Stereoselective Synthesis of Highly Functionalized 2,3-Dihydro-4-pyranones Using Phosphine Oxide as Catalyst

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2,3-Dihydro-4-pyranones were synthesized stereoselectively using a chiral phosphine oxide as the catalyst. The phosphine oxide sequentially activated silicon tetrachloride and promoted the double aldol reaction of 4-methoxy-3-buten-2-one with aldehydes. Subsequent stereoselective cyclization afforded the corresponding highly functionalized 2,3-dihydro-4-pyranones bearing three contiguous chiral centers in good yields and with high diastereo- and enantioselectivities.

Key words aldol reaction; phosphine oxide; pyranone; cyclization; stereoselectivity

Fig. 1. Stereoselective Synthesis of 2,3-Dihydro-4-pyranones Using Phosphine Oxide-Catalyzed Double Aldol Reaction/Cyclization Cascade

Note

Pyran and its derivatives are common and versatile structures in bioactive natural products and medicines. Therefore, it is important to develop efficient methods for the synthesis of diverse pyran structures. Recently, we reported the synthesis of 2-acyl-1,3-diols bearing two stereogenic centers by the phosphine oxide-catalyzed asymmetric double aldol reaction of methyl ketones with aldehydes. It is possible that the double aldol products, obtained from β-alkoxy enones and aldehydes, are cyclized in situ, affording the corresponding highly functionalized 2,3-dihydro-4-pyranones with three contiguous stereogenic centers (Fig. 1). Herein, we report the asymmetric synthesis of 2,3-dihydro-4-pyranones by asymmetric double aldol reaction/cyclization cascade.

First, the reaction of 4-methoxy-3-buten-2-one (1A) with benzaldehyde (2a) was performed in the presence of 10 mol% (S)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl diox ide (BINAP) as the Lewis base catalyst under several reaction conditions (Table 1). The presence of silicon tetrachloride (3 eq) and N,N-disopropylethylamine (5 eq) in CH2Cl2 at −40°C afforded three 2,3-dihydro-4-pyranones 5a, 6a, and 7a as a diastereomeric mixture in total 68% yield, whereas the non-cyclized product 8a was not isolated (entry 1). Furthermore, the major isomer 5a showed a promising enantioselectivity. When propionitrile was used as the solvent, the enantioselectivity improved; however, the product yield decreased (entry 2). The use of a mixture of solvents (1:1, v/v) afforded well-balanced yields and selectivities (entry 3). The reaction of β-benzoyloxy enone 1B afforded only non-cyclized adduct 8B in a moderate yield and with good enantioselectivity (entry 4). The reaction of β-phenoxoy enone 1C resulted in a similar yield and selectivity as 1A, accompanied with non-cyclized adduct 8C (entry 5). A screening of quenching reagents showed that the prior addition of methanol (3 mL) before 1.5 M KF/3.0 M HCOOH solution promoted the cyclization of 8C, affording the corresponding 2,3-dihydro-4-pyranones in 72% yield (entry 6). When the reaction was conducted at a lower concentration of 0.03 M in CH2Cl2–EtCN (1:4, v/v), the enantioselectivity increased to 91% enantiomeric excess (ee) (entry 7).

The probable stereochemical course of the reaction is shown in Fig. 2. The double aldol reaction of enone 1 with aldehyde 2 affords two types of double aldolates, 9 and 10. Isomer 9 is optically active, whereas isomer 10 is optically inactive because of its meso-structure. It is predicted that chelation occurs between one silyloxy group and the carbonyl group, leading to the cyclization of the other silyloxy group, which is located closer to the β-position of the enone, through path A and affording the major isomer 5. When the reaction proceeds via path B, the minor isomer 6 is obtained in almost the same enantioselectivity as the major isomer 5. Isomer 10 reacts through path C and D equally, affording isomer 7 as a racemate.

With the optimized reaction conditions, the reactions of enone 1C with various aldehydes 2 were conducted (Table 2). Regardless of the electronic nature of the phenyl ring, similar yields and enantioselectivities of 5 were obtained (entries...
The use of \( p \)-anisaldehyde (2b) bearing an electron-donating group decreased the diastereoselectivity because of the generation of the \( \text{meso} \)-isomer in the double aldol reaction. The reactions of naphthaldehydes 2d and 2e afforded the corresponding products with good enantioselectivities (entries 4, 5).

