



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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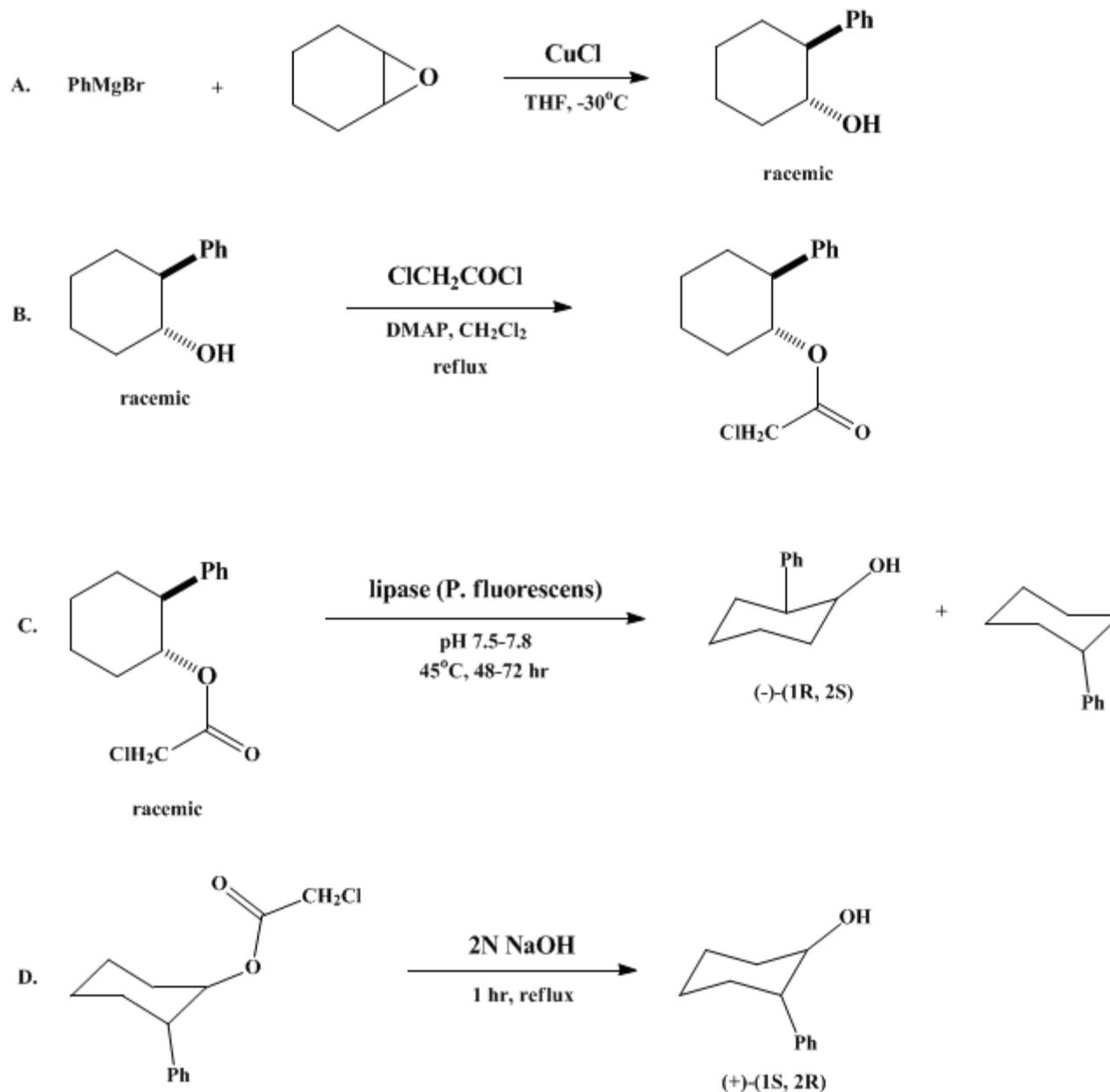
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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**LIPASE-CATALYZED KINETIC RESOLUTION OF ALCOHOLS
VIA CHLOROACETATE ESTERS: (-)-(1*R*,2*S*)-*trans*-2-
PHENYLCYCLOHEXANOL AND (+)-(1*S*,2*R*)-*trans*-2-
PHENYLCYCLOHEXANOL**

