

Diels-Alder Reaction

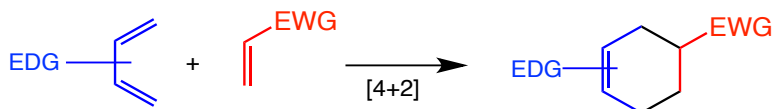
Reviews:

Nicolaou et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668

Kagan, Riant *Chem. Rev.* **1992**, *92*, 1007

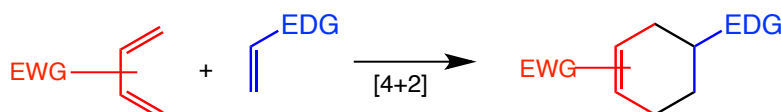
Kurti, Laszlo, Czako *Elsevier*, **2005**, 140-141

Normal Diels-Alder reaction



EDG (electron donating group)
= alkyl, O-alkyl, N-alkyl

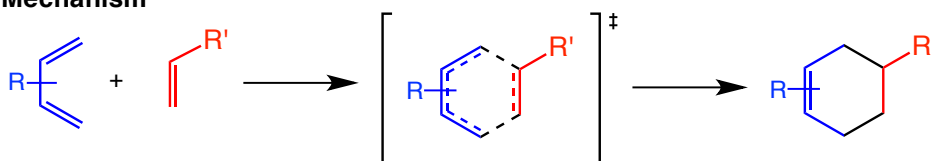
Inverse Electron Demand Diels-Alder reaction



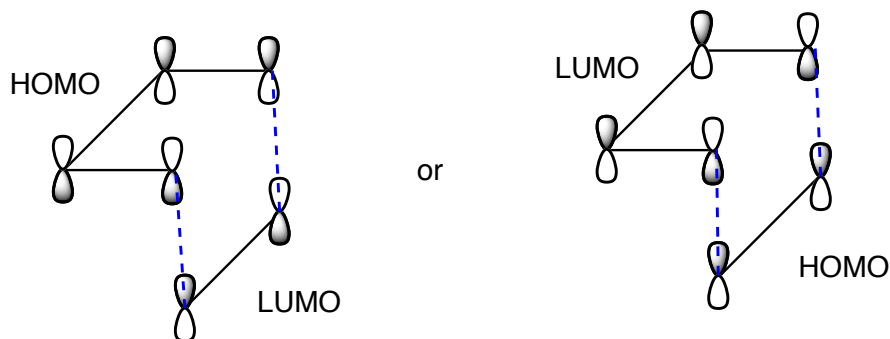
EWG (electron withdrawing group) = COR, CO₂R, COAr, NO₂, etc.

- [4 π + 2 π] cyclization of diene and dienophile
- dienophiles also include substituted alkynes, benzyne, and allenes
- reaction is **regioselective** and **stereospecific**
- reaction can be **enantioselective** using chiral catalysts
- with another atom being other than a carbon, reaction is known as **hetero Diels-Alder reaction**

