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5-Carboxymethyl-2-(4-methylthiophenyl)-1,3,2-dioxaborolan-4-one: synthesis, characterization and application in enantioselective reduction of ketones

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The reaction of arylboronic acids with L-*O*-benzoyl-tartaric acid and D,L-malic acid has been studied. The obtained (acyloxy)boranes are moderately stable in solution and decompose to give boroxines. 5-Carboxymethyl-2-(4-methylthiophenyl)-1,3,2-dioxaborolan-4-one was obtained in the reaction of 4-methylthiophenylboronic acid with D,L-malic acid and characterized by X-ray structural analysis. The use of L-(−)-malic acid afforded the optically pure product which can be used as the powerful chiral reagent in the enantioselective reduction of ketones. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: (acyloxy)boranes; boronic acids; tartaric acid; malic acid

Introduction

Reaction of arylboronic acids with tartaric acid derivatives occurs with formation of chiral (acyloxy)boranes (CAB), which have attracted great attention for their catalytic formation ability of complex carbocyclic frameworks in an enantiomerically enriched form.[1] The application of CAB involves the formation of dihydropyrone derivatives,[2] 3-cyclohexene-1-carboxaldehydes[3,4] and 1,4-bicyclo-2,5-diene-carboxaldehydes[5] via Diels–Alder reactions, Sakurai–Hosomi reaction,[6] synthesis of homoallylic alcohols[7] and β-hydroxyesters[8] in Aldol-type reactions,[9] polyaddition of bis(allyl)silanes and dialdehydes.[10] These reactions proceed smoothly and require usually 10–20 mol% of the CAB complex. The enantiomeric excess is strongly dependent on the substituent at the phenyl ring bonded to the boron atom. Despite some work on the mechanism of catalysis,[11,12] there is a lack of study on the formation and structure of the catalyst. The CABs have been synthesized without isolation and used immediately in the reactions. The proposed structure is based on the molecular weight, found cryoscopically in benzene, and the carbonyl absorption at 1821 cm^{-1} characteristic of the five-membered ring carbonyl compound.[1] In this work we present our results on the reaction of arylboronic acids with L-*O*-benzoyl-tartaric acid and D,L-malic acid. We obtained and fully characterized 5-carboxymethyl-2-(4-methylthiophenyl)-1,3,2-dioxaborolan-4-one, the first crystalline CAB.

We were interested in the preparation of the CAB catalysts **3a–d** derived from the L-*O*-benzoyl-tartaric acid **1** and arylboronic acids **2a–d** (Scheme 1). Thus, the equimolar amounts of the reagents were dissolved in THF at room temperature to form the clear solutions. After 24 h the samples of the reaction mixtures were collected and evaporated. The remaining solids were dissolved in dmso-d_6. The ^{1}H-NMR showed the presence of four signals in the range of 4.6–5.6 ppm. The comparison of the obtained spectra with the ^{1}H-NMR spectrum of **1**: ^{1}H-NMR (dmso-d_6, 400 MHz) δ 13.23 (s, 2H), 8.04 (d, 2H), 7.68 (t, 1H, J = 6.8 Hz), 7.54 (d, 2H), 6.00 (s, OH), 5.48 (d, C–H, J = 2.4 Hz), 4.68 (d, C–H) revealed the presence of the unreacted starting material. Integration of the C–H signals revealed that the reaction yield varies in the range 40–60% depending on boronic acid used. These results were supported by the ^{11}B and ^{19}F-NMR resonances. The ^{11}B-NMR spectra in dmso-d_6 revealed the presence of two broad signals at 30 and 11 ppm respectively. The signal at 11 ppm resulted from the presence of tetravalent boron atom in the CAB*DMSO adduct. The ^{19}F-NMR spectrum of **3b** showed 2 singlets at −60.80 and −61.31 ppm. The formation of the mixture caused problems in isolation and purification of products. However, the formation of **3a–d** was confirmed by MS spectra. Concentration of the reaction mixture containing **3d** followed by cooling to −15 °C afforded colorless crystals after 2 weeks. Unexpectedly, the analysis revealed the presence of the boroxine $(2\text{-F-C}_6\text{H}_4\text{BO})_3$, **4d**. According to our hypothesis the formation of **4d** can be initiated by the intramolecular protonation of the oxygen atom and the subsequent substitution on the carbonyl carbon atom (Scheme 2).

