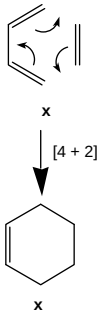
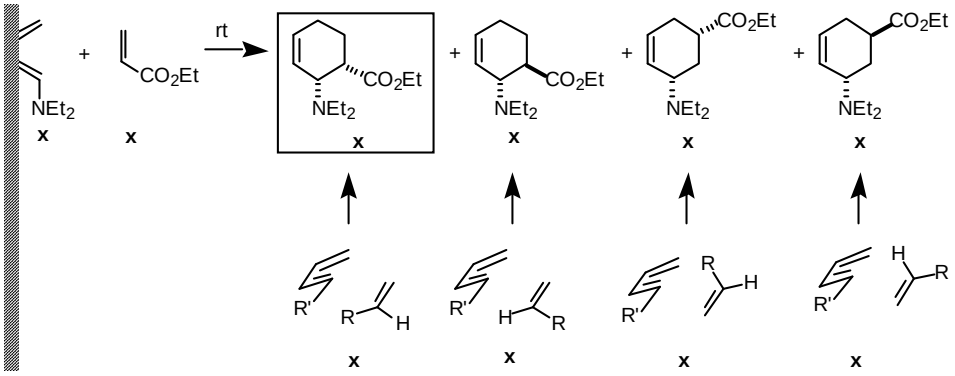
Chapter X. Diels – Alder Cycloadditions

Inter-molecular
Trost-aggarwal

The Diels-Alder reaction is clearly one of the most powerful synthetic transformations in chemistry. This [4 + 2] sigmatropic reaction, depicted in its simplest all-carbon form as the reaction of X to X, has been employed as a key transformation in the total synthesis of many natural products. In a single reaction two new carbon-carbon bonds are formed in addition up to four new stereocenters. The presence of nearby chiral centers often induces a high degree of diastereoselectivity, thus making the reaction ideally suited a vehicle for asymmetric synthesis. The most common reaction partners employed in the Diels-Alder reaction for natural product synthesis involve electron rich dienes and electron poor dienophiles. However, a remarkably wide variety of other components participate in [4 + 2] rearrangements, including heteroatoms, systems with inverse electron demand and both intra- or inter-molecular partners. Another noteworthy feature of the Diels-Alder reaction is that often a single isomeric product is selectively formed although four isomeric products are possible.



As an illustration of the selectivity of the Diels-Alder reaction, the cycliztion of **X** with **X** affords exclusively bicycle **X**.[1] Three other isomeric products, namely **X**, **X** and **X**, could be formed by combinations of **X** and **X** involving regional (i.e, head-to-tail) and facial (i.e., endo vs. exo) orientations, but there were no other reported reaction products. An analysis of the stereochemistry of the product **X** suggests a transition state where **X** and **X** have the orientation as shown in **X**. Note that compared to the three other transition states **x-x** the arrangement **X** places the two bulky groups R and R' in close proximity to each other. The regional preference for the "ortho-like" or 1,2-disubstituted cyclohexene **X** over 1,3-substitution clearly conflicts with a normal steric repulsion model. Additionally, the orientation of the carboxyl group R' is placed below the diene X instead of being positioned away from the more sterically congested portion of the molecule.



A frontier molecular orbital (FMO) analysis of the Diels-Alder reaction adequately explains the observed with X and X and similar Diels-Alder reactions for the "ortho-like" endo products.[2] The relative energies of butadiene and ethylene are shown in figure 1a. Without transition metal catalysis (see

below) the energy difference between the diene and dienophile is great and forcing conditions are necessary for reactivity, usually resulting in loss of selectivity. By adding electron donating and electron withdrawing groups to the diene and dienophile moeities, respectively, the relative energy difference of their frontier orbitals becomes smaller compared to electronically neutral reacting partners (figure 1b). Specifically, with electron donation the HOMO of the diene raises and is closer to the lower energy level of the LUMO of the dienophile. This arrangement is refered to as a normal electron demand Diels-Alder reaction. Switching the placement of the electronic donating or electron withdrawing groups to the other olefin results in compatible reaction partners through the LUMO of the diene and the HOMO of the dienophile, a situation refered to as an inverse electron demand Diels-Alder reaction (figure 1c). In both normal- and inverse-electron demand Diels-Alder reactions the smallest energy difference between the HOMO and LUMO orbitals is less than for the unsubstituted partners.

