

Merged Cycloaddition–Cycloreversion Processes

Evans Group Seminar

May 3, 2002

George Borg

Outline:

1. Retro-Diels-Alder reactions
2. [4 + 1] cycloreversions (cheletropic extrusion)
3. [3 + 2] cycloreversions
4. [2 + 2] cycloreversions

Leading References:

Retro-Diels-Alder Reactions:

Rickborn, B. "The Retro–Diels–Alder Reaction. Part I. C-C Dienophiles." *Org. React. (N. Y.)* **1998**, 52, 1-393.

Rickborn, B. "The Retro–Diels–Alder Reaction. Part II. Dienophiles With One or More Heteroatom." *Org. React. (N. Y.)* **1998**, 53, 223-630.

[3 + 2] Cycloreversions:

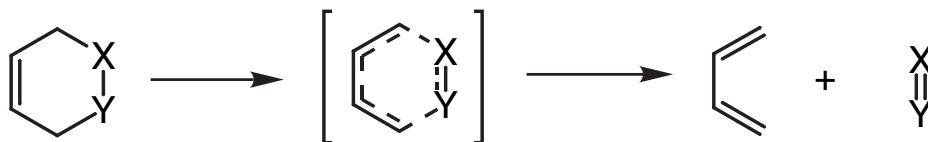
Bianchi, G.; Gandolfi, R. in *1,3 Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 14, pp. 451-543.

[4 + 1] Cycloreversions:

SO₂ extrusion: Chou, T.; Tso, H. *Org. Prep. Proced. Int.* **1989**, 21, 257-296.

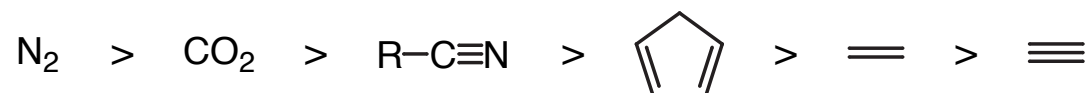
CO extrusion: Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965**, 65, 261-365.

The retro-Diels-Alder (rDA) Reaction: Reactivity Comparisons

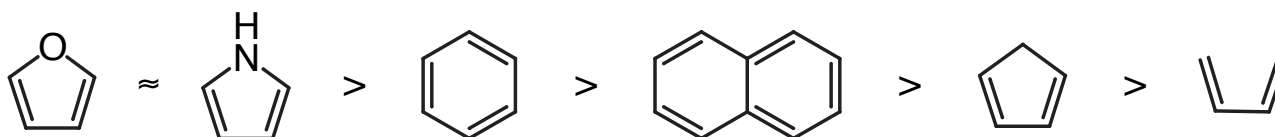


- The ease of expulsion of the diene and dienophile determines reaction conditions and selectivities.

Dienophile:



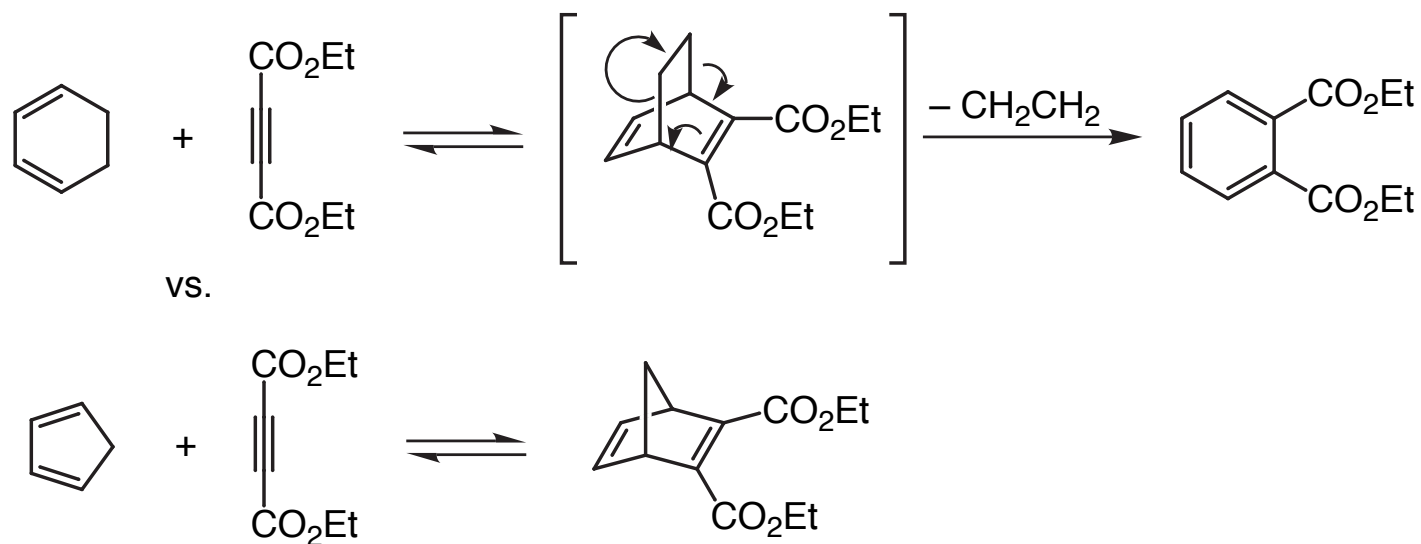
Diene:



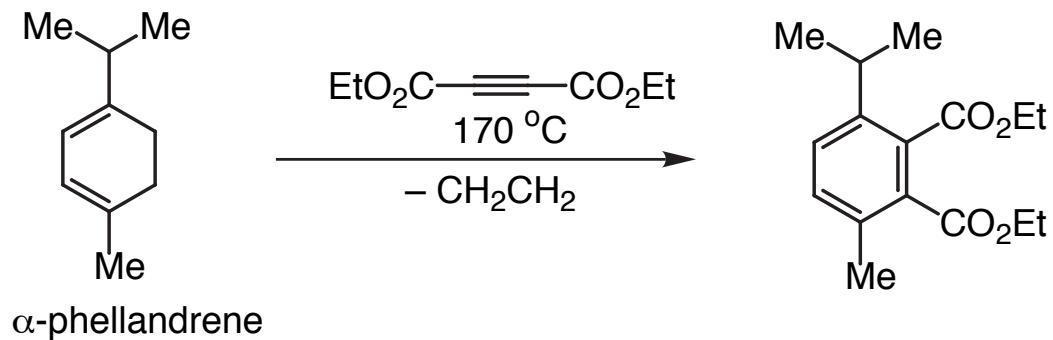
Rickborn, *Organic React.* (N. Y.) **1998**, 52, 1-393.

DA-rDA Reactions with C-C Dienophiles: The Alder-Rickert Reaction

- The Alder-Rickert reaction was an early method for distinguishing 1,3-cyclohexadienes from other dienes.

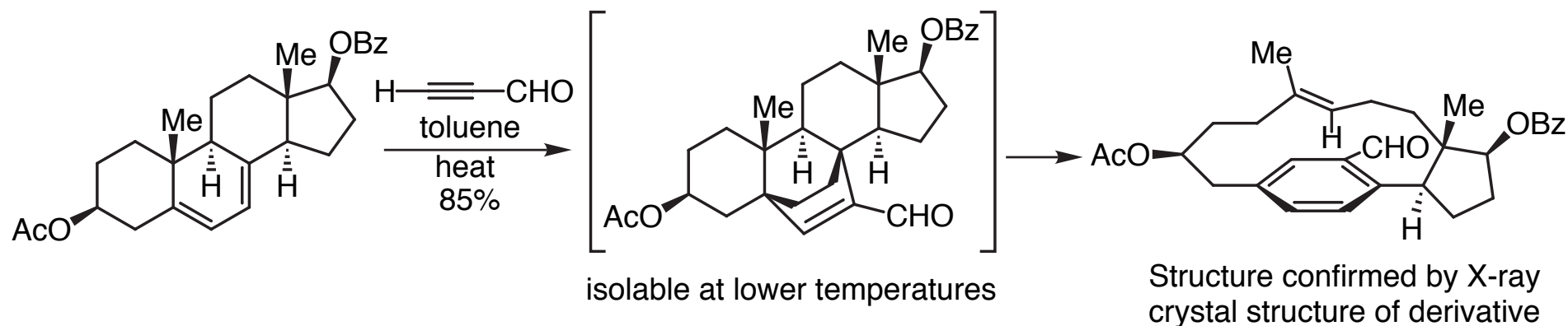


Alder, Rickert, *Justus Liebigs Ann. Chem.* **1936**, 524, 180-189.



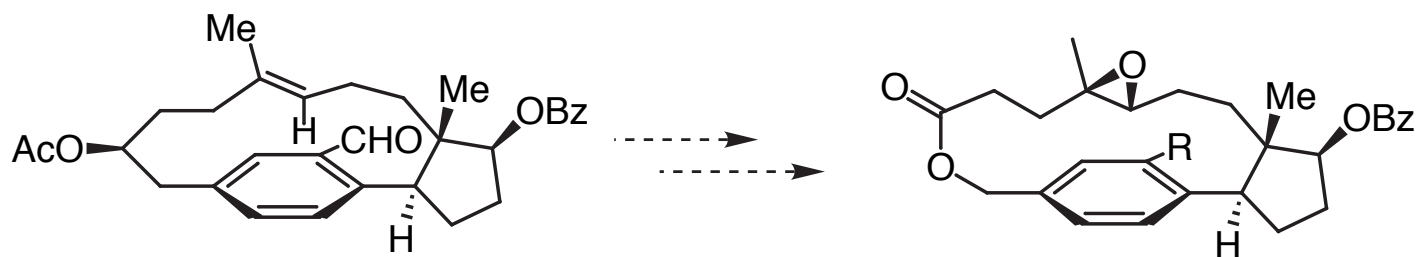
Alder, Rickert, *Chem. Ber.* **1937**, 70, 1364-1369.

The Alder-Rickert Reaction: Synthetic Applications



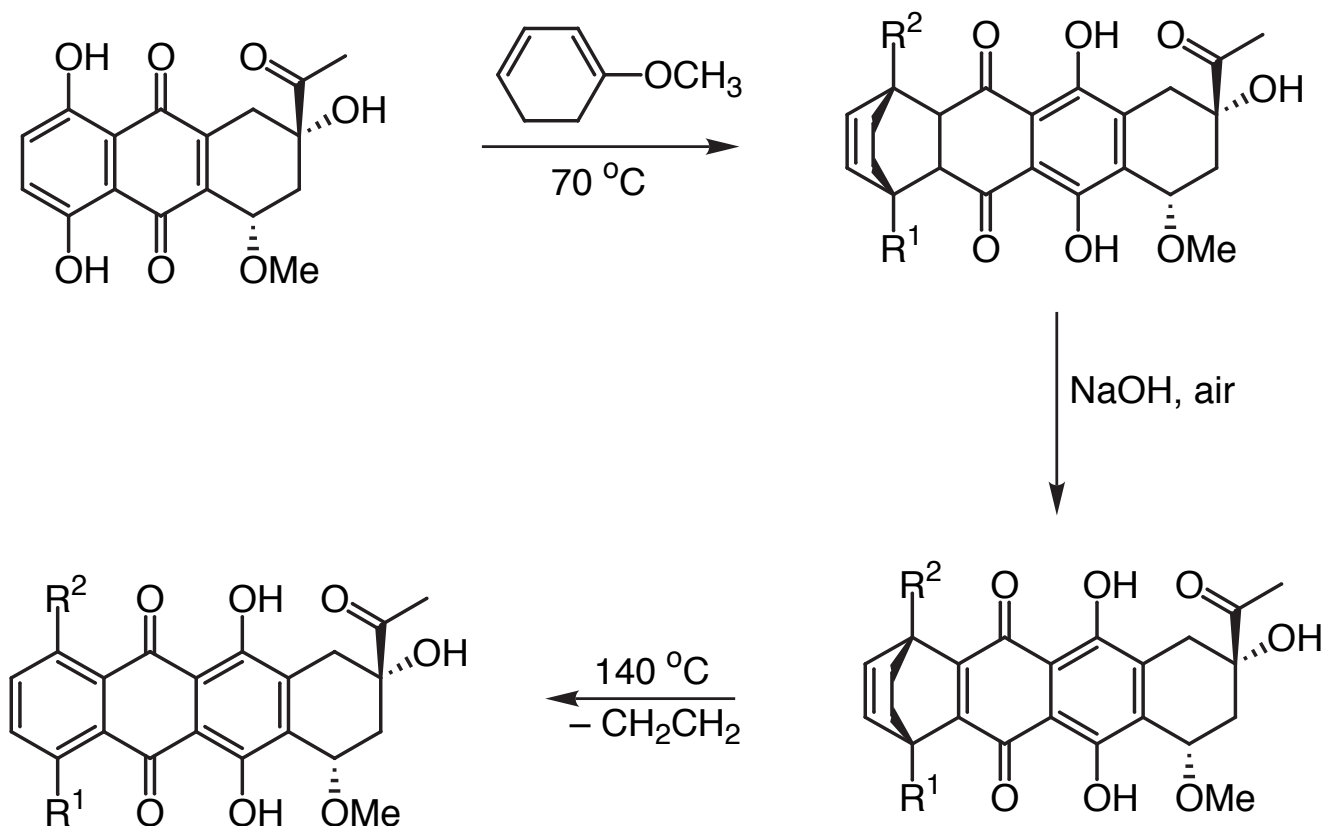
Winterfeldt, *Tetrahedron Lett.* **1985**, 26, 1705-1706.

- The product was used as a starting material for the synthesis of macrolides.



Winterfeldt, *Heterocycles*, **1989**, 28, 333-346.

An Alder–Rickert Reaction Variant: Total Synthesis of Daunomycinone



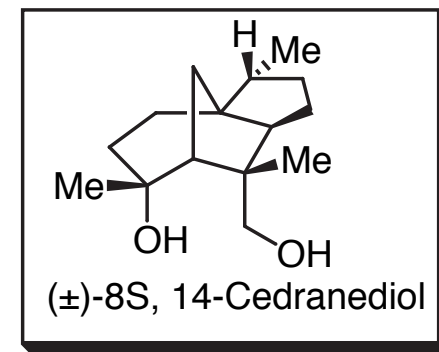
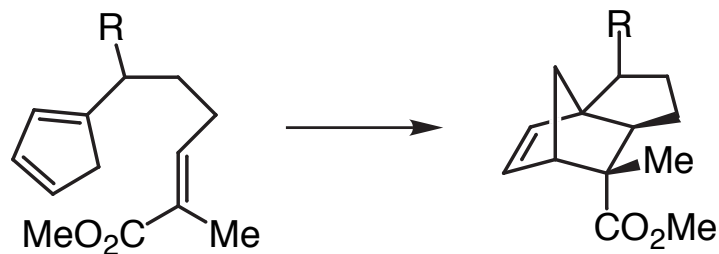
Daunomycinone: $\text{R}^1 = \text{OMe}$, $\text{R}^2 = \text{H}$ (17%)

Isodaunomycinone: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OMe}$ (32%)

- The facile air oxidation of the cycloadduct intermediates allows the quinone to serve as an "acetylene equivalent."
- There is no purification during the DA-oxidation-rDA sequence.

