Diastereoselective Aldol Addition Reactions of a Chiral Methyl Ketone Trichlorosilyl Enolate under Lewis Base Catalysis

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Abstract: The trichlorosilyl enolate of a chiral methyl ketone bearing an oxygen substituent (OTBS) on the β-position undergoes highly diastereoselective aldol addition to a variety of achiral aldehydes in good yield. The stereochemical course of the reaction is primarily controlled by the configuration of the chiral phosphoramidate which serves as an effective catalyst for this transformation.

Key words: aldol addition, trichlorosilyl enolate, Lewis base catalysis, diastereoselection

The stereocontrolled aldol addition reaction remains one of the most powerful and versatile carbon-carbon bond forming reactions in organic synthesis. Among the manifold variants of this venerable process, the addition of unsubstituted (i.e. methyl ketone) enolates has presented a particular challenge. Although the reasons for this behavior are still under investigation, one popular rationalization is the availability of competing diastereomeric transition structures (twist-boats) resulting from the reduced steric demand of the nucleophile.

As part of our exploration of the chemistry of enoxytrichlorosilanes, we have recently described a broad investigation of the catalytic enantioselective addition of methyl ketone trichlorosilyl enolates, Scheme 1. These reactive enolates can be generated in situ by simple mercuric acetate catalyzed exchange of the TMS enol ethers with silicon tetrachloride. Subsequent aldol reactions are catalyzed by chiral phosphoramides to afford the addition products in excellent yield and good enantioselectivities (3.2-24.0/1 er).

To expand the synthetic utility of these enolates, we also studied the addition reactions of chiral methyl ketone enolates bearing an α oxygen substituent, e.g. ii, Scheme 2. This enolate (also readily generated in situ from the TMS enol ether i) undergoes addition in the matched case with phosphoramidate (R,R)-1a (Chart 1) to generate the aldol product iii with high 1,4-syn diastereoselection. However, it was not possible to reverse the sense of diastereoselection by the use of (S,S)-1a.

In continuation of our generalization of this process, we have now extended the scope of chiral methyl ketone structures to include those bearing an oxygen substituent at the β-position, 2, Figure 1. Whereas structures of this type do not give highly diastereoselective aldol additions as their lithium enolates, Paterson has shown that the dicyclohexylboron enolates can give good 1,4-syn diastereoselection. Interestingly, the use of the (-)-IPC ligand significantly improves selectivity, but the (+)-IPC ligand gives the same selectivity as the achiral group. We describe herein the in-situ generation and aldol reaction of the trichlorosilyl enolate 4 derived from 2 and the ability of chiral phosphoramides to control the diastereoselectivity of the addition.

The methyl ketone 2 was easily prepared in three steps from enantiopure (S)-(+)methyl β-hydroxyisobutyrate, Scheme 3. Conversion of the methyl ester to the Weinreb amide 5 proceeded in 88% yield with the agency of trimethylaluminum. Following protection of 5 as a tert-bu-
Diastereoselective Aldol Addition Reactions

For initial studies, the trichlorosilyl enolate 4 was prepared in bulk and purified by distillation. By following our established procedure (1 mol% \( \text{Hg(OAc)}_2 \), 2.0 equiv \( \text{SiCl}_4 \)) the metathesis of 3 to 4 proceeded readily, but the distilled product was contaminated with residual \( \text{Hg(OAc)}_2 \). This problem was circumvented by the use of \( \text{Pd(OAc)}_2 \) (5 mol%) which we have found also to be an effective catalyst for this transformation.

The rate, yield and selectivity of the aldol reactions of 3 were sufficiently interesting to examine the generality of the process with other aromatic, olefinic, acetylenic and aliphatic aldehydes possessing various substitution patterns (Figure 2). However, to further illustrate the synthetic utility of these reagents, we performed all of these additions with in-situ-generated 4. For this purpose, we returned to the use of \( \text{Hg(OAc)}_2 \) because lower loadings were needed to accomplish the metathesis compared to \( \text{Pd(OAc)}_2 \) (1 mol% vs. 5 mol%) and we wished to avoid complications arising from phosphoramide poisoning by the metal salt. To assure complete reaction with a variety of aldehydes, we chose to use 10 mol% catalyst at 0.5 M concentration as the standard condition and simply varied reaction time. The results of this study are collected in Table 2.

