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Nonparallelism between Reaction Rate and Dienophile–Catalyst Affinity in Catalytic Enantioselective Diels–Alder Reactions

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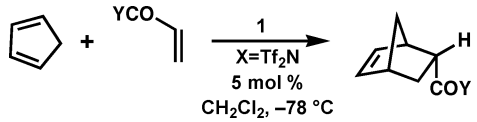
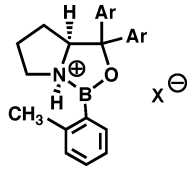
ABSTRACT



The above reaction is much faster with Y = CF_3CH_2O than with Y = CH_3O. However, the methyl ester is a strong inhibitor of the Diels–Alder reaction of the trifluoroethyl ester, since it has a higher affinity for the catalyst 1.

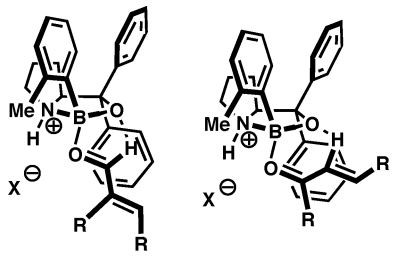
Over the past few years, oxazaborolidinium salts such as **1** and **2** have emerged as remarkably potent, useful, and versatile chiral catalysts, especially for enantioselective Diels−Alder reactions.[1,2]



1, Ar = phenyl
2, Ar = 3,5-dimethylphenyl (mexyl)
X = TfO or Tf_2N

These reactions proceed with very good yields and enantioselectivities with a wide range of dienes and dienophiles.

The face selectivity of the enantioselective Diels−Alder reaction depends on the structural type of the dienophile component. For 2-substituted α,β-enals, formyl C−H···O hydrogen bonding[3] in the catalyst−dienophile complex leads to a preferred pathway via **3**,[1a,b,3] whereas for α,β-unsaturated carbonyl compounds having an α-C−H substituent (e.g., esters, ketones, quinones) α-C−H···O hydrogen bonding favors reaction via complex **4**.[1b,c]



3 **4**

X = TfO or Tf_2N

This mechanistic rationale is powerfully predictive of the absolute stereochemical course of many different Diels−Alder reactions.[1−4] Because only 5−10 mol % of the catalyst is generally required and because the commercially available chiral ligand can be recovered readily and efficiently, these

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(1) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808−3809. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390. (d) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979−3982. (e) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800−4802. (f) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984−5986. (g) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708−13713.

(2) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106−8107.

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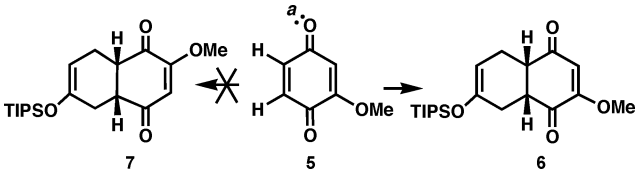
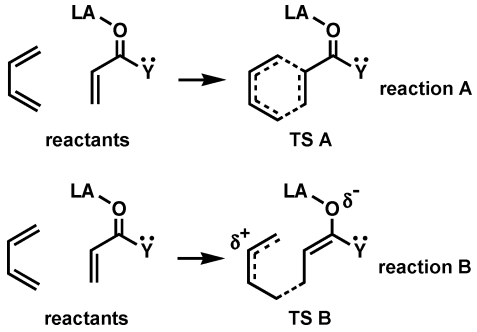
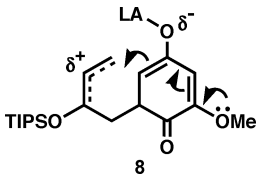
reactions are sufficiently practical for widespread use. Fortunately, inhibition of the reaction by coordination of the Diels−Alder product with the catalyst is not a major problem. Of considerable interest are previous results on the relationship between the coordinating ability of the dienophile and the reaction rate or pathway which showed a clear duality. For instance, in the case of the reactions of trifluoroethyl acrylate and ethyl acrylate with dienes under catalysis by **1**, X = TfO, the latter dienophile reacts more slowly than the former even though it might be expected to coordinate more strongly with the catalyst.[1b] This difference is also seen with this ester of other acids, e.g., crotonates or fumarates.[1b,d] However, in the case of 1,4-benzoquinones as dienophiles, the major pathway is generally that which follows from catalyst coordination to the more basic of the two quinone carbonyl groups.[1b,e,5] Thus, the reaction of 2-methoxy-1,4-benzoquinone (**5**) with 2-triisopropylsilyloxy-1,3-butadiene under catalysis by **1** produces the adduct **6** instead of **7**.[1e] In this reaction, the coordination of catalyst **1** with the lone pair *a* of the more basic quinone oxygen leads to the more productive pathway, so that there is a parallelism between coordinating affinity and reaction rate.



