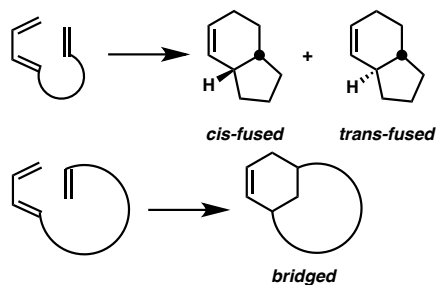


Intramolecular Diels-Alder Reaction (IMDA)

Reference: Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, 38, 2983.
 Vavsari, V. F.; Heravi, M. M. *RSC Adv.* **2015**, 5, 50890
 Roush, W. R., Intramolecular Diels-Alder Reactions; *In Comprehensive Organic Synthesis*;
 Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5,
 p 513–550

Type I and Type II:

- **Type I: tether is attached at the 4-position of the diene.**

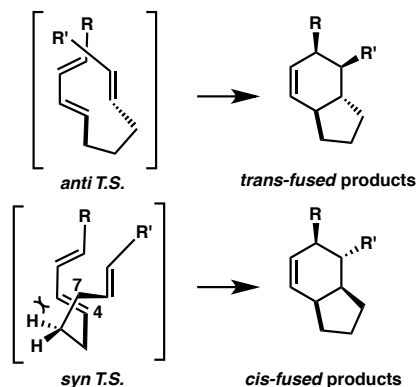


- * Fused products usually have 3- or 4-atom tethers.
- * Bridged products are rarely observed (tether must be >9 atoms)

- **Syn vs. Anti Transition State:**

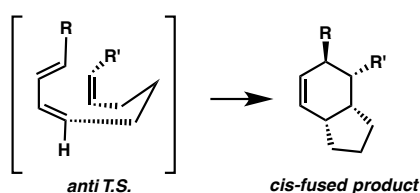
- * To determine the stereochemistry of the IMDA, both **steric** and **electronic** factors should be considered.
- * Although the IMDA is concerted, bond formation is **asynchronous** in the transition state.
- * Effects of asynchronicity are less pronounced for decatriene systems.

- **E-diene:**



- * The representative example above with *E*-diene, *anti* T.S. is **sterically** favored, and *syn* T.S. experiences non-bonding interactions between C4-C7.
- * Internal bond formation is more advanced in the T.S. -> *anti* T.S., *trans* product.
- * External bond formation is more advanced in the T.S. -> *syn* T.S., *cis* product.

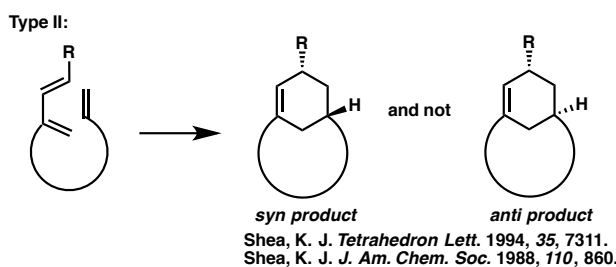
- **Syn vs. Anti Transition State of Z-diene:**



- * No matter the length or nature of the tether, **cis-fused** adduct is the only product.

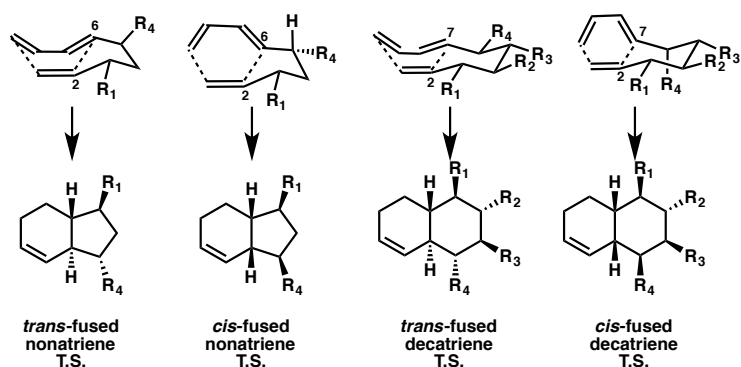
Intramolecular Diels-Alder Reaction (IMDA)

- **Type II: tether is attached at 3-position of diene:**



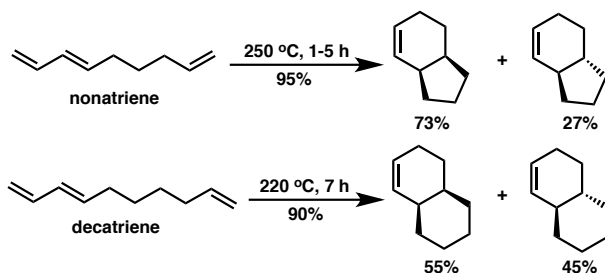
- * Type II IMDA is always cyclized to **syn product** not *anti product* (Bredt's rule says that <4 atom tether won't work).

