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of Reliable Methods
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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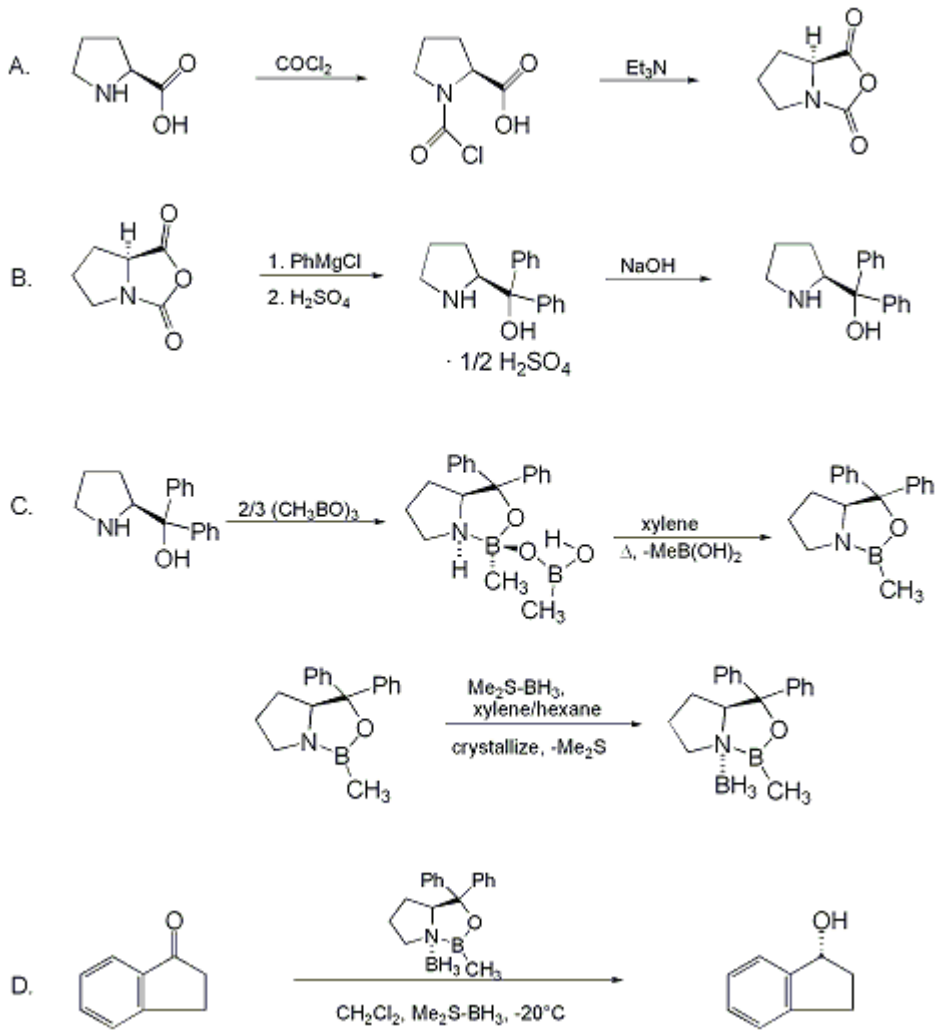
(S)-TETRAHYDRO-1-METHYL-3,3-DIPHENYL-1H,3H-PYRROLO-[1,2-*c*][1,3,2]OXAZABOROLE-BORANE COMPLEX

[Boron, trihydro(tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-*c*][1,3,2] oxazaborole-N[7])-, [I-4-(3aS-cis)]-]



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1. Procedure

CAUTION! This reaction should be carried out in a fume hood since phosgene is an insidious poison.

A. *(S)-Proline-N-carboxyanhydride*. A dry, 3-L, three-necked flask, fitted with a mechanical stirrer, nitrogen inlet tube, 500-mL, pressure-equalized addition funnel and a Teflon-coated thermocouple probe, containing dry tetrahydrofuran (THF) (600 mL) is charged with (S)-proline (60.0 g, 0.521 mol) (Note 1). To the cooled (15–20°C) suspension is added phosgene (324 mL, 0.625 mol, 1.93 M in toluene), via a pressure-equalized addition funnel, over a 0.5–1.0 hr period maintaining a temperature of

15–20°C (Note 2). The reaction mixture is then aged for 0.5–0.75 hr at 30–40°C. The reaction mixture should become homogeneous as the proline reacts with the phosgene to afford the intermediate N-carbamoyl chloride. Once homogeneous, the reaction mixture is aged an additional 0.5 hr, then concentrated under reduced pressure (15–20°C, 1000 down to 50 mBar) to a volume of 80 mL (Note 3). Dry tetrahydrofuran (600 mL, KF < 50 μg/mL) is added to the mixture and it is cooled to 0–5°C. Dry triethylamine (72.6 mL, 0.521 mol, KF < 50 μg/mL) is added over 0.25 hr (Note 4). The mixture is aged for 0.5 hr at 0–5°C, then filtered through an enclosed, 2-L, medium-frit Schlenk funnel under an atmosphere of nitrogen (with careful exclusion of moisture). The triethylammonium hydrochloride cake is washed with dry tetrahydrofuran (3 × 105 mL, KF < 50 μg/mL). The filtrate and washes are combined and used as is in the next reaction (Note 5) and (Note 6).