We believe that the simplest explanation of this dichotomy is one based on the degree of synchronicity of the cycloaddition. In principle, there are two extremes of the possible spectrum of transition states (TS) for a Lewis acid-catalyzed Diels−Alder reaction. At one end of the spectrum (reaction A) lies the perfectly synchronous TS in which the two new C−C bonds for ring formation are formed to the same extent (structure TS A). At the other end is the extreme (reaction B) in which one of the two bonds is formed to a considerable extent and the other has not yet started to develop (structure TS B).



In reaction B, electron delocalization of the unshared lone pair on Y is much diminished in going from the initial catalyst-coordinated dienophile to TS B, whereas in reaction A that delocalization is not significantly decreased. Thus, the synchronicity of the TS and also the rate of Diels−Alder reaction can be expected to depend on the nature of Y or, more generally, on the structure of the dienophile. If the TS leading to the quinone Diels−Alder product **6** is synchronous (reaction type A), it is easy to rationalize the formation of this product since the strength of the bond between the coordinated oxygen and the catalyst will be undiminished in the TS. It would seem logical that transition states for Diels−Alder reactions of quinones would tend toward the synchronous end of the mechanistic spectrum[6] because both terminal carbons of C=C undergoing addition are substituted by electron-withdrawing carbonyl groups (accounting for the high relative reactivity of quinones in these reactions). In addition, if one imagines an asynchronous TS for the reaction **5** → **6**, as in **8**, it is clear that the effect of the methoxy group would be to favor ring closure, thus favoring a more synchronous pathway.



On the other hand, if the reactions of ethyl acrylate and trifluoroethyl acrylate are asynchronous (reaction B) and electron donation from Y is decreased in going from the coordinated transition state, the trifluoroethyl ester would be expected to react faster than the ethyl ester, as observed. These ideas provided the basis for the present studies of the catalytic enantioselective Diels−Alder reactions that have utilized reaction competition between pairs of dienophiles to probe the relationships between (1) the catalyst affinity of a coordinating dienophile and the Diels−Alder reaction rate and (2) the structure of the dienophile and the reaction rate. A greater knowledge of these elements would enhance the understanding of the Diels−Alder reactions catalyzed by **1** and **2** and their value in the planning and execution of new syntheses. Although the results that are described herein underscore the mechanistic intricacy of catalytic enantioselective Diels−Alder reactions, they also provide useful insights and guidelines for planning.

Basicity Versus Reactivity for 1,4-Benzoquinones. Detailed studies of the enantioselective Diels−Alder reactions of a wide variety of 1,4-benzoquinones with dienes under catalysis by **1** or **2** have led to the development of a set of six selection rules for the prediction of the absolute configuration and structures of the products,[1e] e.g., the formation of **6** rather than **7** from 2-methoxy-1,4-benzoquinone (**5**) and 2-triisopropylsilyloxy-1,3-butadiene. Generally, the favored

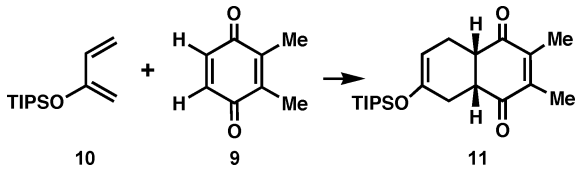
(3) Corey, E. J.; Lee, T. W. *J. Chem. Soc., Chem. Commun*. **2001**, 1321−1329.

(4) For a review of related studies, see: Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

(5) For a detailed discussion of the selection rules for product formation in Diels−Alder reactions of 1,4-benzoquinones under catalysis by **1** or **2**, see ref 1e.