Krohn, *Chem. Ber.* **1979**, *112*, 3453-3471.

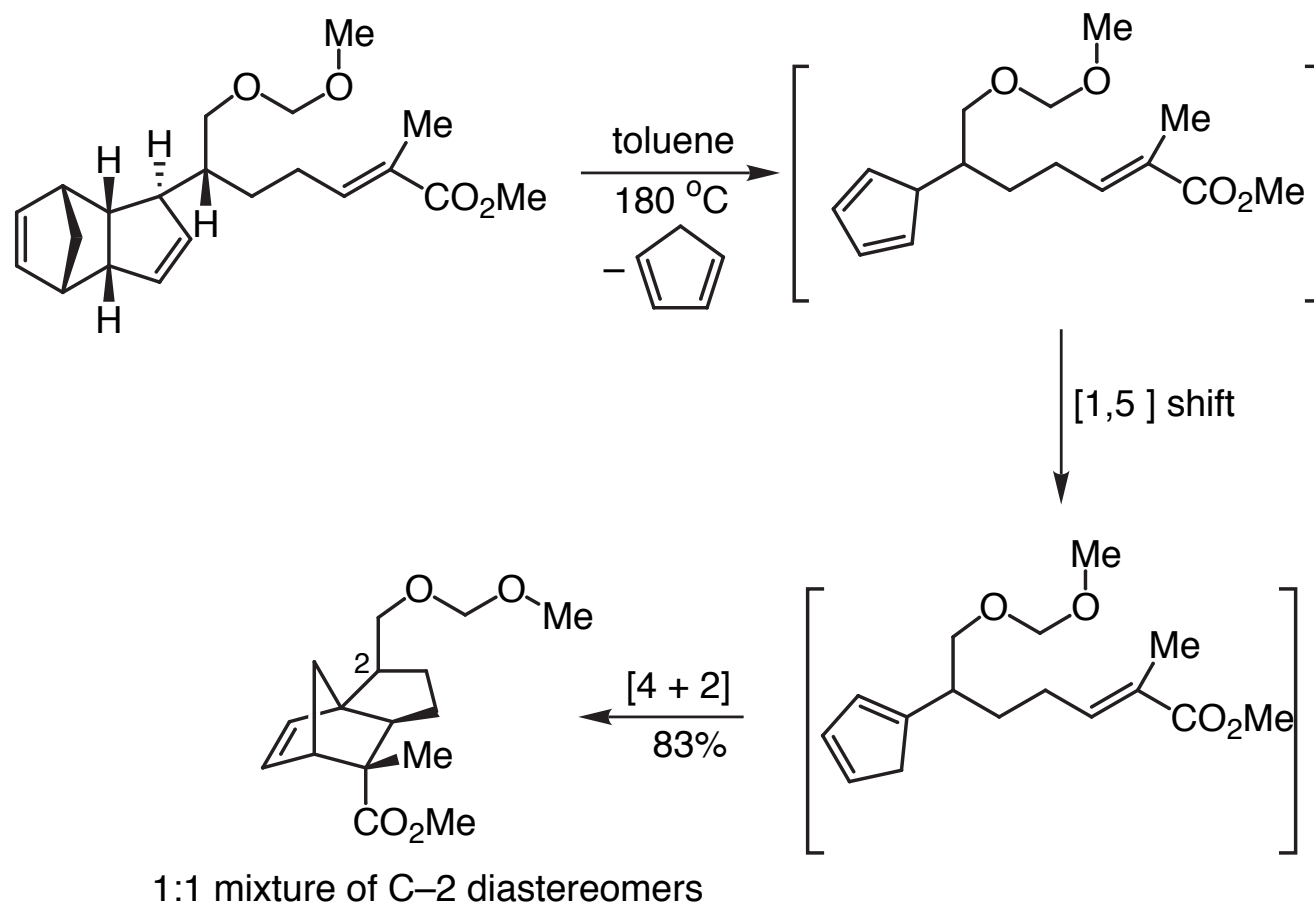
CP as a Diene Protecting Group: Synthesis of (\pm)-8S, 14-Cedranediol



- Due to the facile polymerization of cyclopentadienes, late-stage introduction of the cyclopentadiene was sought.
- The diene was masked as a dicyclopentadiene until the key step.

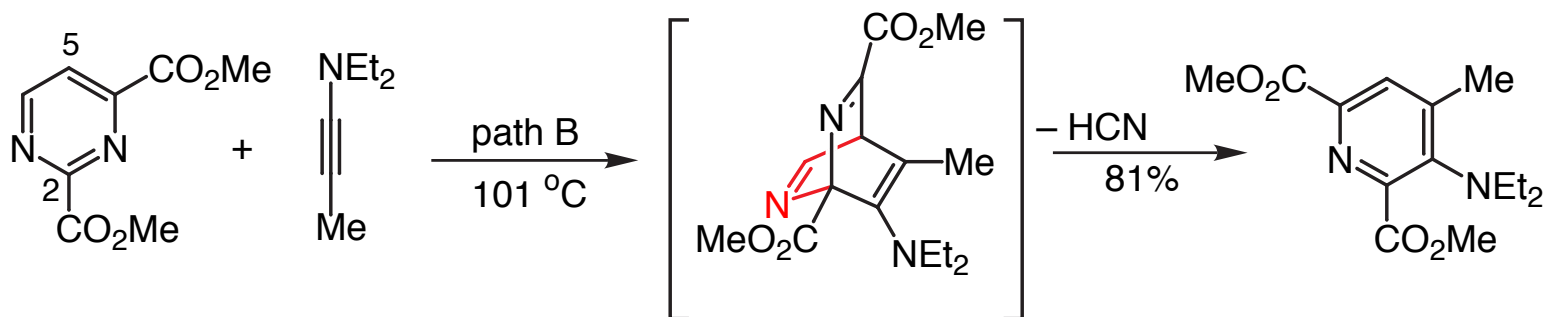
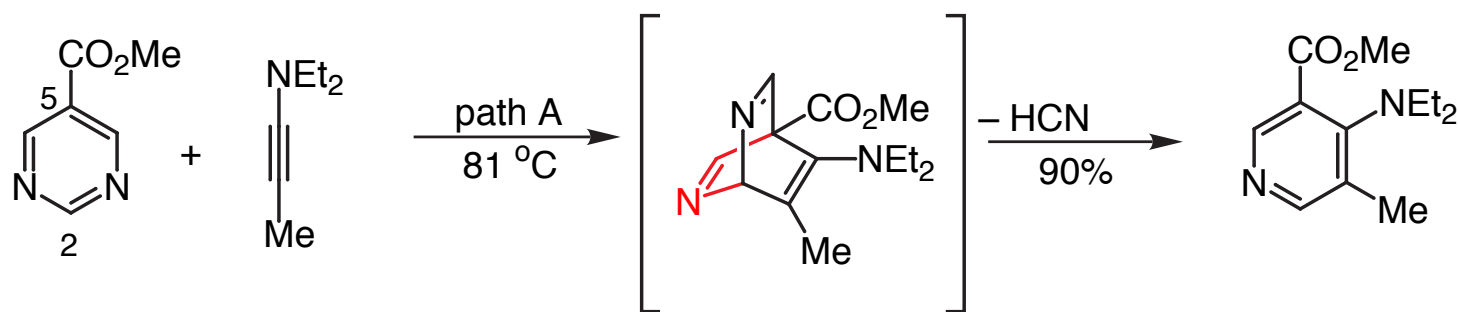
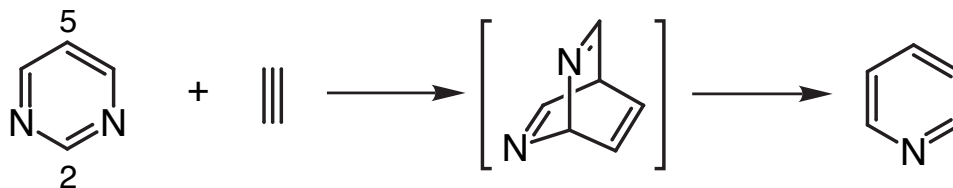
Landry, *Tetrahedron* **1983**, 39, 2761-2768.

CP as a Diene Protecting Group: Synthesis of (±)-8S, 14-Cedranediol



Landry, *Tetrahedron* **1983**, 39, 2761-2768.

Nitriles as Expelled Dienophiles: Pyridines From Pyrimidines

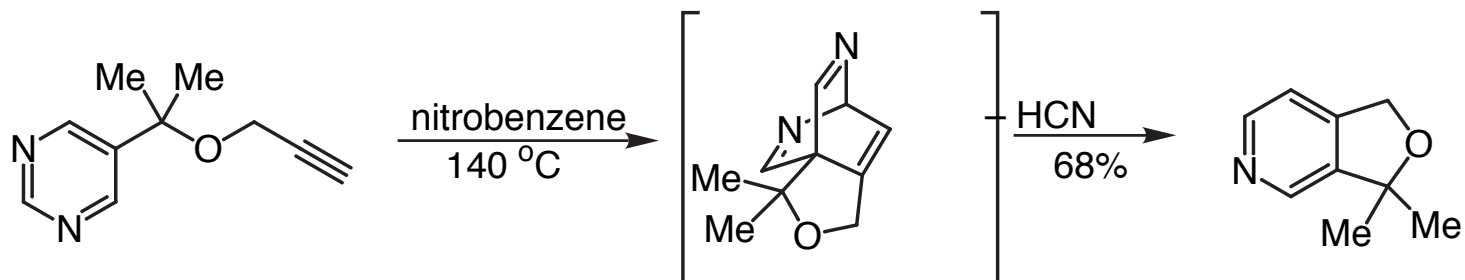


Rationale:

- The dienophile attacks at C-2 and C-5 of the pyrimidine ring.
- The dienophile is oriented so as to allow secondary orbital overlap with the ester.

Neunhoeffer, *Justus Liebigs Ann. Chem.* **1974**, 1190-1194.

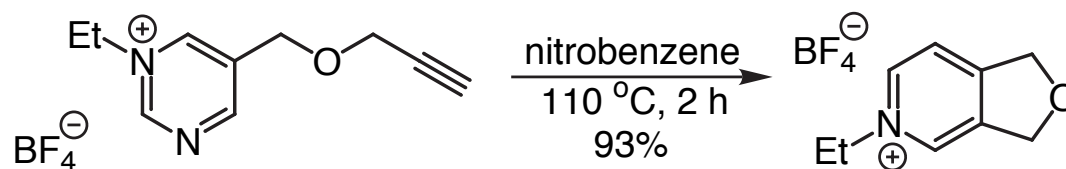
Intramolecular DA-rDA Reactions of Pyrimidines: van der Plas



- Geminal substitution at the α -position increases the reaction rate.

van der Plas, *Tetrahedron* **1989**, 5622-5620.

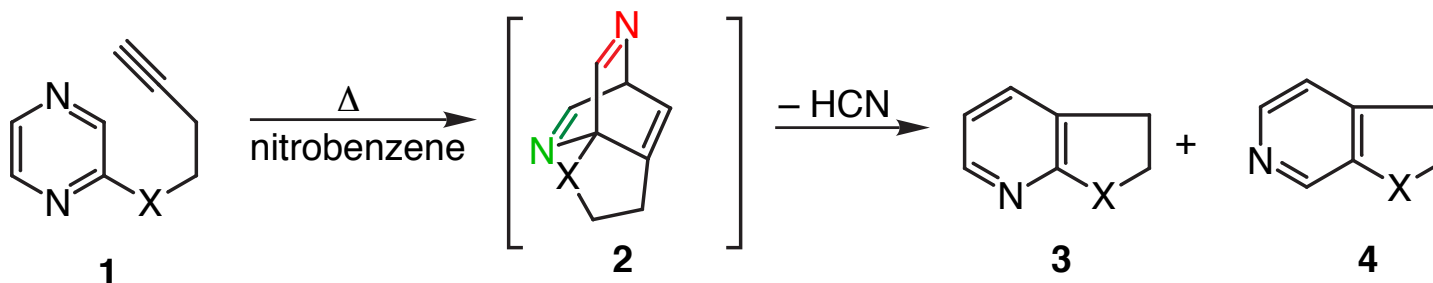
- *N*-Alkylation accelerates the reaction:



- The neutral compound required heating at 140 °C for 17 hours.

van der Plas, *Tetrahedron* **1990**, 595-606.