The difficulties in the synthesis of CAB using **1** prompted us to look for a simpler hydroxy-carboxylic acid and we decided to use D,L-malic acid. The reactions of **1a** with arylboronic acids **2a** and **2b** were carried out in THF solution using CaH_2 to remove water

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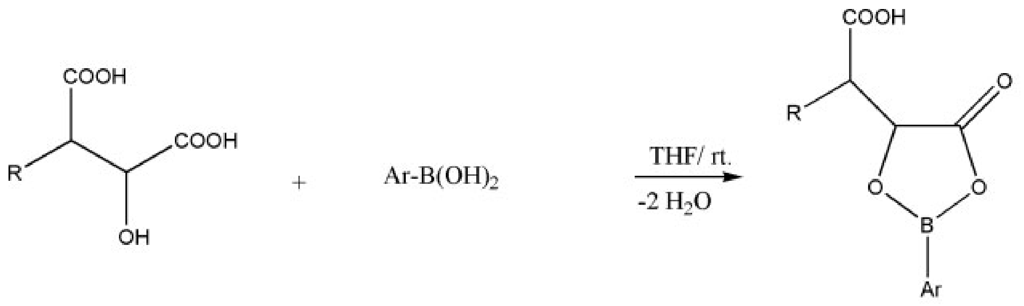
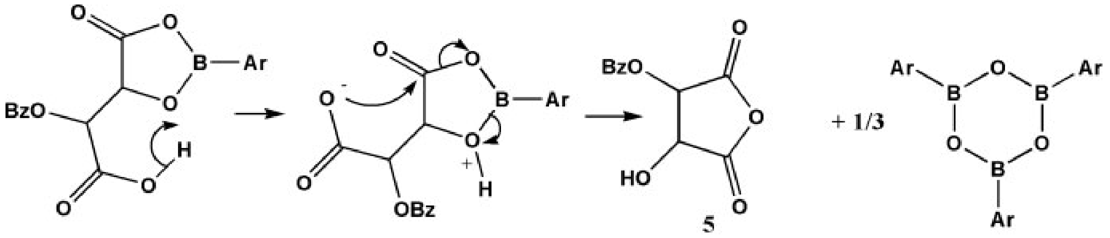


(1) R= C_6H_5COO-
(1a) R= H

(2a) Ar= 4-MeS-C_6H_4-
(2b) Ar= 4-CF_3-C_6H_4-
(2c) Ar= 4-CH_3O-C_6H_4-
(2d) Ar= 2-F-C_6H_4-

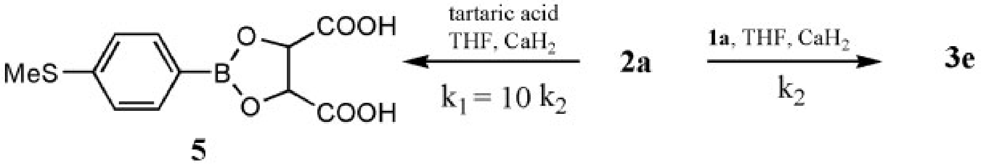
(3a) R= C_6H_5COO-, Ar= 4-MeS-C_6H_4-
(3b) R= C_6H_5COO-, Ar= 4-CF_3-C_6H_4-
(3c) R= C_6H_5COO-, Ar= 4-CH_3O-C_6H_4-
(3d) R= C_6H_5COO-, Ar= 2-F-C_6H_4-
(3e) R= H, Ar= 4-MeS-C_6H_4-
(3f) R= H, Ar= 4-CF_3-C_6H_4-

Scheme 1. General reaction scheme for the reaction of arylboronic acids with L-*O*-benzoyl-tartaric acid and malic acid.



Bz =benzoyl, Ar = 2-F-C_6H_4-

Scheme 2. The mechanism of the formation of boroxines.



