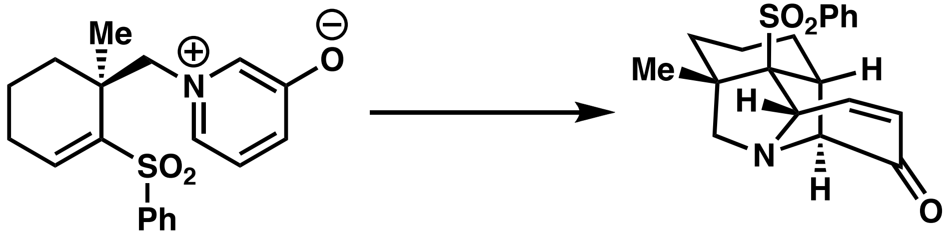
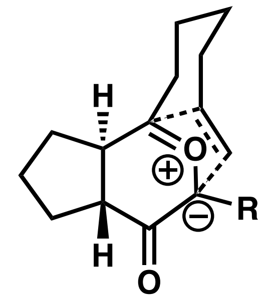


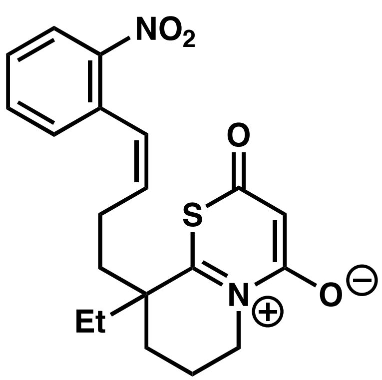


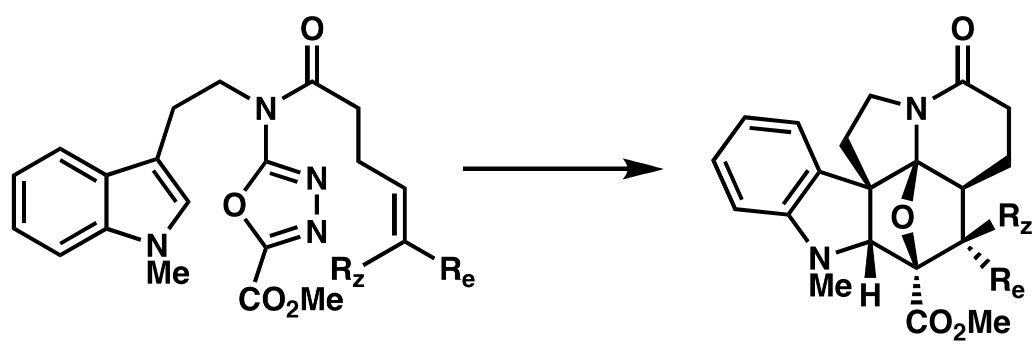
Dipolar Cycloadditions

You Love Them. You Hate Them. You Need Them.

Mike Meyer

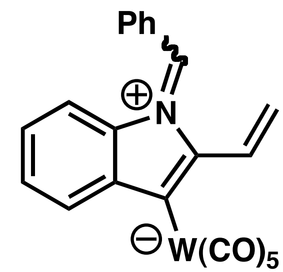
Stoltz Group Meeting, April 3rd, 2006





A Guide for the Discussion of Dipolar Cycloadditions:

1. Types and Classification of 1,3 Dipoles



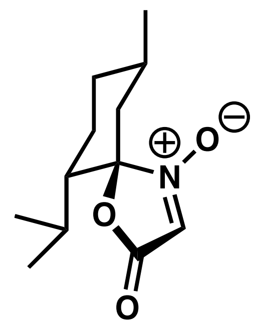
2. Molecular Theory Behind 1,3-Dipolar Cycloadditions

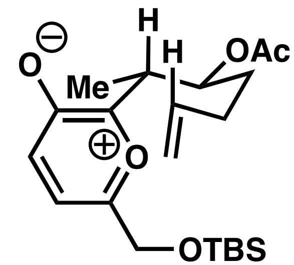
3. Types of Dipoles

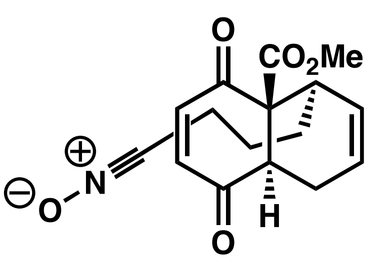
- **a. Nitrones**
- **b. Nitrile Oxides**
- **c. Carbonyl Ylides**
- **d. Diazoalkanes**
- **e. Azomethine ylides**
- **g. Miscellaneous**

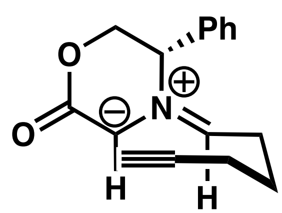
Good Sources:

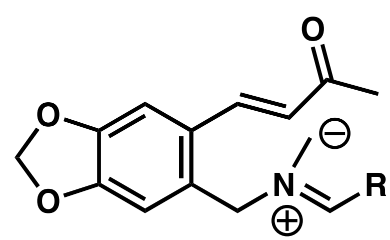
Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.
Gothelf,K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
Padwa, A. *Synthetic applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* John Wiley & Sons, **2002**, p. 269-301.







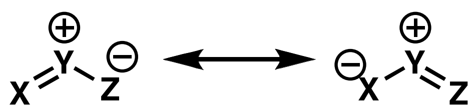




Types and Classification of 1,3-Dipoles

Two Types of Dipoles:

(1) Allyl anion

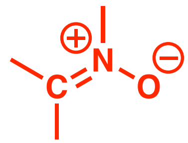


- Bent
- Y = N, O, S

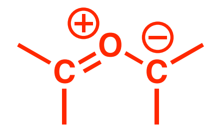
(2) Propargyl/allenyl anion

- Linear
- Y = Nitrogen

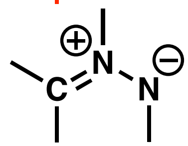
Classification of the Allyl Anion Type 1,3-Dipoles



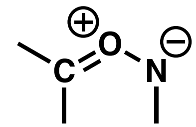
Nitrones



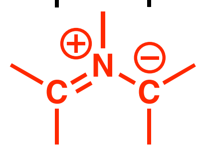
Carbonyl Ylide



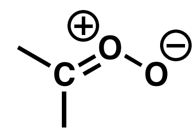
Azomethine Imines



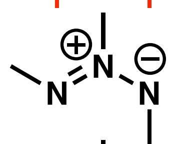
Carbonyl Imines



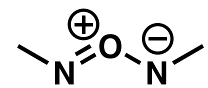
Azomethine Ylides



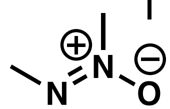
Carbonyl Oxides



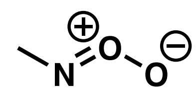
Azimines



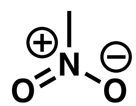
Nitrosimines



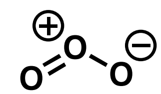
Azoxy Compounds



Nitrosoxides

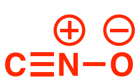


Nitro Compounds

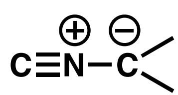


Ozone

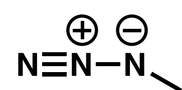
Classification of the Propargyl/Allenyl Anion Type 1,3-Dipoles



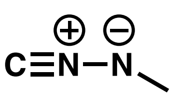
Nitrile Oxides



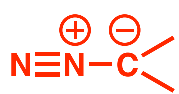
Nitrile Ylides



Azides



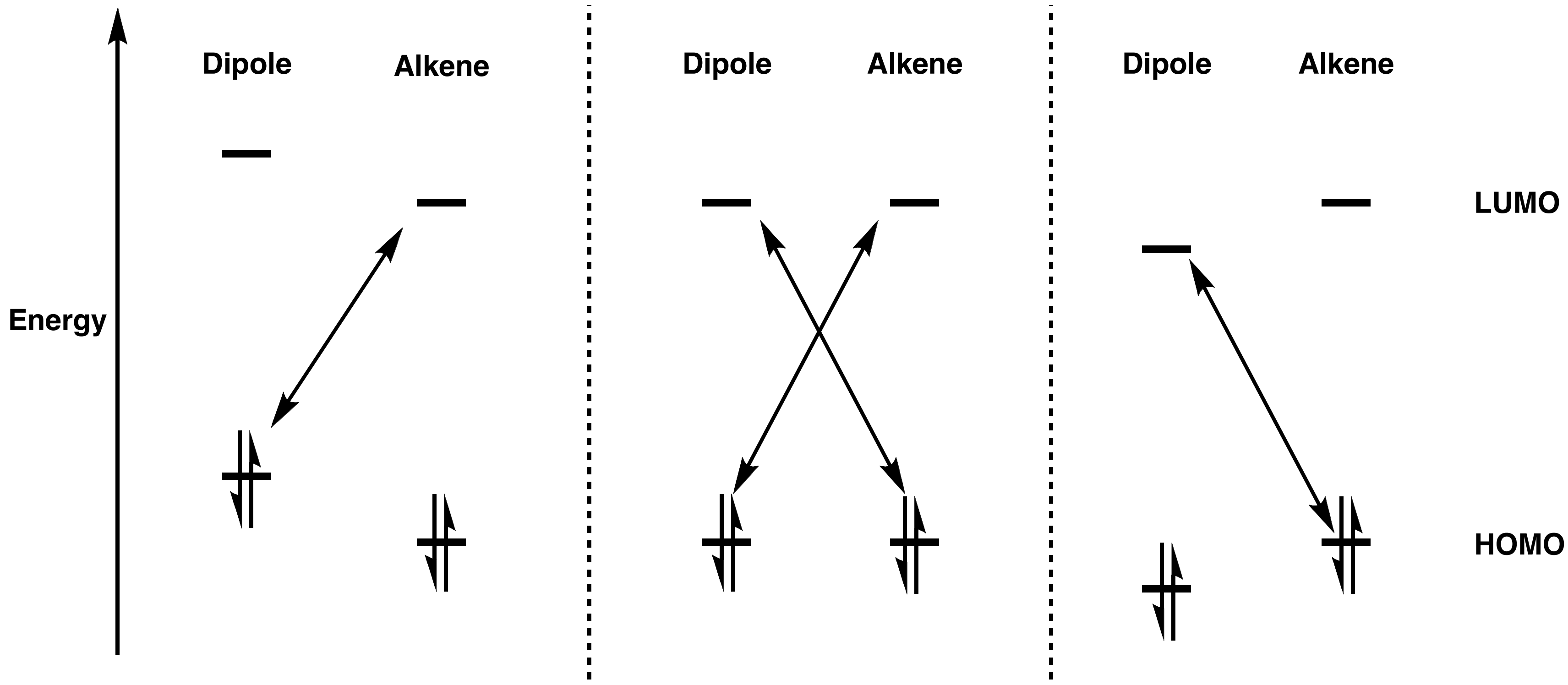
Nitrile Imines



Diazoalkanes

Nitrous Oxide

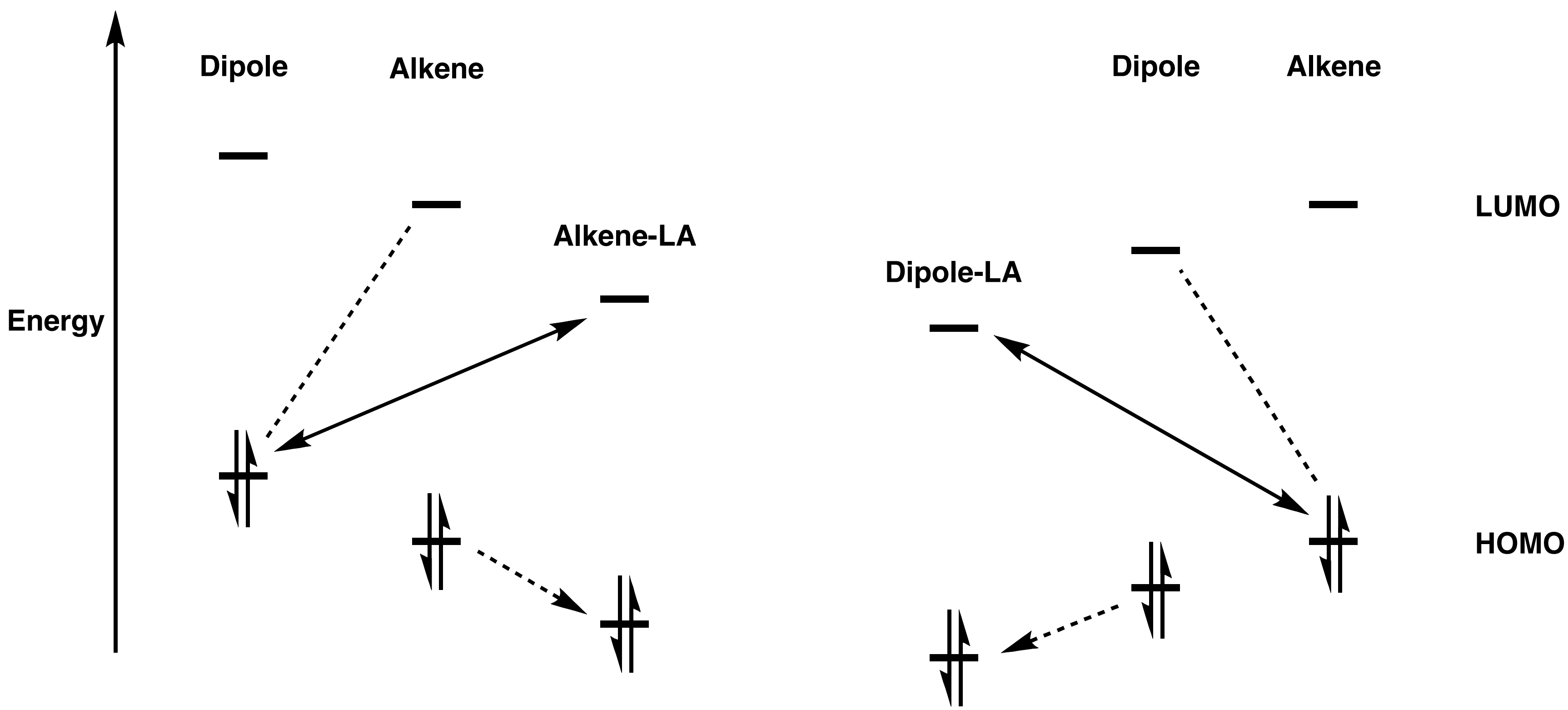
Molecular Theory Behind 1,3-Dipolar Cycloadditions



	Type I	Type II	Type III
	$HOMO_{dipole}-LUMO_{alkene}$	$HOMO_{dipole}-LUMO_{alkene}$ + $HOMO_{alkene}-LUMO_{dipole}$	$HOMO_{alkene}-LUMO_{dipole}$
Types of Dipoles	azomethine ylides, azomethine imines, nitrile ylides	nitrones, nitrile oxides	ozone, nitrous oxide

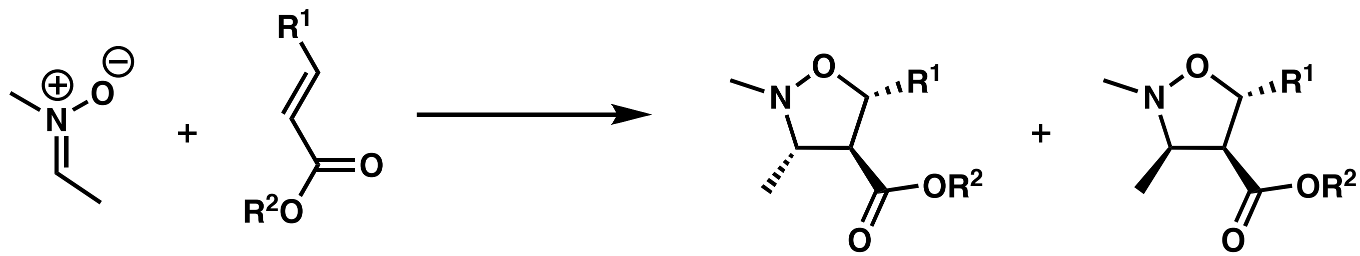
Molecular Theory Behind 1,3-Dipolar Cycloadditions (cont'd)

What about Lewis acid activation?



