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(*S*,*S*)-DIISOPROPYLETHANEDIOL ("DIPED"): A NEW CHIRAL DIRECTOR FOR THE α-CHLORO BORONIC ESTER SYNTHESIS

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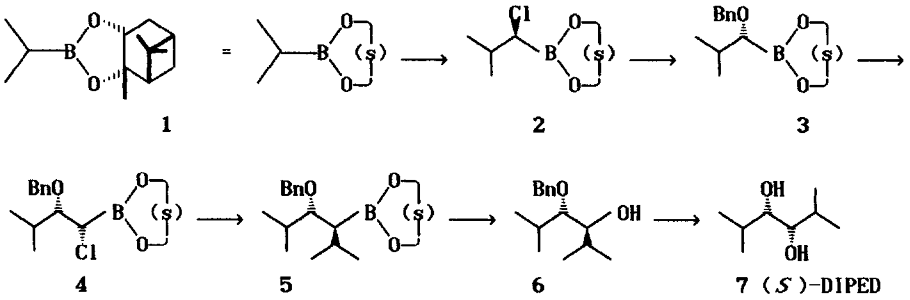
Summary: (*S*,*S*)-Diisopropylethanediol, "DIPED", has been synthesized by means of our new general chiral diol synthesis based on α-chloro boronic esters, and has in turn been shown to be an effective chiral (*R*)-directing group in this synthesis, consistently yielding (*R*)/(*S*)-ratios in the 25:1 to 30:1 range with a series of typical substrates.

Directed chiral synthesis based on α-chloro boronic ester chemistry can lead to a wide variety of structures.[1,2] We have used pinanediol as chiral director to achieve 99% chiral selectivity.[1] However, pinanediol boronic esters are too sterically hindered for some purposes, including hydrolysis of the pinanediol group from the boron.[2] Also, pinanediol lacks C_2 symmetry, and pinanediol (dichloromethyl)boronate reacts unselectively with organometallic reagents.[3] Oxygenated diols having C_2 symmetry (tartrate esters, diacetone mannitol) have not given promising results,[2] but (*R*,*R*)-2,3-butanediol as chiral director commonly yields 95/5 (*S*)/(*R*)-ratios and its boronic esters are very easily hydrolyzed.[4] Substituents larger than the methyl groups of the butanediol appeared likely to improve the chiral directing properties and impart hydrolytic stability in a useful medium range. Chiral diols are easily synthesized by our new chemistry,[1] and we have prepared (*S*,*S*)-diisopropylethanediol, "(*S*)-DIPED" [(3*S*,4*S*)-2,5-dimethylhexane-3,4-diol], from pinanediol isopropylboronate in an overall yield of 55%.

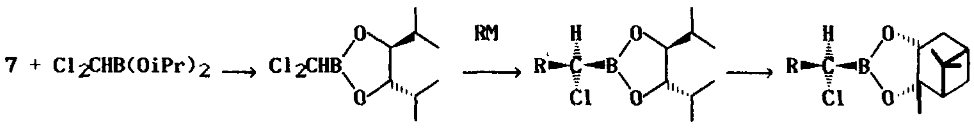
The synthesis of (*S*)-DIPED began from 88.8 g (0.4 mol) of (s)-pinanediol [= (+)-pinanediol][1] isopropylboronate (1),[5] which was added to 0.44 mol of (dichloromethyl)lithium[6] at -100 °C, then treated with 300 mL of 1 M anhydrous zinc chloride in THF and allowed to warm to 20-25 °C overnight. The solution was concentrated and worked up with saturated ammonium chloride in the manner previously described.[1] After concentration, the crude (s)-pinanediol (*S*)-1-chloro-2-methylpropylboronate (2) (96.3 g) was added to lithium benzyloxide prepared from 0.4 mol of butyllithium and 0.4 mol of benzyl alcohol in 400 mL of THF at -78 °C. The mixture was stirred for 18 h at 20-25 °C and worked up with saturated ammonium chloride.[1] Vacuum distillation yielded 90.1 g (74%) of (s)-pinanediol (1*R*)-1-benzyloxy-2-methylpropylboronate (3), bp 200 °C (0.3 torr); ^{1}H NMR ($CDCl_3$): δ 4.55 (q, 2, OCH_2Ph), 3.08 (d, 1, OC*H*B), plus typical[1] Ph and pinanediol peaks; $C_{21}H_{31}BO_3$ calcd: C, 73.68; H, 9.06; B, 3.21. Found: C, 74.03; H, 9.25; B, 3.33.