- **Diastereoselectivity of the IMDA Reactions:**



- * Diastereoselectivity in the IMDA reactions of conformationally mobile, monosubstituted 1,6,8-nonatrienes and 1,7,9-decatrienes: **sterically favored T.S.**

- **Unactivated Trienes:**

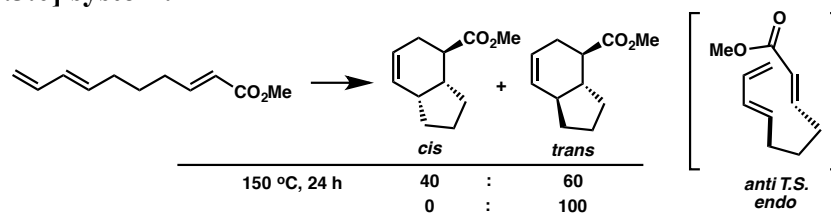


- * The ratios of product can be improved or reversed by using substituents on the triene or additives such as Lewis acids.
- * In both systems, some preference for *cis*-fused products.

- **Terminally Activated Dienophiles:**

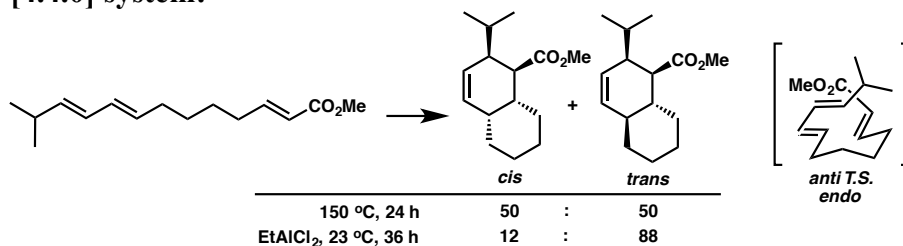
- * *E*-dienophiles, [4.3.0] and [4.4.0] bicycles

[4.3.0] system:



Intramolecular Diels-Alder Reaction (IMDA)

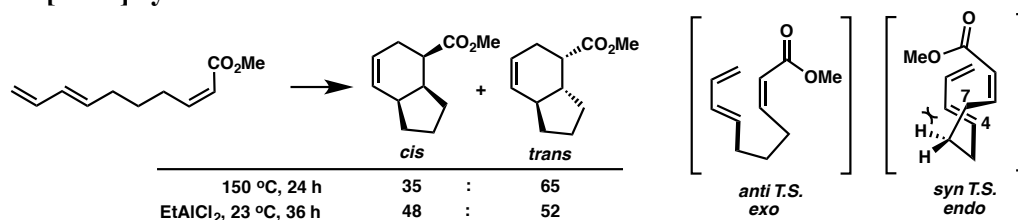
[4.4.0] system:



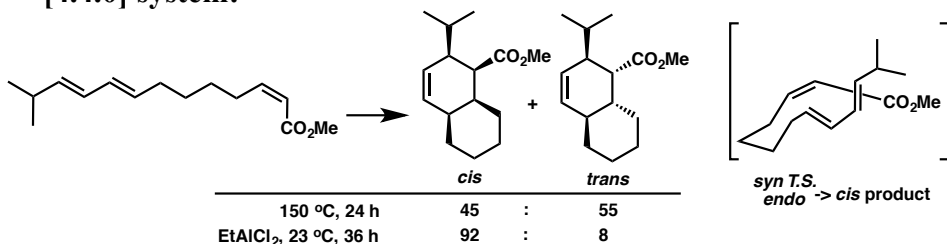
* Terminally activated *E*-dienophiles are **sterically** and **electronically** favored to give *trans* products.

* *Z*-dienophiles, [4.3.0] and [4.4.0] bicycles

[4.3.0] system:



[4.4.0] system:

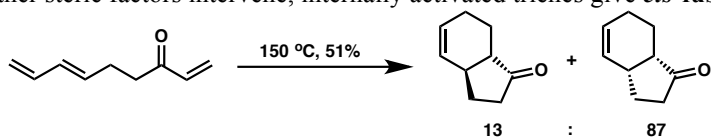


* *Trans* product is favored **sterically** and *cis* product is favored **electronically** with terminally activated *Z*-dienophiles.