Caution! Benzene is generated in this reaction. Benzene is a known carcinogen.

B. *(S)-1,1-Diphenylprolinol*. A 3-L, three-necked flask, fitted with a mechanical stirrer, nitrogen inlet tube, 1-L addition funnel and Teflon-coated thermocouple probe, is charged with phenylmagnesium chloride (0.80 L, 1.6 mol, 2.0 M in tetrahydrofuran) (Note 7) and cooled to −10°C (Note 8). To the suspension is added, with stirring, the tetrahydrofuran solution of (S)-proline-N-carboxyanhydride over a 1-hr period maintaining the temperature at −15° to −10°C (Note 9). After the addition is complete, the reaction mixture is aged for 3 hr at −15°C, then 1 hr at 0°C (Note 10). The reaction is quenched into a 5-L, mechanically-stirred flask containing 2 M aqueous sulfuric acid (1.05 L, 2.1 mol) (0°C) over a 0.5–1.0 hr period (Note 11). The reaction mixture is aged for 1 hr at 0–5°C, filtered, and the magnesium sulfate cake washed with tetrahydrofuran (3 × 500 mL) (Note 12). The filtrate and tetrahydrofuran washes are combined and concentrated (1 atm) to a volume of 1.0 L (Note 13). The mixture is cooled to 0°C, aged 1 hr, and then filtered. The cake is washed with water (5°C, 2 × 100 mL) and ethyl acetate (3 × 180 mL) (Note 14). The cake is dried under reduced pressure (40°C, 50 mBar) to yield 79–88 g (50–56% based on proline) of (S)-diphenylprolinol sulfate as a free-flowing white crystalline solid, mp 275–290°C (Note 15).

A 3-L, three-necked flask, fitted with a mechanical stirrer, nitrogen inlet tube, and Teflon-coated thermocouple, is charged with (S)-diphenylprolinol sulfate (81.0 g, 0.268 mol), tetrahydrofuran (268 mL), and 2 M aqueous sodium hydroxide (268 mL). The mixture is stirred at 20–25°C until all the solid dissolves (0.5 hr) (Note 16). Toluene (1.1 L) is added and the mixture is aged 0.5 hr. The two-phase mixture is filtered through a medium frit sintered glass funnel and partitioned (Note 17). The upper layer is washed with water (130 mL) and the toluene is removed under reduced pressure to afford a light-tan colored oil that crystallizes upon standing at ambient temperature (Note 18). Recrystallization of the resulting light-tan crystals from heptane (ca. 2 mL of heptane per gram of prolinol) affords (S)-1,1-diphenylprolinol; [yield 64–68 g (94–99% yield based upon diphenylprolinol sulfate)] as white crystals, mp 76–78°C, >98% ee (Note 19),(Note 20)).

Caution! Neat (10 M) borane-methyl sulfide is an air- and moisture-sensitive flammable liquid. Dimethyl sulfide has a noxious odor. All reactions should be conducted in an efficient fume hood.

C. *(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole-borane complex*. A 500-mL, four-necked, round-bottomed flask (Note 21) is equipped with a Teflon-coated thermocouple probe, 60-mL pressure-equalizing addition funnel, nitrogen inlet, mechanical stirrer, and distillation head connected to a wide-bore, air-cooled condenser. The flask is charged with 200 mL of xylenes (Note 22) and (S)-diphenylprolinol (50.0 g, 198 mmol). To the vigorously stirred solution at 20° C is added a 50% (w/w) solution of trimethylboroxine (TMB) in tetrahydrofuran (38 g, containing 19 g, 152 mmol of TMB) (Note 23) dropwise over a 15-min period. The addition funnel is rinsed with dry xylenes (10 mL). During the addition an exothermic reaction occurs (warming the mixture to ca. 35°C) resulting in the formation of the bismethylboronic acid adduct as a white precipitate (Note 24). After the addition, the mixture is stirred for 0.5 hr, then heated and concentrated by distillation (1 atm) (Note 25) to a volume of ca. 100 mL (Note 26). The mixture is allowed to cool to ca. 60°C, and is charged with additional dry xylenes (200 mL) (Note 22). The distillation and nitrogen sweep are continued, this time until essentially all the solvent is removed. The mixture is then heated so that the internal temperature is

maintained between 160–180°C for a 0.5-hr period. The pale yellow oil (free oxazaborolidine) is cooled to 20°C (Note 26) and (Note 27), and diluted with dry xylenes (Note 22) to a volume of 100 mL. The distillation head is replaced with a 500-mL, pressure-equalizing addition funnel. At this point, the nitrogen sweep is discontinued; however, the vessel is maintained under a static atmosphere of nitrogen for the remainder of the reaction. To the well stirred solution is added neat (10 M) borane-methyl sulfide (21 mL, 210 mmol) (Note 23) over a 5-min period via syringe. The mixture is stirred for 0.5 hr at 20°C, then slowly diluted with dry hexane to a volume of 450 mL over a 1–2 hr period (Note 28). After the addition is complete, the mixture is aged for 1 hr at 20°C, cooled to −10°C, and then aged for 2 hr at −10°C. The mixture is filtered in an enclosed Schlenk filter (Note 29). The cake is washed with dry hexane (3 × 50 mL) (Note 30). The product is dried under reduced pressure (100 mBar, nitrogen sweep, 20°C) for 1 hr to afford 51–53 g of the title compound as a free-flowing white crystalline solid (Note 31),(Note 32).

