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Bromination of tri(isopropyl)boroxine and asymmetric synthesis of (2-cyano-3,3-dimethylcyclopropyl)boronic esters

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Abstract

Bromination of triisopropylboroxine to tris(1-bromo-1-methylethyl)boroxine is far more facile than α-bromination of *sec*-alkylboronic esters. Normal fluorescent room light is sufficient to initiate the free radical reaction, which can be carried out as a titration. The steric environment for replacement of the bromine by lithioacetonitrile and subsequent asymmetric insertion of a chloromethyl group into the carbon–boron bond is more highly hindered than what has been studied previously, and the pinanediol ester proved to be the only useful chiral boronic ester in such circumstances. Cyclization of the cyano-substituted boronic ester to the corresponding cyclopropylboronic ester yielded a mixture of diastereomers, presumably the result of base-induced epimerization of the initially formed major isomer having the boronic ester and cyano groups *trans*.

Keywords: Boroxine; Boronic ester; Asymmetric synthesis; Cyclopropylboronic ester; Pinanediol

1. Introduction

This investigation began with the observation that α-bromination of triisopropylboroxine, the cyclic anhydride of isopropylboronic acid, is unexpectedly facile. An early attempt to brominate trimethylboroxine with *N*-bromosuccinimide had been totally unsuccessful [1]. Although *tert*-butyl hypochlorite chlorinated the *B*-methyl group of di-*tert*-butyl methylboronate in low yield, similar treatment of trimethylboroxine resulted only in B–C bond cleavage [1]. Bromination of 2-(2-phenylethyl)-1,3,2-dioxaborolane has yielded only the benzylic bromination product [2]. Allylic bromination of dibutyl 1-butenylboronate yielded a 1:1 mixture of α- and γ-bromination products [3]. Bromination of 2-(1-methylpentyl)-1,3,2-dioxaborolane to the 1-bromo-1-methylpentyl derivative appears to have been the first successful α-bromination of a simple (*sec*-alkyl)boronic ester [4]. 2-(*sec*-Alkyl)-1,3-2-dioxaborinanes have proved to be superior boronic esters for preparative α-bromination, which can be initiated by a sunlamp [5]. The same procedure applied to 2-isopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane yielded 82% of isolated α-bromoisopropyl boronic ester [6].

With a plentiful source of α-bromoisopropyl boronic esters available, we began an investigation of their utility as starting material for asymmetric synthesis via the reaction with (dichloromethyl)lithium [7,8]. In view of the dicyanocyclopropane synthesis discovered some time ago [9] and the cyanocyclobutane synthesis reported recently [10], it seemed appropriate to test the new system by replacing the bromine by cyanomethyl, running the asymmetric CHCl insertion, and ring closing the intermediate to a (2-cyano-3,3-dimethylcyclopropyl)boronic ester. Although α-halo-*sec*-alkylboronic esters have been synthesized previously and shown to undergo halide substitution [11], the only previous CHCl insertion had been carried out on 2-*tert*-butyl-1,3,2-dioxaborolane [12], which is achiral, lacking

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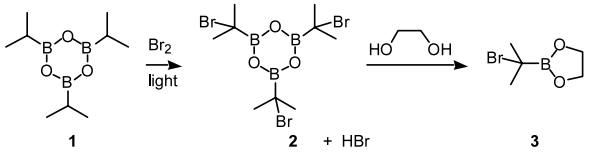
in functionality, and not as sterically crowded as the compounds reported here.

2. Results

Since the initial products isolated from the reaction of Grignard reagents with methyl or isopropyl borate and aqueous work up are boronic acids and these can easily be converted quantitatively to trialkylboroxines (boronic anhydrides) via azeotropic distillation of water, bromination of a tris(*sec*-alkyl)boroxine was tested. Rather surprisingly, the bromination proved so facile that the fluorescent room lights initiated the process immediately, and dropwise addition of the bromine to the stirred boroxine resulted in consumption of the bromine up to the equivalent amount as fast as it was added, with copious evolution of hydrogen bromide. The reaction of tri(isopropyl)boroxine (**1**) to form tris(2-bromo-2-propyl)boroxine (**2**) is essentially quantitative. No solvent is required, since the rate of addition of bromine governs the rate of the exothermic reaction.

