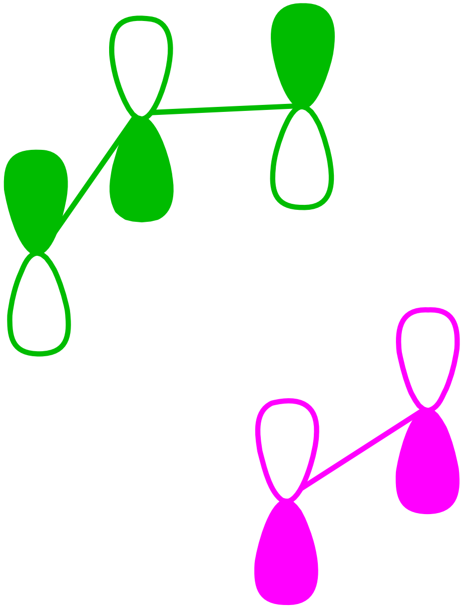
Asymmetric 1,3-Dipolar Cycloadditions



Jeff Frein

1-26-05

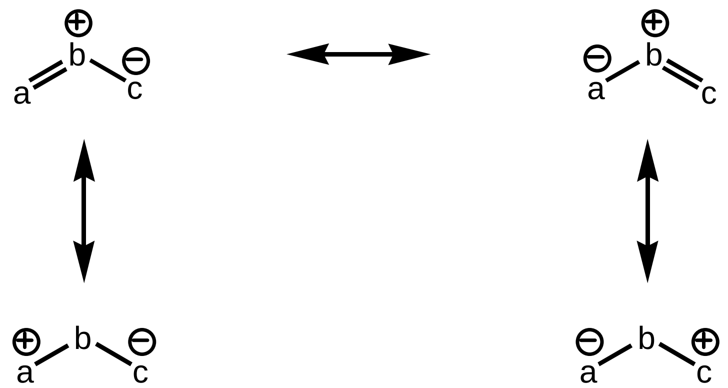
4th Year Seminar

Types of 1,3-Dipoles

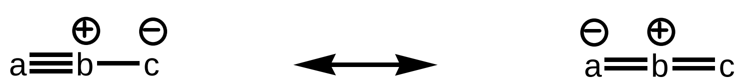
- **Allyl anion**

octet structure

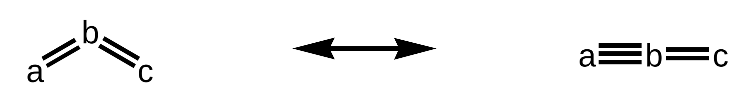
sextet structure



- **Propargyl / Allenyl anion**

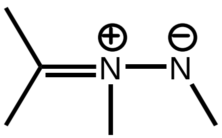


- **Hypervalent representations**

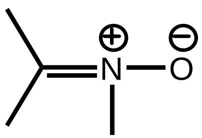


Allyl Anion 1,3-Dipoles

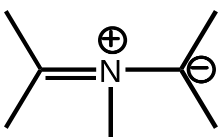
- **Nitrogen in the Middle**



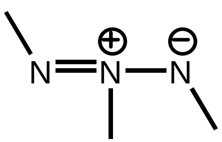
Azomethine Imines



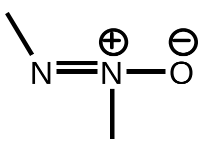
Nitrones



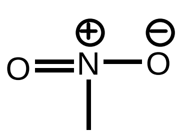
Azomethine Ylides



Azimines

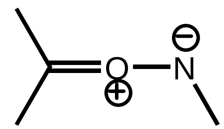


Azoxy Compounds

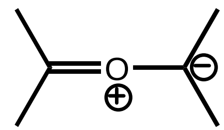


Nitro Compounds

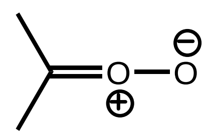
- **Oxygen in the Middle**



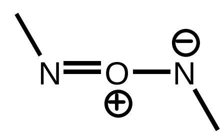
Carbonyl Imines



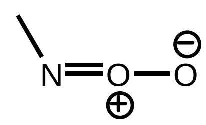
Carbonyl Ylides



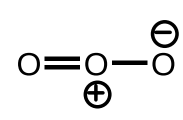
Carbonyl Oxides



Nitrosimines



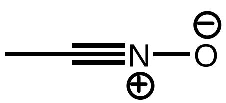
Nitrosoxides



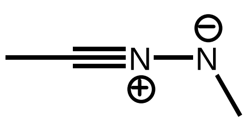
Ozone

Propargyl/Allenyl 1,3-Dipoles

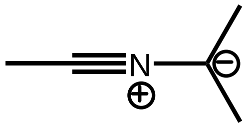
- **Nitrillium Betaines**



Nitrile Oxides

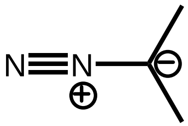


Nitrile Imines

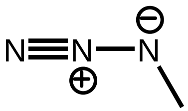


Nitrile Ylides

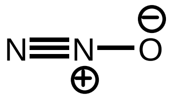
- **Diazonium Betaines**



Diazoalkanes

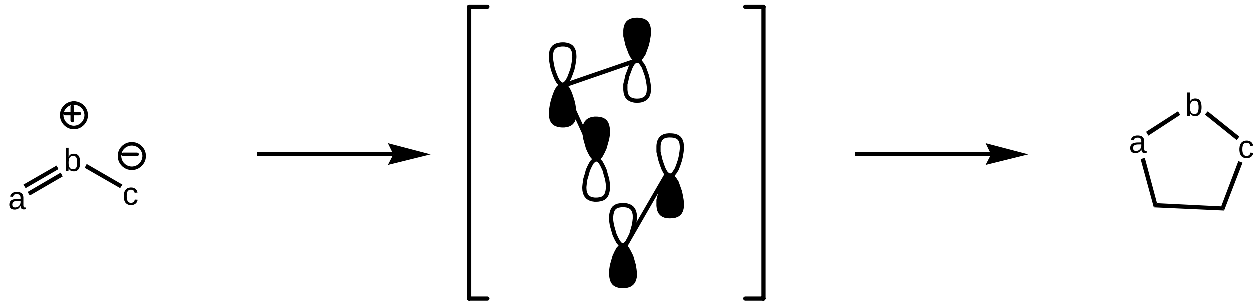


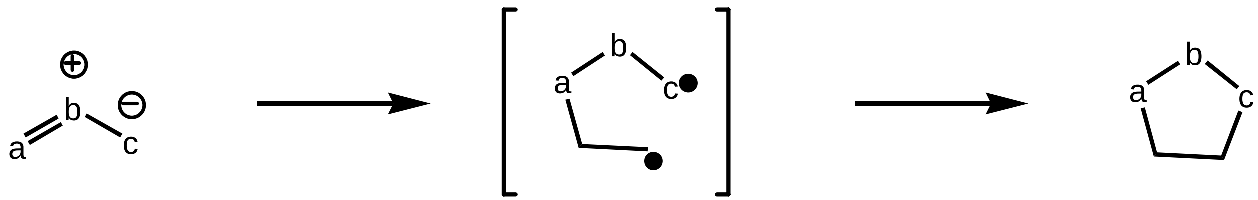
Azides

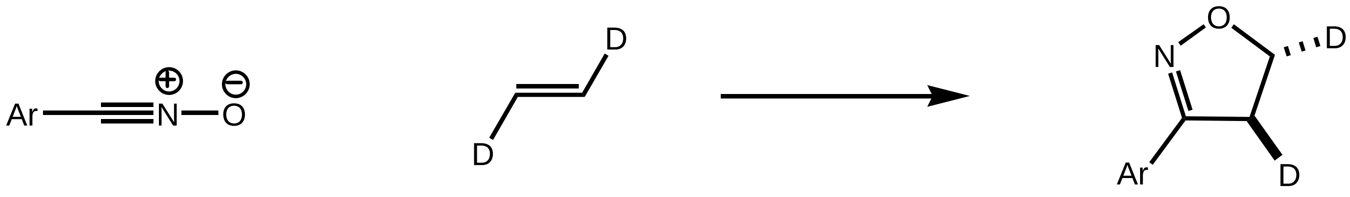


Nitrous Oxide

Concerted or Stepwise?

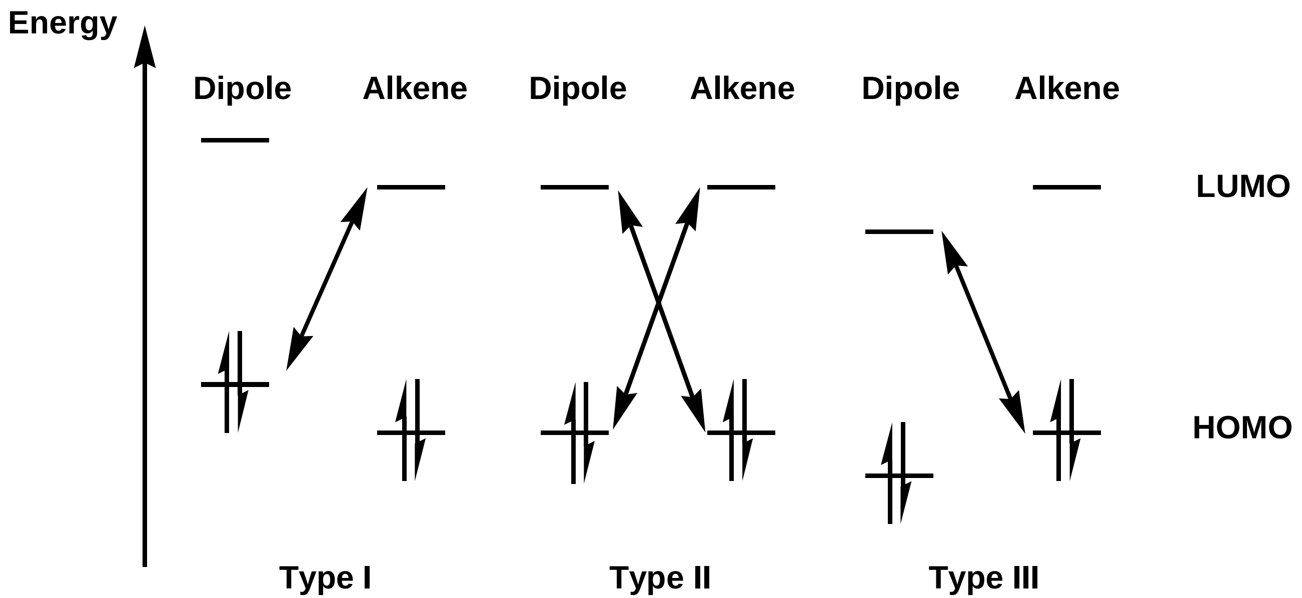






Huisgen, R. *Angew. Chem.* **1963**, *75*, 604.
Firestone

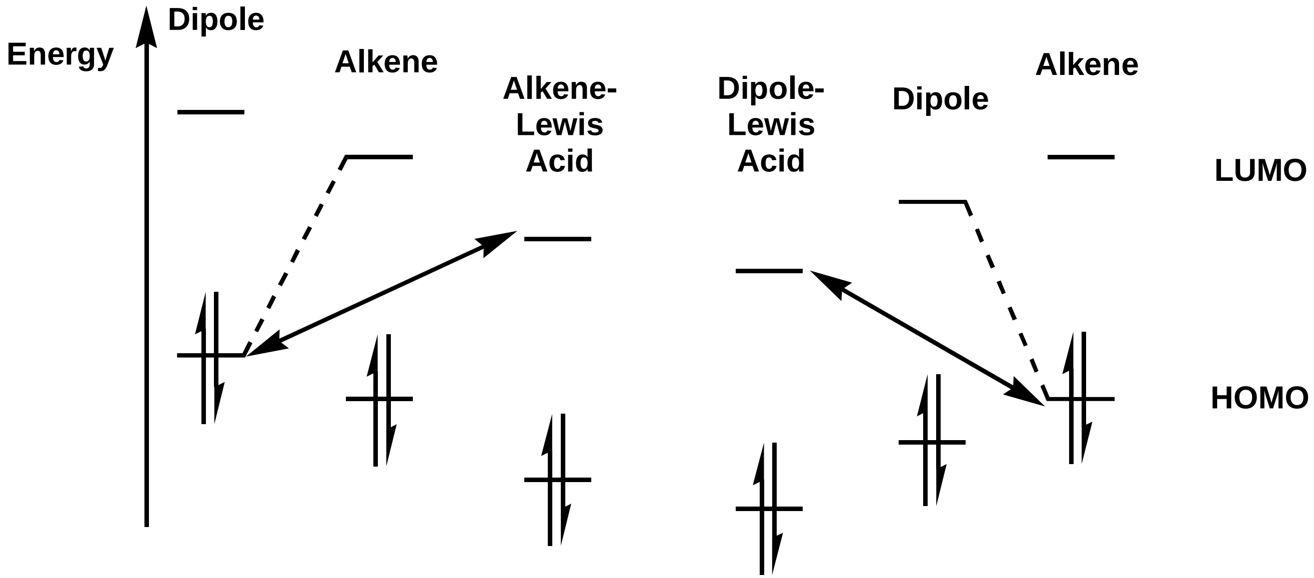
FMO Theory



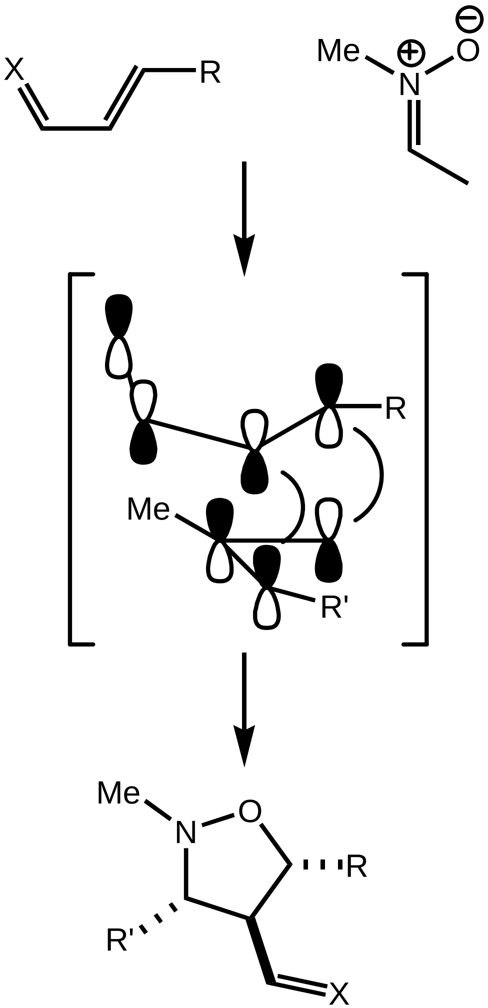
Energy
Dipole
Alkene
Dipole
Alkene
Dipole
Alkene
LUMO
HOMO
Type I
Type II
Type III

