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A Study of Transesterification of Chiral (–)-Pinanediol Methylboronic Ester with Various Structurally Modified Diols†

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Summary. The transesterification of chiral (−)-pinanediol methylboronic ester was studied with various structurally modified diols by ^{1}H NMR to understand the factors influencing the unusual stability of this boronic ester as well as to find ways of recovering pinanediol from its methylboronic ester. In all the cases, reactions were allowed to proceed to equilibrium. The preliminary experiments indeed have shown some encouraging results (displacement of pinanediol up to 40–53%). Amongst cyclopentane-based *cis*-1,2-diols, *endo*-2-phenyl-*exo*,*exo*-2,3-norbornane-diol appeared to be the most effective diol in displacing pinanediol (38%). In the cases of pinane-based diols, the best result was obtained with 2-ethyl-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (53%). It was interesting to observe that the transesterification with 2-phenyl-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol resulted in a 50% conversion after 4 days only, whereas the former diol took 24 days to reach equilibrium.

Keywords. Pinanediol; Boronic ester; Diol; Transesterification.

Introduction

Boronic acids and their esters are highly versatile building blocks in organic synthesis, which have found a broad range of applications in the areas of synthetic and pharmaceutical chemistry over the last decade [1–4]. α-Pinene-based chiral reagents and directors have been used extensively by *Brown* and *Zweifel* [5] and *Matteson* [6], especially in the asymmetric homologation of boronic esters. The stability of boronic esters is a key factor both in the protection of diols as well as in introducing and retrieving the chiral auxiliaries in a chiral auxiliary directed multistep organic synthesis. Pinanediol boronic esters appeared to be remarkably resistant toward hydrolysis, transesterification, or ligand exchange, which posed tremendous difficulties in introducing new chiral director of interest or recovering the chiral auxiliary. Transesterification is a convenient and gentle procedure that not only can introduce but also recover the chiral auxiliary to or from boronic ester, provided the former boronic ester is thermodynamically less stable than the latter. Although, we and others developed few procedures for the recovery of pinanediol from pinanediol boronic esters [7], there is only one report on the successful removal of pinanediol as pinanediol phenylboronic ester using *Ph*B(OH)$_2$ in a biphasic system from *Boc*-protected dipeptide of proline boronic acid utilizing mild transesterification [8].

The main objective of this exercise is to understand the unusual stability of pinanediol boronic ester as well as to find ways of recovering pinanediol from its methylboronic ester by transesterification using various diols. During the study on the relative stability of various achiral and chiral boronic esters utilizing transesterification methodology [9],

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† This paper is dedicated to the memory of my mentor, the late Professor *Herbert C. Brown* (1912–2004). Professor *Herbert C. Brown* deceased on December 19, 2004. The work described herein was performed at Purdue University during my stay as a post-doctoral research associate (1997–2001)

we observed that certain substituted cyclopentane- and norbornane-based diols were comparatively very effective, as reflected by the extent of transesterification. Consequently, we designed and synthesized several diols having cyclopentane and norbornane skeleton as well as few structurally modified pinanediols and tested their effectiveness in transesterification of pinanediol methylboronic ester and the preliminary results of such study are presented in this short communication.

Results and Discussion

All the structurally modified diols were prepared by OsO_4-catalysed *cis*-dihydroxylation [10] of the corresponding olefins (commercial or synthesized) in >75% chemical yields (Figs. 1 and 2). 2-Phenylapopinanediol **14** was synthesized starting from β-pinene as illustrated in Fig. 1. The ozonolysis of β-pinene provided nopinone, which was reacted with the *Grignard* reagent, *Ph*MgBr in *EE* at −40°C to room temperature for 20 h to get 6,6-dimethyl-2-phenylbicyclo[3.1.1]heptan-2-ol (60%) [11]. A similar result was obtained when the nopinone was treated with *Ph*Li at −25°C to room temperature for 20 h. The resulting alcohol was dehydrated to 6,6-dimethyl-2-phenylbicyclo[3.1.1]hept-2-ene (75%) using $POCl_3$ in pyridine at 0°C to room temperature for 24 h. The product olefin was subjected to OsO_4-catalyzed *cis*-dihydroxylation to afford 2-phenylapopinanediol **14** in 80% yield. A similar synthetic strategy was followed to obtain other alkyl- or aryl-substituted diols.

