A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

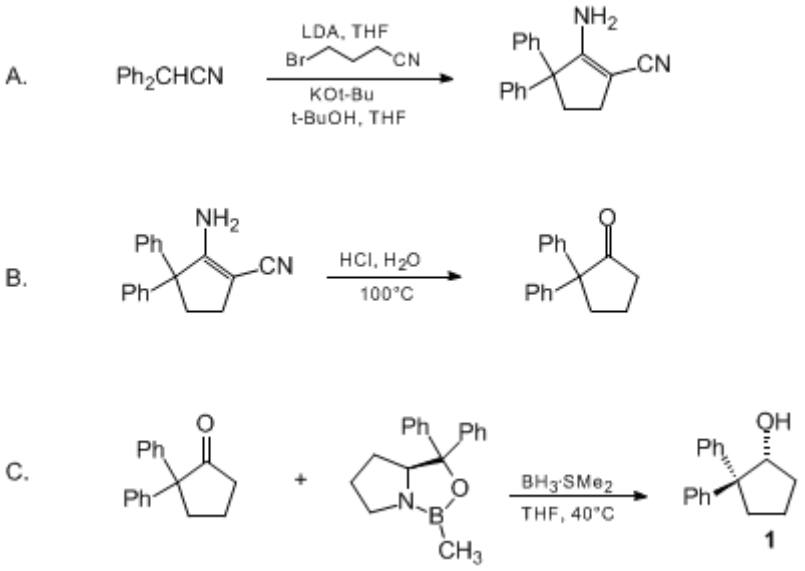
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.074.0033

Organic Syntheses, Coll. Vol. 9, p.362 (1998); Vol. 74, p.33 (1997).

(R)-(−)-2,2-DIPHENYLCYCLOPENTANOL

[Cyclopentanol, 2,2-diphenyl-, (R)-]



Submitted by Scott E. Denmark, Lawrence R. Marcin, Mark E. Schnute, and Atli Thorarensen[1].
Checked by David J. Mathre, Khateeta M. Emerson, and Ichiro Shinkai.

1. Procedure

A. *2-Amino-3,3-diphenyl-1-cyclopentene-1-carbonitrile*. To a 2-L, three-necked, round-bottomed flask equipped with a 250-mL, pressure-equalizing addition funnel, magnetic stirrer, nitrogen/vacuum adapter, and a thermometer is added 39.9 mL (0.29 mol) of diisopropylamine and 200 mL of tetrahydrofuran (THF) (Note 1), (Note 2). The solution is cooled to 0°C, and 101.6 mL of butyllithium (2.55 M in hexane, 0.26 mol) is added slowly (Note 3). After 10 min, a solution of 50.0 g (0.26 mol) of diphenylacetonitrile (Note 4) in 200 mL of THF is added over 30 min forming a deep yellow solution. A solution of 28.3 mL (0.29 mol) of 4-bromobutyronitrile (Note 5), (Note 6) in 200 mL of THF is then added over 20 min. The resulting bright-yellow solution is allowed to warm slowly to room temperature overnight (10 hr) (Note 7). The reaction mixture is quenched by the slow addition of water (25 mL) and then is diluted with 400 mL of tert-butyl methyl ether (MTBE), and washed with water (2 × 100 mL) and brine (100 mL). The aqueous layers are back-extracted with MTBE (100 mL). The combined organic layers are dried with sodium sulfate (Na_2SO_4), concentrated on a rotary evaporator, and the resulting crude dinitrile is placed under high vacuum (0.2 mm) for 1 hr. The dinitrile is transferred to a 2-L, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirrer, nitrogen/vacuum adapter, and a thermometer and is dissolved in a mixture of tert-butyl alcohol (400 mL) and THF (200 mL). To the solution is added 23.25 g (0.21 mol) of potassium tert-butoxide, and the suspension is heated at 60°C (internal temperature) for 2 hr. After the reaction mixture is cooled to room temperature, it is quenched with water (25 mL), diluted with MTBE (500 mL), and washed with water (100 mL) and brine (3 × 100 mL). The aqueous layers are back-extracted with MTBE (100 mL), and the combined organic layers are dried (Na_2SO_4) and concentrated on a rotary evaporator to afford an off-white granular solid. The crude product is suspended in MTBE (75 mL), cooled (0°C), filtered, and recrystallized from absolute ethanol (400 mL). The mother liquor is concentrated on a rotary evaporator, purified by column chromatography on silica gel (330 g) (Note 8) eluting with hexane/EtOAc (4/1), and recrystallized from absolute ethanol to afford a combined yield of 57.7 g (86%) of the enaminonitrile as a white solid (Note 9),(Note 10).

