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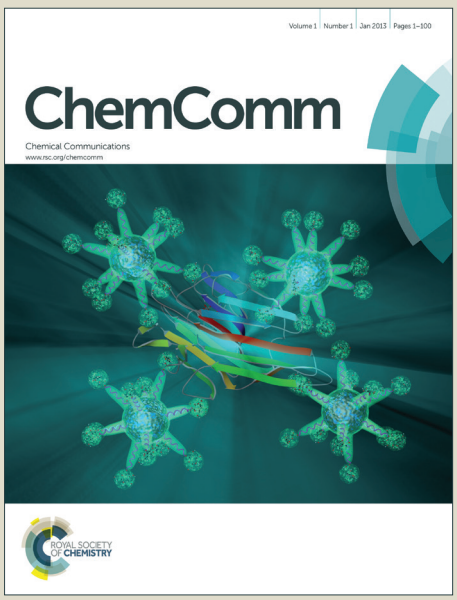

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bis(Mandelato)borate: An Effective and Inexpensive Spiroborate Anion for Chiral Resolution

Received 16th June 2015,
Accepted 00th August 2015

DOI: 10.1039/x0xx00000x

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bis(Mandelato)borate $[B(Man)_2]^-$ (R- or S-) anions are simply prepared and appear widely effective for resolution of racemic cations. Three examples demonstrate their scope; the alkaloid tetrahydropalmatine (THP), 1,2-diaminopropane (1,2-dap) and the metal-organic complex $[Co(phen)_3]^{3+}$ are readily resolved, either by a facile one-pot procedure, or via counter-ion metathesis.

A frequent stumbling block in modern organic chemistry is the need for enantiomeric resolution. The prevalence of chiral compounds in modern pharmaceuticals means the industrial availability of key enantiopure starting reagents for chiral building blocks is of great commercial value.[1]

The selective crystallization of diastereomeric solids offers one of the best resolution methods, applicable to scale-up.[2] The classical method of resolving molecular cations or anions is the formation of diastereomeric salts.[3] An analogous method for neutral molecules through chiral co-crystal formation[4] or host-guest inclusion[5] is a rapidly developing area.

Traditionally racemic mixtures of cations have often been resolved using anions based on tartrates, mandelates[6] or their esters. Notable efforts to develop synthetic anions with high chiral discriminating power for resolution include the TRISPHAT anions $[P(O_2C_6Cl_4)_3]^-$ of Lacour,[7] based on non-labile tris-chelation of substituted catecholates. These have been shown to be of good efficiency in a wide variety of chiral resolutions, for example of metal complexes[8] and dyes,[9] but remain relatively expensive. Boron is capable of chelation of various diols, acid-alcohols, catechols and salicylic acids to form spiroborate anions which can have a variety of uses.[10] Some, such as bis(catecholato)borate $[BCat_2]^-$, have been demonstrated to be effective crystallizing anions.[11]

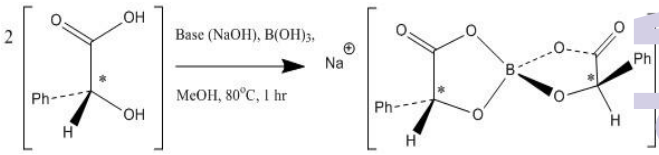

Fig 1. Preparation of **1-R** $[Na][B(R\text{-}Man)_2]$

The resolution of several common racemic amines was already reported by Periasamy[12] based on borate esters of BINOL.[13] Despite this promising work the use of spiroborates for resolution has not gained much momentum, though these anions have been reinvestigated[14] and resolution using a chiral diborate has been recently demonstrated.[15] One issue is that, unlike the octahedral tris-phosphates, the chiral borate centres are labile and prone to racemization. Use of ligand based chirality, as in the BINOL case, is thus necessary.

