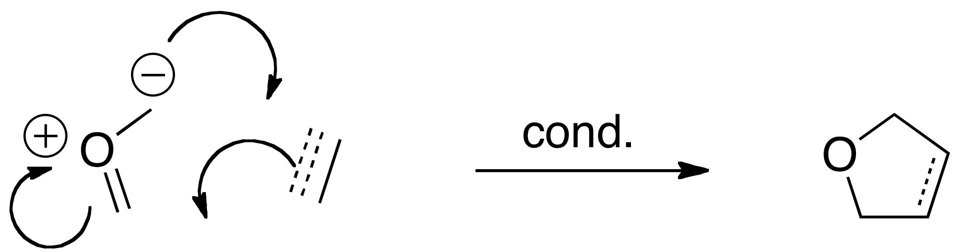
Carbonyl Ylide Cycloadditions

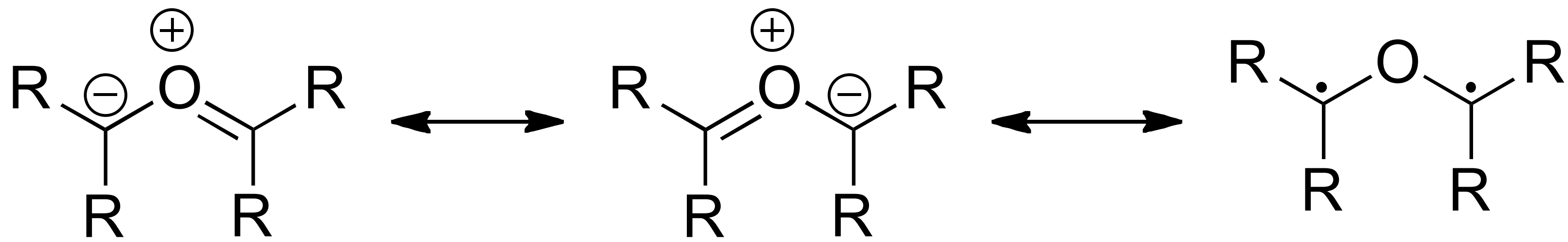


Nicholas Anderson

Denmark Group Meeting

07/13/10

Carbonyl Ylides

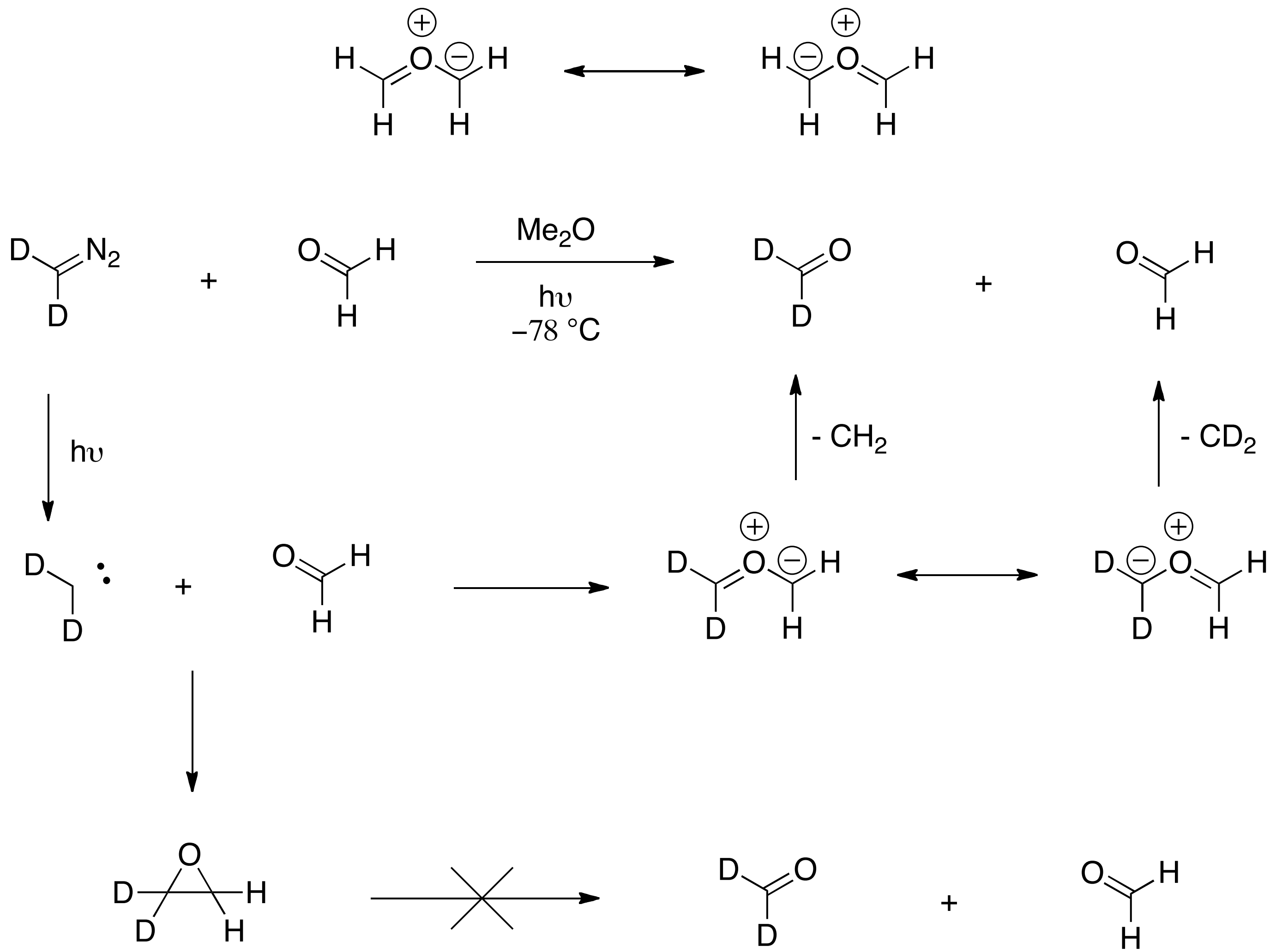


- Uncharged 1,3-Dipole
- Conjugated π-system

- Highly reactive
- Non-isolable

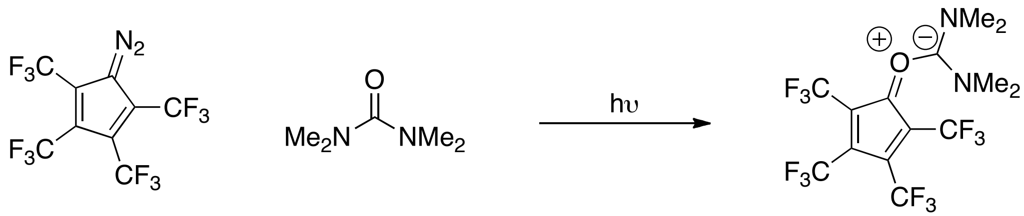
- Generate *in-situ*

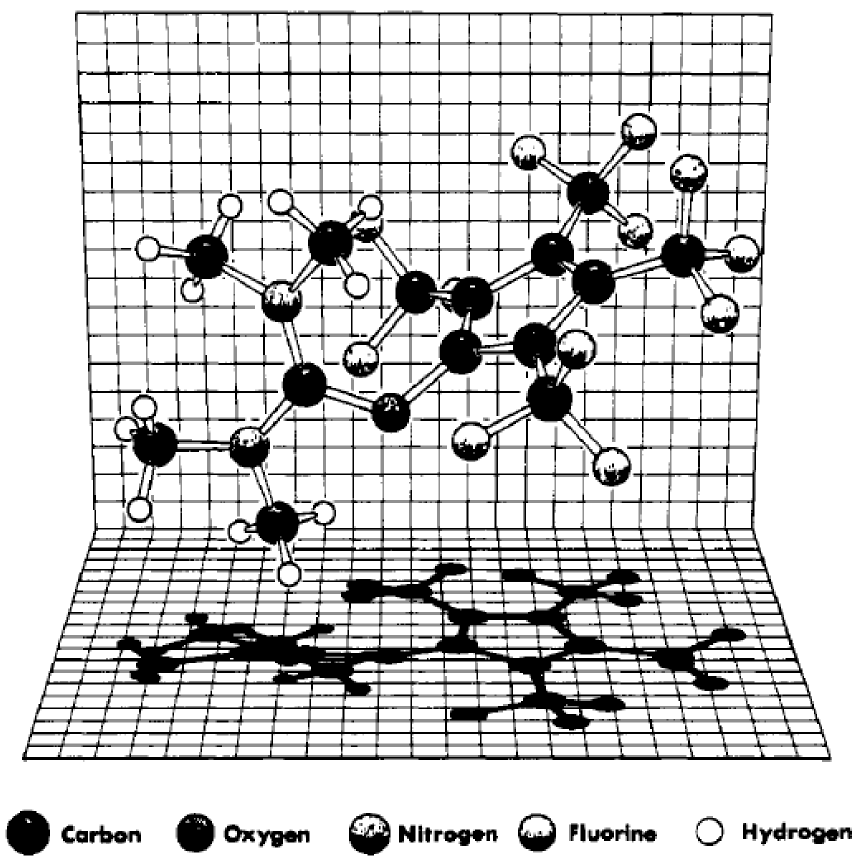
Carbonyl Ylide Stability

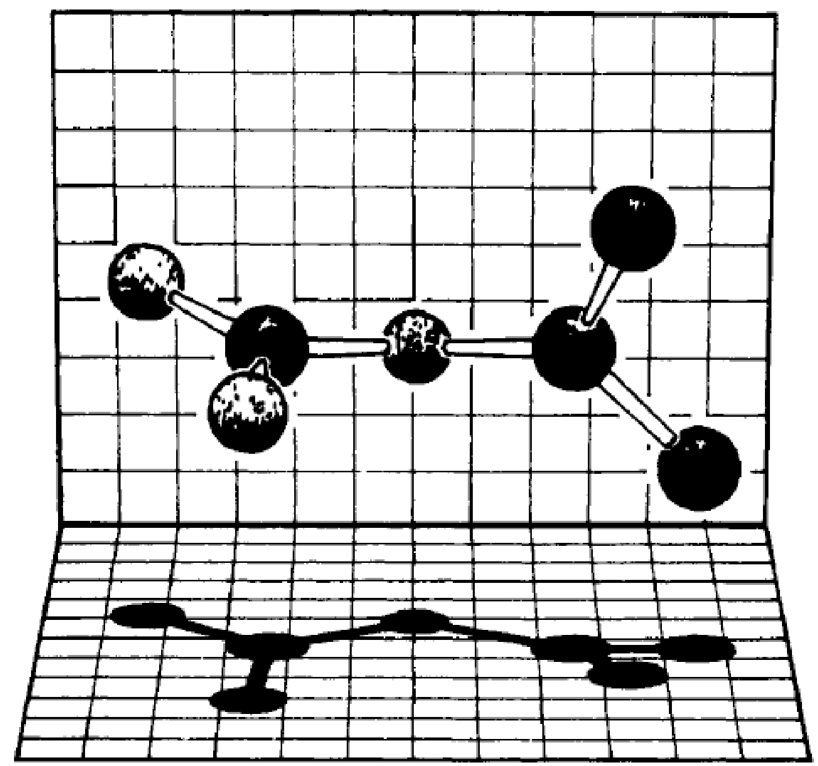


Prakash, G. K. S.; Ellis, R. W.; Felberg, J. D., Olah, G. A. *J. Am. Chem. Soc.*, **1986**, *108*, 1341-1342.

Carbonyl Ylide Stability



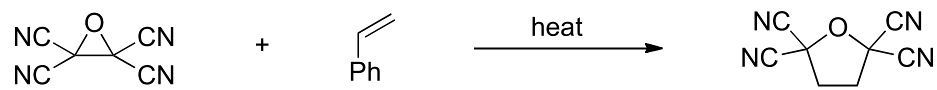




COC of the carbonyl ylide

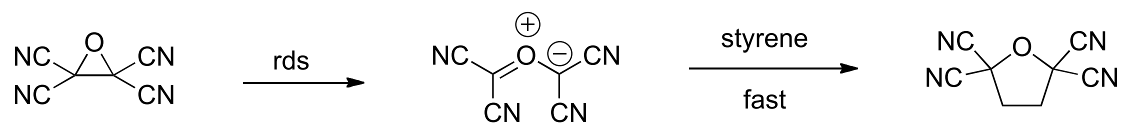
Janulis, E. P.; Arduengo, A. J. *J. Am. Chem. Soc.*, **1983**, *105*, 5929-5930.

