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Asymmetric synthesis of *trans*-disubstituted aryl-vinyl epoxides: a *p*-methoxy effect

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Abstract

It was found that *trans*-aryl-vinyl epoxides could be synthesized with 77–100% conversion from conjugated aldehydes (which could also behave as Michael acceptors and lead to cyclopropanes) and chiral sulfonium salts with ee's ranging from 95 to 100%. When a *p*-methoxy group was present on the arylsulfonium salt, the epoxide was the sole product whatever the solvent.

Keywords: asymmetric reactions; epoxides; sulfonium salts; phosphazenes.

Disubstituted aryl-vinyl epoxides are important synthetic intermediates and attractive precursors of functionalized four-carbon sequences. As an application of our asymmetric synthesis of diaryl epoxides, which have been shown to give almost total enantioselectivities,[1] we present here the enantioselective synthesis of aryl-vinyl epoxides **1a,b** to **3a,b** (Scheme 1).

Although the aldehydes **7–9** are Michael acceptors and could, in principle, provide cyclopropanes as already observed,[2] asymmetric synthesis of the epoxides **1–3** has been successfully carried out from ylides **6a** and **6b** following our method (Scheme 1). The results are gathered in Table 1.

The sulfonium salt **5a** was prepared from (*R*,*R*,*R*)-(+)-oxathiane **4** using Vedejs' triflate method[3] (68% isolated yield) and the sulfonium salt **5b** was synthesized from *p*-methoxybenzyliodide and (*R*,*R*,*R*)-(+)-oxathiane **4** in the presence of AgOTf (1 equiv.) in CH_2Cl_2[4] (57% isolated yield). In both cases, only one diastereomer was formed, as seen from 400 MHz ^{1}H NMR spectra of the crude products of the reactions, and the (*R*,*R*,*R*,S_S)-configuration was assigned to the single diastereomer of **5b**[5] from ^{1}H NMR experiments and by comparison with **5a**.[6]

In a typical experiment, 1 equiv. of the commercially available phosphazene base EtP_2 was added, at –78°C, to a stirred solution of the benzylic sulfonium salt (**5a** or **5b**: 1 equiv., 1.5 mmol) in anhydrous CH_2Cl_2. After stirring for 10–15 min, the aldehyde (1 equiv.) was added dropwise.

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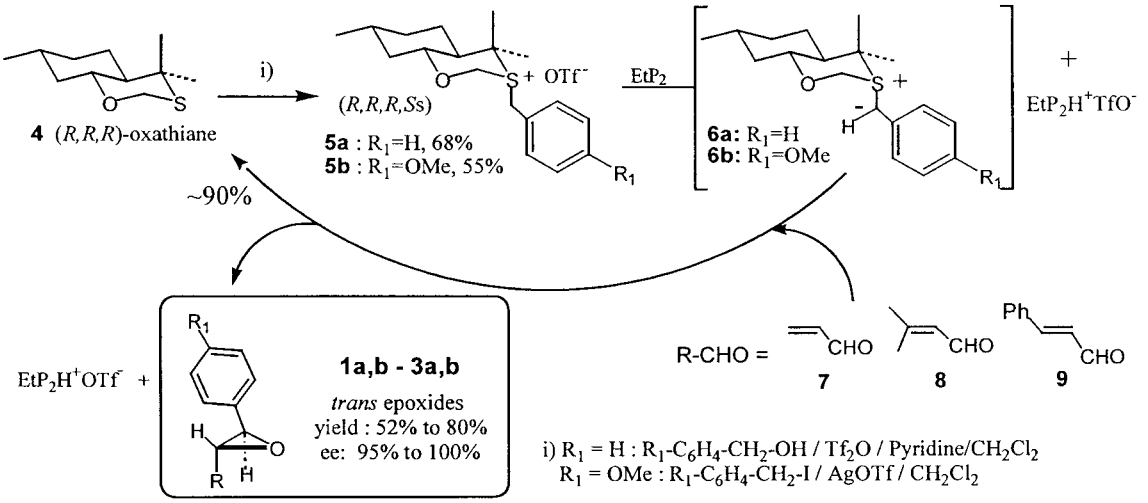

Scheme 1.

