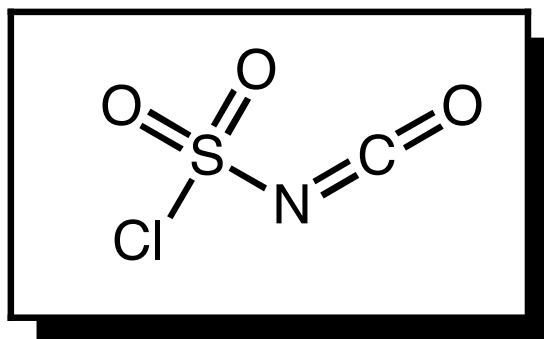


General Reactivity and Applications of Chlorosulfonyl Isocyanate (CSI)



Daniel Tzvi Cohen
Long Literature Presentation
January 7, 2010

Overview

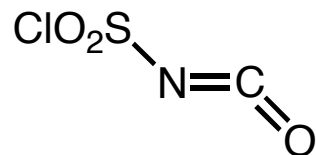
- ❑ Background/Discovery/Applications
- ❑ Basic Functional Groups Reactivity with CSI
- ❑ Total Synthesis of (+)-Blastmycinone

Discovery/Background

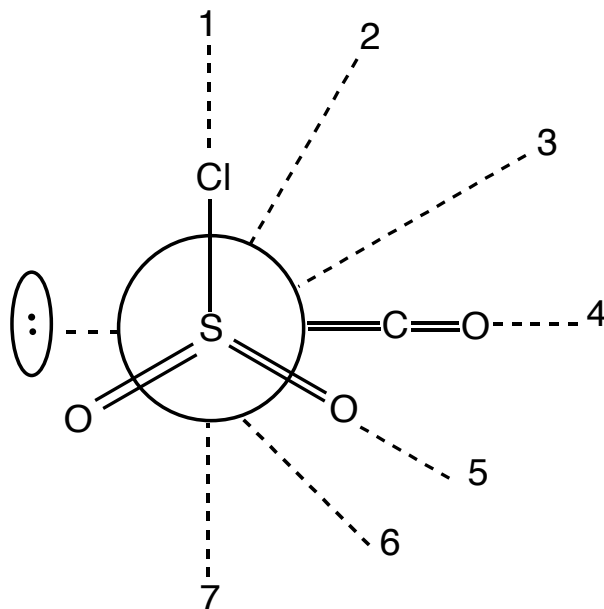
- CSI was discovered by Graf and coworkers in Germany in the early 1950's



- Liquid at room temperature
- Fumes in moist air and reacts violently with water
- Incompatible with protic solvents
- Thermally stable up to 300°C
- NCO lowest energy geometry is bent (118°) based on microwave spectroscopic data

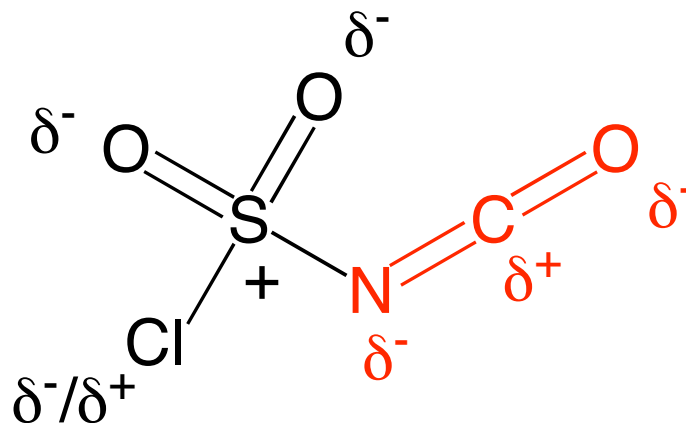


Dihedral Angle Rational



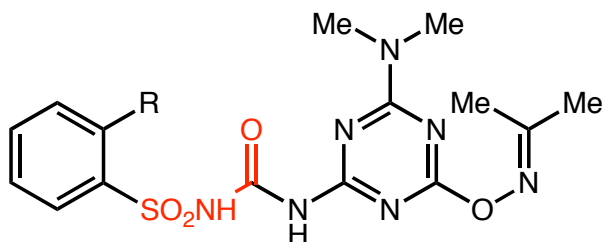
- Positions 1 and 5 repulsion between C=N bond and lone pairs of O/Cl
- Positions 3 and 7 repulsion between nitrogen lone pairs and O/Cl lone pairs
- Position 2 the C=N bond is near the Cl lone pairs
- Position 6 the nitrogen lone pairs are near the Cl lone pairs
- Position 4 Dihedral angle of $\sim 94^\circ$ is preferred (confirmed by X-ray diff.)

Reactivity Pattern



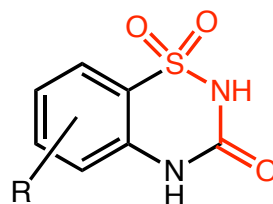
- Complexity of this reactant allows for various products
- Reactivity is dependent on temp/solvent and other reactant(s)
- Isocyanate is the most reactive part of CSI

CSI Applications



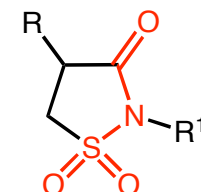
Phenylsulfonyl ureidotriazoles

Increases leaf length in corn



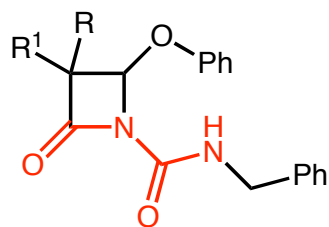
Phenylaminosulfonyl ureas

Pesticides for protecting crops



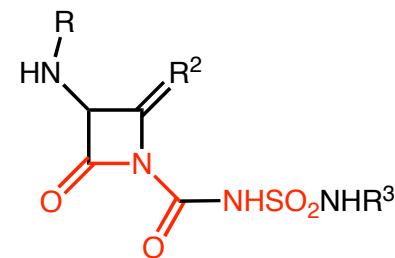
Isothiazolidinones

Anti-inflammatory and anti-metastatic agent



Acylated β -Lactams

Useful in the treatment of leukemia

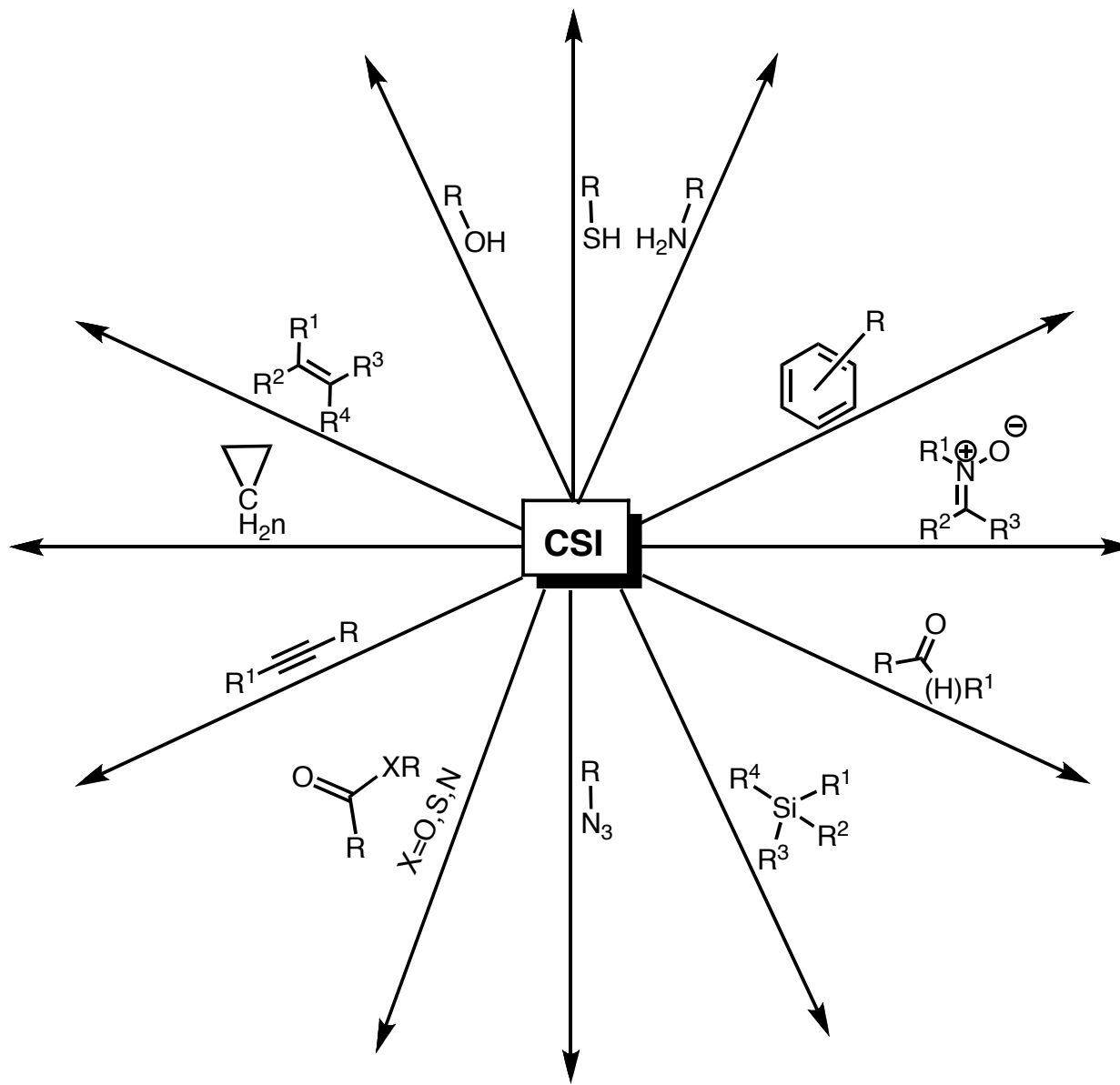


Acylated β -Lactams, derived from ketenes

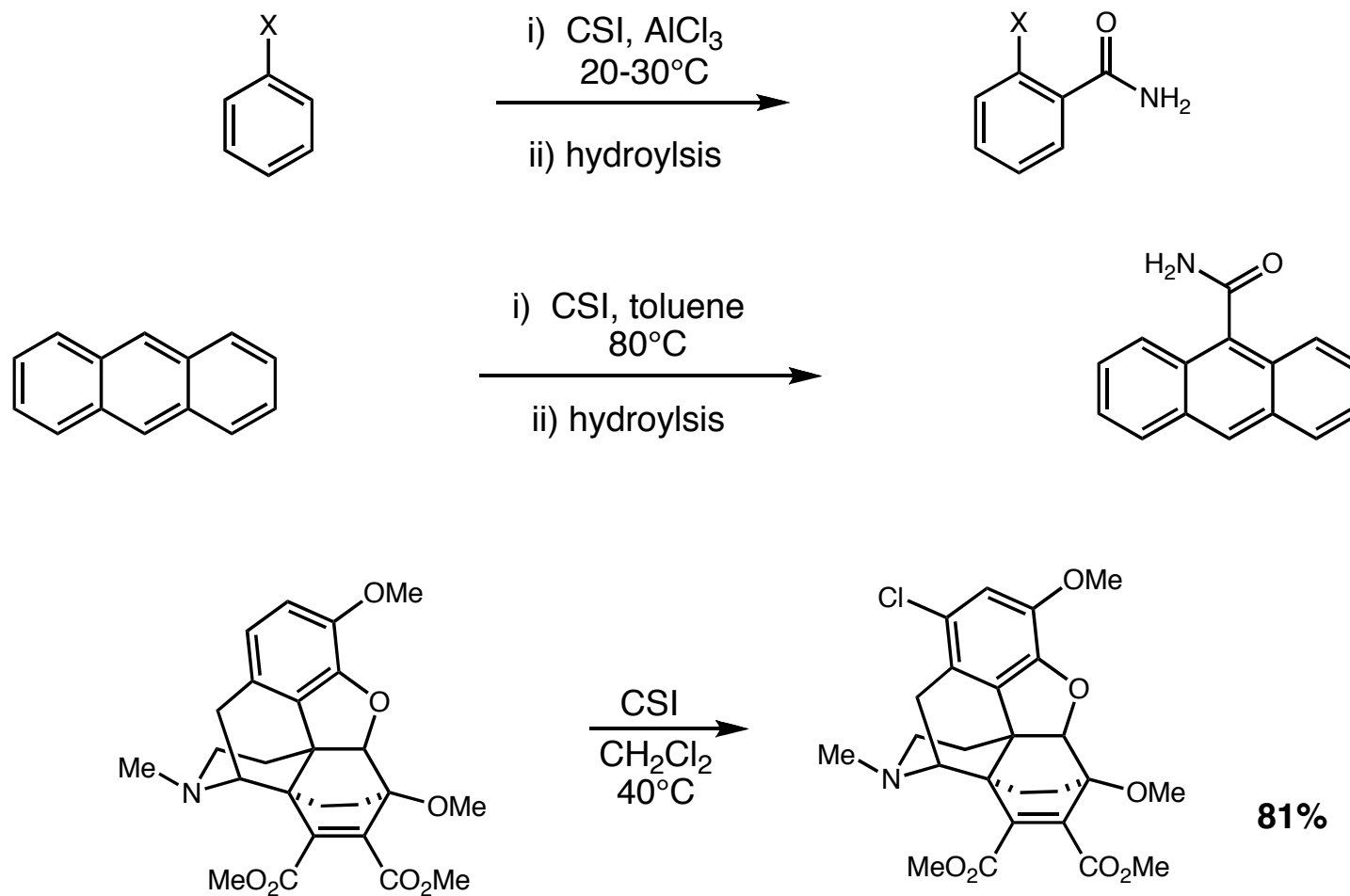
Antibacterial agents

CSI is used to produce many commercially available products for agricultural, biological, and body ailments.

Reactivity of *CSI* with different Functional Groups

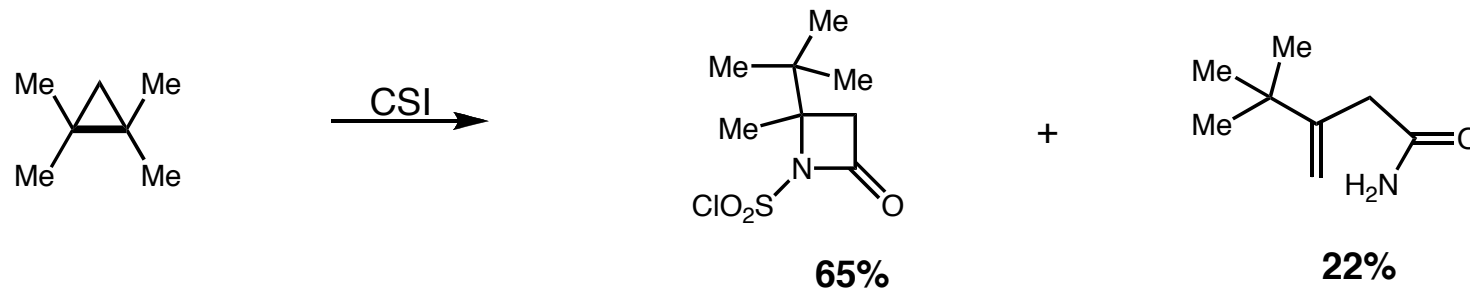


Aromatics

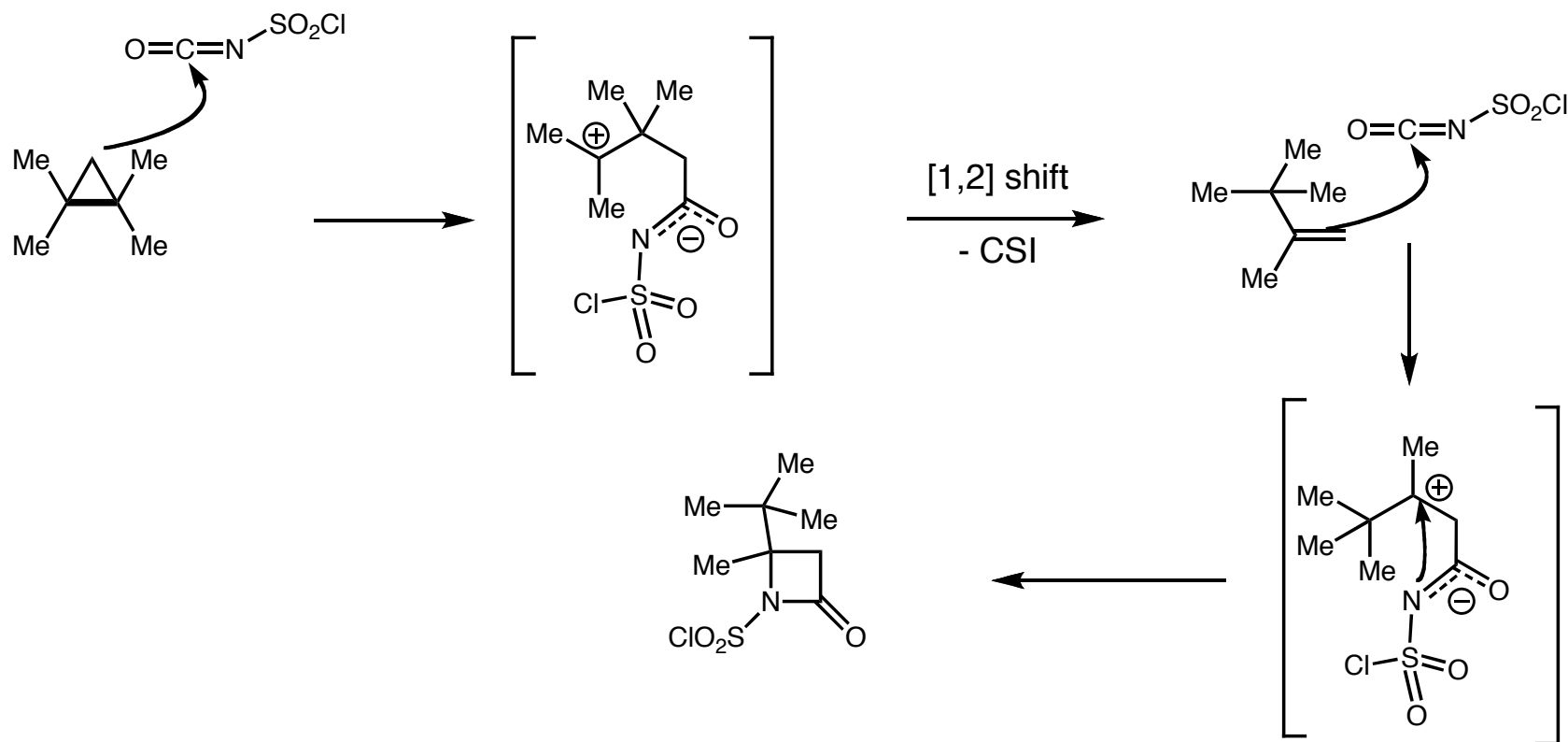


- 1) Graf, R. *Justus Liebigs Annalen der Chemie*, **661**, 111
- 2) Giger, R., et al. *Tetrahedron*, **29**, 2392

Cycloalkanes

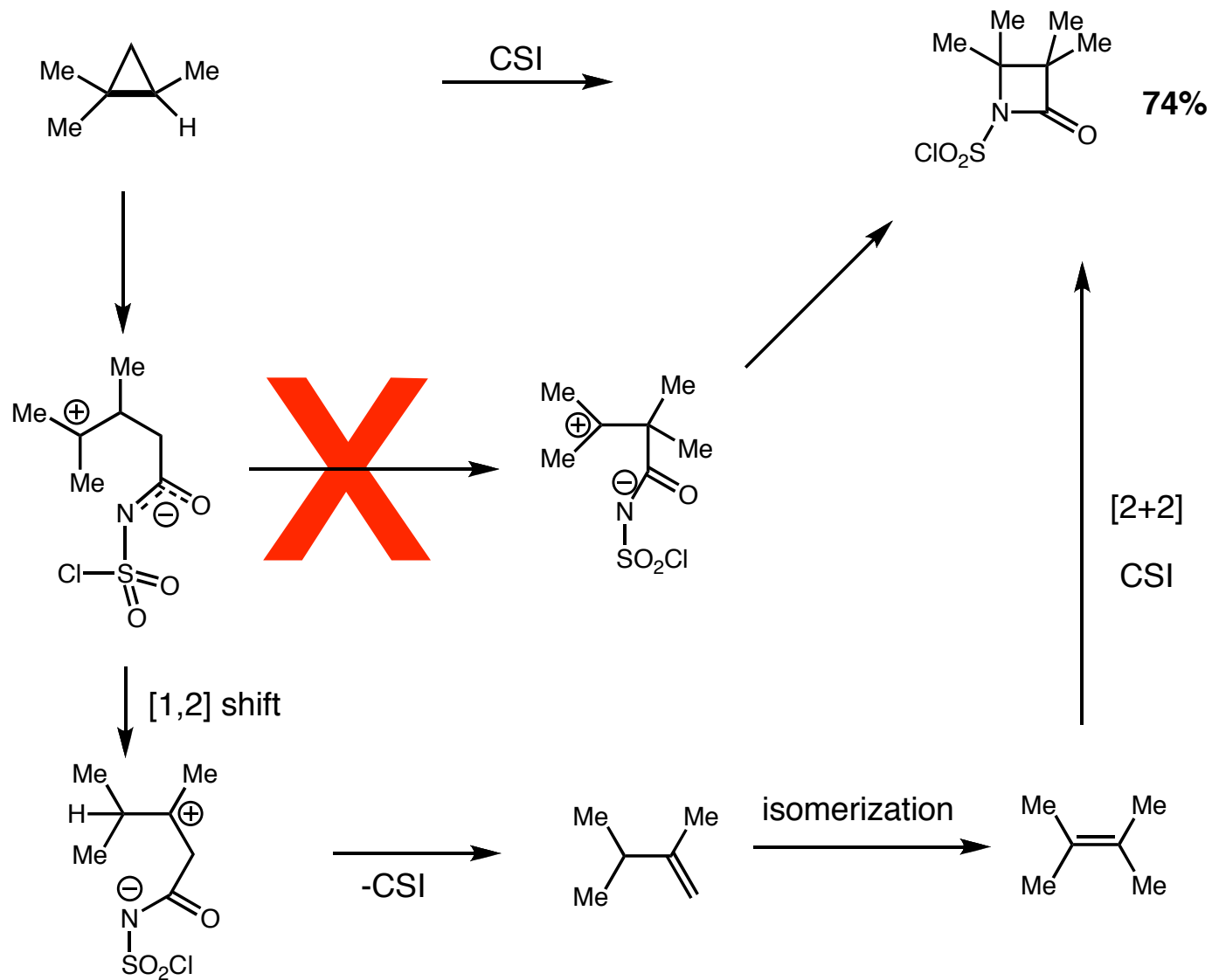


Mechanism

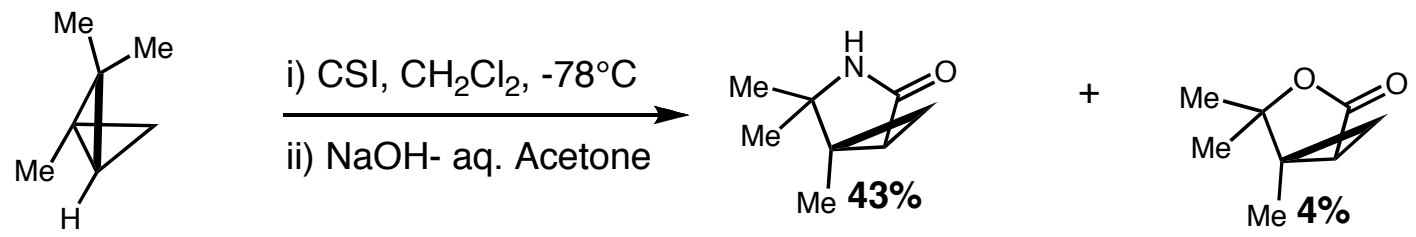
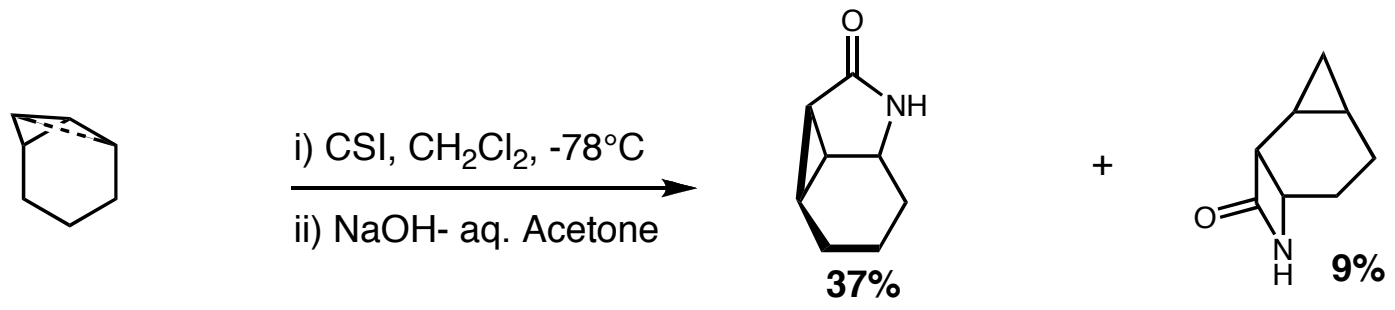