Caution! Neat (10 M) borane-methyl sulfide is an air- and moisture-sensitive flammable liquid. Dimethyl sulfide has a noxious odor. All reactions should be conducted in an efficient fume hood.

D. *(R)-2,3-Dihydro-1H-inden-1-ol*. A 250-mL, three-necked, round-bottomed flask (Note 33) is equipped with a Teflon-coated thermocouple probe, a 125-mL pressure-equalizing addition funnel, nitrogen inlet, and Teflon-coated magnetic stirring bar. The flask is charged with the (S)-oxazaborolidine-borane complex (2.91 g, 10.0 mmol) (Note 34), purged with nitrogen, and charged with dry dichloromethane (10 mL) (Note 35). To the stirred solution is added borane-methyl sulfide (10 M, 20 mL, 200 mmol) (Note 36). The solution is cooled to −20°C (Note 37) and the addition funnel charged with a solution of 1-indanone (26.4 g, 200 mmol) (Note 38) in dry dichloromethane (75 mL) (Note 35). The 1-indanone solution is then added dropwise over a 4–6 hr period while maintaining the internal temperature of the reaction mixture at −20±5°C. After the addition is complete, the reaction mixture is stirred for 2 hr at −20°C (Note 39). After the reaction is complete, the mixture is cautiously poured into a 1-L flask containing magnetically-stirred, pre-cooled (−20°C) methanol (300 mL) (Note 40). The cooling bath is removed, and the stirred mixture allowed to warm to room temperature (20–25°C). After evolution of hydrogen ceases, the mixture is concentrated by distillation (1 atm) to a volume of ca. 50 mL. Methanol (200 mL) is added, and the distillation repeated (Note 41). The residue containing the product and diphenylprolinol is diluted with methanol (100 mL) and then loaded onto a 2.5 × 30-cm column packed with Amberlyst 15 (NH_4^+) (Note 42) at ca. 2.5 mL/min, collecting 40-mL fractions. The column is rinsed with methanol until the product is eluted (Note 43). The column is then rinsed with 1 M methanolic ammonia until the diphenylprolinol is eluted. The fractions containing the product (2–15) are combined, and then concentrated under reduced pressure (40°C, 100 mm) to give 26.2 g of crude product as a white crystalline solid (Note 44). The crude product is dissolved in hexane (260 mL) at 50–60°C in a 500-mL, round-bottomed flask fitted with a mechanical stirrer. The product is allowed to crystallize as the stirred mixture is slowly cooled to 20–25°C. The mixture is stirred for 4 hr at 20–22°C, filtered, and the cake washed with hexane (2 × 25 mL). The product is dried in a vacuum oven (30°C, 10 mm) to constant weight to yield 24.1–25.2 g (90–94%) of the title compound as a white crystalline solid (Note 45) and (Note 46).

2. Notes

1. The submitters used reagent grade tetrahydrofuran (EM Science) dried over 4 Å or 5 Å molecular sieves (Aldrich Chemical Company, Inc.), and determined the water content in the solvents by Karl Fisher titration (KF). The submitters report that the tetrahydrofuran should be dry (KF < 50 μg/mL) and *MUST NOT* contain any DMF (≤ 1 ppm). Also, the KF of the tetrahydrofuran/proline suspension should be < 50 μg/mL. The submitters used (S)-proline obtained from Ajinomoto while the checkers used (S)-proline from Aldrich Chemical Company, Inc. The proline should be milled and/or delumped prior to use, if necessary, to insure complete reaction. The enantiomeric purity of the (S)-proline should be > 99.5%, and can be assayed via the procedure of Marfey.[2] The checkers used HPLC grade THF (Fisher Scientific Company) that was dried over 4 Å molecular sieves.
2. Phosgene (1.93 M in toluene) was obtained from Fluka Chemical Company. Neat phosgene (Matheson Gas Products) and triphosgene (Aldrich Chemical Company, Inc.) (98%) can also be used. *Phosgene is an insidious poison so all manipulations with it must be performed in a fume hood with*

good ventilation. Any excess phosgene should be CAREFULLY decomposed in cold aqueous sodium hydroxide or aqueous ammonia. Since the addition is slightly exothermic, the rate of addition and external cooling is adjusted to maintain the internal temperature at 15–20°C.

3. The vacuum is decreased gradually in order to prevent bumping as the hydrogen chloride, excess phosgene, and tetrahydrofuran are removed. The checkers concentrated the reaction mixture using a rotary evaporator (a drying tube was placed in-line between the water aspirator and the rotary evaporator) under aspirator pressure (bath temp < 30°C), in an efficient fume hood The temperature must be maintained < 20°C during the concentration. At a volume of 80 mL the mixture is viscous but can still be stirred. The reaction can be assayed at this point by ^{1}H NMR; an aliquot withdrawn (ca. 30 mg) and dissolved in $CDCl_3$ (0.6 mL) giving ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.35 (s, toluene), 1.83–2.44 (m, 4 H, C-3-H_2 and C-4-H_2), 3.54–3.86 (m, 2 H, C-5-H_2), 4.47–4.52 (dd, 0.6 H, C-2-H rotamer),4.58–4.61 (dd, 0.4 H, C-2-H rotamer), 7.12–7.29 (m, toluene), 10.6–10.8 (br s, CO_2H). The ^{1}H NMR spectrum should not contain resonances at δ 4.9 (dd, 0.4 H, C-2-H) and 4.7 (dd, 0.6 H, C-2-H) (i.e., those corresponding to the N-carbamoyl chloride, acid chloride derivative of proline).