FMO-re Theory

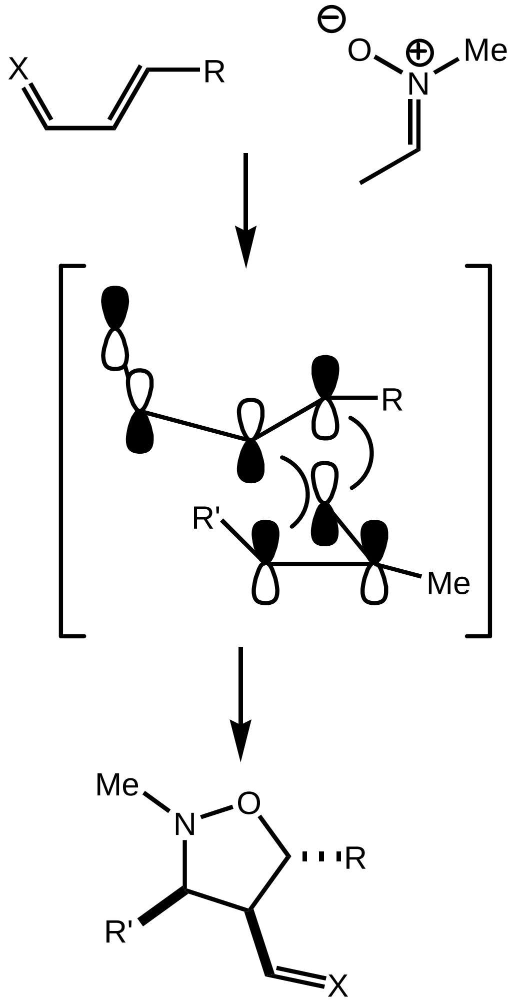
- With Lewis acid



Transition States

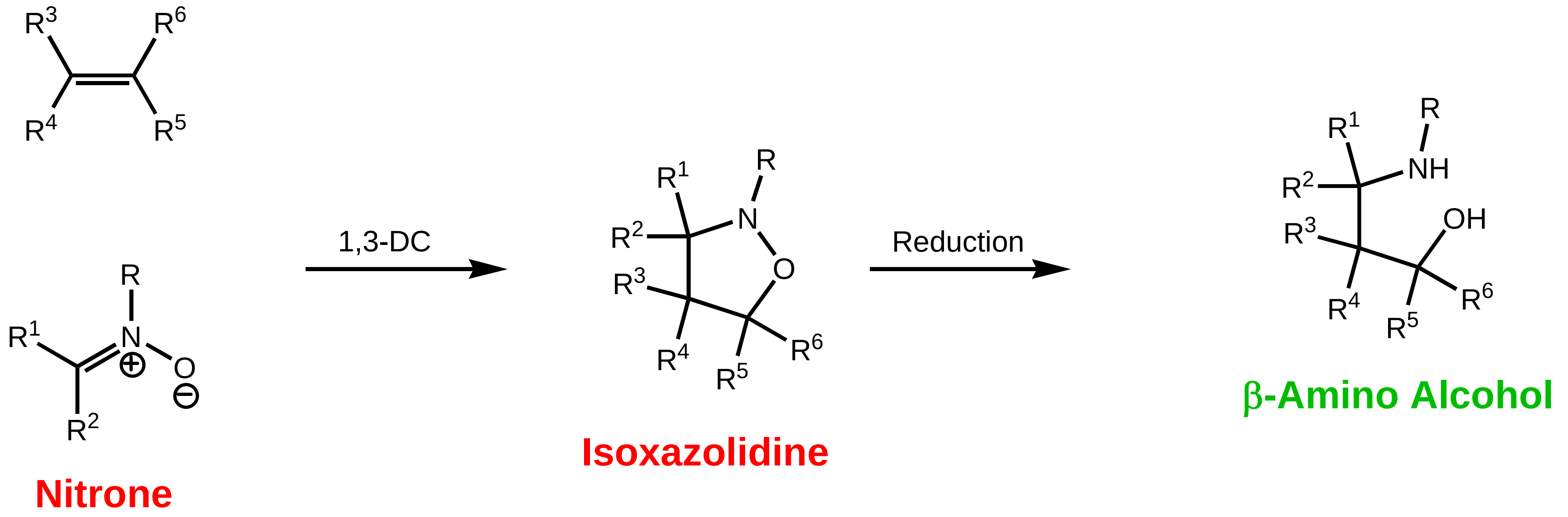


Endo



Exo

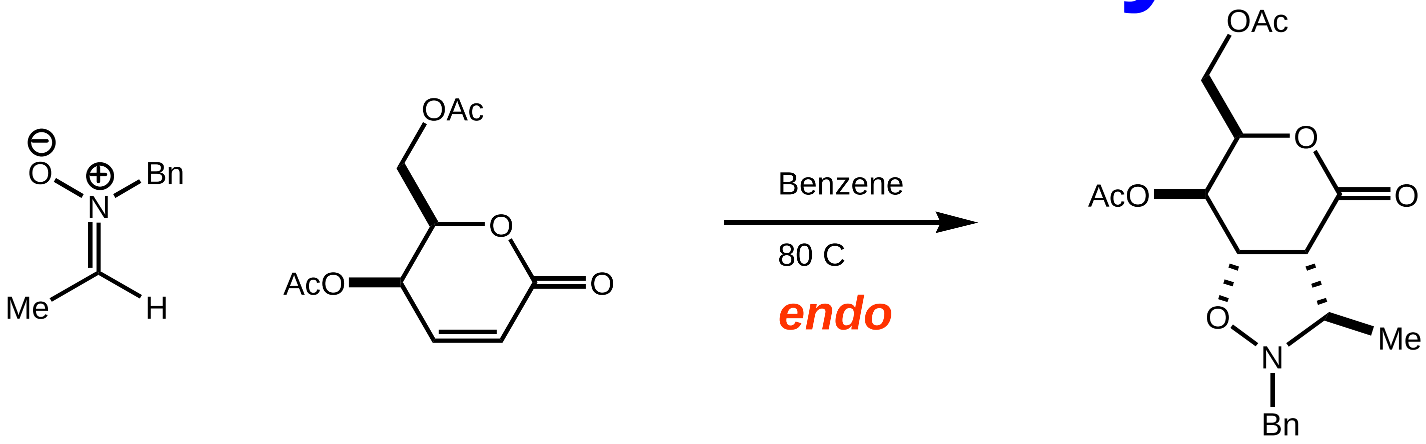
Why Nitrones?



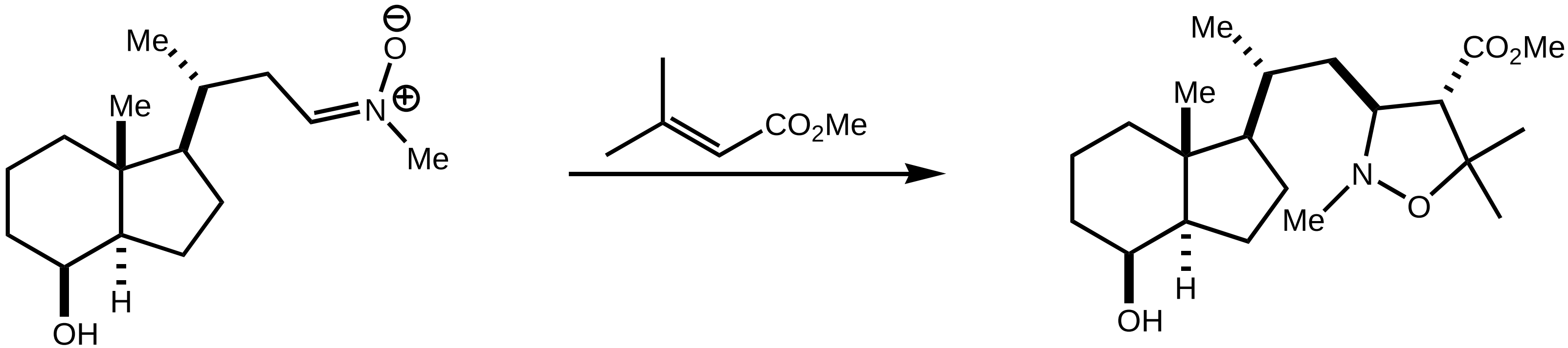
Breakdown

- Chiral Dipolarophiles & Dipoles
- Intramolecular Reactions
- Catalyzed Reactions
- Applications in Total Synthesis

Carbon Chirality



Single Diastereomer



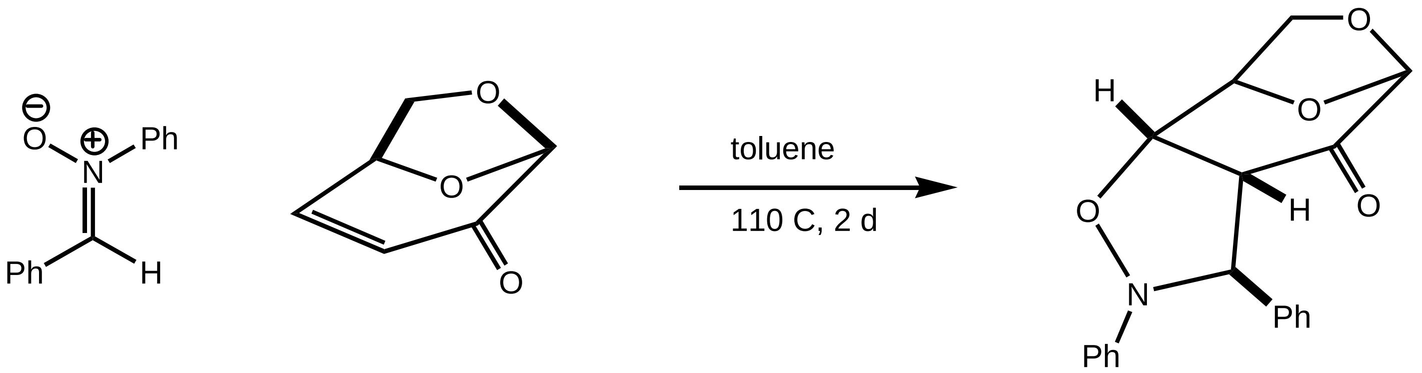
***endo* : *exo* = 100 : 0**

***de**$_{endo}$* **= 0 %**

Baggiolini, E. G.; Iacobelli, J. A.; Hennesy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org.Chem.* **1986**, *51*, 3098.

Panfil, I.; Belzecki, C.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **1991**, *49*, 10087.

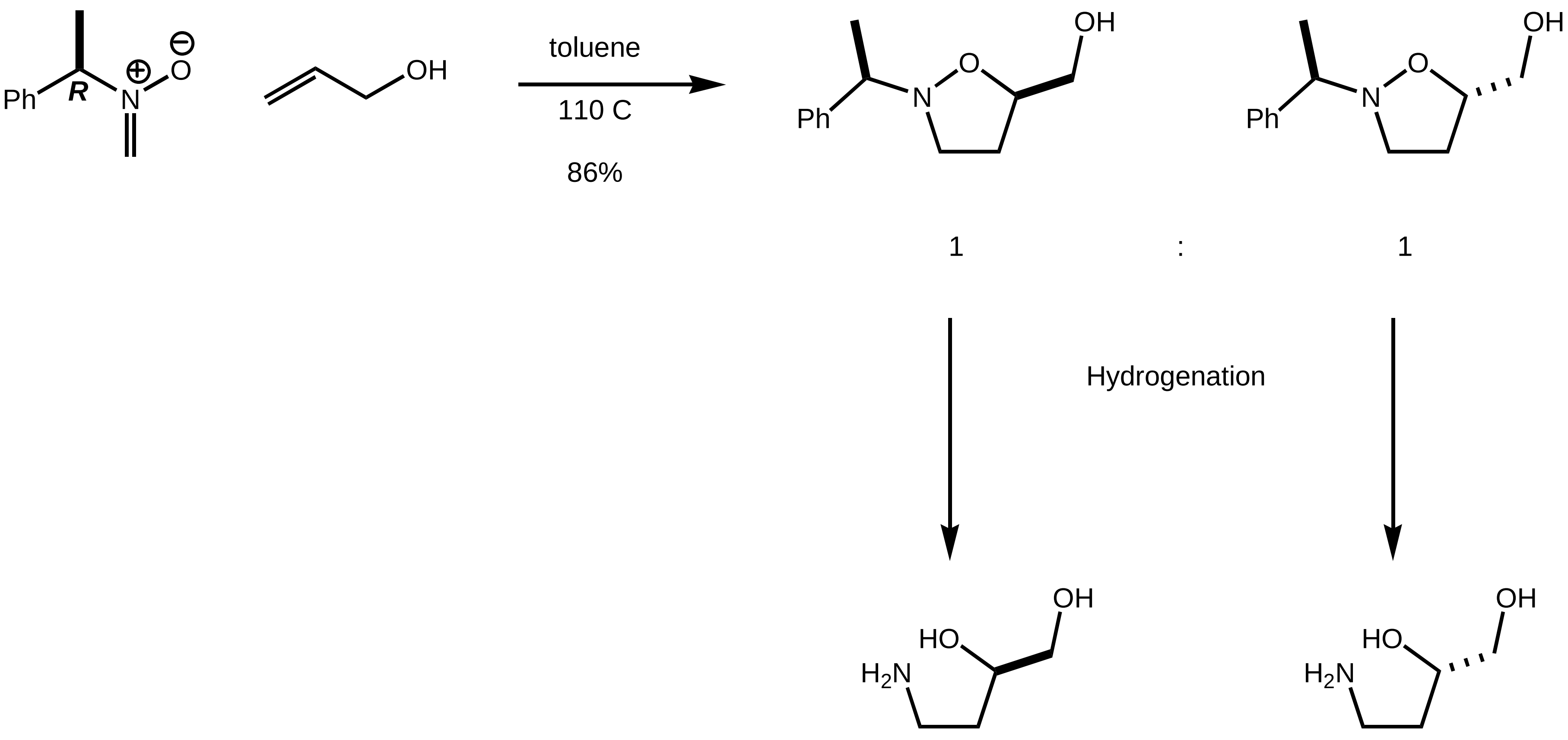
Bicyclic Chirality



Single Diastereomer

Blake, A. J.; Cook, T. A.; Forsyth, A. C.; Gould, R. O.; Paton, R. M. *Tetrahedron* **1992**, *48*, 8053.

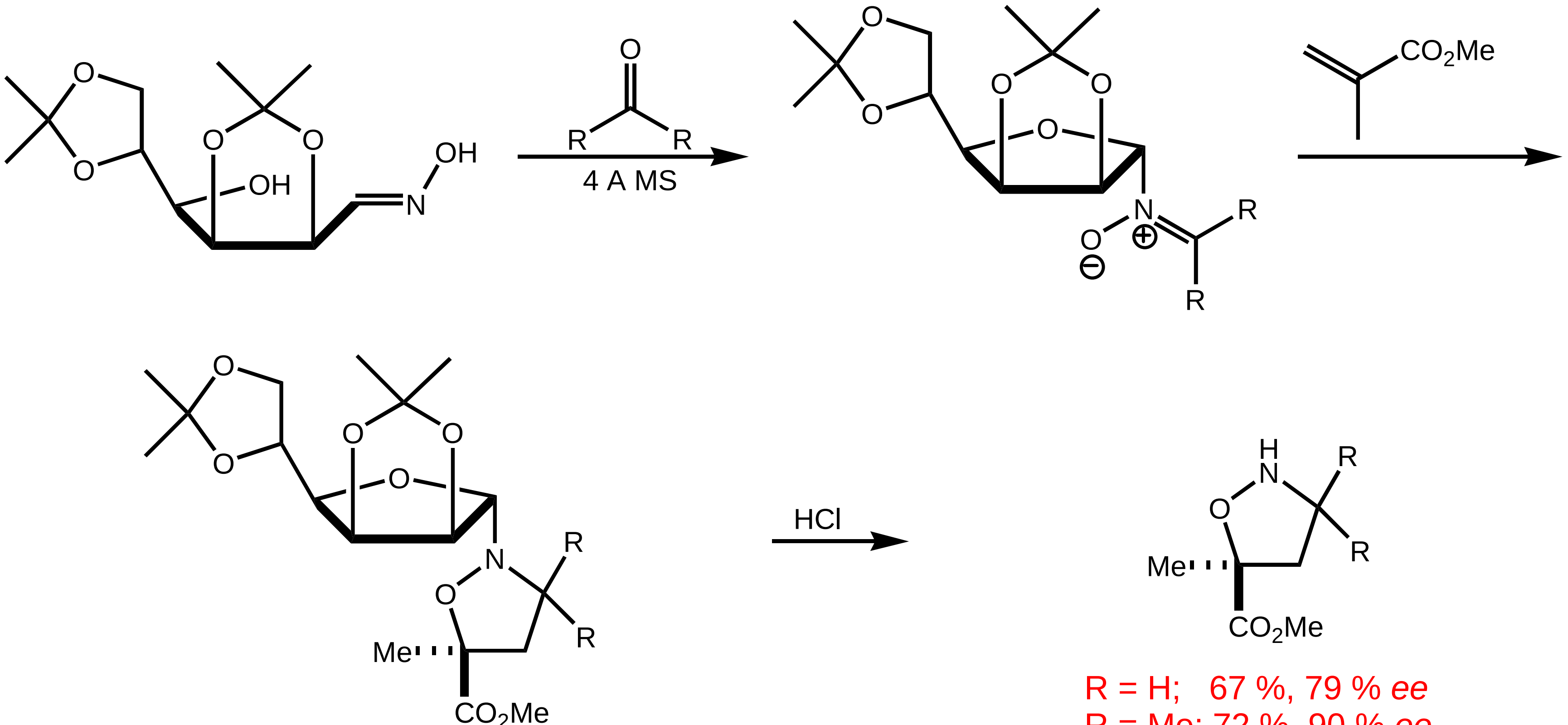
Chirality On Dipole



Enantiomerically Pure Products

Tice, C. M.; Ganem, D. *J. Org.Chem.* **1983**, *48*, 5048.

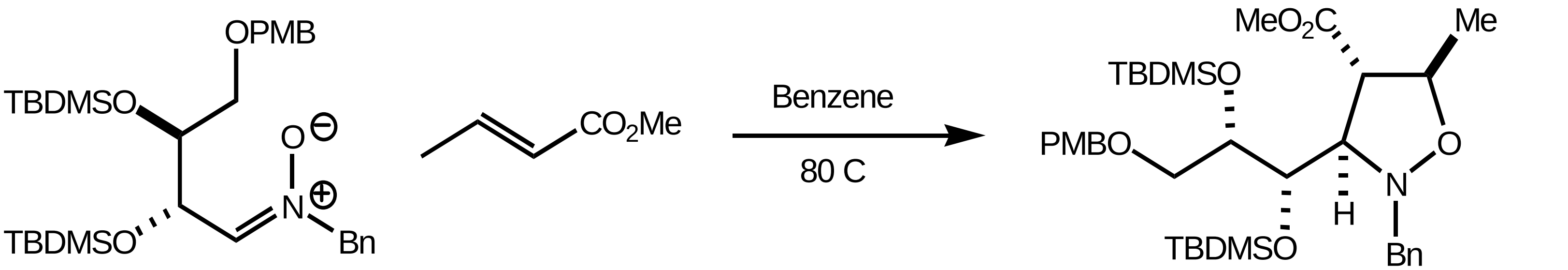
Sugar Based Chirality



R = H;   67 %, 79 % *ee*
R = Me; 72 %, 90 % *ee*

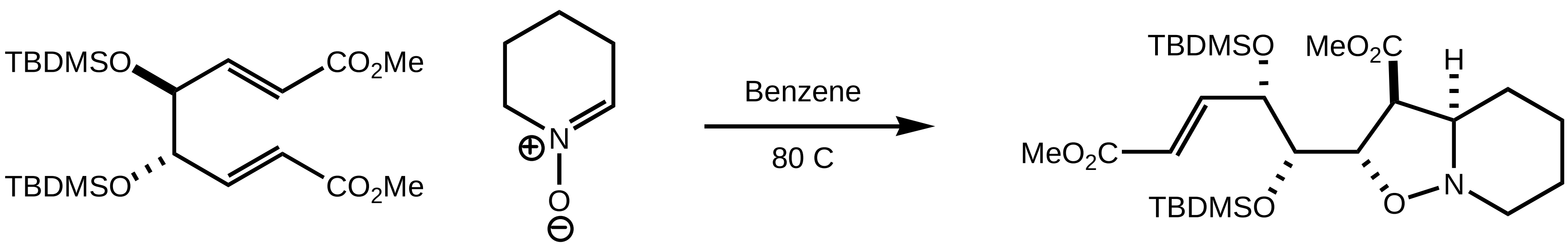
Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33.

