Alkene Ozonolysis: Various Transformation of Ozonide

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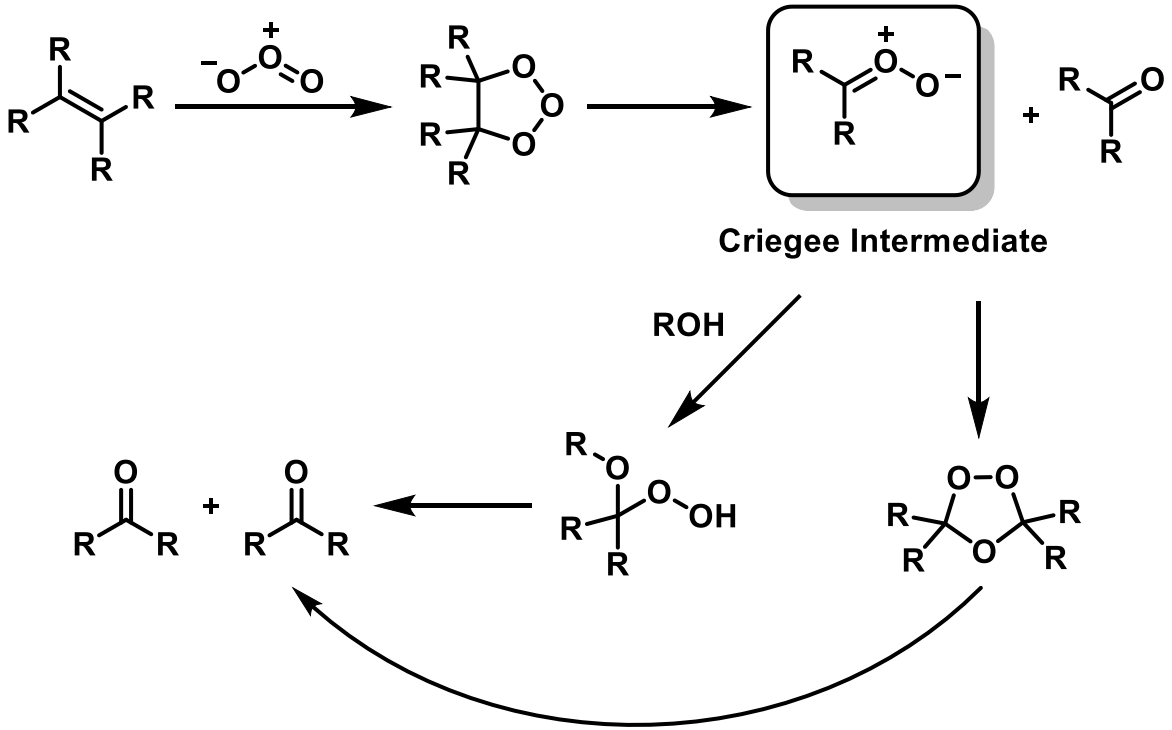
Outline

- **Introduction & Earlier Capture Reactions**
- **Criegee Intermediates: Generation & Transformation**
- **Transformation of Secondary Ozonides**
- **Photoexcited Nitroarenes**
- **Summary**

Introduction

- Ozone: a very electrophilic 1,3-dipole
- Alkene: More reactive than alkyne or C-H
- General & Selective method of cleaving double bonds
- **A Reservoir of High Oxidation State**



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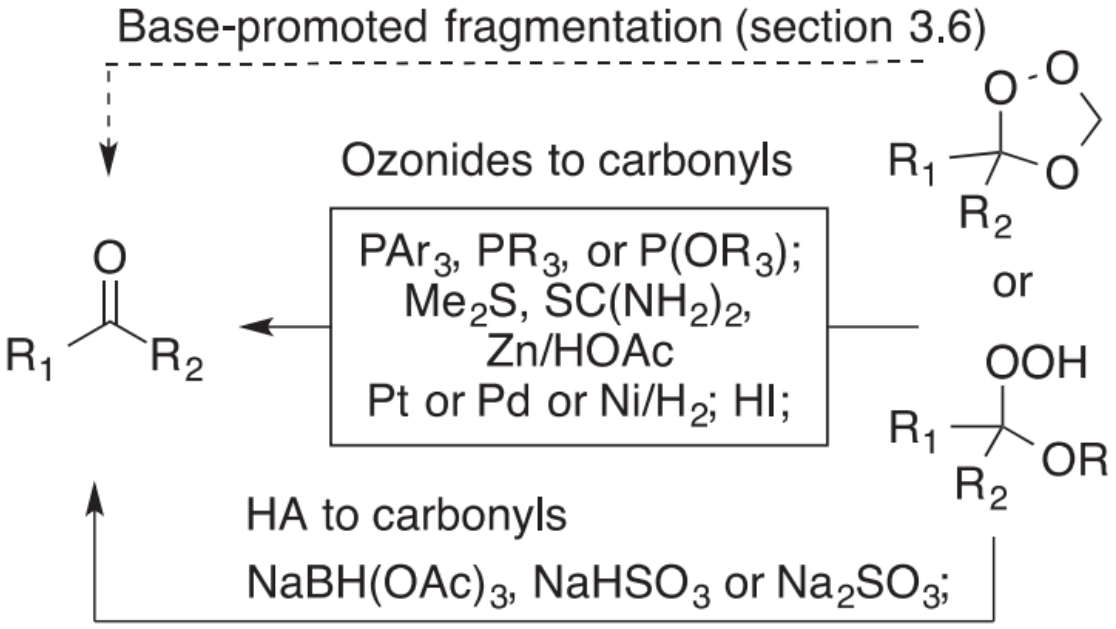
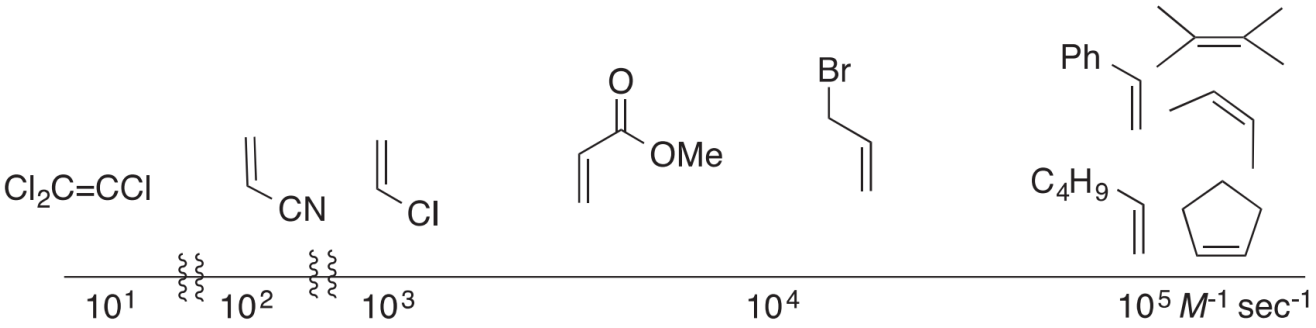
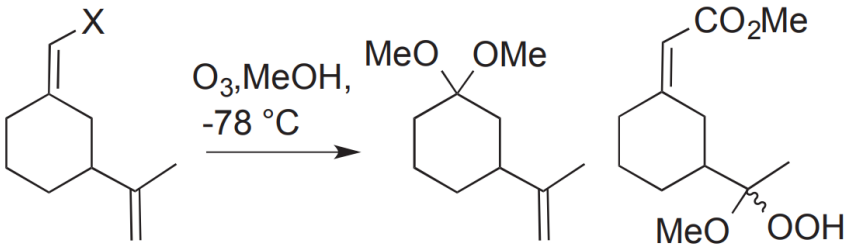
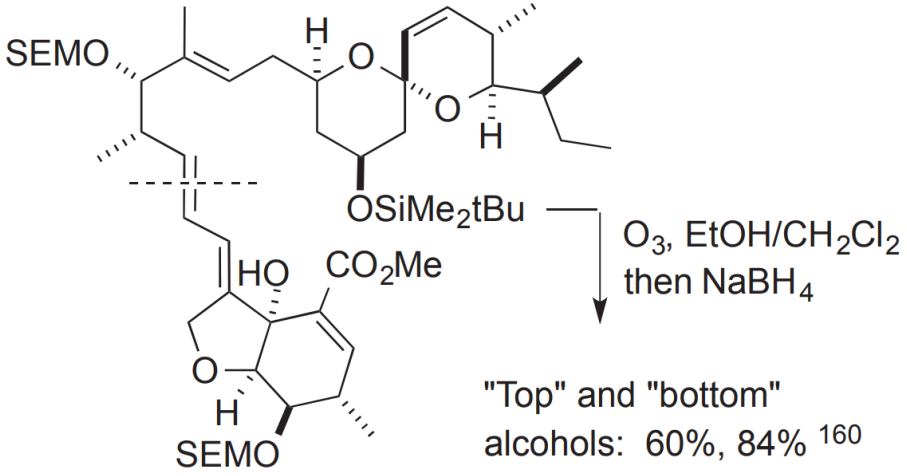


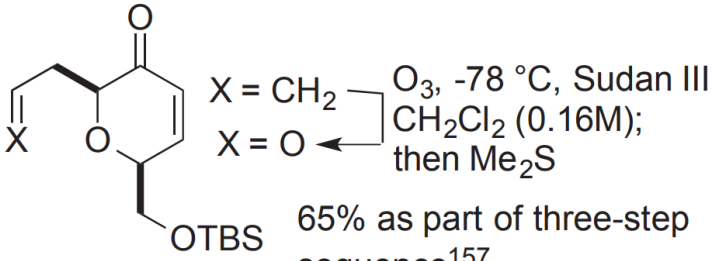
Fisher, T. et al. *Tetrahedron* **2017**, *73*, 4233.

Regioselectivity about Alkenes



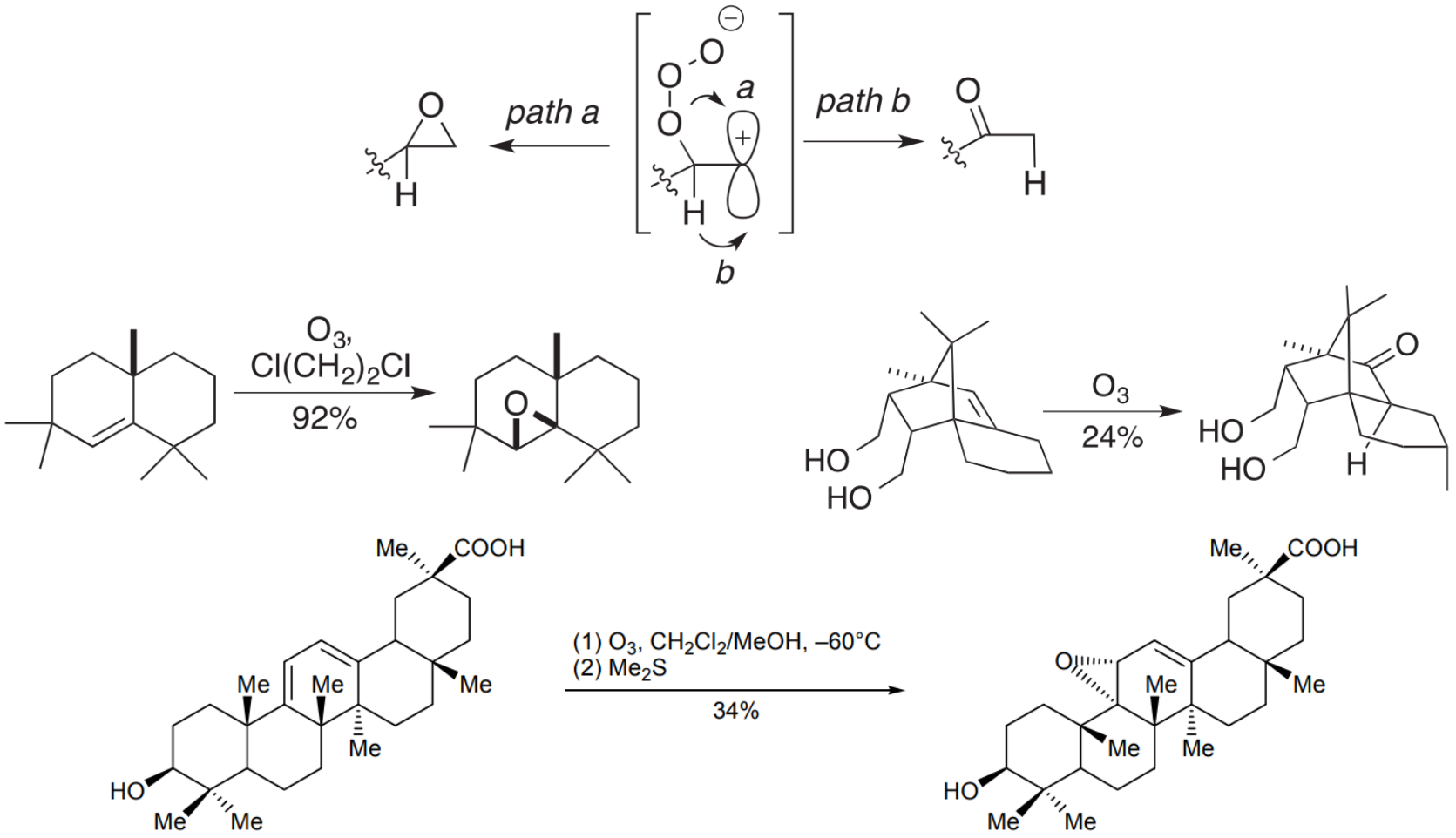






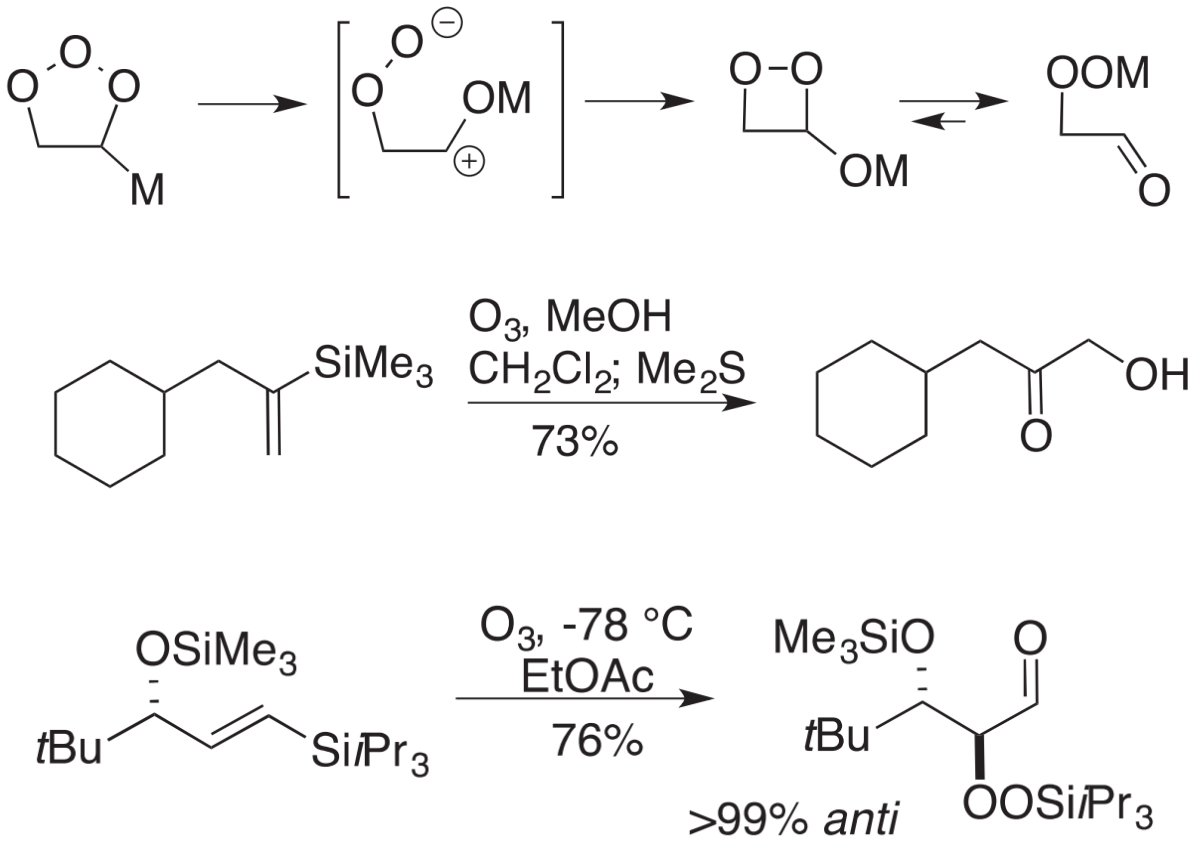
Tokuyasu, T. et al. *Tetrahedron* **2001**, *57*, 5979; Ghosh, A. et al. *Org. Lett*. **2011**, *13*, 66; White, J. et al. *J. Am. Chem. Soc.* **1995**, *117*, 1908.

