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An Efficient Preparation of (*R**,*R**)-1,2-Dicyclohexylethane-1,2-diol, a Superior Chiral Director for Synthesis with Boronic Esters

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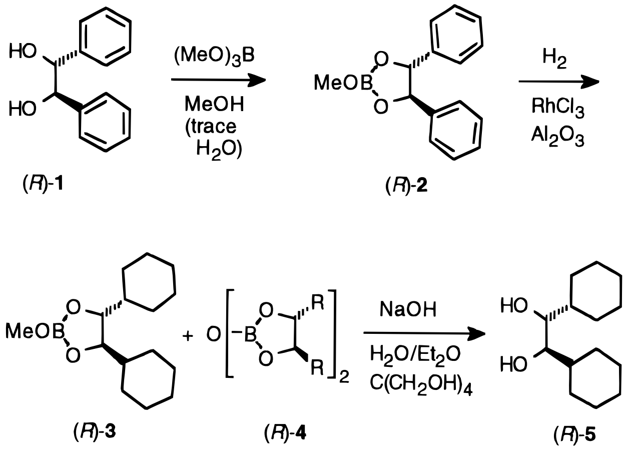
(*R**,*R**)-1,2-Dicyclohexylethane-1,2-diol (**5**) is a valuable chiral director for the insertion of a chloromethyl group into boronic esters with (dichloromethyl)lithium to form chain-extended α-chloro boronic esters,[1,2] and the recent Wang−Sharpless preparation[3] of (*R**,*R**)-1,2-diphenylethane-1,2-diol (**1**) from stilbene makes this precursor to **5** readily available in kilogram lots.[4] The original procedure for hydrogenation of **1**, 14% in methanol, over rhodium on alumina at 60 °C, 7 atm, by Hoffmann and co-workers yielded 84% of **5**,[1] and with the best of the variable lots of catalyst we encountered, we obtained 98% of **5**.

However, several obstacles remained to the routine preparation of large batches of **5**. Large batches of **1** could be hydrogenated at 1 atm and 25 °C but the reaction required weeks to complete.[2] Some batches of **1** poisoned the catalyst even after extensive efforts at purification. Addition of a small amount of acetic acid[2] sometimes seemed to help and sometimes did not, and sometimes the catalyst became poisoned when the hydrogenation was partially complete.

Some batches of commercial rhodium on alumina were active and yielded clean **5**, but others showed low or no activity, and some yielded several percent of the benzylic hydroxyl hydrogenolysis products 1,2-dicyclohexylethanol [distinguished by ^{1}H NMR at δ 0.70−0.95 (m) and 3.37−3.49 (m)] and 1,2-dicyclohexylethane [^{1}H NMR δ 0.70−0.95 (m)]. Rhodium on carbon was a much more active catalyst than rhodium on alumina, but yielded nearly 30% hydrogenolysis products. Rhodium trichloride was also active, but caused 5−10% benzylic cleavage.

In the hope that benzylic hydrogenolysis might be suppressed by conversion of the diphenylethanediol (**1**) to a stable cyclic borate ester, excess trimethyl borate was added to **1** to form (4α,5β)-2-methoxy-4,5-diphenyl-1,3,2-dioxaborolane (**2**). Because **2** is a liquid, it could be used in higher concentrations than **1**.

This approach proved successful. Up to 27% **2** by volume has been hydrogenated successfully at 50 °C under 11 atm of hydrogen within 3 days, and the proportion of **2** that was dehydroxylated to 1,2-dicyclohexylethanol was never more than 2% with any commercial rhodium catalyst, including the relatively active rhodium on carbon. Rhodium trichloride hydrate costs less per gram atom than the commercial catalysts, is easily recyclable, and yielded similar results when used together with alumina.[5] Treatment of the crude hydrogenation product **3** (and/or **4**) with aqueous 2 M sodium hydroxide and pentaerythritol yielded free diol **5** (95% isolated).