Mechanism

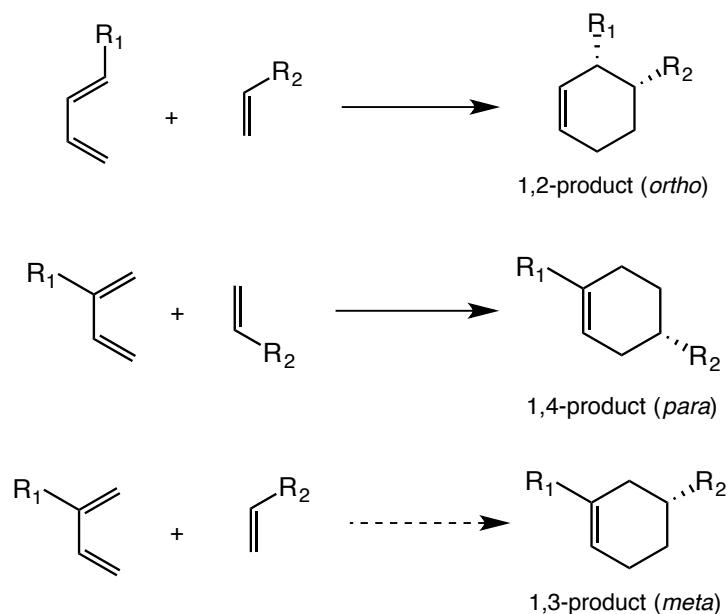


- concerted, pericyclic reaction with an aromatic transition state
- forms two new σ -bonds
- forms the endo product as shown by the HOMO-LUMO orbital interactions



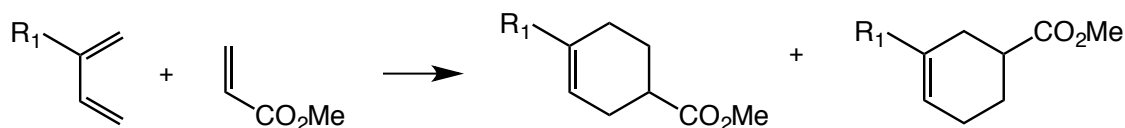
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Regioselectivity



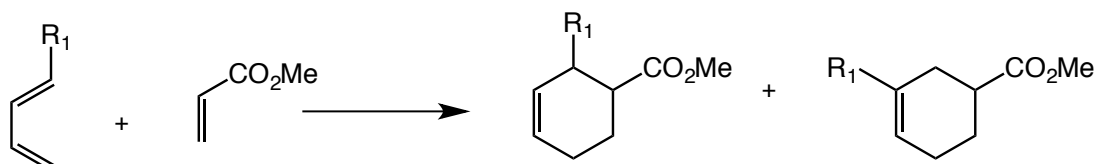
- “*ortho*” and “*para*” products are favored over “*meta*” products
- may be explained by the electronic effects from the substituents R_1 and R_2 creating partial negative or positive charges on the diene and dienophile.
- Lewis acid catalysts decrease the activation energy, favoring the endo-cycloaddition and the *ortho/para* products over *meta*
- the percentage of the “*meta*” product can be observed with an increase of electron-withdrawing groups on the diene
- “*meta*” product ratio is always less

para-favored



R	1,4-product (<i>para</i>)	1,3-product (<i>meta</i>)
Ph	80	20
Me	70	30
CF ₃	55	45

