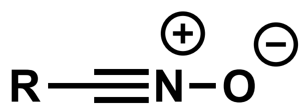
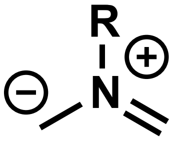
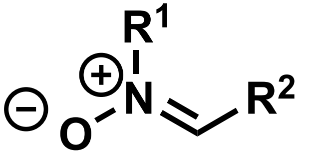
Dipolar Cycloadditions

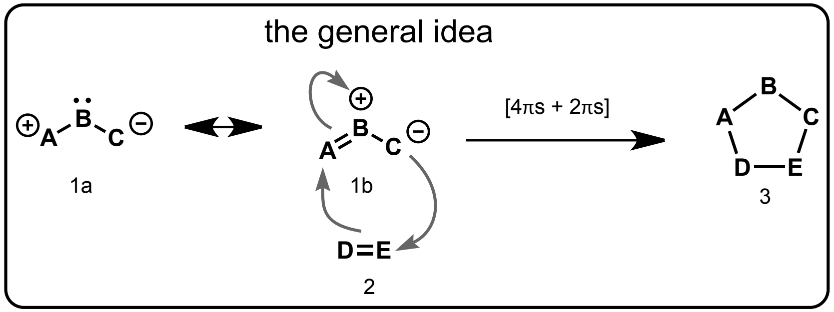




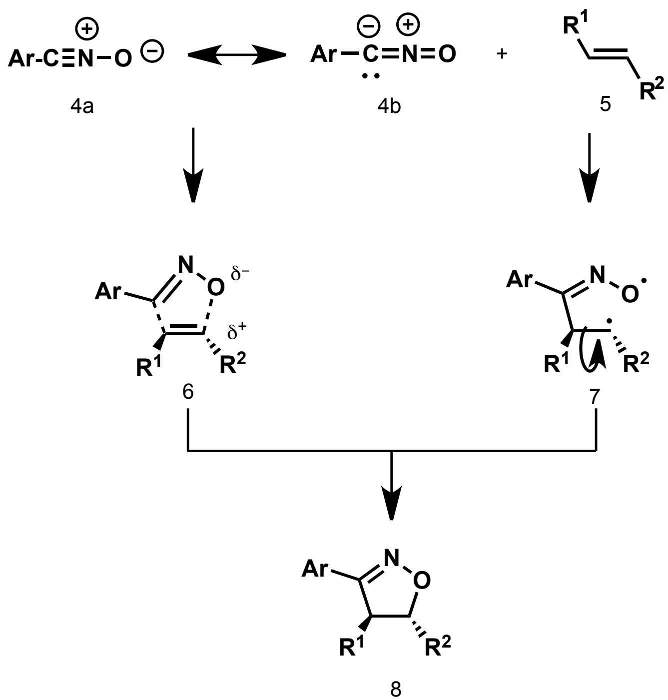


Nitrile oxides, azomethin ylides and nitrones in total synthesis

Introduction

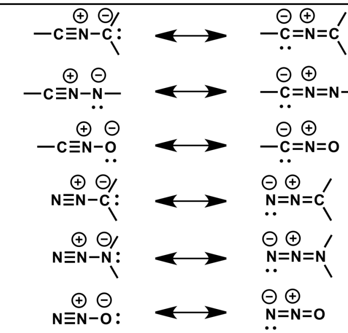


Huisgen vs. Firestone
60's & 70's



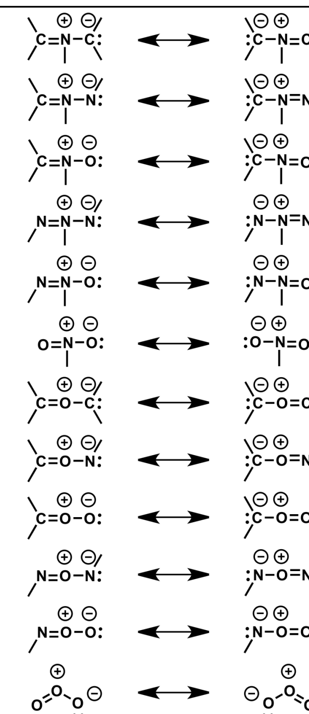
Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403-419

Propargyl/allenyl anion type



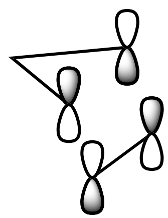
Nitrile ylides	
Nitrile imines	
Nitrile oxides	
Diazo alkanes	
Azides	
Nitrous oxide	

Allyl anion Type



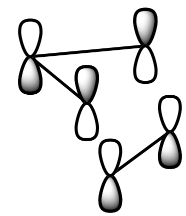
Azomethine ylides	
Azomethine imines	
Nitrones	
Azimes	
Azoxy compounds	
Nitro compounds	
Carbonyl ylides	
Carbonyl imines	
Carbonyl oxides	
Nitrosimines	
Nitrosoxides	
Ozone	

