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Oxathiaborolium: A Type of Chiral Lewis Acid Catalyst and Its Application in Catalytic and Highly Enantioselective Diels–Alder Reactions

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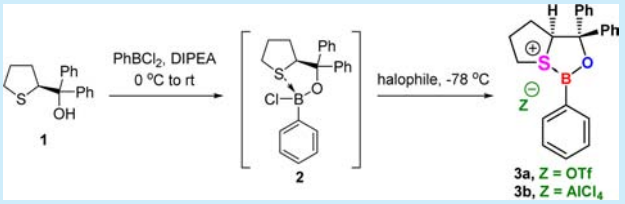
Supporting Information

ABSTRACT: The first reported sulfur-stabilized borenium cations were synthesized through halide abstraction of a haloborane intermediate by halophilic reagents. Different from the well-known cationic oxazaborolidines, a sulfide instead of an amine was used to not only simplify the preparation of the catalysts but also increase Lewis acidity of the boron atom. The in situ generated borenium salts showed exceptional Lewis acidity and successfully catalyzed asymmetric Diels–Alder reactions of cyclopentadiene and dienophiles in excellent yields and enantioselectivities. The NMR studies of these oxathiaborolium structures were reported as well.



The reactive intermediates **I**, known as borenium cations according to Noeth's classification system,[1] are three-coordinate species that comprise two σ-bound substituents (R) and one dative interaction with a ligand (L) capable of occupying a third coordination site through π-backbonding (Figure 1).[2] The positive charge can reside on the ligand itself

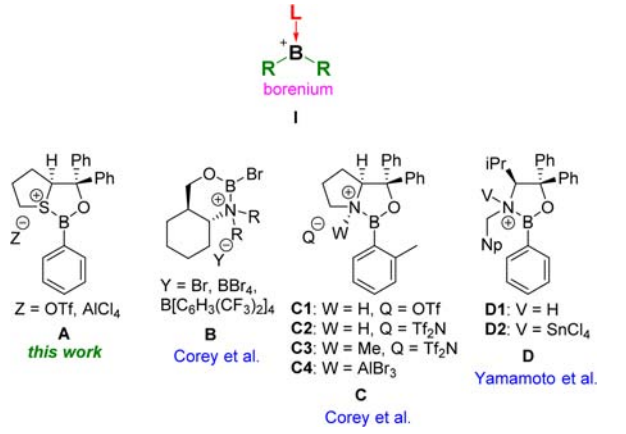


Figure 1. Borenium chemistry from the perspective of organic chemistry.

or on a boron atom with a dative bond coordinated to a ligand. Despite early interest in the chemistry of borenium cations, especially in the field of enantioselective synthesis, their applications have been slow to unfold until recently. In 1996, Corey and co-workers[3] successfully introduced bicyclic oxazaborinane **B** (Figure 1) as a highly efficient catalyst for enantioselective Diels–Alder reactions,[4] which made chiral borenium Lewis acids powerful tools in the field of organic synthesis. The subsequent flourishing development of activated cationic oxazaborolidines **C** and **D** led by Corey and Yamamoto, respectively, further highlights the potential for such species to be used as catalysts for asymmetric organic transformations[5] and the synthesis of many biologically interesting complex molecules.[6] Aside from Diels–Alder reactions, cyanosilylation,[7] [3 + 2] cycloaddition,[5g] Michael aldol addition,[8] Morita–Baylis–Hillman reaction,[9] Mukaiyama aldol,[10] cyclopropanation,[11] and Roskamp reactions[12] have all been shown to be amenable to enantioselective catalysis of cationic oxazaborolidines. This pioneering work inspired us to explore the possibility of forming chiral borenium complex **A**. By using a disubstituted sulfide instead of a secondary amine, the dative bond of borenium cation can be formed directly, avoiding the use of a strong Brønsted acid such as triflic acid (TfOH)[13] and triflimide $(CF_3SO_2)_2NH$[14] as activator. The preparation of catalyst can then be simplified to an one-pot operation. Furthermore, S is a weaker donor than N, O, and P, which may increase Lewis acidity of boron atom toward stronger acid–base interaction, and, to the best of our knowledge, no intra- or intermolecularly sulfur-stabilized boreniums have been previously reported. Herein, we report the syntheses, characterization, and investigation of the reactivity of type-A sulfur-coordinated aryl oxaborenium cations. The abilities of these borenium cations to catalyze asymmetric Diels–Alder reactions are demonstrated.