Tartaric Acid Derived Chirality



***endo* : *exo* = 91 : 9**

***de*$_{endo}$ = >95 %**

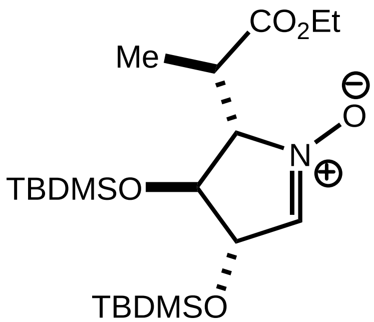


***endo* : *exo* = 94 : 6**

***de*$_{endo}$ = >98 %**

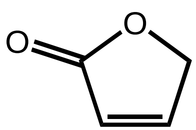
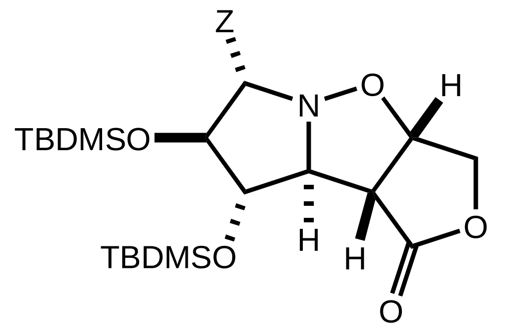
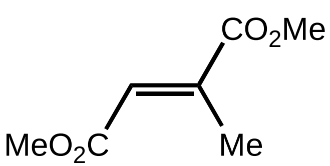
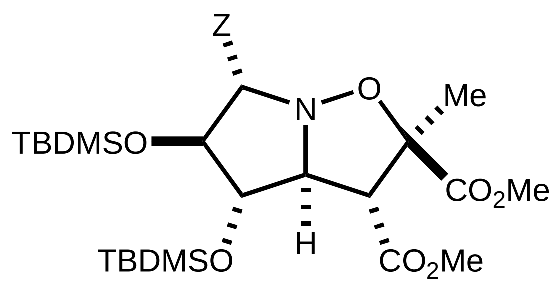
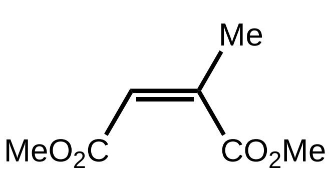
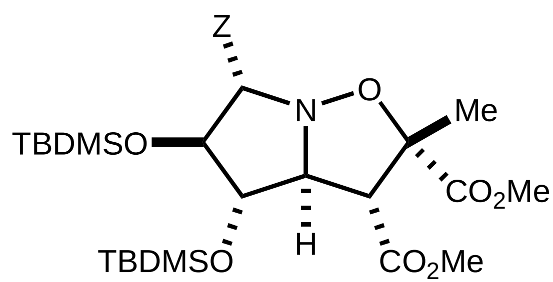
Saito, S.; Ishikawa, T.; Kishimoto, N.; Kohara, T.; Moriwake, T. *Synlett* **1994**, 282.

Chiral Cyclic Nitrone



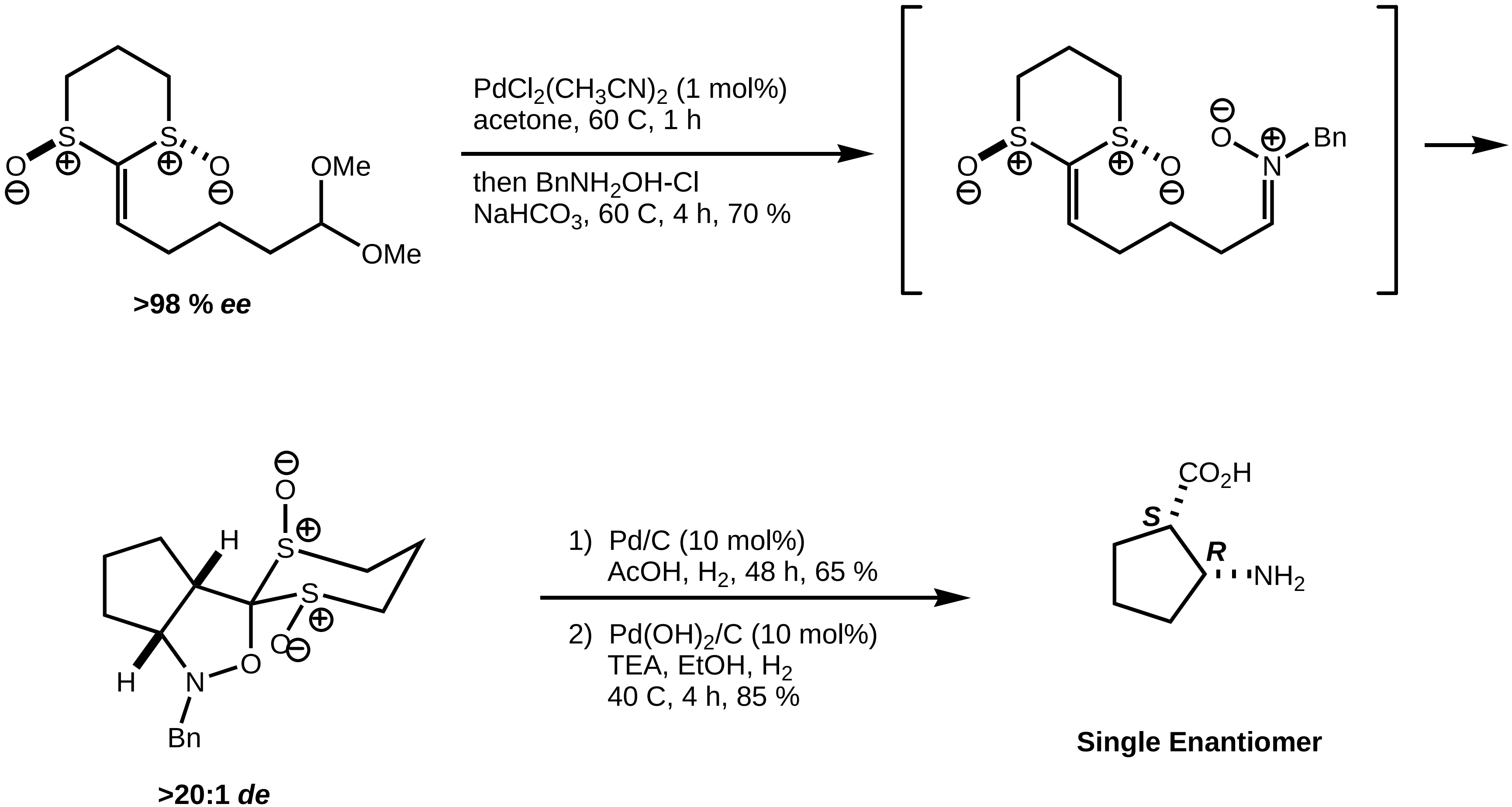
\+ **Dipolarophile** —(Benzene, 70 C)→ **Cycloaddition Product**

Exo Only

Dipolarophile	Cycloaddition Product	Yield (%)
		84
		62
		60

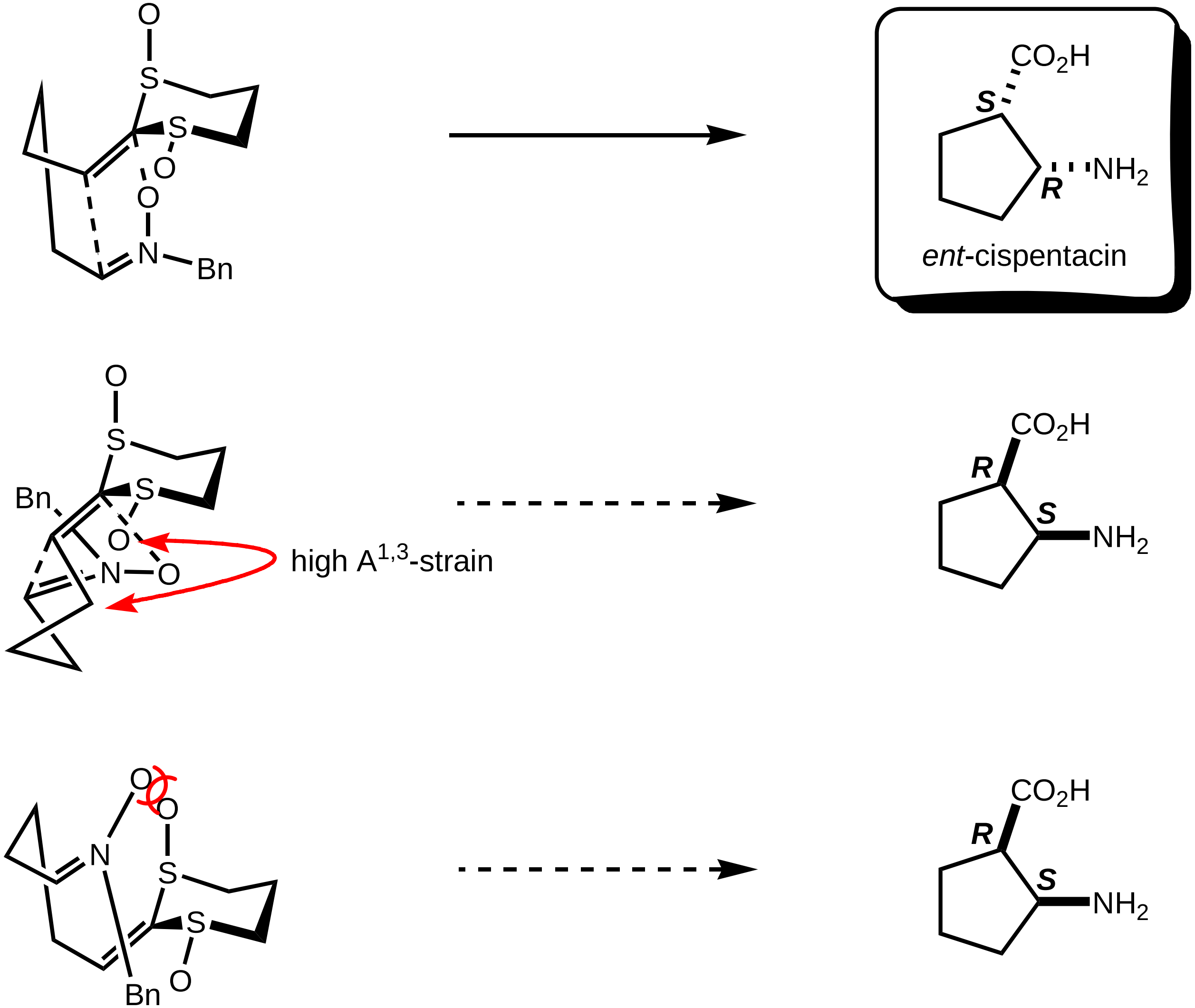
Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem. Int. Ed.* **1996**, *35*, 1863.

Chiral Ketene Equivalents



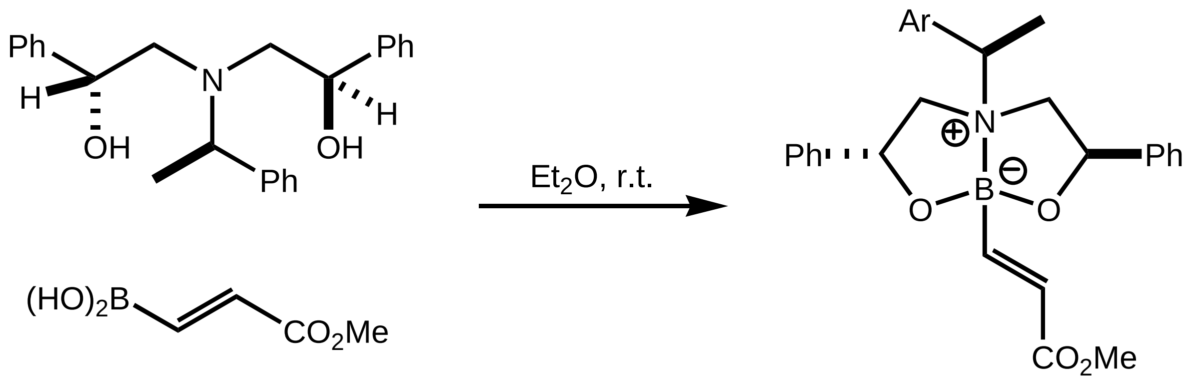
Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227.

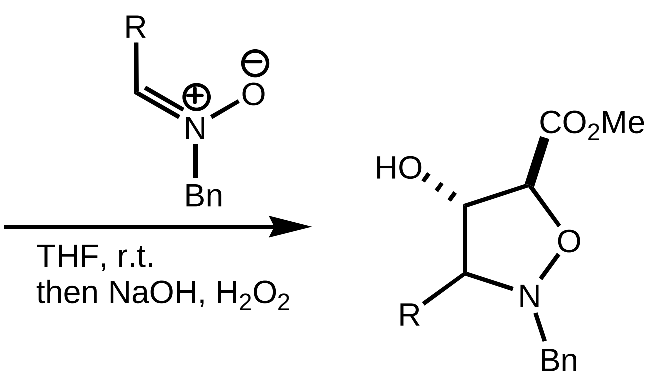
Competing Transition States



Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227.

Asymmetric Induction



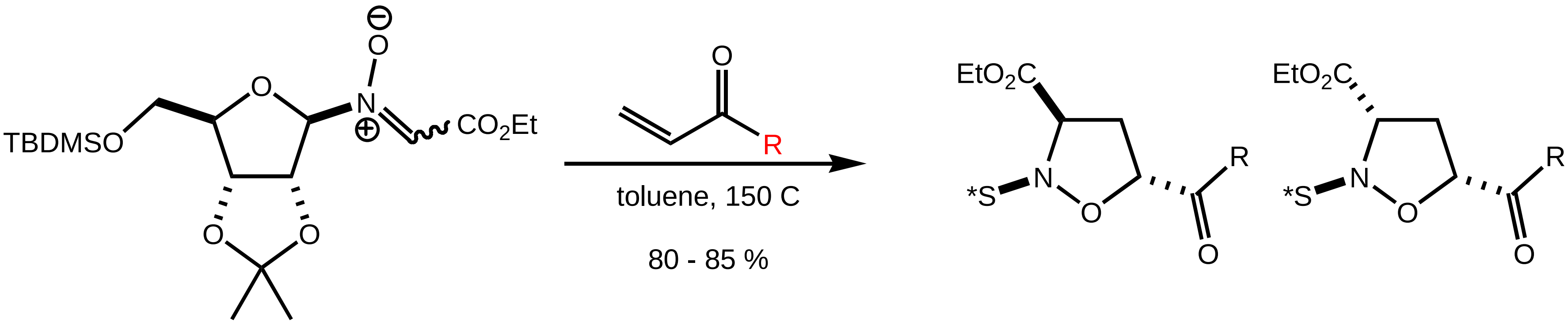


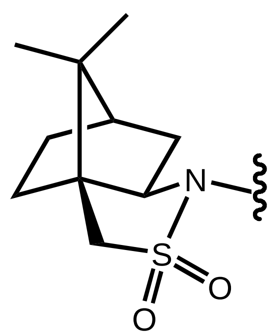
R	Yield (%)	*ee* (%)
H	42	65
CO_2Et	20	74

Exo Only

Davies, C. D.; Marsden, S. P.; Stokes, E. S. E. *Tetrahedron Lett.* **2000**, *41*, 4229.

Dueling Chirality

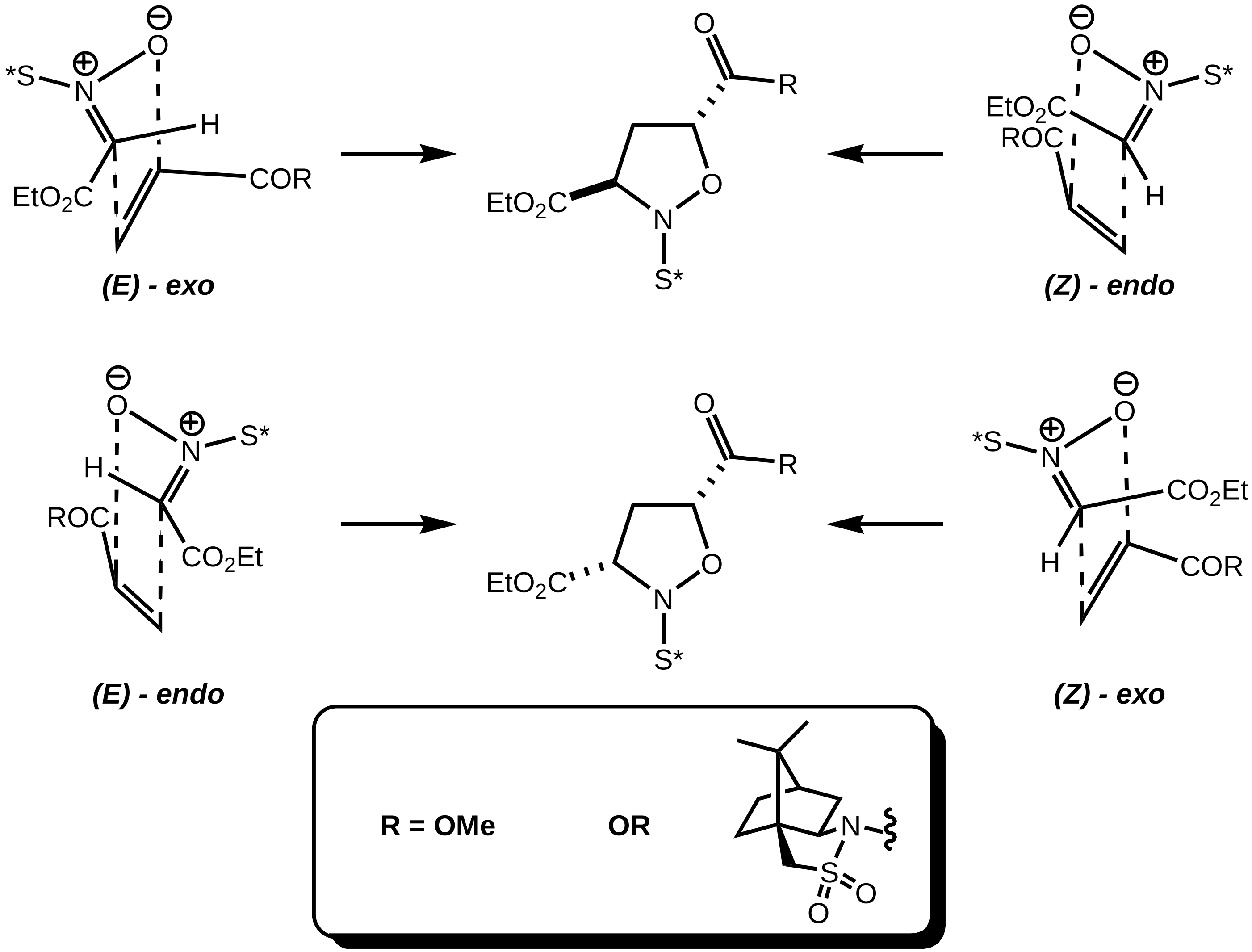


R		
OMe	**2**	**1**
	**20**	**1**

Endo T. S.