Electrocyclic Epoxide Openings

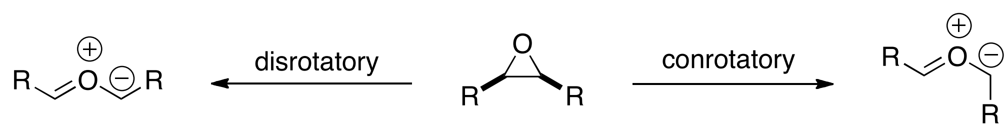


1st order in epoxide

0th order in styrene

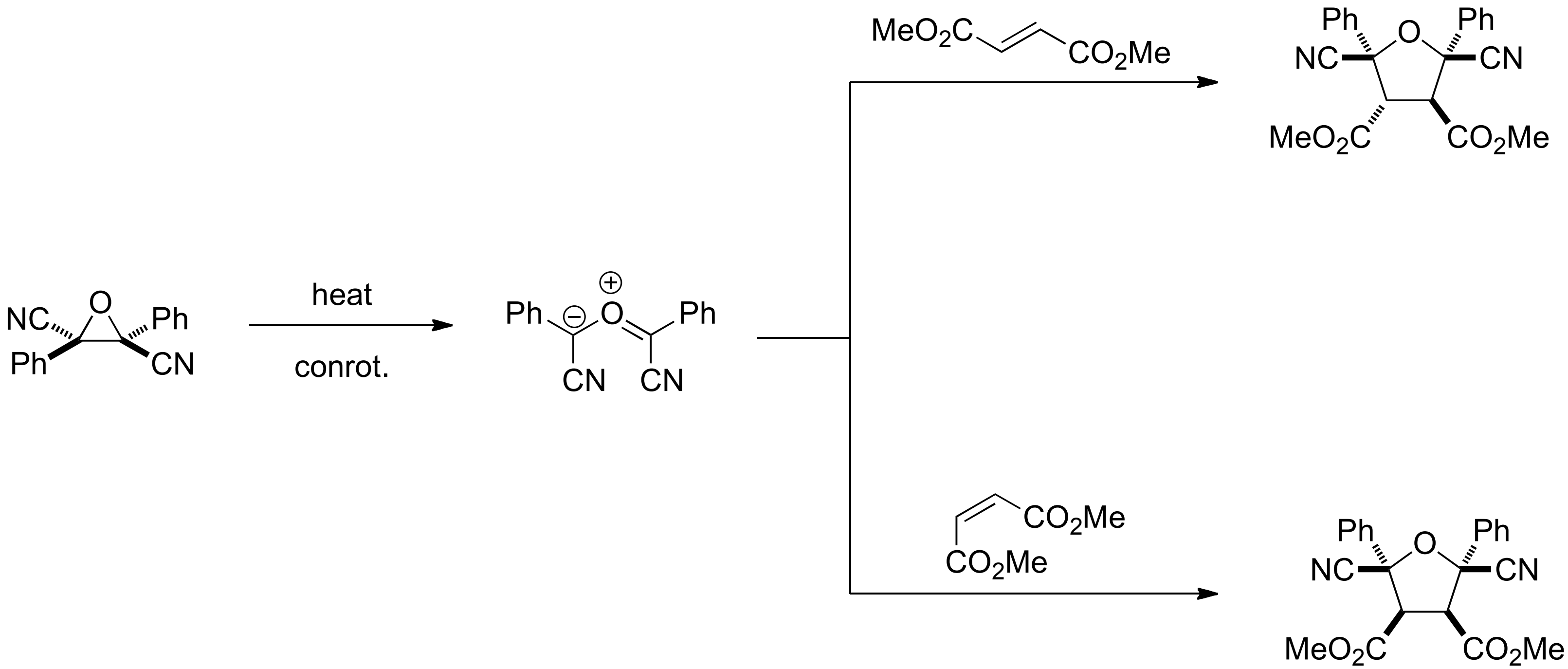


Photochemically Allowed   Thermally Allowed



Huisgen, R. *Angew. Chem. Int. Ed.*, **1977**, *16*, 572-585.

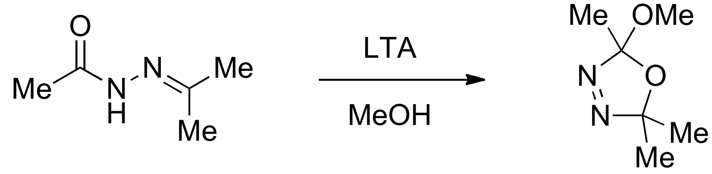
Electrocyclic Epoxide Openings

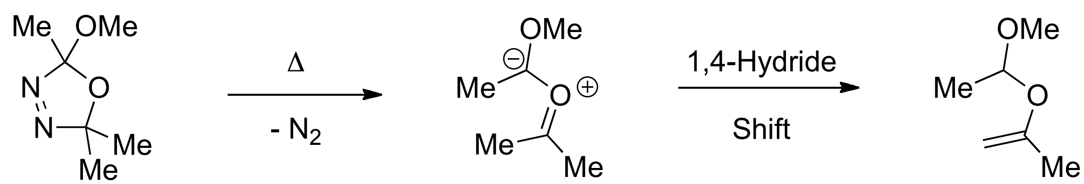


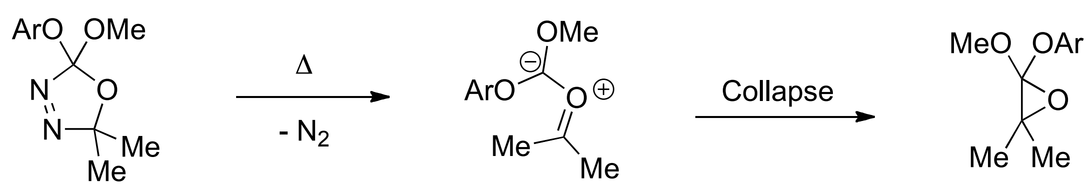
Limitations: requires highly EWG on at least one side of the epoxide

Huisgen, R. *Angew. Chem. Int. Ed.*, **1977**, *16*, 572-585.

Retrocycloadditions - Oxadiazolines

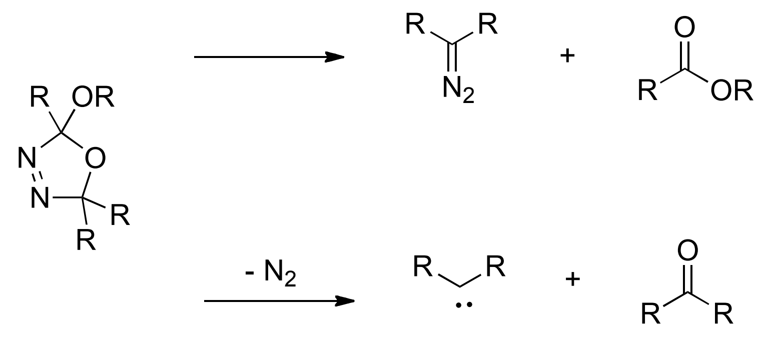


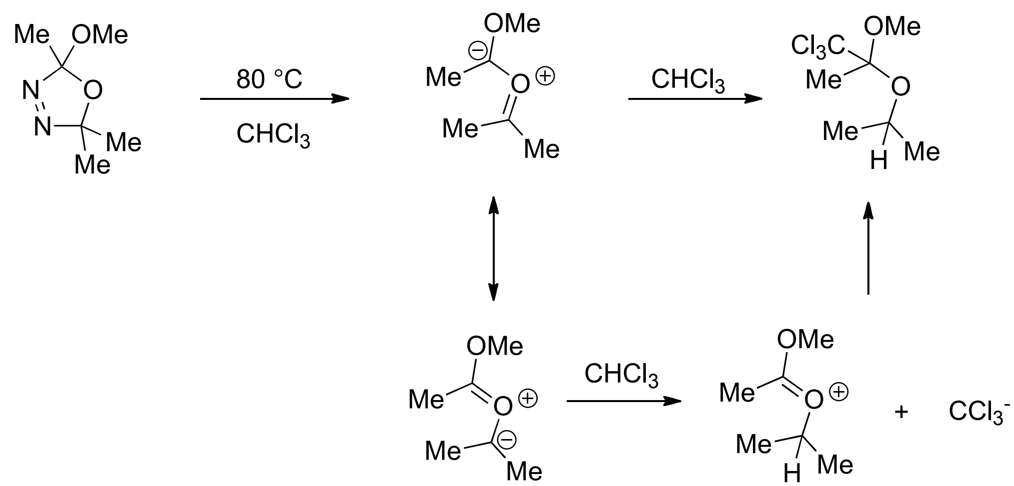




Bekhazi, M.; Warkentin, J. *J. Am. Chem. Soc.*, **1983**, *105*, 1289-1292.
Warkentin, J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2161-2169.

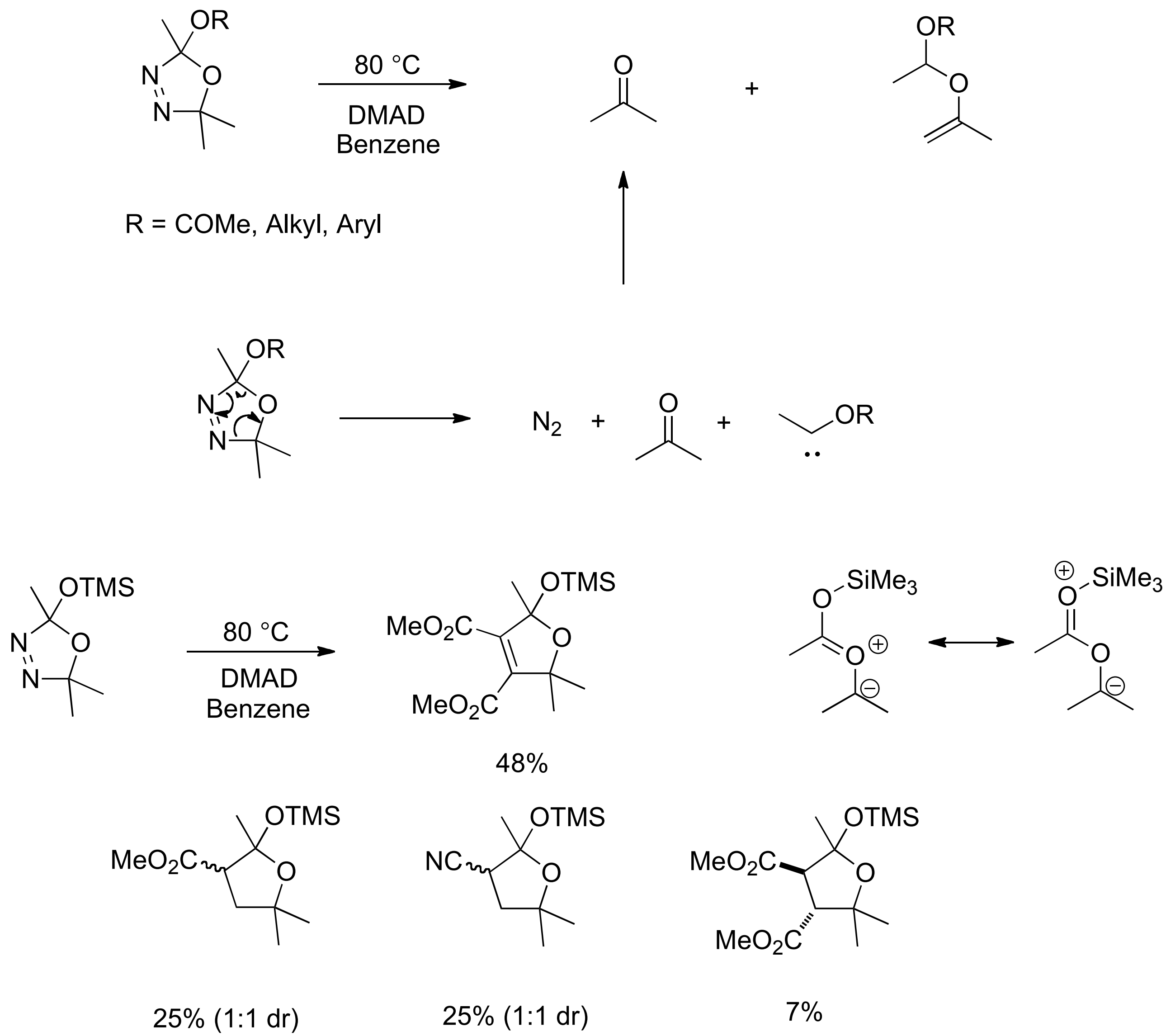
Retrocycloadditions - Oxadiazolines





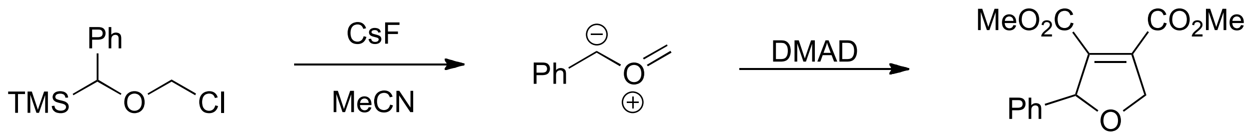
Bekhazi, M.; Lawrynowicz, W.; Warkentin, J. *Can. J. Chem.-Rev. Can. Chim.*, **1991**, *69*, 1507.
Warkentin, J. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2161-2169.