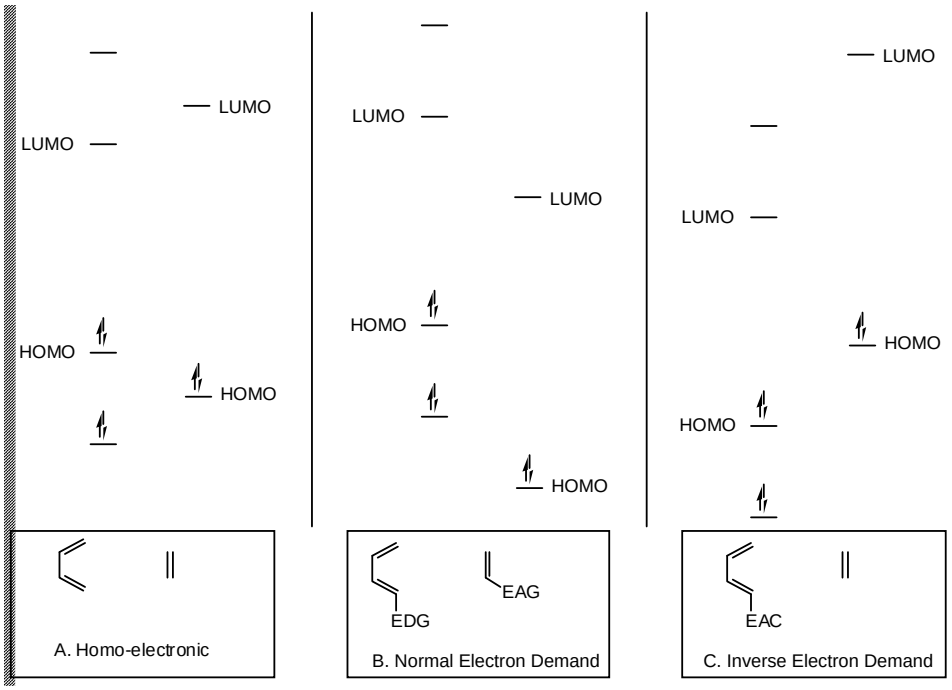


Figure 1. Relative frontier orbtial energies in [4 + 2] cycloadditions

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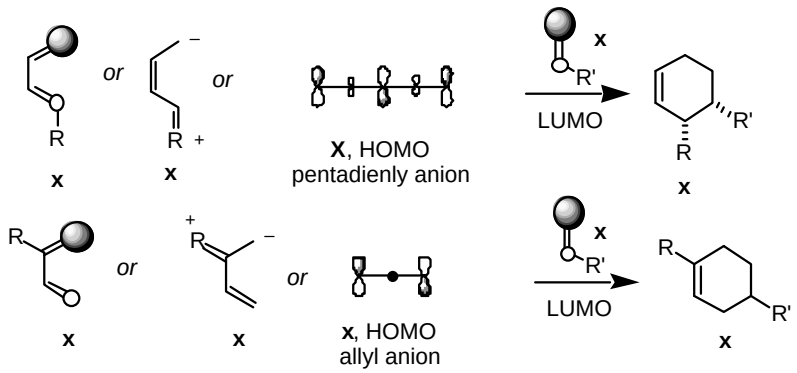
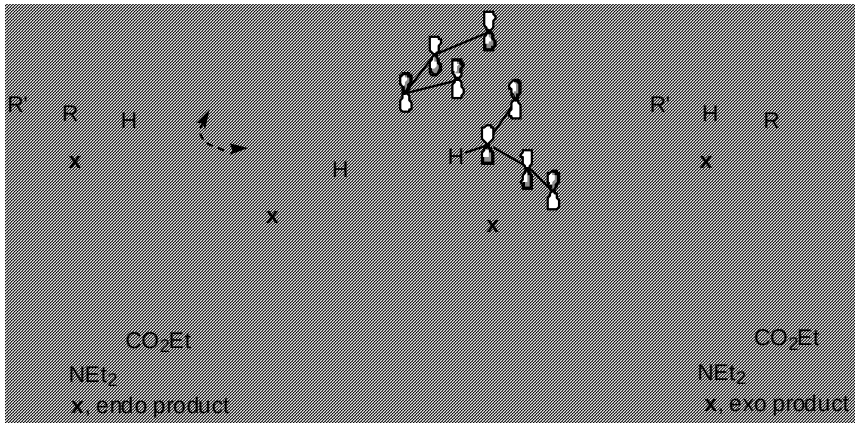
For the normal electron demand Diels-Alder reaction of X and X the relevant frontier molecular orbitals are those shown in figure 2. Electron donation at the diene terminious results in the HOMO orbital coefficient of the diene carbon remote from the donor to be larger relative to the ipso carbon. Either an extreme resonance structure (**X**) or comparison to the HOMO of pentadienyl anion (**X**) helps provide a qualitative rationalization of these relative coefficients. For the dienophile the larger LUMO orbital coeficient would be larger. Mixing of the two orbitals of most similar size places the diene and dienophile in a head-to-head or "ortho-like" orientation (x). When C2 of the diene is substituted with an electon donating group, a similar frontier molecular orbitial analysis predicts the relative orbital coeficients shown in X. Cycloaddition through an orientation with the larger orbitals interacting would provide the "para-like" or 1,4-disubstituted cyclohexene X.



The preference for endo products is due to a more subtle orbital interaction than is responsible for the regiochemical selectivity. That is, orbtital interplay between the diene and dieophile causes the prefered reactive orientation to lead to endo products, but does not lead to new bond formation between. The phase of the diene HOMO and dienophile LUMO orbitals is shown in figure 2a. The double headed arrow shows that the sp^2 carbon of the carbonyl is of the same phase and may therefore interact with the C2 orbital of the diene. This extra stablilizing orbital interaction is absent in the orientation leading to the exo products.

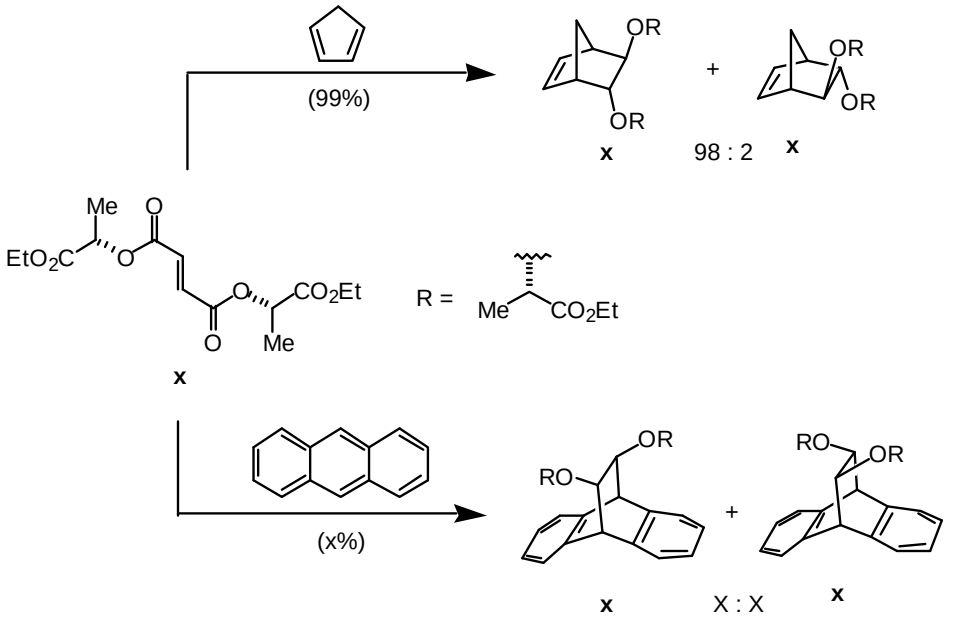


Additionally, predicting the stereochemical outcome of Diels-Alder reactions is relatively uncomplicated with a qualitative FMO analysis. The ease of accurately predicting the stereochemical outcome of Diels-Alder reactions is impressive given the number of possible products and reaction parameters one must consider in an analysis.

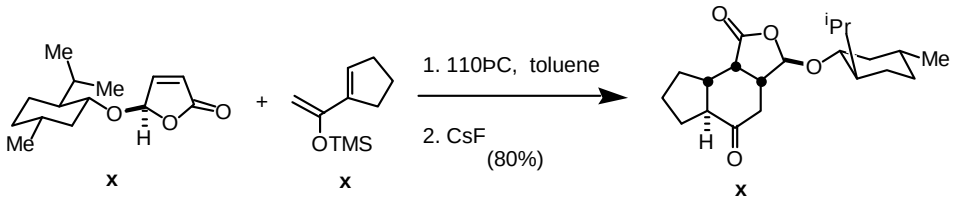
X.X Diastereoselective Intermolecular Diels-Alder Reactions

Many highly diastereoselctive variations on intra- and inter-molecular Diels-Alder reactions wherein the resident chirality on one or both of the reacting participants is transferred to the newly formed carbon-carbon bonds have been documented. This section presents a number of examples that illustrate the scope and selctivity of diastereoselective intermolecular cyclizations. The section is further divided into chiral dienes and dienophiles.