Addition of 85.5 g (0.25 mol) of 3 to 0.275 mol of (dichloromethyl)lithium in 200 mL of THF at -100 °C according to the usual procedure[6] and workup with saturated ammonium chloride followed by concentration of the organic phase yielded a residue of crude (s)-pinanediol (1*S*,2*S*)-1-chloro-2-benzyloxy-3-methylbutylboronate 4, which in THF at -78 °C was directly treated with isopropylmagnesium chloride (0.26 mol, 2M in ether) and stirred 18 h at 20-25 °C. Workup with saturated ammonium chloride was followed by flash chromatography of the nonvolatile organic material in 20-g batches on silica with 5% ether/light petroleum to yield 92.5 g (93%) of (s)-pinanediol (1*S*,2*R*)-1-isopropyl-2-benzyloxy-3-methylbutylboronate (5); ^{1}H NMR ($CDCl_3$): δ 3.42 (t, 1, $CHC\mathit{H}(OCH_2Ph)CH$), 4.69 (2, AB, $C\mathit{H}_2Ph$), plus pinanediol, alkyl, and aromatic peaks. Calcd. for $C_{25}H_{39}BO_3$: C, 75.37; H, 9.79; B, 2.76. Found: C, 75.50; H, 9.96; B, 2.82. To deboronate, 15.9 g (0.04 mol) of 5 was stirred with 0.17 mol of hydrogen peroxide (30%) and 0.072 mol of sodium hydroxide in 65 mL of 4:1 THF/water 1 h at 0 °C and overnight at 20-25 °C. After filtration (solid sodium pinanediol borate) the aqueous layer was extracted with ether. After concentration the (3*S*,4*S*)-5-benzyloxy-4-hexanol 6 was chromatographed on silica with 5:1 light petroleum/ethyl ether; 8.0 g (95%); ^{1}H NMR ($CDCl_3$): δ 0.94-1.04 (12, 2 d, $CH(C\mathit{H}_3)_2$), 1.55-2.15 (2, m, $C\mathit{H}(CH_3)_2$), 2.42 (1, d, $O\mathit{H}$), 3.15-3.41 (2, m, $C\mathit{H}OH$ + $C\mathit{H}OBn$), 4.62 (2, AB, $OC\mathit{H}_2Ph$), 7.31 (5, s, $C_6\mathit{H}_5$). Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 75.75; H, 10.35. Hydrogenolysis of 34 mmol of 6 in 80 mL of absolute ethanol at 1 atm. over 800 mg of 10% palladium on charcoal for 18 h followed by filtration, concentration, and recrystallization from cyclohexane yielded 4.7 g (95%) of (3*S*,4*S*)-2,5-dimethyl-3,4-hexanediol (7, "(*S*)-DIPED"); mp 72-74 °C; ^{1}H NMR ($CDCl_3$): δ 0.95 (12, d, $C\mathit{H}_3$), 1.15-2.02 (2, m, $C\mathit{H}(CH_3)_2$), 2.45 (2, broad d, $O\mathit{H}$), 3.31 (2, broad t, $C\mathit{H}OH$); 22.6 MHz ^{13}C NMR ($CDCl_3$): δ 18.23, 20.26, 31.34, 77.76. Calcd. for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.32; H, 12.23.

To prepare (*S*)-DIPED dichloromethylboronate (8), equimolar quantities of (*S*)-DIPED (7) and diisopropyl dichloromethylboronate[4,7] were stirred at 20-25 °C 18 h and distilled, bp 100-103 °C (2.5 torr); 90 MHz ^{1}H NMR ($CDCl_3$): δ 0.90 + 1.5-1.8 (d + m, $C\mathit{H}(C\mathit{H}_3)_2$), 4.01 (2, m, $C\mathit{H}O$), 5.41 (1, s, $C\mathit{H}Cl_2$). Calcd. for $C_9H_{17}BCl_2O_2$: m/e 238.0698. Found: 238.0704.