4. Triethylamine obtained from J. T. Baker Inc. was dried over 4 Å or 5 Å molecular sieves to a KF < 50 μg/mL. The checkers used triethylamine (Fisher Scientific Company) dried over 4 Å molecular sieves. The reaction is slightly exothermic so the rate of addition and external cooling are adjusted to maintain the internal temperature at 0–5°C. During the addition, a white precipitate of triethylammonium hydrochloride is formed.

5. The tetrahydrofuran solution of the proline-N-carboxyanhydride must be used immediately since on standing the material can polymerize and release CO_2. The reaction can be assayed at this point by ^{1}H NMR: (1.0 mL of the THF solution is concentrated under reduced pressure, and the residue dissolved in 0.6 mL of $CDCl_3$) δ: 1.83–2.39 (m, 4 H), 3.29–3.39 (m, 1 H, C-5-H), 3.70–3.81 (m, 1 H, C-5-H), 4.35–4.39 (dd, 1 H, C-2-H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 26.7, 27.2, 46.2, 62.8, 154.6, 168.8. The amount of triethylammonium hydrochloride, δ3.12 (q, 6 H) and 1.4 (t, 9 H), should be less than 5 mol%.

6. Alternate work-up: The filtered tetrahydrofuran solution is concentrated under reduced pressure (20° C, 50 mm) to a volume of 80 mL. Dry hexane (KF < 50 μg/mL, 600 mL) is slowly added with stirring. The product should begin to crystallize during the addition; seed if necessary. The mixture is stirred at 20–25°C for 1 hr, then filtered. The cake is washed with dry hexane (2 × 25 mL). Filtration is performed in an enclosed, medium-frit Schlenk funnel, under an atmosphere of nitrogen (with careful exclusion of moisture). The cake is dried under reduced pressure (30°C, < 100 mm) for 2 hr to yield 70.5 g (95%) as a free-flowing white crystalline solid, mp 51.5–52°C. The product should be stored cool, protected from moisture. By microanalysis, the product contains 1–4 wt% of triethylammonium hydrochloride. It is also possible to concentrate the THF to precipitate the product as a white solid.

7. Phenylmagnesium chloride (2.0 M in tetrahydrofuran) was obtained from Aldrich Chemical Company, Inc. The vessel must be dry and flushed with nitrogen prior to the addition of the phenylmagnesium chloride.

8. The reaction should not be cooled lower than −10°C because the Grignard reagent can crystallize. This can cause the stir shaft to break. It is best to add a small portion of the proline-N-carboxyanhydride, slurry the solution, and then cool to −10°C. Crystallization of the Grignard reagent does not affect the reaction yield.

9. The reaction is exothermic; therefore the rate of addition and external cooling are adjusted to maintain the internal temperature at −15 to −10°C.

10. The checkers allowed the reaction mixture to warm to ambient temperature overnight before quenching the reaction. If desired, the progress of the reaction may be monitored by the following HPLC assay. An aliquot (0.5 mL, accurately measured) is quenched into water (5 mL) containing 6 M aqueous sulfuric acid (200 μL). The solution is diluted to 100 mL with 1:1 H_2O/MeCN and analyzed by HPLC. The checkers did not monitor the reaction by HPLC. Column: 4.6 × 250-mm ZORBAX RX ; Eluent A: H_2O (0.01 M KH_2PO_4); Eluent B: MeCN; Linear Gradient: 80:20 (A:B) to 20:80 over 12 min; Flow Rate: 1.0 mL/min; Injection: 10.0 μL; Detection: UV (210 nm); Retention Times: Proline, N-benzamide 4.82 min; Diphenylprolinol 6.68 min; Benzene 11.45 min; Triphenylmethanol 14.66 min.

11. Sulfuric acid (Mallinckrodt Inc.) is diluted to the desired concentration with deionized water. Since the quench is exothermic the rate of addition and external cooling are adjusted to maintain the internal temperature below 20°C. During the quench a white precipitate of magnesium sulfate is formed. The amount of water and sulfuric acid used is important. Insufficient water results in the product (sulfate salt) precipitating with the magnesium sulfate. Excess water reduces the amount of magnesium

removed. Insufficient sulfuric acid results in non-filterable gels of magnesium hydroxide. Excess sulfuric acid increases the solubility of the diphenylprolinol sulfate, therefore reducing the yield of isolated product.

12. A large sintered glass funnel is required because of the amount of magnesium sulfate solution produced (~700 mL). Analysis of the magnesium sulfate cake by HPLC detected < 1 g of diphenylprolinol.

13. During concentration, a precipitate of diphenylprolinol sulfate and triphenylmethanol is formed. *CAUTION: Benzene (43 g), formed during the quench of the excess phenylmagnesium chloride, is removed during the concentration.*

14. Water is used to remove excess sulfuric acid, and ethyl acetate to remove triphenylmethanol, benzophenone and the N-benzamide derivative of proline.