B. *2,2-Diphenylcyclopentanone*. To a 3-L, three-necked, round-bottomed flask equipped with a

mechanical stirrer, thermometer, and wide inner-spiral reflux condenser (Note 11) is added 57.5 g (0.22 mol) of the enaminonitrile from step A and 800 mL of concd hydrochloric acid (HCl, (Note 12)). The mixture is stirred for 5 min, and 800 mL of water is added. The reaction mixture is heated to reflux (heating mantle, 110°C internal temperature) with vigorous stirring for 4 days (Note 13), (Note 14), (Note 15). The reaction mixture is cooled to room temperature, and extracted with dichloromethane (CH_2Cl_2, 5 × 200 mL). The organic layers are washed with saturated aqueous sodium bicarbonate ($NaHCO_3$, 100 mL) and brine (100 mL), and the aqueous layers are back-extracted with dichloromethane (100 mL). The combined organic layers are dried ($MgSO_4$) and concentrated on a rotary evaporator. The crude product is recrystallized from MTBE (300 mL). The mother liquor is concentrated on a rotary evaporator, and purified by column chromatography on silica gel (250 g) eluting with hexane/EtOAc (4/1), decolorized with carbon, and recrystallized from MTBE to afford a combined yield of 48.2 g (92%, (Note 16)) of the ketone as a white solid (Note 17), (Note 18)).

C. *(R)-(−)-2,2-Diphenylcyclopentanol* **1**. In a 500-mL, three-necked, round-bottomed flask, equipped with a 125-mL graduated, pressure-equalizing addition funnel, 30-mm, egg-shaped magnetic stir bar, nitrogen/vacuum adapter, and an internal temperature probe is placed 1.76 g (6.34 mmol) of the B-methyloxazaborolidine catalyst (Note 1), (Note 19), (Note 20). The apparatus is evacuated, flushed with nitrogen, charged with 86 mL of dry THF and 6.34 mL (63.4 mmol) of borane-methyl sulfide complex, and then warmed to 40°C (internal temperature) (Note 21). In a 250-mL, three-necked, round-bottomed flask, equipped with a nitrogen/vacuum adapter and magnetic stirrer is placed 15 g (63.4 mmol) of 2,2-diphenylcyclopentanone. The flask is evacuated, flushed with nitrogen, and charged with 111 mL of dry THF. After dissolution, the ketone solution is transferred to the addition funnel via cannula and added dropwise over 8 hr to the stirred catalyst solution maintained at 40°C (Note 22). After complete addition, the funnel is rinsed into the reaction vessel with 10 mL of dry THF, and the resulting reaction mixture is stirred at 40°C for an additional 30 min. Finally, the reaction mixture is cooled to 0–5°C and carefully quenched by the dropwise addition of 100 mL of methanol (*CAUTION: considerable hydrogen evolution occurs after a short induction period*) (Note 23). The cold bath is removed and the reaction is stirred until gas evolution ceases (Note 24). The resulting solution is poured into a 1-L, round-bottomed flask and the reaction vessel is rinsed with 50 mL of methanol. A simple distillation head is attached to the 1-L flask and 100 mL of solvent is distilled (*CAUTION: the distillate contains malodorous methyl sulfide*). An additional 100 mL of fresh methanol is added and 100 mL of solvent is again distilled. The residue is cooled to room temperature and concentrated on a rotary evaporator to afford a slightly yellow oil. The oil is dissolved in MTBE (250 mL), washed with aqueous 0.1 N aqueous hydrochloric acid (3 × 100 mL), and the combined acidic, aqueous phases are back-extracted with MTBE (100 mL). The combined organic phases are washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator to afford 15.1 g of an off-white solid. The solid is purified by bulb-to-bulb distillation (bp 180°C/0.2 mm) to afford 14.7 g (97%) of (R)-(−)-2,2-diphenylcyclopentanol (92% ee) as an analytically-pure, white solid (Note 25), (Note 26). Multiple recrystallizations of the product from hexane afford 11.3 g (75%) of (R)-(−)-2,2-diphenylcyclopentanol (>97% ee) (Note 26), (Note 27), (Note 28). To recover the catalyst precursor, (S)-α,α-diphenyl-2-pyrrolidinemethanol, the acidic, aqueous phase is made basic (blue to litmus) by addition of 25 mL of aqueous 25% sodium hydroxide solution. The aqueous phase is extracted with dichloromethane (3 × 100 mL), and the combined organic phases are washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator to afford a clear oil that crystallizes under high vacuum (0.1 mm, several hours). The solid is recrystallized from hexane to afford 1.5 g (93% recovery) of (S)-α,α-diphenyl-2-pyrrolidinemethanol as a white crystalline solid (Note 29).

2. Notes

1. All glassware was dried in an oven (140°C) and after assembly was allowed to cool under an atmosphere of dry nitrogen.
2. THF was freshly distilled from sodium/benzophenone. tert-Butyl alcohol was purchased from Aldrich Chemical Company, Inc., and was used without further purification. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane ($CaCl_2$); dichloromethane ($CaCl_2$); tert-butyl methyl ether (MTBE) ($CaSO_4/FeSO_4$); ethyl acetate (K_2CO_3).
3. Butyllithium was freshly titrated by the method of Gilman.[2] Excess strong base, either butyllithium or lithium diisopropylamide (LDA), (exceeding 1 equiv per diphenylacetonitrile) should be avoided since

the resulting Thorpe-Ziegler cyclization product is susceptible to fragmentation under the reaction conditions to afford 1,1-dicyano-4,4-diphenylbutane.

4. Diphenylacetonitrile was purchased from Aldrich Chemical Company, Inc., and recrystallized from hexane (mp 73–75°C).

5. 4-Bromobutyronitrile was purchased from Aldrich Chemical Company, Inc., and was freshly distilled (bp 95–98°C, 15 mm).

