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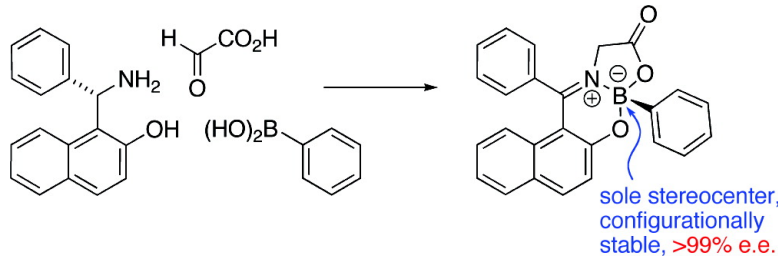

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Enantioselective Preparation of a Stable Boronate Complex Stereogenic Only at Boron

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Chiral organoboron reagents are among the most versatile reagents used in asymmetric synthesis,[1] catalyzing a diverse range of asymmetric transformations. Most chiral boron reagents (e.g., isopinocampheyl boranes,[2,3] allylboranes,[3−5] CBS oxazaborolidines,[6] chiral boronates,[7] and boron enolates[8]) contain chiral organic groups attached to B. However, studies of chiral reagents containing stereogenic B atoms are much less common, mostly due to the labile nature of tetracoordinate B, which is configurationally stable only under certain conditions.[9−12]

The generation of configurationally stable organoboron complexes has been achieved by Vedejs and co-workers (**I** and **II**),[9,10] Contreras, Farfán and co-workers (**III** and **IV**),[13] Braun and co-workers (**V**),[12] and others (Figure 1).[5,11,14] In all of these examples containing stereogenic B atoms, however, the boronate complexes either contain fixed carbon stereocenters (types **I**−**III**) or are racemic (types **IV** and **V**). Vedejs has reported the asymmetric synthesis of disubstituted amino acids from fluoroboronate complex **I** via an intermediate enolate that contains a stereogenic B as the sole stereocenter, and which ultimately directs the stereochemical outcome of the reaction.[9] To our knowledge this remains the only example of asymmetric synthesis of a chiral, nonracemic organoboron species in which the chirality is imparted exclusively by a B stereocenter. However, the enolate species is a reactive intermediate and is not isolated.

We report the first enantioselective preparation of a stable boronate complex stereogenic *only* at B, employing a "chirality transfer" process. Our approach employs Betti base **1** as a chiral *o*-hydroxybenzylamine derivative.[15] Mixing Betti base, glyoxylic acid, and phenylboronic acid in DMF at 50 °C for 24 h gives boronate complex **6** directly in 97% yield. Importantly, complex **6** is stereogenic only at B. Formation of **6** must involve three processes: condensation of amine and aldehyde components to give the corresponding imine, complexation of phenylboronic acid, and isomerization of the aldimine to the corresponding ketimine with concomitant loss of the carbon stereocenter.

Several pathways to the boronate complex **6** are possible. Complexation of aldimine **3** with phenylboronic acid would generate boronate complex **4**, with subsequent tautomerization of the aldimine to the ketimine generating final complex **6** (path A, Scheme 1). Alternatively, tautomerization of the aldimine to the ketimine **5** could precede complexation with the boronic acid (path B, Scheme 1). To achieve enantioselective formation of boronate complex **6**, the reaction must proceed by path A, with diastereoselective formation of glyoximine−boronate complex **4** controlled by the configuration at the carbon stereocenter. The alternative reaction sequence (path B), in which tautomerization of the aldimine **3** to the achiral ketimine **5** precedes complexation with boronic acid, would result in formation of complex **6** as a racemate.[16]

Chiral-HPLC analysis of complex **6** prepared from enantiopure Betti base (*S*)-**1** showed that only one enantiomer of the product

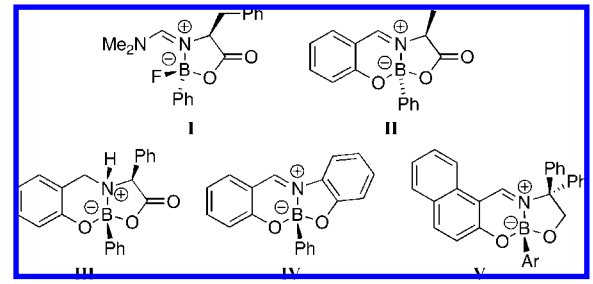
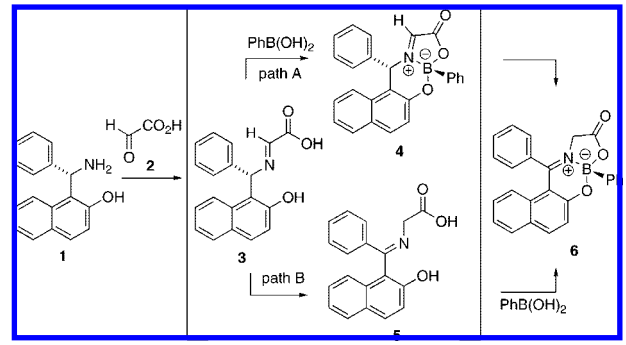


Figure 1. Chiral boronate complexes containing stereogenic boron centers.

Scheme 1. Possible Pathways to Boron Complex **6**



was present, indicating that complex **6** was formed in >99% ee (see Supporting Information, SI). Further analysis of the complexes derived from (*R*,*S*)-**1** and (*S*)-**1** was performed by NMR spectroscopy in the presence of a chiral-shift reagent. The NMR spectrum of (*R*,*S*)-**6** in the presence of europium tris[3-heptafluoropropylhydroxymethylene-(+)-camphorate] exhibited splitting of each of the diastereotopic methylene proton signals, with the upfield signal (δ 4.7−4.8 ppm) cleanly resolved into two distinct doublets (see SI). Analysis of the complex **6** derived from (*S*)-**1** showed only one set of resonances, providing further evidence for the highly enantioselective formation of complex **6**.