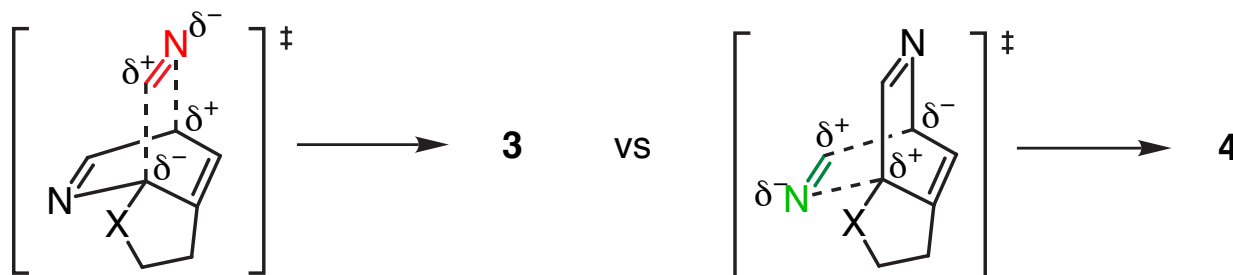
Nitriles as Expelled Dienophiles: Pyrazines



pyrazine	X	products (% yield)
1a	NC(O)CH ₃	3a (17), 4a (83)
1b	O	3b (12), 4b (44)
1c	S	3c (24), 4c (68)
1d	SO	3d (57)
1e	SO ₂	3e (88)

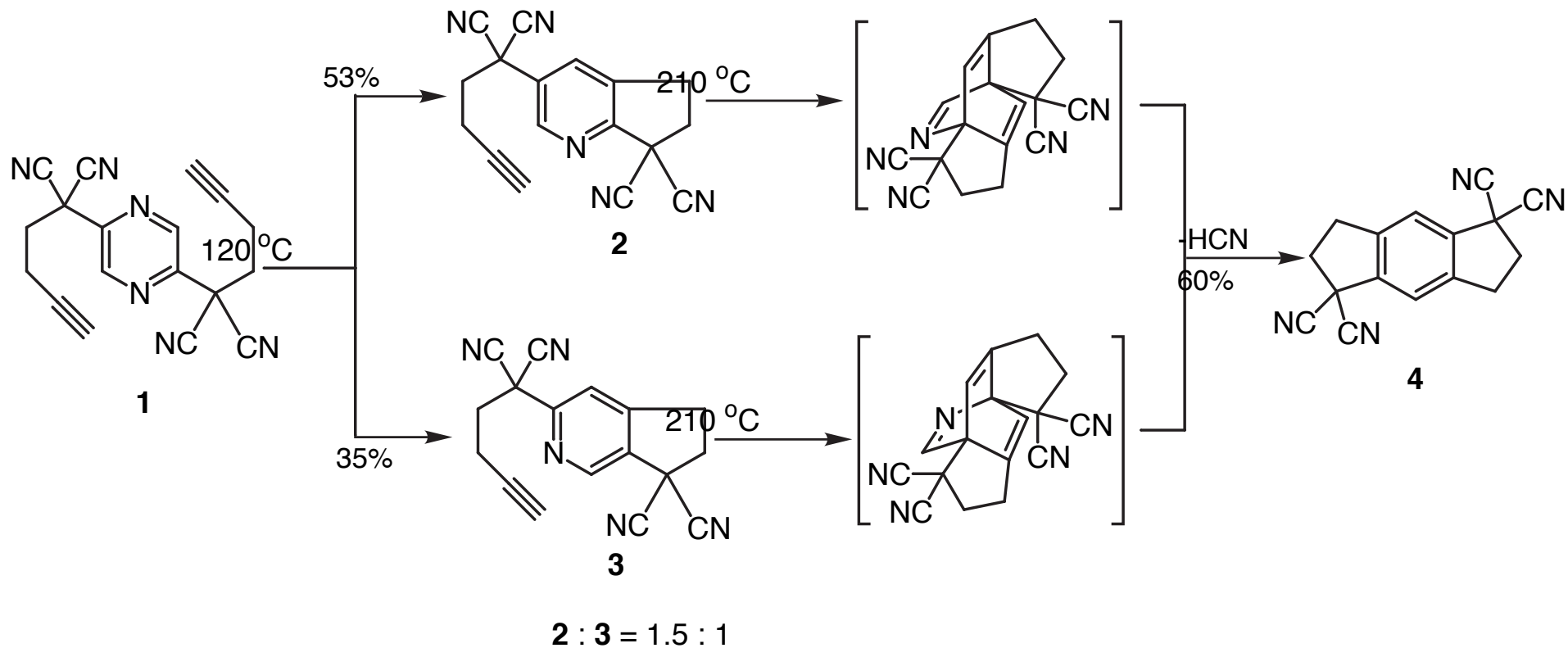
Rationale:

- Electron-donating substituents X favor the development of an adjacent positive charge in the transition state, which leads to **4**.



van der Plas, *Tetrahedron* **1988**, 2977-2983.

Nitriles as Expelled Dienophiles: Pyrazines

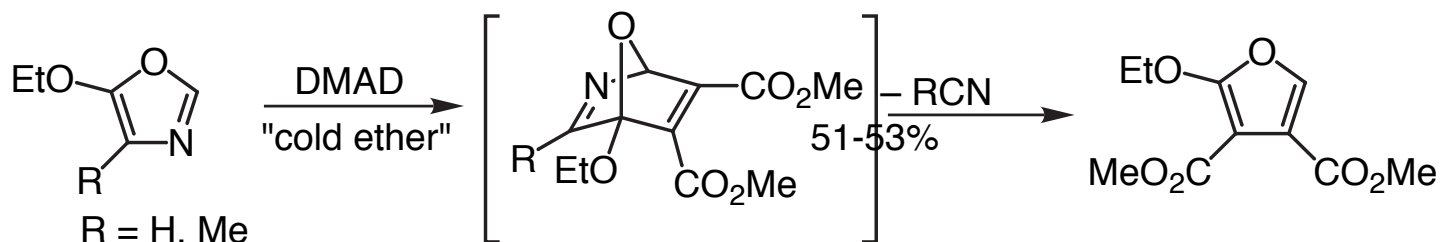


- **4** could also be obtained in one step by heating **1** at 210 °C.

van der Plas, *Tetrahedron* **1988**, 2977-2983.

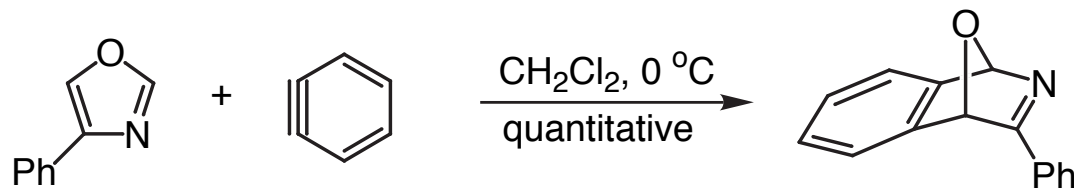
Nitriles as Expelled Dienophiles: Oxazoles

- Initial observation:



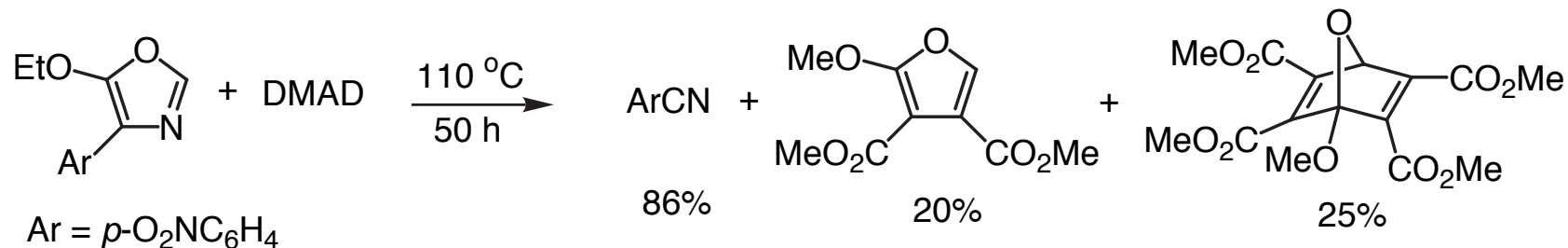
Grigg, *J. Chem. Soc., Chem. Commun.* **1969**, 1167-1168.

- The intermediate cycloadduct can be isolated at low temperatures:



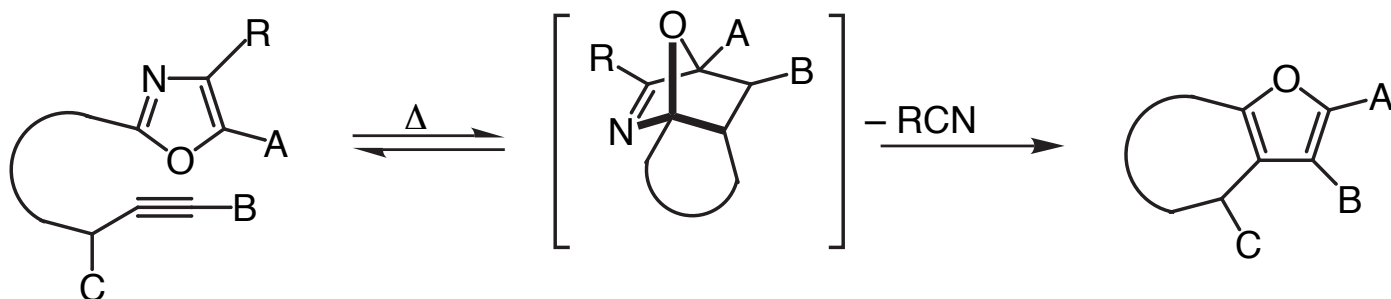
Rickborn, *J. Org. Chem.* **1988**, 53, 5595-5596.

- The furan produced in this reaction can react further:

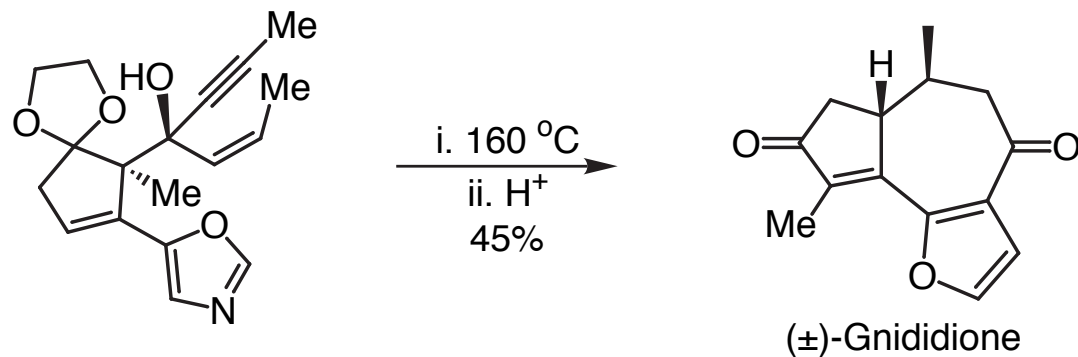


Ibata, *Bull. Chem. Soc. Japan* **1986**, 59, 433-437.

Jacobi: Bis-Heteroannulation

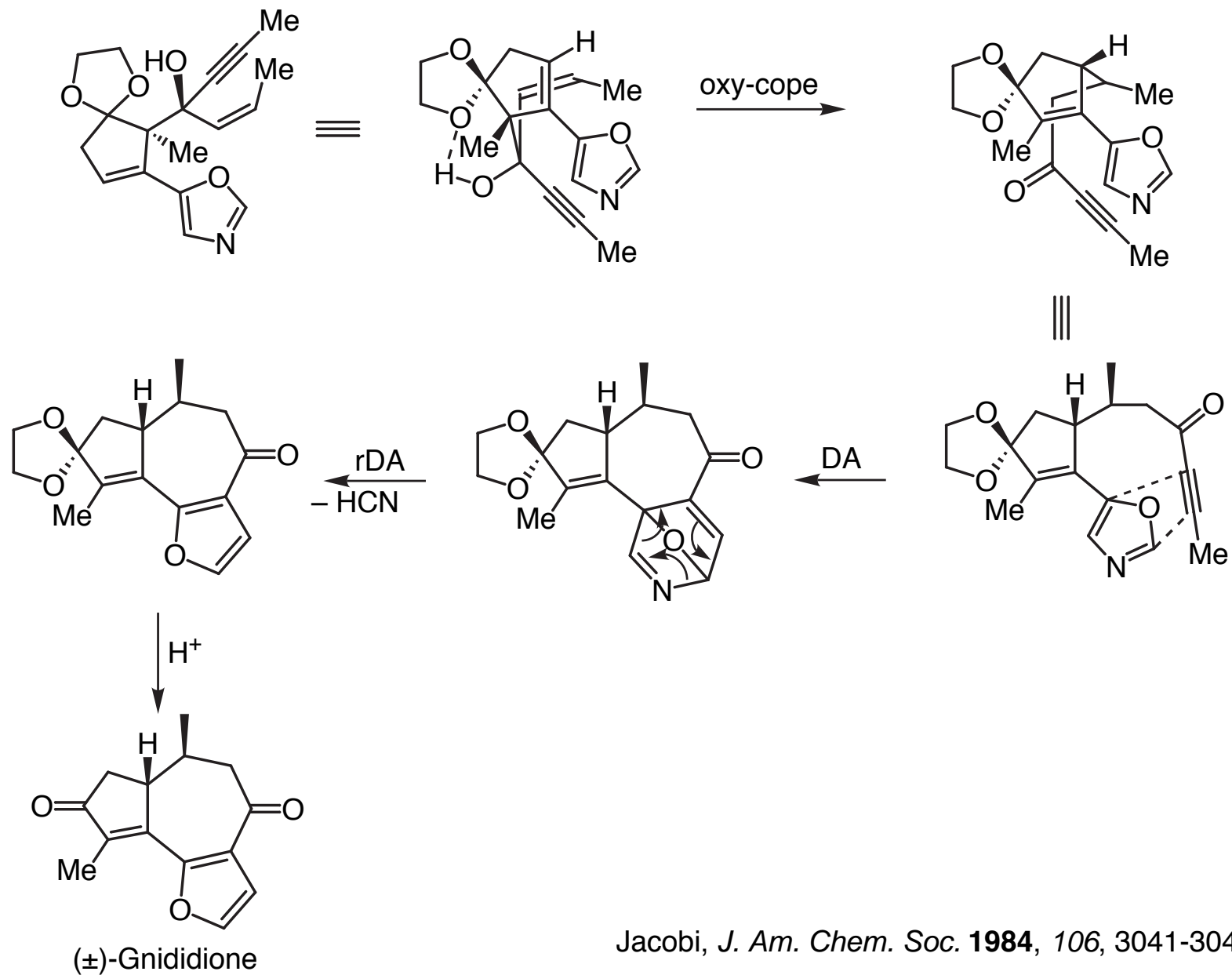


Jacobi, *Adv. Heterocycl. Nat'l Prod. Synth.* **1992**, 2, 251.