Moriconi, E.J., *et al. JOC*, **33**, 3448 (1968)

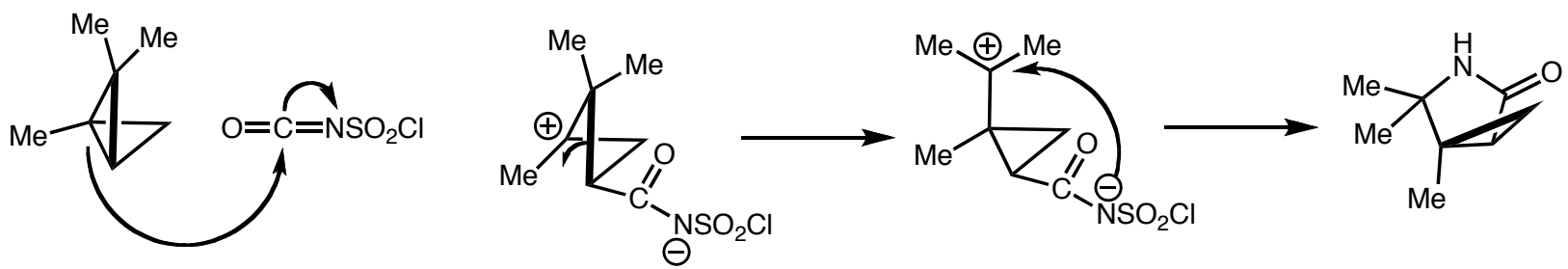
Rearrangement Rational



Cycloalkanes Continued

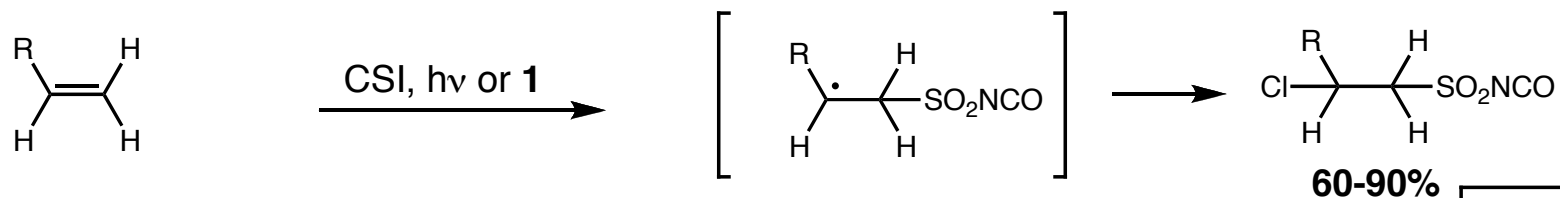


Mechanism

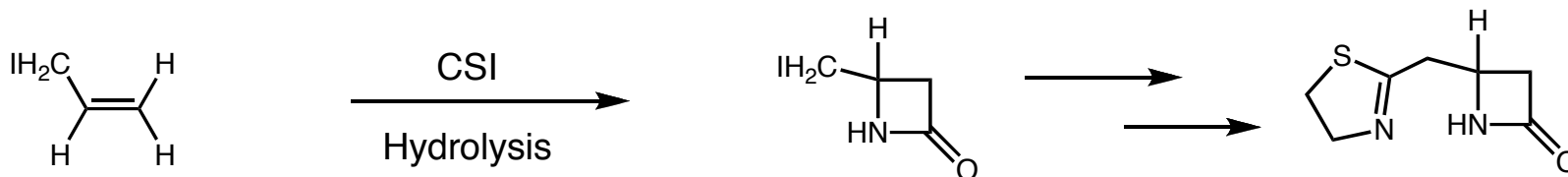
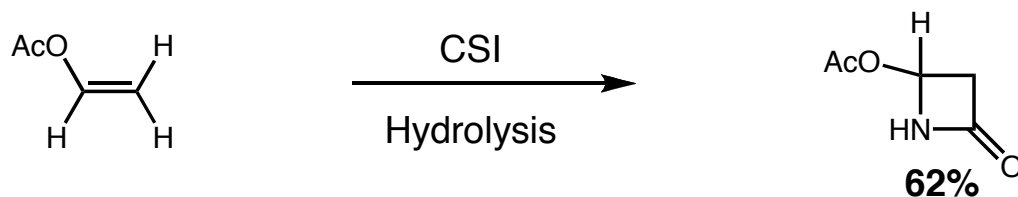
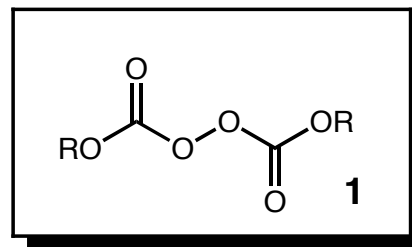


Paquette, L.A., et al. *J. Am. Chem. Soc.*, **93**, 3448 (1971)

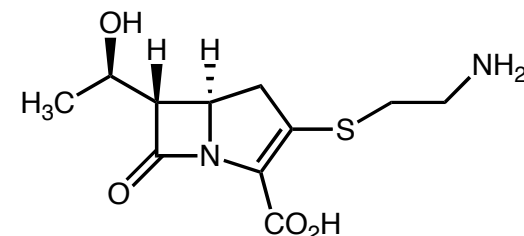
Monosubstituted Alkenes



R = H, Me, Et, Bu, ClCH₂, Cl₂CHCH₂

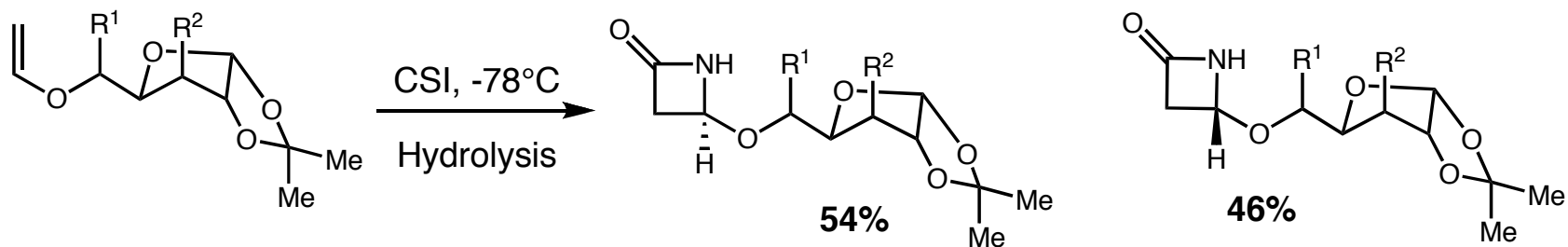
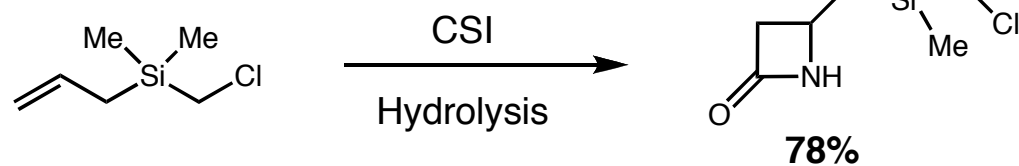
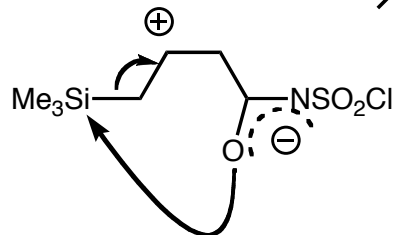
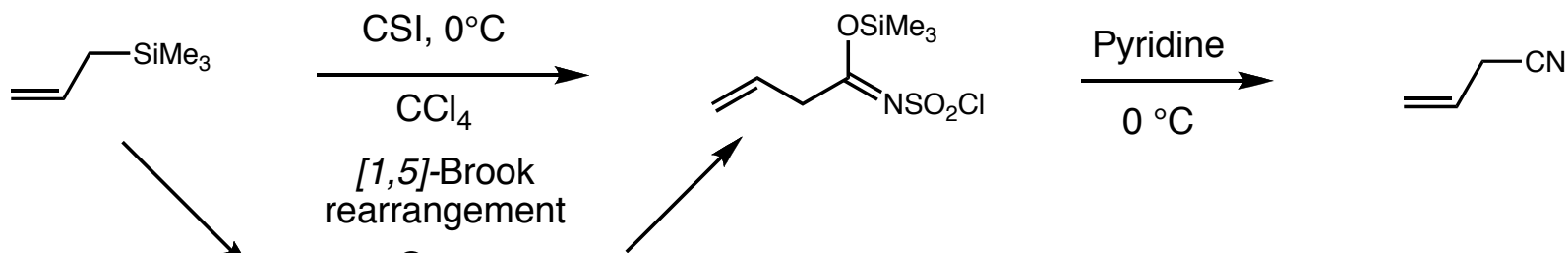


thienamycin intermediate



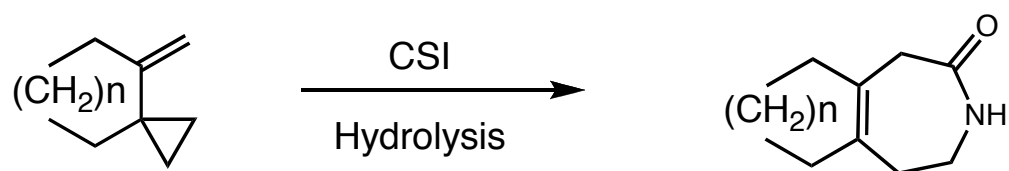
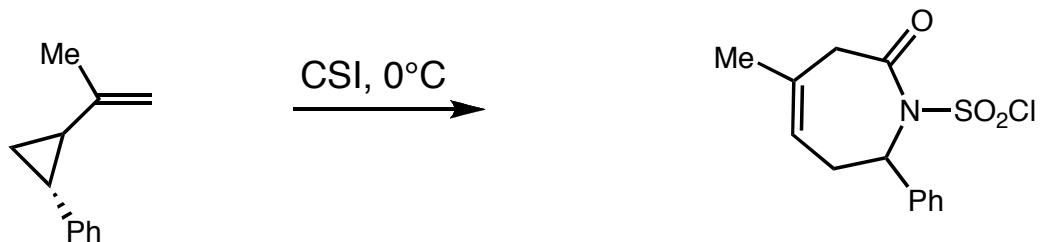
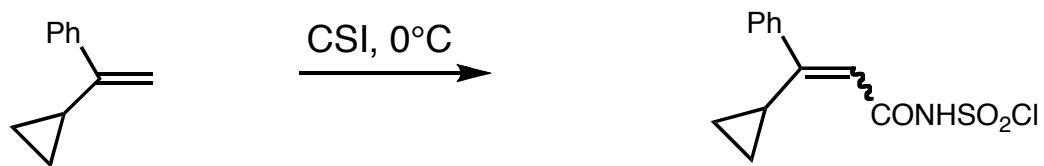
- 1) *Eur. Pat. Appl.* E.P. 53, 331, C.A. **97**, 144359^z (1982)
- 2) Mickel, S. J. *et al. Org. Syn.* **65**, 135
- 3) Miyavdera, T., *et al. Heterocycles* **19**, 1497

More Monosubstituted Alkenes



- 1) Dunogues, J., *et al.*, *J. Organomet. Chem.*, **116**, C45-C48
- 2) Gehanne, S., *et al.*, *Tet. Lett. Syn.* **35**, 2047
- 3) Kaluza, Z., *et al.* *Tet. Asymm.* **6**, 1719

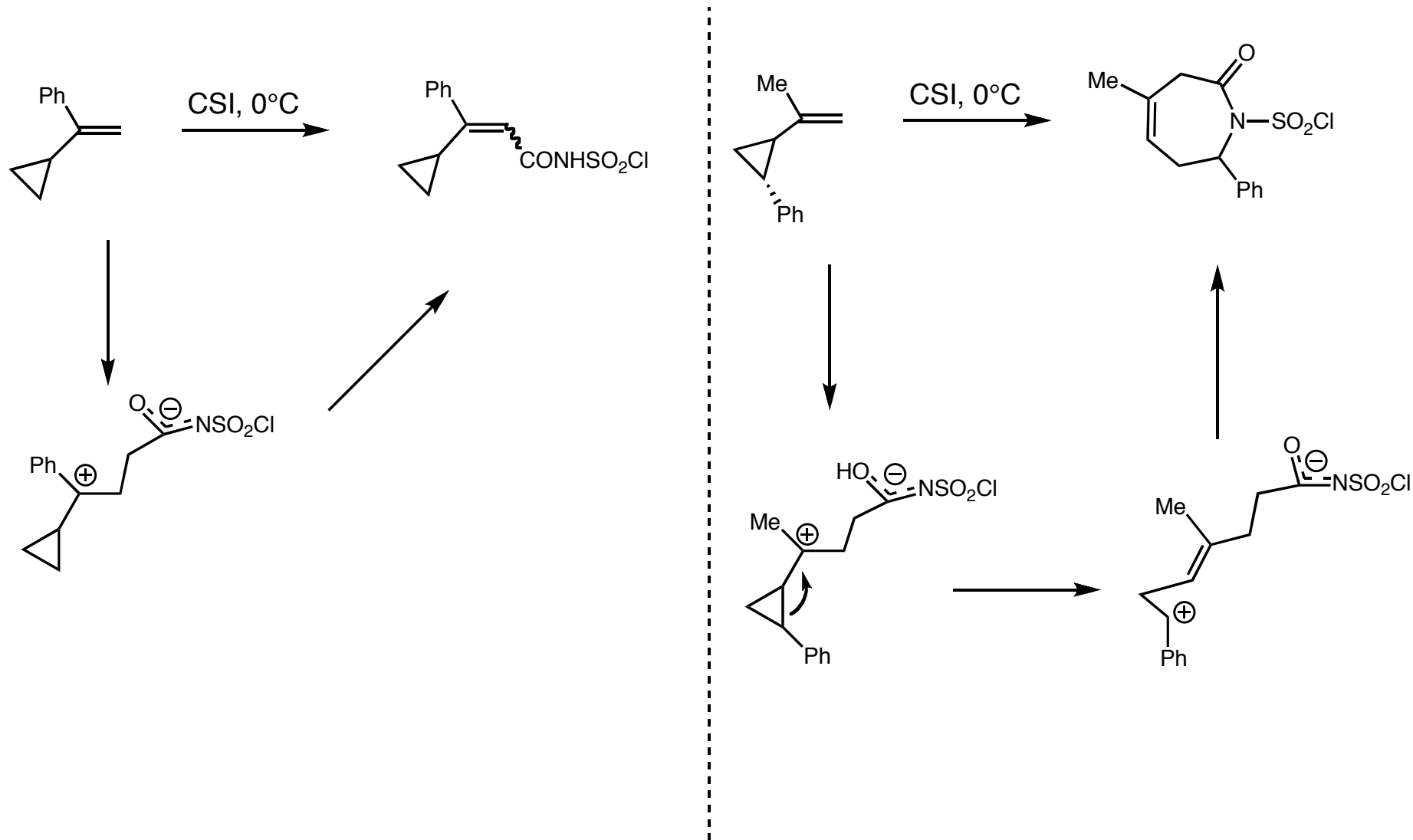
1,1 Disubstituted Alkenes



1) Pasto, D.J., *et al.*, *Tet. Lett.* **14**, 713

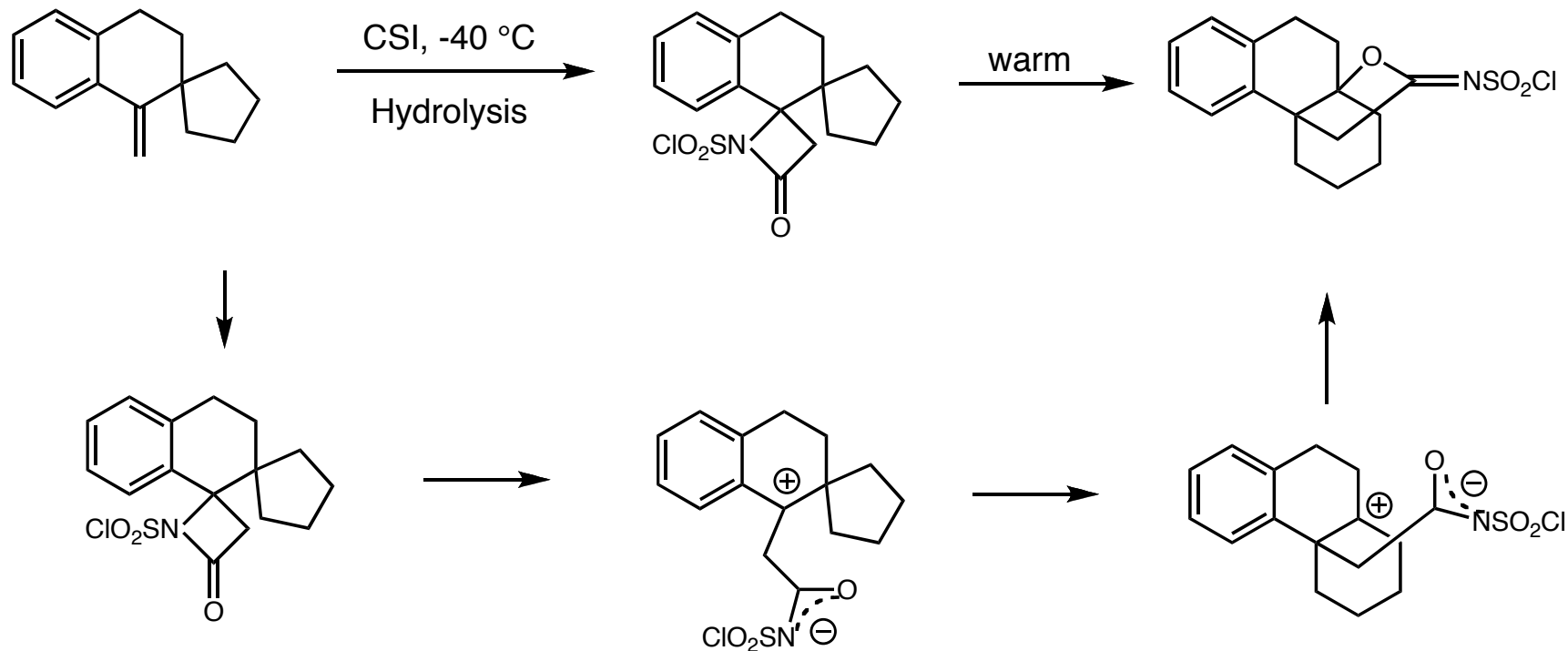
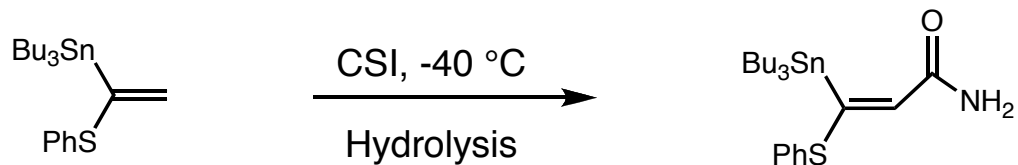
2) Sarel, S., *et al.*, *Tet. Lett.* **17**, 451

Mechanism to Explain Product Formation



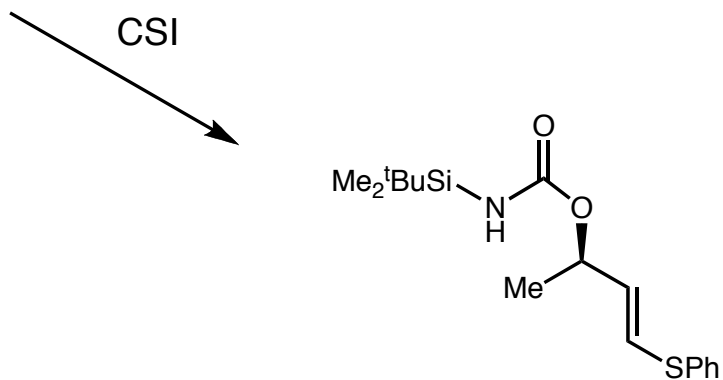
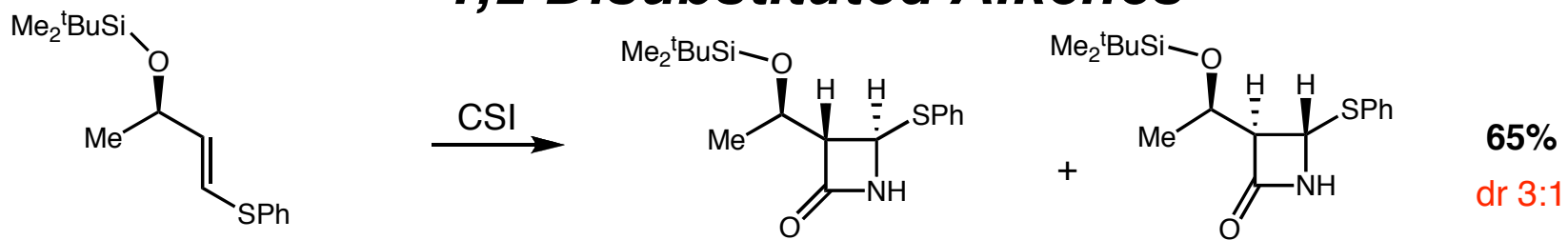
Pasto, D.J., et al., *Tet. Lett.* **14**, 713

More 1,1-Disubstituted

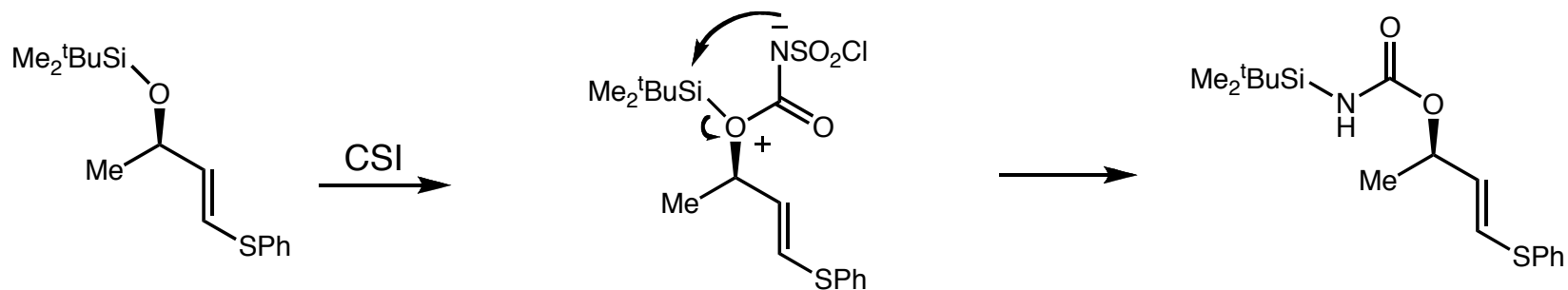


- 1) Imanieh, H., *et al.*, *Tet. Lett.* **30**, 2689
- 2) Doyle, T. W., Conway, T. T., *Tet. Lett.* **10**, 1889