Heterolysis of boron–halogen bonds is the most widely used and successful method for preparing borenium ions; other

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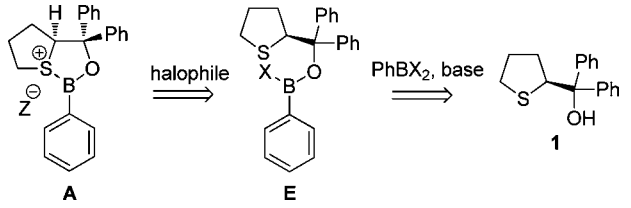
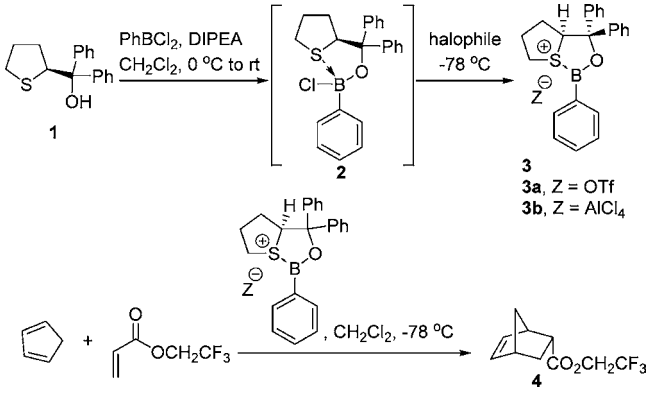
methods include electrophilic activation by protonation or Lewis acids, nucleophilic displacement, electrophilic attack at boron−nitrogen bonds, and metathesis.[1,2,5b] On the basis of these methods, we planned a straightforward approach to synthesize borenium cation **A** through halide abstraction of haloborane **E** using a halophile (Scheme 1); the sulfur−boron

Scheme 1. Retrosynthetic Route for the Synthesis of Type A Oxathiaborolium



bond was expected to form in the presence of an internal tetrahydrothiophene ligand. Intermediate **E** could be readily synthesized through the nucleophilic displacement of dihalo(phenyl)borane by (thiolan-2-yl)diphenylmethanol **1**, which is a very useful sulfur ligand for asymmetric organocatalysis and has been reported by our research group several times.[1S] Accordingly, ligand **1** was first treated with commercially available dichloro(phenyl)borane, and *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base) was used as the base to prepare intermediate **2**. The resulting solution was then mixed with a range of halophilic Lewis acids, as listed in Table 1, to break the

Table 1. Screening of Halophiles in an Oxathiaborolium-Catalyzed Asymmetric Diels−Alder Reaction



entry	halophile	cat. loading[a] (mol %)	time (h)	yield[b] (%) (endo/exo)[c]	ee[d] (%)
1	none	10	48	NR[e]	NA[f]
2	TMSOTf	10	16	NR[e]	NA[f]
3	BBr_3	10	48	31 (99:1)	0
4	BCl_3	10	48	25 (97:3)	2
5	$SbCl_5$	10	48	17 (96:4)	0
6	$AgBF_4$	10	48	26 (92:8)	0
7	AgOTf	10	16	7 (>99:1)	75
8	$AlCl_3$	10	16	13 (97:3)	91
9	AgOTf	20	44	78 (>99:1)	97
10	$AlCl_3$	20	24	96 (98:2)	>99
11[g]	$AlCl_3$	20	24	82 (99:1)	60

[a]Ratio of halophile/ligand/$PhBCl_2$ = 0.9:1:1. [b]Isolated yield. [c]*Exo*/*endo* ratios were determined by ^1H NMR. [d]ee was determined by GC with a Hydrodex *β*-6TBDM column. [e]No reaction occurred. [f]Not available. [g]Toluene was used as the solvent.

boron−halogen bond. The presence of borenium complex **3** was examined by experimentally determining the ability for asymmetric catalysis in the Diels−Alder reaction of cyclopentadiene and 2,2,2-trifluoroethyl acrylate.