We reasoned that bis(mandelato)borate anions $[B(Man)_2]$[16] which have been recently applied to chiral ionic liquids[17] and as anti-fungal wood preservatives[18] might also have promise as resolving agents. They can be readily prepared and isolated as simple salts such as $Na[B_S(R\text{-}Man)_2]$, **1-R**.‡ (Fig 1)

Herein their use in resolving racemic cation mixtures *via* metathesis crystallizations, or even through facile one-pot procedures is described. Three disparate examples (Fig 2) are given to illustrate the variety and effectiveness of the system which requires only boric acid, R- or S-mandelic acid and a reasonably polar or protic solvent, such as methanol. The first system presented is tetrahydropalmatine (THP), an isoquinoline alkaloid of which the S-(-)-isomer is a dopamine antagonist,[19] has promise as an anxiolytic[20] and for treatment of addiction.[21]

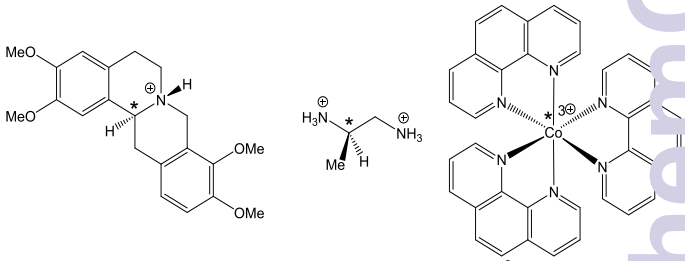

Fig 2 Three cations resolved by $[B(R\text{-}Man_2]$: $[THP\text{-}H]^+$, $[1,2\text{-}dap\text{-}H_2]^{2+}$ and $[Co(phen)_3]$

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‡ Electronic Supplementary Information (ESI) available: [Synthesis and characterization data, powder X-ray diffractograms, chiral HPLC chromatograms, circular dichroism (CD) spectra, DFT calculations and single-crystal X-ray structure determination summaries]. See DOI: 10.1039/x0xx00000x

The compound occurs in a number of plants especially in certain *Cordyalis* and *Stephania* genera,[22] frequently in racemic form, which like the related berberine is commercially available in kg quantity. A resolution based on the benzoyltartrate ester salt of $[THP\text{-}H]^+$ has been established, but the method is not optimal.[23]

Resolution of THP can be readily achieved through stirring $Na[B(R\text{-}Man)_2]$ **1-R** with rac-THP at reflux in methanol for 3h. Crystals of $[S\text{-}THP][B_S(R\text{-}Man)_2]$ **2-R** form in 80% yield upon cooling. Chiral HPLC indicated the enantiopurity of the THP in the solid from this initial crystallization was between 94-97% ee. A big advantage of the mandelate system is that both R- and S- mandelic acids are inexpensive and readily available; thus **2-S** crystals can be similarly obtained by employing S-mandelic acid in the formation of the sodium salt. The segregation of the THP enantiomers between the solid and solution phases can be close to complete, as shown by the circular dichroism spectra taken from solutions based on dissolved solid and the residual solution. The $[THP\text{-}H]^+$ cations are non-planar and possess an asymmetric condensed ring system the molecular twist of which would appear to pack more favourably with one $[B(Man)_2]^-$ ion rather than the other, Fig 3.

The second example presented here is a rather different challenge; 1,2-diaminopropane is a small difunctional molecule possessing a chiral centre with -H and $-CH_3$ groups which can be challenging to discriminate between in solid state molecular packing arrangements. In this case we can use a facile one-pot procedure to give effectively complete resolution. Rac-1,2-diaminopropane, boric acid and R-mandelic acid were heated in methanol for 3 h followed by slow cooling to ambient temperature. Crystals of **3-R** $[R\text{-}1,2\text{-}dap\text{-}H_2][B_S(R\text{-}Man)_2]$ .MeOH are formed phase pure in 80% yield. High enantiopurity of the 1,2-dap within a crystal of **3-R** is indicated since the H and CH_3 positions show no apparent site disorder. HPLC of the bis-benzamide of the 1,2-dap derived from **3-R** showed a 93.7% ee from this single crystallization step.

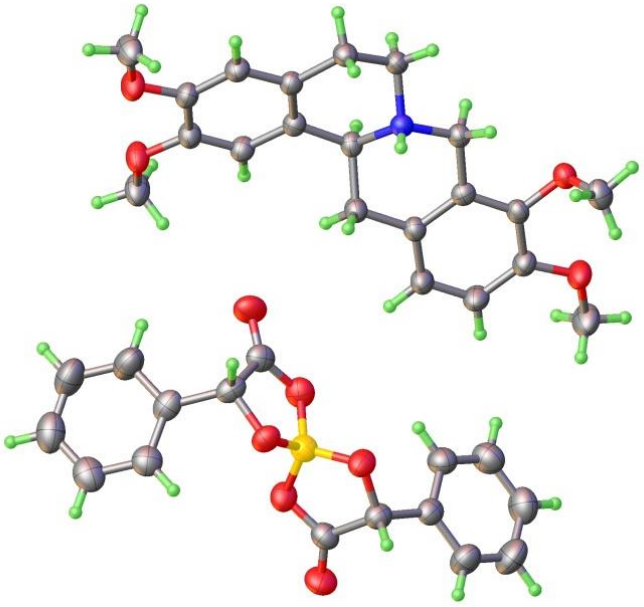

Fig 3. An ion pair from the crystal structure of **2-R** $[S\text{-}THP][B_S(R\text{-}Man)_2]$.

