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Stereoselective dioxirane hydroxylations and the synthesis of tripod boronic acid esters

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Abstract—Methyl(trifluoromethyl)dioxirane (TFDO, **1b**), a powerful yet selective oxidant, was employed to achieve in high yield the direct stereoselective hydroxylation at *tert*-CH of *cis*,*cis*-1,3,5-trimethylcyclohexane (**4**), yielding triol **7** bearing all-axial disposition of the three OH groups. Similarly, TFDO oxidation of 1,3- and of 1,4-dimethylcyclohexane gave the corresponding *Z*-diols **5** and **6**, respectively. Triol **7** was a convenient starting material to synthesize a novel borate—that is, 1-bora-2,8,9-trioxa-3,5,7-trimethyladamantane (**8**)—having a peculiar cage-shaped 'tripod' structure. From triol **7**, novel tripod arylboronic Brönsted-assisted Lewis acids (BLA) could be obtained, as exemplified by **10a** and **10b**.

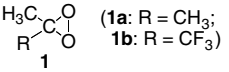
1. Introduction

In the past decades, a great deal of interest was devoted to the chemistry of borate esters and boronic acid derivatives because of their applications in chemistry and biology.[1,2] These remarkable organic intermediates have been widely employed to carry out a number of synthetic transformations, including Diels–Alder reactions, enantioselective syntheses, and Suzuki cross-coupling reactions.[3,4] Actually, the chemical stability of boronic acids $R^1B(OH)_2$ and their esters, coupled with favorable steric properties, make them excellent reagents for geometrically controlled syntheses. Also, it was found that boronic acid analogues of natural substrates could function as effective enzyme inhibitors.[1]

Recently, much interest has attracted research focusing on employing boronic acid compounds for the development of sensors, based on the renowned ability of boronic acids to bind tightly with saccharides and other polyols.[1,5] In fact, several comprehensive studies were devoted to establishing the various features and the binding constants of reactions between compounds containing OH functionalities and arylboronic acids, such as phenylboronic acid $PhB(OH)_2$.[1,5b]

It is well recognized that in aqueous solution the derived boronic esters—as well as the parent boronic acids—can exist in a trigonal planar form in equilibrium with the corresponding tetrahedral anionic form $[ArB(OR)_2OH]^-$, the position of the equilibria depending upon the pK_a values. A thorough understanding of these equilibria is desirable in order to design effective boronic ester-based sensors.

In borates $B(OR^2)_3$ and boronic acid esters $R^1B(OR^2)_2$, reversible exchange between them and water (or in general a given protic species ROH) is usually fairly rapid, so that acyclic esters must be protected from moisture. However, sterically hindered cyclic borates or boronic esters (which represent the most useful synthetic intermediates) are not easily hydrolyzed and can be handled similarly to stable organic compounds. The general properties of boronic esters and borates have been reviewed in detail.[2]



1 (**1a**: R = CH_3; **1b**: R = CF_3)

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Based on the above background, during our work on stereoselective oxidations[6] employing isolated dimethyldioxirane (DDO) (**1a**)[7a,b] and methyl(trifluoromethyl)dioxirane (TFDO) (**1b**),[6,8] we set out to obtain stable borates having a sterically strained framework and novel Brönsted acid-assisted Lewis acids (BLA)[3] that display a unique 'tripod' architecture. Our initial results are described herein.

2. Results and discussion

It was documented that a novel approach to the efficient oxygenation of hydrocarbons under mild conditions consists in the selective O-insertion into C–H bonds using dioxiranes.[6] Actually, it is recognized that oxidations of 'unactivated' hydrocarbon C–H bonds generally require reaction times of hours and excess oxidant employing DDO (**1a**).[7,8] Instead, the powerful TFDO (**1b**) allows one to carry out these transformations often in a matter of minutes and with a high selectivity.[6]

For instance, illustrating the high stereoselectivity of the dioxirane O-insertion, a specific case is the exclusive bridgehead hydroxylation of *cis*-decalin, which gives only the tertiary *cis*-decalinol; a similar stereoselective configuration retention was also observed for *trans*-decalin.[8] Previously it had been shown that the C–H hydroxylation of *cis*- and *trans*-1,2-dimethylcyclohexanes by dioxiranes is also highly stereocontrolled.[7,8]

We now report that a similar high stereoselectivity can be achieved in the TFDO hydroxylation of commercial[9] *cis*-1,3- and of *cis*-1,4-dimethyl substituted cyclohexanes (**2** and **3**), as well as in the hydroxylation of 1,3,5-trimethyl cyclohexane **4** (Chart 1).[10] Starting with these, the corresponding all-*cis*-diols **5**[11] and **6**,[12] and all-*cis* triol **7**[13] could be obtained in high yield and with no epimerization at the *tert*-C–H reaction centers, as illustrated by Eqs. 1–3, in Chart 1. The transformations reported therein are representative of the typical reaction conditions adopted.

