[2+2] Cycloadditions of Ketenes

An Evans Group Afternoon Seminar
Jake Janey
October 8, 1999

Leading References:

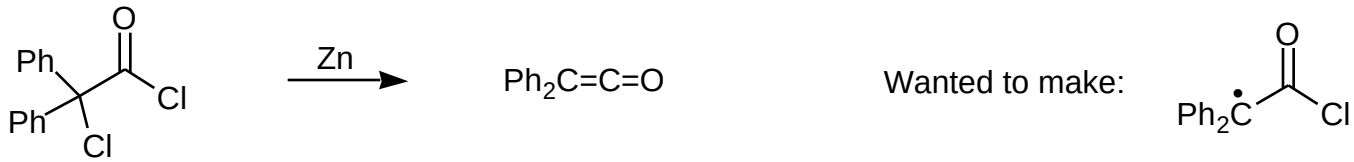
Tidwell, T. T. *Ketenes*, John Wiley and Sons, **1995**.

Ghosez, L.; Marchand-Brynaert, J. *Comprehensive Organic Synthesis*, Vol. 5, Pergamon, **1991**, p. 85-122.

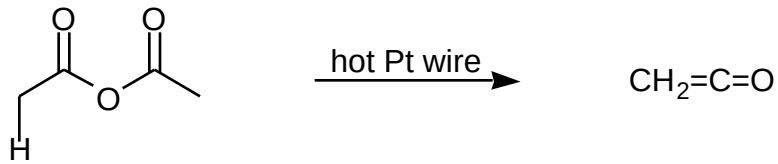
Patai, S. *Chemistry of Ketenes, Allenes, and Related Compounds*, John Wiley and Sons, **1980**.

Staudinger, H. *Die Ketenes*, Verlag Enke, **1912**.

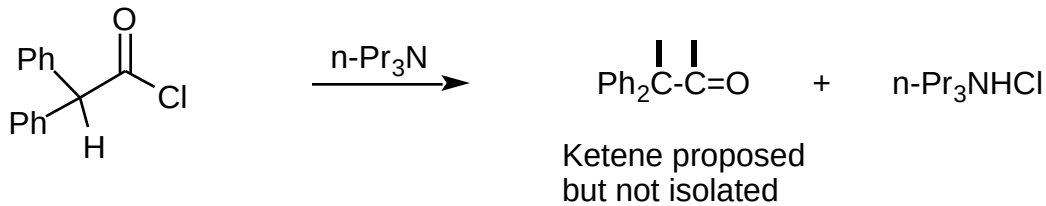
A Brief History



Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735-1739.

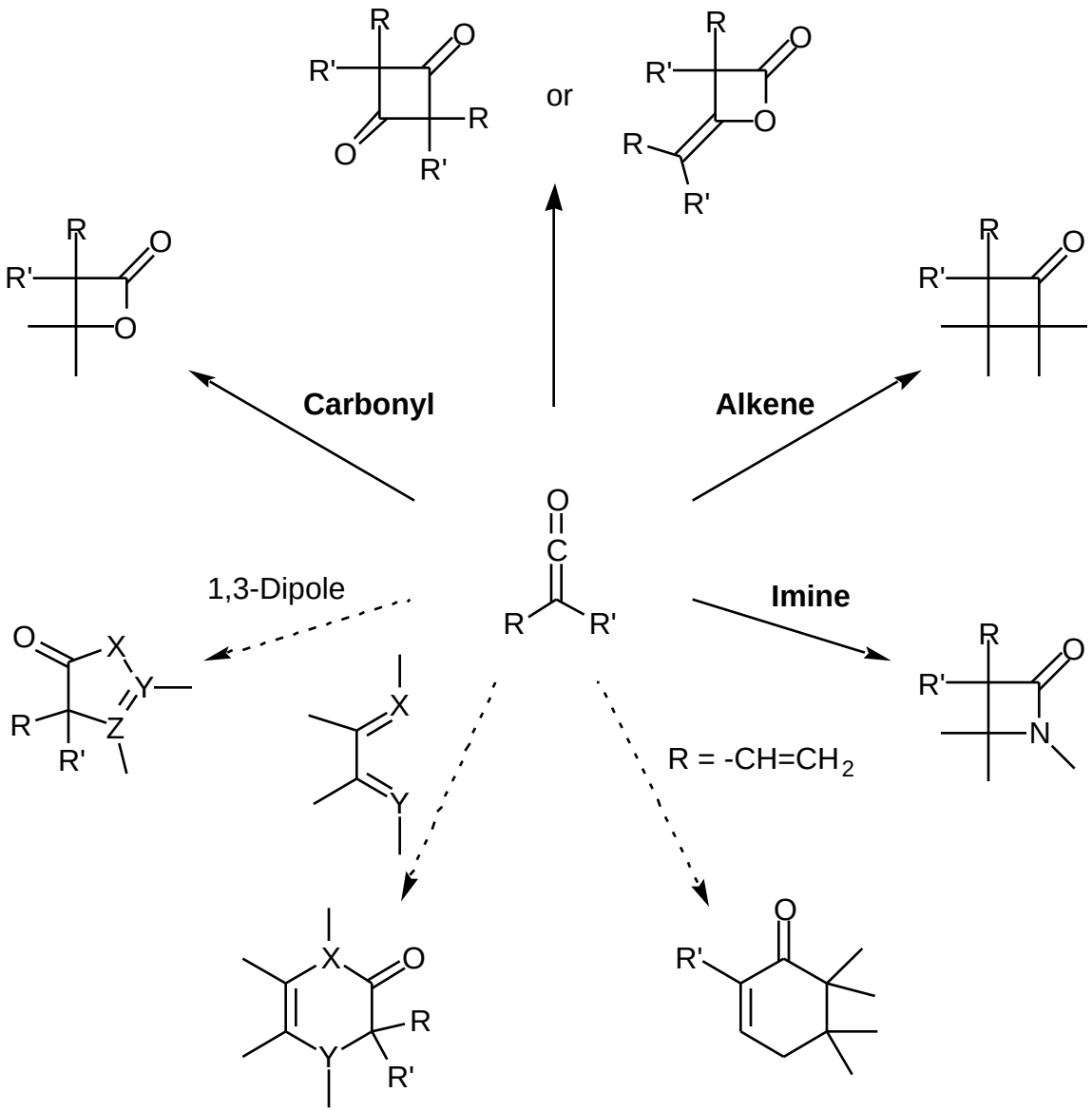


Wilsmore, N. T. M. *J. Chem. Soc.* **1907**, *91*, 1938-1941.



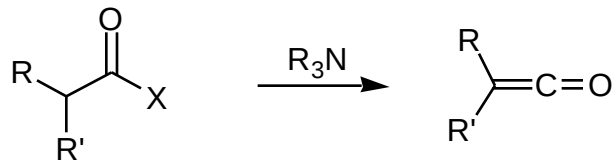
Wedekind, E. *Chem. Ber.* **1901**, *34*, 2070-2077.
Wedekind, E. *Liebigs Ann. Chem.* **1901**, *323*, 246-257.

Summary of Ketene Cycloadditions



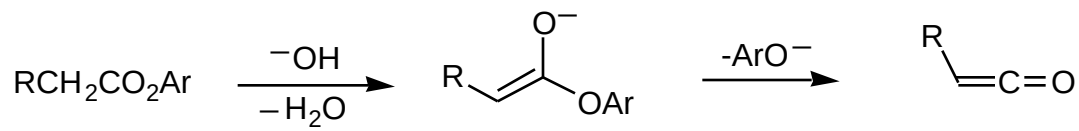
Ketene Preparation

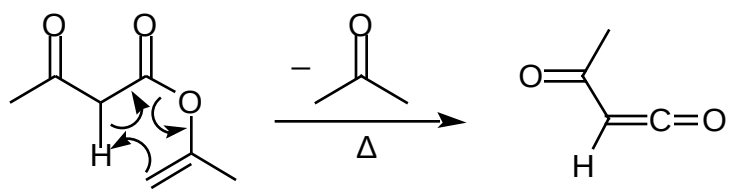
From Carboxylic Acid and Their Derivatives:

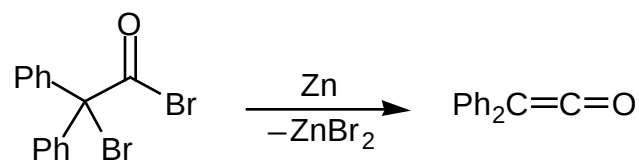


Staudinger Reaction (very general)

X = Cl, Ts, AcO, DCC, etc...

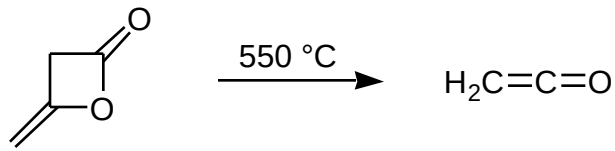


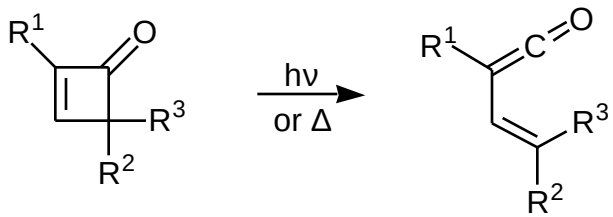


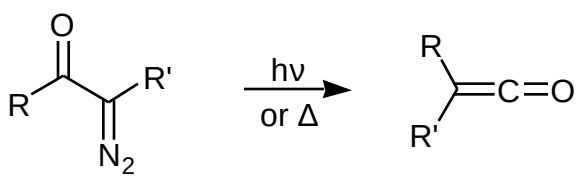


Ketene Preparation

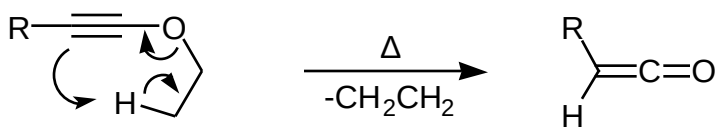
Other Methods:





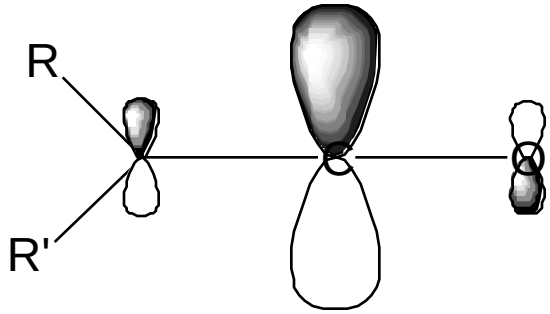


Wolff Rearrangement (variable yields)

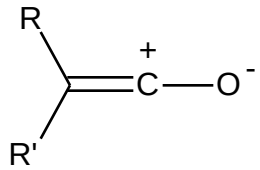


Ketene Frontier Orbitals

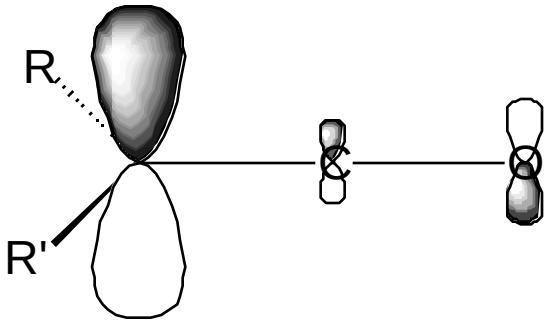
LUMO
(π* of C=O)



or



HOMO
(π of C=C)