[Cyclohexanol, 2-phenyl-, (1*R*-*trans*)- and cyclohexanol, 2-phenyl-, (1*S*-*trans*)-]



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1. Procedure

A. *Racemic trans*-2-phenylcyclohexanol. A 3-L, round-bottomed flask equipped with a mechanical

stirrer, an addition funnel, a reflux condenser, and a nitrogen inlet is charged with 35.3 g (1.47 g-atom) of magnesium turnings (Note 1) and 170 mL of dry tetrahydrofuran (THF). To this stirred mixture a solution of 155 mL (1.47 mol) of bromobenzene (Note 2) in 250 mL of dry THF is added dropwise over a 1.5-hr period (Note 3) and (Note 4). After the addition of bromobenzene is complete, 1 L of dry THF is added. The solution is cooled to -30°C (dry ice–nitromethane slush bath) and 6.53 g (0.066 mol) of purified (Note 5) copper(I) chloride is added. The resulting mixture is stirred for 10 min, and then a solution of 101 mL (1.0 mol) of cyclohexene oxide (Note 6) in 100 mL of THF is added dropwise over a 1.5-hr period. On completion of the addition, the reaction mixture is allowed to warm to 0°C and stirred for 2 hr, then quenched by adding 500 mL of saturated ammonium sulfate $[(\text{NH}_4)_2\text{SO}_4]$ solution (aqueous). The layers are separated and the organic layer is washed with 100 mL of saturated $(\text{NH}_4)_2\text{SO}_4$ (Note 7). The combined aqueous layers are extracted with ether, the organic layers are combined and dried over anhydrous MgSO_4 , and the solvent is removed via rotary evaporator to give 175.5 g (99.6% crude) of the desired product as a light-yellow solid. The solid is recrystallized from pentane to give 142.3 g (80%), mp $55.5\text{--}57.0^{\circ}\text{C}$ (lit.³ $57\text{--}58^{\circ}\text{C}$) (Note 8).

B. *Racemic trans-2-phenylcyclohexyl chloroacetate*. A 1-L, round-bottomed flask equipped with a magnetic stirrer and a condenser is charged with 100 g (0.567 mol) of racemic *trans*-2-phenylcyclohexanol, 50 mL (0.625 mol) of chloroacetyl chloride (Note 9), 300 mg (0.0025 mol) of 4-dimethylaminopyridine (DMAP) (Note 10), and 250 mL of dichloromethane. This mixture is rapidly stirred and heated at reflux for 6 hr. The mixture is cooled and a solution of 350 mL of saturated sodium bicarbonate is carefully added to the rapidly stirring mixture (Note 11). Stirring is maintained for 3 hr (Note 12). The organic layer is separated and dried over anhydrous potassium carbonate. After filtration the filtrate is concentrated on a rotary evaporator (30°C) to a dark-brown oil. This oil is distilled through a 2- or 4-in. column packed with glass beads to give, after collecting a small forerun (ca. 2 g), 135 g (94%) of racemic *trans*-2-phenylcyclohexyl chloroacetate as a colorless liquid, bp $118\text{--}122^{\circ}\text{C}$ at 0.3 mm.

