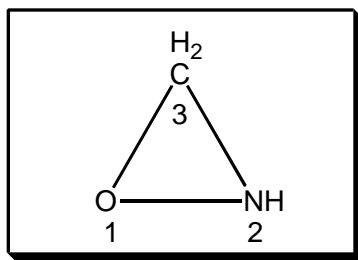


Chemistry of Oxaziridines

An Evans Group Afternoon Seminar

Nabi Magomedov

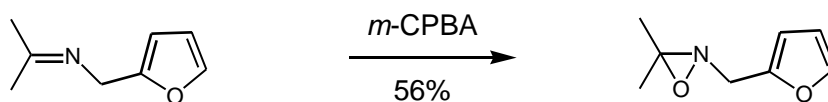
December 1, 2000



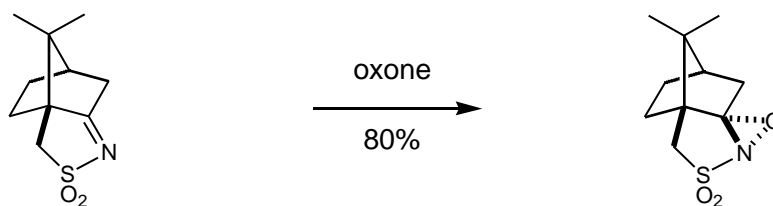
1. Preparation
2. Configurational stability
3. Acid- and base-catalyzed reactions of oxaziridines
4. Heteroatom transfer reactions: 4.1 O-transfer reactions
4.2 N-transfer reactions
5. Rearrangements
6. Single electron transfer chemistry

Leading references: Emmons, W. D. *J. Am. Chem. Soc.* **1957**, 79, 5739
Haddadin, M. J.; Freeman, J. P. in *Small Ring Heterocycles-Part 3*, J. Wiley & Sons, NY 1985, p. 284
Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, 45, 5703
Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, 92, 919

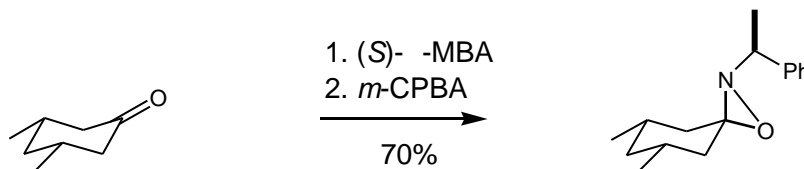
Preparation: Imine Oxidation with Peroxy Compounds



Wilmer *Helv. Chim. Acta* **1974**, 57, 657



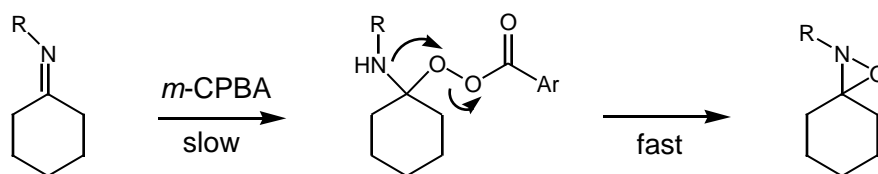
Davis *J. Am. Chem. Soc.* **1988**, 110, 8477



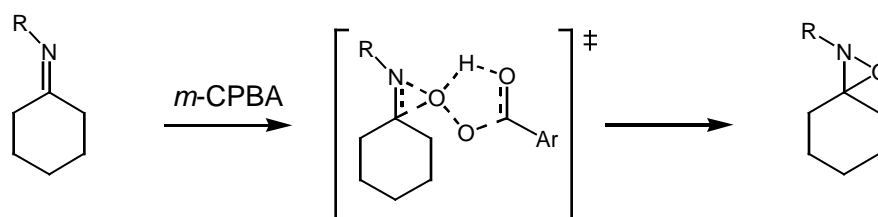
Aube *J. Am. Chem. Soc.* **1995**, 117, 5169