2-(β-Aminoethyl)apopinanediol **17** was prepared from the readily available starting material, nopol (Fig. 2). (*R*)-(−)-Nopol was converted to nopol tosylate by treating with *p*-toluenesulfonyl chloride in pyridine at 0°C for 40–45 h in 83% yield [12]. Under OsO_4-catalyzed *cis*-dihydroxylation conditions, the nopol tosylate underwent solvolytic rearrangement. Therefore, the nopol tosylate was converted to the phthalimide derivative using potassium phthalimide (prepared *in situ* by reacting phthalimide with freshly powdered anhydrous K_2CO_3 in *DMF* at 130–140°C

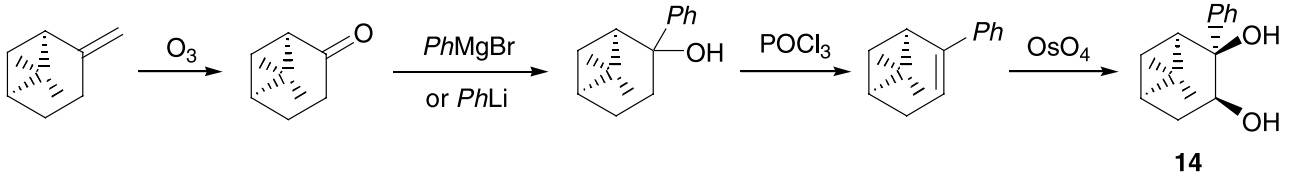

Fig. 1. Synthesis of 2-phenylapopinanediol **14**

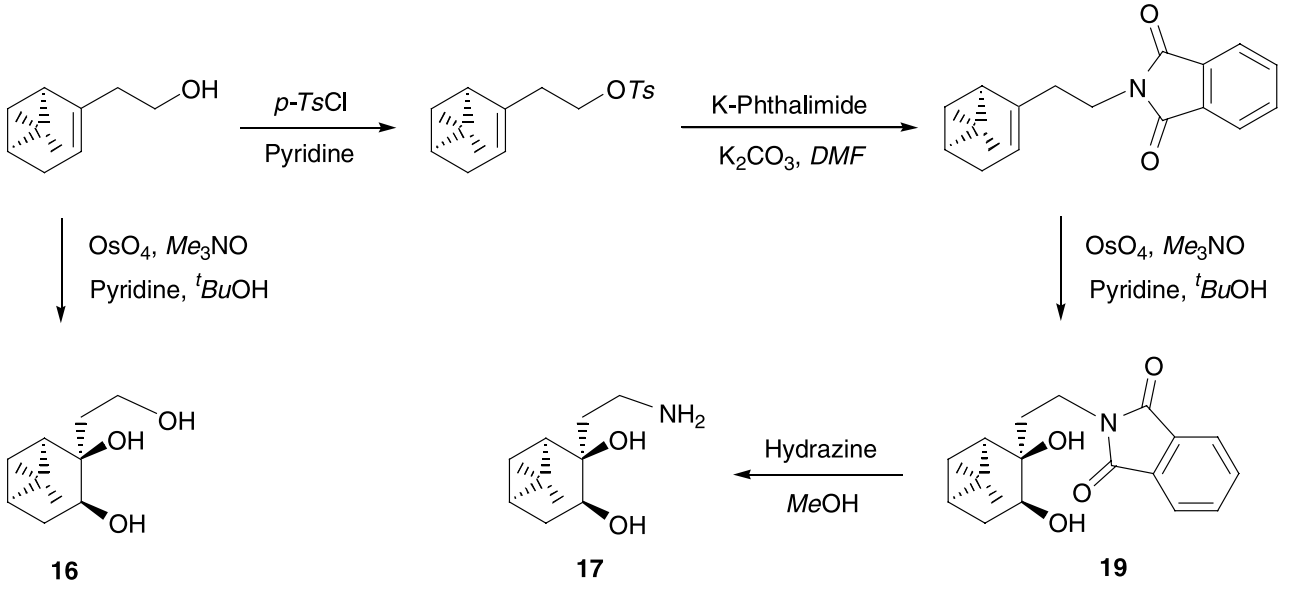

Fig. 2. Preparation of 2-(β-hydroxyethyl)apopinanediol **16** and 2-(β-aminoethyl)apopinanediol **17**

for 2 h) in *DMF* at 130°C for 15 h in 75% chemical yield. This phthalimide derivative underwent *cis*-dihydroxylation very smoothly to give corresponding diol in good chemical yield (73%). Finally, the desired compound, 2-(β-aminoethyl)apopinanediol was obtained by the reduction of imido group with hydrazine in methanol in excellent yield (85%).