FMO Analysis



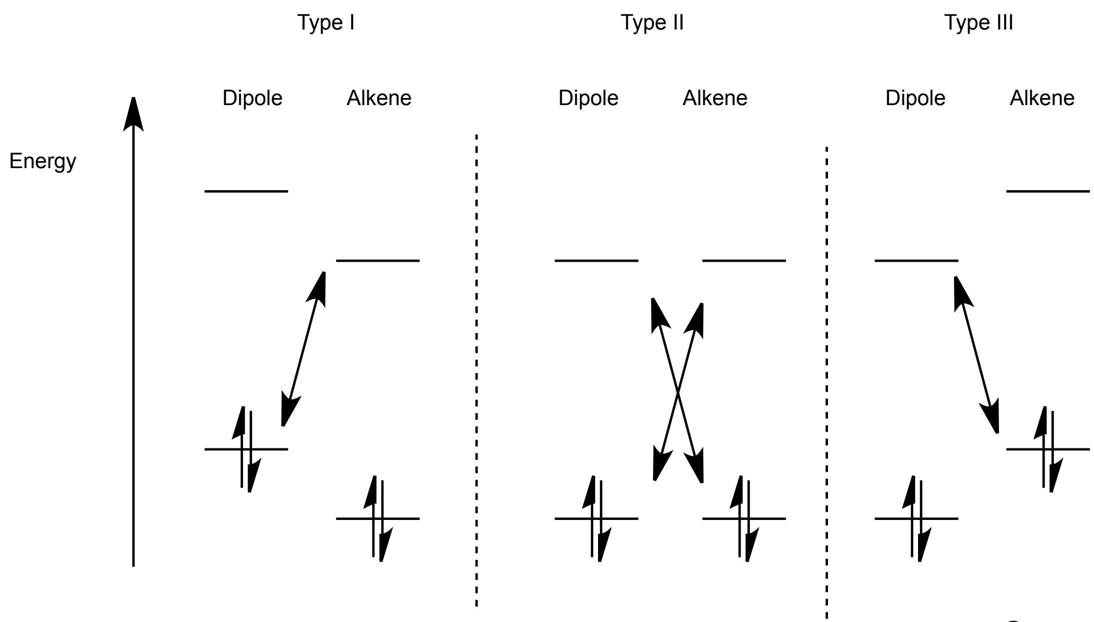
HOMO dipole

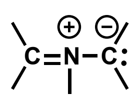
LUMO dipolarophile



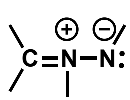
LUMO dipole

HOMO dipolarophile

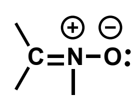




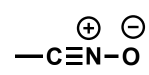
Azomethine ylides



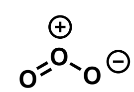
Azomethine Imines



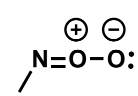
Nitrones



Nitrile Oxides

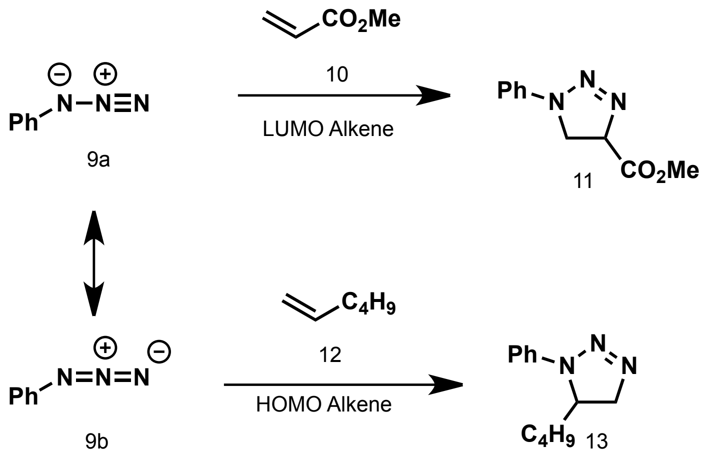


Ozone

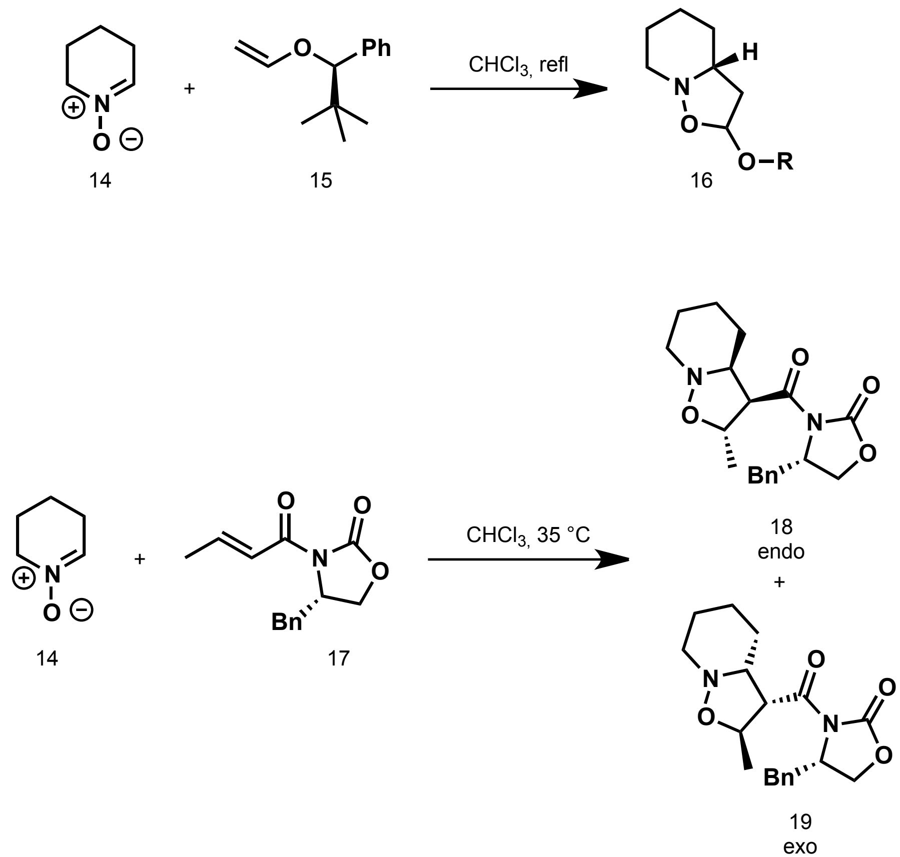


Nitrosoxides

Regiochemistry



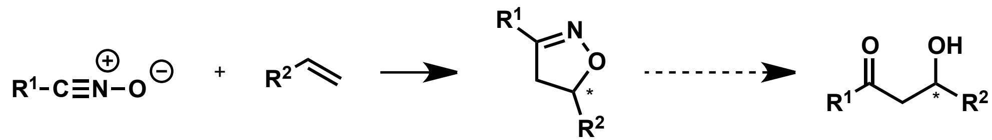
Reaction partners as well as Lewis acids have a big impact on reactivity and selectivity



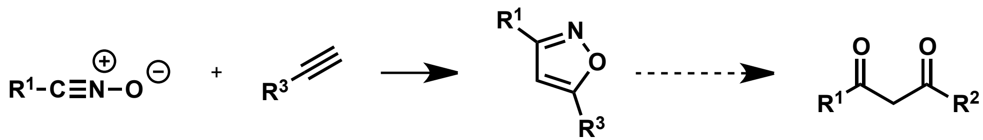
Carruthers, W.; Coggings, P.; Weston, J.B. *J. Chem. Soc., Chem. Commun.* **1991**, *2*, 117 – 118
Murahashi, S.-I.; Imada, Y.; Kohno, M.; Kawakami, T. *Synlett*, **1993**, *6*, 395 - 396

Nitrile oxides: introduction

The basic reaction



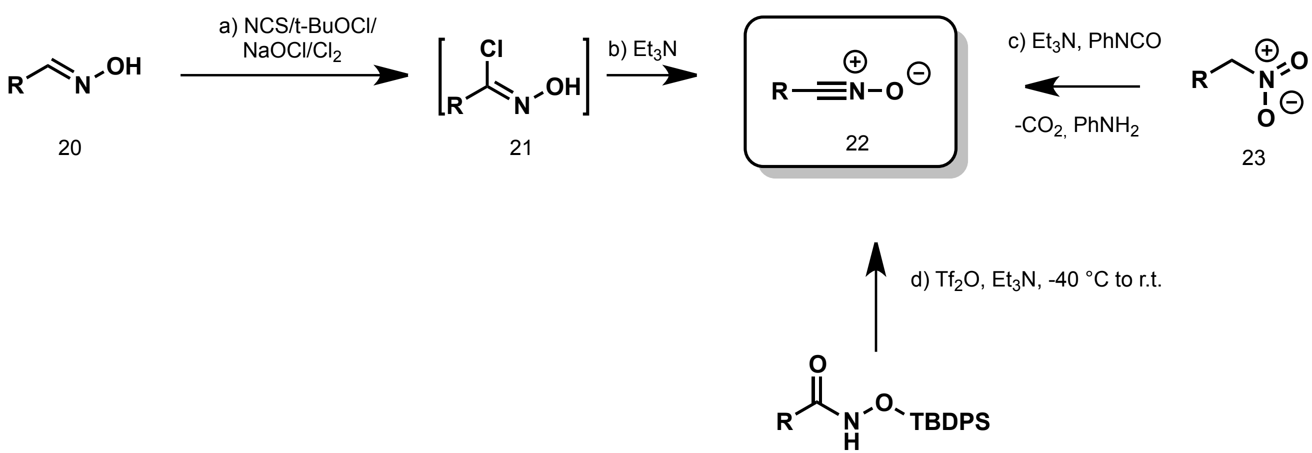
Isoxazolines β-hydroxy ketone



Isoxazoles 1,3 diketone

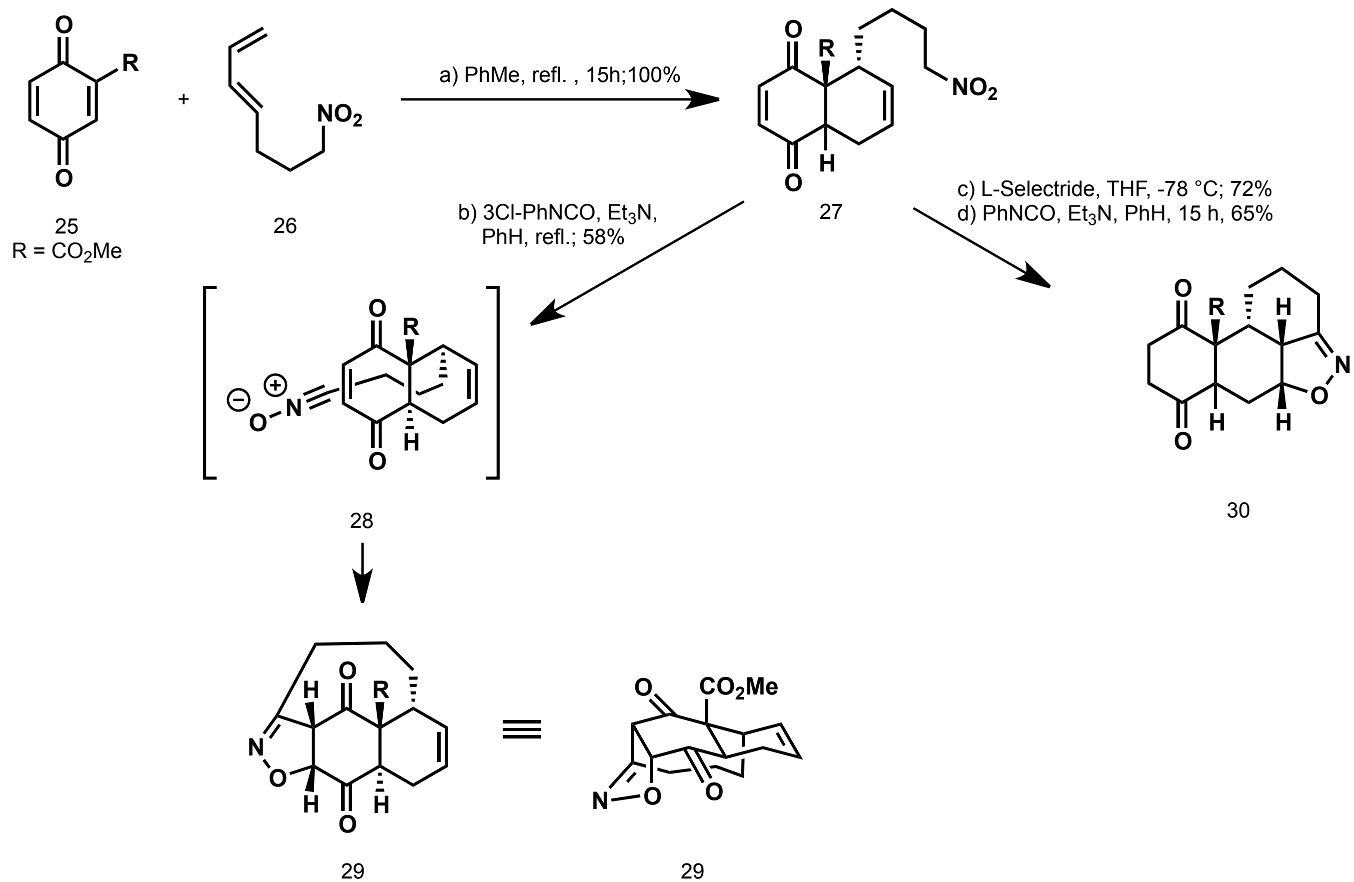
Nitrile Oxides are generally not stable and therefore formed in situ.
If no other reaction partner is present, they may dimerize

