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Synthesis and Application of a Chiral Diborate

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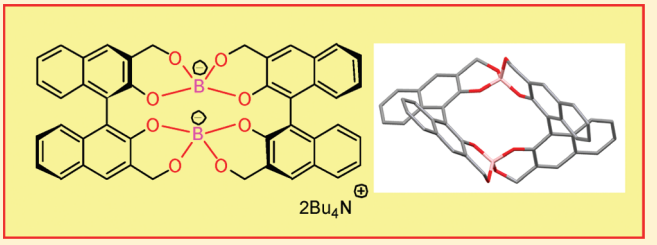
Supporting Information

ABSTRACT: A chiral diborate with different counterions is reported whose structure was unambiguously confirmed by X-ray analysis. This chiral dianion was used in the resolution of *trans*-1,2-diamines and also as a chiral shift reagent for NMR analysis of triphenylphosphonium salts.



Many transformations in organic chemistry feature an ionic reactant, product, or an ionic intermediate. In particular, the latter species, mostly cationic intermediates, open up the possibility of influencing the transformation by a charged catalyst thereby enhancing the reactivity and outcome of the reaction. Application of a chiral counteranion can lead to stereoselective ion pairing that can influence the stereochemical outcome of a transformation.[1,2] List et al.,[3] Rueping et al.,[4] and Toste et al.[5] showed that chiral phosphates like **1** can be useful catalysts in hydroalkoxylations, hydroaminations, asymmetric transfer hydrogenations, and reductive aminations reactions (Figure 1). Other noteworthy applications of chiral anions include the recent work of Lacour et al. They reported the tris(tetrachlorobenzenedolato)phosphate(V) anion **2**[6] that can be used as a chiral shift reagent for phosphonium salts[7] and several cationic metal complexes.[8,9] Besides phosphates, chiral borates are also known to influence the stereochemical outcome of reactions. Borates **3** consisting of two chiral BINOL units have been used as additives (10−50 mol %) in the reaction of prochiral cationic starting materials such as iminium ions or aziridinium ions.[10] The borate **3** has been used as a chiral counteranion to induce enantioselectivity in the copper-catalyzed olefin aziridination and cyclopropanation.[11] Additionally, a new class of back to back twin bowls of D_3-symmetric tris(spiroborate) cyclophanes, which are cyclic trimers resembling **3** has been uncovered very recently.[12] Furthermore, Yamamoto et al. showed that borates like **4** are efficient Brønsted acid assisted chiral Lewis acids for cycloaddition reactions.[13,14]

Against this literature backdrop and in view of the efficient ion pairing of a chiral anion and different cations, we surmised the introduction of a second negative charge to be interesting for effective ion-pairing. A dianion could have a strengthening effect on the interaction with a cation and also allow interactions with dicationic molecules. This might provide access to new applications and establish a new class of catalysts. Examples of borates[15] of type **4** suggested the possibility of a similar diborate. Herein, we report the synthesis of a chiral diborate with different counterions and show its application in the resolution of *trans*-1,2-diamines and also as a shift reagent in NMR analysis.

Our study commenced with the synthesis of tetraol **5**[16] by the introduction of two additional hydroxy groups in a (*R*)-BINOL backbone in the 3- and 3′-positions, which was realized in four steps.[17] Treatment of tetraol **5** with boric acid in the presence of aqueous tetrabutylammonium hydroxide and heating to 60 °C for 1 h provided dianion **6** exhibiting a unique architecture (Scheme 1).

The structure of the chiral diborate **6** was elucidated by spectroscopic analysis and confirmed unequivocally by X-ray crystallography.[17] The crystal structure revealed two concave anionic pockets formed by the diborate, in which the tetrabutyl ammonium cations are located. Although the structure seems to be very sterically crowded, the average B−O bond distance of 1.472 Å is similar to the value found for the monoborate (1.471 Å).[15] In view of this interesting result, we then focused our attention on the synthesis of chiral borate salts derived from secondary amines. Gratifyingly, treatment of **5** with a solution of boric acid and R_2NH resulted in the formation of chiral borate anions **7**−**10** in moderate yield (Table 1).