Alkenes with Large Steric Hindrance



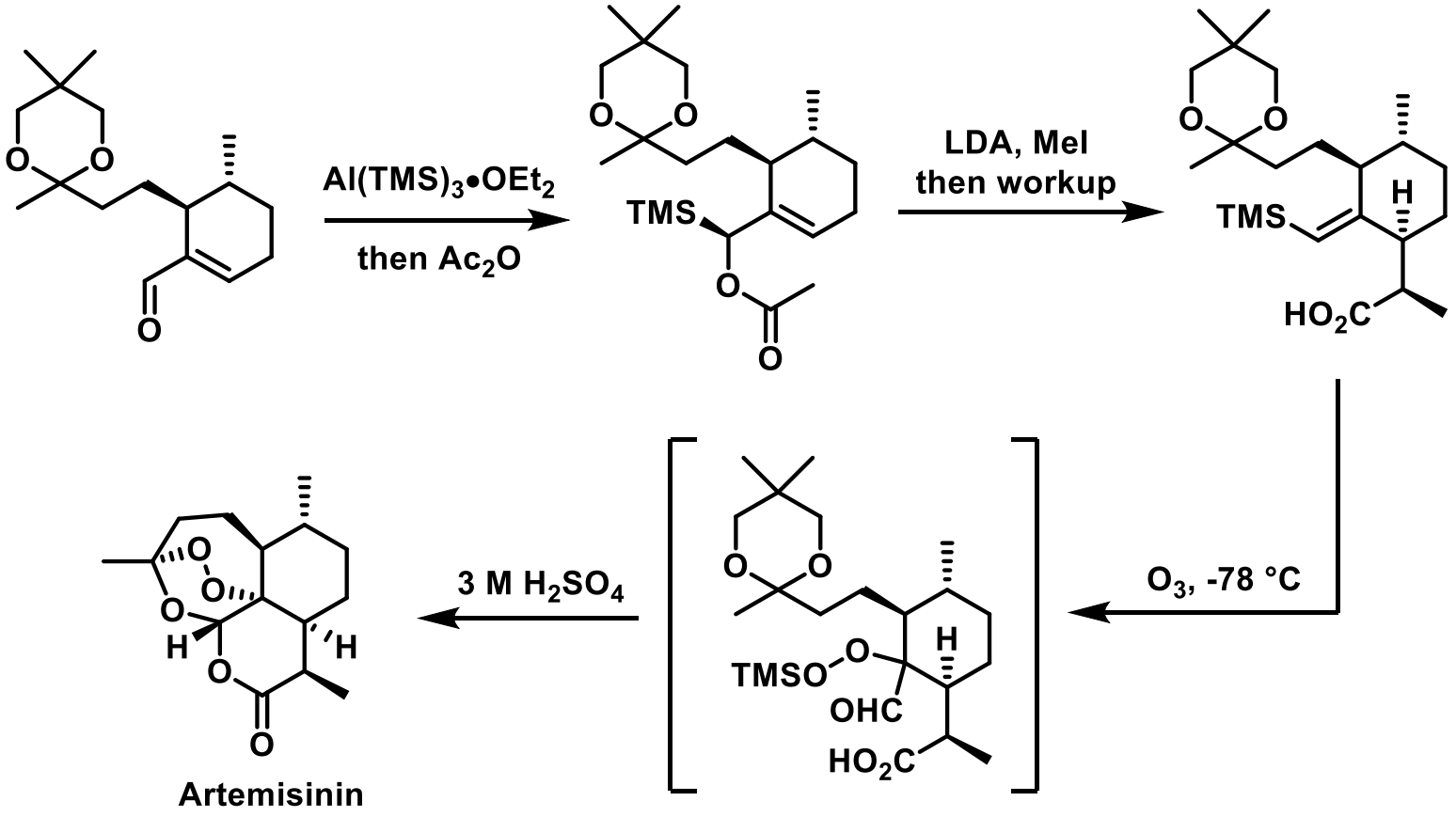
Budaev, A. et al. *Chem. Nat. Compd.* **2014**, *50*, 302; Hochstetler, A. *J. Org. Chem.* **1975**, *40*, 1536; Kondolff, I. et al. *Tetrahedron* **2007**, *63*, 9100.

Interrupted at Primary Ozonide



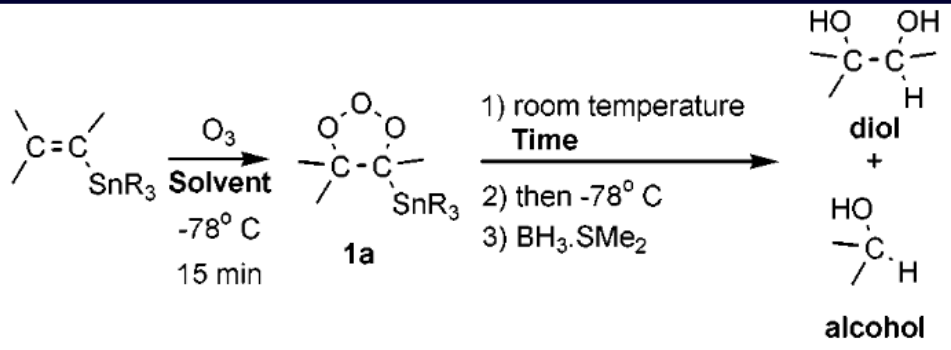
Avery, M. et al. *J. Am. Chem. Soc.* **1992**, *114*, 974; Murakami, M. et al. *Org. Lett.* **2006**, *8*, 4023.

Synthesis of Artemisinin

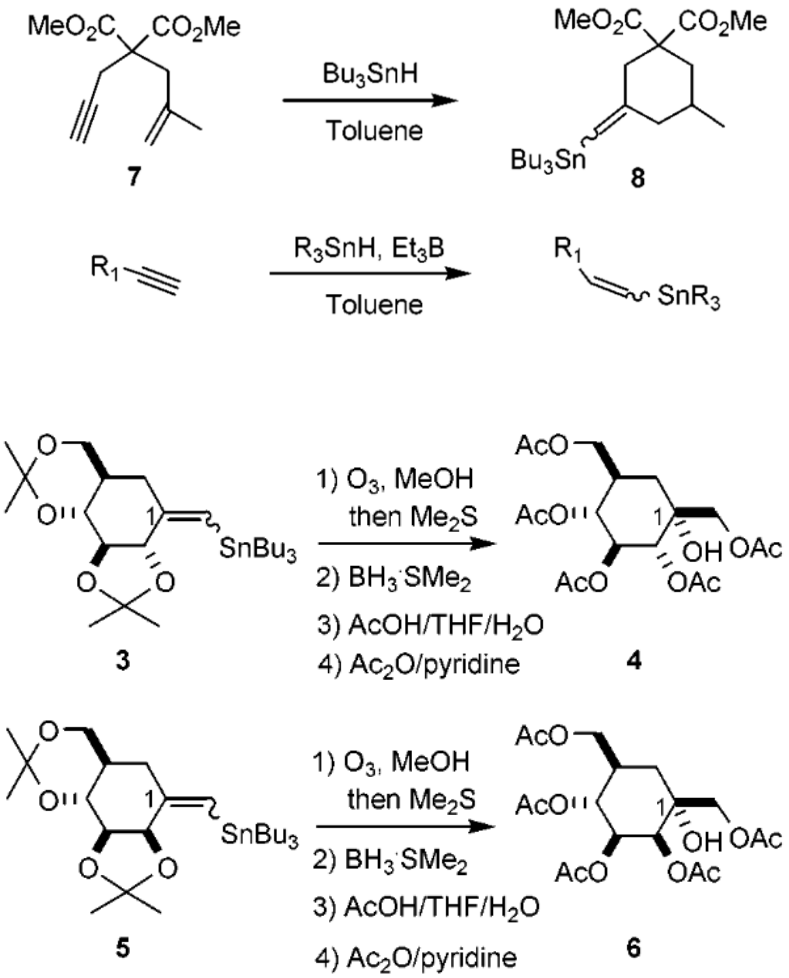


Avery, M. et al. *J. Am. Chem. Soc.* **1992**, *114*, 974.

Unusual Stable Primary Ozonide: Tin

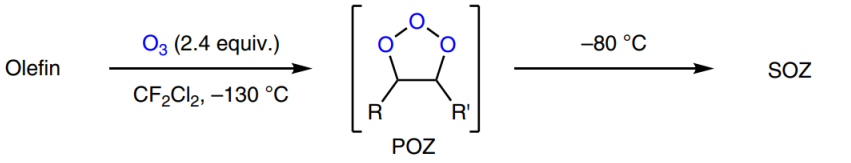


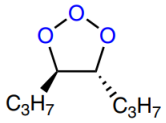
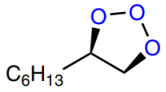
entry	substrate	solvent	time (h)	ratio diol:alcohol	yield (%)
i	**8**	MeOH	0[a]	1:0	67
ii	**8**	MeOH	0.5	1:2	62
iii	**8**	MeOH	2	1:8	63
iv	**8**	MeOH	4	0:1	65
v	**8**	EtOAc	0[a]	1:0	59
vi	**8**	EtOAc	2	1:1	63
vii	**8**	CH_2Cl_2	0[a]	1:0	65
viii	**8**	CH_2Cl_2	2	1:2	61
ix	**10a**	MeOH	0[a]	5:1	71
x	**10a**	MeOH	2	1:3	68
xi	**10a**	EtOAc	0[a]	2:1	69
xii	**10a**	EtOAc	2	1:5	66
xiii	**10a**	CH_2Cl_2	0[a]	4:1	62
xiv	**10a**	CH_2Cl_2	2	1:7	58
xv	**10a**	toluene	0[a]	1:1.5	59

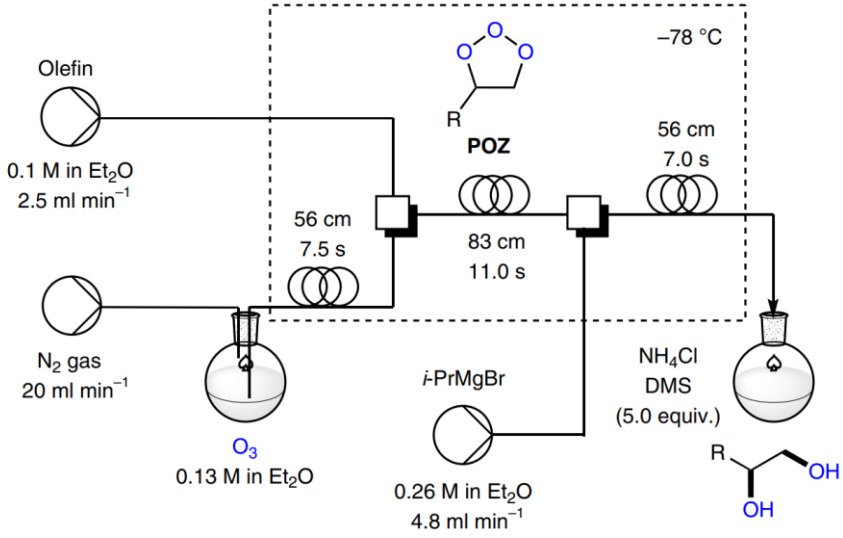


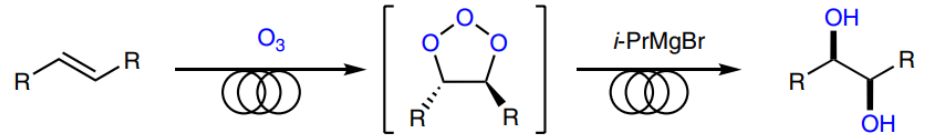
Go´mez, A. et al. *Org. Lett.* **2002**, *4*, 383.

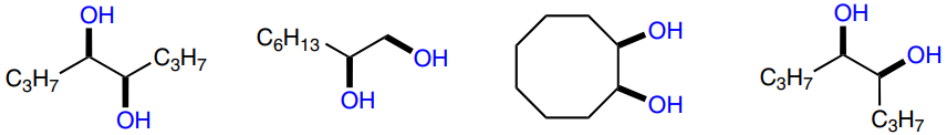
Capture of POZ: Continuous Flow



Entry	Structure	$k_{obs} \times 10^{-3}$ (s^{-1})	k_{rel}	$t_{1/2}$ (min)
POZ 1		1.68 ± 0.02	1.0	6.8 ± 0.2
POZ 2		2.49 ± 0.05	1.48	4.6 ± 0.1







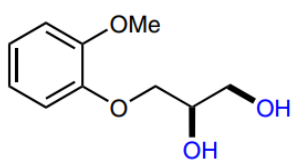
8
69%
Flow 1.5 g h^{-1}

17
68%
Flow 1.4 g h^{-1}

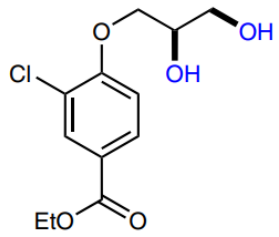
9
63%
Flow 1.3 g h^{-1}

10[a]
19%
Flow 0.4 g h^{-1}

Pharmaceuticals



1 Guiafenisin (Mucinex)
65%
Flow 1.5 g h^{-1}



2 Ponesimod precursor
51%
Flow 1.7 g h^{-1}

Arriaga, D. et al. *Nat. Chem.* **2023**, *15*, 1262.

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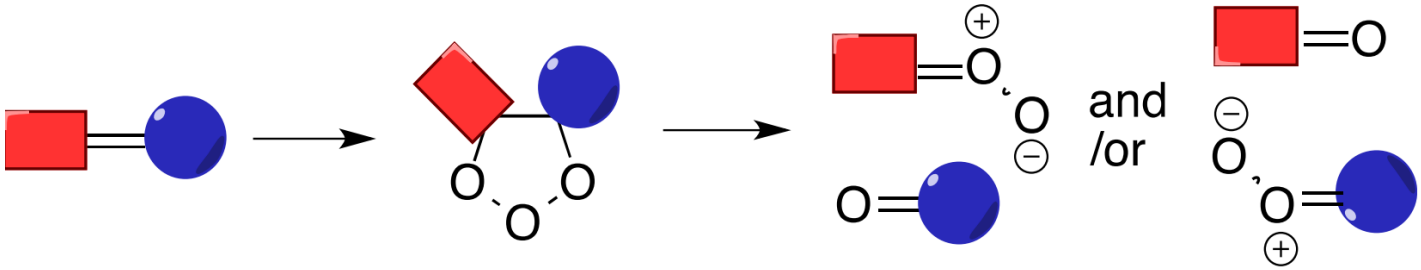
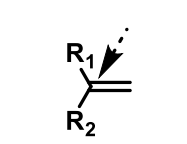
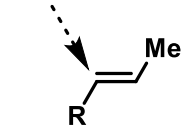
Generated from POZ: Selectivity?

