as shown in Scheme 3. The pure **3a** was converted to the corresponding (*R*)- and (*S*)-(2-naphthyl)methoxyacetic acid (2NMA) esters **8**, $^1$H-NMR analysis determined the absolute configuration of C4-carbon in **8** to be *S*.[16] The $\Delta\delta$ ($\delta_R$-$\delta_S$) (ppm) values are indicated in Scheme 3. Thus, the configuration of the major enantiomer of **3a** was determined to be *R,R*.

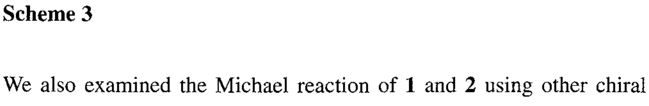


**3a** (major isomer) **8**

(a) $H_2$-Pd/C, AcOEt, RT; (b) $LiAlH_4$, THF, 0°C-RT ; (c) TBDPSi-Cl, Py-DMAP, $CH_2Cl_2$; (d) (*R*)- and (*S*)-2NMA, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, DMAP, $CH_2Cl_2$.

**Scheme 3**

We also examined the Michael reaction of **1** and **2** using other chiral Lewis acid catalysts and found that the reaction using $Cu(OTf)_2$-bis(oxazolines) **9**[17] complex as a catalyst proceeded in the presence of HFIP with high enantioselectivity, though *anti*-selectivity was moderate especially in the reaction of **1a**.[18] Configuration of the product **3a** obtained with (*S,S*)-**9** was determined to be *S,S* by chiroptical comparison.

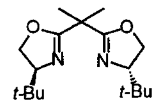


**1a**: $R^1$=H **2**
**1b**: $R^1$=Me

**3a**: $R^1$=H
**3b**: $R^1$=Me

**Table 2.** Michael addition of 2-(trimethylsilyloxy)furans using chiral copper complex.

| entry | substrate | ligand | additive | solvent | yield (%) | *anti*:*syn* | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | **9** | HFIP | $CH_2Cl_2$ | 89 | 8.5:1 | 95 |
| 2 | **1b** | **9** | HFIP | $CH_2Cl_2$ | 95 | 24:1 | 91 |



(*S,S*) -**9**

Typical experimental procedure is as follows: $Sc(OTf)_3$ (6.2 mg, 13 µmol) and diamine **5b** (6.8 mg, 15 µmol) were dissolved in 0.5 ml of $CH_2Cl_2$ in the presence of activated molecular sieves 4A (30 mg) and stirred for 30 min at 0 °C under nitrogen atmosphere. To the mixture were added a $CH_2Cl_2$ solution (0.5 ml) of **2** (38.8 mg, 0.25 mmol), HFIP (26 µl, 0.25 mmol), and **1a** (50 µl, 0.3 mmol) and the whole mixture was stirred for 15 h at the temperature. The mixture was quenched with water and filtered through a pad of Celite to remove insoluble materials. The filtrate was diluted with $CH_2Cl_2$ and separated from the water layer. The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (EtOAc:hexane = 7:3) to afford **3a** (48 mg, 80% yield) as a mixture of *anti*- and *syn*-isomers. The mixture was recrystallized twice from hexane-ethyl acetate to give *anti*-**3a** (27 mg, 45%) of >99% ee.

The reaction with $Cu(OTf)_2$-**9** complex was carried out in the same manner as described for the reaction with $Sc(OTf)_3$-**5b** complex, except that $Cu(OTf)_2$-**9** complex was used instead of $Sc(OTf)_3$-**5b** complex.

In conclusion, we could demonstrate that chiral Lewis acid-promoted Michael addition of 2-(trimethylsiloxy)furans proceeded in the presence of HFIP with good chemical yield and high stereoselectivity. To the best our knowledge, this is the first example of asymmetric and catalytic Michael addition of 2-(trimethylsilyloxy)furans. Further studies are in progress in our laboratory.

**Acknowledgment.** The authors would like to thank Mr. Masami Yamashita, Yoshitomi pharmaceutical industries, Ltd. for X-ray analysis. Financial supports from the Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan and from Japan Tobacco Co. Ltd., are greatly acknowledged.

## Reference and Notes

(1) a) Rao, Y.S. *Chem. Rev.* **1964**, *64*, 353. b) Jefford, C. W.; Jaggi, D.; Sledeski, A. W.; Boukouvalas, J. In *Studies in Natural Products Chemistry*; Atta-er-Rahman, Ed.; Vol. 3, Elsevier: Amsterdam, 1989; p 157.