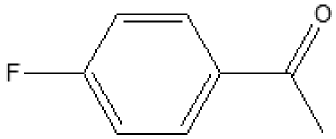
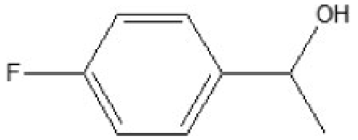
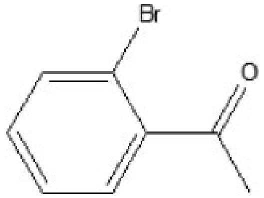
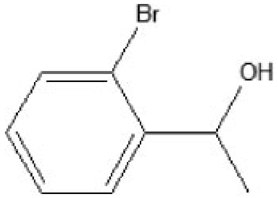
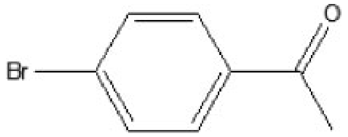
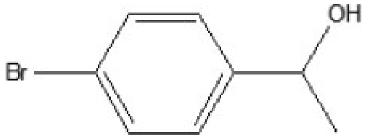
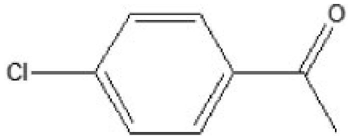
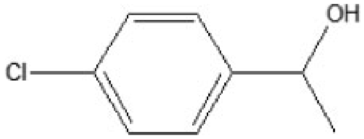
Scheme 3. The influence of the ring strain on the reaction rate.

from the reaction system. The reaction progress was controlled by measurement of the amount of the hydrogen evolved. After the reaction was completed, the reaction mixture was decanted from CaH_2 and concentrated. For the reaction of **1a** with **2b**, the concentration gave the thick oil which solidified after 1 h under vacuum, whereas for the reaction of **1a** with **2a**, the crystalline solid was obtained after removal of *ca* 25% of the solvent. The ^{1}H-NMR spectra revealed that **3e** and **3f** were formed selectively. Single crystals of **3e** were obtained by slow concentration of the reaction mixture.

The X-ray structure determination of **3e** revealed that the boron atom is involved in a five-membered ring which is essentially flat and coplanar with the benzene ring and thiomethyl group (Fig. 1). The carboxylic group is endo-oriented to the five-membered ring with the carbonyl oxygen atom positioned towards the ring center. The angle O5–C4–C3 is significantly declined from the value 120° characteristic for sp^2 hybridized carbon atom, which results in the ring tension. This fact influences strongly the kinetics of the formation of **3e**. In two independent experiments **2a** was reacted with **1a** or with tartaric acid[13,14] and the rate of the hydrogen evolution was controlled. The experiments revealed that reaction with **1a** is much slower than the reaction with tartaric acid (Scheme 3). The explanation lies in the rising of the $\Delta G^{\ddagger}$ in the formation of **3e** because of the introduction of the ring strain. The five-membered ring in **5** is not strained because of the presence of two sp^3 hybrydized carbon atoms. Although the crystal structure of many boronic acids like 4-tolylboronic acid or its catechol ester have been already published,[15–17] the number of crystal structures of aromatic organo-oxyboranes containing sulfur atoms is limited to 2-benzylthiophenylboronic acid which forms characteristic dimers through hydrogen bonds.[18] However, the structures of 4-methylthiophenyl-bis-mesitylborane[19] and related sulfur-containing triarylboranes were also recently published.[20,21]

The new (acyloxy)borane **3e** is moderately stable in air. It forms a strong adduct with DMSO which results in significant changes in the NMR spectra. In the IR spectrum of **3e** we found the absorption peak at 1800 cm^{-1}. This value differs from the 1821 cm^{-1} frequency reported for the other CABs. The reactivity of the optically active **3e** obtained from L-(−)-malic acid was tested in the reduction of ketones in the presence of $NaBH_4$.[14]

Table 1. Reduction of acetophenones using **3e**–$NaBH_4$ system

Ketone	Product	Yield, e.e. (configuration)
		96%; 99.5% (*R*)
		94%; 99.2% (*R*)
		84%; 95.6% (*R*)
		81%, 87.1% (*R*)

The reduction of selected acetophenones yielded the respective secondary alcohols with high enantioselectivity (Table 1).

In conclusion, the reaction of arylboronic acids with L-*O*-benzoyltartaric acid afforded the respective CAB in moderate yields. The reaction of 4-methyltiophenylboronic acid with D,L-malic acid occurs selectively in the THF–CaH_2 system to give 5-carboxymethyl-2-(4-methylthiophenyl)-1,3,2-dioxaborolan-4-one. The presented procedure can be the general way to synthesize (acyloxy)boranes from malic acid. The use of L-(−)-malic enables the synthesis of the optically active **3e**, which shows remarkable reactivity in the enantioselective reduction of acetophenones.