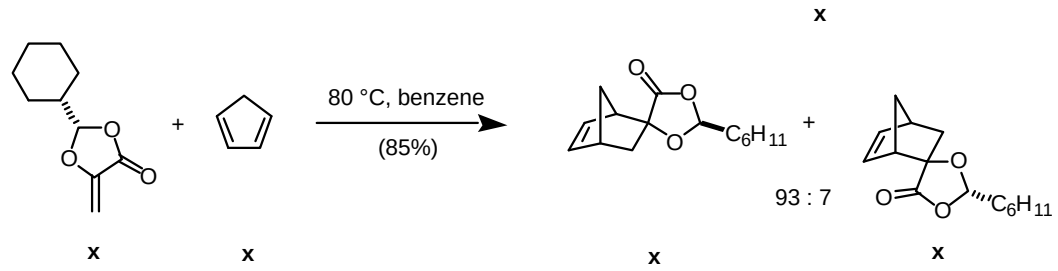
Chiral Dienophiles. The classification of resident chiral centers in dienophiles often fall cleanly into two categories: auxiliary and non-auxiliary. Although the distiction is primarily semantical it serves as a helpful guideline. Specifically, dienophiles with chiral groups readily cleaved from the olefinic portion of the molecule are classified as auxiliary controlled dienophiles. One of the best examples of this approach to transfering asymmetry in Diels-Alder reactions is in the cyclization of fumarates. Fumarate esters of lactate (X) and menthol[3] participate in Diels-Alder reactions with a variety dienes to provide adducts with high levels of diastereoselectivity. For example, reaction of lactol fumarate X with cyclopentadiene[4] or anthracene[5] provides adducts in >9 : 1 selectivity. The ratio may be improved by removal of the minor diastereomer.



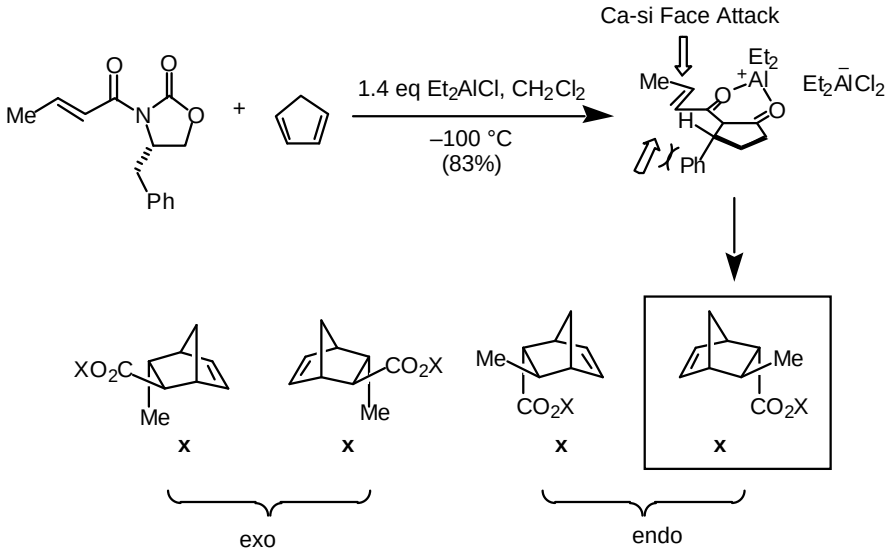
Dienophiles bound to a single chiral substitutent also can show high levels of diastereoeselectivity. The electron rich diene X reacts with chiral dienophile X to afford the single isomer X in 80% yield.[6]



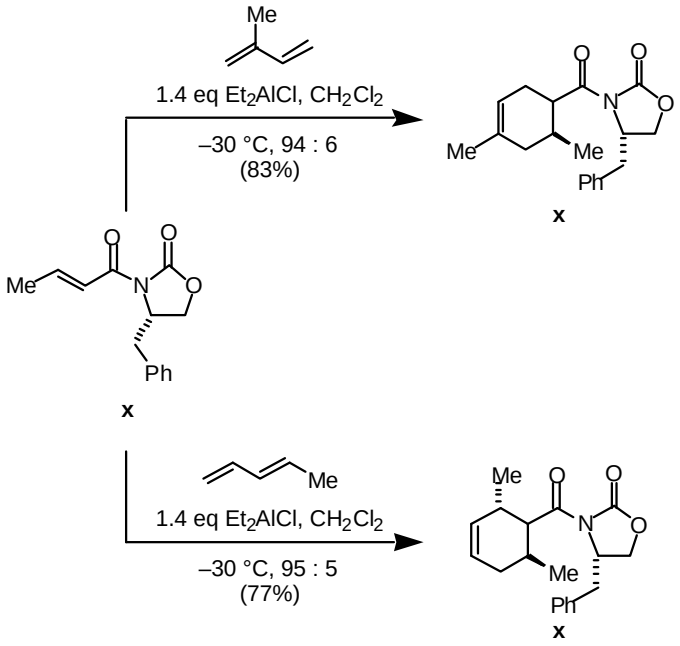
Exocyclic methylenes as part of a chiral dioxilinone have seen extensive use in asymmetric Diels-Alder reactions.[7,8] The reaction of **X** with cyclopentadiene in benzene provides predominately the endo isomer with >13 : 1 selectivity. Furthermore, the endo isomer is formed exlusively as a single diastereomeric product.8



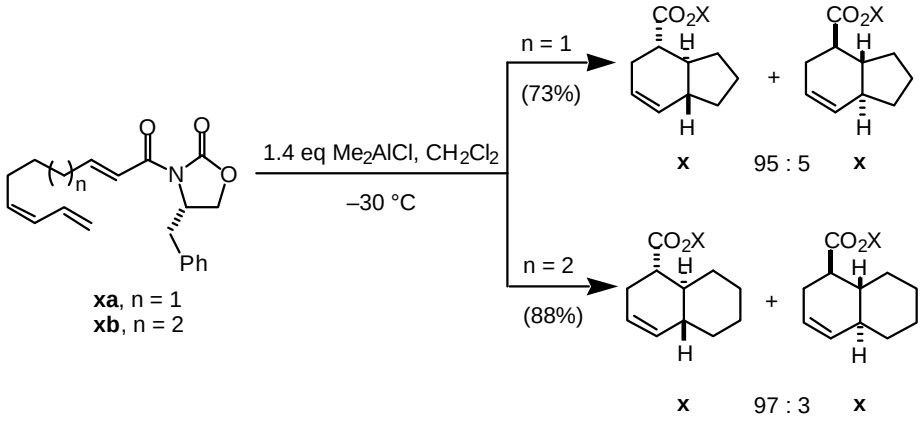
The chiral oxizolidinones successfully developed by Evans for asymmetric aldol reactions also perform admirably as auxiliaries in Diels-Alder reactions. Cycloadducts with high levels of facial- and diastereo-selectivity have been obtained with the utilization of these auxiliaries. For example, the Diels-Alder reaction with cyclopentadiene is greater than 90% selective for a single cycloadduct **x**.[9]