1,2 Disubstituted Alkenes

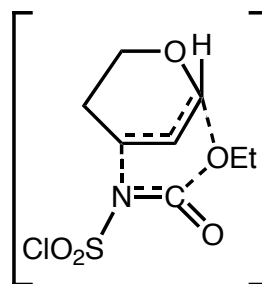
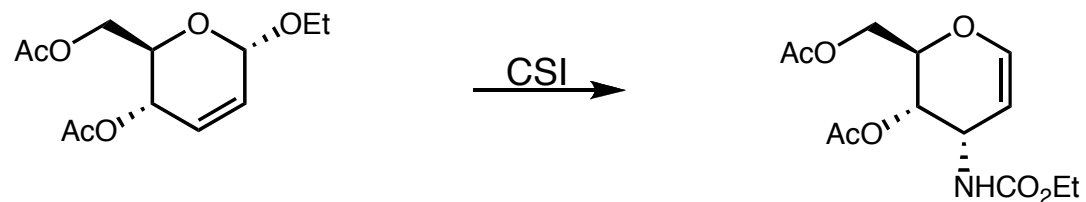
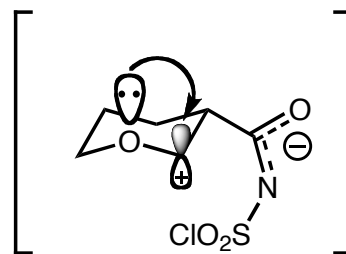
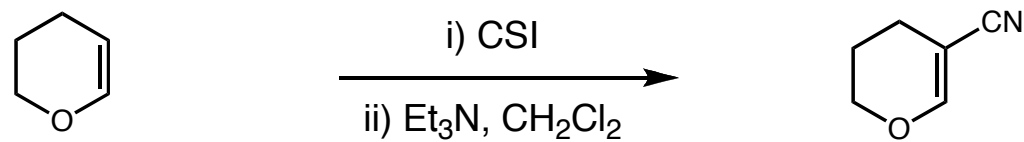


Mechanism Path B



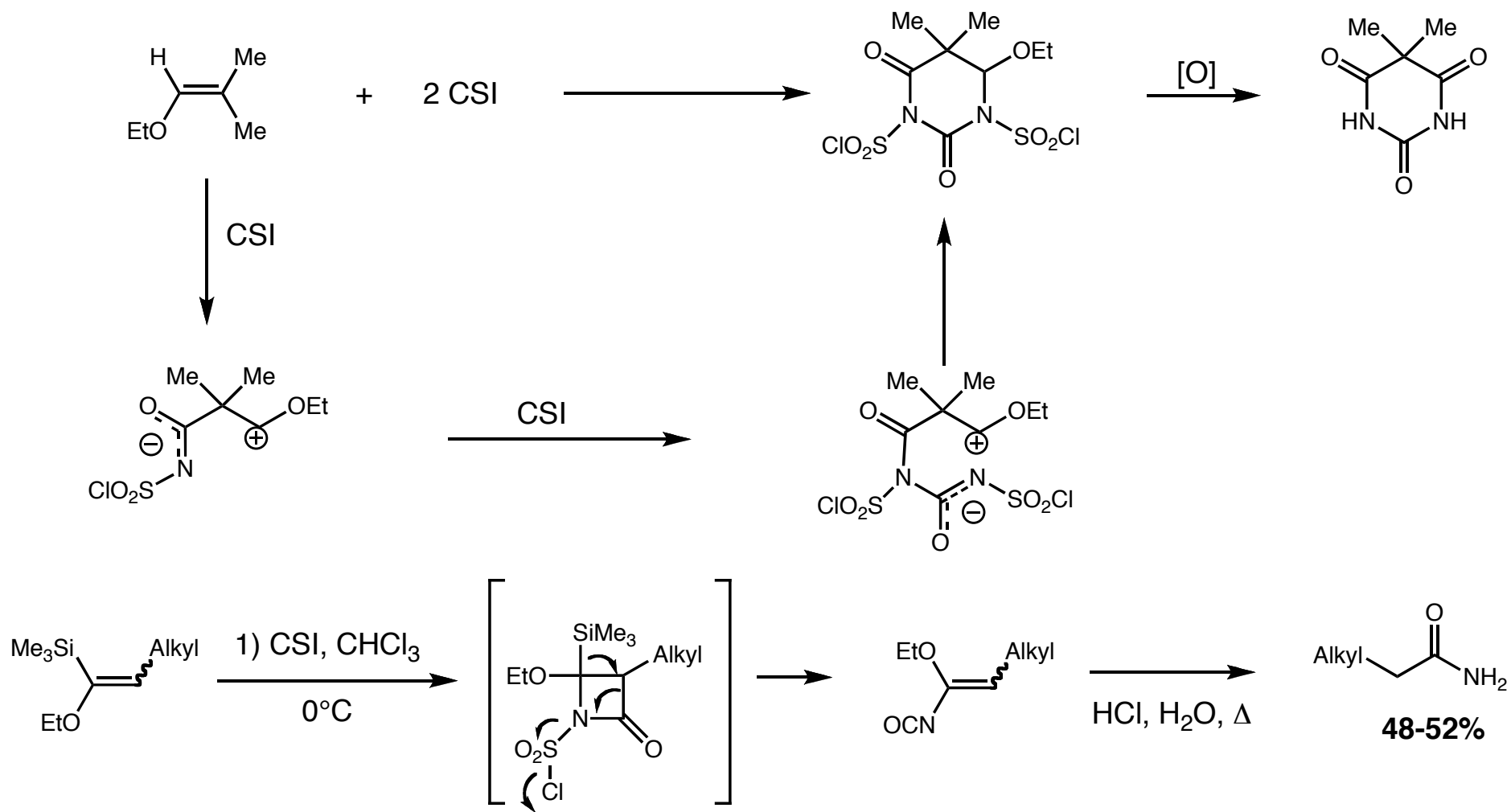
Nakatsuka, T, *et al.*, *JCS Chem. Comm.*, 662 (1991)

More 1,2-Disubstituted



- 1) Vorbruggen, H., *et al.*, *Tetrahedron*. **50**, 6549
- 2) Hall, R.H., *et al.*, *JCS Perkins Trans. I*, 38 (1973)

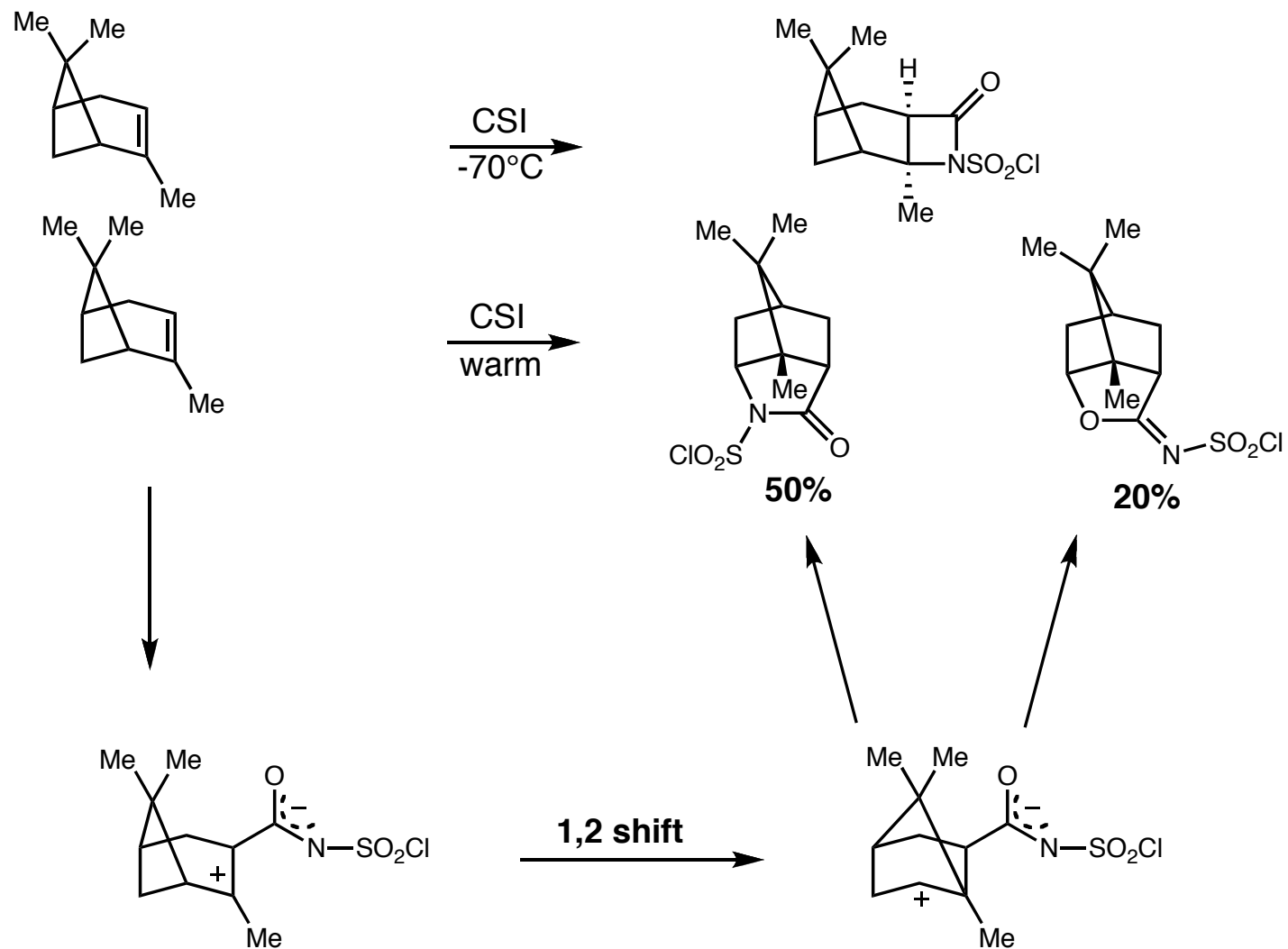
Tri-Substituted Alkenes



1) Graf. R., *Angew. Chem. Int. Ed. Engl.* **7**, 172

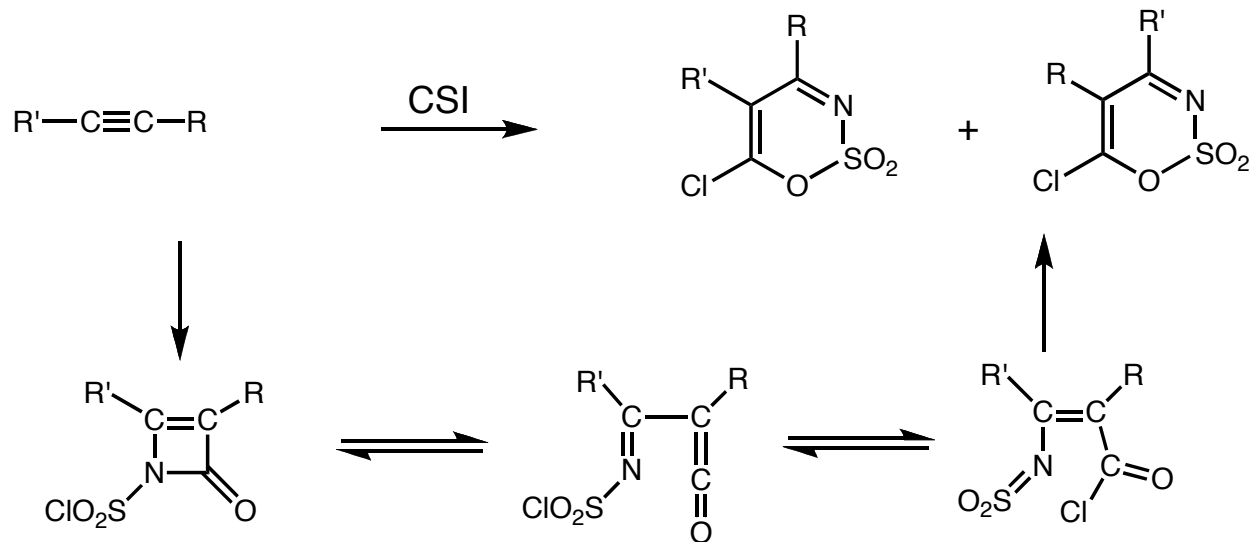
2) Rosenthal, S., Williams, R.V., *Synthesis*, 621(1988)

More Tri-Substituted Alkenes

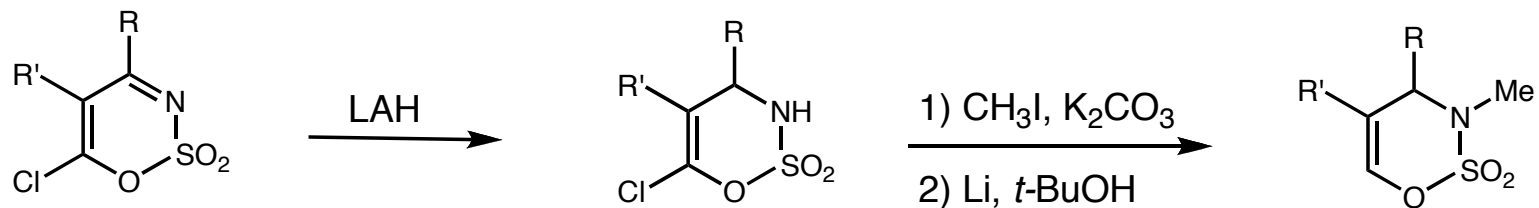
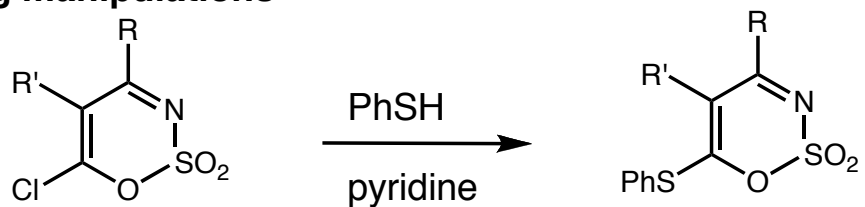


Malpass, J.R., *Tet. Lett.*, **13**, 4951

Alkynes



Ring manipulations

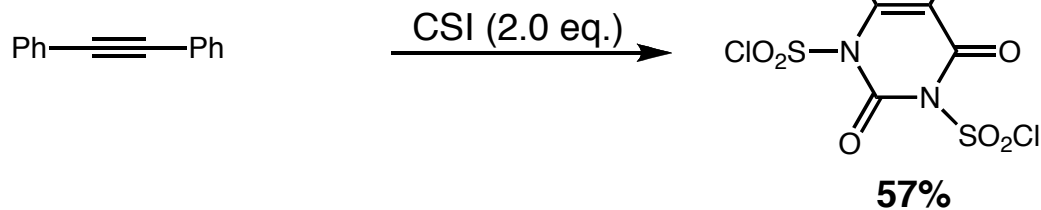
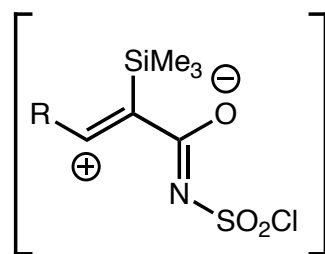
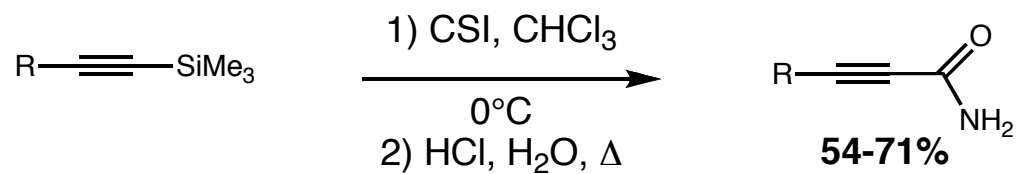
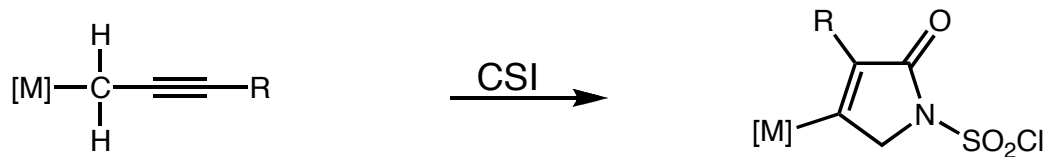


1) Kobelt, D., *et al.*, *Tet Lett.* **12**, 1211 and 3627

2) Moriconi, E. J. *Shimakawas, Y.*, *JOC*, **37**, 196

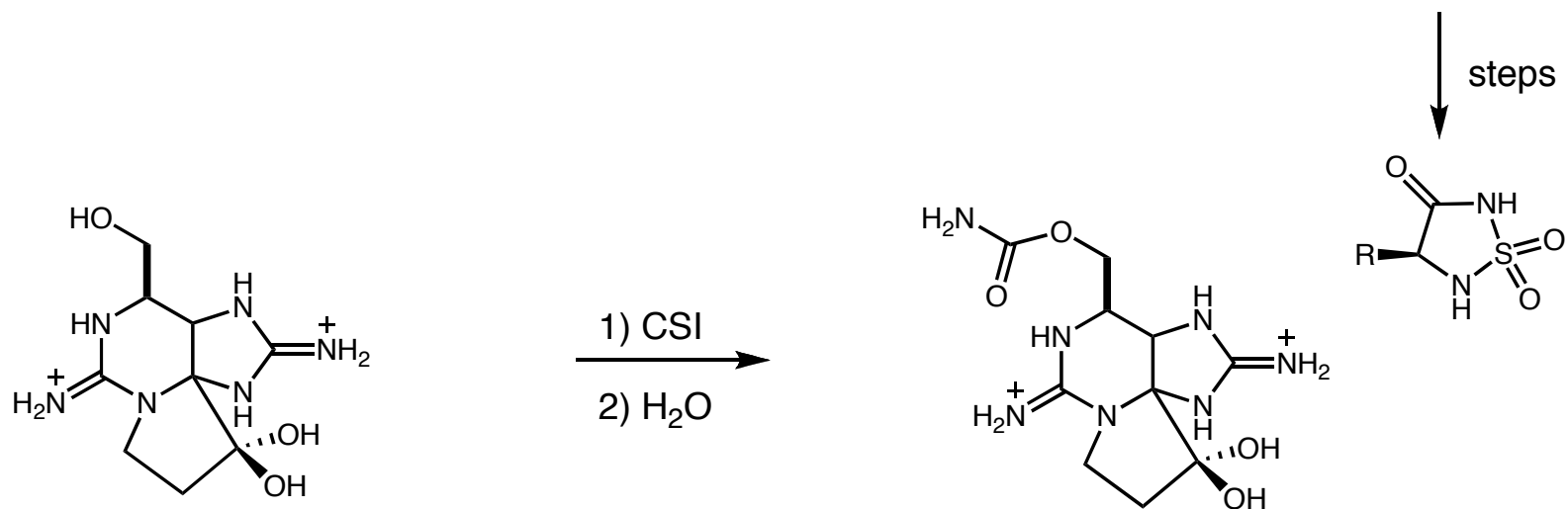
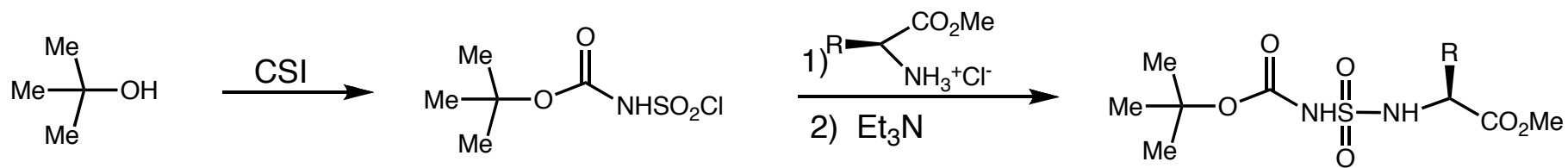
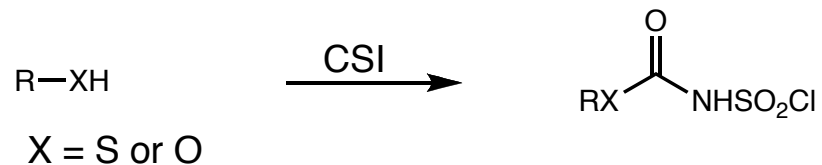
3) Kobrigh, G., *et al.*, *Chem. Ber.*, **105** 1683

More Alkynes



- 1) Giering, W. P., *et al.*, *JACS*, **94**, 8251
- 2) Rosenthal, S., Williams, R.V., *Synthesis*, 621(1988)
- 3) Moriconi, E. J., Shimakawa, Y., *JOC*, **37** 196

Alcohols/Thiols

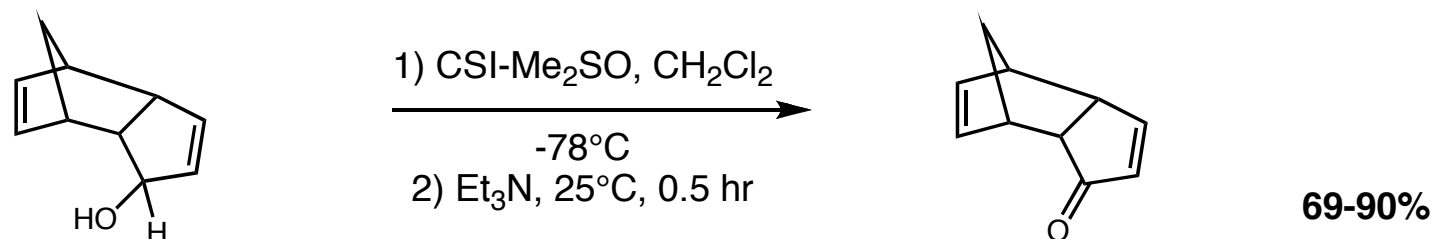
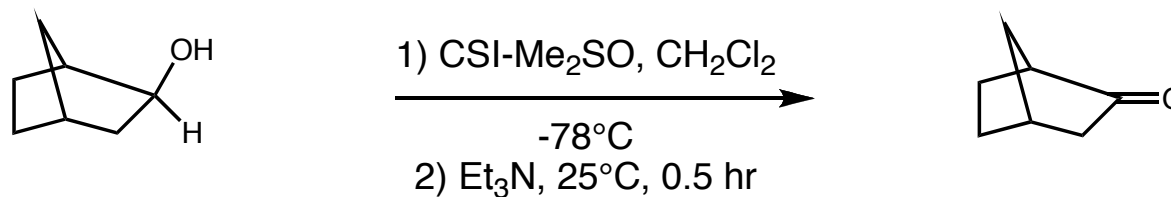