Table 1: Optimization of Aldol Additions of 4 with Phosphoramides 1a, 1b, 1c.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conc., M</th>
<th>loading, mol %</th>
<th>time, h</th>
<th>yield, %</th>
<th>syn/anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-1a</td>
<td>0.1</td>
<td>5</td>
<td>2</td>
<td>43c</td>
<td>14/1</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-1a</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>79</td>
<td>10/1</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-1a</td>
<td>0.5</td>
<td>10</td>
<td>1</td>
<td>73</td>
<td>10/1</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-1a</td>
<td>0.1</td>
<td>15</td>
<td>3</td>
<td>57c</td>
<td>1/9</td>
</tr>
<tr>
<td>5</td>
<td>(S,S)-1a</td>
<td>0.2</td>
<td>10</td>
<td>2</td>
<td>81</td>
<td>1/6</td>
</tr>
<tr>
<td>6</td>
<td>(S,S)-1a</td>
<td>0.2</td>
<td>15</td>
<td>2</td>
<td>72</td>
<td>1/6</td>
</tr>
<tr>
<td>7</td>
<td>(S,S)-1a</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>76</td>
<td>1/6</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>0.1</td>
<td>5</td>
<td>5</td>
<td>51c</td>
<td>5/1</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>0.1</td>
<td>15</td>
<td>12</td>
<td>31c</td>
<td>2/1</td>
</tr>
</tbody>
</table>

Optimization of the aldol addition reactions of 4 with benzaldehyde involved a survey of the reaction concentration, catalyst loading and structure. The results are collected in Table 1. The chiral phosphoramides (R,R)-1a could effectively promote the addition with as little as 5 mol% catalyst at a 0.5 M reaction concentration. The configurational assignment of the major diastereomer as syn-7 was secured by single crystal X-ray analysis of the diol obtained by deprotection with PPTS in EtOH. Interestingly, the reaction selectivity was not dependent on the loading of the catalyst (cf. entries 2-4). The enantioselective catalyst (S,S)-1a, was also effective in promoting the addition with as little as 5 mol% at 0.5 M concentration. Lower reaction concentrations can be used if the catalyst loading is increased. Although the selectivities are not as high as from (R,R)-1a, we were pleased that the catalyst was able to reverse stereoselectivity seen with (R,R)-1a and produce the anti-7 as the major product. To establish the intrinsic, internal diastereoselectivity in this catalyzed process the achiral phosphoramides 1b and 1c were tested. The methyl derivative 1b showed as similar reactivity as (R,R)-1a and produced syn-7 with modest selectivity as the major isomer.

The first entry in Table 2 shows clearly that the in-situ procedure is not only operationally simpler, but also leads to superior results. The overall yield for reaction with benzaldehyde is higher and the selectivities for both
The persistence of internal control with chirally modified catalysts is markedly improved. Similarly 1-naphthaldehyde gives high yields and good selectivities in both directions. The olefinic aldehydes (entries 3–7) all give good yields, but selectivities are quite variable and generally incomplete reaction.12 Nonetheless, the selectivities follow near the carbonyl group. Not surprisingly then, the acetylenic aldehyde is the least selective of the cases (entry 6) further supports the importance of branching.

Extension of these studies to chiral ethyl ketones as well as chiral ketones with more remote stereocenters is in progress.