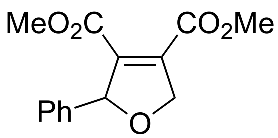
Retrocycloadditions - Oxadiazolines



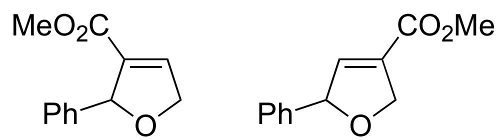
Sharma, P. K.; Warkentin, J. *Tet. Lett.*, **1995**, *36(42)*, 7591-7594.

1,3-Elimination of Ethers

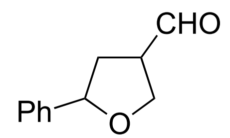




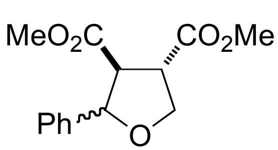
65%



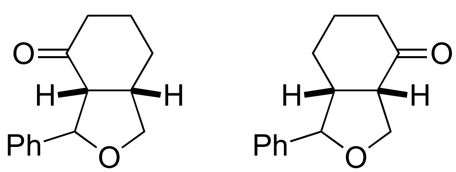
79% (3:1)



43% (59:16:14:11)



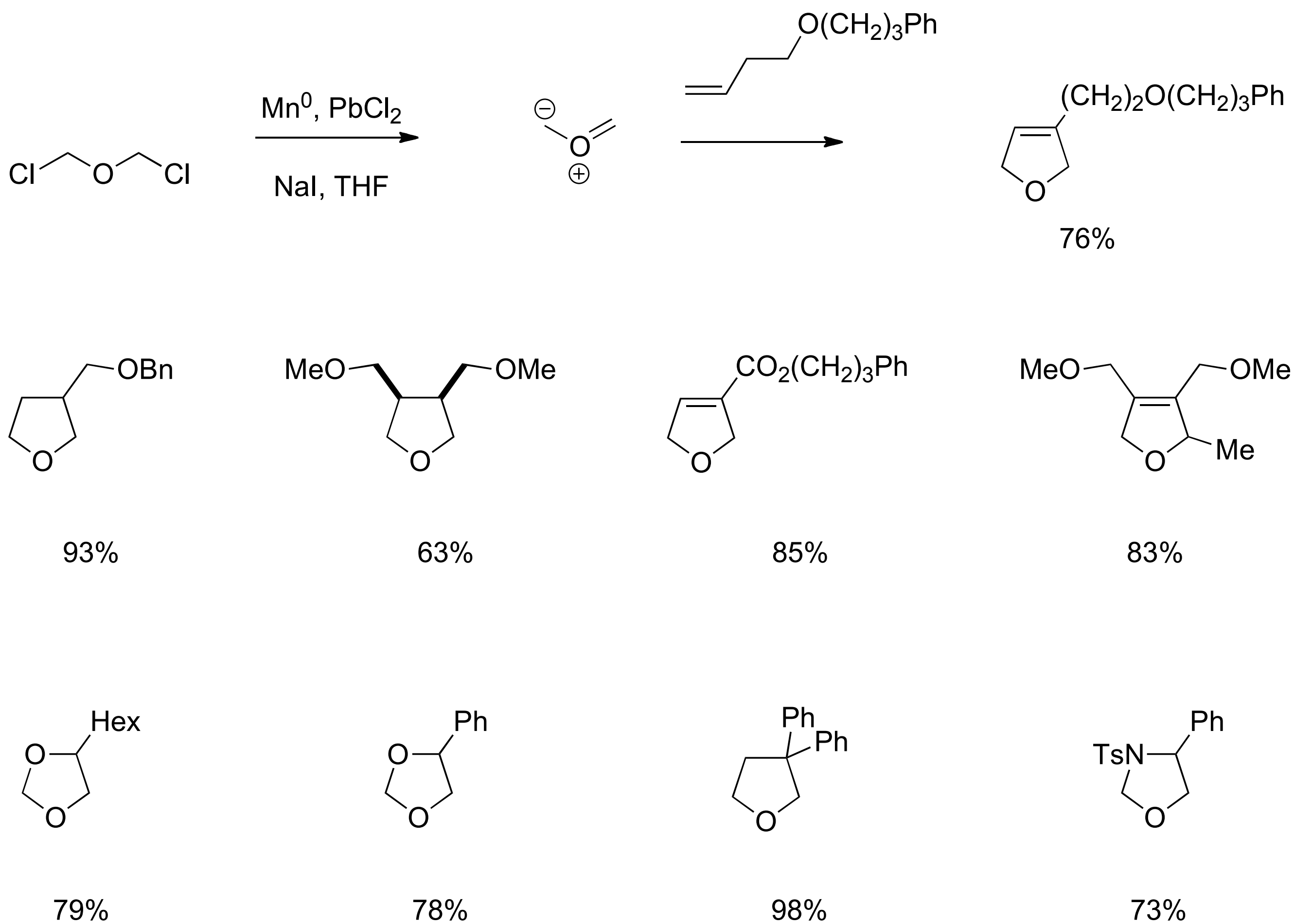
81% (1:1 dr)



81% (1:1)

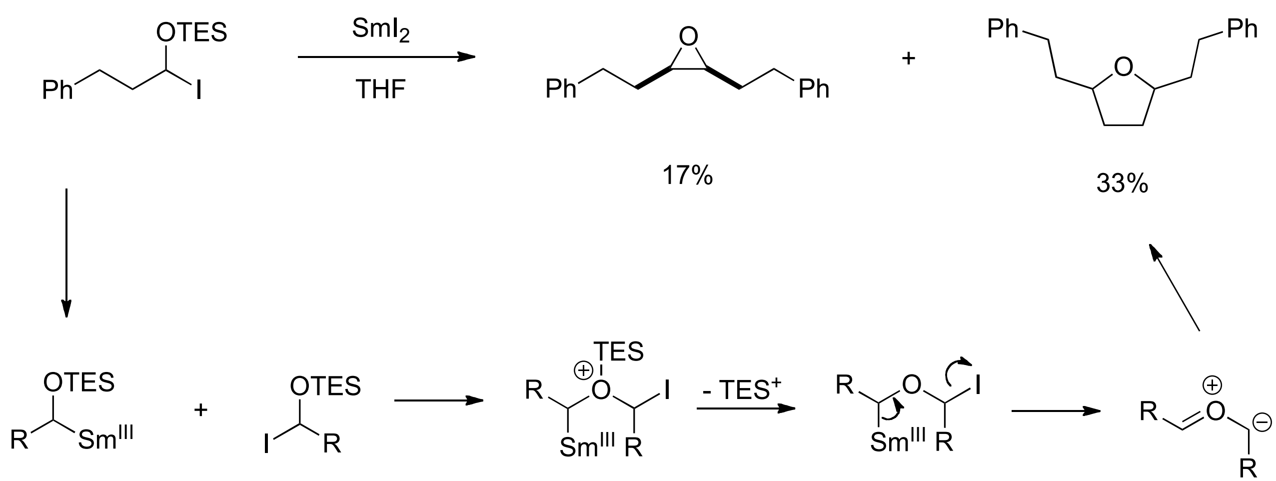
Hojo, M.; Ohkuma, M.; Ishibashi, N.; Hosomi, A. *Tet. Lett.*, **1993**, *34*(*37)*, 5943-5946.

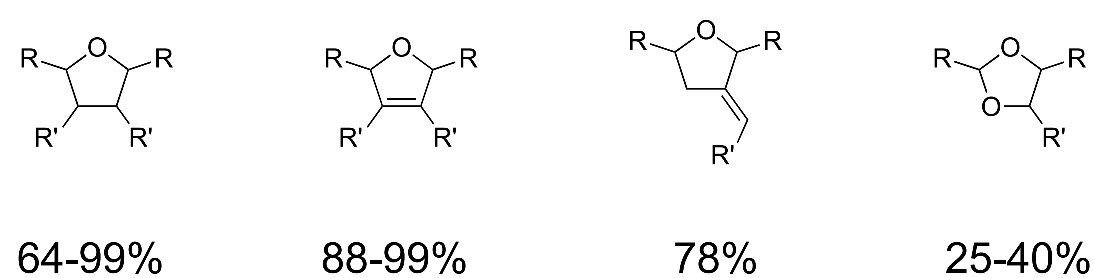
1,3-Elimination of Ethers



Hojo, M.; *et al*. *J. Org. Chem.*, **1997**, *62*, 8610-8611

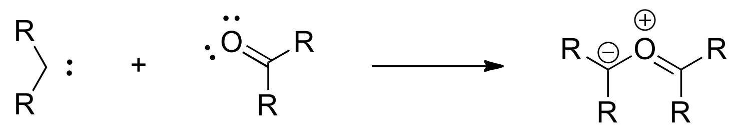
Samarium(II) Iodide Mediated Carbonyl Ylide Formation

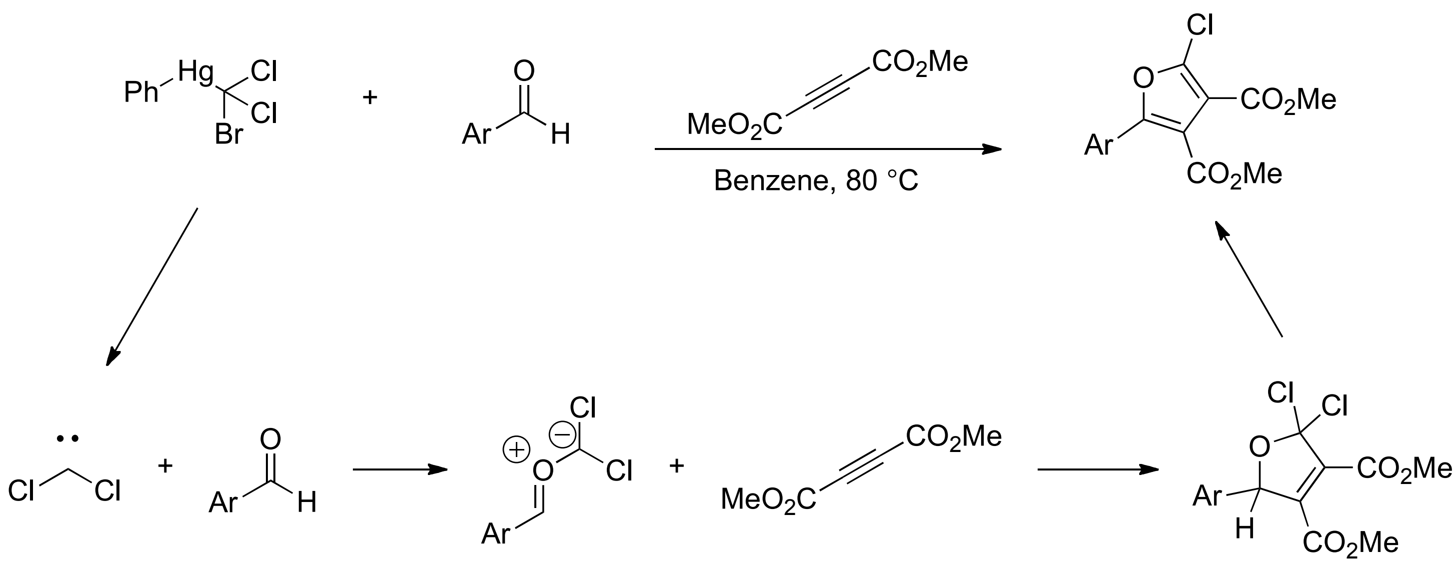


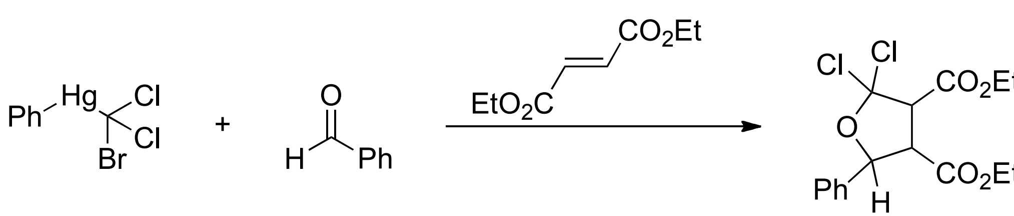


Hojo, M.; Aihara, H.; Hosomi, A., *J. Am. Chem. Soc.*, **1996**, *118*, 3533-3534.