Transesterification of (1S,2S,3R,5S)-(−)-2α,3α-Pinanediol Methylboronic Ester (**21**)

In order to follow the exchange very accurately and precisely, transesterification reactions were conducted in $CDCl_3$ in NMR tubes under an inert atmosphere and the progress of each reaction was monitored by ^1H NMR. The stoichiometric ratios of both the boronic ester **21** and the diol were 0.05 mmol in 1 cm^3 $CDCl_3$ and all the exchange reactions were allowed to proceed to equilibrium. Depending upon the fastness of the reactions (as reflected by the exchange values obtained soon after mixing), the reactions were frequently monitored (every 10 min to 1 h to 12–24 h) and the % transesterification were determined by integrating and comparing the distinct proton signals originated from the reactant boronic ester and the product boronic ester. The equilibrium proportions and the time after mixing which ^1H NMR used to determine those proportions were recorded are used to indicate the efficacy of the diols at displacing the pinanediol.

The initial exchange reaction of the boronic ester **21** [7b, 13] with commercially available *cis*-1,2-cyclopentanediol in $CDCl_3$ showed 11% exchange (as was observed by ^1H NMR spectroscopy) which was quite encouraging considering the fact that no diol was reported to show any detectable amount of pinanediol exchange from its boronic ester (Fig. 3). Among the various substituted *cis*-1,2-cyclopentanediols [15], the best result was obtained with 1-isopropyl-*cis*-1,2-cyclopentanediol (**4**) which showed 31% transesterification (Fig. 4). Although the steric bulk of the substituents present on the diols slow down the transesterification, but they lead to the thermodynamically more stable boronic esters. In the case of 1,2-dimethyl-*cis*-1,2-cyclopentanediol (**6**) [16], the ineffectiveness (<5%) was attributed to the steric factors. To confirm this, the boronic ester derived from the diol **6** was prepared and subjected to transesterification with (−)-pinanediol under similar conditions. As expected, no significant transesterification (<5%) occurred even after 15 days, which confirmed the above conclusion. When boronic ester **21** was treated with *exo*,*exo*-2,3-norbornanediol (**7**) [17], 25% exchange was observed. 2,3-Norbornanediol, being a rigid 3,5-disubstituted analog of 1,2-cyclopentanediol, appeared to be much more effective. Substitution at C_4-, C_5- and C_6-positions (**9** and **10**) [18–20] had no appreciable effects on the equilibrium compositions whereas the substitution at C_2-position by phenyl group **8** had positive effect on equilibrium

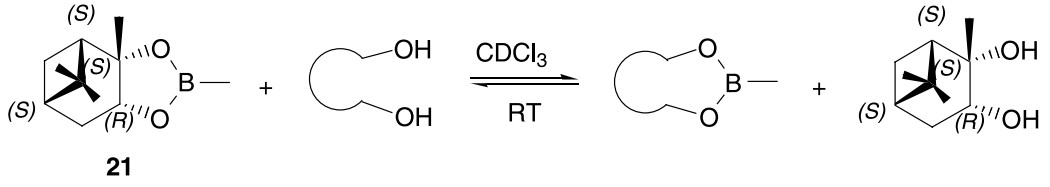

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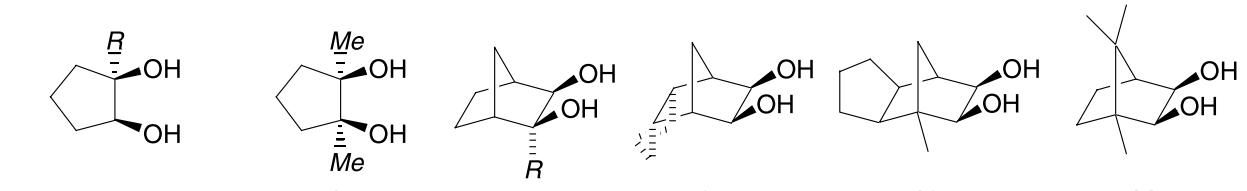
Fig. 3. Transesterification of chiral (−)-pinanediol methylboronic ester **21**