ortho-favored

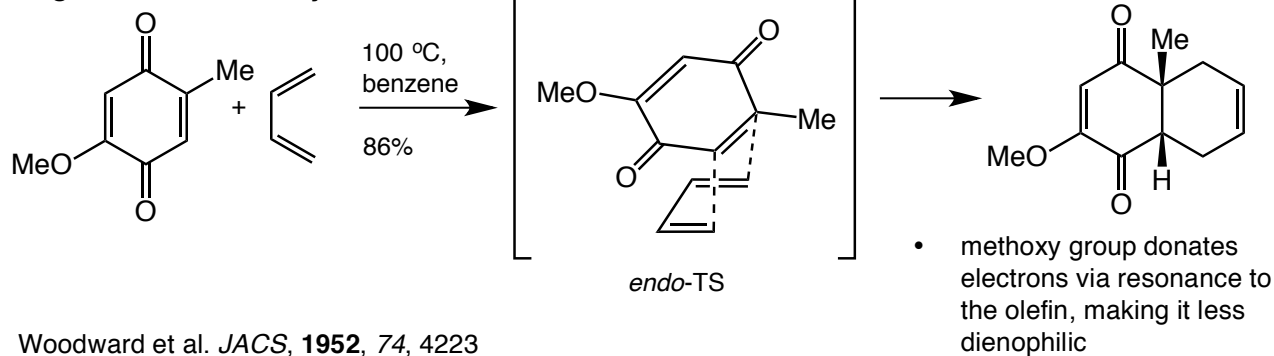


R	1,2-product (<i>ortho</i>)	1,3-product (<i>meta</i>)
Me	90	10

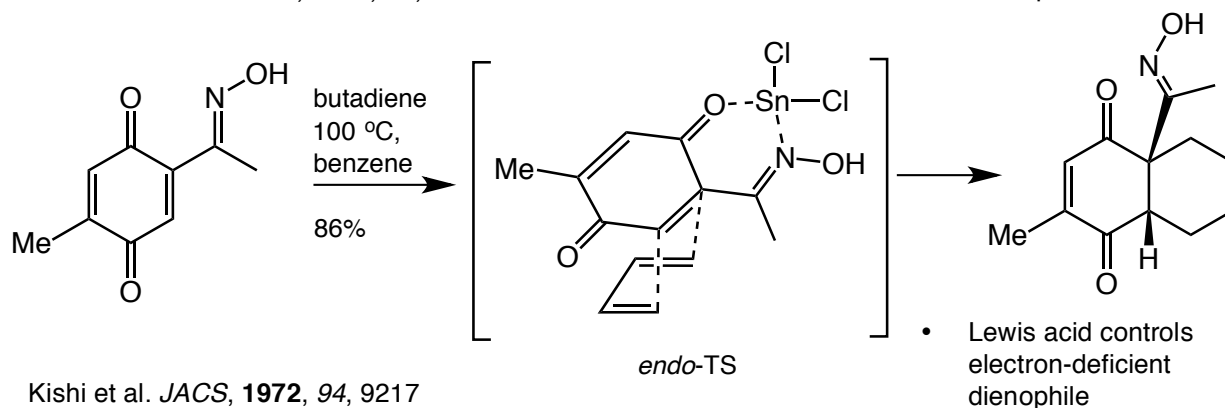
Inukai, Kojima *J. Org. Chem.*, **1971**, *36*, 924

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Regiocontrol in Total Synthesis