15. Assay for enantiomeric purity: To a magnetically stirred suspension of diphenylprolinol sulfate (30 mg) in tetrahydrofuran (1 mL) is added 1 M aqueous sodium hydroxide (210 μL). The mixture is stirred for 15 min, then (R)-Mosher acid chloride (20 μL) is added. By TLC (EM Si-60, 8:2 hexane/EtOAc, R_f diphenylprolinol = 0.05, R_f Mosher amide = 0.4) the reaction is complete in 1 hr. The reaction mixture is diluted into hexane (9 mL), then eluted through a Baker Silica SPE (1 g) column (previously washed with hexane). The column was eluted with additional 9:1 hexane/tetrahydrofuran (5 mL). The combined eluates were than analyzed by capillary GC: Column: 0.33 mm × 30 m DB-23 (J&W Scientific); Oven Temperature: 250°C; Injector/Detector Temperature: 275°C; Carrier Gas: Helium (21 lbs/in^2), ca. 30:1 split; Injection: 1 μL; Detection: FID; Retention Times: (R,R)-Mosher amide 25.9 min; (R,S)-Mosher amide 29.6 min. The enantiomeric purity is 99:1.

16. There are occasions when a small amount of material does not dissolve. This does not affect the reaction.

17. Filtration is necessary to remove a small amount of polymeric solid that interferes with the phase separation.

18. Toluene is removed with a rotary evaporator (water aspirator, 40°C bath temperature). If desired, a toluene flush (300 mL) may be employed to remove residual traces of water. Concentration serves both to remove THF and azeotropically dry the solution. The last traces of solvent are removed by placing the oil under high vacuum (ca. 1 mBar) at room temperature overnight.

19. The physical properties are as follows: lit. mp: 76.5–77.5°C;[2] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.57–1.79 (m, 4 H, C-3-H_2, C-4-H_2), 2.93–2.98 (m, 1 H, C-5-H), 3.02–3.07 (m, 1 H, C-5-H), 4.27 (t, J = 7.6, C-2-H), 7.16–7.21 (m, 2 H, Ar-H), 7.28–7.34 (m, 4 H, Ar-H), 7.53–7.72 (m, 4 H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.4, 26.3 (C-3, C-4), 46.7 (C-5), 64.5 (C-2), 125.5, 125.8, 126.3, 126.4, 127.9, 128.2, (C-2'-C-6', C-2"-C-6"), 145.4 (C-1"), 148.1 (C-1').

20. If desired, the diphenylprolinol may be assayed for enantiomeric purity as described in (Note 15).

21. The glassware was oven-dried (110°C) before use. The 500-mL round-bottomed flask was graduated in 100-mL increments. The checkers used argon in place of nitrogen.

22. The xylenes (EM Science) were dried over 4 Å molecular sieves. Residual water content < 20 μg/mL by Karl Fisher titration. The checkers dried hexanes (Fisher Scientific Company), tetrahydrofuran, and xylenes over 4 Å molecular sieves. The checkers did not measure the residual water content of the solvents.

23. Trimethylboroxine (as a 50 wt% solution in THF) and borane-methyl sulfide (10 M) were obtained from Callery Chemical Company. The checkers employed 50 wt% trimethylboroxine/THF solution (prepared from neat trimethylboroxine (Aldrich Chemical Company, Inc.) and dry THF). The checkers used borane-methyl sulfide obtained from Aldrich Chemical Company, Inc.

24. The submitters report that a two-stage exotherm occurs during the addition. The first exotherm occurs as the trimethylboroxine reacts with the diphenylprolinol, and the second occurs as the intermediate bismethylboronic acid adduct crystallizes. Typically, the intermediate begins to crystallize after ca. one third of the trimethylboroxine is added. The reaction should not be run more concentrated. The checkers observed an exothermic reaction (warming from 20 to 45°C) after approximately one half to two thirds of the trimethylboroxine/THF solution was added.

25. The vessel is swept with a gentle stream of nitrogen during the distillation and subsequent operation to ensure the complete removal of the reaction by-products. The condenser should be air-cooled during the initial stages of the distillation to prevent it from being plugged with methylboronic acid. The checkers heated the stirred mixture rapidly to the boiling point (over ca. 20–30 min period) and used an argon sweep in place of nitrogen during the distillation.

