# Effective Synthesis of 5-Substituted Butenolide Derivatives by Using Cinchonidine-derived Quaternary Ammonium Phenoxide Catalyst

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A vinylogous aldol-type reaction between 4-methyl-2-(trimethylsiloxy)furan and aldehydes catalyzed by cinchonidine-derived quaternary ammonium phenoxide proceeded smoothly to afford the corresponding 5-substituted butenolide derivatives in high yields with good to excellent diastereo- and enantio-selectivities.

5-Substituted butenolide derivatives are useful building blocks in organic synthesis,[1] and therefore, many methods to synthesize chiral 5-substituted butenolides are reported; for example, asymmetric aldol-type reactions of siloxy furans with electrophiles such as aldehyde, ketone, and enone. These reactions are usually catalyzed by chiral Lewis acid,[2] but to apply them to the reagents having pyridyl or amino group was not easy. Thus, it was desired to develop a method that is applicable to such aldehydes.

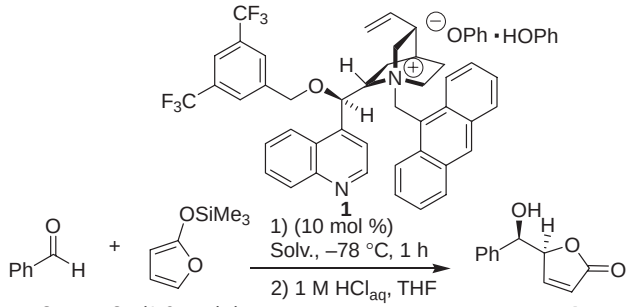
Recently, it was reported that cinchonidine-derived quaternary ammonium phenoxides were useful in the asymmetric reactions between $\alpha,\beta$-unsaturated ketones and various silyl enolates from our laboratory.[3] In order to find further applicability of this ammonium phenoxide, vinylogous aldol-type reactions between siloxyfurans and aldehydes were tried. In this communication, we would like to report highly diastereo- and enantio-selective synthesis of 5-substituted butenolide derivatives[4] via vinylogous aldol-type reactions between aldehydes and siloxyfurans by using the cinchonidine-derived quanternary ammonium phenoxide as a Leiws base catalyst.

In the first place, a reaction of benzaldehyde **2a** and 2-(trimethylsiloxy)furan (**3a**) by using 10 mol % of cinchonidine-derived quaternary ammonium phenoxide **1** was tried at $-78\,^{\circ}C$ for 1 h whose results are summarized in Table 1. While the use of polar solvents such as THF or EtCN gave the 5-substituted butenolide **4a** in moderate enatioselectivity (65% ee or 55% ee, Entries 1 and 2), a nonpolar solvent, $CH_2Cl_2$, increased the enantiomeric excess of **4a** up to 76% ee (Entry 3). In order to decrease the polarity of the solvent, reactions in toluene/$CH_2Cl_2$ or in hexane/$CH_2Cl_2$ were examined. However, no sufficient improvements in enantiomeric excess were observed (Entries 4 and 5).

Next, the effect of substituent on siloxyfurans was examined and the results are summarized in Table 2. A substituent at 3- or 5-position of a furan ring lowered enantioselectivities (Entries 1 and 3). On the other hand, the one at 4-position was found effective and gave the corresponding butenolide in 91% yield with excellent diastereo- and enantio-selectivities (*syn*:*anti* = 93:7, *syn* = 93% ee, Entry 2).

Next, reactions of 4-methyl-2-(trimethylsiloxy)furan (**3b**) with various aldehydes were tried in the presence of cinchonidine-derived quaternary ammonium phenoxide **1** under the optimized conditions (Table 3),[6] and the reactions of both aromatic and aliphatic aldehydes afforded the corresponding butenolides in high yields with good to excellent diastereo- and enantio-selectivities (Entries 1–6). When an aldehyde having a 2-pyridyl group that is not easily used in the conventional Lewis acid-mediated aldol-type reactions was employed, the corresponding butenolide **4h** was obtained in 94% yield with moderate stereochemical control (*syn*:*anti* = 67:33, *syn* =

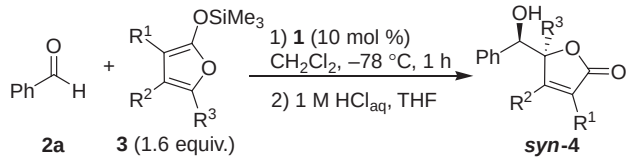
**Table 1.** Effect of solvents




| Entry | Solv. | Yield[a]/% | *syn*:*anti*[b] | % ee (*syn*)[c] |
|---|---|---|---|---|
| 1 | THF | 88 | 90:10 | 65 |
| 2 | EtCN | 88 | 78:22 | 55 |
| 3 | $CH_2Cl_2$ | 92 | 88:12 | 76 |
| 4 | Toluene/$CH_2Cl_2$=1/1 | 85 | 87:13 | 74 |
| 5 | Hexane/$CH_2Cl_2$=1/1 | 88 | 86:14 | 69 |

[a]Isolated yield. [b]Diastereomeric ratio was determined by $^1$H NMR analysis.[5] [c]Enantiomeric excess of major *syn*-**4a** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AS-H) with hexane/2-propanol (volume ratio = 5:1) as an eluent.