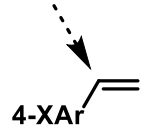




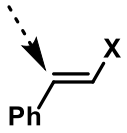
R_1	R_2	
Me	H	62%
Me	Ph	93%
Ph	H	60%
Cy	H	86%



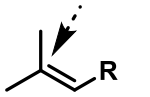
R	
^{t}Bu	88%
^{i}Pr	71%
Ph	82%



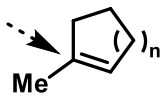
X	
H	60%
Me	71%
OMe	79%
NO_2	14%



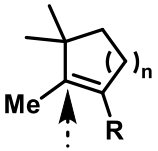
X	
CH_2OH	74%
CH_2Cl	83%
CO_2Me	77%
COMe	10%



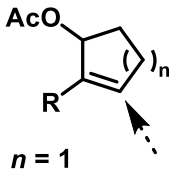
R	
Me	77%
Ph	95%



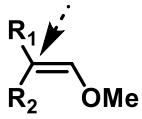
n = 1 : 95%
n = 2 : 100%



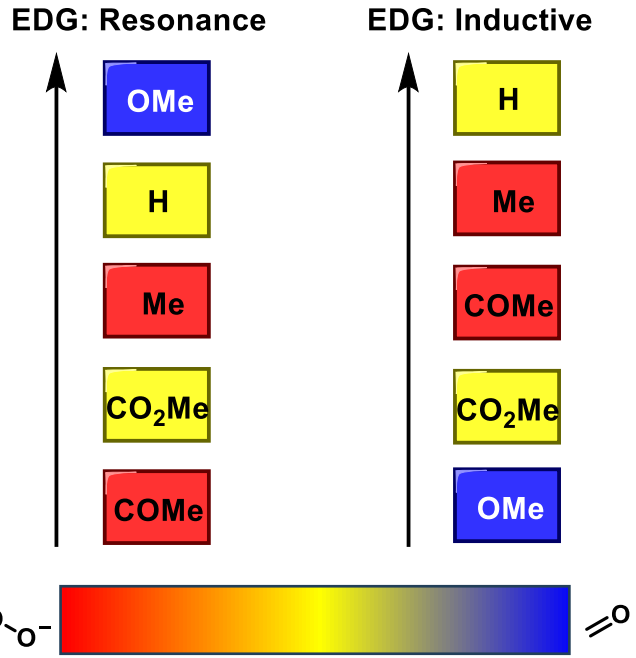
n = 1
R = H: 95%
n = 2
R = H: 100%
R = Me: 0%



n = 1
R = H: 98%
R = Me: 81%
n = 2
R = H: 100%
R = Me: 67%



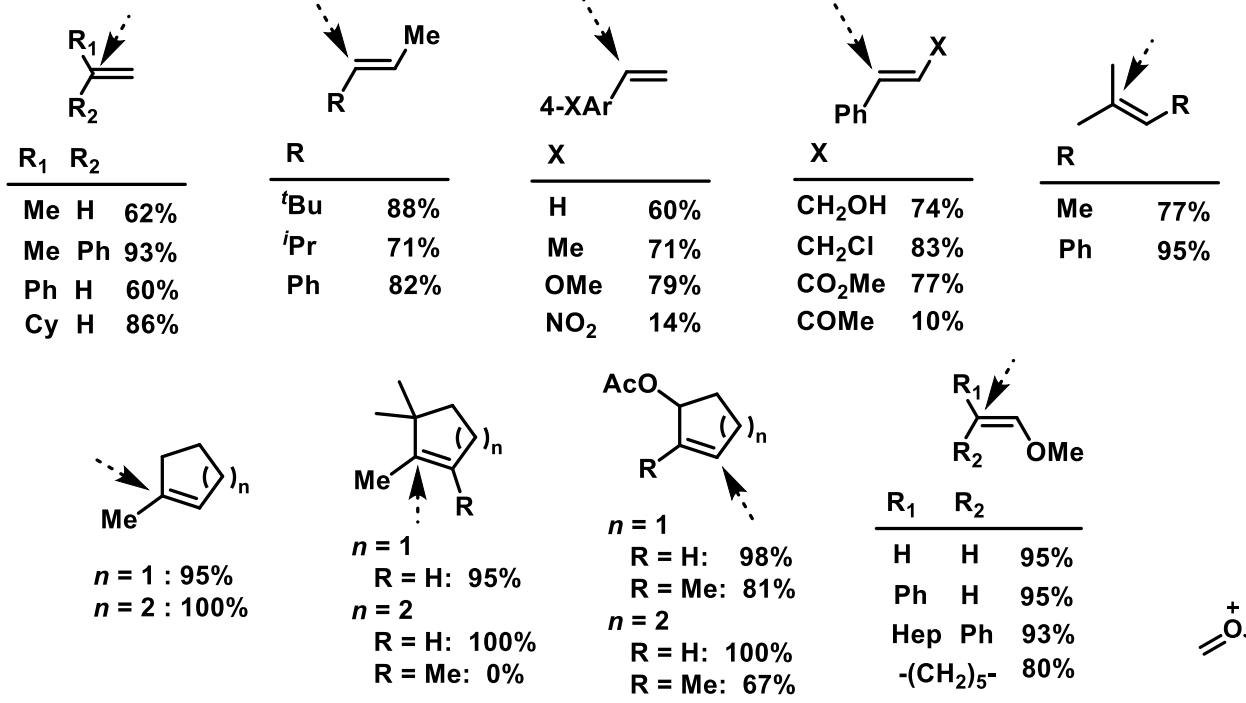
R_1	R_2	
H	H	95%
Ph	H	95%
Hep	Ph	93%
-$(CH_2)_5$-		80%



Fisher, T. et al. *Tetrahedron* **2017**, *73*, 4233.

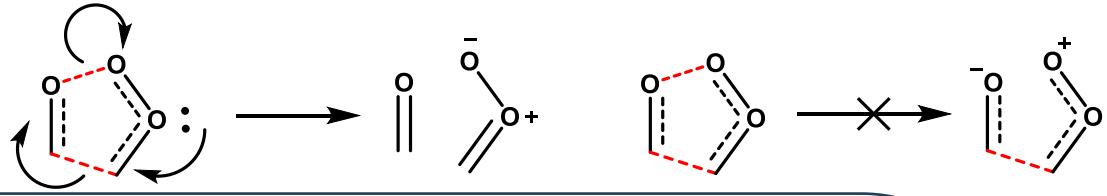
Generated from POZ: Selectivity?

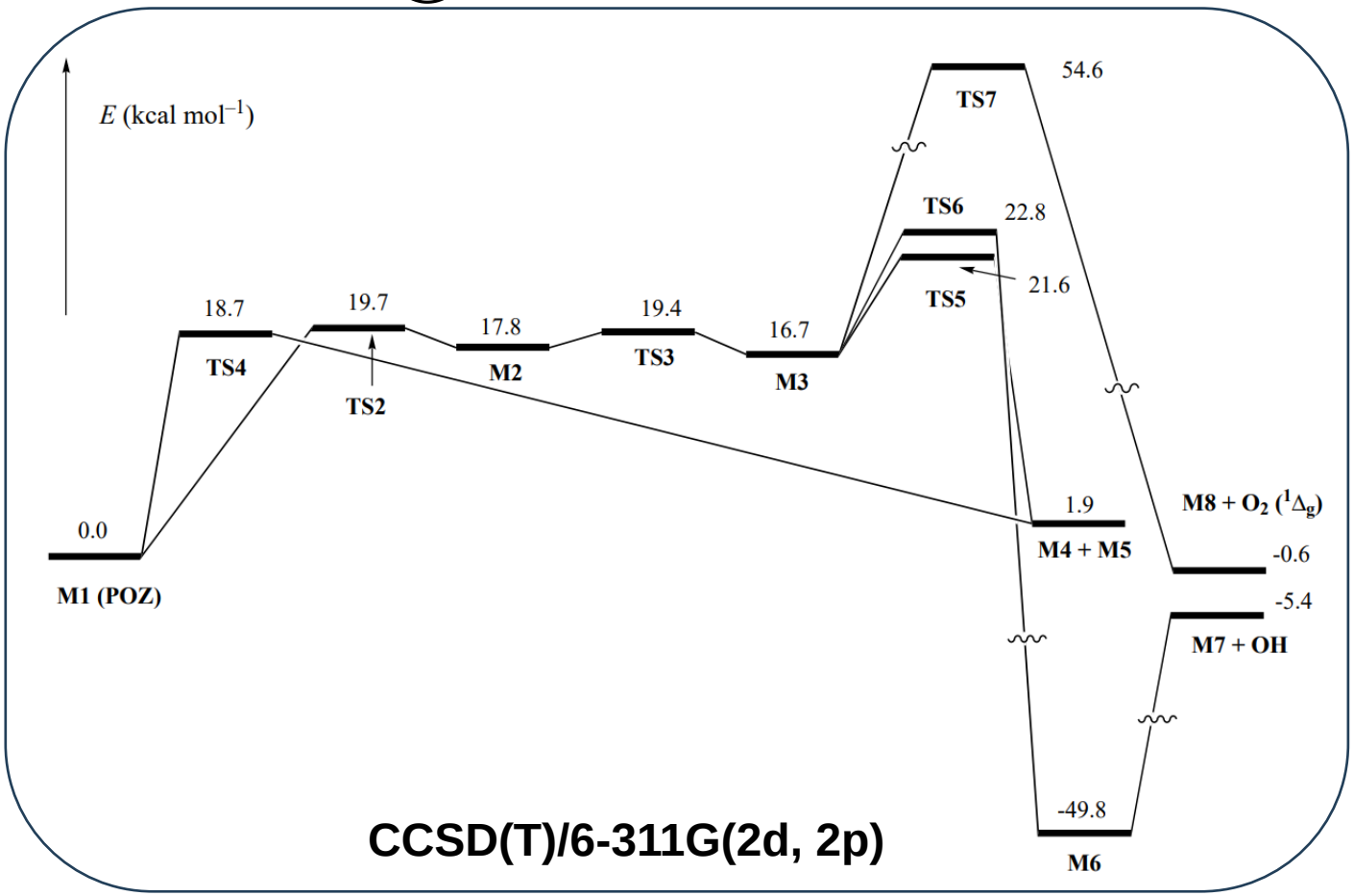
Criegee Tendency:
$COCH_3 > CH_3 > COOH > Ph > H > CH_2OH > CO_2CH_3$

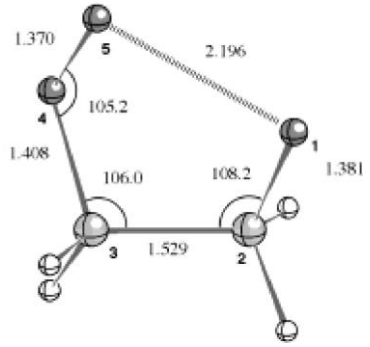


Fisher, T. et al. *Tetrahedron* **2017**, *73*, 4233.

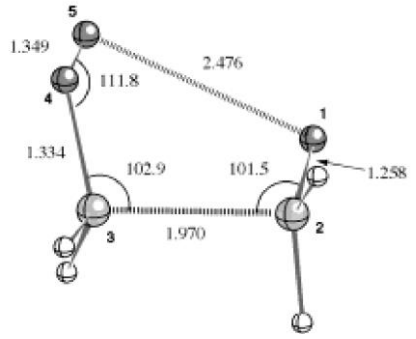
Which Bond Heterolysis First?







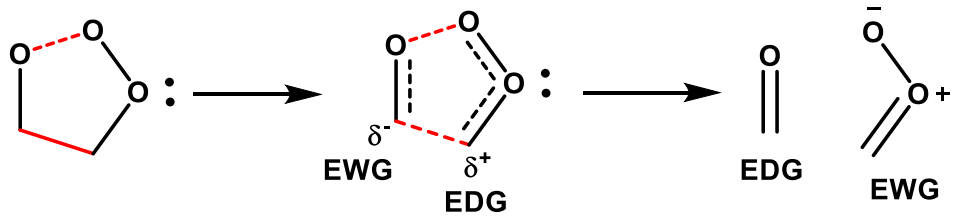
TS2



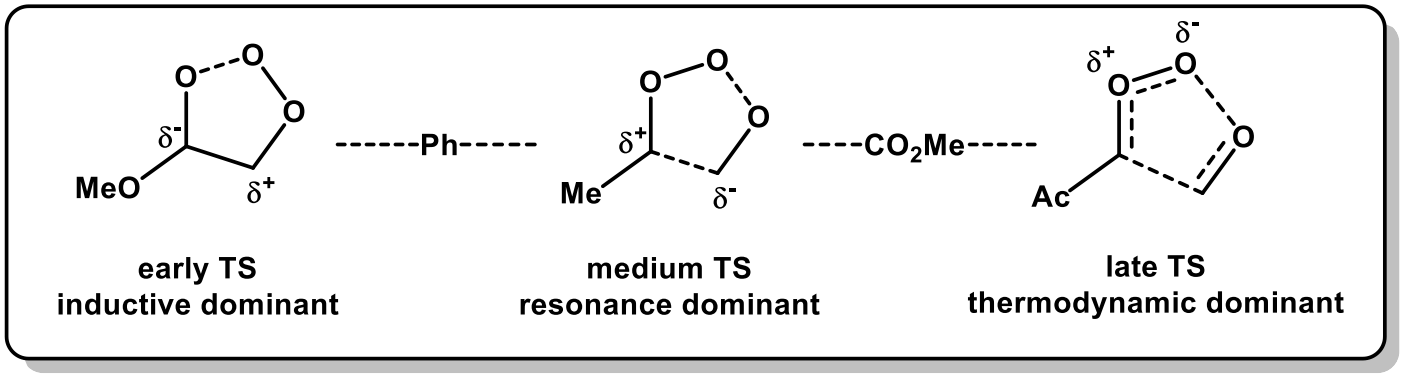
TS4

Anglada, J. et al. *Chem. Eur. J.* **1999**, *5*, 1809.

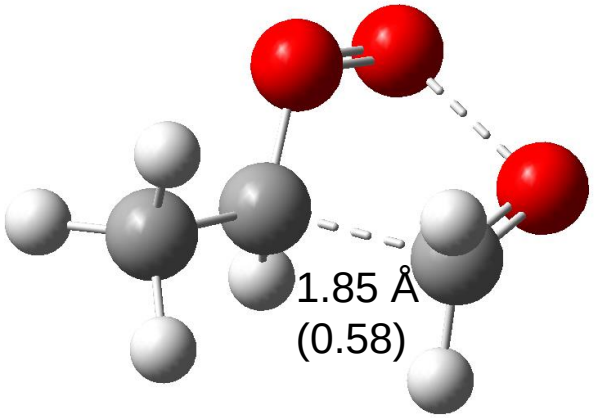
A Proposal: Reaching TS at What Point?

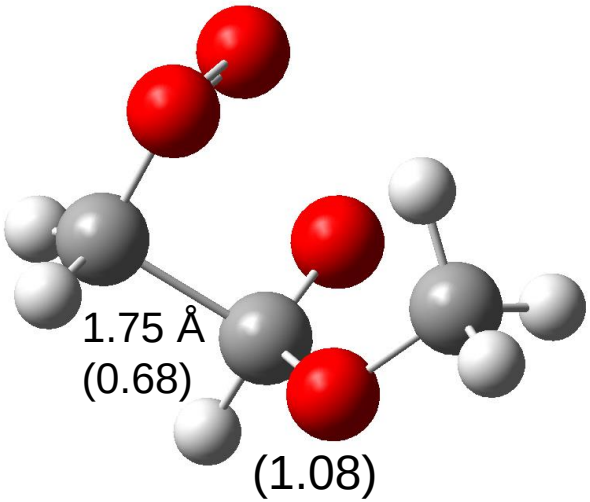


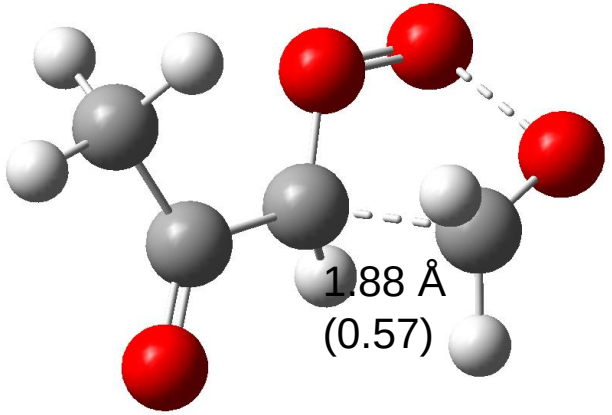
- C-C bond polarization: Criegee to Carbonyl
- Electron-rich degree: Criegee > Carbonyl
- Determining factor: **Early** or **Late** **TS**?
- **EDG**s cause **Negative** **ΔH** & **Early** **TS**



Computation: What is the Critical Point?