To convert **8** to α-chloro boronic esters, a solution of 0.31 g (1.3 mmol) of **8** in THF (3 mL) was stirred at -78 °C under argon during the dropwise addition of 1.3 mmol of a solution of the Grignard or lithium reagent over a period of 5 min. The mixture was stirred 5 min at -78 °C, 1.04 mL of a 1.0 M solution (0.8 equivalent) of anhydrous zinc chloride[1] in THF was added dropwise, and the mixture was stirred 18 h at 20-25 °C (except that for R = phenyl or vinyl, stirring was 2 h while the bath and solution warmed from -30 to +20 °C). The reaction mixture was poured into light petroleum (bp 30-60 °C) (20 mL) containing approx. 5 g of anhydrous magnesium sulfate, filtered, and concentrated to yield the (*S*)-DIPED (α*R*)-α-chloro boronate (**9**). For analytical purposes, the crude **9** was treated with an equivalent amount of (+)-pinanediol (99% ee) in hexane to form **10** and, after flash chromatography to remove gross impurities, the 200 MHz ^{1}H NMR spectrum was examined. The results are summarized in Table 1.



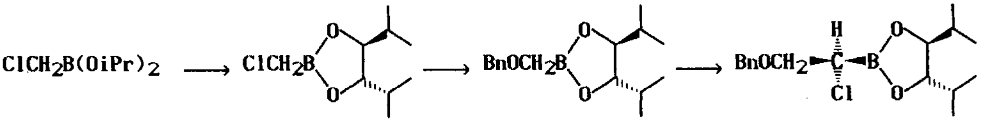
8 **9** **10**

Table 1. Yields and Isomer Ratios from Reactions of (*S*)-DIPED Dichloromethylboronate (**8**) with Organolithium or Grignard Reagents (RM).

R of RM	Yield, %	% (α*R*)[a]	NMR Peak	δ, (α*R*)	δ, (α*S*)
n-C_4H_9	79	97	Pinyl *H*	1.173	1.182
$(CH_3)_2CH$	97	96-97	BC*H*Cl	3.303	3.325
$C_6H_5CH_2$	86	96-97	BC*H*Cl	3.634	3.652
$CH_2{=}CH$	87	97	Pinyl *H*	1.155	1.173
C_6H_5	93	96-97	Pinyl *H*	1.025	1.142
CH_3	87	97[b]	Pinyl *H*	1.158	1.169
$PhCH_2OCH_2$[c]	62	93-95	^{13}C	87.08	87.02

[a] Estimated from magnitudes of clearest portions of NMR multiplets. [b] The MeLi contained 1 mol of LiBr, and 1.8 equivalents of zinc chloride was used. With 0.8 equivalent, the proportion of (α*R*)-isomer fell to 91-92%. [c] Reaction of (*S*)-DIPED benzyloxymethylboronate with (dichloromethyl)lithium.

The benzyloxymethyl group was introduced as (*S*)-DIPED benzyloxymethylboronate (12). DIPED chloromethylboronate (11) was prepared by reacting diisopropyl chloromethylboronate[8] with an equimolar amount of DIPED and was used without purification; ^{1}H NMR ($CDCl_3$): δ 3.02 (s, 2, $C\mathit{H}_2Cl$), plus DIPED peaks. Refluxing 22.4 g (109.5 mmol) of 11 and 120.5 mmol of lithium benzyloxide in 200 mL of dimethoxyethane 18 h yielded 21.5 g (71%) of 12, bp 138-140 °C (0.4 torr); ^{1}H NMR ($CDCl_3$): δ 3.38 (s, 2, $OC\mathit{H}_2B$), other peaks characteristic of DIPED and benzyl. Calcd. for $C_{16}H_{25}BO_2$: m/e 276.1896. Found: 276.1738. Reaction with (dichloromethyl)lithium at -100 °C followed by addition of 1.8 equivalents of zinc chloride (1 M in THF) and stirring at 20-25 °C for 48 h followed by the usual workup yielded 62% of (*S*)-DIPED (1*R*)-1-chloro-2-benzyloxyethylboronate (13).



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