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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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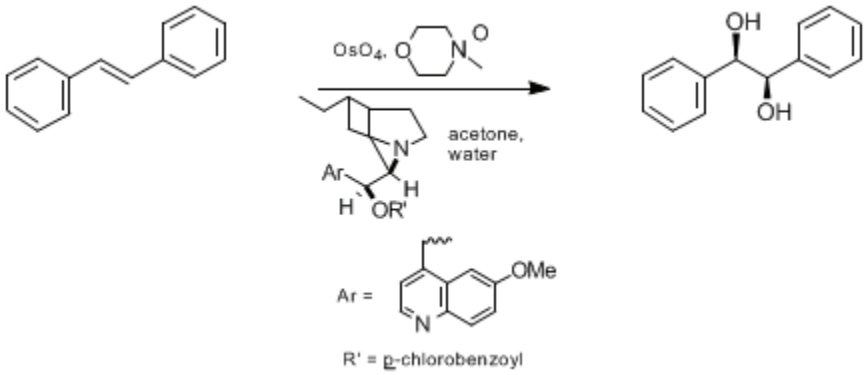
(R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL (STILBENE DIOL)

[1,2-Ethanediol, 1,2-diphenyl-[R-(R,R)]-]



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Checked by Aaron Balog and Robert K. Boeckman, Jr..

1. Procedure

To a 3-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and two glass stoppers at room temperature are added (E)-1,2-diphenylethene (trans-stilbene) (180.25 g, 1.0 mol, 1.0 equiv) (Note 1), 4-methylmorpholine N-oxide (NMO) [260 mL of a 60% by wt. aqueous solution (1.5 mol, 1.5 equiv) (Note 1) and (Note 2)], dihydroquinidine 4-chlorobenzoate (23.25 g, 0.05 mol, 0.05 equiv) (Note 3) and (Note 4), 375 mL of acetone and 7.5 mL water. [The solution is 0.1 M in alkaloid (Note 5), 2 M in olefin, and the solvent is 25% water/75% acetone (v/v) (Note 6)]. The flask is immersed in a 0°C cooling bath and stirred for 1 hr. Osmium tetroxide (1.0 g, 4.0 mmol, 4.0×10^{-3} equiv) is added in one portion, producing a milky brown-yellow suspension (Note 7). The reaction mixture is then stirred at 0°C for 33 hr and monitored by silica TLC (3:1 CH_2Cl_2:Et_2O v/v) until complete. At this point, the mixture is warmed to room temperature, diluted with 500 mL of dichloromethane, and sodium metabisulfite (285 g, 1.5 mol) is added in several portions while the internal temperature is maintained at room temperature with an ice bath as needed. After addition is complete and the exothermic reaction has subsided, stirring is continued at room temperature for 1 hr (Note 8). Anhydrous sodium sulfate (50 g) is added and the mixture is stirred at room temperature overnight (Note 9). The suspension is filtered through a 20-cm Büchner funnel, the filtrand is rinsed thoroughly with acetone (3 × 250 mL), and the filtrate is concentrated to a brown paste (Note 10). The paste is dissolved in 3.5 L of ethyl acetate, transferred to a 6-L separatory funnel, and washed sequentially with water (2 × 500 mL) (Note 11), 0.25 M sulfuric acid (2 × 500 mL) (Note 12), and brine (1 × 500 mL). The initial, aqueous washes are kept separate from the subsequent acid washes which are retained for alkaloid recovery (Note 13) and (Note 14). The organic layer is dried (Na_2SO_4), and concentrated to give the crude diol in quantitative yield (222.7 g, 1.04 mol, 104%). The ee of the crude product is determined by ^1H NMR analysis of the derived bis-Mosher ester to be 90%. One recrystallization[3] from hot aqueous 95% ethanol (3 mL/g) affords 155–162 g (72–75%) of enantiomerically pure stilbene diol as a white solid, mp 144.5–146.5°C, $[\alpha]_D^{25}$ 90.0° (abs EtOH, *c* 1.96) (Note 15).

2. Notes

1. trans-Stilbene and N-methylmorpholine N-oxide were obtained from the Aldrich Chemical Company, Inc.
2. This solution contains 173.7 g of NMO and 117.5 mL of water. Its density is 1.130 g/mL.
3. Dihydroquinidine 4-chlorobenzoate is available from the Aldrich Chemical Company, Inc. The optical rotation of the commercial sample employed by the checkers had an $[\alpha]_D^{25}$ of −68.9° (EtOH, *c*