Carbonyl Ylides from Carbenes

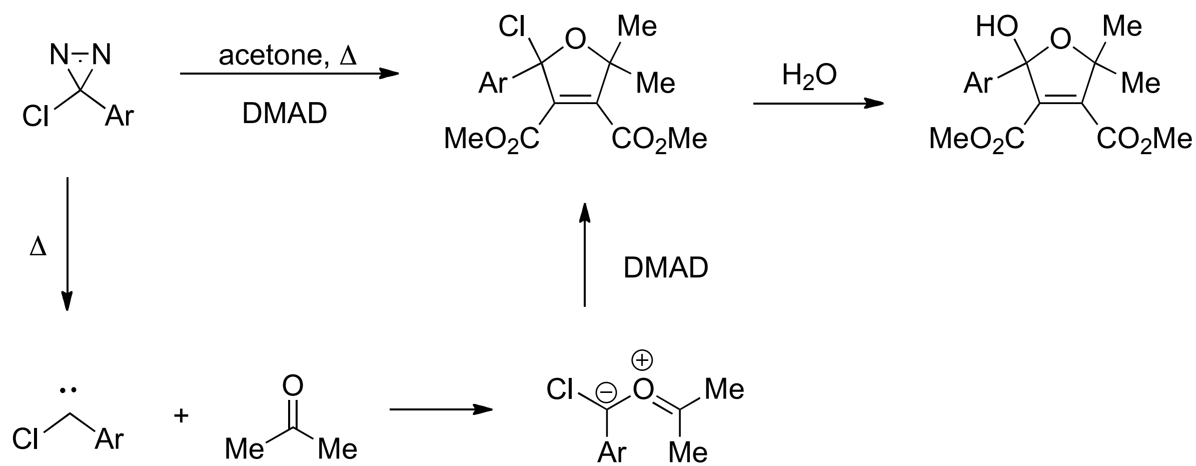


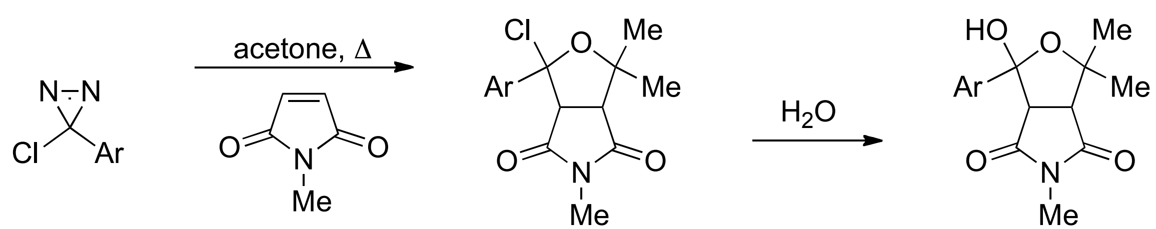




Gill, H. S.; Landgrebe, J. A. *J. Org. Chem.*, **1983**, *48*, 1051-1055.

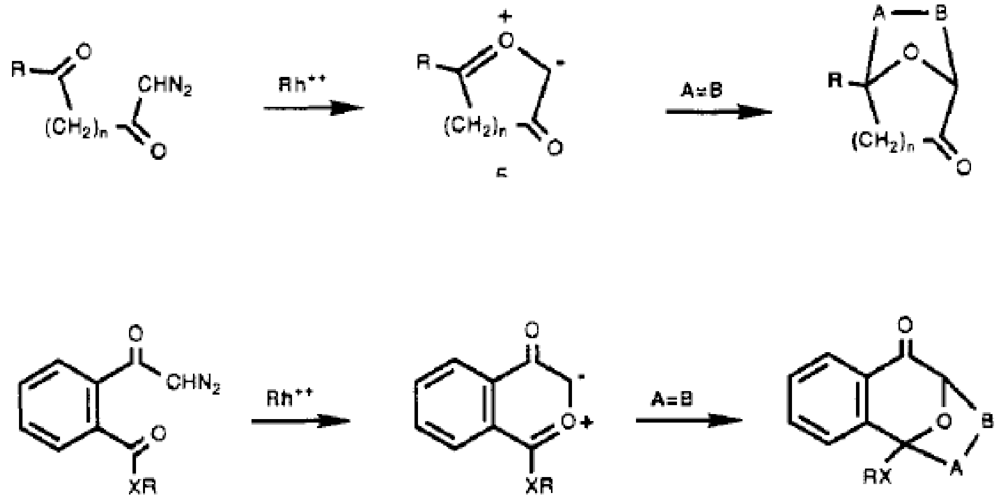
Diazirine Decomposition

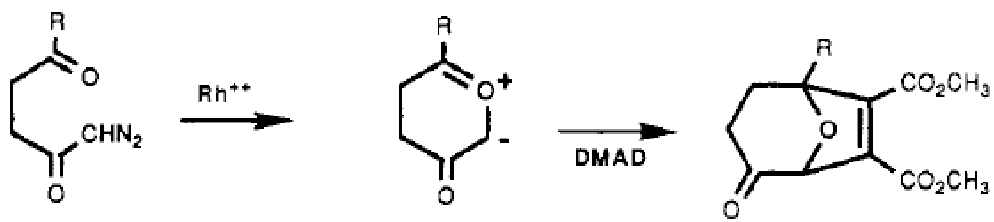




Ibata, T.; Liu, M. T. H.; Toyoda, J. *Tet. Lett.*, **1986**, *27*, 4383-4386.

Rhodium Catalysis





7; R=CH_3
8; R=Ph

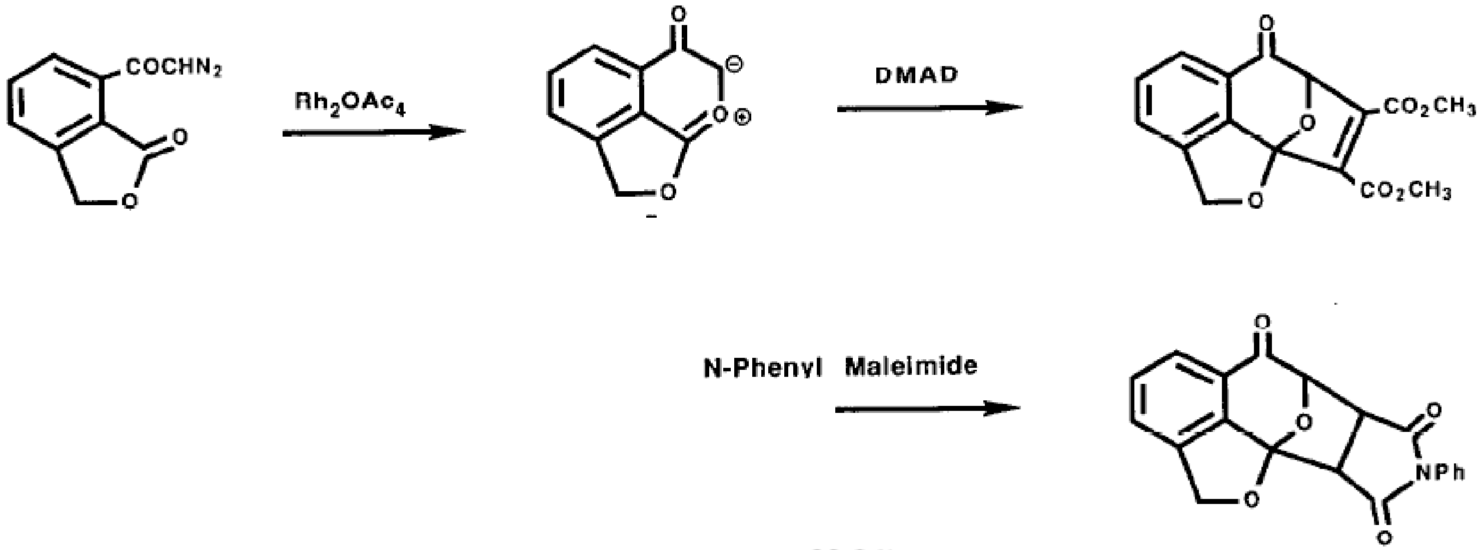
9

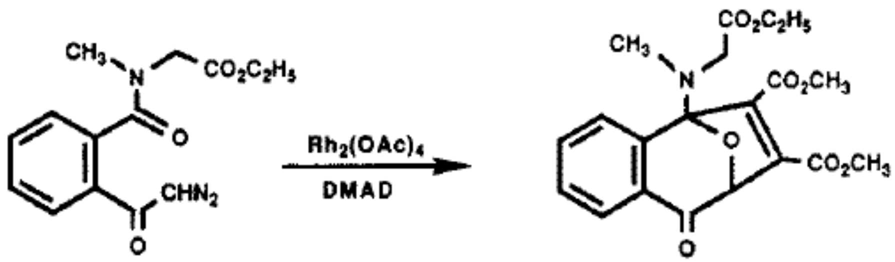
10; R=CH_3 [88%]
11; R=Ph [93%]

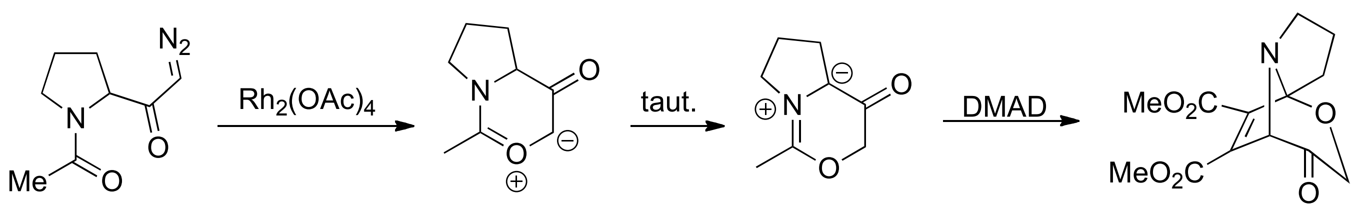
$Rh^{++} = Rh_2(OAc)_4$

Padwa, A.; Fryxell, G. E.; Zhi, L., *J. Am. Chem. Soc.*, **1990**, *112*, 3100-3109.

Diazocompounds and Amides/Esters

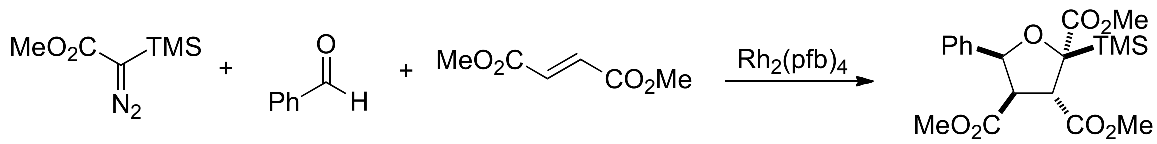


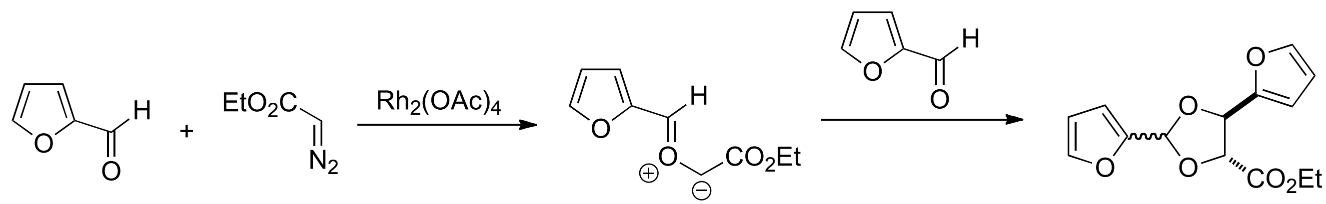


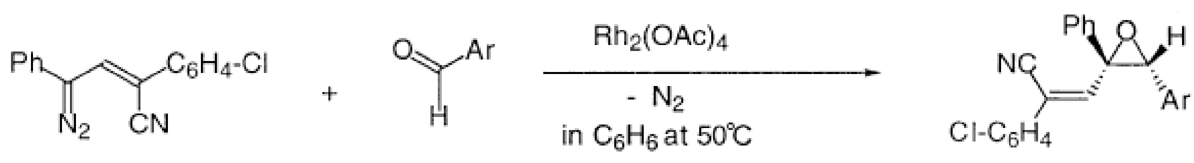


Padwa, A.; Stull, P. D., *Tet. Lett.*, **1987**, *28(45)*, 5407-5410.
Padwa, A.; Zhi, L., *J. Am. Chem. Soc.*, **1990**, *112*, 2037-2038.