Coordination of the LA to either the dipole or the alkene results in LUMO lowering, and a faster reaction rate.

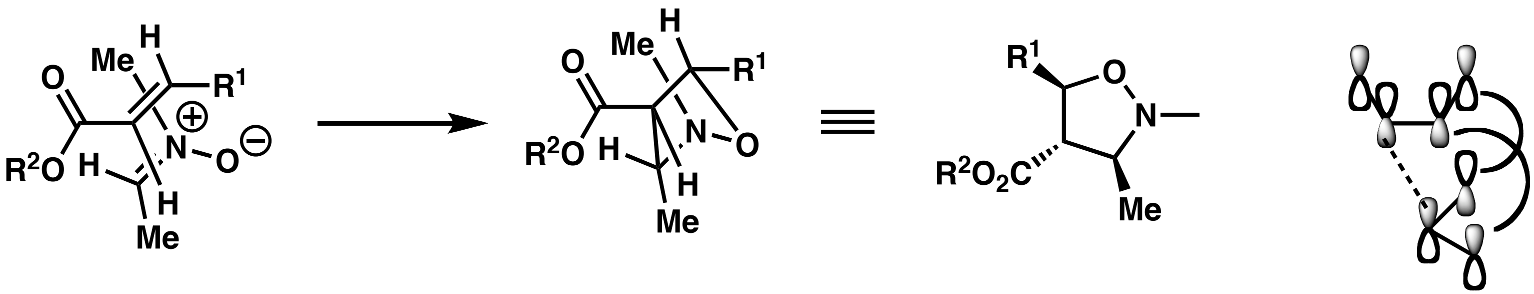
Another Consideration: Endo vs. Exo



endo *exo*

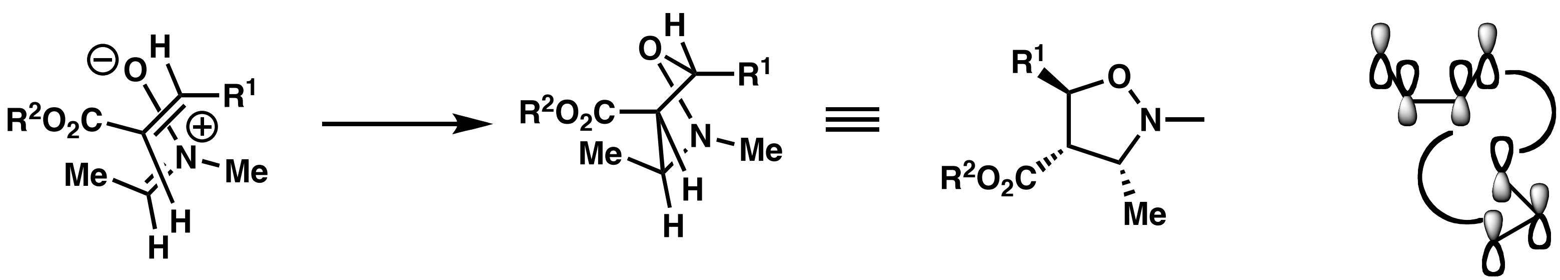
2 diastereomers (racemic)

Endo:



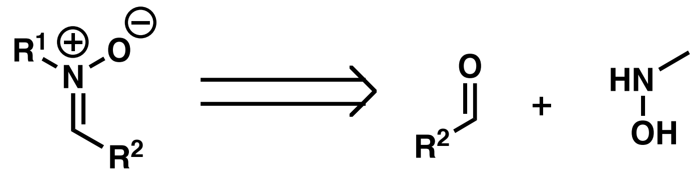
Secondary overlap is minimal

Exo:



A Usefull Dipole: Nitrones (a.k.a. Azomethine Oxides)

What is a nitrone?



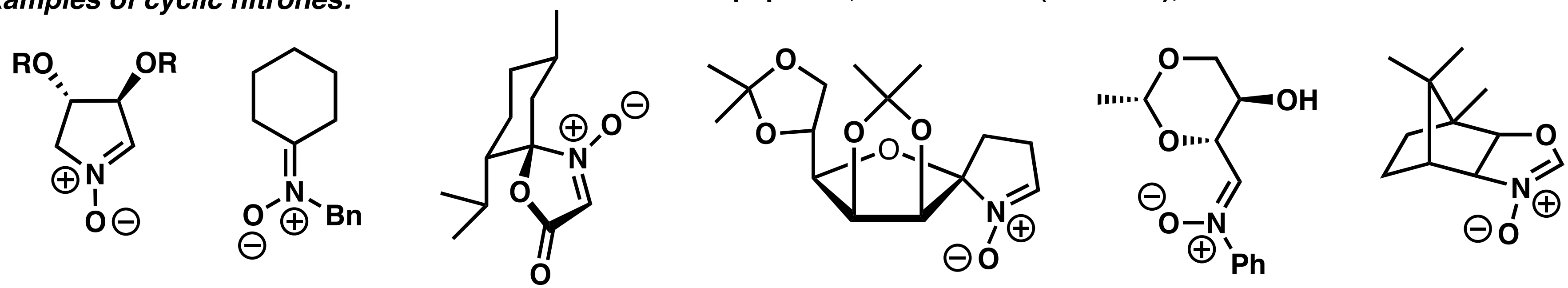
nitrone species

- E/Z mixtures of the nitrone can occur, resulting in mixtures of stereoisomers

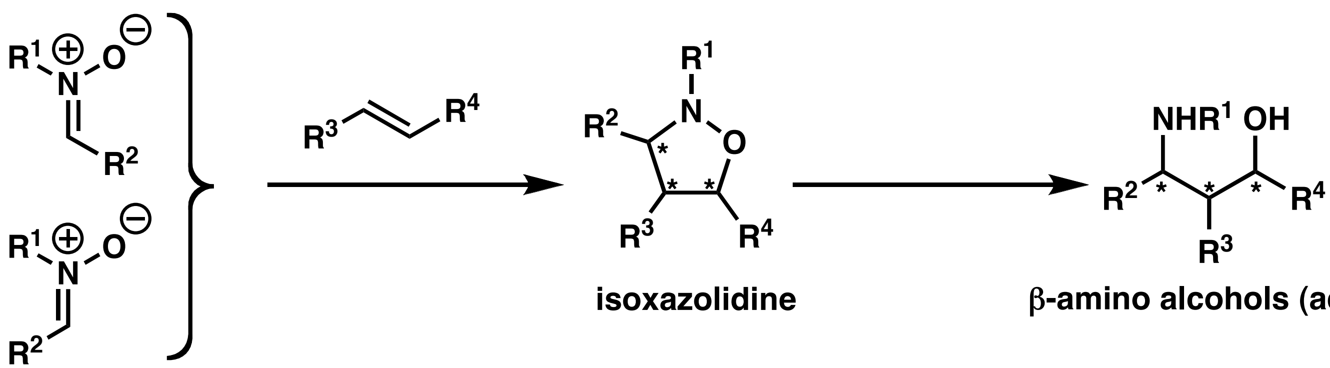
- Cyclic nitrones avoid geometrical isomers, and generally give better selectivity

- Dipolar cycloadditions with nitrones can produce: isoxazolidines, nucleosides, lactams, quinolizidines, indolizidines, pyrrolizidines, peptides, amino acids (alcohols), and more

Examples of cyclic nitrones:



Most common reaction with nitrones:



isoxazolidine

β-amino alcohols (acids)

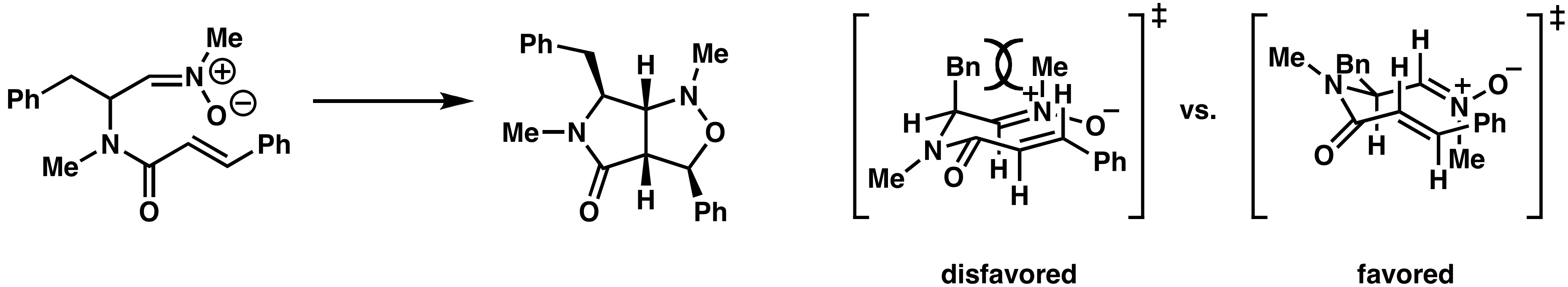
- 1,3-DC with nitrones can create upto three stereogenic centers

Nitrones: In the Beginning

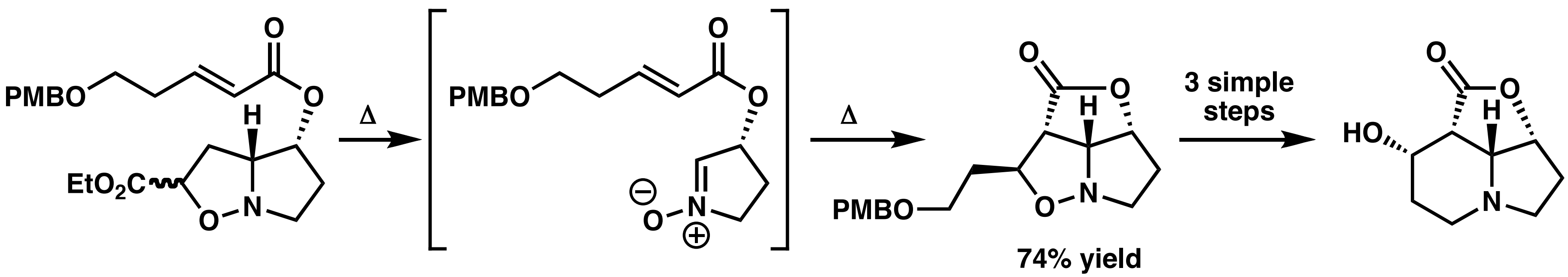
In the early 1970's, organic chemists began to use 1,3 DC to build complex intermediates and important building blocks in the realm of total synthesis.

- Huisgen was the first chemist to successfully prove that 1,3 DC occur through a concerted mechanism.

Some examples involving nitrones:



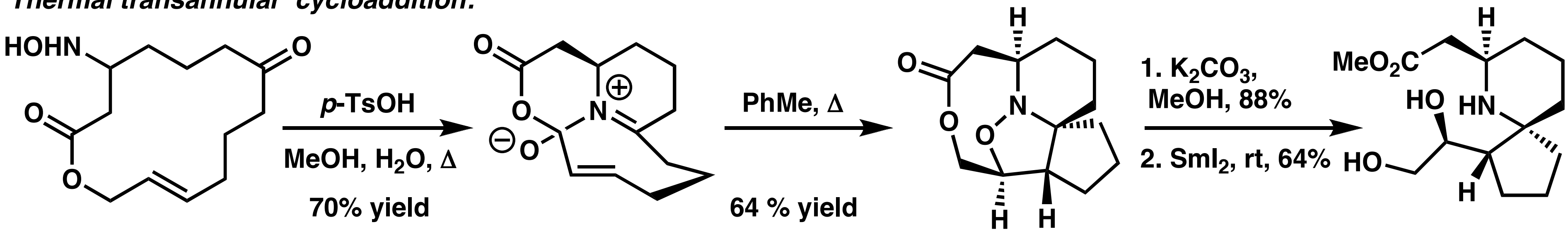
White, J. D., et. al.; *Tetrahedron*, **1989**, *45*, 6631.



Cordero, F.M., et. al.; *Org Lett.* **2000**, *2*, 2475.

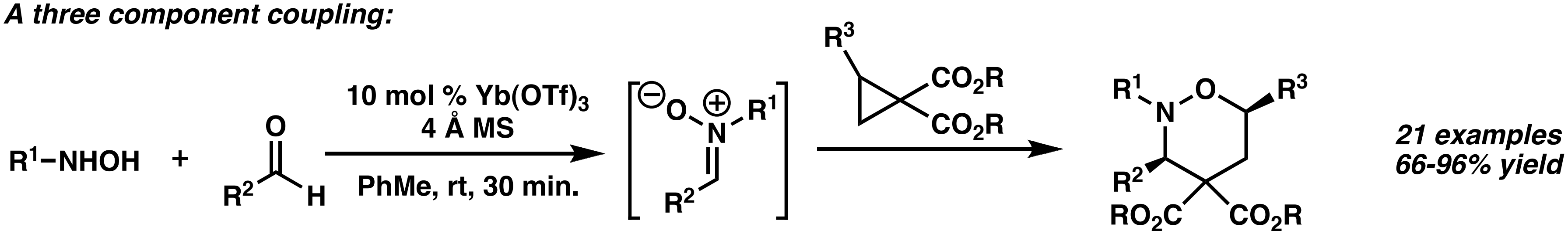
Nitrones: Getting More Complicated

Thermal transannular cycloaddition:



White, J. D., et. al.; *Org. Lett.* **2001**, *3*, 413.

