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# Molar Scale Synthesis of Enantiopure Stilbene Oxide

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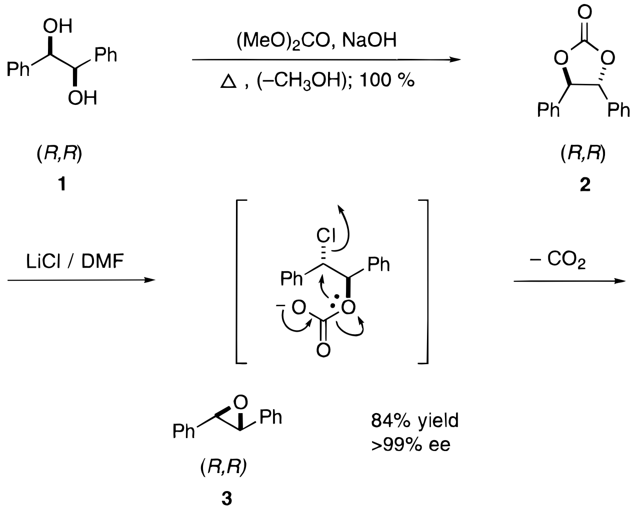
The enantiomerically pure stilbene oxides (*R,R* and *S,S*) are useful precursors to the various heterosubstituted stilbene derivatives[1] which have found uses as chiral ligands,[2] chiral building blocks,[3] and chiral auxiliaries.[4] Previous methods of preparation of enantiomerically enriched stilbene oxide include catalytic epoxidation of stilbene by chiral manganese and chromium salen complexes,[5] epoxidation of stilbene with chiral sulfonyloxaziridines or with chiral perborates,[6] condensation of benzaldehyde with chiral sulfonium and arsonium ylides,[7] and several enzymatic kinetic resolutions of appropriate racemic precursors.[8] Each of these methods was only described on a small scale and most of them also gave modest enantioselectivities. In our continuing efforts to develop practical applications for the asymmetric dihydroxylation (AD) of olefins,[9] we report here a 1 mol scale synthesis of enantiomerically pure (*R,R*)-stilbene oxide (**3**) from (*R,R*)-hydrobenzoin (**1**). The latter is readily available by AD of stilbene in a process described on a 1 kg scale and needing only a 5-L reaction vessel.[10]

**Scheme 1**



The conversion of diol **1** to epoxide **3** is achieved in two simple steps: first, the cyclic carbonate **2** is prepared by transesterification with dimethyl carbonate; and second, LiCl catalyzes nucleophilic opening of carbonate **2** to give an intermediate which collapses to epoxide **3** with loss of $CO_2$. Both steps are very easy to perform and neither involves extraction or chromatography.

The efficient large-scale formation of cyclic carbonate **2** relies on NaOH-catalyzed transesterification of hydrobenzoin by dimethyl carbonate with distillative removal of the methanol produced.[11] The workup procedure simply requires dilution with THF, filtration through Celite to remove the solids, and concentration. Carbonate **2** was both chemically and enantiomerically pure by $^1$H NMR and HPLC, respectively, and was subjected directly to epoxide formation.

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In our previous study on the nucleophilic opening of cyclic carbonates for the synthesis of 1,2-amino alcohols,[11c] epoxide is the predominant byproduct under anhydrous conditions. This observation indicates that, especially in the absence of a proton source, the intermediate azido carbonate salt can extrude $CO_2$ and azide, leading to formation of the epoxide. Indeed, Shapiro reported in 1969 that ethylene oxide is obtained by pyrolysis of ethylene carbonate in the presence of alkali metal halides,[12] and several Texaco patents have reported that monosubstituted ethylene carbonates, such as propylene carbonate, undergo the analogous transformation.[13] Here, we have extended this methodology to show that the process can be stereoselective (i.e. *threo*-carbonate **2** gives *threo*-epoxide **3**).

