The [3+2] Cycloaddition Reaction

Lecture Notes

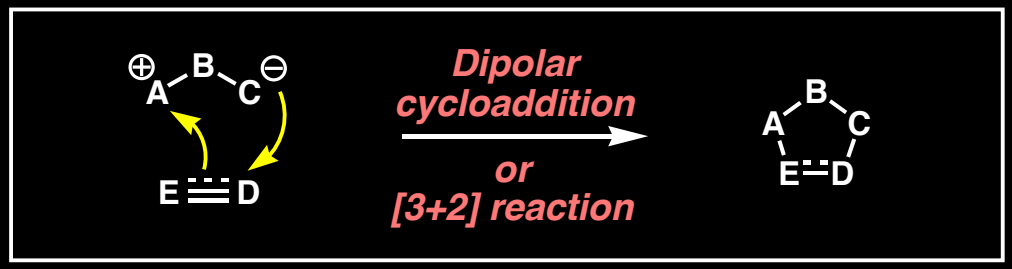
Key Reviews:

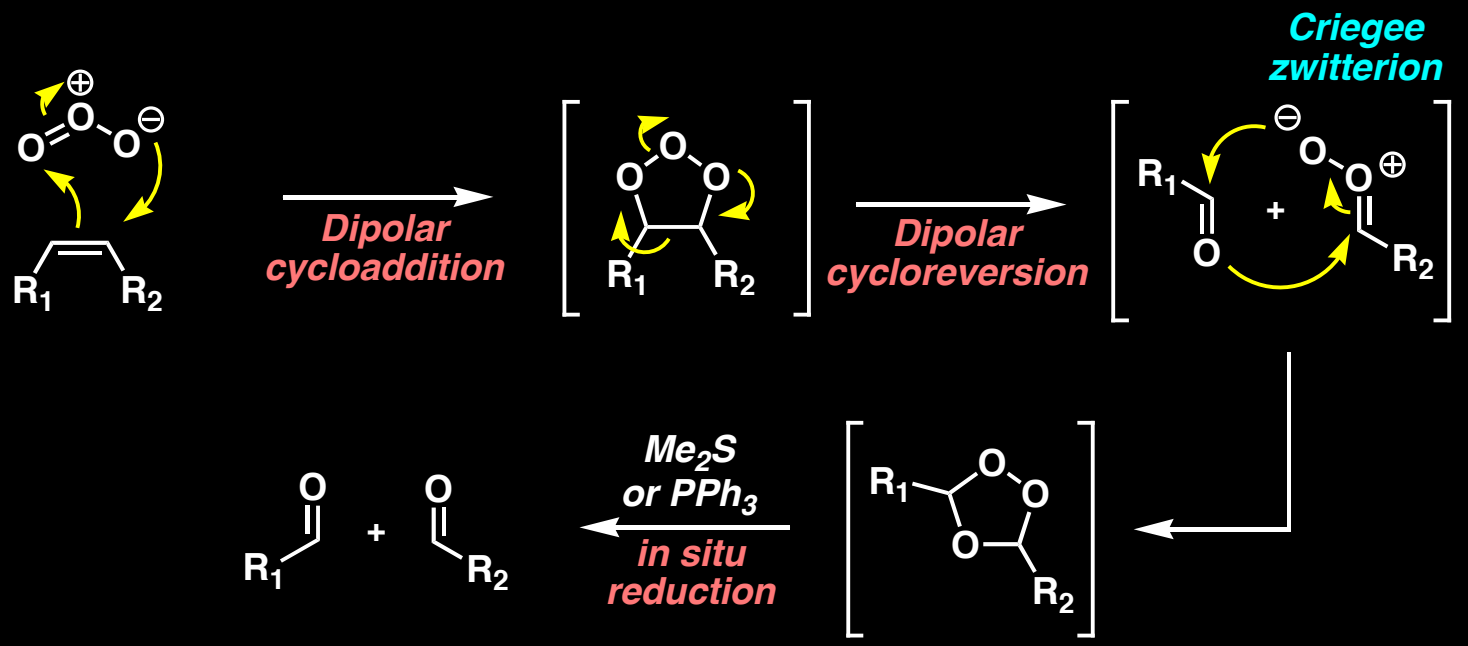
Asymmetric
K. V. Gothelf, K. A. Jorgensen, Chem. Rev. 1998, 98, 863.

Nitrones
P. N. Confalone, Org. React. 1988, 36, 1.

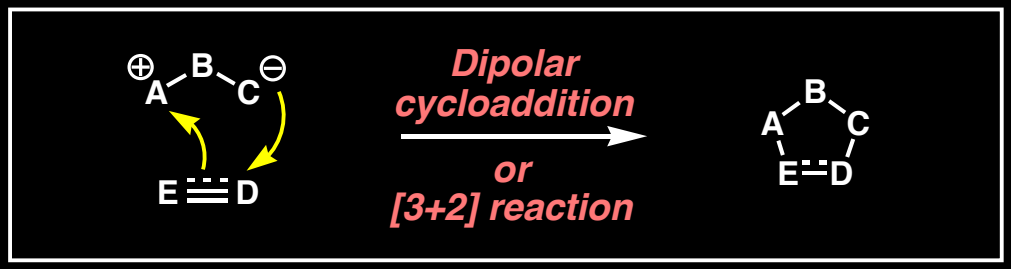
Azomethine Ylides
I. Coldhaim, R. Hufton, Chem. Rev. 2005, 105, 2765.

[3+2] Dipolar Cycloadditions: A Reaction You Have Seen Before

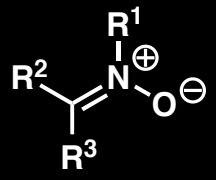




[3+2] Dipolar Cycloadditions: General Reaction and Classes of 1,3-Dipoles

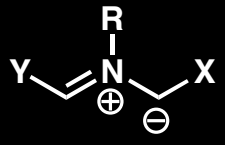


nitrile oxides

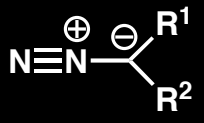


nitrones

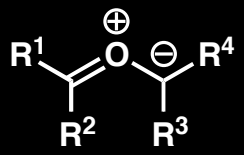
azides



azomethine ylides



diazoalkanes

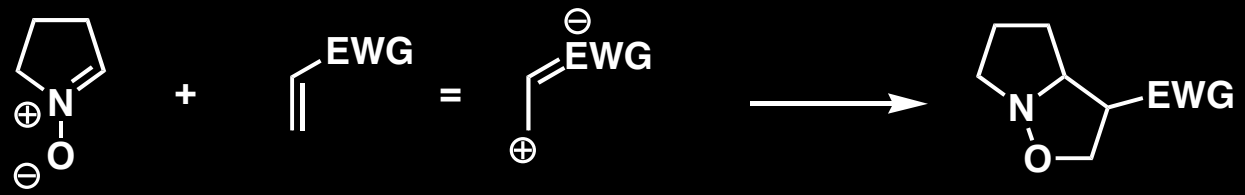


carbonyl ylides

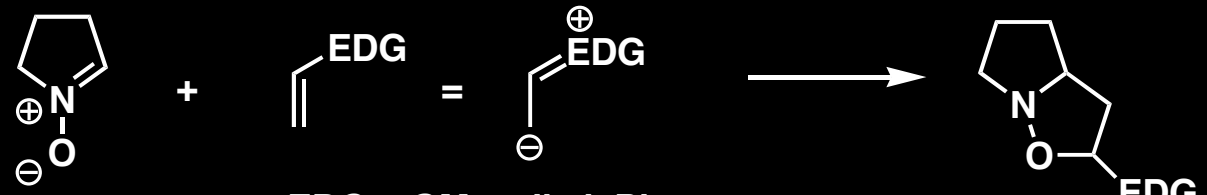
X = electron withdrawing group
Y = electron donating group

[3+2] Cycloadditions: Understanding Regio- and Diastereoselectivity

Regioselectivity



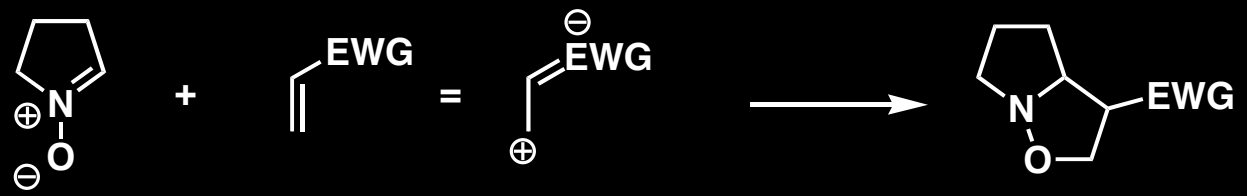
EWG = CO_2Et, NO_2



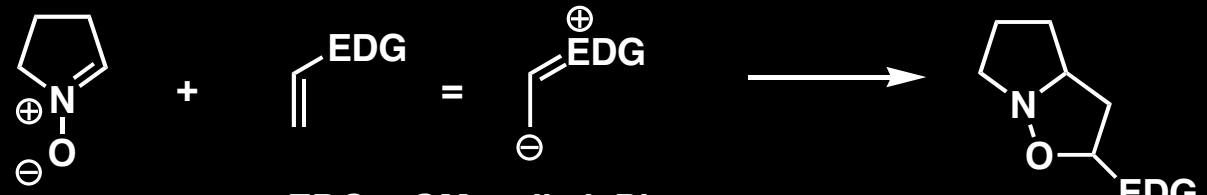
EDG = OMe, alkyl, Ph

[3+2] Cycloadditions: Understanding Regio- and Diastereoselectivity

Regioselectivity



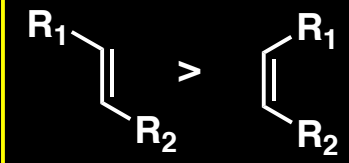
EWG = CO_2Et, NO_2



EDG = OMe, alkyl, Ph

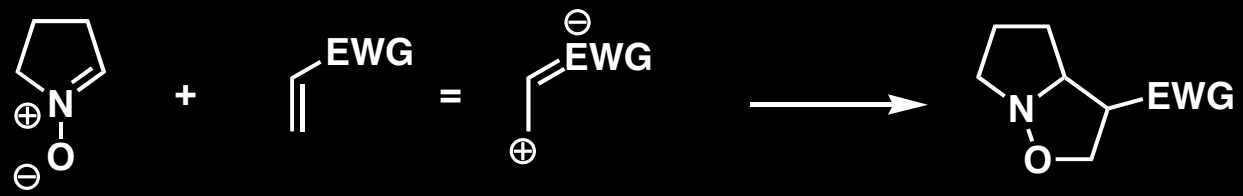
Note:
azides do not follow this trend

Reactivity:

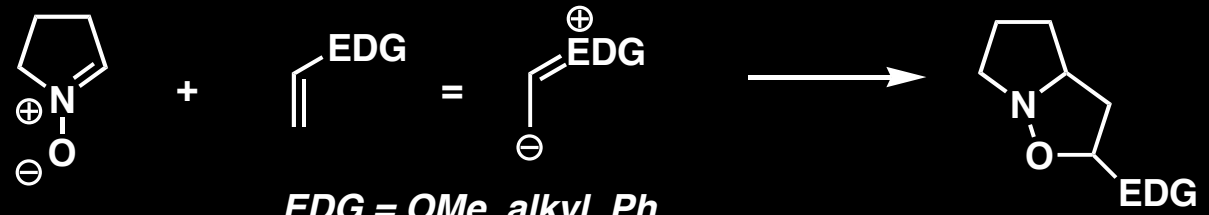


[3+2] Cycloadditions: Understanding Regio- and Diastereoselectivity

Regioselectivity



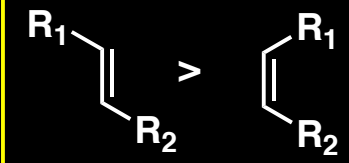
EWG = CO_2Et, NO_2



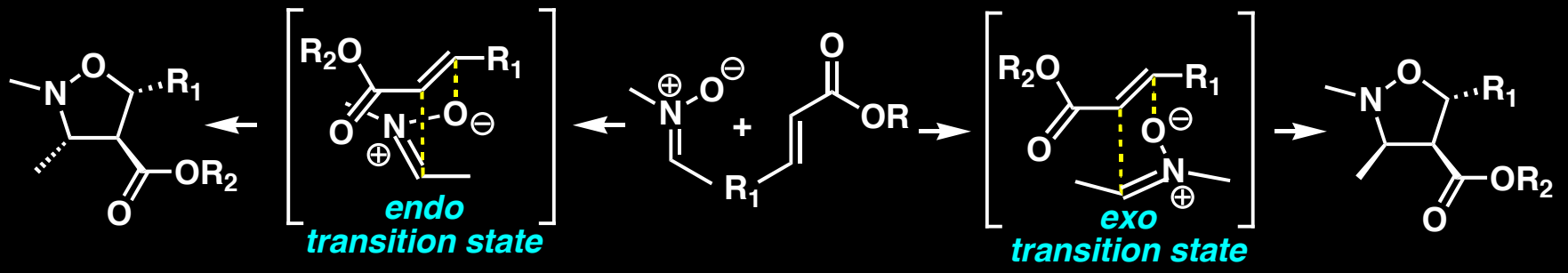
EDG = OMe, alkyl, Ph

Note: *azides do not follow this trend*

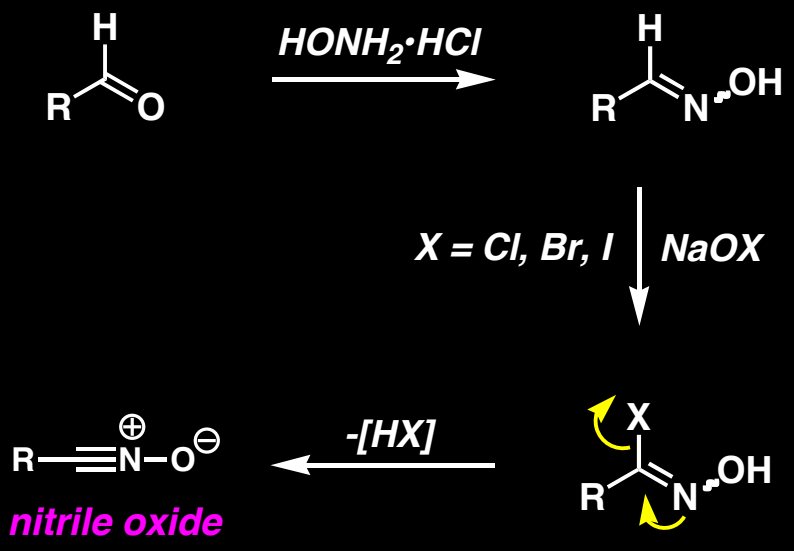
Reactivity:



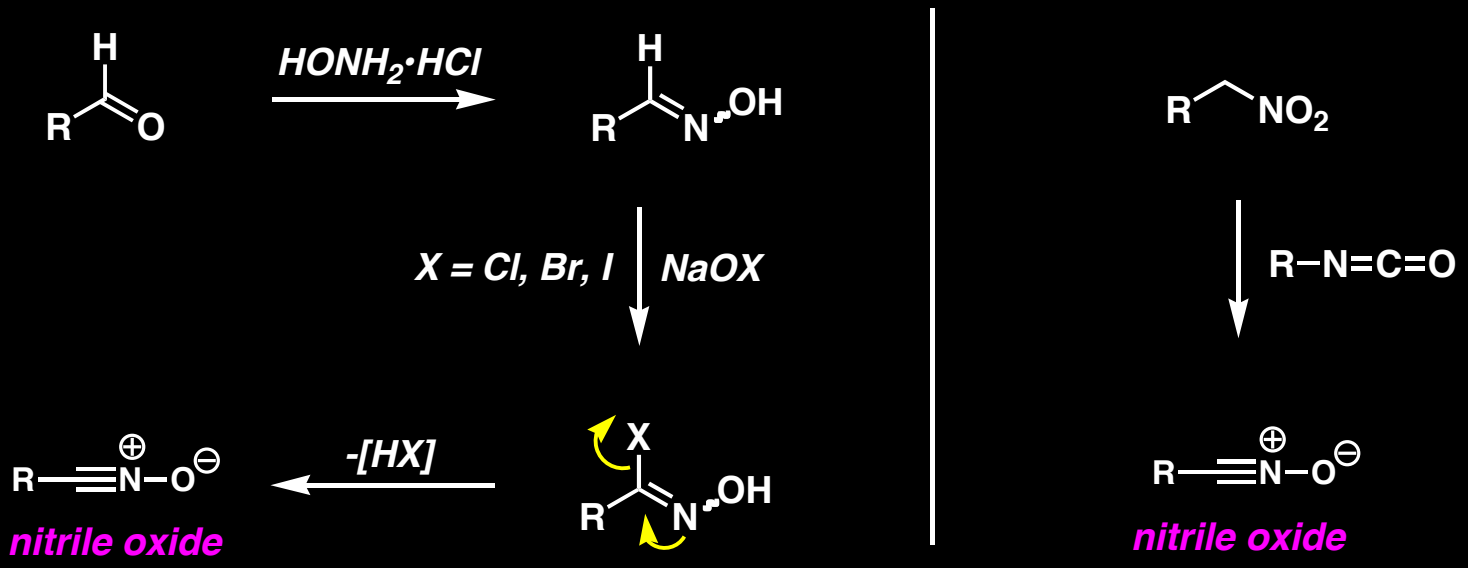
Diastereoselectivity



Nitrile Oxides: Synthesis

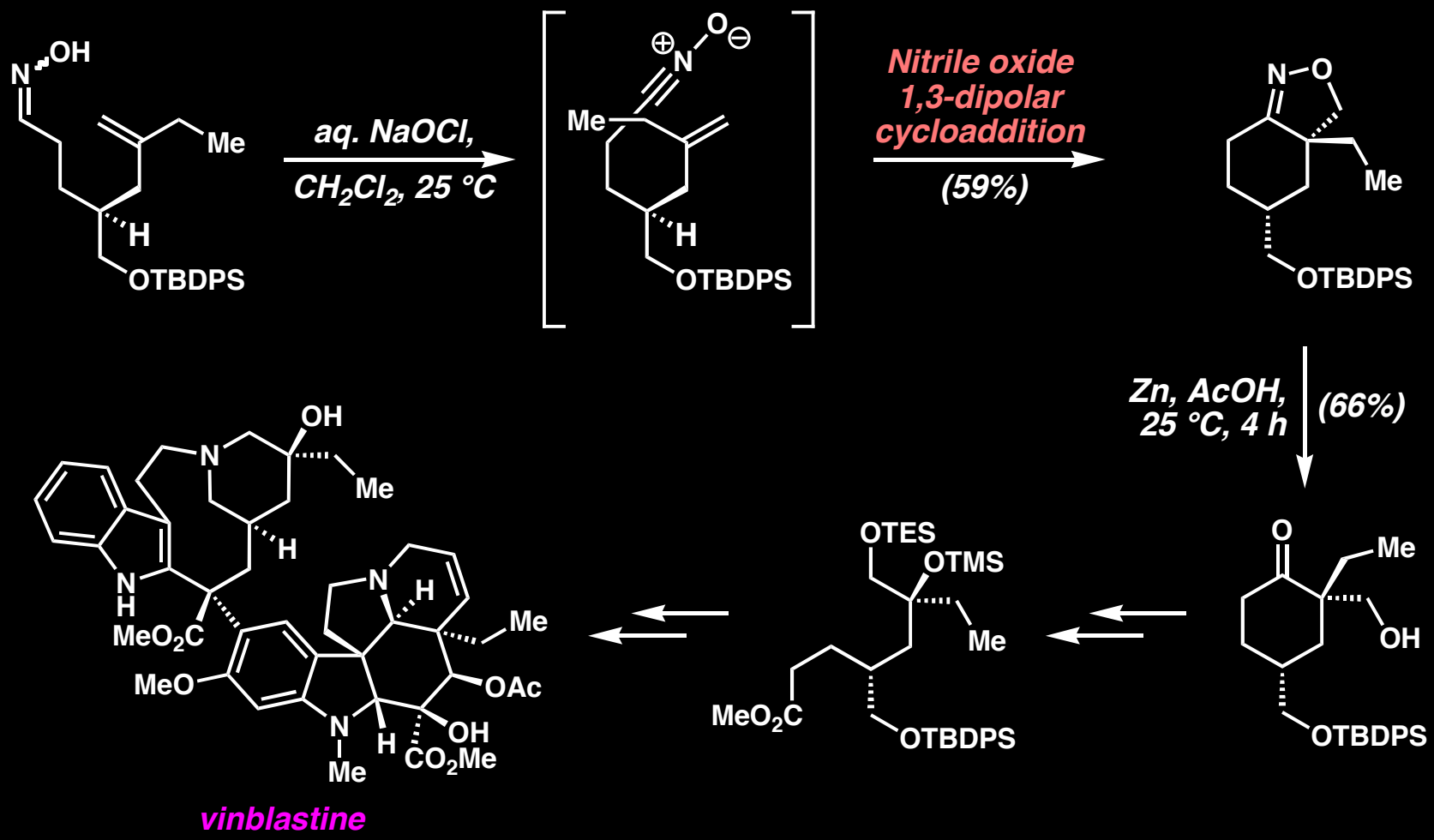


Nitrile Oxides: Synthesis



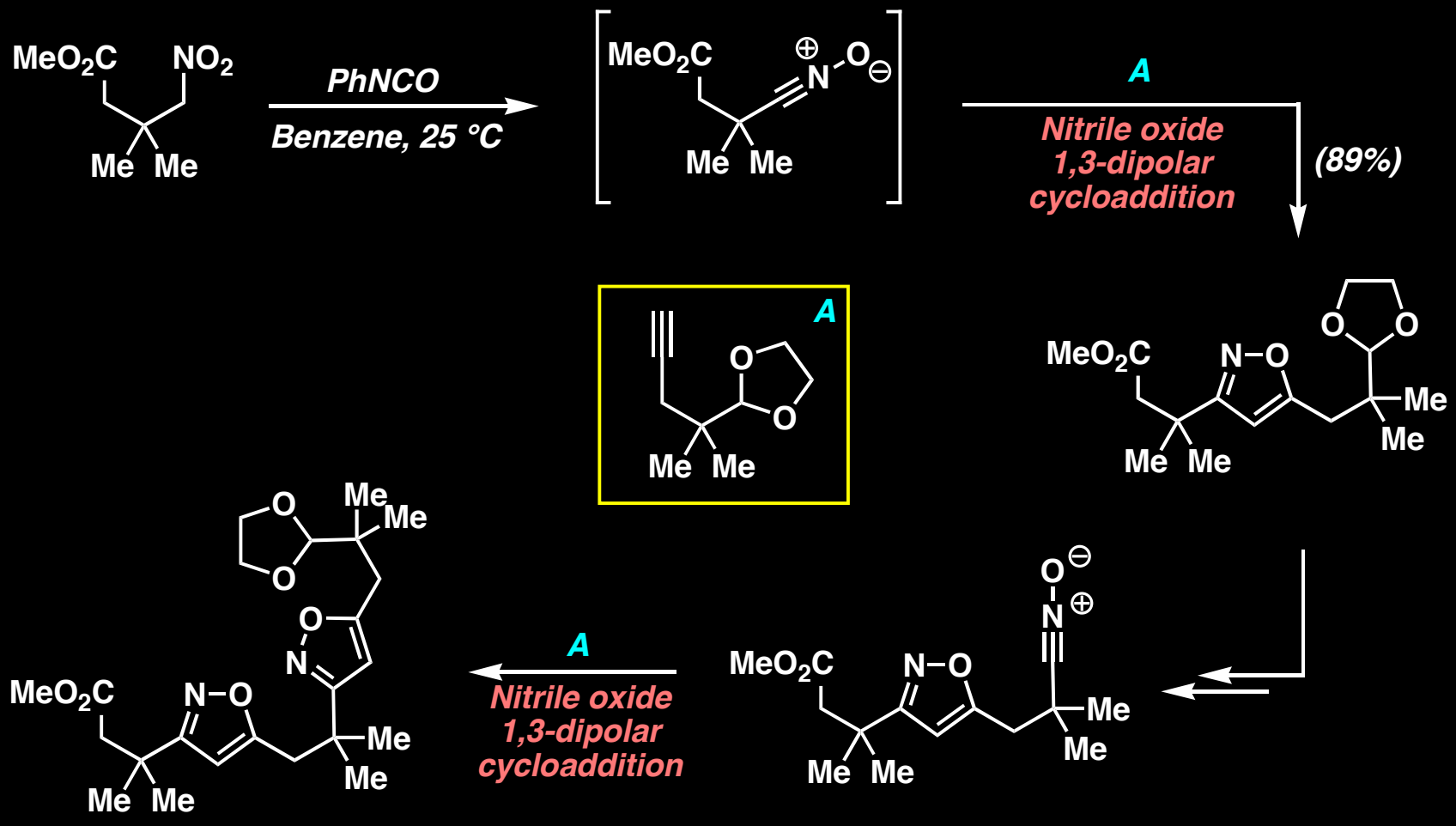
The isocyanate is serving as a dehydrating reagent; can you rationalize a mechanism?

Nitrile Oxides: Applications in Total Synthesis



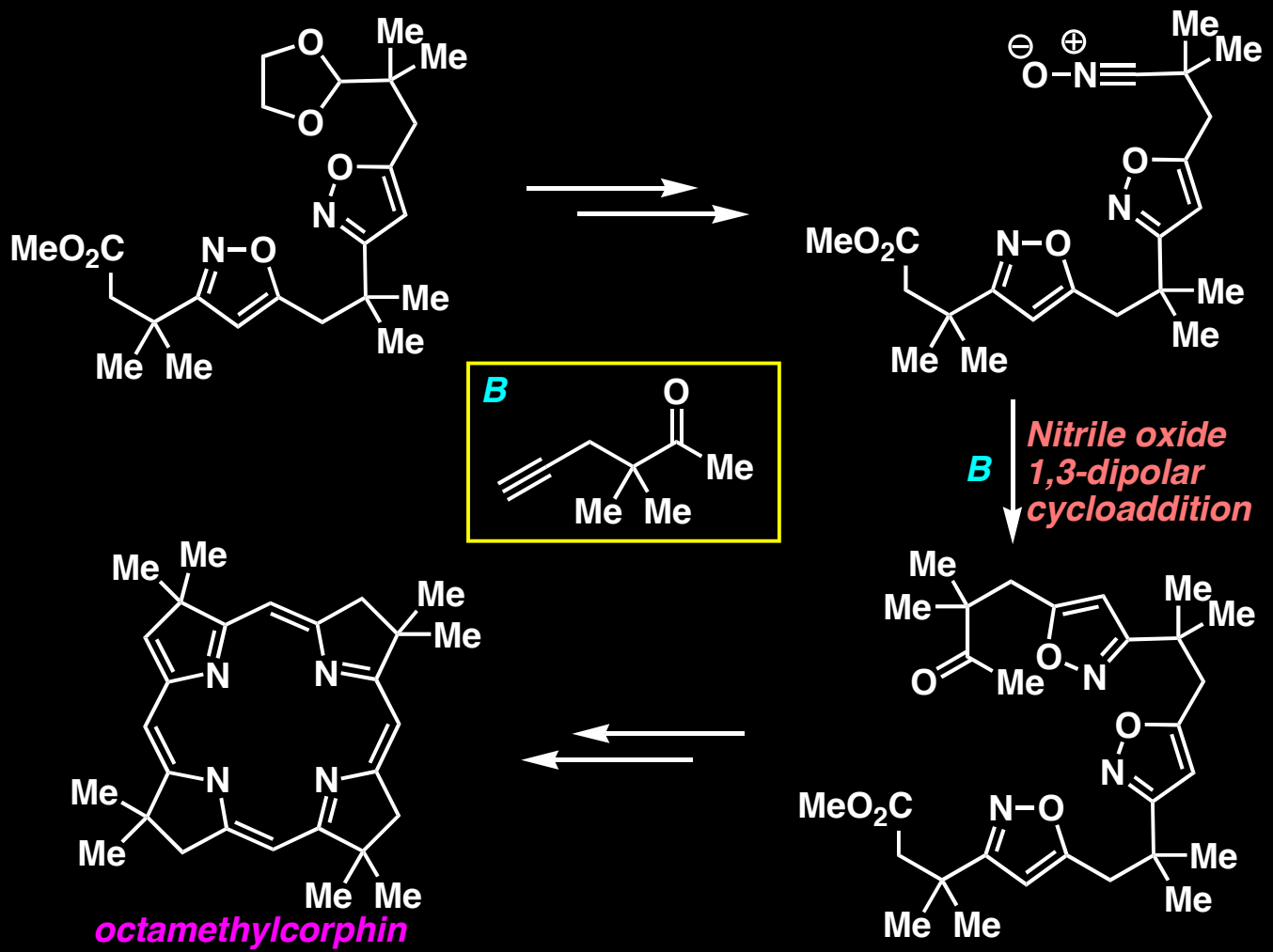
T. Fukuyama and co-workers, J. Am. Chem. Soc. 1999, 121, 3791
For a review, see Classics in Total Synthesis II, Chapter 18

Nitrile Oxides: Applications in Total Synthesis



R.V. Stevens, J. Am. Chem. Soc. 1975, 97, 5940.

Nitrile Oxides: Applications in Total Synthesis



R.V. Stevens, J. Am. Chem. Soc. 1975, 97, 5940.