6. 4-Iodobutyronitrile may also be used as a less expensive alternative available from 4-chlorobutyronitrile[3] by a modification of the above procedure. The increased reactivity of the iodide, however, requires a more tedious procedure, but is provided as follows:

A. *4-Iodobutyronitrile*. To a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is placed a solution of 70 mL (0.77 mol) of 4-chlorobutyronitrile in 420 mL of acetone. To the solution is added 123.4 g (0.82 mol) of sodium iodide, and the resulting clear solution is heated to reflux for 23 hr. Over time, the formation of large amounts of a white precipitate is observed. The resulting suspension is cooled to room temperature, filtered, and the filter cake is washed with dichloromethane (200 mL). The combined organic layers are concentrated on a rotary evaporator. The residue is redissolved into dichloromethane (200 mL), washed with saturated aqueous sodium thiosulfate ($Na_2S_2O_3$, 50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator. The resulting oil is distilled (bp 80–92°C/0.8 mm) to afford 141.6 g (92%) of 4-iodobutyronitrile as a clear colorless oil.

B. *2-Amino-3,3-diphenyl-1-cyclopentene-1-carbonitrile*. In a 1-L, three-necked, round-bottomed flask, a solution of 53.8 mL (0.38 mol) of diisopropylamine in 250 mL of dry THF is cooled to −70°C. To the solution is slowly added 118 mL of butyllithium (2.95 M in hexane, 0.34 mol) at such a rate that the internal temperature never exceeds −50°C. The resulting solution is cooled to −70°C, and a solution of 67.5 g (0.34 mol) of diphenylacetonitrile in 250 mL of dry THF is added over 30 min forming a black solution that is stirred an additional 20 min. In a 2-L, three-necked, round-bottomed flask, a solution of 4-iodobutyronitrile (74.9 g, 0.38 mol) in 250 mL of dry THF is cooled to −77°C. Using a Teflon cannula (0.5-cm diameter) the anion of diphenylacetonitrile is added very rapidly to the 4-iodobutyronitrile solution (internal temperature rose by only 3°C). The resulting light-yellow solution is stirred for 80 min at −78°C, warmed to 0°C for 60 min, and allowed to stir at room temperature for 30 min. The reaction mixture is quenched with water (34 mL), diluted with MTBE (500 mL), and washed with water (2 × 250 mL) and brine (250 mL). The aqueous layers are back-extracted with MTBE (200 mL), and the combined organic layers are dried (Na_2SO_4) and concentrated on a rotary evaporator. The resulting crude dinitrile is dissolved in a mixture of tert-butyl alcohol (540 mL) and THF (270 mL). To the solution is added 31.0 g (0.28 mol) of potassium tert-butoxide, and the suspension is heated at 60°C (internal temperature) for 2 hr. After the reaction mixture is cooled to room temperature, it is diluted with MTBE (600 mL), and washed with water (150 mL) and brine (3 × 150 mL). The aqueous layers are back-extracted with MTBE (150 mL), and the combined organic layers are dried ($MgSO_4$) and concentrated on a rotary evaporator. The crude product is suspended in MTBE (75 mL), cooled, filtered, and recrystallized from absolute ethanol (600 mL) to afford 67.5 g of pure ketone. The mother liquor is concentrated on a rotary evaporator, purified by column chromatography [hexane/EtOAc (8/1, 4/1)], and crystallized from absolute ethanol to afford 8.6 g (9.5%) of additional material for a combined yield of 76.1 g (84%) of analytically pure enaminonitrile as a white solid giving identical spectral data to that reported above (Anal. Calcd for $C_{18}N_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.06; H, 6.20; N, 10.74).

7. The following reverse-phase HPLC assay was developed to monitor steps A-C. Column: YMC J'Sphere H80 (4.6 × 250 mm); eluent: 45:55 H_2O (20 mM H_3PO_4)/MeCN; flow rate: 1.0 mL/min; column temp.: 45°C; detection: UV (210 nm). Retention times: "diphenylprolinol" (1.85 min, with solvent front); 4-bromobutyronitrile (4.0 min); "enaminoamide" (6.1 min); "dinitrile" (11.4 min); diphenylacetonitrile (12.0 min); "cyanoketone" (12.5 min); diphenylcyclopentanol (13.1 min); "enaminonitrile" (14.4 min); "diphenylcyclopentanone" (19.5 min).

8. Kieselgel 60 (230–400 mesh) was purchased from EM Science.

9. Rather than purifying the mother liquors by column chromatography, the checkers obtained a second crop of crystals for a combined yield of 57.3 to 60.3 g (85–89%). The checkers also note that the crude product can be used "as is" in the next step after being suspended and washed with cold MTBE.

10. The physical properties are as follows: mp 145–148°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (dd, 2

H, J = 6.8, 5.6), 2.63 (dd, 2 H, J = 7.6, 6.3), 4.38 (br, 2 H, NH_2), 7.23–7.37 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.94, 41.48, 62.76, 76.19, 118.77, 127.08, 128.19, 128.40, 142.82, 164.78; IR (CCl_4) cm^{-1}: 3490 (w), 3395 (w), 3063 (w), 2954 (w), 2863 (w), 2197 (m), 1643 (s), 1595 (m); MS (EI, 70 eV) 260 (M^+, 100), 259 (31), 183 (49), 182 (36); TLC R_f = 0.38 (hexane/EtOAc, 4/1). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.05; H, 6.19; N, 10.76. Found: C, 83.34; H, 6.07; N, 10.84.