(6) Reaction of 2-triisopropylsilyloxy-1,3-butadiene with 2-methoxy-1,4-benzoquinone (**5**) is clearly not perfectly synchronous since the product **6** is formed with high position selectivity.

product with unsymmetrical components is that expected from coordination of the oxazaborolidinium ion to the *more basic* of the two quinone oxygens. This led us to do an *intermolecular* competition experiment between two different quinones, one more basic than the other, and a diene. The reactions of 2,3-dimethyl-1,4-benzoquinone (**9**) and of 2-methoxy-1,4-benzoquinone (**5**) with 2-triisopropylsilyloxy-1,3-butadiene (**10**) were selected for this analysis. The quinone **5** is clearly more basic than **9**. The reaction of quinone **9** and diene **10** (3 equiv) in the presence of 5 mol % **1**, X = Tf_2N in CH_2Cl_2 at −95 °C for 2 h affords 98% yield of adduct **11** having >99% ee.[7]

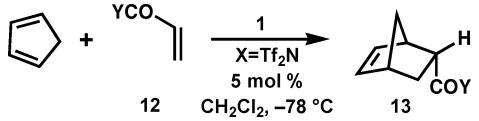


10 **9** **11**

In contrast, when this experiment was conducted with a 1:1 mixture of the methoxyquinone **5** and quinone **9** with 5 mol % catalyst **1** at −95 °C for 2 h, the yield of **11** was reduced to 8% and only ca. 2% of the adduct **6** was formed from **5**. This result proves that the methoxyquinone **5** inhibits the reaction of **10** with **9** because it bonds to the catalyst **1** more strongly. It also shows that the quinone **5** undergoes the Diels−Alder reaction with **10** somewhat more slowly (ca. 4 times) than does **9**. At −78 °C, the reaction of diene **10** with the quinone **9** was approximately 3 times faster than that with the methoxyquinone **5**, as measured for conversion of a 1:1 mixture of **9** and **5** as a function of time. Thus, although tighter catalyst binding correlates with faster reaction for the *intramolecular* competition between the two regioisomeric pathways for **5**,[1e] it does not correlate with the *intermolecular* competition results for **5** and **9**. The preferential formation of **6** from **5** rather than **7** may be due to a more synchronous TS pathway leading to **6** as compared to **7**.

Basicity Versus Reactivity for Acrylate Esters. We have also conducted pairwise competition experiments between several acrylate esters and also acrylyl chloride for reaction with cyclopentadiene in the presence of catalyst **1**, X = Tf_2N. This Diels−Alder reaction proceeded to form the *endo* adduct as shown in Scheme 1. The competition between trifluoroethyl acrylate and methyl acrylate was immediately instructive. Whereas the reaction of trifluoroethyl acrylate and cyclopentadiene (3 equiv) with **1**, X = Tf_2N, (5 mol %) as the catalyst in CH_2Cl_2 at −78 °C for 16 h produces **13** Y = CF_3CH_2O, in 42% yield (complete conversion occurs after a longer reaction time), when the same experiment was conducted with a 1:1 mixture of trifluoroethyl acrylate and the less reactive methyl acrylate neither of the Diels−Alder adducts **13**, Y = CF_3CH_2O or CH_3O, was formed in a measurable amount.[7] Thus, the less reactive methyl acrylate inhibits the Diels−Alder reaction of trifluoroethyl acrylate because it coordinates more strongly with the catalyst **1**. For this pair also there is a divergence of dienophile basicity and Diels−Alder reactivity. This result also argues for an asynchronous transition state for these catalytic acrylate Diels−Alder reactions with cyclopentadiene.

Scheme 1



12 **13**

Pairwise competition experiments were also conducted for (1) trifluoroethyl acrylate vs hexafluoroisopropyl acrylate, (2) trifluoroethyl acrylate vs *p*-nitrophenyl acrylate, and (3) trifluoroethyl acrylate vs *p*-trifluoromethylphenyl acrylate. In each case, it was observed that the trifluoroethyl ester reacted much faster with cyclopentadiene (rate factors > 30 times) using **1**, X = Tf_2N, as the catalyst. This leads to the following order of reactivity: **12** (Y = CF_3CH_2O) ≫ **12** (Y = $(CF_3)_2CHO$, *p*-$NO_2C_6H_4O$, or *p*-$CF_3C_6H_4O$).[8] The sharply diminished reactivity of the last three esters relative to trifluoroethyl acrylate indicates that there is a point at which coordination of the ester to the catalyst is so attenuated that the catalyzed reaction is shut down.[9] The attenuated coordination is to be expected with these last three esters on both electronic and steric grounds.