A three component coupling:

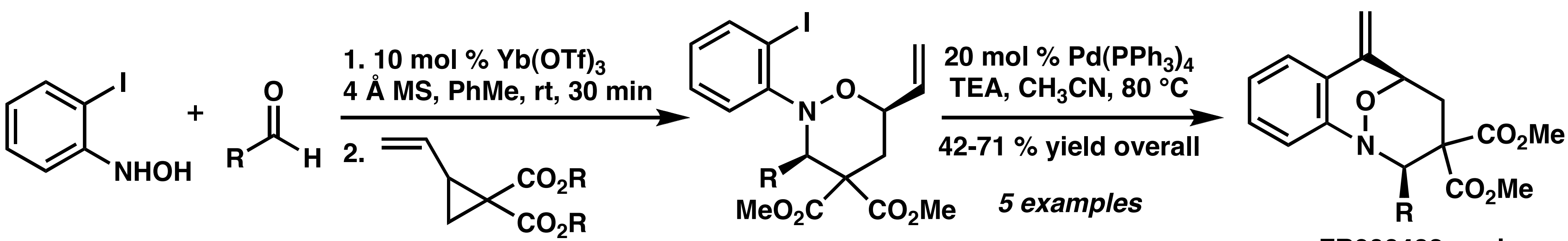


R^1 = aryl, benzyl

R^2 = alkyl, alkenyl, aryl, heteroaryl

R^3 =alkyl, alkenyl, phenyl, heteroaryl

tetrahydro-1,2-oxazines



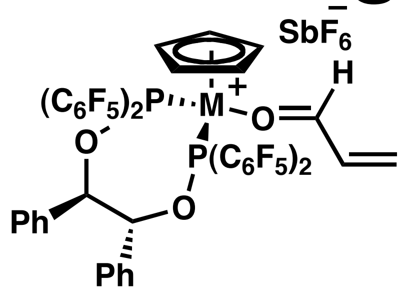
FR900482 analogs
antitumor, antibiotic

Young, I. S.; Kerr, M. A. *Org. Lett.* **2003**, *6*, 139.

For a cat. enantiosel. 1,3-DC using a heterochiral Yb catalyst, see: Kobayashi, JACS, **1998**, *120*, 5840.

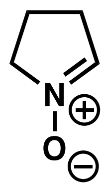
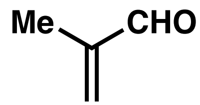
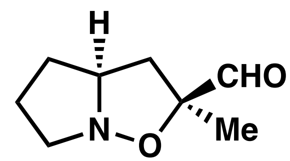
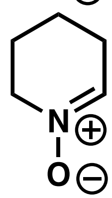
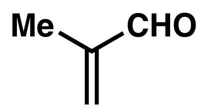
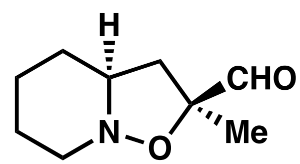
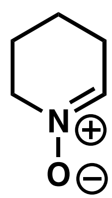
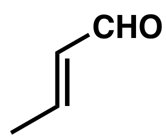
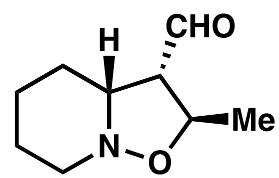
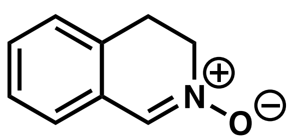
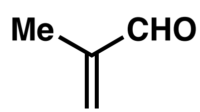
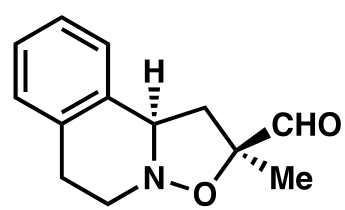
Examples of Asymmetric 1,3-Dipolar Cycloadditions using Nitrones

Chiral Metal Complex:



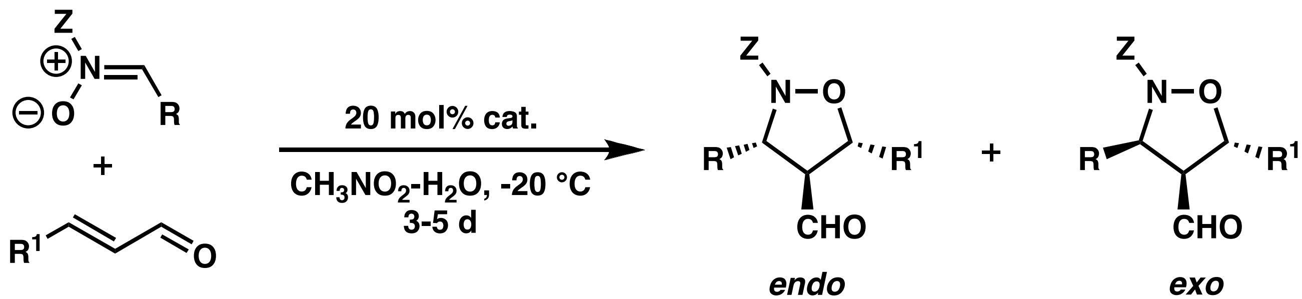
M = Fe, Ru

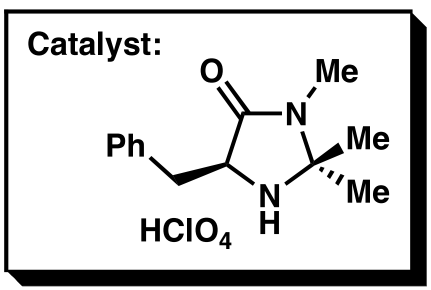
M = Fe for the following table

entry	nitrone	enal	yield (%)	product	ee (%)
1			92		96
2			71		>96
3			75		75
4			71		94

Kündig, E. P., et. al.; *J. Am. Chem. Soc.* **2002**, *124*, 4968.
For a similar system using a Co(salen)* complex, see: Yamada, T., et. al.; *Org Lett.* **2002**, *4*, 2457.
For a similar system using a bis-TiL_2* complex, see: Maruoka, K., et. al.; *J. Am. Chem. Soc.* **2005**, *127*, 11926.

The One and Only, Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition using Nitrones





Note: The shown table is abbreviated.

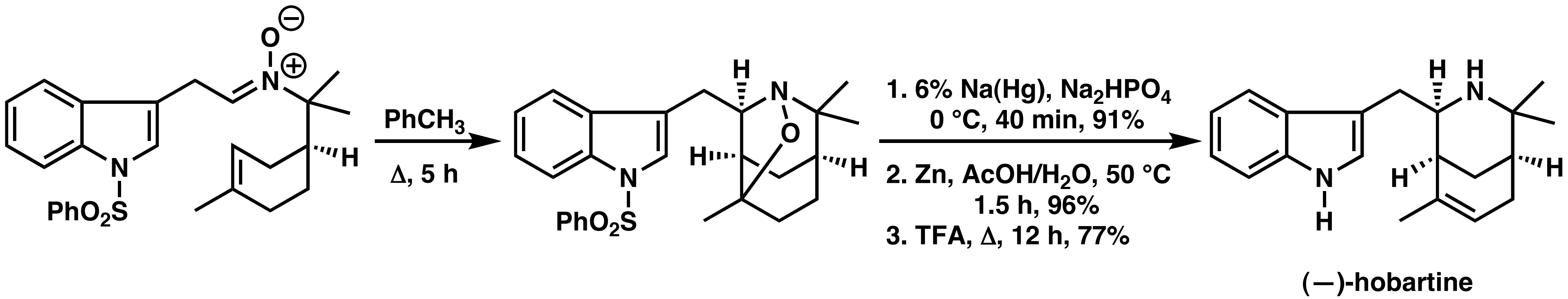
Overall: *15 examples*
70-98% yield
90-99% ee

entry	Z	R	R^1	*endo:exo*	yield	% ee (*endo*)
1	Bn	Ph	Me	94:6	98	94
2	Allyl	Ph	Me	93:7	73	98
3	Me	Ph	Me	95:5	66	99
4	Bn	C_6H_4Cl-4	Me	92:8	78	95
5	Bn	Cy	Me	99:1	70	99
6	Bn	C_6H_4Cl-4	H	80:20	80	91

Jen, W. S.; Weinger, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

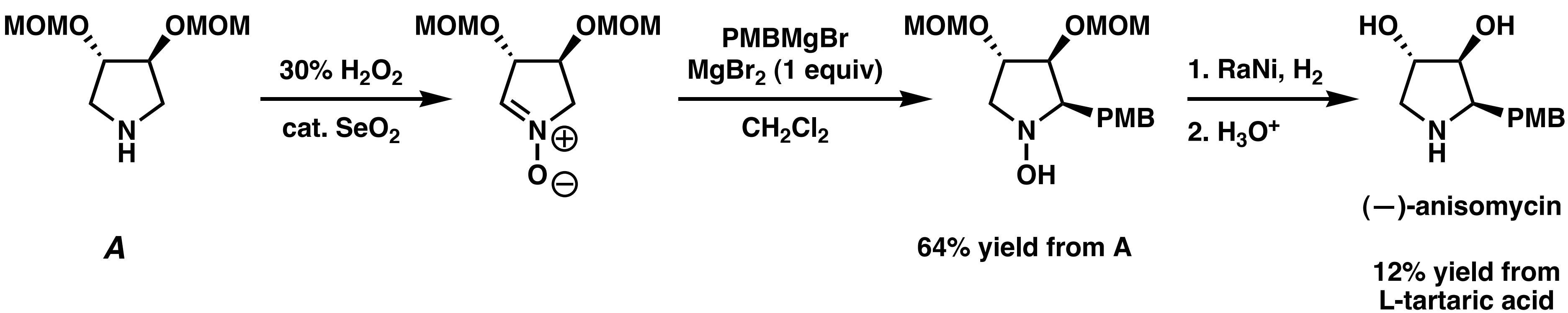
Synthetic Applications of Nitrones Toward Natural Product Syntheses

Gribble:



Gribble, G. W.; Barden, T. C. *J. Org. Chem.* **1985**, *50*, 5902.

Petrini (not a 1,3-DC):



Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316.

A Guide for the Discussion of Dipolar Cycloadditions:

1. Types and Classification of 1,3 Dipoles

2. Molecular Theory Behind 1,3-Dipolar Cycloadditions

3. Types of Dipoles:

   a. Nitrones

   b. Nitrile Oxides

   c. Carbonyl Ylides

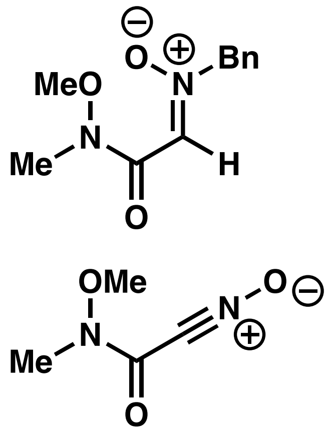
   d. Diazoalkanes

   e. Azomethine ylides

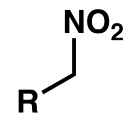
   g. Miscellaneous

Nitrile Oxides: Powerfull Dipoles in 1,3-Dipolar Cycloadditions

What is a nitrile oxide, and how is it made?



A. K., Parhi; R. W. Franck *Org. Lett.* 2004, *6*, 3063



alkyl nitro moiety

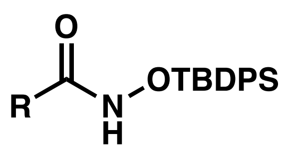
PhNCO, DCC cat. base

"Mukaiyama method"

T., Mukaiyama; T., Hoshino *J. Am. Chem. Soc.* **1960**, *82*, 5339.

M. J., Kurth, et. al.; *J. Org. Chem.* **2000**, *65*, 499.

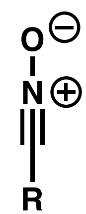
A. P., Kozikowski; H., Ishida *J. Am. Chem. Soc.* **1980**, *102*, 4265.



***O*-silylated hydroxamates**

Tf_2O, TEA

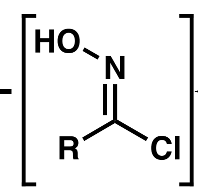
-40 °C to 0 °C



nitrile oxide

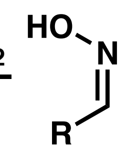
TEA

- HCl



hydroximinoyl chloride

NCS/NaOCl/Cl_2



oxime

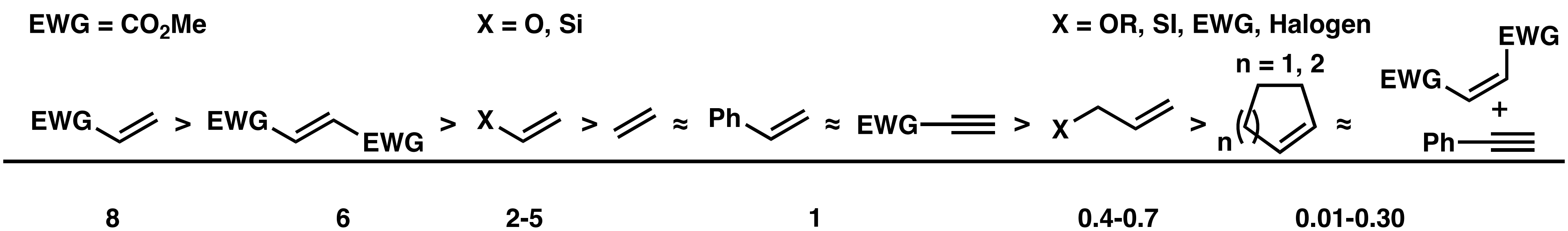
E. M., Carreira, et. al.; *Org. Lett.* **2000**, *2*, 539.

J. W., Bode; E. M. Carreira *J. Am. Chem. Soc.* **2001**, *123*, 3611.

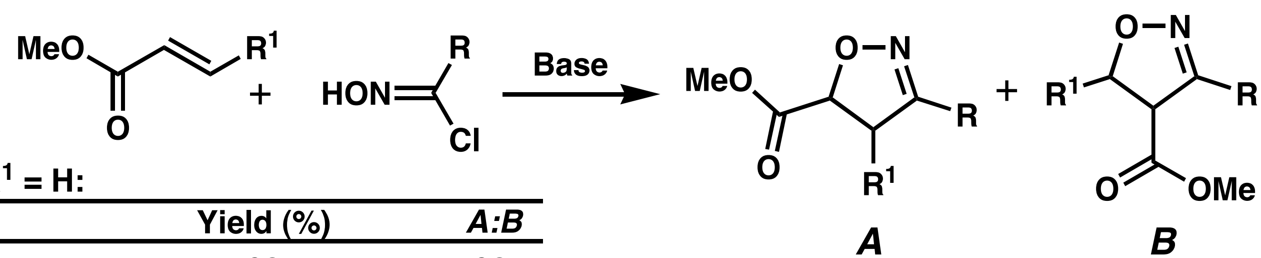
M. J., Kurth, et. al.; *Tet. Lett.* **1999**, *40*, 3535.