To carry out oxidations in Eqs. 1–3, isolated TFDO (**1b**) solutions that were 0.7–0.8 M in its parent ketone 1,1,1-trifluoropropanone (TFP) were prepared and employed as already reported in detail.[8] On a 2–5 mmol scale, the simple oxidation procedure merely involved the addition of an aliquot of standardized[8] dioxirane solution in one portion to the substrate dissolved in CH_2Cl_2 (5–10 mL) and kept at 0 °C. A moderate excess of dioxirane **1b** was applied in order to achieve complete substrate conversions, as monitored by GC and GC/MS. Removal of the solvent in vacuo and column chromatography (silicagel) gave products **5**, **6**, or **7**, respectively, in practically quantitative yield.

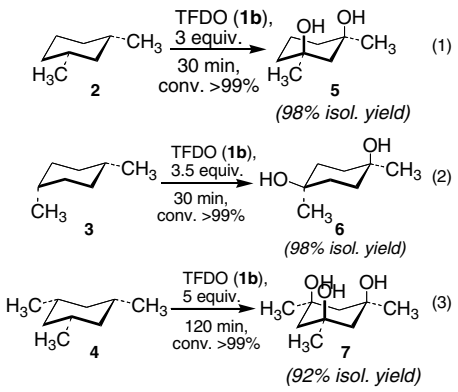

Chart 1.

The novel triol **7** (a solid, mp 134–135 °C) was fully characterized by ^1H and ^{13}C NMR, yielding spectra in complete agreement with the given structure.[13] The all-axial disposition of the three hydroxy functionalities was further unambiguously determined by X-ray crystallography (Fig. 1).[14]

The feat of obtaining **7** *directly* as a single diastereomer is in itself remarkable; actually, other approaches to its synthesis that could be envisaged would necessarily be more elaborate, requiring multiple steps. Because of the precise stereochemistry of **7**, it is perhaps no surprise that, from this, 'tripod' borate **8** could be easily obtained in high yield upon reaction with BCl_3/Py under the conditions given in Eq. 4, Chart 2.

It should be noted that the analogue of tripod borate **8** lacking the three methyl substituents, that is, 3,5,7-trimethyl-2,8,9-trioxa-1-boraadamantane appears to have been synthesized (method, yields, and characteristics undisclosed); it was patented and claimed to be an efficient catalyst in homogeneous olefin polimerization.[15]

The novel tripod borate ester **8** displays a geometry around tricovalent boron, that is, somewhat distorted (O–B–O 113.9°, MM2 output) with respect to the planar structure typical of open-shaped borates, for instance $B(OPh)_3$.[3a] In fact, the caged borate (^{11}B NMR, δ 18.3) has the structure of fourfold heterosubstituted adamantane, that is, 1-bora-2,8,9-trioxa-3,5,7-trimethyladamantane. Remarkably stable, it could be isolated as a white solid (mp 62–64 °C) and fully characterized by ^1H, ^{13}C, and ^{11}B NMR.[16] We find that **8** is resistant to

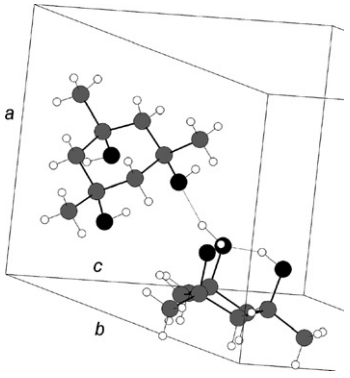

Figure 1. Partial view of unit cell assembling four molecules (two are shown) of triol **7**, computer-generated (ball-and-stick models) from X-ray crystallographic data. $a = 9.939(2)$, $b = 9.986(4)$, $c = 11.696(5)$ Å. Selected H-bond lengths within H···O 1.8 Å are shown.

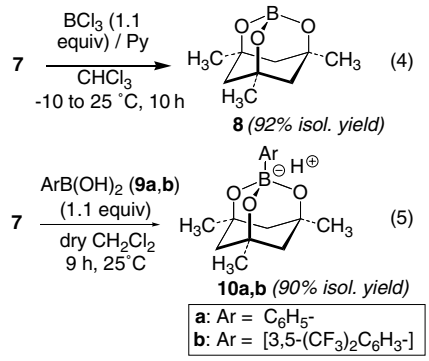

Chart 2.

hydrolysis upon moderate exposure to atmospheric moisture at 25 °C; however, it can be perhydrolyzed using alkaline H_2O_2,[17] regenerating triol **7** with unchanged stereochemistry.

