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Enantioselective and Structure-Selective Diels−Alder Reactions of Unsymmetrical Quinones Catalyzed by a Chiral Oxazaborolidinium Cation. Predictive Selection Rules

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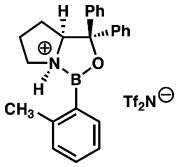
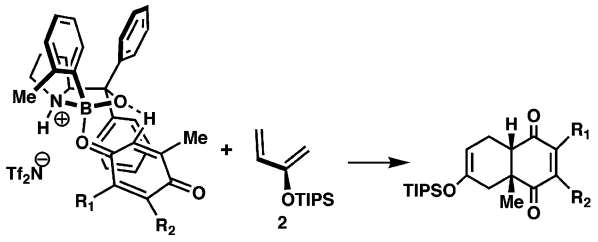
The chiral cationic oxazaborolidinium ion **1**[1,2] (and the corresponding triflate[3,4]) are useful and potent catalysts for promoting a wide variety of highly enantioselective Diels−Alder reactions.[5] One particularly important area of application is to the Diels−Alder reactions of unsymmetrical 1,4-benzoquinones and 1,3-dienes, which is especially challenging because of the multiple requirements of high enantioselectivity, orientational selectivity (i.e., only one of the two possible modes of coupling the ends of the diene and dienophile), and site-selectivity (i.e., reaction at only one of the two C=C subunits of the quinone). Achievement of all these selectivities with a broad range of dienes and 1,4-benzoquinones would be a major advance since the quinone subcategory of the Diels−Alder reaction is one of the most powerful versions of [4 + 2]-cycloaddition and one of the most useful for the synthesis of many complex natural products.[6] In a previous paper we have described a number of highly successful enantioselective reactions of 1,3-dienes with 1,4-benzoquinones in which one of the components is symmetrical.[1] However, only a few cases were studied in which both components were unsymmetrical.[1] Some of these afforded a single chiral product, but others gave a mixture of positional (or regio) isomers. We describe herein a wide-ranging study of many different unsymmetrical quinones with the test diene 2-triisopropylsilyloxy-1,3-butadiene that gave substantially one product with high enantioselectivity. The results reported herein provide powerful guidance for the use of catalytic enantioselective quinone Diels−Alder reactions in the synthesis of complex targets. Taken together, they allowed the development of predictive rules for the preferred course of reactions between unsymmetrical 1,3-dienes and quinones, which are summarized below. The selection rules also depend on the predictive mechanistic model that has been derived previously.[1,3,7]

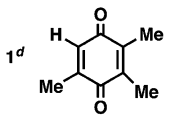
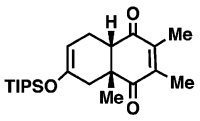
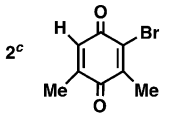
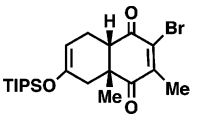
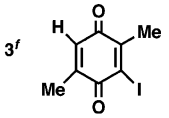
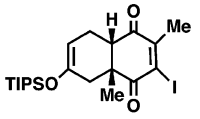
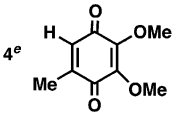
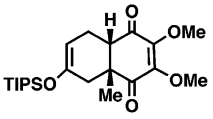
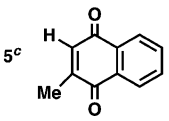
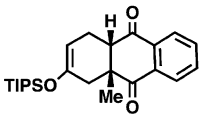


1

Table 1 summarizes the results of the Diels−Alder reactions catalyzed by **1** (0.2 equiv) between 2-triisopropylsilyloxy-1,3-butadiene (**2**) and five trisubstituted 1,4-benzoquinones. These reactions all proceed with very good yields and enantioselectivities. They all conform to the mechanistic path outlined at the top of Table 1 in which the catalyst coordinates to the least sterically shielded C=O lone pair, uniquely that which is syn to the benzoquinone C_α−H subunit, to produce the major enantiomer.[1,3,7] Chromatographic analysis of the crude reaction mixtures and the high yields of isolated pure product demonstrate that each of these reactions is highly site-selective and regioselective as well as highly enantioselective. The site selectivity indicates that diene attack on the less substituted double bond is favored. In addition, the reactive double bond is in each case syn to the catalyst-coordinated oxygen lone pair. The orientational (or regio) selectivity can be explained by attack of the nucleophilic end (C-1) of the 2-substituted diene at the carbon β to the coordinated carbonyl, i.e., the olefinic carbon expected to the most electrophilic in the quinone complex with catalyst **1**.