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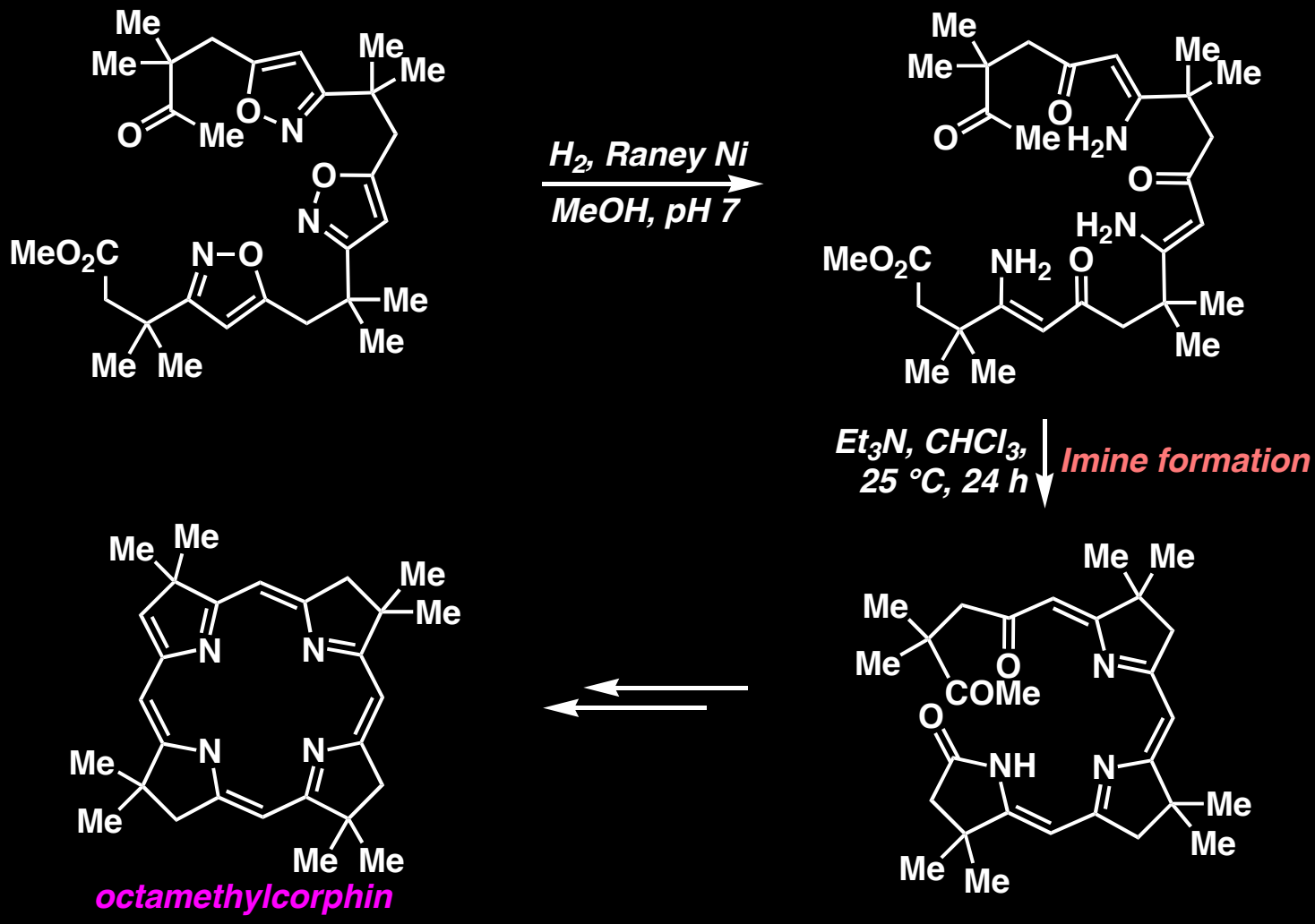

R.V. Stevens, J. Am. Chem. Soc. 1975, 97, 5940.

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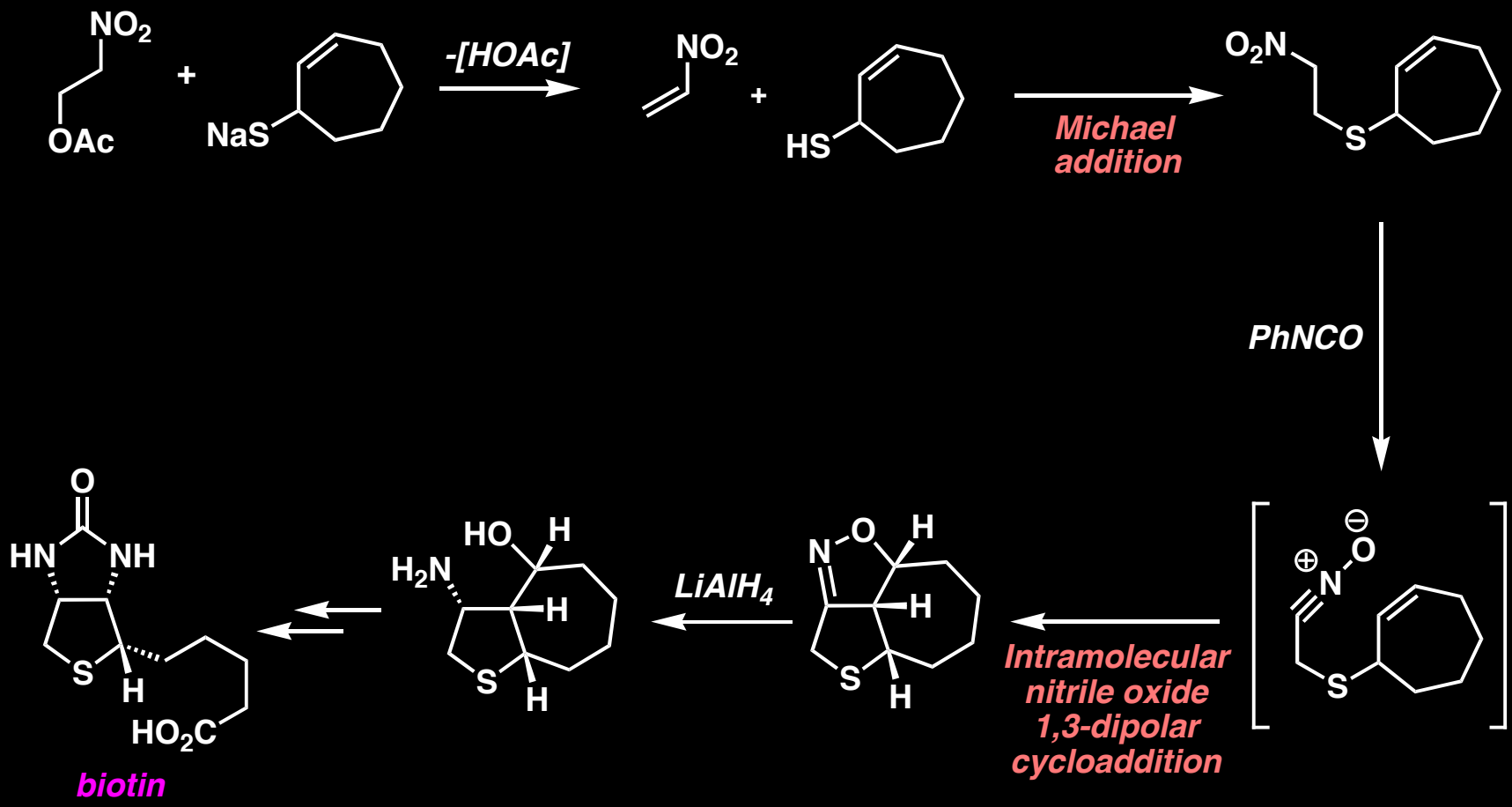
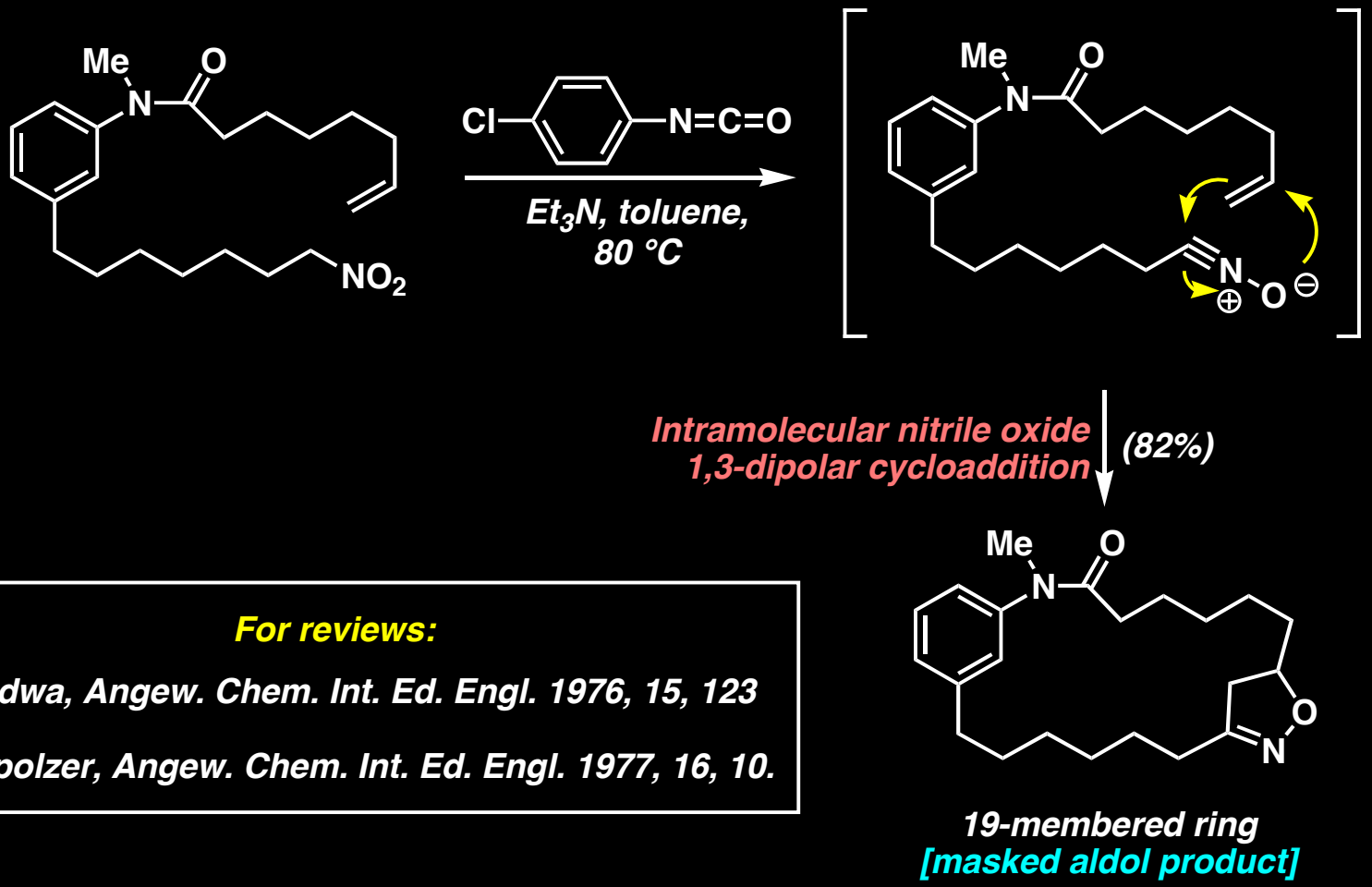


P. N. Confalone, J. Am. Chem. Soc. 1980, 102, 1954.

Nitrile Oxides: Applications in Total Synthesis



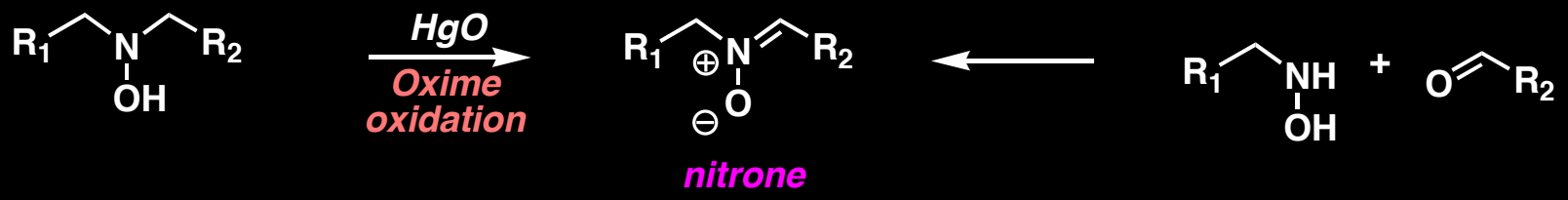
For reviews:

A. Padwa, Angew. Chem. Int. Ed. Engl. 1976, 15, 123

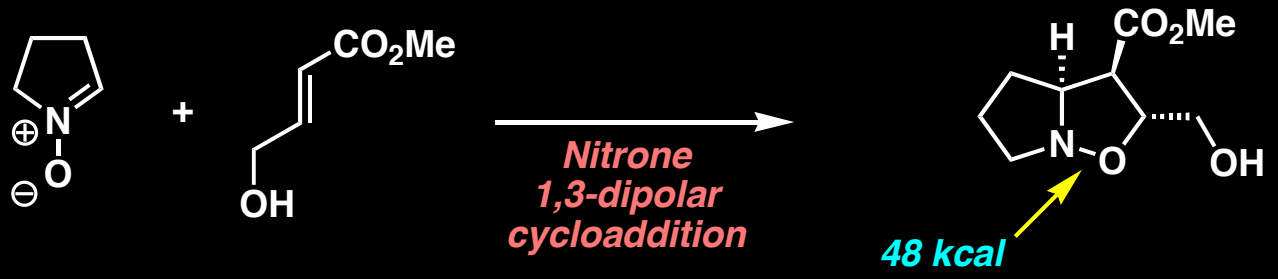
W. Oppolzer, Angew. Chem. Int. Ed. Engl. 1977, 16, 10.