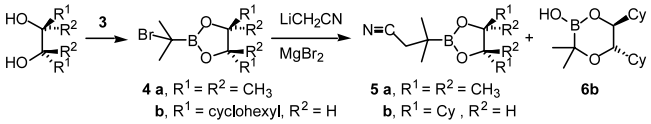


The reactivity of tri(isopropyl)boroxine (**1**) toward bromine parallels its sensitivity to atmospheric oxygen. Attempts to obtain a satisfactory ^{1}H-NMR sample of tri(isopropyl)boroxine by rapid transfer from the flask in which it had been prepared into the NMR tube invariably led to the presence of a few percent of isopropoxy derivative from air oxidation. Rigorous anaerobic transfer was not attempted. The brominated product **2** appeared much less sensitive to oxygen.

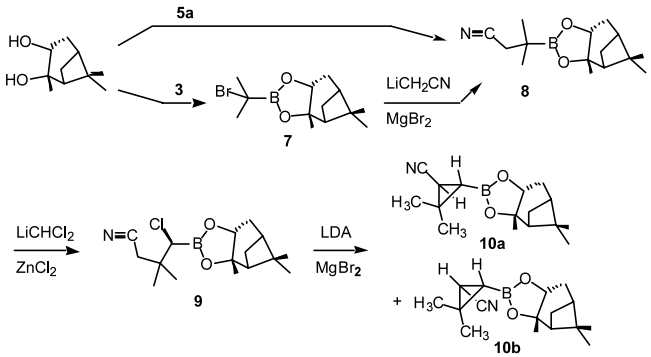
Brief exploration of the behavior of other trialkylboroxines has indicated that bromination of tricyclohexylboroxine is similarly facile, but primary alkylboroxines reacted only under sunlamp irradiation and yielded mixtures of bromination products [13]. Products were insufficiently characterized to report in detail, though it appeared that α-bromination of tripentylboroxine was favored to some extent.

Attempted displacement of bromide from **3** by ethyl lithioacetate or lithioacetonitrile was unsuccessful. Transesterification of **3** to the propanediol ester followed by reaction with lithioacetonitrile in the presence of magnesium bromide in tetrahydrofuran (THF) appeared to yield ca. 16% 2-(1,1-dimethyl-2-cyanoethyl)-1,3,2-dioxaborinane, but this product was incompletely characterized.

More promising results were obtained with the pinacol ester **4a** or the (*S*)-DICHED boronic ester **4b**, prepared from **3** by transesterification with pinacol or (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol, respectively. Reaction of **4a** with lithioacetonitrile promoted by magnesium bromide yielded 80% 2-(1,1-dimethyl-2-cyanoethyl)-4,4,5,5-dimethyl-1,3,2-dioxaborolane (**5a**), and **4b** with lithioacetonitrile promoted by magnesium bromide yielded ca. 69% (*S*,*S*)-2-(1,1-dimethyl-2-cyanoethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**5b**) in a mixture with what appeared to be the product of ring expansion of the 1,3,2-dioxaborolane to the 1,4,2-dioxaborinane **6b**. Reaction of **5b** (of questionable purity) with (dichloromethyl)lithium yielded a mixture of products and only ca. 30% of the chloromethyl insertion product could be isolated.



In contrast to the preceding frustrating results, reaction of the pinanediol ester **8** with (dichloromethyl)lithium proceeded efficiently. Access to **8** was readily achieved most efficiently by transesterification of the pinacol ester **5a** with pinanediol (88%). The alternative route via the pinanediol bromoalkylboronate **7** (96% from **3**) with lithioacetonitrile (50%) was less efficient. Reaction of **8** with (dichloromethyl)lithium proceeded nearly quantitatively to **9**, which was cyclized efficiently to a mixture of diastereomers **10a** and **10b**.