Both TMSOTf and the control reaction (entries 1 and 2) showed no reaction and did not generate the Diels−Alder adduct. Although tribromoborane, trichloroborane, antimony pentachloride, and silver tetrafluoroborate afforded product **4** in 31%, 25%, 17%, and 26% yields after 2 days, respectively, no enantioselective induction was observed (entries 3−6). When AgOTf was used as a halophile (entry 7), 7% of product **4** was isolated with 75% ee. The use of $AlCl_3$ further improved the enantiomeric excess to 91% with a small increase in the reaction rate (entry 8). Because $AlCl_3$ is only slightly soluble in dichloromethane, the dissolution of $AlCl_3$ indicated the successful reaction of this halophile with phenyl boron chloride **2**. These results encouraged us to use a larger amount (20 mol %) of catalyst **3a** or **3b** (entries 9 and 10), which generated a satisfactory outcome. Product **4** was synthesized in 96% yield with excellent endo/exo selectivity (98:2) and almost perfect enantioselectivity (>99% ee) after 24 h of reaction in dichloromethane at −78 °C. The use of dichloromethane as a solvent was also critical for achieving high reactivity and enantioselectivity in comparison with reactions conducted in toluene (entry 11).

The successful use of oxathiaborolium **3b** in the catalytic asymmetric Diels−Alder reaction of cyclopentadiene and 2,2,2-trifluoroethyl acrylate prompted us to examine the scope of the dienophile substrates, especially the less reactive ester ones; the outcomes are highlighted in Table 2. Compound **3b** effectively catalyzed the reaction of cyclopentadiene with less active acrylates (entries 1−4) at a higher temperature (−20 °C) in a highly stereoselective manner, generating dominant *endo* Diels−Alder adducts **4a**−**d** in excellent yields (>92%) and excellent enantiomeric excess (96%−97%). Reactions with dialkyl fumarates (entries 5 and 6) and cyclohexenone (entry 7) also generated products **4e**−**g** in excellent yields (>90%) and excellent enantioselectivities (92%, 97%, and 95%, respectively). When cycloheptenone (entry 8) was used as dienophile, high yield (93%) and good enantioselectivities (87%) were obtained; nevertheless, the enantioselectivity decreased to 60% when cyclopentenone was employed as dienophile (entry 9). Overall, the reactivity and stereoselectivity of compound **3b** are not only universal but also comparable with type **C** and **D** catalysts in adducts **4**,[5c,e,14a] including **4a**,[5d,f] **4f**,[5c−e,14a] and **4g**[5c,e] (entries 1, 6, and 7). Entries 2−5 are not covered by the previously reported cationic oxazaborolidine catalysts. With less reactive dienophiles such as ethyl crotonate (entry 10), no reaction was observed at 0 °C.

To further characterize oxathiaborolium **3b**, a series of NMR studies were carried out at various temperatures, as summarized in Scheme 2. The reaction of ligand **1** with dichloro(phenyl)-borane and DIPEA in CD_2Cl_2 partially converted the ligand to chloro(methoxy)(phenyl)borane **2**, as determined by ^1H and ^{11}B NMR analyses. The lower field shift of H_a (δ = 4.97 ppm) on **2** suggests that the combination of formally positive sulfur and tetracoordinate boron (δ 11B = 17.6 ppm) was responsible for deshielding the proton on the adjacent carbon atom ($\Delta\delta$ = 0.25 ppm). When the solution was further treated with $AlCl_3$ at −78 °C, a new broad peak that appeared at δ 5.61 ppm was assigned to borenium structure **3b**; this chemical shift is greater than the reported H_a chemical shifts of cationic oxazaborolidines C and D (δ H_a = 4.85−5.44 ppm),[5b] which support the

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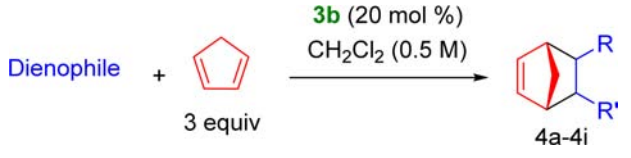
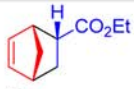
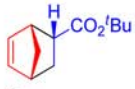
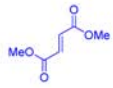
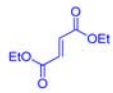
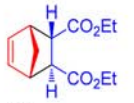
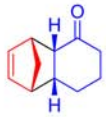
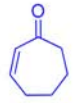
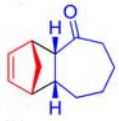
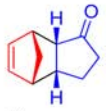
Table 2. Scope of Dienophile Substrates