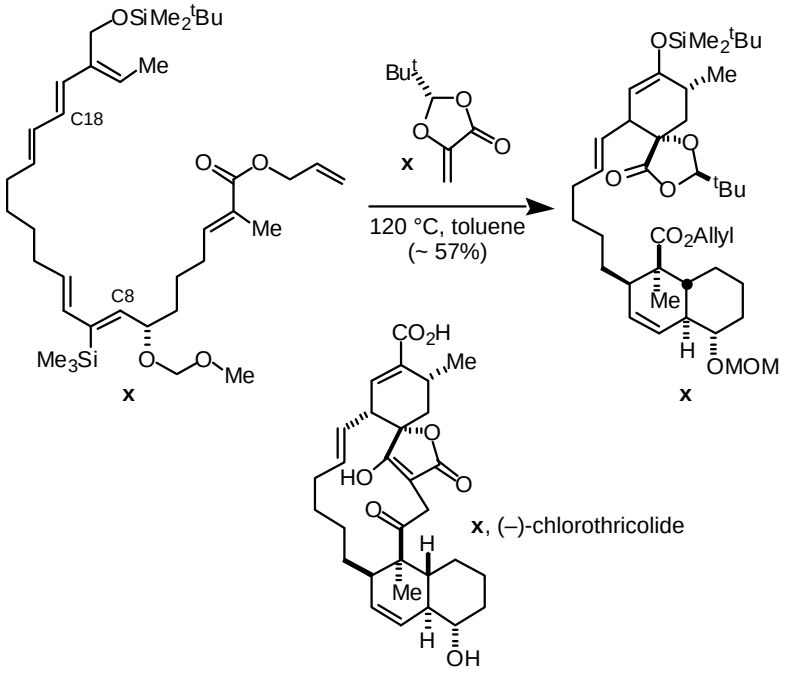
Key to achieving high diastereoselectivity for a variety of cyclic and acyclic dienophiles with these auxilaries was the discovery that the ideal bidentate Lewis acid was generated *in situ* by the chloride metathesis of dimethyl or diethyl aluminum chloride. Both isoprene and piperylene are excellent reaction partners and provide products with 94 : 6 selectivity or better that are readily purified to single isomers.[9]



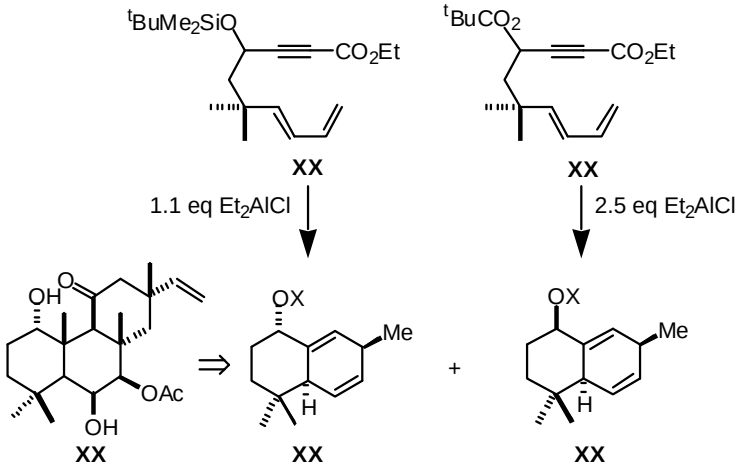
The oxazoline auxiliary even shows good levels of stereocontrol with intramolecular Diels-Alder variations. For example, triene X is stable at room temperature. However, spontaneous cyclization occurs at –30 °C in the presence of Me_2Al affords endo diastereomer **X** with >97 : 1 preference over endo diastereomer **X**. Over major isomer **X** may be obtained in >99 : 1 isomeric purity after purification.[9]



Roush has applied Diels-Alder methodology to the synthesis of several natural products.[10] A particularly impressive example of selectivity in Diels-Alder cyclizations was reported by Roush in his total synthesis of chlorothricolide X. The key step in the synthesis selectivley achieves both an intramolecular cyclization from the α,β-unsaturated ester and the C8-C11 diene and an intermolecular cyclization with dienophile **X** and the more electron rich C18-C20 portion of the triene. Remarkably, these reactions are achieved in about 57% yield. The intermolecular cyclization demonstates chirality transfer by an auxiliary approach and the stereochemistry of the intramolecular reaction is controlled by an allyic stereocenter.

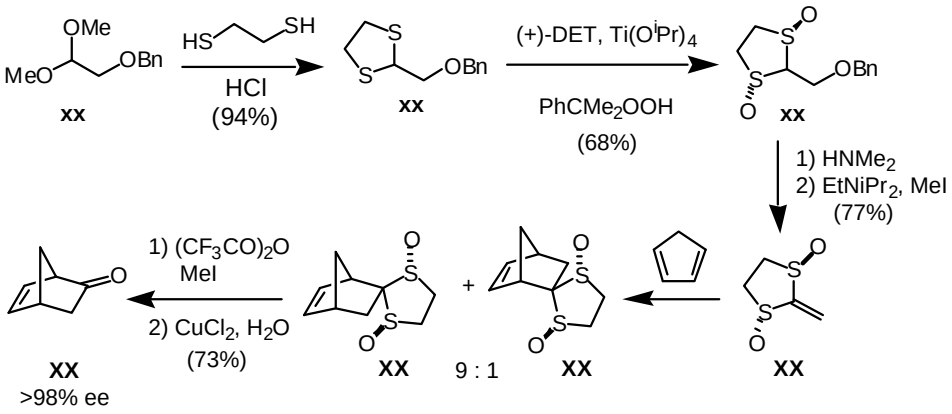


A propargylic hyroxyl or ether function can also provide bias for facial selectivity in intramolecular Diels-Alder reactions. In studies on the synthesis of forsolin **XX**, Trost observed some remarkable directing effects of the propargylic substituent wherein either cycloaddition product **Xx** or **XX** could dominate in the reaction by careful selection of oxygen protecting group in combination with reactions conditions.[11] In the two cases shown below, each cycloaddition proceeds to give only the product drawn directly below it, under nearly identical reaction conditions. Whether the stereochemical course of this reaction is due to steric differences or stereoelectronic effects is unclear.



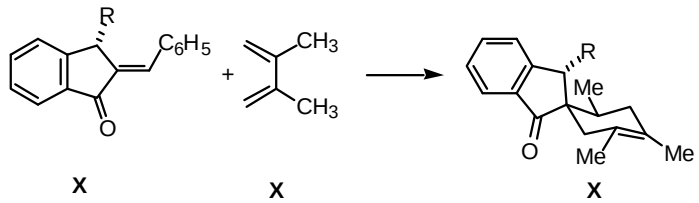
Another auxiliary based methodology developed by Aggarwal provides the synthetic equivalent of a chiral ketene, and performs well with a variety of dienes.[12] The optically active (-)-2-methylene-1,2-dithiolane 1,3-dioxide **XX** is prepared by oxidation of the corresponding dithiolane **XX** with dimethylbenzyl

peroxide in the presence of titanium tetraisopropoxide and (+)-diethyl tartrate. The dioxide **XX** is secured in >99% ee before recrystallization as 10:1 mixture of the desired compound and the meso dioxide **XX**. A two step substitution and elmination sequence affords the final product.