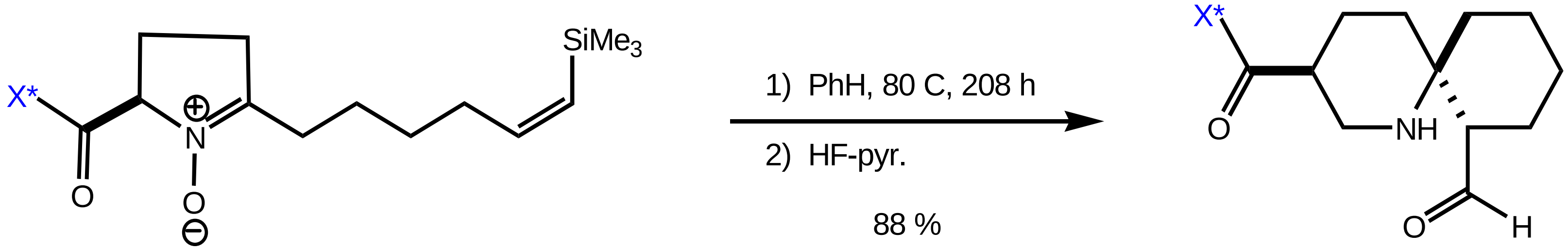
Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymm.* **2002**, *13*, 167.

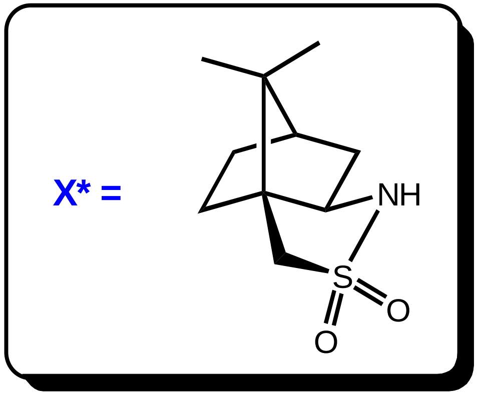
Possible TSs



Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymm.* **2002**, *13*, 167.

Spirocyclic Cores



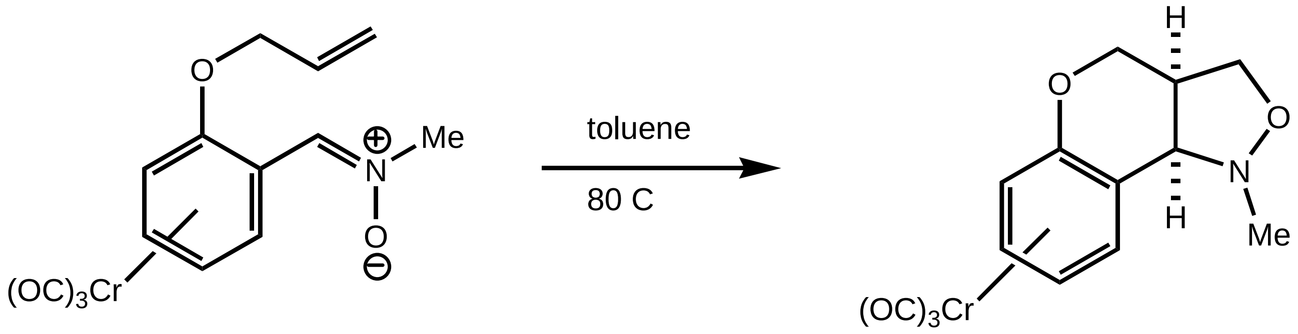


Single Diastereomer

Exo T.S.

Oppolzer, W.; Bochet, C. G. *Tetrahedron: Asymm.* **2000**, *11*, 4761.

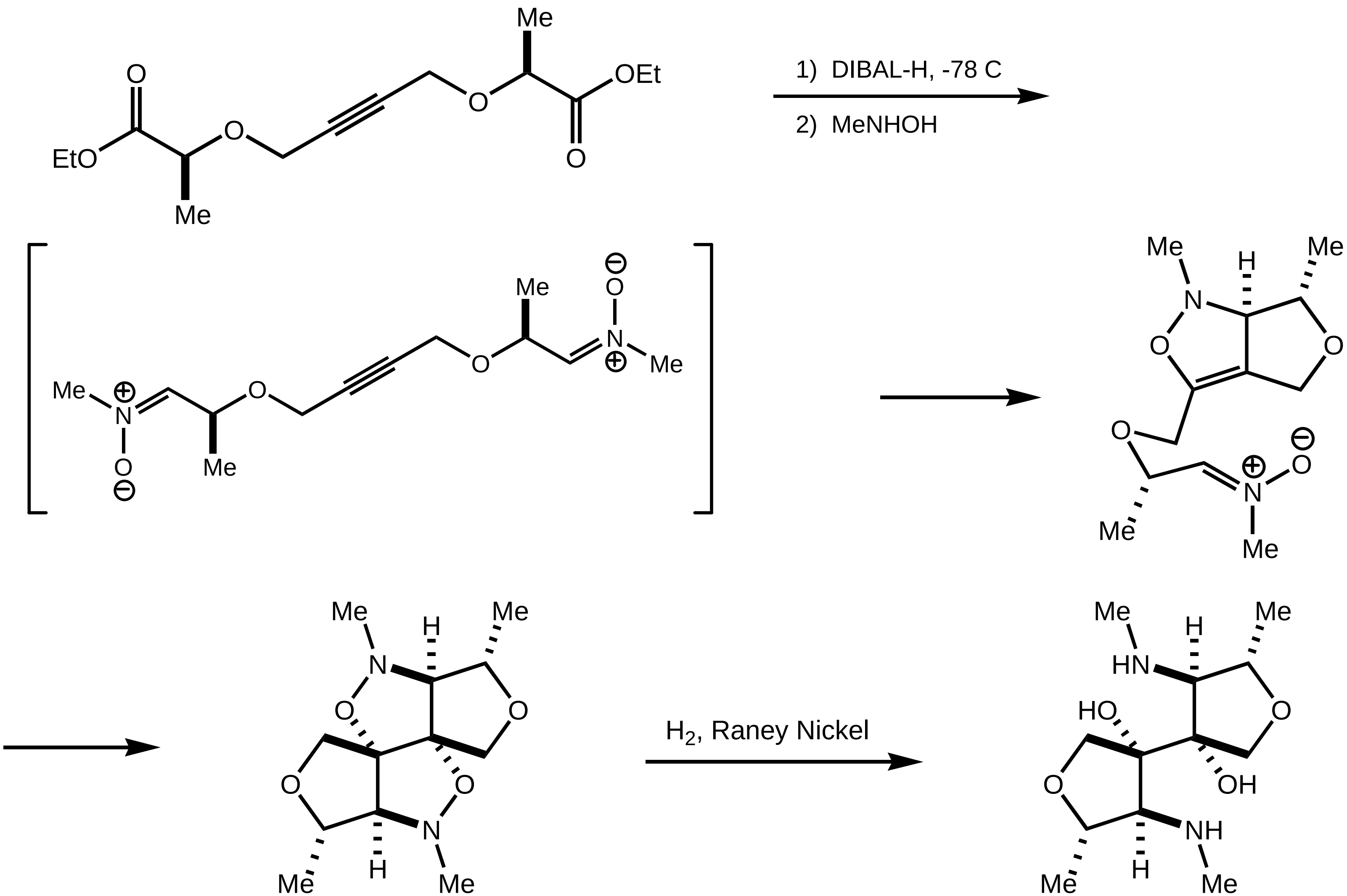
Arene-Complexed Chirality



Single Isomer

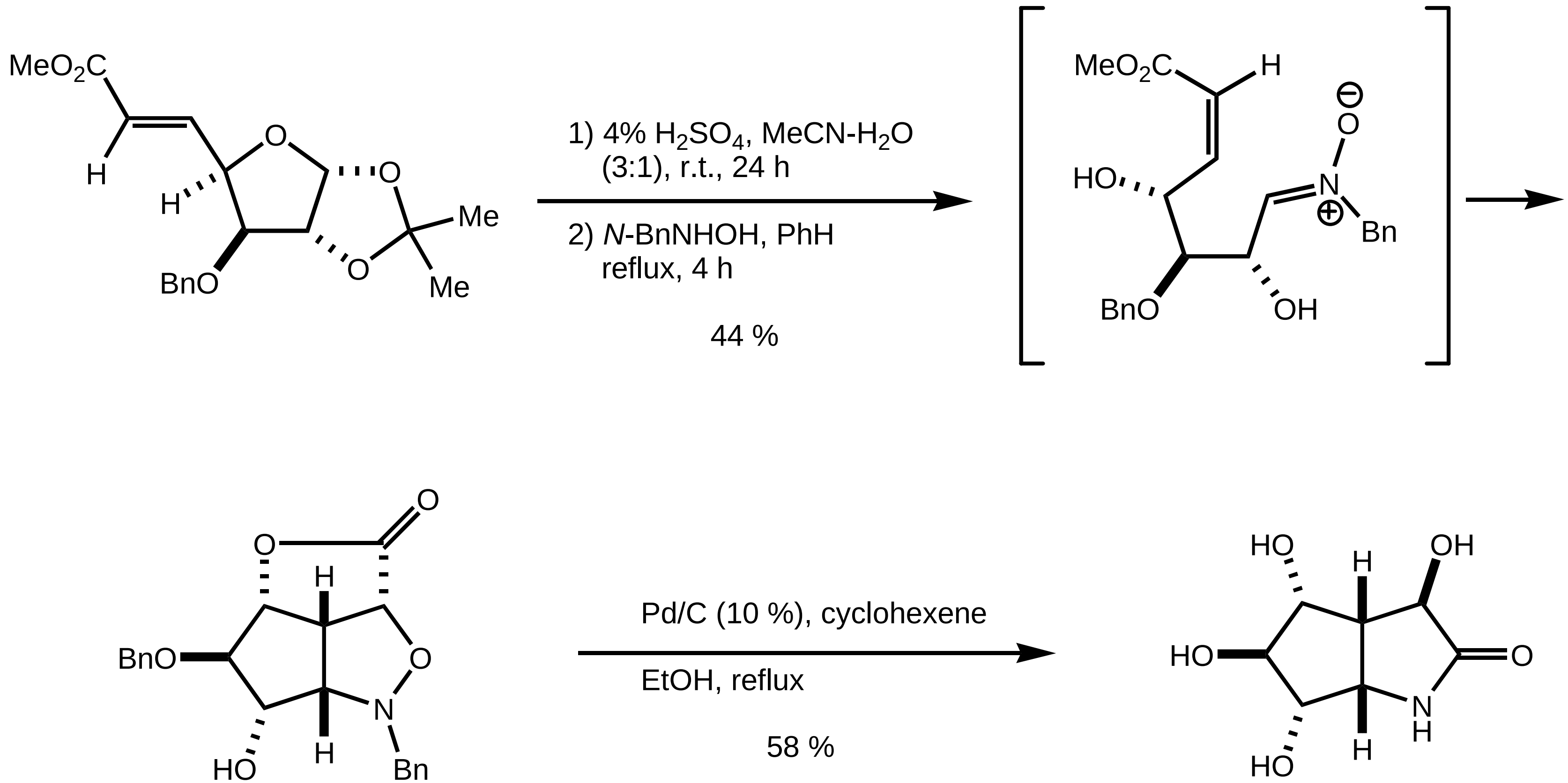
Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *Tetrahedron: Asymm.* **1995**, *6*, 1711.

Two Successive 1,3-DCs



Aurich, H. G.; Biesemeier, F.; Harms, K. *Lieb. Ann.* **1997**, 469.

Fused Bicycles



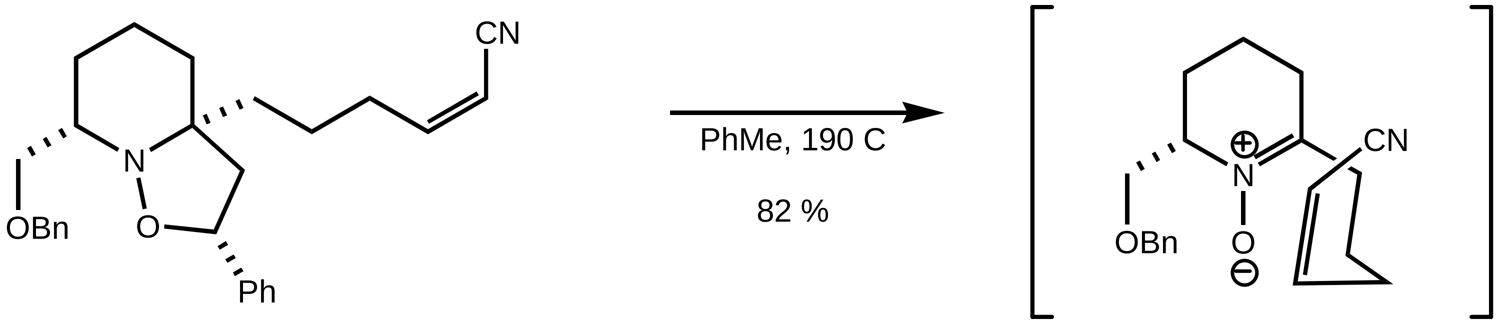
Single Diastereomer

Exo T.S.

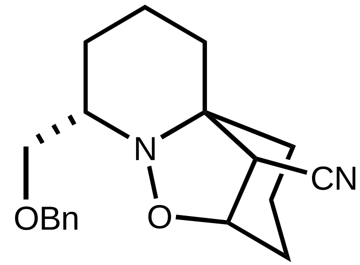
Roy, A.; Roy, B. G.; Achari, B.; Mandal, S. B. *Tetrahedron Lett.* **2004**, *45*, 5811.

Swap Meet

- Cycloreversion-cycloaddition reaction



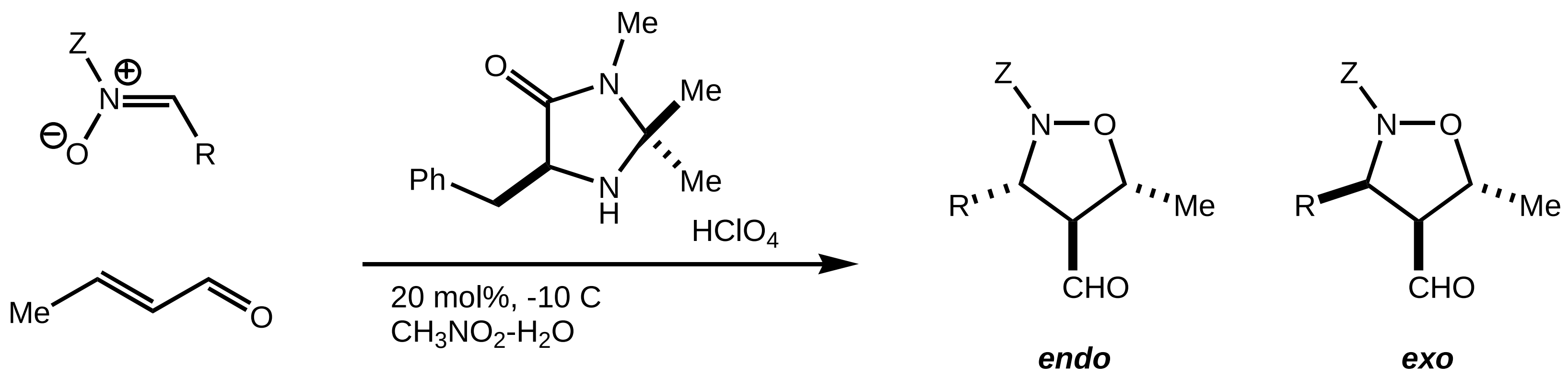
Exo T.S.

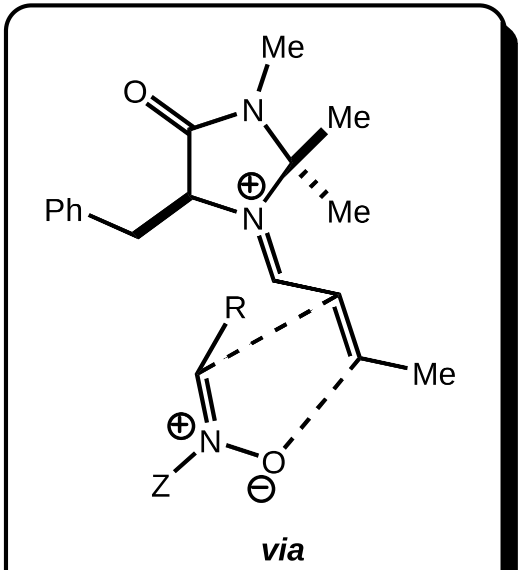


Sole Isomer

Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. M.; Davies, J. E.; Raithby, P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *J. Chem. Soc., Perkin Trans. I* **2002**, 1494.