1) Graf, R., *Chem. Ber.*, **96**,56

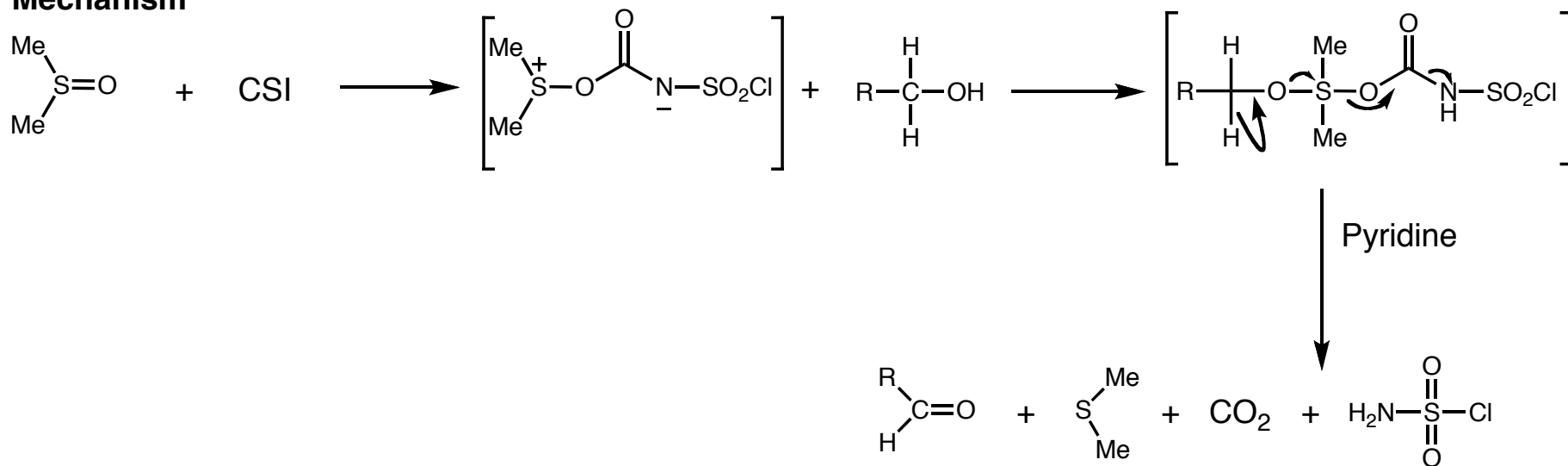
2) Dewynter, G., *et al.*, *Tetrahedron*, **52**, 993

3) Tanino, H., *et al.*, *JACS*, **99** 2818

CSI as an Oxidant for Alcohols

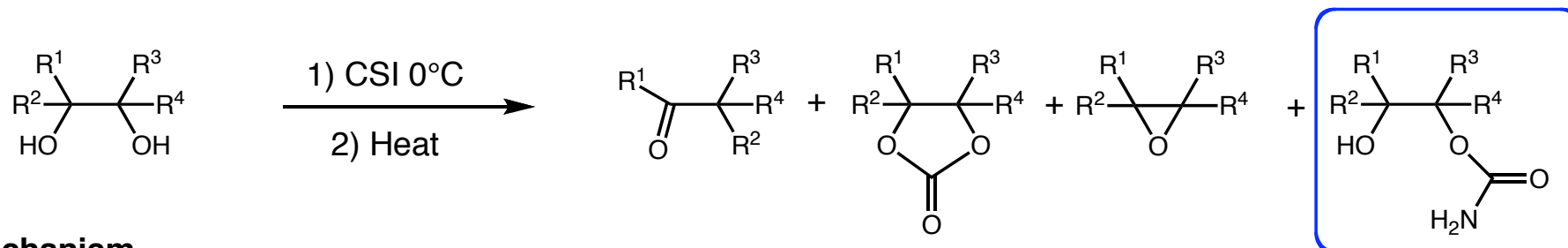


Mechanism

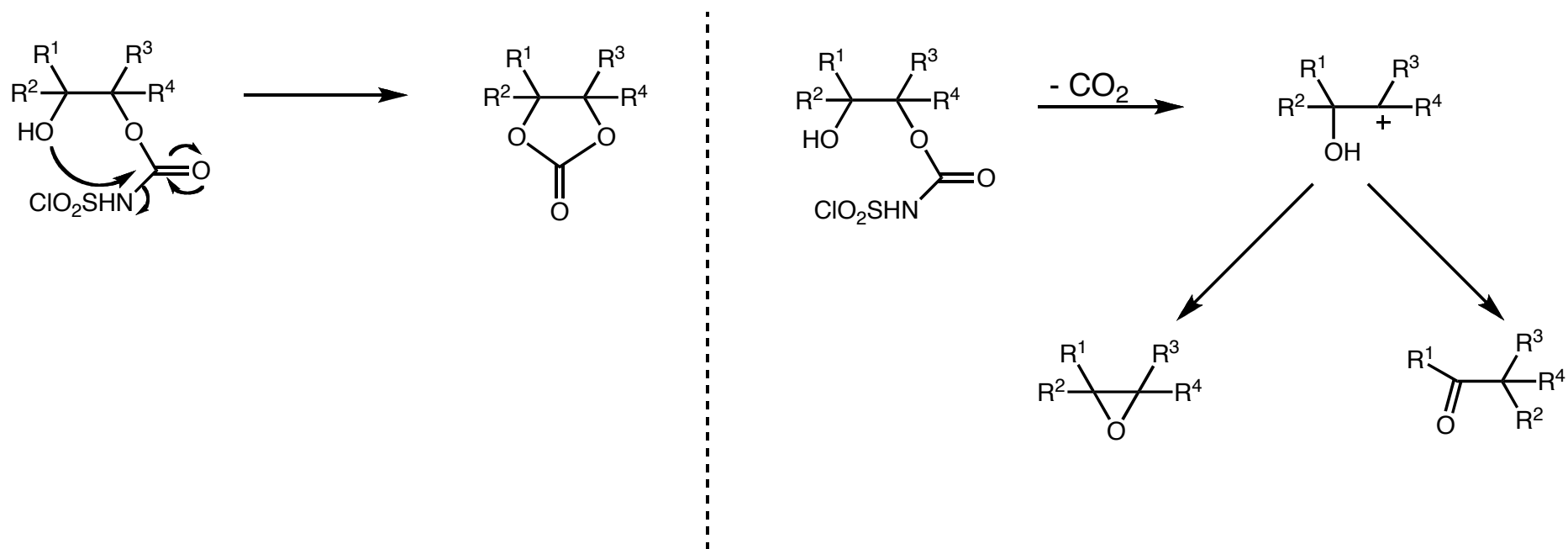


Olah, G., *Synthesis*,(2) **141**, (1980)

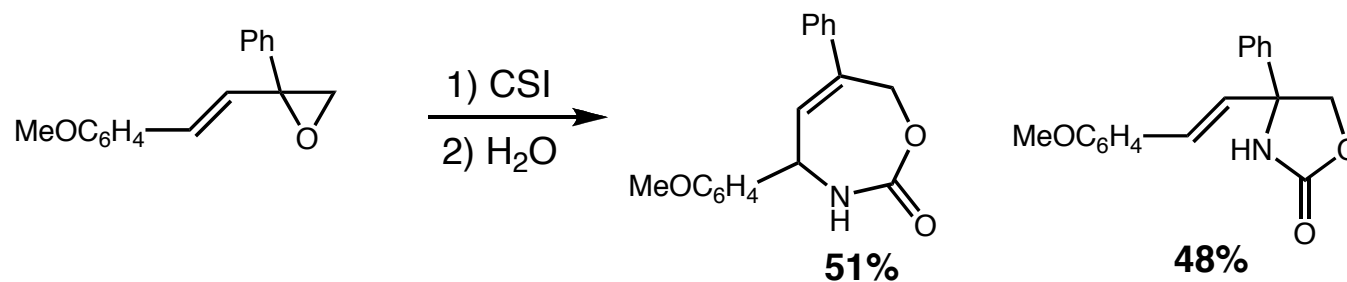
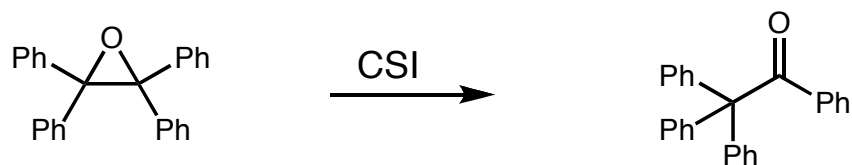
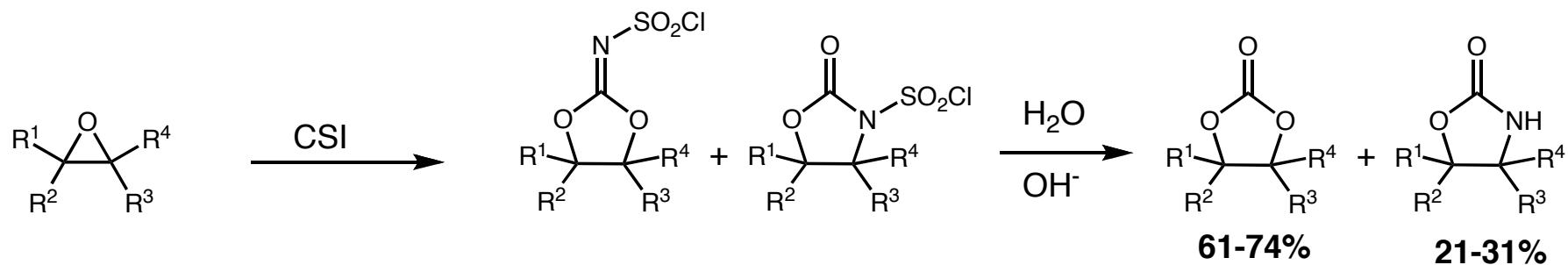
Vicinal Diols



Mechanism

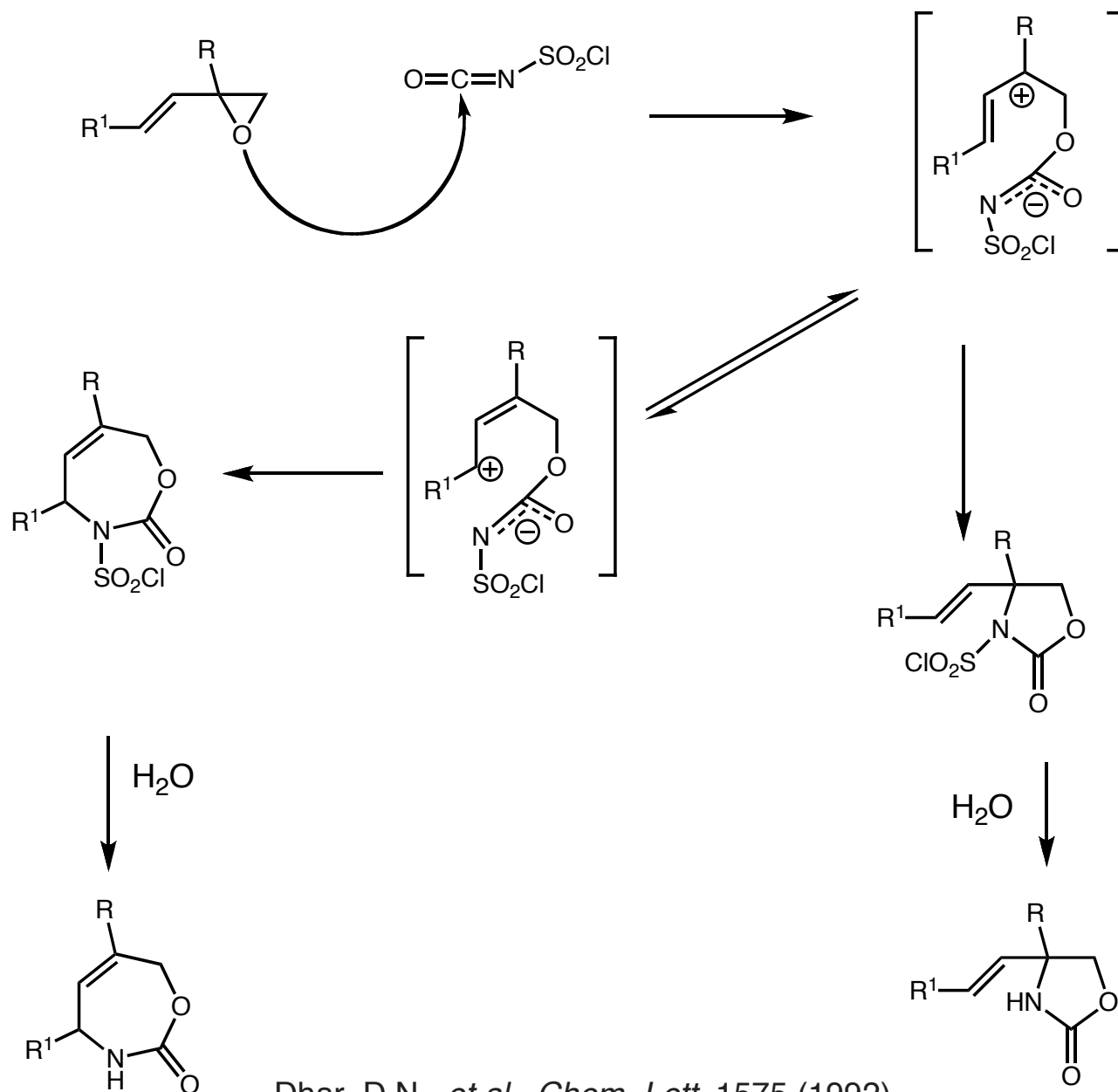


Epoxides



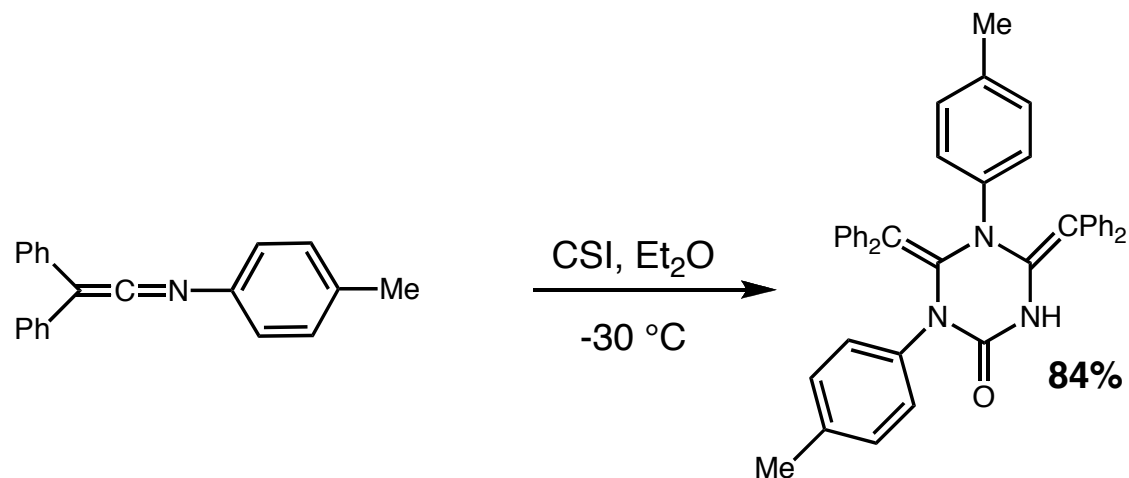
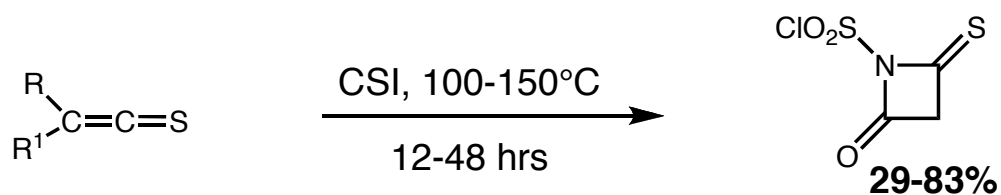
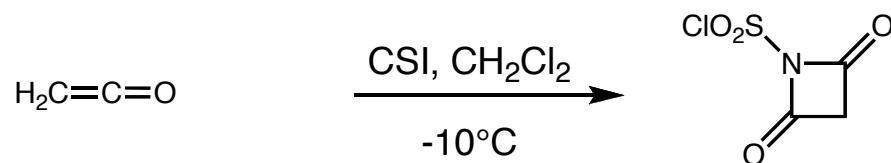
- 1) Keshava Murthy, K.S., Dhar, D.N., *Synth. Comm.*, **14**, 687
- 2) Keshava Murthy, K.S., Dhar, D.N., *J. Heterocycl.chem.*, **21**, 1721
- 3) Dhar, D.N., *et al.*, *Chem. Lett.* 1575 (1992)

Mechanism



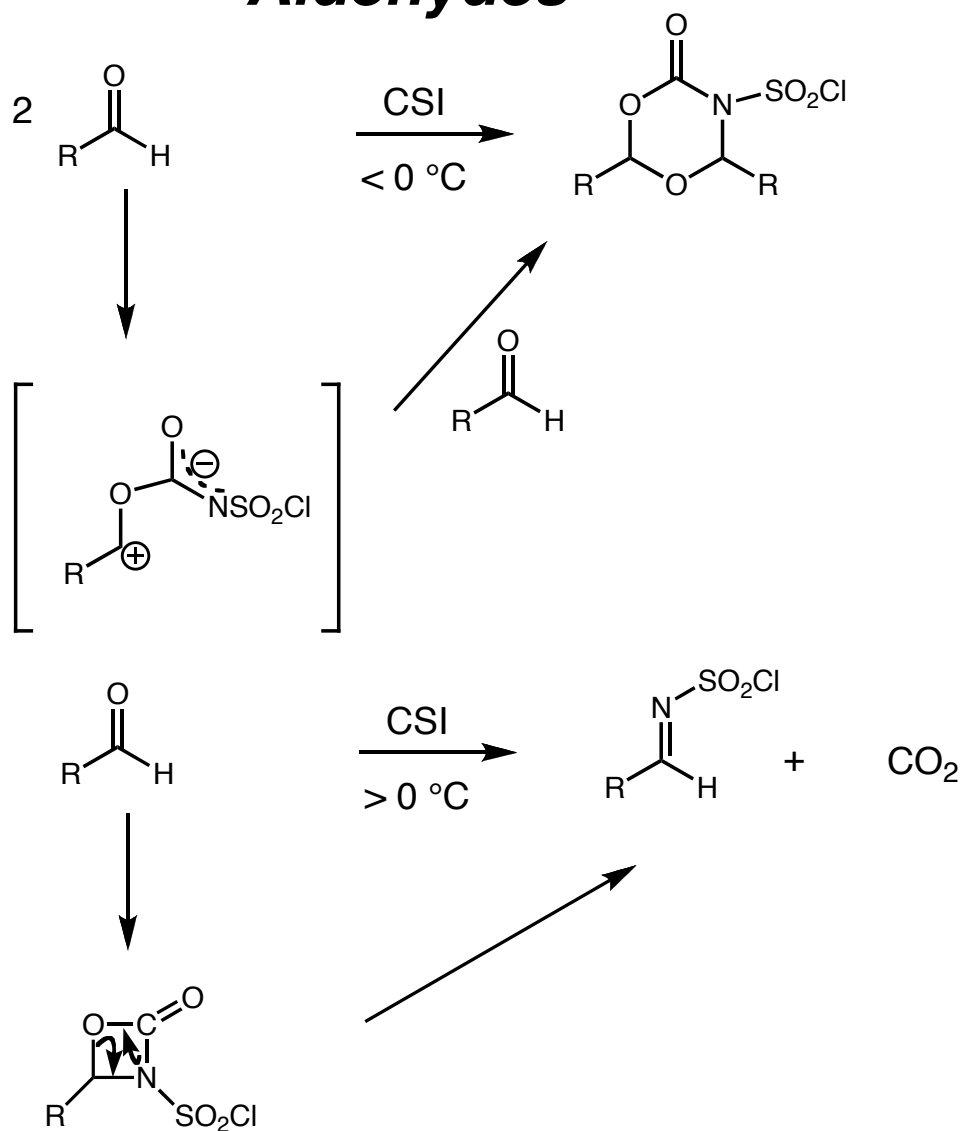
Dhar, D.N., *et al.*, *Chem. Lett.* 1575 (1992)

Ketenes/Thioketenes

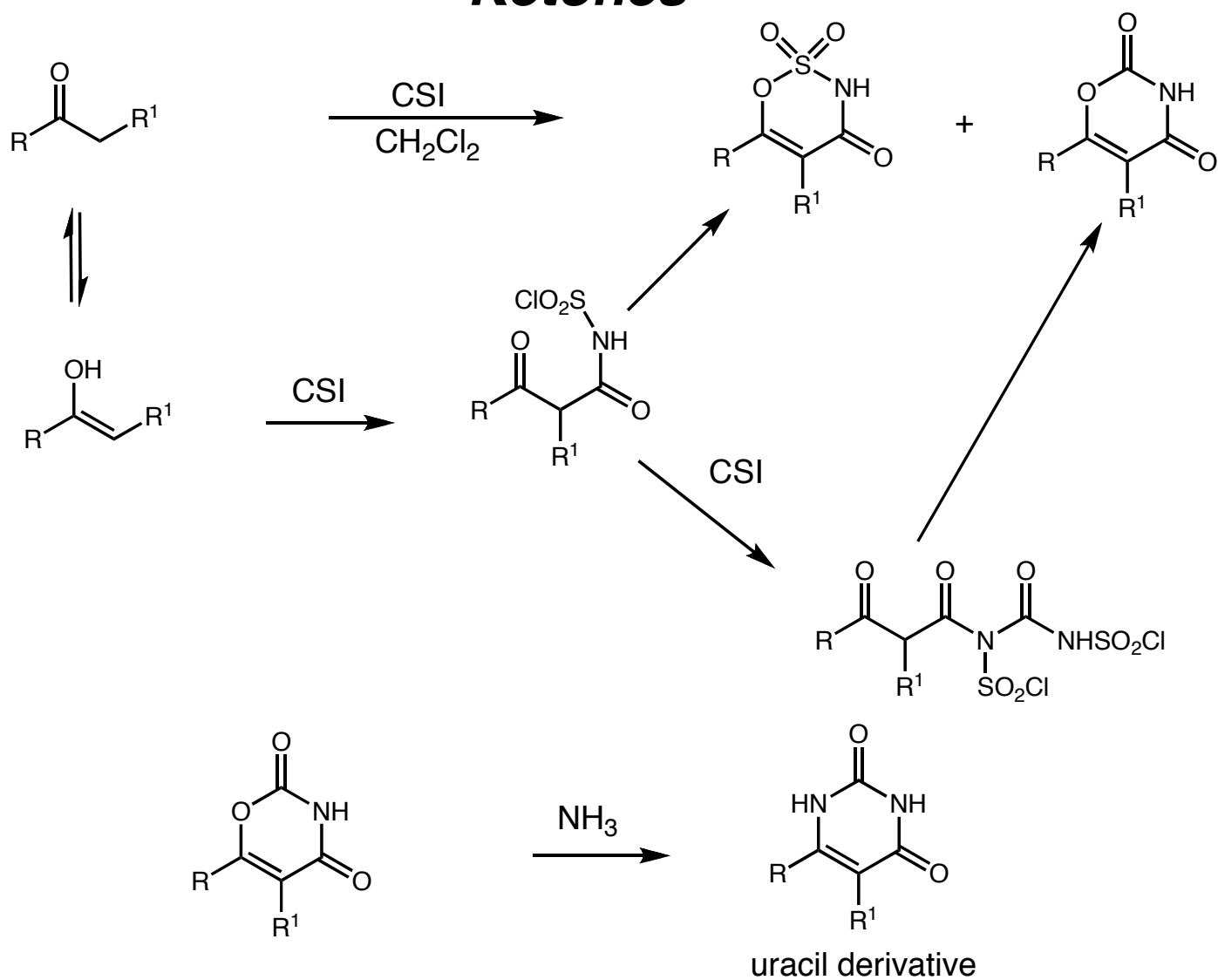


- 1) Mundloss, E., Graf, R., *Ann.*, **677**, 108
- 2) Schaumann, E., *et al.*, *Tet. Lett.* **21**, 4247
- 3) Romming, C., Skatteboel, L., *Acta Chem. Scand.*, **43**, 819