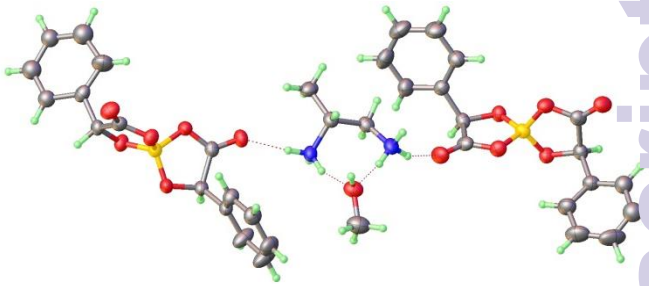

Fig 4. Asymmetric unit of **3-R** & role of methanol solvate in 1,2-dap resolution.

This compares favourably with the classic resolution of 1,2-da using tartaric acid, which involved a tedious number o recrystallizations.[24] In this case of **3-R** the methanol has a crucial role in the structure as a double hydrogen bond accepto from the 1,2-dap-H_2 dication (Fig 4). Resolutions using other solvents are possible, though details differ and in this syste the diastereomeric salt can be a contaminant, or a m product, depending on the solvent used. The resolution of THP can also be carried out by a similar one-pot procedure to 1,2-dap, but gives products polymorphic to **2-R** and **2-S**.

The third example selected shows the resolution o octahedral Δ and Λ metal-organic coordination enantiomers o the well-known tris-1,10-phenanthroline cobalt(III) cation $[Co(phen)_3]^{3+}$. This offers a different resolution scenario fro the previous two examples, in that shape alone is involved an the cations have no hydrogen bond donors to interact with th spiroborate anions. In this system a highly efficient enantio separation can be obtained using a metathesis procedur Heating a solution of rac-$[Co(phen)_3]Cl_3$ with 3 equivalents o $Na[B(R\text{-}Man)_2]$ **1-R** for several hours followed by slow cooling back to room temperature leads to precipitation of orange crystals **4-R**, whilst still leaving an orange solution. The cryst structure of **4-R** reveals that it is a 1:3 salt of idealized formula $[(\Lambda)\text{-}Co(phen)_3][B_s(R\text{-}Man)_2]_3.2MeOH$. The asymmetric has three independent trications, nine $[BMan_2]^-$ anions and sites for six MeOH. One site is split and disordered about a 2-fold axis and is partially occupied and/ or hydrated.The geometry o the anions is closely preserved in as shown in Figure 5.

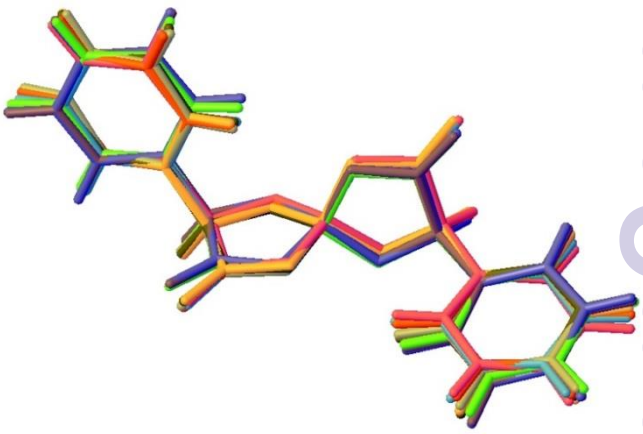

Fig 5. Overlay of the nine crystallographically independent anions in **4-R**.