In conclusion, we have demonstrated asymmetric 2,3-dihydro-4-pyranone synthesis using a chiral phosphine oxide as the catalyst. The chiral phosphine oxide effectively facilitated the double aldol reaction of 4-methoxy-3-buten-2-one with aldehydes and subsequent stereoselective cyclization afforded the corresponding highly functionalized 2,3-dihydro-4-pyranones in good yields and with good diastereo- and enantioselectivities. This method offers an alternative to the existing methods for the synthesis of 2,3-dihydro-4-pyranones from the corresponding ketones and aldehydes.

**Experimental**

**General** All the reactions were performed under argon atmosphere using dried glasswares equipped with a rubber septum and a magnetic stirring bar. The column chromatography purifications were performed using Kanto Chemical Silica Gel 60N (spherical, neutral, \( 63–210 \mu\text{m} \)). The IR spectra were recorded using a JEOL JIR 6500-W. The \( 1^H \)- and \( 13^C \)-NMR spectra were recorded in CDCl\( _3 \) using a JEOL JNM-ECX-400 spectrometer. The chemical shifts are reported in ppm relative to the internal tetramethylsilane (TMS) standard (\( \delta \) 0.00 ppm) for the \( 1^H \)-NMR spectra and solvent signals (\( \delta \) 77.0 ppm) for the \( 13^C \)-NMR spectra. The mass spectra were recorded using a JEOL JMS-700MStation mass spectrometer. The HPLC analyses were performed using JASCO P-2080 and UV-2075.

**Typical Procedure for the Synthesis of 2,3-Dihydro-4-pyranones** Silicon tetrachloride (3 eq) was added to a solution of ketone 1 (0.5 mmol), aldehyde 2a (2.5 eq), \( \text{Pr}_2\text{NEt} \) (5.0 eq), and (S)-BINAPO (10 mol%) in a solvent (5 mL) at \(-40^\circ\text{C} \), and quenched with aq. 1.5 M KF/3.0 M HCOOH (5 mL).

### Table 1. Optimization of Reaction Condition\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
<th>( \text{dr}, \text{5a}/\text{6a}/\text{7a})</th>
<th>ee of 5a(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1A</td>
<td>CH(_2)Cl(_2)</td>
<td>4</td>
<td>68</td>
<td>92/2/6</td>
</tr>
<tr>
<td>2</td>
<td>1A</td>
<td>EtCN</td>
<td>4</td>
<td>39</td>
<td>92/1/7</td>
</tr>
<tr>
<td>3</td>
<td>1A</td>
<td>CH(_2)Cl–EtCN=1:1</td>
<td>4</td>
<td>60</td>
<td>85/2/13</td>
</tr>
<tr>
<td>4</td>
<td>1B</td>
<td>CH(_2)Cl–EtCN=1:1</td>
<td>2</td>
<td>0 (52)(^i)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>1C</td>
<td>CH(_2)Cl–EtCN=1:1</td>
<td>6</td>
<td>58 (22)(^j)</td>
<td>79/3/18</td>
</tr>
<tr>
<td>6(^k), 7(^h)</td>
<td>1C</td>
<td>CH(_2)Cl–EtCN=1:1</td>
<td>24</td>
<td>72</td>
<td>82/3/15</td>
</tr>
<tr>
<td>6(^k), 7(^h)</td>
<td>1C</td>
<td>CH(_2)Cl–EtCN=1:4</td>
<td>48</td>
<td>69</td>
<td>85/1/14</td>
</tr>
</tbody>
</table>

\(a\) Unless otherwise noted, the reactions were carried out by adding SiCl\(_4\) (3.0 eq) to a solution of ketone 1 (0.5 mmol), aldehyde 2a (2.5 eq), \( \text{Pr}_2\text{NEt} \) (5.0 eq), and (S)-BINAPO (10 mol%) in a solvent (5 mL) at \(-40^\circ\text{C} \), and quenched with aq. 1.5 M KF/3.0 M HCOOH (5 mL).

\(b\) Combined yields of diastereomers.

\(c\) Determined by \( 1^H \)-NMR and HPLC analyses.

\(d\) Determined by HPLC analysis.

\(e\) Results of noncyclized adduct 8 in the parenthesis.

\(f\) The reaction was conducted at \(-60^\circ\text{C} \).

\(g\) The reaction was quenched with methanol (3 mL) before the addition of aq. 1.5 M KF/3.0 M HCOOH.

\(h\) The reaction was conducted at a concentration of 0.03 M.