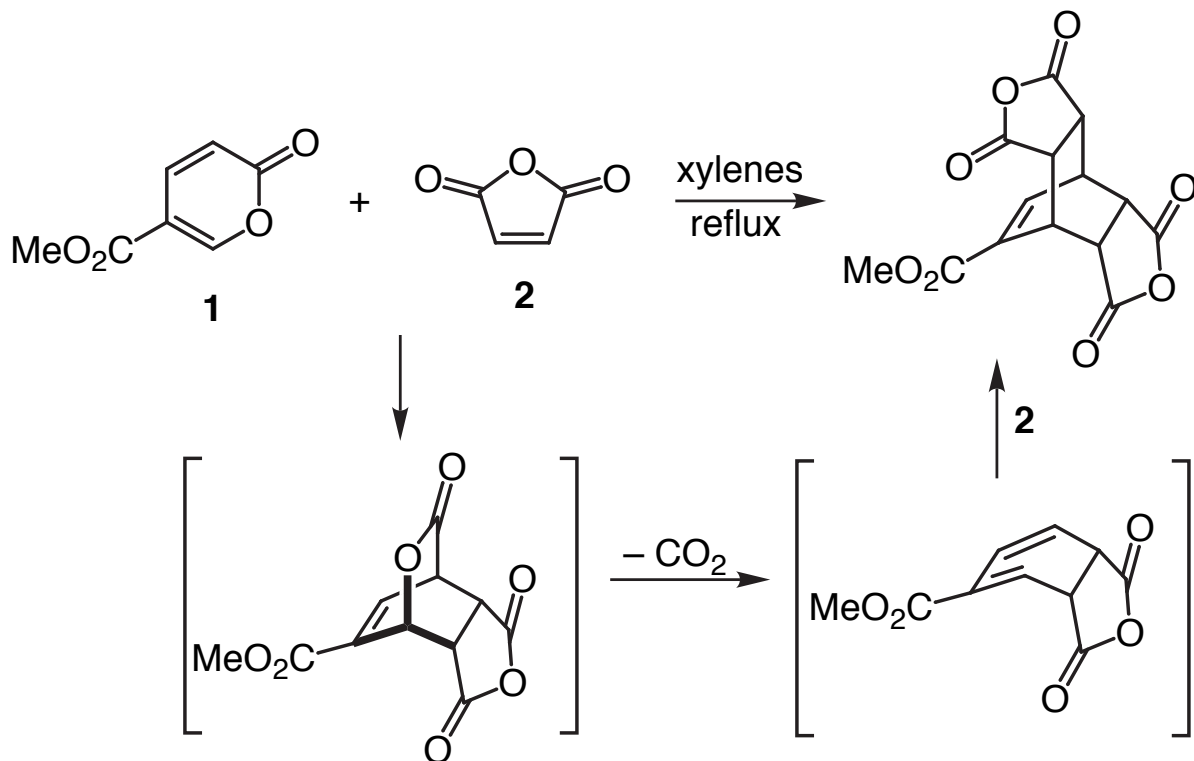
Jacobi, *J. Am. Chem. Soc.* **1984**, 106, 3041-3045.

An Oxy-Cope-DA-rDA Sequence



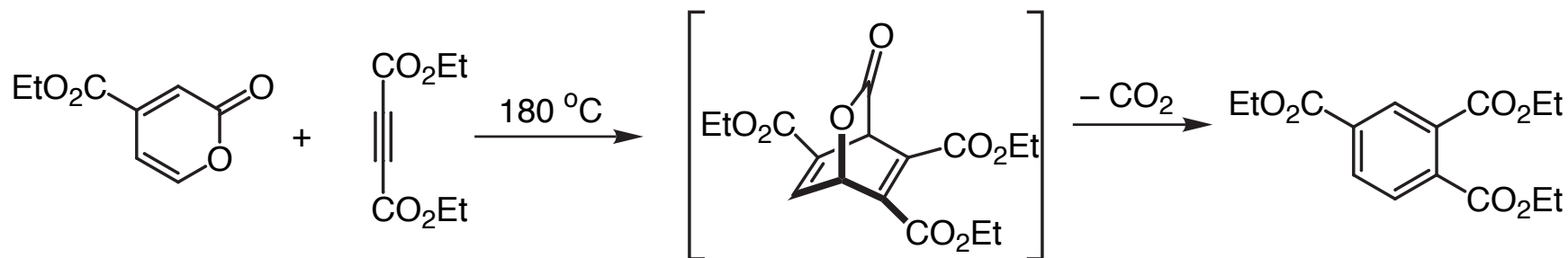
Jacobi, *J. Am. Chem. Soc.* **1984**, *106*, 3041-3045.

CO₂ as the Expelled Dienophile: 2-Pyrones



Diels, Alder, *Justus Liebigs Ann. Chem.* **1931**, 490, 257-266.

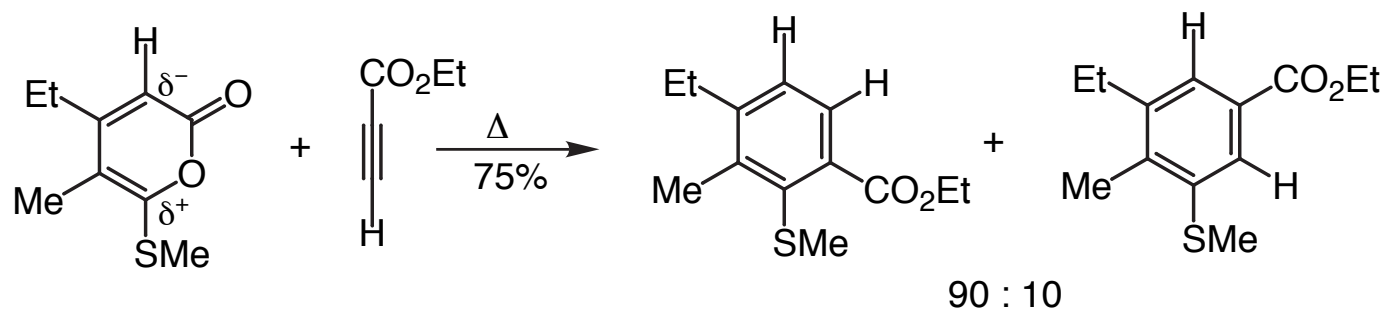
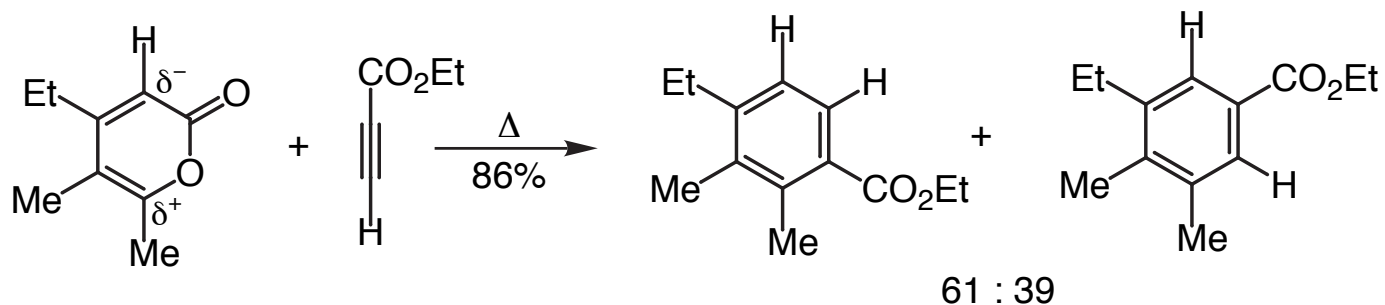
- With alkynes:



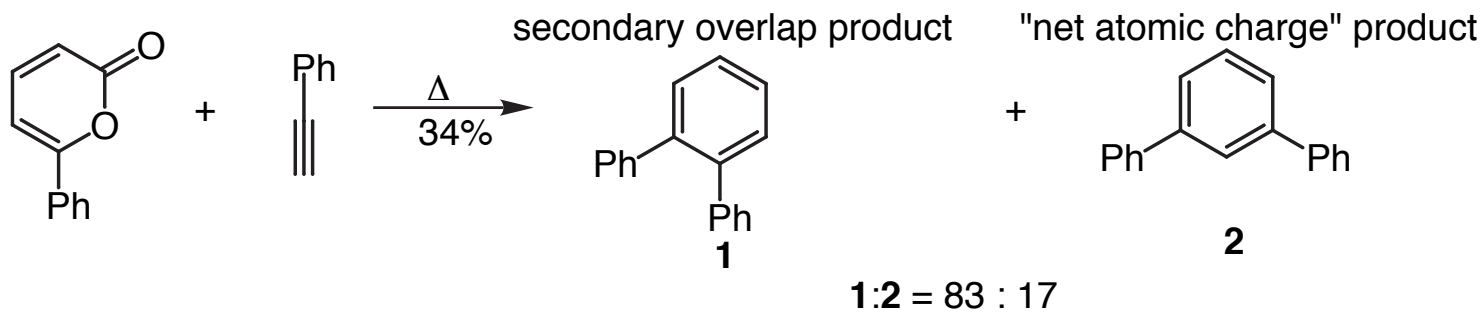
Alder, *Chem. Ber.* **1937**, 70, 1354-1363.

DA-rDA Reactions of 2-Pyrones: Regioselectivity

- The regioselectivity of the cycloaddition is consistent with an asynchronous transition state.
- Secondary orbital overlap can dramatically affect the regioselectivity.

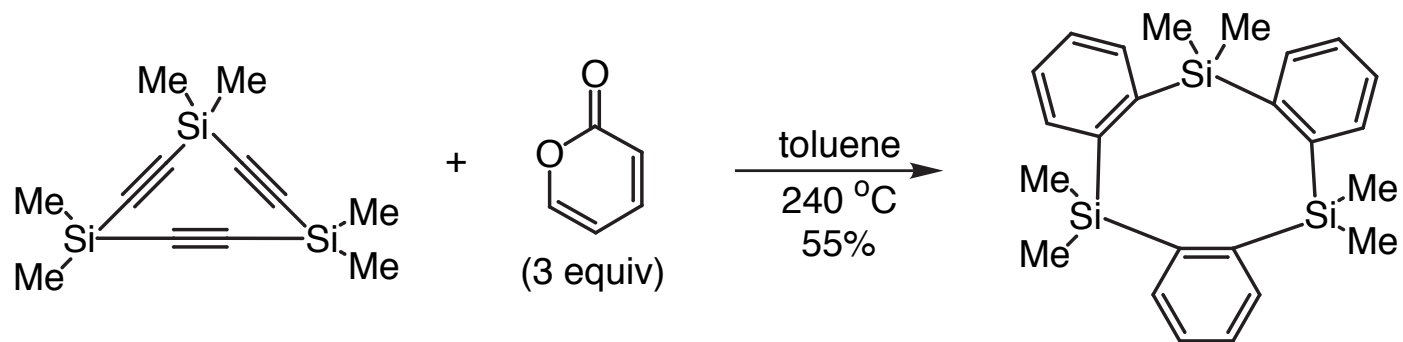


Dieter, *Tetrahedron* **1988**, 70, 1915-1924.

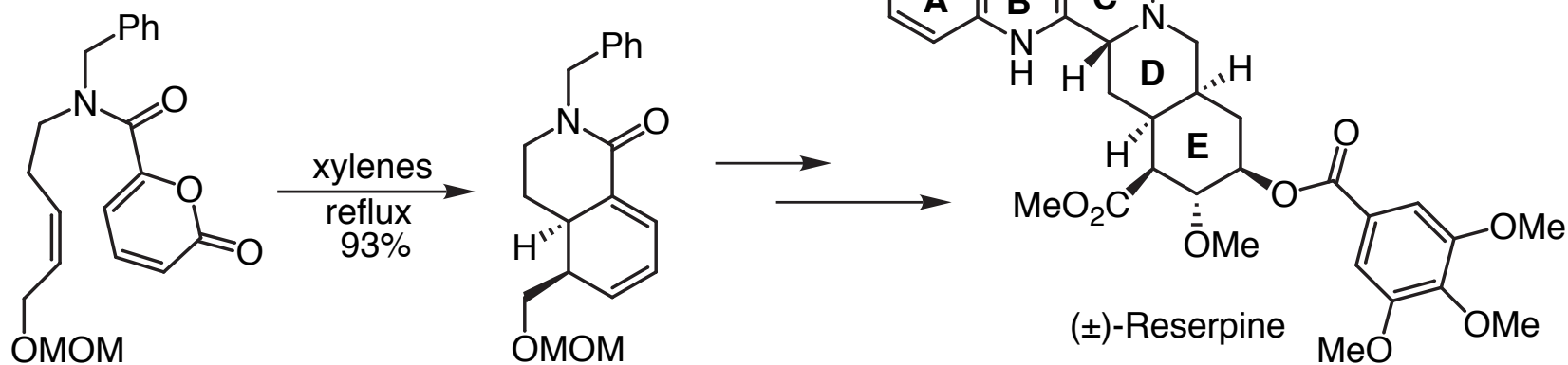


Stille, *Macromolecules* **1978**, 11, 340-343.

DA-rDA Reactions of 2-Pyrones: Applications

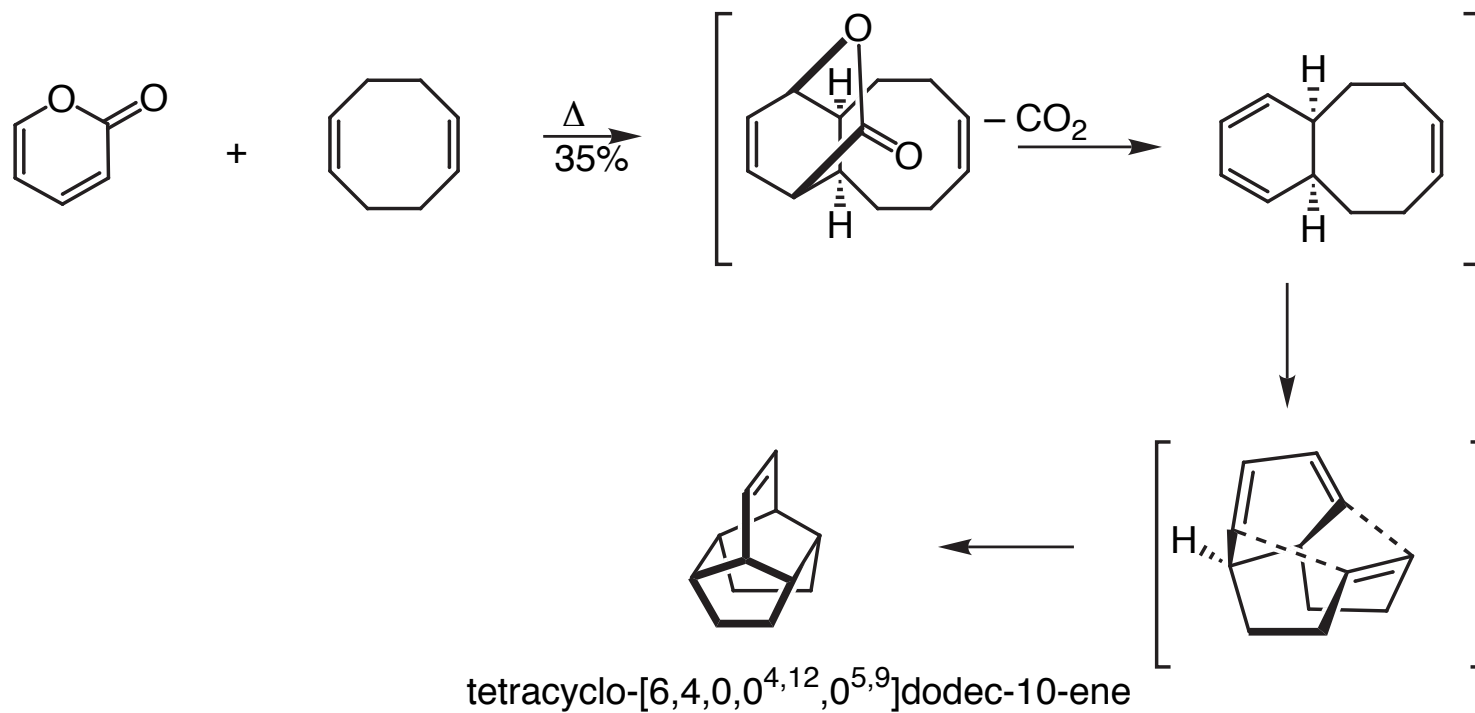


Sakurai, *Chemistry Lett.* **1984**, 595-598.