Generation of nitrile oxides



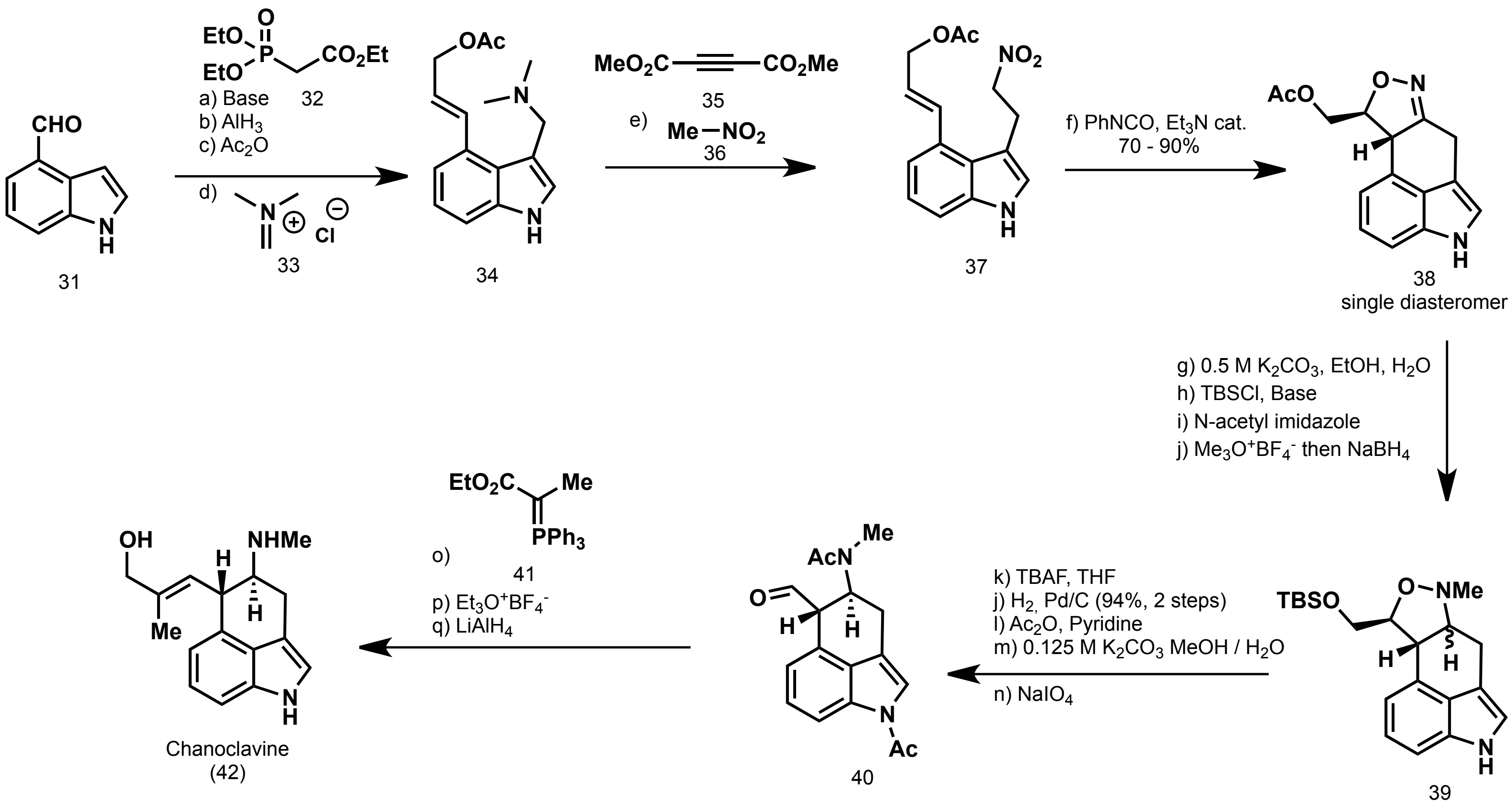
Reactivity example of nitrile oxides

Kozikowski, A.P.; Hiraga, K.; Springer, J.P.; Wang, B.C.; Xu, Z.-B. *J. Am. Chem. Soc.* **1984**, *106*, 1845-1847



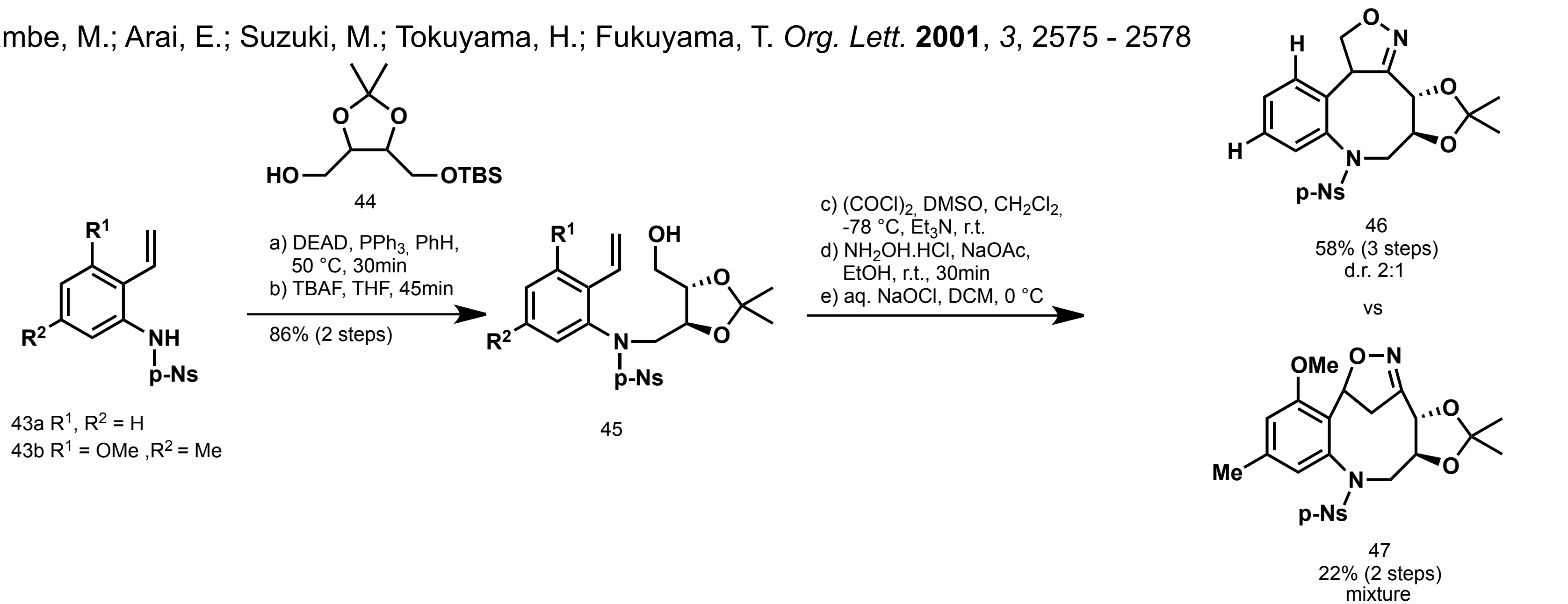
Nitrile oxides in total synthesis

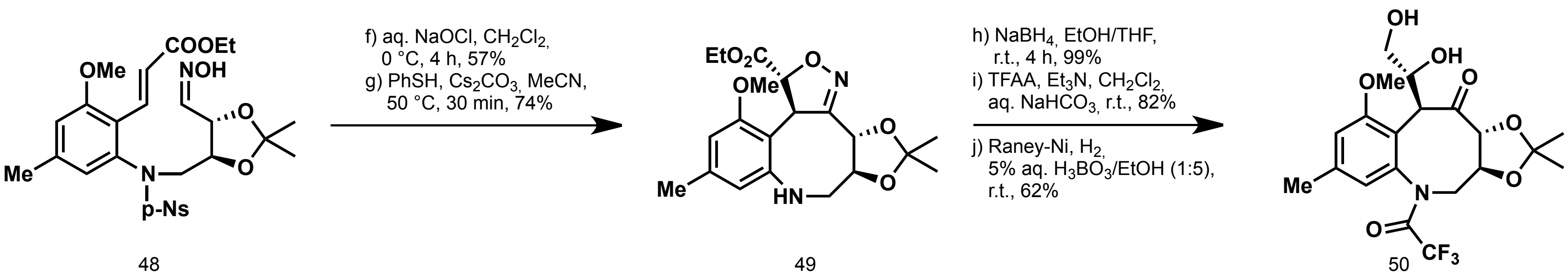
Kozikowski, A.P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265 - 4267