Table 1
Epoxides **1a,b**, **2a,b** and **3a,b** from addition (at –78°C) of aldehydes **7–9** on ylides **6a** and **6b** using EtP_2 as base

Entry	Alde hydes	Ylides	Epox.	Solvent	Epox./ Epoxycyclop./ Cyclop.[a]	Epoxide *trans*/*cis*[b]	Epoxide *Trans*[c] ee	Epoxide *Cis*[c] ee
1	**7**	**6a**	**1a**	CH_2Cl_2	**77**/11/12	**100**	**97**	-
2	**7**	**6a**	**1a**	THF	32/37/31	100	-	-
3	**7**	**6b**	**1b**	CH_2Cl_2	100/0/0	**77**/23	95	98
4	**7**	**6b**	**1b**	THF	**100**/0/0	**97**/3	**97**	-
5	**8**	**6a**	**2a**	CH_2Cl_2	**100**/0/0	**97**/3	**100**	-
6	**8**	**6a**	**2a**	THF	**100**/0/0	**97**/3	**99**	-
7	**8**	**6b**	**2b**	CH_2Cl_2	100/0/0	90/10	93	99
8	**8**	**6b**	**2b**	THF	**100**/0/0	**97**/3	**95**	-
9	**9**	**6a**	**3a**	CH_2Cl_2	**100**/0/0	**97**/3	**100**	-
10	**9**	**6a**	**3a**	THF	63/24/13	97/3	100	-
11	**9**	**6b**	**3b**	CH_2Cl_2	100/0/0	91/9	99	-
12	**9**	**6b**	**3b**	THF	**100**/0/0	**96**/4	**99**	-

[a] Determined by 400MHz ^{1}H NMR of crude products. [b] Determined by 400MHz ^{1}H NMR of isolated products. [c] Determined by chiral HPLC, *cf.* ref. 14.

The reaction mixture was then stirred for 30 min at –78°C. After addition of water, the organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The dried combined organic phases were concentrated under vacuum and then re-dissolved in a 1:1 mixture of Et_2O:*n*-hexane. The phosphazene-base salt ($EtP_2H^+TfO^-$) which precipitated, was filtered off and the solution concentrated under vacuum to give the crude product, which was analyzed before separation.

It is worth noting that, with ylide **6a**, the desired epoxides (**1a**,**2a**,**3a**)[7] were always the *major* product (Table 1, entries 1, 5, 6, 9 and 10), except in the case of aldehyde **7** in THF, which provided up to 68% of other products identified by NMR as being cyclopropanes[8] (Table 1, entry 2). Aldehyde **9** and ylide **6a** in THF also led to cyclopropanes,[8] but as *minor* products (37%; Table 1, entry 10). However, using CH_2Cl_2 instead of THF allowed us to maximize formation of the epoxide, which was obtained as the *major* or sole product (100% for **3a** and 77% for **1a**; Table 1, entries 1 and 9).

Interestingly, ylide **6b** provided the epoxide (**1b**,**2b** or **3b**)[9] as the sole product with all aldehydes regardless of the solvent. It thus appears that the methoxy group leading to a less stabilized and more reactive ylide (**6b**) favors formation of the epoxide to the detriment of the cyclopropanes, suggesting that the rate constants leading to formation of epoxides become large compared to those leading to cyclopropanes.

When *cis*-epoxides are formed,[10] higher percentages were obtained in CH_2Cl_2 than in THF (Table 1, entries 3, 7 and 11). This is consistent with less reversibility in formation of the *syn*-betaine in solvents of low polarity (CH_2Cl_2) compared to polar solvents (THF).[11]

The percentages of conversion[12] were about 95% in all cases, as usually observed with this method.[1] However, while oxathiane **4** is almost fully recovered (~90% after purification) and can be reused, significant amounts of epoxides are often lost during chromatography. This difficulty can be overcome through in situ opening[13] (or further reaction) of these epoxides.

In all cases, the enantiomeric excesses[14] (ee) obtained for the desired *trans*-isomers ranged from 95 to 100% (Table 1, entries 1, 4, 5, 8, 9 and 12). From the (+) sign of its optical rotation (in EtOH), the *trans*-epoxide **3b** was assigned the (*R*,*R*)-configuration according to the literature.[15] This is consistent with our previous results[1,2a,6] and our model of approach of the reactants.[6] Therefore, the (*R*,*R*)-configuration can also be assigned to the other *major trans*-epoxides obtained (**1a**,**1b**,**2a**,**2b**,**3a**).

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5. Compound **5b**: m.p. 104–105°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, 3H, ^3J = 6.5 Hz, CH_3), 1.1–1.3 (m, 3H), 1.55 (m, 1H), 1.70 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.8 (m, 2H), 2.05 (m, 1H), 3.78 (td, 1H, $^3J_{ae}$ = 4 Hz, $^3J_{aa}$ = $^3J_{aa}$ = 10 Hz, CH–O), 3.80 (s, 3H, methoxy), 4.61 (s, 2H, S^+–CH_2–Ph), 4.83 (A from AB, 1H, $^2J_{AB}$ = 12 Hz,, S^+–CH_2–O), 5.52 (B from AB, 1H, $^2J_{AB}$ = 12 Hz, S^+–H_2–O), 6.92 (~d, 2H arom., J = 8.5 Hz), 7.42 (~d, 2H arom., J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0 (CH_3), 21.8 (CH_3), 23.6 (CH_2), 25.8 (CH_3), 30.9 (CH), 33.8, 36.1 (CH_2),

40.0 (S^+–CH_2–arom), 43.1 (CH), 55.5 (methoxy), 57.7 (O–CH_2–S^+), 70.7 (Cq$(Me)_2$), 76.01 (O–CH), 115.3 (CH arom.), 117.9 (Cq arom.), 132.3 (CH arom.), 161.0 (Cq arom.); IR ($CHCl_3$) 1040 cm^{-1} (C–S^+).