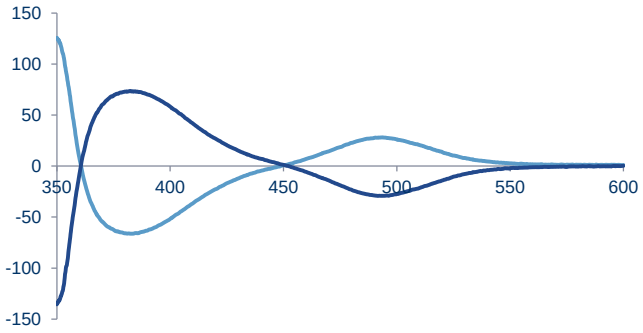

Fig 6. Circular dichroism spectra of resolved **4-R** and **4-S** $[Co(phen)_3][B(Man)_2]_3$

The circular dichroism (CD) spectra of the dissolved salts **4-R** and **4-S** obtained from different crystallizations employing R-Man and S-Man respectively, are shown in Figure 6. Comparison with literature values of $[Co(phen)_3]^{3+}$ complexes indicates that ee of 90% have been obtained. It is worth noting that in this case isolation of the salt is just greater than 50% yield limiting the ee of the resolved salt, since dynamic equilibrium between the Δ and Λ-cations will be minimal.[25]

Crystallization of a wide range of counter cations using the bis(mandelato)borate anions may be facilitated in part by their semi-rigid nature; they have two independent degrees of freedom on the two Ph dihedral angles and displacement of the B atom of up to 0.12Å from the chelate plane introduces a hinge angle in the 5-membered chelate rings that can modify the molecular shape by displacements of up to 2Å. Metathesis appears most effective in polar and protic solvents such as MeOH, MeCN and EtOH for which the RT solubility of $Na[B(Man)_2]$ **1-R** varied from around 1M to 0.4M. As indicated in the examples here the choice of solvent can play a critical role and it should be noted that for some systems we have observed gel formation rather than crystallization.

The effectiveness of chiral resolutions in these salts is no doubt greatly attributable to the shape differentiation of the $[B_S(R\text{-}Man)_2]^-$ and the mirror image anion $[B_R(S\text{-}Man)_2]^-$ ions, which are overlayed for comparison in Figure 7. It is thus reasonable that resulting diastereomeric salts of one such anion with racemic cations may have reasonably differing packing efficiencies and solubilities.

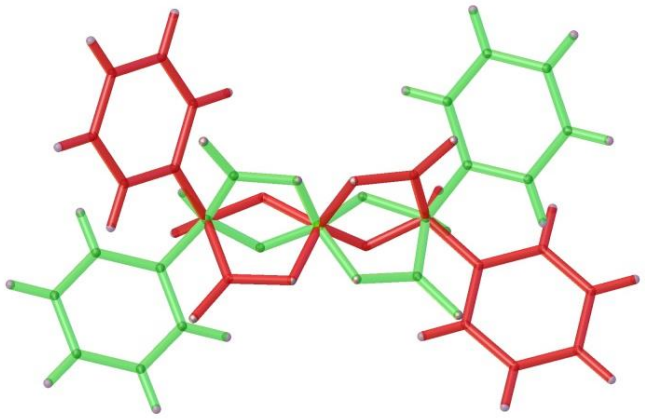

Fig 7. Shape differentiation of $[B_S(R\text{-}Man)_2]^-$ (red) and $[B_R(S\text{-}Man)_2]^-$ anions.

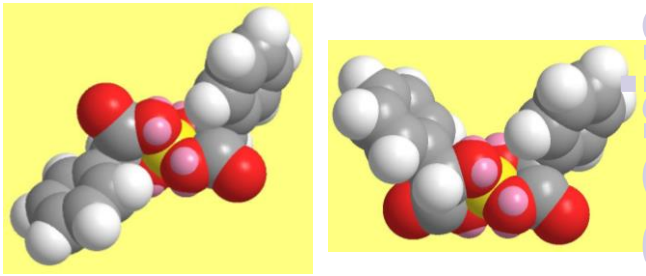

Fig 8. Comparison of "twisted" $[B_R(S\text{-}Man)_2]^-$ and "V-shaped" $[B_S(S\text{-}Man)_2]^-$ anions

However the degree to which the enantio-separations were attained was still mildly surprising and might indicate an additional factor is at play.