Aldehydes

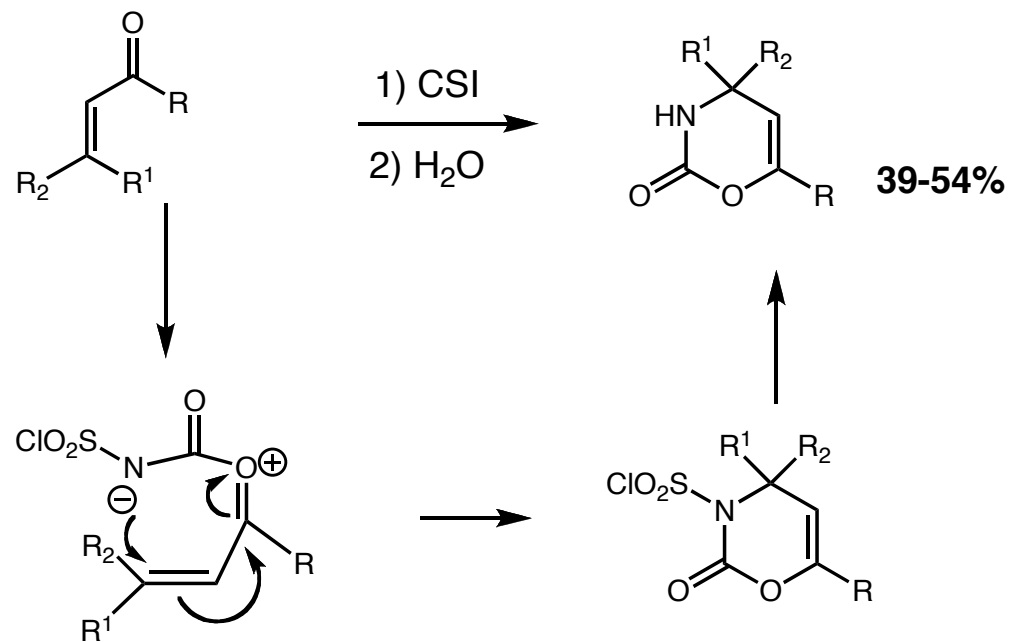
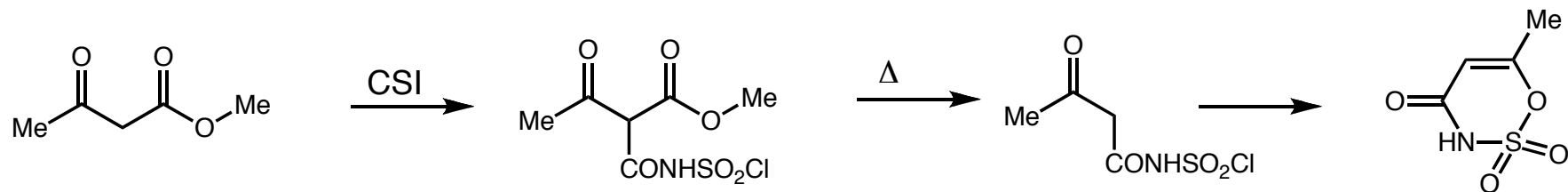
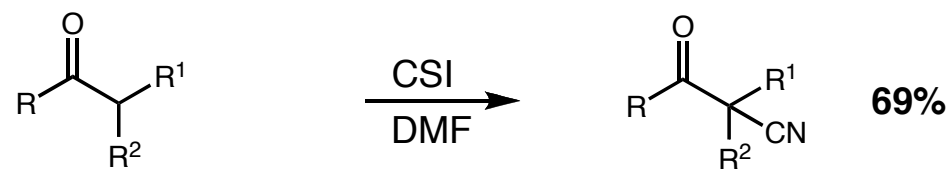


Ketones



Rasmussen, J.K., Hassner, A., *JOC*, **38**, 2114

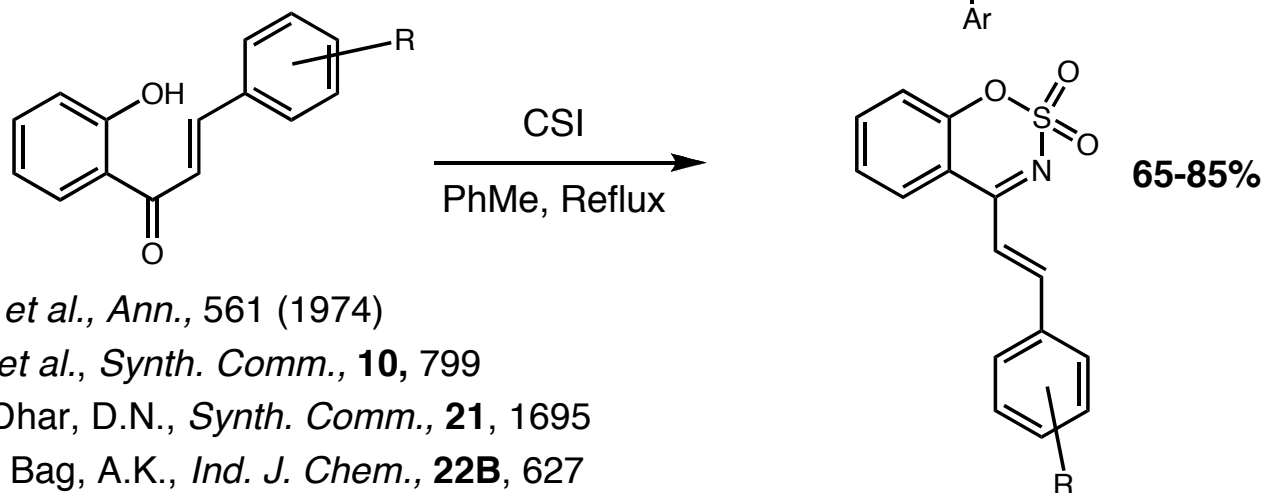
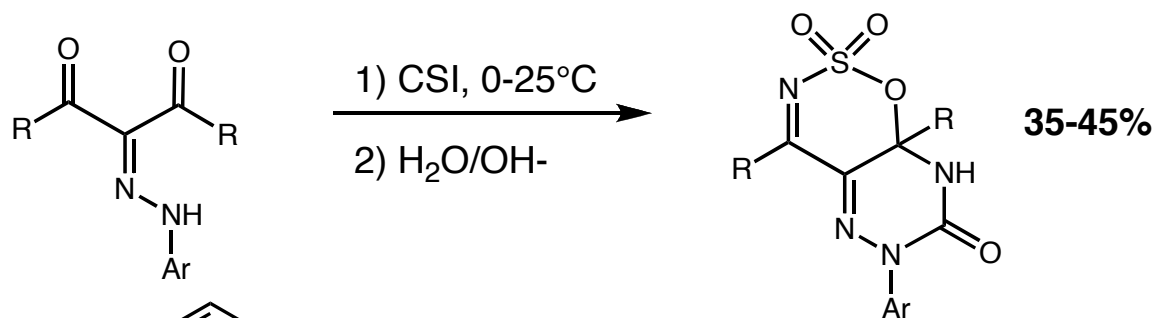
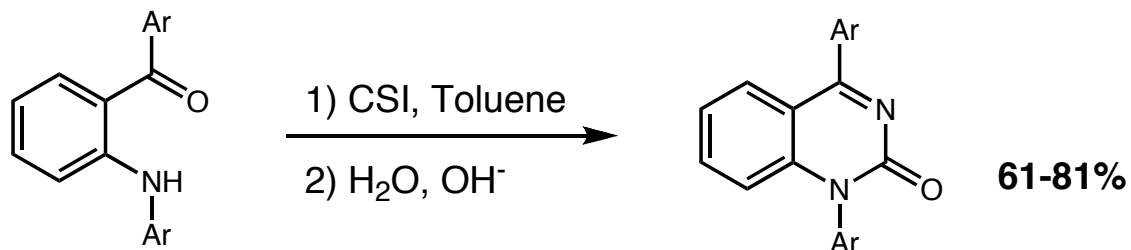
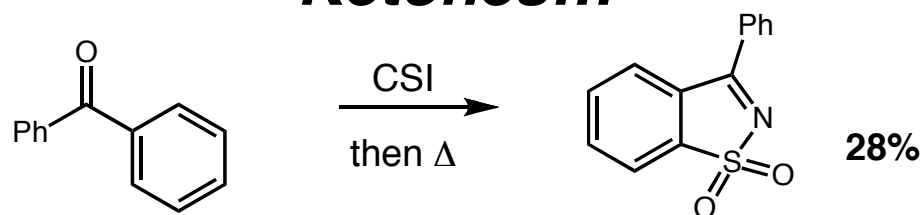
More Ketones



1) Rasmussen, J.K., Hassner, A., *JOC*, **38**, 2114

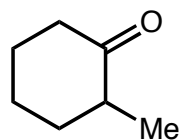
2) (Hoechst, A.G.), German Patent, 2, 327, 804 C.A. **82**, 171097 (1975)

Ketones...



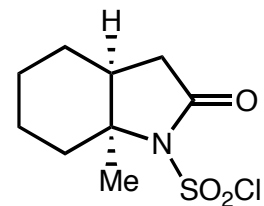
- 1) Clauss, K., *et al.*, *Ann.*, 561 (1974)
- 2) Kamal, A., *et al.*, *Synth. Comm.*, **10**, 799
- 3) Daniel, J., Dhar, D.N., *Synth. Comm.*, **21**, 1695
- 4) Dhar, D.N., Bag, A.K., *Ind. J. Chem.*, **22B**, 627

...Ketones...

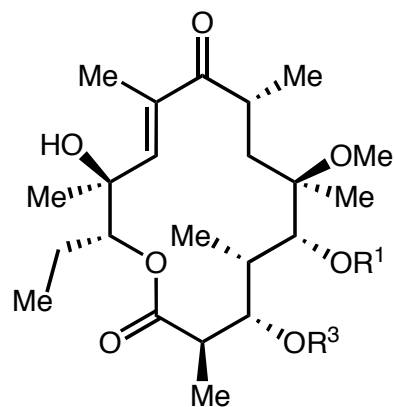


1) CH_2I_2 , Zn, TiCl_4

2) CSI, 23°C

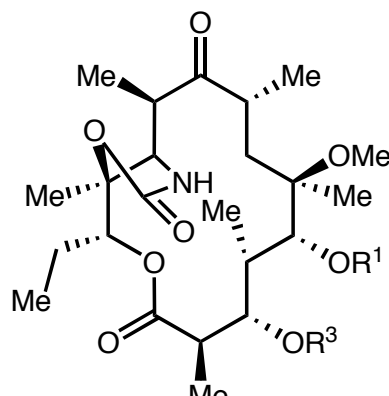


75%



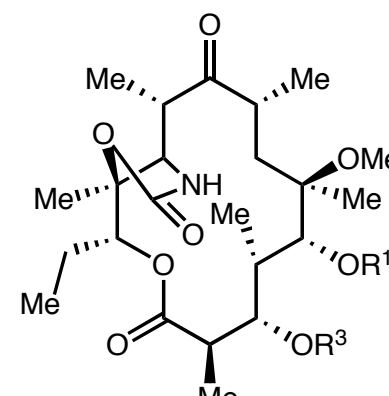
CSI, CH_2Cl_2

-5°C

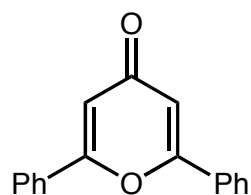


6%

+

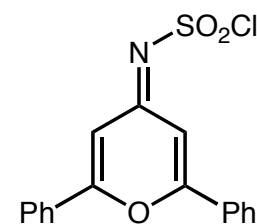


4%



CSI, MeCN

23°C , 1 hr



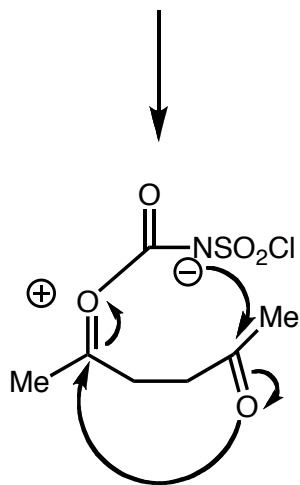
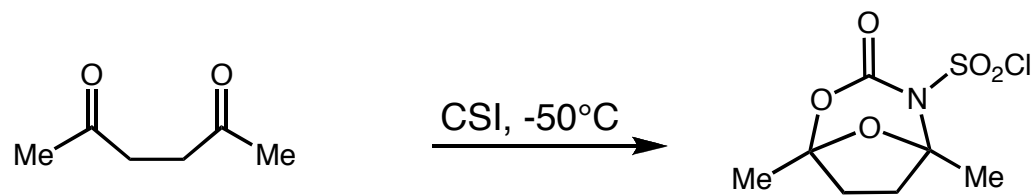
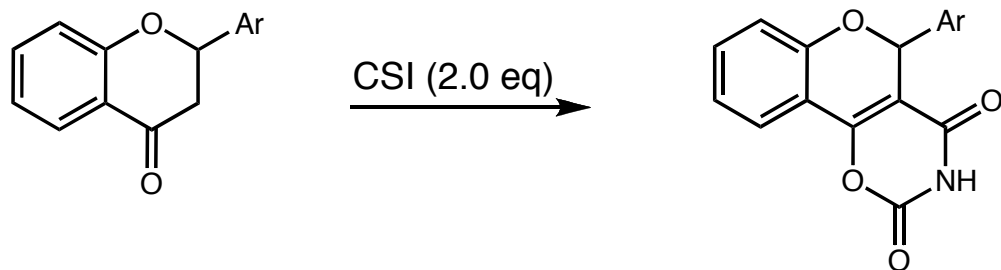
72-92%

1) Black, H. T., *et al.*, *Synth. Comm.*, **22**, 2729

2) Baker, W. R., *et al.*, *JOC*, **53**, 2340

3) Van Allan, J. A., *et al.*, *Heterocycl. Chem.*, **11**, 195

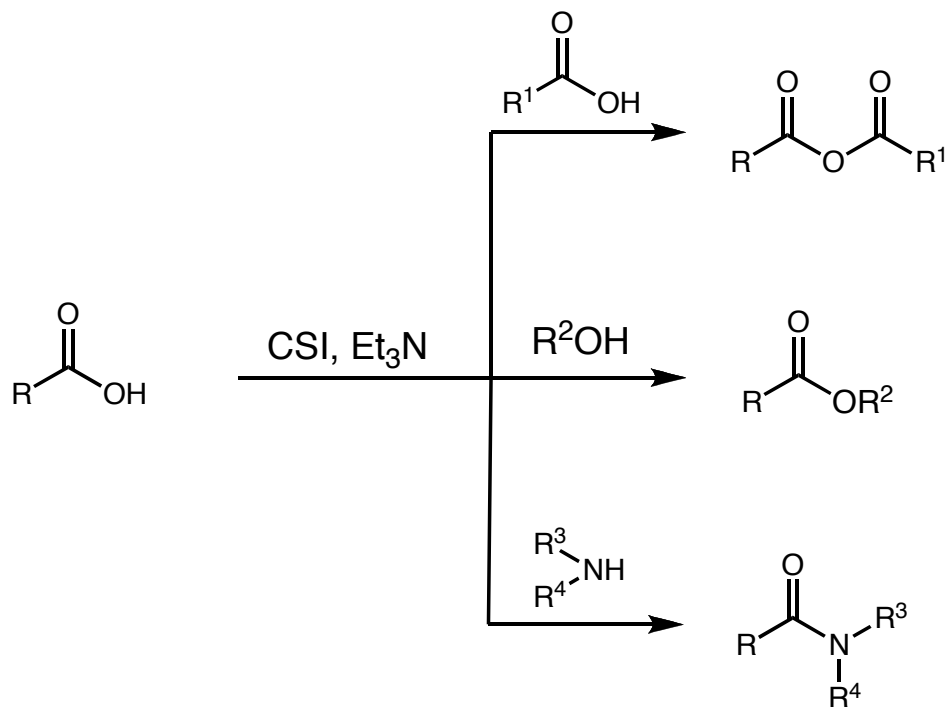
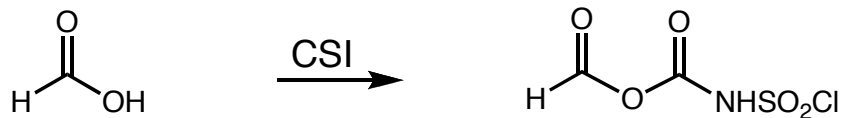
... 2 more



1) Tripathi, M., Dhar, D. N., *Ind. J. Chem.*, **26B**, 1082

2) Clauss, K., *et al.*, *Ann.*, 561 (1974)

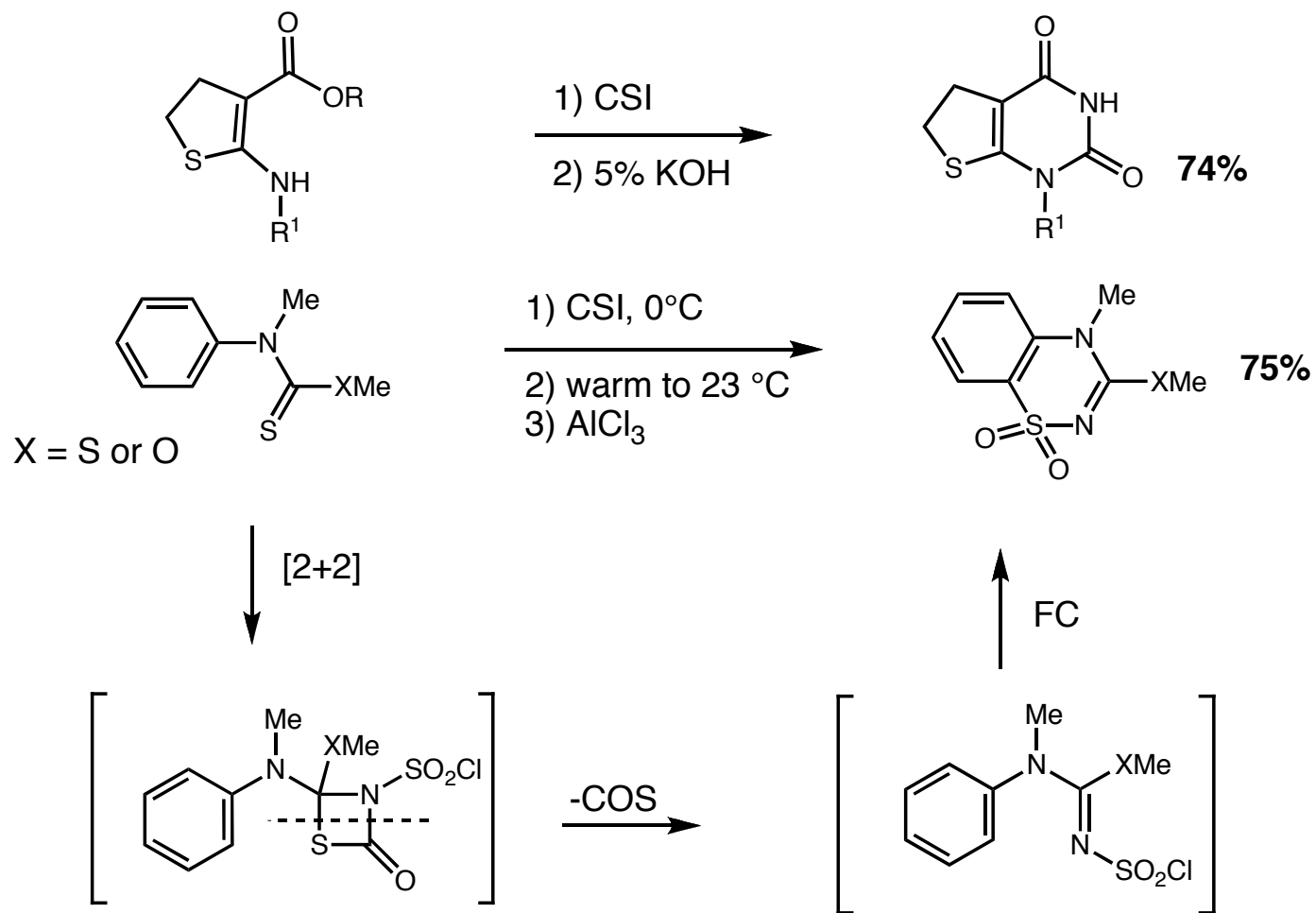
Carboxylic Acids



1) Graf. R., (Farbwke Hechst A.G.) German Patent, 931, 225, 1952

2) Keshava Murthy, K. S., *et al.*, *Synthesis*, 506 (1982)

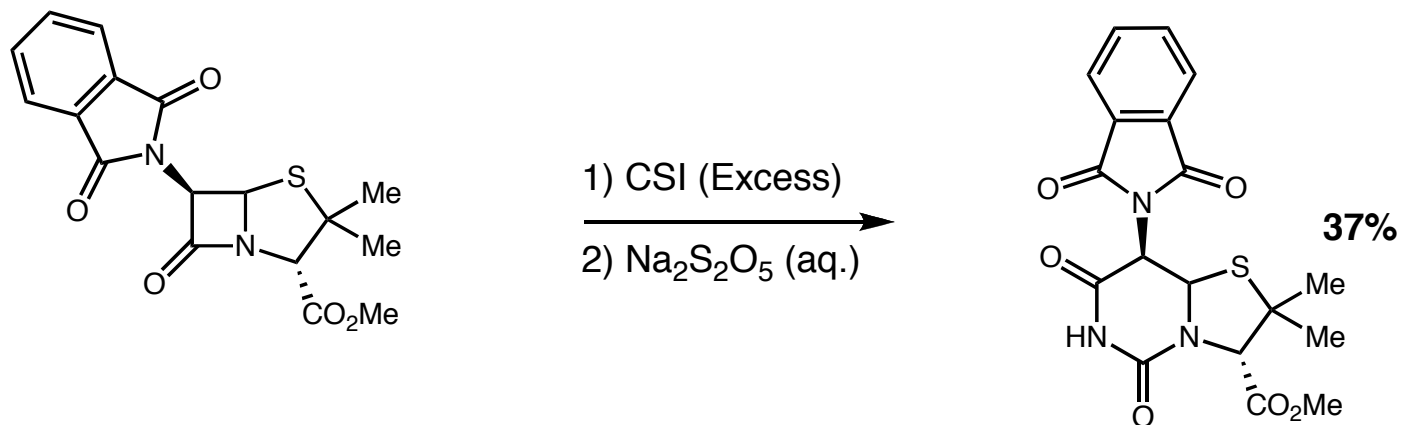
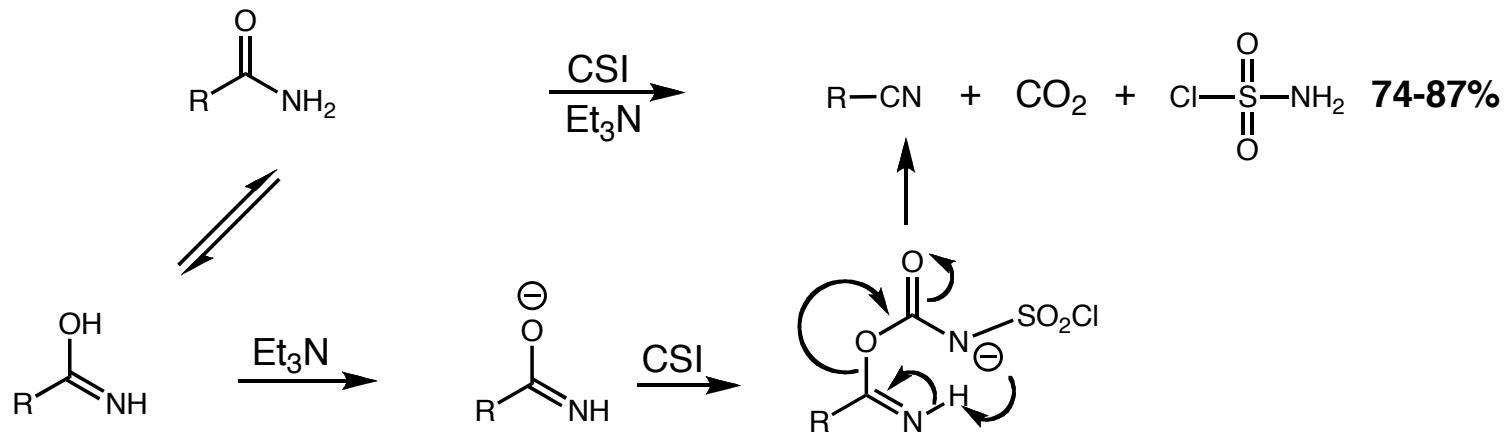
Esters/Thioesters