P. N. Confalone, J. Heterocyclic Chem. 1990, 31.

Nitrones: Preparative Methods

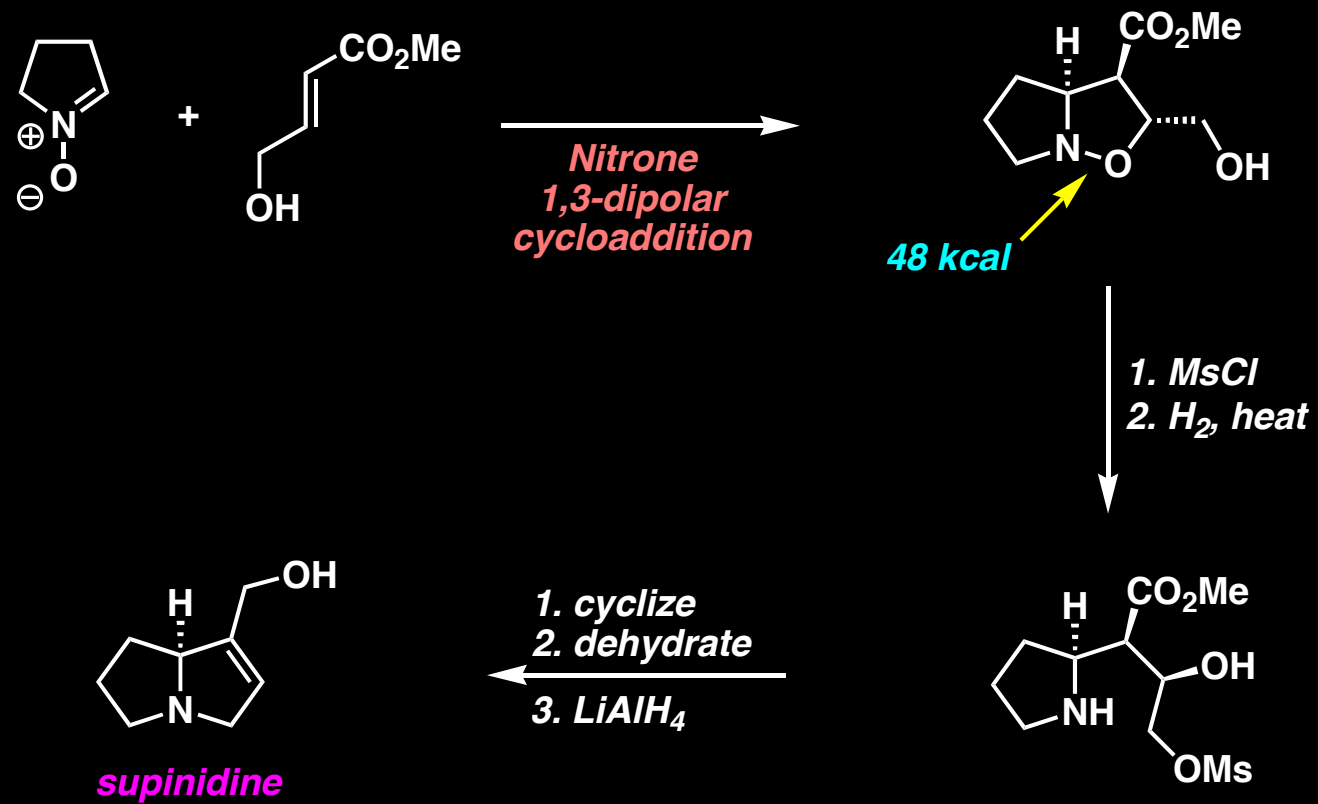


Nitrones: Applications in Total Synthesis



J. Tufariello, Acc. Chem. Res. 1979, 12, 396.

Nitrones: Applications in Total Synthesis



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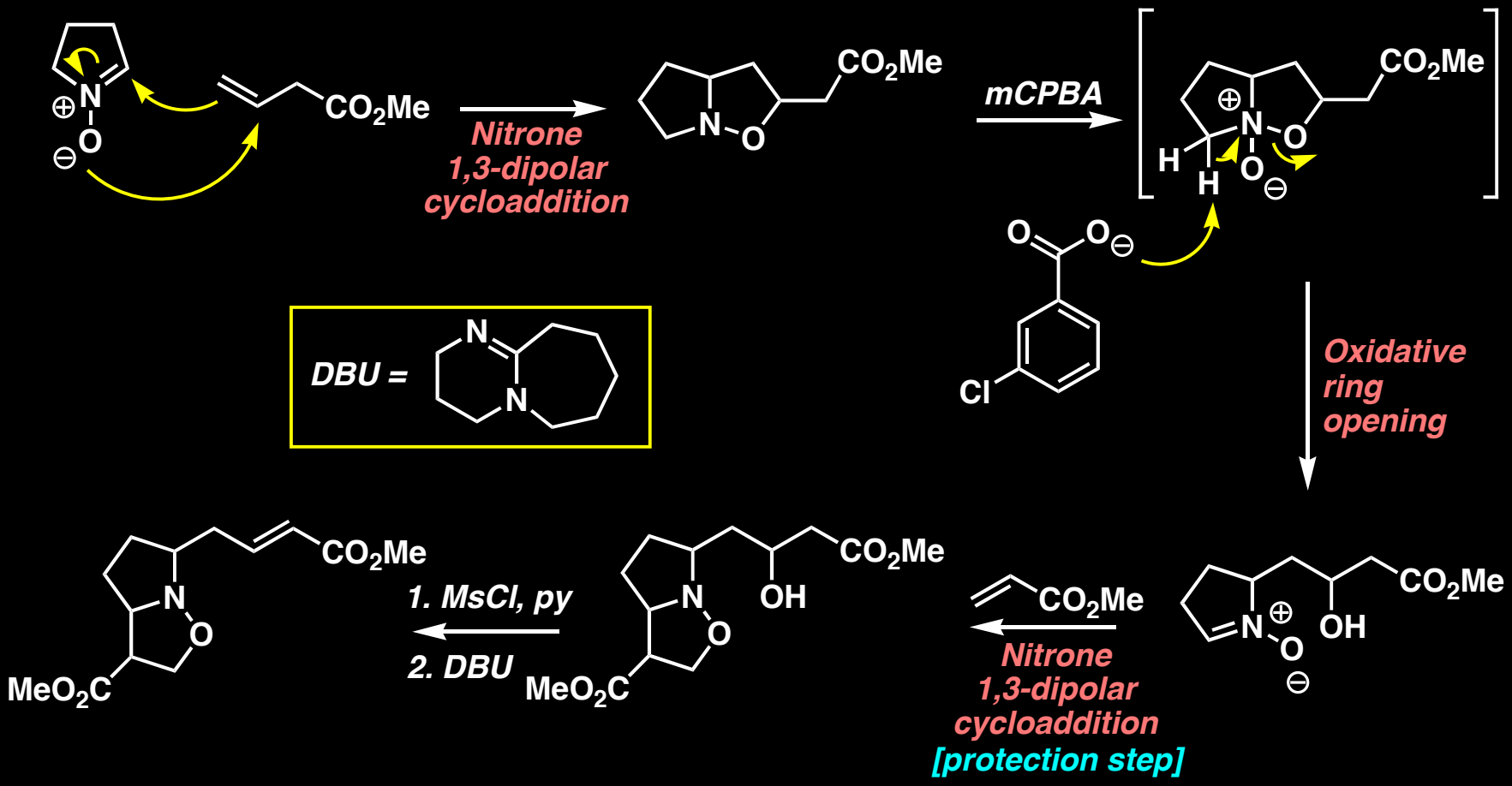

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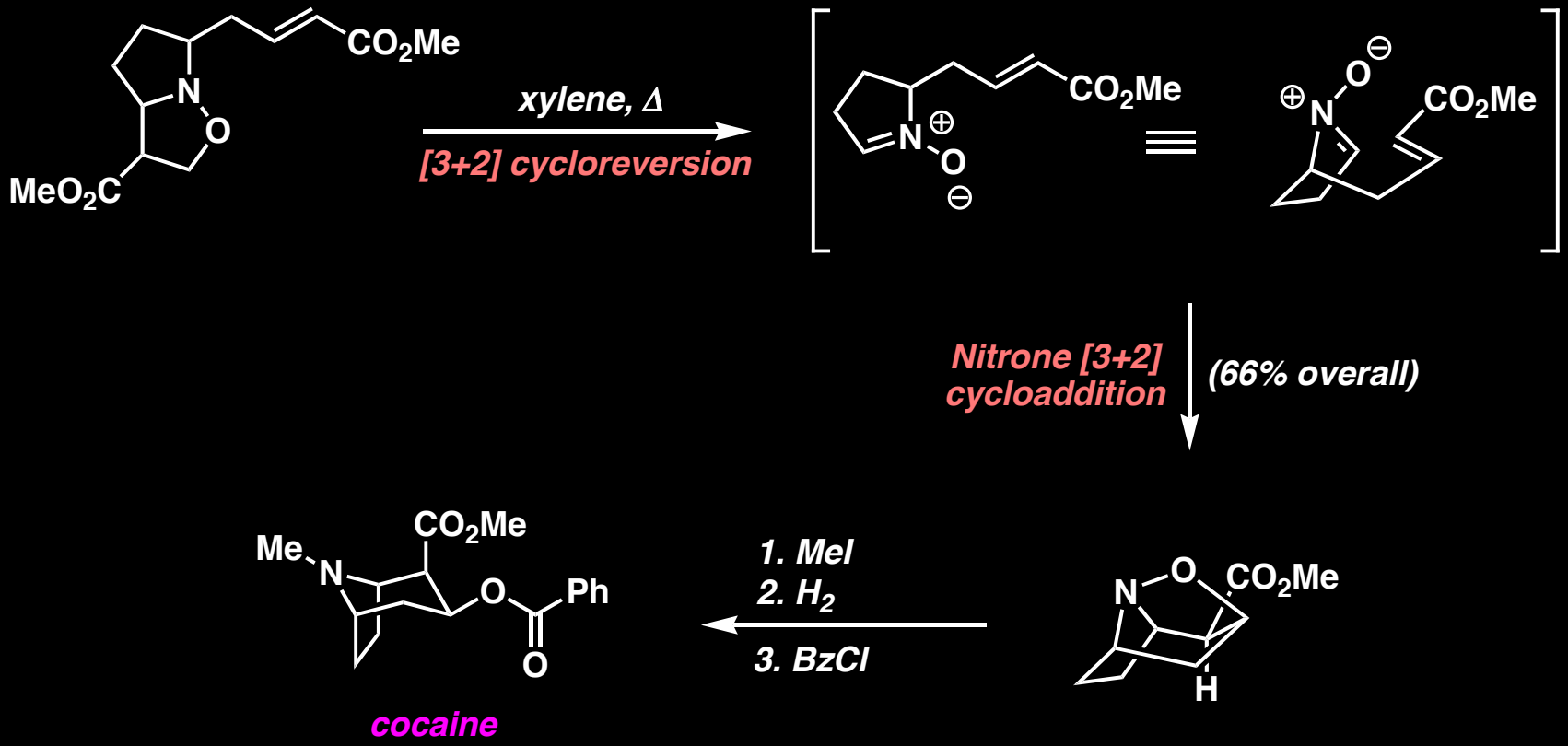

J. Tufariello, J. Am. Chem. Soc. 1978, 100, 3638.
J. Tufariello, J. Am. Chem. Soc. 1979, 101, 2435.

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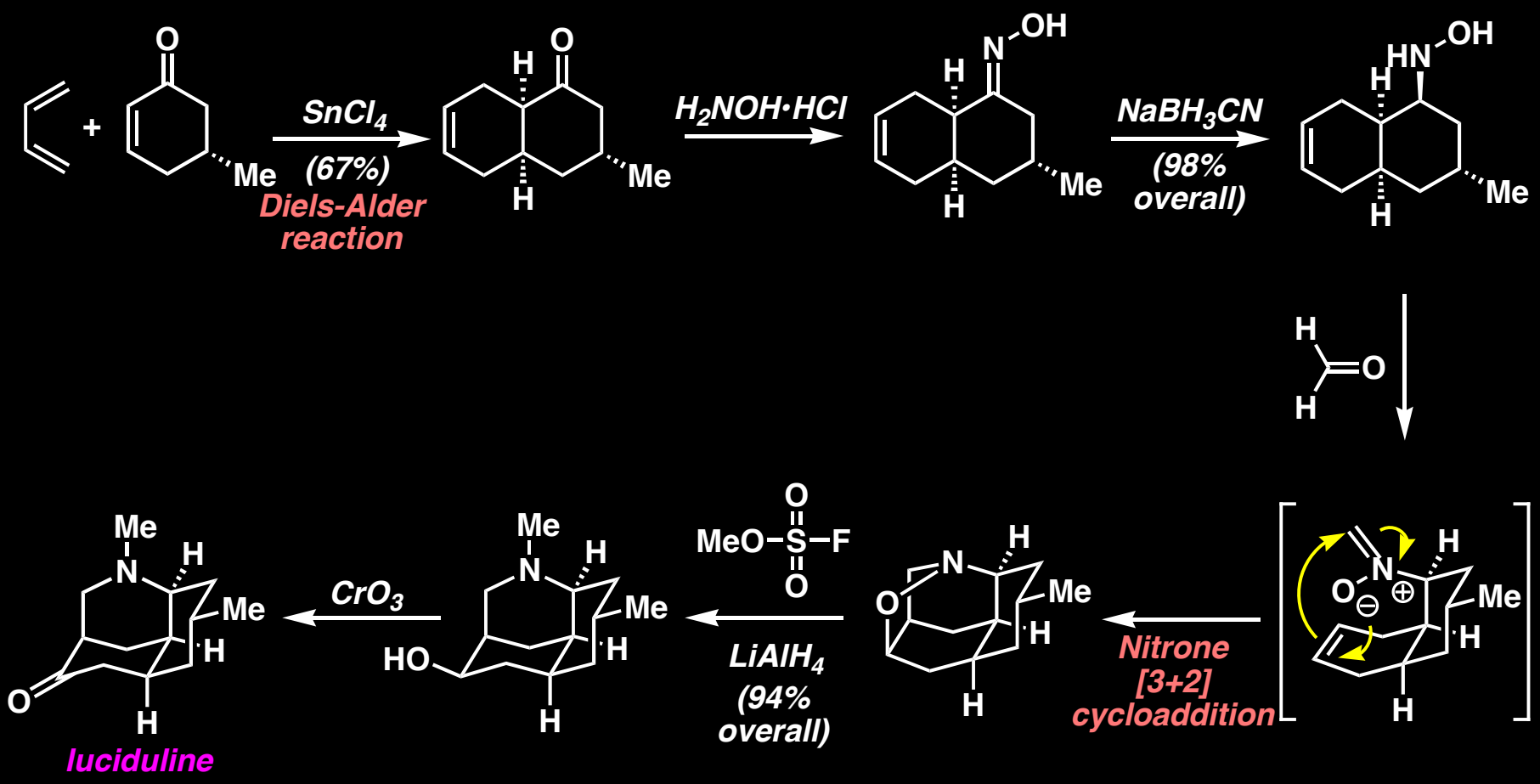
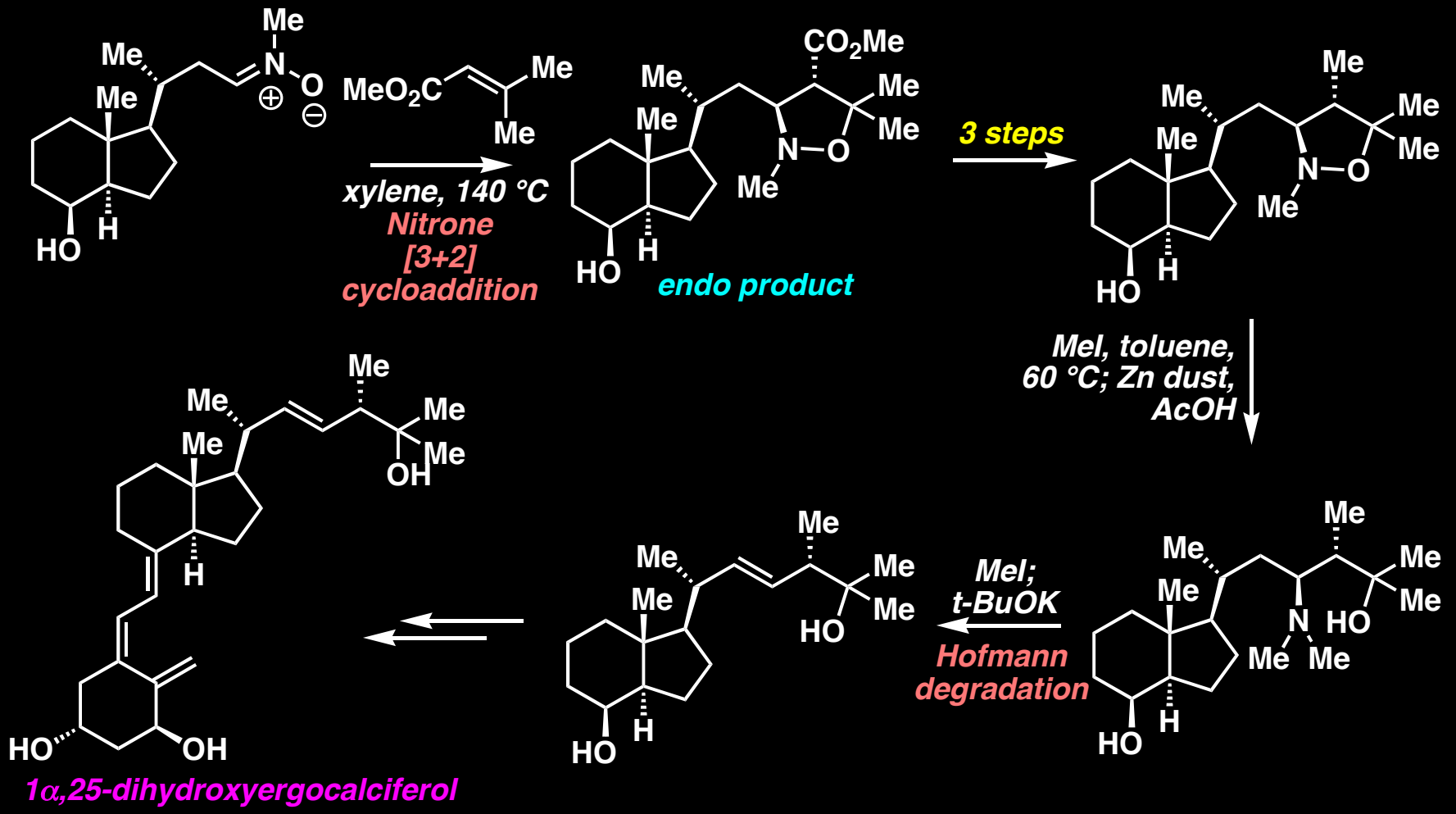