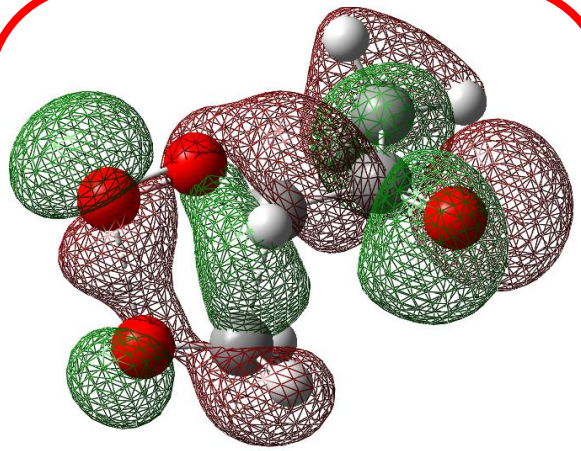




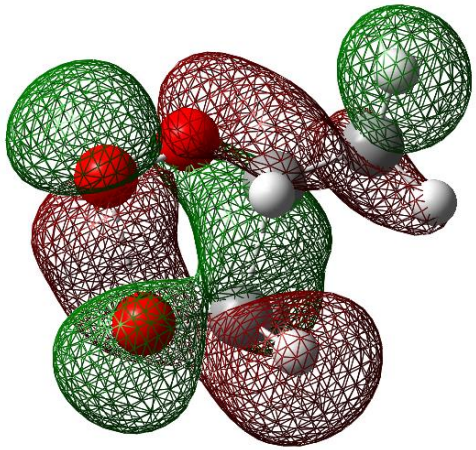
- Me vs Ac: Similar bond length & order in TS
- Only dimension for **Early** or **Late**?
- Orbital Interaction
- **Microscopic Reversibility**

M06-2X(D3)/def2SVP SMD = Methanol

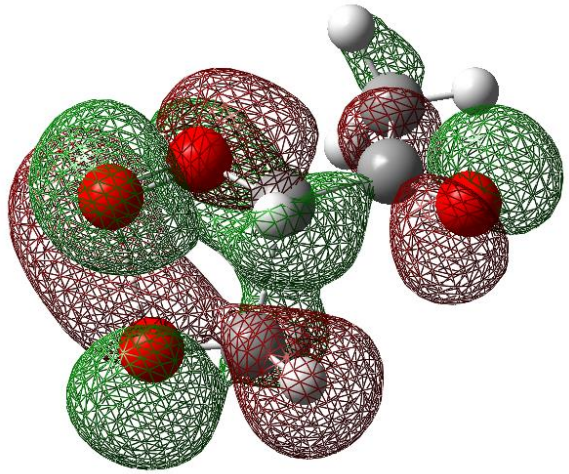
Product-Like Orbital Interaction?



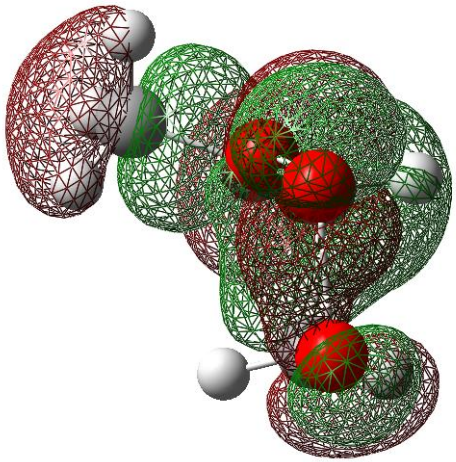
HOMO-1 (Ac)

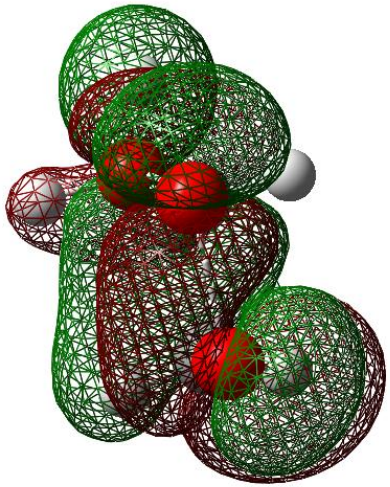


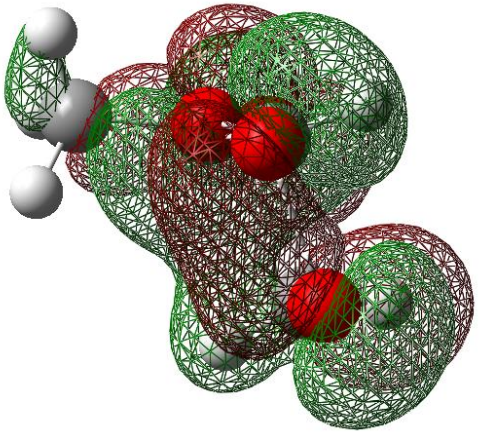
HOMO-1 (Me)



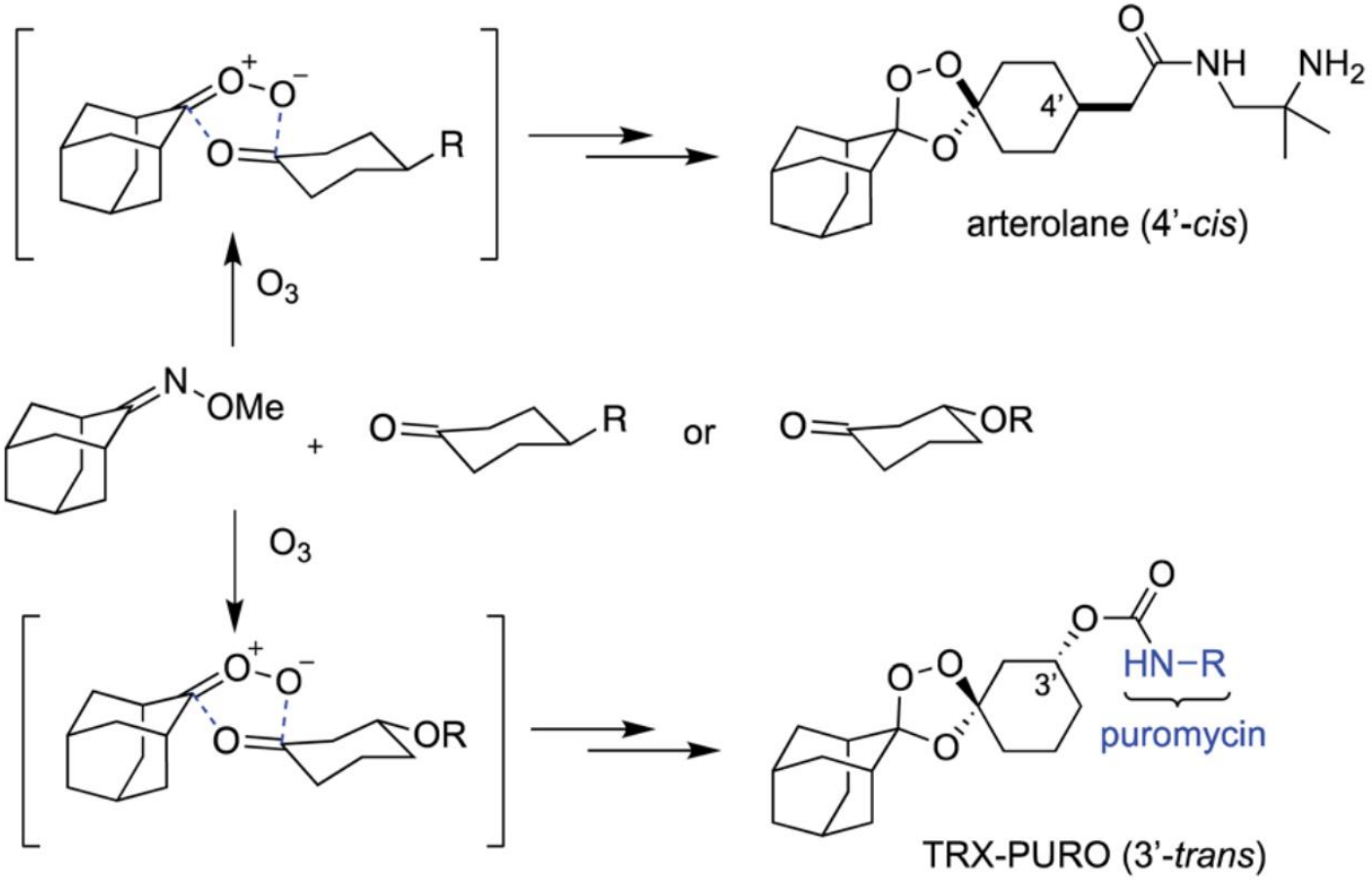
HOMO-2 (Ac)





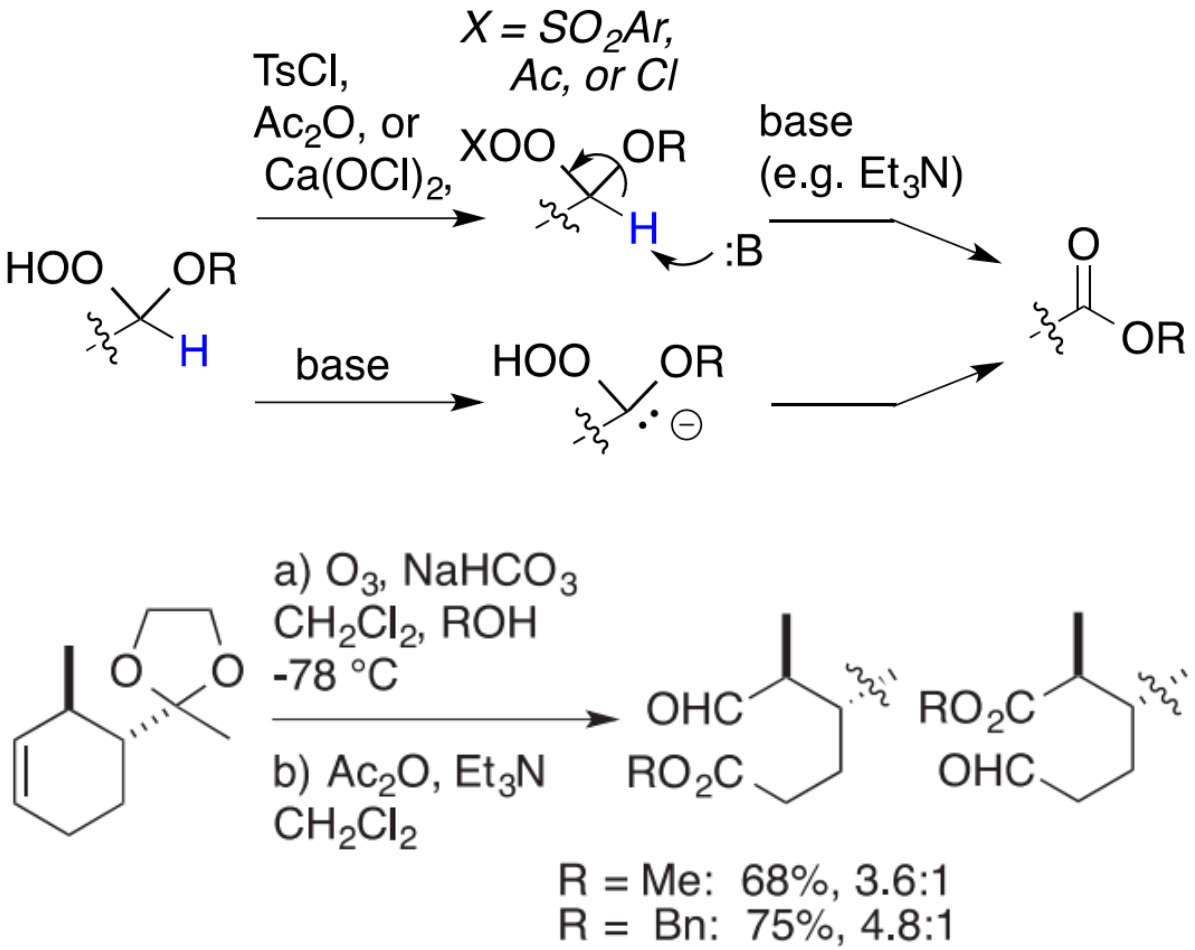


Griesbaum Ozonolysis



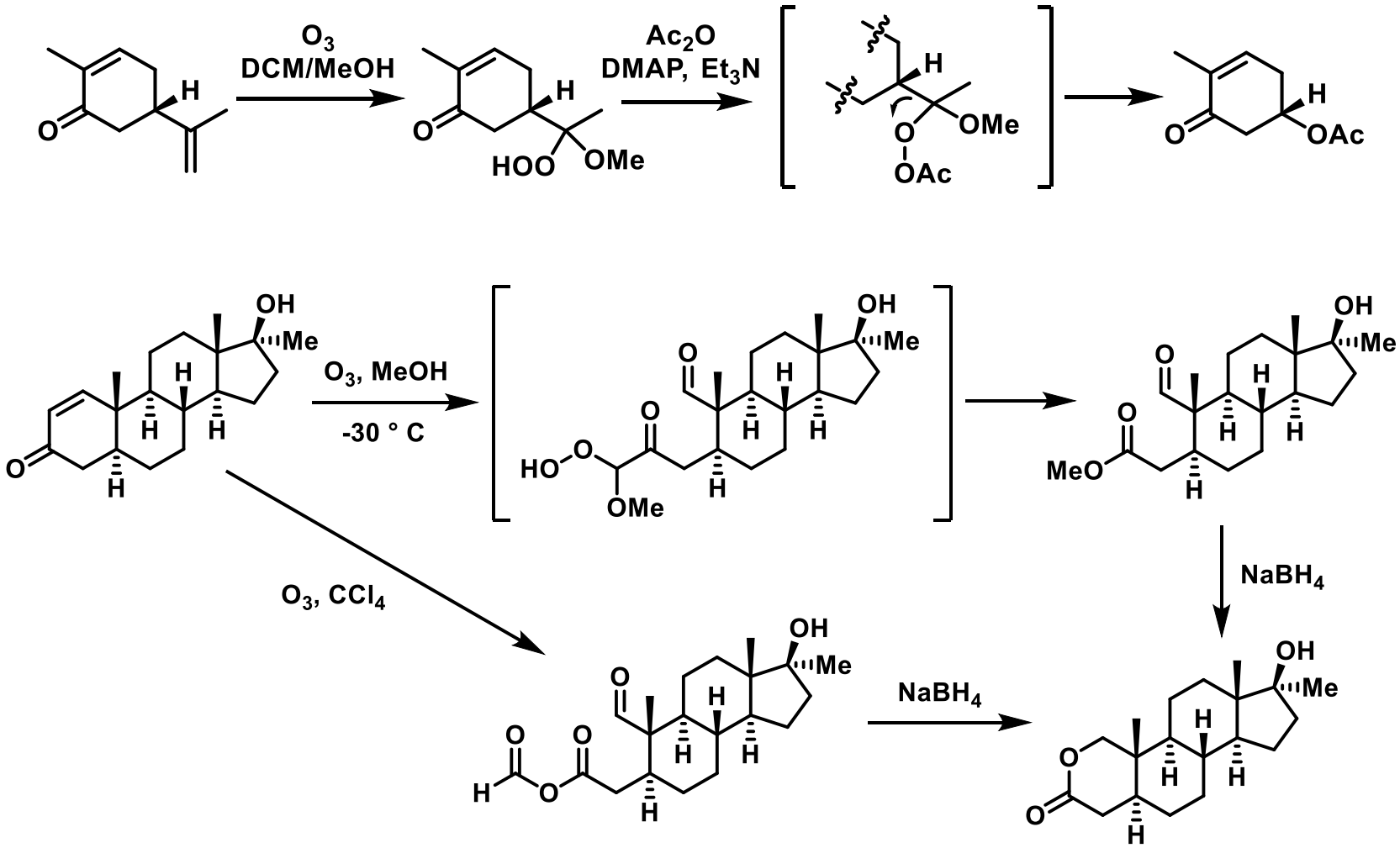
Chen, J. et al. *RSC Adv.* **2021**, *11*, 34338.