• Internally Activated Dienophiles [4.3.0] and [4.4.0] Bicycles:

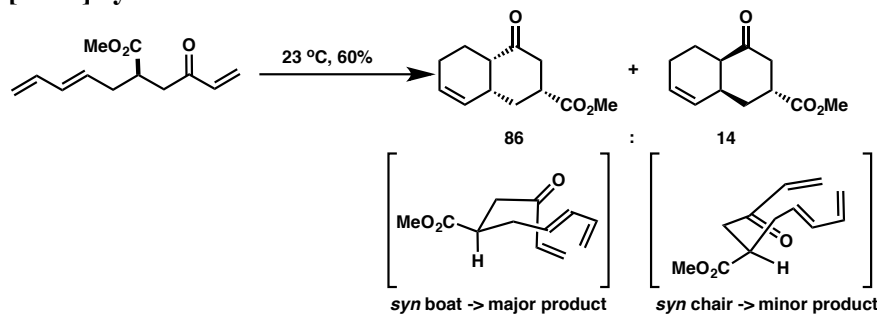
[4.3.0] system:

* Unless other steric factors intervene, internally activated trienes give *cis*-fused products.



Roush, W. R. *J. Am. Chem. Soc.* 1981, 103, 6696

[4.4.0] system:



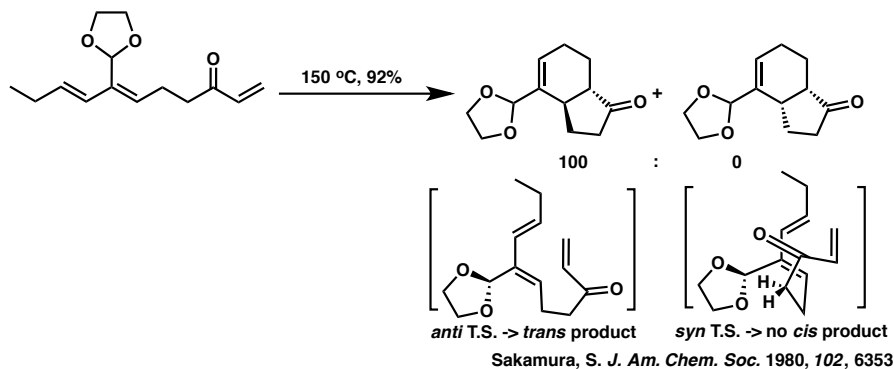
Zschiesche, R. *Angew. Chem. Int. Ed. Engl.* 1986, 25, 1086

* Decatrienes with internal carbonyls adjacent to dienophile cyclized through boat T.S. to give *cis*-fused products.

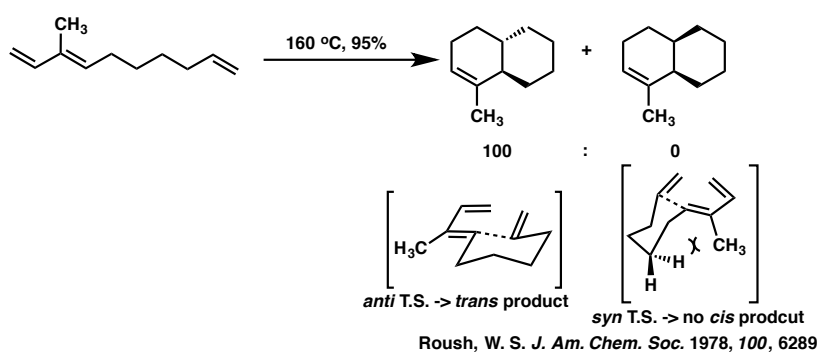
Intramolecular Diels-Alder Reaction (IMDA)

- Internally Substituted Dienes [4.3.0] and [4.4.0] Bicycles:

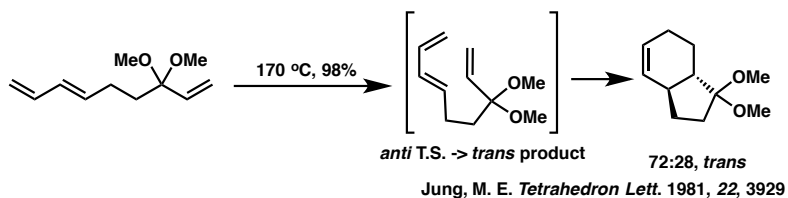
* [4.3.0] system:



* [4.4.0] system:

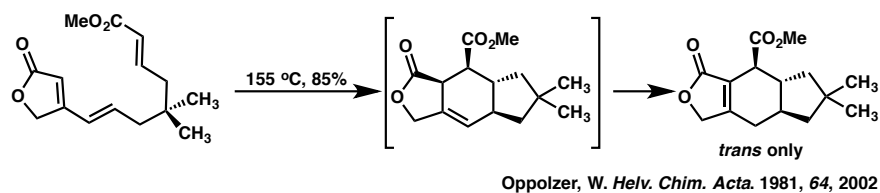


- Effects of Substitution on tether:
[4.3.0], α,α -disubstitution system



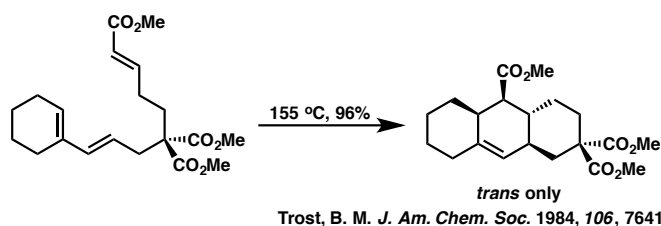
* Nonbonding interactions in *anti* T.S. give predominantly *trans* product.

[4.3.0], β,β -disubstitution system



Intramolecular Diels-Alder Reaction (IMDA)

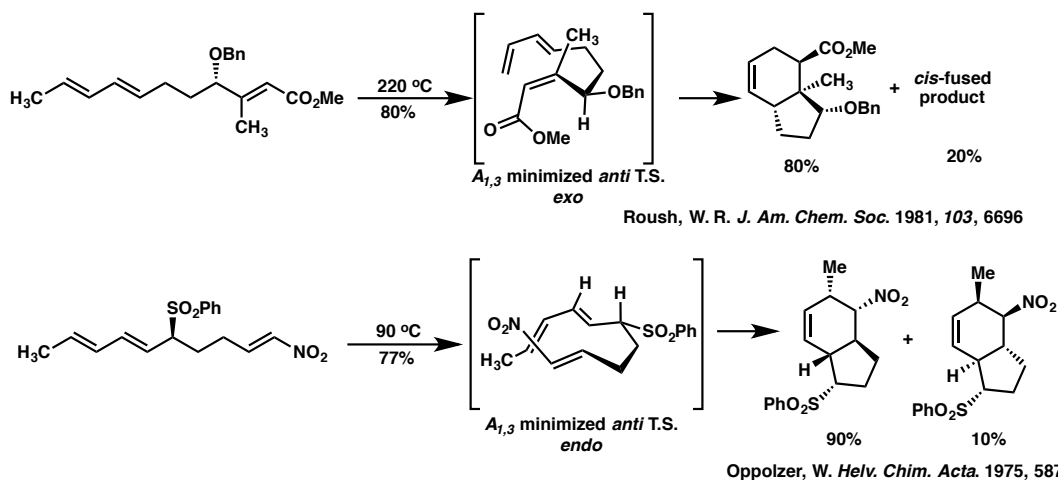
[4.4.0], dialkyl substitution system



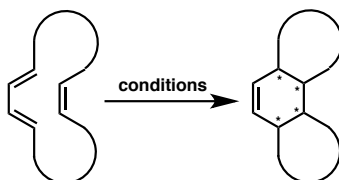
* Thorpe-Ingold effect: Dialkyl substitution improved the reaction rates.

$A_{1,3}$ effect:

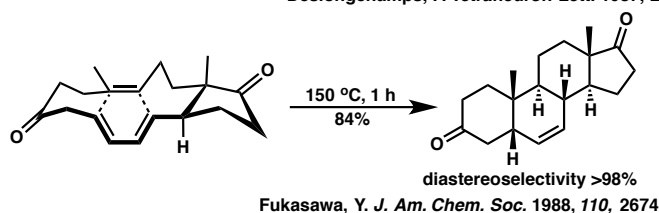
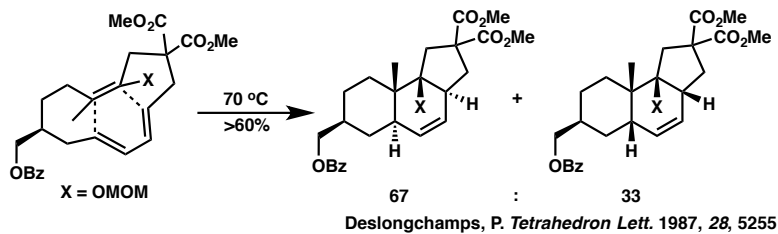
[4.3.0], stereocenter adjacent to dienophile



• Transannular Intramolecular Diels-Alder Reactions (TADA):



* Transannular intramolecular Diels-Alder reactions are a subgroup of IMDA reactions, and are often very chemo-, regio-, and stereo-selective processes in general.