In order to test triol **7** as a probe for boronic acid sensors, we made it react with two widely employed boronic acids, that is, benzeneboronic acid (**9a**) or 3,5-bis(trifluoromethyl)benzeneboronic acid (**9b**)[1,3c] under the conditions given in Eq. 5, Chart 2. These reactions were run on a 0.2 mmol scale in 5–10 mL of methylene chloride solvent, affording the corresponding BLA acids **10a** or **10b** in practically quantitative yields (Chart 2, Eq. 5). Both **10a** (^{11}B NMR, δ −17.1) and **10b** (^{11}B NMR, δ −17.2) could be successfully isolated as white solids and were fully characterized.[18,19] The recorded ^{1}H- and ^{13}C NMR spectra were in excellent agreement with their highly symmetrical structure; for instance, in line with their C_3 symmetry, in their proton spectra both presented a singlet C*H*$_3$ resonance (**10a**, 1.29; **10b**, 1.31 ppm), and again just one *C*H$_3$ signal (**10a**, 30.9; **10b**, 29.7 ppm) in the proton-decoupled ^{13}C NMR spectra for the three methyl groups.

Soluble in organic solvents such as CH_2Cl_2, $CHCl_3$, THF, MeCN, the BLA acids above have a limited solubility in water. By dissolving solid **10a** in warm water (50–60 °C), solutions that were ca. 5×10^{-3} M in BLA could be prepared; an apparent pH of 2.5 was measured for such solutions at 25 °C.

Significant changes were monitored in the fluorescence spectra of both boronic acids **9a** and **9b** upon binding to triol **7**. For instance, benzene boronic acid **9a** (UV λ_{max1} 242 and λ_{max2} 263 nm), upon irradiation at 263 nm (c 0.015 M, CH_2Cl_2), yields an emission spectrum with λ_{max} 299 nm and intensity (*I*) of 15.1 au. Its BLA derivative **10a** (UV λ_{max1} 234 and λ_{max2} 267 nm), when irradiated at the 267 nm at a similar concentration in the same solvent, gives an emission spectrum with λ_{max} 288 nm, with a *more than 25-fold increase* in emission intensity ($I = 388$ au).

By contrast, proceeding in a similar manner we find that—on going from 3,5-bis(trifluoromethyl)benzeneboronic acid (**9b**) (UV λ_{max1} 236 and λ_{max2} 263 nm) to BLA **10b** (UV λ_{max1} 231 and λ_{max2} 263 nm)—the intensity of the emission is *depressed*, being $I = 247$ au (λ_{max} 294 nm) for **9b** and $I = 95.8$ au (λ_{max} 305 nm) for the corresponding BLA acid **10b**.

In summary, we provide herein one more example showing that the high reactivity and selectivity achievable using dioxiranes, chiefly TFDO **1b**, in electrophilic O-insertions into unactivated C–H bonds can be exploited to obtain synthons that are useful in building compounds presenting peculiar architecture and properties. Obviously, organic compounds displaying several OH or OR moieties that are favorably arranged sterically can be effective ligand systems for various metal complexes. These might show enhanced or peculiar properties as catalysts. For instance, cage-shaped borates display enhanced catalytic activity in hetero Diels–Alder reactions with respect to open-shaped borates. This was rationalized in terms of reduced π-electron overlap between boron and its ligand oxygens.[3a]

Besides its value in designing effective metal catalysts, all-*cis* triol **7** might also find useful applications in testing the capability of simple and complex boronic acids to act as selective sensors toward certain natural target molecules.[1,5]