Hydroperoxyl Acetal to Ester



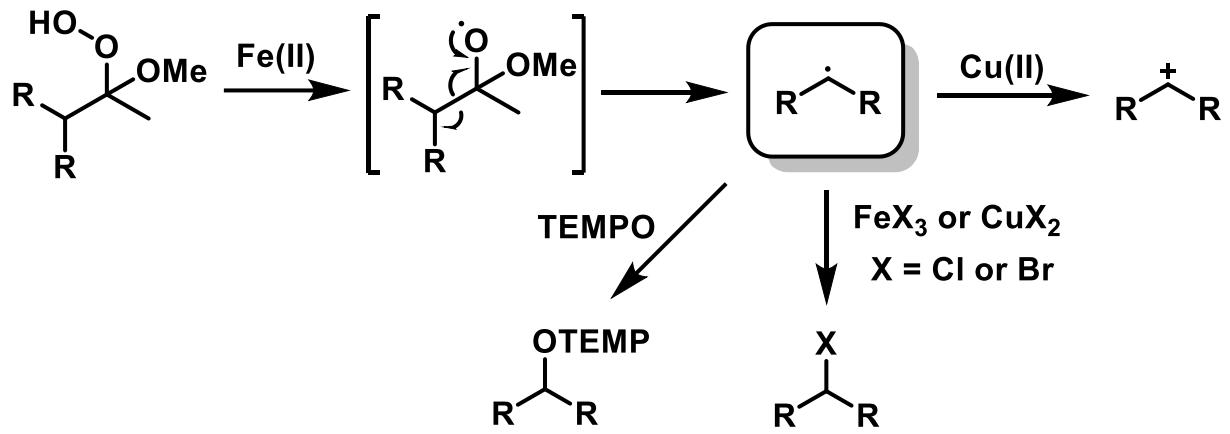
Taber, D. et al. *J. Org. Chem.* **2001**, *66*, 2515.

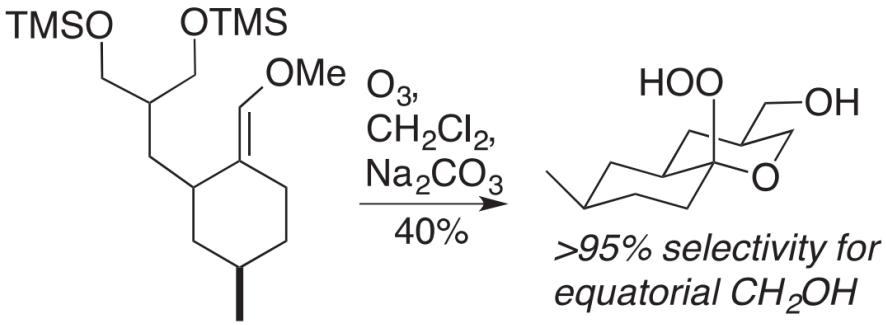
Formal Baeyer-Villiger Oxidation

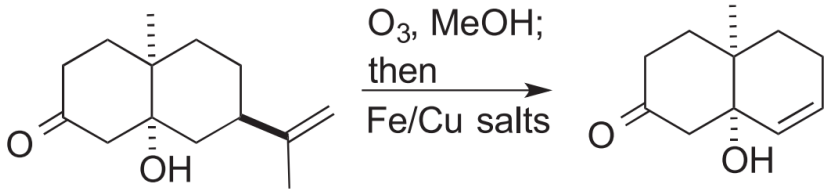


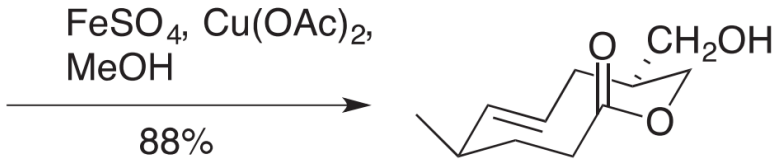
Schreiber, S. et al. *Tetrahedron Lett.* **1983**, *24*, 2363; Bailey, P. *J. Am. Chem. Soc.* **1957**, *79*, 3120.

As Radical Precursor







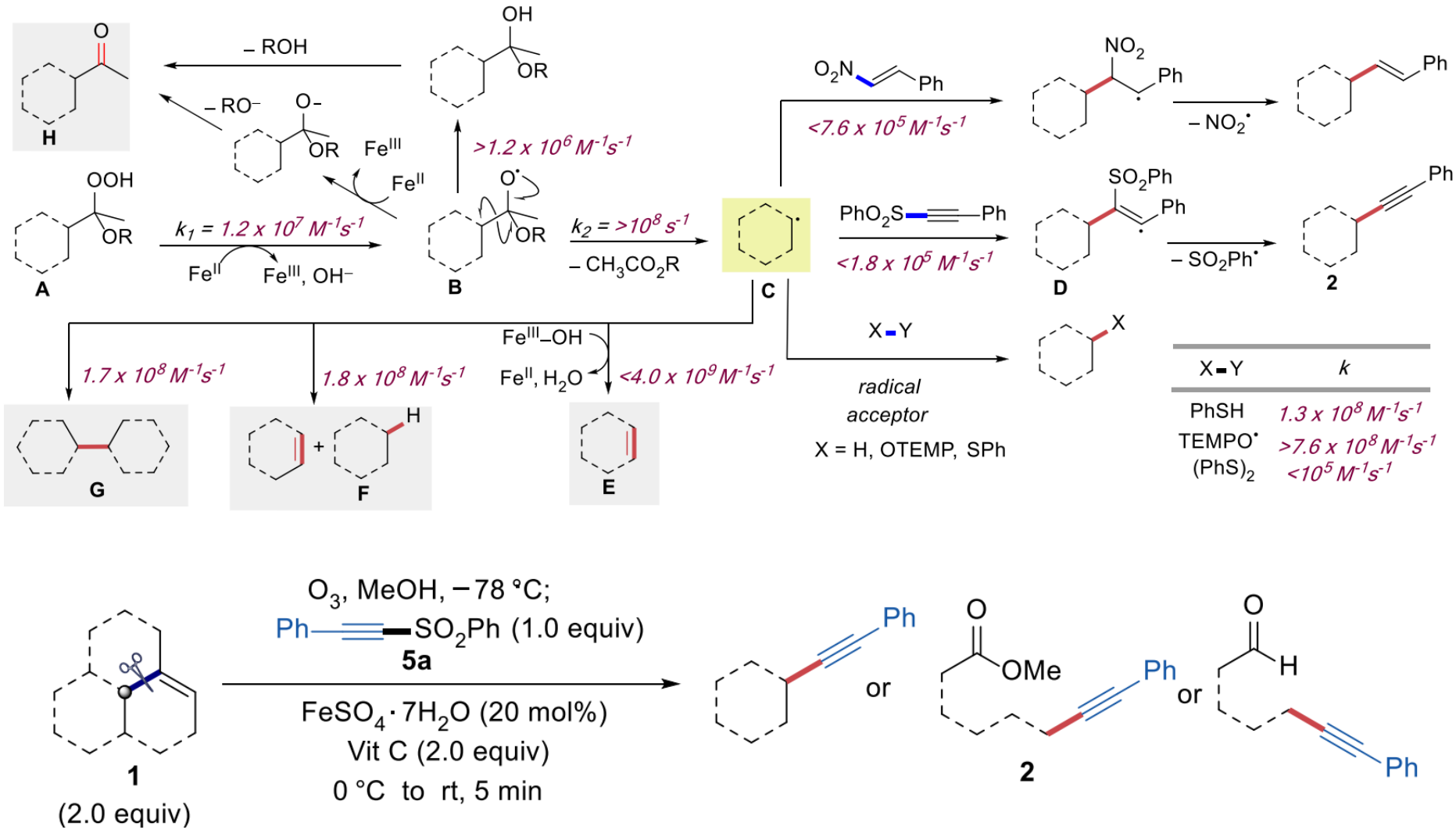


FeSO$_4$•7H$_2$O, Cu(OAc)$_2$•H$_2$O (77%)

aq. Fe(BF$_4$)$_2$, aq. Cu(BF$_4$)$_2$ (71%)

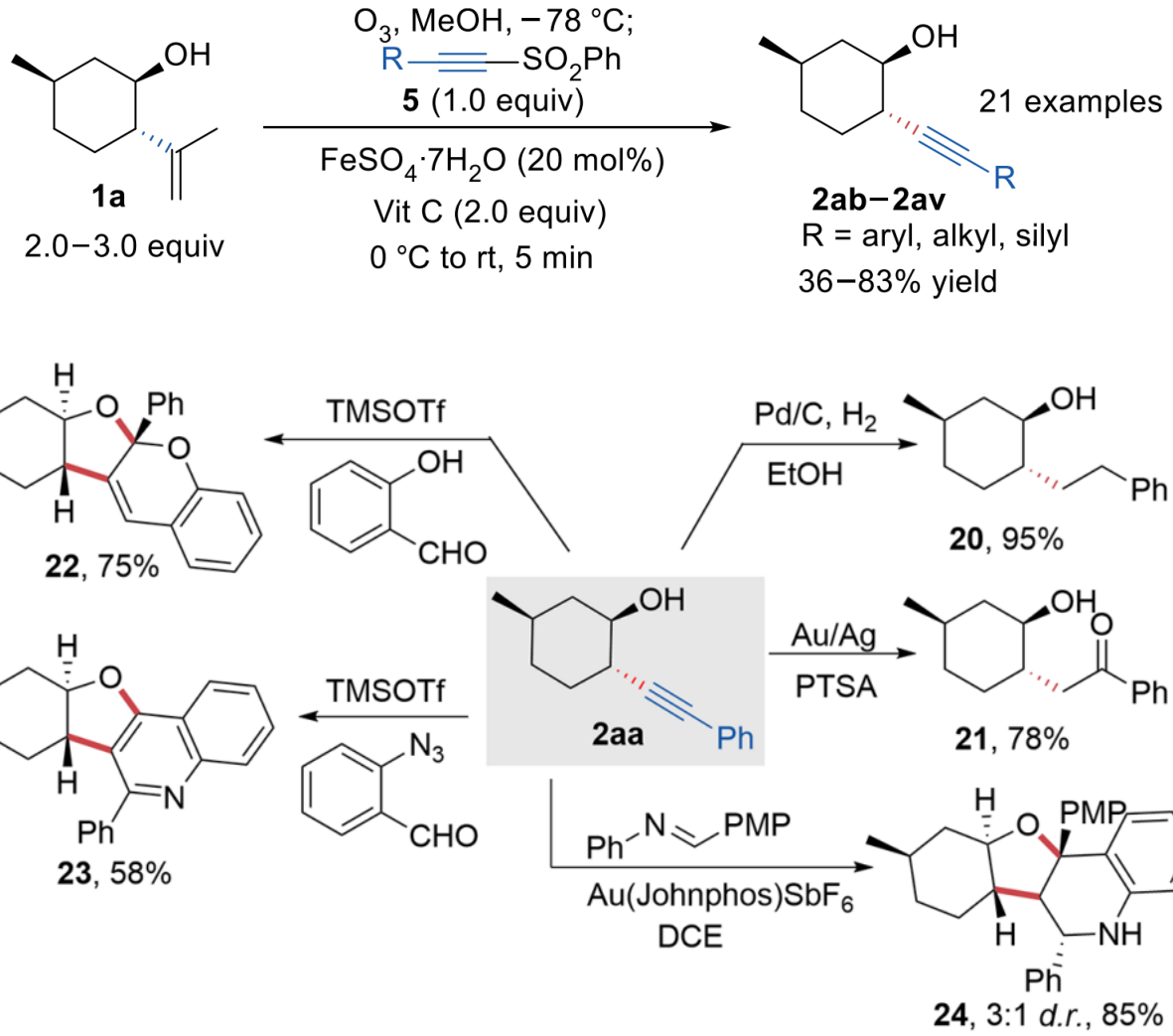
Schreiber, S. et al. *Tetrahedron* **1986**, *42*, 2945; White, J. et al. *Org. Synth.* **2005**, *82*, 108.

Radical Addition Reaction?

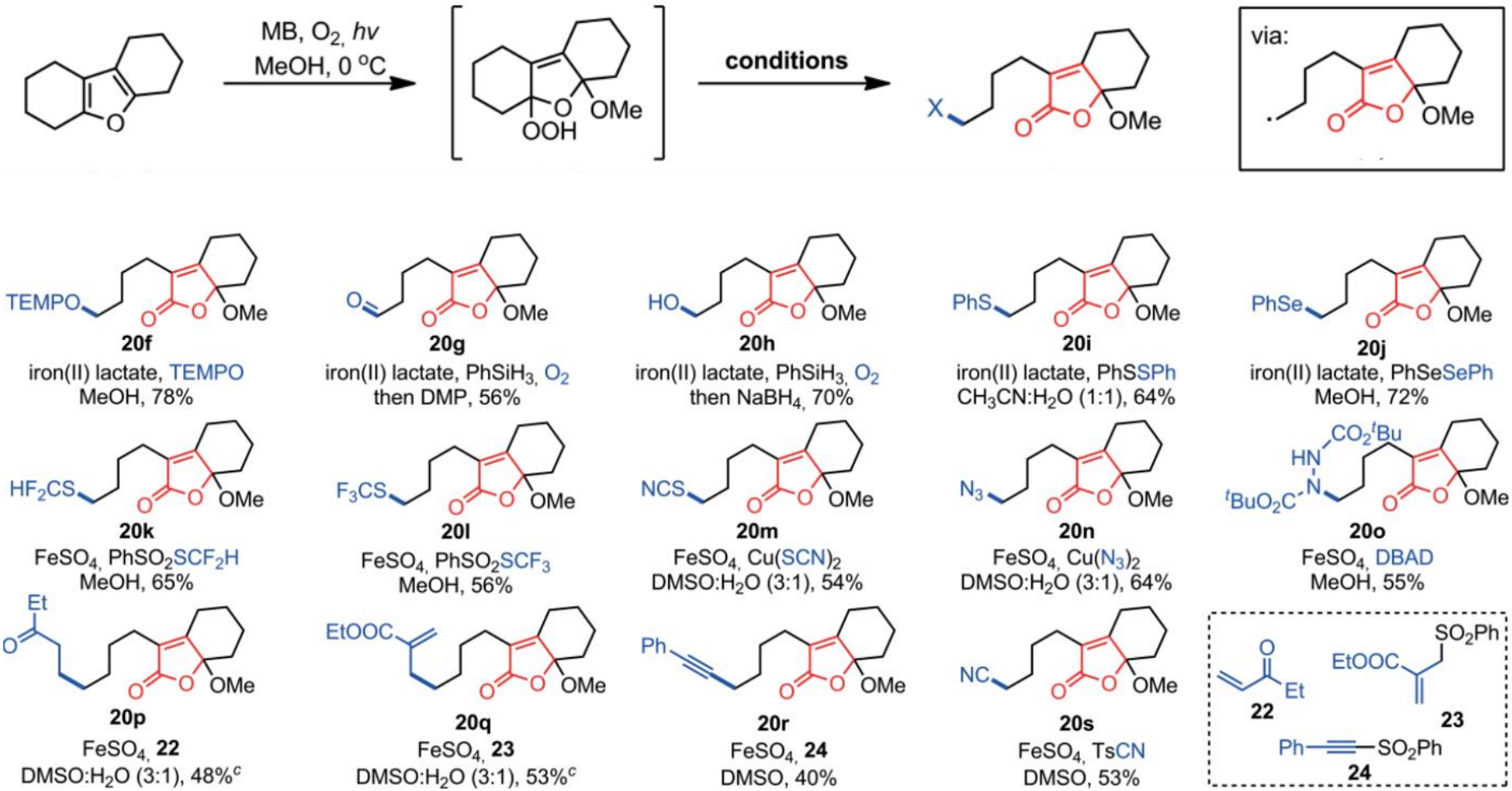


Swain, M. et al. *J. Am. Chem. Soc.* **2022,** *144*, 14828.