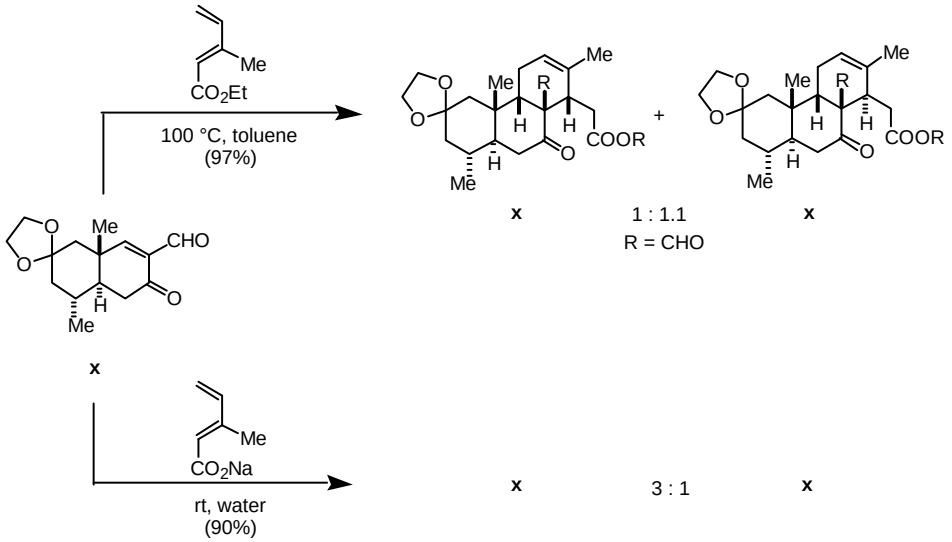
The chiral ketene equivalent **XX** displays excellent levels of diastereocontrol in Diels-Alder reactions with a variety of dienes. For example, treatment of **XX** with cyclopentadiene at room temperature for 24 hours affords a 9:1 mixture of cycloaddition adducts **Xx** and **XX** in 96% combined yield. Similarly impressive results are obtained with 1-methoxybutadiene (>93:3, 83%), 1-methoxy-3-trimethylsilyloxybutadiene (>93:3, 90%) and furan (>97:3, 65%). Hydrolytic removal of the bis-sulfoxide is achieved with a two-step reduction and hydrolysis procedure to afford the optically pure cycloaddition product **XX**.

The following examples do not fit into the classification of auxiliary based dienophiles as the chirality residing within the dienophile is connected to the olefin by carbon-carbon bonds or non-hydrolyzable heterobonds. Furthermore, these examples illustrate the structural diversity and complexity compatible with the Diels-Alder reaction. The cyclization of **X** and **X** affords the spirocycle X in 64% yield as a single isomer, and illustrates the utility of the Diels-Alder reaction in forming hindered, asymmetric quaternary centers.[13]

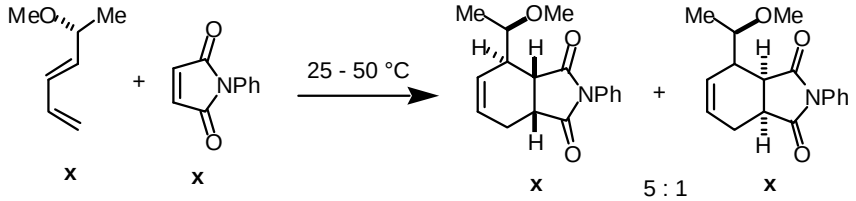


Diels-Alder reactions often show a strong dependence on the reaction media. For example, cyclization of **X** and **X** in toluene proceeded with only 1 : 1.1

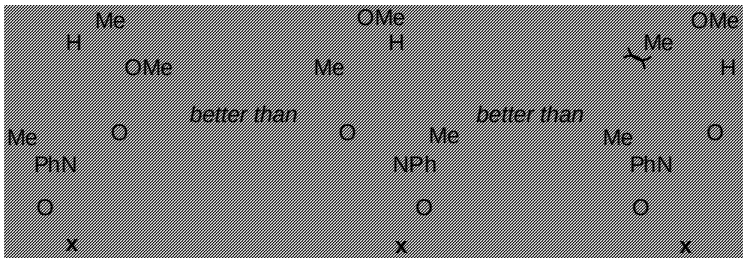
selectivity. However, performing the cyclization with the sodium salt **x** in water increased the selectivity to 3 : 1.[14] A review of synthetic reactions that benefit from aqueous media has recently appeared.[15]



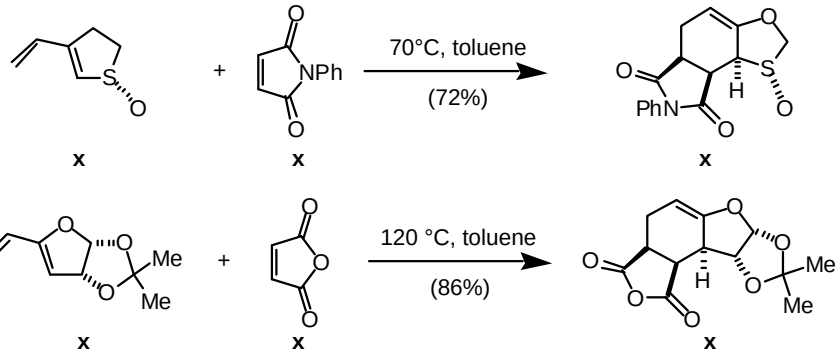
Chiral Dienes. As seen above in the synthesis of chlorothricolide X by Roush, an allylic stereocenter in a chiral diene can serve as an effect stereocontrolling element in Diels-Alder cycloadditions. Studies by Franck have illuminated the parameters that determine the facial selectivity in asymmetric Diels-Alder reactions of allylic substituted dienes.[16] In the cyclization of diene X and maleimide X a 5 : 1 facial selectivity was observed.



A transition state conformational analysis suggests that structure **X** would be disfavored due to allylic A1,3 strain between the diene and the methyl group. The prefered reactive conformation would place the smaller group in the most hindered position, thus favoring transition states **X** or **X**. A stereoelectronic preference for transition states with the better electron donor (methyl) anti to the new bond formation then makes **X** the most favored transition state conformation.