3. Discussion

A recent extensive experimental and theoretical study of α-boryl radicals has indicated that the planar configuration of 1,3,2-dioxaborolanyl-substituted radicals [$R_2C^{\bullet}$-$B(OCH_2)_2$] is favored over the transition state for rotation around the C–B bond by ca. 3 kcal mol^{-1} [14]. This modest stabilization of α-dioxyboryl radicals appears to be in accord with the earliest observations of the radical chemistry of boronic esters [15]. A higher rotation barrier was found for radicals derived from more reactive species such as trialkylboranes.

In view of the possibility of delocalizing the odd electron over the boroxine ring in a manner analogous to the delocalization of benzyl radicals, the high reactivity of tris(*sec*-alkyl)boroxines might have been anticipated. However, a search of Chemical Abstracts with the aid of SciFinder failed to find any previous example of bromination of a trialkylboroxine or of a tris(α-bromoalkyl)boroxine.

The chemistry of the substitution products derived from 2-(1-bromo-1-methylethyl)-1,3,2-dioxaborolanes studied as examples implies that there are severe steric restraints on substitution reactions. The apparent formation of **6b** via migration of oxygen instead of carbon from boron to the α-carbon is not entirely unprecedented, having been observed in a different kind of sterically constrained system [16], though the intermediate in this process, *B*-(α-alkoxyalkyl)-*B*-(alkyl)-*B*-(alkoxy)borane, is clearly not the thermodynamically favored product [17]. The precursor to **6b** would have a cyanomethyl substituent on boron, which would hydrolyze readily to **6b** under the work up conditions.

It is of interest that the pinanediol boronic ester series is the only one that works properly in the reaction sequence tested. It appears that pinanediol boronic esters are less sterically hindered than 1,2-dicyclohexyl-1,2-ethanediol boronic esters and that the rigidity of the pinanediol unit protects the boronic esters from such side reactions as ring expansion of the 1,3,2-dioxaborolane ring instead of alkyl migration.

It was disappointing that the high *trans* selectivity for the boronic ester and cyano groups seen in the cyclobutyl series [10] could not be duplicated with the cyclopropylboronic ester **10a**. There is a strong possibility that the cyclopropyl proton α to the cyano group of **10a** is more acidic than the protons α to the cyano group in precursor **9** and that the initially formed *trans* product **10a** epimerizes under the reaction conditions.

4. Experimental

4.1. General

THF was freshly distilled from sodium benzophenone ketyl. All operations involving air-sensitive compounds were carried out under an argon atmosphere. NMR spectra were recorded on a Varian Mercury 300 NMR instrument. Mass spectra were obtained with a VG Instruments 7070 EHF mass spectrometer. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

4.2. Tri(isopropyl)boroxine (*1*)

Following a standard procedure [18], isopropyl magnesium chloride (1.6 mol, 800 ml, 2 M in ether) and trimethyl borate (176 g) were added simultaneously over a period of 1 h to vigorously stirred anhydrous ether (1 l) at −78 °C. After overnight, the solution was cooled to 0 °C and hydrochloric acid (266 ml, 6 M, 1.6 mol) was added dropwise with stirring until the precipitate dissolved (pH < 4). The organic layer was separated and the aqueous phase was extracted with ether (3 × 200 ml). The combined organic phase was concentrated by distillation at atmospheric pressure under argon. Cyclohexane (430 ml) was added and the solution was refluxed under a Dean-Stark trap for 3 days. The cyclohexane was distilled through a short fractionating column (1 atm) and **1** was distilled at 70 °C (10 torr) (or 180–185 °C (700 torr)); 76.7 g (69%); 300-MHz ^{1}H-NMR ($CDCl_3$) δ 1.02 (d, $J = 6.6$ Hz, 18), 1.16 (m, $J =$ 6.3 Hz, 3H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 18.6; HRMS Calc., 210.1770; Found, 210.127 (not internally calibrated in this case). This compound oxidizes rapidly in air and was stored under argon.

