Design, Synthesis, and Characterization of a New Class of Amino Acid-Based Chiral Borate Counteranions

David B. Llewellyn and Bruce A. Arndtsen*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 2K6, Canada

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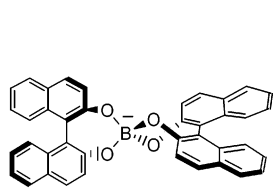
Summary: A new class of α-amino acid-tethered borate counteranion has been prepared from α-amino acid, tartaric acid, and $HBBr_2$ building blocks. This anion can be incorporated into transition metal complexes via ion exchange, providing a straightforward nonbonding method to associate metal complexes within a peptide environment.

The association of transition metal complexes with peptides, or peptide-like environments, is important to a range of biologically relevant issues, including the creation of models for bioinorganic structures,[1] therapeutic development,[2] and the design of synthetic metalloenzymes.[3] In addition, there has been significant recent interest in designing selective metal catalysts by their attachment to chiral peptide or α-amino acid residues.[4] In general, the approach employed to create metal-peptide adducts is to coordinate a peptide fragment to the metal center. However, this typically requires the initial preparation of a peptide-containing ligand and subsequent synthesis of the metal-peptide complex. In addition, the coordination of the ligand directly to a metal center often alters the structural and reactivity properties of both the metal and the peptide, which can complicate the rational design of specific features into the complex.[5]

We have been interested in the use of weak, formally nonbonding interactions as a method to associate reactive transition metal complexes within various environments. In particular, we have recently demonstrated that ion-pairing of a chiral counteranion to a cationic metal catalyst is sufficient to induce asymmetry into metal-catalyzed reactions.[6,7] X-ray structural analysis of this complex indicates that the counteranion creates a chiral pocket wherein the metal complex resides. These results suggest that cation/anion interactions might also be used as an alternative to rigid coordination to associate metal complexes to bioenvironments such as peptides. We report below the synthesis of a new class of amino acid-bound borate counteranions and their direct association to a Cu(I) complex via ion exchange. The degree of contact between the counteranion and copper center has been probed by examining the behavior of this complex in the asymmetric copper-catalyzed cyclopropanation of styrene. These results show that ion-pairing can provide a simple, yet effective, method to place transition metals within an α-amino acid environment.



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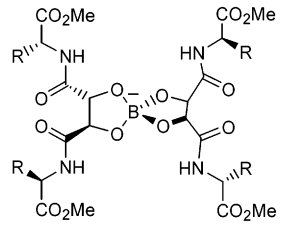

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Our previous studies have demonstrated that bis(binaphthol)borate anion **1** provides a noncoordinating chiral environment within which $Cu(NCMe)_4^+$ can associate through ion-pairing. However, to incorporate amino acid residues about the counteranion, a more easily modified scaffold than binaphthol was desired. The system employed herein is derived from the chelation of two tartaric acid derivatives onto boron (**2**).

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Scheme 1

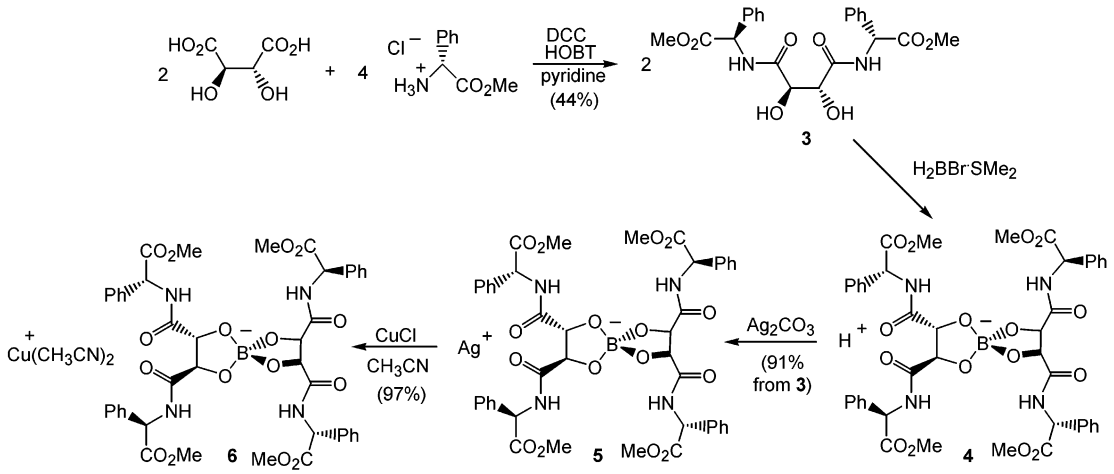
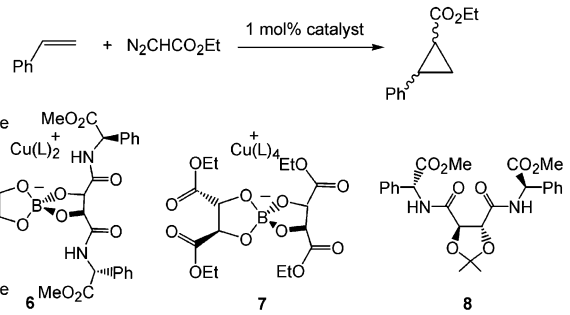