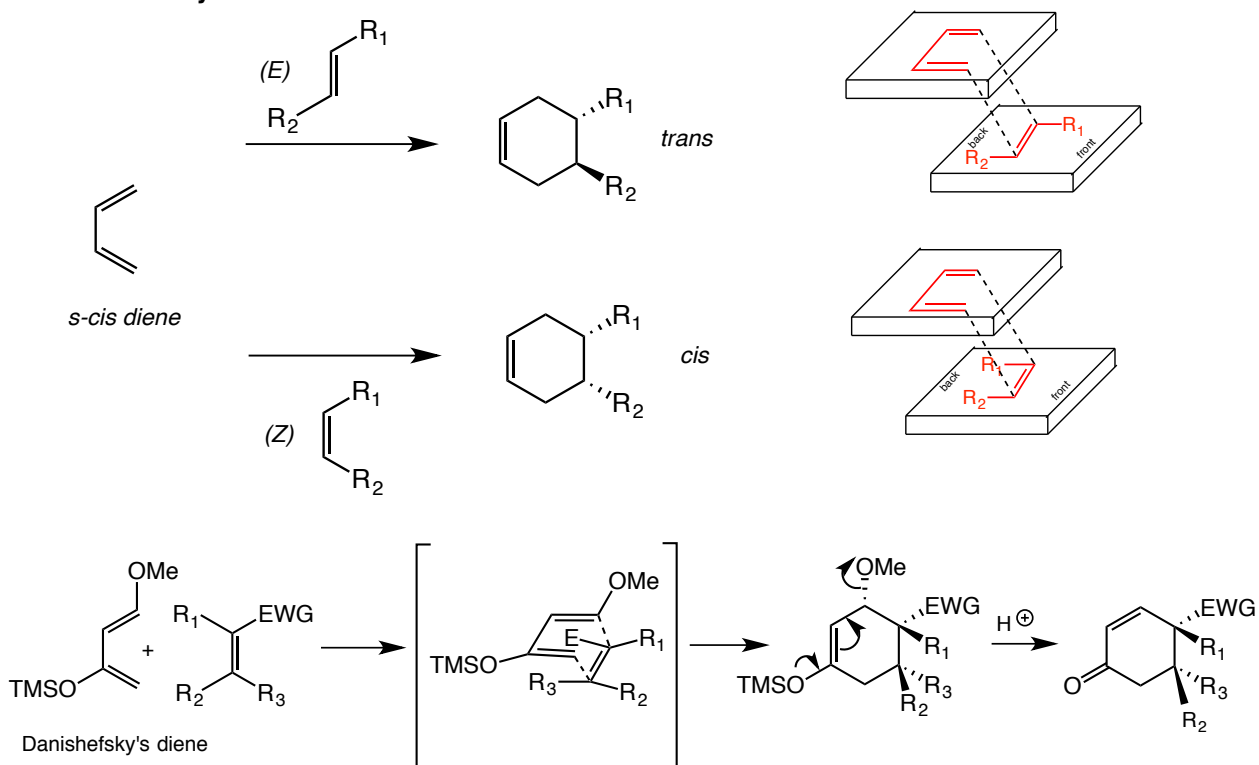


Woodward et al. *JACS*, **1952**, 74, 4223



Kishi et al. *JACS*, **1972**, 94, 9217

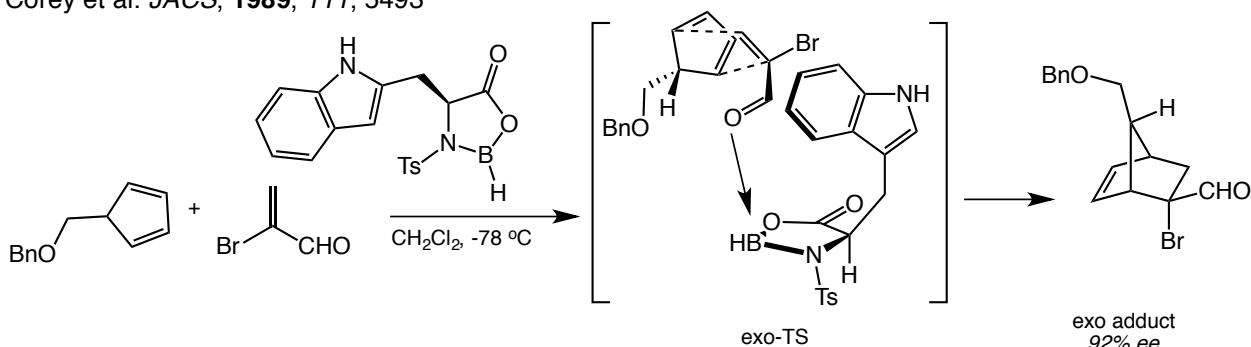
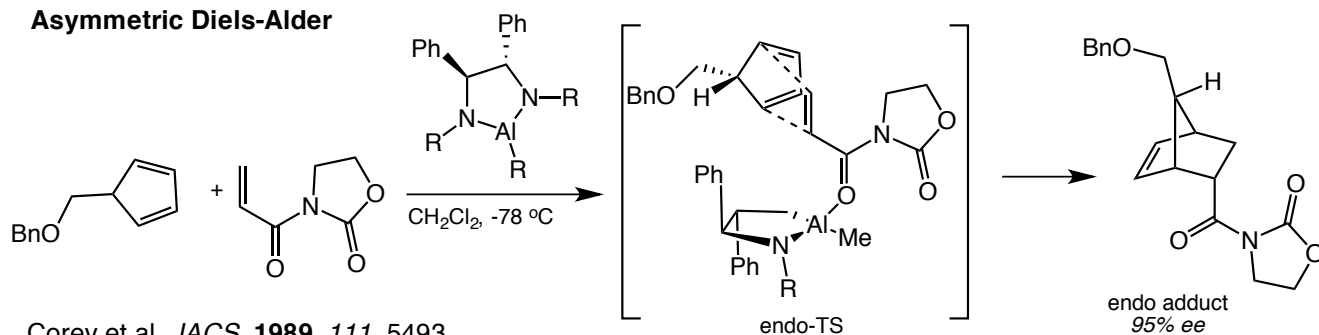
Stereoselectivity