Relative Reactivity of Dipolarophiles with Nitrile Oxides

A relative reactivity guide for achiral dipolarophiles:



Regioselctivity with nitrile oxides:



When R[1] = H:

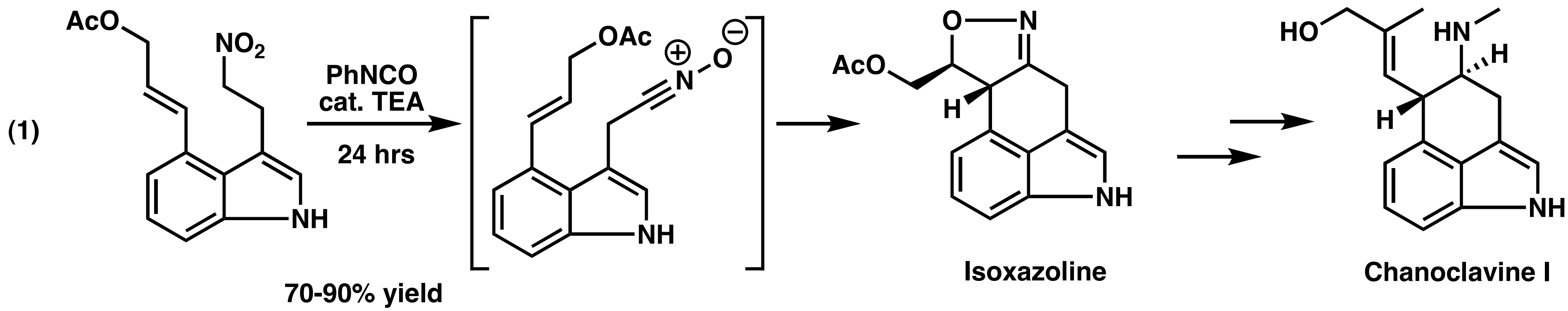
R	Yield (%)	*A:B*
2,6-$Cl_2C_6H_3$	93	93:7
CO_2Et	94	>99:1
C_6H_5	99	>99:1
COMe	97	>99:1
Br	89	95:1
COPh	76	>99:1
2,4,6-$Me_3C_6H_2$	99	95:5

When R[1] ≠ H, the selectivity breaks down to give unpredictable mixtures.

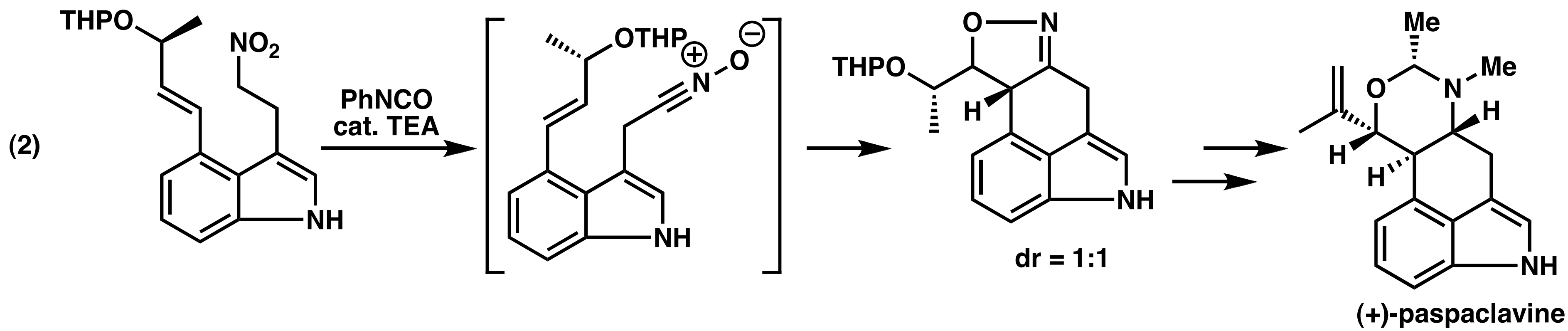
A., Padwa *Synthetic applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* John Wiley & Sons, **2002**, p. 377-380.

Synthetic Examples of Nitrile Oxides in 1,3-DC reaction: In the 1980's

In the Beginning, it was Kozokowski:



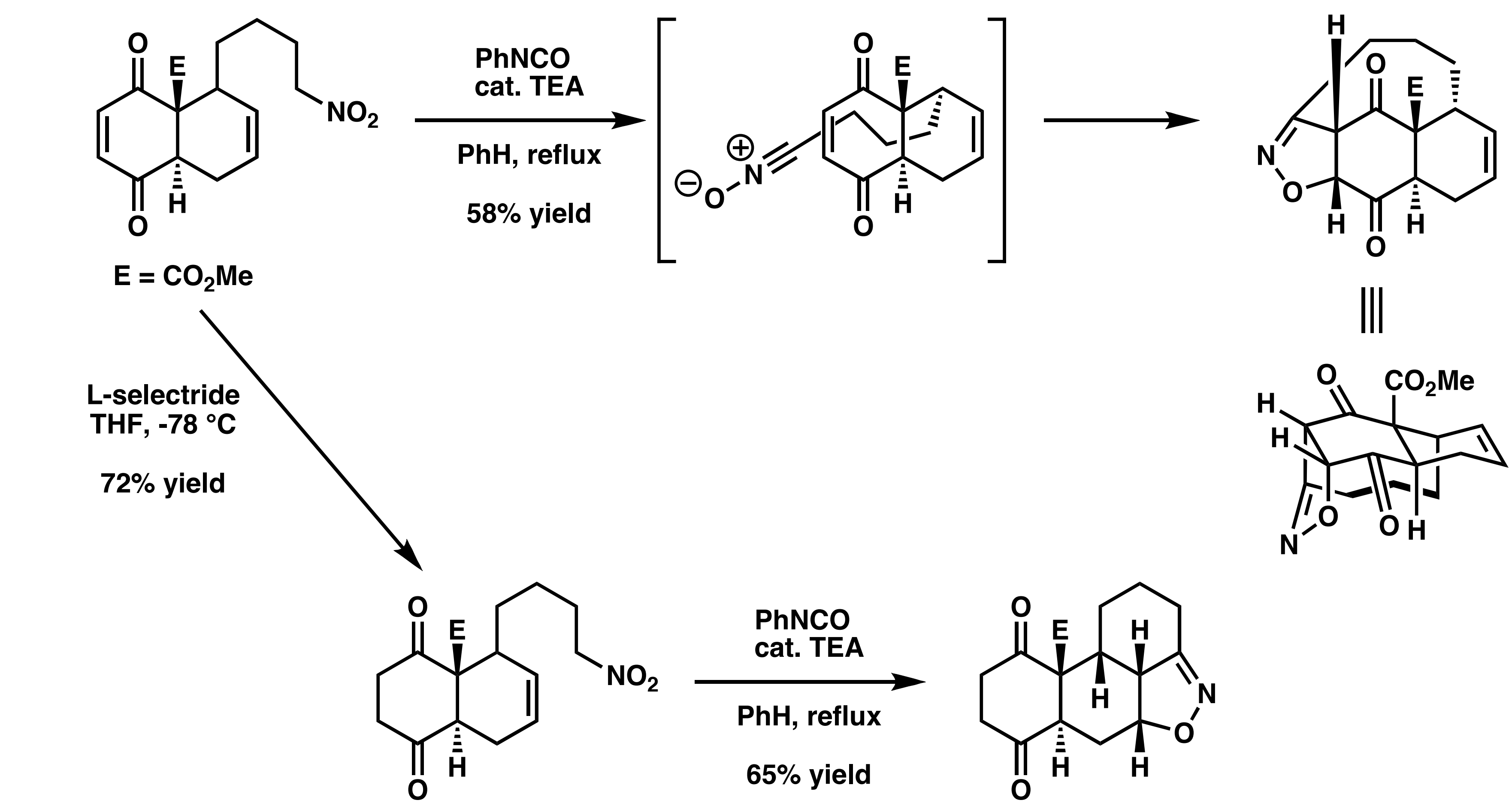
A. P., Kozikowski; H., Ishida *J. Am. Chem. Soc.* **1980**, *102*, 4265.



A. P., Kozikowski; Y. Y. Chen *J. Org. Chem.* **1981**, *46*, 5250.

1,3-Dipolar Cycloadditions using Nitrile Oxides in the 1980's (cont'd)

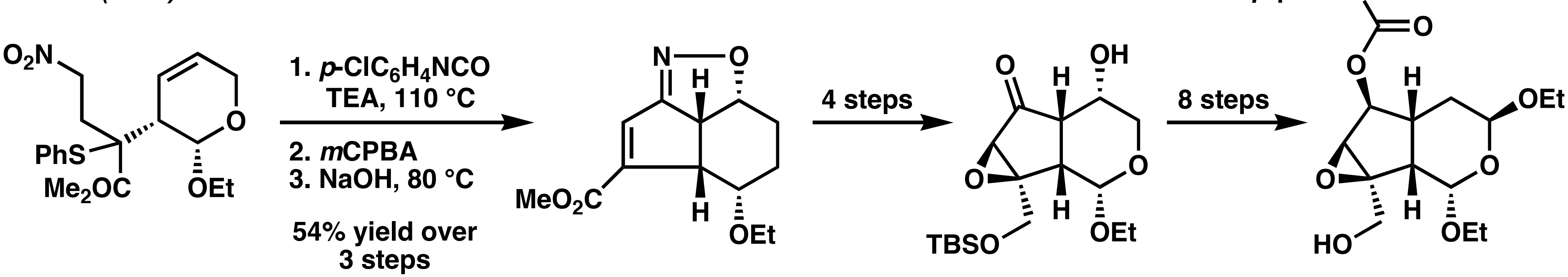
More Kozikowski:



A. P. Kozikowski, et. al.; *J. Am. Chem. Soc.* **1984**, *106*, 1845.

1,3-Dipolar Cycloadditions using Nitrile Oxides moves into the 1990's

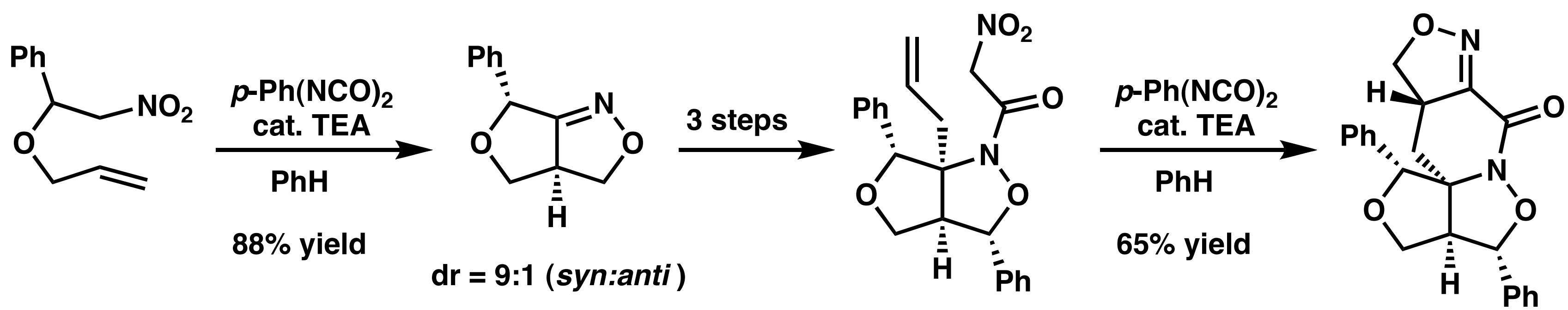
***Curran(1987)*:**



Specionin

D. P., Curran, et. al; *J. Am. Chem. Soc.* **1987**, *109*, 5280.

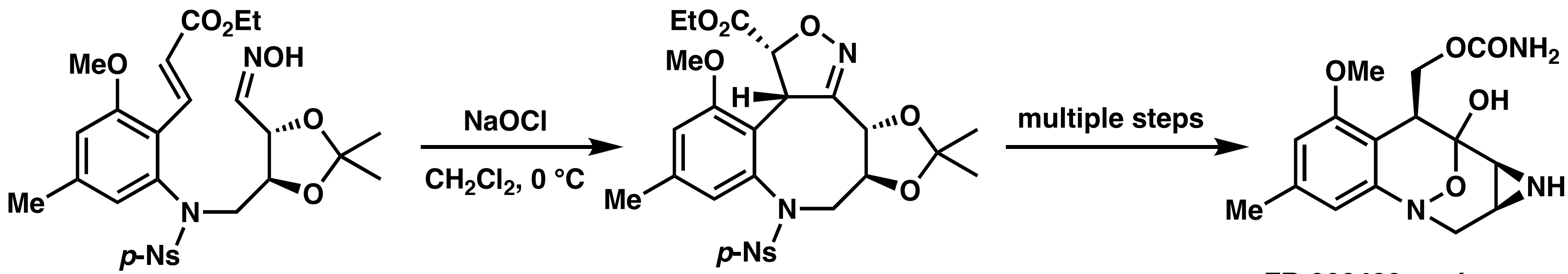
Kurth:



M. J., Kurth, et. al; *J. Org. Chem.* **2000**, *65*, 499.

1,3-Dipolar Cycloadditions using Nitrile Oxides in the New Millennium

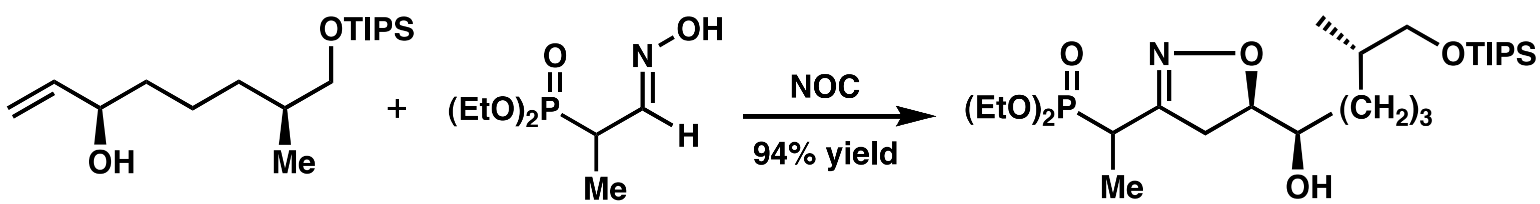
Dr. Mitomycin (Fukuyama):

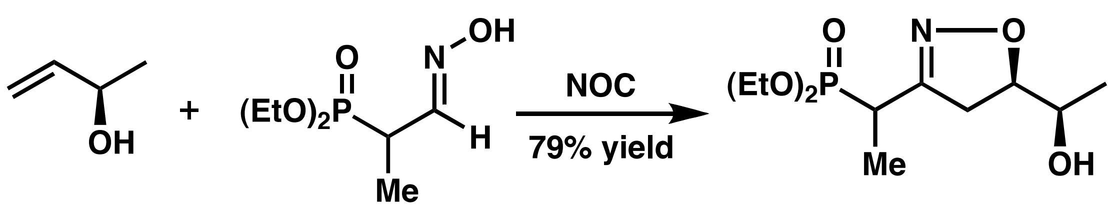


FR-900482 analogue

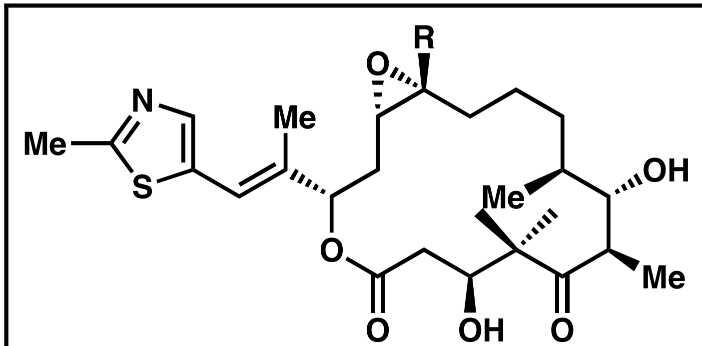
T., Fukuyama, et. al.; *Org. Lett.* **2001**, *3*, 2575.

