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[4 + 2] Cycloaddition Reactions Catalyzed by a Chiral Oxazaborolidinium Cation. Reaction Rates and Diastereo-, Regio-, and Enantioselectivity Depend on Whether Both Bonds Are Formed Simultaneously

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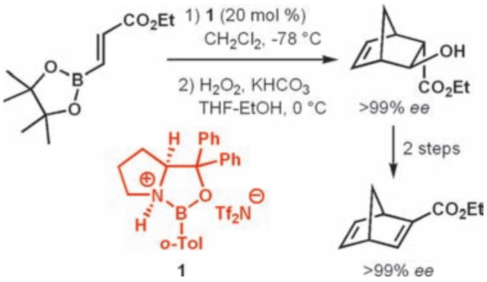
ABSTRACT



The reaction rates and products in enantioselective Diels−Alder reactions with a range of dienophiles correlate with the expected degree of concertedness of bond formation in the transition state.

Proton-activated chiral oxazaborolidine cations such as **1** (Figure 1) have been shown to be highly effective reagents in enantioselective synthesis, especially as catalysts for a wide range of Diels−Alder reactions.[1] A major advantage of these catalysts in addition to ready availability,[2] widespread applicability, and excellent absolute stereocontrol is the success of a mechanistic model that reliably predicts the absolute configuration of a Diels−Alder product. For example, in the case of the Diels−Alder reaction of trifluoroethyl acrylate and 1,3-cyclopentadiene, the model of the pre-transition state assembly **2** leads to the observed product (**3** in Figure 1). A further consequence of these mechanistic insights is the possibility to probe more deeply other aspects

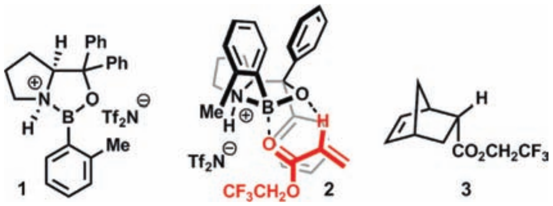


Figure 1. Oxazaborolidinium cation, predicted pre-transition state assembly, and the observed Diels−Alder product.

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[1] Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117.

[2] The very potent Lewis acid **1** can be generated in situ from the corresponding oxazaborolidine (available from Sigma-Aldrich Co.) simply by addition of triflimide.

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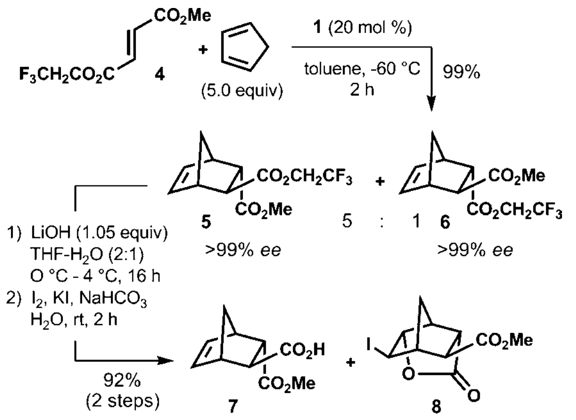
of these Diels−Alder reactions, including the behavior of various useful dienophiles.

We reported earlier[3] that a dichotomy exists between the rate of reaction and the binding of the dienophile to the catalyst. In the case of acrylate esters, the more strongly binding methyl acrylate is less reactive than the weaker coordinator trifluoroethyl acrylate. On the other hand, the regioselectivity of the Diels−Alder reactions with a series of 1,4-benzoquinones indicates that the faster pathway corresponds to that expected for coordination of the quinone to the catalyst at the more basic of the two oxygens.[3,4]

In this paper we explore binding versus reactivity further and present additional information regarding the relationship between catalyst affinity, dienophile structure, and preferred reaction pathway.

Although both methyl and trifluoroethyl acrylate undergo highly enantioselective Diels−Alder reaction with cyclopentadiene, the methyl ester reacts much more slowly than the latter and in a 1:1 mixture inhibits adduct formation from the more reactive trifluoroethyl ester. This was interpreted to result from a decidedly asynchronous [4 + 2] cycloaddition pathway and the strong dependence of rate on the amount of positive charge at the β-carbon of the acrylate−catalyst complex.[3] In the case of 1,4-benzoquinones, the cycloaddition reaction is more synchronous and the rate is less sensitive to positive charge β to the coordinated carbonyl group.