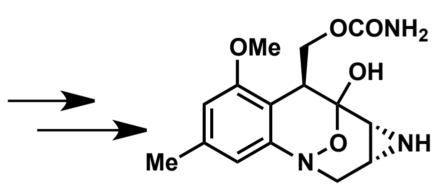


Nitrile oxides in total synthesis

Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2001**, *3*, 2575 - 2578



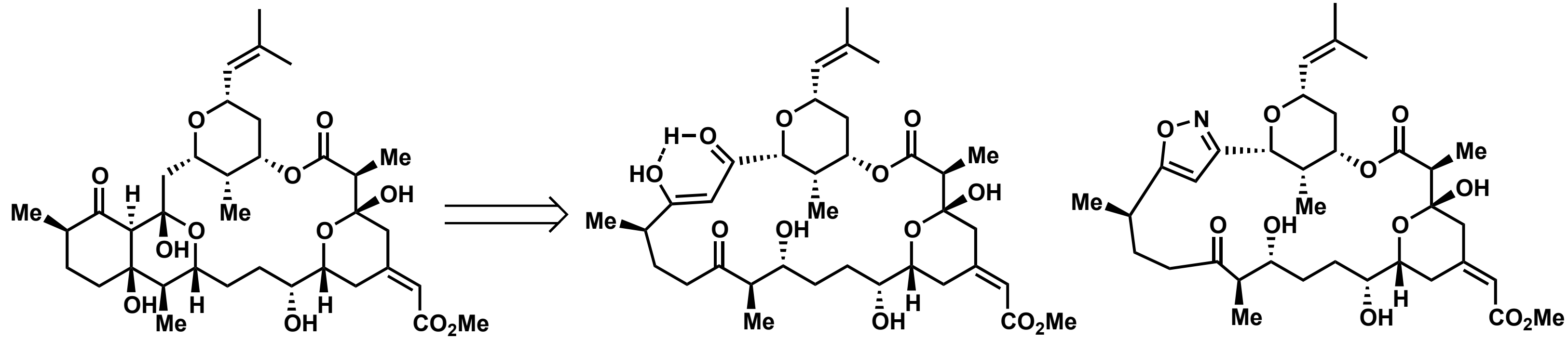




51
Analogue to FR-9000482
antitumor activities via DNA crosslinking

Nitrile oxides as aldol equivalents

Evans, D. A.; Ripion, D.H.B.; Halstead, D.P.; Campos, K.R. *J. Am. Chem. Soc.* **1999**, *121*, 6816-6826

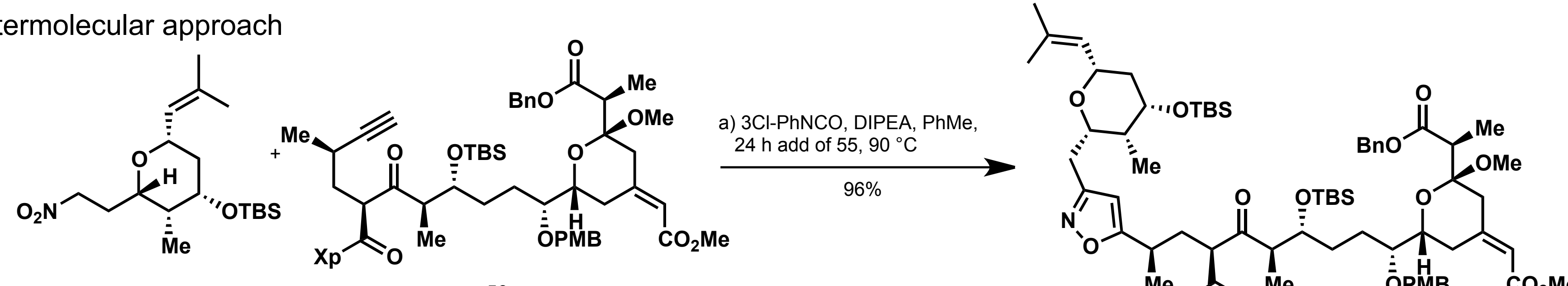


(+)-Miyakolide (52)

53 proposed: trans-annular aldol reaction

54 precursor to aldol

intermolecular approach



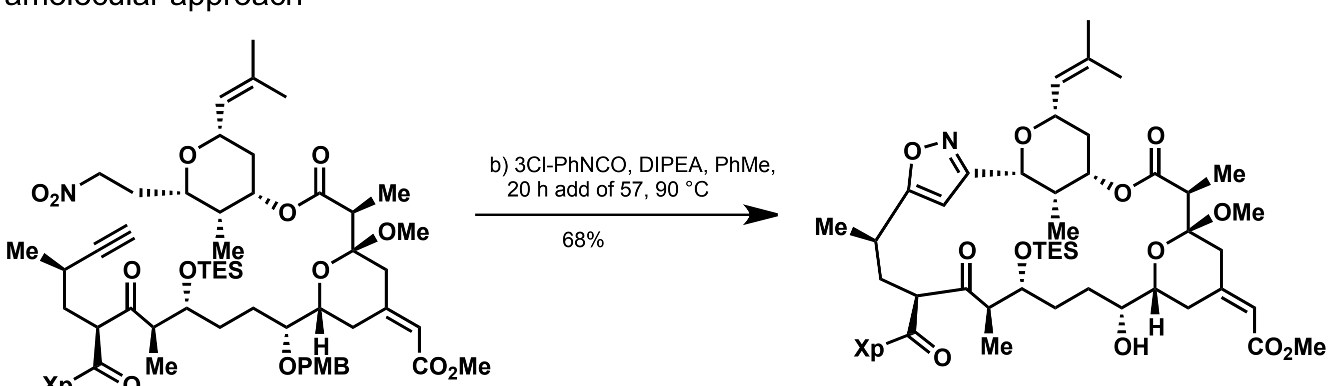
55

Xp: Evans Auxilliary

56

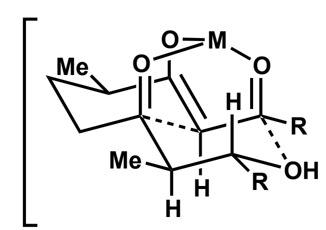
57 5 steps to 54

intramolecular approach



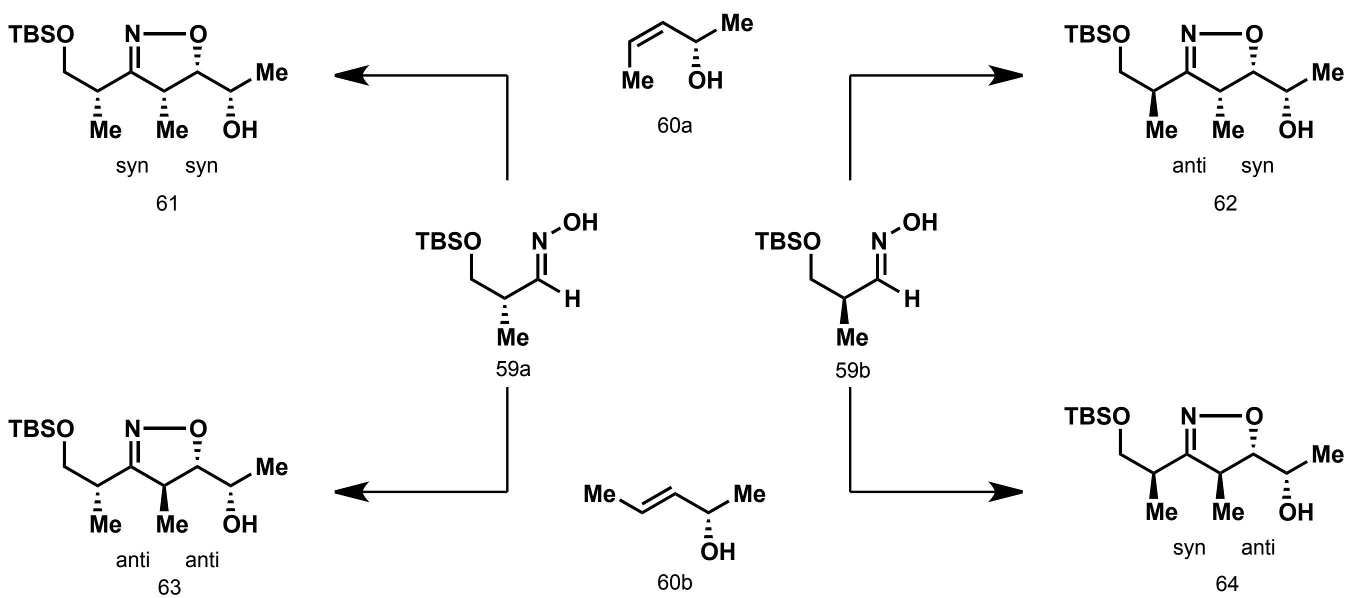
57

58 3 steps to 54



Nitrile oxides as aldol equivalents

Bode, J.W.; Carrreira, E.M. *J. Am. Chem. Soc.* **2001**, *123*, 3611 – 3612
After work from Kanemasa *et. al.*:
Kanemasa, S.; Nishiuchi, M.; Kamimure, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324

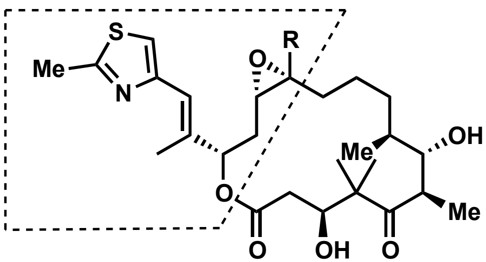


a) t-BuOCl, -78 °C b) 3 equiv EtMgBr, to r.t. 12 h
"all cycloadducts were regiochemically and sterochemically pure by ^{1}H and ^{13}C NMR analyses"