Mechanism of Peroxy Acid Oxidation of Imines

Two-step mechanism



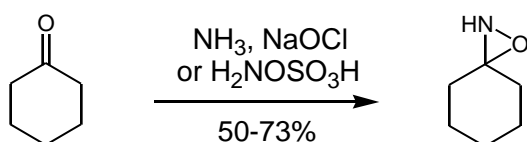
Concerted mechanism



1. Reaction is stereoselective but *not* stereospecific.
2. Imines are oxidized in preference to olefins at low temperature.
3. Kinetic study and study of solvent effects support the two-step mechanism.
Ogata *J. Am. Chem. Soc.* **1973**, 95, 4687
4. Theoretical study also suggests the two-step mechanism.
Plesnicar *J. Am. Chem. Soc.* **1979**, 101, 1107

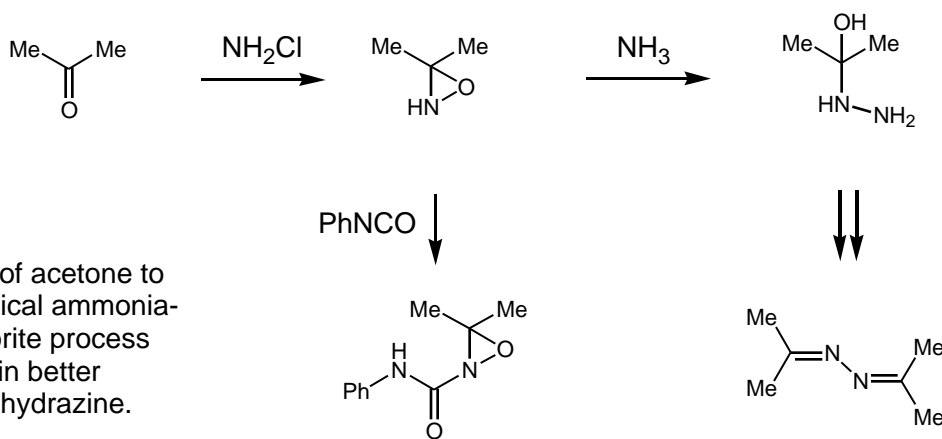
Aube *J. Org. Chem.* **2000**, 65, 5120

Preparation via Electrophilic Amination of Ketones



Reaction is preferred for preparation of oxaziridines unsubstituted at nitrogen. Success of reaction is highly substrate dependent: works well also with PhCHO , butanone, and chloral.

Modified Raschig's process

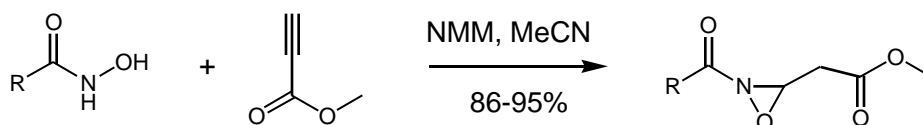


Addition of acetone to the classical ammonia-hypochlorite process resulted in better yields of hydrazine.