Preparation of (+)-(S)-N-Methoxy-N-methyl-3-tert-butyldimethylsilyloxy-2-methylpropionamide (6)

To a solution of the hydroxy amide 5 (5.84 g, 39.7 mmol) in 120 mL of THF were added tert-butyldimethylchlorosilane (7.78 g, 51.6 mmol, 1.3 equiv), 4-dimethylamino.pyridine (485 mg, 3.97 mmol, 0.1 equiv) and triethylamine (13.8 mL, 99.3 mmol, 2.5 equiv). The reaction mixture was stirred at r.t. for 12 h. The solvent was removed under reduced pressure and the residue was triturated in 100 mL of ether. The insoluble material was removed by filtration. The filtrate was washed sequentially with 10 mL of 15% v/v aqueous acetic acid, 10 mL of water and 10 mL of sat. aq. NaHCO₃. The ether solution was dried (MgSO₄) and was concentrated to give 12.3 g of crude material. The crude product was distilled to afford the silyl amide 6 (10.0 g, 97%) as a colorless oil. Data for 6: bp: 103 °C/0.6 mmHg, 1H NMR: (500 MHz, CDCl₃) 3.82 - 3.85, 3.51 - 3.54 (ABX, 2H); 3.71 (s, 3H); 3.19 (s, 3H); 3.13 - 3.22 (m, 1H); 1.54; [D]_24 = +24.4 (CHCl₃, c = 1.0) Anal. Calc for C₁₂H₂₇NO₃Si: C 55.13%; H 10.41%; N 5.36%; Found: C 55.05%; H 10.16%; N 5.35%

Preparation of (+)-(S)-4-tert-Butyldimethylsilyloxy-3-methyl-2-butanone (2)

The amide 6 (2.70 g, 10.3 mmol) was dissolved in 30 mL of diethyl ether at 0 °C. To this solution was slowly added 3.0 M solution of MeMgBr in ether (4.48 mL, 13.4 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, then was gradually warmed up to r.t. over 11 hours. The reaction mixture was quenched by slow addition of sat. aq. NaHCO₃ (ca. 30 mL). The layers were separated and the aqueous layer was extracted twice with 50 mL of ether. The extracts were combined, dried (MgSO₄) and concentrated to give 2.48 g of crude oil. The crude product was purified by chromatography (pentane/ether, 3/1, SiO₂) followed by distillation to afford 2 (2.02, 91%) as a colorless liquid. Data for 2: bp: 55 °C/1.0 mmHg, 1H NMR: (500 MHz, CDCl₃) 3.63 - 3.74 (ABX, 2H); 2.74 (sext, J = 7.1, 1H); 2.18 (s, 3H); 1.07 (d, J = 6.8, 3H); 0.87 (s, 9H); 0.03 (d, J = 4.4, 6H); 13C NMR: (125 MHz, CDCl₃) 212.24; 65.90; 61.68; 38.23; 31.17; 26.03; 18.43; 13.95; -5.29; -5.31; IR (neat) 1666 (s); MS: (F1) 261 (M⁺, 0.57), [M]₂⁺ = +24.4 (CHCl₃, c = 1.0) Anal. Calc for C₁₁H₁₉NO₃Si (261.43), Calc. C 55.13%; H 10.41%; N 5.36%; Found: C 55.05%; H 10.16%; N 5.35%

Preparation of (+)-(S)-4-tert-Butyldimethylsilyloxy-3-methyl-2-trimethylsilyloxy-1-butene (3)

n-Butyllithium (1.54 M in hexane, 11.1 mL, 17.8 mmol, 1.4 equiv) was added dropwise to a solution of disopropylamine (1.67 mL, 11.9 mmol, 1.5 equiv) in 30 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 10 min then was cooled to -78 °C. To the reaction mixture were added TMSCl (1.51 mL, 11.9 mmol, 1.5 equiv) and the ketone 2 (1.71 g, 79.0 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was gradually warmed up to 0 °C and was quenched with 40 mL of cold H₂O. The layers were separated and the aqueous layer was extracted twice.
with tetramethylene glycol. The combined extracts were washed with 50 mL of sat. aq. Na₂SO₄, 25 mL of water and 50 mL of brine. The organic extracts were dried (Na₂SO₄) and were concentrated to give 2.32 g of crude oil. After distillation the enolate 3 was isolated as colorless oil.