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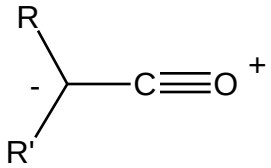
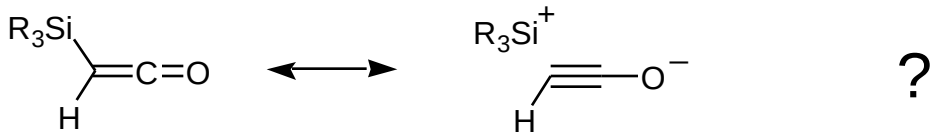


- Ketenes are ambiphilic
- HOMO is orthogonal to the plane of the LUMO

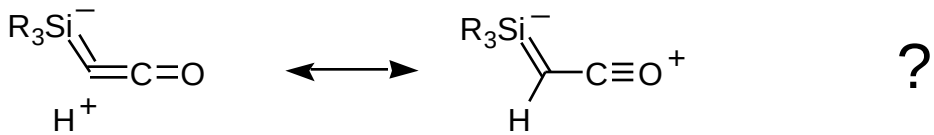
Silyl Ketene Stability

Hyperconjugation:



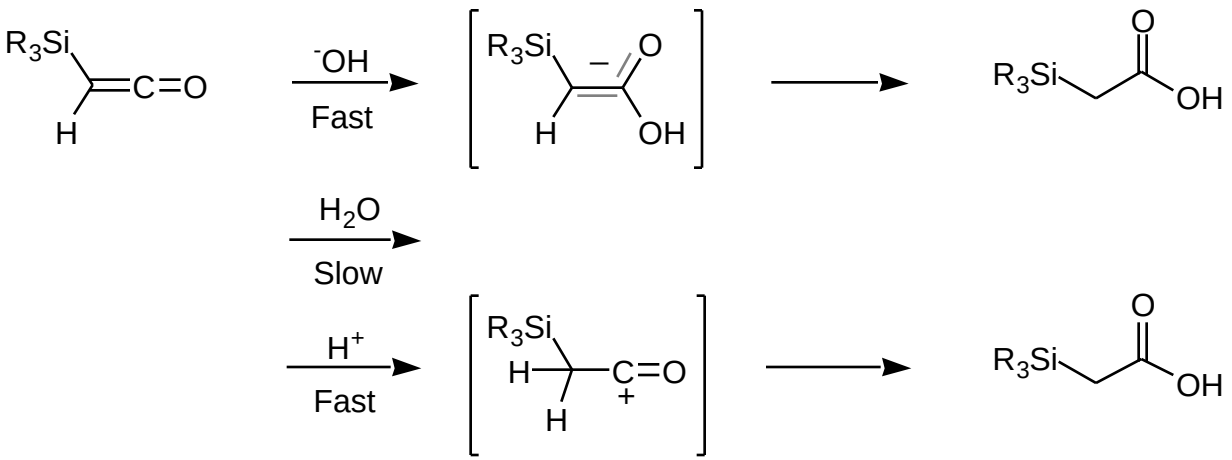
Brady, W. T.; Cheng, T. C. *J. Org. Chem.* **1977**, 42, 732-4.

π -> d Donation to Si:



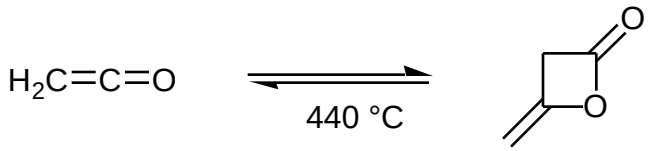
Runge, W. *Prog. Phys. Org. Chem.* **1981**, 13, 315-484.

Si σ −> πDonation:



Gong, L.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1991**, 113, 6021-8.

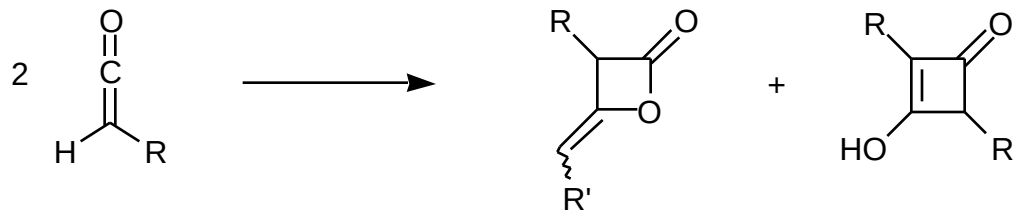
Dimerization

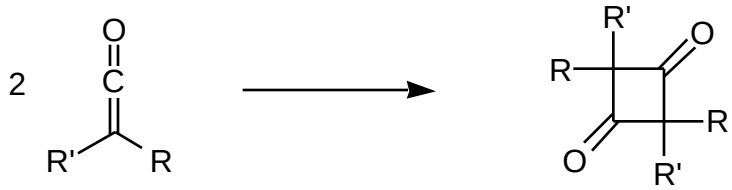


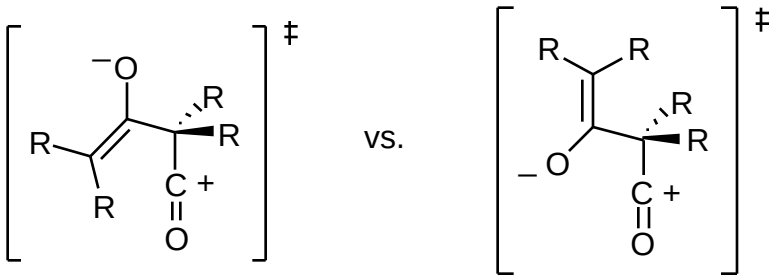
- Valuable synthetic intermediate
  Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241-318.

Wilsmore, N. T. M. *J. Chem. Soc.* **1907**, *91*, 1938-1941.

In General:

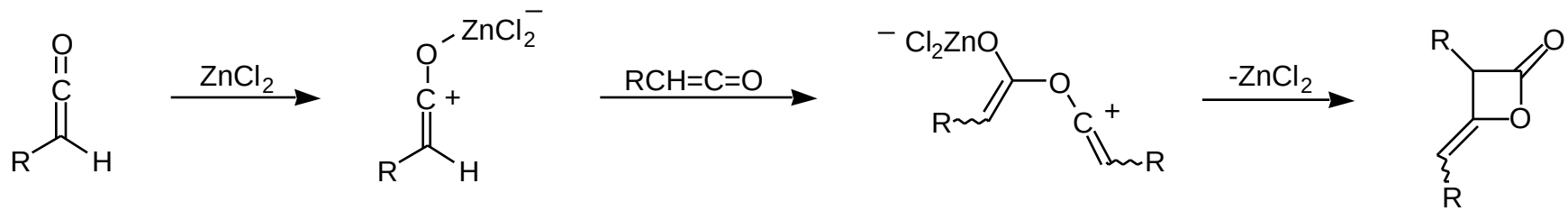




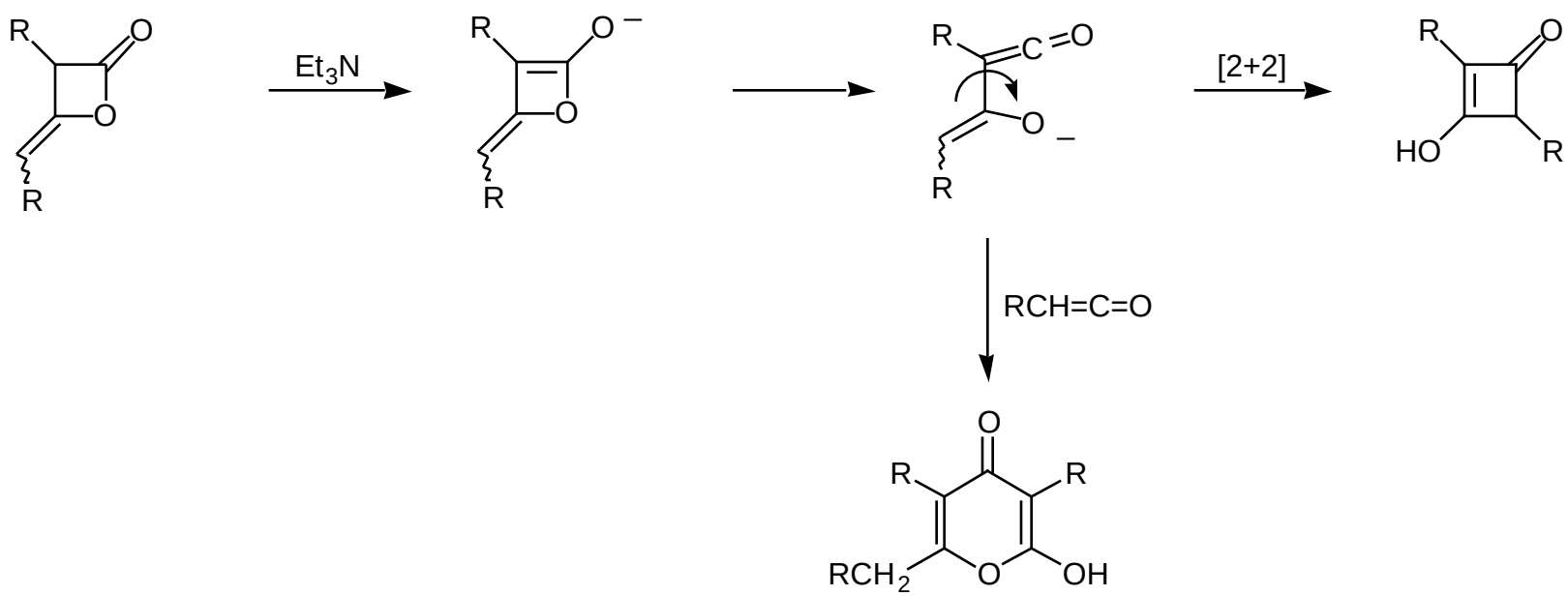


Catalyzed Dimerization

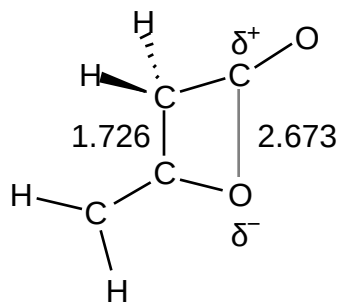
Favors β-lactones:



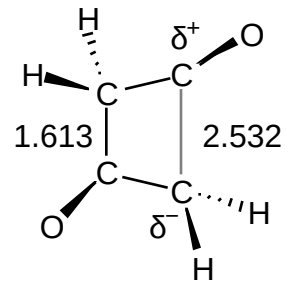
Base catalyzed isomerization:



Dimerization Mechanism

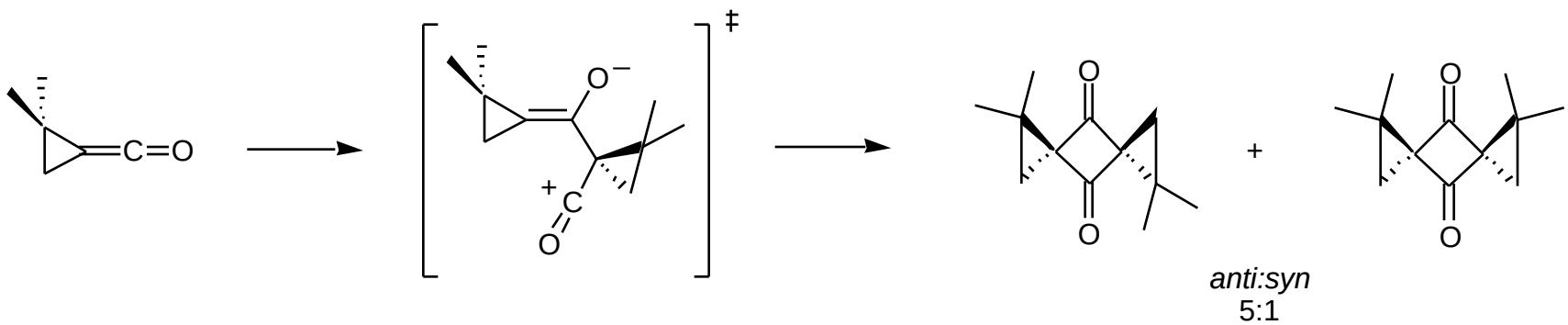


$\Delta G^{\ddagger}$ = 32 kcal/mol



$\Delta G^{\ddagger}$ = 36 kcal/mol

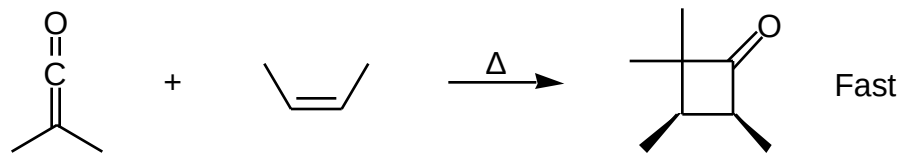
Seidl, E. T.; Schaeffer, H. F. *J. Am. Chem. Soc.* **1991**, *113*, 5195-5200.

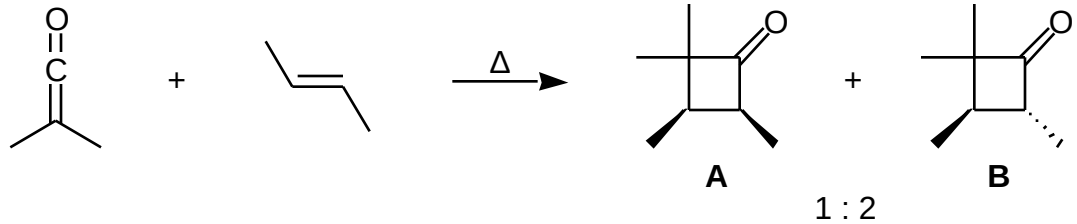


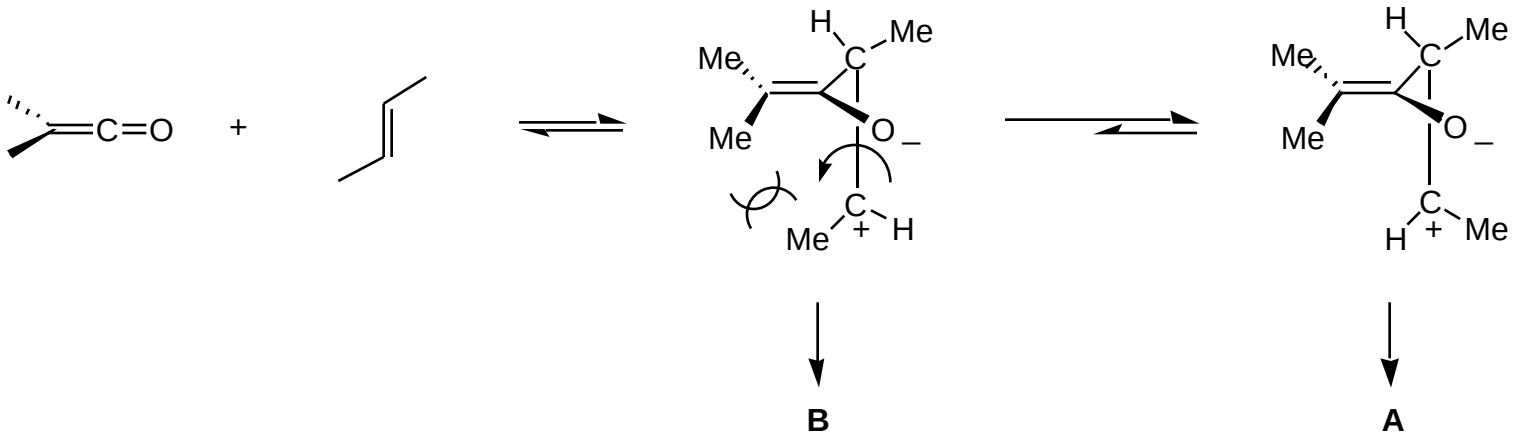
"A one step concerted process has never been proven for any one example."

Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Eng.* **1985**, 607-608.

Ketene-Alkene [2+2]

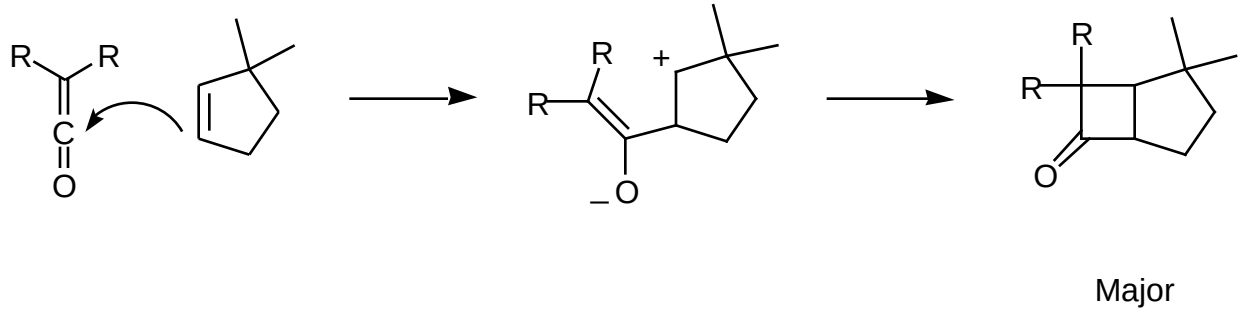




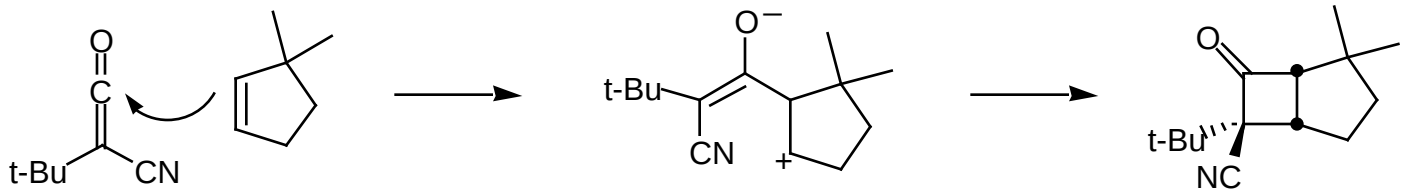


Frey, H. M.; Isaacs, N. J. *J. Chem Soc. B,* **1970**, 830-832.

Regiochemistry



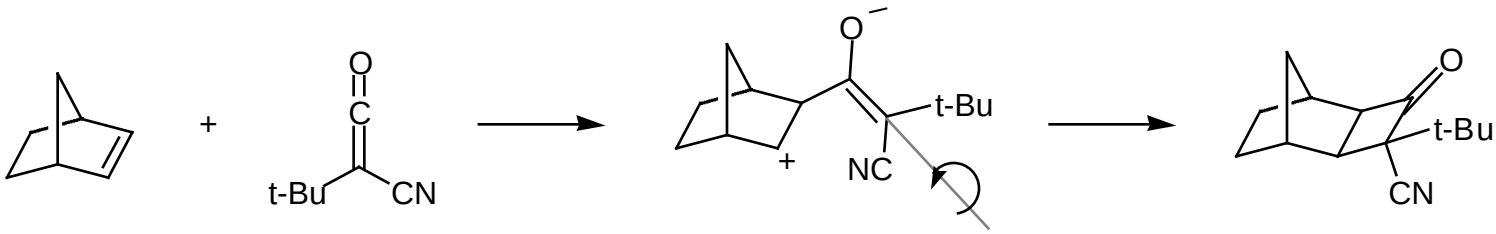
Major



Exclusive

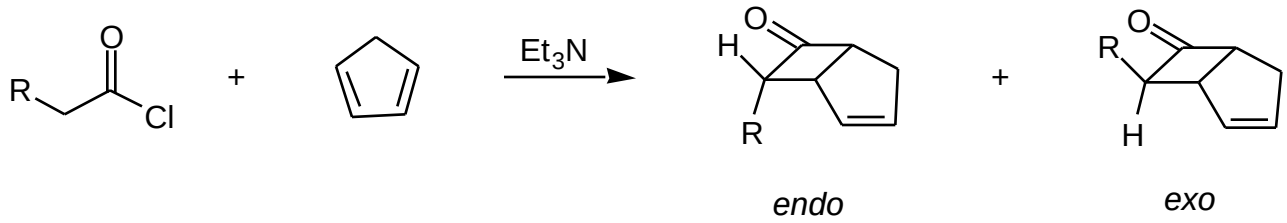
Hassner, A.; Cory, R.; Sartoris, N. J. *J. Am. Chem. Soc.* **1976**, *98*, 7698-7704.

Diastereoselectivity:



Gheorghiu, M. D.; Draghici, C.; Parvulescu, L. *Tetrahedron*, **1977**, *33*, 3295-3299.