11. The product may sublime into the condenser causing it to become clogged. This can be prevented by periodically washing down the solids with 6 N HCl.

12. To ensure complete consumption of the intermediate cyano ketone, the ratio of enaminonitrile to solvent volume cannot be altered.

13. Efficient stirring and heating to a vigorous reflux is crucial for complete consumption of the intermediate cyano ketone.

14. The reaction progress can be monitored by ^1H NMR integration of the signals of the ketone (dt, 1.95 ppm, 2 H) and the cyano ketone intermediate (t, 3.43 ppm, 1 H) determined from a crude reaction sample following the same work-up as reported above. Spectral data for 2-cyano-5,5-diphenylcyclopentanone are as follows: ^1H NMR (400 MHz, $CDCl_3$) δ: 2.22 (m, 1 H), 2.47 (m, 1 H), 2.70 (ddd, 1 H, J = 12.5, 9.8, 6.1), 2.90 (dt, 1 H, J_d = 12.5, J_t = 6.1), 3.43 (t, 1 H, J = 9.0), 7.15–7.40 (m, 10 H). Alternatively, high pressure liquid chromatography (HPLC) analysis may be used employing a Supelco LC-Si (5μ, 250 × 4.5 mm) column (hexane/EtOAc, 9/1, 1.5 mL/min, detector λ = 254 nm); R_t: "ketone" (4.6 min, response factor = 1.50), R_t: "cyano ketone" (16.8 min, response factor = 0.76).

15. The progress of the reaction was monitored by HPLC. The checkers found the reaction to take from 4 to 7 days to reach > 99% completion.

16. Yields ranged from 84% to 92%.

17. Rather than purifying the mother liquors by column chromatography, the checkers obtained a second crop of crystals for a combined yield of 87–95%.

18. The physical properties are as follows: mp 85–88°C; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.95 (dt, 2 H, J_d = 13.4, J_t = 7.3) 2.46 (t, 2 H, J = 7.7), 2.73 (t, 2 H, J = 6.6), 7.21–7.32 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.79, 38.07, 38.16, 62.44, 126.69, 127.96, 128.31, 142.02, 217.77; IR (CCl_4) cm^{-1}: 3061 (m), 3033 (m), 2969 (m), 2886 (m), 1744 (s), 1494 (s), 1446 (m), 1406 (m), 1143 (m), 1104 (m); MS (EI, 70 eV) 236 (M^+, 47), 208 (11), 180 (100), 179 (37), 178 (25), 165 (43); TLC R_f = 0.48 (hexane/EtOAc, 8/1). Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.57; H, 6.75.

19. A Baxter Diagnostics Inc. Type K Thermo-Couple Thermometer was used to monitor the internal temperature of the reaction solution.

20. (S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole was prepared from (S)-proline in two steps according to the literature procedure[4] and purified by bulb-to-bulb distillation (170°C, 0.2 mm). The enantiomeric purity of the intermediate, (S)-α,α-diphenyl-2-pyrrolidinemethanol, was determined to be >99% ee by chiral HPLC analysis of its corresponding N-p-toluenesulfonamide derivative (DIACEL Chiralcel OD column; hexane/ethanol, 92/8; 1.0 mL/min; R_t(S) 8.6 min; R_t(R) 12.8 min). The checkers used the crystalline β-methyloxazaborolidine-borane complex (1.84 g, 6.34 mmol) as the catalyst.

21. Borane-methyl sulfide complex was purchased from Aldrich Chemical Company, Inc., and was used without purification.

22. Addition of the ketone solution over a 6-hr period affords almost identical results. However, variation of the reaction temperature can have a dramatic effect on product ee.[5]

23. Anhydrous, reagent-grade methyl alcohol was purchased from Mallinckrodt Inc. and used without purification.

24. Hydrogen evolution stops after 2–3 hr; however, for convenience the reaction can be allowed to stand at room temperature overnight with no deleterious effect on yield or enantioselectivity.

25. Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.65; H, 7.63.

26. Enantiomeric excess is determined by chiral HPLC analysis (DIACEL Chiralcel OJ column; hexane/ethanol, 70/30; 1.0 mL/min; R_t: S-isomer (8.8 min); R_t: R-isomer (17.9 min).

27. The checkers determined enantiomeric purity by supercritical fluid chromatography (SFC) using a Chiralpak AD (4.6 × 250 mm) column. Eluent: carbon dioxide (300 Bar); modifier: methanol (24%); flow rate: 1.5 mL/min; detection: UV (210 nm). Retention times were as follows: "diphenylcyclopentanone" (3.9 min); (R)-diphenylcyclopentanol (5.9 min); (S)-diphenylcyclopentanol (10.4 min).