Table 1. Enantioselective Diels−Alder Reactions of Trisubstituted 1,4-Benzoquinones Catalyzed by **1** (0.2 Equiv)



Quinone	Product	Temp. (°C), Time (h)	% Yield;[a] *ee*[b]
1[d] 		−78, 12	98; 99
2[c] 		−78, 3	96; 97
3[f] 		−78, 16	99; >99
4[e] 		−50, 48	85; 95
5[c] 		−60, 36	96; 91

[a] Isolated yield. [b] Enantioselectivities were determined by HPLC analysis. [c] Absolute configuration proved by X-ray analysis. [d] Absolute configuration determined by synthesis from product in entry 3. [e] Absolute configuration assigned from optical rotatory data. [f] Absolute configuration, ref 1.

Table 2 summarizes the results of five reactions, catalyzed by **1** (0.2 equiv), between 2-triisopropylsilyloxy-1,3-butadiene and various 2,3- or 2,6-disubstituted 1,4-benzoquinones. In entries 1 and 2, the quinones are C_2 symmetric so that there is no issue of orientational selectivity. The major product results from coordination of catalyst to the least shielded oxygen lone pair (*a*) and addition of diene to the less substituted C=C. The absolute

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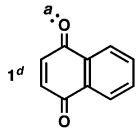
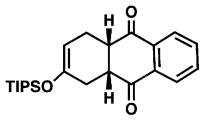
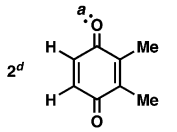
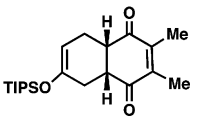
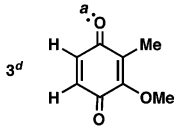
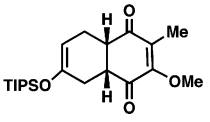
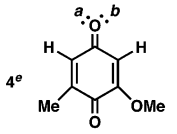
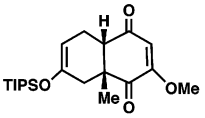
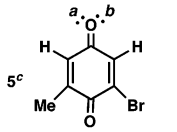
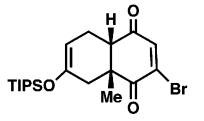
Table 2. Enantioselective Diels−Alder Reactions of 2,3- or 2,6-Disubstituted 1,4-Benzoquinones and 2-Triisopropylsilyloxy-1,3-butadiene Catalyzed by **1** (0.2 Equiv)

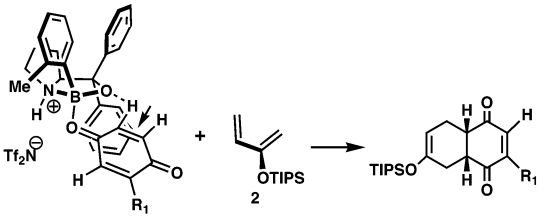
Quinone	Product	Temp. (°C), Time (h)	% Yield[a]; ee[b]
 1[d]		−78, 2	98; 97
 2[d]		−95, 2	98; >99
 3[d]		−78, 12	84; 90
 4[e]		−50, 96	98; 92
 5[c]		−78, 4	95; 91

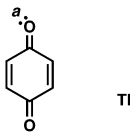
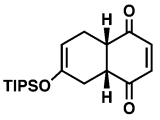
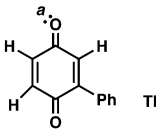
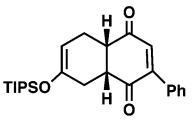
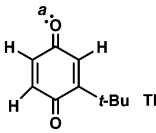
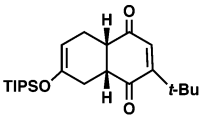
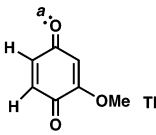
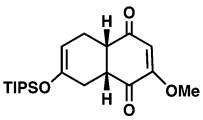
[a] Isolated yield. [b] Enantioselectivities were determined either by HPLC or ^{1}H NMR MTPA analysis. [c] Absolute configuration proved by X-ray analysis. [d] Absolute configuration assigned from optical rotatory data. [e] Absolute configuration from chemical correlation.