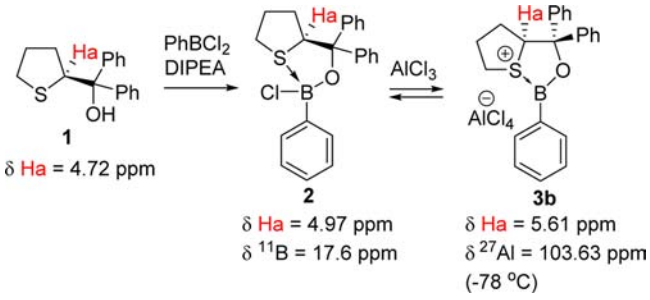


entry	dienophile	major product	t (°C)	time (h)	yield %[a] (*endo:exo*)[b]	ee[c] (%)
1		 4a	-20	16	95 (97:3)	97
2		 4b	-20	22	95 (95:5)	96
3		 4c	-20	60	97 (98:2)	96
4		 4d	-20	36	92 (97:3)	97
5		 4e	-50	18	90	92
6		 4f	-60	24	91	97
7[d]		 4g	-20	24	91 (93:7)	95
8[d]		 4h	-20	16	93 (96:4)	87
9[d]		 4i	-50	22	92 (93:7)	60
10		NR[e]	0	70	NR[e]	NA[f]

[a]Isolated yield. [b]*Exo/endo* ratios were determined by ^{1}H NMR. [c]ee was determined by GC with a Hydrodex β-6TBDM column. [d]1 M concentration, 5 equiv cyclopentadiene used. [e]No reaction occurred. [f]Not available.

higher Lewis acidity of oxathiaborolium **3b**. The ^{1}H NMR data also suggest that the catalytically active and super Lewis acidic borenium cation **3b** was present in equilibrium with the tetracoordinate boron complex **2** and that only approximately 20% of compound **1** was converted into **3b**; as observed, the intrinsic catalytic reactivity was sufficiently large to catalyze the Diels–Alder reaction. When the temperatures of the NMR experiments were increased to above −10 °C, the equilibrium gradually collapsed. Enhanced quadrupolar relaxation at low temperatures is a recurring issue with most of the cationic oxazaborolidine catalysts;[2,16] thus, no information could be obtained from the ^{11}B NMR experiment of **3b**. We then turned to ^{27}Al NMR, and the resulting spectrum showed a sharp signal for $AlCl_4^-$ (δ ^{27}Al = 103.63 ppm, $h(1/2)$ = 51 Hz, see the Supporting Information).

Scheme 2. NMR Studies of Oxathiaborolium 3b in CD_2Cl_2



Finally, we aimed to further demonstrate that the formation of a sulfur–boron dative bond was critical for the catalytic ability of this novel oxathiaborolium species. When sulfoxides **5a** and **5b** (see SI) were used to prepare catalysts, both of which contained sulfur atoms masked by oxygen atoms, the Diels–Alder reactions of cyclopentadiene and 2,2,2-trifluoroethyl acrylate proceeded slowly, and only a 15% racemic mixture of compound **4** was isolated after 24 h at −78 °C. These data, the absolute stereochemical outcome of the catalytic reaction, and the NMR results all support the hypothesis that the highly enantioselective formation of the Diels–Alder adducts resulted from the preferred pre-transition-state assembly **6** (see the SI), which was similar to the activity of chiral oxazaborolidium cations proposed by Corey et al.[3,5h,17] The complexation of the catalyst with acrylate involved the coordination of the carbonyl oxygen to boron and a synergistic electronic interaction between the α-C–H group and the oxygen on boron from the less hindered, convex face of the bicyclic borenium core, which led to face selectivity.

To summarize, we have reported the development of a novel oxathiaborolium catalyst that was readily synthesized in a single step using chiral tetrahydrothiophene ligand **1** and commercial materials (see SI); this catalyst exhibits excellent catalysis of asymmetric Diels–Alder reactions at low temperatures. Oxathiaborolium type **A** compounds functioning as potent chiral Lewis acids have strong potential to be used in other Lewis acid catalyzed reactions where borenium cations serve as activating agents.[18] Although further developments are required for better stability at higher temperature, compounds **3a** and **3b** are the first sulfur-stabilized borenium Lewis acids reported to date, which paves the way for expanding the applications of chiral sulfur ligands in organic syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03147.

Detailed experimental procedures, characterization data, and NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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