First Organocatalytic 1,3-DC

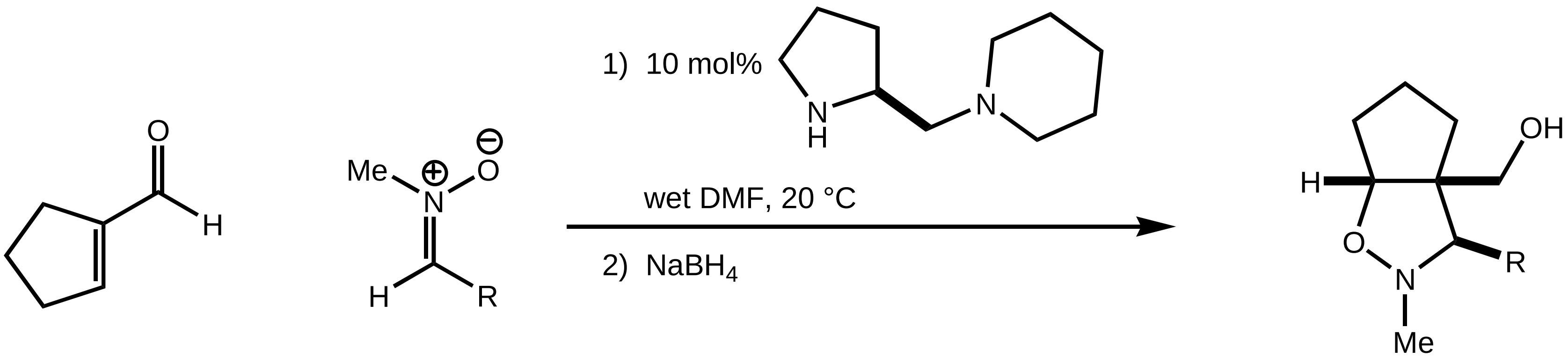


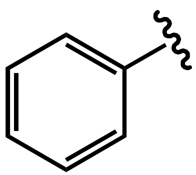
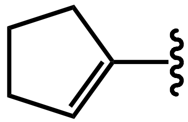
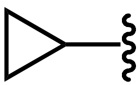
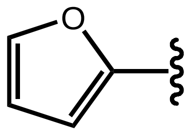


Z	R	*endo:exo*	Yield(%)	*ee* (%)
allyl	Ph	93:7	73	98
Me	Ph	95:5	66	99
Me	C_6H_4Me-4	93:7	82	97
Bn	*c*-hex	99:1	70	99

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

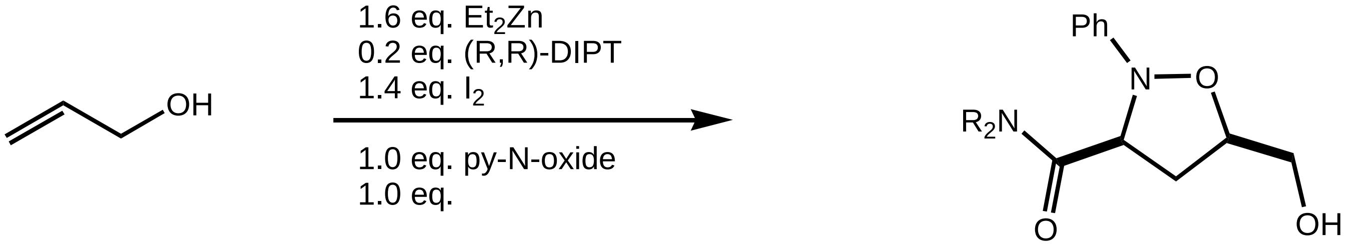
^{M}-Or^{e}ganocatalysis

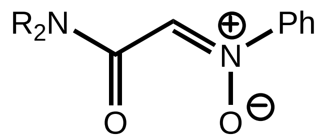


R	Time (h)	Yield (%)	*dr (exo:endo)*	*ee (exo)*
	72	49	97:3	92
	120	68	99:1	>99
	24	58	>99:1	41
	144	51	98:2	53

Karlsson, S.; Hogberg, H-E. *Eur. J. Org. Chem.* **2003**, 2782.

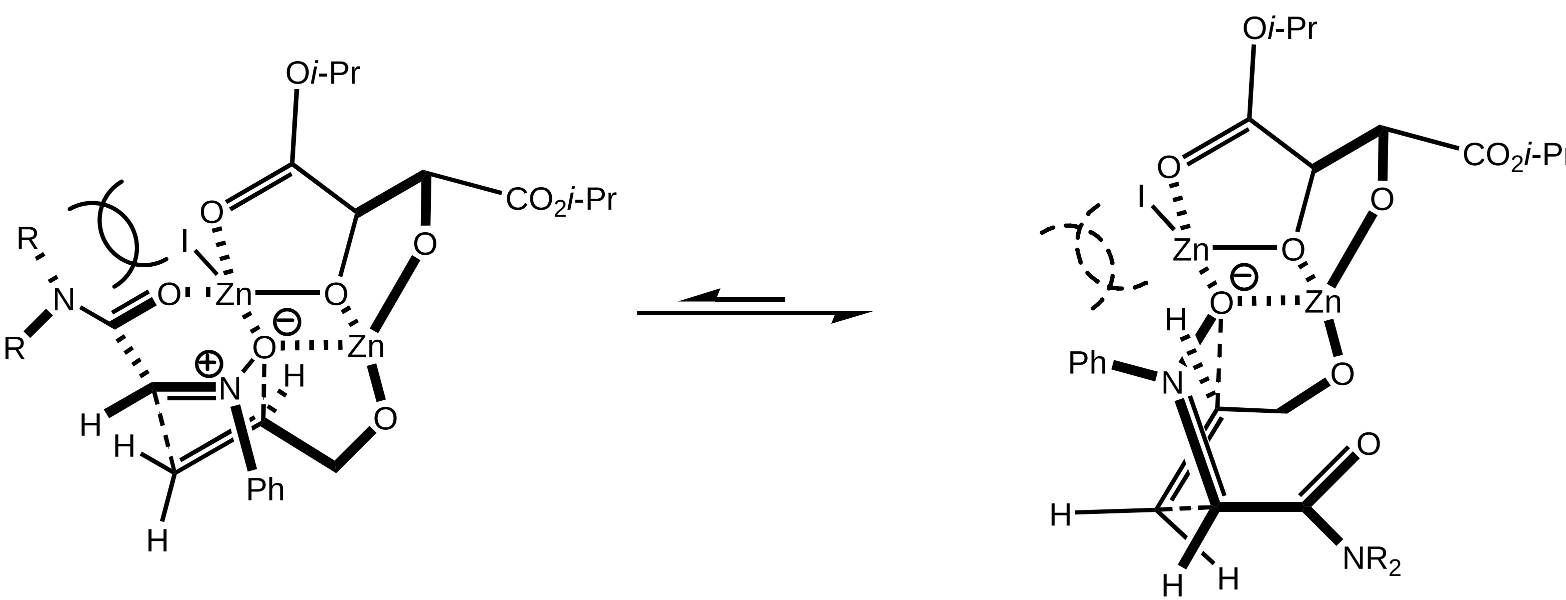
Zinc Catalyzed





0 C, 24 h, $CHCl_3$

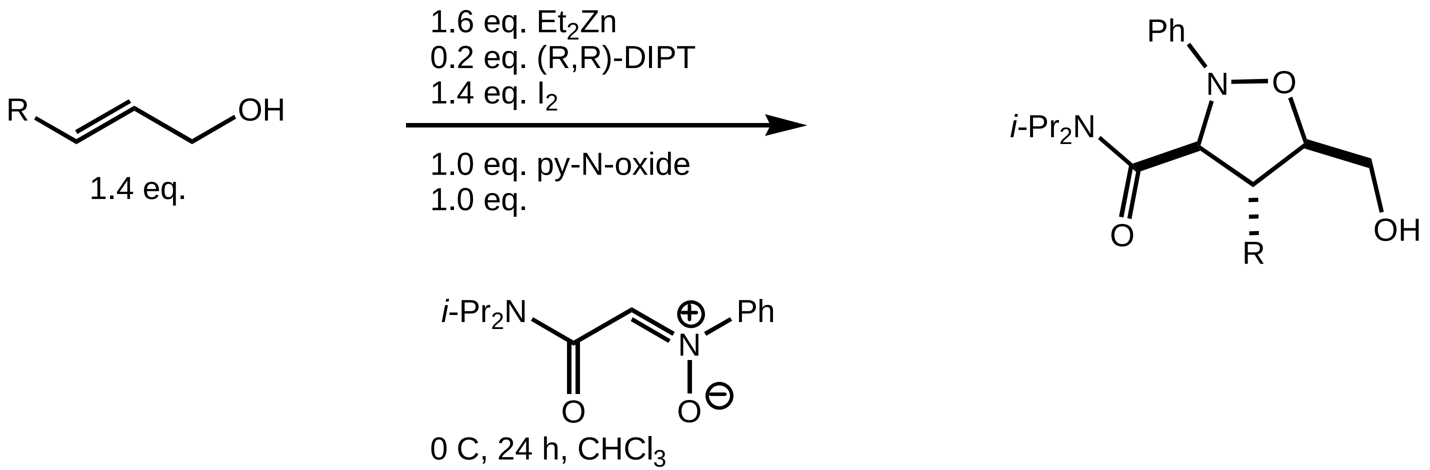
R	Yield (%)	ee (%)
Bn	70	64
Et_2CH	41	93
i-Pr	69	98



endo ***exo***

Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2001**, 468.

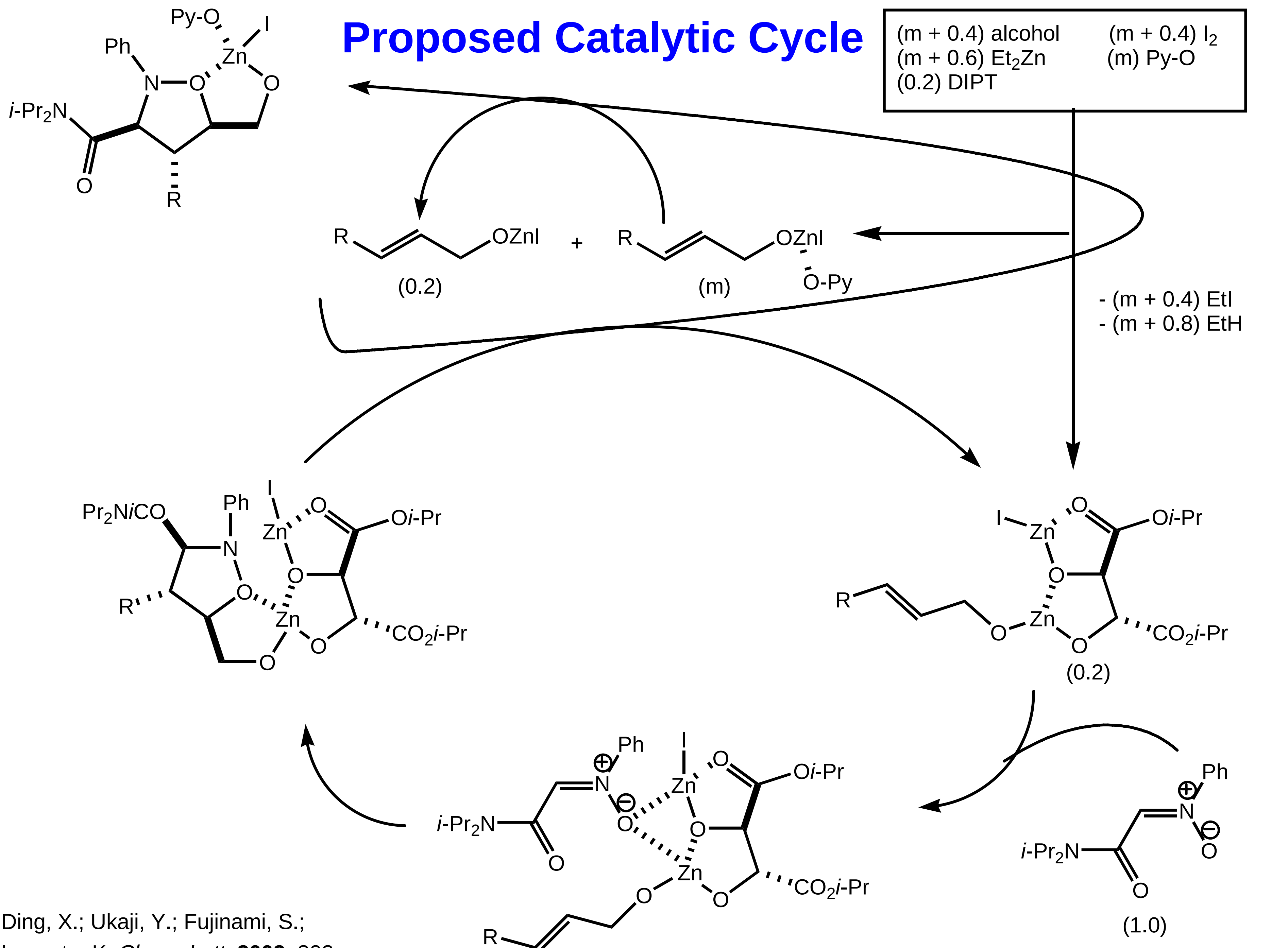
More Zinc Results



R	Yield (%)	*ee* (%)
Me	64	>99
Pr	48	>99
CO_2Me	53	95
CO_2Et	61	92

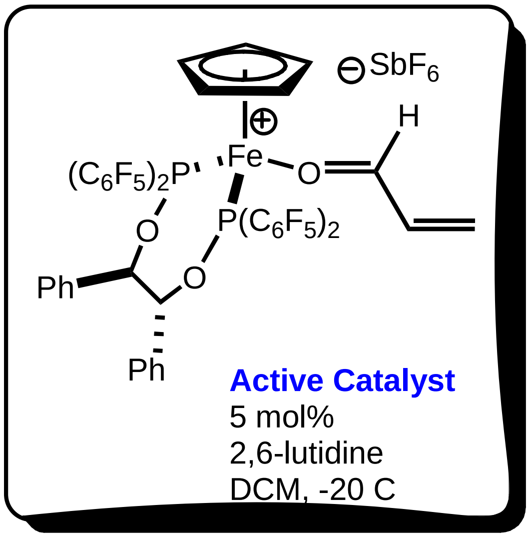
Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett*. **2002**, 302.

Proposed Catalytic Cycle

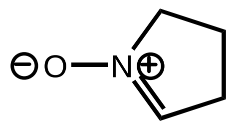
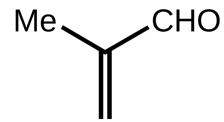
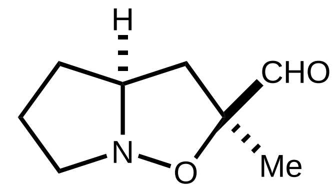
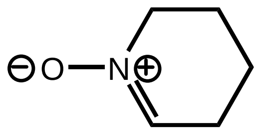
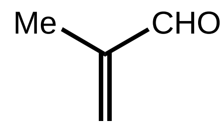
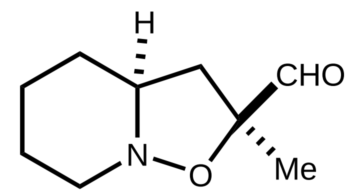
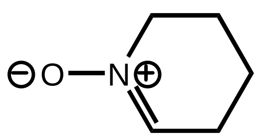
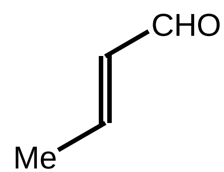
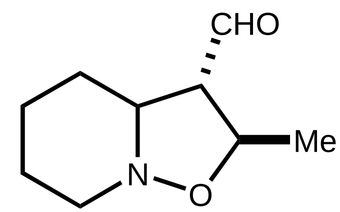
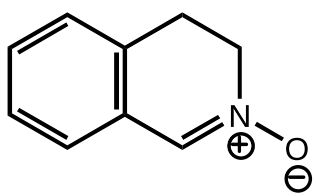
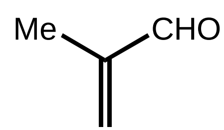
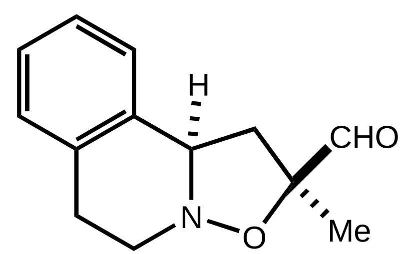


Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett*. **2002**, 302.

Iron Catalyzed

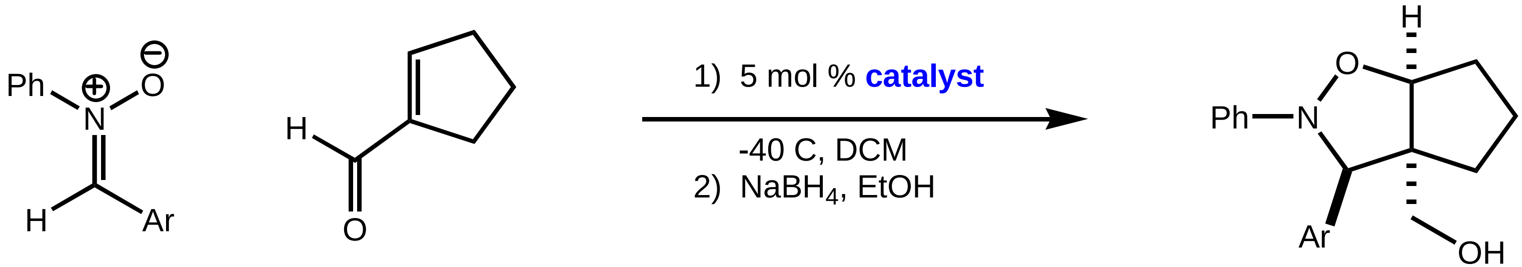


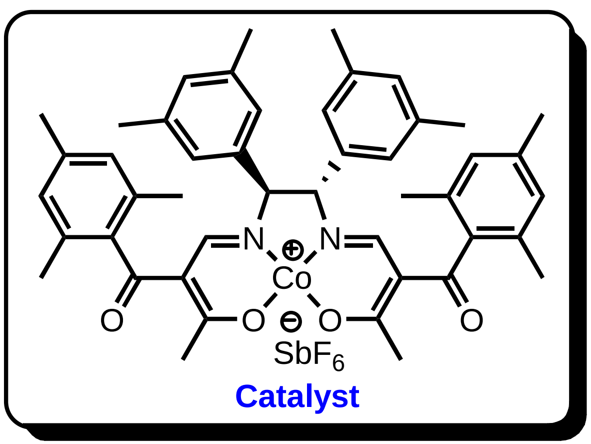
Invokes Endo T.S.