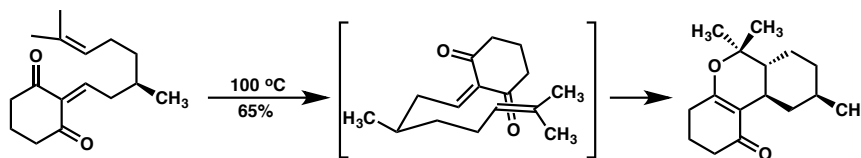


* An important synthetic method to form a polycyclic ring system.

Intramolecular Diels-Alder Reaction (IMDA)

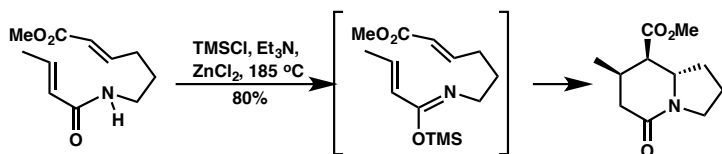
- Formation of Heterocycles *via* IMDA:

- Heterodienes:



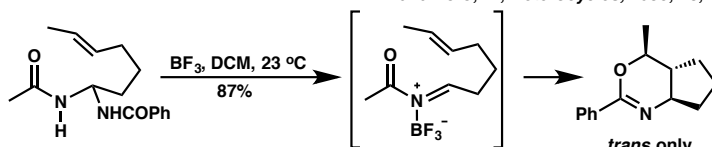
Jung, M. E., *J. Org. Chem.* 1982, 47, 1084

- * Because of the stereocenter at the 3-position of the diene, the methyl is placed equatorial in a chair-like T.S. and promotes an *anti* T.S. to give the only product.



trans : *cis* = 90 : 10

Fukumoto, K., *Heterocycles*, 1985, 23, 1097



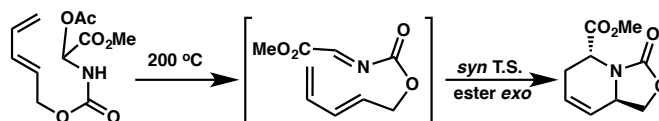
trans only

Weinreb, S. M. *J. Org. Chem.* 1986, 51, 3248

- * The diastereoselectivity of the substrates with diene heteroatoms follows the same rules as all-carbon dienes.

- Heterodienophiles:

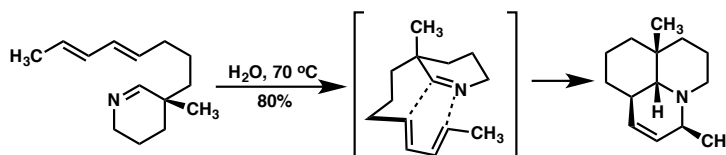
- Acyl-amine dienophile:



Weinreb, S. M. *J. Am. Chem. Soc.* 1981, 103, 7573

- * One diastereomer is obtained. It is usually the opposite diastereomer as when the all-carbon triene is used.

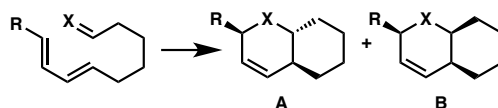
- Imino dienophile:



Grieco, P. A. *J. Org. Chem.* 1999, 64, 6041-8

Intramolecular Diels-Alder Reaction (IMDA)

- **Other Heterodienophile:**



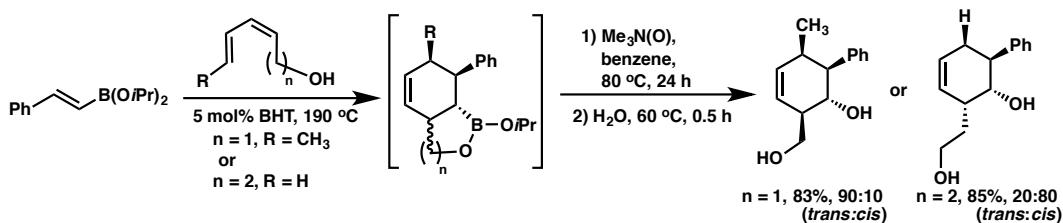
X	R	conditions	yield	selectivity (A:B)
NBz	Me	70 °C	63%	71:29
Se	Me	55 °C	70%	45:55
S	H	36 °C	71%	33:67

Grieco, P. A. *J. Am. Chem. Soc.* 1985, 107, 1768
 Segi, M. *Tetrahedron Lett.* 1988, 29, 6965
 Wilde, R. G. *J. Org. Chem.* 1988, 53, 2220

* Heteroatom substituents at the dienophile terminus have a significant effect on diastereoselectivity.