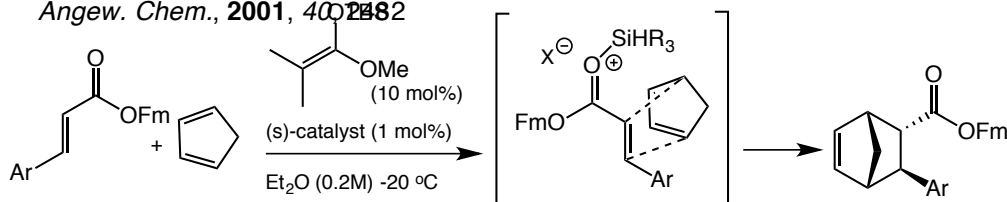
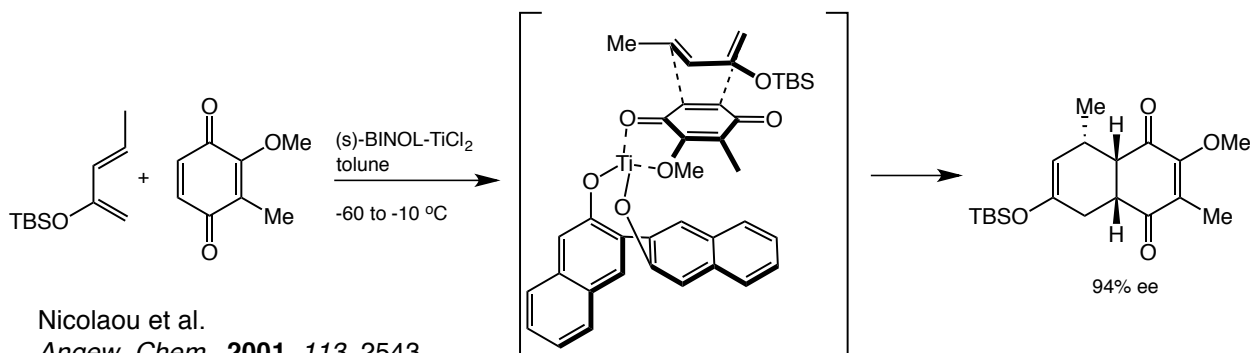
Danishefsky, Kitahara *JACS*, **1974**, 96, 7807

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Asymmetric Diels-Alder

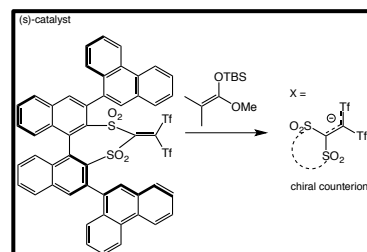


Lewis acid catalyzed asymmetric Diels-Alder



- silylium ion as lewis acid catalyst
- chirality at the counterion
- Aromatic groups can be electron rich or deficient
- >90% ee

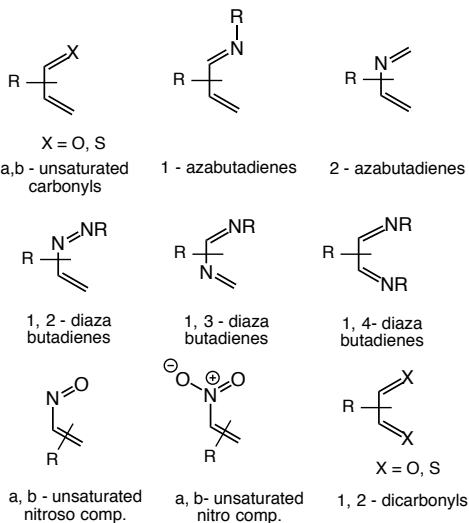
Gatzenmeier, Gemmeren *Science*, **2016**, *26*, 949



