A Novel and Highly Efficient Asymmetric Synthesis of Epoxides via Chiral Telluronium Ylides

Wen-Hua Ou, Zhi-Zhen Huang*
School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. China
Fax +86(25)83686240; E-mail: huangzhizhen0226@163.com
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Abstract: The one-pot reaction of telluronium salt 8, aldehyde, and potassium tert-butoxide proceeded smoothly via chiral benzyl telluronium ylide, producing trans-(2S,3S)-diaryl epoxides with good yields as well as excellent diastereoselectivities and enantioselectivities (up to 99% ee).

Key words: telluronium ylide, asymmetric synthesis, chiral epoxide, enantioselectivity, one-pot reaction

Owing to their significant biological activities and versatile chemical transformations, chiral epoxides have become one of the most important synthetic intermediates. The development of new and efficient syntheses of chiral epoxides is still a challenging subject. Among various syntheses of chiral epoxides, the chiral ylide route is one of the most important methods due to the formation of a carbon–carbon bond and epoxidation in the one reaction. Recently, novel and efficient methods for asymmetric synthesis of epoxides via C2 symmetric sulfonium ylide and selenonium ylide have been developed (Figure 1). However, the formation of chiral epoxides via selenonium ylide results in a mixture of diastereomers (1:1 to 1:2). The enantioselectivities of the sulfonium ylide and selenonium ylide reactions are high and the ee ranges from 64–94%, however, further improvements to the stereoselectivity are still required. Although there are many reports concerned with the application of telluronium ylides in the synthesis of epoxides, to our knowledge, there is no report on their application to the asymmetric synthesis of epoxides. Furthermore, considering that telluronium ylides are more reactive than their corresponding sulfonium ylides, better diastereoselectivity is achieved with the telluronium ylide, which is more sterically hindered than the corresponding sulfonium and selenonium ylide. Therefore, we prepared new telluronium ylides and tried to develop a more efficient method for the asymmetric synthesis of chiral epoxides.

We found that allyl telluronium salt could be prepared in good yield by the reaction of allyl bromide with telluride which was prepared from (2S,5S)-hexanediol. Subsequently, telluronium salt was reacted with aldehydes in the presence of a base under a range of reaction conditions. It was found that the reaction via allyl telluronium ylide could proceed in one-pot to give the desired 2-phenyl-3-vinyl epoxide predominantly as the trans-product. However, under the range of reaction conditions tested (Table 1), yields, stereoselectivities, and enantioselectivities were poor at room temperature. When the reaction was carried out at a lower temperature even poorer yields resulted (10–30%).

Scheme 1 Formation of telluronium salt and the formation of chiral epoxide via allyl telluronium ylide.

Compared with allyl telluronium ylide, benzyl telluronium ylide is more sterically hindered, this may lead to increased stereoselectivity. It was found that the reaction of telluride with benzyl bromide proceeded smoothly giving telluronium salt in good yield (Scheme 2). Next, salt was reacted with 2-chlorobenzaldehyde in the presence of potassium hydroxide in acetonitrile at room temperature. We were pleased to find that the one-pot reaction via benzyl telluronium ylide took place smoothly to give epoxide in 75% yield, almost exclusively as the trans isomer, and with high enantioselectivity (84% ee). Encouraged by this result, the synthesis of a chiral epoxides

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Formation of Chiral Epoxides via Allyl Telluronium Ylide

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Method*</th>
<th>Reaction time (h)</th>
<th>Yieldb (%)</th>
<th>trans/cis</th>
<th>trans ee (S,S)d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC6H4CHO</td>
<td>A</td>
<td>24</td>
<td>61</td>
<td>72:28</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>B</td>
<td>36</td>
<td>51</td>
<td>80:20</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>C</td>
<td>36</td>
<td>36</td>
<td>75:25</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>D</td>
<td>36</td>
<td>55</td>
<td>65:35</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>C6H5CHO</td>
<td>A</td>
<td>36</td>
<td>45</td>
<td>75:25</td>
<td>32</td>
</tr>
</tbody>
</table>