26. The essentially pure free oxazaborolidine will slowly solidify on standing (mp 79–81°C). Although this material can be stored and used "as is" if scrupulously protected from adventitious moisture, the submitters recommend that it be converted to the more stable borane complex.
27. The physical properties are as follows: mp 80–83°C (corr); ^{1}H NMR (500 MHz, 0.15 M in $CDCl_3$) δ: 0.46 (s, 3 H, B-CH_3), 0.85–0.93 (m, 1 H, C-4-H), 1.64–1.85 (m, 3 H, C-4-H, C-5-H_2), 3.08–3.13 (m, 1 H, C-6-H), 3.38–3.43 (m, 1 H, C-6-H), 4.40–4.43 (dd, 1 H, J = 5.5, 9.8, C-3a-H), 7.23–7.43 (m, 8 H, Ar-H), 7.59–7.61 (m, 2 H, Ar-H); ^{11}B NMR (64.2 MHz, 0.15 M in $CDCl_3$) δ: 34.6; ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.7 (br, B-CH_3), 26.3 (C-5), 30.1 (C-4), 42.8 (C-6), 72.6 (C-3a), 87.7 (C-3), 126.1, 126.2, 126.5, 127.0, 127.6, 128.0 (C-3', C-3", C-4', C4", C-5', C-5"), 143.9, 147.5 (C-1', C-1"); IR (CCl_4) cm^{-1}: 3060, 3025, 2980, 2875, 1445, 1335, 1315, 1235, 995, 695; low-resolution EIMS: m/z 277.2 $[M]^+$. The solvent used for the NMR spectra must be dry and free of HCl or DCl (molecular sieves and/or anhydrous potassium carbonate).
28. During the addition, the oxazaborolidine-borane complex crystallizes. A slow addition of dry hexane favors the formation of larger crystals.
29. During the filtration it is important to keep the operation under an atmosphere of dry nitrogen to prevent moisture from condensing on the product. The submitters have also isolated the product in a 600-mL, sintered-glass funnel contained in a large bag maintained under an atmosphere of dry nitrogen. The checkers performed the filtration in a 600-mL, medium-frit sintered glass funnel contained in a large plastic glove bag maintained under an argon atmosphere.
30. The three hexane washes are first used to rinse product remaining in the reaction vessel.
31. The physical properties are as follows: mp 124–127°C (dec); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.77 (s, 3 H, B-CH_3), 1.0–1.9 (very br s, 3 H), 1.28–1.37 (m, 1 H, C-4-H), 1.56–1.68 (m, 1 H, C-5-H_2), 1.89–2.0 (m, 2 H, C-5-H_2), 3.19–3.24 (m, 1 H, C-6-H), 3.37–3.43 (m, 1 H, C-6-H), 4.66 (t, 1 H, J = 7.9, C-3a-H), 7.2–7.4 (m, 8 H, Ar-H), 7.6 (m, 2 H, Ar-H); ^{11}B NMR ($CDCl_3$) δ: 34.5 (oxazaborolidine-B), −14.5 (complexed H_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −3.9 (br, B-CH_3), 24.9 (C-5), 31.4 (C-4), 57.7 (C-6), 76.2 (C-3a), 90.6 (C-3), 125.0 (C-2", C-6"), 125.4 (C-2', C-6'), 127.1 (C-4"), 127.3 (C-4'), 128.1 (C-3", C-5"), 128.2 (C-3', C-5'), 143.5 (C-1"), 144.6 (C-1'). Anal. Calcd for $C_{18}H_{23}B_2NO$: C, 74.29, H, 7.97; N, 4.81. Found: C, 74.34; H, 8.00; N, 4.69.
32. The product is stored at room temperature protected from moisture. A nitrogen atmosphere is recommended for long term storage. Unlike the free oxazaborolidine that readily reacts with and is decomposed by atmospheric moisture, the oxazaborolidine-borane complex is significantly more stable, allowing it to be handled briefly in the open.
33. The glassware was oven-dried (110°C) before use. The checkers used argon in place of nitrogen.
34. The checkers observed gas evolution upon dissolution of the (S)-oxazaborolidine-borane complex in dichloromethane (CH_2Cl_2) at room temperature.
35. Dichloromethane (Fisher Scientific Company) was dried over 4 Å molecular sieves before use (water content < 20 mg/mL by Karl Fisher titration). The checkers did not measure the residual water content of the solvent.
36. Borane-methyl sulfide (10 M) was obtained from Callery Chemical Company. The checkers purchased borane-methyl sulfide (10 M) from Aldrich Chemical Company, Inc.
37. The reaction temperature was controlled using a cooling bath of methanol/ice and sufficient dry ice to maintain the indicated temperature.
38. 1-Indanone (Aldrich Chemical Company, Inc., 99+%) was used as received.
39. The progress of the reaction was followed by capillary GC. An aliquot (50 µL) is quenched into methanol (5 mL) and then analyzed using a 30-m × 0.32-mm DB-23 (J&W Associates) column (He carrier, 15 Ibs/in^2; ca. 30:1 split; oven temp: 50 to 150°C at 10°C/min; injector/detector temp: 250°C). 1-Indanol (t_R 10.9 min); 1-indanone (t_R 11.1 min).
40. *CAUTION: Hydrogen is evolved during the quench. The flask should be flushed with nitrogen. The reaction mixture is added at a rate to control the foaming.*
41. Methanol distillation serves to remove the majority of the boron species, as $B(OMe)_3$and $MeB(OMe)_2$
42. The Amberlyst (NH_4+) resin column is prepared as follows: Amberlyst 15 (H^+) (56 g, 100 mL dry, Rohm & Haas Co.) is suspended in an open beaker containing methanol (100 mL). [*CAUTION: the slurry exotherms to ca. 40°C without external cooling, and expands to ca. 1.5 times its initial volume.*] The slurry is poured into a 2.5 × 30-cm column and is eluted with 1 M methanolic ammonia (ca. 1 L) until a sample of the eluent diluted 1:1 with water is basic. The resin is then eluted with methanol (ca.