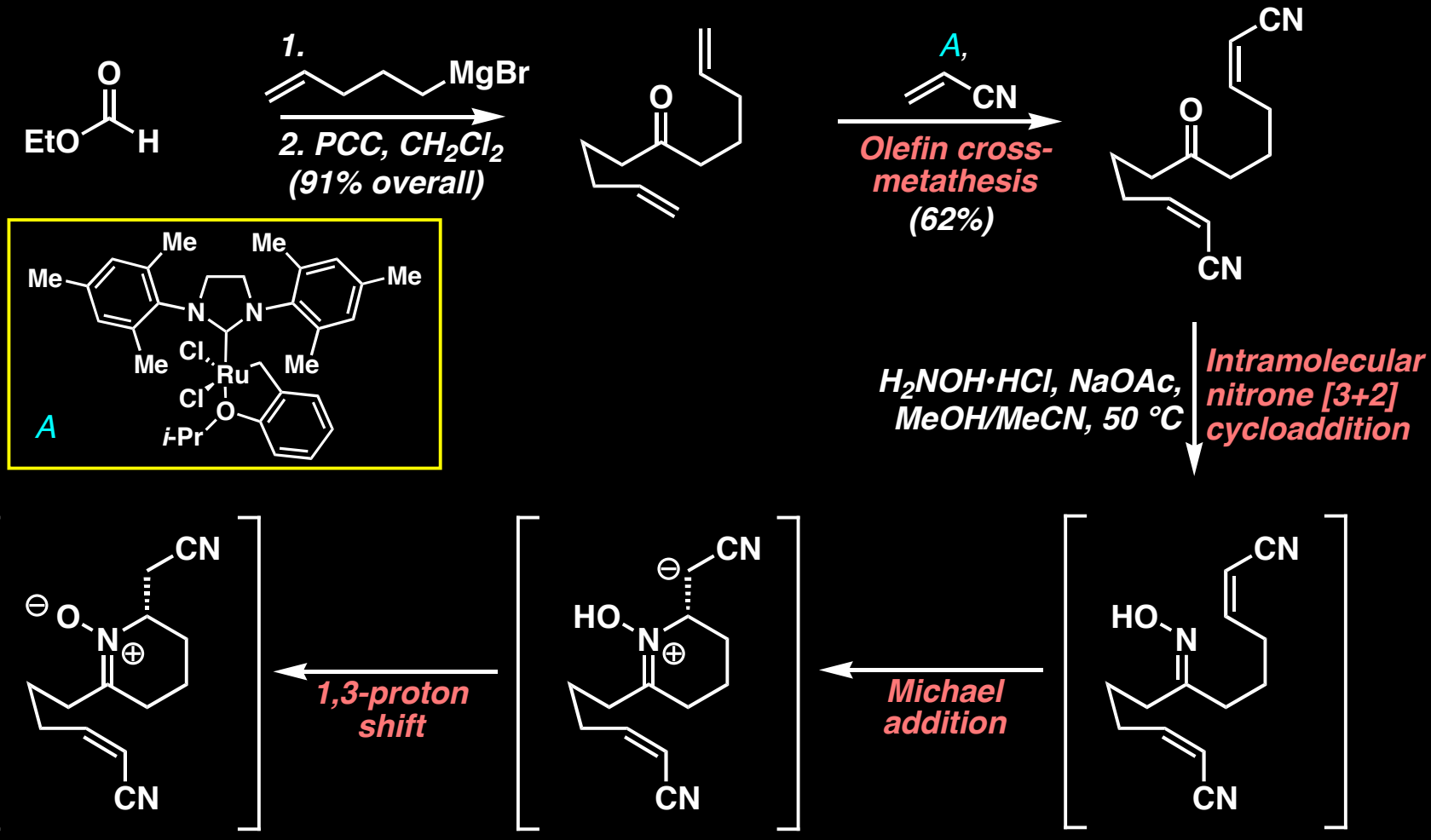
W. Oppolzer, M. Petrzilka, J. Am. Chem. Soc. 1976, 98, 6722.
W. Oppolzer, M. Petrzilka, Helv. Chim. Acta 1978, 61.

Nitrones: Applications in Total Synthesis



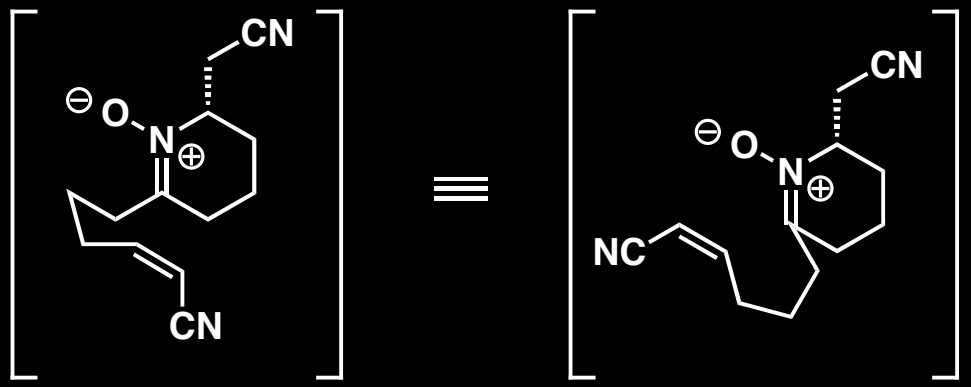
E. G. Baggiolini and co-workers, J. Org. Chem. 1986, 51, 3098.

Nitrones: Applications in Total Synthesis



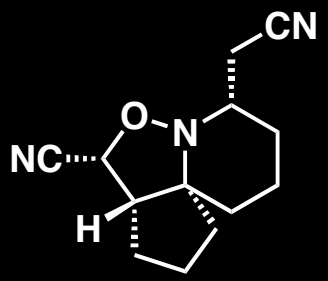
P. L. Fuchs and co-workers, J. Am. Chem. Soc. 2006, 128, ASAP.
D. L. Hughes and co-workers, J. Org. Chem. 2004, 69, 1598.

Nitrones: Applications in Total Synthesis



Intramolecular nitrone [3+2] cycloaddition

(89% overall)

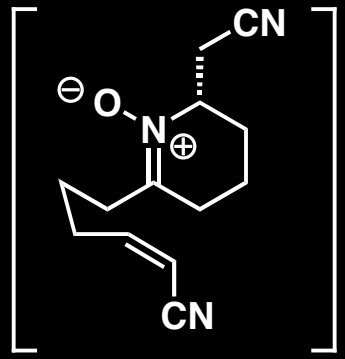


kinetic product

toluene, 180 °C
sealed tube

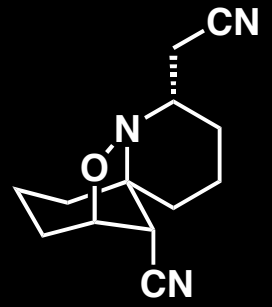
Retro [3+2] cycloaddition

For original concept, see:
R. Grigg, J. Chem. Soc., Perkin Trans. 1 1984, 47

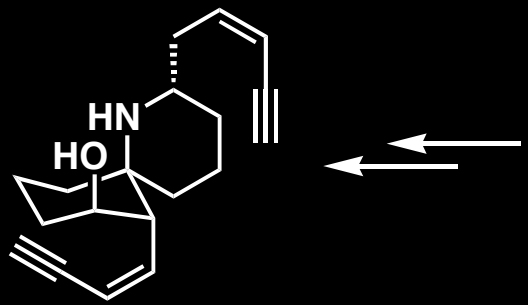


Intramolecular nitrone [3+2] cycloaddition

(95%)



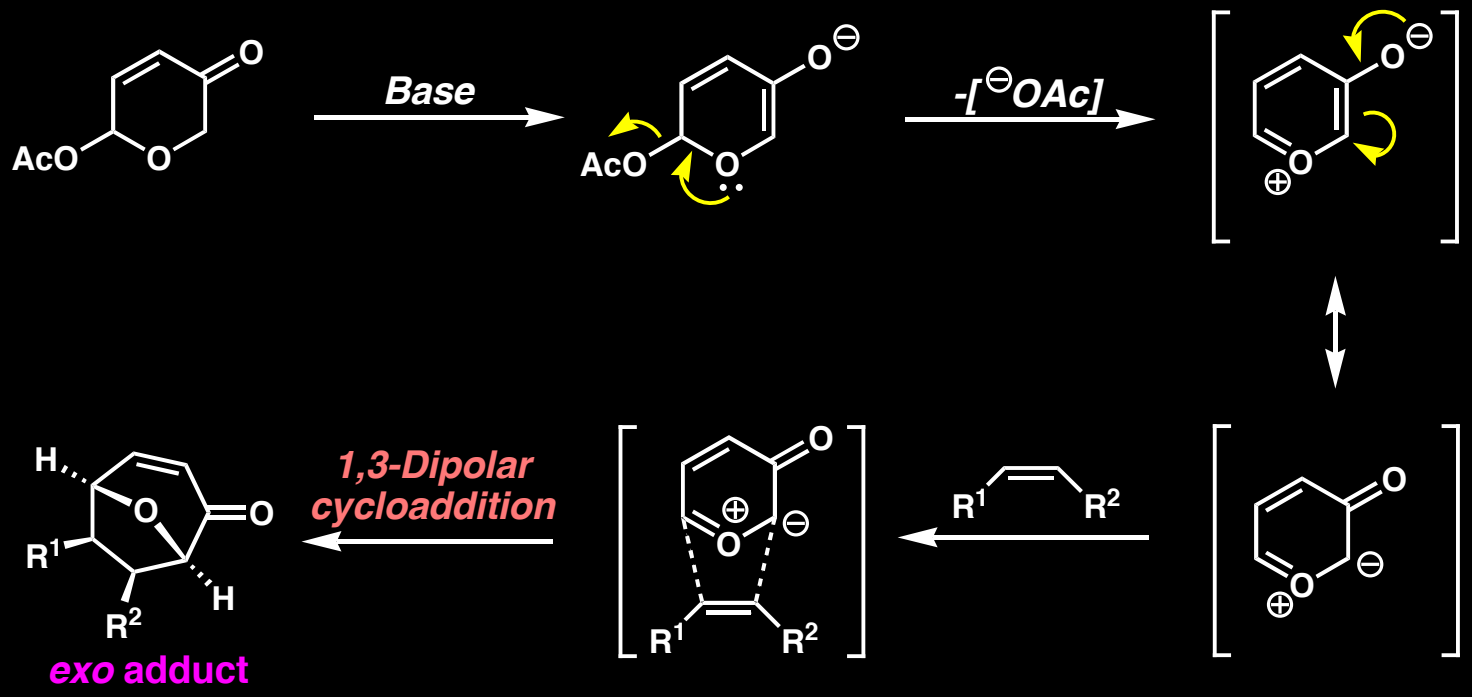
thermodynamic product



histrionicotoxin

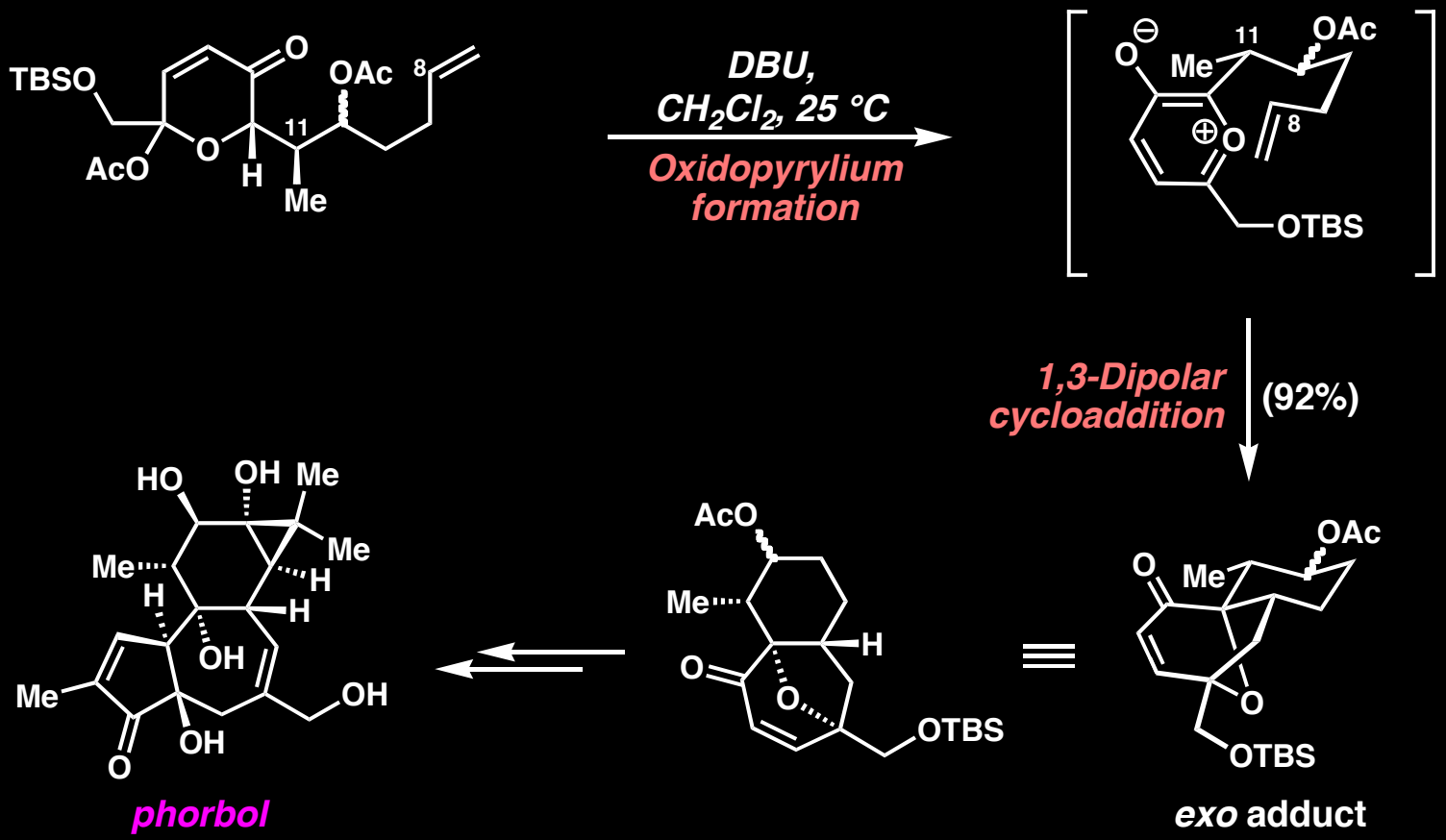
P. L. Fuchs and co-workers, J. Am. Chem. Soc. 2006, 128, ASAP.
D. L. Hughes and co-workers, J. Org. Chem. 2004, 69, 1598.