**1H NMR:** (500 MHz, CDCl₃) 7.47 – 7.38 (m, 7H); 5.98 (m, J = 9.5, 1H); 5.44 (d, J = 15.5, 6.6, 1H); 4.52 (m, J = 9.0, 2.8, 1H); 3.68 – 3.78 (ABX, 2H); 3.30 (m, 1H); 1.16 (d, J = 6.6, 3H); 0.87 (s, 3H); 0.05 (d, J = 2.9, 6H); 2.89 – 2.91 (m, 3H); 1.67 (dd, J = 15.0, 6.6, 1.0, 1H); 7.21 (t, J = 7.2, 1H); 6.58 (s, 1H); 4.62 (dt, J = 9.5, 2.6, 1H); 3.67 – 3.77 (ABX, 2H); 3.27 (d, J = 3.0, 1H); 2.77 – 2.89 (m, 3H); 1.88 (s, 3H); 1.06 (d, J = 7.1, 3H); 0.88 (s, 9H); 0.06 (d, J = 2.9, 6H); SFC (7.5% MeOH): tᵢₚ (2S, 5R)-syn-7d 2.76 min (91%); (2R, 5S)-anti-7d 3.03 min (9%).

**(2S,5S)-1-tert-Butyldimethylsilyl-2-methyl-5-hydroxy-5-(1-naphthyl)-3-pentanone (7b)**

**1H NMR:** (500 MHz, CDCl₃) 7.73 (s, J = 8.6, 1H); 7.73 (d, J = 5.6, 1H); 7.30 (t, J = 7.7, 2H); 7.23 (t, J = 7.2, 1H); 6.65 (d, J = 16.2, 1H); 6.21 (dd, J = 16.0, 6.0, 1H); 4.77 (m, 1H); 3.66 – 3.77 (ABX, 2H); 3.31 (d, J = 3.4, 1H); 2.75 – 2.90 (ABX, 2H); 2.82 (m, 1H); 1.06 (d, J = 7.1, 3H); 0.88 (s, 9H); 0.05 (d, J = 3.9, 6H); SFC (12.5% MeOH): tᵢₚ (2S, 5S)-anti-7b 3.15 min (89%); (2S, 5R)-syn-7b 4.11 min (11%), Anal. Calc for C₁₂H₁₂O₂Si (372.57), Calc. C 70.92%; H 8.66%, Found: C 70.74%; H 8.60%

**General Procedure for the Aldol Reaction of 3:**

**1H NMR:** (500 MHz, CDCl₃) 7.37 (d, J = 8.6, 1.0, 1H); 7.37 (d, J = 7.7, 1.0, 1H); 7.31 (t, J = 7.7, 2.2H); 7.23 (t, J = 7.2, 1.1H); 6.67 (d, J = 16.1, 1.4, 1.0H); 6.22 (dd, J = 15.9, 6.0, 1.0H); 4.75 (m, 1H); 3.67 – 3.78 (ABX, 2H); 3.34 (d, J = 3.4, 1.0H); 2.77 – 2.92 (ABX, 2H); 2.84 (m, 1.0H); 1.07 (d, J = 7.1, 3.0H); 0.88 (s, 9.0H); 0.05 (d, J = 5.7, 6.0H); SFC (7.5% MeOH): tᵢₚ (2S, 5R)-syn-7c 2.74 min (89%); (2S, 5S)-anti-7c 3.26 min (11%), Anal. Calc for C₁₂H₁₂O₂Si (348.55), Calc. C 68.92%; H 9.38%, Found: C 68.59%; H 9.02%

**Preparation of (S)-4-tert-Butyldimethylsilyl-3-methyl-2-tributylstannyl-1-butene (4):**

**1H NMR:** (500 MHz, CDCl₃) 7.37 (d, J = 8.6, 1H); 7.37 (d, J = 7.7, 1H); 7.31 (t, J = 7.7, 2H); 7.23 (t, J = 7.2, 1H); 6.65 (d, J = 16.2, 1H); 6.21 (dd, J = 16.0, 6.0, 1H); 4.77 (m, 1H); 3.66 – 3.77 (ABX, 2H); 3.31 (d, J = 3.4, 1H); 2.75 – 2.90 (ABX, 2H); 2.82 (m, 1H); 1.06 (d, J = 7.1, 3H); 0.88 (s, 9H); 0.05 (d, J = 5.7, 6.0H); SFC (7.5% MeOH): tᵢₚ (2S, 5R)-syn-7d 2.76 min (91%); (2S, 5S)-anti-7d 3.03 min (9%), Anal. Calc for C₁₂H₁₂O₂Si (348.55), Calc. C 68.92%; H 9.38%, Found: C 68.56%; H 9.14%