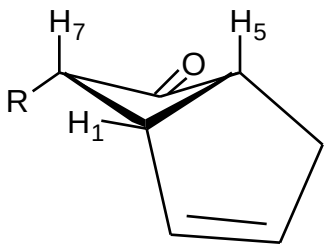
Endo -Exo Selectivity



R	*endo*	*exo*
F	89	11
Cl	87	13
Me	76	24
Ph	67	33
Et	64	36
i-Pr	57	43
t-Bu	10	90

- Product ratios at equilibrium

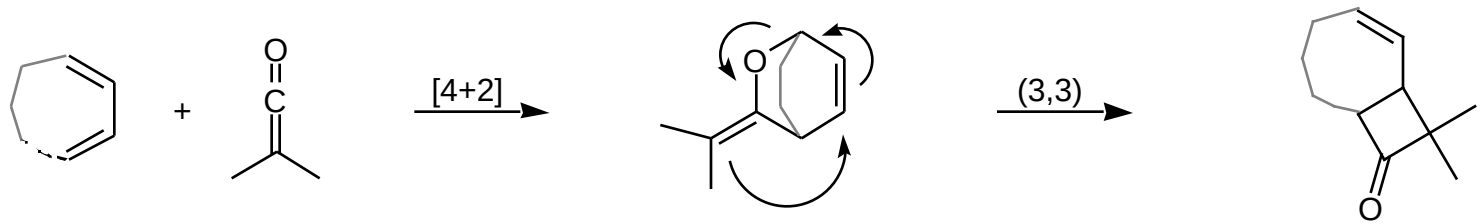
^{1}H NMR Conformation

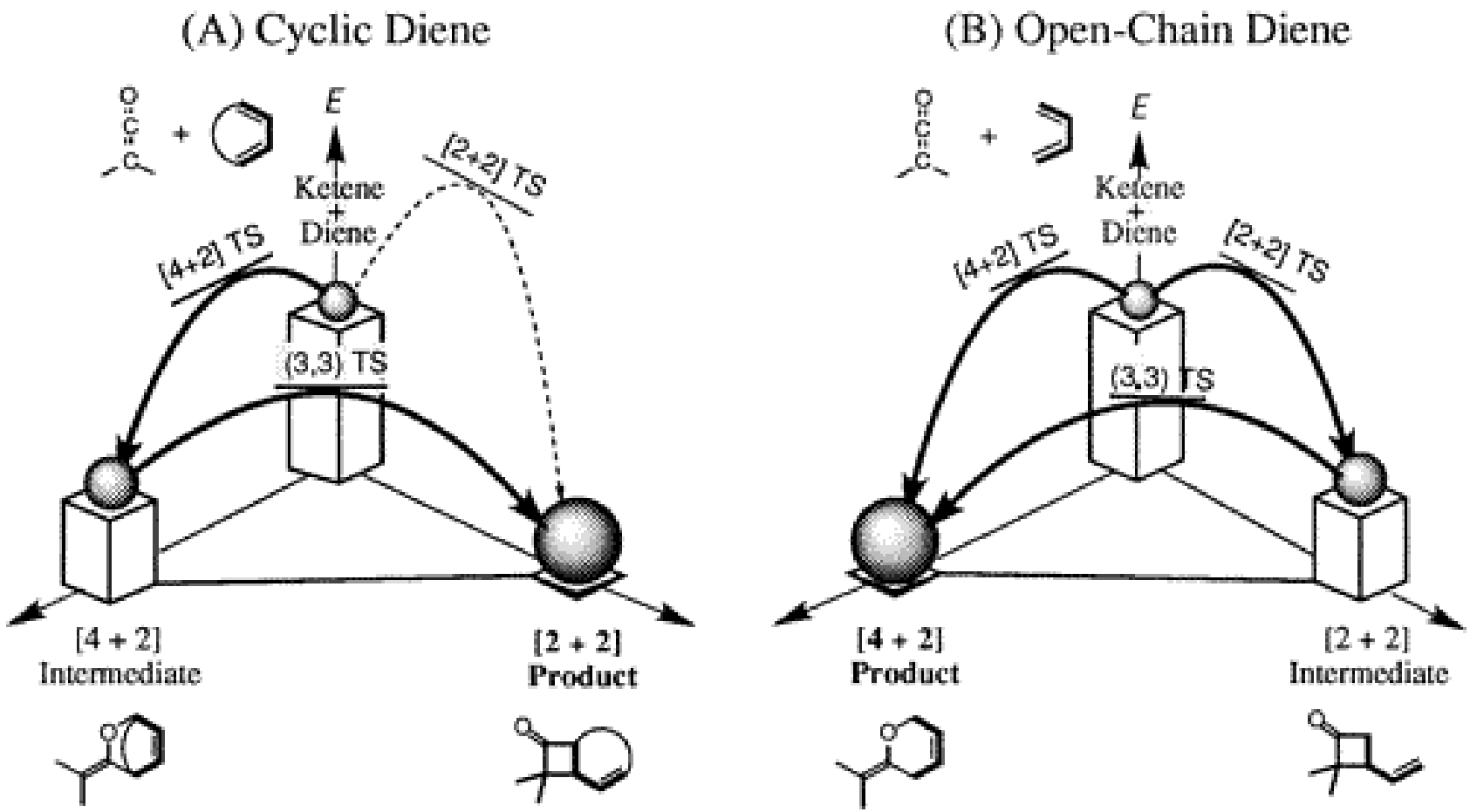


- Hyperconjugative interaction between H_5, H_7 and π^* of C=O
- Endo position is more sterically crowded

Ghosez, L.; et. al. *Helv. Chim. Acta,* **1982**, *65*, 703-720.

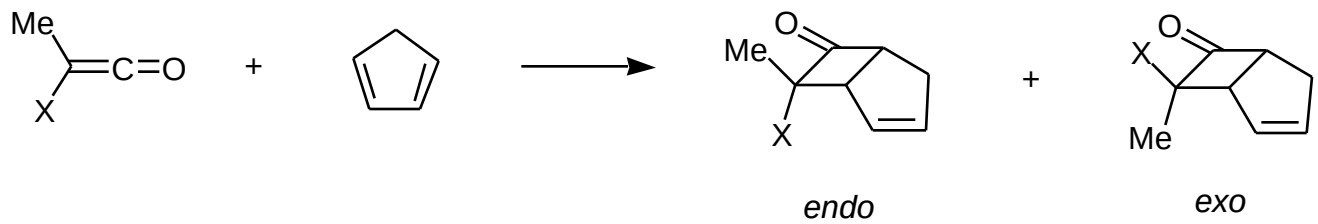
[2+2] Versus [4+2]





Machiguchi, T.; Yamabe, S.; et. al. *J. Am. Chem. Soc.* **1999**, *121*, 4771-4786.

Solvent Effects

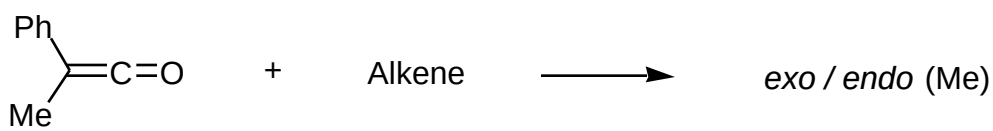


X	Solvent	*endo / exo*
Cl	hexane	4.3 / 1
Cl	Et_3N	2.2 / 1
Cl	$CHCl_3$	1.6 / 1
Cl	CH_3CN	0.59 / 1

X	Solvent	*endo / exo*
Br	hexane	0.71 / 1
Br	Et_3N	0.28 / 1
Br	CH_3CN	0.14 / 1

- Solvent effects implicate a zwitterionic intermediate

Brady, W. T.; Roe, R. Jr.; Hoff, E. F.; Parry, F. H., III, *J. Am. Chem. Soc.* **1970**, *92*, 146-148.



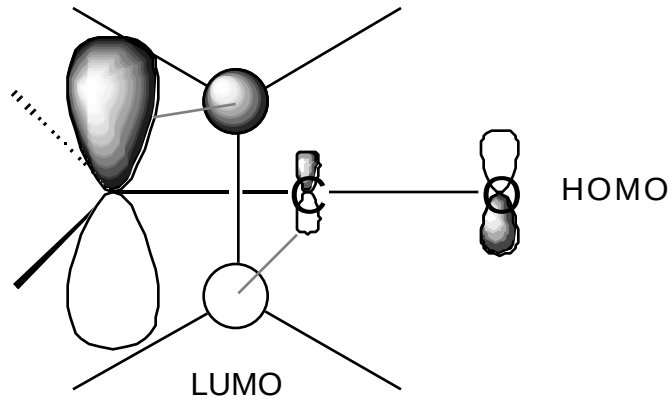
Alkene	*exo / endo* (Me)
Cp	>20
$EtOCH{=}CH_2$	2.3
Dihydropyran	1.7
Cyclohexene	2
Cyclooctene	1

- Not a highly ordered transition state

Brady, W. T.; Parry, F. H., III; Stockton, J. D. *J. Org. Chem.* **1971**, *36*, 1486-1489.