Martin, *J. Am. Chem. Soc.* **1987**, 6124-6134.

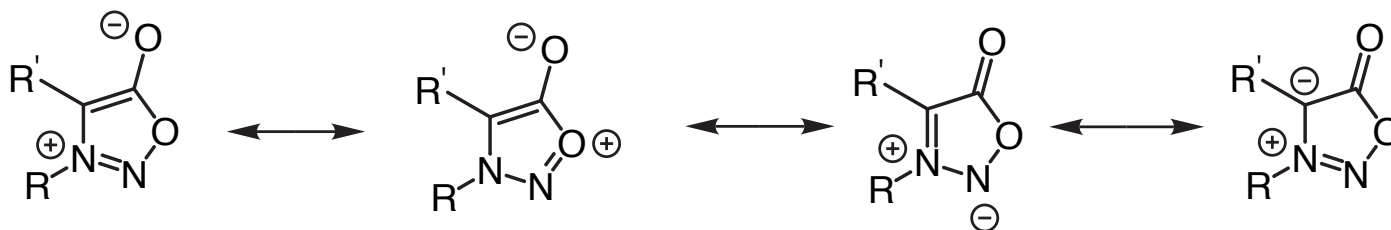
Reactions of 2-Pyrones with Alkenes



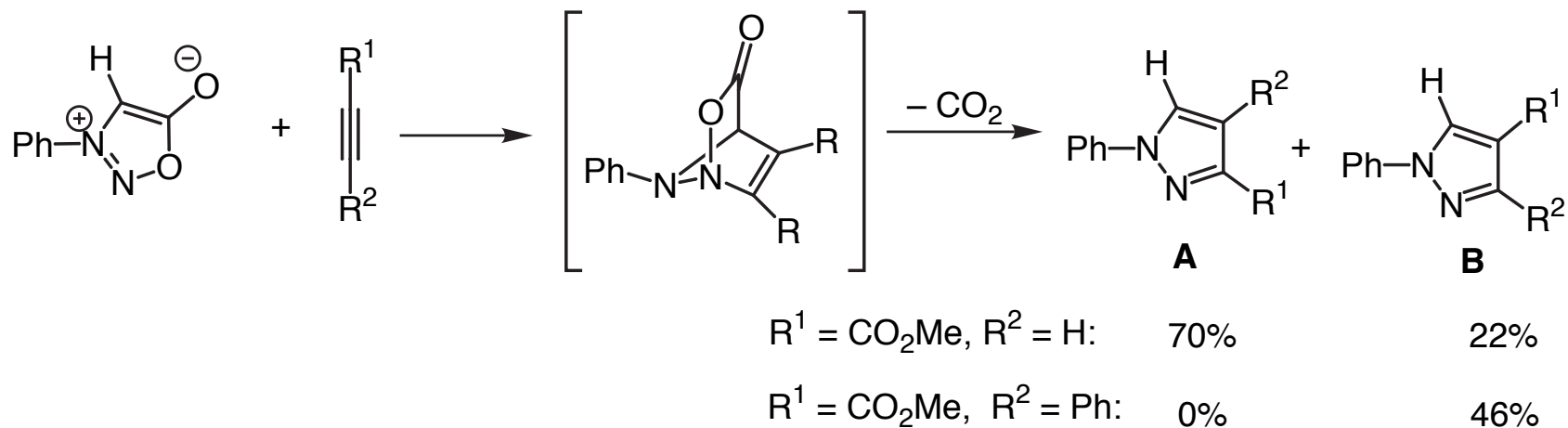
Fray, *J. Chem. Soc. (C)* **1968**, 812-815.

Reactions of Mesionics with Alkynes

- Mesionics: a class of heterocycles for which zwitterionic 1,3-dipolar resonance forms can be written.



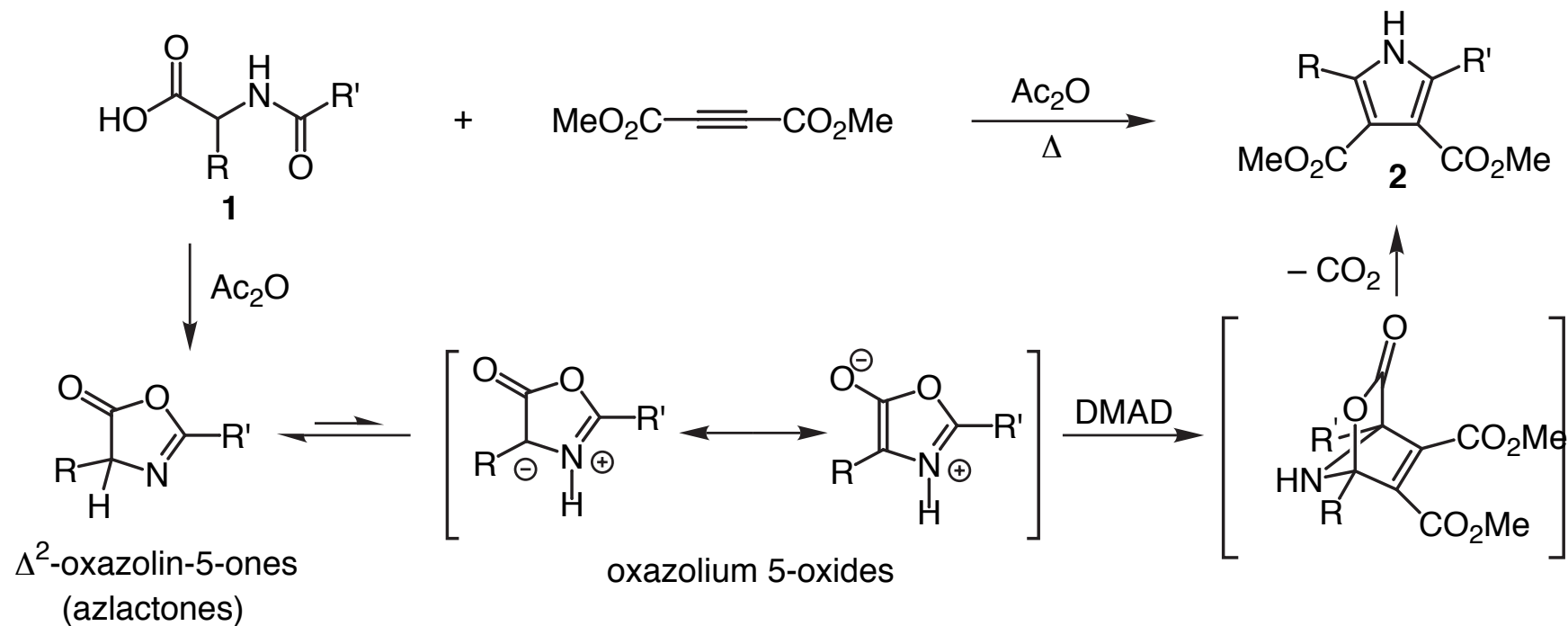
- Sydnones react with alkynes via a [3 + 2]-rDA sequence to afford pyrazoles.



- Monosubstituted alkynes can afford mixtures of products.
- Ph substitution reverses the regioselectivity.

Huisgen, *Chem. Ber.* **1968**, *101*, 536-551.

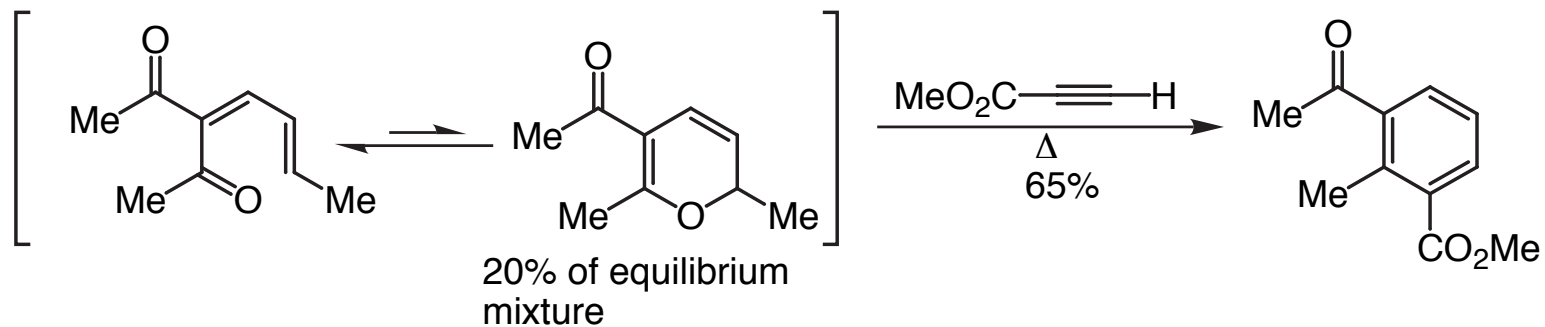
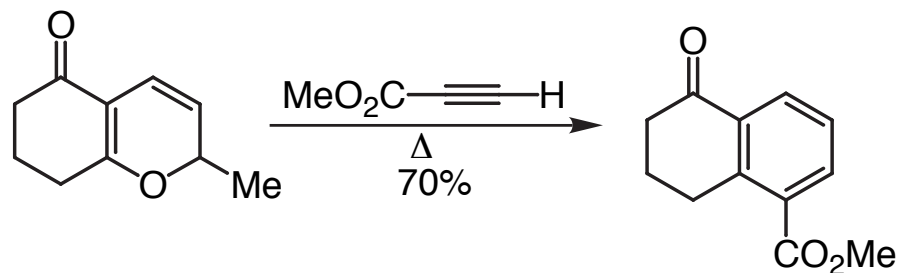
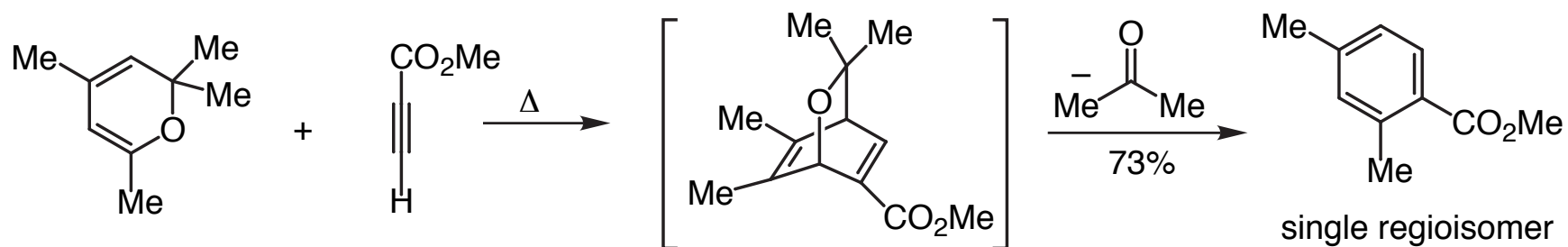
Synthesis of Pyrroles from Amino Acids and Alkynes



entry	1	R	R'	pyrrole 2	% yield
1	a	Ph	Ph	a	93
2	b	Ph	<i>p</i> -MeO-Ph	b	98
3	c	Ph	α -naphthyl	c	85
4	d	Ph	<i>p</i> -Cl-Ph	d	99
5	e	Ph	CH_3	e	78
6	g	Ph	cyclohexyl	g	93

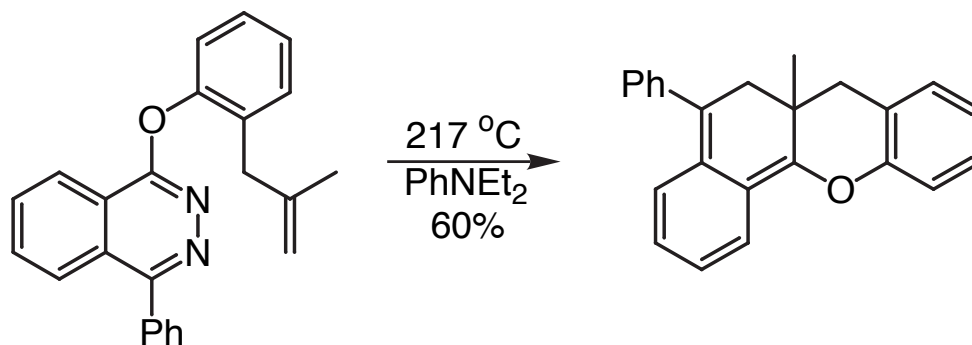
Huisgen, *Chem. Ber.* **1970**, 103, 2356-2367.

Carbonyl Compounds as Expelled Dienophiles

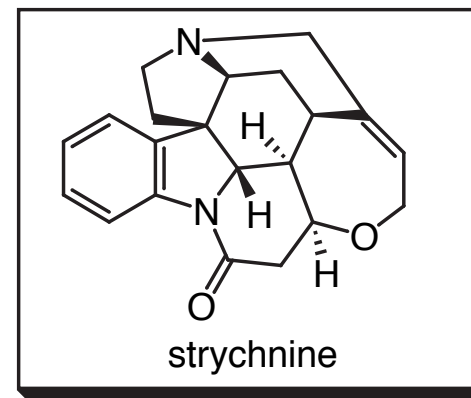
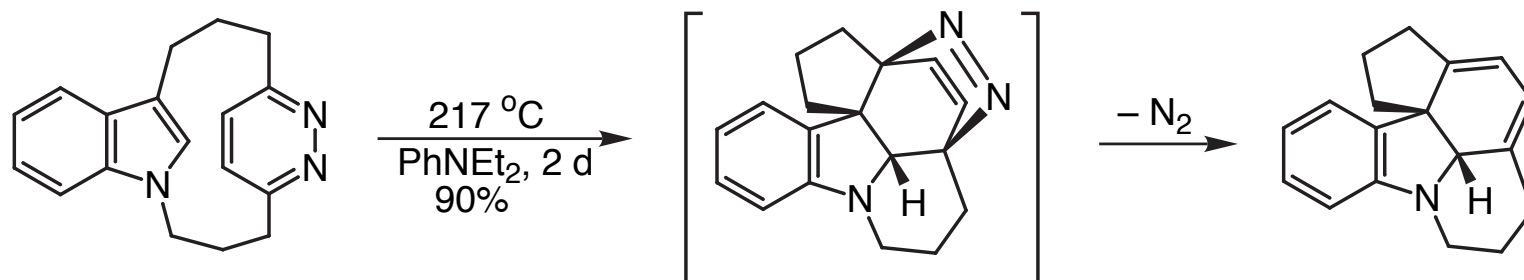


Salomon, *J. Org. Chem.* **1976**, *41*, 2918-2920.