*Method A: KOH, CH3CN; Method B: t-BuOK, THF; Method C: NaH, THF; Method D: KOH, THF, and trace water. All reactions were carried out at r.t.

b All products are known compounds and were confirmed by 1H NMR, IR, and mass spectroscopy.

c Determined by 1H NMR spectroscopy or GC.

d Determined by chiral HPLC on a Chiralcel OB-H column.

via ylide 9 was carried out in a range of solvents – Et2O, CH3CN, CH2Cl2, and THF. These results are different from telluronium ylide 6; the modified conditions resulted in excellent diastereoselectivities (trans/cis, 98:2 to 100:0) in all solvents, however THF gave optimal yield (81%) and enantioselectivity (90% ee). In an attempt to optimize the reaction conditions further, a range of bases (NaOH, KOH, NaH, and t-BuOK) were applied to the one-pot reaction of salt 8 with 2-chloroazaldehyde in THF at room temperature. The experiment showed all the bases furnished chiral epoxides via ylide 9 as the desired trans-diarylepoxydes 10b in good yields (53–88%) with excellent diastereoselectivity (trans/cis, 98:2–100:0). Potassium tert-butoxide and salt 8, in a ratio of 1:3, gave the best results producing trans-diarylepoxydes in good yield (88%) with excellent enantioselectivity (91% ee).

Following this optimization, a variety of aromatic aldehydes were reacted with telluronium salt 8 at –5 °C or –40 °C in the presence of potassium tert-butoxide in THF. Our experimental results showed that the yields of trans-diarylepoxydes 10 are good and the diastereoselectivities are excellent (Table 2). In many cases, only the trans-isomer was obtained and no cis-isomer was observed. Therefore the diastereoselectivity of our protocol via telluronium ylide 9 for the synthesis of chiral epoxides is much better than that via selenonium ylide 2. Moreover, quite different from allyl telluronium ylide 6, the enantioselectivities of the chiral epoxides via benzyl telluronium ylide 9 are excellent and up to 99% ee could be achieved. Noticeably the enantioselectivities achieved via telluronium ylide 9 are also better than that via the sulfonium ylide 1 and selenonium ylide 2. As expected, the reaction via telluronium ylide 9 proceeded faster than that via sulfonium ylide 1 and took only 12–24 hours. The absolute configurations of 10a–h were assigned by comparison of the sign of optical rotation with that of the known compound and all 2S,3S isomers of 10a–h are levorotatory in ethanol.

In conclusion, optically pure telluronium salts 5 and 8 were synthesized in good yields; these are the precursors of two new chiral telluronium ylides. We found that the one-pot reaction via telluronium ylide 6 proceeded readily to give the desired vinyl epoxides 7. However, yields, stereoselectivities, and enantioselectivities for the synthesis of chiral epoxides were not satisfactory. Furthermore we found that the one-pot reaction via more hindered telluronium ylide 9 proceeded faster than the telluronium ylide 6 and took only 12–24 hours. The absolute configurations of 10a–h were assigned by comparison of the sign of optical rotation with that of the known compound and all 2S,3S isomers of 10a–h are levorotatory in ethanol.

Table 2

<table>
<thead>
<tr>
<th>Salt</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
<th>trans/cis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10g</td>
<td>88</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>53</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>ArCHO</td>
<td>36</td>
<td>75:25</td>
</tr>
<tr>
<td>8</td>
<td>PhCHO</td>
<td>12</td>
<td>65:35</td>
</tr>
</tbody>
</table>

Scheme 2

Formation of telluronium salt 8 and the synthesis of chiral epoxide via benzyl telluronium ylide 9.
Asymmetric Synthesis of Epoxides via Chiral Telluronium Ylides

Telluronium Salts 5 and 8; General Procedure

A mixture of telluride 4 (1.23 g, 5.78 mmol) and allyl bromide (0.64 g, 5.96 mmol) or benzyl bromide (1.02 g, 5.96 mmol) was stirred in Et2O at r.t. for 12 h. The mixture was filtered and the residue was washed with Et2O to give telluronium salt 5 or 8. Salt 5 or 8 could be recrystallized from CH2Cl2–Et2O.