configurations of the products shown correspond to those expected from the mechanistic model. In the remaining cases of Table 2 (entries 3−5), although each of the reactants is unsymmetrical, good site-selectivity and regio- and enantioselectivity are observed. In each case the favored pathway is that predicted for catalyst coordination to the oxygen lone pair that is labeled *a*. Entry 3 of Table 2 is an especially interesting example, since that reaction was not totally regioselective, with the product shown being formed in 84% yield and the regioisomer in 15% yield. In this case the major pathway involves catalyst coordination to the more basic oxygen (lone pair *a*), whereas the minor, regioisomeric product results from coordination to the sterically less screened lone pair of the other oxygen. Examples 4 and 5 of Table 2 illustrate an interesting new selectivity in catalyst coordination that results in the favoring of the pathway for [4 + 2]-cycloaddition at the double bond that is syn to the coordinated lone pair *a*. Coordination to lone pair *b* would have led to the enantiomer of the observed product. Methoxy substituents on the quinone exert two important effects because of their strong electron donation into the π-system of the catalyst−quinone complex: (1) methoxy greatly favors catalyst complexation at the carbonyl β to the methoxy group (the more basic oxygen) and (2) methoxy lowers the electrophilicity of the olefinic carbon to which it is attached so much that that C═C of the quinone is unreactive.

Table 3 presents the results of experiments on the Diels−Alder reactions with 0.2 equiv of **1**, 2-triisopropylsilyloxy-1,3-butadiene, and 1,4-benzoquinone or three monosubstituted 1,4-benzoquinones. For the parent 1,4-benzoquinone (entry 1), the observed predominating enantiomer accords with the model shown in the heading of Table 3, with endo addition of the diene to that double bond which

Table 3. Enantioselective Diels−Alder Reactions of Unsubstituted or Monosubstituted 1,4-Benzoquinones and 2-Triisopropylsilyloxy-1,3-butadiene Catalyzed by **1** (0.2 Equiv)



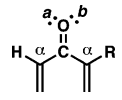
Quinone	Product	Temp. (°C) Time (h)	% Yield;[a] ee[b]
 1[c]		−78, 6	85; 88
 2[d]		−78, 24	87;[e] 94
 3[d]		−78, 12	92; 91
 4[c]		−78, 16	95; 91

[a] Isolated yield. [b] Enantioselectivities were determined either by HPLC or ^{1}H NMR MTPA analysis. [c] Absolute configuration determined by X-ray analysis. [d] Absolute configuration assigned from optical rotatory data. [e] In addition, 3% of the regioisomer was formed.

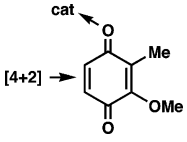
is syn to the coordination site. In remaining cases (Table 3, entries 2−4), the favored site of diene attack is the less substituted C═C subunit, catalyst coordination occurs to the lone pair of the oxygen β to the electron-supplying substituent, and the product is that expected from addition of diene syn to that coordination site.

The data summarized in this study allowed the derivation of the following set of selection rules for Diels−Alder reactions of unsymmetrical 1,3-butadienes with unsymmetrical 1,4-benzoquinones, which when used together are predictive of the structure and absolute configuration of the predominant product with **1** as a chiral catalyst.

(1) For a quinone carbonyl flanked by C_α−H and C_α−R, the major product will result from catalyst coordination preferentially at the oxygen lone pair on the C−H side (*a*) rather than the C−R side (*b*) because *a* is sterically more accessible than *b*.

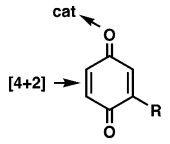


(2) Catalyst coordination at the more basic of the two 1,4-quinone oxygens will predominate, and this mode will lead to the preferred Diels−Alder adduct.



(3) If a double bond of the quinone in 1,3-diene addition bears two hydrogens, it will be more reactive than that bearing substituent(s), especially one or two π-electron donor groups.

(4) For monosubstituted 1,4-quinones (or *p*-benzoquinone itself), the major product pathway will involve coordination of catalyst at C═O syn to the HC═CH subunit that undergoes [4 + 2]-cycloaddition.