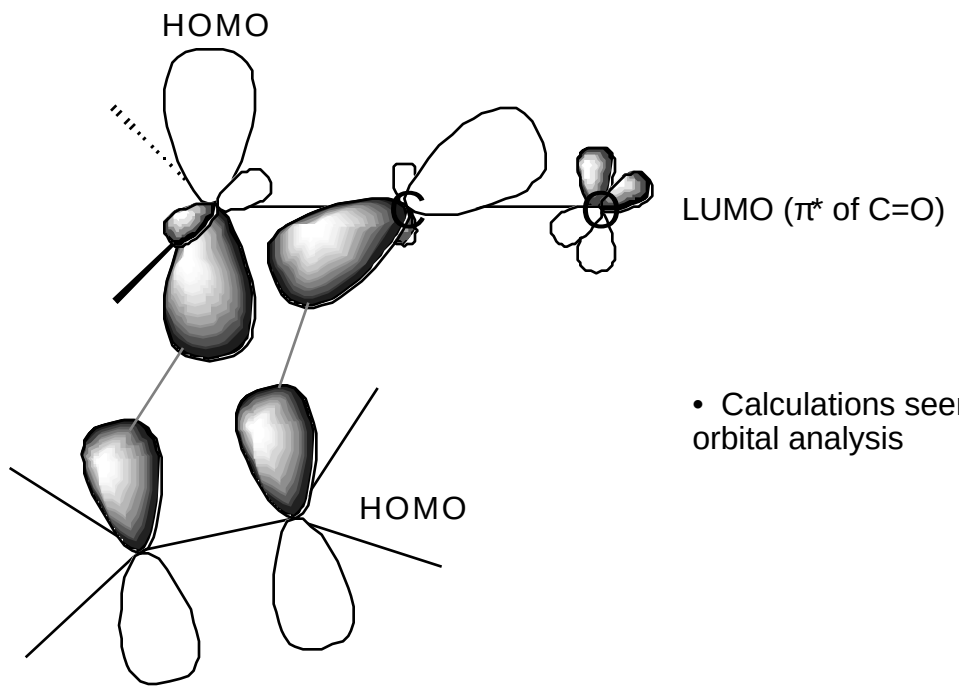
Woodward-Hoffmann Analysis

$(\pi^2_s + \pi^2_a)$



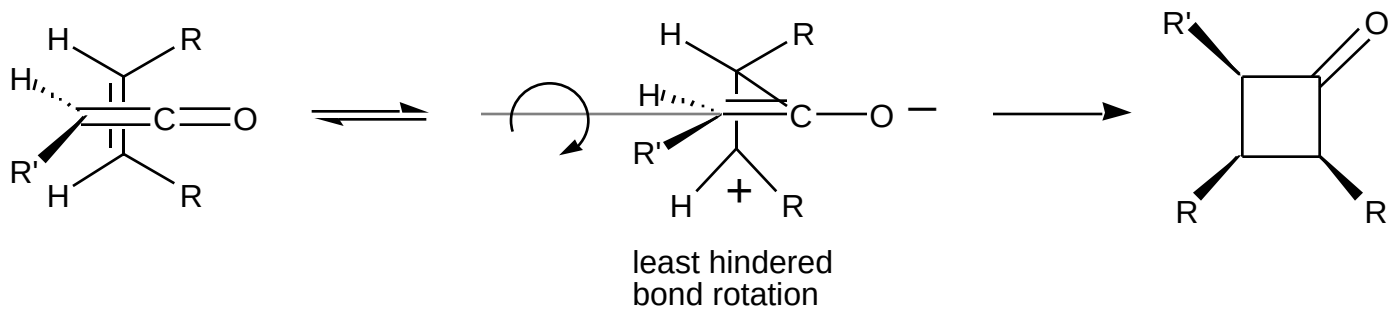
Or

$\pi^2_s + (\pi^2_s + \pi^2_s)$



- Calculations seem to support this orbital analysis

Stepwise Versus Concerted



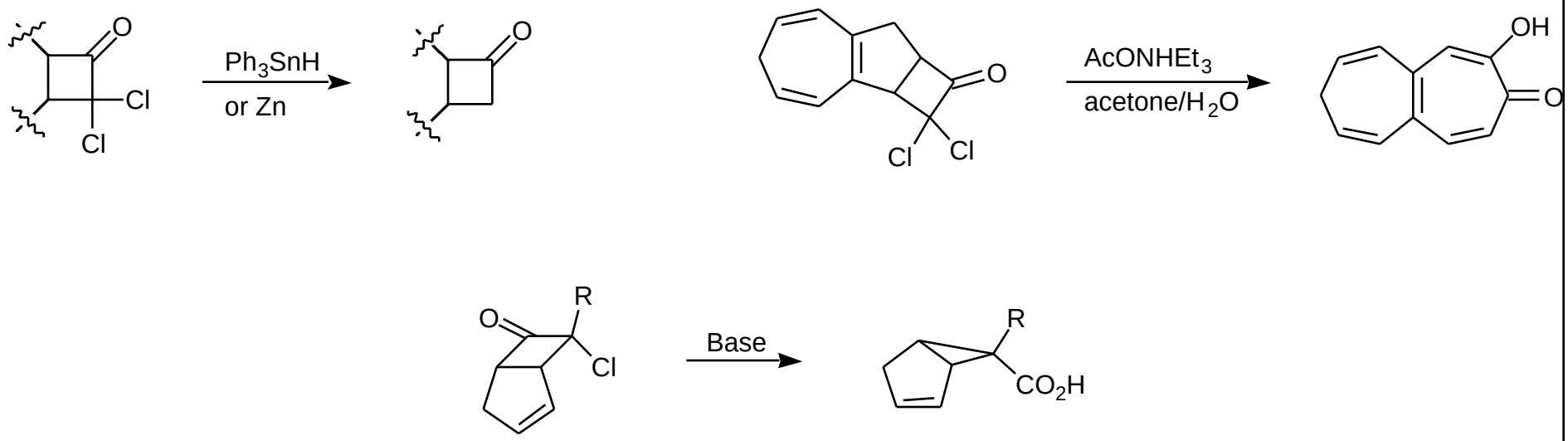
Stepwise

- Very large polar effects
- E olefins yield a mixture of *cis* and *trans* products
- Solvent effects observed, but it could merely be a ground state effect
- KIE seen for many reactions support stepwise mechanism
- Calculations (Wang and Houk) show a highly asynchronus transition state in the gas phase reaction
- All stereochemical outcomes can be rationalized assuming a stepwise mechanism

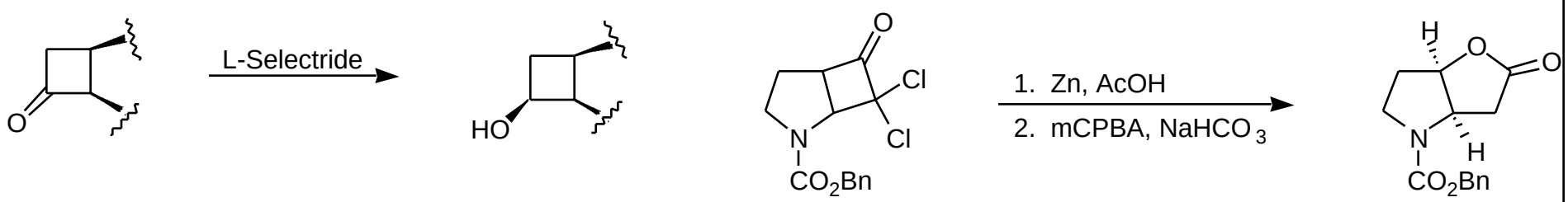
Concerted

- Ketenes add stereoselectively to Z alkenes
- Z olefins are much more reactive than E

Transformations of Cyclobutanones



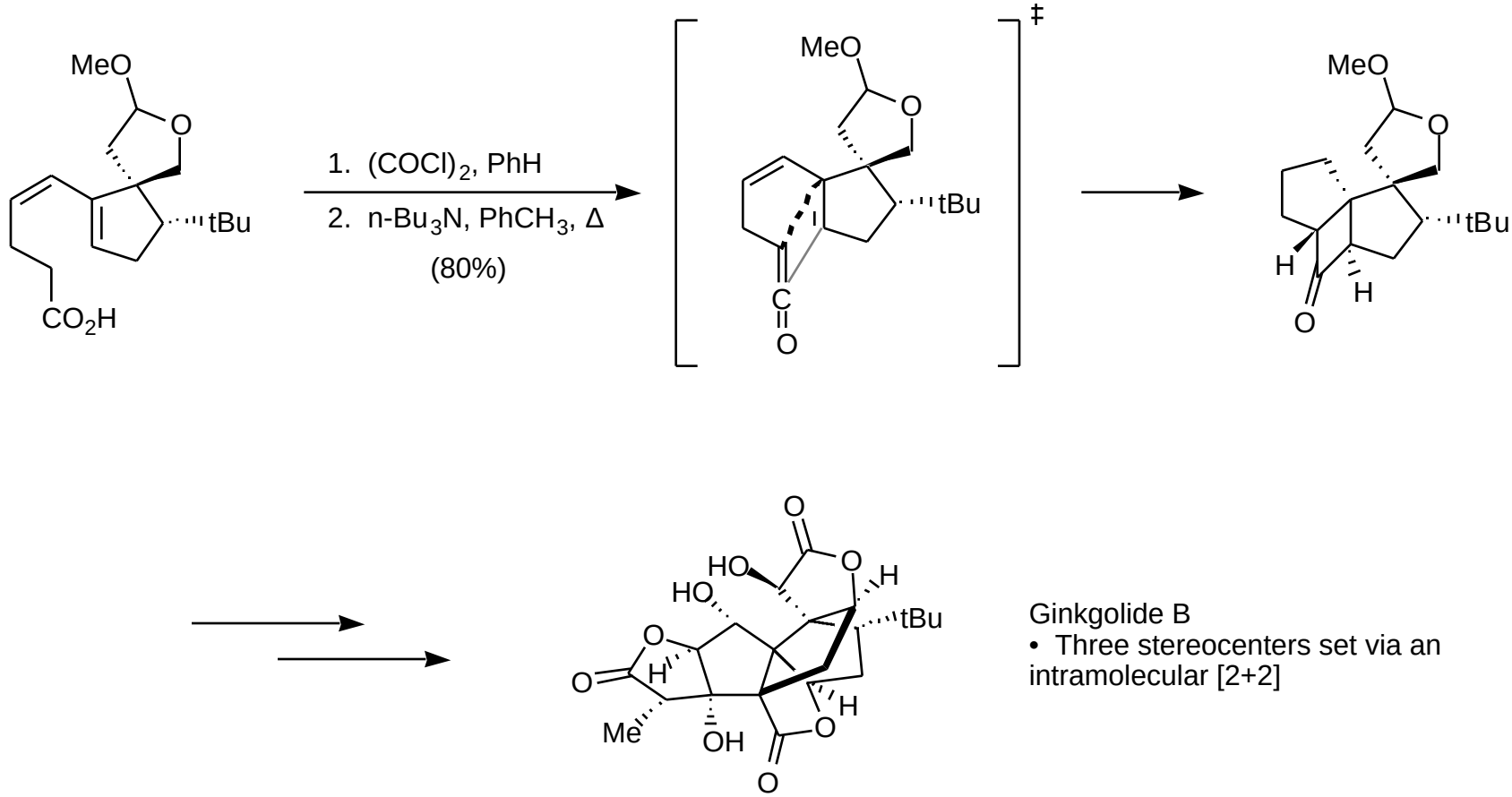
Brady, W. T. In *The Chemistry of Ketenes, Allenes, and Related Compounds* ; Patai, S. Ed.; Wiley: New York, **1980**, part 1, ch. 8.



Recent Progress in the Chemical Synthesis of Antibiotics ; Lukacs, G.; Ohno, M. Eds.; Springer-Verlag: Berlin, **1990**.

Lorreia, C. R. D. et. al. *Tetrahedron Lett.* **1993**, 27-30.

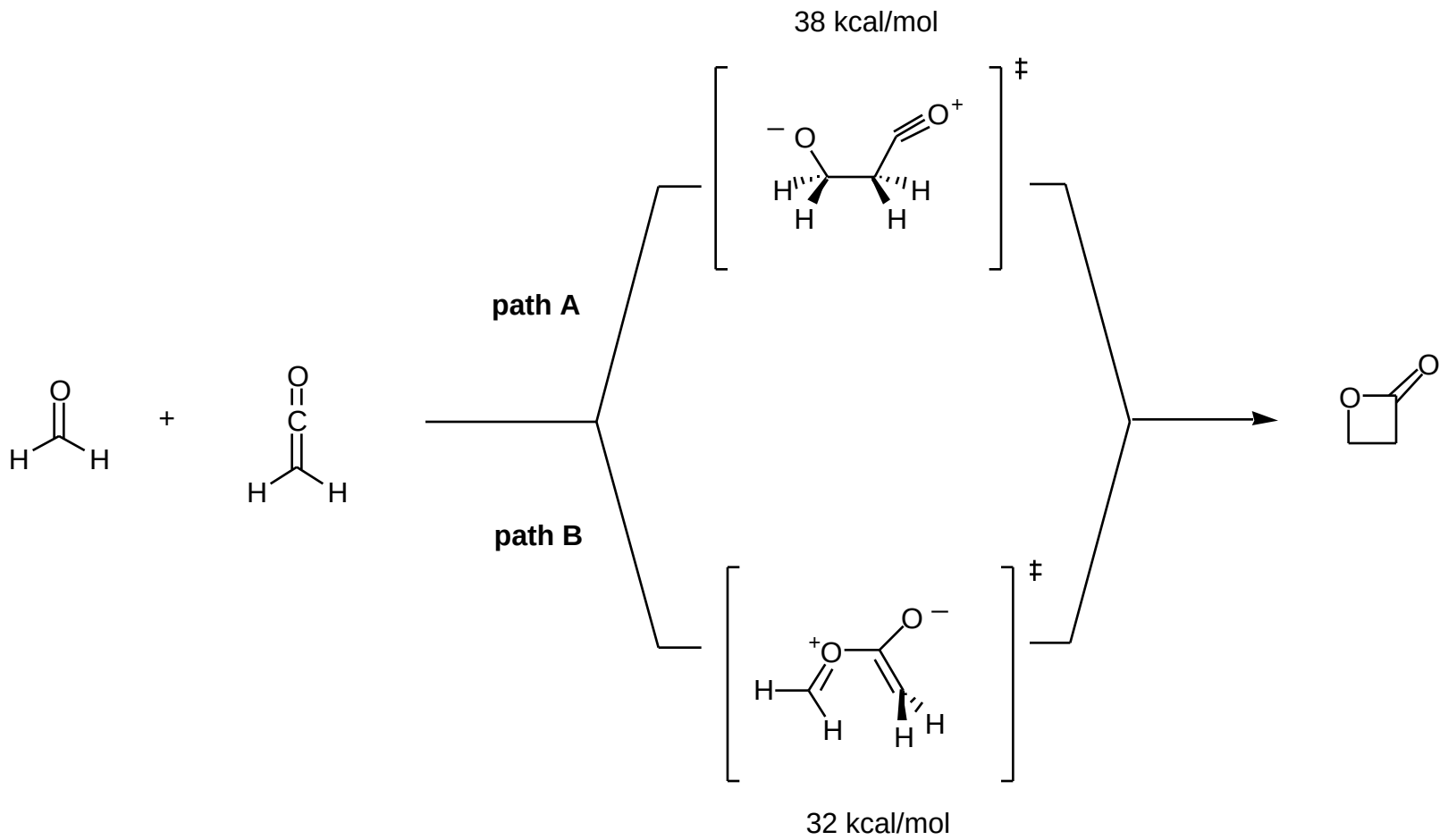
Application to Ginkgolide B



Ginkgolide B
- Three stereocenters set via an intramolecular [2+2]