The enantioselective formation of **6** from (*S*)-**1** must therefore proceed via path A, with complexation of phenylboronic acid to aldimine ligand **3** occurring with high stereoselectivity to generate a single diastereomer of **4**. Complexation of the imine N to B would significantly increase the acidity of the benzylic proton, promoting the tautomerization event after B complexation. The driving force for the tautomerization step would presumably be the extended conjugation through the naphthol portion and removal of the destabilizing effect of adjacent δ^+-carbons in the glyoximine **4**. Isomerization abolishes the C stereocenter, generating a compound stereogenic exclusively at the B atom. Ultimately, the configuration

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at the C stereocenter in Betti base **1** determines the configuration of the B stereocenter in **6**, through a novel chirality transfer process.

To assess the configurational stability of the boronate complex, a solution of **6** in toluene was heated at reflux for 24 h. HPLC and NMR analysis indicated the enantiopurity of **6** was preserved (<0.5% racemization). The remarkable configurational stability of the B stereocenter presumably results from several factors, including the tridentate nature of the boron ligand, the acyl coordinating group, and the conformational rigidity of the naphthylphenylimine moiety.[10−12] Racemization of **6** would require dissociation of the B−N bond,[11] rotation about several bonds within the resultant dioxazaboronane ring (including rotation about C2−C23 to project the phenyl group to the opposite side of the naphthyl group), and recoordination of the N to the B from the opposite (*re*) face.

While the chiral-HPLC and chiral shift NMR experiments reveal that **6** is formed with high enantioselectivity, they cannot establish the absolute configuration of **6**. We surmised that the reaction proceeds via **4** with the two phenyl groups derived from Betti base and phenylboronic acid situated *trans* to each other, but further evidence was required to prove this configuration.

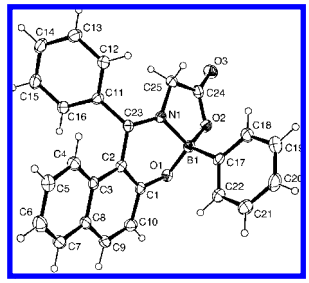


Figure 2. ORTEP diagram of (*R*,*S*)-**6** (ellipsoids at 20% probability level).

The racemic boron complex (*R*,*S*)-**6** was suitable for X-ray crystallographic analysis (Figure 2). However, samples of the enantiopure B complex were not suitable for X-ray crystallography. To both facilitate crystallization and provide a heavy atom, the *p*-bromo derivative **7** was prepared in the same manner as enantiopure **6**, using *p*-bromophenylboronic acid in place of phenylboronic acid. The brominated complex **7** was suitable for X-ray crystallographic analysis and was virtually identical to complex **6** (Figure 3). The Flack parameter of **7** refined to 0.030(18), confirming the (*S*)-configuration at the B stereocenter, and by inference, the configuration of (*S*)-**6**.

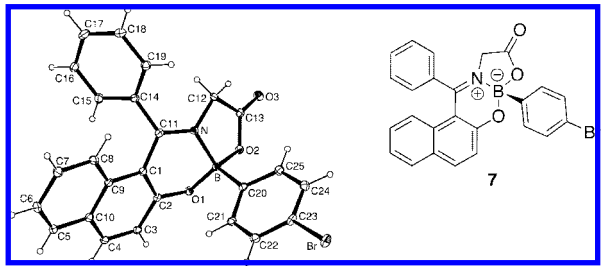
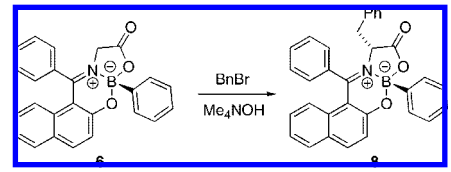


Figure 3. ORTEP diagram of (*S*)-**7** (ellipsoids at 20% probability level).

Utility of the chiral boronate complexes was demonstrated through stereoselective alkylation to generate phenylalanine derivative **8**. Treatment of (*S*)-**6** with benzyl bromide in the presence of tetramethylammonium hydroxide generated the alkylated product **8** in 60% yield (brsm) and 10.5:1 dr (Scheme 2). This route is analogous to Vedejs' alkylation of complex **I**[9] but, with complex **6** being a glycine imine derivative and possessing no C stereocenter, is not limited to the preparation of α,α-disubstituted amino acids. The alkylation may be limited, however, in the same manner as Vedejs reported for enolates of similar systems:[10] bulkier and more functionalized benzylic bromides gave complex mixtures of products.

Scheme 2



In conclusion, we have developed a stereoselective asymmetric synthesis of a compound stereogenic exclusively at boron. Our results demonstrate that formation of complexes **6** and **7** occurs in a highly enantioselective manner, through a novel chirality transfer process from the original carbon stereocenter, which is subsequently abolished. To our knowledge, this is the first enantioselective synthesis of a configurationally stable, nonracemic boronate complex stereogenic only at boron.

Supporting Information Available: Experimental details, NMR spectra of (*S*)-**6**, (*R*,*S*)-**6**, **7**, and **8**, chiral HPLC traces and chiral shift-reagent NMR spectra of (*S*)-**6** and (*R*,*S*)-**6**, and crystallographic data in CIF format for (*R*,*S*)-**6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) A further possibility suggested by a reviewer is that **3** exists as a single atropisomer (about the naphthyl−methine carbon bond) and that, upon isomerization to **4**, the atropisomer does not undergo rotation either to the opposite atropisomer or to bring the C=N bond into planarity with the naphthyl group, prior to coordination to phenylboronic acid.

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