Carreira:





J. W., Bode; E. M., Carreira *J. Am. Chem. Soc.* **2001**, *123*, 3611.



Epothilone A (R = H), B (R = Me)

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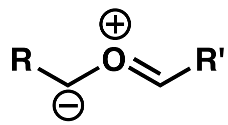
3. Types of Dipoles:

- **a. Nitrones**
- **b. Nitrile Oxides**
- **c. Carbonyl Ylides**
- **d. Diazoalkanes**
- **e. Azomethine ylides**
- **g. Miscellaneous**

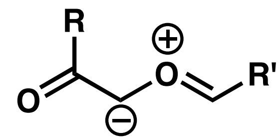
Carbonyl Ylides: How to Make the Dipole

3 types of carbonyl ylides:

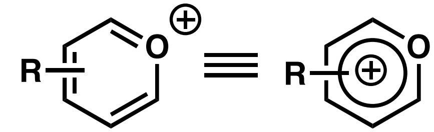
(1) Unstablized ylides



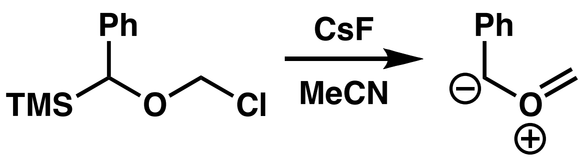
(2) Stablized ylides



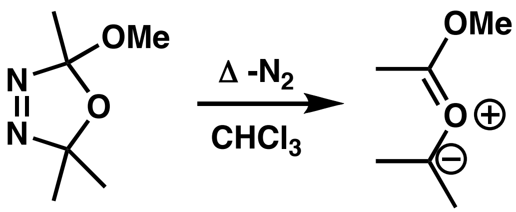
(3) Oxidopyrylium ion



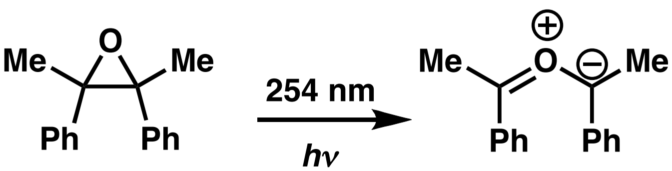
Generation of the ylides:



A., Hosomi, et. al.; *J. Org. Chem.* **1997**, *62*, 8610.

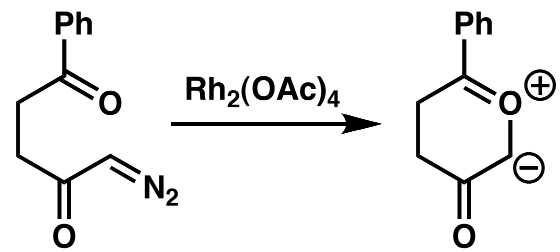


P. K. Sharma; J., Warkentin *Tetrahedron Lett.* **1995**, *36*, 7637.

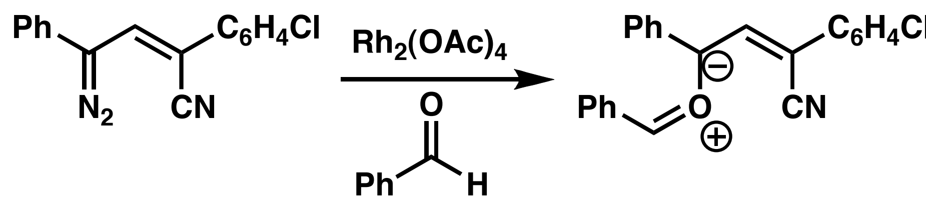


G. W., Griffin, et. al.; *Tetrahedron* **1981**, *37*, 3345.

The most common method to generate a carbonyl ylide is from a metallocarbenoid:



A., Padwa, et. al.; *J. Am. Chem. Soc.* **1990**, *112*, 3100.



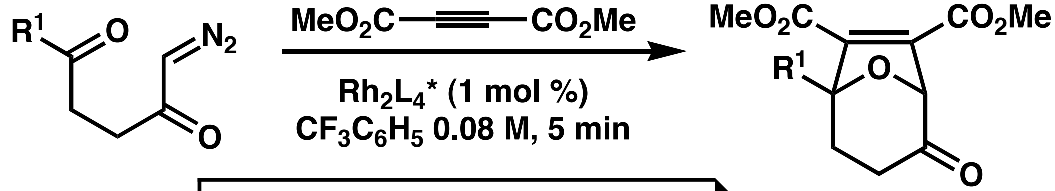
M., Hamaguchi, et. al.; *Tetrahedron Lett.* **2000**, *41*,1457.

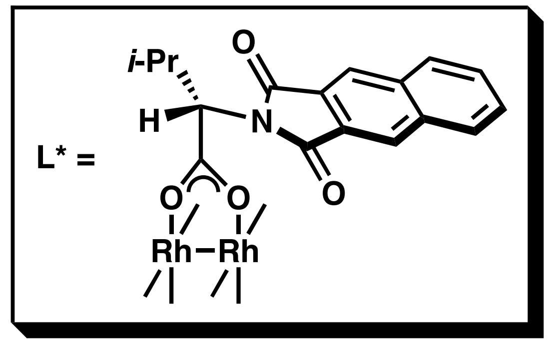
For a plethora of examples using metallocarbenoids to generate carbonyl ylides, see: A., Padwa *Synthetic applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* John Wiley & Sons, **2002**, p. 269-301.

Enantioselective Catalyzed 1,3-Dipolar Cycloaddtions using Carbonyl Ylides

Hashimoto:

entry	R^1	temp (°C)	yield (%)	% ee
1	C_6H_5	0	77	90
2	C_6H_5	-23	54	92
3	4-MeC_6H_4	0	67	92
4	4-$MeOC_6H_4$	0	65	90
5	4-ClC_6H_4	0	78	87



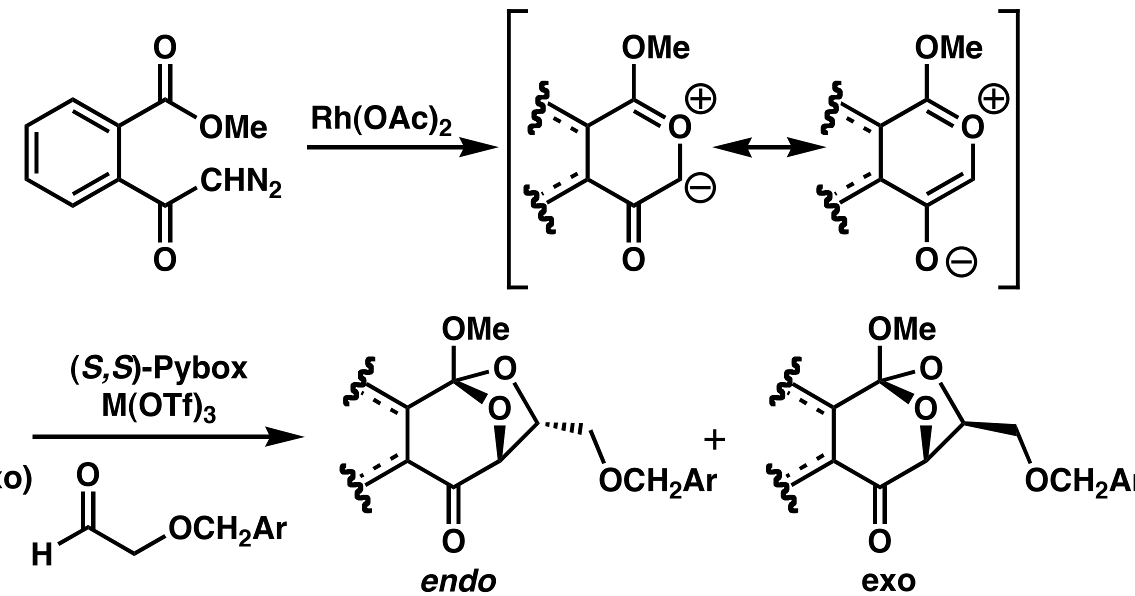


Note: The full table conatins 11 examples with 68-92 % ee

S.-i., Hashimoto, et. al.; *J. Am. Chem. Soc.* **1999**, *121*, 1417.

Suga:

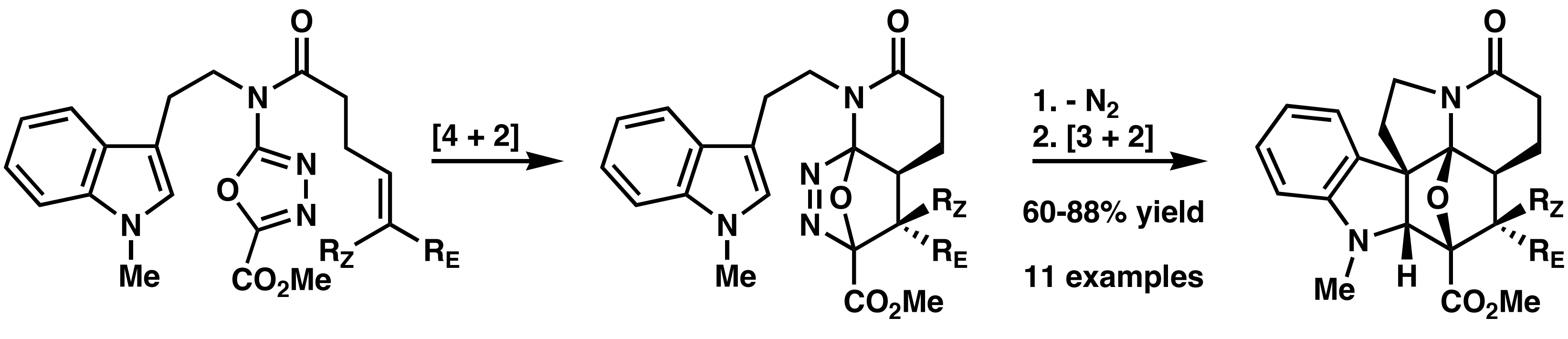
entry	temp (°C)	yield (%)	*endo:exo*	% ee
1	-10	96	88:12	91
2	-10	82	85:15	82
3	-10	53	91:9	89
4	-10	97	82:18	93
5	-25	84	73:27	86
6	-25	77	67:37	83
7	-10	84	12:88	45 (exo)



H., Suga, et. al; *J. Am. Chem. Soc.* **2002**, *124*, 14836.

Recent Examples of Carbonyl Ylides used in Natural Product Syntheses

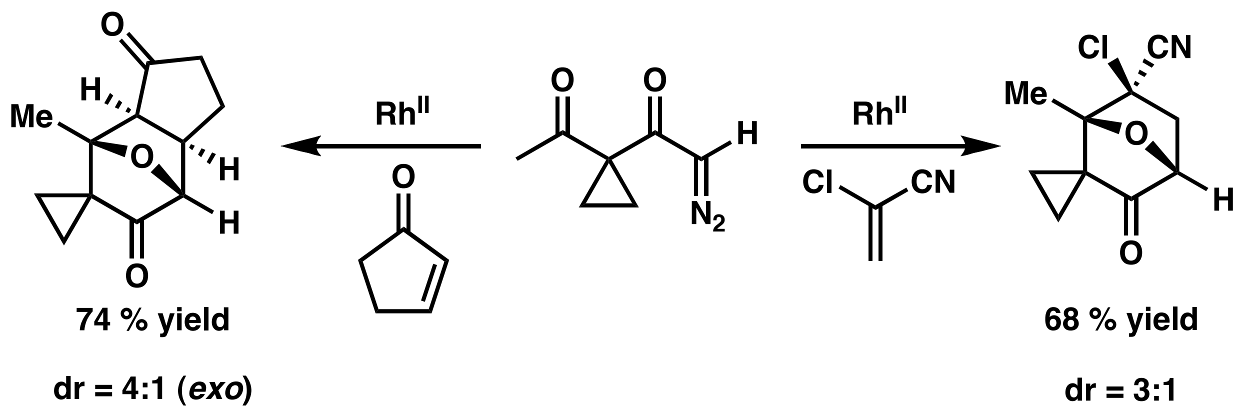
Boger:



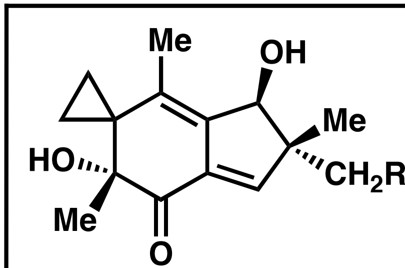
Core of vinoline

D. L., Boger; et. al.; *J. Am. Chem. Soc.* **2002**, *124*, 11292.

Padwa:



A ⟶ **illudin core and ptaquilosin core** ⟵ ***B***

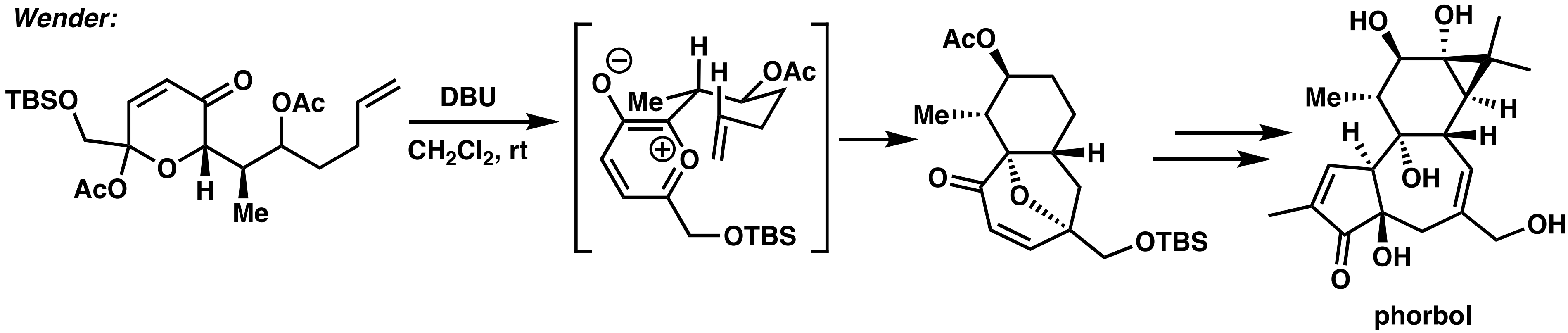


Illudin M (R = H)
Illudin S (R = OH)

A., Padwa, et. al.; *J. Am. Chem. Soc.* **1994**, *116*, 2667.