28. The product is recrystallized two times by dissolution in boiling hexane (60 mL and 50 mL) and

cooling to room temperature to provide 9.8 g of material with greater than 97% ee. The mother liquors are then combined, concentrated and recrystallized four times from hexane (20 mL, 15 mL, 10 mL and 10 mL) to provide 1.5 g of additional (R)-(−)-2,2-diphenylcyclopentanol with greater than 97% ee. The physical properties are as follows: mp 76–77°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (dd, 1 H, J = 4.9, 0.7), 1.55–1.75 (m, 2 H), 1.93 (m, 1 H), 2.10 (m, 1 H), 2.32 (ddd, 1 H, J = 12.9, 8.7, 3.3), 2.66 (dt, 1 H, J_t = 12.9, J_d = 8.9), 4.88 (dd, 1 H, J = 9.7, 4.8), 7.14–7.33 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.95, 31.67, 34.60, 59.71, 77.57, 125.89, 126.33, 126.92, 128.17, 128.44, 128.53, 144.26, 146.87; MS (EI, 70 eV) 239 (8), 238 (M^+, 44), 78 (12), 167 (100), 115 (16), 91 (11); IR (CCl_4) cm^{-1}: 3585 (m), 3061 (m), 3025 (w), 2967 (s), 2916 (w), 1495 (s), 1446 (s), 1288 (w), 1094 (m), 1074 (m), 1034 (m), 1015 (m); $[\alpha]_D^{26}$ −114.8° (EtOH, *c* 1.17). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.65; H, 7.59.

29. The solid is recrystallized by dissolution in boiling hexane (20 mL) and cooling to 0°C to afford 1.37 g of (S)-α,α-diphenyl-2-pyrrolidinemethanol. The mother liquor is then concentrated and recrystallized from hexane (10 mL) to afford an additional 0.13 g of material. The physical properties are as follows: mp 75–76°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.58–1.74 (m, 4 H), 2.96 (m, 1 H), 3.02 (m, 1 H), 4.26 (t, 1 H, J = 7.6), 7.14–7.59 (m, 10 H).

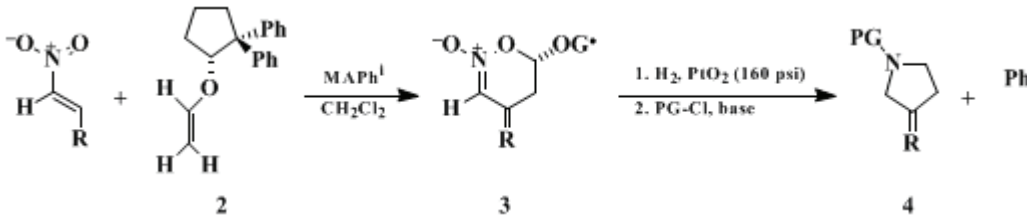
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. The malodorous, methanol distillate resulting from the borane reduction was first treated with commercial bleach before disposal.

3. Discussion

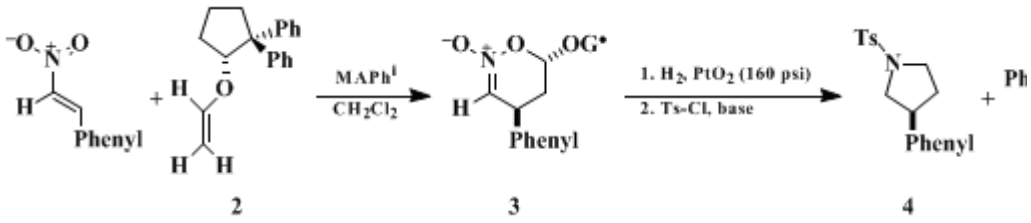
(R)-(−)-2,2-Diphenylcyclopentanol **(1)** is a highly effective chiral auxiliary in asymmetric synthesis. Hydrogenation of chiral β-acetamidocrotonates derived from this alcohol has afforded the corresponding β-amido esters with high diastereoselectivity (96% de).[6] In addition, (R)-**1** has been used as a chiral auxiliary in Mn(III)-based oxidative free-radical cyclizations to provide diastereomerically enriched cycloalkanones (60% de).[7] Our interest in (R)-(−)-2,2-diphenylcyclopentanol is its utility as a chiral auxiliary in Lewis acid-promoted, asymmetric nitroalkene [4+2] cycloadditions. The 2-(acetoxy) vinyl ether derived from alcohol (R)-**1** is useful for the asymmetric synthesis of 3-hydroxy-4-substituted pyrrolidines from nitroalkenes (96% ee).[8] In a similar fashion, a number of enantiomerically enriched (71–97% ee) N-protected, 3-substituted pyrrolidines have been prepared in two steps from 2-substituted 1-nitroalkenes and (R)-2,2-diphenyl-1-ethenoxycyclopentane **(2)** (see Table).[9]