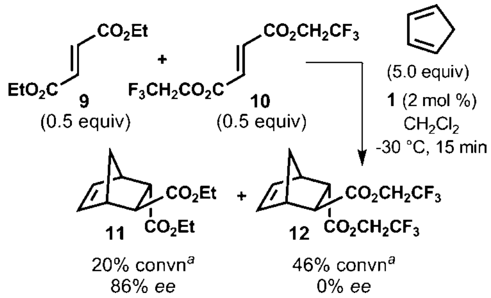
Scheme 1



In view of the interesting difference in behavior of acrylate ester and 1,4-benzoquinone dienophiles, we examined the reaction of 1,3-cyclopentadiene with methyl trifluoroethyl fumarate (**4**).[5] The reaction proceeded well at −60 °C with 20 mol % of catalyst **1** to give after 2 h in 99% yield a 5:1 mixture of adducts **5** (>99% *ee*) and **6** (>99% *ee*) as shown in Scheme 1.

The structures of **5** and **6** were revealed by selective hydrolysis of the more reactive $CO_2CH_2CF_3$ subunit (LiOH/THF/H_2O) and treatment with I_2 at pH 10, which afforded easily separable **7** and **8**, respectively. These results indicate that the pathway via the complex of CO_2Me with **1** is five times faster than that via the complex of $CO_2CH_2CF_3$ with **1**. This ratio represents at least a 100-fold reversal of the reactivity as compared to methyl acrylate and trifluoroethyl acrylate. Thus, it appears that the Diels−Alder reaction is considerably more synchronous with fumarate esters than with acrylate esters, the former behaving more like 1,4-benzoquinone substrates.

Scheme 2



[a] Conversions are based on the total amount of dienophiles employed.

To follow up on this result we have carried out an intermolecular competition between diethylfumarate (**9**) and bis(trifluoroethyl)fumarate (**10**) in Diels−Alder addition to cyclopentadiene using **1** as catalyst. The results of such an experiment are summarized in Scheme 2.

Using equimolar amounts of the ethyl ester **9** and trifluoroethyl ester **10** at −30 °C with catalyst **1** and an excess of cyclopentadiene for just 15 min to ensure only partial conversion, the catalytic pathway gave *only* the adduct **11** from the ethyl ester **9**. Although the adduct **12** from the trifluoroethyl ester was also formed, it arose from an *uncatalyzed* process, since it was found to be totally racemic (0% *ee*). The catalyzed reaction of **10** and cyclopentadiene produces adduct **12** with 99% *ee*.[6] Furthermore, a control experiment at −30 °C with trifluoroethyl ester **10** and cyclopentadiene but without catalyst **1** gave the same conversion to the racemic adduct **12**. The much faster catalytic pathway with ethyl ester **9** compared with that of trifluoroethyl ester **10** again contrasts sharply with the relative reactivity of the corresponding acrylate esters. It is also noteworthy that in the experiment summarized in Scheme 2, diethyl fumarate **9** actually inhibited the catalytic pathway of the trifluoroethyl ester **10** as a result of its higher affinity for catalyst **1**.

Another interesting fumarate derivative for this investigation was the mixed trifluoroethyl ester amide **13** (Scheme 3).

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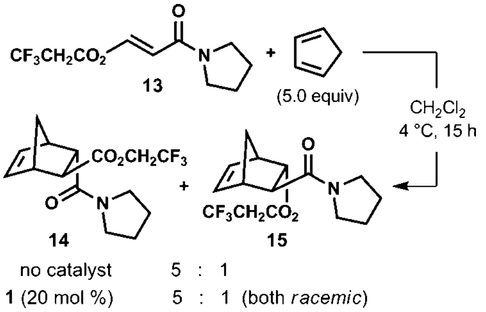
(3) Ryu, D. H.; Zhou, G.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1633–1636.

(4) Also see: Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800–4802.

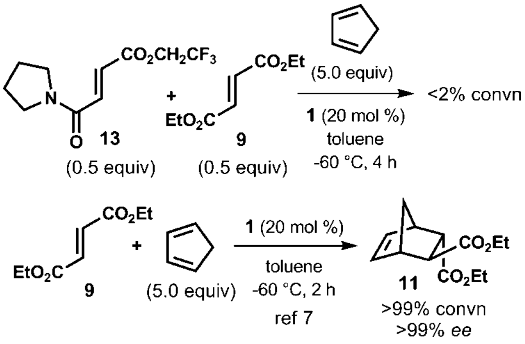
(5) For a report on chiral auxiliary-controlled *diastereoselective* Diels−Alder reactions of unsymmetrical maleates, see: Maruoka, K.; Akakura, M.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6153–6158.

(6) The reaction was carried out with 20 mol % **1** in CH_2Cl_2 at −78 °C and found to be complete within 1.5 h. For the determination of *ee* and absolute configuration see Supporting Information.