1, *R* = H; **2**, *R* = *Me*
3, *R* = *Et*; **4**, *R* = ^{i}*Pr*
5, *R* = *Ph*

6

7, *R* = H
8, *R* = *Ph*

9 **10** **11**

Fig. 4. Cyclopentane- and norbornane-based structurally modified diols **1**–**11**

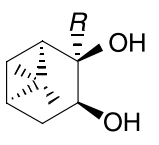
(from 25 to 38%). The extent of transesterification with various cyclopentane-based *cis*-1,2-diols are tabulated in the Table 1.

After examining various cyclopentane- and norbornane-based diols, we turned our attention to test the effectiveness of few pinane-based diols (Fig. 5). These structurally modified pinanediols [10, 21], some of them having suitably substituted coordinating sites (−OH, $-NH_2$, O*Me*, $-N(C{=}O)_2$), which were hoped to provide an additional stability to the product boronic esters possibly by chelation. It is clear from the data (Table 2) that the nature of the

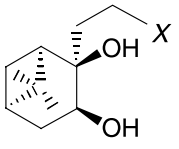
Table 1. Transesterification of the boronic ester **21** with various cyclopentane-based diols **1–11**

Entry	Diol	Time/d	Equilibrium compositions %[a] RBE⇋PBE
1	*cis*-1,2-Cyclopentanediol (**1**)	4	89⇋11
2	1-Methyl-*cis*-1,2-cyclopentanediol (**2**)	7	87⇋13
3	1-Ethyl-*cis*-1,2-cyclopentanediol (**3**)	14	78⇋22
4	1-Isopropyl-*cis*-1,2-cyclopentanediol (**4**)	45	69⇋31
5	1-Phenyl-*cis*-1,2-cyclopentanediol (**5**)	16	86⇋14
6	1,2-Dimethyl-*cis*-1,2-cyclopentanediol (**6**)	7	No equilibrium
7	*exo*,*exo*-2,3-Norbornanediol (**7**)	10	75⇋25
8	*endo*-2-Phenyl-*exo*,*exo*-2,3-norbornanediol (**8**)	28	62⇋38
9	Octahydro-4,7-methanoindene-*exo*,*exo*-5,6-diol (**9**)	6	74⇋26
10	*exo*,*exo*-4-Methyloctahydro-4,7-methanoindene-5,6-diol (**10**)	7	72⇋28
11	1,7,7-Trimethylbicyclo[2.2.1]heptane-*exo*,*exo*-2,3-diol (**11**)	20	88⇋12

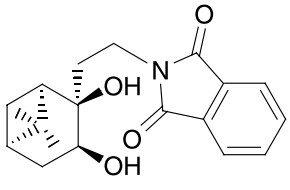
[a] The exchange reaction was carried out in an NMR tube under nitrogen (boronic ester:diol = 1:1; 0.05 mmol each in 1 cm^3 $CDCl_3$). RBE (reactant boronic ester) and PBE (product boronic ester)



12, *R* = H; **13**, *R* = *Et*
14, *R* = *Ph*



15, *X* = Cl; **16**, *X* = OH
17, *X* = NH_2; **18**, *X* = OCH_3



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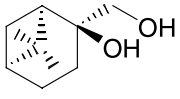

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Fig. 5. Pinane-based structurally modified diols **12–20**

Table 2. Transesterification of (−)-pinanediol methylboronic ester **21** with various pinane-based diols **12–20**