Carbonyl Ylides (Oxidopyryliums): Using Cyclic Systems



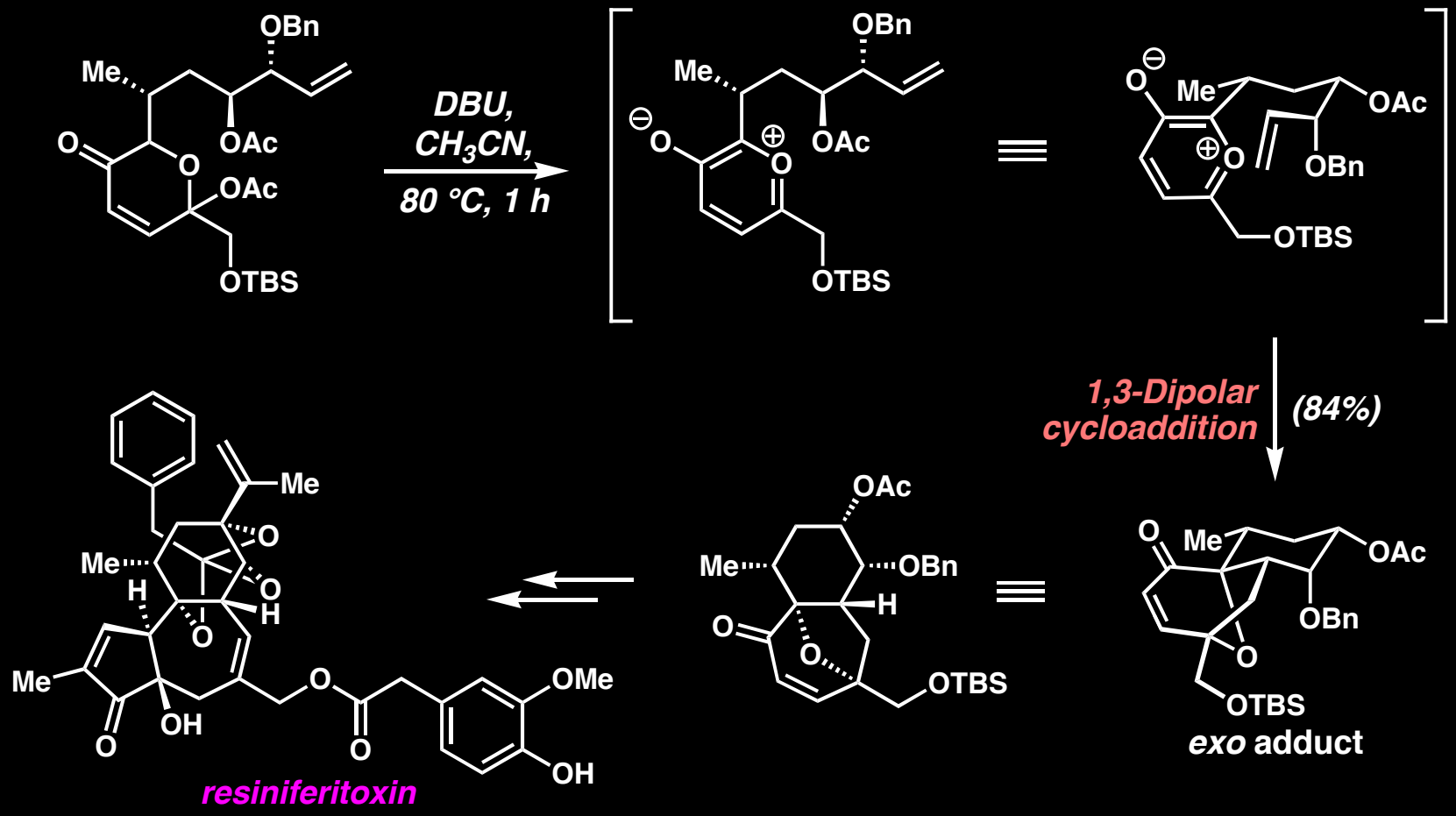
In cyclizations of this type, the ENDO isomer places the substituents on the dipolarophile anti to the oxido bridge. Accordingly, the EXO isomer is the one in which these substituents are syn to the resultant oxygen bridge.

Carbonyl Ylides (Oxidopyryliums): Using Cyclic Systems



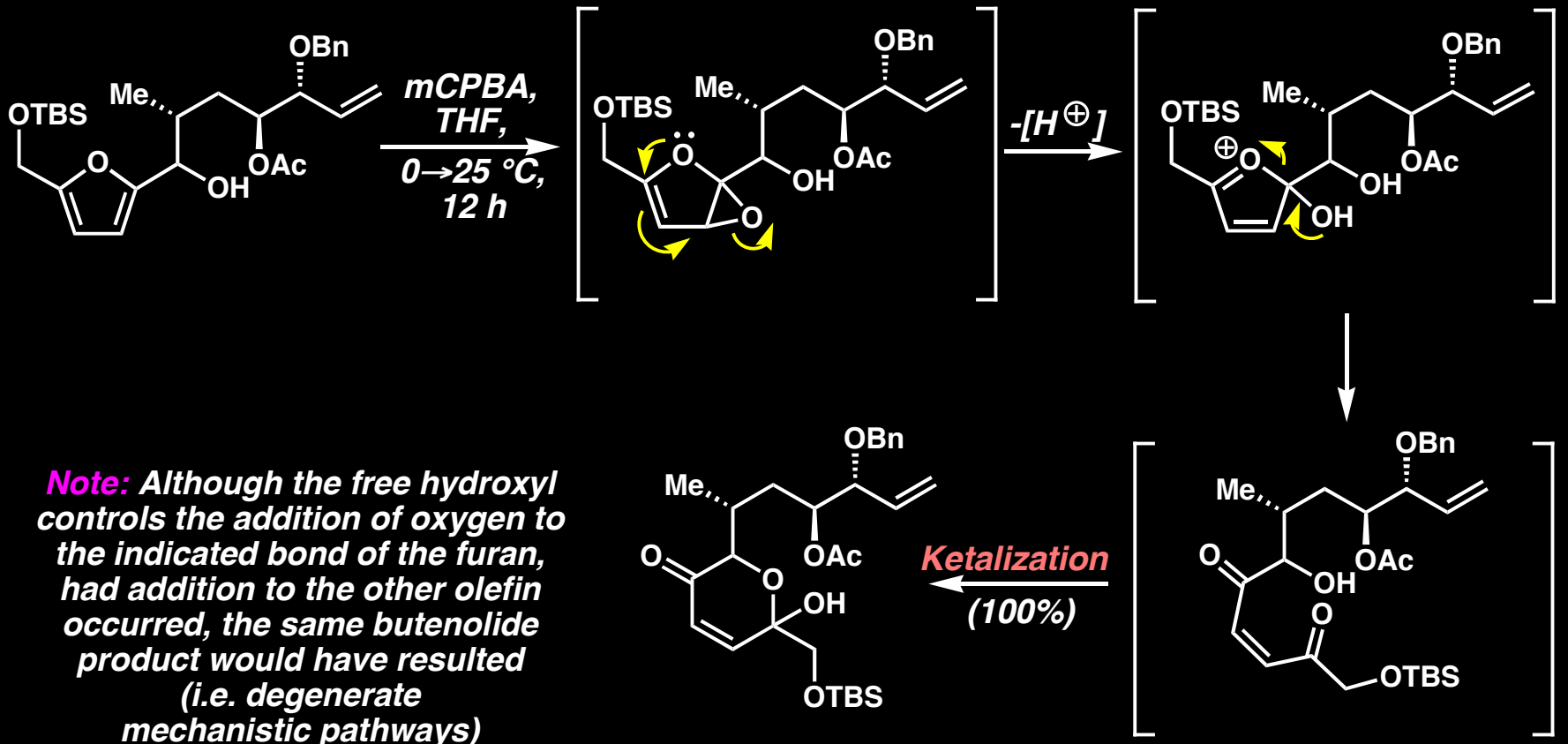
P.A. Wender and co-workers, J. Am. Chem. Soc. 1989, 111, 8954 and 8957.

Carbonyl Ylides (Oxidopyryliums): Using Cyclic Systems



P.A. Wender and co-workers, J. Am. Chem. Soc. 1997, 119, 12976.
For a review, see: Classics in Total Synthesis II, Chapter 6

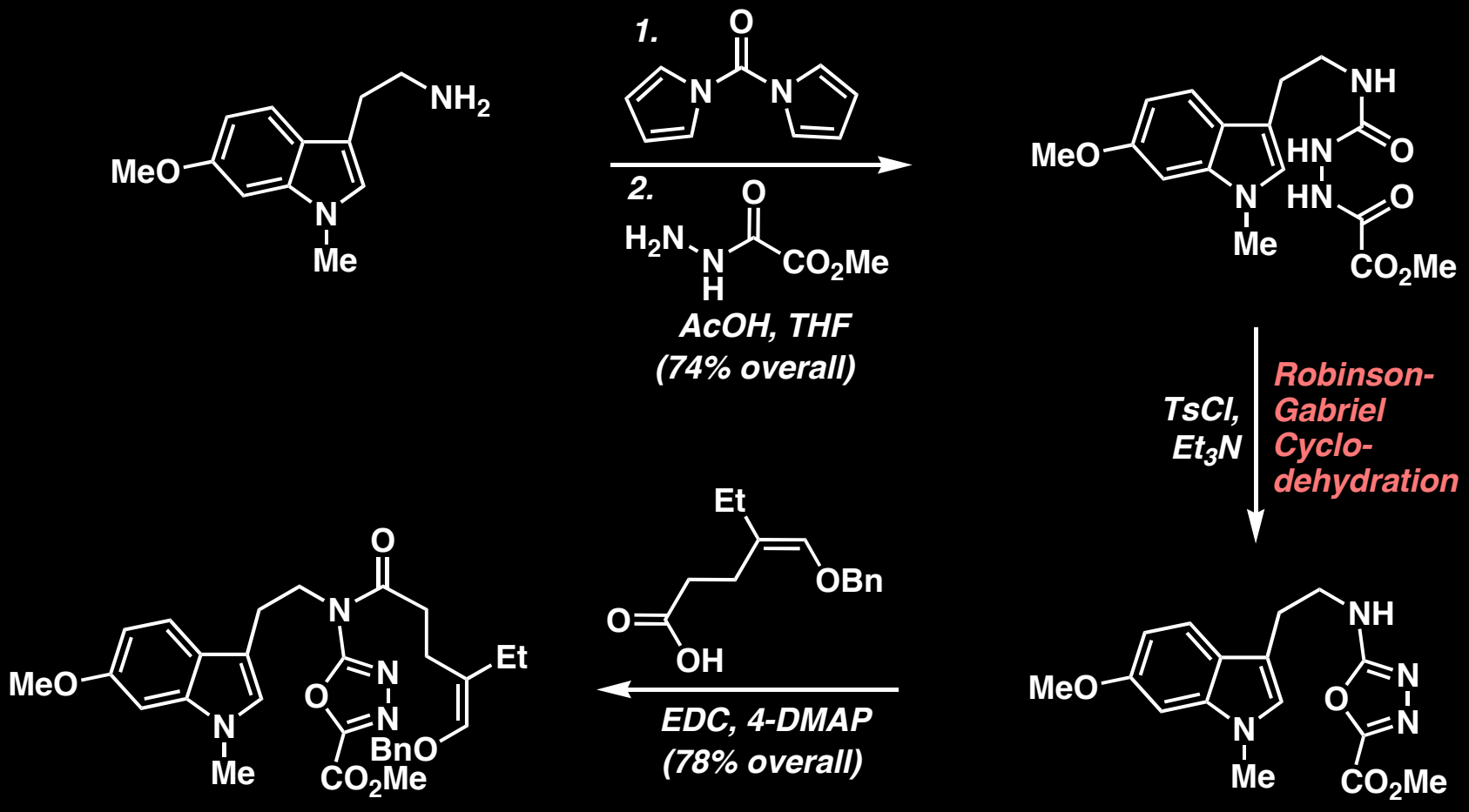
Carbonyl Ylides (Oxidopyryliums): How to Make Precursors



Note: *Although the free hydroxyl controls the addition of oxygen to the indicated bond of the furan, had addition to the other olefin occurred, the same butenolide product would have resulted (i.e. degenerate mechanistic pathways)*

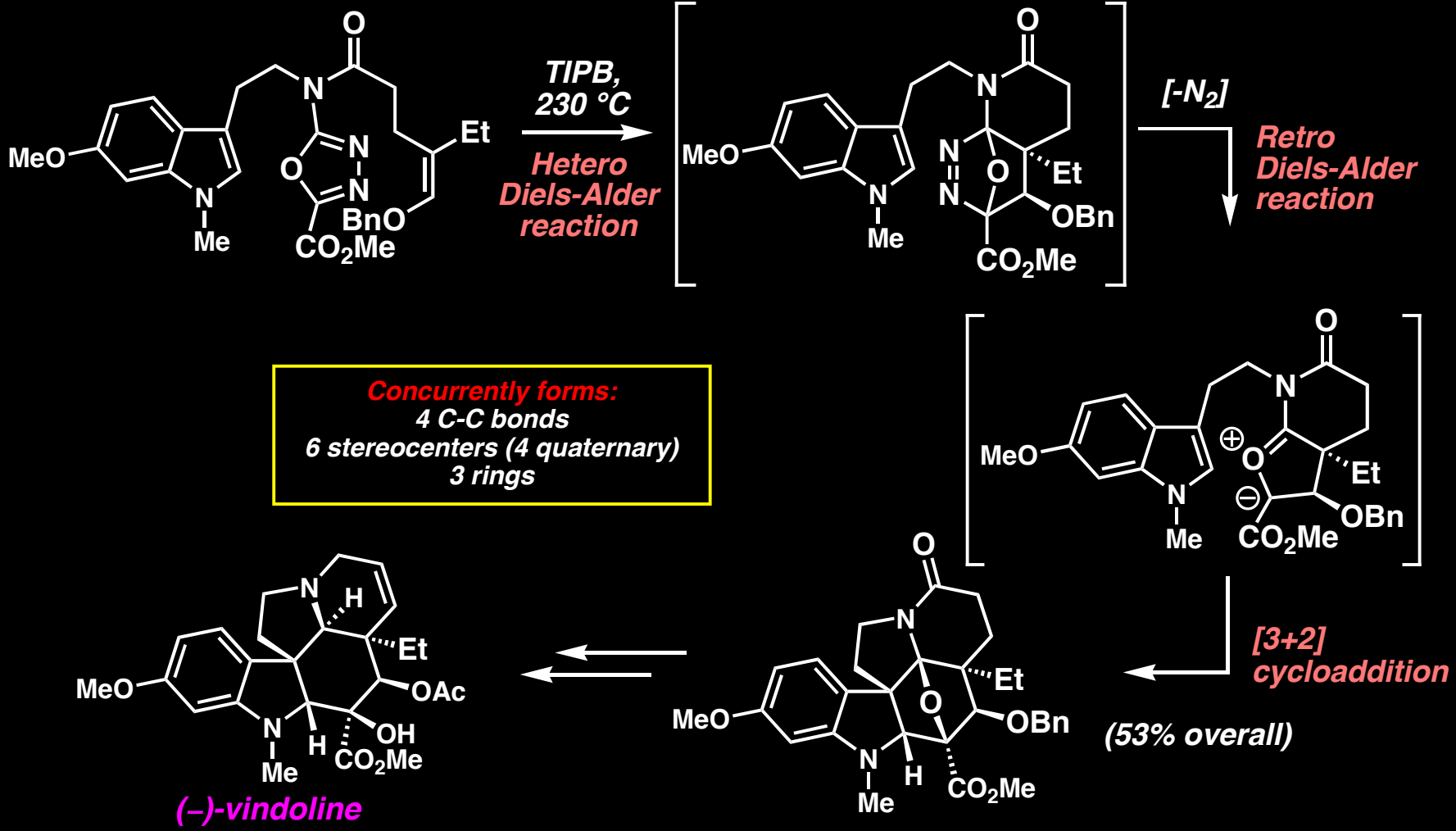
P.A. Wender and co-workers, J. Am. Chem. Soc. 1997, 119, 12976.
For a review, see: Classics in Total Synthesis II, Chapter 6