TABLE I
SYNTHESIS OF OPTICALLY ACTIVE 3-SUBSTITUTED PYR

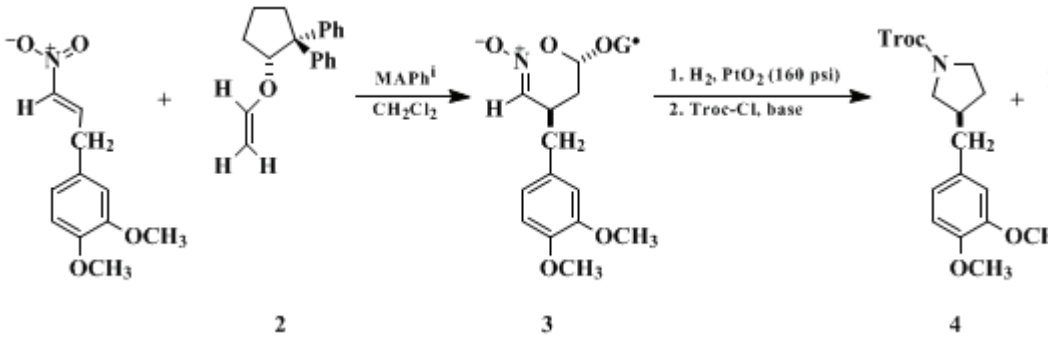


R

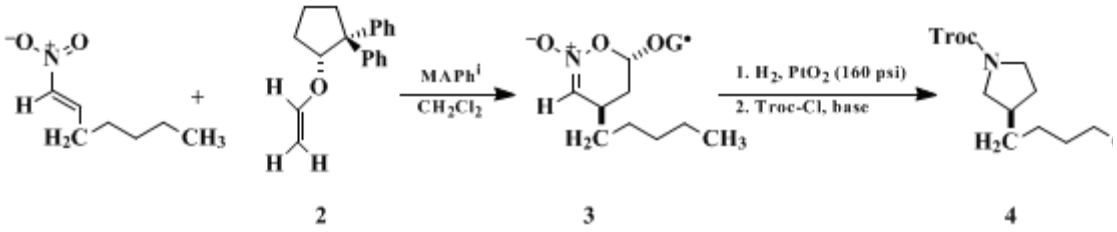
phenyl



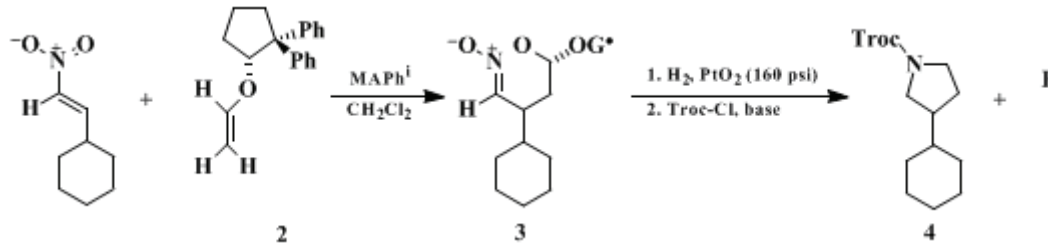
veratryl



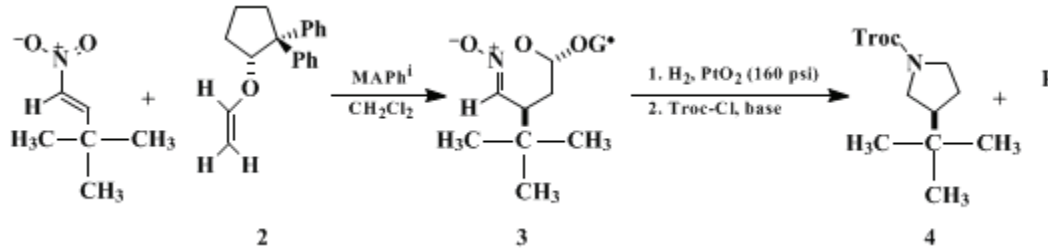
pentyl



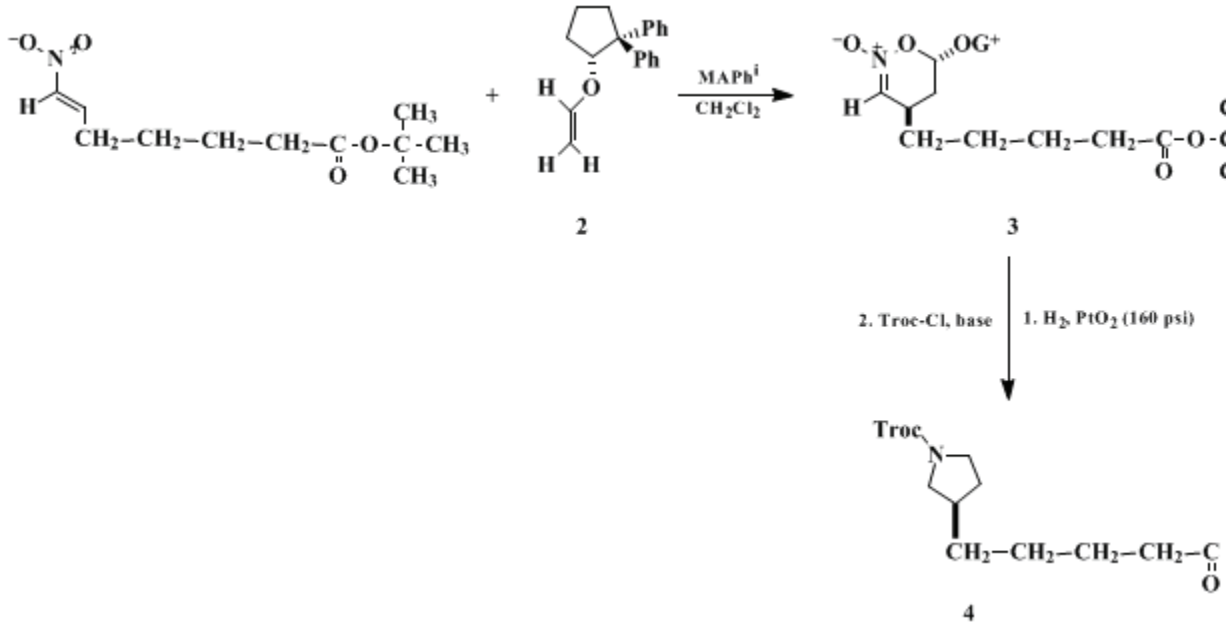
cyclohexyl



tert-butyl



$-(CH_2)_4CO_2$-tert-Bu



i) Methylaluminum bis-2,6-diphenylphenoxide.

2,2-Diphenylcyclopentanone previously has been synthesized several times employing three general approaches.[10 11 12 13,14 15,16] The most common approach involves alkylation of diphenylacetonitrile with a 4-halobutyronitrile followed by Thorpe-Ziegler cyclization and acid hydrolysis to afford the ketone.[10,11,12,13] One- and two-step preparations of the enaminonitrile have been reported. The best results have been obtained by using sodium amide in liquid ammonia (70% yield).[11] Acid hydrolysis (H_2SO_4) of the enaminonitrile is reported to afford the desired ketone in only moderate yields employing tedious procedures. Alternatively, the ketone is available by allylation of diphenylacetic acid followed by Lewis acid promoted Friedel Crafts acylation to afford the 5,5-diphenyl-2-cyclopentenone.[14,15] Subsequent reduction provided the ketone, however, only in 20% overall yield.[15] A more recent and more conceptually attractive approach involves the one step diphenylation of cyclopentanone trimethylsilyl enol ether with diphenyliodonium fluoride (DIF) giving the desired ketone in 51% yield.[16] The disadvantage of this approach lies in the preparation of the DIF reagent, available in one step from very expensive diphenyliodonium iodide or in five steps from inexpensive, available starting materials.

The procedure described here represents a reliable modification of the alkylation/Thorpe-Ziegler approach to 2,2-diphenylcyclopentanone applicable to large-scale preparations. The use of LDA as the alkylation base, in exact stoichiometry, has been found to avoid over-reaction and the undesired fragmentation pathway of the enaminonitrile observed with sodium amide. The Thorpe-Ziegler cyclization proceeds smoothly employing modified literature conditions[10] with potassium tert-butoxide as the base. Hydrolysis of the enaminonitrile with hydrochloric acid,[17] was found to be superior to previously reported methods, which led to incomplete consumption of the intermediate cyano ketone in our hands. The ratio of solvent volume to enaminonitrile is very important and more concentrated reaction mixtures result in incomplete conversion of the cyano ketone even after prolonged heating.