1) Wamhoof, H., Ertas, M., *Synthesis*, 190 (1985)

2) Iwakawa, T., *et al.*, *Chem. Pharm. Bull.*, **38**, 1075, and **39**, 1939

Amides

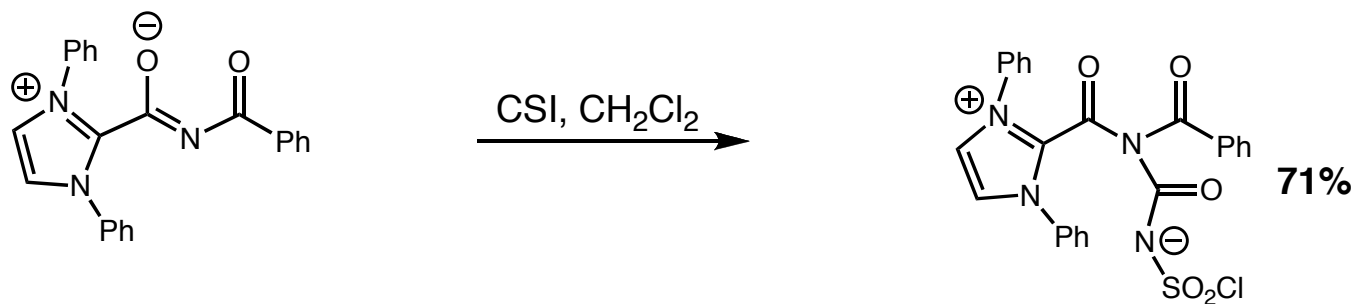
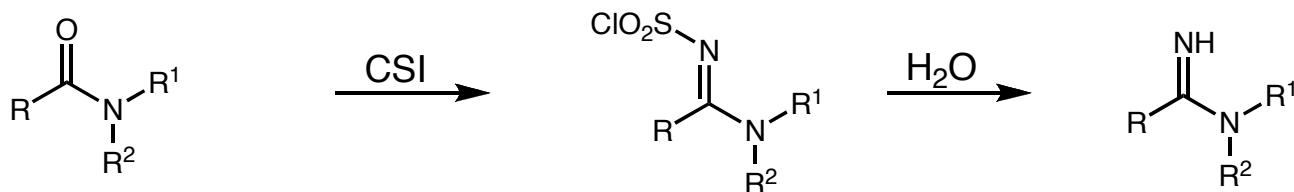
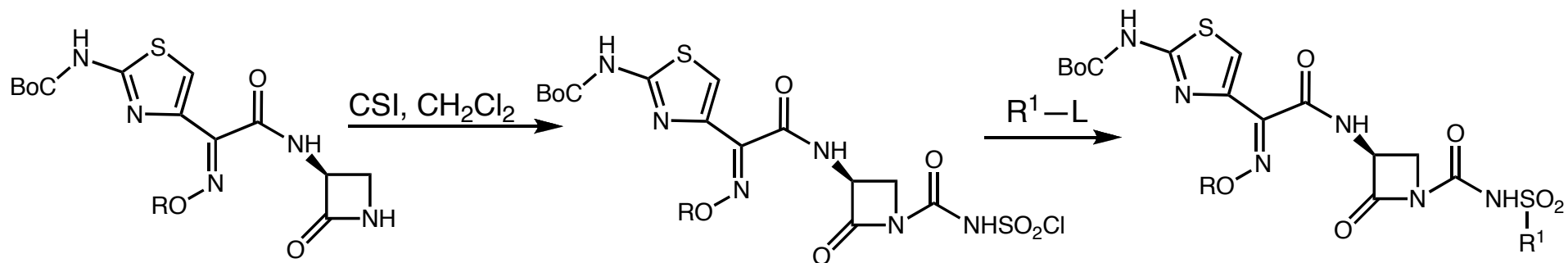


1) Olah, G., *et al.*, *Synthesis*, 227 (1979)

2) Graf, R., *et al.*, (Farbwke Hechst A.G.) German Patent, 1144718, *Chem. Zbl.*, 20282 (1963)

3) Campbell, M. M., *et al.*, *JCS Pekin Trans. I*, 817 (1978)

Amides Continued

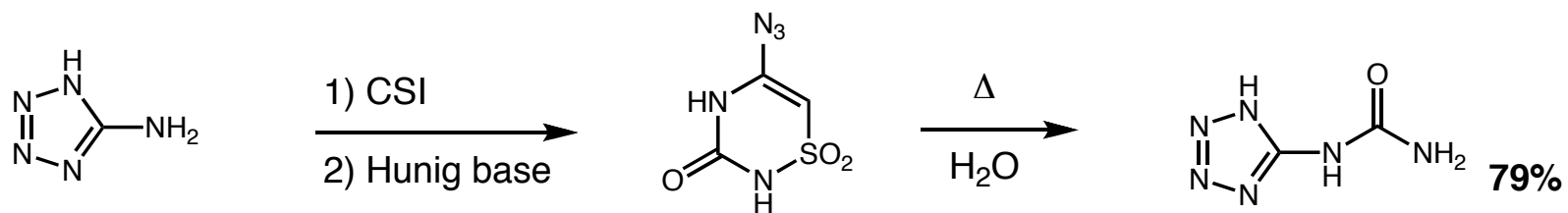
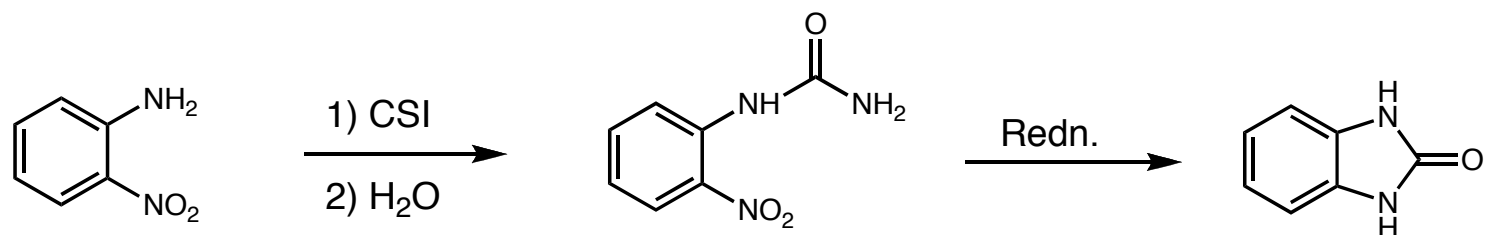


1) Barbachyn, M.R., Tuominen, T. C., *J. Antibiot.*, **43**, 1199

2) Graf, R., *et al.*, (Farbwke Hechst A.G.) German Patent, 1144718, *Chem. Zbl.*, 20282 (1963)

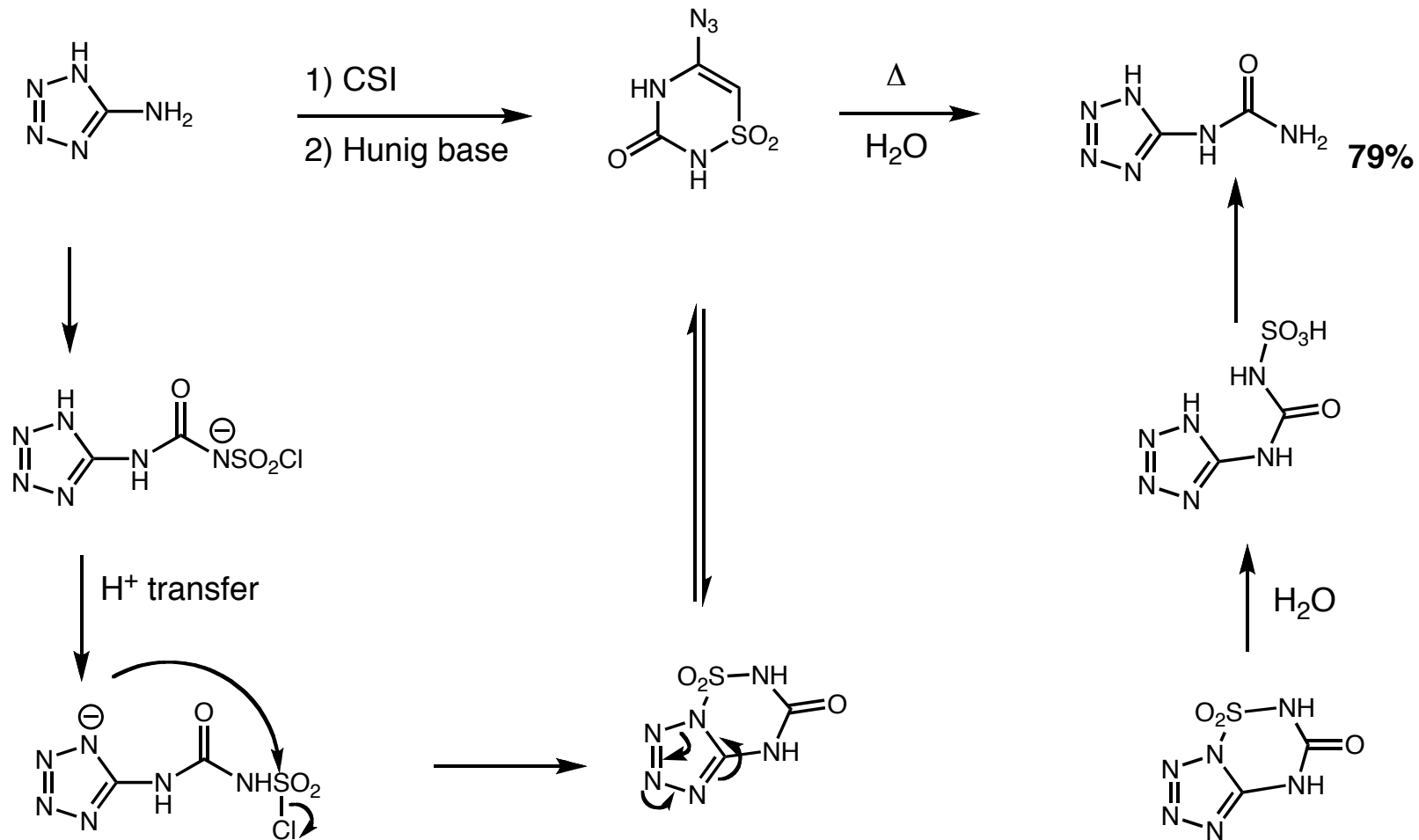
3) Schossler, W., Regitz, M., *Chem. Ber.*, **107** 1931

Amines

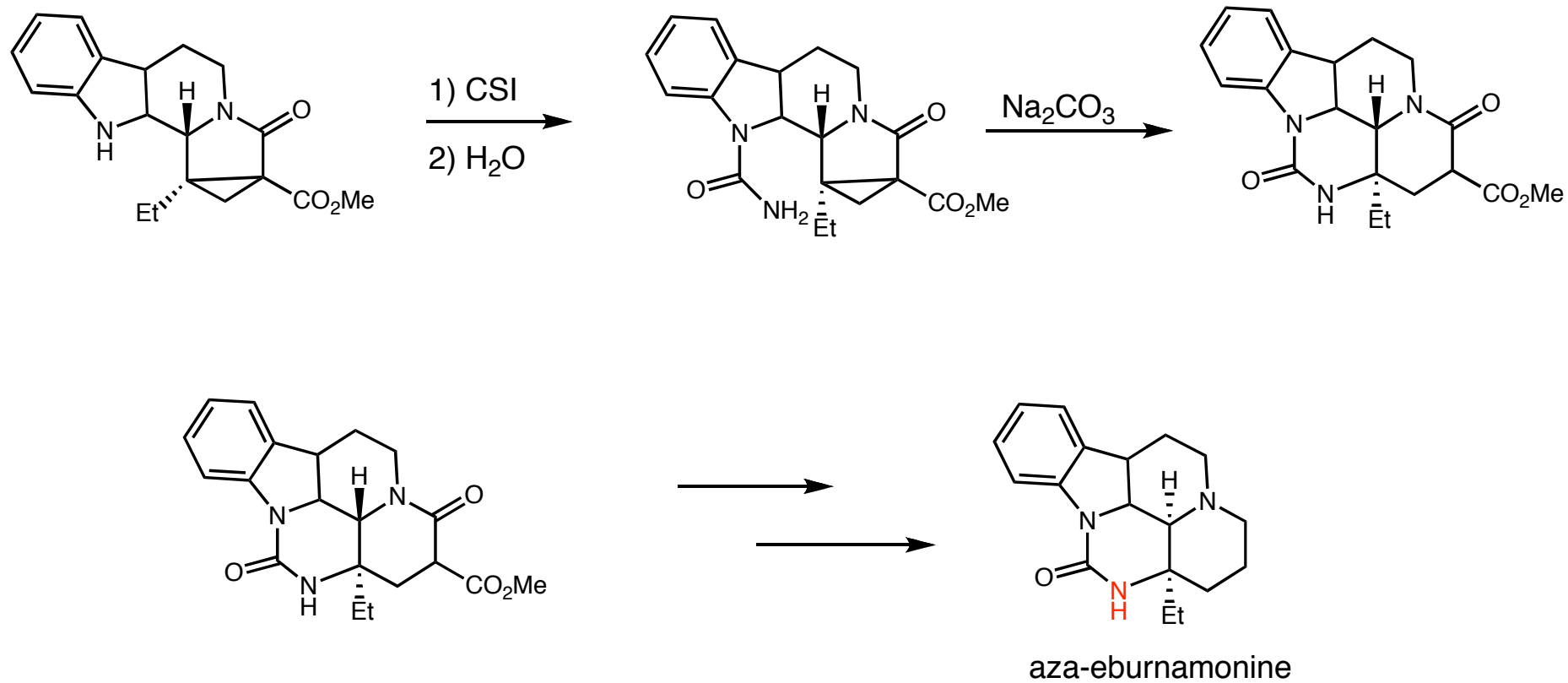


- 1) Hoechst. A. G., German Patent 2, 1855, 884. C.A. **94**, 15413(1981)
- 2) Pasto, D. J., Chen, A. F. T., *Tet. Lett*, **14**, 713

Mechanism

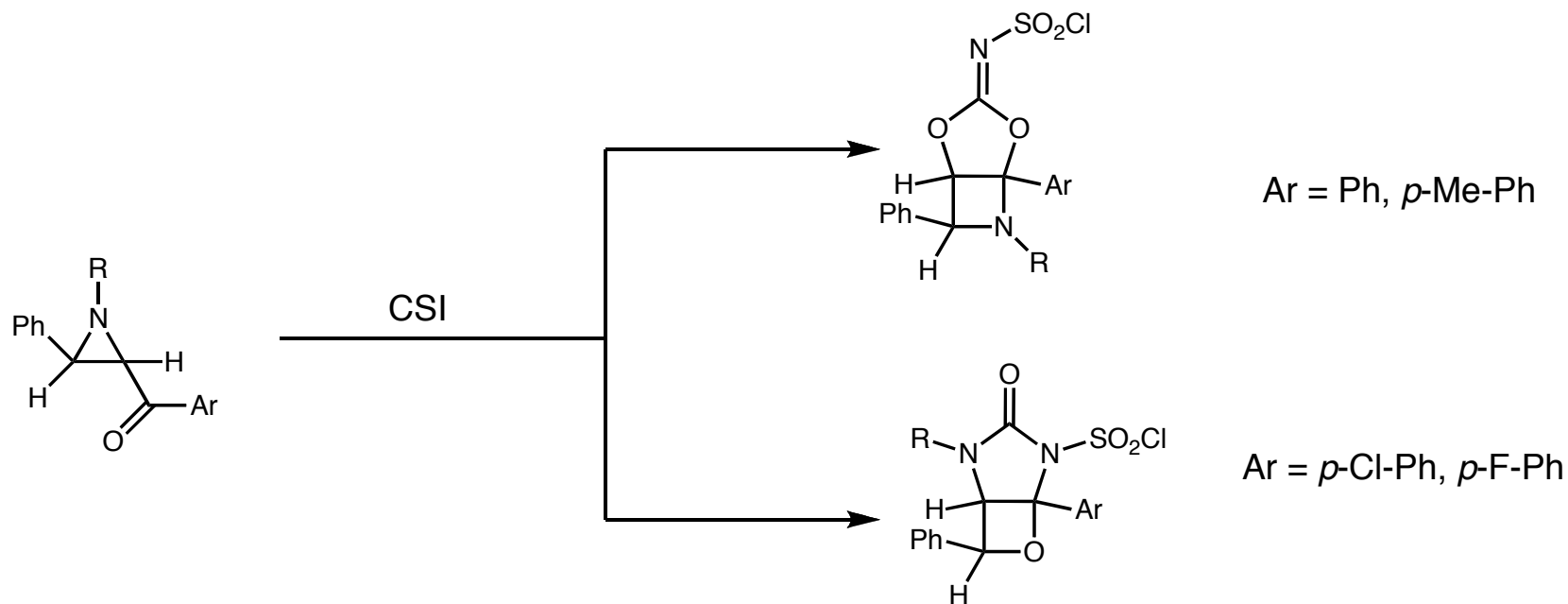
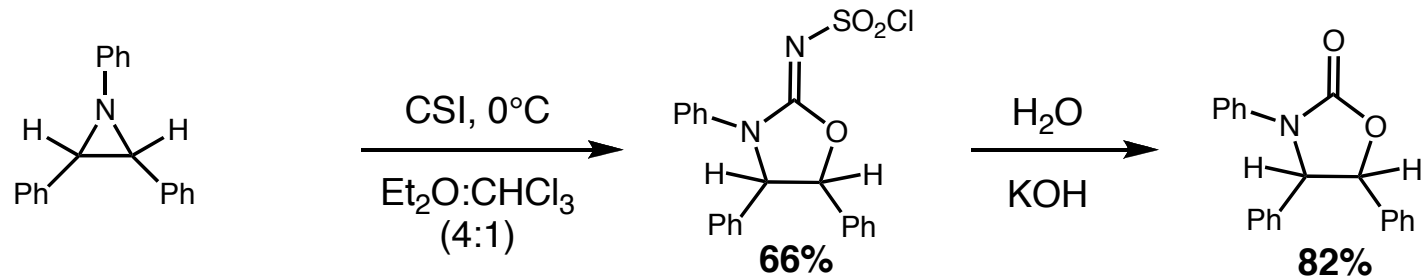


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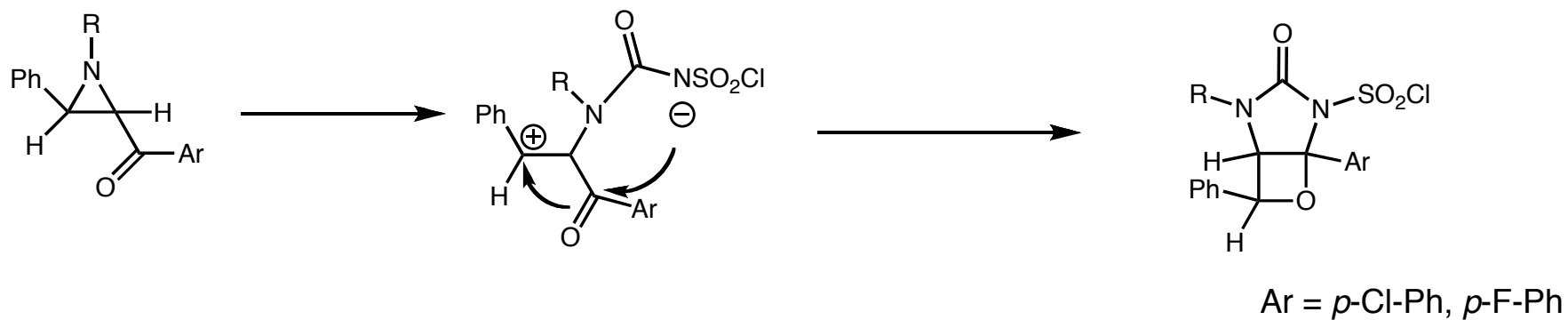
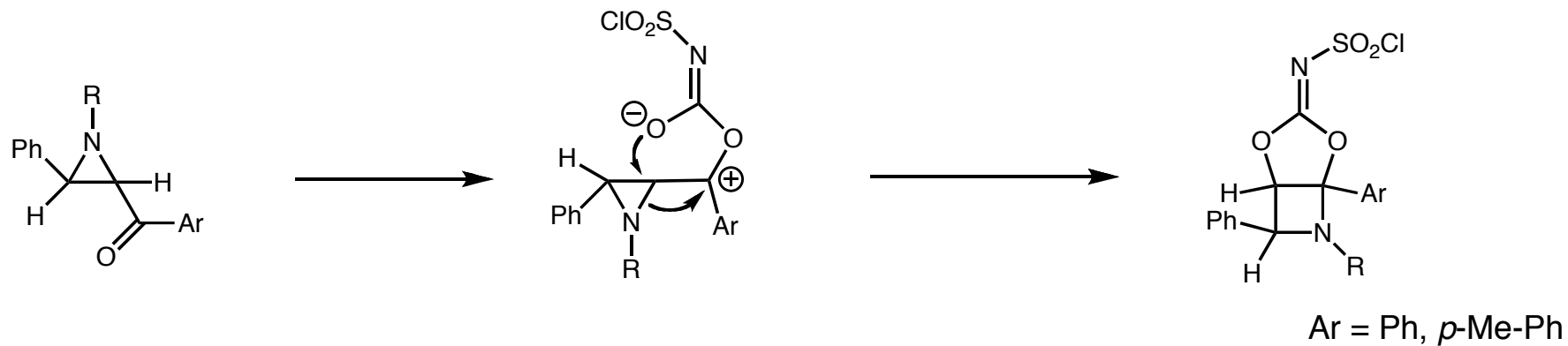


Hammer H., Winterfeldt, E., *Tetrahedron* **37**, 3609

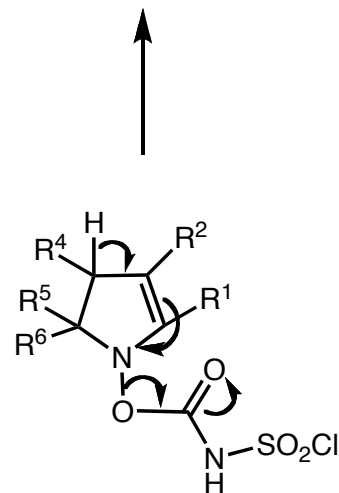
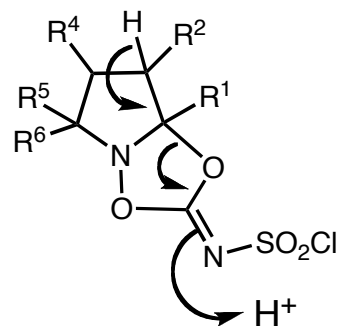
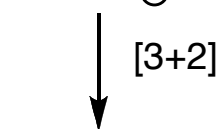
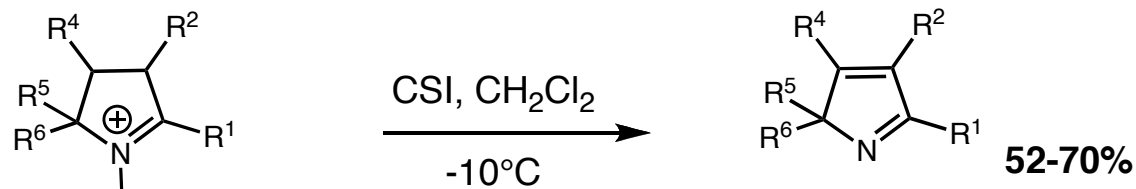
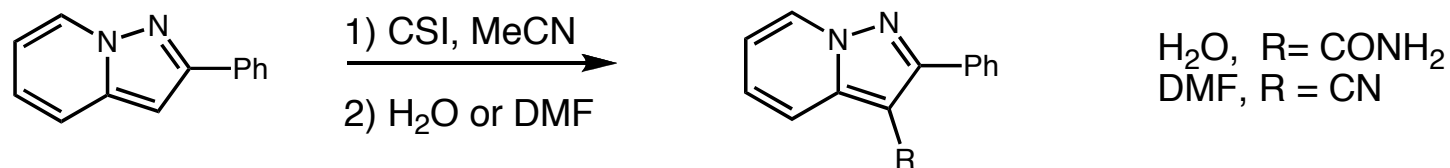
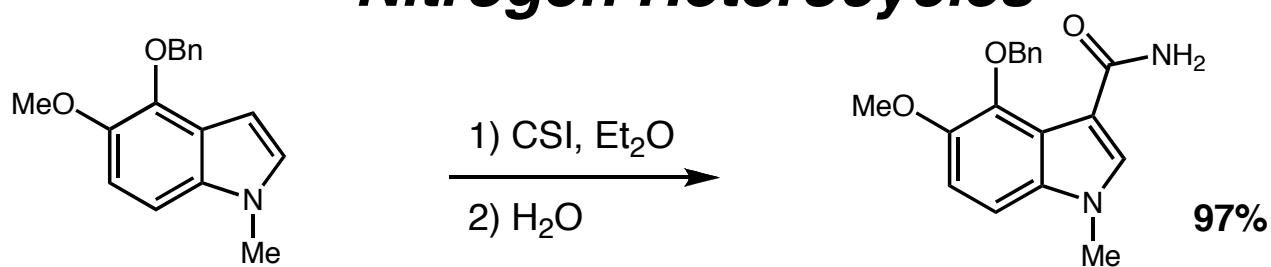
Aziridines