RESOLUTION

With this new chiral diborate in hand, we envisioned its application in resolution of racemic amines inspired by the report of Periasamy et al.[18] They reported the resolution of racemic BINOL by stereoselective formation of a monoborate **3** with a chiral ammonium counterion using the readily available (*R*)-(+)-α-methylbenzylamine to induce stereoselectivity. We proposed to invert this procedure and achieve resolution of racemic amines by using chiral tetraol **5** for the diborate formation following our idea that a chiral dianion can lead to enhanced interactions with cations. Chiral diamines in general are often used as ligands in metal complexes[19] and serve as scaffolds for several other successful ligands, e.g., the Trost ligand.[20] Access to a variety of chiral diamines allows tuning of the ligands and

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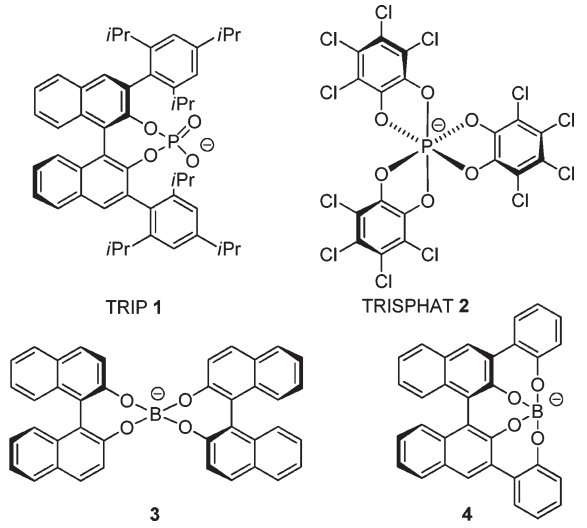


Figure 1. Examples of chiral anions.

Scheme 1. Synthesis of Chiral Diborate 6

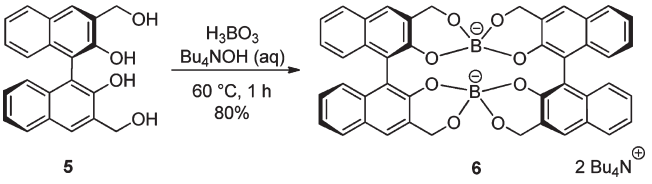
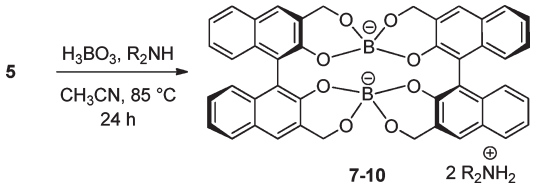


Table 1. Synthesis of Diborates Derived from R_2NH[a]



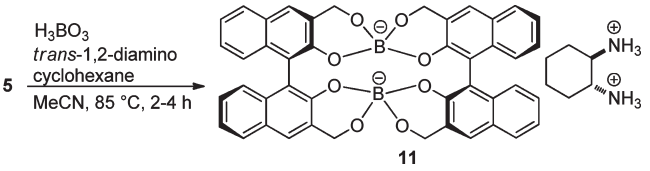
entry	R_2NH	product	yield (%)
1	diethyl amine	**7**	36
2	dibenzyl amine	**8**	48
3	piperazine	**9**	36
4	morpholine	**10**	33

[a] Conditions: **5** (1.0 equiv) was added to a solution of boric acid (1.1 equiv) and the amine (3.0 equiv) in MeCN (4.0 mL for 0.5 mmol of the tetraol) and the mixture stirred for 24 h at 85 °C in a sealed tube.

optimization for different applications to find more efficient catalysts.[21] Indeed, diamines are more suitable in this resolution reaction, supporting our assumption of a stronger interaction of the borate with dications.

Treatment of **5** with boric acid and different amounts of *trans*-1,2-diaminocyclohexane resulted in the formation of chiral diborate **11** (Table 2). The best result was obtained with 2.0 equiv of the diamine giving 64% ee. We expected the selectivity to rise by using excess of diamine, but with 10.0 equiv

Table 2. Formation of Diborate 11 with Different Amounts of Racemic *trans*-1,2-Diaminocyclohexane[a]



entry	amount of diamine used (equiv)	yield[b] (%)	ee[c] (%)
1	1.0	44	52
2	2.0	81	64
3	10.0	87	42

[a] Reaction conditions: **5** (2.0 equiv) was added to a solution of boric acid (2.0 equiv) and *trans*-1,2-diaminocyclohexane (amounts given in Table) in MeCN, and the reaction mixture was stirred for 2−4 h at 85 °C in a sealed tube. The formed diborate salt precipitated and was filtered off and washed with MeCN. [b] Yields of the diamine referred to the borate formed. [c] ee was determined by chiral GC analysis.