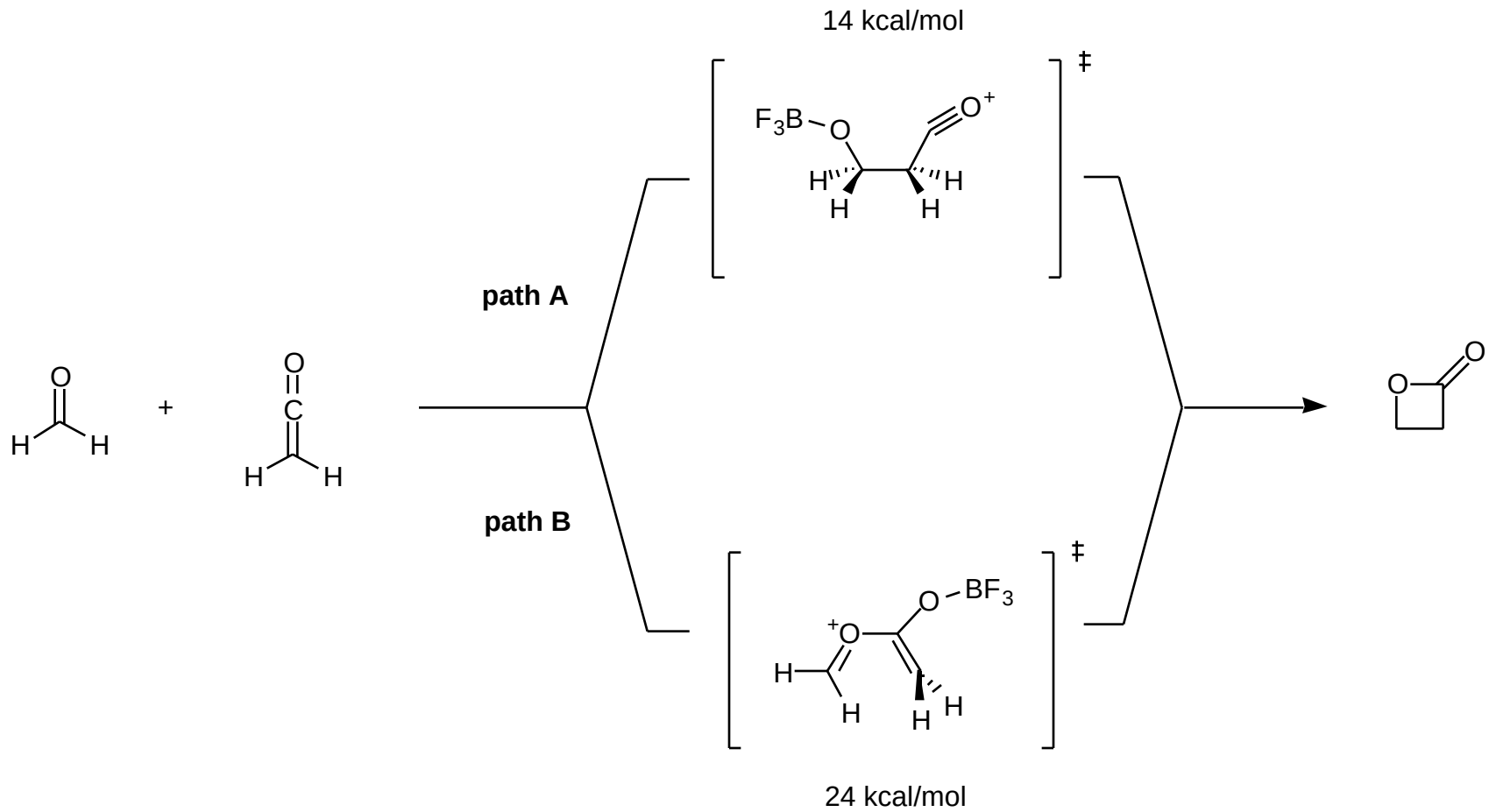
Corey, E. J.; Kang, M. -C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988,** 110, 649.

Un-catalyzed [2+2] Mechanism



Pons, J. -M.; et. al. *J. Am. Chem. Soc.* **1997**, *119*, 3333.

BF_3 Catalyzed [2+2] Mechanism

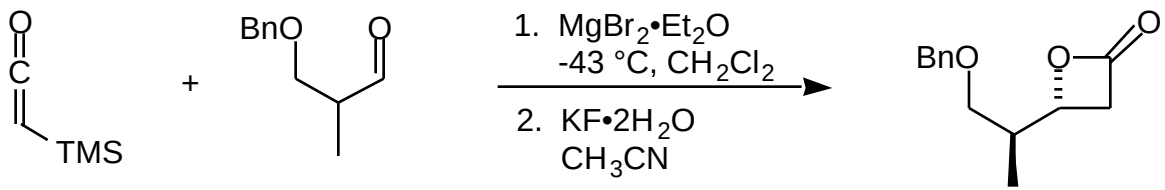


Pons, J. -M.; et. al. *J. Am. Chem. Soc.* **1997**, *119*, 3333.

- Concerted, asynchronus early transition state with a half electron charge on boron as calculated by Gaussian (MP2/G-31 and HF/G-31) with ZPE corrections and solvent effects.

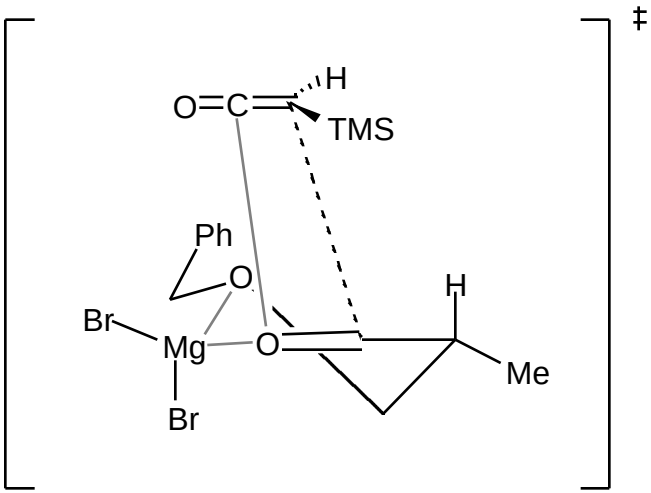
Cossio, F. P.; et. al. *J. Am. Chem. Soc.* **1994**, *116*, 9613.

Chelation Controlled Ketene-Aldehyde [2+2]



98:2 = *anti:syn*
94% yield

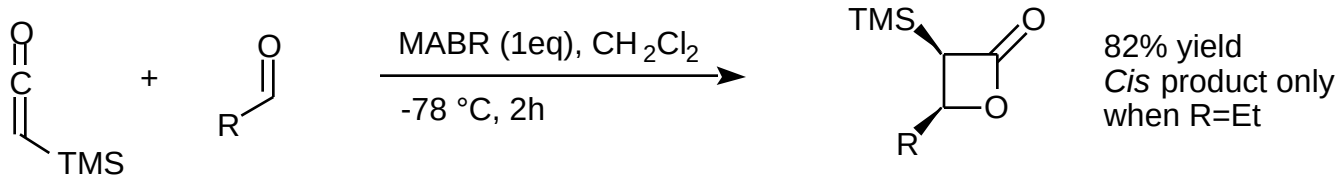
• d.e. with TMS group not reported

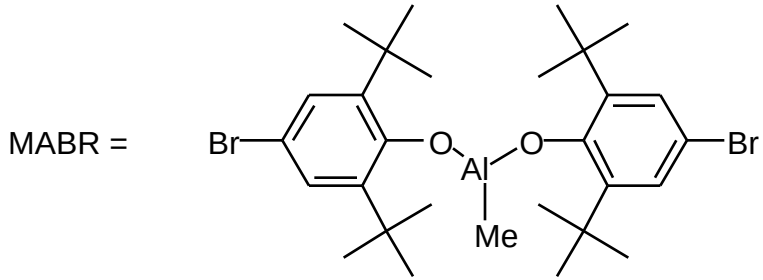


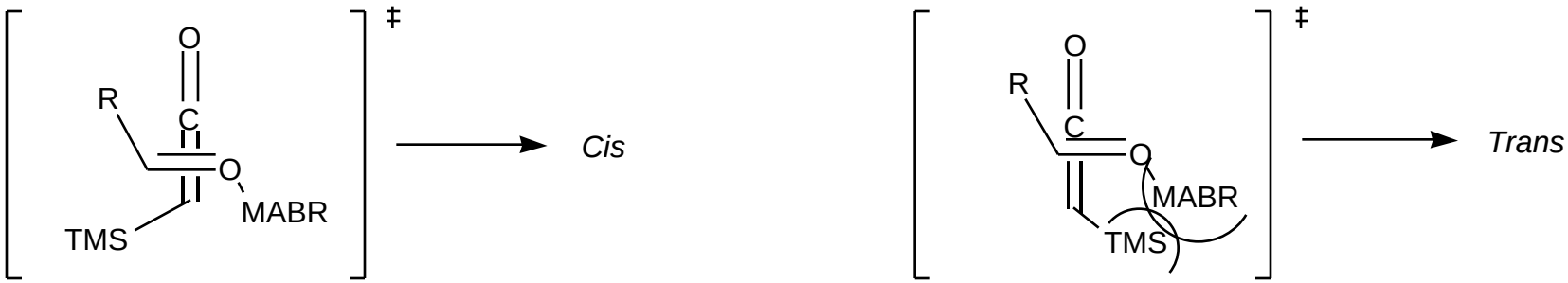
Vemribo, R.; Romo, D. *Tetrahedron Lett.* **1995**, *36*, 4159.

see also: Pommier, A.; Pons, J.-M.; Kocienski, P.J.; Wong, L. *Synthesis* **1994**, 1294.