Dealkenylative Alkynylation

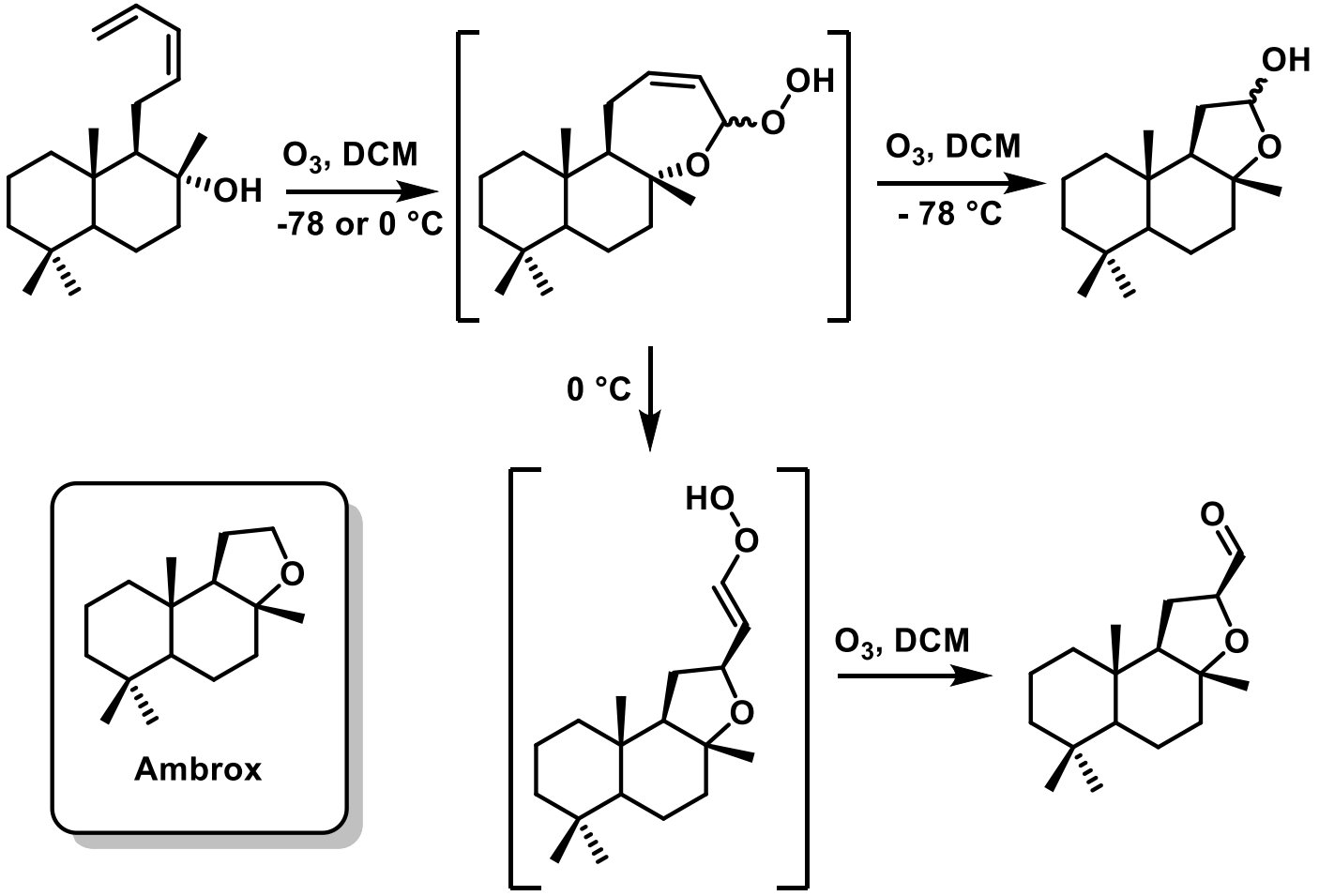


Hydroperoxyl Ketal from Furan



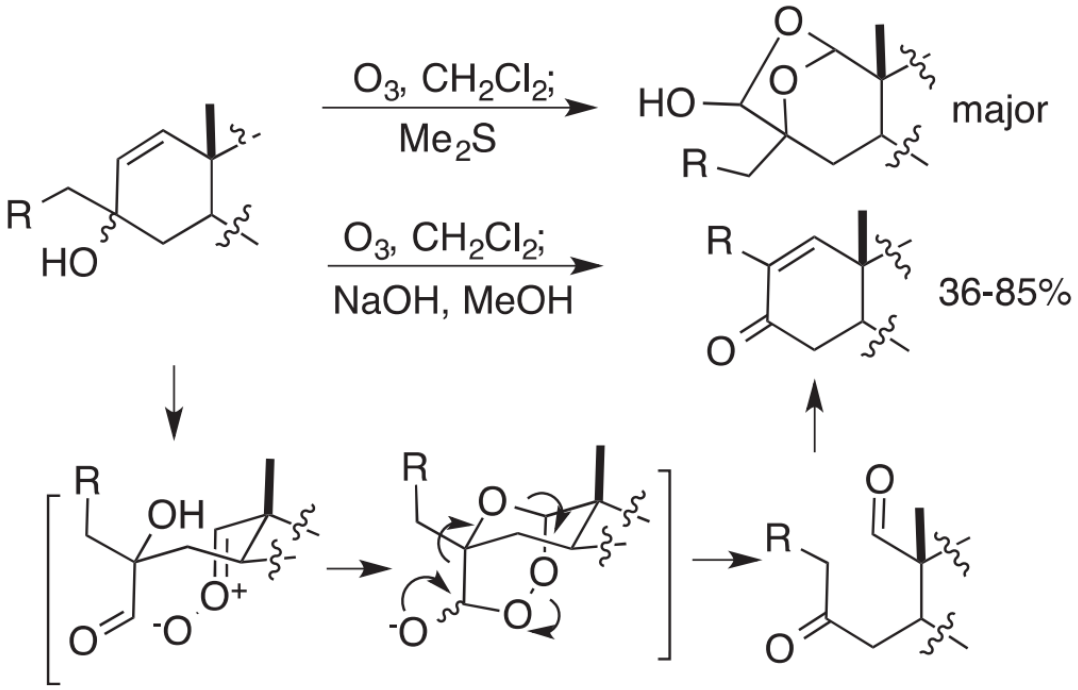
Bao, J. et al. *Eur. J. Org. Chem.* **2020**, 339.

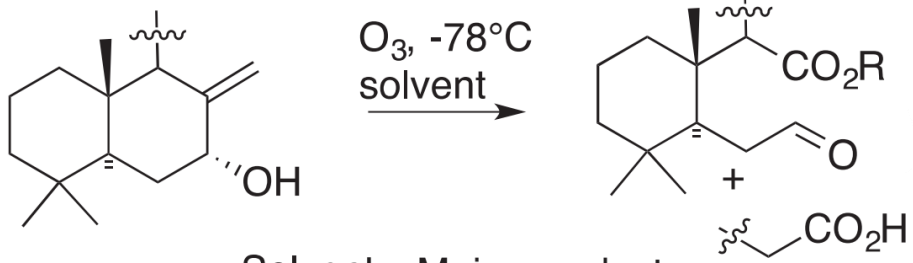
Diene: 1,2 to 1,4 Rearrangement



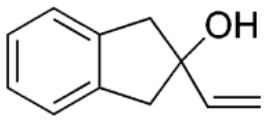
Kulcitki, V. et al. *Tetrahedron Lett.* **2010**, *51*, 4079.

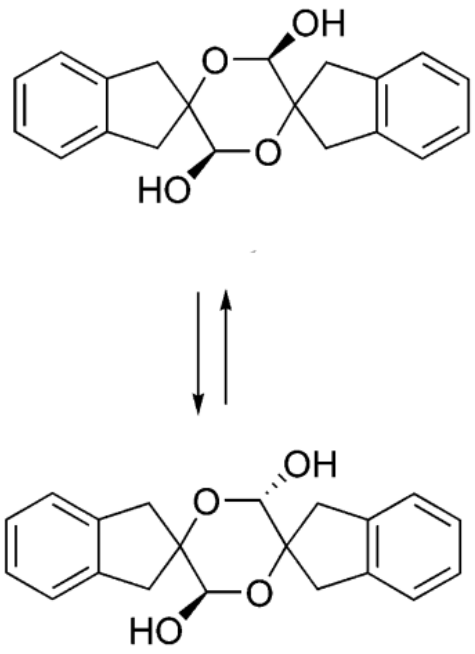
Allyl Alcohol: Fragmentation





Solvent	Major product
CH_2Cl_2	R = H
MeOH	R = Me

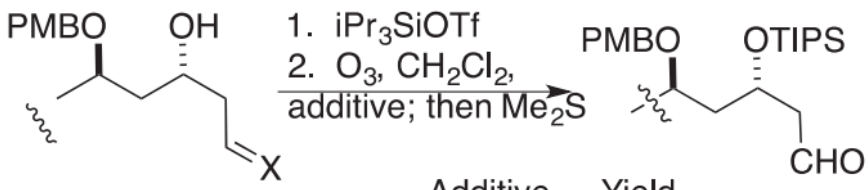




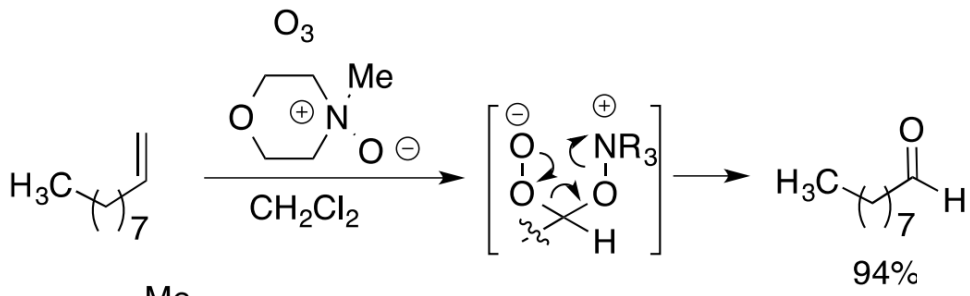
Ragan, J. et al. *Org. Process. Res. Dev.* **2003**, *7*, 155;
Everest, D. et al. *Aust. J. Chem.* **1988**, *41*, 1025;
DeNinno, M. et al. *J. Am. Chem. Soc.* **1995**, *117*, 9927.

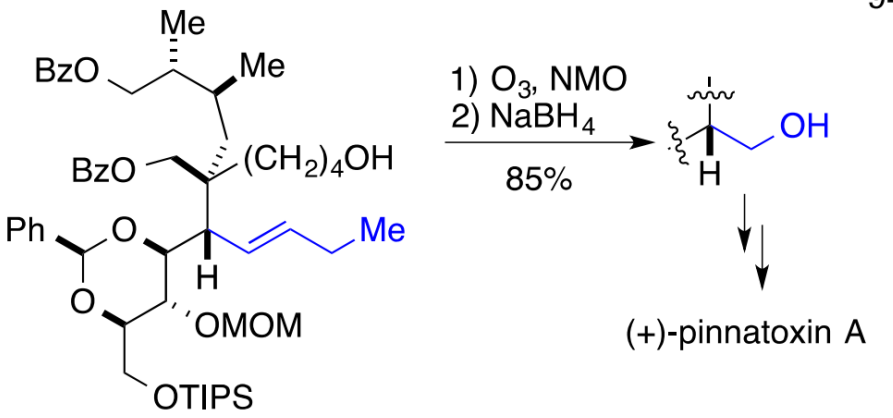
In Situ Reductive Ozonolysis

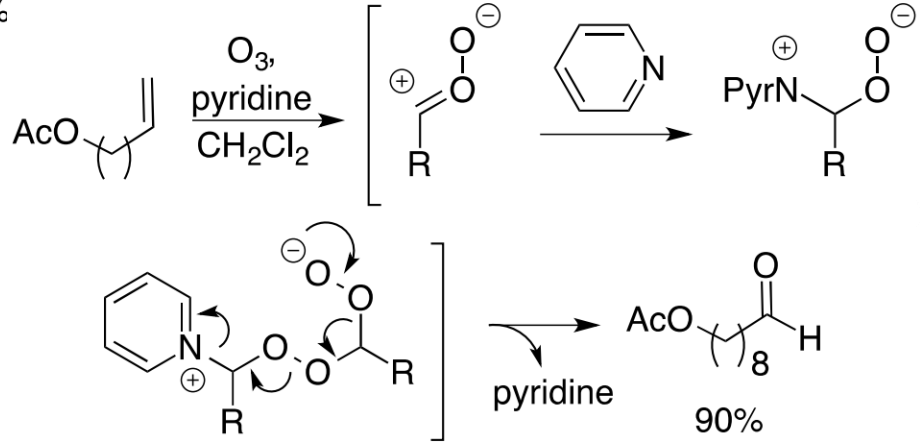
- Avoid peroxide accumulation
- Inhibit side reactions of CIs



Additive	Yield
None	55-68%
Pyridine	99%

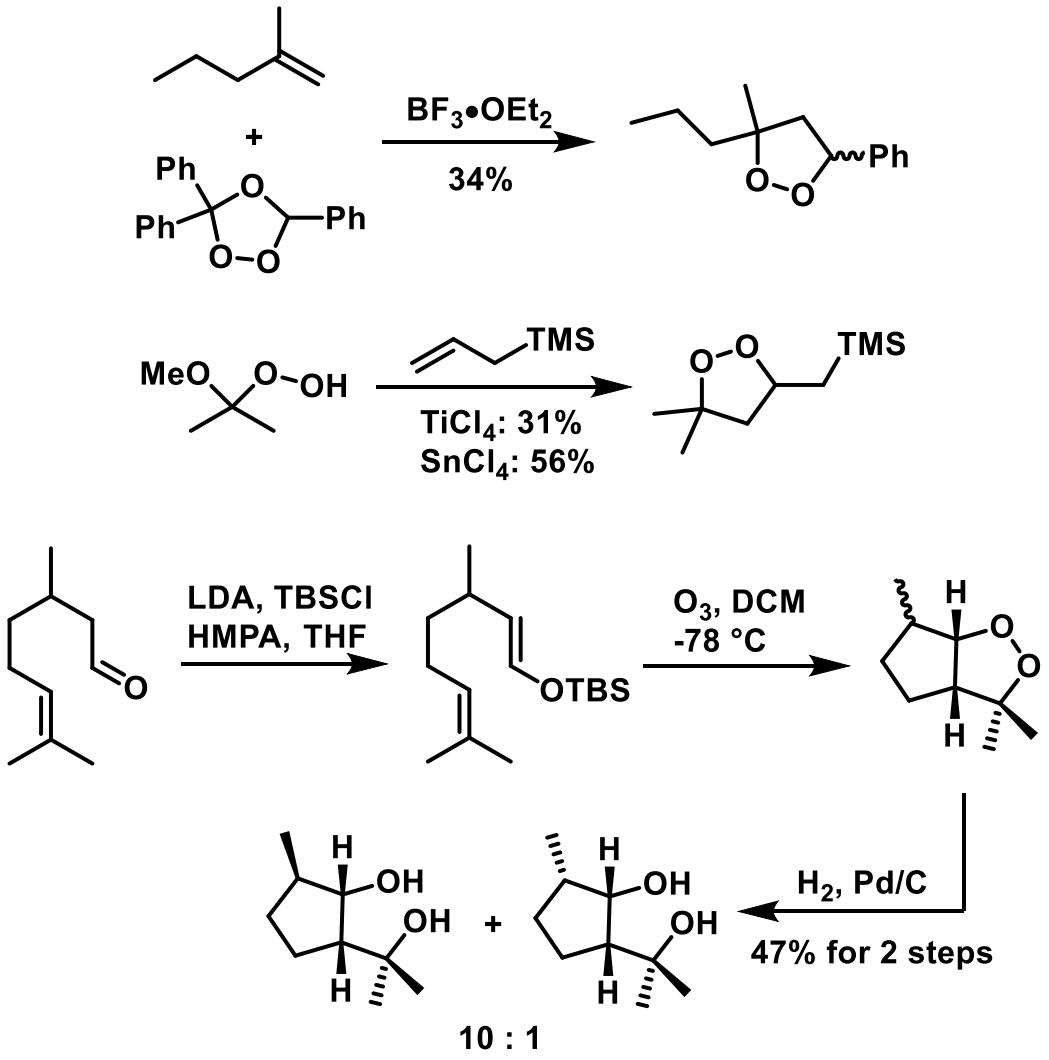






Stivala, C. et al. *J. Am. Chem. Soc.* **2008**, *130*, 3774; Schwartz, C. et al. *Tetrahedron* **2006**, *62*, 10747; Schreiber, S. *J. Am. Chem. Soc.* **1990**, *112*, 5583; Smith III A. et al. *J. Am. Chem. Soc.* **1992**, *114*, 1438.