**Diastereoselective Aldol Addition Reactions: (2S,5R)-1-tert-Butyldimethylsilyl-2-methyl-5-hydroxy-5-phenyl-6-hepten-3-one (syn-7c)**

**1H NMR:** (500 MHz, CDCl₃) 7.37 (d, J = 8.6, 1H); 7.37 (d, J = 7.7, 1H); 7.31 (t, J = 7.7, 2H); 7.23 (t, J = 7.2, 1H); 6.67 (d, J = 16.1, 1.4, 1.0H); 6.22 (dd, J = 15.9, 6.0, 1.0H); 4.75 (m, 1H); 3.67 – 3.78 (ABX, 2H); 3.34 (d, J = 3.4, 1.0H); 2.77 – 2.92 (ABX, 2H); 2.84 (m, 1.0H); 1.07 (d, J = 7.1, 3.0H); 0.88 (s, 9.0H); 0.05 (d, J = 5.7, 6.0H); SFC (7.5% MeOH): tᵢₚ (2S, 5R)-syn-7e 2.55 min (93%); (2S, 5S)-anti-7e 2.96 min (81%), Anal. Calc for C₁₂H₁₂O₂Si (348.55), Calc. C 68.92%; H 9.38%, Found: C 68.56%; H 9.14%

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benzoyloxy-7g (2S,5R)-syn-5-benzoxyl-7e 4.47 min (26%); (2S,5S)-anti-5-benzoxyl-7e 5.14 min (74%). Anal. Calc. for C_{15}H_{20}O_{3}Si (286.48). Calc. C 62.89%; H 10.55%. Found: C 62.70%; H 10.57%.

(2S,SR)-1-tert-Butyldimethylsilyloxy-2,6-dimethyl-5-hydroxy-6-heptan-3-one (syn-7f)

1^H NMR: (500 MHz, CDCl_3) 7.17 - 7.30 (m, 5H); 4.07 (m, 1H); 3.62 - 3.73 (ABX, 2H); 3.24 (d, J = 3.5, 0.8, 1H); 2.56 - 2.85 (m, 5H); 1.65 - 1.86 (2m, 2H); 1.02 (d, J = 7.0, 3H); 0.86 (s, 9H); 0.03 (d, J = 9.0, 6H); SFC (5% MeOH): t_f (2S,5R,syn-7i) 3.45 min (91%); (2S,5S)-anti-7i 3.87 min (9%). Anal. Calc. for C_{15}H_{20}O_{3}Si (350.57). Calc. C 68.52%; H 9.78%. Found: C 68.59%; H 9.91%.

(2S,SS)-1-tert-Butyldimethylsilyloxy-2-methyl-5-hydroxy-7-phenyl-3-heptanone (anti-7i)

1H NMR: (500 MHz, CDCl_3) 7.17 - 7.30 (m, 5H); 4.03 (m, 1H); 3.62 - 3.75 (ABX, 2H); 3.28 (d, J = 3.2, 0.7, 1H); 2.56 - 2.85 (m, 5H); 1.66 - 1.87 (2m, 2H); 1.03 (d, J = 7.0, 3H); 0.87 (s, 9H); 0.04 (d, J = 3.2, 6H); SFC (5% MeOH): t_f (2S,5R)-anti-7i 3.51 min (29%); (2S,5S)-anti-7i 3.88 min (71%). Anal. Calc. for C_{16}H_{21}O_{3}Si (357). Calc. C 68.52%; H 9.78%. Found: C 68.64%; H 9.78%.