Lewis Acid Catalyzed [2+2]

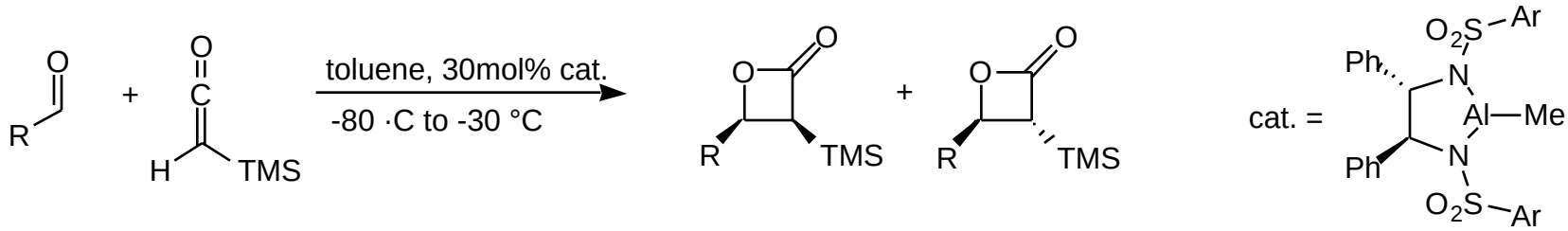






Concepcion, A. B.; Maruoka, K.; Yamamoto, H. *Tetrahedron*, **1995**, *51*, 4011.

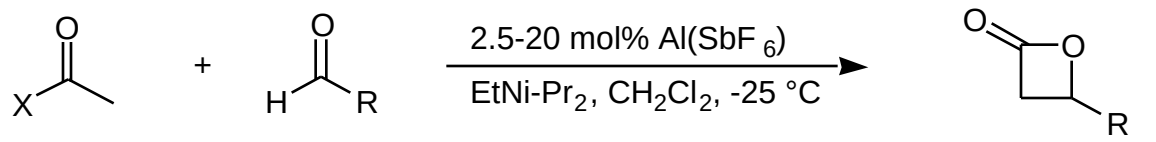
Catalytic, Enantioselective [2+2]



Entry	R	*cis:trans*	Yield (%)	ee (%)
1	Bn	100:0	43	40
2	$BnCH_2$	100:0	43	44
3	c-hex	95:5	57	55
4	Bn	83:17	56	83
5	$BnCH_2$	90:10	80	44
6	c-hex	85:15	32	68
7	$C_{11}H_{23}$	94:6	67	47
8	p-$MeOC_6H_4CH_2$	99:1	77	83
9	Bn	79:21	82	62
10	$BnCH_2$	90:10	85	30
11	c-hex	77:23	57	53
12	Bn	75:25	72	82
13	$BnCH_2$	94:6	82	36
14	c-hex	69:31	43	67
15	$C_{11}H_{23}$	82:18	67	48
16	p-$MeOC_6H_4CH_2$	70:30	81	75

Dymock, R. W.; Kocienski, P. J.; Pons, J. -M. *Chem. Commun.* , **1996**, 1053

in-situ Ketene-Aldehyde [2+2]



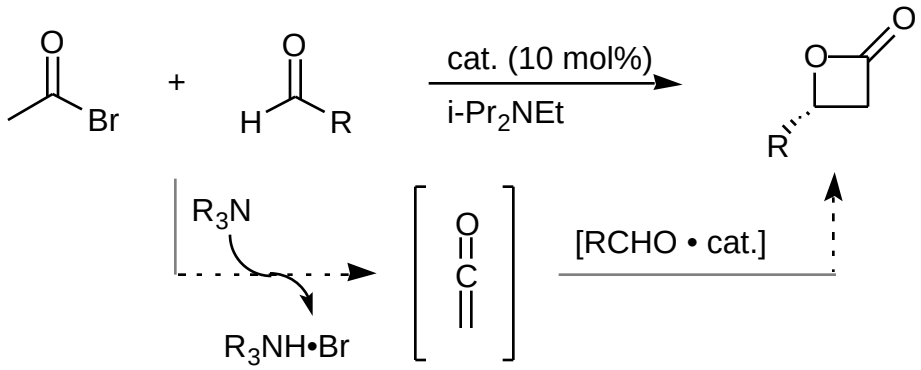
1.5 eq.
(X = Cl or Br)

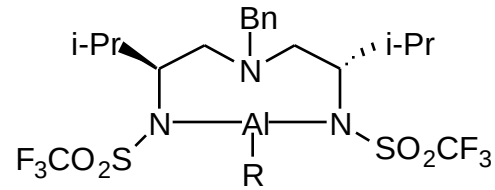
60-93% yield

- Only cis product observed when EtCOCl utilized

Nelson, S. G. et. al. *Tetrahedron Lett.* **1999**, *65*, 35-39.

"Masked Aldol"



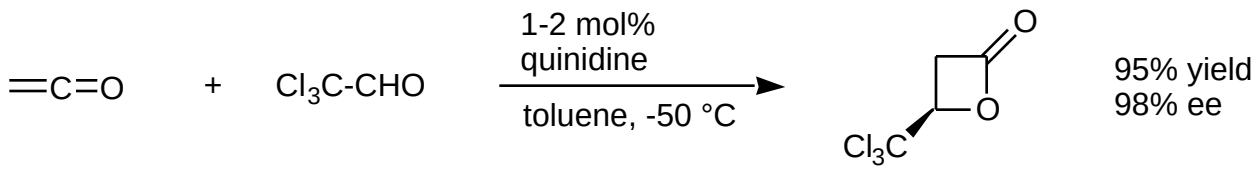


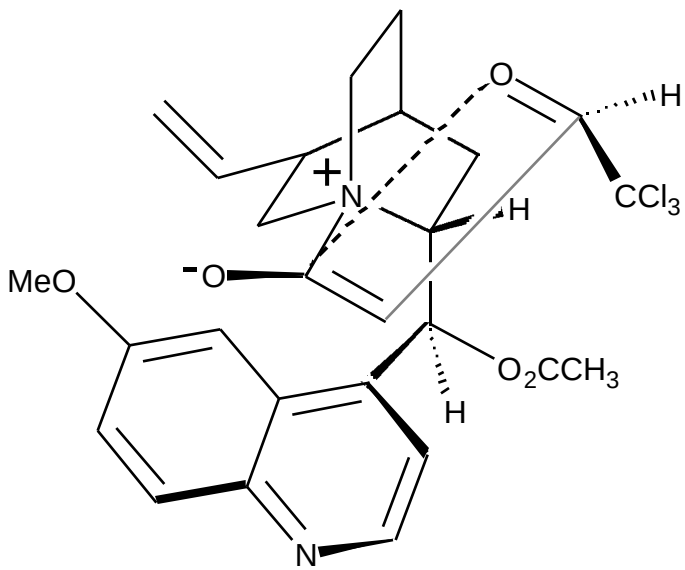
cat. = **5a**: R = Me
5b: R = Cl

entry	Aldehyde **2** (R)	catalyst [time (h), temp (°C)]	% yield	% ee **3** (configuration)
a	$BnOCH_2$—	**5b** (8, -40)	91	92 (*R*)
b	$PhCH_2CH_2$—	**5a** (16, -50)	93	92 (*S*)
	$PhCH_2CH_2$—	**5a** (72, -78)	89	95 (*S*)
c	$CH_2CH(CH_2)_8$—	**5b** (16, -50)	91	91 (*S*)
d	Me_2CHCH_2—	**5a** (24, -50)	80	93 (*S*)
e	$BnOCH_2CH_2$—	**5b** (16, -40)	90	91 (*S*)
f	$TBDPSOCH_2$—	**5b** (16, -40)	74	89 (*R*)
g	$BnOCH_2$—≡—	**5a** (16, -50)	86	93 (*R*)
h	Me_3C—≡—	**5a** (16, -50)	91	85 (*R*)
i	C_6H_{11}—	**5b** (24, -40)	56	54 (*R*)

Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* Web ASAP Oct. 4, **1999**.

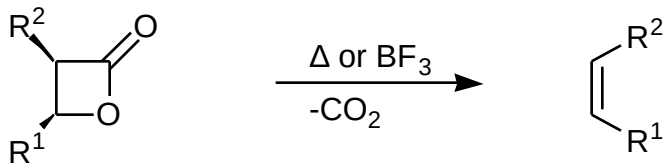
Enantioselective Base Catalyzed [2+2]

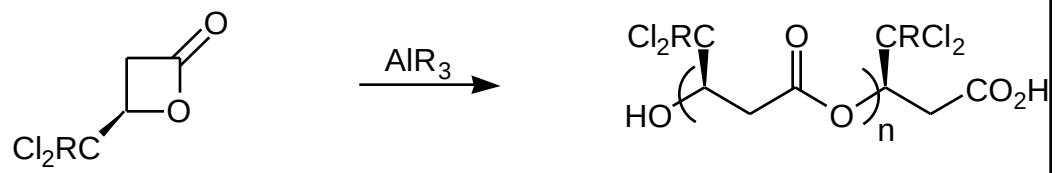




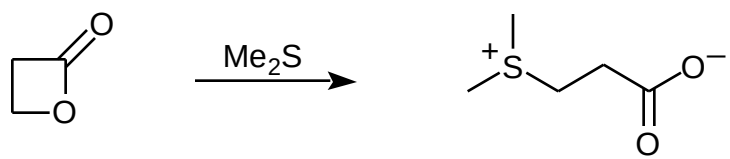
Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977.

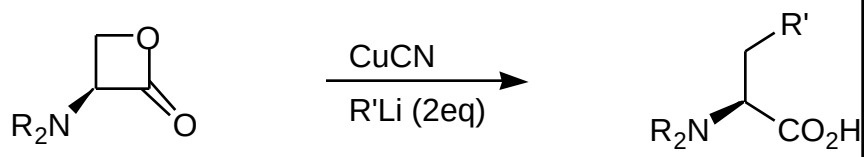
Transformations of β-Lactones



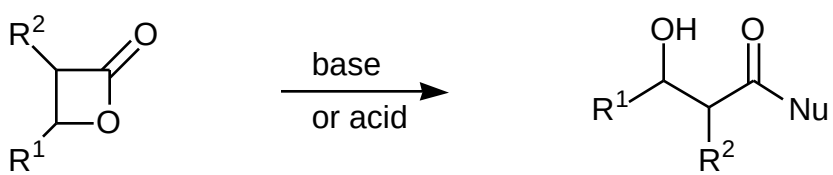


Lavallee, C. et. al. *Macromolecules*, **1984**, *17*, 2457.