0.95).
4. Many other dihydroquinidine derivatives have been assayed in the catalytic, asymmetric dihydroxylation reaction (ADH)[4] and the submitters have recently found that the benzoate and 2-naphthoate esters are slightly better for aryl-substituted alkenes while certain ethers are better for other substrates.[5] However, since the level of asymmetric induction is already high, there is little advantage to be gained from their use in this case.
5. When the alkaloid concentration is increased to 0.25 M there is a slight increase in ee; when the concentration is decreased below 0.067 M there is a drastic decrease in ee.[6,7]
6. These solvent conditions have been optimized. The low solubility of stilbene in the reaction mixture approximates "slow addition" conditions.[8]
7. Osmium tetroxide is volatile and toxic and therefore should be used only in a well-ventilated hood. On a 1-mole scale, osmium tetroxide was added as a solid. On a smaller scale, it was added as a solution (ca. 0.5 M) in toluene.[6]
8. The checkers noted a significant exotherm upon addition of the sodium metabisulfite and warming to room temperature that caused the temperature of the methylene chloride solution to rise to the boiling point. Addition of the bisulfite in small portions at 0°C had no beneficial effect in moderating the exotherm that occurred after warming to room temperature.
9. This time can be reduced to 30 min without any deleterious effects.[8]
10. The filtrate is concentrated on a rotary evaporator with slight heating (bath temperature 30–40°C). In some runs with other substrates, stronger heating (bath temperature 70–80°C) caused the reaction mixture to turn black. However, there was no significant effect on either yield or enantiomeric excess in those cases.
11. These washes remove 4-methylmorpholine as well as any remaining acetone. Subsequent contact of the diol with acetone should be avoided to prevent any chance of acetonide formation.
12. It is important to use sulfuric acid at this point to ensure efficient extraction. The sulfate salt of the alkaloid is more soluble in water and less soluble in organic solvents than the hydrochloride salt. In the ADH of other alkenes the preferred system is sulfuric acid/diethyl ether. However, stilbene diol is only sparingly soluble in diethyl ether, which necessitates the use of ethyl acetate. Chlorinated hydrocarbon solvents should be avoided since both alkaloid salts have appreciable solubility in them. When diethyl ether is used as the organic phase, not all of the reaction mixture dissolves in it, but the material that remains undissolved is derived solely from 4-methylmorpholine.
13. Back extraction of the acid layer yields an insignificant amount of diol in this case. However, it may be necessary for more water-soluble diols. For example, in the case of the diol from methyl 2-octenoate the yield is increased by 30% with one back extraction, while styrene glycol requires repeated prolonged extraction.
14. The alkaloid was recovered by raising the pH of the acidic washes to 11 with sodium carbonate, transferring the solution to a 6-L separatory funnel and extracting with methylene chloride (3 × 500 mL). The alkaloid was recovered in 84–85% yield as a white foam and was used without further purification in subsequent dihydroxylations. The use of recovered alkaloid by the checkers resulted in a decrease in the ee of the crude diol to 80%. The submitters, however, report ee's of 90% from repeated use of recovered alkaloid. Note that the alkaloid is stable for several days in the acidic aqueous extract. Once the solution is made alkaline, however, it should be extracted immediately.
15. Optically pure S,S-stilbene diol can be similarly obtained in 66% yield using dihydroquinine-4-chlorobenzoate. The crude ee before recrystallization is 74%.

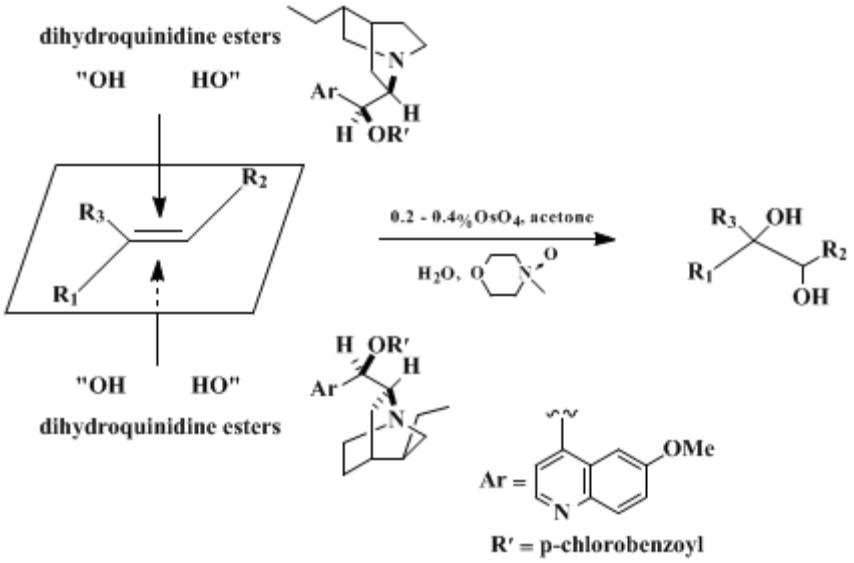
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure describes a convenient preparation of threo-stilbene diol on a 1-mole scale and illustrates the utility of the catalytic, asymmetric dihydroxylation (ADH) of solid substrates on a large scale. Note that this procedure calls for more water than initially reported.[6] The extra water leads to higher ee (90% cf. 78%[6]) by better approximating the slow addition conditions that are now almost always used for liquid olefins.[8,9] In the meantime a new procedure employing the $(DHQD)_{2}PHAL$

ligand has been developed to perform the oxidation on a 1 kilo scale.[10]



Recently reported uses of optically pure stilbene diol in asymmetric synthesis include. (1) the dimethyl ether as a ligand for effecting enantioselective conjugate addition;[10] (2) the preparation of α,β-unsaturated ketals for achieving diastereoselective Simmons–Smith cyclopropanation;[11] (3) the preparation of enantiomercially pure β-halohydrins;[12] and (4) the preparation of chiral crown ethers.[13]

[14]

References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium metabisulfite

brine

(R,R)-1,2-DIPHENYL-1,2-ETHANEDIOL (STILBENE DIOL)

(E)-1,2-diphenylethene (trans-stilbene

dihydroquinine-4-chlorobenzoate

ethanol (64-17-5)

sulfuric acid (7664-93-9)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

dimethyl ether (115-10-6)

acetone (67-64-1)

toluene (108-88-3)

methylene chloride,
dichloromethane (75-09-2)

stilbene

osmium tetroxide (20816-12-0)

styrene glycol

dihydroquinidine 4-chlorobenzoate

trans-Stilbene (103-30-0)

STILBENE DIOL,
S,S-stilbene diol

1,2-Ethanediol, 1,2-diphenyl-[R-(R,R)]- (52340-78-0)

4-methylmorpholine N-oxide,
N-methylmorpholine N-oxide (80913-66-2)

4-methylmorpholine (109-02-4)

methyl 2-octenoate