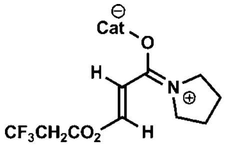
Scheme 3



Scheme 4



The catalyzed reaction of **13**, cyclopentadiene and 20 mol % of the oxazaborolidinium salt **1** proceeded not at all at temperatures of −78 °C. At 4 °C for 15 h only the noncatalyzed Diels−Alder reaction occurred to form the *racemic adducts* **14** and **15** in a ratio of 5:1, respectively, *with* or *without* catalyst **1** (20 mol %). The failure of the catalytic reaction to compete with the uncatalyzed reaction is probably due to the coordination of **1** solely to the more basic amide carbonyl and the overwhelming distribution of positive charge on the amide nitrogen (see **16**, below) rather than the carbon beta to the amide carbonyl.



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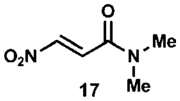

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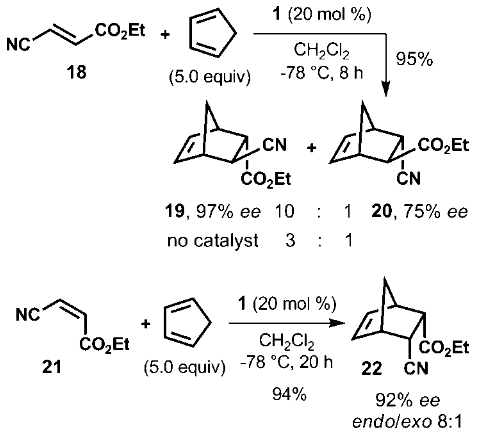
Such a nonproductive coordination of amide carbonyl to the catalyst was supported by the competition experiment between trifluoroethyl ester amide (**13**) and diethylfumarate (**9**) in Diels−Alder addition to cyclopentadiene using **1** as depicted in Scheme 4. Although **9** is known to undergo complete conversion to the cycloadduct **11** (with >99% *ee*) within 2 h in the presence of 20 mol % of **1** at −60 °C,[7] no product formation was observed under identical reaction conditions even after 4 h when equimolar amounts of **9** and **13** were employed as substrates. Similar reactivity trend was also found for β-nitroacrylamide **17**[8] even though the corresponding β-nitroacrylates are excellent dienophiles for Diels−Alder reaction (vide infra).

A study of the fumaric nitrile ester **18** was also instructive as shown by the results with **1** and cyclopentadiene that are outlined in Scheme 5. It is evident that the productive catalytic pathway is that in which **1** is coordinated to the ester carbonyl rather than the cyano group. Similar results were obtained using the mixed (*Z*)-nitrile-ester **21** in the maleic series to form **22**.

Scheme 5



Although the Diels−Alder reactions of **1** with (*E*)-cyano ethyl ester **18** and (*Z*)-cyano ethyl ester **21** were highly enantioselective, the corresponding reactions of the cyano trifluoroethyl esters were considerably less so[9] and also slower (probably allowing the noncatalytic pathway to compete). The data revealed in Scheme 5 indicate that coordination of catalyst to the ester carbonyl rather than the cyano group leads to the most productive pathway.

We next directed our attention to a study of the mixed ethyl ester vinyl boronate **23**.[10,11] The reaction of **23** with cyclopentadiene and catalyst **1** afforded the *endo*-ethoxycarbonyl adduct **24** cleanly and enantioselectively (Scheme 6), as predicted by the mechanistic model. The adduct represents a versatile chiral synthetic intermediate since, in principle the boronic ester unit may be replaced by a variety of other substituents.[12]

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(7) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390.

(8) Two diastereomers were formed at a ratio of >20:1 *with* or *without* the catalyst **1**. For further details see Supporting Information.