Asymmetric reduction of the ketone on a 1.0-g (4.0-mmol) scale to provide (R)-(−)-2,2-diphenylcyclopentanol (96% ee) has been reported employing (+)-β-chlorodiisopinocampheylborane; however, the reaction is extremely slow and inefficient [70% yield, 5 days, 2.6 equiv of (+)-β-chlorodiisopinocampheylborane].[6] Other efforts to obtain enantiomerically pure **1** by means of enzymatic hydrolysis of the corresponding racemic acetates using horse liver acetone powder (HLAP) and pig liver acetone powder (PLAP) have been only moderately successful and are of limited utility [4.0-mmol scale, 28% yield, 96.5% ee (R)].[18]

The oxazaborolidine-catalyzed borane reduction of 2,2-diphenylcyclopentanone provides an efficient and useful alternative for the asymmetric synthesis of (R)-**1** on a preparative scale. Variation of

several reaction parameters such as catalyst loading, solvent, temperature, and addition order, have led to the development of an optimized procedure for this reduction. To achieve a selectivity of >90% ee, the reaction requires the use of 10 mol% of the oxazaborolidine catalyst, which is easily prepared in two steps from natural proline[4] or in one step from commercially available (S)-α,α-diphenylpyrrolidinemethanol. When using a smaller catalyst loading a significant decrease in selectivity is observed [5 mol% cat. provides 87% ee (R)-**1**]. The oxazaborolidine catalyst used in these experiments was purified by bulb-to-bulb distillation prior to use and quickly weighed in the open atmosphere. Examination of the purified catalyst by ^{1}H NMR confirmed the presence of B-methyloxazaborolidine as well as varying amounts of the hydrated adduct (approximately 7–20%).[4] Unfortunately, it is not clear whether the hydrated adduct was the result of trace amounts of water in the NMR solvent, exposure to atmospheric moisture, or simply insufficient purification. Regardless, the use of different batches of the catalyst provided reproducible results that are within experimental error [(R)-**1** with 91–94% ee]. Several solvents such as toluene, dichloromethane and THF have been reported to be useful in oxazaborolidine reductions;[19] however, for the reduction of 2,2-diphenylcyclopentanone the use of THF was found to provide the highest enantioselectivity. An extremely important parameter in this reaction is temperature. The reaction displays an inverse temperature effect with respect to enantioselectivity, where decreased selectivity is observed at lower temperatures. This interesting phenomenon in oxazaborolidine-catalyzed reductions has precedents,[5] and can be attributed to the slow breakdown of the catalyst-product complex at low temperatures. The catalyst-product complex is a highly active but less selective catalyst for the reduction of the starting ketone.[20] Accumulation of this undesired intermediate can be avoided by running the reaction at higher temperatures (40°C) as well as using a slow inverse addition of the ketone to the catalyst-borane mixture.

