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

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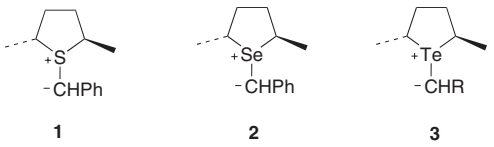
Abstract: The one-pot reaction of telluronium salt **8**, aldehyde, and potassium *tert*-butoxide proceeded smoothly via chiral benzyl telluronium ylide, producing *trans*-(2*S*,3*S*)-diaryl epoxides with good yields as well as excellent diastereoselectivities and enantioselectivities (up to 99% ee).

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



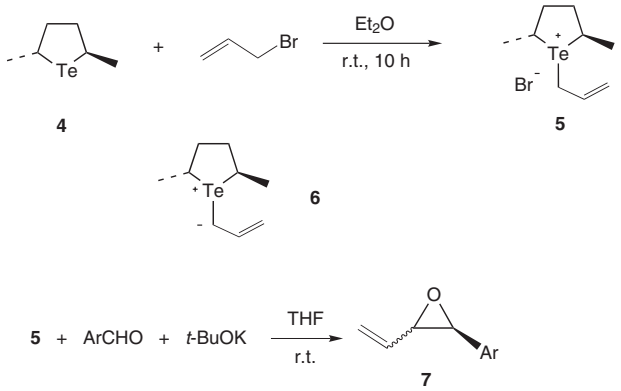
1 2 3

R = vinyl, phenyl

Figure 1 Sulfonium **1**, selenonium **2**, and telluronium ylides **3**.

Owing to their significant biological activities[1] and versatile chemical transformations,[2] chiral epoxides have become one of the most important synthetic intermediates.[3] 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.[4] Recently, novel and efficient methods for asymmetric synthesis of epoxides via C_2 symmetric sulfonium ylide **1**[5] and selenonium ylide **2**[6] have been developed (Figure 1). However, the formation of chiral epoxides via sulfonium ylide **1** takes two to six days while that via selenonium ylide **2** results in a mixture of distereomers (1:1 to 1:2). The enantioselectivities of the sulfonium ylide **1** and selenonium ylide **2** 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,[7] 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 **3** and tried to develop a more efficient method for the asymmetric synthesis of chiral epoxides.

We found that allyl telluronium salt **5** could be prepared in good yield by the reaction of allyl bromide with telluride **4** which was prepared from (2*S*,5*S*)-hexanediol[5,8] (Scheme 1). Subsequently, telluronium salt **5** 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 **6** could proceed in one-pot to give the desired 2-phenyl-3-vinyl epoxides **7** 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%).



4 5 6 7

7a: Ar = 4-$CH_3C_6H_4$
7b: Ar = C_6H_5

Scheme 1 Formation of telluronium salt **5** and the formation of chiral epoxides via allyl telluronium ylide **6**.

Compared with allyl telluronium ylide **6**, benzyl telluronium ylide **9** is more sterically hindered, this may lead to increased stereoselectivity. It was found that the reaction of telluride **4** with benzyl bromide proceeded smoothly giving telluronium salt **8** in good yield (Scheme 2). Next, salt **8** 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 **9** took place smoothly to give epoxide **10b** in 75% yield, almost exclusively as the *trans* isomer, and with high enantioselectivitiy (84% ee). Encouraged by this result, the synthesis of a chiral epoxides

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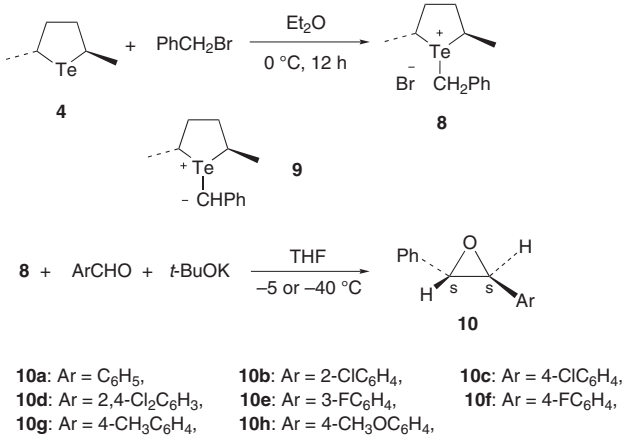
Table 1 Formation of Chiral Epoxides via Allyl Telluronium Ylide **6**

Entry	Aldehyde	Method[a]	Reaction time (h)	Yield[b] (%)	*trans*/*cis*[c]	*trans* ee (*S*,*S*)[d] (%)
1	4-MeC_6H_4CHO	A	24	61	72:28	50
2	–	B	36	51	80:20	46
3	–	C	36	36	75:25	53
4	–	D	36	55	65:35	44
5	C_6H_4CHO	A	36	45	75:25	32

[a] Method A: KOH, CH_3CN; 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[9] 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 – Et_2O, CH_3CN, CH_2Cl_2, 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-chlorobezaldehyde in THF at room temperature. The experiment showed all the bases furnished chiral epoxides via ylide **9** as the desired *trans*-diaryl epoxides **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*-diaryl epoxides in good yield (88%) with excellent enantioselectivity (91% ee).



Scheme 2 Formation of telluronium salt **8** and the synthesis of chiral epoxide via benzyl telluronium ylide **9**.

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*-diaryl epoxides **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 2*S*,3*S* isomers of **10a–h** are levorotatory in ethanol.[5,9]

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 smoothly to give the *trans*-(2*S*,3*S*)-diaryl epoxides **10a–h** in good yields, with excellent diastereoselectivities and enantioselectivities (ee up to 99%). This protocol via telluronium ylide **9** is better than that via sulfonium ylide **1** or selenonium ylide **2** in terms of both enantioselectivity and diastereoselectivity. The facile preparation of chiral telluronium ylide **9**, good yields, excellent diastereoselectivities, and enantioselectivities of the reaction make this protocol a novel and highly efficient synthetic method for the synthesis of chiral epoxides which may have practical application in organic synthesis and industry.