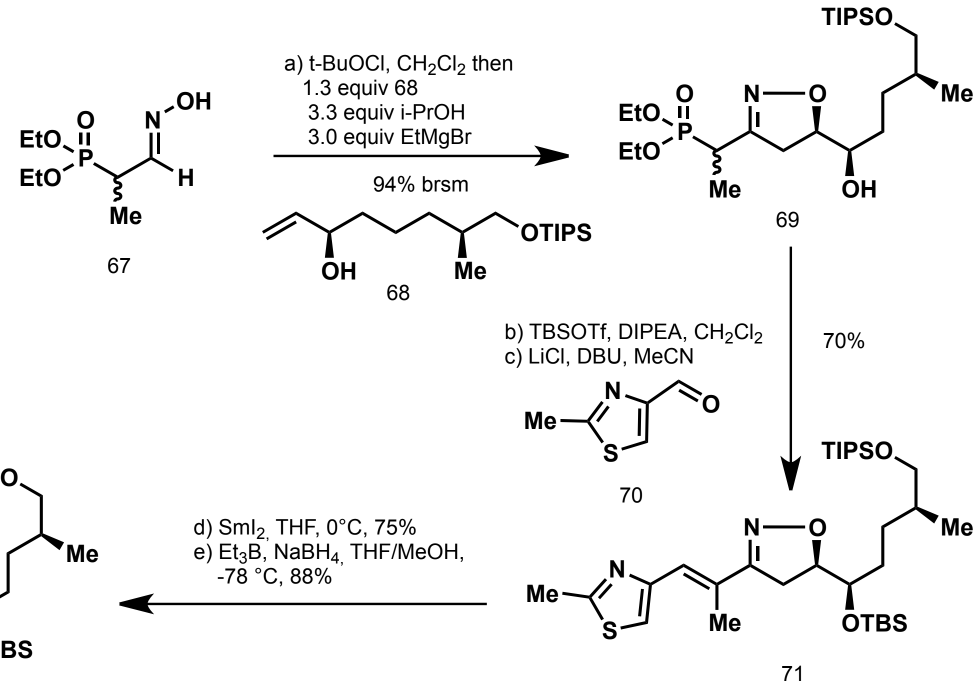
65a

Nitrile oxides as aldol equivalents

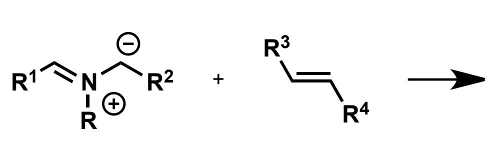
Bode, J.M.; Carreira, E.M. *J. Am. Chem. Soc.* **2001**, *123*, 3611-1612

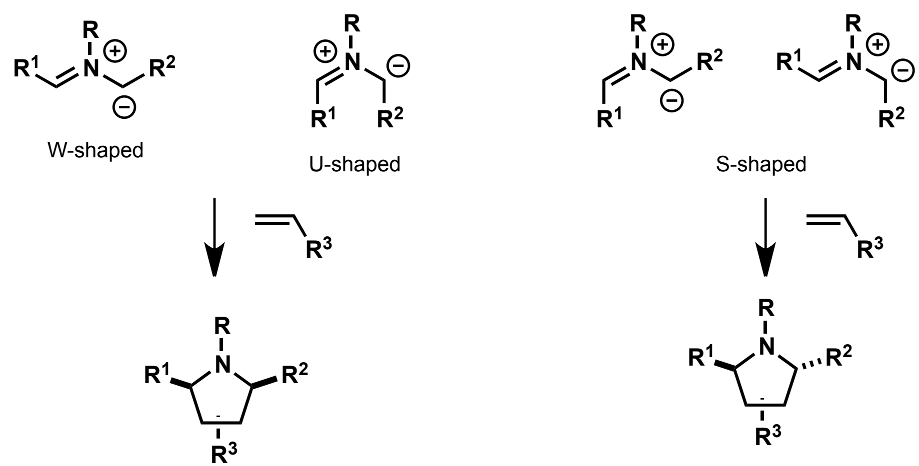


Epothilone A (R = H) (66a)
Epothilone B (R = Me) (66b)