C. *(-)-(1R,2S)-trans-2-Phenylcyclohexanol*. A 500-mL, three-necked Morton flask (Note 13) equipped with a mechanical stirrer, a pH probe (connected to a pH controller, (Note 14)), and a base inlet (connected to a syringe pump regulated by the pH controller and a calibrated 250-mL reservoir (Note 15) of 1 N sodium hydroxide) is charged with 106.0 g (0.419 mol) of racemic *trans*-2-phenylcyclohexyl chloroacetate, 10 mL of pH 7 buffer (Note 16), and 90 mL of deionized water. This heterogeneous mixture is rapidly stirred and heated to between 45° and 50°C using a constant temperature bath. The pH is adjusted to 7.5 with 1 N sodium hydroxide and after a steady pH reading is achieved (Note 17), 1 g of lipase (*P. fluorescens*, (Note 18)) is added. Immediately 1 N sodium hydroxide begins to flow into the reaction mixture as the pH begins to drop (indicating hydrolysis of the chloroacetate). The pH controller regulates the addition of base so as to maintain the pH between 7.5 and 7.8. After 2 hr, an additional 1.5 g of lipase is added to the reaction mixture and the rate of hydrolysis becomes noticeably faster (Note 19). After 45 hr, ca. 200 mL ($\sim 95\%$ of theory) of 1 N sodium hydroxide has been added and the rate of hydrolysis has become very slow. After ca. 50 hr, 210 mL of 1 N sodium hydroxide (0.21 mol, 100% of theory) has been added to the mixture and the rate of base addition has nearly stopped (Note 20). The mixture is cooled to room temperature and extracted with three 200-mL portions of ether. The organic layer is filtered through a small pad of Celite to remove traces of enzyme emulsion and the Celite is rinsed with three 100-mL portions of ether. The combined organic layers are dried over anhydrous sodium sulfate and after filtration are concentrated on a rotary evaporator (35°C) and finally dried at 0.5 mm for 1 hr to give 93 g of a colorless oil. Fractional crystallization from 100 mL of petroleum ether ($30\text{--}60^{\circ}\text{C}$) at -20°C (freezer) overnight affords 19.8 g (53.5% of theory, (Note 21)) of *(-)-(1R,2S)-trans-2-phenylcyclohexanol* as colorless needles, mp $63\text{--}65^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} -54.3^{\circ}$ (methanol, c 18). An additional 15.8 g of the (-) alcohol is obtained by chromatography of the mother liquors (vide infra) to afford a total of 35.6 g (96.2% of theory, (Note 21) and (Note 22)).

The mother liquors are concentrated on a rotary evaporator (35°C) to give a colorless oil that is redissolved in 100 mL of hexanes and poured onto a 250-g pad of silica gel (Note 23) contained in a 500-mL sintered-glass funnel, preequilibrated with hexanes. Using this simple silica pad, 100-mL fractions are collected, diluting first with 1 L of hexanes, followed by 3 L of 9:1 hexanes: ethyl acetate, and finally with 600 mL of ethyl acetate. After TLC analysis of the eluants (Note 24), fractions 3–18 are

combined and concentrated initially on a rotary evaporator (40°C) and finally dried at 0.5 mm to afford 52.0 (98% of theory) of (-)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl chloroacetate as a colorless oil, $[\alpha]_{\text{D}}^{25} -14.3^{\circ}$ (benzene, *c* 10). Fractions 20–28 are combined and concentrated as above to afford 15.8 g of the (-)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol, mp 62–65°C, $[\alpha]_{\text{D}}^{25} -54.9^{\circ}$ (methanol, *c* 2.1).

D. (+)-(1*S*,2*R*)-*trans*-2-Phenylcyclohexanol. A 500-mL, round-bottomed flask is charged with a mixture of 52.0 g (0.206 mol) of (-)-(1*S*,2*R*)-*trans*-2-phenylcyclohexyl chloroacetate, 250 mL of 2 *N* sodium hydroxide, and 100 mL of methanol and then stirred at reflux for 3 hr. TLC analysis (Note 24) indicates complete reaction. The mixture is cooled to room temperature, adjusted to pH 7 with ca. 35 mL of 3 *N* sulfuric acid and poured into 500 mL of water. The mixture is extracted with two 150-mL portions of dichloromethane and the organic layer is dried over anhydrous sodium sulfate and concentrated on a rotary evaporator (35°C) to afford 37.0 g of a colorless solid. Recrystallization from 100 mL of petroleum ether (30–60°C) at –20°C gives in two crops, 35.8 g (96% of theory) of (+)-(1*S*,2*R*)-*trans*-2-phenylcyclohexanol as colorless needles, mp 60–62°C, $[\alpha]_{\text{D}}^{25} +52.8^{\circ}$ (methanol, *c* 5.4) (Note 25).