- **Removable Tethers for IMDA Reactions:**

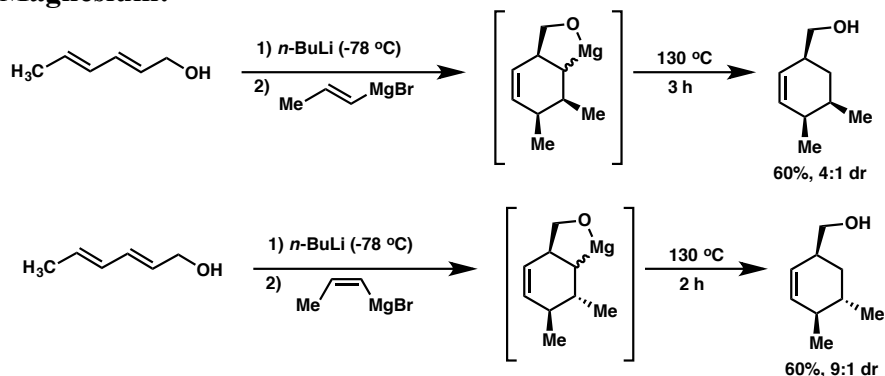
- * **Boron:**



Batey, R. A. *J. Am. Chem. Soc.* 1999, 121, 450-1

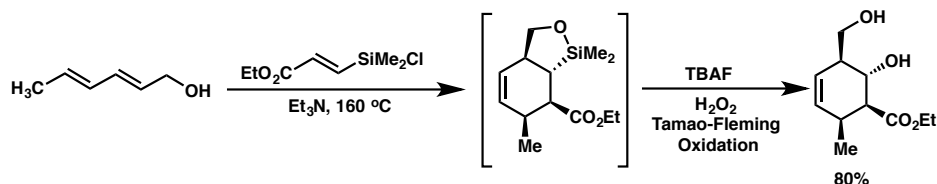
* Notice that the diastereoselectivity was not the same when different chains were applied.

- **Magnesium:**



Stork, G. *J. Am. Chem. Soc.* 1995, 117, 6595

- **Silicon:**



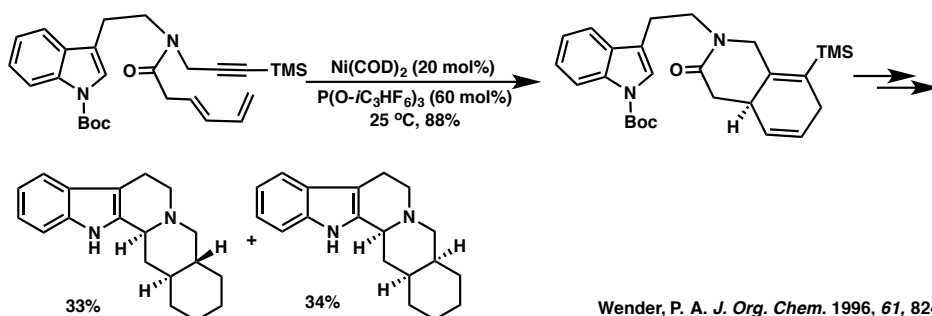
Stork, G. *J. Am. Chem. Soc.* 1992, 114, 7578

* IMDA of silyl ether gave *trans*-fused product.

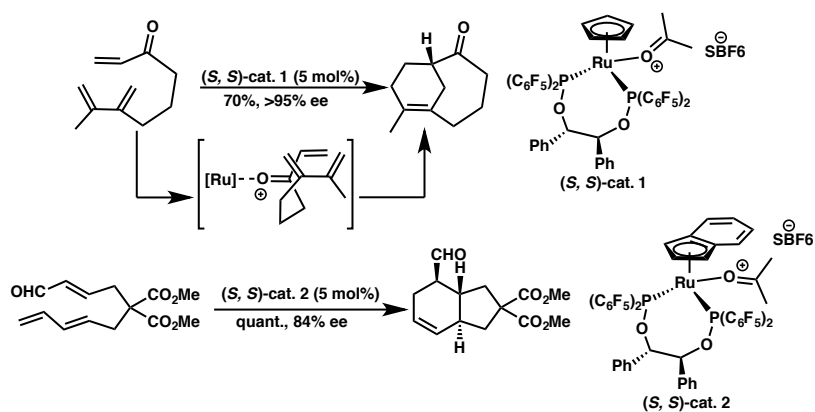
* Reference of other removable tethers for IMDA: Metz, P. *Tetrahedron*, 2000, 56, 873; Overman, L. E. *J. Am. Chem. Soc.* 1999, 121, 700.