4.3. Tris(2-bromo-2-propyl)boroxine (*2*)

The system was equipped with a suitably trapped gas outlet tube for release of hydrogen bromide. Tri(isopropyl)boroxine (76.7 g, 0.366 mol) was stirred rapidly under argon and fluorescent room lighting during the dropwise addition of bromine (56.5 ml, 1.01 mol), until the color of bromine persisted in the reaction mixture. At this point the product **2** began to crystallize to a low-melting solid and was directly suitable for use in the next step; 300-MHz ^{1}H-NMR ($CDCl_3$) δ 1.87 (s). This compound was not further characterized but was converted to ethylene glycol ester **3** and further derivatives. A distilled sample of **2**, b.p. 135–145 °C (5–6 torr), was obtained in 90% yield from an alternative procedure in which the bromination was carried out in dichloromethane as solvent.

4.4. 2-(1-Bromo-1-methylethyl)-1,3,2-dioxaborolane (*3*)

The crude **2** described above was dissolved in dichloromethane (80 ml). Ethylene glycol (67.25 ml, 1.21 mol) was added slowly under argon. When three-fourths of ethylene glycol had been added crystal formation was seen, but when the rest of the ethylene glycol had been added the crystals disappeared. An aqueous layer formed (ca. 30 ml), which was separated and extracted with dichloromethane (3 × 10 ml). The organic phase was dried over anhydrous magnesium sulfate. Distillation yielded **3**, b.p. 42 °C (1 torr); 168.3 g (79.5%); 300-MHz ^{1}H-NMR ($CDCl_3$) δ 4.31 (s, 4H), 1.81 (s, 6H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 66.6, 30.7. GC–MS for $C_5H_{10}BBrO_2$: $[M]^+$ Calc., 192 + 194; Found, 192 + 194.

4.5. 2-(1-Bromo-1-methylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4a**)

A solution of 2-(1-bromo-1-methylethyl)-1,3,2-dioxaborolane (**3**) (10.0 g, 51.85 mmol) and pinacol (6.13 g, 51.85 mmol) in diethyl ether (100 ml) was stirred for 16 h under argon. Two phases formed. The ether phase was separated and washed with saturated aqueous ammonium chloride (50 ml). The combined aqueous and ethylene glycol phases were extracted with diethyl ether (3 × 50 ml). The ether phase was dried over magnesium sulfate and concentrated on a rotary evaporator to yield a residue of **4a**, 11.87 g (92%); 300-MHz ^{1}H-NMR ($CDCl_3$) δ 1.77 (s, 6H), 1.28 (s, 12H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 84.4, 30.5, 24.7, *C*–B not observed; HRMS: Calc. for $C_9H_{18}BBrO_2$ [$M^+ + H$], 249.0662; Found (EI), 249.0658 (VG Instruments 7070 EHF mass spectrometer).

4.6. 2-(2-Cyano-1,1-dimethylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5a**)

A solution of LDA was prepared from diisopropylamine (17.0 ml, 121 mmol) in THF (40 ml) treated with butyllithium (45.4 ml, 1.6 M, 72.6 mmol) under argon. The solution was stirred at −78 °C during the dropwise addition of acetonitrile (4.79 ml, 91.0 mmol) along the side of the flask. A solution of 2-(1-bromo-1-methylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4a**) (15.0 g, 60.5 mmol) in THF (20 ml) was added dropwise from a syringe. Freshly prepared magnesium bromide solution in THF (500 ml, 0.2 M) (from 1,2-dibromoethane and magnesium turnings) was added and the mixture was allowed to warm to 20–25 °C and kept 24 h, then concentrated on a rotary evaporator. Work up with saturated aqueous ammonium chloride (150 ml) and ethyl acetate (3 × 150 ml) followed by drying over magnesium sulfate and concentration under vacuum yielded oily crude **5a**. A solution of this product in pentane was filtered through a short silica column to yield crystalline **5a**, m.p. 42–43 °C, 10.1 g (80%); 300-MHz ^{1}H-NMR ($CDCl_3$) δ 2.30 (s, 2H), 1.24 (s, 12H), 1.10 (d, 6H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 119.1, 84.2, 28.2, 24.9, 24.2, C–B not identified. HRMS: Calc. for $C_{11}H_{20}BNO_2$ [$M^+ - CH_3$], 194.1352; Found, 194.1349. Anal. Calc. for $C_{11}H_{20}BNO_2$: C, 63.19; H, 9.64; B, 5.17; N, 6.70; O, 15.30. Found: C, 62.86; H, 9.68; B, 5.37; N, 6.56%.