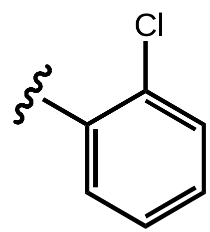
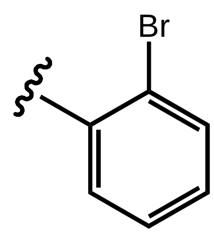
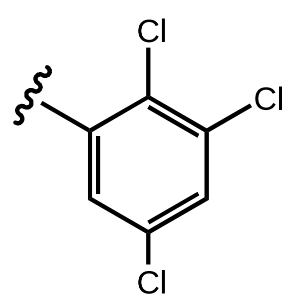
Nitrone	**Enal**	**Yield (%)**	**Product**	***ee* (%)**
		92		96
		71		>96
		75		75
		71		94

Viton, F.; Bernardinelli, G.; Kundig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968.

Colbalt Catalyzed



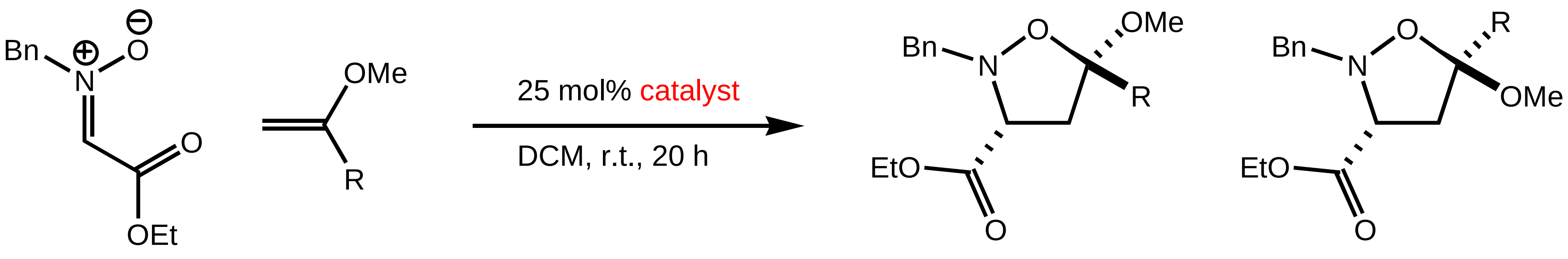


Ar	time (h)	yield (%)	*endo / exo*	*ee (endo)*
	96	96	99 / 1	80
	96	85	99 / 1	85
	83	93	>99 / 1	85

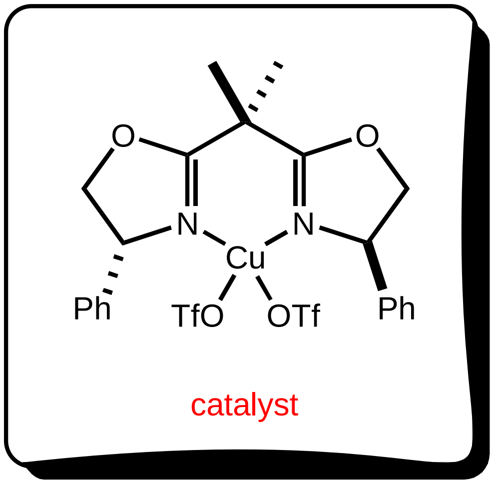
Invokes Endo T.S.

Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457.

Copper Bisoxazoline Catalyzed



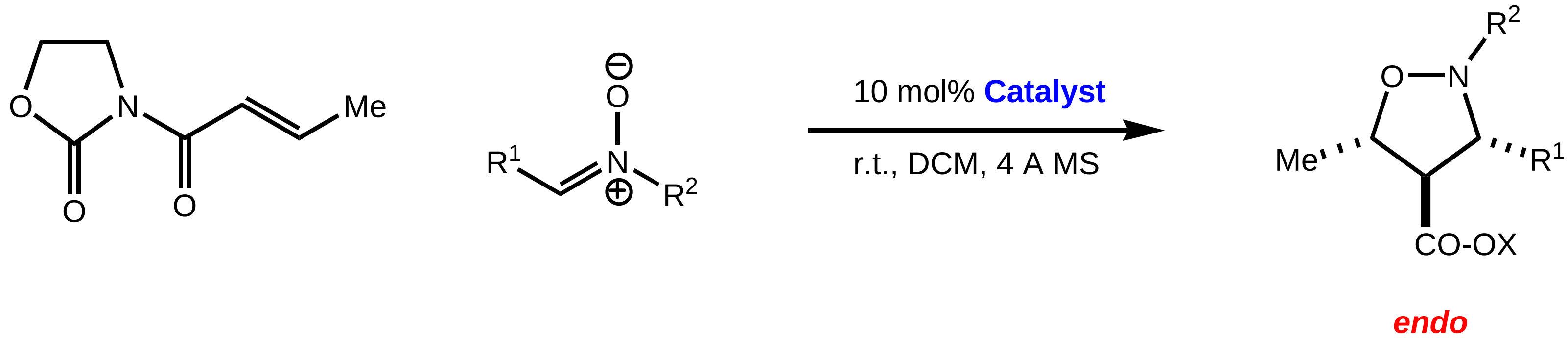
exo *endo*

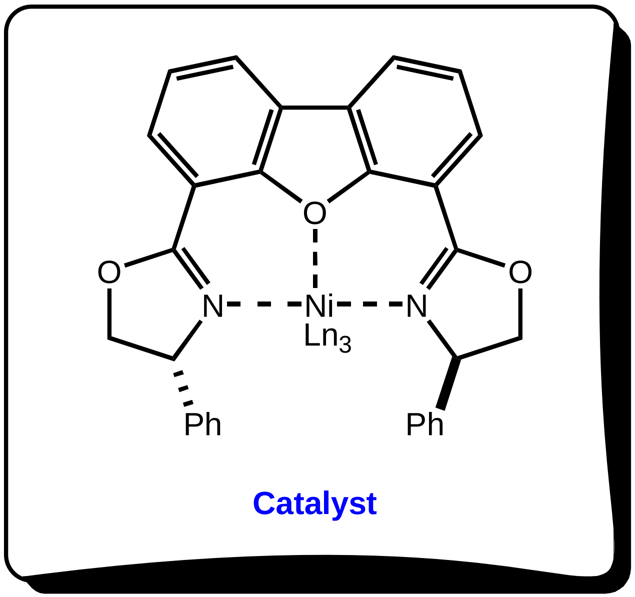


R	Yield (%)	*exo : endo*	*ee* (*exo : endo*) %
H	83	77 : 23	89 / 16
Me	83	31 : 69	90 / 94

Jensen, K. B.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353.

Nickel Catalyzed

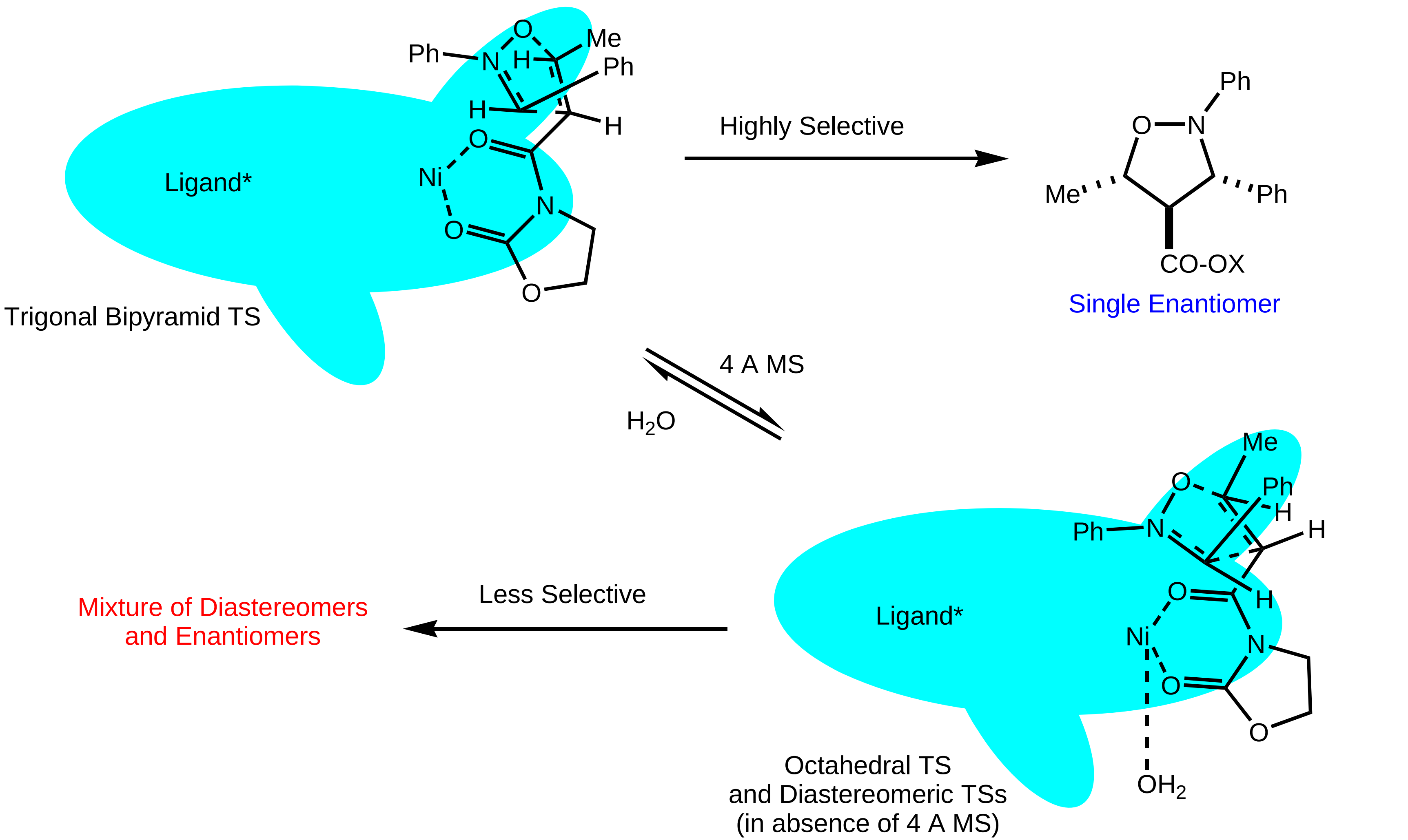




R^1	R^2	Time (h)	Yield (%)	*ds* (*endo*:*exo*)	*ee* (%)
Ph	Me	72	63	99:1	>99
p-MeC_6H_4	Ph	36	100	99:1	>99
Et	Bn	48	92	94:6	97

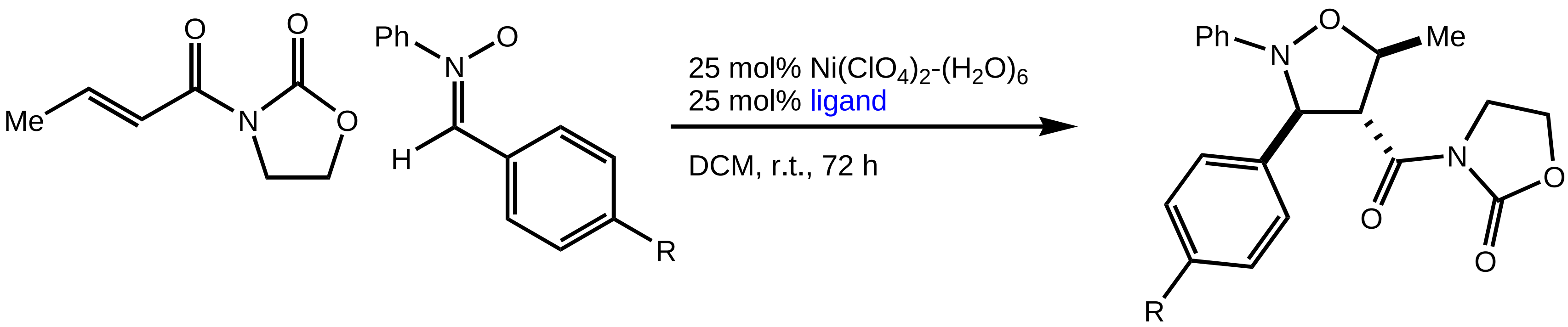
Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355.

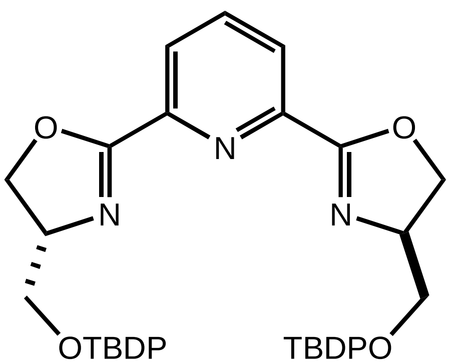
Why Do You Need Sieves?



Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355.

Nickel & Electron Rich Dipoles



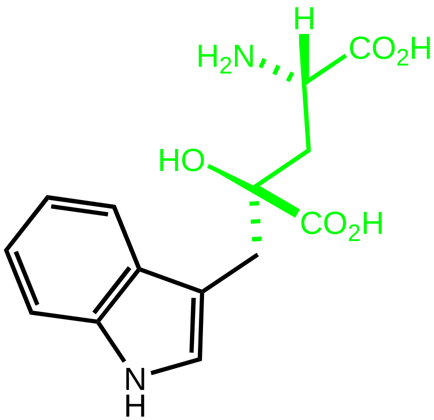


Ligand

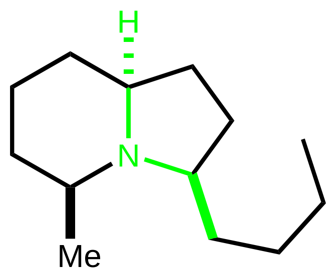
R	Yield (%)	*endo:exo*	ee of *endo* (%)
H	99	>99:1	97
Me	99	>99:1	95
OMe	99	>99:1	94

Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715.