Proposed Mechanism

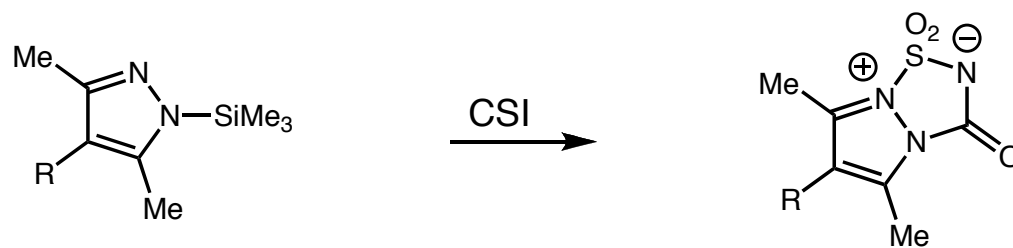
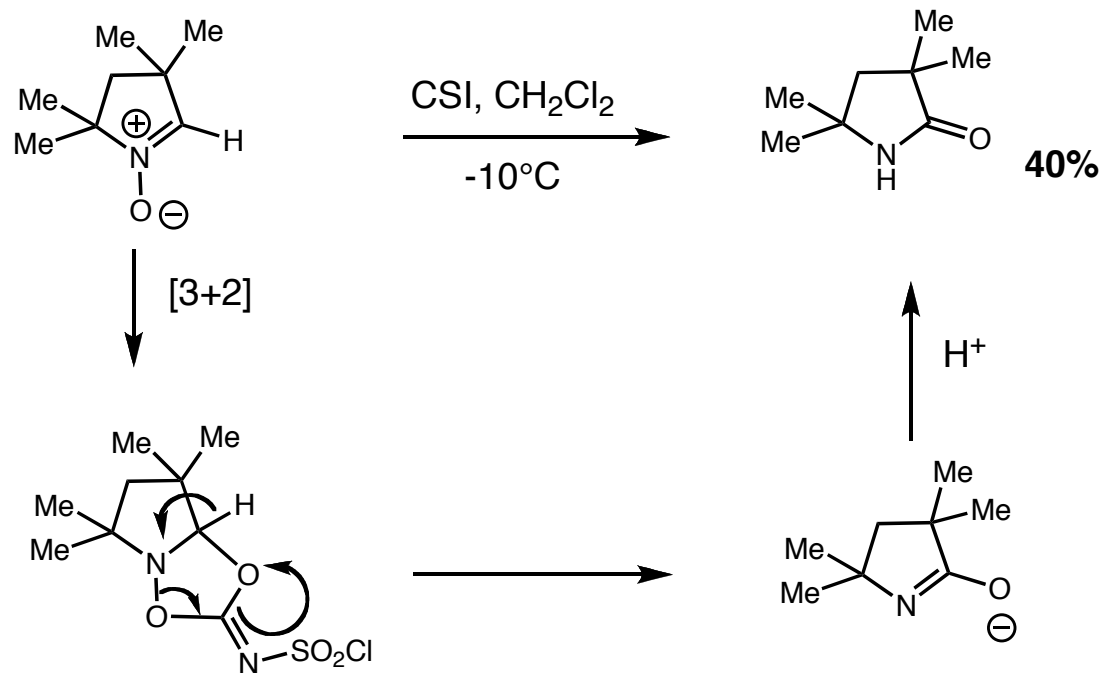


Nitrogen Heterocycles



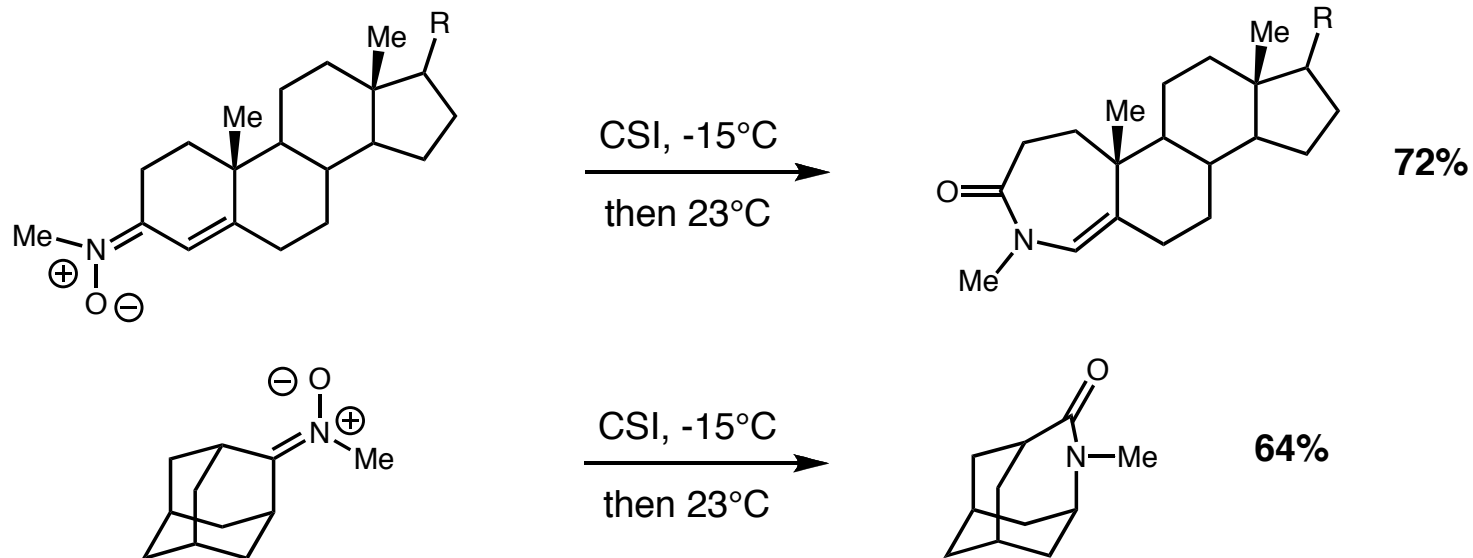
- 1) Moddy, J. C., Swann, E., *Tet. Lett.*, **34**, 1987
- 2) Yasuyoshi, M., *et al.*, *Heterocycles*, **38**, 1881
- 3) Joseph, S. P., Dhar, D.N., *Tetrahedron*, **44**, 5209

More Nitrogen Heterocycles

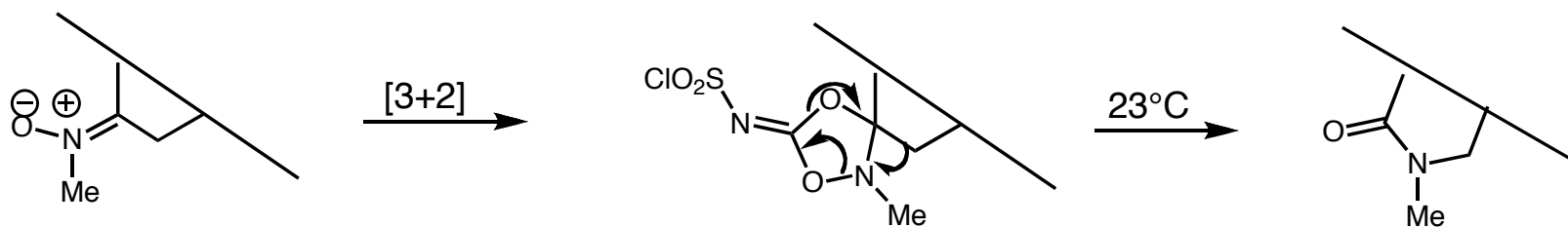


- 1) Joseph, S. P., Dhar, D.N., *Tetrahedron*, **44**, 5209
- 2) Friedrichsen, W., *et al.*, *Heterocycles*, **20**, 845

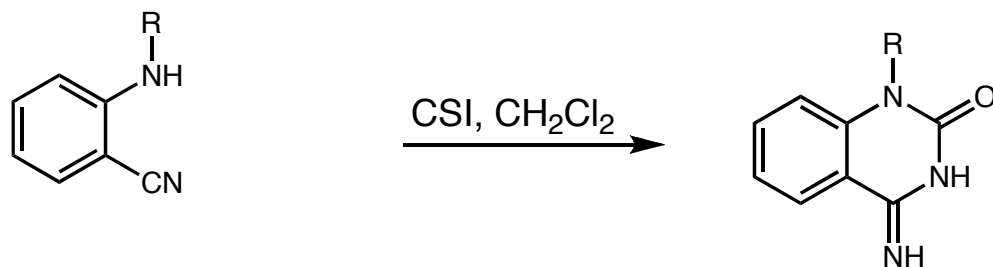
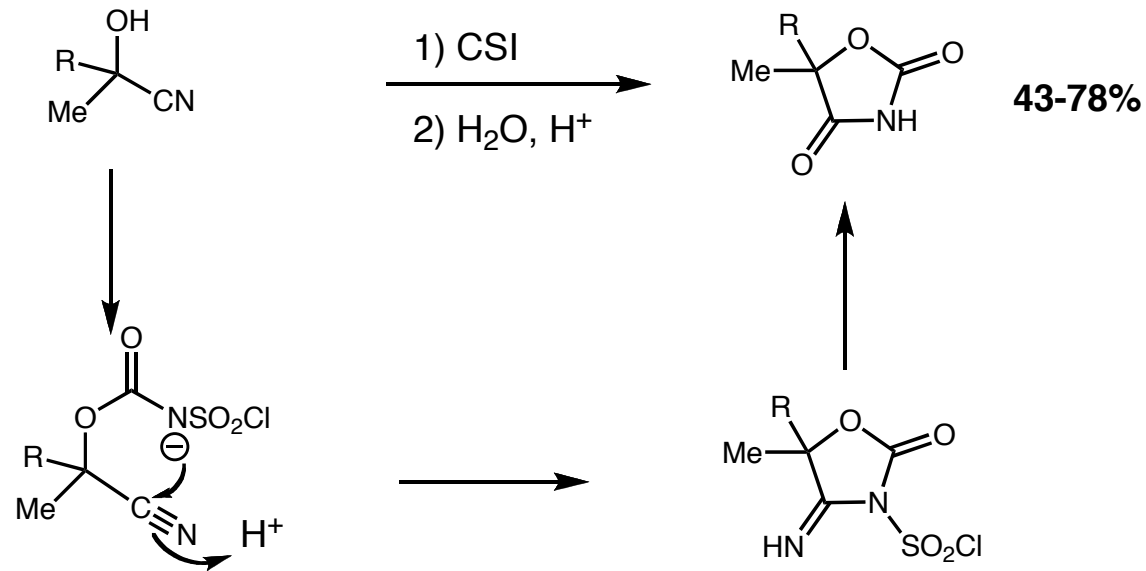
Nitrones for Ring Expansion



Mechanism

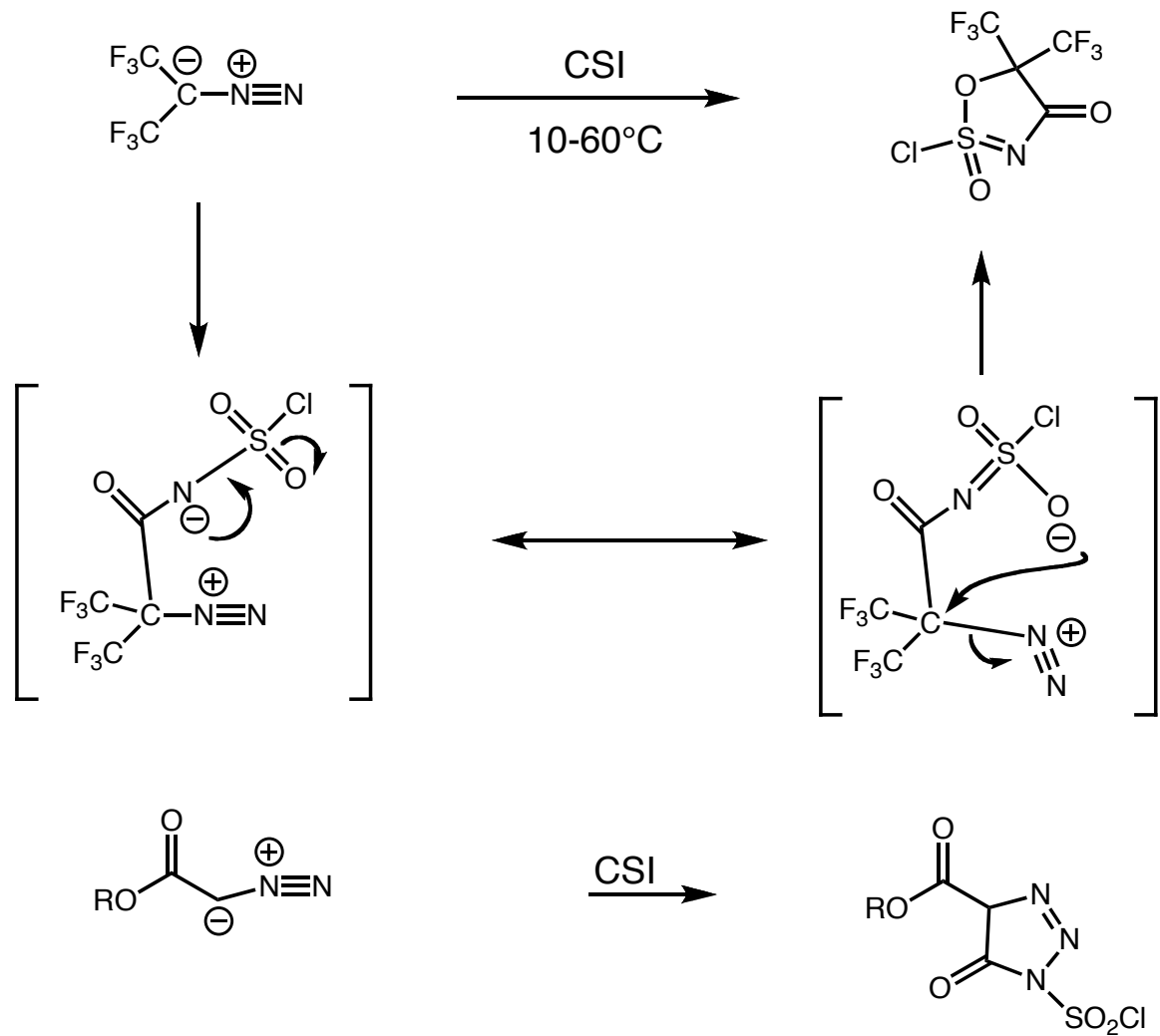


Cyanides with Adjacent Heteroatom



- 1) Garcia, M. V., *et al.*, *Synthesis*, 6978 (1991)
- 2) Reddy, A. V. N., *et al.*, *Synth. Comm.*, **18**, 525

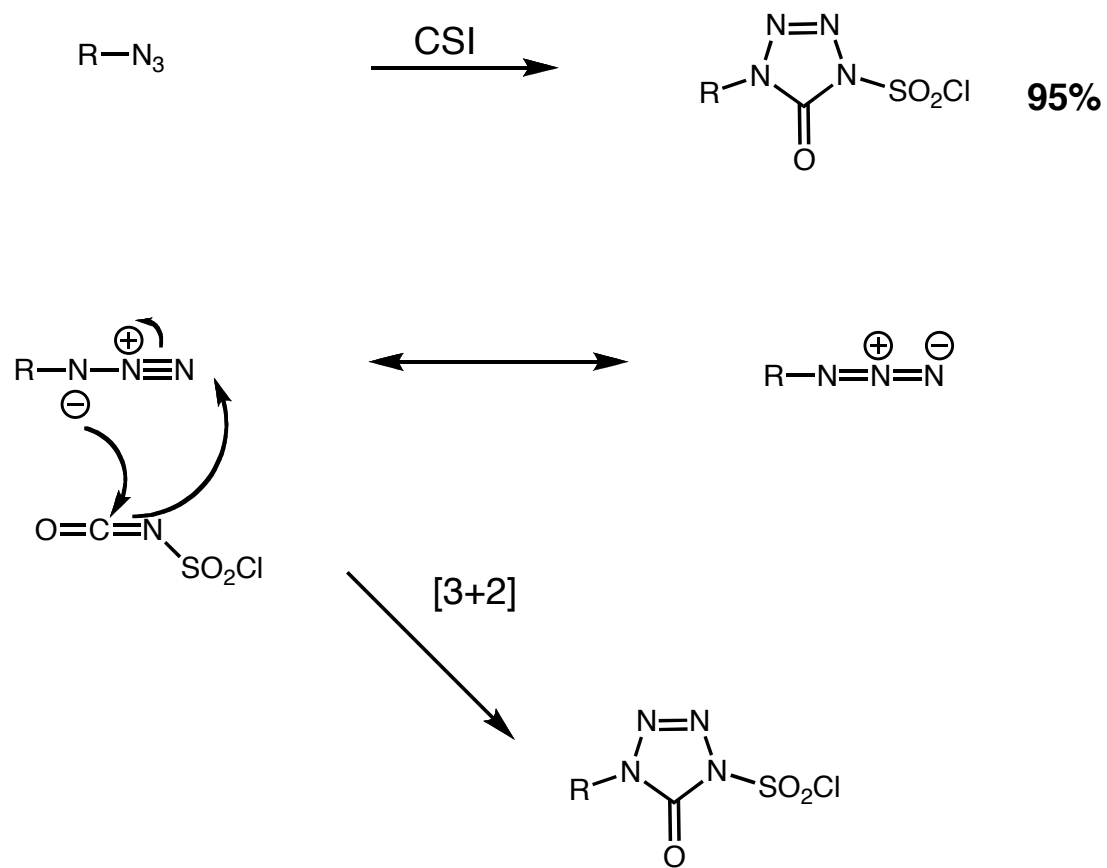
Diazo Compounds



1) Steinbeisser, H., *et al.*, *Anorg. Allg. Chem.*, **406**, 299

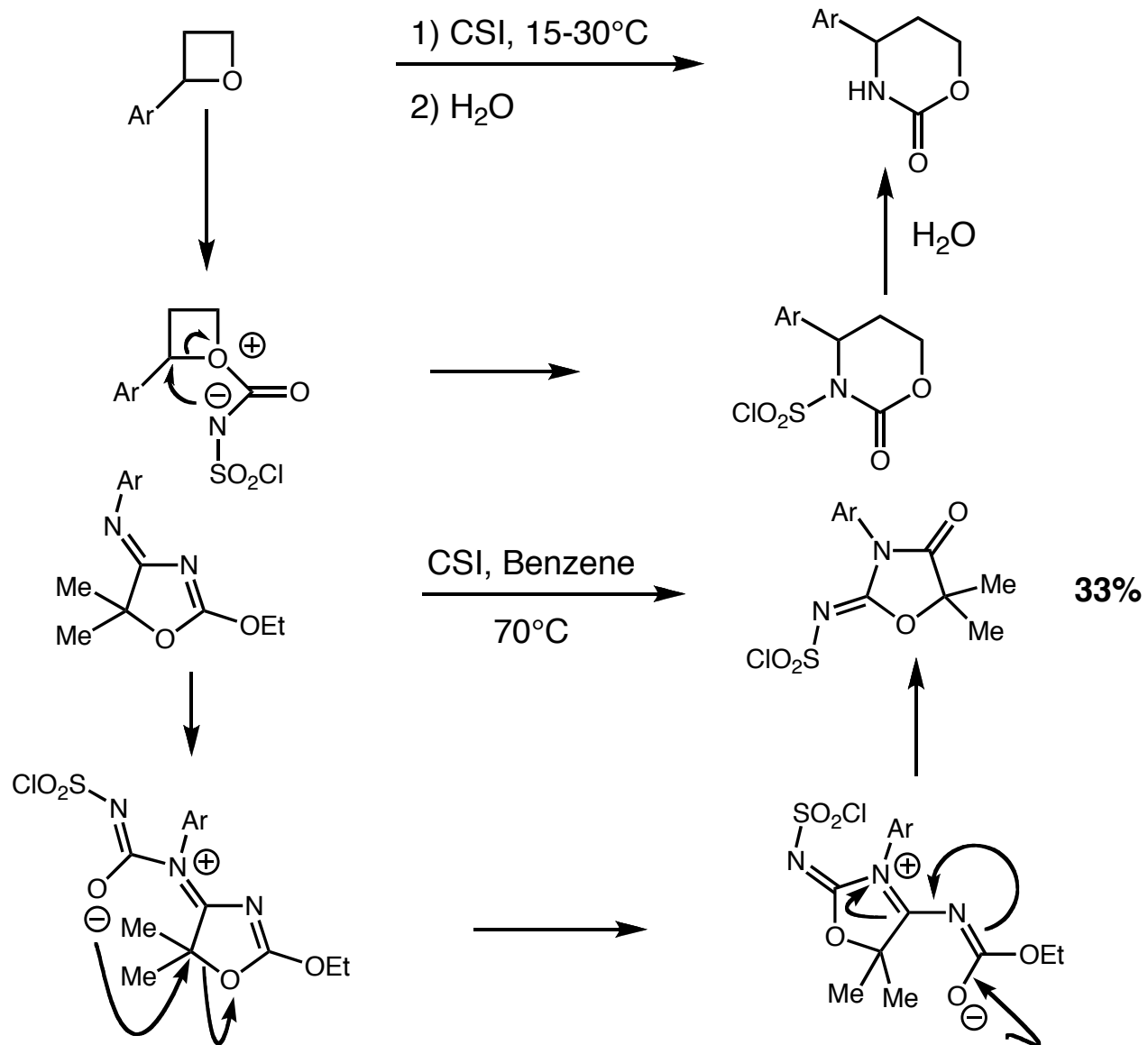
2) Graf, R., *Angew. Chem. Int. Ed. Engl.*, **7**, 172