The oxazaborolidine-catalyzed borane reduction to prepare (R)-**1** is an improvement over existing methods such as the β-chlorodiisopinocampheylborane reduction,[6] and enzymatic resolution[18] for several reasons. First, the reaction uses an easily obtained *catalytic* reducing agent that provides the chiral alcohol in 92% ee. Secondly, the reaction proceeds at a reasonable rate (6–8 hr) and affords the chiral alcohol (92% ee) in nearly quantitative yield (97%). Finally, the work-up, isolation and purification of the product is straightforward and requires no column chromatography, only bulb-to-bulb distillation and recrystallization, affording (R)-**1** in 75% yield with 97% ee. In addition, the catalyst precursor, (S)-α,α-diphenylpyrrolidinemethanol, can be easily recovered in excellent yield.

References and Notes

1. Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801. We are grateful to Dr. David J. Mathre (Merck) for valuable discussions and the generous gift of B-methyloxazaborolidine catalyst.
2. Gilman, H.; Cartledge, F. K. *J. Organometal. Chem.* **1964**, *2*, 447.
3. Ruzicka, L.; Koolhaas, D. R.; Wind, A. H. *Helv. Chim. Acta* **1931**, *14*, 1151.
4. Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751; Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corley, E. G.; Desmond, R. *Org. Synth., Coll. Vol. IX* **1998**, 676.
5. Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465.
6. Potin, D.; Dumas, F.; d'Angelo, J. *J. Am. Chem. Soc.* **1990**, *112*, 3483.
7. Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640.
8. Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576.
9. Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221.
10. Easton, N. R.; Nelson, S. J. *J. Am. Chem. Soc.* **1953**, *75*, 640;
11. Sneen, R. A.; Jenkins, R. W., Jr.; Riddle, F. L., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 1598;
12. Salmon-Legagneur, F.; Neveu, C. *Bull. soc. chim. France* **1956**, 929;
13. Salmon-Legagneur, F.; Rabadeux, J. *Bull. soc. chim. France* **1967**, 1310.
14. Craig, P. N.; Witt, I. H. *J. Am. Chem. Soc.* **1950**, *72*, 4925;
15. Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690.

16. Chen. K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764.
17. Snider, T. E.; Morris, D. L.; Srivastava, K. C.; Berlin, K. D. *Org. Synth., Coll. Vol. VI* **1988**, 932.
18. Randrianasolo-Rakotozafy, L. R.; Azerad, R.; Dumas, F.; Potin, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1993**, *4*, 761.
19. Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880.
20. Personal communication with Dr. David J. Mathre of Merck Research Laboratories.

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

(+)-β-chlorodiisopinocampheylborane

β-chlorodiisopinocampheylborane

brine

(R)-(−)-2,2-DIPHENYLCYCLOPENTANOL

Methylaluminum bis-2,6-diphenylphenoxide

β-methyloxazaborolidine

ethanol (64-17-5)

hydrochloric acid,
HCl (7647-01-0)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

methyl alcohol,
methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

acetone (67-64-1)

carbon (7782-42-5)

pyridine (110-86-1)

toluene (108-88-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

4-chlorobutyronitrile (628-20-6)

Diphenylacetic acid (117-34-0)

sodium iodide (7681-82-5)

dichloromethane (75-09-2)

borane (7440-42-8)

methyl sulfide (75-18-3)

sodium amide (7782-92-5)

butyllithium (109-72-8)

proline,
(S)-proline (147-85-3)

Tetrahydrofuran (109-99-9)

4-bromobutyronitrile (5332-06-9)

Diphenylacetonitrile (86-29-3)

DIPHENYLIODONIUM IODIDE (2217-79-0)

hexane (110-54-3)

cyano ketone (1115-12-4)

tert-butyl alcohol (75-65-0)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

Cyclopentanol, 2,2-diphenyl-, (R)- (126421-67-8)

2-Amino-3,3-diphenyl-1-cyclopentene-1-carbonitrile (3597-67-9)

tert-butyl methyl ether (1634-04-4)

potassium tert-butoxide (865-47-4)

2,2-Diphenylcyclopentanone (15324-42-2)

B-methyloxazaborolidine

1,1-dicyano-4,4-diphenylbutane

4-Iodobutyronitrile (6727-73-7)

diphenylcyclopentanol

2-cyano-5,5-diphenylcyclopentanone (2674-76-2)

(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole (112022-81-8)

N-p-toluenesulfonamide (70-55-3)

2-(acetoxy)vinyl ether

5,5-diphenyl-2-cyclopentenone

diphenyliodonium fluoride

oxazaborolidine

(S)-α,α-diphenyl-2-pyrrolidinemethanol

(R)-diphenylcyclopentanol

(S)-diphenylcyclopentanol

(R)-2,2-diphenyl-1-ethenoxycyclopentane

(S)-α,α-diphenylpyrrolidinemethanol