Diazocompounds and Aldehydes



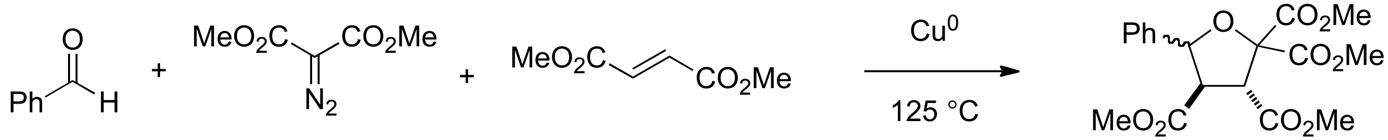




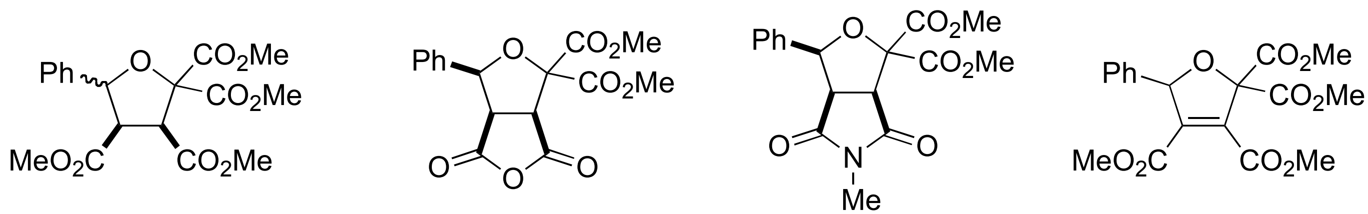
Major product

Alt, M. Maas, G., *Tetrahedron*, **1994**, *50(25)*, 7435-7444.
Wenkert, E.; Khatuya, H., *Tet. Lett.*, **1999**, *40*, 5439
Hamaguchi, M.; *et al.*, *Tet. Lett.*, **2000**, *41*, 1457-1460.

Diazocompounds and Aldehydes

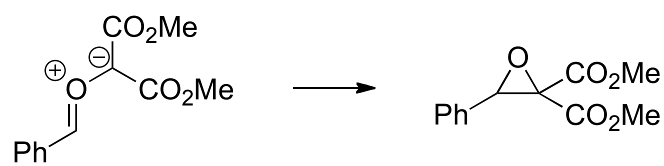


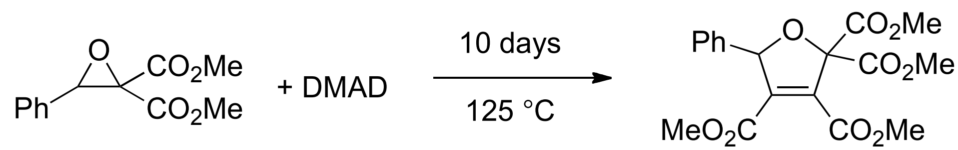
58% (54:46 dr)



24% (55:45 dr) | 42% | 59% (83:17 dr) | 58%

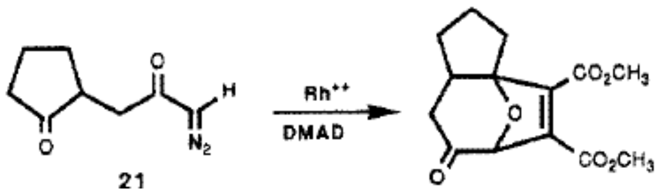
mass balance was typically epoxide:

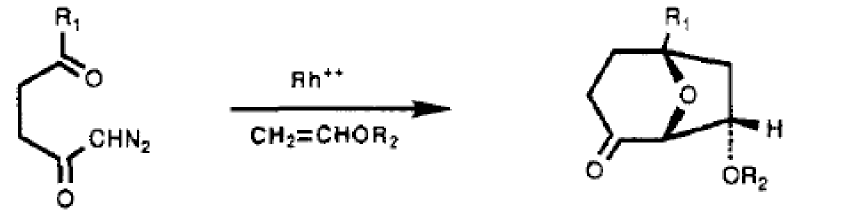




Huisgen, R.; De March, P., *J. Am. Chem. Soc.*, **1982**, *104*, 4953-4954.

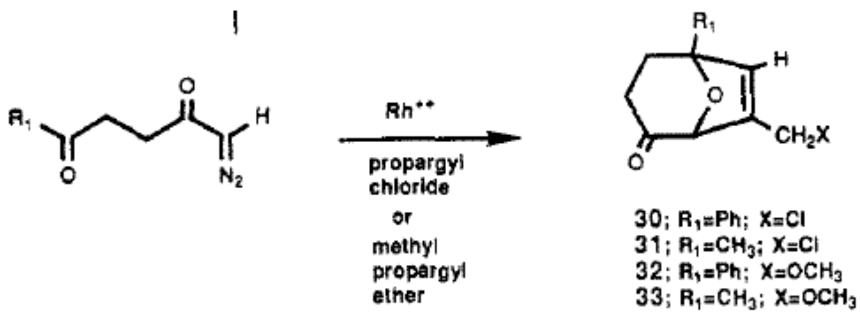
Diazocompounds and Ketones

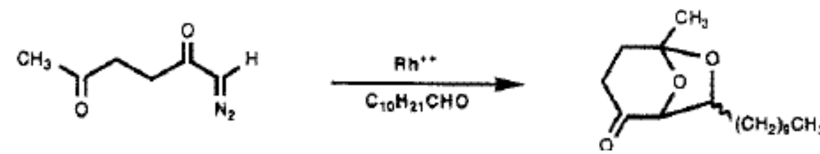




53; R_1=CH_3; R_2=$COCH_3$
55; R_1=Ph; R_2=$COCH_3$
57; R_1=CH_3; R_2=C_2H_5
59; R_1=Ph; R_2=C_2H_5

25-70%, mixture of isomers





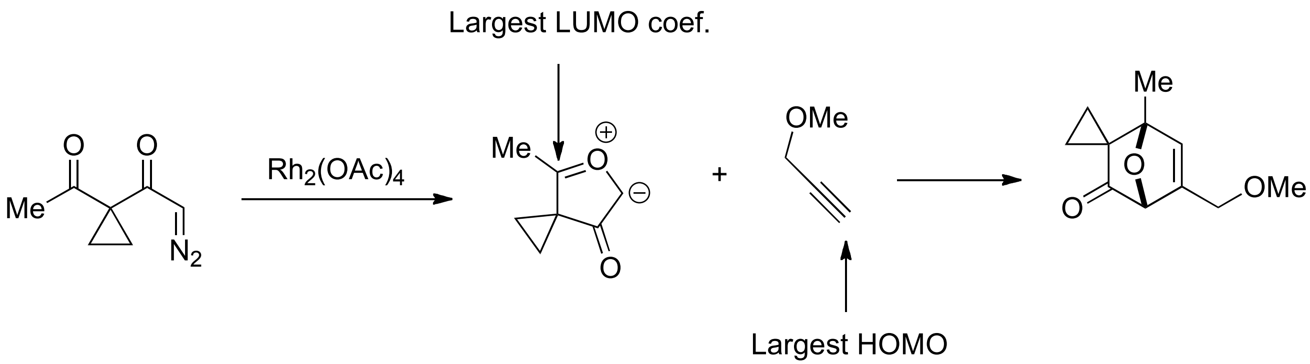
50% (1:1 dr)

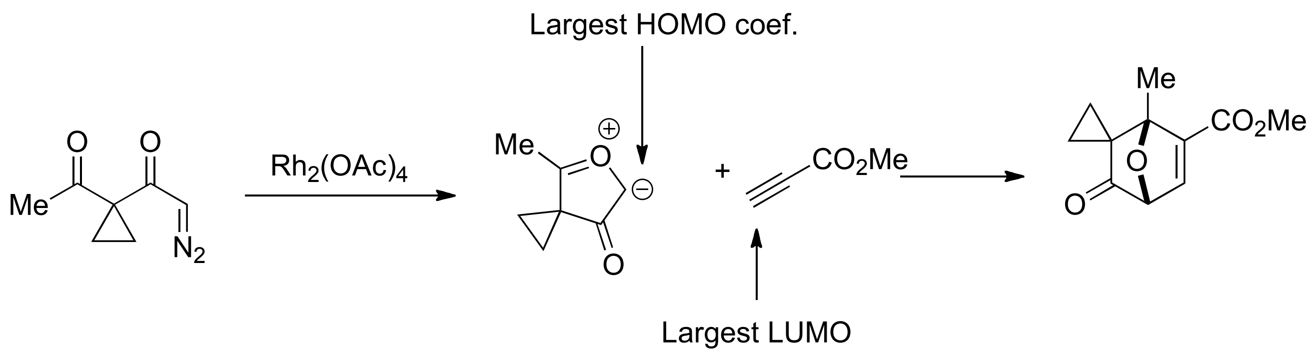
68-85%
No isomers observed

Padwa, A., et al. *Tet. Lett.*, **1989**, *30(3)*, 301-304.

Selectivity Rationalization

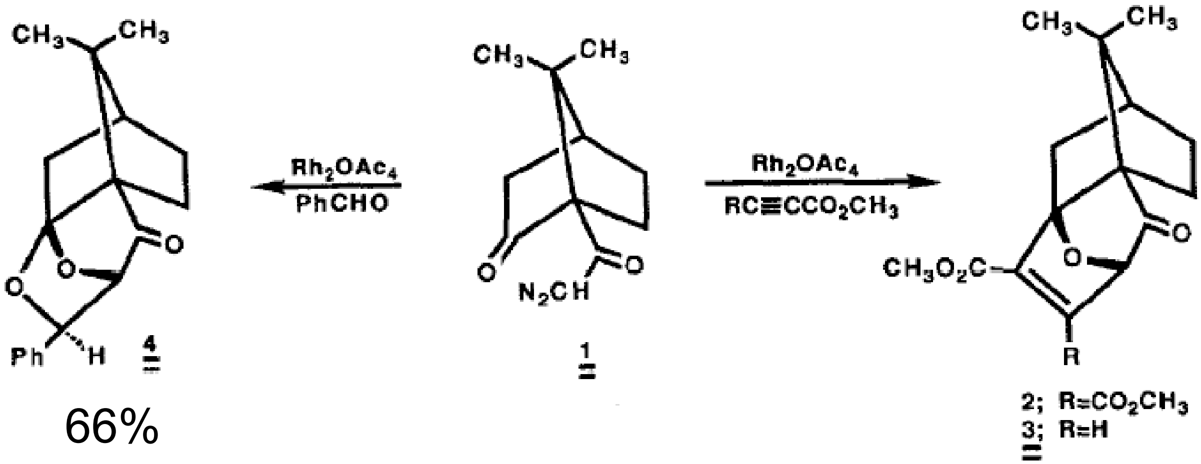
FMO can explain selectivity:
HOMO dipole – LUMO dipolarophile for e$^-$ poor dipolarophiles
LUMO dipole – HOMO dipolarophile for e- rich dipolarophiles





Padwa, A., et al. *Tet. Lett.*, **1989**, *30(3)*, 301-304.