Intramolecular Diels-Alder Reaction (IMDA)

- Transition Metal-Catalyzed IMDA:**



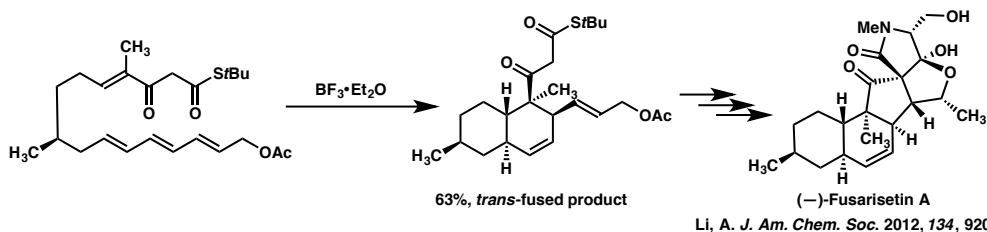
- * The alternative thermal reaction to form the IMDA product required a temperature of 150 °C, which caused the cleavage of the Boc protecting group and lowered the yield to 45%.



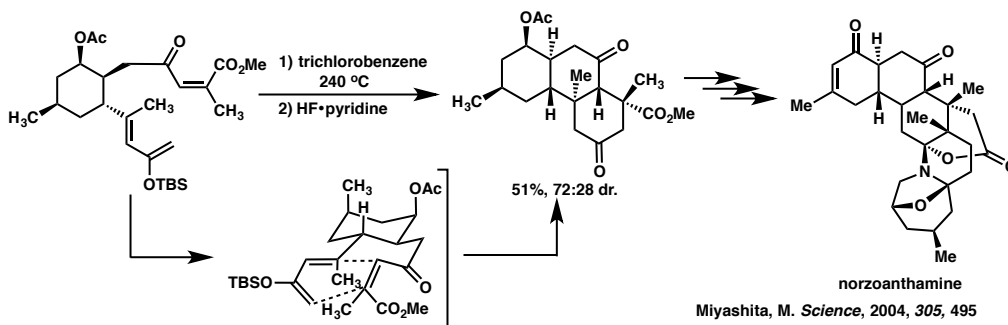
- * Ruthenium catalysts could act as a Lewis acid to promote Type I and Type II IMDA reactions.

- The Application of IMDA in the Total Synthesis of Natural Products.**

- Type I IMDA reactions:**

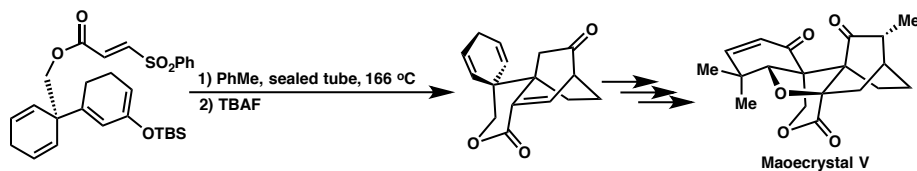


- * The key step in the total synthesis of (–)-Fusarisetin A used a type I IMDA to afford the *trans*-fused decalin core with a Lewis acid catalyst.



- * The IMDA product was formed *via* the *exo* transition state.

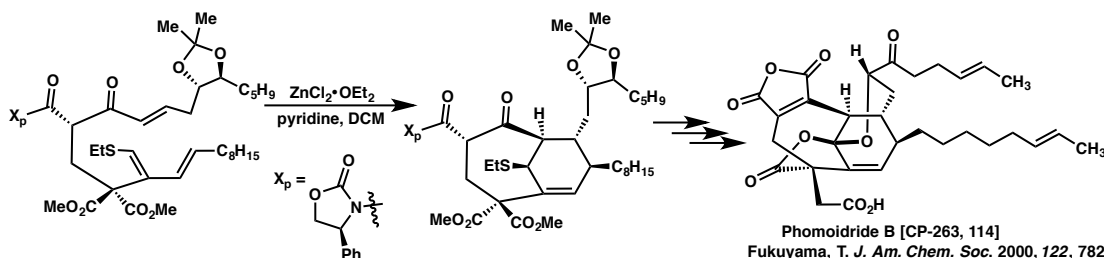
Intramolecular Diels-Alder Reaction (IMDA)



Danishefsky, S. J. *Tetrahedron Lett.* 2011, 52, 2104

- * After the IMDA reaction, upon exposure to TBAF, the TBS group was hydrolyzed, and the phenyl sulfone part spontaneously eliminated to give the pentacyclic core.