The reaction of trifluoroethyl acrylate with cyclopentadiene with 5 mol % catalyst **1**, X = Tf_2N, was only slightly retarded by the presence of 1 equiv of acrylyl chloride, as expected. However, Diels−Alder adducts were formed at comparable rates for the two dienophiles in the 1:1 admixture. The product from acrylyl chloride was completely racemic (0% ee of adduct **13**, Y = Cl, measured after conversion to the methyl ester **13**, Y = CH_3O). About half of the adduct was shown, by control experiments with acrylyl chloride and cyclopentadiene alone in CH_2Cl_2, to arise by an uncatalyzed pathway.

We have also determined from competition experiments that methacrolein is much more reactive toward a diene than methyl acrylate even though the latter coordinates more strongly with catalyst **1**, X = Tf_2N. Thus, the reaction of methacrolein with isoprene and 5 mol % **1**, X = Tf_2N, in CH_2Cl_2 at −78 °C is 80% complete in 2 h. However, in the presence of 1 equiv of methyl acrylate there is only 20% conversion to the acrolein adduct and 0% conversion to the methyl acrylate adduct under the same conditions.

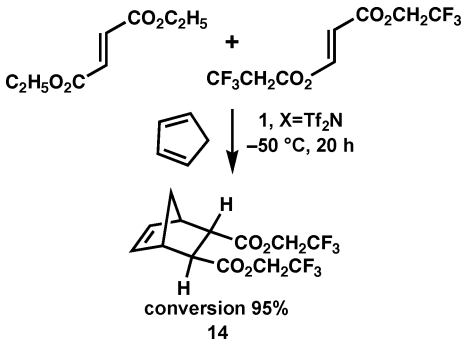
A surprising result was obtained in a competition experiment between trifluoroethyl acrylate and acrylic acid with

(7) Results of approximate measurements of the conversion of starting materials to Diels−Alder product(s) as a function of time in this study were determined by 500 MHz ^{1}H NMR analysis of isolated reaction mixtures.

(8) For example, with 1 mmol each of trifluoroethyl acrylate and *p*-trifluoromethylphenyl acrylate, 3 mmol of cyclopentadiene, and 5 mol % catalyst **1** in 5 mL of CH_2Cl_2, the following conversions to the adduct **13**, Y = CF_3CH_2O, were determined experimentally: 2% at −78 °C for 2 h, 7% at −78 °C for 10 h, 40% at −50 °C for 6 h, and 99% at −20 °C for 10 h; however, in each case, none of the adduct **13**, Y = *p*-$CF_3C_6H_4O$, could be detected.[7]

(9) Rate of the Diels−Alder reaction of trifluoroethyl acrylate with cyclopentadiene under catalysis by **1**, X = Tf_2N, was not appreciably slowed by the presence of an equimolar amount of the esters **12**, Y = $(CF_3)_2CHO$, *p*-$NO_2C_6H_4O$, or *p*-$CF_3C_6H_4O$.

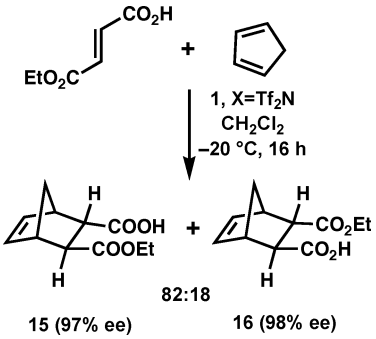
Scheme 2



cyclopentadiene and catalyst **1**, X = Tf_2N, in CH_2Cl_2 at −78 °C. The rate of the Diels−Alder reaction was about 6 times faster with the acid than with the trifluoroethyl ester; both products had the absolute configuration shown by **13**, and in each case the enantioselectivities were high (at least 98%).[1b] We are currently investigating in more detail the reasons for the unexpectedly fast rate of the acrylic acid reaction and the mechanistic bases of the observed enantioselectivity.

Basicity Versus Reactivity for Fumarate Esters. As predicted from the above results for acrylate esters, the reaction of equimolar amounts of bistrifluoroethyl fumarate and diethyl fumarate with cyclopentadiene in the presence of 5 mol % catalyst **1**, X = Tf_2N, in CH_2Cl_2 afforded exclusively the adduct of bistrifluoroethyl fumarate (**14**), as shown in Scheme 2. The rate of the reaction was considerably diminished by the presence of diethyl fumarate. In the absence of diethyl fumarate, only 2 h is required at −78 °C for 95% conversion to **14**. Thus, the behavior of fumarate esters parallels that of acrylate esters, despite there being electron-withdrawing groups at both terminals of the fumarate dienophile.