Azides



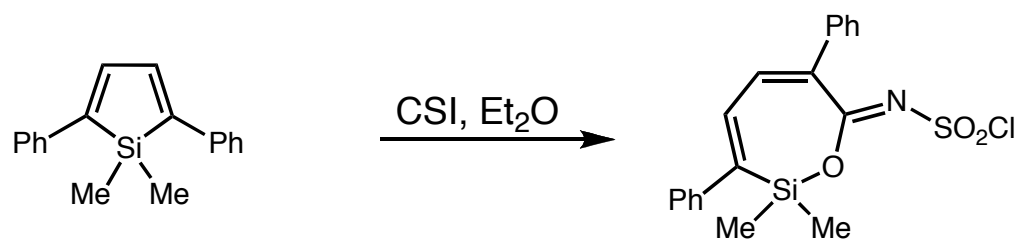
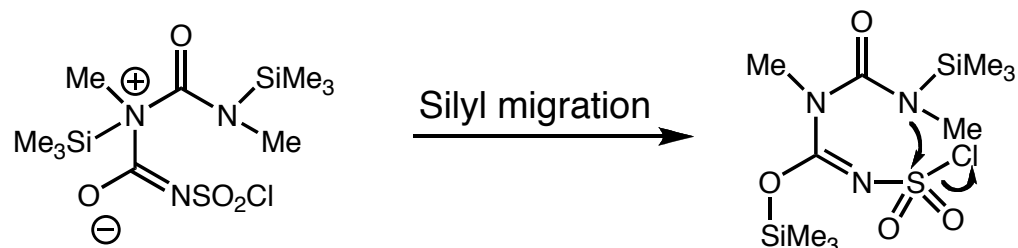
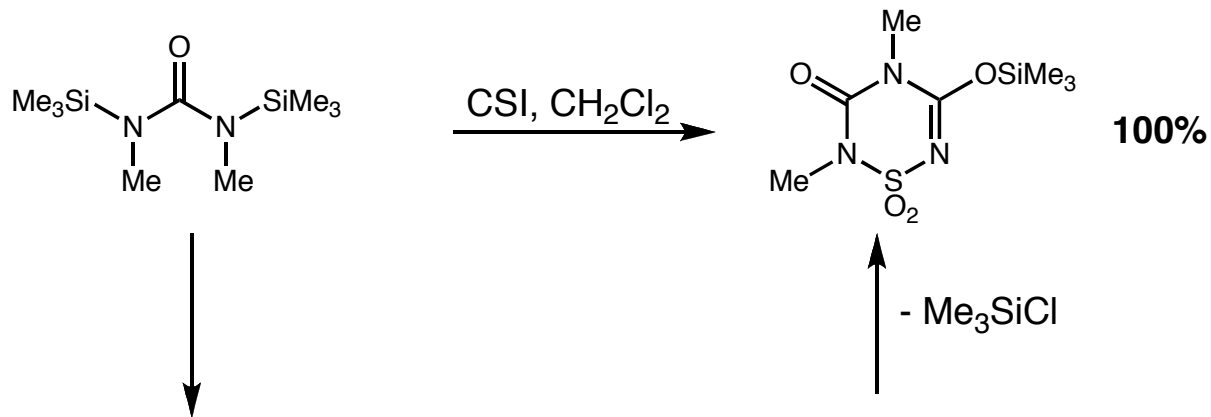
Vander Sarel, J-M., *et al.*, *JOC*, **38**, 675

Oxygen Heterocycles



- 1) Sampath Kumar, E., Dhar, D.N., *Synth. Comm.*, **25**, 1939
- 2) L'Abbe', G., Destexhe, R., *Chem. Comm.*, 1614 (1985)

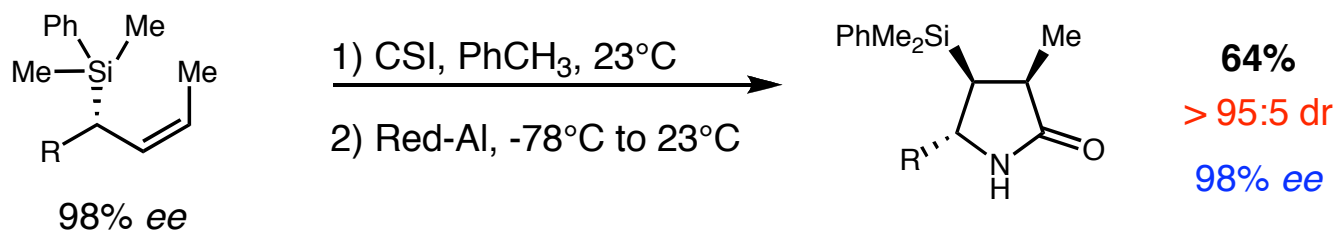
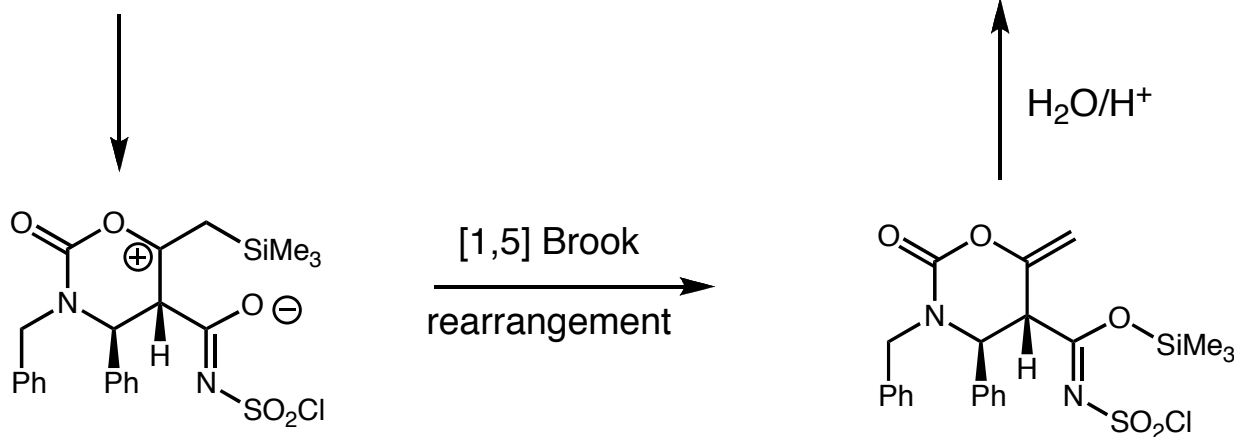
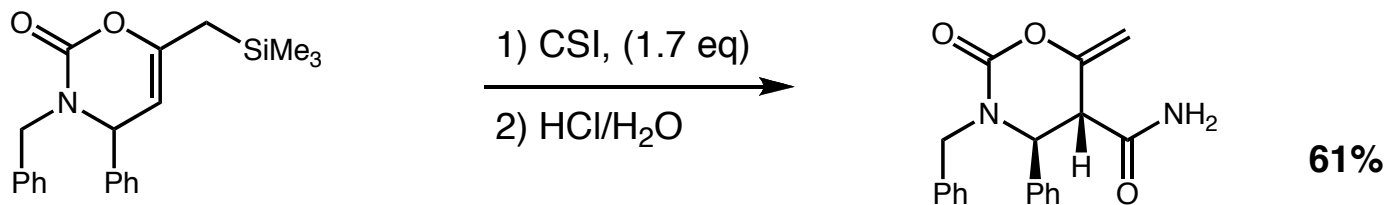
Organo-Silicon Compounds



1) Barton, T.J., Rogido, R.J., *Chem. Comm.*, 878 (1972)

2) Barton, T.J., Rogido, R.J., *JOC*, **40**, 582

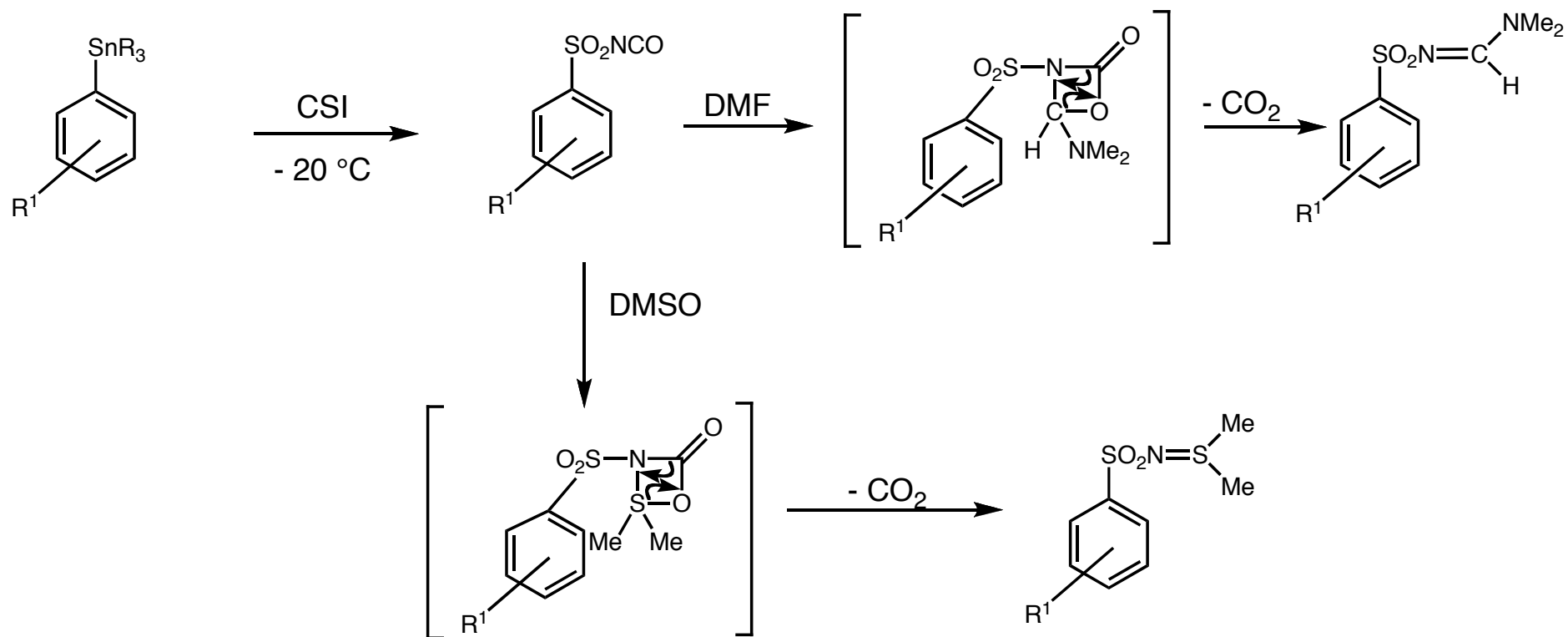
Organo-Silicon Compounds Continued



1) Esch, P. M., *et al.*, *Tetrahedron*, **48**, 3445

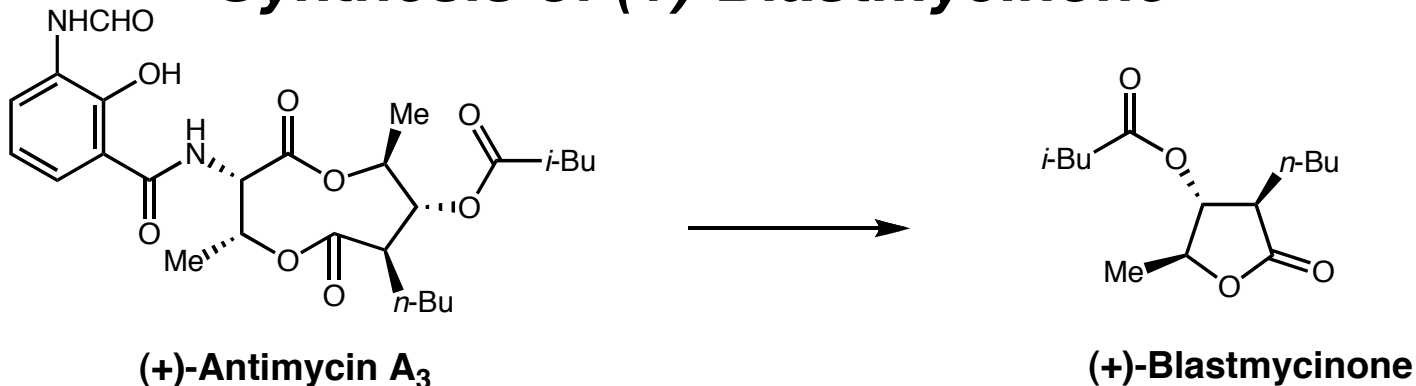
2) Roberson C., Woerpel, K., *JOC*, **64**, 1434

Miscellaneous Reactions



Arnswald, M., Neumann, W.P., *JOC*, **58**, 7022

Synthesis of (+)-Blastmycinone



- Degradation product of the macrocyclic dilactone (+)-antimycin A₃
- γ -Butyrolactone an important core structure in many biological active natural products
- Three contiguous stereogenic centers with a cis/trans/cis relationship
- Two major Challenges:

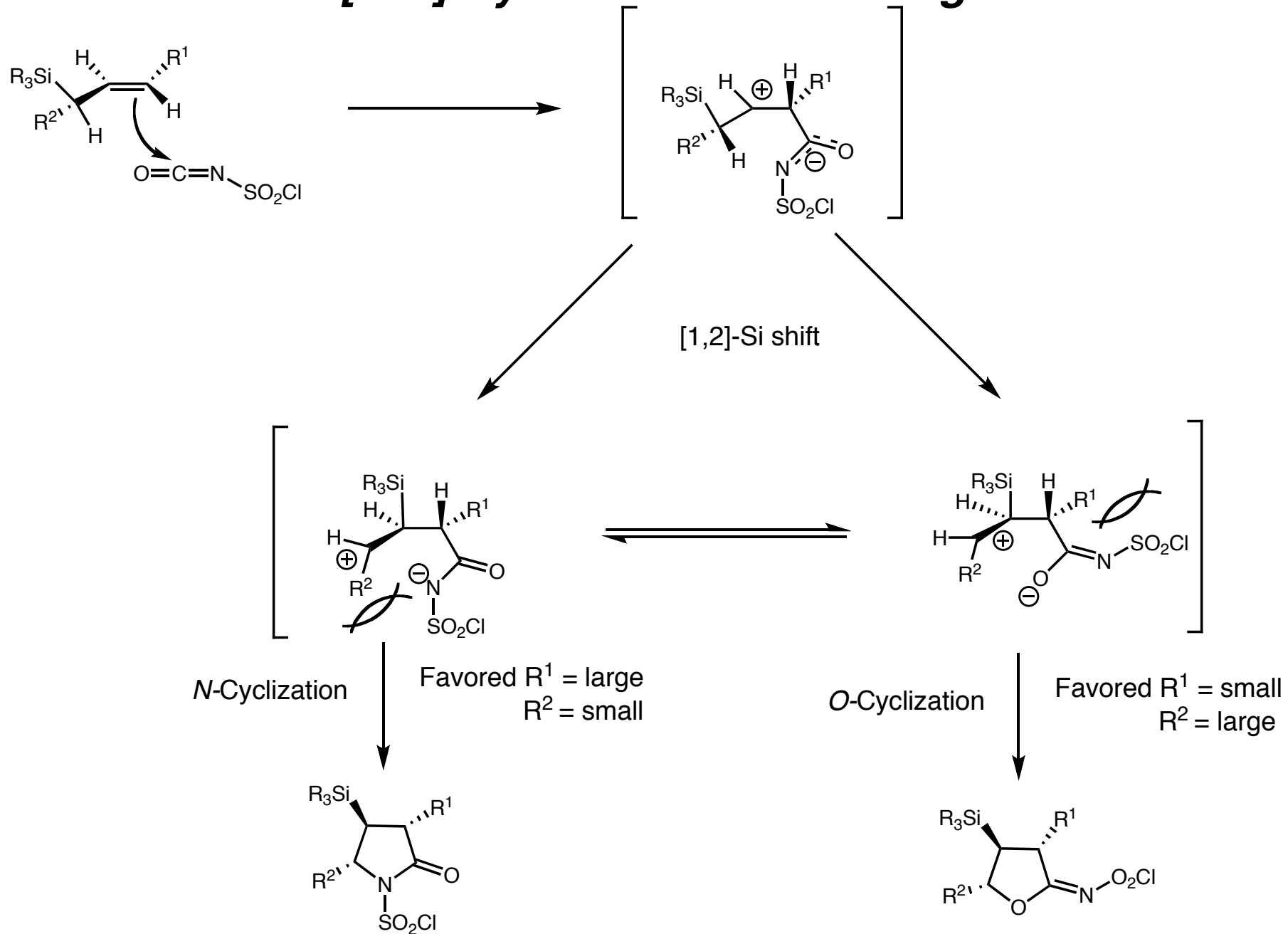
A) [3+2] cycloaddition C=O Vs. C=N

B) controlling the selectivity of the [1,2]-silyl shift

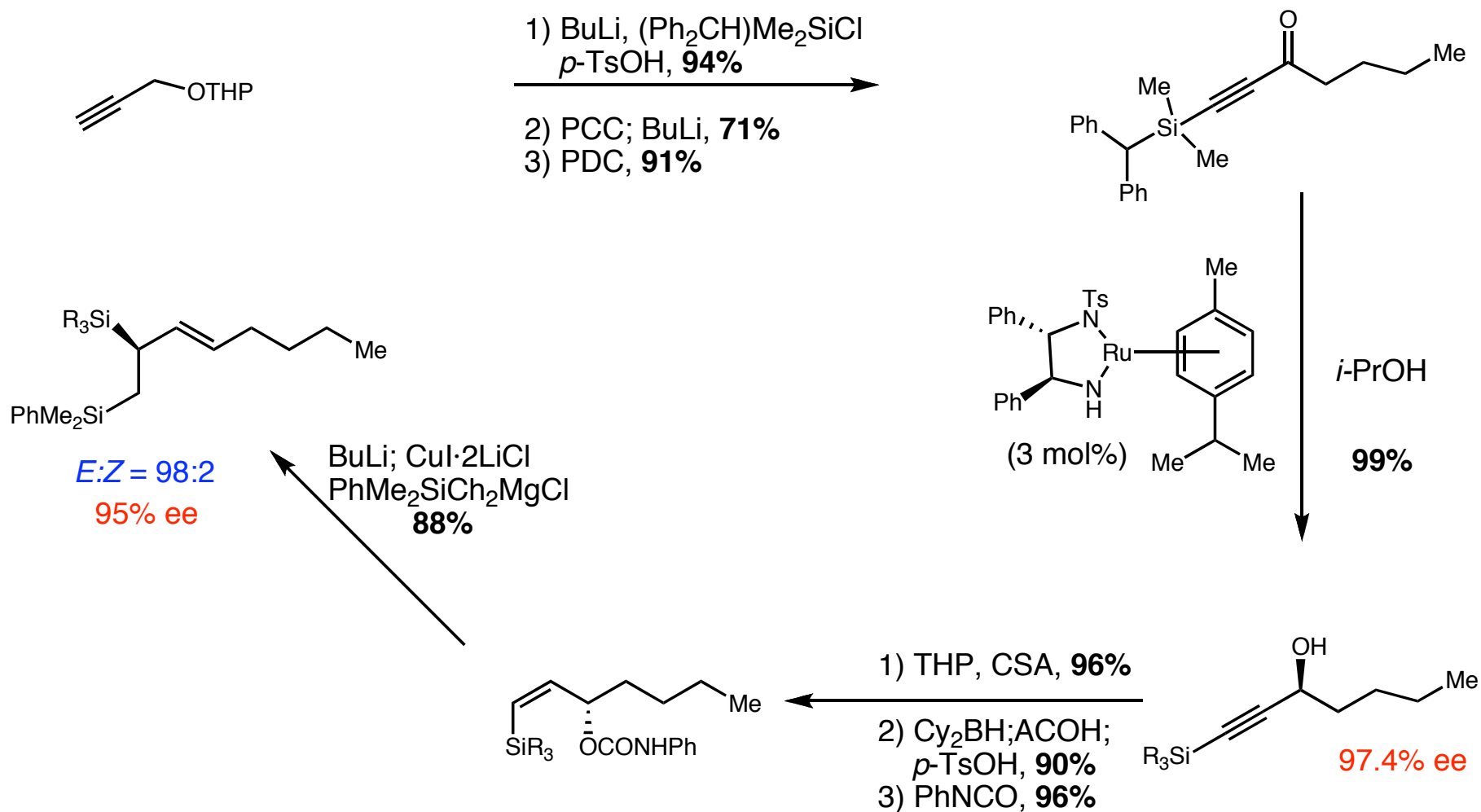
1) Peng, Z. H., Woerpel, K. A., *Org. Lett.*, **5**, 675

2) Wasserman, H. H, Gambale, R. J., *JACS*, **107**, 124

[3+2] Cycloaddition Challenge

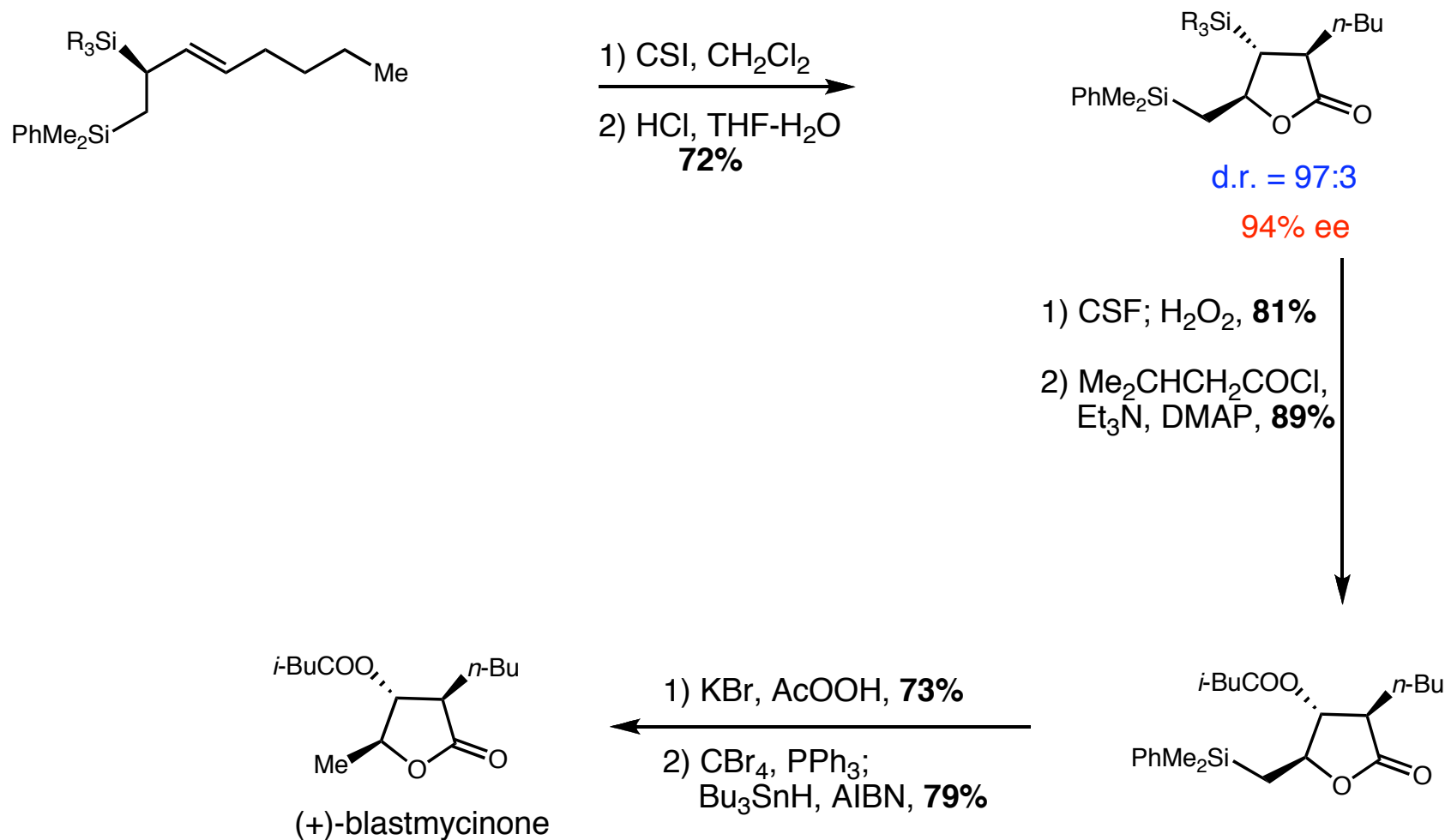


Stepwise Synthesis of (+)-Blastmycinone



Peng, Z. H., Woerpel, K. A., *Org. Lett.*, **5**, 675

Final Steps in the Synthesis (+)-Blastmycinone



Peng, Z. H., Woerpel, K. A., *Org. Lett.*, **5**, 675

Summary & Conclusions

- Powerful and versatile reagent
- Can be used to access valuable motifs for:
 - A) Biological
 - B) Pharmaceutical
 - C) Agricultural

Thank You!