N₂ as the Expelled Dienophile: DA-rDA Reactions of Pyridazines



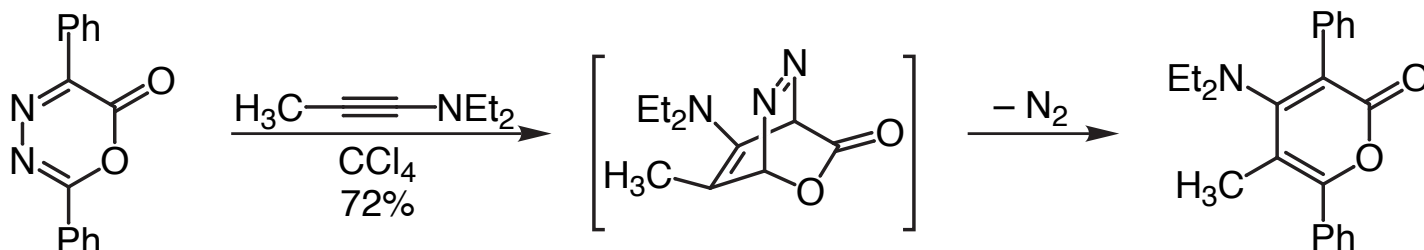
Jojima, *Chem. Pharm. Bull.* **1976**, 24, 1581-1587.



Bodwell, *Org. Lett.* **2002**, 127-130.

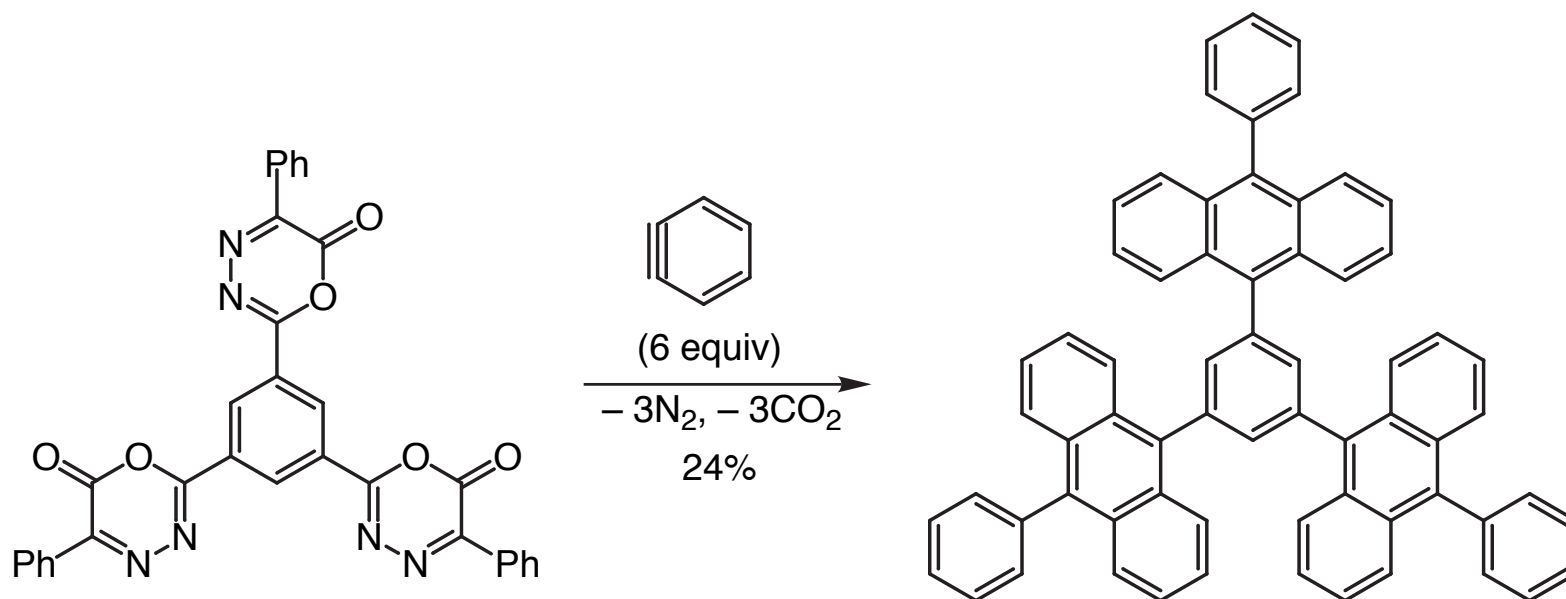
Cycloadditions of 1,3,4-Oxadiazin-6-ones

- 1,3,4-oxadiazin-6-ones behave like pyridazines in DA-rDA processes:



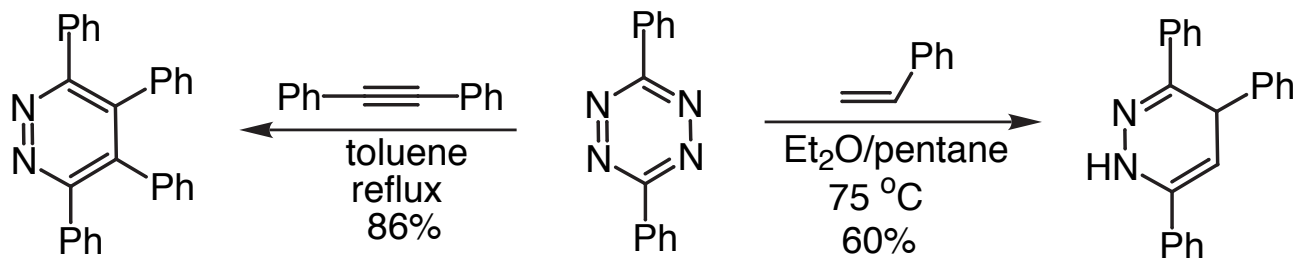
Steglich, *Synthesis* **1977**, 252-253.

- With more reactive dienophiles, the loss of N_2 is followed by a second DA-rDA sequence:

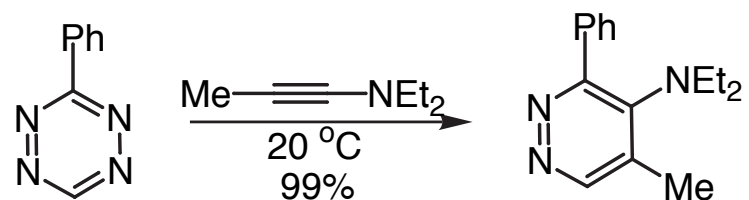


Gansen, G. Dissertation, Universität Bonn, 1983. Cited in: Christl, M. *Gazz. Chim. Ital.* **1986**, 116, 1-17.

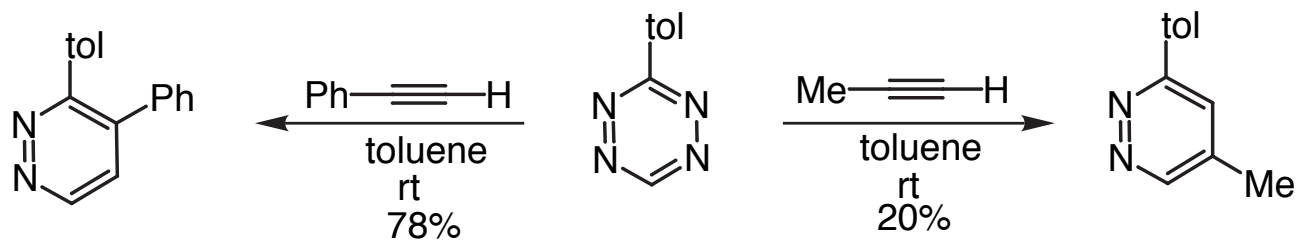
Tetrazines: The Carboni-Lindsey Reaction



Carboni, Lindsey, *J. Am. Chem. Soc.* **1959**, *81*, 4342-4346.



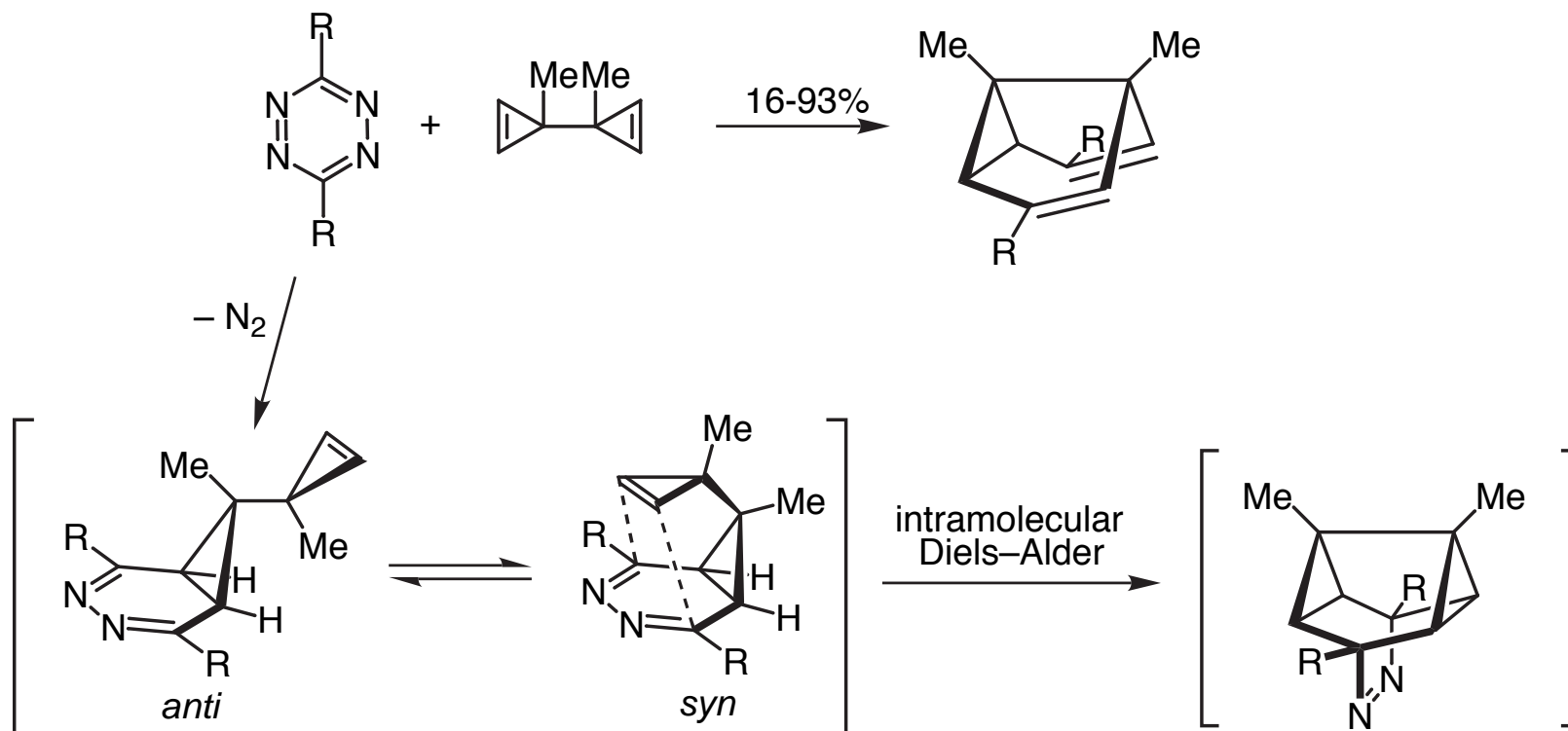
Steigel, Sauer, *Tetrahedron Lett.* **1970**, *38*, 3357-3360.



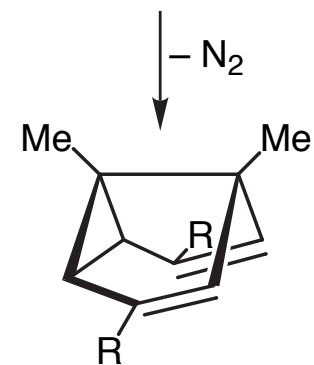
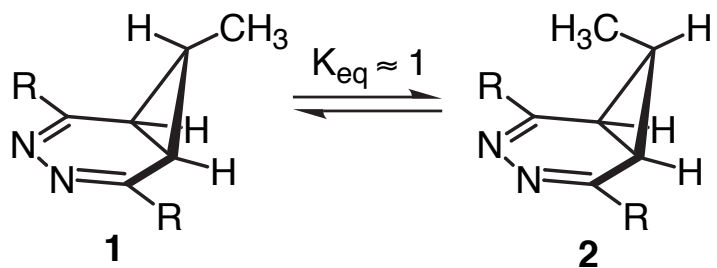
Meresz, *J. C. S. Chem. Comm.* **1972**, *16*, 950-951.

- The authors propose that the total change in the regioselectivity of this reaction with phenyl acetylene is due to a secondary orbital overlap effect.

A One-Pot Synthesis of Semibullvalenes



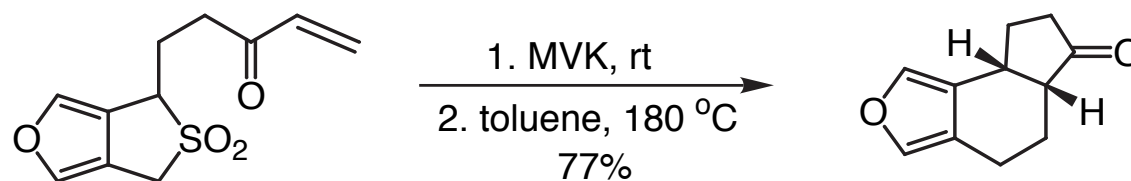
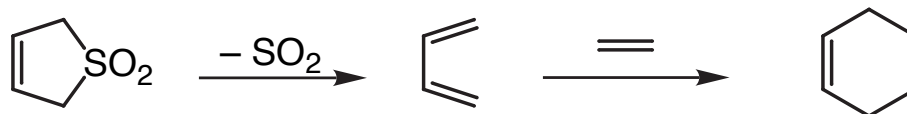
- The *anti* isomer could be observed when R = aryl.
- Additional evidence for this mechanism was provided by the observation that **1** slowly isomerizes to **2** at room temperature.