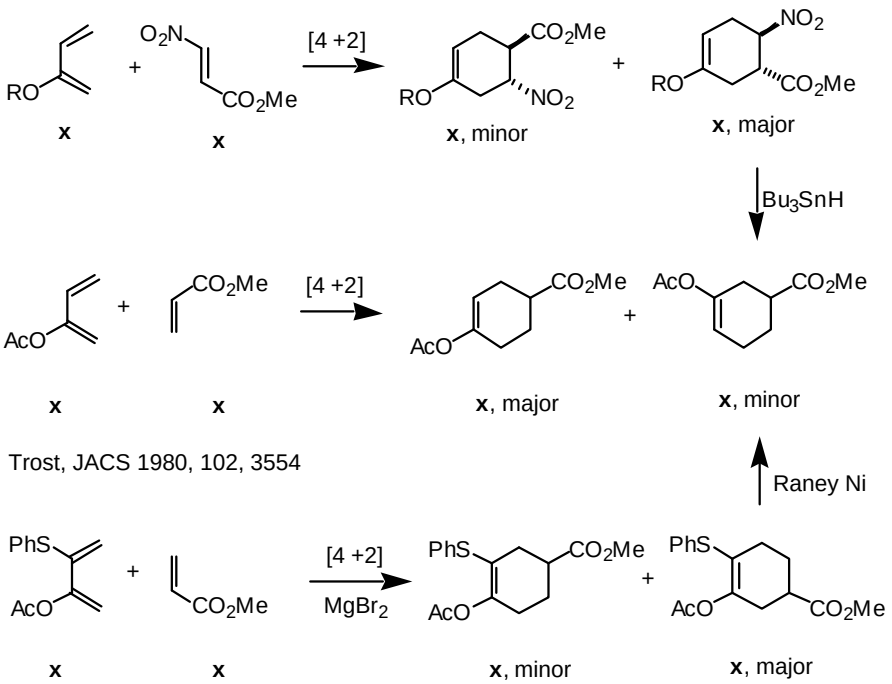


The mechanistic rationale for the stereochemical outcome of Diels-Alder cycloadditions with dienes of type **X** has been examined extensively by Overman.[17] Unlike the mechanistic models acyclic dienes of type **X**, the facial selectivity with cyclic dienes can be explained by a simple steric model. For example, cyclization of diene **X** with maleimide occurs from the less hindered face of the diene anti to the sulfoxide oxygen to form exclusively the endo adduct **X**. Analogously, glucose-derived diene **X** also shows complete selectivity in the cyclization with maleic anhydride.[18]



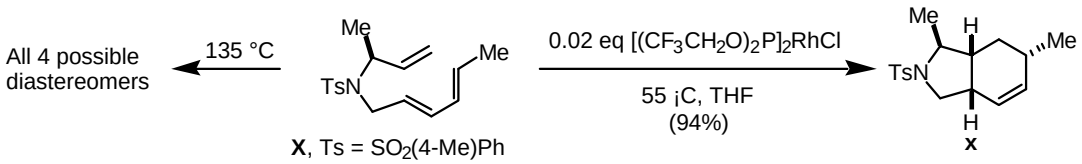
X.X Reversal of Regioselectivity

If one wanted to find fault with a reaction that consistently provides products with high stereoselectivity, it might be in a situation where the minor diatereomer is desired. In certain instances, Lewis acid additives can influence or even overwhelm the natural stereochemical course or a reaction. However, Lewis acids typically only increase the inherent bias in Diels-Alder reactions and do not facilitate entry to divergent stereochemical pathways. Two creative solutions relying on subsequent chemical manipulations of Diels-Alder adducts have circumvented the natural stereochemical preference. In pioneering investigations on regiocontrol in Diels-Alder cycloadditions Danishefsky reported that when a diene is substituted with a nitro group, the normal regiochemical influencing elements relenquish contol to the nitro group (**x** → **x**).[19] Reduction or elimination of the nitro cyclization adduct then affords the product formally obtained as the minor diastereomer in a standard Diels-Alder reaction ((**x** → **x**)).[20] An alternative strategy devised by Trost employs an arylsulfenyl ether to preferentially generate the "meta" product.[21] Reductive desulfurization generates the cyclohexene **x** that again corresponds to the minor isomer in a standard Diels-Alder reaction.

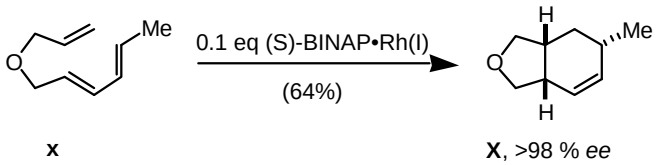


X.X Homo-electronic Diels-Alder Reactions.

The examples illustrated so far in this chapter rely on electron donating or withdrawing substiutents to lower the engery difference between the reacting orbitals (figure 1). Applying more focing conditions such as high temperatures can promote reactivity but often have a detrimental effect on the reaction stereoselectivity. In his landmark publication in 1990, Livinghouse disclosed that Rh(I) phosphine complexes catalyze the Diels-Alder reaction between electronically similar dienes and dienophiles.[22] The power of the rhodium catalyst system is apparent when comparing the reactivity of a few representative substrates. Cycliztion of triene X requires heating to 135 °C to promote cyclization and a diastereomeric mixture of all four possible diastereomeric Diels-Alder products is obtained as a 1 : 1 : 2 : 2 mixture.[23] In contrast, in the presence of 2 mol % of $[(CF_3CH_2O)_2P]_2RhCl$ at 55 °C in THF the cyclization proceeds smoothly to afford the major diastereomer X with 19 : 1 stereoselectivity 94% yield.