Experimental Section

^1H-, ^{13}C-, ^{19}F- and ^{11}B-NMR as well as IR spectra were recorded at room temperature. Chemical shifts are given in ppm relative to TMS in ^1H- and ^{13}C-NMR spectra, relative to C_6F_6 in ^{19}F-NMR spectra and relative to $Et_2O{*}BF_3$ in ^{11}B-NMR spectra. All chemicals were received from Aldrich. THF was stored over sodium and DMSO-d_6 was distilled over CaH_2 prior to use. All reactions were carried out under dry argon using standard Schlenk techniques. The enantiomeric excess was measured using *S*(+)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride as the chiral selector. The absolute configurations were obtained by comparison of optical rotation with values measured for enantiopure compounds obtained from Aldrich.

Synthesis of 3e†

4-Methylthiophenylboronic acid (1.68 g, 0.01 mol), D,L-malic acid (1.34 g, 0.01 mol) and CaH_2 (1.68 g, 0.04 mol) were placed in the reaction flask and THF (40 ml) was added via a syringe maintaining the vigorous stirring. The reaction flask was tightly closed and only the connection to the gas evolution measurement apparatus was left open. The reaction started immediately, which was indicated as the rapid gas evolution. The reaction mixture was left on stirring until the stoichiometrical amount of hydrogen evolved (*ca* 24 h). After this time the stirrer was turned off and the reaction mixture was left to clarify (*ca* 48 h). A clear solution over precipitate was obtained. This solution was transferred to another reaction flask via cannula. Concentration of this solution by 25% under vacuum at room temperature afforded colorless crystals. The crystals were separated and the remaining solution was placed to the freezer (−15 °C). After 2 days the new portion of crystals was obtained. Both of the fractions were combined and dried under vacuum

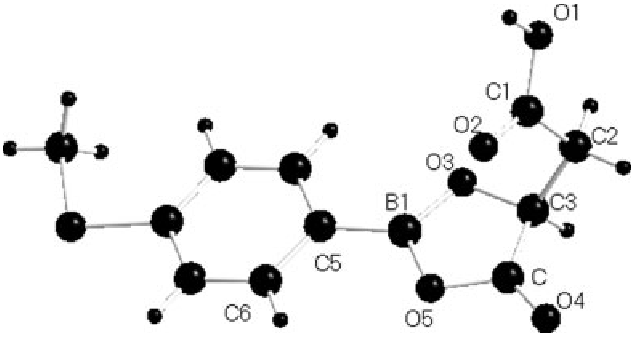


Figure 1. Structure of **3e** with thermal ellipsoids at the 50% probability level. Selected bond lengths (Å) and angles (deg): B1–C5 1.539(3), B1–O51.406(3), C4–O4 1.983(2), C4–C31.519(3), C4–O5 1.366(2), C3–O31.441(2), O5–C4–O4 123.01(2), O5–C4–C3 107.90(2), C4–C3–O3 104.31(2), O2–C1–O1 124.18(2), O4–C4–C3 129.02(2), C3–C2–C1–O2 37.33(3). Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 781172.

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† PL patent applied for

to obtain **3e**. Yield: 2.7 g (92%). ^{1}H-NMR (THF-d_8, 400 MHz) δ 7.66 (d, 2H, $J = 4.4$ Hz), 7.20 (d, 2H), 4.82 (dd, 1H$_X$, $J = 4.4$ Hz, $J = 4.8$ Hz), 2.90 (dd, 1H$_A$, $J^2 = 11.2$ Hz, $J^3 = 4.4$ Hz), 2.83 (dd, 1H$_B$, $J^2 = 11.2$ Hz, $J^3 = 4.8$ Hz), 2.41 (s, 3H). ^{13}C-NMR (THF-d_8, 100 MHz) δ 176.30 (COOH), 171.29 (C=O), 146.57 ($C_{Ar}-S$), 136.25 (C_{Ar}), 125.91 (C_{Ar}), 74.12 (C–H), 36.64 (CH_2), 14.81 (CH_3). ^{11}B-NMR (THF-d_8, 64 MHz) δ 32. MS, EI–HR: calcd for $C_{11}H_{11}O_5BS$ 266.04203. Found: 266.04311. Elemental analysis: calcd for $C_{11}H_{11}O_5BS$: C, 49.65; H,4.17. Found: C, 49.96; H,4.21.