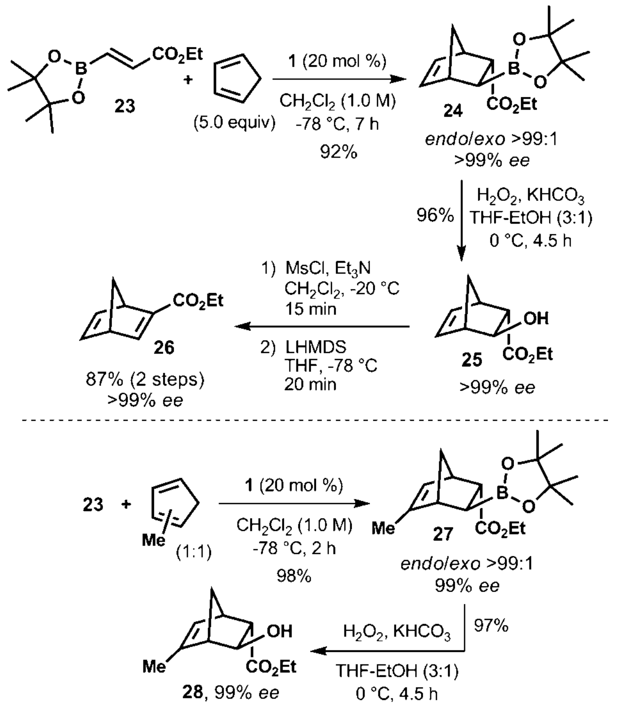
(9) Under the same reaction conditions using (*E*)-cyano trifluoroethyl ester as the substrate, two diastereomeric products were obtained in 3.5:1 ratio with 42% and 15% *ee*, respectively. Product derived from (*Z*)-cyano trifluoroethyl ester was obtained in 6:1 *endo*/*exo* ratio with 62% *ee* for the *endo* diastereomer.

(10) Vinyl boronate **23** was prepared by Cu-catalyzed addition of bis(pinacolato)diboron to ethyl propiolate. Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733–734.

(11) For a catalytic enantioselective Diels−Alder reaction of vinyl boronate and it application in total synthesis of (+)-paniculide A, see: Yamamoto, I.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3327–3333.

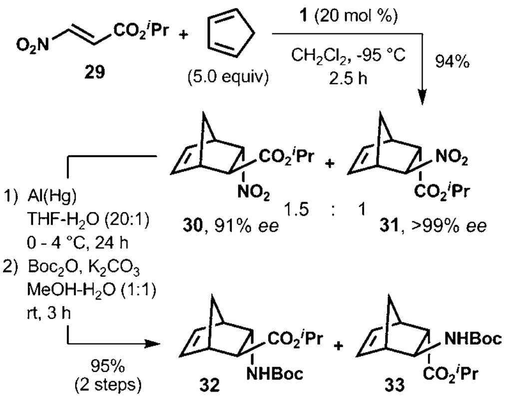
As shown in Scheme 6, the adduct **24** was efficiently transformed into the *β*-hydroxy ester **25** and the chiral bicyclo[2,2,1]heptadiene **26**.[13] Starting with a mixture of 1- and 2-methylcyclopentadienes,[14] the mixed boronate-carboxylic ester **23** was converted into the chiral bicyclic ester **27**, which could be oxidized cleanly to **28** (Scheme 6).

Scheme 6



Finally, we have studied the reaction of isopropyl *β*-nitroacrylate **29** with cyclopentadiene and **1**. The Diels−Alder reaction proceeded well at −95 °C to give a mixture of adducts **30** and **31** in a ratio of 1.5:1 as summarized in Scheme 7. From the data shown we surmise that the pathway in which the catalyst coordinates to the nitro group to form **30** is more productive but also less enantioselective than the $CO_2{}^iPr$ coordination pathway to produce **31**. Even though **30** and **31** are not separable at this stage, reduction of nitro group followed by Boc-protection produced easily separable *β*-amino acid derivatives **32** and **33** as crystalline solids.

Scheme 7



separable by column chromatography

In summary, the experiments reported herein show that strong binding to the chiral catalyst **1** is less important for Diels−Alder reactions that are asynchronous than for those in which the two new bonds are formed almost simultaneously. Such considerations led to the development of the highly useful boron-containing dienophile **23** (Scheme 6), which behaves more like a fumarate than an acrylate type dienophile.[15,16]

Acknowledgment. We thank Dr. Nathan Wallock of Sigma-Aldrich Co. for a gift of the precatalyst for **1** and triflimide.

Supporting Information Available: Experimental procedures and spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Miyaura, Y.; Yamamoto, Y. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M. P., Crabtree. R. H., Eds.; Elsevier: London, 2007; Vol. 9, pp 145−244.

(13) For other approaches to this type of chiral norbornadiene, see: (a) Brown, M. K.; Corey, E. J. *Org. Lett.* **2010**, *12*, 172–175. (b) Payette, J. N.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 8060–8062.

(14) For a recent report on asymmetric Diels−Alder reactions of substituted cyclopentadiene, see: Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9536–9537.

(15) In this regard ethyl acrylate, **1**, and cyclopentadiene do not react at −78 °C in contrast to diethylfumarate, **1**, and cyclopentadiene.

(16) For a recent application of chiral cationic oxazaborolidines, see: Mukherjee, S.; Corey, E. J. *Org. Lett.* **2010**, *12*, 632–635.