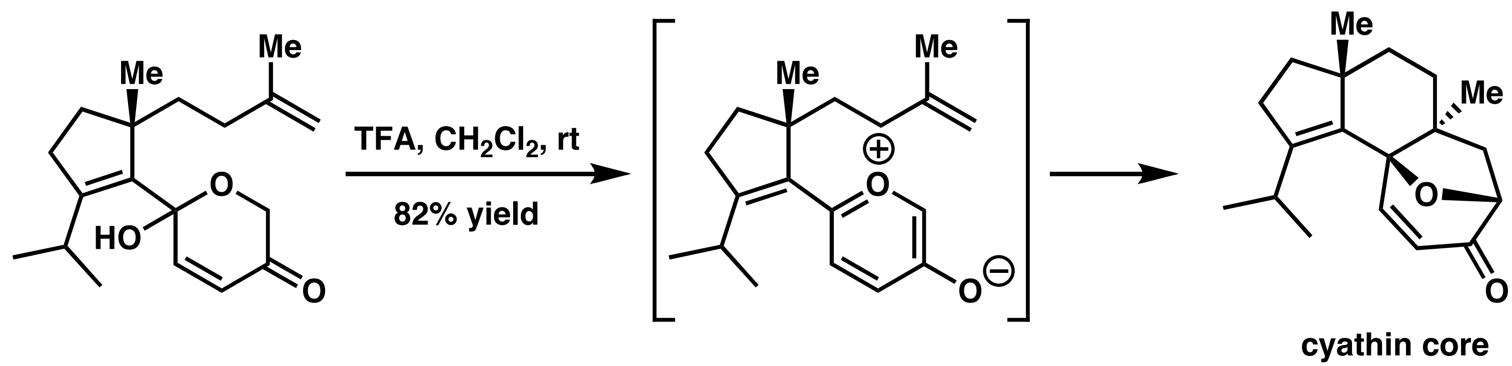
Synthetic Examples of 1,3-Dipolar Cycloadditions Using Oxidopyrylium Ylide

Wender:



K. C., Nicolaou; S. A., Snyder *Classics in Total Synthesis II* Wiley-VCH, **2003**, Ch. 6.

Magnus:



P., Magnus; L., Shen *Tetrahedron*, **1999**, *55*, 3553.

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   b. Nitrile Oxides

   c. Carbonyl Ylides

   d. Diazoalkanes

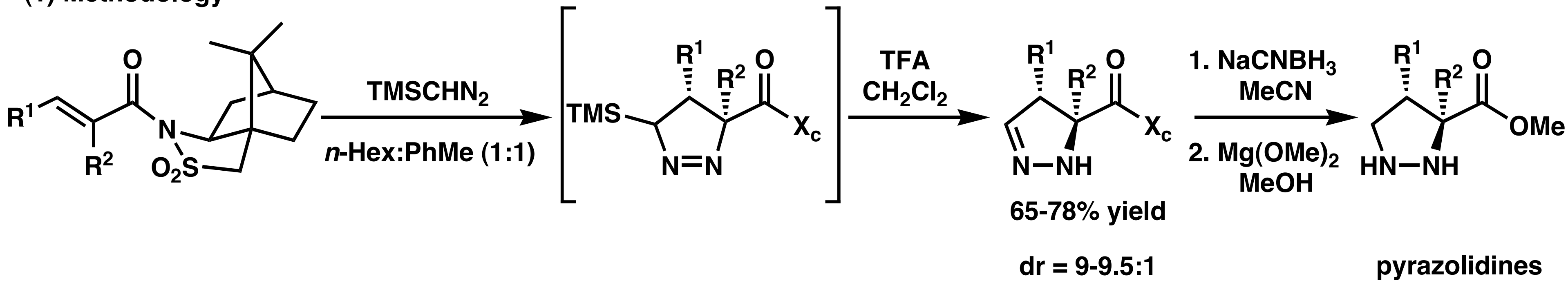
   e. Azomethine ylides

   g. Miscellaneous

Using $TMSCHN_2$ in 1,3-Dipolar Cycloadditions

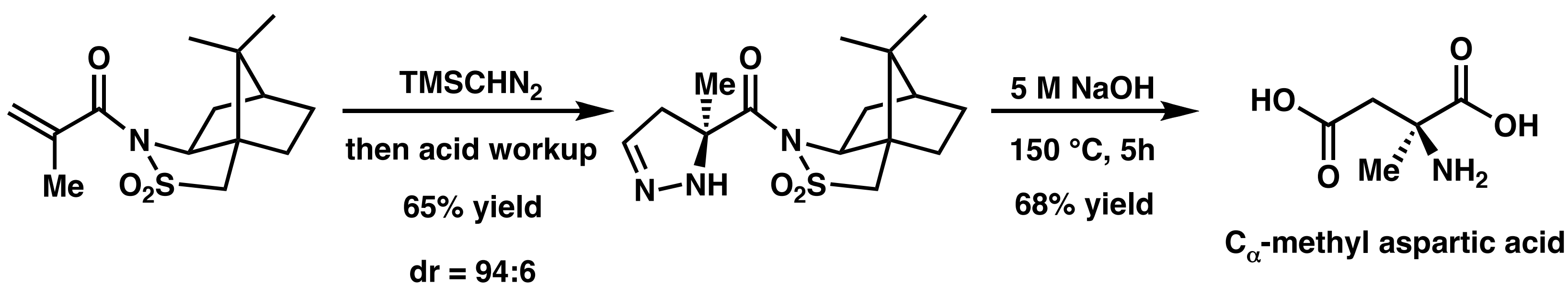
Carreira:

(1) Methodology

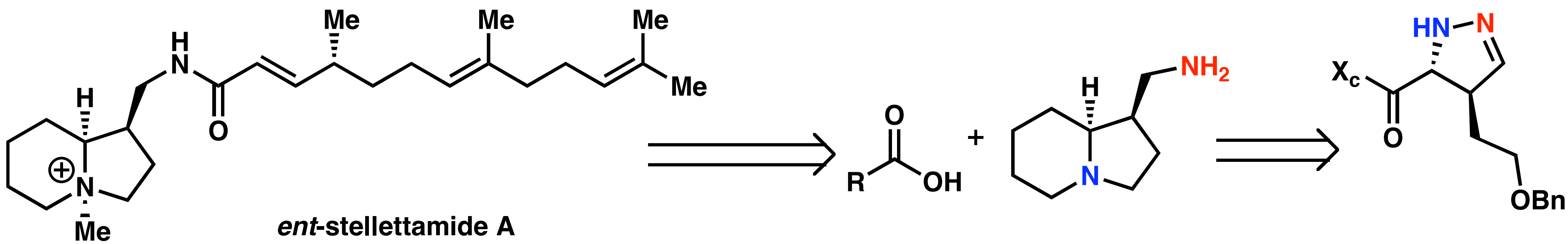


Carreira, E. M., et. al.; *J. Am. Chem. Soc.* **1997**, *119*, 8379.

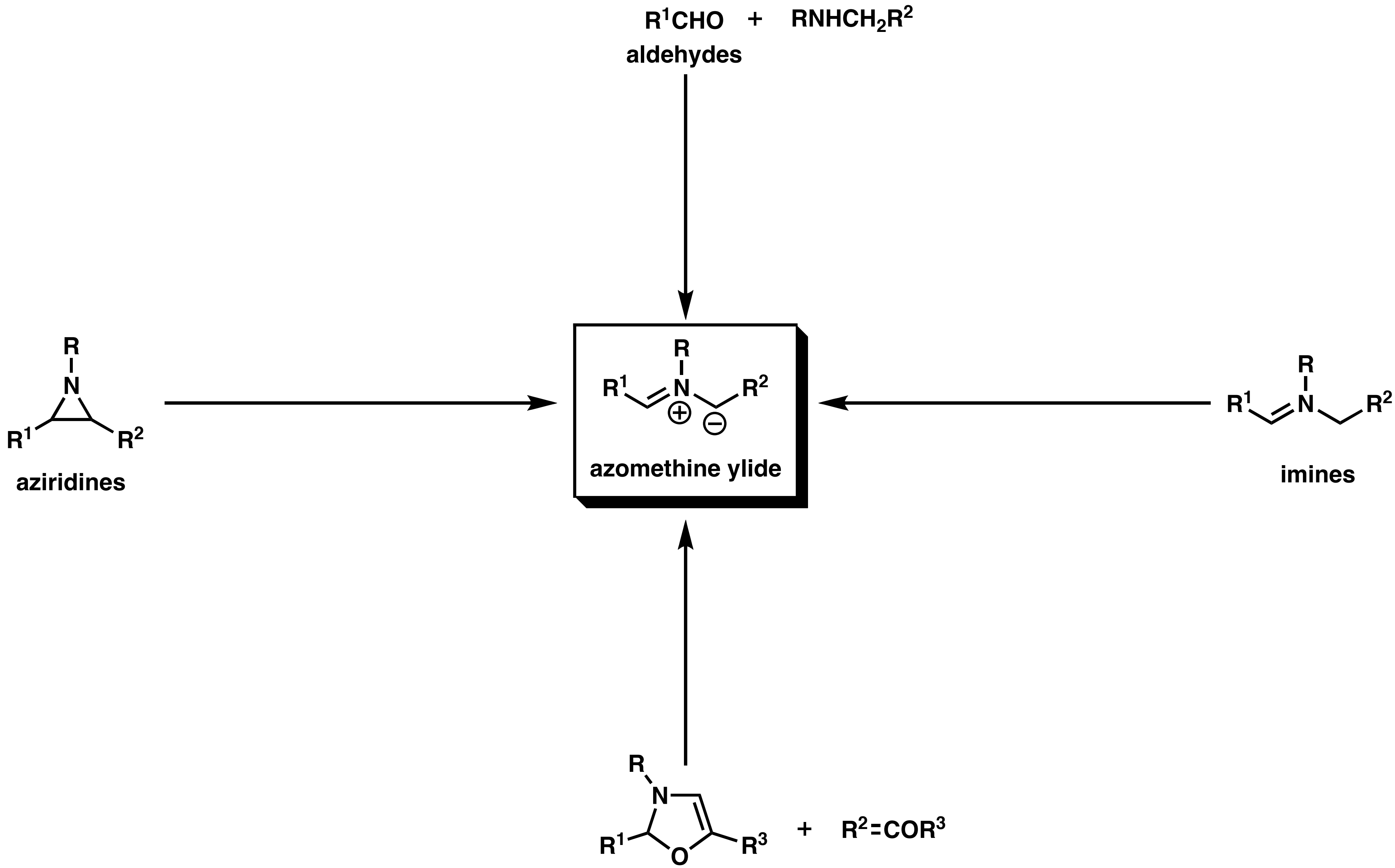
(2) Total Synthesis



H., Sasaki; E. M., Carreira *Synthesis* **2000**, *1*, 135.

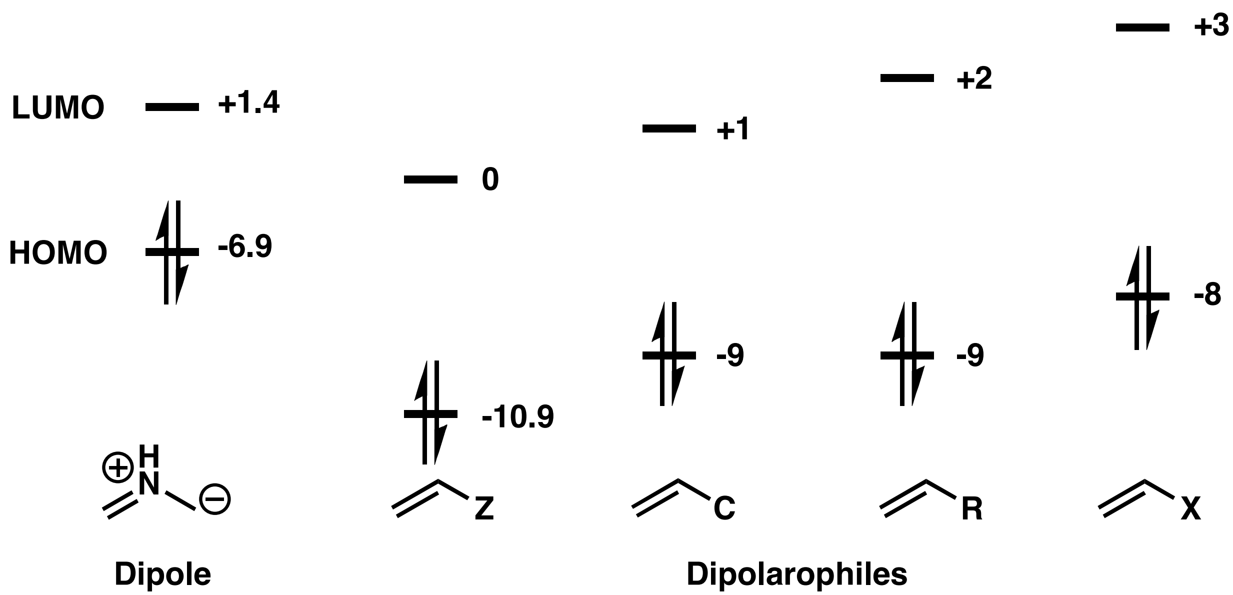


Azomethine Ylides: How they are generated



For a general review of azomethine ylides, see: I., Coldham; R., Hufton *Chem. Rev.* **2005**, *105*, 2765.