4.7. (*S*,*S*)-2-(1-Bromo-1-methylethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**4b**)

A mixture of 2-(1-bromo-1-methylethyl)-1,3,2-dioxaborolane (**3**) (4.27 g, 0.022 mol) and (*S*,*S*)-1,2-dicyclohexyl-1,2-ethanediol (5.0 g, 0.022 mol) in diethyl ether (100 ml) was stirred for 16 h at 20–25 °C under argon. The mixture was concentrated on a rotary evaporator, dissolved in pentane (50 ml), and extracted with aqueous ammonium chloride. The aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic phase was dried over magnesium sulfate and concentrated under vacuum. The residue (92% crude yield) was dissolved in pentane and filtered through a silica gel plug with additional pentane. Concentration yielded **4b**, m.p. 85–87 °C; 300-MHz ^{1}H-NMR ($CDCl_3$) δ 3.96 (d, $J = 4.8$ Hz, 2H), 1.76−0.96 (m, 22H), 1.80 (s, 6H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 84.0, 42.9, 30.7, 30.6, 28.2, 27.3, 26.5, 26.0, 25.9, *C*–B not detected. HRMS: Calc. for $C_{17}H_{30}BBrO_2$ [$M^+ - C_6H_{11}$], 273.0661; Found (EI), 273.0650.

4.8. (*S*,*S*)-2-(2-Cyano-1,1-dimethylethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**5b**)

A solution of LDA (13.4 mmol) in THF (20 ml) was stirred at −78 °C during the addition of acetonitrile (0.71 ml, 13.4 mmol) dropwise along the side of the flask. After 30 min, a solution of (*S*,*S*)-2-(1-bromo-1-methylethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**4b**) (4.00 g, 11.2 mmol) in THF (8 ml) was added dropwise at −78 °C. Magnesium bromide in THF (110 ml, 0.2 M) was added via cannula and the mixture was kept at 20–25 °C for 48 h. The solution was concentrated on a rotary evaporator and the residue was treated with saturated aqueous ammonium chloride (150 ml) and extracted with pentane (3 × 100 ml). The organic phase was dried over magnesium sulfate and concentrated. The residue of crude **5b** and alternative product **5c** was distilled in a Kugelrohr (bath 140 °C, 0.8–1.2 mm). Data for **5b**: Yield ca. 69%; 300-MHz ^{1}H-NMR ($CDCl_3$) δ 3.89 (dd, $J = 3.0$ Hz, 2H), 2.34 (d, $J = 1.5$ Hz, 2H), 1.13 (d, $J = 1.5$ Hz, 6H), 1.80−0.87 (m, 22H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 118.6, 83.9, 43.0, 28.3, 28.0, 27.2, 26.5, 26.0, 25.9, 24.4, 24.3, *C*–B not detected. HRMS: Calc. for $C_{19}H_{32}BNO_2$ [M^+], 317.2526; Found, 317.2511. Byproduct 1,4,2-dioxaborinane **6c** crystallized from the viscous product mixture, ca. 25%; 300-MHz ^{1}H-NMR ($CDCl_3$) δ 3.8 (s, 1H), 3.79 (d, $J = 8.4$, 1H), 3.15 (d, $J = 8.7$ Hz, 1H), 1.73−1.13 (m, 28H).

4.9. (*S*)-Pinanediol (1-bromo-1-methylethyl)boronate (7)