Synthesis of 3e*DMSO-d_6

3e (0.021 g) was dissolved in DMSO-d_6 (0.6 ml) to form the clear solution. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 7.31 (d, 2H, $J = 6.4$ Hz), 7.11 (d, 2H), 4.50 (dd, 1H$_X$, $J^3 = 4.0$ Hz, $J^3 = 4.4$ Hz), 2.67 (dd, 1H$_A$, $J^2 = 15.2$ Hz, $J^3 = 4.0$ Hz), 2.45 (dd, 1H$_B$, $J^2 = 15.2$ Hz, $J^3 = 4.4$ Hz), 2.41 (s, 3H). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 177.68 (COOH), 171.90 (C=O), 140 (C–B, br), 136.36 ($C_{Ar}-S$), 132.27 (C_{Ar}), 125.17 (C_{Ar}), 71.87 (CH), 39.01 (CH_2), 15.01 (CH_3). ^{11}B-NMR (DMSO-d_6, 64 MHz) δ 11. Elemental analysis: calcd for $C_{13}H_{11}D_6O_6BS_2$: C, 44.58; H,6.62. Found: C, 44.76; H,6.69.

Example Procedure for the Reduction of Ketones

3e obtained from L-(−)-malic acid (1.01 g, 0.003 mol) and 4-fluoroacetophenone (0.41 g, 0.003 mol) was placed in the Schlenk flask and THF (30 ml) was added maintaining the stirring. $NaBH_4$ (0.11 g, 0.003 mol) was added to the obtained solution causing the rapid gas evolution. After 1 h the reaction mixture was poured onto water (50 ml) and extracted with hexane (30 ml). The organic phase was dried with $MgSO_4$ and evaporated to give 4-fluoro-α-methylbenzyl alcohol. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.23 (m, 2H), 6.93 (m, 2H), 4.77 (q, 1H), 2.06 (br, 1H), 1.36 (d, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 161.3 (d, $J^1_{C-F} = 253$ Hz), 136.5, 128.1, 115.7, 75.7, 22.6. Elemental analysis: calcd for C_8H_9OF: C, 68.56; H,6.47. Found: C, 69.01; H,6.56.

Determination of Enantiomeric Excess

Equimolar amounts (100 μmol) of 4-fluoro-α-methylbenzyl alcohol and *S*(+)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride were placed into vial and dissolved in 0.2 ml of hexane. The excess of K_2CO_3 was added and the obtained mixture was kept at 50 °C for 1 h. The sample of the reaction mixture was next examined by GC [COL-ELITE-5 MS column, $t_R = 7.8$ min for (*R*)-enantiomer].

Crystal Data for 3e

Single crystal data were collected on a Gemini A Ultra Diffractometer (Oxford Diffraction Ltd). The *CrysAlisPro* program was used for data collection, cell refinement, data reduction and the empirical absorption corrections using spherical harmonics, implemented in multi-scan scaling algorithm. The structure was solved using direct methods, and refined with the full-matrix least-squares technique using the *SHELXS97* and *SHELXL97* programs, respectively. $C_{11}H_{11}O_5BS{*}C_4H_8O$, FW = 338.17, monoclinic, space group $P2_1/c$, $D_{calcd} = 1.399$ g cm^{-3}, $Z = 4$, $a = 12.6498(3)$ Å, $b = 5.43210(13)$ Å, $c = 23.5827(5)$ Å, $\alpha = 90.00°$, $\beta = 97.667(2)°$, $\gamma = 90.00°$, $V = 1606.00(7)$ Å^3, $T = 100(2)$ K, Gemini A Ultra Diffractometer, λ (Cu/K$_\alpha$) = 1.5418 Å, $\mu = 2.041$ mm^{-1}. Of 10 319 reflections measured, 1993 were unique ($R_{int} = 0.045$). Refinement on F^2 concluded with the values $R_1 = 0.0490$ and $wR_2 = 0.0892$ for 226 parameters and 2502 data with $I > 2\delta_I$.

Acknowledgments

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