0.5 L) until a sample of the eluent diluted 1:1 with water is neutral. Once prepared, the column can be reused multiple times.
43. The progress of the column is monitored by UV (260 nm) or capillary GC (Note 39).
44. Chiral HPLC assay (4.6 × 250-mm Chiralcel-OB, 90:10 hexane/isopropyl alcohol, 0.5 mL/min, UV 254 nm): 1-indanone (t_R 29.6 min, < 0.1%), (R)-carbinol (t_R 10.3 min, 98.9%), (S)-carbinol (t_R 15.3 min, 1.1%). The sample was taken as a homogenous solution in methanol (prior to crystallization) to avoid enantiomeric enrichment. The checker's weight of crude (R)-1-indanol (prior to recrystallization); was 26 g, ca. 90% ee. The checkers also recovered crude (S)-diphenylprolinol (1.9 g) from the column.
45. The physical properties are as follows: Mp 73.0–73.5°C [lit.[3] 72.0°C]; HPLC (Chiralcel-OB) (R)-carbinol (t_R 10.3 min, > 99.9%), (S)-carbinol (t_R 15.3 min, <0.1%); $[\alpha]_D^{29}$ −45.5° (MeOH, *c* 1.184) [lit.[4] (S)-carbinol $[\alpha]_D^{25}$ +22.6° ($CHCl_3$, *c* 4.2) reported for the enantiomer]; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.2–2.25 (br s, 1 H, OH), 1.91–1.98 (m, 1 H, C-2-H), 2.46–2.53 (m, 1 H, C-3-H), 2.81–2.87 (m, 1 H, C-3-H), 3.04–3.10 (m, 1 H, C-3-H), 5.23 (t, 1 H, J = 6.0, C-1-H), 7.27–7.45 (m, 4 H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 29.7, 35.7, 76.2, 124.1, 124.7, 126.5, 128.1, 143.2, 144.9. Checkers yield of (R)-2,3-dihydro-1H-inden-1-ol after recrystallization was 19.6–20.3 g (73–76%); mp (corr): 73–74°C, $[\alpha]_D^{29}$ −18.1° (MeOH, *c* 1.3).
46. From the mother liquors was obtained an additional 1.75 g (6.5%) of 1-indanol of lower enantiomeric purity (HPLC: 85:15 R/S). The checkers concentrated the mother liquors to afford additional (R)-1-indanol (6.5–6.9 g) of lower enantiomeric purity (60–70% ee).

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

A-B. Enantiomerically pure (R)- and (S)-α,α-diaryl-2-pyrrolidinemethanols are precursors to several useful asymmetric catalysts,[5 6 7 8 9] including the corresponding oxazaborolidines.[19 10 11 12 13 14 15] Although several routes have been reported for making these compounds, none were suitable for our purposes (poor yields, multiple steps, difficult isolations).[16 17,18,20 21,22,23] We therefore developed a practical two-step synthesis of (R)-α, α-diaryl-2-pyrrolidinemethanols from (R)- or (S)-proline based on the addition of proline-N-carboxyanhydride to phenylmagnesium chloride.[24,25 26 27] This investigation led to the development of a reliable procedure for oxazaborolidine preparation based on the reaction of trimethylboroxine with diphenylprolinol.[24] Using this the submitters prepared a series (see Table) of enantiomerically pure α,α-diphenyl-2-pyrrolidinemethanols and their corresponding B-alkyl- and B-aryloxazaborolidines beginning with either (R)- or (S)-proline.

TABLE
α,α-DIARYL-2-PYRROLIDINEMETHANOLS

Entry	R	Yield[a]	e.e.[b]
1	Phenyl	73%	99.4%
2	4-Fluorophenyl	89%	99.4%
3	4-Chlorophenyl	59%	99.4%
4	4-Methylphenyl	57%	99.4%
5	4-(CF_3)-Phenyl	46%	99.4%
6	4-tert-Butylphenyl	50%	99.4%
7	4-Methoxyphenyl	53%	99.4%
8	3-Chlorophenyl	62%	99.4%
9	3,5-Dichlorophenyl	68%	99.4%
10	3,5-Dimethylphenyl	60%	99.4%
11	2-Naphthyl	64%	99.4%

[a]Isolated yield. [b]Enantiomeric excess (e.e.) determined by capillary GC analysis of

the (R)-α-methoxy-α-(trifluoromethyl)phenylacetic acid amide derivative.

The yield obtained for the preparation of (S)-α,α-diaryl-2-pyrrolidinemethanol was 67% at −10°C. It was found that addition of the Grignard reagent to the proline-N-carboxyanhydride resulted in a lower yield; therefore the proline-N-carboxyanhydride is added to the Grignard. The reaction is successful with meta- and para-substituted aryl Grignards, but with ortho-substituted aryl Grignard reagents only one equivalent adds, affording an unstable ketone intermediate too hindered for further addition. Alkyl Grignards do not afford the desired product so the submitters recommend the procedure described by Enders.[23]

The methods reported for the preparation of the oxazaborolidine include the reaction of diphenylprolinol with methylboronic acid 1) in toluene at 23°C for 1.5 hr with 4 Å molecular sieves present and 2) in toluene at reflux for 3 hr using a Dean-Stark trap, both followed by evaporation of solvent and molecular distillation (0.1 mm, 170°C).[19] An alternate method involved heating a toluene solution of 2-naphthylprolinol and methylboronic acid at reflux for 10 hr using a Soxhlet extractor containing 4 Å molecular sieves.[12] These methods afforded erratic results. The submitters therefore developed an alternate synthesis.