All reactions were carried out under a nitrogen atmosphere. ^1H NMR spectra were determined in $CDCl_3$ on a Brucker ARX-300 (300 MHz) with TMS as the internal standard. MS were obtained on a VG-ZAB-HS mass spectrometer. IR spectra were taken with a 5DX-FT-2 spectrometer. Melting points were uncorrected. Elemen-

Table 2 Asymmetric Synthesis of *trans*-Diaryl Epoxides via Telluronium Ylide **9**

Entry	Aldehyde	Product[a]	Time (h)	Yield (%)[d]	*trans*/*cis*[e]	ee (*S*,*S*)[f] (%)
1	C_6H_5CHO	**10a**	12[b]	72	98:2	99
2	2-ClC_6H_4CHO	**10b**	12[b]	90	100:0	94
3	–	**10b**	24[c]	78	99:1	95
4	4-ClC_6H_4CHO	**10c**	12[b]	92	92:8	96
5	2,4-$Cl_2C_6H_3CHO$	**10d**	12[b]	85	99:1	86
6	–	**10d**	24[c]	82	100:0	93
7	3-FC_6H_4CHO	**10e**	12[b]	80	98:2	93
8	–	**10e**	24[c]	75	100:0	95
9	4-FC_6H_4CHO	**10f**	12	77	99:1	94
10	–	**10f**	24[c]	81	100:0	97
11	4-MeC_6H_4CHO	**10g**	12[b]	87	95:5	91
12	4-$MeOC_6H_4CHO$	**10h**	12[b]	64[g]	99:1	91

[a] All products are known compounds[10] and were confirmed by ^{1}H NMR, IR, and mass spectroscopy .
[b] –5 °C.
[c] –40 °C.
[d] Isolated yields.
[e] Determined by ^{1}H NMR spectroscopy or GC.
[f] Determined by chiral HPLC on a Chiralcel OD-H column.
[g] Product unstable on silica gel.[5d]

tal analyses were determined on Perkin-Elmer 240C. Enantiomeric excesses were determined by HPLC analysis under the following conditions: Daicel Chiralcel OB-H column, hexane–*i*-PrOH, 95:5, 0.5 mL/min, l = 254 nm or Daicel Chiralcel OD-H column, hexane–*i*-PrOH, 95:5 to 99:1, 0.5 mL/min, λ = 254 or 234 nm.

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 Et_2O at r.t. for 12 h. The mixture was filtered and the residue was washed with Et_2O to give telluronium salt **5** or **8**. Salt **5** or **8** could be recrystallized from CH_2Cl_2–Et_2O.

Allyl Telluronium Salt 5
Yield: 81% (1.49g); colorless prisms; mp 114–115.5 °C; $[\alpha]_D^{20}$ +109.7 (*c* 0.62, $CHCl_3$).

IR (KBr): 3085, 2795, 1635, 891 cm^{-1}.

^{1}H NMR: δ = 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, 7H).

MS (EIS, positive): *m*/*z* = 255 (M – Br).

Anal. Calcd for $C_9H_{17}TeBr$: 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; $[\alpha]_D^{20}$ +218.6 (*c* 0.61, $CHCl_3$).

IR (KBr): 2915, 2862, 2846, 1595, 1489, 1448, 1230, 761 cm^{-1}.

^{1}H NMR: δ = 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).

MS (EIS, positive): *m*/*z* = 305 (M – Br).

Anal. Calcd for $C_{13}H_{19}TeBr$: C, 40.79; H, 5.00. Found: C, 40.98; H, 4.89.

***trans*-(2*S*,3*S*)-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*-(2*S*,3*S*)-2-(4-Methylphenyl)-3-vinyloxirane (7a)**
Pale yellow oil.[9]

IR (KBr): 1488, 1372, 1251, 1075, 923, 876, 823, 726 cm^{-1}.

^{1}H NMR: δ = 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*-(2*S*,3*S*)-2-Phenyl-3-vinyloxirane (7b)**
Pale yellow oil.[9]

IR (KBr): 1495, 1446, 1251, 1183, 1061, 985, 921, 871, 790 cm^{-1}.

^{1}H NMR: δ = 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*-(2*S*,3*S*)-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 *trans*-(2*S*,3*S*)-diaryl epoxides **10**.

***trans*-(2*S*,3*S*)-2,3-Diphenyloxirane (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*-(2*S*,3*S*)-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*-(2*S*,3*S*)-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*-(2*S*,3*S*)-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).

MS (EI): *m*/*z* (%) = 248 (68.36) [M^+], 264 (49), 248 (52), 235 (74), 212 (24), 194 (48), 178 (100), 165 (68), 123 (86), 105 (28), 89 (90).

Anal. Calcd for $C_{14}H_{10}Cl_2O$: C, 63.42; H, 3.80. Found: C, 64.03; H, 3.86.

***trans*-(2*S*,3*S*)-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*-(2*S*,3*S*)-2-(4-Fluorophenyl)-3-phenyloxirane (10f)**
White solid; mp 76–78 °C (Lit.[10c] 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*-(2*S*,3*S*)-2-Phenyl-3-*p*-tolyloxirane (10g)**
White solid; mp 60–61 °C (Lit.[10a] 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*-(2*S*,3*S*)-2-(4-Methoxyphenyl)-3-phenyloxirane (10h)**
White solid; mp 76–78 °C (Lit.[5d] 76–78 °C).

IR (KBr): 3043, 2967, 1614, 1517, 1254, 1032, 826 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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