Sauer, *Eur. J. Org. Chem.* **2002**, 791-801.

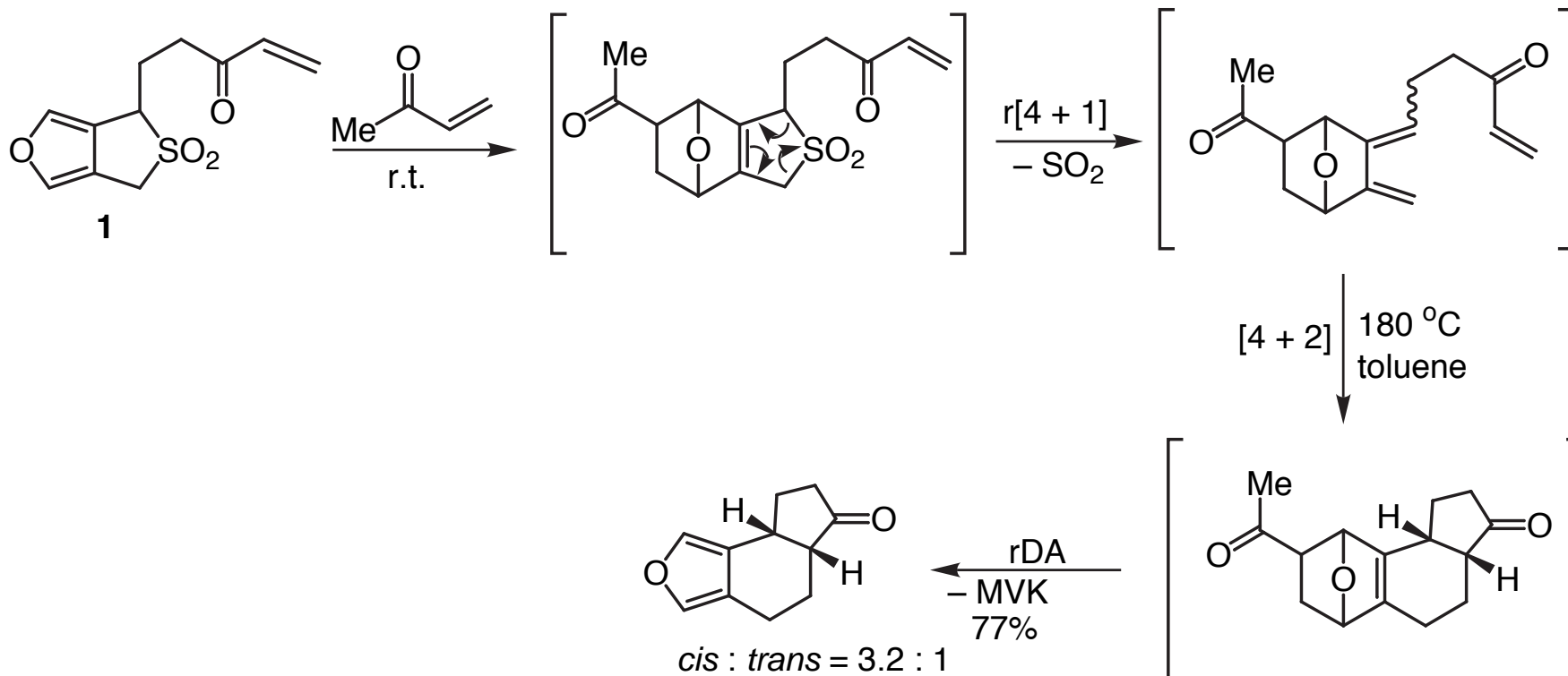
Merged Cycloaddition-Retro [4 + 1] Processes: SO₂ Extrusion

- 3-sulfolenes can serve as masked 1,3-butadienes:



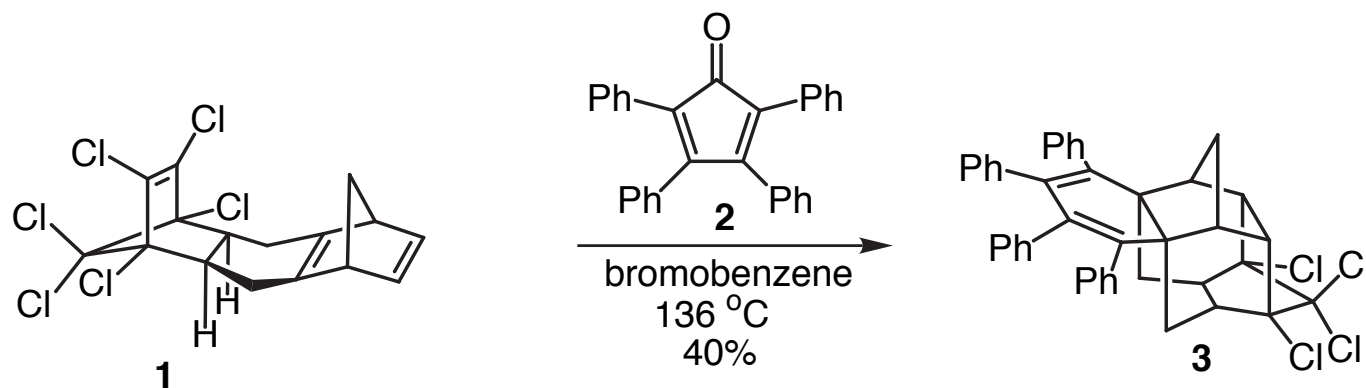
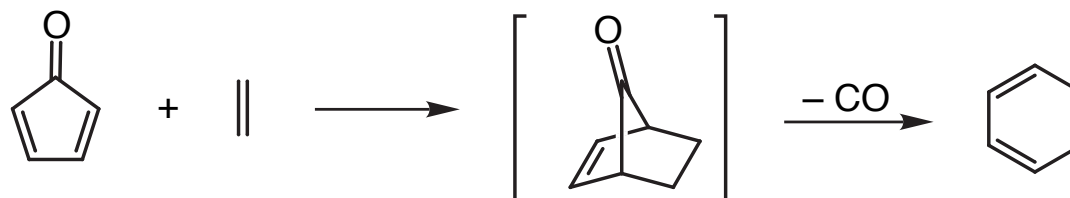
Takayama, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2263-2268.

Merged Cycloaddition-Retro [4 + 1] Processes: SO₂ Extrusion



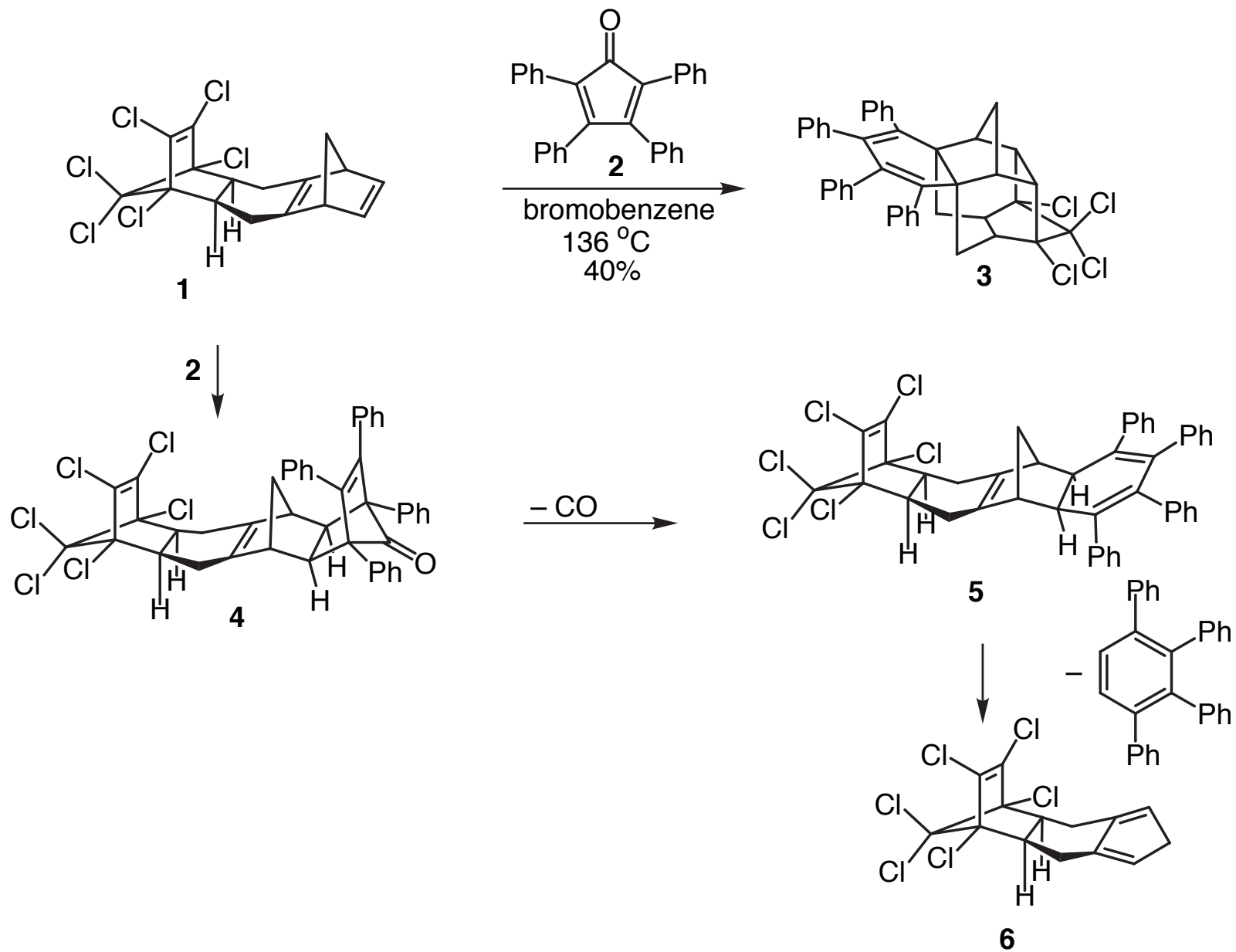
Takayama, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2263-2268.

Merged Cycloaddition-Retro [4 + 1] Processes: CO Extrusion

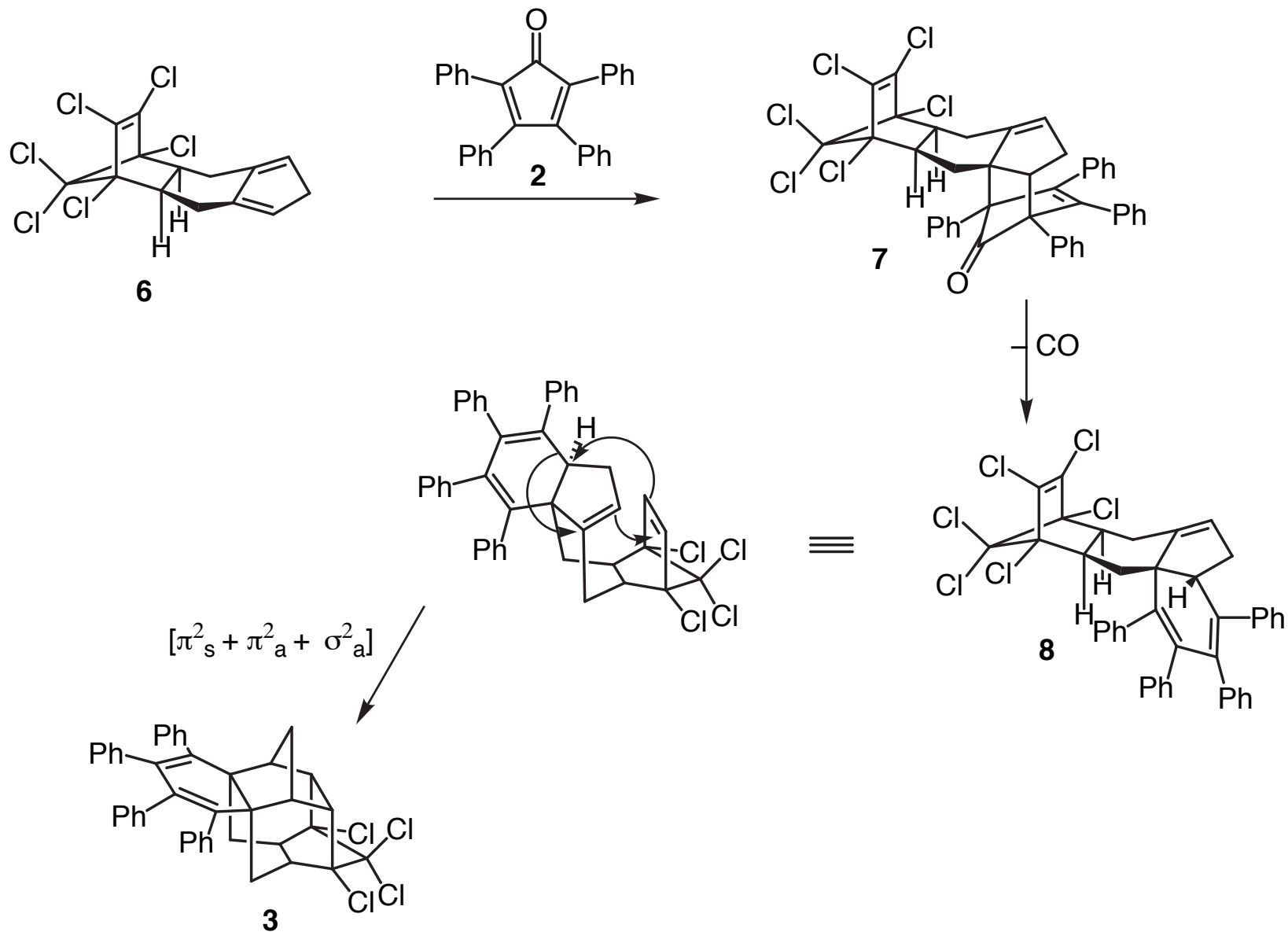


Howard, Mackenzie, *Tetrahedron* **1993**, 4699-4710.