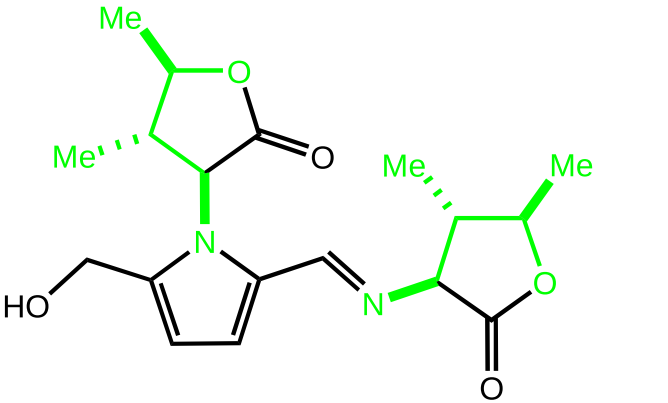
Applications in Total Synthesis



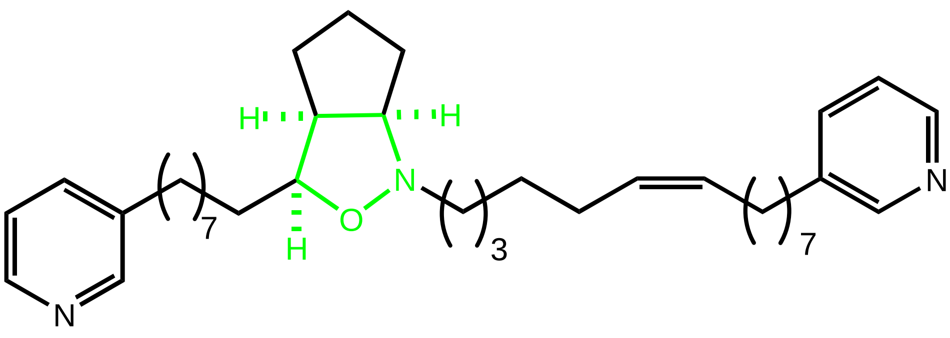
Monatin



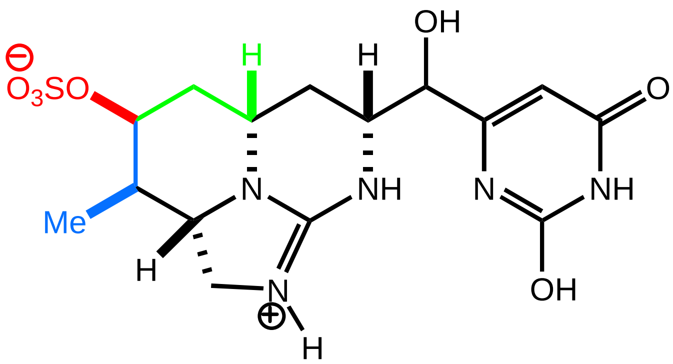
Monomorine I



Funebrine

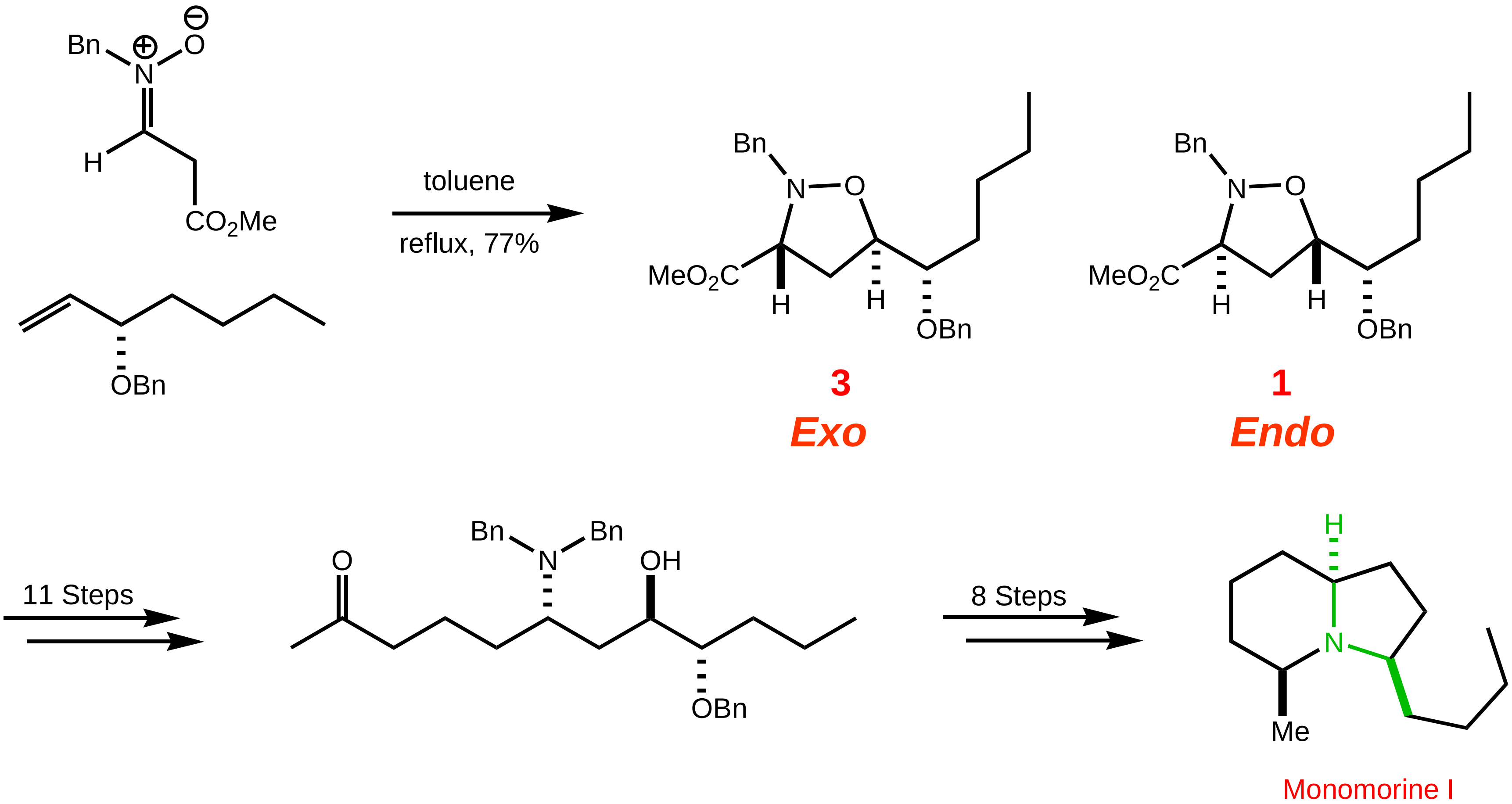


Pyrinodemin A



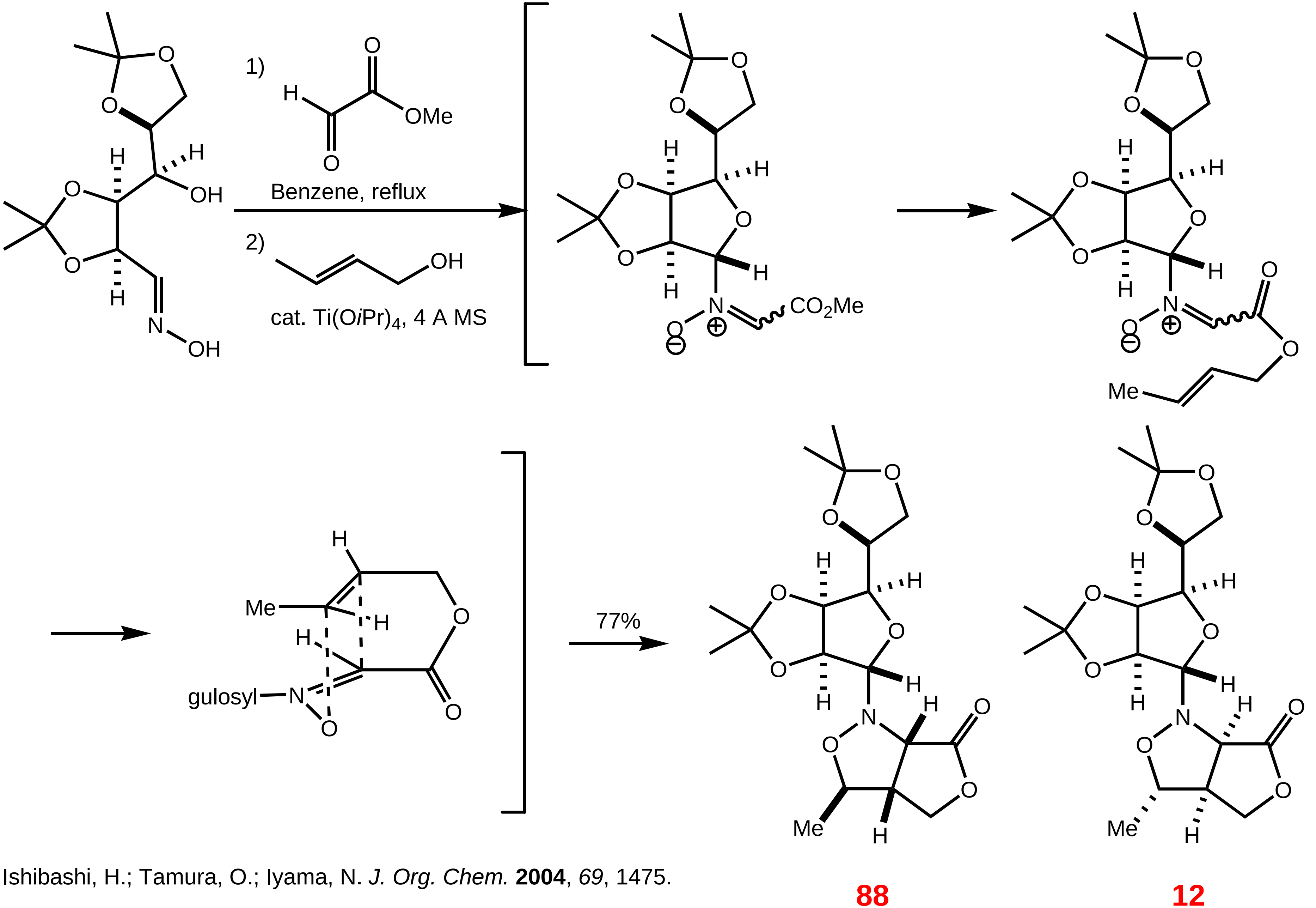
7-Epicylindrospermopsin

Monomorine I



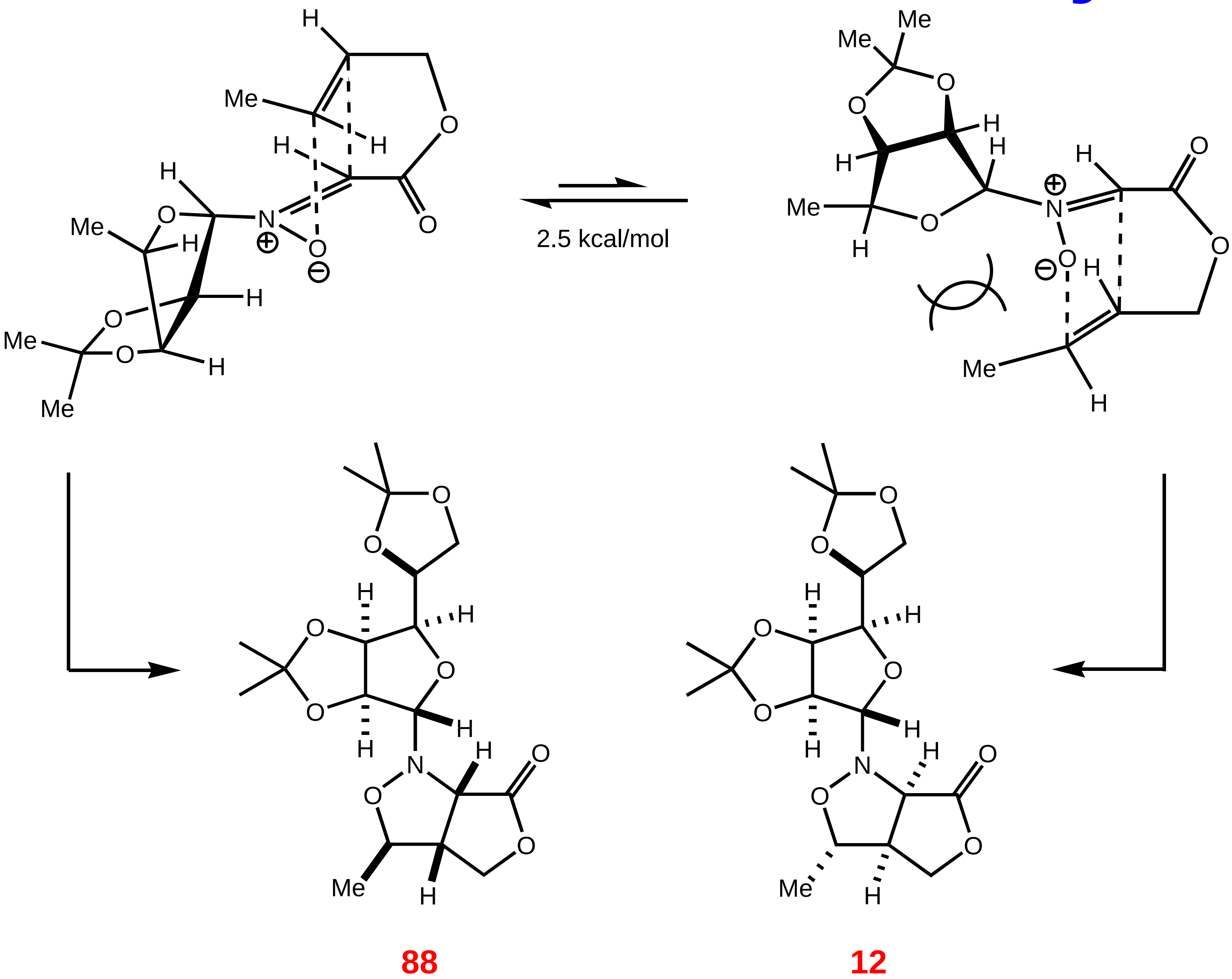
Kibayashi, C.; Ito, M. *Tetrahedron* **1991**, *47*, 9329.

Funebrine



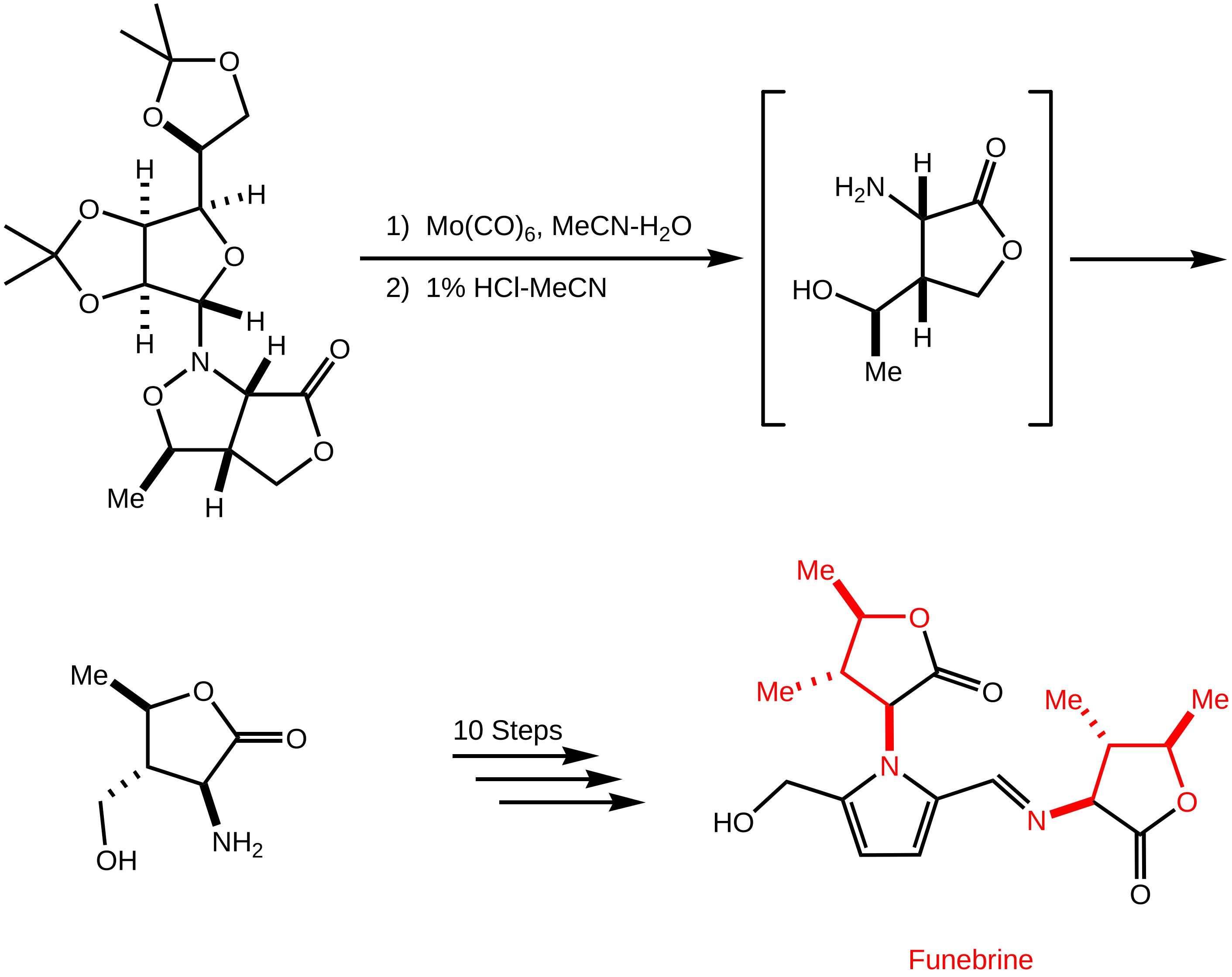
Ishibashi, H.; Tamura, O.; Iyama, N. *J. Org. Chem.* **2004**, *69*, 1475.

Reason For Selectivity



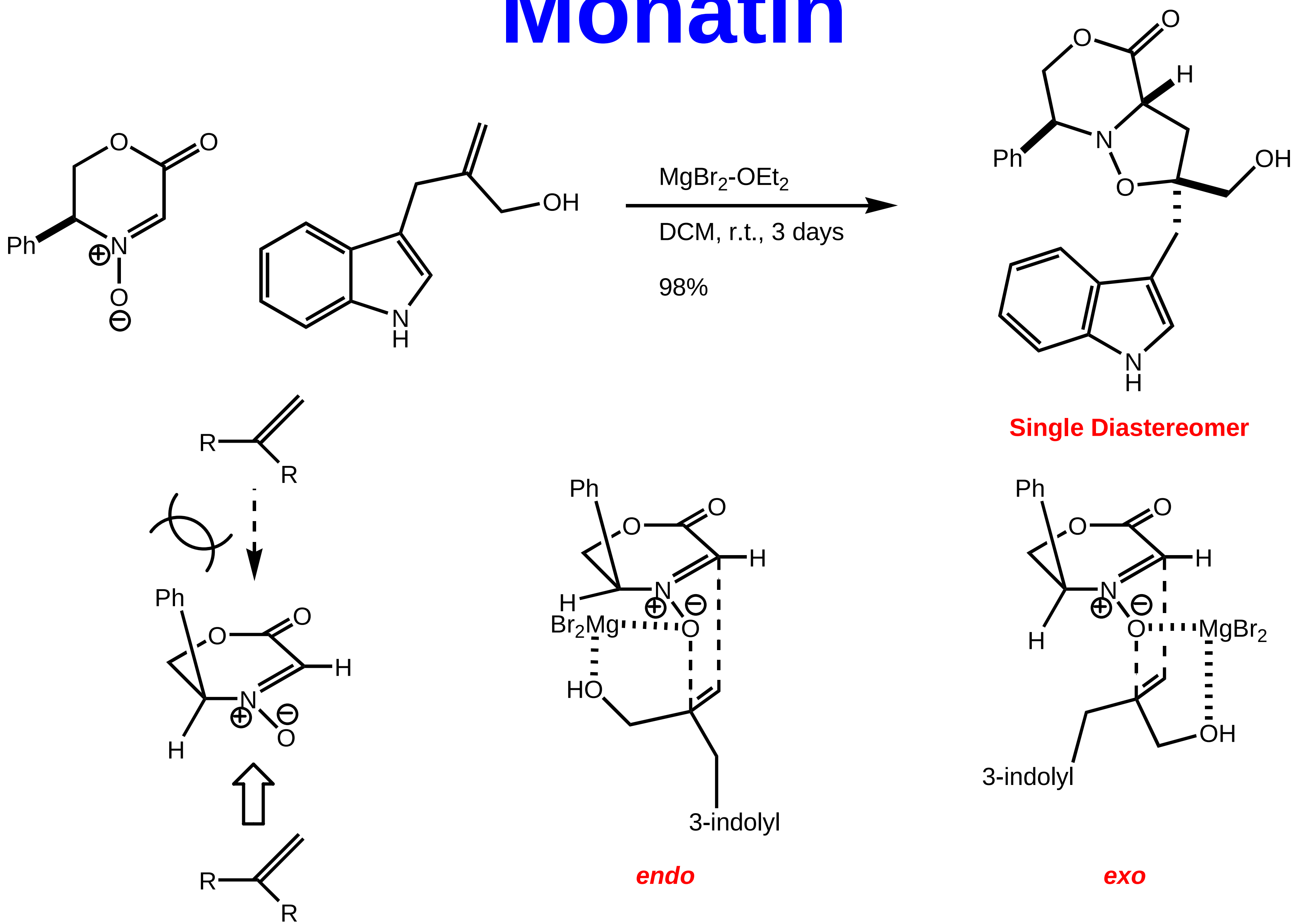
Ishibashi, H.; Tamura, O.; Iyama, N. *J. Org. Chem.* **2004**, *69*, 1475.