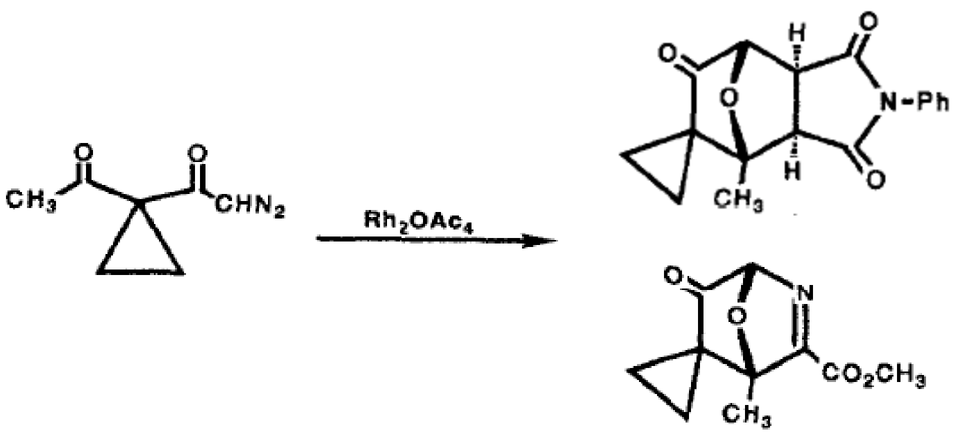
Polycycles Through Carbonyl Ylides



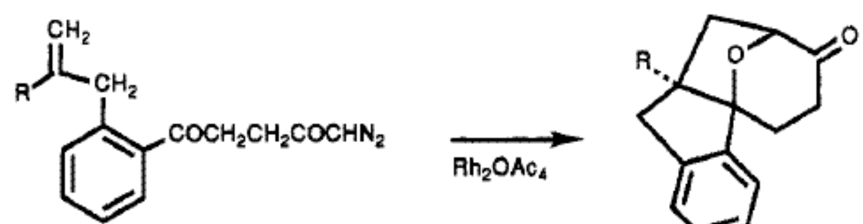
66%

85%

72%



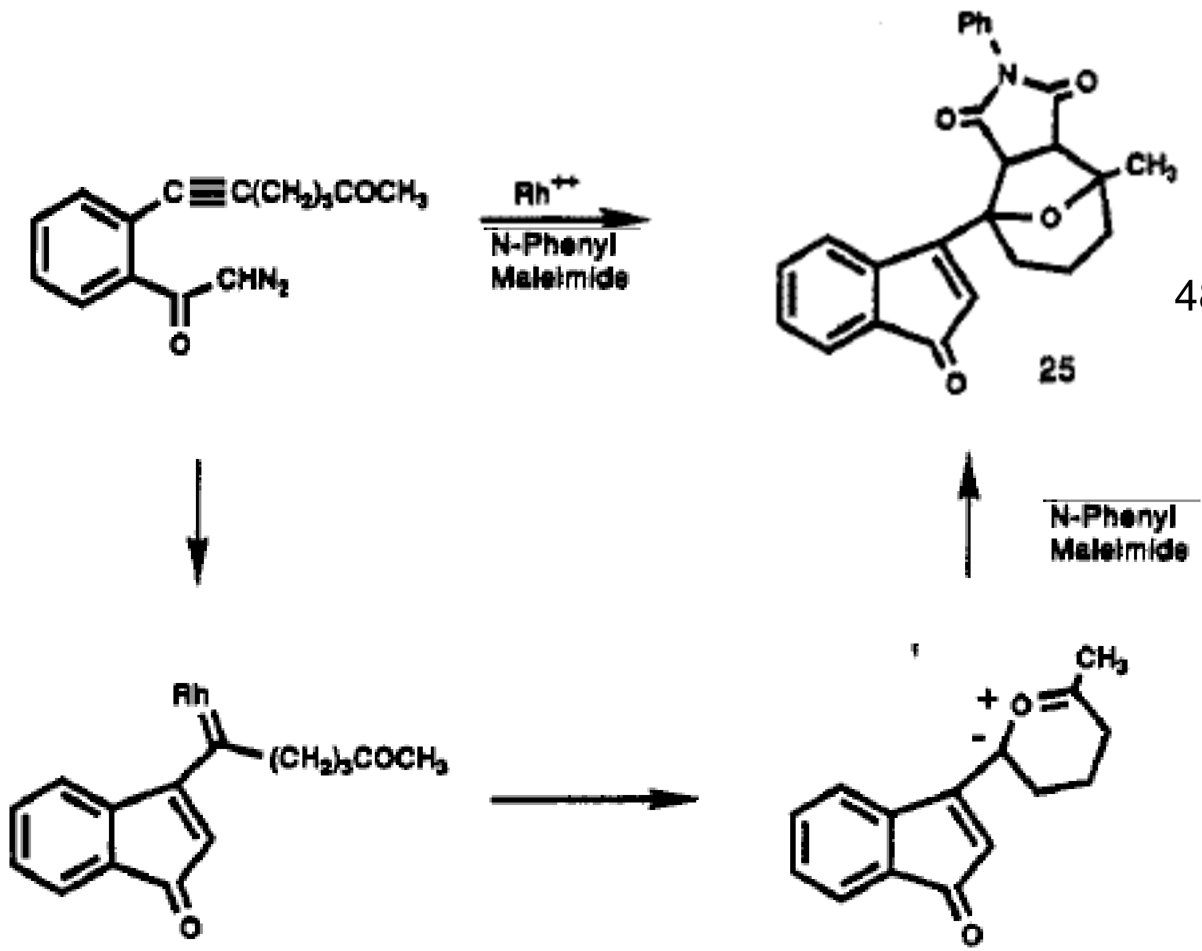
"high yield"



88%

Padwa, A., et al. *Tet. Lett.*, **1989**, *30(3)*, 301-304.

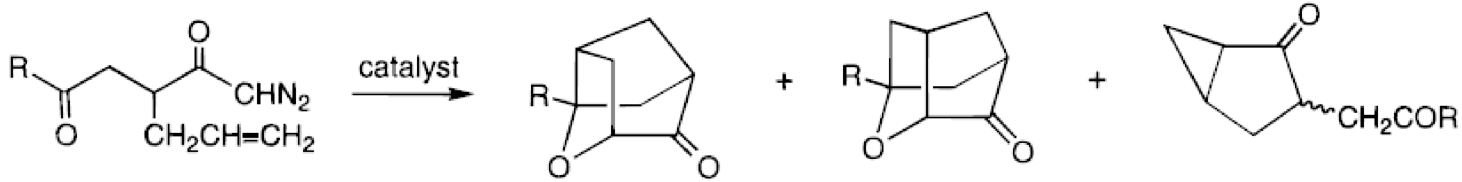
Increase Complexity



48%

Padwa, A., *et al*. *J. Org. Chem.*, **1991**, *56(7)*, 2523-2530.

Ligand Effects on Selectivity

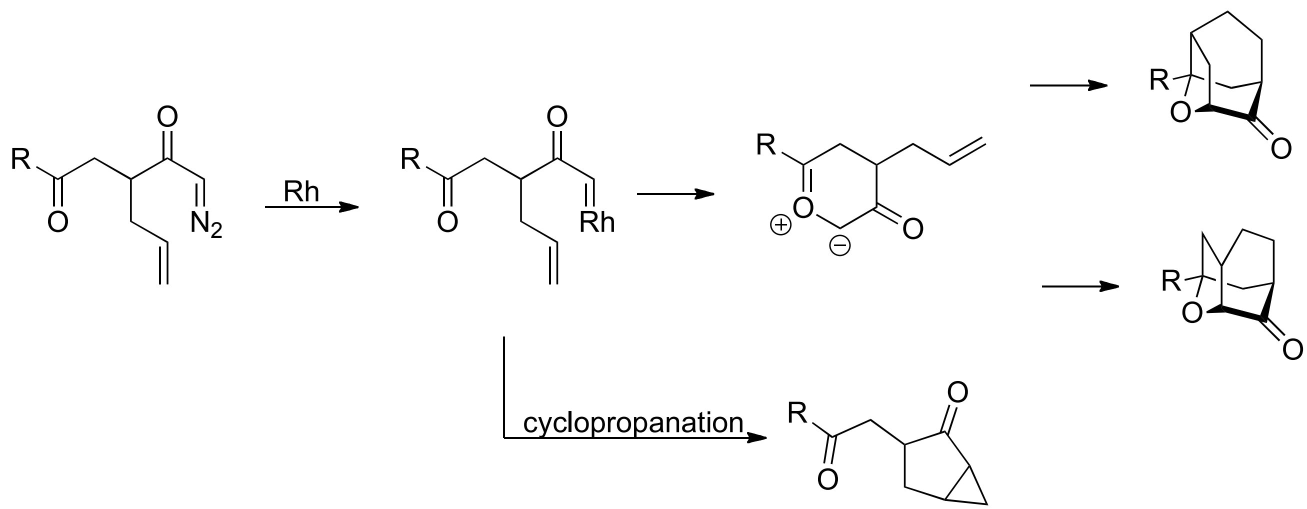


1; R=Me
5; R=Ph

2; R=Me
6; R=Ph

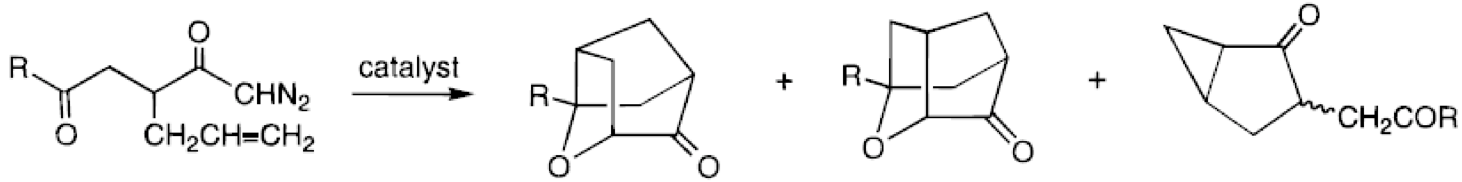
3; R=Me
7; R=Ph

4a; R=Me (*trans*)
4b; R=Me (cis)
8a; R=Ph (*trans*)
8b; R=Ph (cis)



Padwa, A.; Austin, D. J.; Hornbuckle, S. F., *J. Org. Chem.*, **1996**, *61*, 63-72.

Ligand Effects on Selectivity



1; R=Me
5; R=Ph

2; R=Me
6; R=Ph

3; R=Me
7; R=Ph

4a; R=Me (*trans*)
4b; R=Me (cis)
8a; R=Ph (*trans*)
8b; R=Ph (cis)

diazo ketone	Rh_2L_4	isolated yield, %	relative yield, %			
			2	**3**	**4a**	**4b**
1	$Rh_2(OAc)_4$	83	6	41	22	14
1	$Rh_2(cap)_4$	82	8	25	34	15
1	$Rh_2(pfb)_4$	58	0	18	27	13
1	$Rh_2(tfa)_4$	71	0	35	24	12
1	$Cu(acac)_2$	94	0	9	75	10
1	$PdCl_2(PhCN)_2$	89	0	0	83	6

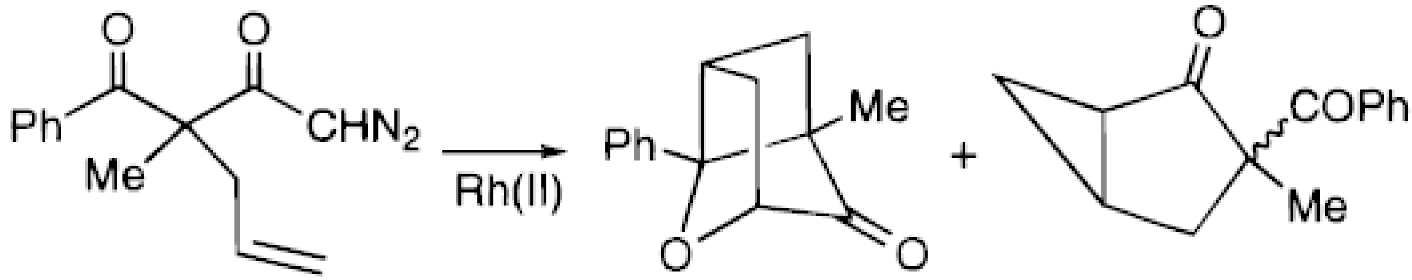
diazo ketone	Rh_2L_4	isolated yield, %	relative yield, %			
			6	**7**	**8a**	**8b**
5	$Rh_2(OAc)_4$	94	10	47	23	14
5	$Rh_2(cap)_4$	96	12	52	28	4
5	$Rh_2(pfb)_4$	87	33	12	25	17
5	$Rh_2(tfa)_4$	93	34	12	17	30
5	$Cu(acac)_2$	98	9	35	34	20
5	$PdCl_2(PhCN)_2$	68	0	0	38	30

Ligand affect is unclear
However, ligand IS present during cycloaddition

Cap = caprolactamate
Pfb = perfluorobutyrate
Tfa = trifluoroacetate

Padwa, A.; Austin, D. J.; Hornbuckle, S. F., *J. Org. Chem.*, **1996**, *61*, 63-72.