Azomethine Ylides: A quick look at FMO



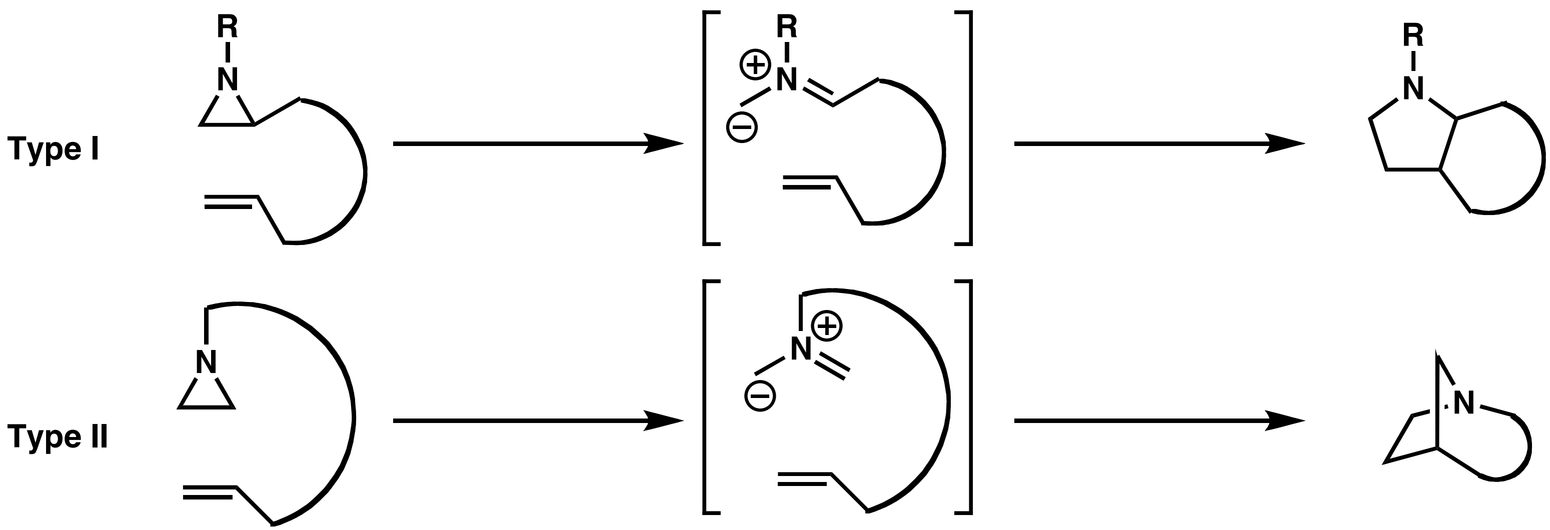
Z = electron deficient

C = conjugated

R = alkyl

X = electron rich

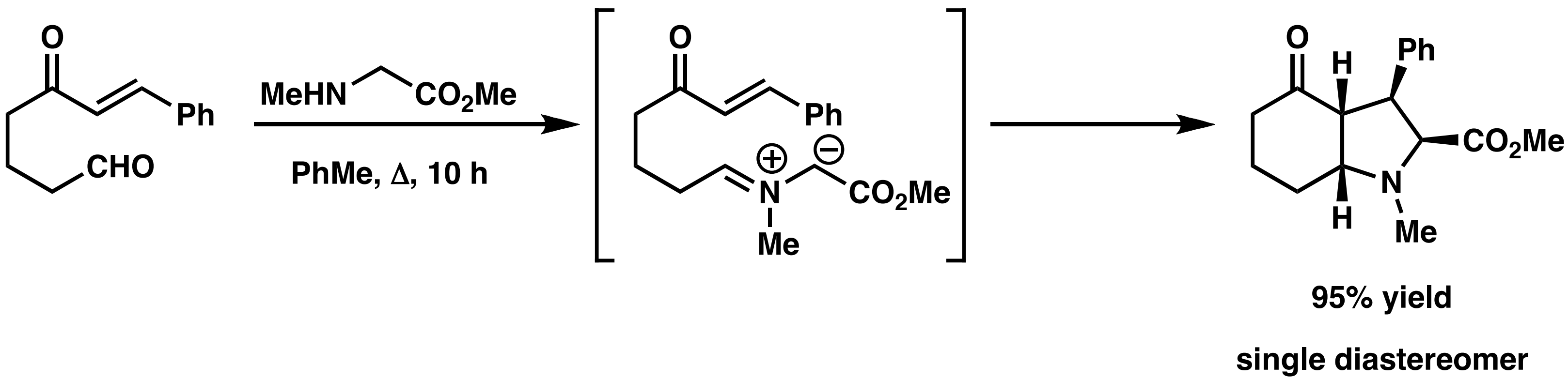
Intramolecular Tethers:



I., Coldham; R., Hufton *Chem. Rev.* **2005**, *105*, 2765.

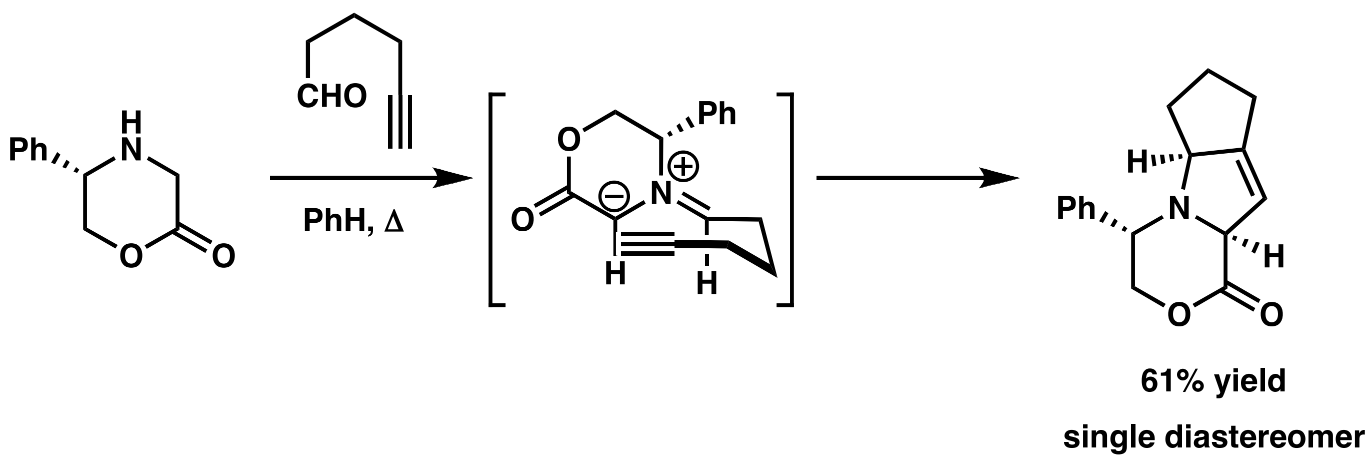
Azomethine Ylides Generated From Aldehydes

Kanemasa:



S., Kanemasa; K., Doi; E., Wada *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2866.

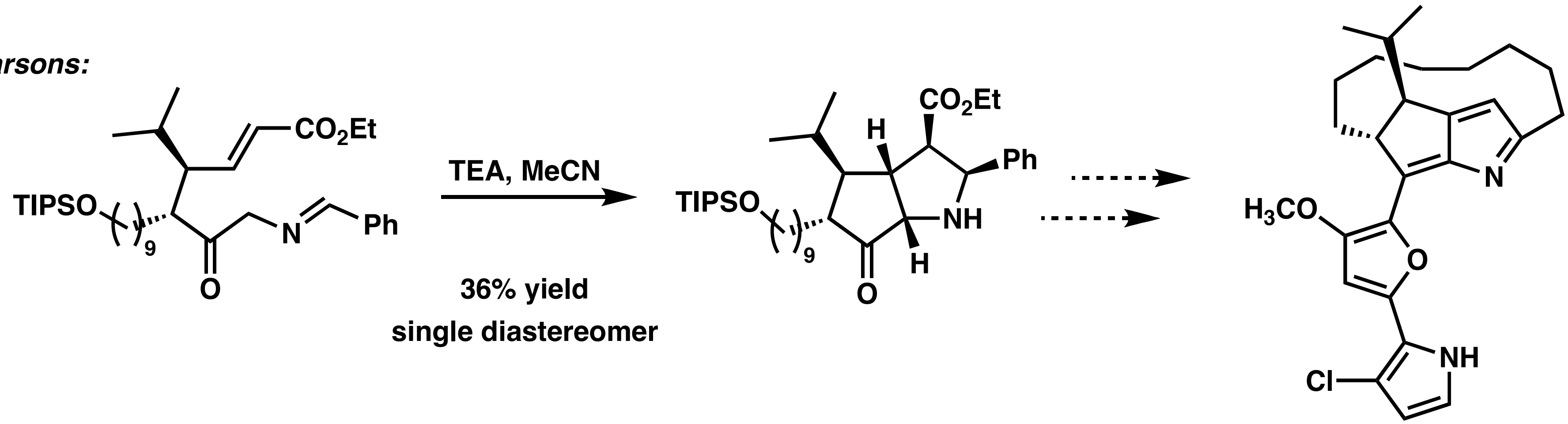
Harwood:



L. M., Harwood; L. C., Kitchen *Tetrahedron Lett.* **1993**, *34*, 6603.

Azomethine Ylides Generated From Imines

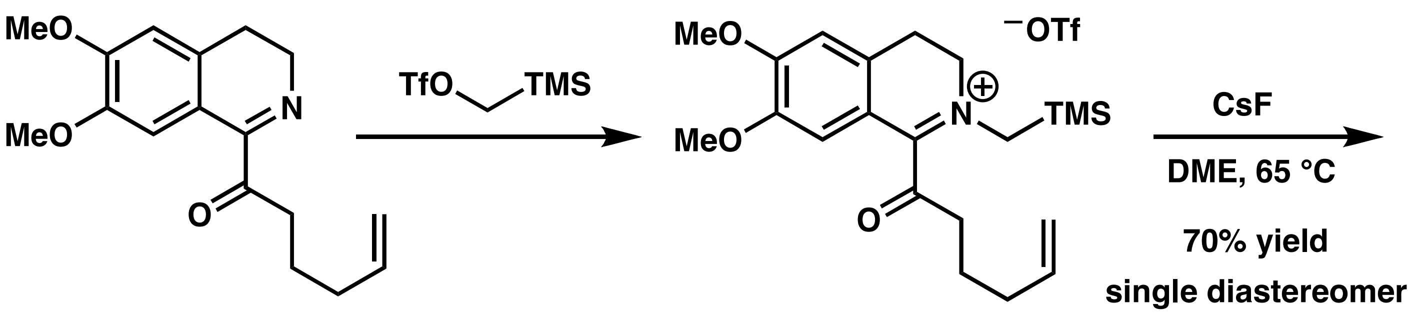
Parsons:



roseophilin

P. J., Parsons, et. al.; *Synlett.* **2003**, 1856.

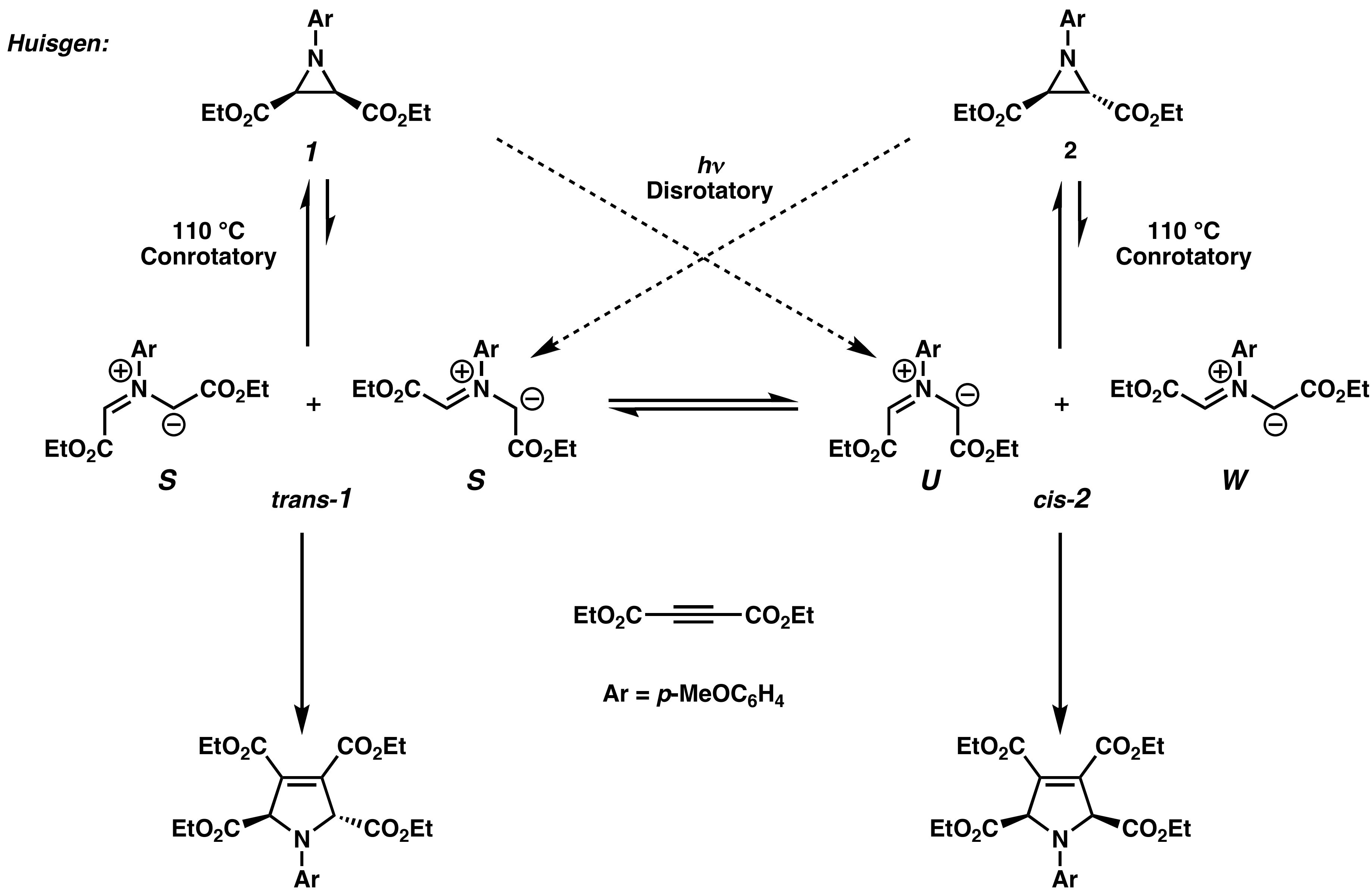
Livinghouse:



erythrinane skeleton

T., Livinghouse, et. al.; *J. Org. Chem.* **1996**, *51*, 1159.

Azomethine Ylides Generated From Aziridines



R., Huisgen, et. al.; *J. Am. Chem. Soc.* **1967**, *89*, 1753.
R., Huisgen, et. al.; *Tetrahedron Lett.* **1966**, 397.