Entry	Diol	Time/d	Equilibrium compositions/%[a] RBE⇋PBE
1	6,6-Dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**12**)	8	67⇋33
2	2-Ethyl-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**13**)	24	47⇋53
3	2-Phenyl-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**14**)	4	50⇋50
4	2-(2-Chloroethyl)-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**15**)	60	57⇋43
5	2-(2-Hydroxyethyl)-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**16**)	2	67⇋33
6	2-(2-Aminoethyl)-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**17**)	1	82⇋18
7	2-(2-Methoxyethyl)-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**18**)	40	90⇋10
8	2-[2-(2,3-Dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl)-ethyl]isoindole-1,3-dione (**19**)	92	56⇋44
9	2-Hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (**20**)	22	No equilibrium reached

[a] The exchange reaction was carried out in an NMR tube under nitrogen (boronic ester:diol = 1:1; 0.05 mmol each in 1 cm^3 $CDCl_3$). RBE (reactant boronic ester) and PBE (product boronic ester)

side chain at C_2-position has a significant effect on stability. The apopinanediol **12**, which lacks the C_2-*Me* group, could exchange only up to 33%. Both apopinanediols **16** and **17** bearing −OH and $-NH_2$ as potential chelating groups did not demonstrate any superiority over the ethyl-substituted apopinanediol **13**. The substitution of C_2-*Me* by C_2-*Ph* group **14** also did not show any advantage. On the contrary, the diols **15** and **19** having β-chloroethyl and β-isoindoledione structures showed relatively higher percentages of transesterification (43–44%). The reason for the lower exchange with diols **16** and **17** is not clear at this stage. The unusual hydrolytic resistance of pinanediol boronic esters is believed to be due to the orientation of hydroxyl groups and rigidity of the free diol [6c]. The influence of the rigid structural framework, 6,6-dimethylbicyclo[3.1.1]heptane can't be underestimated. Other factors that influence the thermodynamics of ligand exchange include the entropies of internal rotations of free diols, the steric repulsion on enthalpy and the chelation. A summary of the best results obtained from diols of diverse structural types is presented in Fig. 6.

In conclusion, we have described the behaviour of (−)-pinanediol methylboronic ester **21** in transesterification reactions with a variety of cyclopentene- and pinane-based diols by ^{1}H NMR. The displacement of the pinanediol from its boronic ester has been achieved to a considerable extent, if not quantitatively. With cyclopentene-based-*cis*-1,2-diols, the pinanediol was only poorly displaced (best result of 38% with diol **8**). In the cases of pinane-based diols, the displacements of pinanediol up to 43–53% could be attained instead, and transesterification with diol **14** resulted in a 50% conversion after 4 days only, though diols **13** and **15** showed similar values after 24 and 60 days, respectively. This study reveals that the equilibrium can be driven towards favoured direction by increasing the steric bulk on one of the carbons bearing an OH group. 1,2-Disubstituted diols were found to be ineffective, possibly due to steric reasons (hard to approach the boron center). Among the pinane-based diols, the nature of the side chain at C_2-position has significant effects on transesterification. The absence of methyl group in the *cis*-apopinanediol **12** makes this boronic ester relatively