Schmitz *Synthesis* **1991**, 327

Other Methods of Preparation

Conjugate addition of hydroxamic acids to propiolates

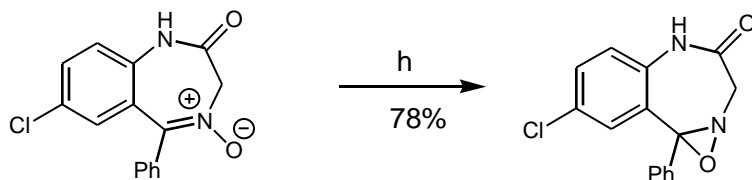


R = aryl, alkyl, alkenyl

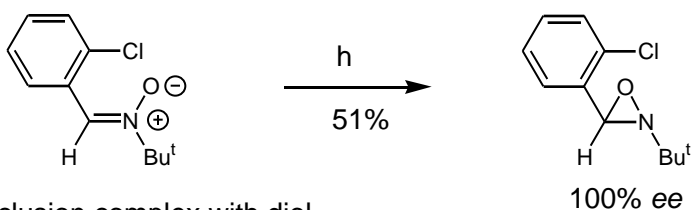
NMM = *N*-methylmorpholine

Ryu *Tetrahedron Lett.* **1998**, 39, 6227

Photolysis of nitrones

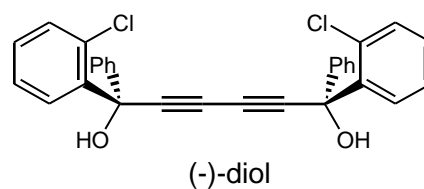


Hoffmann-La Roche
J. Org. Chem. **1970**, 35, 2243



1:1 inclusion complex with diol

100% ee

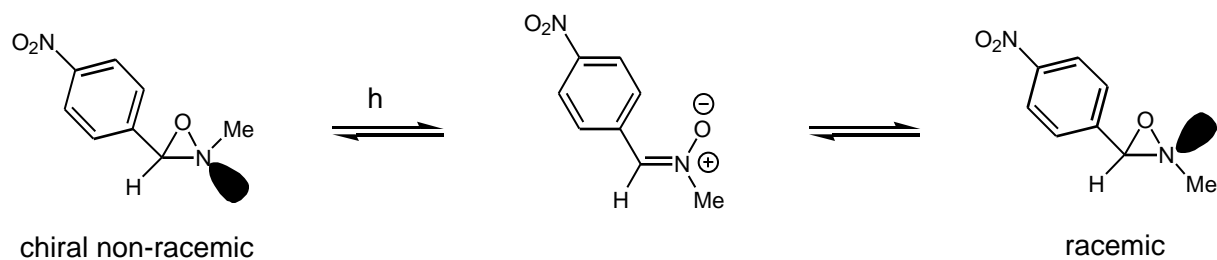


(-)-diol

Toda *Chem. Lett.* **1987**, 2283

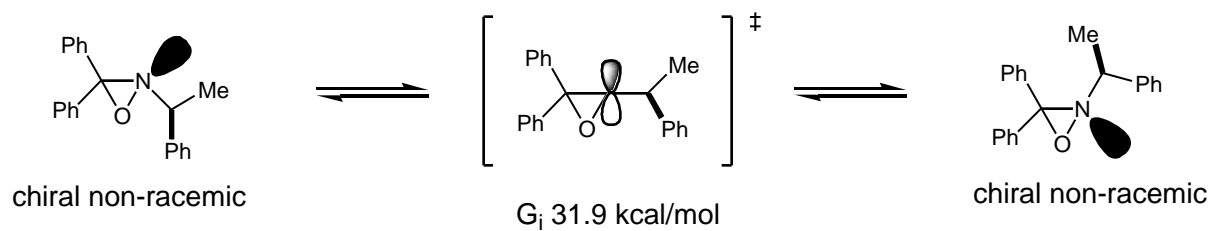
Configurational Stability and Mechanisms of Epimerization at Nitrogen

Photochemical epimerization



Boyd *Chem. Commun.* **1976**, 162

Thermal epimerization

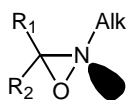


Torre *JCS, Perkin II* **1978**, 401

Barriers for Nitrogen Inversion in Oxaziridines

Two major reasons for high energetic barrier for N inversion:

1. Ring strain increases on going from ground state to the inversion transition state.
2. Inductive effect of adjacent O atom increases the s-character of the lone pair on N and makes it more pyramidal.



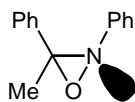
G_i 25-32 kcal/mol

The bigger *N*-alkyl group the smaller the inversion barrier:

Alk = *i*-Pr 32 kcal/mol but Alk = *t*-Bu 26 kcal/mol.

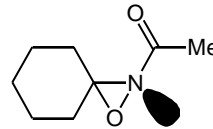
Boyd *JCS, Perkin II* **1973**, 1575

When N atom is connected to substituents capable of π -conjugation or hyperconjugation, the inversion barriers are smaller.