Ligand Effects on Selectivity

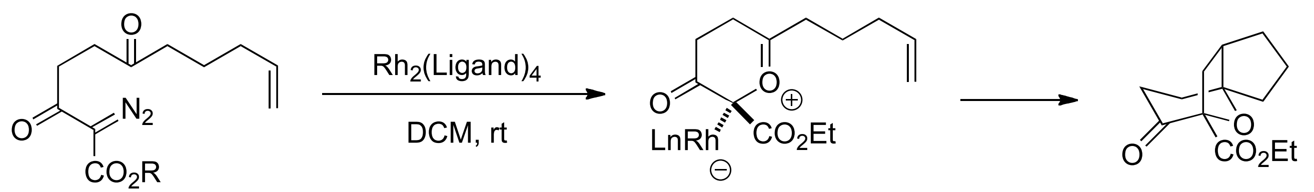


$Rh_2(OAc)_4$	60%	24%
$Rh_2(tfa)_4$	67%	0%
$Rh_2(cap)_4$	70%	28%

The more electron poor ligands cause the intermediate carbene to be more electrophilic favoring formation of the carbonyl ylide.

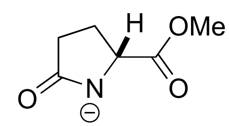
Padwa, A.; Austin, D. J.; Hornbuckle, S. F., *J. Org. Chem.*, **1996**, *61*, 63-72.

Enantioselective Carbonyl Ylide Cycloadditions

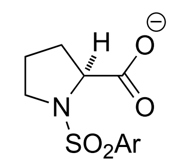


Ligand	Yield	er
OAc	73%	50:50
5R-MEPY	75%	50:50
S-DOSP	NR	54:46
S-DOSP[a]	76%	76:24
R-DDBNP[a]	81%	94:6

a) run in hexane

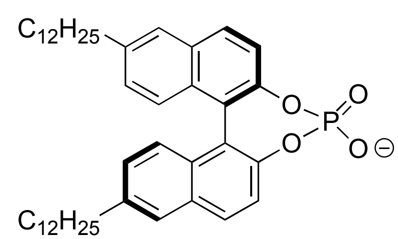


5R-MEPY



Ar= 4-$C_{12}H_{25}C_6H_4$

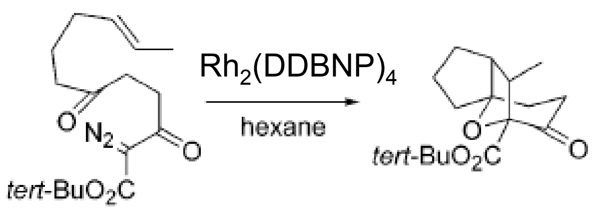
S-DOSP



R-DDBNP

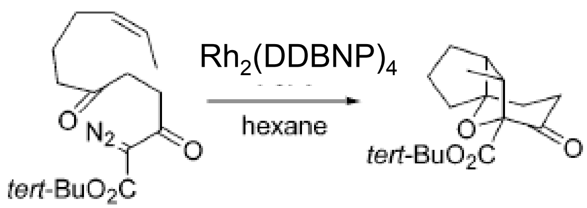
Hodgson, D. M.; Stupple, P. A.; Johnstone, C., *Tet. Lett.*, **1997**, *38(36)*, 6471-6472.
Hodgson, D. M.; *et al.*, *J. Chem. Soc., Chem. Commun.*, **1999**, *2185-2186*.

Enantioselective Substrate Scope



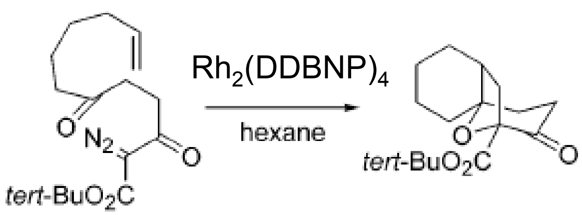
25 (+)–35

63%
82:18 er



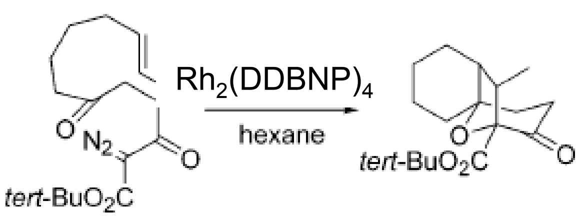
26 (–)–36

67%
88:12 er



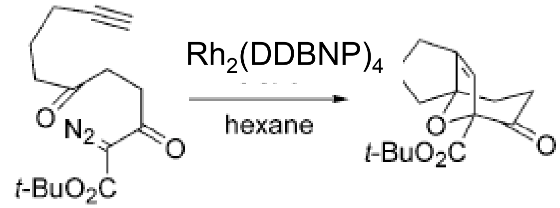
27 (+)–37

73%
93:7 er



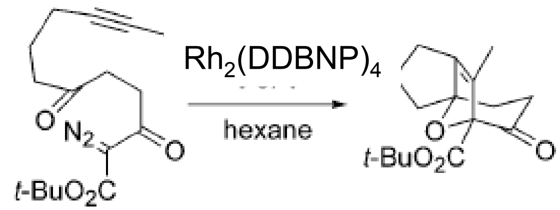
28 (+)–38

44%
75:25 er



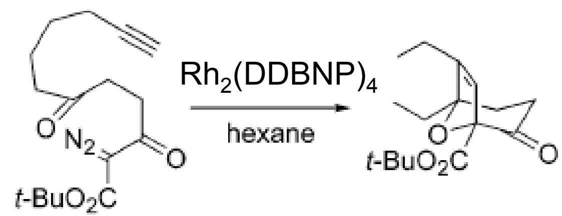
29 (+)–39

77%
87:13 er



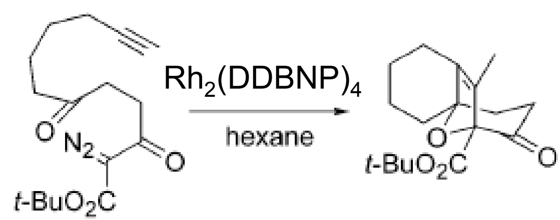
30 (+)–40

76%
80:20 er



31 (+)–41

41%
86:14 er

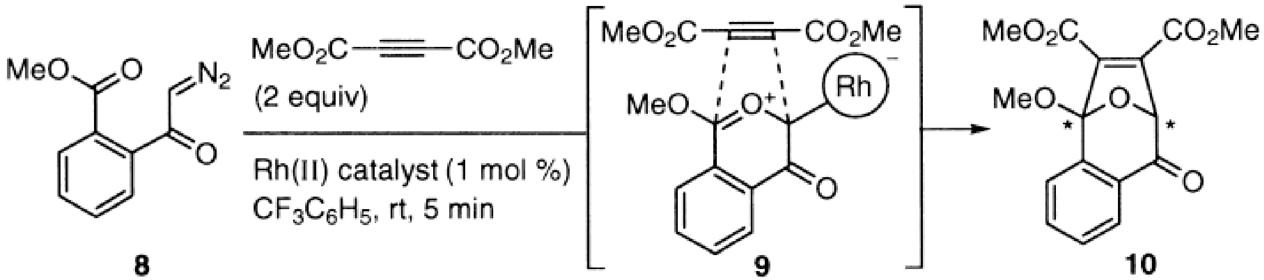


32 (+)–42

38%
83:17 er

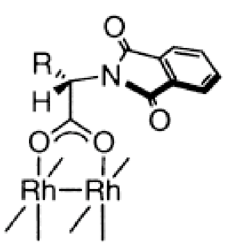
Hodgson, D. M.; *et al.*, *J. Org. Chem.*, **2003**, *68(16)*, 6153-6159.

Asymmetric Cycloadditions from Esters

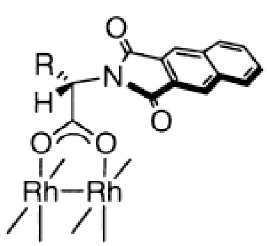


Entry	Rh(II)	Yield[a] (%)	Ee[b] (%)	Entry	Rh(II)	Yield[a] (%)	Ee[b] (%)
1	Rh_2(*S*-PTPA)$_4$	67	44	5	Rh_2(*S*-BPTPA)$_4$	63	52
2	Rh_2(*S*-PTA)$_4$	69	35	6	Rh_2(*S*-BPTA)$_4$	68	34
3	Rh_2(*S*-PTV)$_4$	67	51	7	Rh_2(*S*-BPTV)$_4$	72	62
4	Rh_2(*S*-PTTL)$_4$	67	74	8	Rh_2(*S*-BPTTL)$_4$	68	72

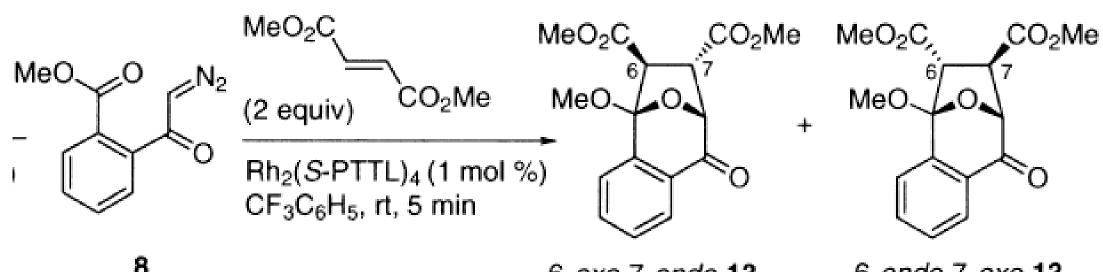
[a]Isolated yield. [b]Determined by HPLC analysis using a Daicel Chiral OD; see ref 13.



R = Bn: Rh_2(*S*-PTPA)$_4$
R = Me: Rh_2(*S*-PTA)$_4$
R = Pr^i: Rh_2(*S*-PTV)$_4$
R = Bu^t: Rh_2(*S*-PTTL)$_4$



Rh_2(*S*-BPTPA)$_4$
Rh_2(*S*-BPTA)$_4$
Rh_2(*S*-BPTV)$_4$
Rh_2(*S*-BPTTL)$_4$

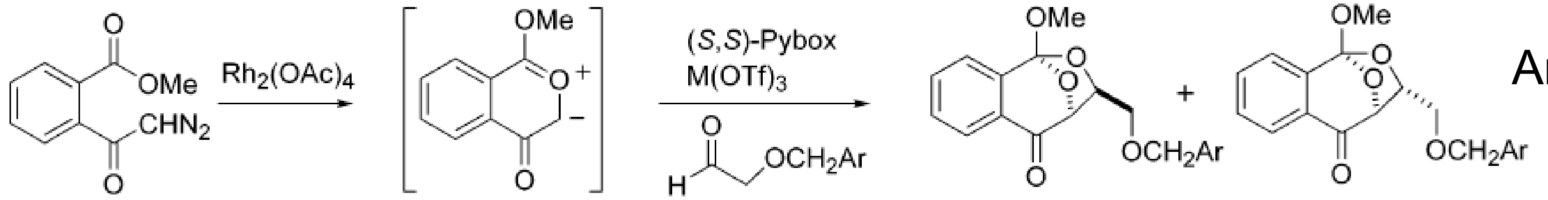


6-*exo*-7-*endo*-**13**
31%, 77% ee

6-*endo*-7-*exo*-**13**
29%, 4% ee

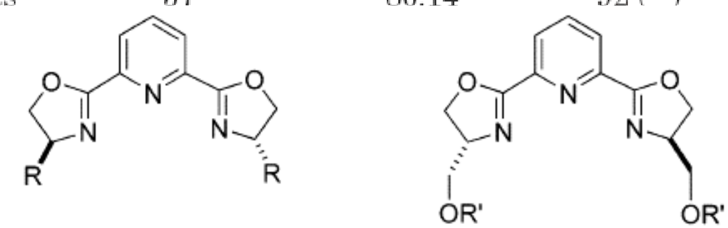
Kitagaki, S.; *et al.*, *Tet. Lett.*, **2000**, *41*, 5931-5935.