Acknowledgments

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11. (a) White solid (mp 92–94 °C, lit.[11b] 92–93 °C); column chromatography (silicagel, *n*-hexane/Et_2O 3:1) yields **5** (purity >98%, GC); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.85 (s, 2H), 1.92 (m, 2H), 1.68 (m, 2H), 1.47 (m, 1H), 1.29 (m, 1H), 1.26 (m, 1H), 1.19 (m, 1H), 1.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 71.3, 47.8, 37.9, 30.8, 17.3; GC/MS (70 eV) *m*/*z* (rel intensity): 126 (3), 101 (5), 83 (7), 71 (8), 58 (12), 43 (100); (b) Meinwald, J.; Yankeelov, J. A., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 5266; (c) Eastman, R. H.; Quinn, R. A. *J. Am. Chem. Soc.* **1960**, *82*, 4249.
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13. White solid, mp 134–135 °C; column chromatography[11a] gives **7** (purity 98%, GC); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.99 (s, 3H), 1.89 (d, 3H, $J = 14.3$ Hz), 1.37 (d, 3H, $J = 14.3$ Hz), 1.18 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 72.1, 48.1, 31.6; FT-IR (CH_2Cl_2): 3367, 2969, 1455, 1390, 1186, 901 cm^{-1}; GC/MS (70 eV) *m*/*z* (rel intensity): 174 (0.1), 159 (1.1), 123 (5), 101 (33), 83 (7), 59 (19), 43 (100); Anal. Calcd for $C_9H_{18}O_3$: C, 62.0; H, 10.4. Found: C, 62.0; H, 10.2.
14. Cambridge Crystallographic Data Centre, CCDC no. 633318. Salient data for **7**: $C_{18}H_{36}O_6$, $M_T = 174.23$ g mol^{-1}, triclinic, space group: *P*-1, $\alpha = 114.01(3)$; $\beta = 100.43(4)$; $\gamma = 91.14(3)$ deg.; cell volume = 1037.2(6) $Å^3$, $Z = 2$, $T = 293(2)$ K, $\rho_c = 1.116$ g cm^{-3}, $\mu = 0.082$ mm^{-1}, ϑ range = 5.07–27.50°. The SHELXL-97 program was employed for refinement. The complete supplementary files can be obtained upon request to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; email: deposit@ccdc.cam.ac.uk.
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16. (a) *3,5,7-Trimethyl-2,8,9-trioxa-1-boratricyclo [3.3.1.-1^{3,7}]decane* (**8**): white solid, mp 62–64 °C (cryst *n*-pentane); ^1H NMR ($CDCl_3$, 500 MHz): δ 1.87 (d, 3H, $J = 13.0$ Hz), 1.45 (d, 3H, $J = 13.0$ Hz), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 71.8, 47.2, 30.5; ^{11}B NMR (128.4 MHz, $CDCl_3$, ext. ref. $Et_2O{\cdot}BF_3$): δ 18.265; FT-IR (CH_2Cl_2) 2960, 2922, 2850, 2358, 1734, 1450, 1396, 1373, 1259, 1093, 1022, 798 cm^{-1}; Anal. Calcd for $C_9H_{15}BO_3$: C, 59.4; H, 8.3. Found: C, 59.9; H, 8.2; (b) Lappert, M. F. *J. Chem. Soc.* **1953**, 667.
17. For instance, see: Pelter, A.; Maddocks, U.; Smith, K. *Chem Commun.* **1978**, 805.
18. BLA (**10a**): white solid, mp 103–104 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.78 (m, 2H), 7.37–7.29 (m, 3H), 1.94 (d, 3H, $J = 14.0$ Hz), 1.54 (d, 3H, $J = 14.0$ Hz), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 133.5 (*C*-B), 129.8, 127.3, 70.9, 47.7, 30.9; ^{11}B NMR (128.4 MHz, $CDCl_3$, ext. ref. $NaBF_4$): δ −17.15; FT-IR (CH_2Cl_2) 3153, 2926, 2873, 1791, 1600, 1473, 1436, 1375, 1365, 1350, 1317, 1207, 1099 cm^{-1}; Anal. Calcd for $C_{15}H_{21}BO_3$: C, 69.3; H, 8.1. Found: C, 66.9; H 8.0.
19. BLA (**10b**): white solid, mp 174–176 °C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.19 (s, 2H), 7.83 (s, 1H), 1.96 (d, 3H, $J = 14.0$ Hz), 1.57 (d, 3H, $J = 14.0$ Hz), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 132.7, 129.7 (q, *C*–CF_3, $J = 32$ Hz), 123.6 (q, *C*F_3, $J = 272$ Hz), 122.5, 71.0, 49.3, 29.7; ^{11}B NMR (128.4 MHz, $CDCl_3$, ext. ref. $NaBF_4$): δ −17.22; FT-IR (CH_2Cl_2) 3150, 2925, 1600, 1375, 1350, 1320, 1202, 1099 cm^{-1}; Anal. Calcd for $C_{17}H_{19}BF_6O_3$: C, 51.5; H, 4.8. Found: C, 50.9; H, 5.1. HRMS (MALDI, TOF) Calcd for $C_{17}H_{18}BF_6O_3^-Na^+$: 418.115. Found: 418.560 [(M−H)+Na^+].