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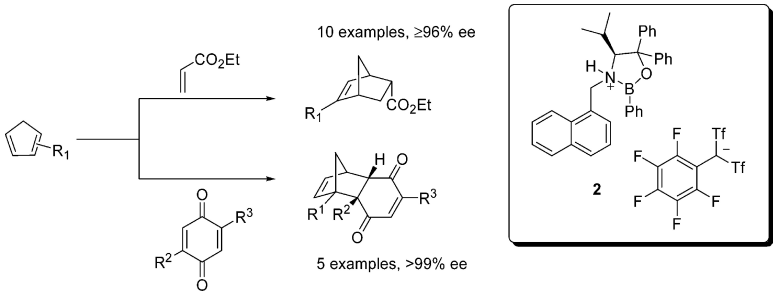

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Regioselective and Asymmetric Diels−Alder Reaction of 1- and 2-Substituted Cyclopentadienes Catalyzed by a Brønsted Acid Activated Chiral Oxazaborolidine

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Diels−Alder adducts derived from 1- and 2-substituted cyclopentadienes are potentially useful building blocks of complex natural products. At temperatures >0 °C, monosubstituted cyclopentadienes undergo a facile [1,5]-sigmatropic rearrangement yielding a ∼1:1 mixture of the 1- and 2-substituted isomers.[1] Under Lewis acid catalysis, only poor to moderate regioselection is achieved for adducts derived from these diene mixtures.[2a,b] Additionally, difficulties with separation of the regioisomeric adducts have severely limited the applicability of these dienes in organic synthesis. We herein report the first catalytic regio- and enantioselective Diels−Alder reaction of 1- and 2-substituted cyclopentadienes catalyzed by a Brønsted acid activated chiral oxazaborolidine.[3a,b]

Previous work in our lab has demonstrated the high catalytic activity of Lewis acid activated valine-derived oxazaborolidine **1**.[4a,b] Subsequent screening of several Brønsted acid activators revealed that $C_6F_5CHTf_2$ yielded an even more reactive catalyst system (Scheme 1).[5] Using cyclopentadiene and ethyl acrylate as test diene and dienophile, respectively, 5 mol % of the catalyst gave the corresponding adduct in 73% yield and >99% ee at −78 °C in 1 h (entry 4, Table 1). The trend in reactivity among Brønsted acid activators, $C_6F_5CHTf_2$ > Tf_2NH > TfOH, may indicate that the larger steric dimensions of the counteranion confer reactivity, presumably due to its lower capacity to coordinate to boron, rather than the pK_a of the Brønsted acid.[6]

In connection with other current work in our lab, we next applied catalyst **2** to the Diels−Alder reaction of 3.0 equiv of methylcyclopentadiene and ethyl acrylate.[7] Gratifyingly, the resultant *endo* adduct was obtained as a single regioisomer in 96% yield and 99% ee, derived solely from 2-methylcyclopentadiene (Table 2, entry 1). Subsequently, the Diels−Alder reaction of ethyl acrylate and various functionalized monosubstituted cyclopentadienes catalyzed by **2** was examined. As seen in Table 2, all adducts are obtained in good to excellent yields as a single regioisomer in ≥96% ee. Reactions of allyl, 2-bromoallyl, and 2-ethylphenyl cyclopentadienes proceed in high yield and asymmetric induction. Dienes with aryl substituents containing electron-withdrawing and electron-donating groups also furnish adducts in excellent yields and enantioselectivities. Furthermore, dienes bearing a 1,3-dioxolane functionality or a Lewis basic ester are easily tolerated. Notably, the bulky cyclohexyl group is well accommodated, giving the product in 70% yield and 99% ee.

To account for the observed regio-discrimination between 1- and 2-substituted cyclopentadienes by catalyst **2**, we propose hypothetical transition state **A** shown in Scheme 2. The mode of dienophile complexation to cationic oxazaborolidine **2** is analogous to that postulated by Corey et al. for their proline-derived catalyst system.[8a,b] HOMO coefficients of each diene determine the orientation of approach to the complexed dienophile. Thus, in **TS1**, the substituents of 1-substituted cyclopentadienes will experience significant steric interactions with the phenyl group appended to boron. However, 2-substituted cyclopentadienes should be oriented with their substituents pointed away from the catalyst−dienophile complex, resulting in a much lower energy transition state as indicated in **TS2**.