Table 3. Summarized Results of Resolution Application[a]

entry	diamine	yield[b] (%)	ee (%)
1	*trans*-1,2-diphenylethane-1,2-diamine	35	24
2	*trans*-1,2-diaminocyclohexane	81	64
3	*cis*-/*trans*-1,2-diaminocyclohexane	83	47[c,d]

[a] Reaction conditions: **5** (1.0 equiv) was added to a solution of boric acid (1.0 equiv) and the amine (1.0 equiv) in MeCN, and the reaction mixture was stirred for 2−4 h at 85 °C in a sealed tube. The formed diborate salt precipitated and was filtered off and washed with MeCN. [b] Yields of the diamine referred to the borate formed. [c] Enantiomeric excess for *trans*-diamine, determined by chiral GC analysis. [d] 10.0 equiv of diamine used.

of *trans*-1,2-diaminocyclohexane the enantiomeric excess dropped to 42%. However, this represents the resolution of a chiral diamine exclusively by ionic interactions with a chiral diborate. In addition, the tetraol can easily be reisolated by extraction of the acidic aqueous media.

Encouraged by these results, we next tested 1,2-diphenylethane-1,2-diamine in the resolution procedure. Unfortunately, with 2.0 equiv of the chiral diamine, only 24% ee could be obtained (Table 3). Surprisingly, with 10.0 equiv, no diborate formation was observed. This might be due to the higher steric demand of the diamine or formation of an undesired borate species. We have also carried out the resolution for a mixture of *cis*-/*trans*-1,2-diaminocyclohexane to see if there is a discrimination of the *cis*-configurated diamine. However, in the formation of the diborate, a little differentiation between *cis* and *trans* configuration has been observed. There was 18% of *cis*-diamine incorporated into the borate and the *trans*-diamine showed an enantiomeric excess of 47%.

USE AS CHIRAL SHIFT REAGENT

Arguably, NMR spectroscopy is a very important method for the analysis of chiral molecules.[9] Usually, chiral derivatizing agents form a coordinative or covalent bond with the enantiomers that are being analyzed (e.g., Mosher's reagent).

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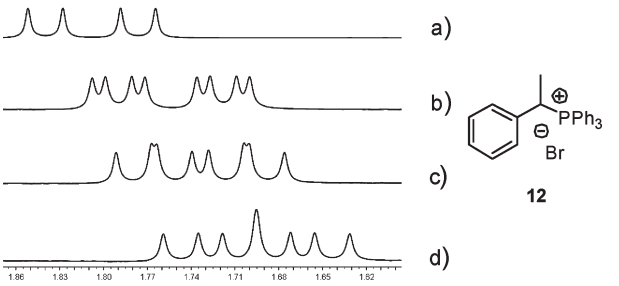

Figure 2. Sections of ^{1}H NMR (300 MHz in $CDCl_3$) of triphenyl(1-phenylethyl)phosphonium bromide **12** showing the proton next to the triphenylphosphonium group (a) without additive and (b) with 0.25 equiv, (c) with 0.5 equiv, and (d) with 1.0 equiv of **6**.

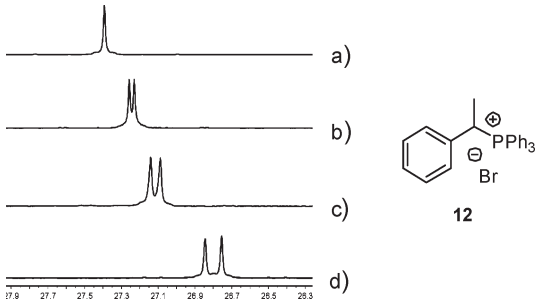

Figure 3. ^{31}P NMR (61 MHz in $CDCl_3$) of triphenyl(1-phenylethyl)-phosphonium bromide **12** (a) without additive and (b) with 0.25 equiv, (c) with 0.5 equiv, and (d) with 1.0 equiv of **6**.