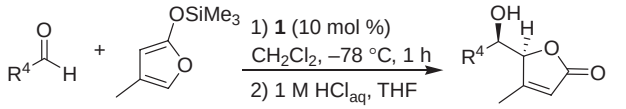
**Table 2.** Reaction of benzaldehyde with various siloxyfuran




| Entry | $R^1$ | $R^2$ | $R^3$ | Yield/%[a] | *syn*:*anti*[b] | % ee (*syn*)[c] |
|---|---|---|---|---|---|---|
| 1 | Me | H | H | 92 | 80:20 | 31 |
| 2 | H | Me | H | 91 | 93:7 | 93 |
| 3 | H | H | Me | 43 | 97:3 | 57 |

[a]Isolated yield. [b]Diastereomeric ratio was determined by $^1$H NMR analysis. [c]Enantiomeric excess of major *syn*-**4** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AS-H) with hexane/2-propanol as an eluent.

**Table 3.** Synthesis of various 5-substituted butenolides




**2a** **3b** (1.6 equiv.) ***syn*-4**

| Entry | $R^4$ | Product | Yield/%[a] | *syn*:*anti*[b] | % ee (*syn*)[c] |
|---|---|---|---|---|---|
| 1 | Ph | **4a** | 91 | 93:7 | 93 |
| 2 | 4-Br-$C_6H_4$ | **4b** | 93 | 83:17 | 93 |
| 3 | 4-MeO-$C_6H_4$ | **4c** | 95 | 89:11 | 93 |
| 4 | $PhCH_2CH_2$ | **4d** | 75 | 78:22 | 97 |
| 5 | *c*-$C_6H_{11}$ | **4e** | 97 | 76:24 | 80 |
| 6 | *t*-$C_4H_9$ | **4f** | 41 | >99:1 | 85 |
| 7 |  | **4g** | 95 | 86:14 | 93 |
| 8 |  | **4h** | 94 | 67:33 | 57 |

[a]Isolated yield. [b]Diastereomeric ratio was determined by $^1$H NMR analysis. [c]Enantiomeric excess of major *syn*-**4** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AS-H or Chiralcel OD-H) with hexane/2-propanol as an eluent. 0.1% $Et_2NH$ was added to the solvent in the case of **4h**.

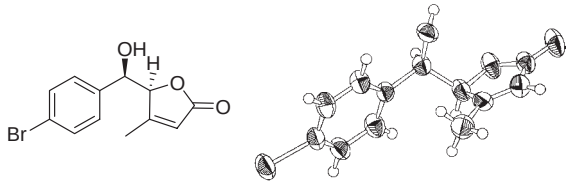



**Figure 1.** ORTEP drawing of compound *syn*-**4b**.

57% ee, Entry 8).

Relative and absolute configurations at two newly created adjacent carbon centers of the major product that formed by the reaction with 4-bromobenzaldehyde (Table 3, Entry 2) were clearly identified as shown in Figure 1 by X-ray crystallographic analysis.[7]

Thus, an efficient synthesis of 5-subsituted butenolide derivatives via vinylogous aldol-type reactions between aldehydes and 4-methyl-2-(trimethylsiloxy)furan (**3b**) was achieved for the first time in high yields with good to excellent diastereo- and enantio-selectivities when cinchonidine-derived quaternary ammonium phenoxide **1** was used as a catalyst.

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4 Recent example of Lewis base-catalyzed conjugate addition of siloxydiene derivatives, see: S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192.

5 Structural assignment of diastereomeric 5-substituted butenolides was based on the $^1$H NMR chemical shift of the characteristic vinyl proton, which resonates at a lower magnetic field in the anti isomer than in the syn isomer. see: M. Szlosek, B. Figadère, *Angew. Chem., Int. Ed.* **2000**, *39*, 1799.

6 Typical experimental procedure for the preparation of **4** is shown in the following (Table 3, Entry 2): To a stirred solution of **1** (27.0 mg, 0.03 mmol) in $CH_2Cl_2$ (0.2 mL) were successively added a solution of 4-bromobenzaldehyde (55.5 mg, 0.3 mmol) in $CH_2Cl_2$ (1.2 mL) and a solution of 4-methyl-2-trimethylsilyoxyfuran (81.7 mg, 0.48 mmol) in $CH_2Cl_2$ (0.6 mL) at $-78$ °C. After the mixture was stirred for 1 h at the same temperature, it was quenched with 1 M $HCl_{aq}$ and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated. The crude product was dissolved in THF and 1 M $HCl_{aq}$ was added at room temperature. After 10 min, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and evaporated. The crude product was purified by preparative TLC (hexane/EtOAc = 1/1) to give butenolide **4b** (79.4 mg, 93%, 93% ee) as a colorless crystal. $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 7.57–7.46 (d, $J = 8.5$ Hz 2H), 7.35–7.26 (d, $J = 8.5$ Hz, 2H), 5.80–5.75 (m, 1H), 5.14–5.03 (m, 2H), 2.70 (d, $J = 4.6$ Hz, 1H), 1.89 (s, 3H). The enantiomeric excess was determined by HPLC analysis using DAICEL Chiralcel OD-H, hexane/2-propanol = 20/1, $\lambda = 254$ nm, flow rate = 1.0 mL/min, retention time = 38.8 min (major) and 75.2 min (minor).

7 The product **4b** was recrystallized from $CH_2Cl_2$. Crystal date: $C_{12}H_{11}BrO_3$ (FW 283.12), monoclinic, $P2_1$, $a = 7.391(4)$, $b = 5.963(5)$, $c = 13.357(3)$ Å, $\beta = 97.12(3)^\circ$, $V = 584.1(5)$ Å$^3$, $Z = 2.0$, $D_{calcd} = 1.610$ g cm$^{-3}$, $T = 295$ K. X-ray intensities were measured on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo K$\alpha$ radiation ($\lambda = 0.710690$ Å). The final $R$ factors was 0.032 ($R$w = 0.093 for all data) for 2406 reflections with $I > 2\sigma(I)$.

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