In contrast to the high temperatures (>200 °C) employed in the earlier pyrolysis,[12,13] we have found that use of DMF as solvent facilitates the reaction, so that useful rates are achieved in the 130−155 °C temperature range. In a typical reaction, carbonate **2** was treated with 5% of dry LiCl in refluxing DMF for 7 to 8 h. Lithium chloride is a better catalyst than LiBr or $Et_4NCl$, which gave more byproducts. Sodium chloride, KCl, and LiF were almost inactive as catalysts (<5% conversion). The effect of water is notable in that reactions using the commercial ACS grade DMF (which contains ≤0.15% water) were *ca.* 3 times slower than those using the commercial anhydrous DMF (which contains ≤0.005% water). During the course of a 1 mol scale reaction, the enantiomeric excess of the crude stilbene oxide (**3**) dropped to 97%, whereas early in the reaction epoxide **3** was present in >99% ee. This slight epimerization is thought to result from Lewis acid-catalyzed processes involving the *meso*-epoxide.[14a] In addition, deoxybenzoin, a major byproduct from the LiCl-catalyzed rearrangement of **3**,[15] is produced rapidly after the starting carbonate **2** has been consumed. The workup procedure consists simply of removal of excess DMF followed by filtration to give the crude epoxide **3** in 98% yield (97% ee). After one recrystallization from hot MeOH (1 g/1 mL), the pure product was obtained in 77% overall yield (151 g, >99.5% ee). Two further recrystallizations of the mother liquor from methanol gave an additional 13.5 g of enantiopure **3**, for a combined yield of 84%.

In conclusion, we have developed a practical synthesis of enantiomerically pure stilbene oxide. This simple preparation should make the useful derivatives of **3** more available. Only the (*R*,*R*)-epoxide is described here, but the (*S*,*S*)-epoxide is of course equally accessible from the (*S*,*S*)-diol.[10]

## Experimental Section

**General.** (*R*,*R*)-hydrobenzoin was prepared by AD as described earlier.[10] Anhydrous DMF (Aldrich) was stored over 3 Å molcular sieves, LiCl (Aldrich) was dried in a vacuum oven at 150 °C overnight before use. Other reagents were purchased from commercial sources and used without further purification. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Melting points are uncorrected. Infrared spectra were recorded using KBr pellets. Enantiomeric excesses were determined by HPLC on Chiralcel AS and OD-H columns (25 cm length × 4.6 mm i.d.).

**(+)-(*R*,*R*)-1,2-Diphenylethylene Carbonate (2).** A 500 mL flask, fitted with a distillation apparatus and a magnetic stir bar, was charged with (*R*,*R*)-hydrobenzoin **1** (214 g, 1 mol), catalytic NaOH (3 g, pellets) and 300 mL of dimethyl carbonate. While being stirred under nitrogen, this solution was heated to 60 °C for 0.5 h and then the bath temperature was raised to 90 °C, whereupon distillative removal of a mixture of methanol and dimethyl carbonate began and was continued until *ca.* 200−250 mL of distillate was collected. The remaining suspension was diluted with 200 mL of THF, filtered through Celite, and concentrated to dryness, leaving 240 g (quantitative yield) of the crude carbonate **2,** which was used directly in the next step. [Crude **2** is a solid and may be recrystallized from methanol (1 g/2 mL) to give white crystalline **2**, mp 110−112 °C]: $^1H$ NMR $\delta$ 5.44 (s, 2H), 7.30−7.33 (m, 4H), 7.43−7.45 (m, 6H); $^{13}C$ NMR $\delta$ 85.35, 126.05, 129.20, 129.73, 134.70; IR (KBr): 1810, 1275, 1167, 1034 cm$^{-1}$; MS FAB calcd for $C_{15}H_{12}O_3$ ($M^+ + H$) 241, found 241; mp 110−112 °C; $[\alpha]_D$ +286° (*c* 1.0, EtOH); >99% ee (Chiralcel AS, 10% *i*-PrOH/hexane, 0.5 mL/min; 22.9, ***26.5***).