2. Notes

1. Magnesium turnings were purchased from Aldrich Chemical Company, Inc.
2. Bromobenzene was purchased from Fisher Scientific and used without further purification.
3. A small amount of 1,2-dibromoethane was used to initiate the reaction.
4. An ice bath was used to control the reaction temperature during Grignard formation.
5. Copper(I) chloride was purified via the procedure in *Inorganic Syntheses*.⁴
6. Cyclohexene oxide was purchased from Aldrich Chemical Company, Inc. and used without further purification.
7. The organic layer was washed until the aqueous layer no longer turned blue.
8. The spectral properties of the product are as follows: ¹H NMR (300 MHz) δ : 1.25–1.53 (bm, 4 H), 1.62 (s, 1 H), 1.76 (m, 1 H), 1.84 (m, 2 H), 2.11 (m, 1 H), 2.42 (ddd, 1 H, *J* = 16.5, 10.8, 5.4), 3.64 (ddd, 1 H, *J* = 10.8, 10.8, 5.4), 7.17–7.35 (m, 5 H); ¹³C NMR (90 MHz) δ : 25.1 (t), 26.1 (t), 33.5 (t), 34.7 (t), 53.0 (d), 74.0 (d), 126.4 (d), 127.9 (d), 128.4 (d), 143.8 (s); IR cm^{-1} : 3592, 3461, 2941, 2863, 1604, 1497, 1451; MS 176 (*M*⁺), 158, 143, 130, 117, 104, 91 (base).
9. Chloroacetyl chloride (99%) was purchased from Fluka and used without further purification.
10. 4-Dimethylaminopyridine was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
11. Rapid addition of the bicarbonate solution may result in uncontrollable foaming.
12. Excess chloroacetyl chloride was slowly hydrolyzed to chloroacetic acid, which was neutralized.
13. A creased or Morton flask was preferable as the rate of hydrolysis of the chloroacetate increases with efficient agitation.
14. The pH controller used was a Horizon Model 5997 available from Cole-Parmer Instrument Co.
15. A 250-mL graduated cylinder, used as a reservoir, was capped with a septum through which base-stable, 1/32-in.-i.d. tubing was run and connected to a peristaltic pump.
16. Fisher pH 7 buffer was used from the bottle as purchased.
17. Traces of chloroacetyl chloride are hydrolyzed to produce chloroacetic acid, producing a fluctuation in pH that will settle down within 5 min.
18. The lipase used was isolated from *Pseudomonas fluorescens* and was commercially available from Amano International Enzyme Co., Inc. (Troy, VA) as a powder, specific activity 32,000 units/g (P-30).
19. The rate enhancement was manifested by a more rapid base uptake.
20. If the hydrolysis was allowed to proceed, small additions of base (≤ 0.1 mL) occurred every 30 min or so.
21. If the hydrolysis was taken to 50% completion, the theoretical yield of each alcohol isomer was 36.96 g.
22. The (-)-(1*R*,2*S*) alcohol had an enantiomeric ratio of (-) : (+) 99.2 : 0.8 corresponding to an enantiomeric excess (ee) of 98.4%. This determination resulted from GC analysis (50-m \times 0.25-mm capillary column, OV-17 on fused silica, 250°C) of the α -methoxy- α -trifluoromethylphenylacetate (MTPA ester). The checkers determined the enantiomeric ratio to be 98.6 : 1.4 (97.2% ee) by ¹H NMR analysis at 300 MHz of the MTPA ester that was prepared as follows. The sample alcohol (0.1 mmol) was placed in a vial along with a solution of (+)- α -methoxy- α -trifluoromethylphenylacetyl chloride

(0.15 mmol) in 1 mL of dichloromethane, triethylamine (0.15 mmol), and a crystal of 4-dimethylaminopyridine, and stirred at room temperature overnight. The excess acid chloride was treated with dimethylaminopropylamine (0.1 mmol). The MTPA ester was isolated in pure form after passing the mixture through a 5-g plug of silica gel and elution with 4 : 1 hexanes : ethyl acetate.