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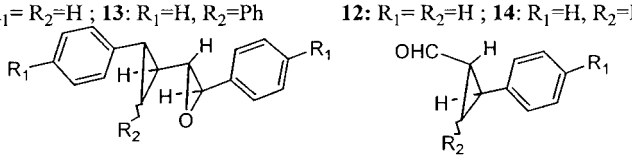
8. The signals of the epoxide ring (d and dd at 3.75 and 3 ppm, respectively) and of the cyclopropane ring (ddd at 2.05 ppm) have been used for identification of compound **11** ($R_1 = R_2 = H$), while the signals of the cyclopropane ring (ddd at 2.65, 2.20 and 1.75 ppm) and of the aldehyde (d at 9.35 ppm) have been used in the case of **12** ($R_1 = R_2 = H$). Similarly, **13** ($R_1 = H$, $R_2 = Ph$) was identified from the epoxide ring signal (d at 3.75 ppm), and **14** ($R_1 = H$, $R_2 = Ph$) from the cyclopropane ring signal (ddd at 2.5 ppm) and the aldehyde (d at 8.95 ppm).

11: $R_1 = R_2 = H$; **13**: $R_1 = H$, $R_2 = Ph$ **12:** $R_1 = R_2 = H$; **14**: $R_1 = H$, $R_2 = Ph$



9. Compound **1b**-*trans*-(*R*,*R*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (dd, 1H, $^3J = 2$ Hz, $^3J = 7.5$ Hz, epoxide ring), 3.74 (d, 1H, $^3J = 2$ Hz, epoxide ring), 3.83 (s, 3H, OMe), 5.35 (dd, 1H, $^3J_{cis} = 10.5$ Hz, $^2J = 0.5$ Hz, CH vinyl), 5.55 (dd, 1H, $^3J_{trans} = 16$ Hz, $^2J = 0.5$ Hz, CH vinyl), 5.75 (ddd, 1H, $^3J = 7.5$ Hz, $^3J_{cis} = 10.5$ Hz, $^3J_{trans} = 16$ Hz, CH vinyl), 6.91 (~d, 2H, arom.), 7.22 (~d, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7 (methoxy), 60.5 (epoxide ring), 63.1 (epoxide ring), 114.4 (CH arom.), 119.7 (CH_2 vinyl), 127.2 (CH arom.), 129.4 (Cq arom.), 135.6 (CH vinyl), 160.2 (Cq arom.). Compound **2b**-*trans*-(*R*,*R*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (bs, 6H, $(CH_3)_2$), 3.53 (dd, 1H, $^3J = 2$ Hz, $^3J = 8.5$ Hz, epoxide ring), 3.73 (d, 1H, $^3J = 2$ Hz, epoxide ring), 3.83 (s, 3H, OMe), 5.02 (sept. d, 1H, $^3J = 8.5$ Hz, $^4J = {}^4J = {}^4J = {}^4J = {}^4J = {}^4J = 1$ Hz, CH vinyl), 6.91 (~d, 2H, arom.), 7.24 (~d, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8 (CH_3 vinyl), 26.3 (CH_3 vinyl), 55.7 (methoxy), 60.1 (epoxide ring), 60.3 (epoxide ring), 114.4 (CH arom.), 122.4 (Cq vinyl), 127.1 (CH arom.), 129.9 (Cq arom.), 140.8 (CH vinyl), 160.0 (Cq arom.). Compound **3b**-*trans*-(*R*,*R*): mp = 100–102°C; $[\alpha]_D^{25}$ +209 (*c* 1.0; $CHCl_3$); $[\alpha]_D^{25}$ +266 (*c* 0.31; EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.52 (dd, 1H, $^3J = 2.5$ Hz, $^3J = 7.5$ Hz, epoxide ring), 3.84 (s, 3H, OMe), 3.85 (d, 1H, $^3J = 2.5$ Hz, epoxide ring), 6.07 (dd, 1H, $^3J = 7.5$ Hz, $^3J = 16$ Hz, CH vinyl), 6.81 (d, 1H, $^3J = 16$ Hz, CH vinyl), 6.90 (~d, 2H, arom.), 7.2–7.45 (m, 7H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7 (methoxy), 61.0 (epoxide ring), 63.3 (epoxide ring), 114.5 (CH arom.), 126.7 (CH arom.), 126.9 (CH), 127.2 (CH arom.), 128.5 (CH), 129.1 (CH arom.), 129.4 (Cq arom.), 134.7 (CH), 136.6 (Cq arom.), 160.2 (Cq arom.).
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