A solution of 2-(1-bromo-1-methylethyl)-1,3,2-dioxaborolane (**3**) (15.0 g, 77.8 mmol) and (*S*)-pinanediol (13.24 g, 77.8 mmol) in ether (200 ml) was stirred at 20–25 °C for 24 h under argon. The ethylene glycol phase that formed was separated, the ether solution was extracted with saturated aqueous ammonium chloride, and the ethylene glycol and aqueous phase were extracted with diethyl ether (3 × 100 ml). After drying over magnesium sulfate the ether phase was concen-

trated on a rotary evaporator, leaving a white solid residue of **7**, 22.55 g (96%); 300-MHz ^{1}H-NMR ($CDCl_3$) δ 4.38 (dd, $J = 6.9$ Hz, 1H), 2.36 (m, 1H), 2.26 (m, 1H), 2.11 (t, $J = 6.0$ Hz, 1H), 1.92 (m, 1H), 1.87 (m, 1H), 1.80 (s, 6H), 1.41 (s, 3H), 1.30 (s, 3H), 1.26 (d, 1H), 0.85 (s, 3H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 86.5, 78.5, 51.4, 39.3, 38.4, 35.5, 30.7, 30.5, 28.445, 27.1, 26.4, 24.1, *C*–B not detected. HRMS: Calc. for $C_{13}H_{22}BBrO_2$ [$M^+ - CH_3$], 285.0661; Found (EI), 285.0658.

4.10. (*S*)-Pinanediol [(1,1-dimethyl-2-cyano)ethyl]boronate (**8**)

4.10.1. Method A: from 2-(2-cyano-1,1-dimethylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**5a**) and (*S*)-pinanediol

(*S*)-Pinanediol (1.63 g, 9.56 mmol), **5a** (2 g, 9.56 mmol), diethyl ether (50 ml), and water (0.5 ml) were stirred together for 16 h at 20–25 °C under argon. The ether phase was extracted with saturated aqueous ammonium chloride (50 ml) and the aqueous phase was extracted with ether (3×50 ml). The combined organic phase was dried over magnesium sulfate and concentrated on a rotary evaporator. The residue (3.6 g) was chromatographed on silica with 1:9 ethyl acetate–hexane to yield **8**, 2.19 g (88%); m.p. 57–58 °C; 300-MHz ^{1}H-NMR ($CDCl_3$) δ 4.30 (dd, $J = 8.7$ Hz, 1H), 2.33 + 2.34 (AB, 2H), 2.39 − 2.19 (m, 3H), 2.05 (t, $J = 5.1$ Hz, 1H), 1.91 (m, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.13 (s, 6H), 1.06 (d, $J = 10.8$ Hz, 1H), 0.84 (s, 3H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 118.8, 86.3, 78.3, 51.2, 39.4, 38.2, 35.5, 28.6, 28.1, 27.1, 26.5, 24.3, 24.2, 24.0, *C*–B not detected. HRMS: Calc. for $C_{15}H_{24}BNO_2$ [M^+], 261.1900; Found, 261.1899. Anal. Calc. for $C_{15}H_{24}BNO_2$: C, 68.98; H, 9.26; B, 4.14; N, 5.36; O, 12.25. Found: C, 68.88; H, 9.10; B, 3.45; N, 5.29%.

4.10.2. Method B: from (*S*)-pinanediol (1-bromo-1-methylethyl)boronate (**7**)

This synthesis was carried out according to the procedure described for preparation of **5a** but with **7** in place of **4a**; yield of chromatographed **8**, 50%.

4.11. (*S*)-Pinanediol (1*S*)-(1-chloro-3-cyano-2,2-dimethylpropyl)boronate (**9**)

(Dichloromethyl)lithium was prepared according to the usual procedure by addition of butyllithium (12.0 mmol) dropwise down the wall of the flask to a stirred solution of dichloromethane (1.24 ml, 19 mmol) in THF at −100 °C [12]. (*S*)-Pinanediol (2-cyano-1,1-dimethylethyl)boronate (**8**) (2.5 g, 9.57 mmol) in THF (10 ml) was added dropwise. After stirring for 5–10 min a white solid formed. The mixture was allowed to warm to −78 °C and stirred for 1 h. Anhydrous zinc chloride solution (24 ml, 1.0 M in diethyl ether, 24 mmol) was added and the solid dissolved. The mixture was allowed to warm up to 20–25 °C and kept for 16 h, then worked up in the usual manner [7]. Evaporation of the solvent in a rotary evaporator yielded **9** of sufficient purity for use in the next step (2.92 g, 99%); 300-MHz ^{1}H-NMR ($CDCl_3$) δ 4.34 (dd, $J = 8.7$ Hz, 1H), 3.42 (s, 1H), 2.60 (s, 2H), 2.48 − 2.23 (m, 2H), 2.11 (t, $J = 6$ Hz, 1H), 1.98 − 1.84 (m, 2H), 1.42 (s, 3H), 1.30 (s, 3H), 1.25 (d, $J = 9.3$ Hz, 6H), 1.15 (d, $J = 9.9$ Hz, 1H), 0.85 (s, 3H); 300-MHz ^{13}C-NMR ($CDCl_3$) δ 118.2, 86.9, 78.5, 51.1, 39.4, 38.3, 36.8, 35.3, 28.5, 28.2, 27.0, 26.5, 25.5, 24.3, 24.1. HRMS: Calc. for $C_{16}H_{25}BClNO_2$ [M^+], 309.1667; Found, 309.1686.