Carbonyl Ylides (Oxidopyryliums): Applications in Total Synthesis



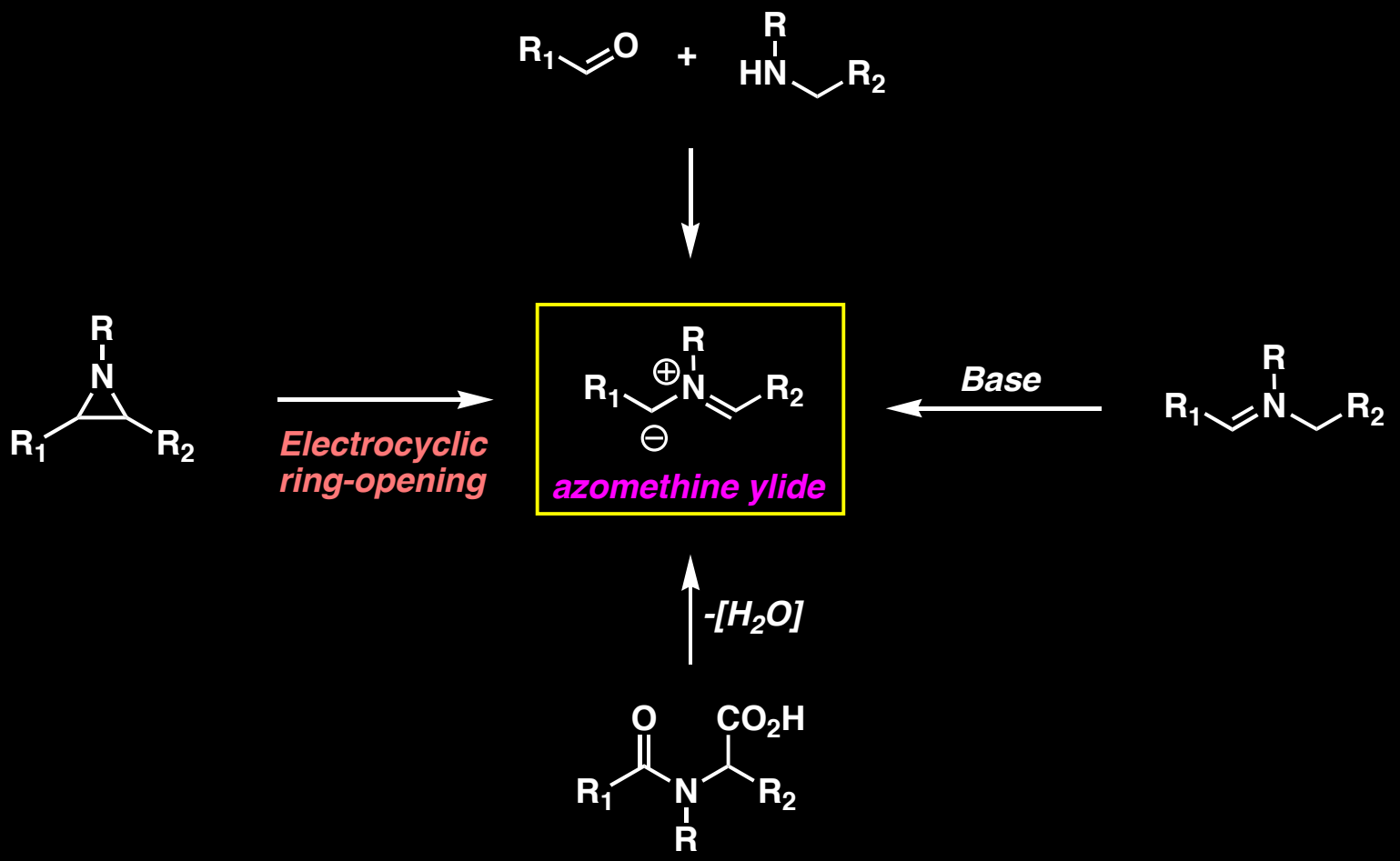
D.L. Boger and co-workers, J. Am. Chem. Soc. 2006, 128, 10597.
D.L. Boger and co-workers, J. Am. Chem. Soc. 2006, 128, 10589.

Carbonyl Ylides (Oxidopyryliums): Applications in Total Synthesis



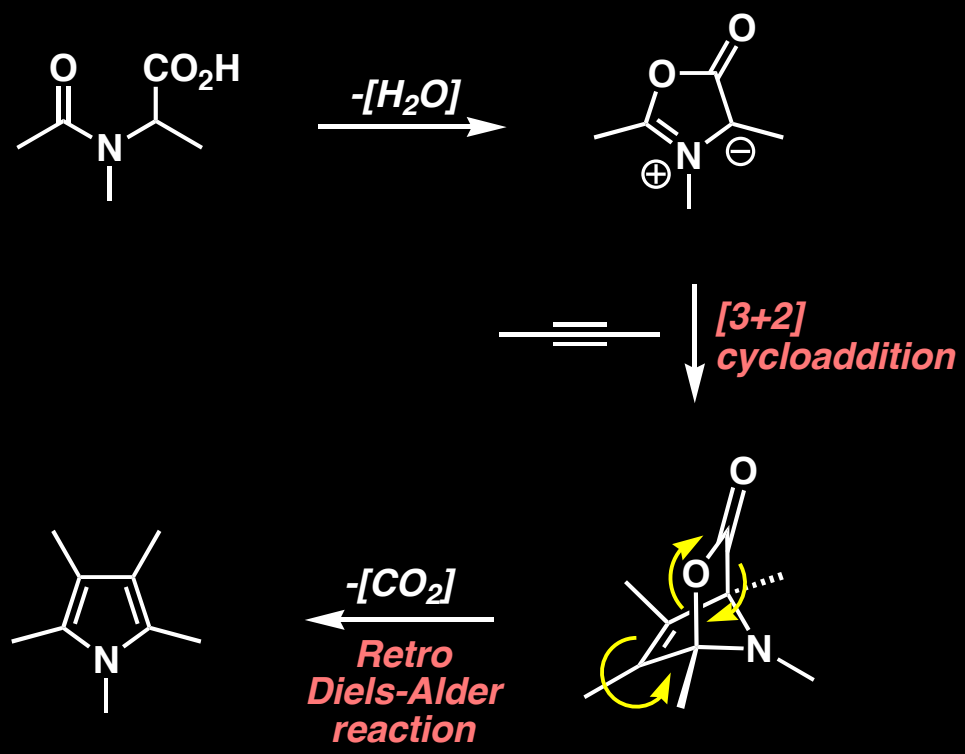
D.L. Boger and co-workers, J. Am. Chem. Soc. 2006, 128, 10597.
D.L. Boger and co-workers, J. Am. Chem. Soc. 2006, 128, 10589.

Azomethine Ylides: Formation

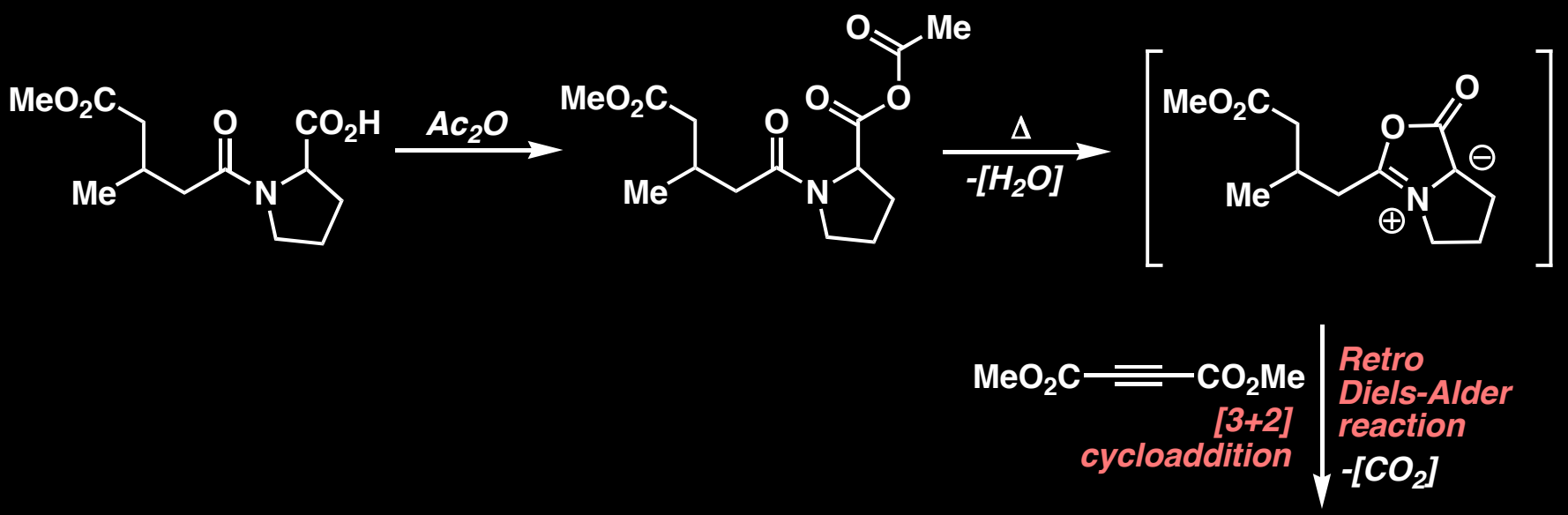


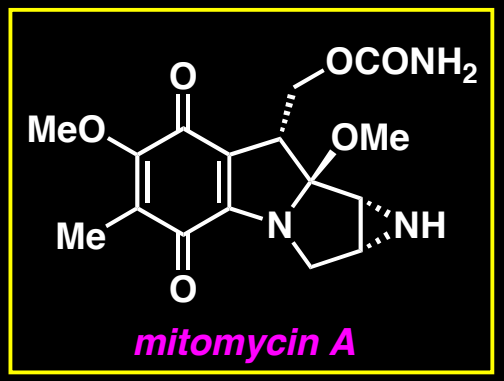
For a review, see: I. Coldham, R. Hufton, Chem. Rev. 2005, 105, 2765.

Azomethine Ylides: Huisgen's Pyrrole Synthesis



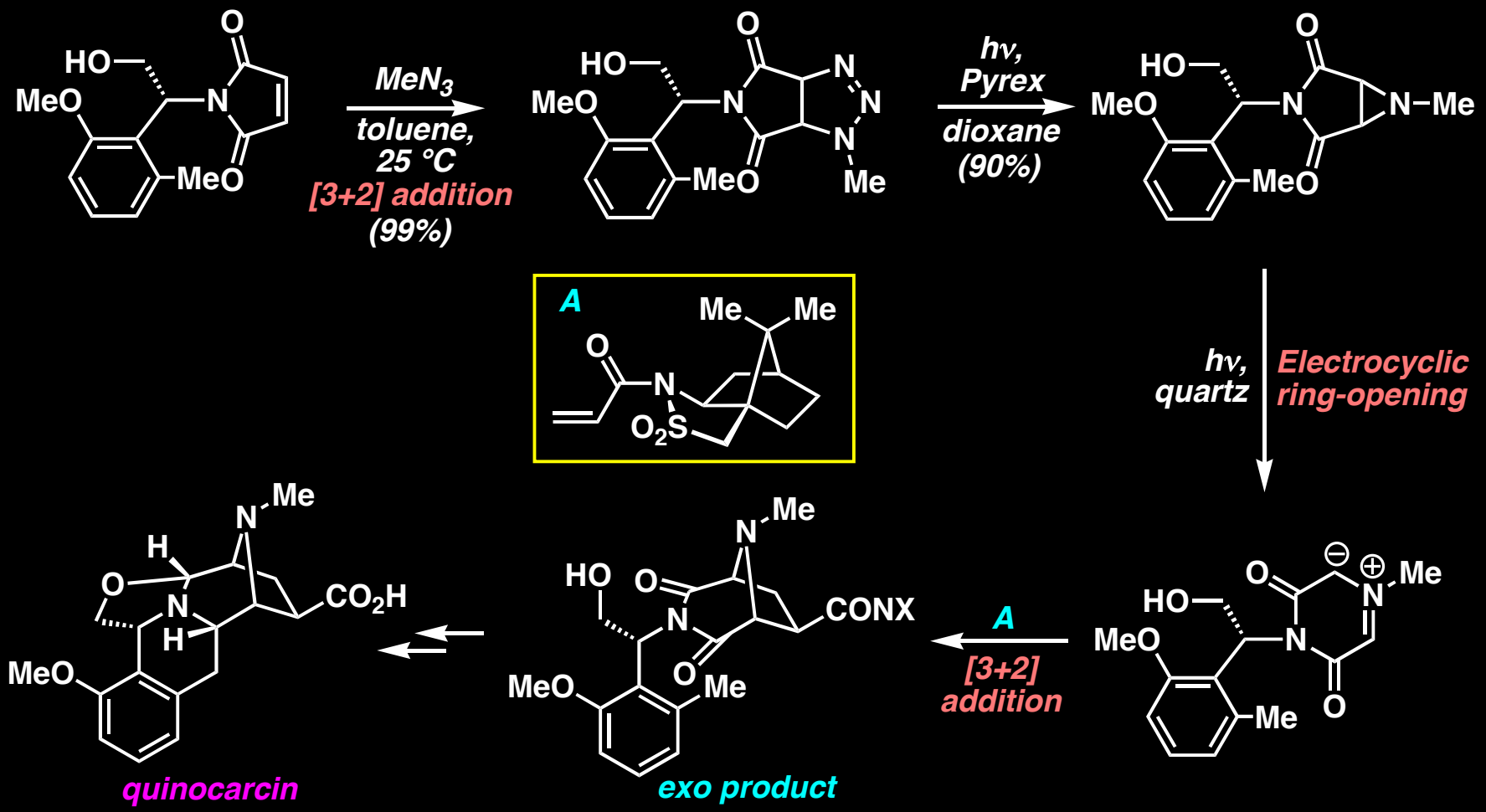
Azomethine Ylides: Applications in Total Synthesis





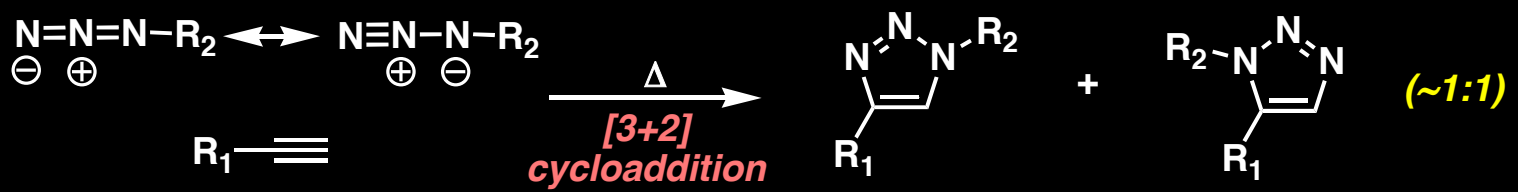
J. Rebek, Tetrahedron Lett. 1977, 3027.