Criegee Intermediate as 1,3-Dipole



Miura, M. et al. *J. Chem. Soc., Perkin Trans* **1980**, *1*, 2909; Dussault, P. et al. *J. Chem. Soc., Perkins Trans* **2000**, *1*, 3006; Casey, M. et al. *Synlett* **1992**, *3*, 214.

Outline

- Introduction & Earlier Capture Reactions
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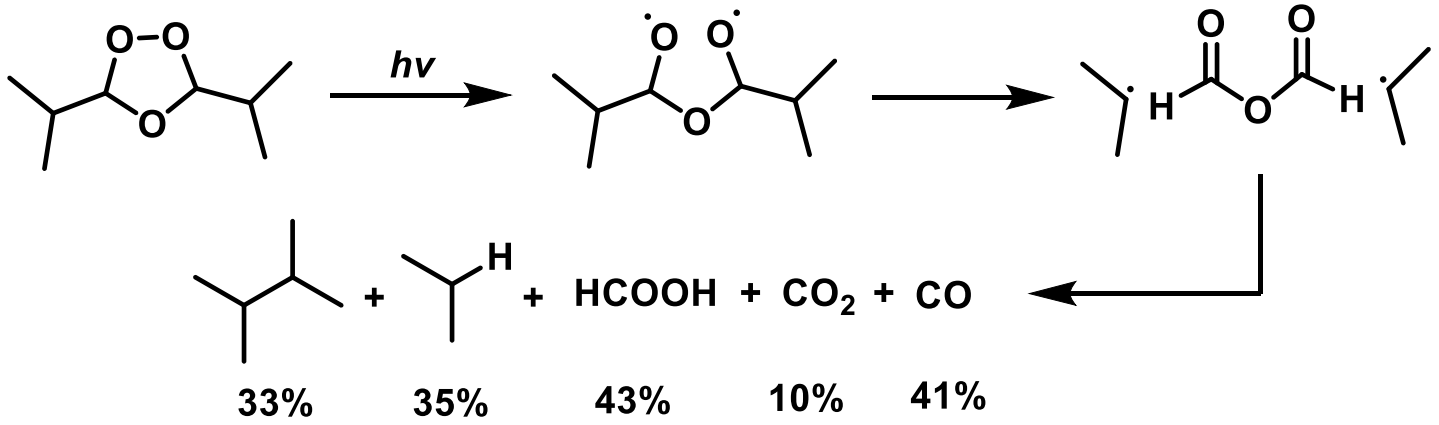
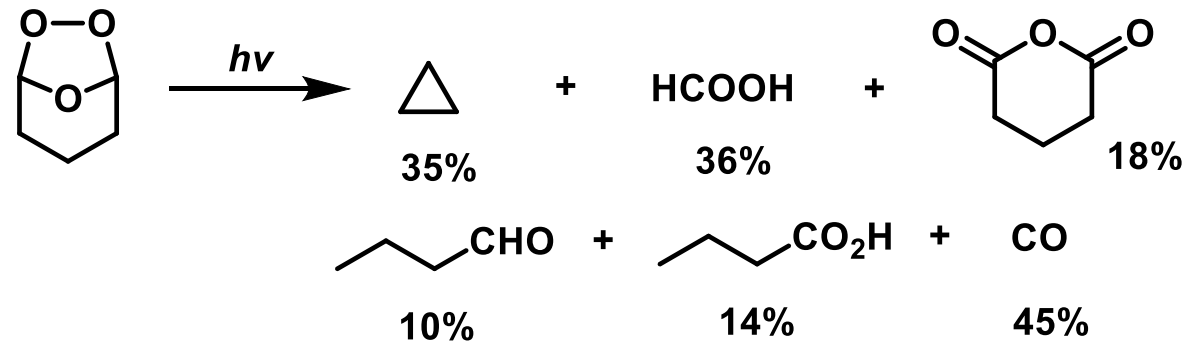
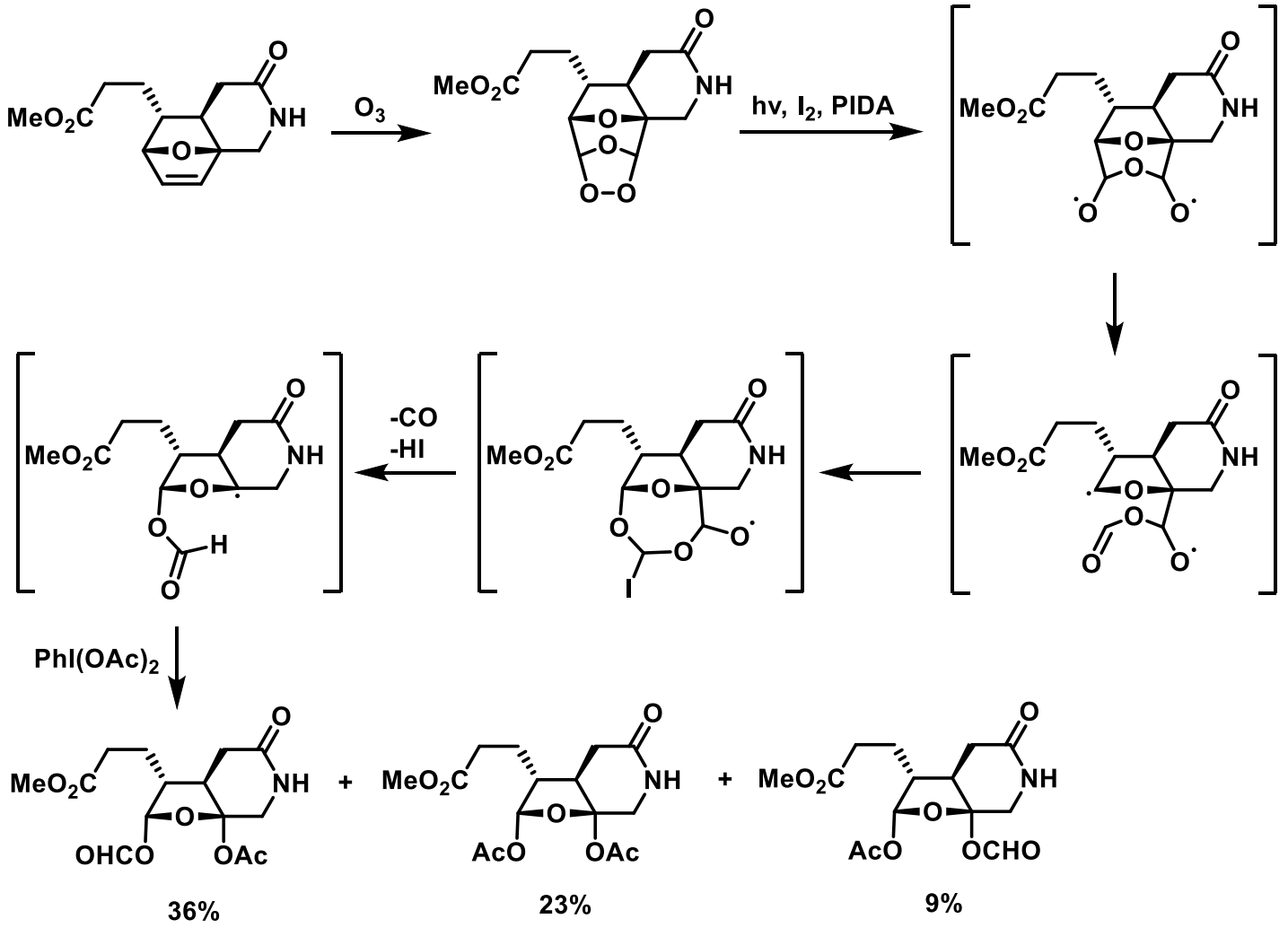
Pyrolysis or Photolysis: Story Reaction





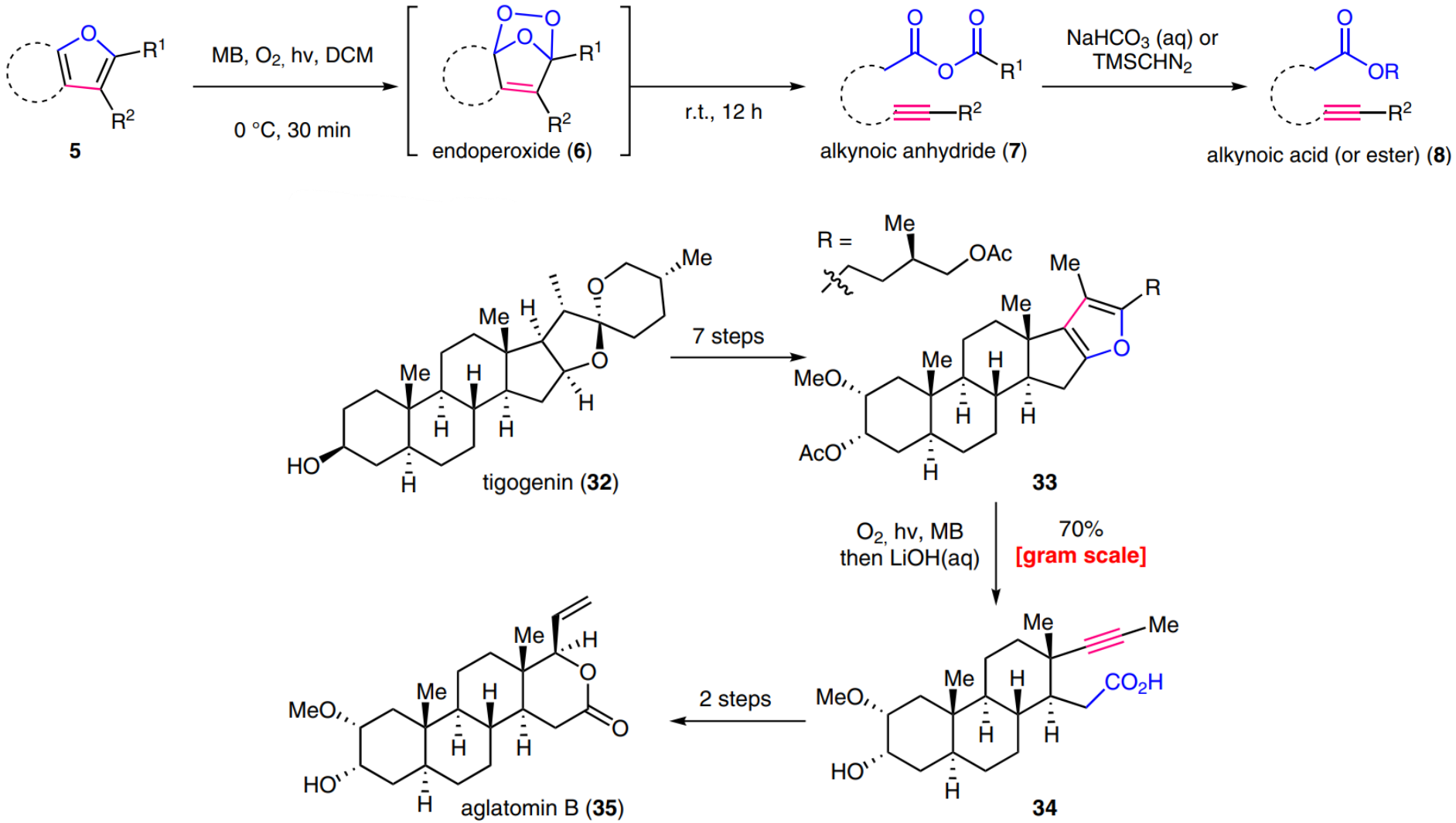
Story, P. et al. *Tetrahedron Lett.* **1968**, *29*, 3291.

Diradical Capture: PIDA



Jacobi, P. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9307.

Alkyne-Forming Furan Fragmentation



Deng, J. et al. *Synlett* **2019**, *30*, 642.

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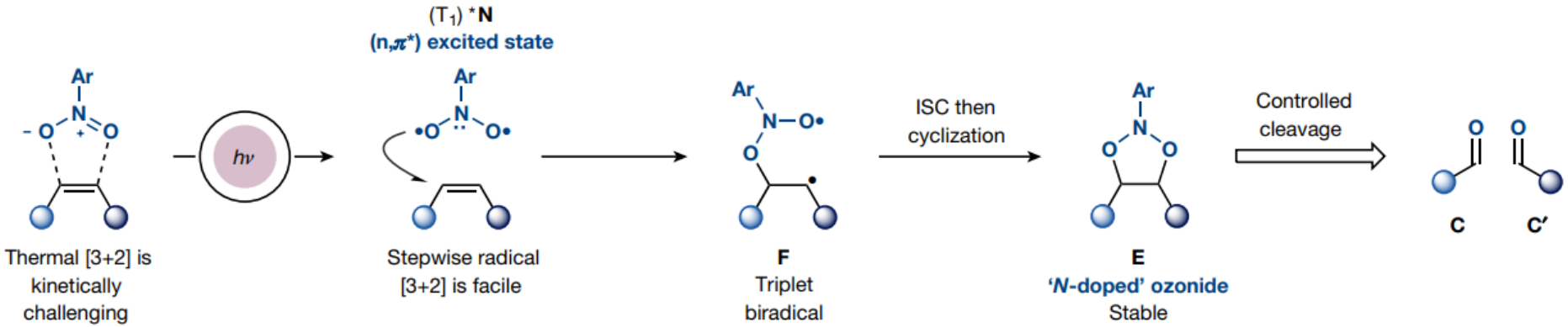
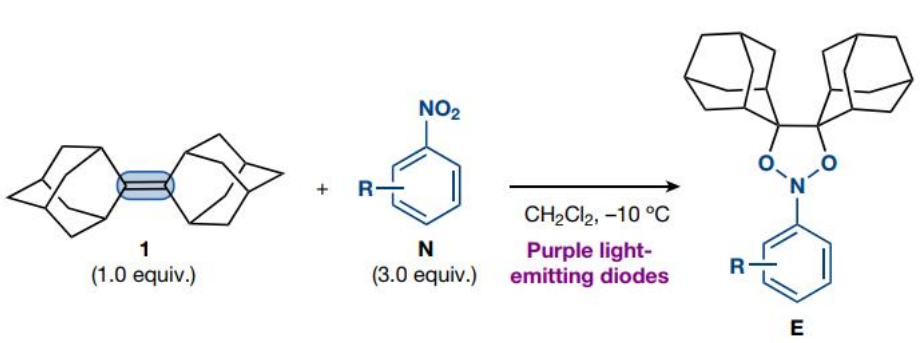
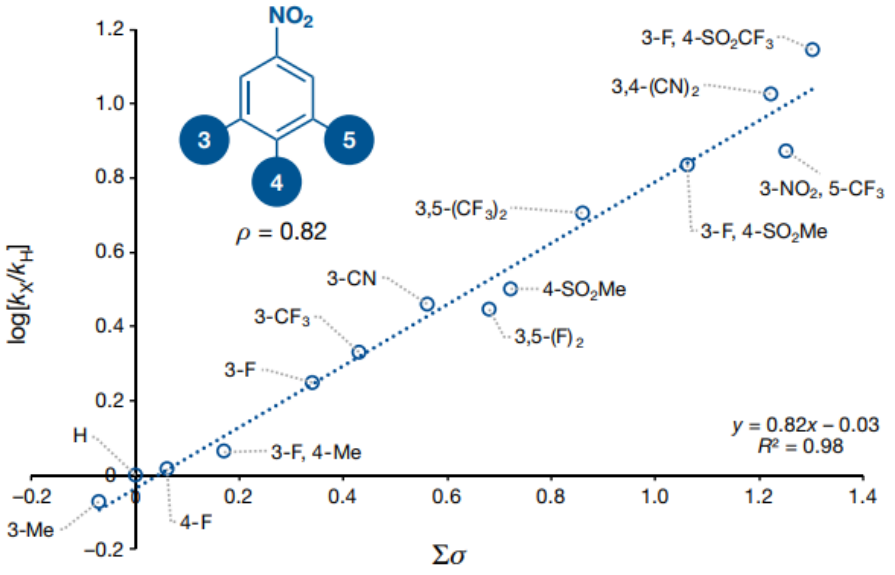
Photoexcited nitroarenes *Ozonolysis*