Instead of making **5**, the dioxaborolane **3** can be used directly in several ways. With simple boronic esters such as methyl or isopropyl alkylboronates, transesterification is fast and quantitative to yield the corresponding 2-alkyl-4,5-dicyclohexyl-1,3,2-dioxaborolanes. If **2** is first purified by distillation[6] and rigorous care is taken to exclude water, the hydrogenation product **3** can be distilled. Ethylation of **3** with ethylmagnesium bromide has been used to prepare 2-ethyl-4,5-dicyclohexyl-1,3,2-dioxaborolane.[2] However, if moisture is not excluded at all stages of the hydrogenation, a significant amount of high boiling oxybis(dioxaborolane) **4** (R = cyclohexyl) is formed as a byproduct if distillation is attempted.

A brief study with a simple boronic ester, (4α,5β)-2-methyl-4,5-diphenyl-1,3,2-dioxaborolane (the analog of **2** having CH_3−B in place of CH_3O−B), resulted in even cleaner hydrogenation, with no visible NMR evidence of hydrogenolysis to 1,2-diphenylethanol.

Recovery of most of the rhodium as the trichloride from spent catalyst can be effected conveniently with hydrochloric acid. Hydrogen ion alone has insufficient oxidizing potential to attack rhodium,[7] and air oxidation of the finely divided metal is likely involved.

Our improved hydrogenation procedure has allowed the use, simple recovery, and regeneration of a reproducible and active rhodium catalyst, rhodium chloride hydrate, which is soluble in methanol and deposits rhodium metal on alumina in situ when the vessel is pressured with hydrogen. Without alumina, the rhodium plated out on the walls of the glass liner in the hydrogenation vessel and was inactive. Alternatively, with

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(1) Hoffmann, R. W.; Ditrich, K.; Köster, G.; Stürmer, R. *Chem. Ber.* **1989**, *122*, 1783−1789.

(2) (a) Matteson, D. S.; Man, H.-W. *J. Org. Chem.* **1993**, *58*, 6545−6547. (b) Matteson, D. S.; Man, H.-W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560−4566.

(3) (a) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302−8303. (b) Some samples of potassium osmate have proved insoluble and inert under the conditions described in (ref 3a), but can be dissolved in water (heated as necessary) to make a 1% solution and then added over a period of ∼15 min. (We thank R. P. Singh for this observation.) Solutions of osmium tetraoxide in 1:1 water/*tert*-butyl alcohol also work well if added over the course of 1 h, but Wang and Sharpless have noted, and our inexperienced helper has reconfirmed, that the mixture overheats and gives a poor ee if the osmium is added all at once.

(4) Unfortunately, (*R**,*R**)-1,2-diphenylethane-1,2-diol is not a useful chiral director for this purpose, as reported in ref 1 and replicated in our laboratory by G. D. Schaumberg.

(5) However, hydrogenation of **2** at 25 °C with rhodium trichloride hydrate and charcoal required more than 1 week to complete and resulted in 6% debenzylation products.

(6) Attempted vacuum distillation of **4**, R = phenyl, at ∼250 °C, resulted in pinacol rearrangement to diphenylacetaldehyde. The thermal stability of **4**, R = cyclohexyl, has not been tested.

(7) *CRC Handbook of Chemistry and Physics*; Weast, R. C., Lide, D. R., Astle, M. J., Beyer, W. H., Eds., 1989; pp D154−D156.

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commercial anhydrous rhodium chloride, which is insoluble in methanol, a catalytically active precipitate of rhodium formed and no alumina was required.

These new developments make either pure enantiomer of (*R**,*R**)-1,2-dicyclohexylethane-1,2-diol (**5**) readily available. The pure enantiomers of pinanediol, the first successful chiral director for the asymmetric boronic ester synthesis,[8] are no longer cheaper than **5**, and pinanediol provides less stereoselectivity than C_2-symmetrical diols such as **5**.[1,2,9] Pinanediol should now be regarded as obsolete, with the possible exception of situations where a boronic ester that is unusually resistant to hydrolysis or transesterification might be required.

Experimental Section

Apparatus. Hydrogenations were carried out in a stainless steel autoclave equipped with a custom fitted removable 200 mL glass test tube as a liner, a magnetic stirrer operable at 1000 revolutions/min, and a heated oil bath with a thermocouple temperature regulator. Hydrogen from a cylinder was held at 10−11 atm gauge pressure via the regulator valve and suitable pressure connections.