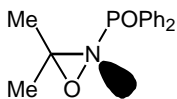
G_i 23.4 kcal/mol

Ono *Tetrahedron Lett.* **1973**, 4107



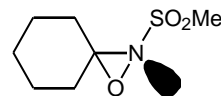
G_i 11.8 kcal/mol; G_r (N-CO) 10.3 kcal/mol

Jennings *JCS, Chem. Commun.* **1992**, 1078



G_i 13.2 kcal/mol

Jennings *JCS, Perkin II* **1991**, 1281

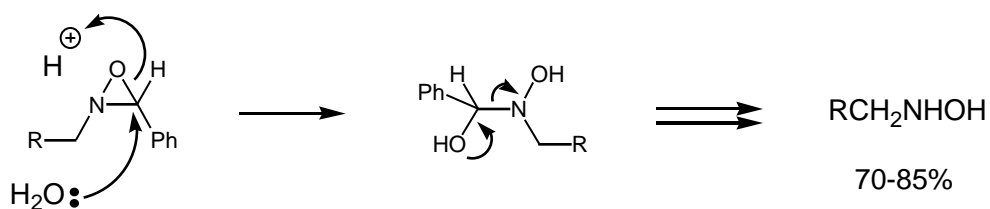


G_i 20.6 kcal/mol

Jennings *J. Am. Chem. Soc.* **1987**, 109, 8099

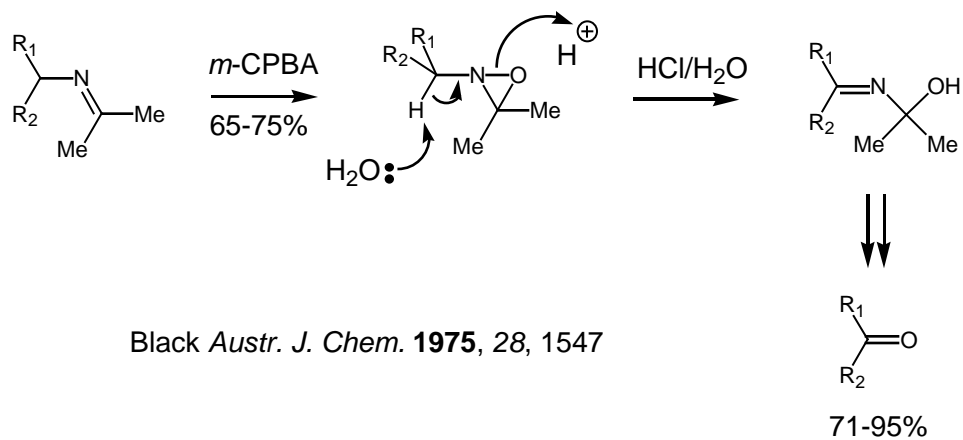
Acid-Catalyzed Ring Opening of Oxaziridines

3-Aryl-substituted oxaziridines



Emmons *Chem. Heteroc. Comp.* **1964**, 19, 624

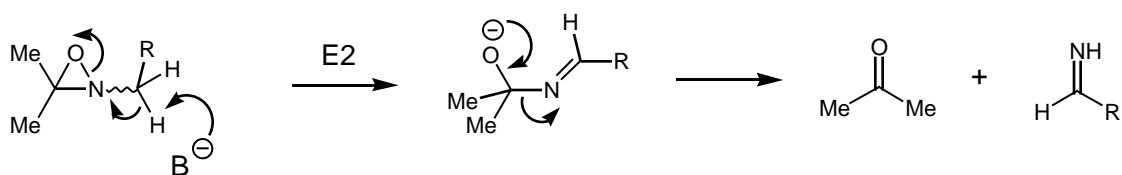
3-Alkyl-substituted oxaziridines



Black *Austr. J. Chem.* **1975**, 28, 1547

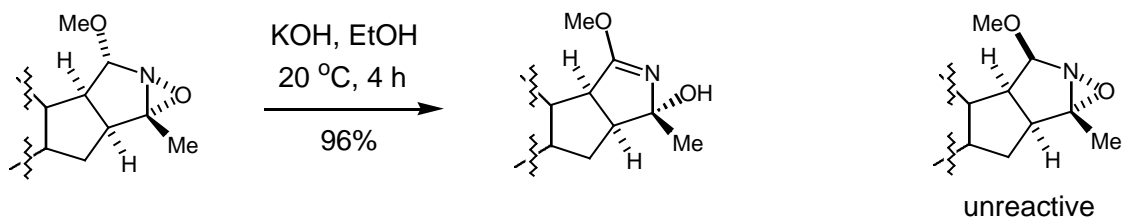
Base-Catalyzed Ring Opening of Oxaziridines