Allyl Telluronium Salt 5

Yield: 81% (1.49 g); colorless prisms; mp 114–115.5 °C; [\(\alpha\)]D\textsubscript{20} +109.7 (c 0.62, CHCl3). IR (KBr): 3085, 2795, 1635, 891 cm\(^{-1}\). 1H NMR: \(\delta = 6.06–6.03\) (m, 1 H), 5.39 (m, 1 H), 5.28 (m, 1 H), 4.30 (m, 1 H), 3.80 (m, 1 H), 3.51–3.41 (m, 2 H), 2.80 (m, 1 H), 2.41–2.37 (m, 2 H), 1.89–1.74 (m, 7 H). MS (EIS, positive): \(m/z = 255\) (M – Br).

Anal. Calcd for C\(9\)H\(17\)TeBr: C, 32.49; H, 5.15. Found: C, 32.78; H, 5.09.

Benzyl Telluronium Salt 8

Yield: 84%; colorless prisms; mp 135–137 °C; [\(\alpha\)]D\textsubscript{0} +218.6 (c 0.61, CHCl3).

IR (KBr): 3085, 2795, 1595, 1489, 1448, 1230, 761 cm\(^{-1}\). 1H NMR: \(\delta = 7.50–7.25\) (m, 5 H), 4.52 (d, \(J = 12\) Hz, 1 H), 3.85 (d, \(J = 12\) Hz, 1 H), 4.38 (m, 1 H), 3.35–3.29 (m, 1 H), 2.94–2.88 (m, 1 H), 2.44–2.37 (m, 2 H), 1.85–1.64 (m, 7 H).

trans-(2S,3S)-2-Aryl-3-vinyl Epoxides (7); General Procedure

To a solution of telluronium salt 5 (1.0 mmol) and aldehyde (1.0 mmol) in THF (10 mL) was added t-BuOK (0.33 g, 3.0 mmol) at r.t. The reaction mixture was stirred for the time indicated in Table 2 at r.t. Then the mixture was filtered and solvent was removed by evaporation. The residue was separated by preparative TLC to give the 2-aryl-3-vinyl epoxide 7.

trans-(2S,3S)-2-(4-Methylphenyl)-3-vinyloxirane (7a)

Pale yellow oil. IR (KBr): 1488, 1372, 1251, 1075, 923, 876, 823, 726 cm\(^{-1}\). 1H NMR: \(\delta = 7.27–7.17\) (m, 4 H), 5.75–5.28 (m, 3 H), 3.76 (d, \(J = 2.0\) Hz, 1 H), 3.40–3.37 (dd, \(J = 2.0\) Hz, 1 H, trans), 2.37 (s, 3 H).

trans-(2S,3S)-2-Phenyl-3-vinyloxirane (7b)

Pale yellow oil. IR (KBr): 1495, 1446, 1251, 1183, 1061, 985, 921, 871, 790 cm\(^{-1}\). 1H NMR: \(\delta = 7.38–7.28\) (m, 5 H), 5.60–5.28 (m, 3 H), 3.79 (d, \(J = 1.9\) Hz, 1 H), 3.40–3.37 (dd, \(J = 1.9\) Hz, 1 H), 2.37 (s, 3 H).

trans-(2S,3S)-2-Diaryl Epoxides 10; General Procedure

To the solution of telluronium salt 8 (1.0 mmol) and aldehyde (1.0 mmol) in THF (10 mL) was added t-BuOK (0.33 g, 3.0 mmol) at –5 °C or –40 °C (Table 2). The reaction mixture was stirred for the time indicated in Table 2 at this temperature. Then the mixture was filtered and solvent was removed by evaporation. The residue was separated by preparative TLC to give the 2-diaryl-3-vinyl epoxide 10.
separated by preparative TLC to give the trans-(2S,3R)-diaryl epoxides 10.