(*R*)-(*R,*R**)-1,2-Dicyclohexylethane-1,2-diol (5) from Hydrogenation of (*R*)-(4α,5*β*)-2-Methoxy-4,5-diphenyl-1,3,2-dioxaborolane (2) with Rhodium Trichloride Hydrate.** (*R*)-(*R**,*R**)-1,2-Diphenylethane-1,2-diol[3] (**1**) (30.6 g, 143 mmol) was stirred with trimethyl borate (30.5 mL, 27.9 g, 269 mmol) for 4.5 h to dissolve all the solid. Methanol (50 mL) was added, and rhodium chloride trihydrate (0.303 g, 1.45 mmol, from recovered catalyst) and alumina (1 g) were added to the stirred solution. The autoclave was flushed with hydrogen, pressurized to 10−11 atm (gauge), and heated at 50 °C. Hydrogenation was incomplete after 48 h (pressure drop when source closed) but complete in 64 h. The autoclave was cooled to 20−25 °C and vented, and TLC analysis indicated complete hydrogenation. The mixture was filtered (suction) through Celite, which was washed with additional methanol (100 mL). (*CAUTION*: There is a possibility, not observed, of pyrophoric rhodium.) The combined methanol solution was stirred vigorously in a 2-L flask during addition of aqueous 2 M sodium hydroxide (150 mL) followed by pentaerythritol (36 g, 264 mmol) and water to 1.5 L total volume. As the mixture was stirred 16 h, **5** precipitated slowly. The solid was filtered, dried (36.9 g), dissolved in acetone (1 L), filtered, and concentrated under vacuum to a residue of fluffy crystalline **5** (31.0 g, 96%). ^{1}H NMR analysis showed 1,2-diphenylethane (distinguished by m at δ 0.70−0.95) and 1,2-diphenylethanol (δ 0.70−0.95, 3.37−3.49) (total <2%), which were removed by washing with pentane.

Hydrogenation of (*S*)-(4α,5*β*)-2-Methyl-4,5-diphenyl-1,3,2-dioxaborolane to (*S*)-(4α,5*β*)-2-Methyl-4,5-dicyclohexyl-1,3,2-dioxaborolane with Rhodium Trichloride Hydrate. (*S*)-(4α,5*β*)-2-Methyl-4,5-diphenyl-1,3,2-dioxaborolane (17.03 g, 68.1 mmol) in methanol (50 mL) was treated with rhodium chloride hydrate (0.181 g, 0.86 mmol) followed by alumina (1.84 g) and hydrogenated at 10−11 atm, 50 °C, for 51 h. The mixture was filtered through Celite with the aid of additional methanol (250 mL) and concentrated under vacuum to a clear liquid (17.1 g, 96%), which slowly solidified at 20−25 °C. NMR analysis showed no detectable (<1%) overreduction products and a trace of free 1,2-dicyclohexyl-1,2-ethanediol. Passage through a short silica column with pentane/ether (3:1) and concentration yielded (*S*)-(4α,5*β*)-2-methyl-4,5-dicyclohexyl-1,3,2-dioxaborolane (16.73 g, 94%), which again solidified; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 3), 0.9−1.8 (m, 22), 3.80−3.83 (m, 2); 75 MHz ^{13}C NMR ($CDCl_3$) δ −6.9 (broad, B−*C*), 25.8, 26.6, 27.2, 28.1, 42.9, 83.3, lit.[10] similar, but lower field, lacks B−*C* peak.

Rhodium Chloride Recovery. Spent rhodium on carbon and/or alumina and Celite filtering agent was refluxed in 5−10 times its volume of concentrated hydrochloric acid for 18 h. The red solution was decanted and filtered through Celite, and the solids were treated with one or two additional portions of hydrochloric acid, until only a pale red solution resulted. Concentration under vacuum resulted in crystallization of rhodium trichloride hydrate, which was collected, washed with cold ethanol, and dried in air. From one hydrogenation in which 0.6 g of rhodium chloride was used with carbon, two acid extractions led to recovery of 78% of the rhodium chloride.

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[9] Tripathy, P. B.; Matteson, D. S. *Synthesis* **1990**, 200−206.

[10] Matteson, D. S.; Man, H.-W. *J. Org. Chem.* **1994**, *59*, 5734−5741.