Table 1. Copper-Catalyzed Cyclopropanation of Styrene



entry	catalyst	solvent	temp (°C)	trans/cis[a]	% ee (cis)[a]	% ee (trans)[a]	yield (%)
1	**6**	CH_2Cl_2	25	1.7	15 (1*R*,2*S*)	8 (1*R*,2*R*)	57
2	**7**	CH_2Cl_2	25	1.9	<2	<2	67
3	**8**/CuOTf	CH_2Cl_2	25	1.5	<2	<2	82
4	**6**	CH_2Cl_2	0	1.3	18 (1*R*,2*S*)	17 (1*R*,2*R*)	35
5	**6**	C_6H_6	0	1.3	26 (1*R*,2*S*)	17 (1*R*,2*R*)	21

[a] Enantiomeric excess and trans/cis ratio determined using literature procedures. Absolute configuration determined by comparison to a literature procedure.[12b] Major enantiomer in brackets (L = CH_3CN).

These anions can be easily derivatized to incorporate α-amino acid residues (vide infra), and complexation of enantiopure diols to boron creates a single C_2-symmetric enantiomer and therefore does not require subsequent resolution. In addition, the anion has four flexible α-amino acid arms that can serve to encapsulate a metal cation.

As shown in Scheme 1, the reaction of R-phenylglycine methyl ester hydrochloride with (*R*,*R*)-tartaric acid under standard coupling conditions leads to the formation of the α-amino acid-tethered diol **3**.[8] Diols such as **3** are known to undergo condensation with various boron reagents to form chelated borates.[9] Similarly, the addition of **3** (2 equiv) to $H_2BBr{\cdot}SMe_2$ in dichloromethane results in the liberation of H_2 and HBr and the in situ generation of the chiral C_2-symmetric borate acid **4**. The latter is not isolated, but instead directly deprotonated with Ag_2CO_3 in acetronitrile, leading to the formation of the silver salt of the tetra-amino acid-tethered borate anion (**5**) in 91% yield from **3**. The ^{1}H NMR ($CDCl_3$) of **5** reveals only a single set of tartrate and amino acid signals, suggesting that racemization has not occurred during synthesis. All other NMR, IR, MS, and elemental analysis data are consistent with the structure shown. Overall, this provides a straightforward three-step method to construct a chiral α-amino acid-based counteranion from inexpensive and flexible starting materials.

With the peptide-based borate counteranion in hand, preliminary experiments have been performed to associate this anion with cationic transition metal complexes. Silver salt **5** can serve as a useful precursor for the incorporation of anion **2** into transition metal salts via ion exchange. This is illustrated in the reaction of **5** with CuCl in acetonitrile, which results in the immediate precipitation of AgCl. Filtration and evaporation of the solvent provides the copper salt **6** as a white solid in 97% yield.[8] Notably, the ^{1}H NMR of **6** in both polar d_3-acetonitrile and nonpolar d_6-benzene shows a symmetrical set of anion α-amino ester and tartrate resonances. Furthermore, the IR spectrum of **6** in both the solid state (KBr) and solution (CH_2Cl_2) reveals only a single set of amide (ν_{CO} = 1646 cm^{-1}) and ester (ν_{CO} = 1740 cm^{-1}) signals, consistent with a symmetrical anion in **6**. These data suggest that the interaction between Cu^+ and the borate anion is predominantly ionic in

(8) For full characterization of **3**, **5**−**8**, see the Supporting Information.