Mechanism



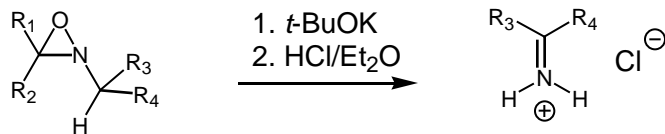
$$k_H/k_D = 4-6$$

Rastetter *J. Org. Chem.* **1982**, 47, 419



Lusinch *Tetrahedron* **1974**, 30, 2825

Synthesis of N-H ketimines



$R_1 = Ph$; $R_2 = H$ or Ph

90% $R_3 = R_4 = Ph$
52% $R_3 = R_4 = Et$

Boyd *Tetrahedron Lett.* **1982**, 23, 2907

Heteroatom Transfer Reactions

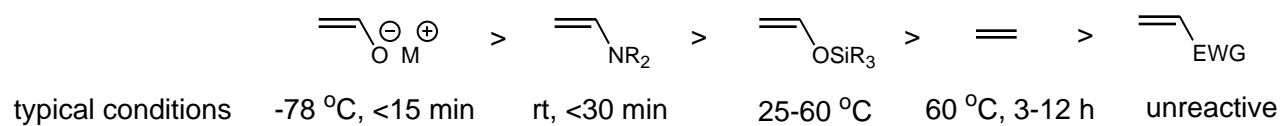
Generally, oxaziridines with small substituents on nitrogen act as aminating agents, whereas those with bulky or electron-withdrawing groups on nitrogen preferentially transfer the oxygen atom.

- Oxygen transfer reagents:
1. *N*-sulfonyl oxaziridines
 2. *N*-phosphinoyl oxaziridines
 3. oxaziridinium salts
 4. perfluorinated oxaziridines

Reactivity order of oxygenating reagents toward olefins:



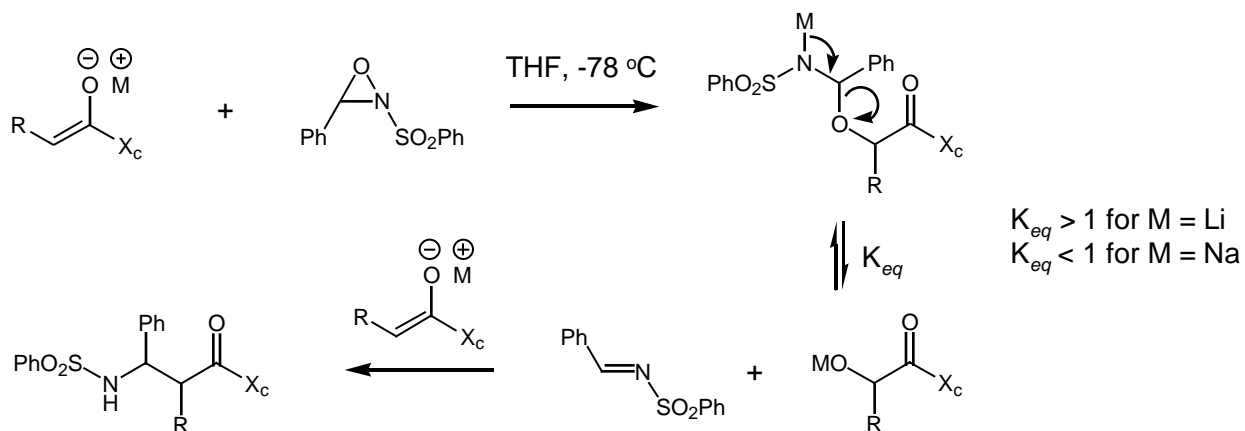
Reactivity order of oxidation substrates in reaction with *N*-sulfonyl oxaziridines:



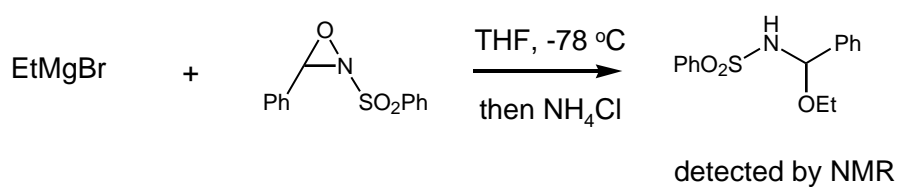
- Nitrogen transfer reagents:
1. *N*-unsubstituted oxaziridines
 2. *N*-alkyl oxaziridines
 3. *N*-acyl oxaziridines

Mechanism of Reaction of Enolates with Oxaziridines

Mechanism involves an S_N2 -type attack of enolate on oxaziridine oxygen to form a hemiaminal intermediate that collapses to give oxygenated product and imine.



Evans *J. Am. Chem. Soc.* **1985**, *107*, 4346

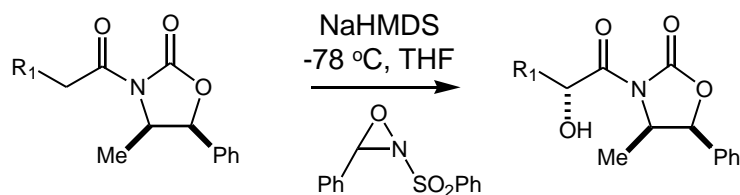


Davis *Tetrahedron Lett.* **1987**, *28*, 5115

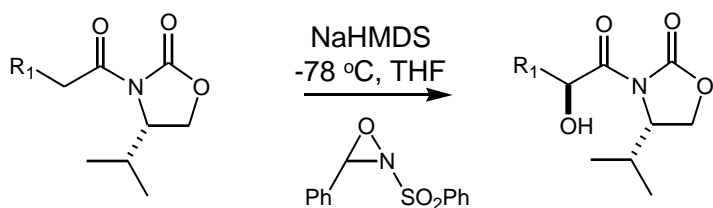
Asymmetric Enolate Oxidation with *N*-Sulfonyl Oxaziridines

1. Auxilliary-induced asymmetric oxidations.
2. Asymmetric oxidation of prochiral enolates with non-racemic oxaziridines.
3. Double asymmetric induction.

Evans' auxiliary method



R_1	<i>dr</i>	yield, %
CH_2Ph	94:6	86
Ph	90:10	77
$CH_2CH=CH_2$	95:5	91

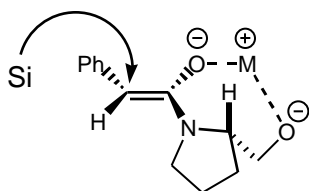
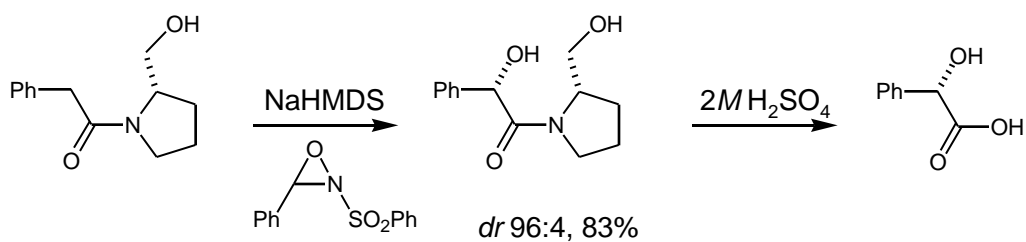
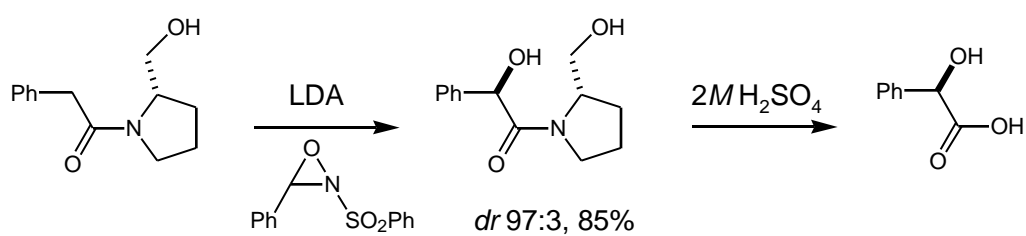