While the current method provides efficient access to Diels−Alder adducts derived from 2-substituted cyclopentadienes, adducts of 1-substituted cyclopentadienes are also desirable since they would contain a quaternary carbon center at the bridgehead position. To

Scheme 1

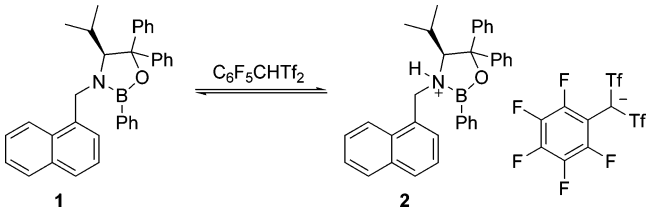
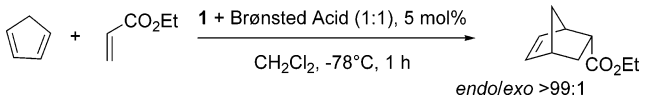


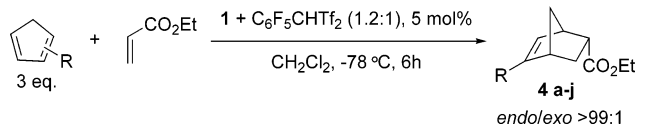
Table 1. Optimization of Brønsted Activator



entry	Brønsted acid	yield (%)[a]	ee (%)[b]
1	MsOH	NR	
2	TfOH	30	97
3	Tf_2NH	43	97
4	$C_6F_5CHTf_2$	73	>99

[a] Yields determined by ^{1}H NMR with $MeNO_2$ as internal standard. [b] Enantiomeric excess determined by GC.

Table 2. Diels−Alder Reaction of 2-Substituted Cyclopentadienes[a]



entry	diene	R	yield (%)[b]	dr	ee (%)
1	**3a**	Me−	96	99:1	99
2	**3b**	CH_2=$CHCH_2$−	98	99:1	97
3	**3c**	CH_2=$CBrCH_2$−	85	99:1	96
4[c,d]	**3d**	cyclohexyl	70	98:2	99
5	**3e**	$PhCH_2$−	97	99:1	97
6	**3f**	*p*-$MeOC_6H_4CH_2$−	96	99:1	99
7	**3g**	*p*-$BrC_6H_4CH_2$−	81	99:1	99
8	**3h**	$PhCH_2CH_2$−	97	99:1	99
9	**3i**	$(CH_2O)_2CHCH_2$−	98	99:1	98
10	**3j**	$MeO_2CCH_2CH_2$−	96	99:1	99

[a] See Supporting Information for details. [b] Isolated yield. [c] 5 equiv of diene used. [d] Reaction conducted at −78 °C for 6 h then −40 °C for 6 h.

10.1021/ja0735958 CCC: $37.00

Scheme 2. Hypothetical Transition State **A** (*endo* Approach)

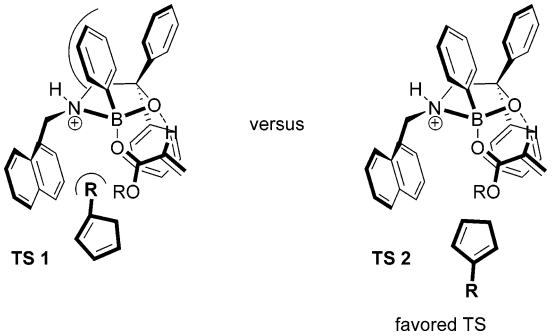
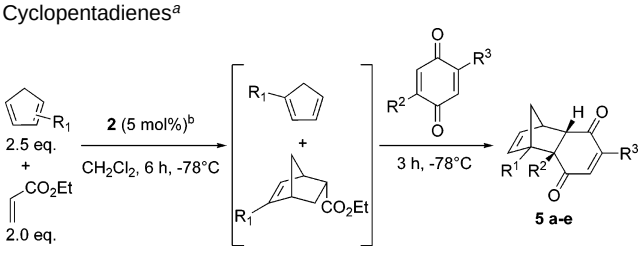


Table 3. Diels−Alder Reaction of 1-Substituted Cyclopentadienes[a]



entry	R^1	R^2	R^3	product	yield (%)[b]	dr	ee (%)
1	$CH_2{=}CHCH_2-$	Me	Me	**5a**	89(95)[c]	>99:1	>99
2	*p*-$BrC_6H_4CH_2-$	Me	Me	**5b**	43	>99:1	>99
3	$MeO_2CCH_2CH_2-$	Me	Me	**5c**	83	>99:1	>99
4[d,e]	$CH_2{=}CBrCH_2-$	Me	OMe	**5d**	70	>99:1	>99
5[d,f]	$CH_2{=}CBrCH_2-$	Br	Me	**5e**	96	>99:1	>99