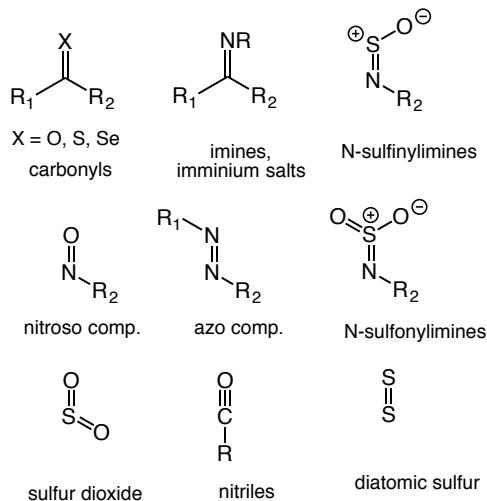
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Hetero Diels-Alder Reaction

Common Heterodienes:

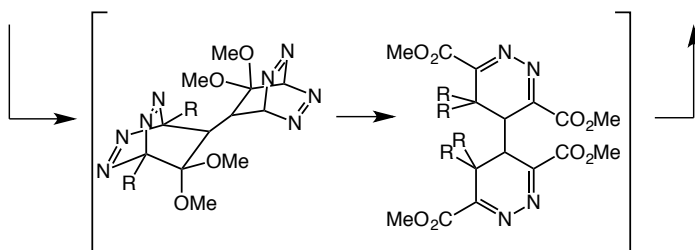
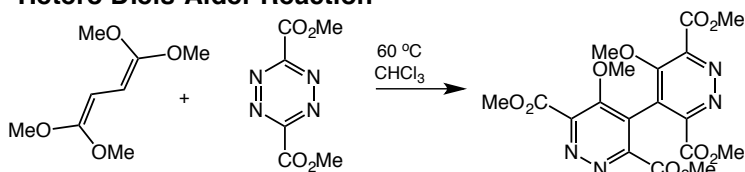


Common Heterodienophiles:



- Normal D-A reaction: diene and heterodienophile (electron-deficient); or heterodiene (electron-rich) and non-heterodienophile can be used
- Inverse D-A reaction: heterodiene (electron-withdrawing) and dienophile; or diene and heterodienophile (electron-rich) can be used

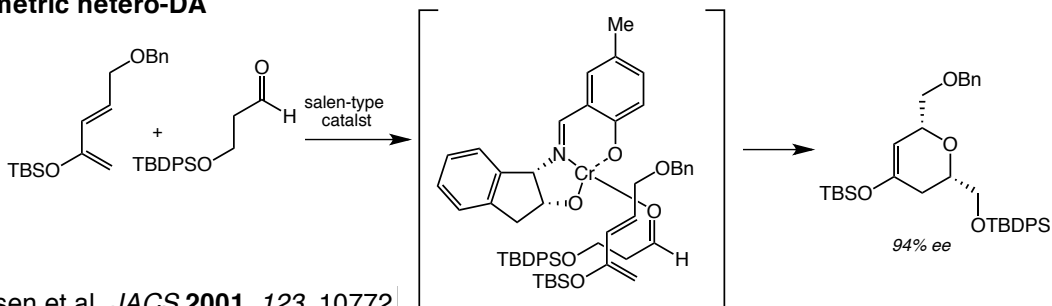
Hetero Diels-Alder Reaction



- Double azadiene DA, following retro-DA to aromatize to final product

J. Am. Chem. Soc. **1993**, *115*, 11418

Asymmetric hetero-DA



Jacobsen et al. *JACS* **2001**, *123*, 10772