**(+)-(*R*,*R*)-Stilbene Oxide (3).** A 500 mL flask, equipped with a condenser and a magnetic stir bar (all equipment oven dried), was charged with (+)-(*R*,*R*)-1,2-diphenylethylene carbonate **2** (240 g, 1 mol), predried LiCl (2.12 g, 0.05 mol), and 250 mL of anhydrous DMF (stored over 3 Å molecular sieves). The mixture was refluxed under nitrogen in an oil bath for 7 h. *It is important to monitor the reaction carefully since the desired epoxide starts to decompose rapidly when all the carbonate starting material is consumed.*[14] A vacuum distillation apparatus is then used for removal of the DMF under reduced pressure (*ca.* 20 mmHg) at a bath temperature of *ca.* 50 °C. The oily residue was diluted with 400 mL of EtOAc and filtered through a 1 in. pad of silica gel[16] topped by 0.5 in. of Celite (in a 2.5 in. diameter sintered-glass funnel) and concentrated to afford 202 g (theory = 196 g) of crude epoxide **3** as a solid (*ca.* 97% ee). Recrystallization of crude **3** from hot methanol (1 g/mL) gave 151 g (>99.5% ee, 77% yield)[17] and 48.75 g (84% ee) from the concentrated mother liquor. The 84% ee material was recrystallized again from methanol to give 23.2 g (94% ee). Another recrystallization of the preceding 23.2 g gave 13.5 g (>99.5% ee, 7% yield). This 13.5 g sample was combined with the original 151 g to give 164.5 g (84% overall yield from the diol (**1**), >99.5% ee): $^1H$ NMR $\delta$ 3.87 (s, 2H), 7.15−7.37 (m, 10H); $^{13}C$ NMR: $\delta$ 62.83, 125.54, 128.30, 128.55, 137.08; IR (KBr): 1455, 1283, 866, 847, 837, 695 cm$^{-1}$; MS FAB calcd for $C_{14}H_{12}O$ ($M^+ + H$) 197, found 197; mp 68−69 °C;[18] $[\alpha]_D$ +361° (*c* 2.05, PhH) [lit.[18] mp 69 °C, $[\alpha]_D$ +374° (*c* 0.5, PhH)]; >99% ee (Chiralcel OD-H, 10% *i*-PrOH/hexane, 0.5 mL/min; 11.3, ***18.1***).

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[13] McEntire, E. E.; Gipson, R. M. US Patent 4 265 821, **1981**; UK Patent GB 2 092 126 A, **1981**; US Patent 4 371 704, **1983**.

[14] (a) The following control experiment was performed: a sample of stilbene oxide (**3**) (99% ee) was subjected to the reaction conditions overnight, whereupon *ca.* 90% of the epoxide had rearranged to deoxybenzoin, the major byproduct in the actual process. The enantiopurity of recovered **3** was reduced to 75% ee, and traces of the *meso*-epoxide and diphenylacetaldehyde were also detected. (b) We find that it is best to monitor the reaction by $^1H$ NMR. Since the DMF resonances do not interfere with the carbonate and epoxide methine resonances, a *ca.* one drop aliquot is added directly to the NMR tube followed by $CDCl_3$. The reaction should be stopped when the epoxide to carbonate ratio is about 20:1.

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[16] *This silica gel filtration is very important.* It removes the LiCl which otherwise causes decomposition of the epoxide during recrystallization from boiling MeOH.

[17] The recrystallization is performed in an Erlenmeyer flask with a magnetic stir bar. The epoxide is added followed by the appropriate volume of MeOH and the mixture is heated to boiling while being stirred. The hot solution is then allowed to cool gradually to room temperature and the crystalline product is collected by filtration.

[18] Epoxide **3** appears to be a racemic compound for which the enantiopure substance and the racemate have coincidentally the same melting point. Read, J.; Campbell, I. G. M. *J. Chem. Soc.* **1930**, 2377.