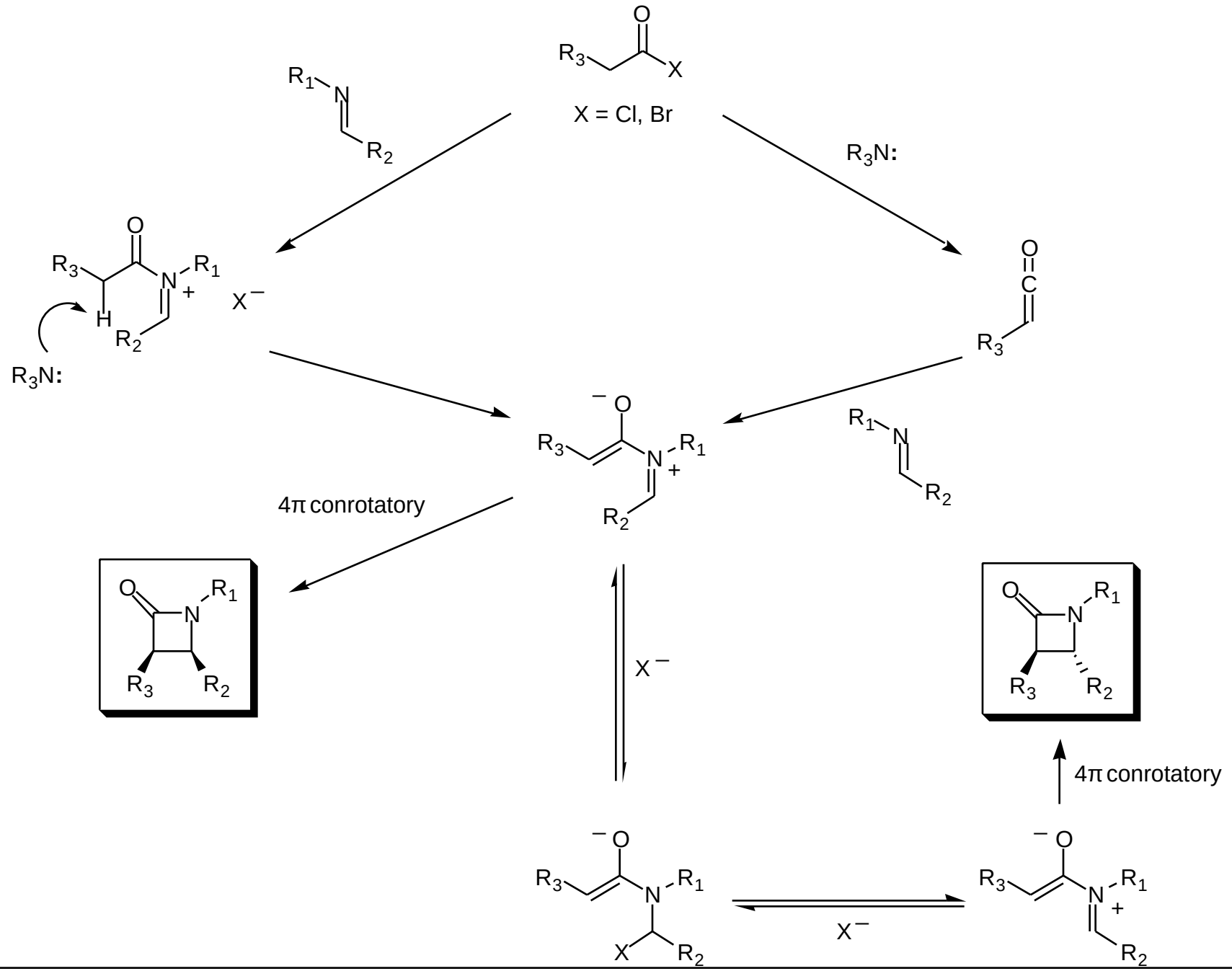
Arnold, L. D.; Drover, J. C. J.; Vederas, J. C. *J. Am. Chem. Soc.* **1987**, *107*, 4649.



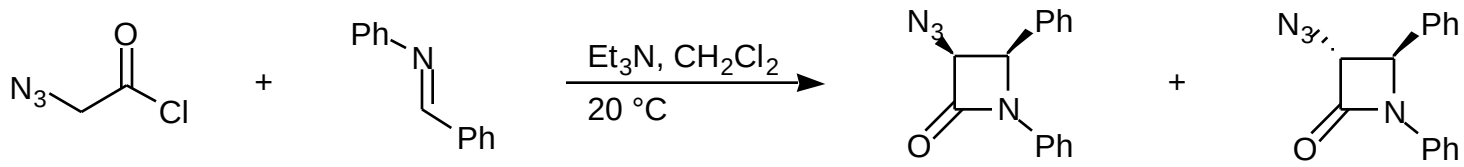
Nu = OH_2, ROH, R_2NH

Zaugg, H. E. *Org. React.* **1954**, *8*, 305.

Staudinger Reaction

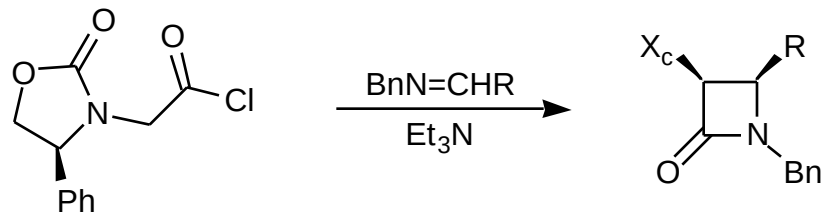


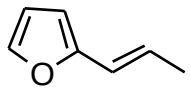
Diastereoselective Staudinger



addition of acid chloride (to imine + Et_3N)	66%	34%
addition of Et_3N (to imine + acid chloride)	33%	67%

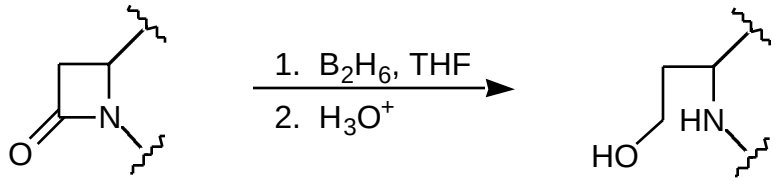
Bose, A. K.; Anjaneyula, B.; Bhattacharya, S. K.; Manhas, M. S. *Tetrahedron* **1967**, *23*, 4769.

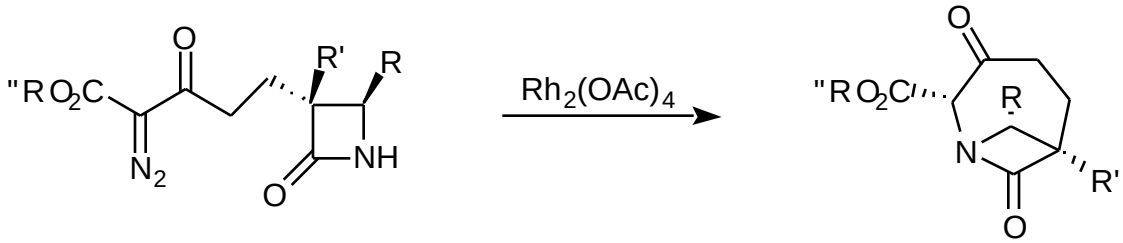


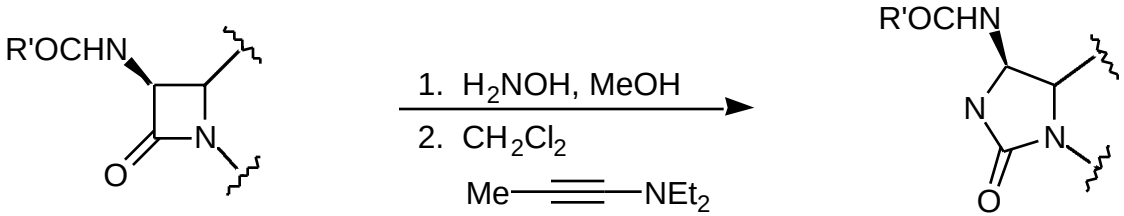
R	yield (%)	de (%)
Ph	90	94
trans-PhCH=CH-	82	90
	80	94

Evans, D.A.; Sjogren, E.B. *Tetrahedron Lett.* **1985,** 3783-6, 3787-90.

Transformations of β-Lactams

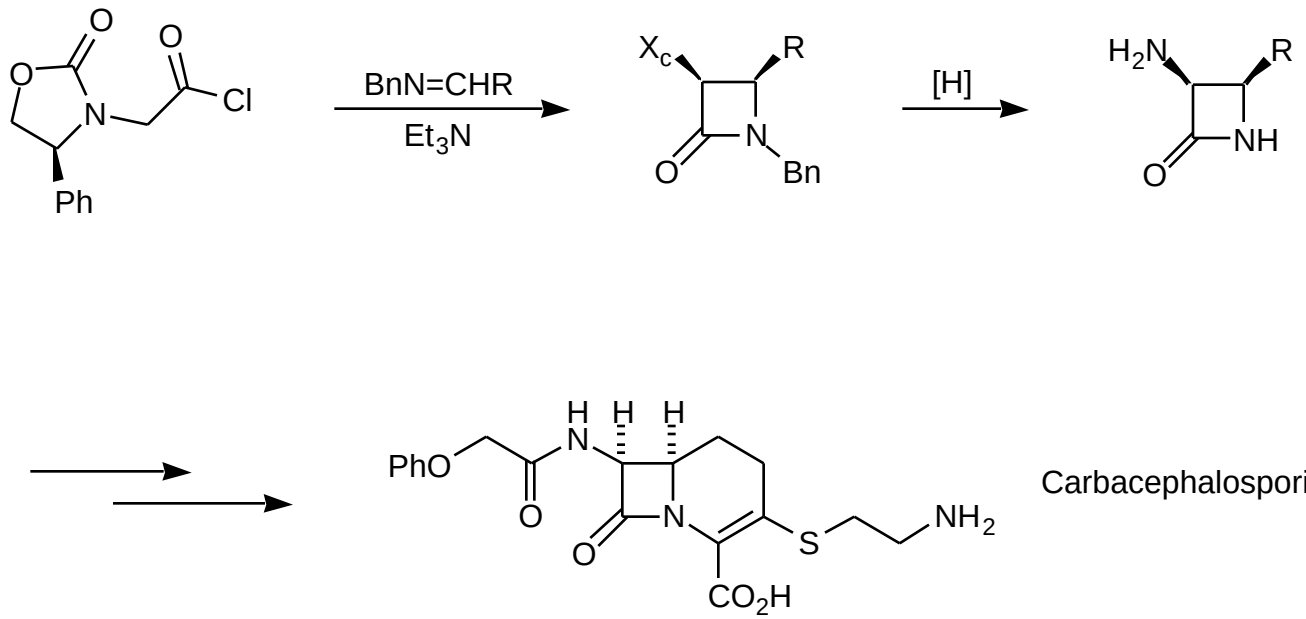






Recent Progress in the Chemical Synthesis of Antibiotics ; Lukacs, G.; Ohno, M. Eds.; Springer-Verlag: Berlin, **1990**.

Application To β-Lactam Antibiotics



Carbacephalosporin Nucleus

Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985,** 3783-6, 3787-90.
Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988,** 5065-8.

Conclusion

- Ketenes undergo [2+2] cycloadditions with alkenes, carbonyls, imines, and other unsaturated functionalities.

- Ketenes are ambiphilic, thus the mechanism of the cycloaddition is stepwise with the ketene acting as either the nucleophile, or the eletrophile.

- Most cycloadditions are highly stereoselective and regioselective, although the stereochemical outcome is not always predictable.

- Ketenes cycloadditions provide access to a variety of useful synthetic intermediates, including β-lactams.