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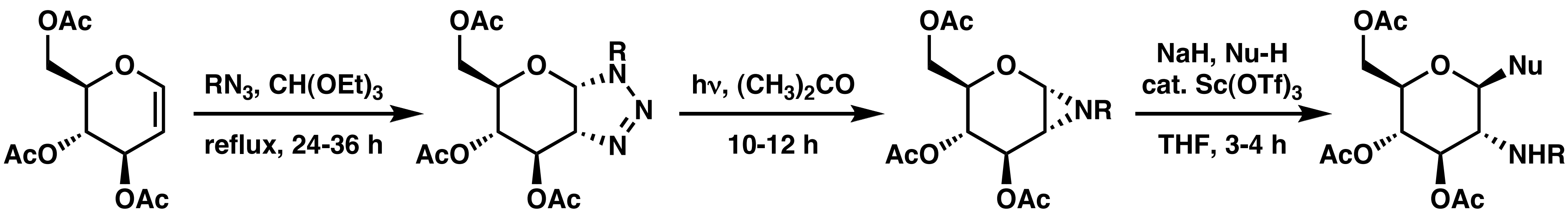
d. Diazoalkanes

e. Azomethine ylides

g. Miscellaneous

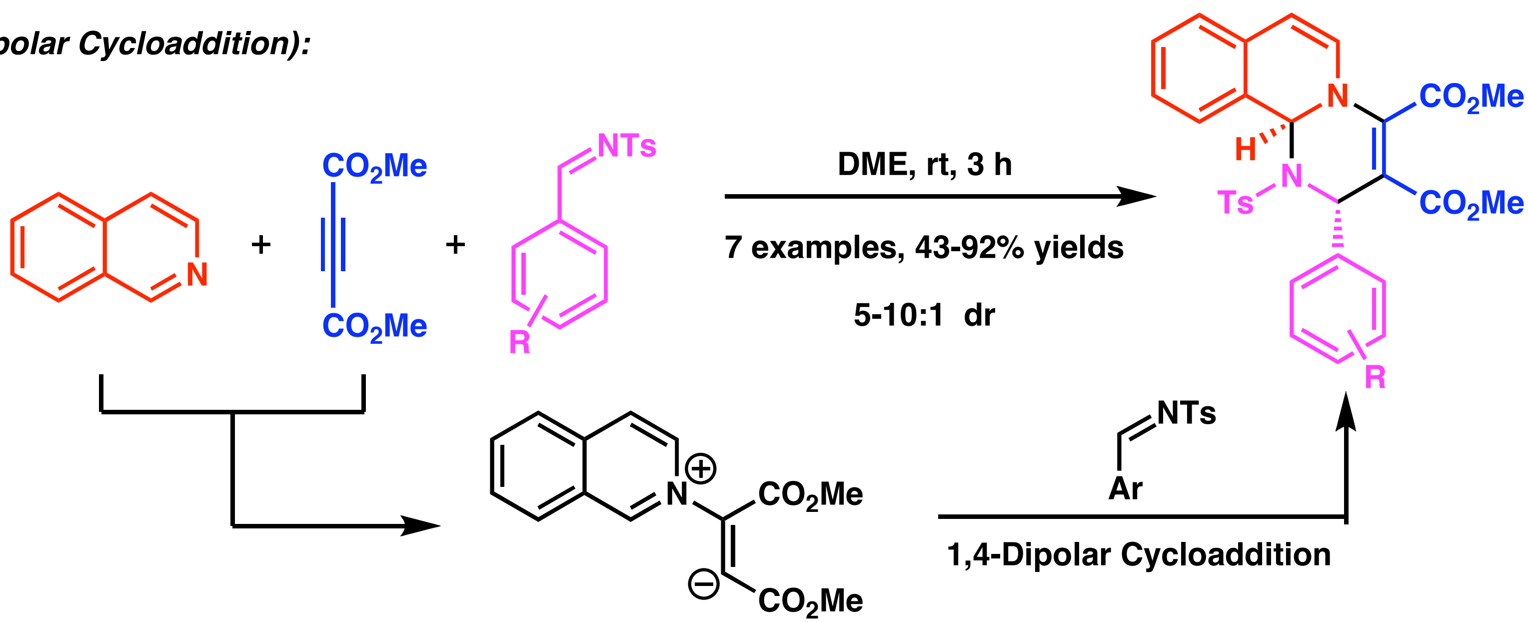
Various Dipoles and Dipolarophiles in Dipolar Cycloadditions

Finney:



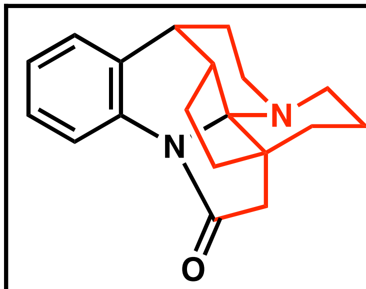
R. S., Dahl; N. S., Finney *J. Am. Chem. Soc.* **2003**, *126*, 8356.

Nair (1,4-Dipolar Cycloaddition):



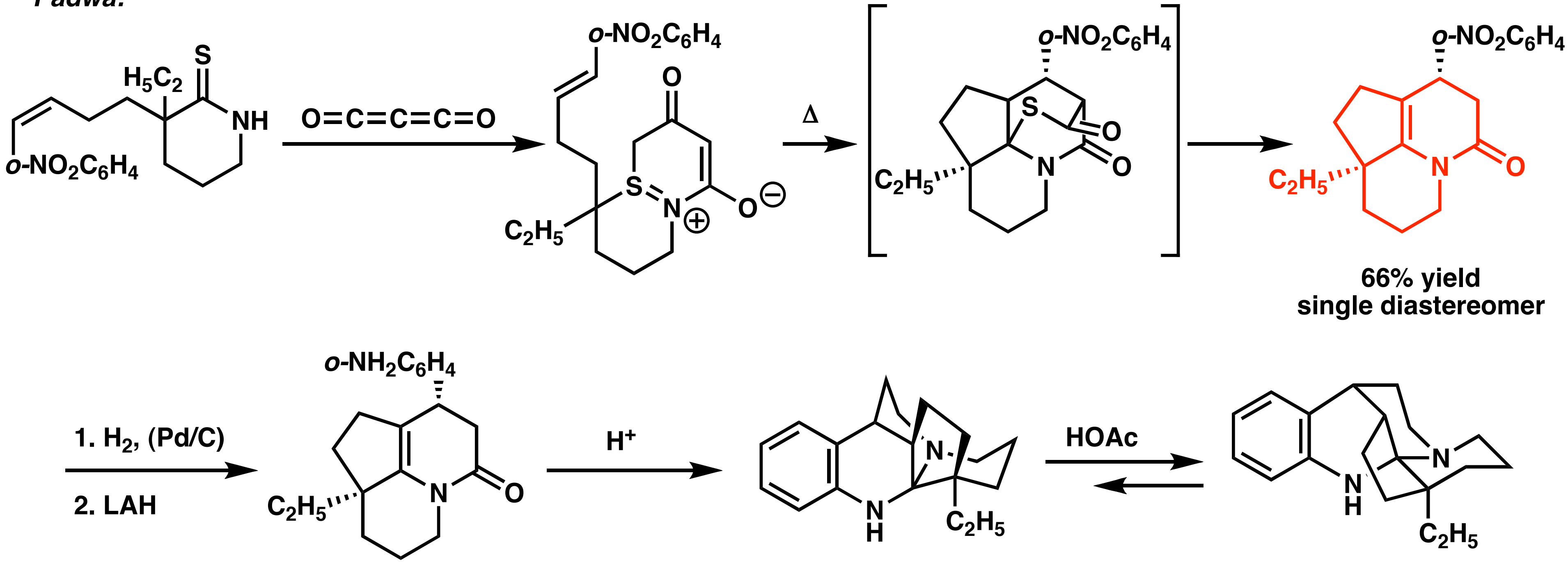
V., Nair, et. al.; *Org. Lett.* **2002**, *4*, 3575.

Various Dipoles Used to Access Complex Alkaloid Core Structures



isoschizizygane core

Padwa:

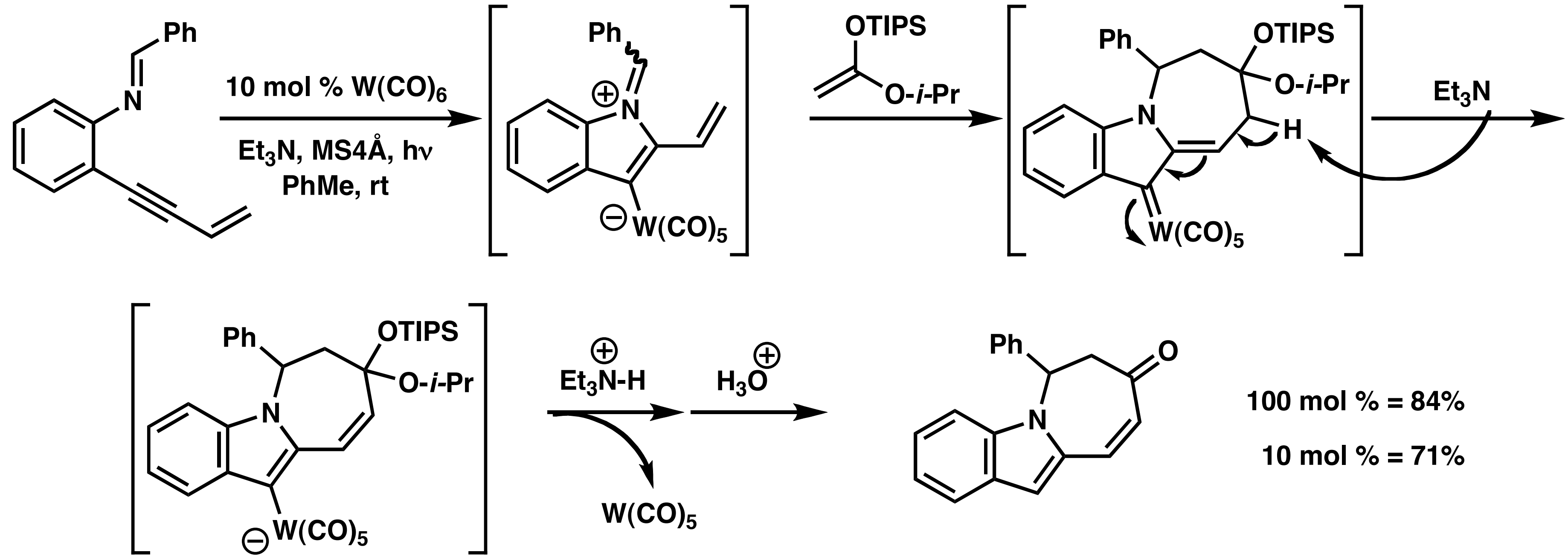


1 : **6**

A., Padwa, et. al.; *Org. Lett.* **2005**, *7*, 2925.

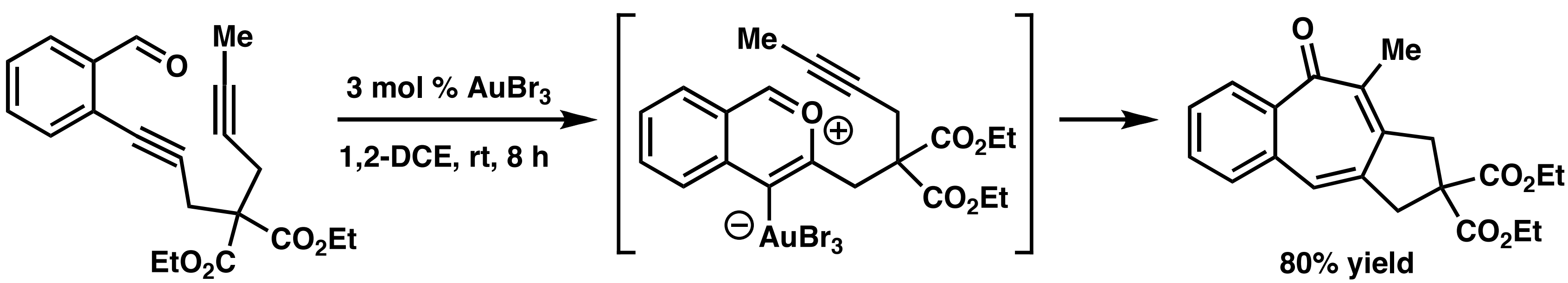
Dipoles Generated by Catalytic Methods Using Various Metals

Iwasawa:



N., Iwasawa, et. al.; *Org. Lett.* **2006**, *8*, 895.

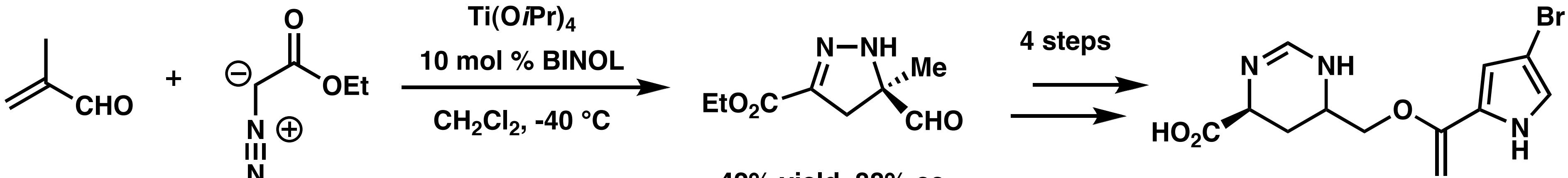
Oh:



C. H., Oh, et. al.; *Org. Lett.* **2005**, *7*, 5289.

One Old Friend, and One Friendly Molecule

Maruoka, Taichi Kano:

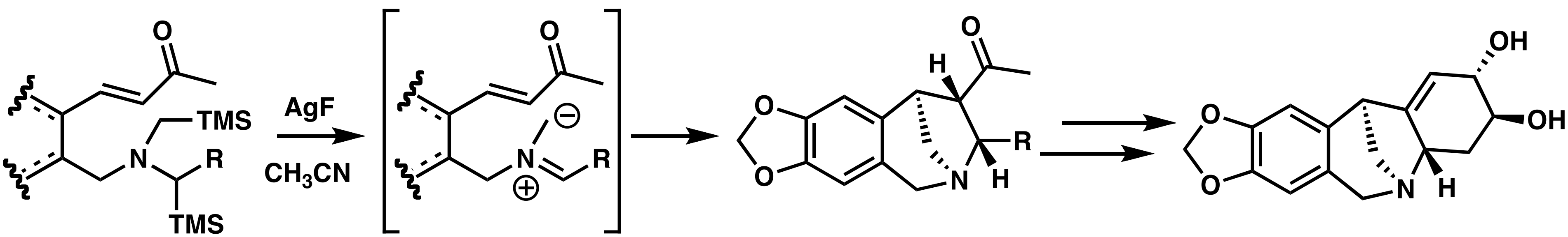


42% yield, 88% ee

Manzacidin A

T., Kano, T., Hashimoto, K., Maruoka *J. Am. Chem. Soc.* **2006**, *128*, 2174.

Pandey:



R = CH_2CH_2OBz

56% yield

Pancracine

"Overman Talk"

G., Pandey, et. al; *Org. Lett.* **2005**, 3713.

Some Conclusions

- 1,3 DC are extremely powerful reactions that can generate multiple chiral centers, various heterocyclic or carbocyclic ring sizes, as well as a wide array of final products.

- There are many different dipoles, and there are various ways to make the more popular dipoles.

- Asymmetric 1,3 DC have good ee's, however lack a wide substrate scope for specific dipoles. This area is still underexplored and will continue to draw interest.

THE END