Remarkable resolution enhancements have been achieved by the 'Dutch method' of the addition of one or more resolving ions from within the same molecular family.[26] A suggested mechanism of this non-intuitive result is that the 'foreign' ions may serve to suppress nucleation of diastereomeric salts.[27] In this respect it is of interest that chelation of asymmetric ligands, such as mandelate, creates a stereochemical centre at boron. Density functional theory (DFT) calculations imply there is little energetic difference in the resulting B_R- and B_S-diastereomers, though they have quite different shape (Fig 8). In the case of $[B(R\text{-}Man)_2]^-$ the 'twisted' B_S anion is favoured by just ca. 0.5 kcal mol^{-1} in MeOH over the 'V-shaped' B_R anion, although it is exclusively preferred in the solid state for all salts studied to-date. However the presence of the B_R anions in solution may play a 'Dutch resolution' role. The ions in Fig. 8 are still identical in shape for half the molecule, so the B_R-ions may disrupt nucleation for the two possible B_S diastereomeric salts. If this occurs to a different extent in each case, the resolving efficiency of $[BMan_2]^-$ should be improved.

In summary we have presented evidence that bis(mandelato)borate anions show promise as widely applicable resolving agents. The systems presented here include 1:1, 1:2 and 1:3 salts with different cation charge, size, shape and functionality. The $[B(Man)_2]^-$ anions can be readily prepared and isolated for use in metathesis crystallizations as simple salts, or can be generated in situ in facile one pot resolutions without need for prior isolation. They are equally available in both hands and significant solubility differences for their diastereomeric salts can lead to facile and quantitative enantio-separation after a single crystallization step. Apart from smaller lab scale separations these systems would also appear to have many ideal characteristics for industrial scale-up. The authors are grateful to Research Grants Council Hong Kong for support of this work through grant 605511.

Notes and references

‡ Experimental details of synthesis and characterization data, powder X-ray diffractograms, chiral HPLC chromatograms, circular dichroism (CD) spectra, DFT calculations and single-crystal X-ray structure determination summaries available in Electronic Supplementary Information.

Crystal data: For **1-R.EtOH** $C_{16}H_{12}BNaO_6.C_2H_5OH$, M = 380.12, monoclinic, a = 9.2739(2) Å, b = 13.4321(3) Å, c = 14.8221(3) Å, α = 87.117(2)°, β = 88.987(2)°, γ = 81.732(2)°, V = 1824.75(7) Å^3, T = 173(2)K, space group P1, Z = 4, μ(CuKα) = 1.083 mm^{-1}, 29,333 reflections measured, with 12,497 independent (R_{int} = 0.024). The final R_1 was 0.0262 ($I > 2\sigma(I)$) and $wR(F^2)$ 0.0680 (all data). The GoF on F^2 was 1.006. CCDC number 1054443. For **2-R**, $C_{37}H_{38}BNO_{10}$, M = 667.49, monoclinic, a = 8.8770(3) Å, b = 13.3291(4) Å, c = 14.6644(4) Å, β = 98.596(3)°, V = 1715.64(9) Å^3, T = 173(2)K, space group $P2_1$, Z = 2, μ(CuKα) = 0.770 mm^{-1}, 14049 reflections measured, with 6000 independent (R_{int} =0.037). The final R_1 was 0.0330 ($I > 2\sigma(I)$) and $wR(F^2)$ 0.0768 (all data). The GoF on F^2 was 1.008. CCDC number 897202. For **3-R**, $C_{36}H_{40}B_2N_2O_{13}$, M = 730.32, monoclinic, a = 12.7917(4) Å, b = 8.7742(2) Å, c = 16.8769(5) Å, β= 103.527(3)°, V = 1841.67(9) Å^3, T = 173(2)K, space group $P2_1$, Z = 2, μ(CuKα) = 0.830 mm^{-1}, 10890 reflections measured, with 6465 independent (R_{int} =0.026). The final R_1 was 0.0425 ($I > 2\sigma(I)$) and $wR(F^2)$ 0.1119 (all data). The GoF on F^2 was 1.003. CCDC number 897203. For **4-R**, $C_{86}H_{68}B_3CoN_6O_{20}$, M = 1596.87, orthorhombic, a = 22.7598(4) Å, b = 74.1769(10) Å, c = 13.0562(3) Å, V = 22,042.1(7) Å^3, T= 143(2)K, space group $P2_12_12$, Z = 12, 60,133 reflections measured, with 38,050 independent (R_{int} = 0.044). The final R_1 was 0.0717 ($I > 2\sigma(I)$) and $wR(F^2)$ 0.1565 (all data). The GoF on F^2 was 1.003. CCDC number 897204.

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