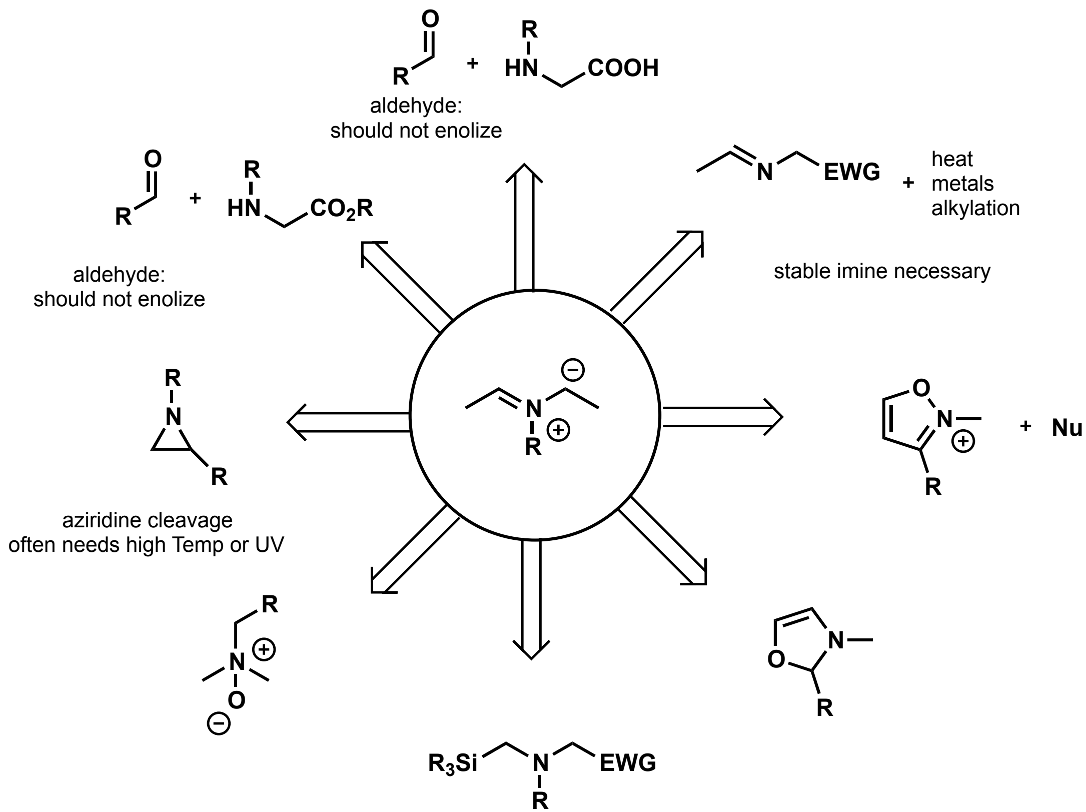


Azomethine ylides

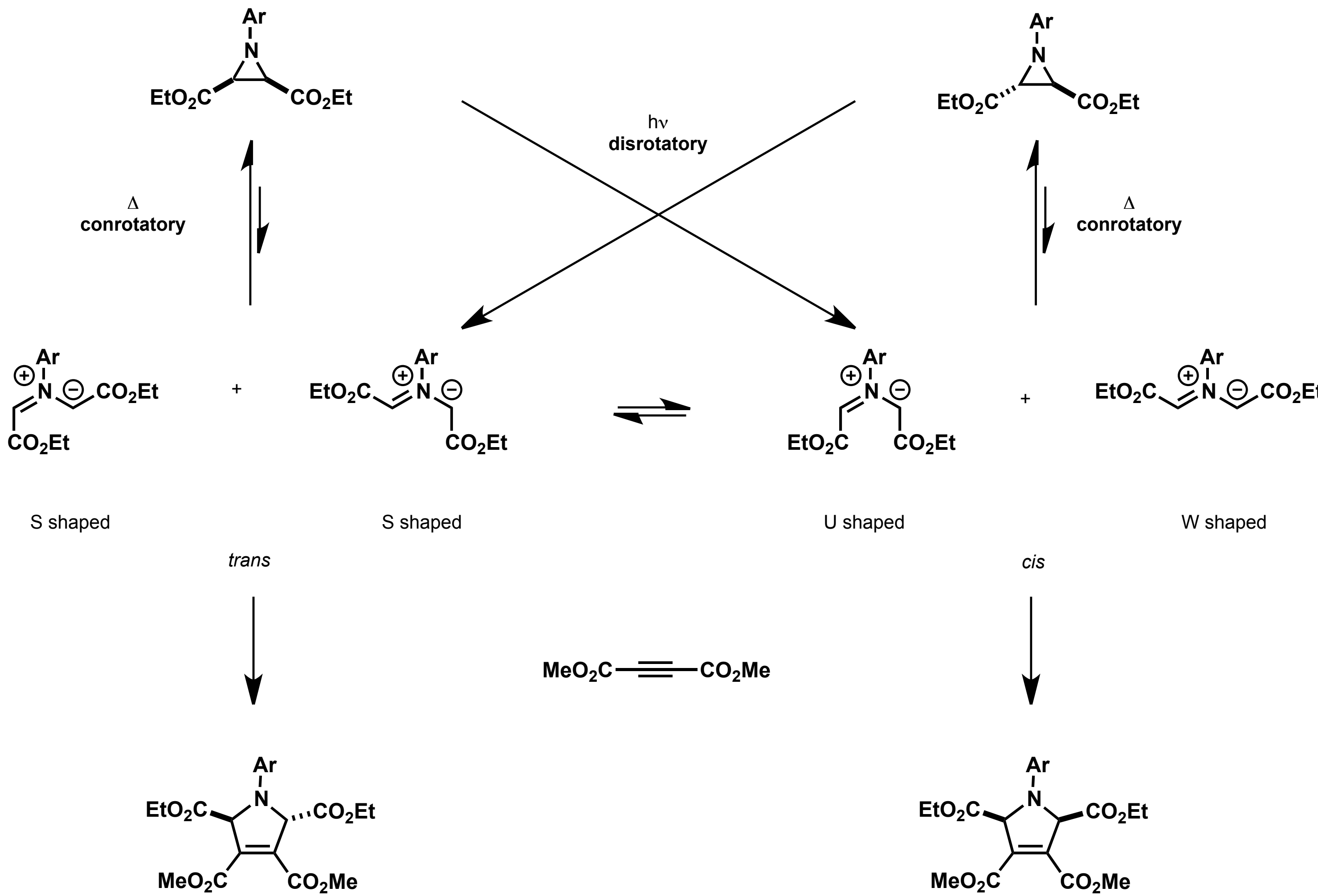




Preparation of azomethine ylides

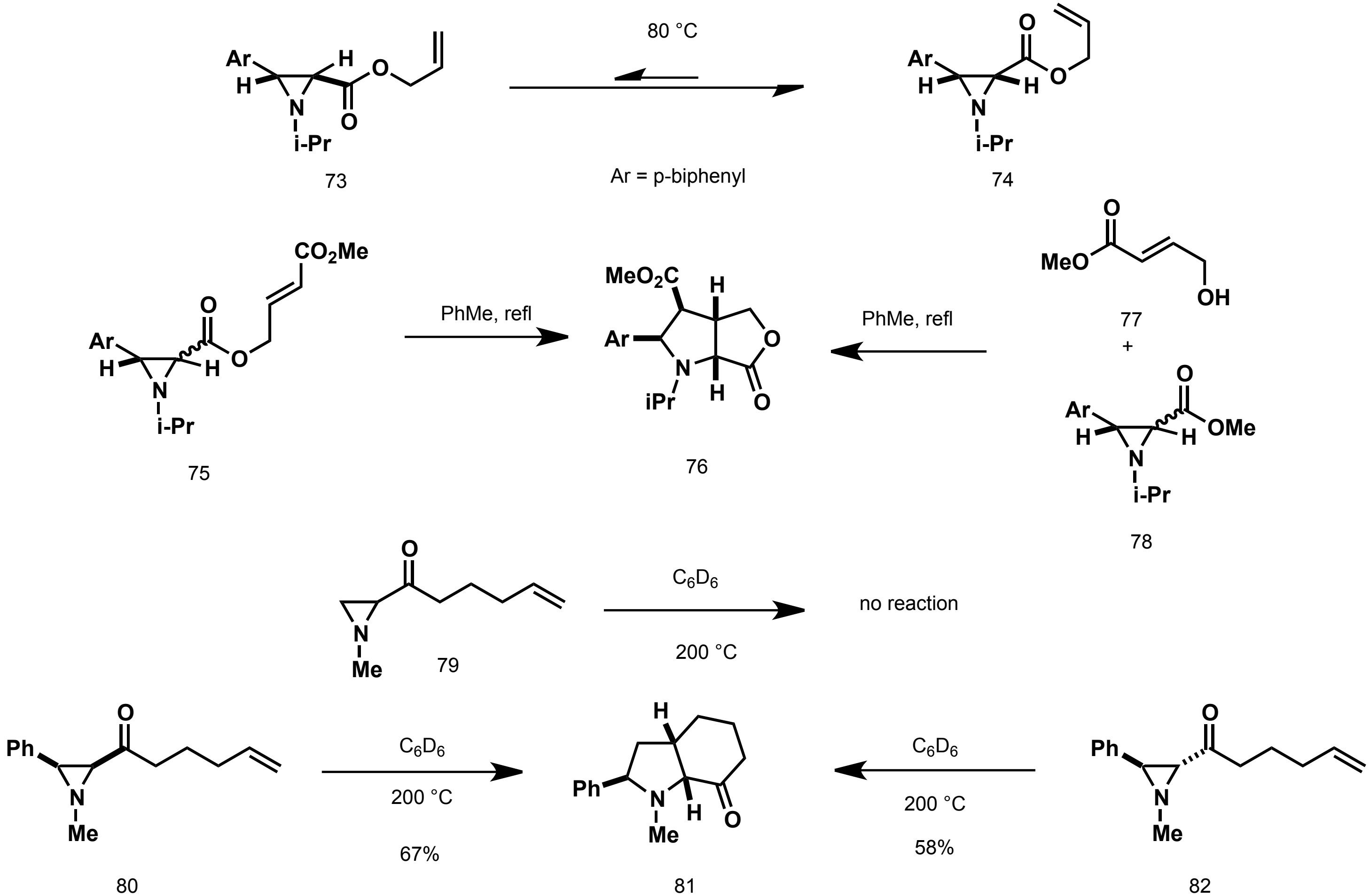


Stereochemistry with azomethinylides



Huisgen, R.; Scheer, W.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 1753 - 1755
Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, *4*, 397 - 404
Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395 - 397

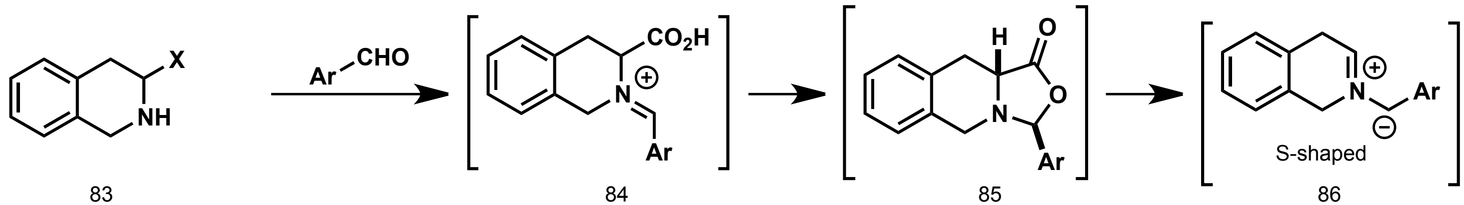
HOMO – LUMO interaction for azomethine ylides

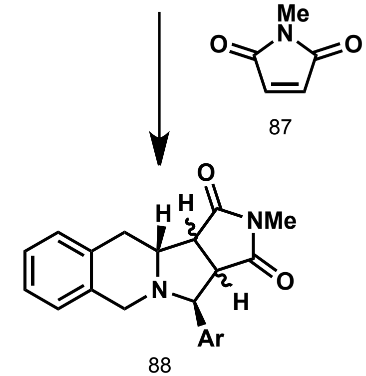


Padwa, A.; Ku, H. *J. Org. Chem.* **1979**, *44,* 255 – 261
Wenkert, D.; Ferguson, S.B.; Porter, B.; Qvarnstrom, A. *J. Org. Chem.* **1985**, *50*, 4114 - 4119

Stereochemistry with azomethinylides

when generating ylides from aldehydes, the S shaped ylid is formed predominantly

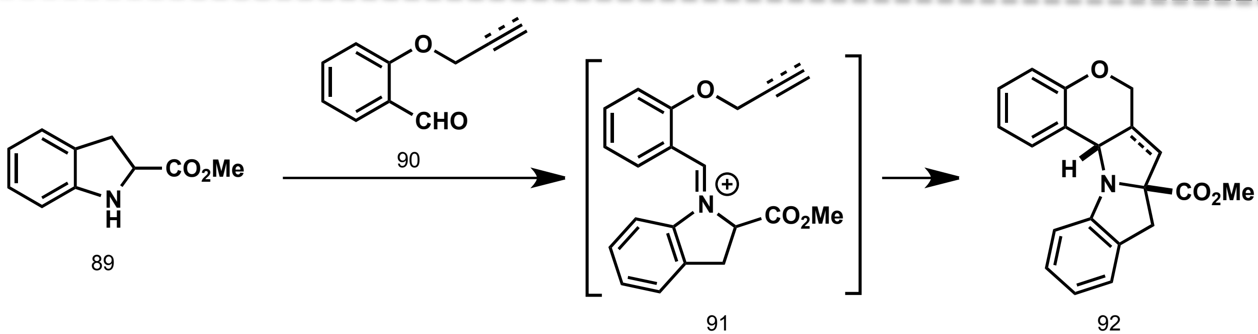




Endo/Exo selectivity varies

selectivities generally > 10

Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D.
J. Chem. Soc., Chem. Commun. **1987**, *2*, 49 - 51