(2) a) Hanessian, S.; Murray, J. P.; Sahoo, P.S. *Tetrahedron Lett.* **1985**, *26*, 5627. b) Hanessian, S.; Murray, J. P. *Can. J. Chem.* **1986**, *64*, 2231. c) Hanessian, S.; Sahoo, P. S.; Maurizio, B. *Tetrahedron Lett.* **1987**, *28*, 1147. d) Mattes, H.; Hamada, K.; Benezra, C. *J. Med. Chem.* **1987**, *30*, 1948. e) Hanessian, S.; Cooke, G. N.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276. f) Pelter, A.; Al-Bayati, H. I. R.; Ayoub, T. M., Lewis, W.; Pardasani, P.; Hansel, R. *J. Chem. Soc. Perkin Trans. 1* **1987**, 717. g) Lange, D. B.; Bolhuis, V. F.; Feringa, L. B. *Tetrahedron* **1989**, *45*, 6799. h) Jong, D. J.; Bolhuis, V. F.; Feringa, L. B. *Tetrahedron: Asymmetry* **1991**, *2*, 1247. i) Pelter, A.; Ward, S. R.; Jones, M. D., Maddocks, P. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2621.

(3) a) Asaoka, M.; Sugimura, N.; Takei, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1953. b) Jefford, W. C.; Jaggi, D.;Bernardinelli, G.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4041.

(4) a) Brown, W. D.; Campbell, M. M.; Taylor, P. A.; Zhang, X. **1987**, *28*, 985. b) Jefford, W. C.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037. c) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *Tetrahedron Lett.* **1989**, *30*, 5325. d) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gasparri, F.; Belicchi, F. M. *Tetrahedron* **1990**, *46*, 5807. e) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1990**, *55*, 2565. f) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *56*, 2135. g) Bauer, T. *Tetrahedron: Asymmetry* **1996**, *7*, 981.

(5) a) Harding, E. K.; Coleman, T. M.; Liu, T. L. *Tetrahedron Lett.* **1991**, 3795. b) Martin, F. S.; Corbett, W. J. *Synthesis* **1992** *93*, 55. c) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5573. d) Pelter, A.; Ward, S. R.; Sirit, A. *Tetrahedron: Asymmetry* **1994**, *5*, 1745. e) Martin, F. S.; Barr, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 3299.

(6) a) Castellari, C.; Poletti, L.; Trombini, C. *J. Org. Chem.* **1994**, *59*, 6843. b) Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059.

(7) a) Fukuyama, T.; Yang, L. *Tetrahedron Lett.* **1986**, *27*, 6299. b) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1987**, *109*, 7881.

c) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303. d) Brimble, A. M.; Brimble, T. M.; Gibson, J. J. *J. Chem. Soc. Perkin Trans. I.* **1989**, 179. e) Brimble, A. M.; Duncalf, J. L.; Reid, C. W. D. *Tetrahedron: Asymmetry* **1995**, *6*, 263.

(8) For a review of stereoselective reaction of 2-(trimethylsilyloxy)furans and analogous dienes, see. Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607.

(9) The review for Sc(OTf)$_3$-catalyzed reactions, see: Kobayashi, S. *Synlett* **1994**, 689.

(10) Tandem Michael-Dieckmann condensation product was also produced.

(11) a) Kobayashi, S.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535. b) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325. c) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. d) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623.

(12) a) Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T., *Chem. Lett.*, **1995**, 1113. b) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207.

(13) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343.

(14) Compound **4** which was prepared according to the reported procedure (ref. 12b), was reduced with LiAlH$_4$ in THF at reflux for 4 h to give 3,3'-bis(dialkylaminomethyl)-BINOL (**5**) without decaying its chiral integrity. For example, **5b** was obtained in a yield of 65% as white powder, mp. 138-139 °C, $[\alpha]^{21}_{D}$ +147° (*c* 0.5, CHCl$_3$). The optical purity (>99% ee) was verified by HPLC analysis using Dicel Chiralcel OD-R.

(15) Mp. 88-89°C, $[\alpha]^{21}_{D}$ -75.4° (*c* 1, CHC13). Crystal data: $C_{11}H_{13}NO_5$ M = 239.23, monoclinic, space group *P*2$_1$, a = 9.490 (1) Å, b = 9.122 (1) Å, c = 6.587 (1) Å, β = 97.74 (1)°, V = 565.1 (2) Å$^3$, Z = 2, μ(Cu Kα) = 0.908 mm$^{-1}$, Dx = 1.405 g· cm$^{-3}$, R = 0.034.

(16) Kusumi, T.; Takahashi, H.; Xu, P.; Fukushima, T.; Asakawa, Y.; Hashimoto, T.; Inoue, Y. *Tetrahedron Lett.* **1994**, *35*, 4397.

(17) For the example of the reactions using Cu(II)-bis(oxazolines) complexes as catalysts, see: Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339, and references cited therein.

(18) The reaction in the absence of HFIP gave the desired Michael adduct of 92% ee in 37% yield, though *anti*-selectivity was slightly increased to 10.5:1.