Asymmetric Induction via a Chiral Lewis Acid



Ar = Ph

entry	Pybox	$M(OTf)_3$	conditions[b]	MS 4A	yield (%)	*endo*:*exo*	% ee[c] *endo* ( )[d]	% ee[c] *exo* ( )[d]
1	TBSm	$Yb(OTf)_3$	rt, 2 h	no	86	6:94	8 (+)	11 (+)
2	*i*-Pr	$Yb(OTf)_3$	rt, 2 h	no	93	9:91	40 (−)	40 (−)
3	*i*-Pr	$Yb(OTf)_3$	rt, 2 h	yes	92	9:91	35 (−)	36 (−)
4	Ph	$Yb(OTf)_3$	rt, 2 h	yes	quant	14:86	38 (+)	7 (−)
5	hm	$Sc(OTf)_3$	rt, 2 h	no	81	5:95	32 (+)	10 (+)
6	TBSm	$Sc(OTf)_3$	rt, 2 h	no	98	29:71	75 (+)	18 (+)
7	TBSm	$Sc(OTf)_3$	rt, 2 h	yes	50	57:43	77 (+)	9 (+)
8	*i*-Pr	$Sc(OTf)_3$	rt, 1 h	no	85	5:95	1	0
9	*i*-Pr	$Sc(OTf)_3$	rt, 2 h	no	91	55:45	85 (−)	16 (−)
10	*i*-Pr	$Sc(OTf)_3$	rt, 6 h	no	94	76:24	86 (−)	34 (−)
11	*i*-Pr	$Sc(OTf)_3$	reflux, 2 h	no	87	77:23	88 (−)	16 (−)
12	*i*-Pr	$Sc(OTf)_3$	rt, 2 h	yes	96	88:12	91 (−)	18 (−)
13[e]	*i*-Pr	$Sc(OTf)_3$	rt, 2 h	yes	93	85:15	87 (−)	15 (−)
14	Ph	$Sc(OTf)_3$	rt, 2 h	yes	57	86:14	92 (−)	14 (−)

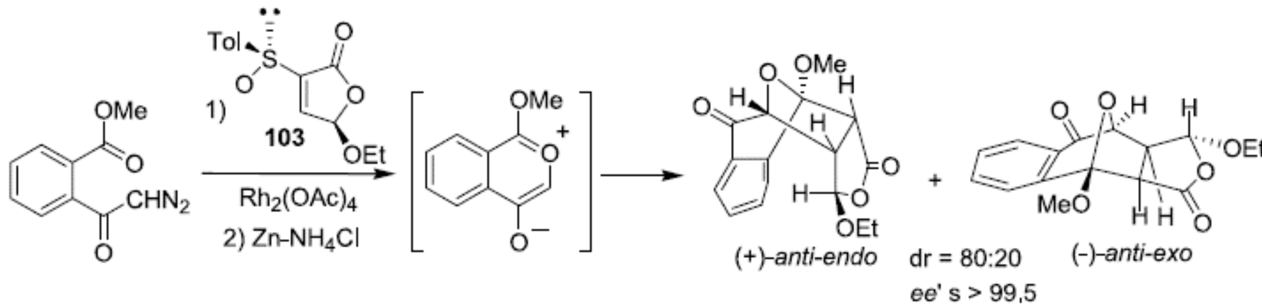


R = *i*-Pr: (*S*,*S*)-Pybox-*i*-Pr
R = Ph: (*S*,*S*)-Pybox-Ph

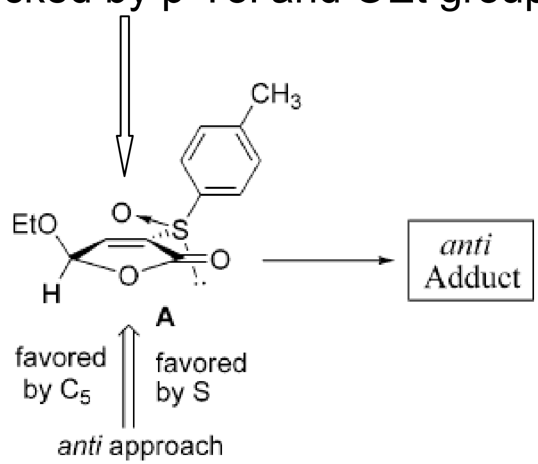
R' = H: (*S*,*S*)-Pybox-hm
R' = $SiBu^tMe_2$: (*S*,*S*)-Pybox-TBSm
R' = $SiBu^tPh_2$: (*S*,*S*)-Pybox-TBDPSm
R' = $SiPh_3$: (*S*,*S*)-Pybox-TPSm

Suga, H.; *et al.*, *J. Org. Chem.*, **2005**, *70*, 47-56.

Asymmetric Induction via Chiral Dipolarophile

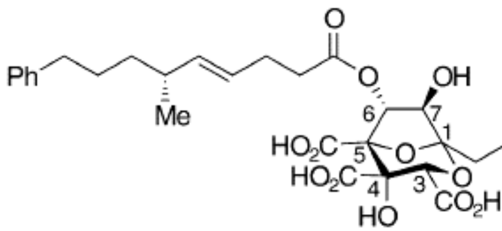


Top face blocked by p-Tol and OEt groups

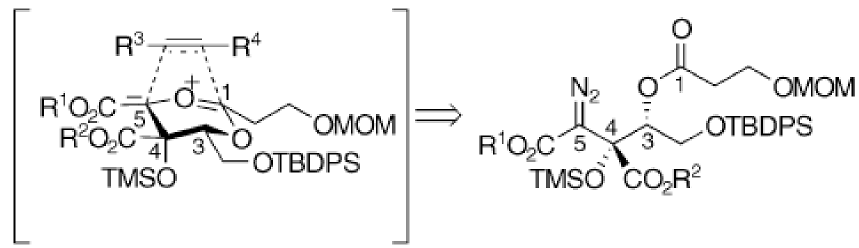


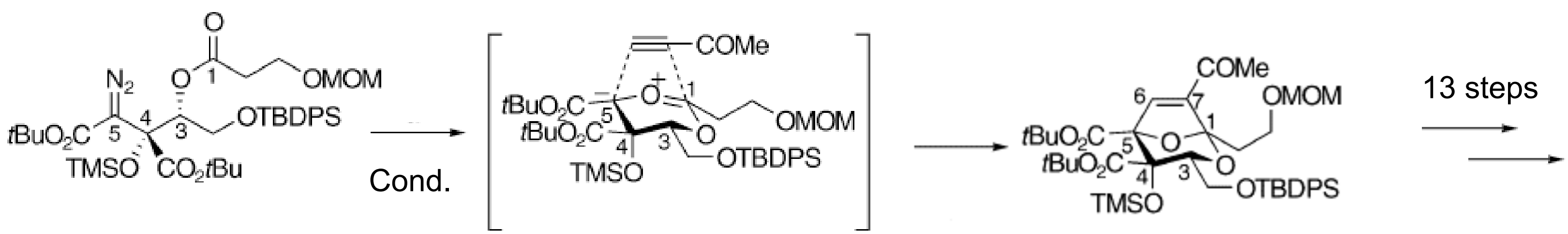
Ruano, J. L. G.; *et al.*, *J. Org. Chem.*, **2006**, *71*, 6536-6541.

Applications to Total Synthesis – Zaragozic Acid C



zaragozic acid C





Conditions: $Rh_2(OAc)_4$ (5 mol%), HC≡CC(O)Me (3 equiv), benzene, reflux, 1 h, 72%

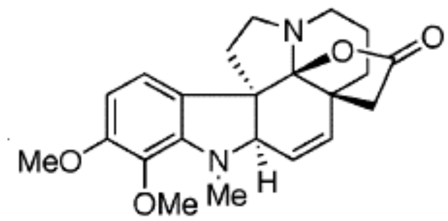
Overall synthesis: 30 steps, 3.7%

Carbonyl Ylide Cycloaddition:

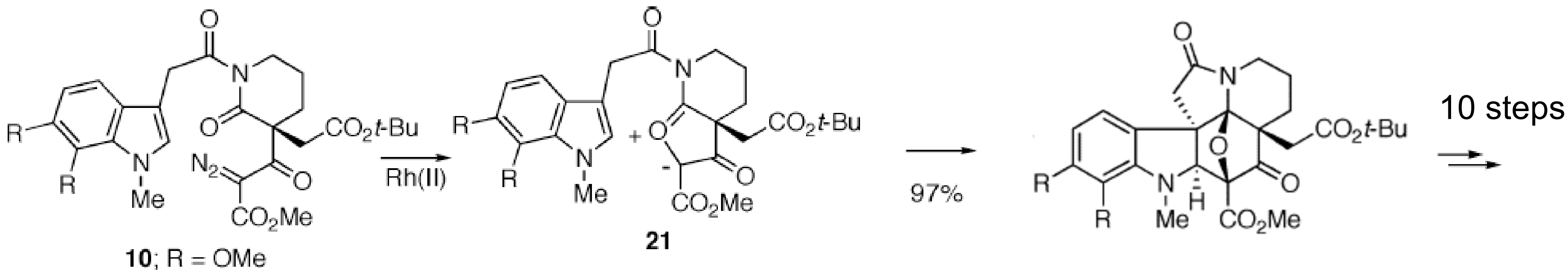
- generates the bicyclic core
- allows for possible mid stage modifications

Nakamura, S.; *et al.*, *Angew. Chem. Int. Ed.*, **2003**, *42*, 5351-5355.

Applications to Total Synthesis – (±)-Aspidophytine



(±)-Aspidophytine



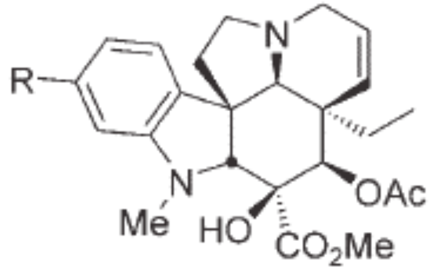
21 steps, 6.5% overall yield

Cabonyl Ylide Cycloaddition:

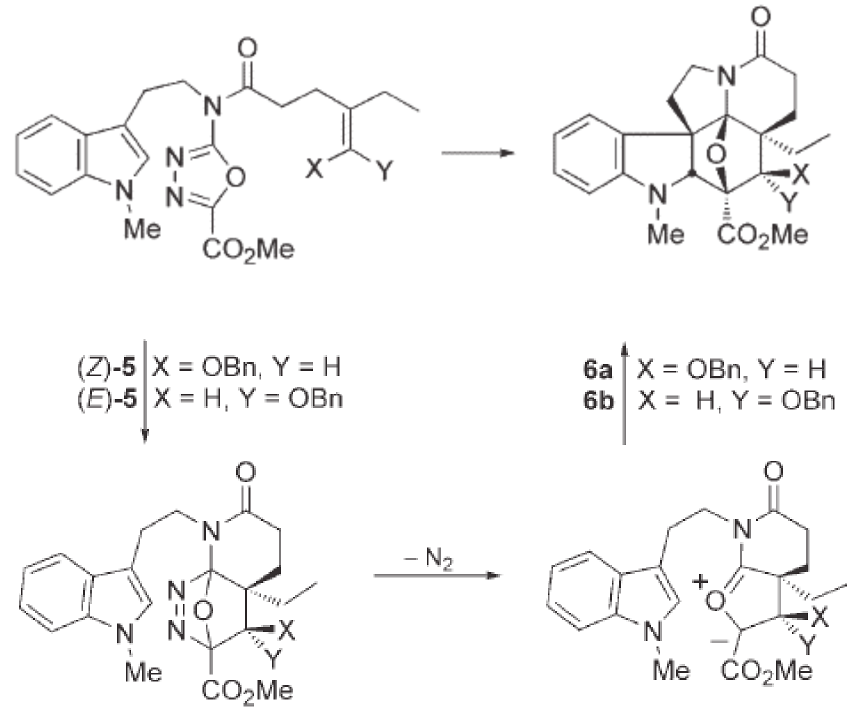
- Forms 2 new rings
- Forms 4 contiguous stereocenters (racemicly)

Mejia-Oneto, J. M.; Padwa, A., *Org. Lett.*, **2006**, *8(15)*, 3275-3278.

Applications to Total Synthesis – Vindorosine



R = H: vindorosine (**1**)



Carbonyl ylide precursor is formed in 4 steps from tryptophan

Four new rings are formed, incorporating six contiguous stereocenters

Conditions: Triisopropylbenzene 230 ^oC, 132 h 0.1 mM, 78% yield

Elliott, G. I.; *et al.*, *Angew. Chem. Int. Ed.*, **2006**, *45*, 620-622.

Conclusions and Outlook

- Dipolar carbonyl ylide cycloadditions provide a unique route to highly functionalized di- and tetrahydrofurans

- Rhodium catalyzed reactions of diazoketones with carbonyl moieties is the most widely utilized method for formation of carbonyl ylides

- Systems for generating enatioenriched tetrahydrofurans have been developed

- More studies on the role of rhodium and the interaction of ligands with the substrate are needed in order to develop more highly enantioselective and general reactions

Further Reading

Padwa, A.; Pearson, W. H., Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, Wiley and Sons, 2003

Muthusamy, S.; Krishnamurthi, J., Heterocycles by Cycloadditions of Carbonyl Ylides Generated from Diazo Ketones, Springer-Verlag Berlin, 2008

Ref., *J. Am. Chem. Soc.*, **1982**, *104*, 4953-4954.