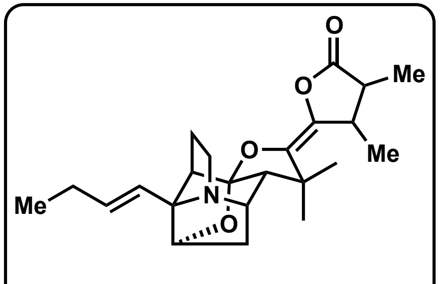


single isomer for the alkyne
2:1 d.r. for the alkene

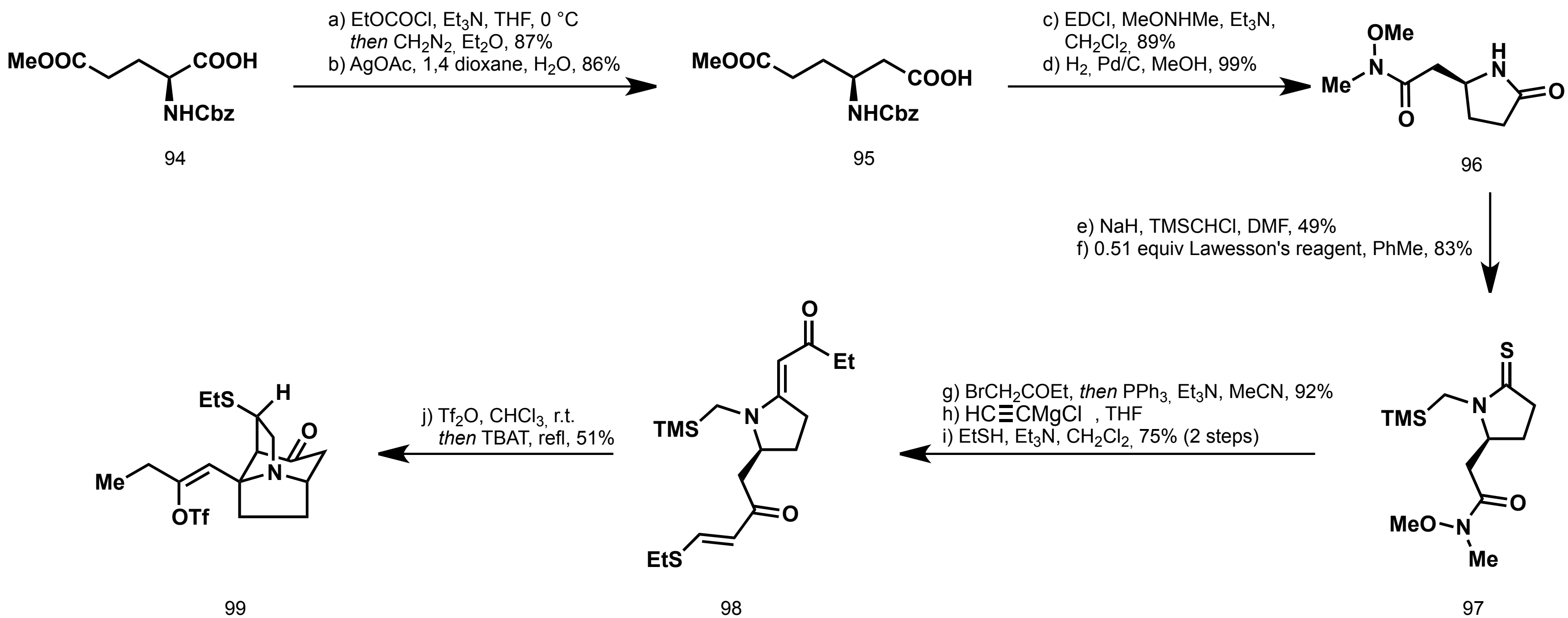
Grigg, R.; Duffy, L.M.; Dorrity, M.J.; Malone, J.F.; Rjaviroongit, S.; Thornton-Prett, M. *Tetrahedron* **1990**, *46*, 2213 - 2230

Azomethine ylides in total synthesis

Epperson, M. T.; Gin, D.Y.
Angew. Chem. Int. Ed.,**2002**, *41*, 1778 - 1780

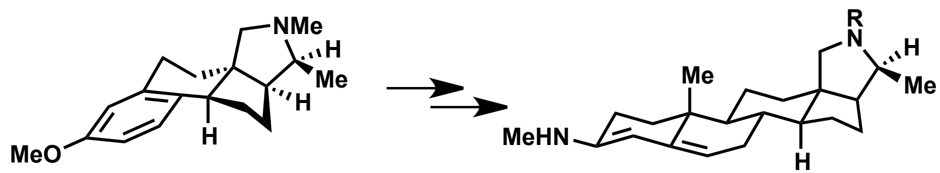


Asparagamine A
(93)



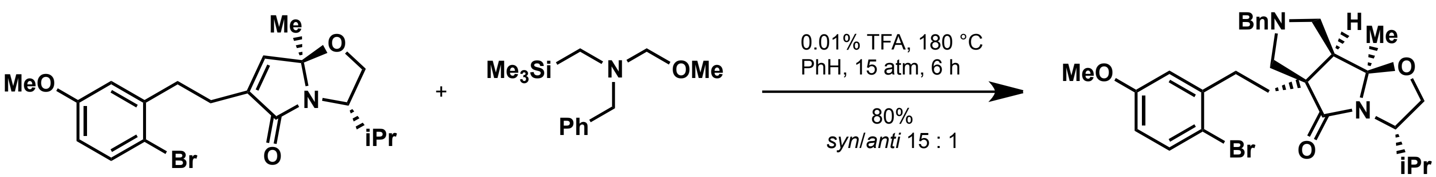
Azomethine ylides in total synthesis

Kopach, M.E.; Fray, A.H.; Meyers, A.I. *J. Am. Chem. Soc.* **1996**, *118*, 9876 - 9883

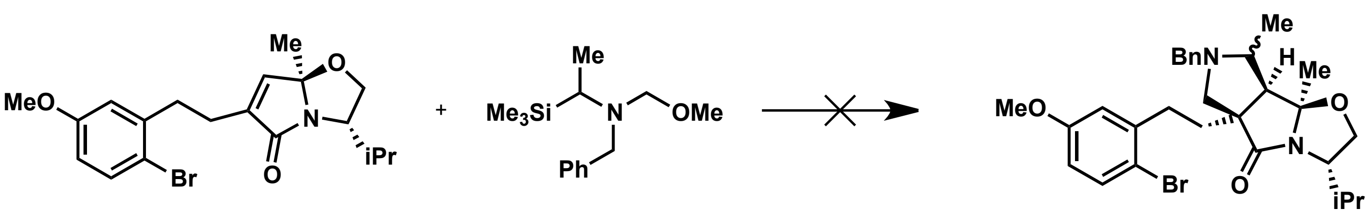


100

R = H, Regholarrhenine C (101a)
R = Me, Conessine (101b)



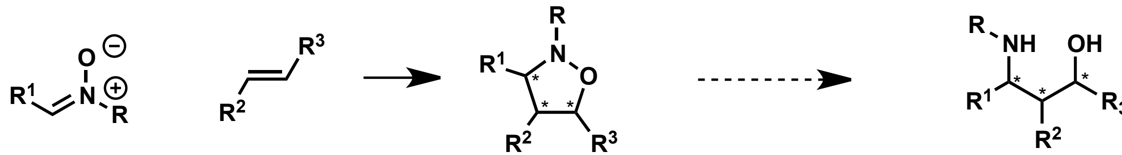
102 103 104



105 106 107

Nitrones

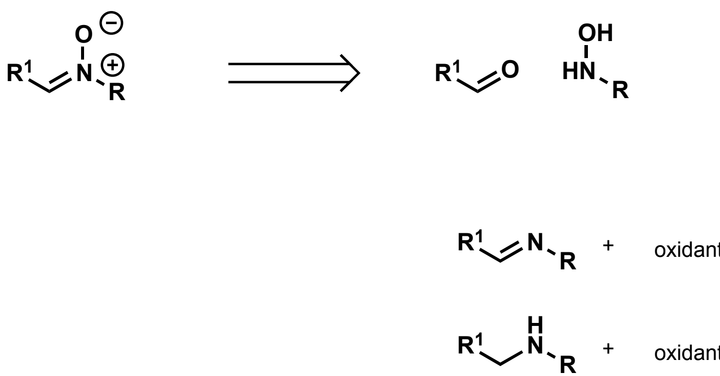
The basic reaction

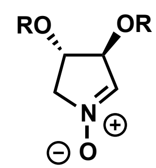


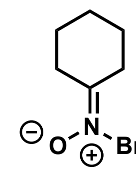
E/*Z* isomers of exist
partially interconversion exists
resulting in stereoisomers