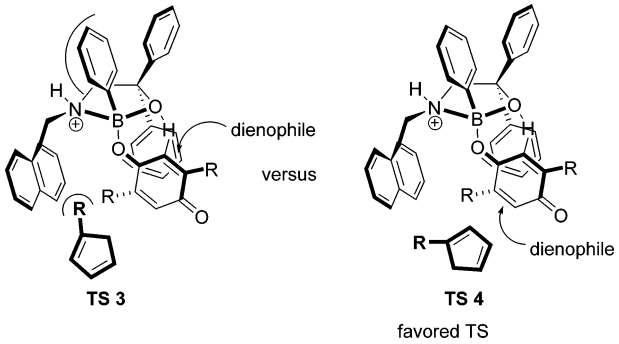
[a] See Supporting Information for details. [b] Based on benzoquinone. [c] Yield after 8 h. [d] 3.0 equiv of diene and 2.2 equiv of ethyl acrylate used. [e] Stir 8 h after benzoquinone addition. [f] Stir 12 h after benzoquinone addition.

this end, we envisioned a one-pot procedure whereby excess ethyl acrylate was employed to consume all 2-substituted cyclopentadiene. Subsequently, a more activated dienophile would be added to react exclusively with remaining 1-substituted cyclopentadiene. To test this hypothesis, excess ethyl acrylate was allowed to react with diene **3b** catalyzed by 5 mol % of **2**. After 6 h, the more reactive dienophile, 2,5-dimethylbenzoquinone, was added to the reaction mixture at −78 °C and allowed to stir for an additional 3 h. Remarkably, the reaction proceeded with complete positional regioselectivity, giving the *endo* adduct **5a** derived from 1-allylcyclopentadiene and 2,5-dimethylbenzoquinone as a single regioisomer in 89% yield and >99% ee.[9,10] The structure was assigned by the observed coupling of the bridgehead proton with the *exo* α proton in the ^{1}H NMR spectrum. This assignment was later supported by X-ray analysis of adduct **5b**.

Table 3 lists several examples of the application of this one-pot procedure with 2,5-dimethylbenzoquinone. Allyl-, benzyl-, and ester-containing cyclopentadienes could be utilized to obtain adducts as a single regioisomer in moderate to excellent yields with excellent enantioselectivities. Further, Table 3 shows the use of asymmetric 2,5-substituted benzoquinones with diene **3c**. In each case, the adduct resulting from reaction at the double bond containing the less basic substituent is obtained as a single regioisomer in high yield and enantioselectivity. This is a rare example of the highly diastereo- and enantioselective construction of compounds containing adjacent all-carbon quaternary stereocenters.[11]

To rationalize the observed positional discrimination between the two quinone double bonds coordinated *anti* and *syn*[9] to catalyst **2**, we propose hypothetical transition state **B** shown in Scheme 3. In accordance with Scheme 2, **TS3** should be disfavored due to a strong steric interaction with the substituents of 1-substituted cyclopentadienes and the phenyl ring of the catalyst. However, in **TS4**, the *anti*-coordinated benzoquinone double bond is placed far enough from the steric sphere of the catalyst to allow the approach of 1-substituted cyclopentadienes to be unimpeded. Lastly, the absolute configuration of these adducts is in full accord with our proposed transition structure.

Scheme 3. Hypothetical Transition State **B** (*endo* Approach)



In conclusion, we have developed the first enantio- and regioselective Diels−Alder reaction of both 1- and 2-substituted cyclopentadienes mediated by the highly reactive cationic oxazaborolidine **2**. Further, adducts containing adjacent all-carbon quaternary stereocenters can be obtained in high enantiomeric purity. We propose that the high levels of regiocontrol observed are an outcome of energy differences in modes of diene approach created by the unique steric environment of the catalyst−dienophile complex.

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Supporting Information Available: Experimental procedures, spectral data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) For a review of cyclopentadiene isomerization, see: Mironov, V. A.; Soboleve, E. V.; Elizarova, A. N. *Tetrahedron* **1963**, *19*, 1939.
(2) (a) For a previous example of a catalytic, asymmetric Diels−Alder reaction of a monosubstituted cyclopentadiene, see: Corey, E. J.; Guzman-Perez, A.; Loh, T. *J. Am. Chem. Soc.* **1994**, *116*, 3611. (b) For example, we found 20 mol % of $EtAlCl_2$ gives the adducts of ethyl acrylate and methyl cyclopentadiene in a 7:3 ratio, favoring the product derived from 2-methylcyclopentadiene.
(3) For other examples of Brønsted acid activation of a chiral oxazaborolidine, see: (a) Corey, E. J.; Shibata, T.; Lee, T. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6389.
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(9) For an interesting study on positional regioselectivity of asymmetrical benzoquinones in the Diels−Alder reaction, see: Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800.
(10) Without ethyl acrylate addition, catalyst **2** gives the adducts of diene **3b** and 2,5-dimethylbenzoquinone in an 8:2 mixture favoring the product derived from 1-allylcyclopentadiene. The minor component consists of a mixture of two regioisomers derived from 2-allylcyclopentadiene from reaction at either benzoquinone double bond.
(11) For a review on construction of contiguous stereogenic quaternary carbon centers, see: Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943.

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