(2S,SR)-1-tert-Butyldimethylsilyloxy-2-methyl-5-hydroxy-7-cyclohexyl-3-pentanone (syn-7j)

1H NMR: (500 MHz, CDCl_3) 3.83 (m, 1H); 3.64 - 3.76 (ABX, 2H); 3.12 (d, J = 3.4, 1H); 2.82 (m, 1H); 2.54 - 2.77 (ABX, 2H); 1.66 - 1.89 (5H); 1.00 - 1.38 (6H); 1.03 (d, J = 7.1, 3H); 0.88 (s, 9H); 0.05 (d, J = 5.6, 6H); SFC (5-benzoyloxy-7j 2% MeOH): t_f (2S,5R)-anti-5-benzoyloxy-7j 4.59 min (94%); (2S,5S)-anti-5-benzoyloxy-7j 5.52 min (6%). Anal. Calc. for C_{16}H_{21}O_{3}Si (328.56). Calc. C 68.50%; H 11.04%. Found: C 65.92%; H 11.26%.

(2S,SS)-1-tert-Butyldimethylsilyloxy-2-methyl-5-hydroxy-7-cyclohexyl-3-pentanone (anti-7j)

1H NMR: (500 MHz, CDCl_3) 3.81 (m, 1H); 3.64 - 3.78 (ABX, 2H); 3.15 (d, J = 3.5, 1.5, 2H); 2.81 (m, 1H); 2.54 - 2.73 (ABX, 2H); 1.66 - 1.89 (5H); 0.97 - 1.42 (6H); 1.05 (d, J = 7.0, 3H); 0.89 (s, 9H); 0.06 (d, J = 2.7, 6H); SFC (5-benzoyloxy-7j 2% MeOH): t_f (2S,5S)-anti-5-benzoyloxy-7j 4.41 min (20%); (2S,5S)-anti-5-benzoyloxy-7j 5.17 min (80%). Anal. Calc. for C_{16}H_{21}O_{3}Si (328.56). Calc. C 65.80%; H 11.04%. Found: C 65.80%; H 11.19%.

(2S,SR)-1-tert-Butyldimethylsilyloxy-2,6,6-trimethyl-5-hydroxy-3-heptanone (syn-7k)

1H NMR: (500 MHz, benzene-d_6) 3.84 (d, J = 10.5, 2.2, 1H); 3.41 - 3.64 (ABX, 2H); 3.17 (d, J = 2.9, 1H); 2.37 - 2.59 (ABX, 2H); 2.48 (m, 1H); 0.95 (s, 9H); 0.91 (s, 9H); 0.82 (d, J = 6.8, 3H); -0.01 (d, J = 1.9, 6H). Anal. Calc. for C_{15}H_{22}O_3Si (302.52). Calc. C 63.52%; H 11.33%. Found: C 63.41%; H 11.44%.

(2S,SS)-1-tert-Butyldimethylsilyloxy-2,6,6-trimethyl-5-hydroxy-3-heptanone (anti-7k)

1H NMR: (500 MHz, benzene-d_6) 3.77 (d, J = 9.2, 3.2, 1H); 3.44 - 3.64 (ABX, 2H); 3.24 (d, J = 3.0, 1H); 2.37 - 2.59 (3m, 9H); 0.94 (s, 9H); 0.93 (s, 9H); 0.85 (d, J = 6.8, 3H); 0.01 (s, 6H). Anal. Calc. for C_{15}H_{22}O_3Si (302.52). Calc. C 63.52%; H 11.33%. Found: C 63.27%; H 11.43%.

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References and Notes


(3) For a general discussion of the aldol transition structures see:

(9) Denmark, S. E.; Pham, S. M. Unpublished results.
(10) For a definition of these terms see: Denmark, S. E.; Almstead, N. G. In Modern Carbonyl Chemistry; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapt. 10.
(11) Assignment of the major diastereomer in all cases is based on analogy to benzaldehyde.
(12) We believe that the slow rate seen for aliphatic aldehydes in general in these reactions does not arise from enolization, but rather from formation of chlorohydrin-type adducts. T. Wynn, S. K. Ghosh, unpublished results from these laboratories.
(13) All chiral stationary phase analytical chromatographic determinations were performed on a Berger Instruments Supercritical Fluid Chromatograph (SFC) operating at 150 bar and 3.0 mL/min fitted with a Chiralpak OD column.

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