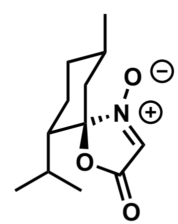
isoxazolidine

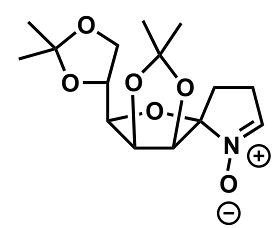
β amino alcohols



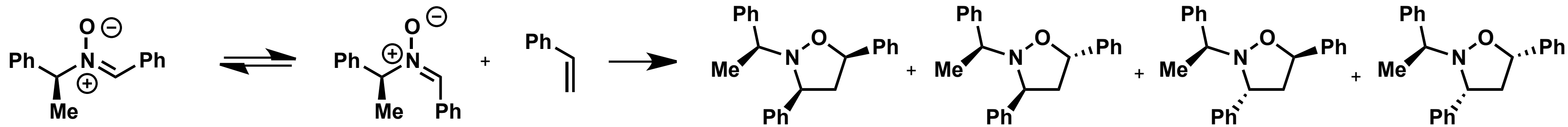








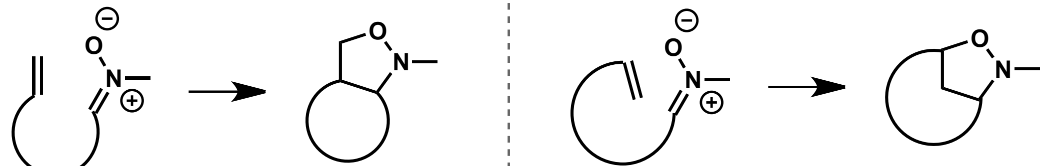
Nitrones in DA: selectivity



108a 108b 109 110a 110b 110c 110d

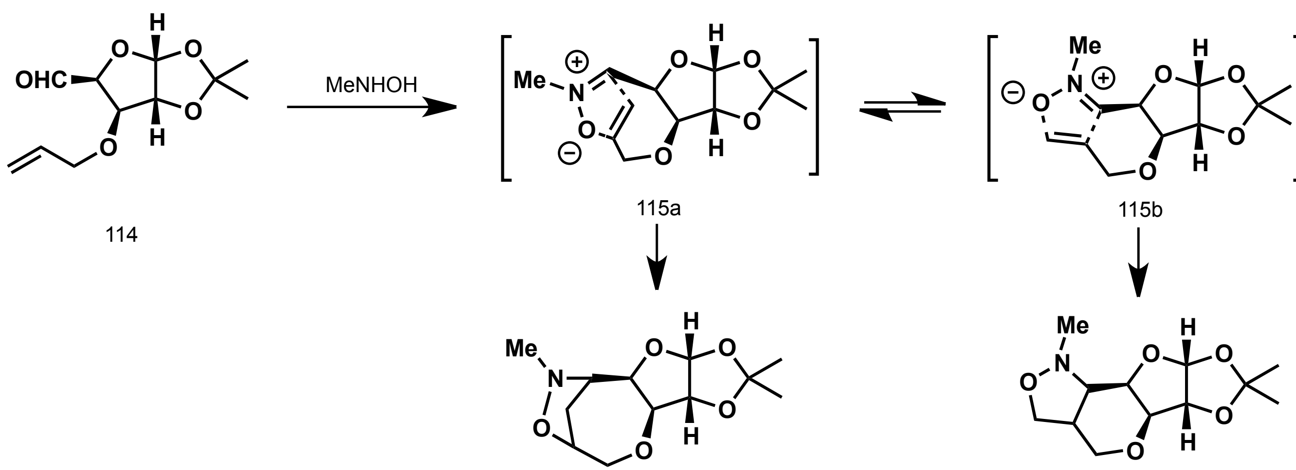
Yield: 90% ratio: 76 : 8 : 11 : 5

Belzecki, C.; Panfil, I. *J. Chem. Soc., Chem. Commun.* ***1977****, 9*, 303 - 304



bicyclo [X,3,0] bicyclo [X,2,1]

111 112 111 113



114 115a 115b

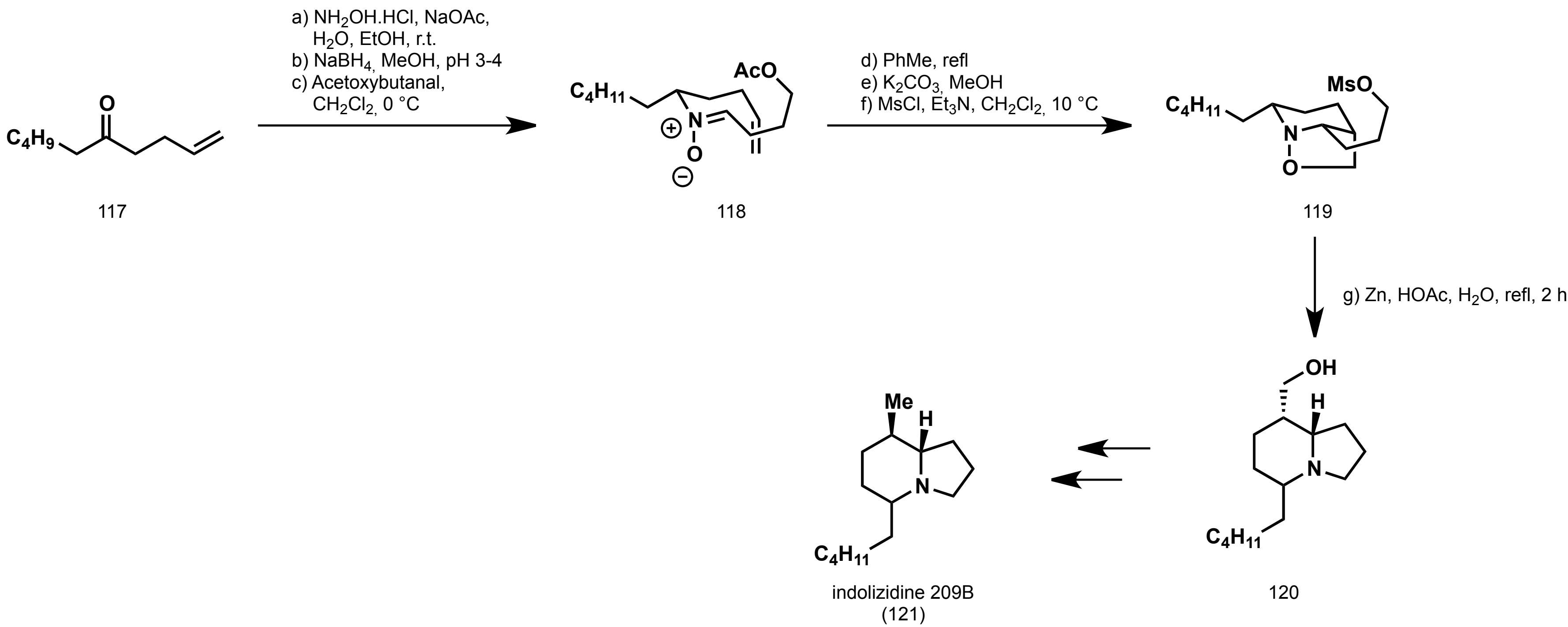
116
76%

117
6%

Shing, T.K.M.; Fung, W.-C.; Wong, C.-H.
J. Chem. Soc., Chem. Commun. **1994**,*4*, 449 - 450

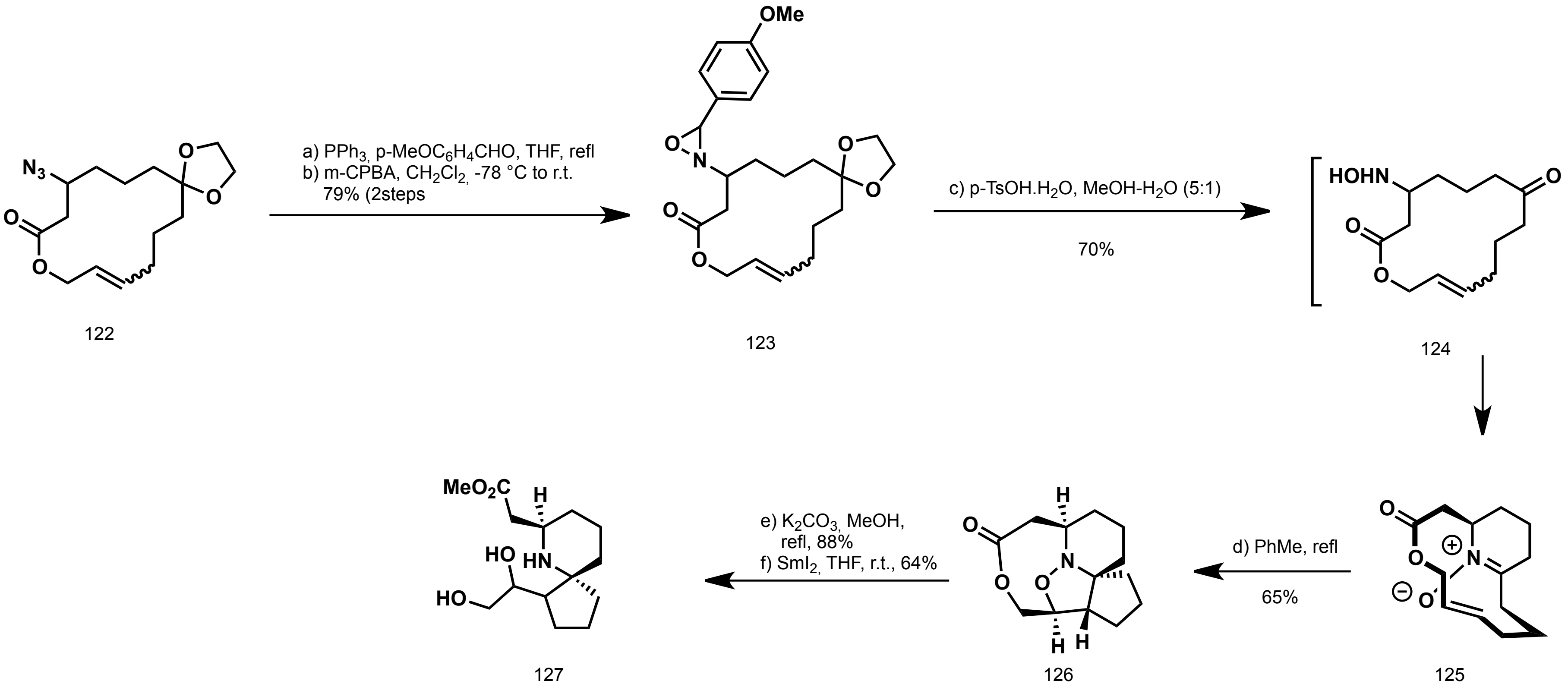
Nitrones in total synthesis

Smith, A.L.; Williams, S.F.; Holmes, A.B. *J. Am. Chem. Soc.* **1988**, *110*, 8696 - 8698



Nitrones in total synthesis

White, J.D.; Blakemore, P.R.; Korf, E.A.; Yokochi, A.F.T. *Org. Lett.* **2001**, *3*, 415 - 415



"A stereocontrolled entry to the spirocyclic Core of Pinnaic Acid"

Summary

- Dipolar Cycloadditions as a means for C-C bond formation
- Controlled formation of stereocenters
- Intramolecular approaches helps with selectivity
- A lot of existing literature
- some reviews:

Gothelf, K.V.; Jorgensen, K.A. *Chem. Rev.* **1988**, *98*, 863 – 909

Coldham, I.; Hufton, R. C *Chem. Rev.* **2005**, *105*, 2765 – 2809

Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry. Towards Heterocycles and Natural Products (Series: Chemistry of Heterocyclic Compounds, Vol. 59.) Padwa, A. Pearson, W. H., 2003, John Wiley & Sons, inc.