(9) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545.

nature and that any formal coordination is a weak, rapid equilibrium process.[10,11] Attempts to grow crystals of **6** suitable for X-ray analysis were unsuccessful.

Complex **6** represents, to our knowledge, the first well-defined example of a transition metal complex ion-paired to a peptide-based borate counteranion. However, since the copper center is not directly coordinated to the borate anion, it is not clear what, if any, contact exists between the metal and the peptide environment in solution. One probe for the degree of cation/anion interaction involves examination of the behavior of copper salt **6** in asymmetric catalysis, where the formation of enantiomerically enriched products would demonstrate communication of the metal center with the α-amino acid-tethered anion. Cationic copper(I) complexes are known to be effective catalysts for the asymmetric cyclopropanation of olefins.[12] As shown in Table 1, **6** is also an effective cyclopropanation catalyst resulting in the formation of cyclopropane in 57% yield (entry 1). Thus, the incorporation of the α-amino acid-based counteranion does not appear to significantly perturb the reactivity of the copper complex. More importantly, however, analysis of the reaction products by chiral GC shows that the cyclopropanes generated are nonracemic, with the cis- and trans-cyclopropanes formed in 15% and 8% ee, respectively. The latter clearly demonstrates that the copper cation is held within the chiral environment created by the counteranion.

The borate counteranion contains two different sources of chirality: the tartrate backbone and the α-amino acid residues. To determine if the α-amino acid residues are a source of chiral induction in this reaction, the non-peptide-containing copper salt **7** was prepared in a fashion similar to **6**.[8] As shown in Table 1 (entry 2), **7** is also an effective catalyst for the cyclopropanation reaction; however, it yields racemic cyclopropane products. Further control experiments demonstrate that the ionic interaction between the counteranion and the metal center is also crucial for chiral induction. The cyclopropanation of styrene with 1 mol % CuOTf in the presence of 1 mol % **8**, which contains the α-amino acid/tartrate backbone but is not associated to the copper center via ion-pairing, does not induce enantioselectivity into the reaction (entry 3). Together, these results strongly suggest that ion-pairing with the borate anion is necessary to hold the copper catalyst within the α-amino acid environment, from which the desired communication between the chiral α-amino esters and copper center induces asymmetry into the reaction products.

As anticipated from this type of interaction, enantioinduction with **6** can be influenced by factors that affect ion-pairing in solution. For example, chiral induction is increased upon lowering of the reaction temperature to 0 °C (cis ee = 18%, entry 4). The use of benzene rather than dichloromethane as solvent leads to an even greater enhancement of enantioselectivity (cis ee = 26%, entry 5). This is likely the result of tighter contact between the copper cation and the counteranion in the nonpolar benzene solution, leading to a greater degree of copper/peptide interaction.[13] The latter result also represents the highest reported enantioselective transition metal-catalyzed reaction using a chiral counteranion as the source of asymmetry.[6]

In summary, we have developed an efficient synthesis for a new and structurally interesting class of α-amino acid-based chiral counteranions. These anions can be readily incorporated into transition metal complexes via ion exchange and provide a new and synthetically straightforward method to place a metal complex within a peptide environment. The observation that **6** can catalyze the cyclopropanation of styrene with up to 26% ee demonstrates that the ion-pairing interaction is sufficient to allow communication between the metal center and peptide unit. Experiments directed toward tuning these counteranions to achieve higher levels of enantioselectivity are currently in progress.

Acknowledgment. We thank NSERC (Canada) and FQRNT (Quebec) for their financial support of this research. D.B.L. thanks NSERC for a graduate fellowship.

Supporting Information Available: Synthesis and characterization of **3** and **5**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Most weakly coordinating anions have been found to show some degree of coordinative interaction with transition metal cations: (a) Strauss, S. H. *Chem. Rev.* **1993**, *93*, 927−942. (b) Macchioni, A. *J. Inorg. Chem.* **2003**, 195, and references within.

(11) The copper salt **6** is isolated with two acetonitrile molecules rather than the expected four for a typical cationic copper(I) complex, suggesting there may be some degree of anion coordination in the solid state.

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