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Fig. 2. Proposed Stereochemical Course

2, 3). The use of \( p \)-anisaldehyde (2b) bearing an electron-donating group decreased the diastereoselectivity because of the generation of the \( \text{meso} \)-isomer in the double aldol reaction. The reactions of naphthaldehydes 2d and 2e afforded the corresponding products with good enantioselectivities (entries 4, 5).
Table 2. Reaction of Various Aldehydes$^{a}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>2</th>
<th>Yield$^{b}$ (%)</th>
<th>dr, 5/6/$^{c}$</th>
<th>ee of 5$^{d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a, R=Ph</td>
<td>69</td>
<td>85/1/14</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>2b, R=4-MeOC$_2$H$_4$</td>
<td>71</td>
<td>72/5/3</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>2c, R=4-BrC$_2$H$_4$</td>
<td>62</td>
<td>81/4/5</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>2d, R=1-Naphthyl</td>
<td>64</td>
<td>80/5/15</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>2e, R=2-Naphthyl</td>
<td>75</td>
<td>84/2/14</td>
<td>84</td>
</tr>
</tbody>
</table>

$^{a}$ All the reactions were carried out by adding silicon tetrachloride (3.0 eq) to a solution of ketone 1C (0.5 mmol), an aldehyde 2 (2.5 eq), N,N-diisopropylethylamine (5.0 eq), and (S)-BINAP (10 mol%) in CH$_2$Cl$_2$-EtCN (16.7 mL, 1:4, v/v) at −60°C. $^{b}$ Combined yields of diastereomers. $^{c}$ Determined by 1H-NMR and HPLC analyses. $^{d}$ Determined by HPLC analysis.

(2S,3R,1'R)-3-[Hydroxy(phenyl)methyl]-2-phenyl-2,3-dihydro-4-pyranone

Data for 5a

TLC: Rf 0.57 (hexane–EtOAc=1:1, stained orange with anisaldehyde); [α]$_D^{20}$ = −195.3 (c=1.0, CHCl$_3$) for 99% ee (after recrystallization); $^1$H-NMR (CDCl$_3$): δ: 5.50 (1H, dd, $J=5.0$, 10.6 Hz), 4.30 (1H, d, $J=7.8$ Hz), 4.89 (1H, dd, $J=5.0$, 7.8 Hz), 5.30 (1H, d, $J=10.6$ Hz), 5.53 (1H, d, $J=6.0$ Hz), 7.10–7.34 (11H, m); $^{13}$C-NMR (CDCl$_3$): δ: 4.54, 72.9, 82.0, 107.6, 126.9, 127.8, 127.8, 128.3, 128.7, 139.2, 135.7, 140.6, 163.1, 194.4; IR (film): 1599, 1672, 3444 cm$^{-1}$; low resolution (LR-MS) (FAB): m/z 303 (M+Na$^+$); high resolution (HR-MS) (FAB): Calcd for C$_{29}$H$_{32}$O$_2$Na 363.1208. Found 363.1213. The ee was determined to be 93% ee using HPLC equipped with Daicel Chiralcel OZ-H column [elucent: hexane–IPA=9:1; flow rate: 1.0 mL/min; detection: 254 nm; $t_R$: 18.5 min (major), 23.1 min (minor)].

3-[4-Bromophenylhydroxymethyl]-2-(4-bromo-phenyl)-2,3-dihydro-4-pyranone

Data for 5c

TLC: Rf 0.29 (hexane–EtOAc=2:1, stained orange with anisaldehyde); [α]$_D^{20}$ = −156.4 (c=1.0, CHCl$_3$) for 99% ee (after recrystallization); $^1$H-NMR (CDCl$_3$): δ: 3.71 (1H, d, $J=4.1$, 11.2 Hz), 3.74 (1H, d, $J=7.4$ Hz), 5.10 (1H, dd, $J=4.1$, 7.4 Hz), 5.30 (1H, d, $J=11.2$ Hz), 5.57 (1H, d, $J=6.0$ Hz), 6.91 (1H, d, $J=8.7$ Hz), 7.07 (1H, d, $J=8.7$ Hz), 7.32 (1H, d, $J=8.3$ Hz), 7.39 (1H, d, $J=6.0$ Hz), 7.42 (1H, d, $J=8.3$ Hz); $^{13}$C-NMR (CDCl$_3$): δ: 54.7, 71.1, 81.4, 107.6, 121.5, 123.6, 128.1, 129.6, 131.3, 131.8, 134.5, 139.7, 163.2, 193.4; IR (film): 1595, 1662, 3410 cm$^{-1}$; LR-MS (FAB): m/z 437, 439, 441 (M+H$^+$); HR-MS (FAB): Calcd for C$_{25}$H$_{23}$BrO$_2$ 436.9368. Found 436.9351. The ee was determined to be 90% ee using HPLC equipped with a Daicel Chiralpak AD-H column [elucent: hexane–IPA=9:1; flow rate: 0.5 mL/min; detection: 254 nm; $t_R$: 28.2 min (major), 41.0 min (minor)].