Merged Cycloaddition-Retro [4 + 1] Processes: CO Extrusion



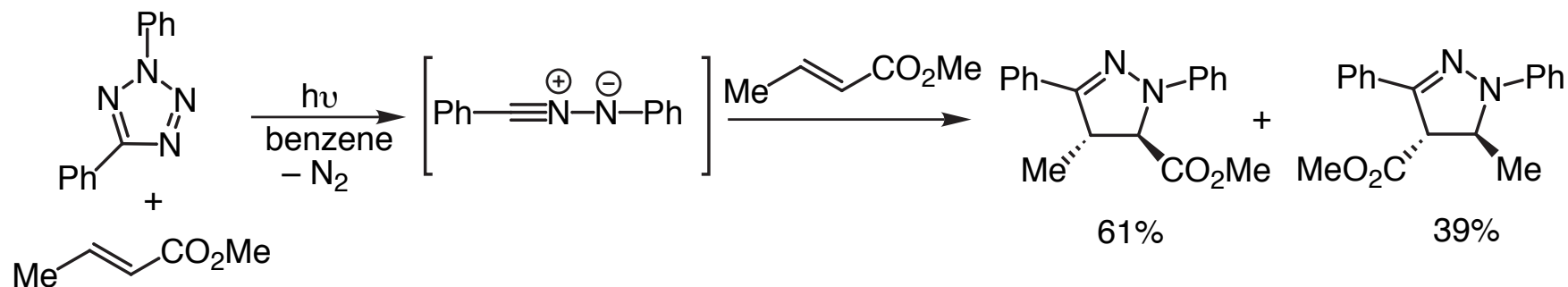
Merged Cycloaddition-Retro [4 + 1] Processes: CO Extrusion



Howard, Mackenzie, *Tetrahedron* **1993**, 4699-4710.

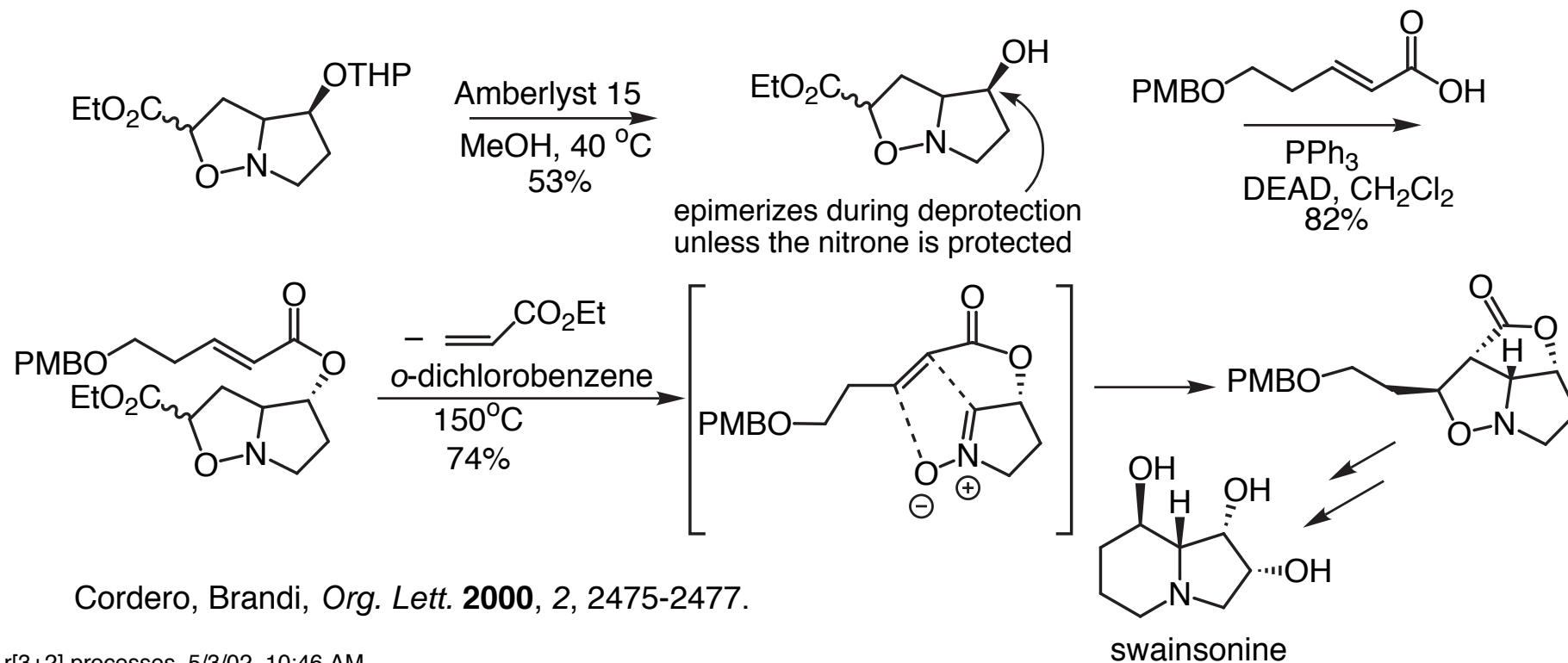
Merged [3 + 2]-Retro [3 + 2] Processes

- Retro [3 + 2] reactions have been used to generate 1,3-dipoles, which can be trapped *in situ* with dipolarophiles.



Huisgen, *Chem. Ber.* **1967**, 100, 60-70.

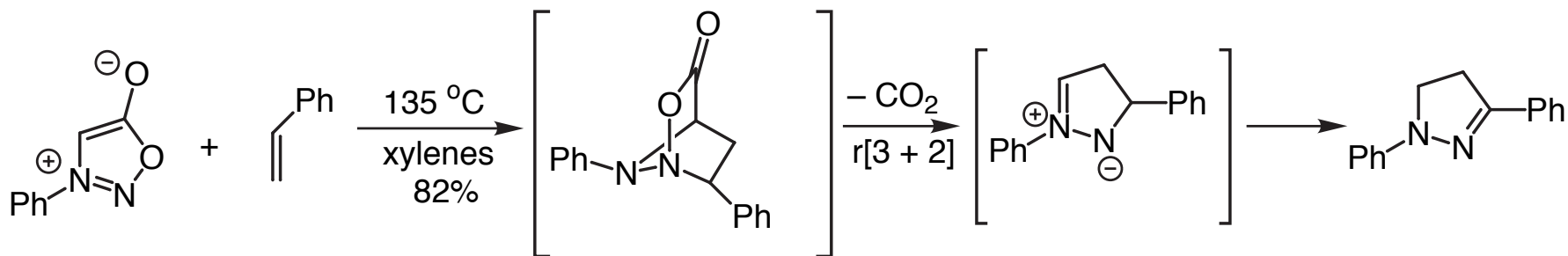
- Nitrones can be protected by cycloaddition, and then deprotected through a cycloreversion:



Cordero, Brandi, *Org. Lett.* **2000**, 2, 2475-2477.

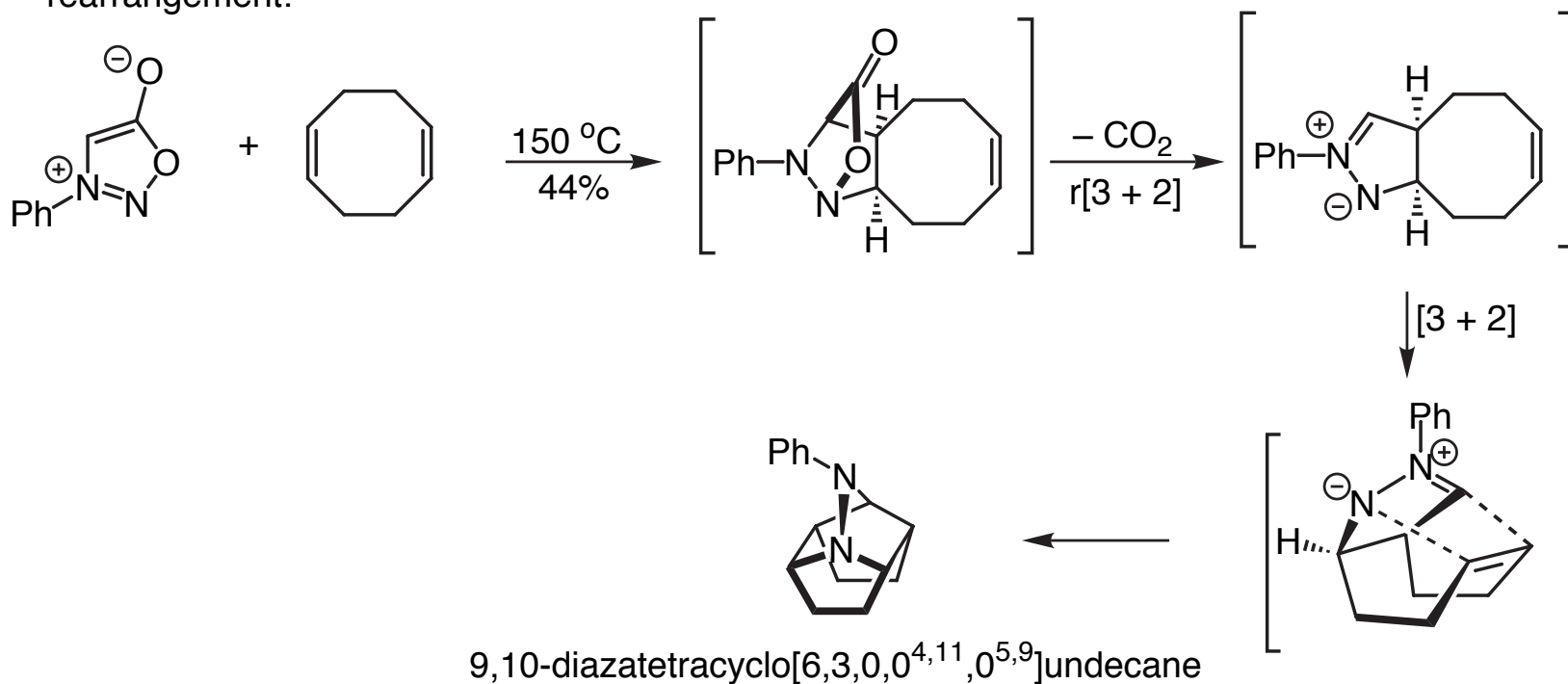
[3 + 2]-r[3 + 2] Reactions of Sydnone

- Reactions of sydnone with alkenes produce 2-pyrazolines:



Huisgen, *Chem. Ber.* **1968**, 101, 552-563.

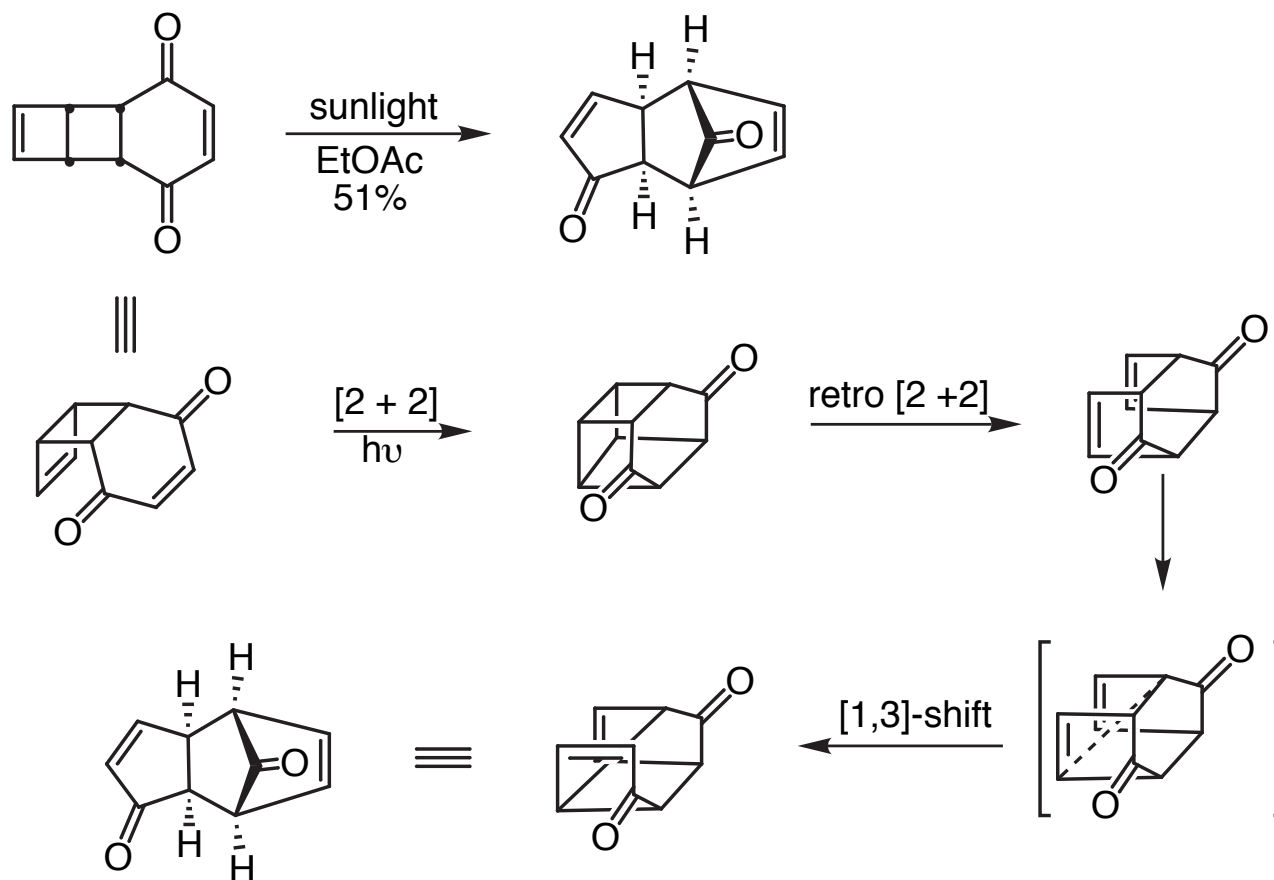
- The reaction of the azomethine intermediate with excess dipolarophile can be competitive with rearrangement:



Weintraub, *Chem. Comm.* **1970**, 101, 760-761.

Merged [2 + 2]-Retro [2 + 2] Processes

- Sunlight-mediated olefin metathesis:



Mehta, *Tetrahedron Lett.* **1991**, 32, 6403-6406.

Summary

- Merged cycloaddition-cycloreversion processes have been widely used for the synthesis of heterocycles and aromatics.
- Heteroatom dienophiles generally increase the rate of the retro-Diels-Alder reaction. Nitriles, CO₂, and N₂ are the most common.
- Cycloreversions are useful for generating dienes and 1,3-dipoles *in situ*.
- Complex polycyclic structures can be produced in one step through cycloaddition-cycloreversion cascades.