Finishing Funebrine



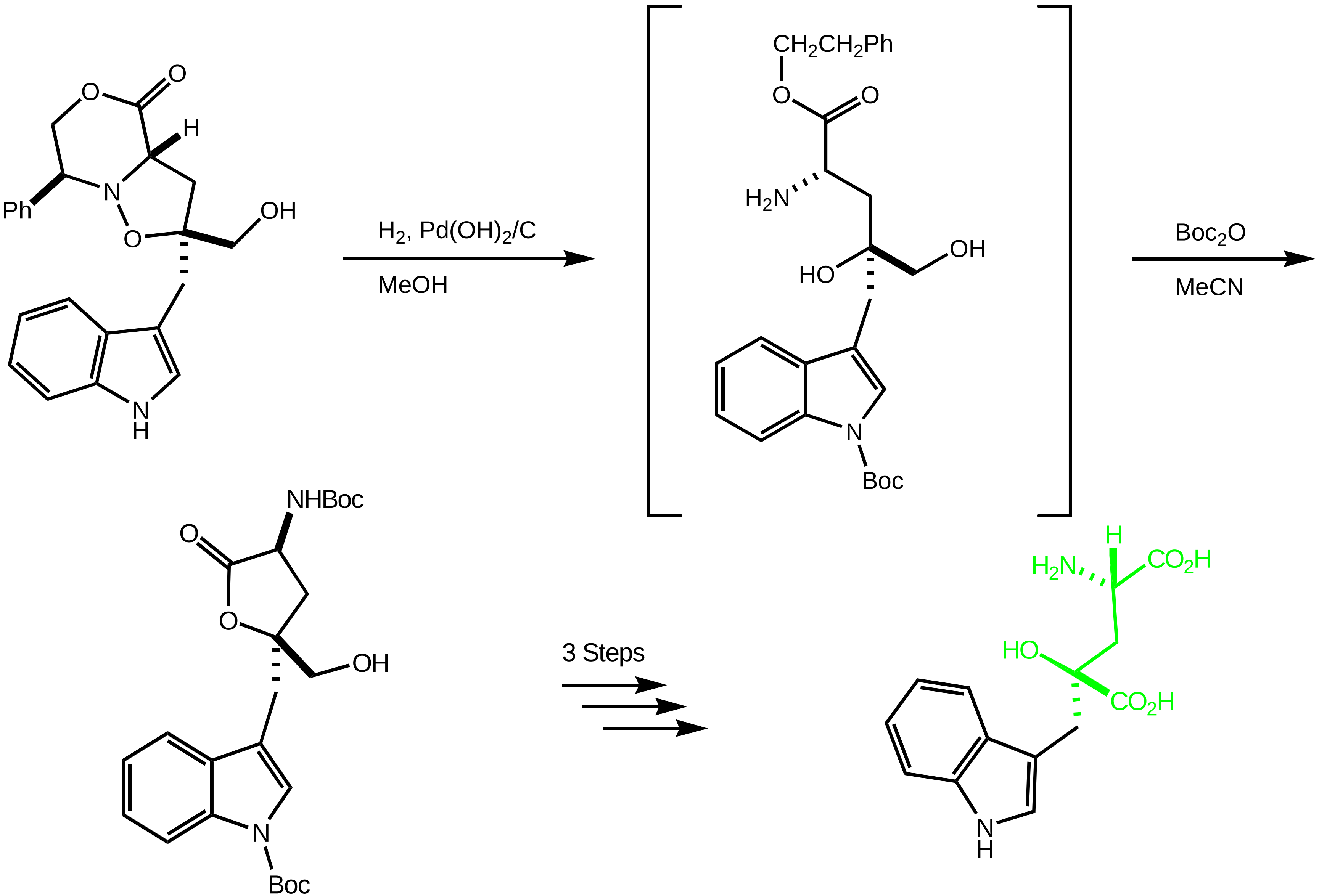
Ishibashi, H.; Tamura, O.; Iyama, N. *J. Org. Chem.* **2004**, *69*, 1475.

Monatin



Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Comm.* **2003**, 2678.

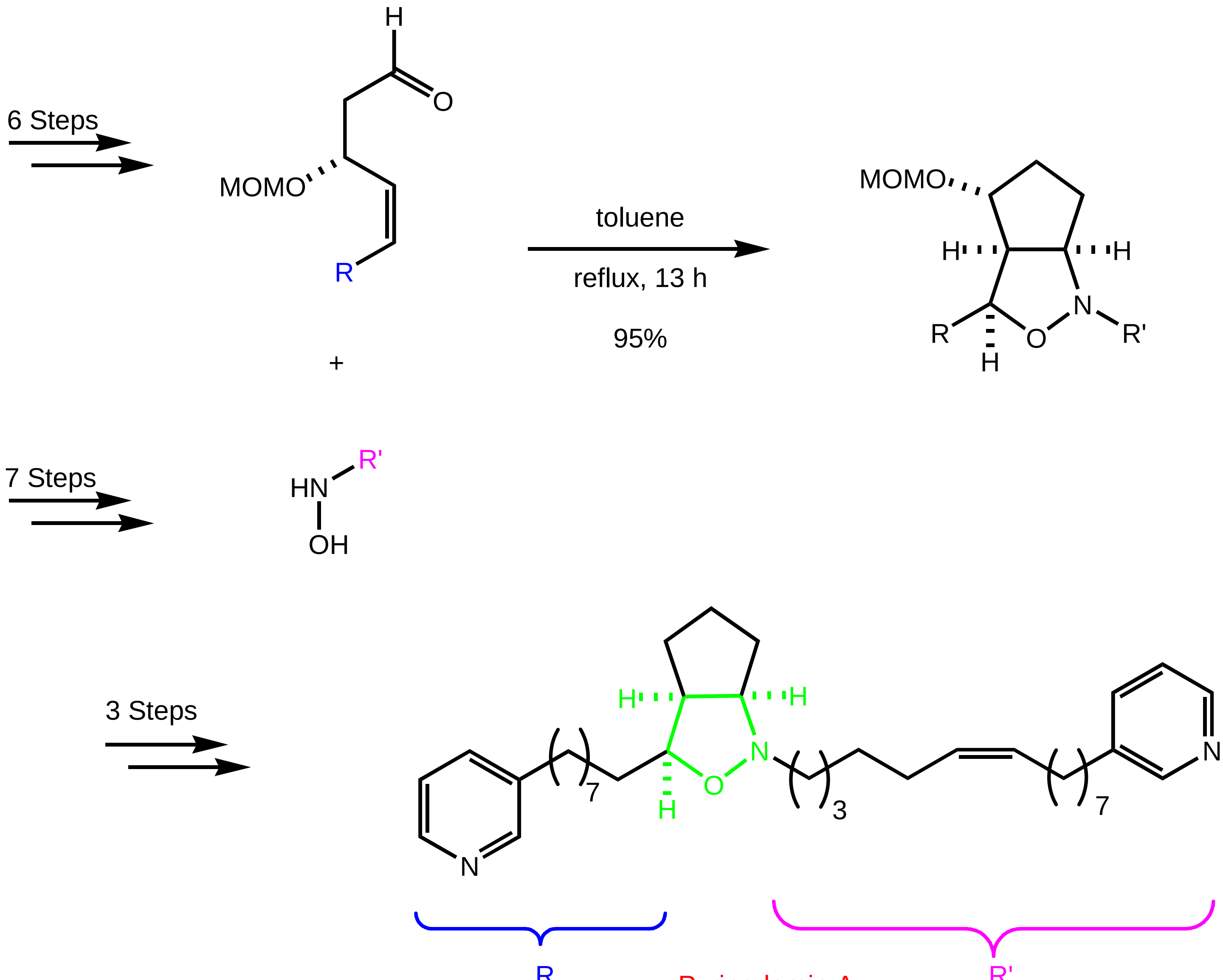
Finishing Monatin



Monatin

Tamura, O.; Shiro, T.; Toyao, A.; Ishibashi, H. *Chem. Comm.* **2003**, 2678.

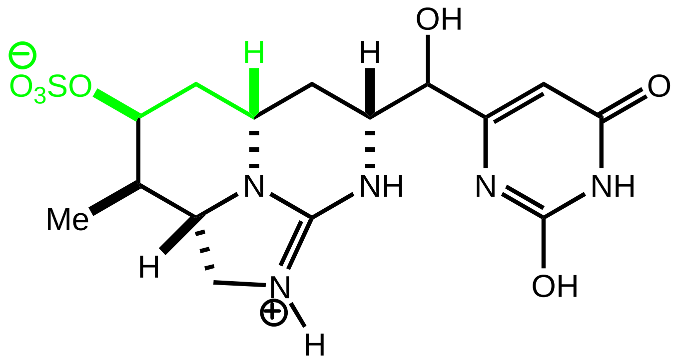
Pyrinodemin A



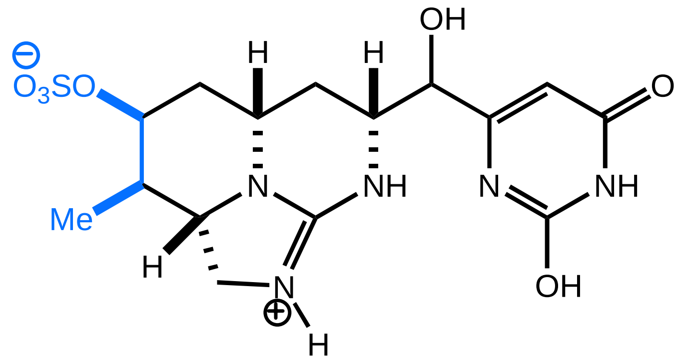
Pyrinodemin A

Morimoto, Y.; Kitao, S.; Okita, T.; Shoji, T. *Org. Lett.* **2003**, *5*, 2611.

7-Epicylindrospermopsin



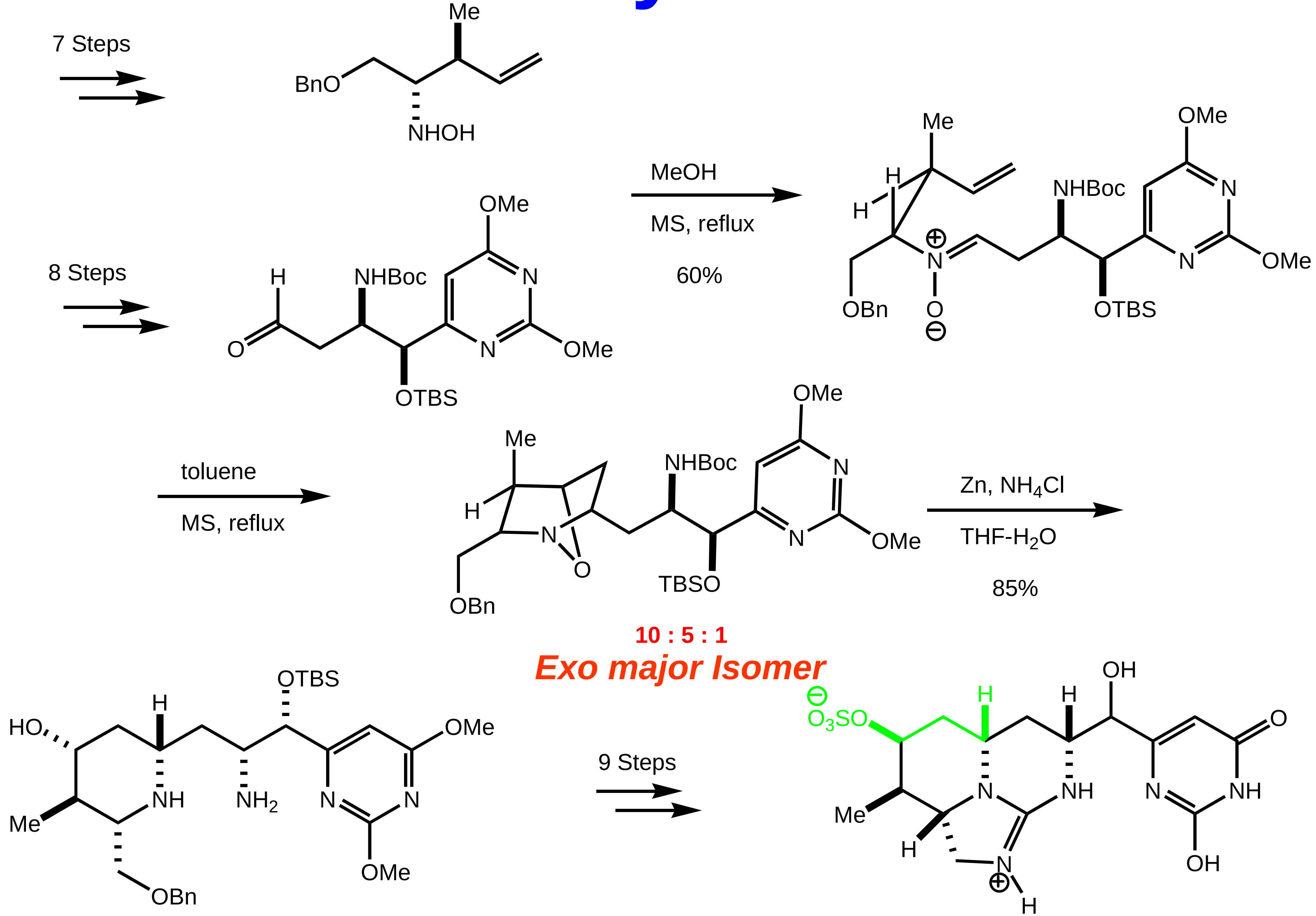
White Synthesis



Williams Synthesis

White, J. D.; Hansen, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4950.
Looper, R. E.; Williams, R. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2.

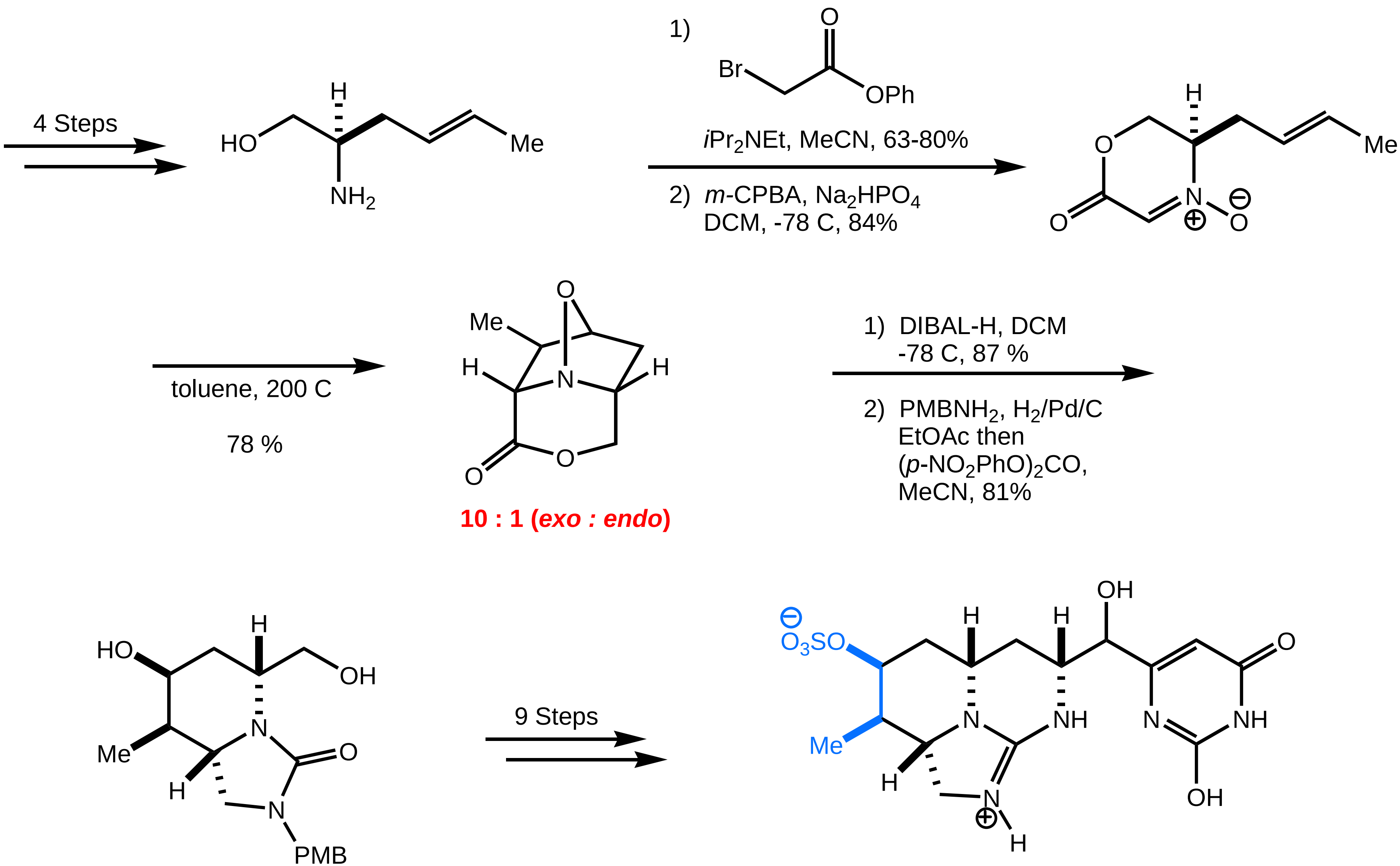
White Synthesis



White, J. D.; Hansen, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4950.

7-Epicylindrospermopsin

Williams Synthesis



7-Epicylindrospermopsin

Looper, R. E.; Williams, R. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2.

THE END