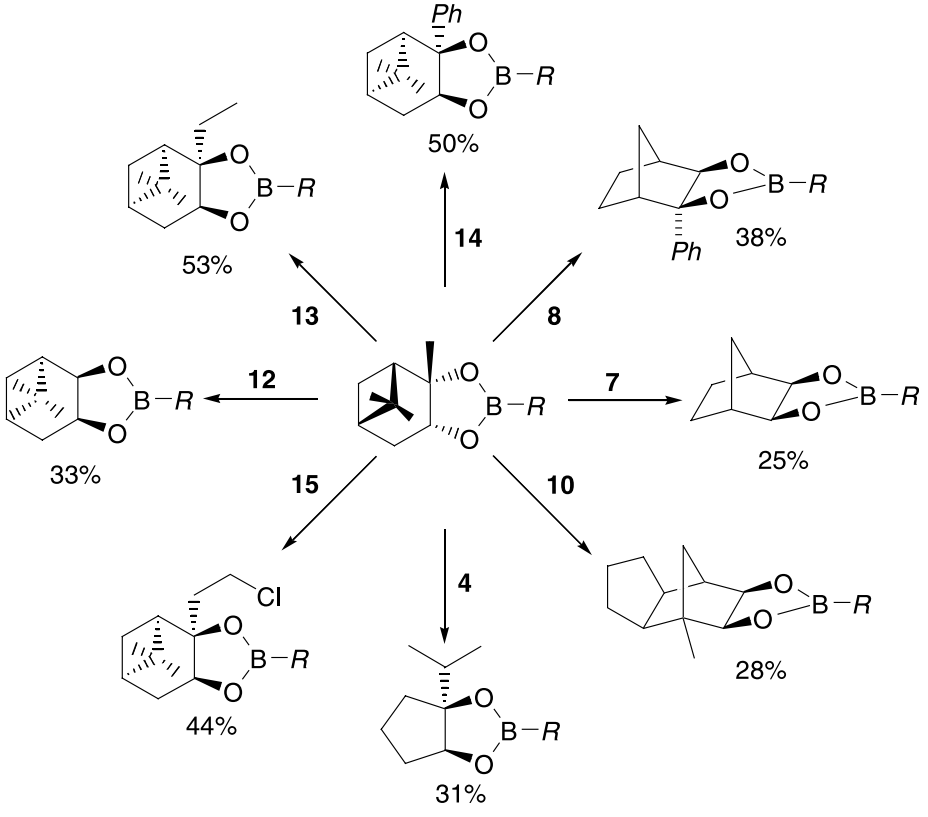

Fig. 6. A brief result summary of transesterification of chiral (−)-pinanediol methylboronic ester with structurally modified diols

less stable, as reflected by the equilibrium compositions ($67 \leftrightharpoons 33$). It was interesting to note that both diols **16** and **17** despite having an additional coordinating or chelating sites ($-$OH and $-NH_2$ groups) did not show any improvements in comparison with 2-ethylapopinanediol **13**. It would be interesting to synthesize other structurally modified diols and test their effectiveness in transesterification.

Experimental

All operations involving organoboranes were carried out under an inert atmosphere. Detailed procedures and techniques for handling air- and moisture-sensitive compounds have been reported elsewhere [14]. The ^{11}B (96 MHz), ^{1}H (300 MHz), and ^{13}C (75 Mhz) NMR spectra were recorded on a Varian Gemini NMR instrument, and the chemical shifts (δ) are given in *ppm* relative to external standard BF_3-Et_2O and internal standards *TMS* and $CDCl_3$. *THF* was freshly distilled from sodium benzophenone ketyl. Octahydro-4,7-methanoindene-*exo*,*exo*-5,6-diol (**9**) and *exo*,*exo*-4-methyl-octahydro-4,7-methanoindene-5,6-diol (**10**) were obtained as gift. β-Pinene, (*R*)-(−)-nopol, camphor, N_2H_4-H_2O, *Ph*Li, *Ph*MgBr, OsO_4, *NMO*, *p-Ts*Cl, phthalimide, *cis*-1,2-cyclopentanediol, (−)-α-pinanediol, and methylboronic acid were purchased from the Aldrich Chemical Co.

Experimental Techniques Used for Transesterification

In order to monitor the progress of the exchange reaction precisely and conveniently, reactions were carried out in $CDCl_3$ solvent in a tightly closed NMR tubes under N_2 atmosphere and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. Both (−)-pinanediol methylboronic ester and the diol (0.05 mmol of each) were dissolved in 1 cm^3 $CDCl_3$ and the NMR tube was flushed with N_2. For fast reactions, the progress of the reaction was followed quite frequently (every 5–15 min) whereas the reactions were monitored every 12–24 h for slow reactions. The starting and product boronic esters always had certain distinguishable protons, which could be followed, compared and integrated to obtain the quantitative values of the transesterification. The ^{1}H NMR spectra were recorded for extended periods of time even after the exchange had ceased (for slow reactions) to get accurate equilibrium compositions. In some cases, product boronic esters were prepared and subjected to transesterification with the corresponding diols to confirm the unfavorable equilibrium due to steric factors or to verify the obtained equilibrium composition values by conducting the reactions in reverse directions.