During their investigations they isolated the methylboronic acid adduct and the water adduct of the catalyst. The submitters found, by NMR experiments, that these were the compounds giving rise to spurious signals that were attributed to a "dimer". It was shown that the methylboronic acid adduct could be synthesized directly by treating 0.667 equiv of methylboronic acid with (S)-α,α-diphenyl-2-pyrrolidinemethanol. Heating at reflux in toluene yielded the catalyst free of any spurious signals. The catalyst prepared this way reproducibly afforded high levels of enantioselection. The oxazaborolidine must, however, be protected from moisture in order to retain high levels of enantioselection.

C. The reported procedure provides a practical preparation of (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-*c*][1,3,2]oxazaborole and conversion to its more stable borane complex.[28] [29] The oxazaborolidine-borane complex has also been prepared by treatment of a toluene solution of the free oxazaborolidine with gaseous diborane followed by recrystallization from a dichloromethane-hexane bilayer.[30] This and other chiral oxazaborolidines have been used to catalyze the enantioselective reduction of prochiral ketones.[31] [32] [33] [34] The yield and enantioselectivity of reductions using catalytic amounts of the oxazaborolidine-borane complex are equal to or greater than those obtained using the free oxazaborolidine.[28,29]

D. The use of chiral oxazaborolidines as enantioselective catalysts for the reduction of prochiral ketones, imines, and oximes, the reduction of 2-pyranones to afford chiral biaryls, the addition of diethylzinc to aldehydes, the asymmetric hydroboration, the Diels-Alder reaction, and the aldol reaction has recently been reviewed.[32,34] The yield and enantioselectivity of reductions using stoichiometric or catalytic amounts of the oxazaborolidine-borane complex are equal to or greater than those obtained using the free oxazaborolidine.[28,29] The above procedure demonstrates the catalytic use of the oxazaborolidine-borane complex for the enantioselective reduction of 1-indanone. The enantiomeric purity of the crude product is 97.8%. A single recrystallization from hexane then affords enantiomerically pure (> 99.8% ee) 1-indanol in 90–94% overall yield.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 362
- Org. Syn. Coll. Vol. 10, 448

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21. Kapfhammer, J.; Matthes, A. *Z. physiol. Chem.* **1933**, *223*, 43–52. In the submitters hands, addition of (S)-proline methyl ester hydrochloride to phenylmagnesium chloride, afforded (S)-α,α-diphenyl-2-pyrrolidinemethanol in 20% yield and 80% e.e. See also ref. [8].
22. Addition of N-(benzyloxycarbonyl)-(S)-proline methyl ester to phenylmagnesium chloride to give (S)-α,α-diphenyl-2-pyrrolidinemethanol (3 steps, 5 isolations, 0–50% yield from (S)-proline): ref. [9] and [10]. It should be noted that 6–10 equiv of the Grignard reagent are required to drive this reaction to completion. Quenching the excess phenylmagnesium bromide affords benzene—an environmental and health hazard.
23. Addition of N-benzyl-(S)-proline ethyl ester to phenylmagnesium chloride followed by catalytic hydrogenolysis affords (S)-α,α-diphenyl-2-pyrrolidinemethanol (4 steps, 3 isolations, 51% yield from (S)-proline: Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belg.* **1988**, *97* , 691–704. This method has also been used to prepare other (S)-α,α-diaryl-2-pyrrolidinemethanols: ref. [12].
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

H_2O

hexanes

(S)-Proline-N-carboxyanhydride

(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2]oxazaborole-borane complex

N-carbamoyl chloride

(S)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole-borane complex

xylenes

proline-N-carboxyanhydride

N-benzamide

Trimethylboroxine

pyrroglutamic acid

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

(R)- or (S)-proline

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrogen chloride,
HCl (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

magnesium (7439-95-4)

nitrogen (7727-37-9)

toluene (108-88-3)

Benzophenone (119-61-9)

isopropyl alcohol (67-63-0)

phosgene (75-44-5)

phenylmagnesium chloride (100-59-4)

magnesium hydroxide

Phenylmagnesium bromide (100-58-3)

dichloromethane (75-09-2)

diethylzinc (557-20-0)

triphenylmethanol (76-84-6)

magnesium sulfate (7487-88-9)

borane (7440-42-8)

1-Indanone (83-33-0)

methyl sulfide,
dimethyl sulfide (75-18-3)

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

Tetrahydrofuran,
THF (109-99-9)

heptane (142-82-5)

hexane (110-54-3)

triethylamine (121-44-8)

argon (7440-37-1)

helium (7440-59-7)

DCl (7698-05-7)

α,α-diphenyl-2-pyrrolidinemethanol (112068-01-6)

N-nitrosopyrrolidine (930-55-2)

triphosgene (32315-10-9)

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

oxazaborolidine

triethylammonium hydrochloride

(S)-1,1-Diphenylprolinol,
diphenylprolinol,
(R)-diphenylprolinol,
(S)-α,α-diphenyl-2-pyrrolidinemethanol,
(S)-diphenylprolinol

(S)-diphenylprolinol sulfate,
diphenylprolinol sulfate

(R)-2,3-Dihydro-1H-inden-1-ol,
(R)-1-indanol (697-64-3)

methylboronic acid (13061-96-6)

1-Indanol (6351-10-6)

2-naphthylprolinol

methyl pyroglutamate (4931-66-2)

(S)-proline methyl ester hydrochloride

N-(benzyloxycarbonyl)-(S)-proline methyl ester

N-benzyl-(S)-proline ethyl ester