Furthermore, use of chiral solvating agents that bind in situ to the compounds through noncovalent interactions is known. These shift reagents very often contain metals like lanthanides, palladium, ruthenium, or others. In addition, metal-free molecules are used as chiral solvating agents. Cyclodextrins and crown ethers, for example, form hydrogen bonds or have dipole−dipole interactions with the different enantiomers. Charged shift reagents are also known, mostly being negatively charged metal complexes.[22]

As mentioned above, Lacour et al. introduced TRISPHAT **2** as a metal-free anionic shift reagent, effectively separating the NMR signals of racemic and positively charged molecules.[6−9] As another example, Arndtsen et al. used chiral monoborates as a shift reagent for enantiomeric copper(I) complexes with tol-BINAP and an oxazoline ligand.[23] Inspired by these, we imagined diborate **6** to act as an efficient shift reagent. To validate our assumption, in several NMR experiments we added different amounts of **6** to triphenyl(1-phenylethyl)phosphonium bromide **12**.[24] Figure 2 shows sections of the ^{1}H NMR spectra focusing on the single hydrogen next to the triphenylphosphonium group. A separation of the signals was achieved by addition of only 0.25 equiv of **6**.

In ^{31}P NMR (Figure 3), the same trend is observed. More additive leads to a higher chemical shift, but separation is already complete with the addition of 0.25 equiv of diborate **6**. These first findings in this area suggest the opportunity to expand the use of **6** in the NMR analysis of enantiomeric mixtures to other cationic molecules, complexes, or even neutral molecules.[25]

In conclusion, we have uncovered a chiral diborate with different counterions, and its structure was unequivocally verified by X-ray crystallography. We could apply this dianion as a chiral shift reagent in NMR analysis of triphenylphosphonium salts. Furthermore, it can be used in the resolution of *trans*-1,2-diaminocyclohexane and *trans*-1,2-diphenylethane-1,2-diamine. It is reasonable to assume that the new class of chiral diborates presented herein and its application as chiral resolution agent and NMR shift reagent will have potential utility in organic synthesis.

EXPERIMENTAL SECTION

Procedure for the Synthesis of Borate (6). In analogy to a known procedure,[26] (*R*)-3,3′-bis(hydroxymethyl)-1,1′-binaphthyl-2,2′-diol (**5**) (104 mg, 0.30 mmol, 1.0 equiv) was added to boric acid (19 mg, 0.30 mmol, 1.0 equiv) and tetrabutylammonium hydroxide (0.2 mL, *c* = 1.5 Mol/L in H_2O, 0.30 mmol, 1.0 equiv). The reaction mixture was stirred for 1 h at 60 °C and the dark red residue dried in high vacuum. Recrystallization from Et_2O/EtOH (10:1) afforded 283 mg (0.24 mmol, 80%) of an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, J = 7.8 Hz, 4H), 6.98−6.96 (m, 4H), 6.89−6.79 (m, 12H), 5.03 (d, J = 13.3 Hz, 4H), 4.60 (d, J = 13.3 Hz, 4H), 2.71−2.49 (m, 16H), 1.09−0.92 (m, 32H), 0.67 (t, J = 7.2 Hz, 24H). It may be noted that ^{1}H NMR of **6** showed additional protons in the aliphatic region presumably due to the presence of tetrabutyl ammonium residue. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.0, 135.0, 131.7, 126.8, 126.7, 125.8, 123.5, 120.9, 120.2, 116.9, 62.5, 58.6, 23.9, 19.4, 13.6. ^{11}B NMR (96 MHz, $CDCl_3$): δ = 3.54. HR-MS (ESI): *m*/*z* calcd for $[(C_{44}H_{28}B_2O_8Na)^-]$ 729.1888, found 729.1882 $[(M + Na)^-]$. IR (ATR): ν /cm^{-1} = 2954, 1458, 1421, 1265, 1112, 956, 875, 744. $[\alpha]^{22}_D$ = +82.0 (*c* = 0.5 in $CHCl_3$).

ASSOCIATED CONTENT

Supporting Information. General experimental methods, full characterization data, and crystallographic data (CIF) for diborate **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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