Azomethine Ylides: Applications in Total Synthesis



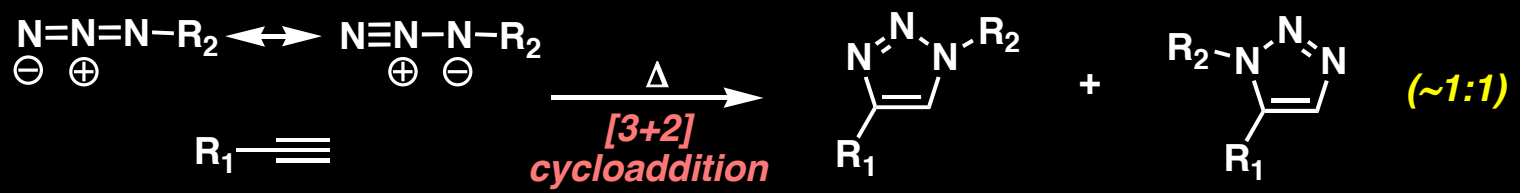
P. Garner, W.B. Ho, H. Shin, J. Am. Chem. Soc. 1993, 115, 10742.

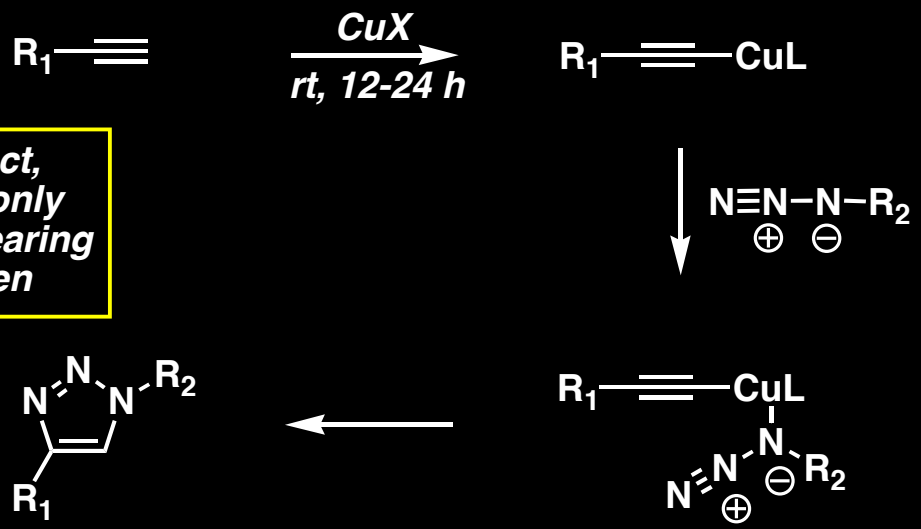
Azides: Regioselectivity and Reactivity



K. B. Sharpless and co-workers, Angew. Chem. Int. Ed. 2002, 41, 2596.
K. B. Sharpless and co-workers, J. Am. Chem. Soc. 2005, 127, 210.

Azides: Regioselectivity and Reactivity

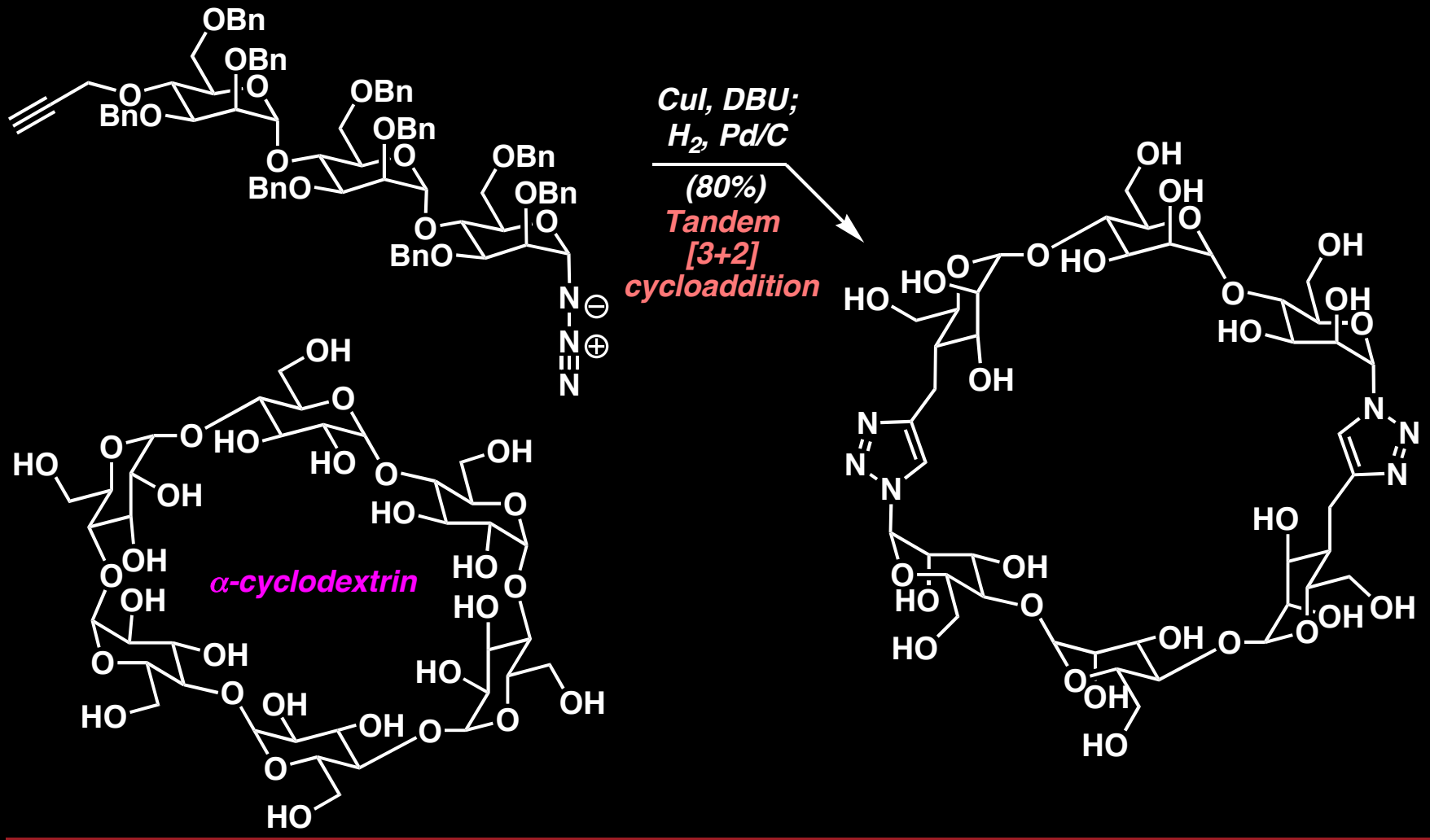




As you might expect, this selectivity can only occur with alkynes bearing a terminal hydrogen

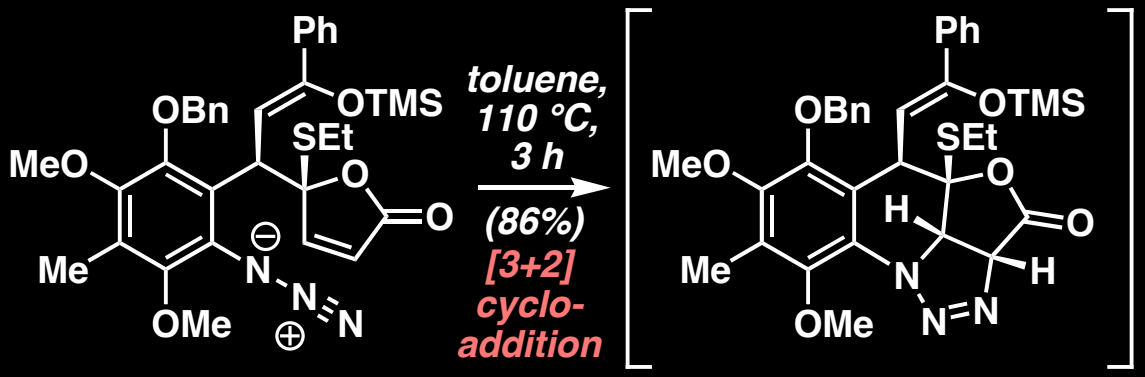
K. B. Sharpless and co-workers, Angew. Chem. Int. Ed. 2002, 41, 2596.
K. B. Sharpless and co-workers, J. Am. Chem. Soc. 2005, 127, 210.

Azides: Applications in Total Synthesis



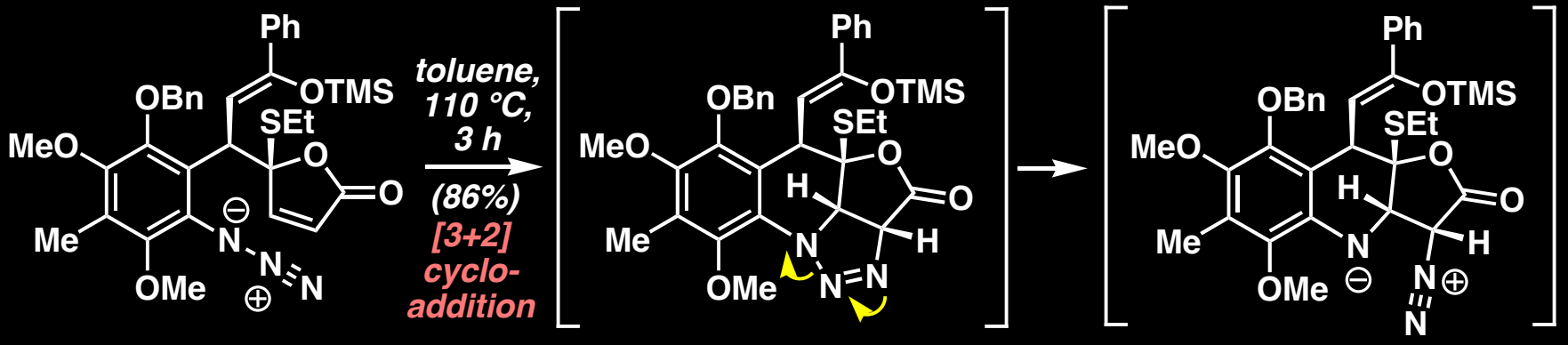
K.D. Bodine, D.Y. Gin, M.S. Gin, J. Am. Chem. Soc. 2004, 126, 1638.

Azides: Applications in Total Synthesis



T. Fukuyama, L. Yang, J. Am. Chem. Soc. 1989, 111, 8303.

Azides: Applications in Total Synthesis



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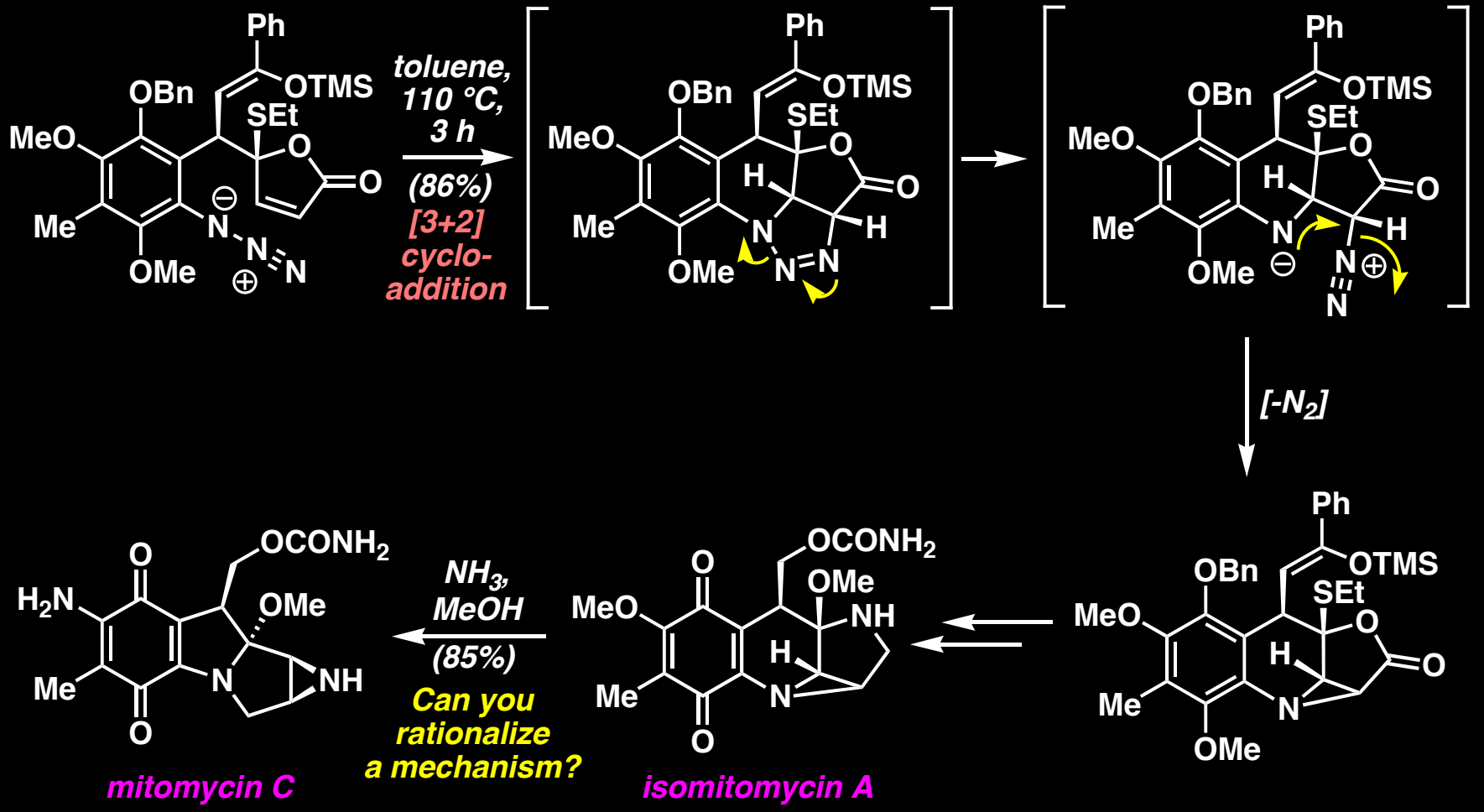
Azides: Applications in Total Synthesis



T. Fukuyama, L. Yang, J. Am. Chem. Soc. 1989, 111, 8303.