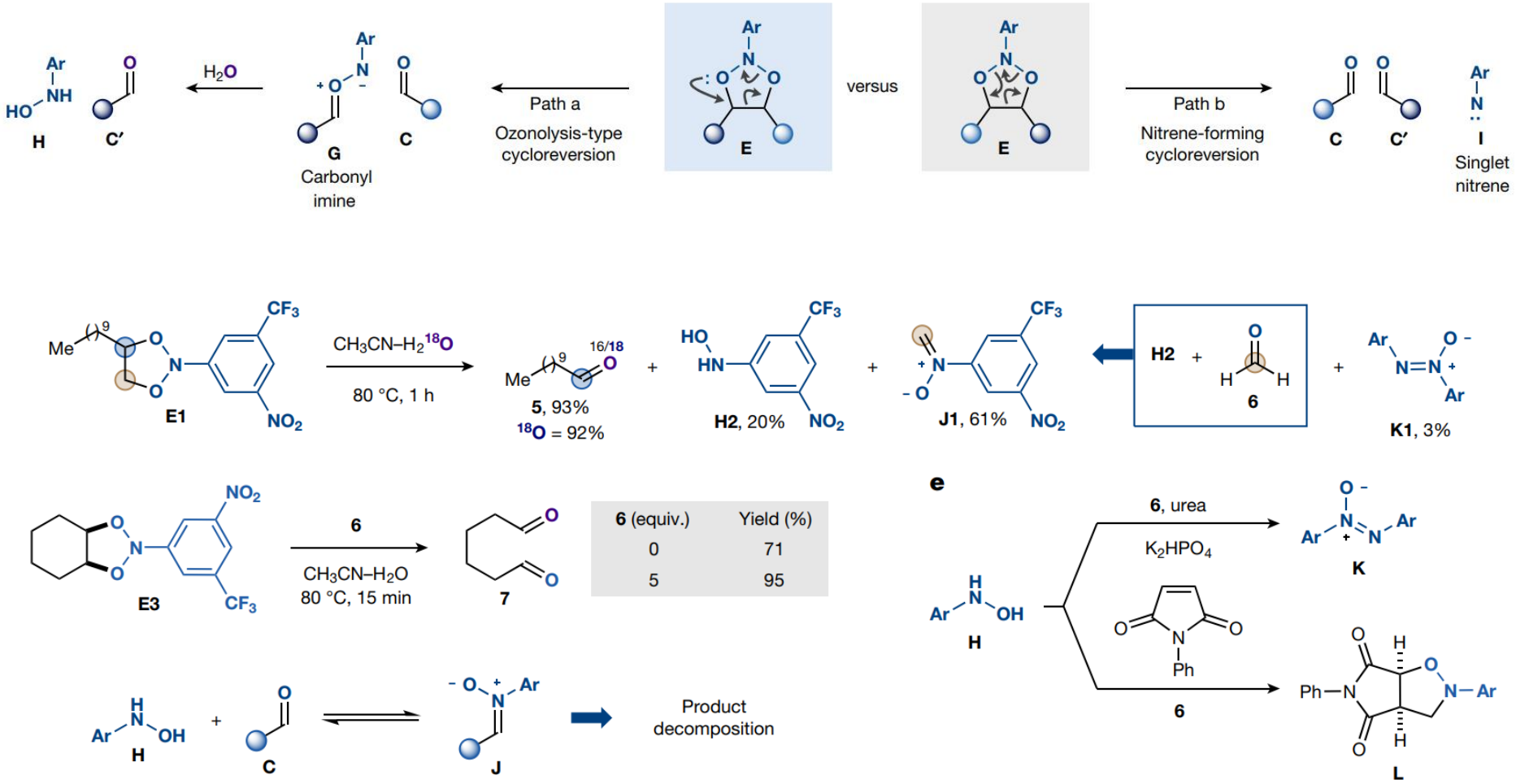




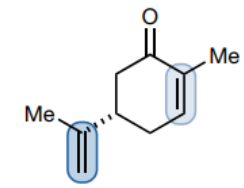


Ruffoni, A. et al. *Nature* **2022**, *610*, 81.

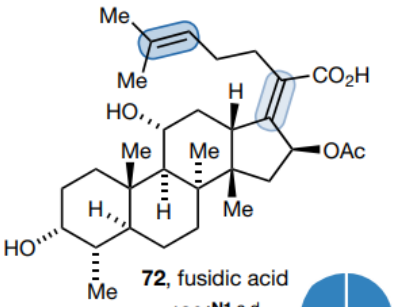
Ozonolysis-Type Fragmentation



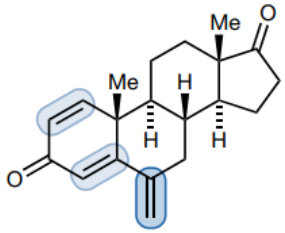
Selective Olefin Oxidation Cleavage



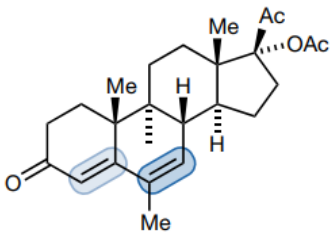
71, (–)-carvone
95%[N1,a,b]
(r.s.m. 43%[c])



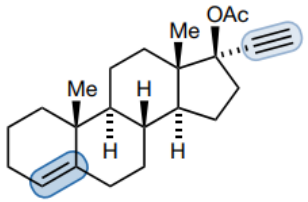
72, fusidic acid
42%[N1,a,d]



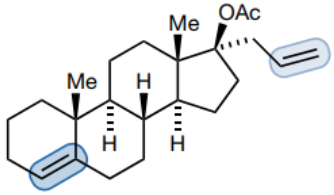
73, exemestane
64%[N3,a,b]
(r.s.m. 68%[c])



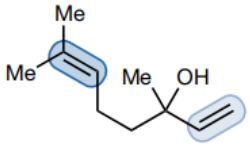
74, megestrol acetate
35%[N7,a,b]
(r.s.m. 63%[c])



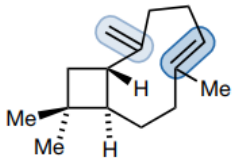
75, lynestrenol
47%[N4,e,f]
(r.s.m. 63%[c])



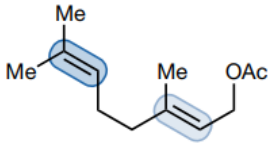
76, allylestrenol acetate
60%[N4,b,e]
(r.s.m. 38%[c])



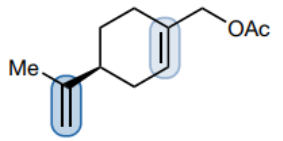
77, linalool
71%[N10,d,e]



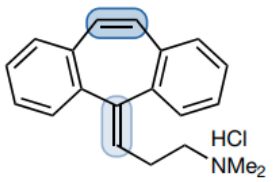
78, (–)-*trans*-caryophyllene
89%[N9,e,f,g]
(r.s.m. 49%[c])



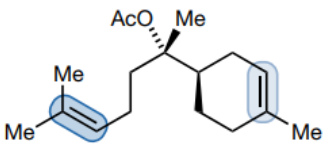
79, geranyl acetate
66%[N4,a,f,h]
(r.s.m. 55%[c]; *E*:*Z* 19:1)



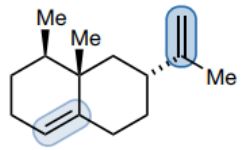
80, (–)-perillyl acetate
73%[N2,a,b]
(r.s.m. 56%[c])



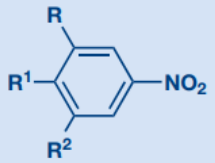
81, cyclobenzaprine•HCl
99%[N1,b,i]
(r.s.m. 42%[c])



82, (–)-bisabolol acetate
78%[N2,b,e,j]
(r.s.m. 55%[c])

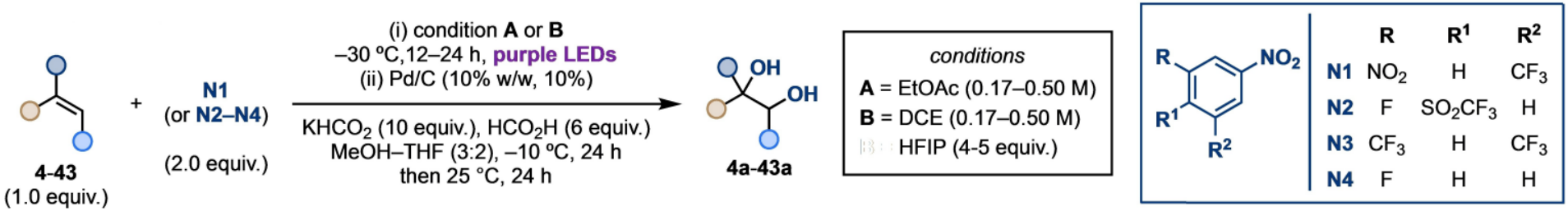


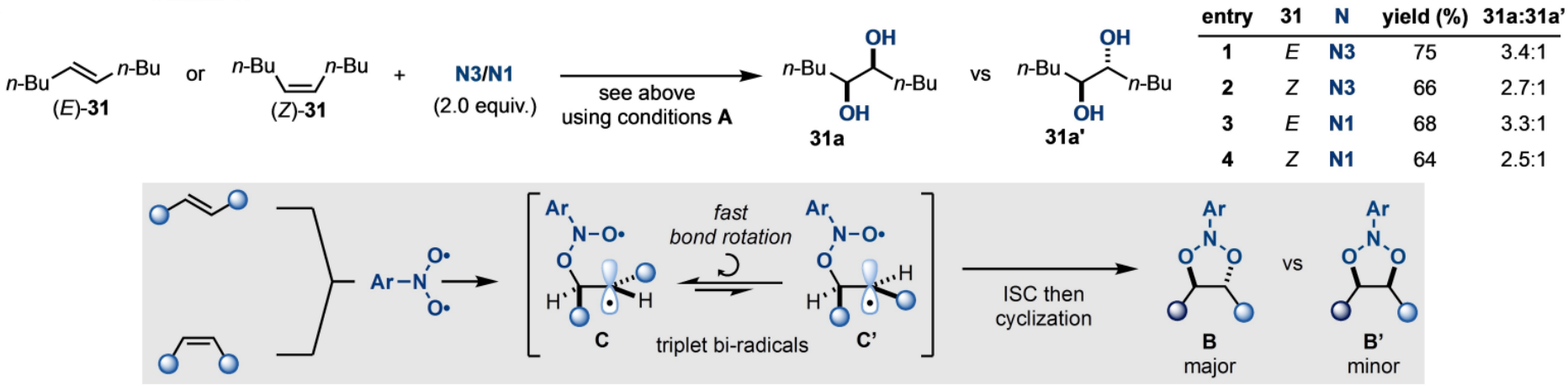
83, (+)-valencene
46%[N2,a,k]
(r.s.m. 91%[c])



	R	R^1	R^2
N1:	NO_2	H	CF_3
N2:	CF_3	H	CF_3
N3:	CN	CN	H
N4:	F	H	H
N7:	F	SO_2CF_3	H
N9:	CN	Me	H
N10:	CN	H	H

Dihydroxylation Using Nitroarenes





Hampton, C. et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202214508.

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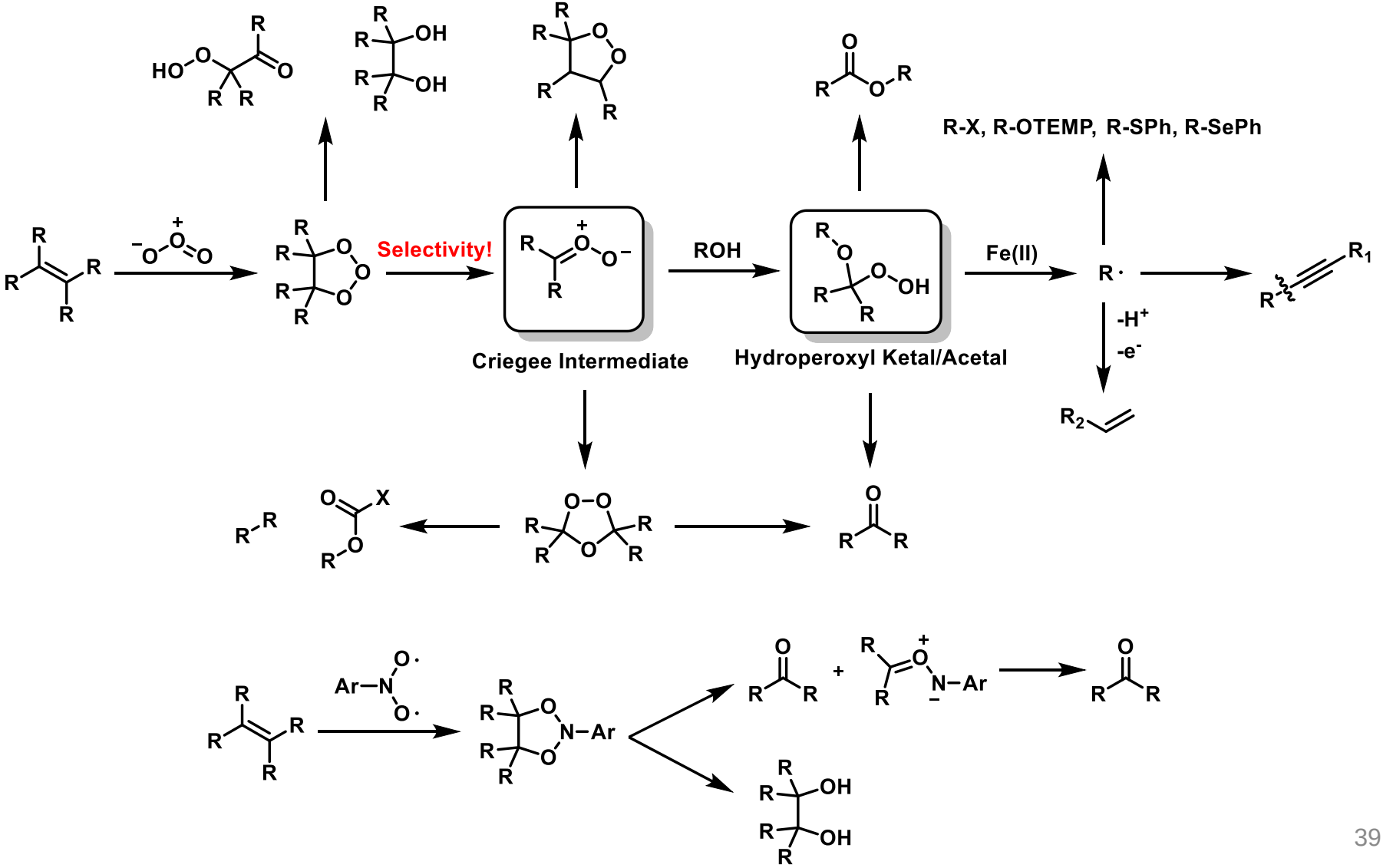
Summary


Selectivity!
ROH
Fe(II)
R-X, R-OTEMP, R-SPh, R-SePh
-H+
-e-
Criegee Intermediate
Hydroperoxyl Ketal/Acetal
Ar–N
N–Ar