23. The silica gel used was 70–230 mesh as purchased from E. Merck.

24. TLC was run on 10 × 20-mm silica plates (E. Merck): TLC solvent was 4 : 1 hexanes : ethyl acetate; visualization was with 5% (NH₄)₂MoO₄ in 10% aqueous sulfuric acid, with heat. In the event that any mixed fractions are obtained, these are combined and evaporated, and the residue is rechromatographed in the same manner.

25. By GC analysis of (+)-MTPA esters (see (Note 22)), an enantiomeric ratio of (+) : (–) 96.5 : 3.5, corresponding to 93% ee, was determined.

3. Discussion

The use of chiral auxiliaries to impart dissymmetry has become a powerful tool for controlling the stereochemical outcome of chemical transformations. Many of these auxiliaries have been drawn from the chiral pool of natural materials. While high levels of asymmetric induction have been achieved in many cases, none of these natural products has emerged as a general agent, in part because typically only one enantiomer of the auxiliary is readily available.

The procedure described here provides ready access to both the (+) and (–) antipodes of *trans*-2-phenylcyclohexanol, a useful chiral auxiliary in ene reactions of its glyoxylate ester⁵ and its *N*-sulfinylcarbamate,⁶ as well as in cycloaddition reactions of dienes with the *N*-sulfinylcarbamate,⁷ and olefins with ketenes.⁸ This simple auxiliary appears to retain⁵ many of the features of 8-phenylmenthol,⁹ a powerful agent difficult to prepare on a large scale.¹⁰ A modest-scale procedure for 8-phenylmenthol is included in this volume.¹¹

Optically pure *trans*-2-phenylcyclohexanol can also be prepared by resolution of the phthalate esters using brucine to obtain the (+)-alcohol and strychnine to obtain the (–)-alcohol (after basic hydrolysis of their respective salts).¹² Enzyme-catalyzed kinetic resolution of the acetate esters using pig liver esterase⁵ and pig liver acetone powder³ has been used to prepare both enantiomers of this chiral auxiliary. The hydroboration of 1-phenylcyclohexene with isopinocampheylborane has been reported to give the chiral auxiliary in 97% enantiomeric excess.¹³

Racemic *trans*-2-phenylcyclohexanol has previously been prepared in a yield comparable to that realized in this procedure via copper-catalyzed phenyl Grignard addition to cyclohexene oxide using the more expensive copper(I) oxide.¹⁴

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 258
- Org. Syn. Coll. Vol. 10, 603

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

petroleum ether

hexanes

Racemic trans-2-phenylcyclohexanol

$(\text{NH}_4)_2\text{SO}_4$

Racemic trans-2-phenylcyclohexyl chloroacetate

(-)-(1S,2R)-trans-2-phenylcyclohexyl chloroacetate

$(\text{NH}_4)_2\text{MoO}_4$

N-sulfinylcarbamate

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium sulfate (7757-82-6)

chloroacetic acid (79-11-8)

copper(I) oxide

bromobenzene (108-86-1)

1,2-dibromoethane (106-93-4)

chloroacetyl chloride (79-04-9)

copper(I) chloride (7758-89-6)

Cyclohexene oxide (286-20-4)

ammonium sulfate (7783-20-2)

Pentane (109-66-0)

dichloromethane (75-09-2)

brucine

MgSO₄ (7487-88-9)

1-phenylcyclohexene (771-98-2)

strychnine

Tetrahydrofuran,
THF (109-99-9)

triethylamine (121-44-8)

dimethylaminopropylamine (109-55-7)

4-dimethylaminopyridine (1122-58-3)

α -methoxy- α -trifluoromethylphenylacetate (56135-03-6)

(+)- α -methoxy- α -trifluoromethylphenylacetyl chloride

trans-2-Phenylcyclohexanol,
(-)-(1R,2S)-trans-2-PHENYLCYCLOHEXANOL,
Cyclohexanol, 2-phenyl-, (1R-trans)- (98919-68-7)

8-phenylmenthol

isopinocampheylborane

(+)-(1S,2R)-trans-2-PHENYLCYCLOHEXANOL,
cyclohexanol, 2-phenyl-, (1S-trans)- (34281-92-0)