3-[Hydroxy(1-naphthyl)methyl]-2-(1-naphthyl)-2,3-dihydro-4-pyranone

Data for 5d

TLC: Rf 0.35 (hexane–EtOAc=2:1, stained orange with anisaldehyde); [α]$_D^{20}$ = −33.1 (c=1.6, CHCl$_3$) for 77% ee; $^1$H-NMR (CDCl$_3$): δ: 2.55 (1H, d, $J=4.6$ Hz), 3.74 (1H, dd, $J=2.8$, 7.8 Hz), 5.70 (1H, d, $J=6.0$ Hz), 6.34 (1H, m), 6.55 (1H, d, $J=7.8$ Hz), 7.03–7.92 (15H, m); $^{13}$C-NMR (CDCl$_3$): δ: 54.1, 69.0, 78.0, 107.1, 122.4, 122.8, 123.6, 124.4, 124.6, 125.3, 125.4, 125.9, 126.2, 127.7, 128.6, 128.7, 129.3, 130.2, 131.9, 133.3, 133.6, 136.2, 163.1, 192.8; IR (film): 796, 1597, 1657, 3417 cm$^{-1}$; LR-MS (FAB): m/z 380 (M$^+$); HR-MS (FAB): Calcd for C$_{34}$H$_{22}$O$_2$ 380.1412. Found 380.1411. The ee was determined to be 77% ee using HPLC equipped with a Daicel Chiralpak AS-H column [elucent: hexane–IPA=9:1; flow rate: 1.0 mL/min; detection: 254 nm; $t_R$: 21.4 min (major), 35.5 min (minor)].
3-[Hydroxyl(2-naphthyl)methyl]-2-(2-naphthyl)-2,3-dihydro-4-pyranone

Data for 5e

TLC: \( R_f \) 0.35 (hexane–EtOAc=2:1, stained orange with anisaldehyde); \( [\alpha]_D^{20} \) = −182.2 (\( c=1.0 \), CHCl\(_3\)) for 84% ee; \( ^1\)H-NMR (CDCl\(_3\)) \( \delta \): 3.71 (1H, dd, \( J=4.6, 11.4 \) Hz), 4.30 (1H, d, \( J=7.8 \) Hz), 5.17 (1H, dd, \( J=4.6, 7.8 \) Hz), 5.45 (1H, d, \( J=11.4 \) Hz), 5.61 (1H, d, \( J=6.0 \) Hz), 7.28–7.76 (15H, m); \( ^{13}\)C-NMR (CDCl\(_3\)) \( \delta \): 54.1, 72.8, 82.4, 107.7, 124.3, 124.4, 125.9, 126.1, 126.2, 126.5, 126.8, 127.4, 127.6, 127.8, 128.0, 128.1, 128.2, 128.6, 132.7, 132.8, 133.5, 137.9, 163.3, 194.6; IR (film): 748, 816, 856, 1597, 1652, 3404 cm\(^{-1}\); LR-MS (FAB): \( m/z \) 403 (M+Na); HR-MS (FAB): Calcd for C\(_{26}\)H\(_{20}\)O\(_3\)Na 403.1310. Found 403.1312. The ee was determined to be 84% ee using HPLC equipped with a Daicel Chiralpak AD-H column [eluent: hexane–IPA=9:1; flow rate: 1.0 mL/min; detection: 254 nm; \( t_R \): 27.6 min (major), 30.6 min (minor)].

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Conflict of Interest The authors declare no conflict of interest.

References and Notes
11) The absolute configuration of the major isomer 5a was determined to be 2S,3R,1’R by X-ray crystallographic analysis after derivatization to the corresponding camphorsulfonate. The crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as a supplementary publication number CCDC 1425234.
12) The treatment of trichlorosilyl aldolate 9 with MeOH appeared to afford trimethoxysilyl aldolate, which could be transformed to 5a.
13) Minor isomer 6a has almost the same enantioselectivity as the major isomer 5a.
14) It is possible to generate two types of meso-isomers in the double aldol reaction. But, one cyclized isomer was isolated after cyclization. The relative configuration of 7a was assigned on the basis of the proton–proton NMR coupling constants.