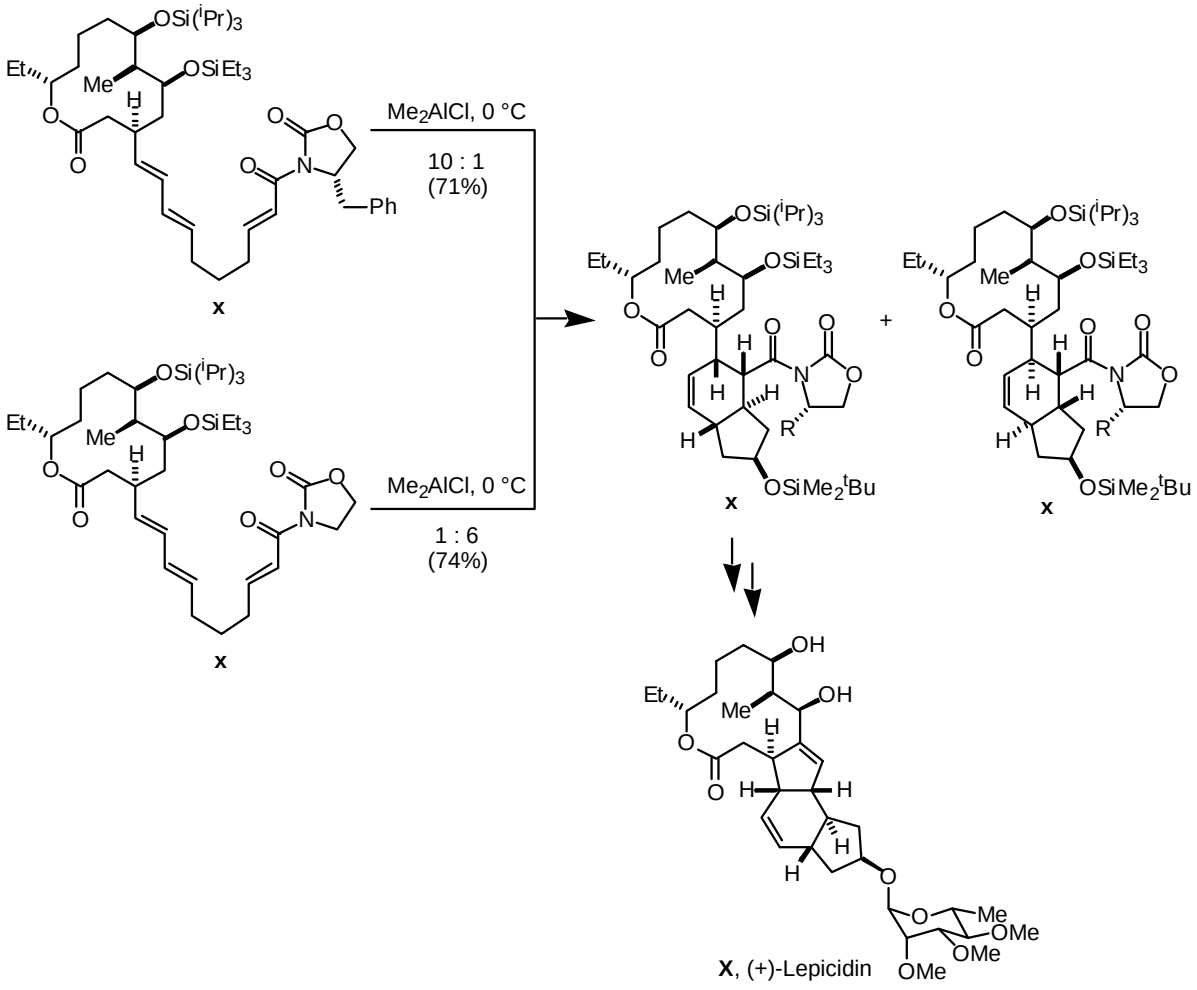
Significant improvements in the enantioselectivivity of cyclization adducts of achiral trienes was realized by the addition of ethyl acetate to the originally published procedures.[24,25] With the ethyl acetate modification, enantioselectivities in excess of 98% have been realized.[24]



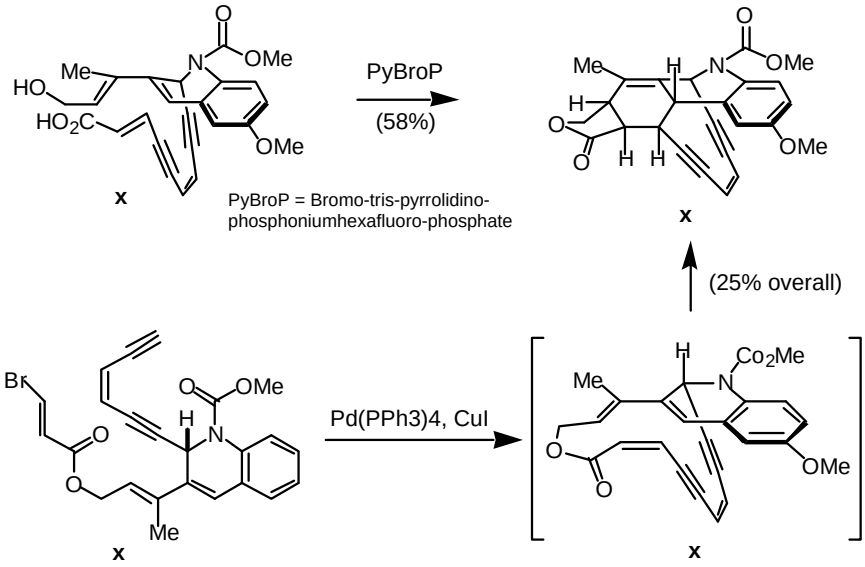
x **X**, >98 % *ee*

X.X Intramolecular Diels-Alder Reactions

Intramolecular Diels-Alder reactions typically display a high level of regioselectivity (head-to-tail) with a sufficiently short tether that precludes a conformation without severe eclipsing interactions that the regioisomeric (tail-to-head) products are seldom observed. The major concern in these cyclizations is the facial selectivity. An example by Evans in his synthesis of (+)-lepicidin A demonstrates both the facial bias imparted by an allylic stereocenter on the diene (see above, section X.X) and the ability of a chiral imide to overwhelm this influence to access selectively the other diastereomer.[26] The intramolecular Diels-Alder cycloaddition of X provided a 10 : 1 mixture of diastereomers, with the major isomer suited for deployment in completing the synthesis of lepin X. The chiral imide portion of X was able to over-ride the natural inherent facial bias of the diene, as evidenced by the cycloaddition of X bearing an achiral imide. In this instance, the undesired diastereomer was formed as the major isomer in a 6 : 1 ratio.

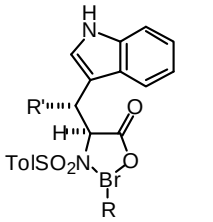


In Schreiber's elegant studies on the synthesis of dynemicin A and related structures, he developed an intramolecular approach to the enediyne core.[27] Intramolecular macrolactonization leads to a spontaneous and efficient cyclization reaction. The sensitive enediyne portion of the molecule remains undisturbed in the cyclization.

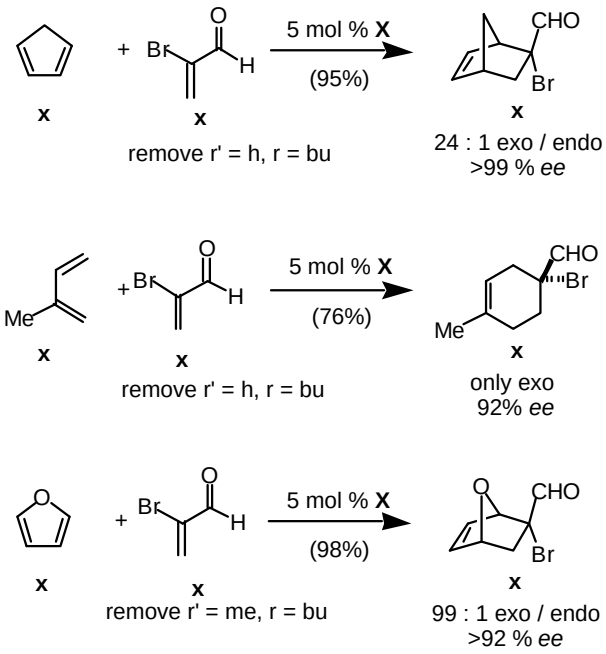


X.X Catalytic, Enantioselective Diels-Alder Reactions

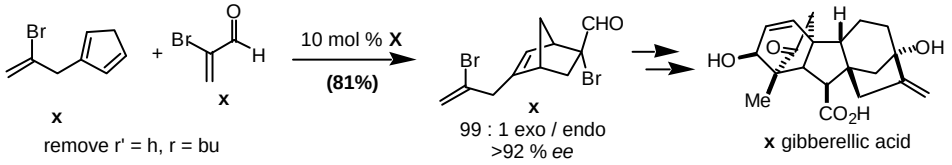
There are now many catalysts capable of effecting the asymmetric Diels-Alder reaction between prochiral diene and dienophile. What differentiates one catalytic method from another is less the reported enantioselectivity, but the breath of substrates that the catalyst remains effective. Two of the most general Lewis acid catalysts displaying wide substrate compatibility and high asymmetric induction are derived from boranes or transition metal chelates with bis-oxazoline ligands.