trans-(2S,3R)-2,3-Diphenylloxirane (10a)
Colorless prisms; mp 68–69 °C (Lit.10a 69 °C)
IR: 3060, 2987, 1452, 1071, 851, 748, 695, 611 cm–1.
1H NMR: δ = 7.43–7.28 (m, 10 H), 3.90 (s, 2 H).

trans-(2S,3S)-2-(2-Chlorophenyl)-3-phenyloxirane (10b)
Colorless oil.10b
IR (KBr): 3065, 2986, 1478, 1275, 1128, 750, 700, 612 cm–1.
1H NMR: δ = 7.42–7.28 (m, 9 H), 4.25 (d, J = 1.9 Hz, 1 H), 3.79 (d, J = 1.9 Hz, 1 H).

trans-(2S,3S)-2-(4-Chlorophenyl)-3-phenyloxirane (10c)
Colorless prisms; mp 99–100 °C (Lit.10a 100 °C)
IR (KBr): 3052, 1492, 1460, 1091, 819, 751, 700 cm–1.
1H NMR: δ = 7.39–7.15 (m, 9 H), 3.86 (d, J = 1.9 Hz, 1 H), 3.84 (d, J = 1.9 Hz, 1 H).

trans-(2S,3S)-2-(2,4-Dichlorophenyl)-3-phenyloxirane (10d)
Colorless prisms; mp 89–92 °C.
IR (KBr): 3084, 3065, 3023, 1588, 1462, 1459, 1096, 821, 733, 692 cm–1.
1H NMR: δ = 7.29–7.45 (m, 8 H), 4.19 (d, J = 1.9 Hz, 1 H), 3.75 (d, J = 1.9 Hz, 1 H).

trans-(2S,3S)-2-(3-Fluorophenyl)-3-phenyloxirane (10e)
Colorless oil.10b
IR (KBr): 3065, 3036, 2988, 1613, 1591, 1490, 1452, 1271, 1256, 861, 782, 768, 692 cm–1.
1H NMR: δ = 7.42–7.05 (m, 9 H), 3.88 (d, J = 1.7 Hz, 1 H), 3.85 (d, J = 1.7 Hz, 1 H).

trans-(2S,3S)-2-(4-Fluorophenyl)-3-phenyloxirane (10f)
White solid; mp 76–78 °C (Lit.10b 76–77 °C).
IR (KBr): 3044, 2990, 1512, 1230, 1087, 831, 778, 697 cm–1.
1H NMR: δ = 7.41–7.09 (m, 9 H), 3.87 (d, J = 1.8 Hz, 1 H), 3.85 (d, J = 1.8 Hz, 1 H).

trans-(2S,3S)-2-Phenyl-3-p-tolyloxirane (10g)
White solid; mp 60–61 °C (Lit.10b 62 °C).
IR (KBr): 3052, 2916, 1406, 1111, 816, 738, 509 cm–1.
1H NMR: δ = 7.40–7.19 (m, 9 H), 3.87 (d, J = 1.8 Hz, 1 H), 3.85 (d, J = 1.8 Hz, 1 H), 2.38 (s, 3 H).

trans-(2S,3S)-2-(4-Methoxyphenyl)-3-phenyloxirane (10h)
White solid; mp 76–78 °C (Lit.10d 76–78 °C).
IR (KBr): 3043, 2967, 1614, 1517, 1254, 825 cm–1.
1H NMR: δ = 7.40–6.91 (m, 9 H), 3.87 (d, J = 1.9 Hz, 1 H), 3.84 (s, 3 H), 3.83 (d, J = 1.9 Hz, 1 H).

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