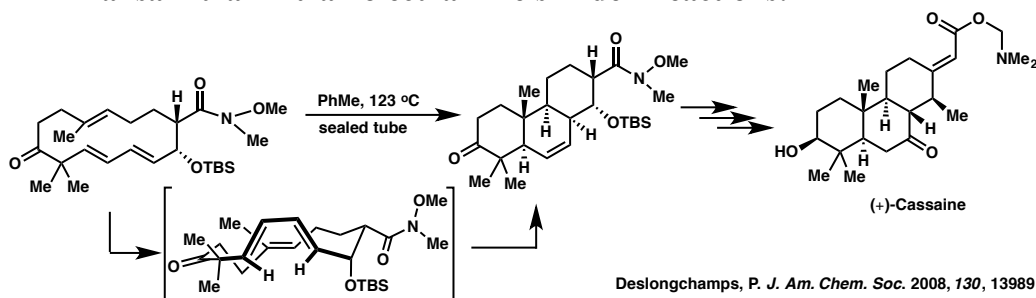
Type II IMDA Reactions:



Fukuyama, T. *J. Am. Chem. Soc.* 2000, 122, 7825

- * The reaction underwent an IMDA reaction smoothly at room temperature, and the crude was used directly in the next step. The overall yield was 53%.

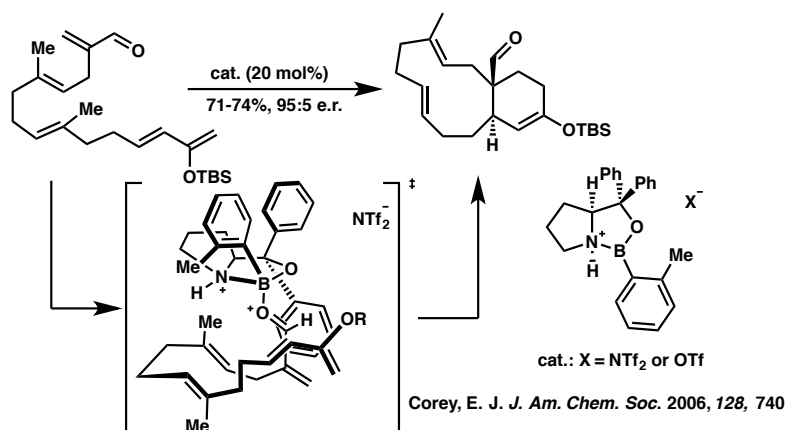
Transannular Intramolecular Diels-Alder Reactions:



Deslongchamps, P. *J. Am. Chem. Soc.* 2008, 130, 13989

Asymmetric IMDA Reactions:

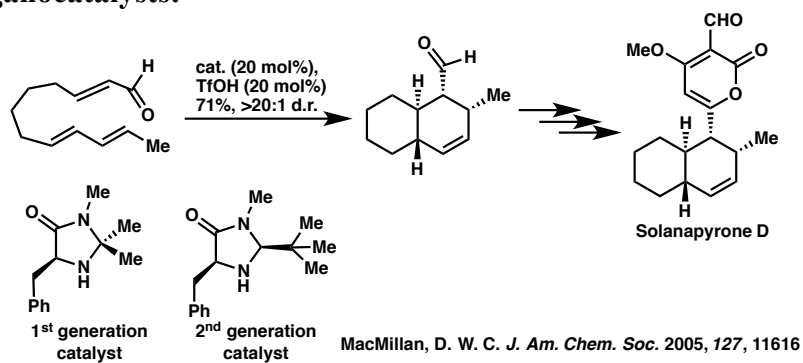
Corey's cationic oxazaborolidine catalysts:



- * Cationic oxazaborolidine catalysts have been applied to the synthesis of the dolabellane natural products. Simple achiral Lewis acids such as Me₂AlCl, MeAlCl₂, or EtAlCl₂ did not promote the reaction to give the racemic product.

Intramolecular Diels-Alder Reaction (IMDA)

- **Organocatalysts:**



* The organocatalysts could react with aldehydes to form an iminium first, which lowered the energy of the LUMO.

* Other representative asymmetric IMDA reactions:

Chiral auxiliaries:

Mukaiyama, T. *Chem. Lett.* **1981**, 28.

Masamune, S. *J. Org. Chem.* **1983**, 48, 1137.

Oppolzer, W. *Tetrahedron Lett.* **1985**, 26, 5437.

Evans, D. A. *J. Am. Chem. Soc.* **1993**, 115, 4497.

Chiral acyloxyborane (CAB): Yamamoto, H. *J. Am. Chem. Soc.* **1996**, 118, 3049.

Ti-TADDOL:

Narasaka, K. *Tetrahedron: Asymm.* **1991**, 12, 1305.

Bis(oxazoline):

Evans, D. A. *J. Org. Chem.* **1997**, 62, 786.