4.12. (*S*)-Pinanediol (3-cyano-2,2-dimethylcyclopropyl)boronate (**10**)

A solution of LDA (10.55 mmol) freshly prepared from butyllithium and diisopropylamine in THF (7 ml) was added dropwise to a solution of (*S*)-pinanediol (1*S*)-(1-chloro-3-cyano-2,2-dimethylpropyl)boronate (**9**) (2.92 g, 10 mmol) in THF (10 ml) at −78 °C under argon. The reaction mixture was kept at 20–25 °C for 16 h. The solution was concentrated on a rotary evaporator. The residue was worked up with diethyl ether (100 ml) and saturated aqueous ammonium chloride (100 ml), and the aqueous phase was extracted with diethyl ether (3×50 ml). The combined organic phase was dried over magnesium sulfate. Concentration under vacuum yielded a residue of both diastereomers of **10** (2.60 g, 94.9%) in a ratio of 2:1, with the isomer believed to have the boronic ester group *trans* to the nitrile predominating. The isomers were separable by chromatography.

The product assigned the *trans* configuration (**10a**) is a solid, m.p. 72–74 °C; 300-MHz ^{1}H-NMR ($CDCl_3$) δ 4.29 (dd, $J = 8.8$ Hz, $J = 2.2$ Hz, 1H), 2.29 (m, 2H), 2.03 (t, $J = 5.2$ Hz, 1H), 1.92 (m, 1H), 1.79 (dt, $J = 14.6$ Hz, $J = 2.2$ Hz, 1H), 1.49 (d, $J = 6.3$ Hz, 1H), 1.38 (d, $J = 3.0$ Hz, 6H), 1.26 (d, $J = 16.5$ Hz, 6H), 1.07 (d, $J = 11.0$ Hz, 1H), 0.83 (s, 3H), 0.51 (d, $J = 6.3$ Hz, 1H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 120.8, 86.4, 78.1, 51.0, 39.4, 38.1, 35.4, 28.6, 27.0, 26.6, 25.8, 24.5, 24.0, 22.0, 15.2, *C*–B not detected. HRMS: Calc. for $C_{16}H_{24}BNO_2$ [M^+], 273.1900; Found, 273.1900.

The other product was assigned the *cis* configuration (**10b**); 300-MHz ^{1}H-NMR ($CDCl_3$) δ 4.35 (dd, $J = 8.8$ Hz, $J = 2.2$ Hz, 1H), 2.30 (m, 2H), 2.08 (t, $J = 5.2$ Hz, 1H), 1.92 (m, 1H), 1.86 (dt, $J = 16.5$ Hz, $J = 2.0$ Hz, 1H), 1.48 (d, $J = 9.6$ Hz, 1H), 1.40 (dd, $J = 7.1$ Hz, $J = 2.8$ Hz, 6H), 1.26 (d, $J = 19.5$ Hz, 6H), 1.16 (d, $J = 11.0$ Hz, 1H), 0.84 (s, 3H), 0.46 (d, $J = 9.6$ Hz, 1H); 75-MHz ^{13}C-NMR ($CDCl_3$) δ 119.6, 86.1, 78.0, 51.0, 39.5, 38.1, 35.5, 28.6, 27.6, 27.1, 26.6, 25.1, 24.1, 19.5, 15.4.

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