^{1}H NMR Spectroscopic Data for Diols

1-Methylcyclopentane-*cis*-1,2-diol (**2**) [15], 1-ethylcyclopentane-*cis*-1,2-diol (**3**) [15], 1-isopropylcyclopentane-*cis*-1,2-diol (**4**) [15], 1-phenylcyclopentane-*cis*-1,2-diol (**5**) [15], 1,2-dimethylcyclopentane-*cis*-1,2-diol (**6**) [16], bicyclo[2.2.1]heptane-*exo*,*exo*-2,3-diol (**7**) [17], 2-phenylbicyclo[2.2.1]heptane-*exo*,*exo*-2,3-diol (**8**) [18], *endo*,*endo*-octahydro-4,7-methanoindene-*exo*,*exo*-5,6-diol (**9**) [19], 1,7,7-trimethylbicyclo[2.2.1]heptane-*exo*,*exo*-2,3-diol (**11**) [20], 2-methoxyethyl-6,6-dimethylbicyclo[3.1.1]heptane-*cis*-2,3-diol (**18**) [10], 2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]-heptan-2-ol (**20**) [21], and (−)-pinanediol methylboronic ester (**21**) [7b] have been well characterized in literature.

6,6-Dimethylbicyclo[3.1.1]heptane-cis-2,3-diol (**12**, $C_9H_{16}O_2$)
^{1}H NMR ($CDCl_3$): $\delta = 4.15$ (m, CHOH), 2.80 (br s, CHOH), 2.50–1.50 (m, CHOH, CH and CH_2), 1.26 (s, CH_3), 0.79 (s, CH_3) ppm.

2-Ethyl-6,6-dimethylbicyclo[3.1.1]heptane-cis-2,3-diol (**13**, $C_{11}H_{20}O_2$)
^{1}H NMR ($CDCl_3$): $\delta = 3.96$ (m, CHOH), 2.60 (d, CHOH), 2.50–1.30 (m, CHOH, CH and CH_2), 1.26 (s, CH_3), 0.95 (t, CH_2CH_3), 0.92 (s, CH_3) ppm.

2-Phenyl-6,6-dimethylbicyclo[3.1.1]heptane-cis-2,3-diol (**14**, $C_{15}H_{20}O_2$)
^{1}H NMR ($CDCl_3$): $\delta = 7.49$–7.25 (m, ArH), 4.55 (m, CHOH), 2.80 (br s, CHOH), 2.50–1.50 (m, C(*Ph*)OH, CH and CH_2), 1.27 (s, CH_3), 0.80 (s, CH_3) ppm.

2-Chloroethyl-6,6-dimethylbicyclo[3.1.1]heptane-cis-2,3-diol (**15**, $C_{11}H_{19}ClO_2$)
^{1}H NMR ($CDCl_3$): $\delta = 4.15$ (m, CHOH), 3.75 (m, CH_2Cl), 3.04 (s, COH), 2.60 (d, CHOH), 2.60–1.30 (m, CH and CH_2), 1.26 (s, CH_3), 0.96 (s, CH_3) ppm.

2-Hydroxyethyl-6,6-dimethylbicyclo[3.1.1]heptane-cis-2,3-diol (**16**, $C_{11}H_{20}O_3$)
^{1}H NMR ($CDCl_3$): $\delta = 4.15$ (m, CHOH), 4.05–3.80 (m and s CH_2OH and COH), 3.40 (d, CHOH), 2.55 (t, CH_2OH), 2.50–1.30 (m, CH and CH_2), 1.27 (s, CH_3), 0.93 (s, CH_3) ppm.

2-Aminoethyl-6,6-dimethylbicyclo[3.1.1]heptane-cis-2,3-diol (**17**, $C_{11}H_{21}NO_2$)
^{1}H NMR ($CDCl_3$): $\delta = 4.00$ (m, CHOH), 3.06 (m, CH_2NH_2), 2.50–1.40 (m, NH_2, COH, CH and CH_2), 1.26 (s, CH_3), 0.93 (s, CH_3) ppm.

2-[2-(cis-2,3-Dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl) ethyl]isoindole-1,3-dione (**19**, $C_{19}H_{23}NO_4$)
^{1}H NMR ($CDCl_3$): $\delta = 7.82$ (m, ArH), 7.70 (m, ArH), 4.10 (m, CHOH), 3.87 (m, CH_2N), 3.30–3.00 (br s, CHOH and COH), 2.60–1.30 (m, CH and CH_2), 1.25 (s, CH_3), 0.93 (s, CH_3) ppm.

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