***Endo*/*exo* Selectivity in the Reactions of Cyclopentadiene with Fumaric Monoester Derivatives.** Given the unforeseen result described immediately above for the reaction of acrylic acid and cyclopentadiene, it was of interest to investigate the *endo*/*exo* ratio in the reaction of fumaric monoesters. The reaction of monoethyl fumarate and cyclopentadiene using 5 mol % catalyst **1**, X = Tf_2N, in CH_2Cl_2 at −20 °C for 16 h afforded in 99% yield an 82:18 mixture of the adducts **15** and **16**. These two products were readily and efficiently separated by the sequence (1) iodolactonization of **15** in the mixture by reaction with I_2−KI and aqueous $NaHCO_3$, (2) extraction and separation of the iodo γ-lactone corresponding to **15** and unreacted **16** in pure form by column chromatography, and (3) reaction of the iodo γ-lactone with Zn−HOAc to regenerate **15** in pure form.



The predominance of **15** in the Diels−Alder reaction is a possible indication that it is formed by the addition of cyclopentadiene to the complex of **1**, X = Tf_2N, with the free carboxylic acid moiety of monoethyl fumarate. It is also of interest in this regard that the reaction of the monoethyl ester−monoacid chloride of fumaric acid with cyclopentadiene and catalyst **1**, X = Tf_2N, at −95 °C for 2 h afforded, after treatment of the crude product with water, a mixture of **15** and **16** in a ratio of 1:2.2.

Conclusions. In summary, the relative rates of oxazaborolidinium ion-catalyzed Diels−Alder reactions of a series of dienophiles have been estimated by a set of pairwise competition experiments.[10] Trifluoroethyl acrylate, which is the most reactive ester studied to date, is more reactive with cyclopentadiene than methyl acrylate even though the methyl ester binds more strongly to the catalyst. On the other hand, the hexafluoroisopropyl, *p*-nitrophenyl, and *p*-trifluoromethylphenyl esters have so little catalyst affinity that they do not react with cyclopentadiene under the same conditions. In the catalyzed Diels−Alder reactions of acrylates, there is clearly an optimum basicity of the carbonyl oxygen for maximum rate. The situation is different with unsymmetrical 1,4-benzoquinones, which have two different oxygens available for coordination to catalyst **1** and, hence, two (or more) reaction paths because of internal competition. The predominating pathway with such quinones is that involving coordination of the more basic oxygen to catalyst **1**. These subtle reactivity effects for acrylate esters and quinones may arise from differing degrees of synchronicity of the transition states for Diels−Alder addition.

Supporting Information Available: Additional experimental procedures and spectral data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **Illustrative Procedure for a Typical Competition Experiment.** The solution of the oxazaborolidinium triflimide (0.1 mmol) in dichloromethane (7.5 mL) was prepared from (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol (30.4 mg, 0.12 mmol), tri-*o*-tolylboroxine (14.2 mg, 0.04 mmol), and triflimide (0.5 mL, 0.2 M in dichloromethane) by the previously reported procedure.[1c] To a stirred solution of trifluoroethyl acrylate (127 μL, 1 mmol) and methyl acrylate (68.6 μL, 1 mmol) in dichloromethane (1 mL) was added the freshly prepared catalyst solution (0.05 mmol, 4 mL) at −78 °C. Half of the catalyst solution was used for the control experiment without methyl acrylate. After 10 min, 1,3-cyclopentadiene (248 μL, 3 mmol) was added at −78 °C. An aliquot (50 μL) was removed from the reaction mixture and quenched quickly with Et_3N (20 μL) solution in $CDCl_3$ (0.6 mL). The progress of the reaction as a function of time was determined by ^1H NMR monitoring with signal integration (500 MHz, $CDCl_3$): δ 4.54 (q, 2H, J = 8.5 Hz, trifluoroethyl acrylate), 4.35 (dq, 1H, J = 12.8, 8.4 Hz, adduct of trifluoroethyl acrylate), 3.75 (s, 3H, methyl acrylate), 3.62 (s, 3H, adduct of methyl acrylate).