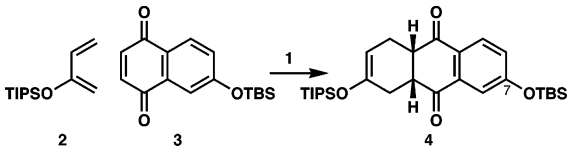


(5) C(1) of 2-triisopropylsilyloxy-1,3-butadiene (**2**), the more nucleophilic end of the diene, will attach to the carbon β to the carbonyl group that coordinates with the catalyst, i.e., the more electrophilic carbon.

(6) The preferred three-dimensional transition state corresponds to the *endo* arrangement of diene and catalyst-coordinated quinone.[1]

We have tested these rules by examining a number of their consequences experimentally. For instance, rule 1 predicts that catalyst **1** will not be effective for tetrasubstituted 1,4-benzoquinones. In fact, the reaction of tetramethyl-1,4-benzoquinone with 2-triisopropylsilyloxy-1,3-butadiene in the presence of 0.2 equiv of catalyst **1** is exceedingly slow at −78 °C. When the reaction was conducted at −40 °C for 16 h, the resulting 1:1 Diels−Alder adduct (35% yield) was totally racemic, indicating that the reaction may occur as a result of proton transfer from catalyst **1** to the quinone rather than by coordination at boron.

Rules 1, 2, and 5 allow the prediction that the reaction of 6-[*tert*-butyldimethylsilyloxy]-1,4-naphthoquinone (**3**) with **2** under catalysis by **1** will generate adduct **4** as the principal Diels−Alder product. In fact, the reaction was found to give **4** of >99% enantiomeric purity in a 92:8 predominance over the regioisomeric adduct (95% total yield after 16 h at −78 °C in CH_2Cl_2 with 0.2 equiv of **1** as catalyst), in full accord with expectations based on the above selection rules.[8] The underlying basis for rule 2 may derive from the possibility that stronger coordination of catalyst **1** to the more basic of the two quinone carbonyls *lowers the energy of the transition state more than that of the complex ground state*.



It is important to note in this context that the coordination of catalyst to the carbonyl persists not only in the transition state but even in the Diels−Alder adduct. Because the steric requirements of the Lewis acid catalyst will play a role in determining the magnitude of this transition-state coordination effect, it is not surprising that different Lewis acids show regioselectivities that diverge from those observed with catalyst **1**. For example, in the case of Table 1, entry 2, an 86:14 mixture of (±)-regioisomeric adducts is obtained at −78 °C with $EtAlCl_2$ as a catalyst, whereas only one adduct is formed with **1** as catalyst.[9]

We believe that the catalytic enantioselective Diels−Alder reactions of quinones described herein with catalyst **1** demonstrate a major advance in synthetic methodology that will prove to have broad utility.[10] The availability of a mechanistic model and a reliable set of selection rules that allow prediction of the structure and absolute configuration of the principal reaction product adds further to the usefulness of the catalyst **1** in the planning of syntheses. Details of the determination of enantioselectivity and absolute configuration of the various products along with several interesting synthetic transformations of the Diels−Alder adducts are presented in Supporting Information.

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Supporting Information Available: Information is provided on the analysis and characterization of reaction products to determine structure, enantioselectivity, and absolute configuration (PDF, CIF). X-ray diffraction data are provided for the products in Table 1, entries 2 and 5; for the product in Table 2, entry 5; and the products in Table 3, entries 1 and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Diels−Alder reaction of **2** with the methoxy analogue of quinone **3** and catalyst **1** was less regioselective and afforded the 7-methoxy analogue of **4** and the 6-methoxy regioisomer in a ratio of 76:24. The lower selectivity in this case relative to **4** is understandable in view of the stronger π-electron donation from OTBS vs methoxy in the quinone substrates.
(9) As is well known, thermal quinone Diels−Alder reactions with unsymmetrical components are relatively nonregioselective. For instance, for the case of Table 1, entry 2, the thermal reaction at 110 °C affords a 43:56 mixture of (±)-regioisomers with that shown in Table 1 being the minor component.
(10) The Mikami binaphthol-$TiCl_4$−molecular sieves system is a known catalyst for enantioselective Diels−Alder addition of 1,3-dienes to quinones; for a leading reference, see: White, J. D.; Choi, Y. *Helv. Chim. Acta*, **2002**, *85*, 4306−4327. In addition, pybox lanthanide catalysts have recently been applied to quinones having a methoxycarbonyl substituent; see: Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162−10163.

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