X, R = nBu, R' = H
X, R = nBu, R' = Me

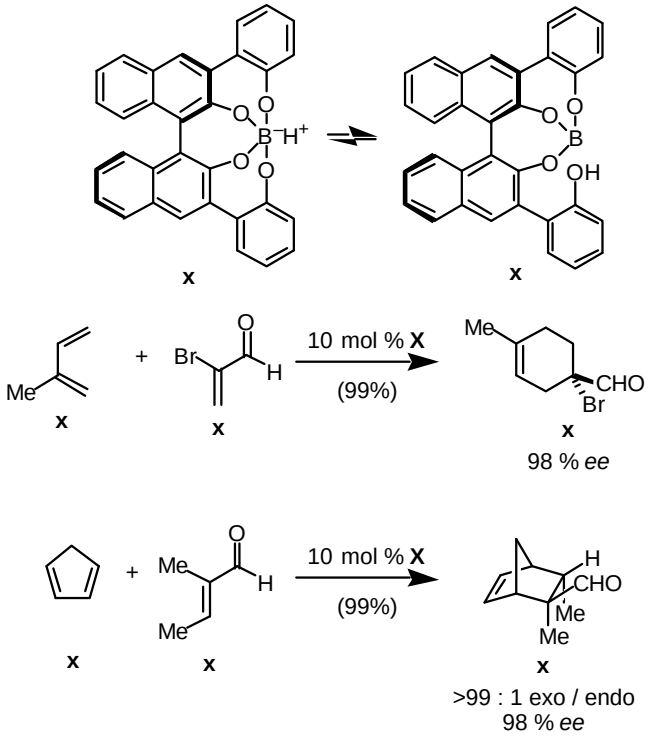
The tryptophan derived oxazaborolidine catalyst **X** reported by Corey stands as abench mark against what many other Diels-Alder catalysts are now measured.[28] These catalyts show exceedingly high levels of exo selectivity, often beyond detection of the minor endo component. Also, many substrates cyclize with greater than 90% enantiomeric induction. For example, cyclopentadiene X, acyclic dienes (X) and furan are suitable substrates.[28,29] In these cases, the best enantioselectivity is obtained with a-bromo acrolein as dienophile.



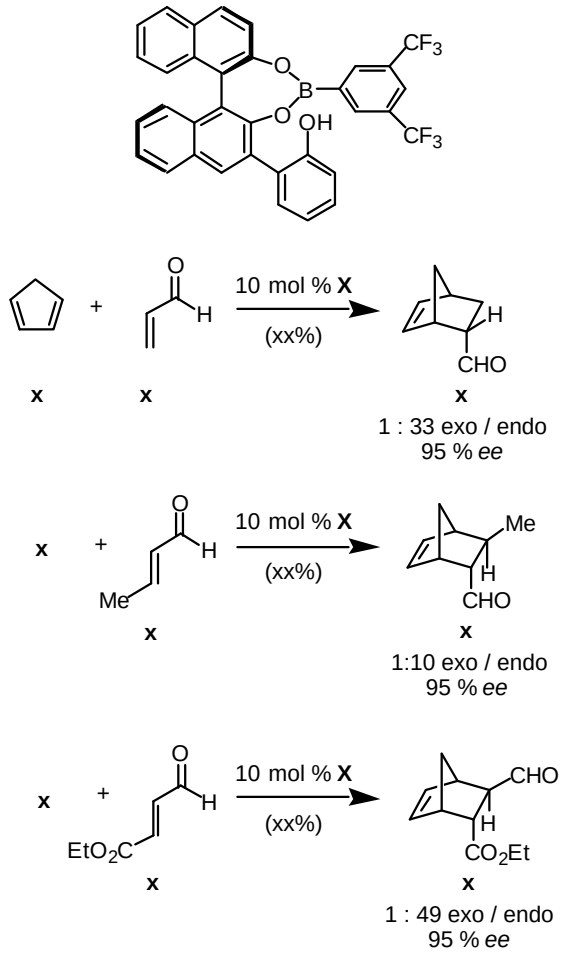
Catalyst **X** was utilized as the first key reaction in the total synthesis of Gibberellic Acid. The Diels-Alder with a-bromoacrolein and the substituted cyclopentadiene X was achieved in >99 % ee with only 10 mol % catalyst.[30]



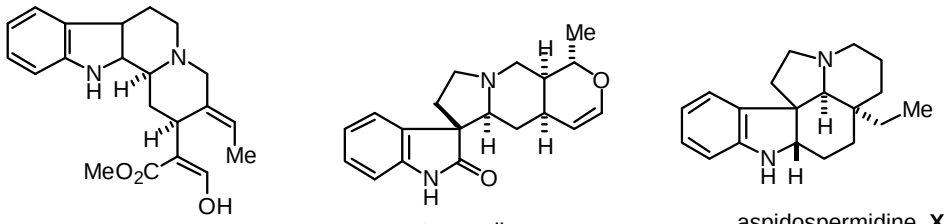
Another boron derived Lewis acid complex that serves as a catalyst for the asymmetric Diels-Alder between a variety of dienes and substituted acroleins was devised by Yamamoto and Ishihara.[31] Tetravalent, zwiterionic complexes of this type are categorized as Brönsted acid-assisted chiral Lewis acid (BLA) complexes. The ate-complex is in equilibrium with the coordinatively unsaturated boron species **X** or similar isomer that presumably functions in the catalytic cycle.[31] Complex **X** effectively catalyzes the Diels-Alder addition between α-bromoacrolein **x** and substituted acrolein derivatives **x** with >99 : 1 exo selectivity and >98 % enantiomeric exess.



The closely related BLA complex **X** is a second-generation catalyst reported by Yamamoto, that futher extends the scope of compatible dienophiles. For example, with this more recent catalyst acrolein and crotonaldehye participate in the Diels-Alder to afford products in >95% *ee*.



X.X Applications of Diels-Alder Cycloadditions to Natural Product Synthesis



geissoschizine, **x**
da

pteropodine, **x**
hda

aspidospermidine, **X**

Figure X. geissoschizine **x** (DA),[32] pteropodine **x** (HDA),[32] aspidospermidine **X** (DA).[33]

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