R_1	<i>dr</i>	yield, %
CH_2Ph	95:5	85
<i>i</i> -Pr	99:1	86

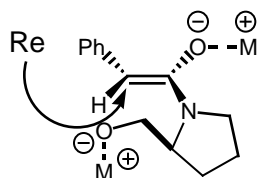
Evans *J. Am. Chem. Soc.* **1985**, *107*, 4346

Oxidation of Chiral Amide Enolates with *N*-Sulfonyl Oxaziridines

2-Pyrrolidinemethanol auxiliary



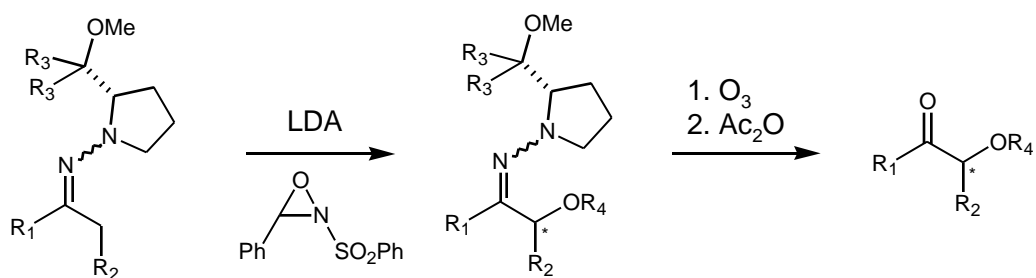
Li as a counterion



Na as a counterion

Davis
Tetrahedron Lett. **1985**, 26, 3539

Oxidation of Enders' Hydrazones with *N*-Sulfonyl Oxaziridines

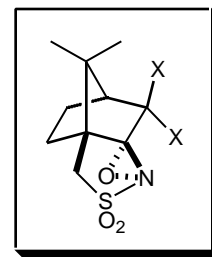
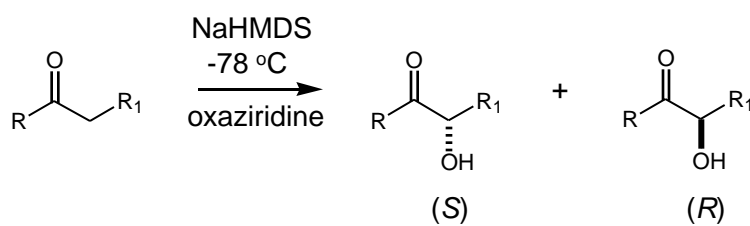


For R₁=H O-benzylation (NaH/DMF then BnCl) was required before the oxidative cleavage of the auxiliary.

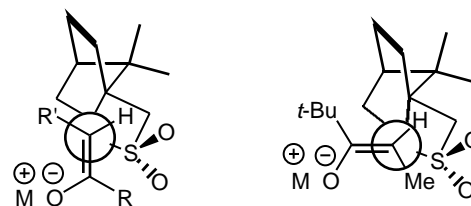
R ₁	R ₂	R ₃	R ₄	overall yield, %	ee, %	conf.
Ph	Me	H	COMe	51	93	<i>R</i>
Ph	Me	Me	COMe	73	88	<i>R</i>
Ph	Ph	H	COMe	74	>96	<i>S</i>
H	<i>n</i> -Hex	H	Bn	63	56	<i>R</i>
H	<i>n</i> -Hex	Et	Bn	55	>96	<i>S</i>

Enders *Tetrahedron Lett.* **1988**, 29, 2437

Oxidation of Prochiral Enolates with Non-racemic Oxaziridines



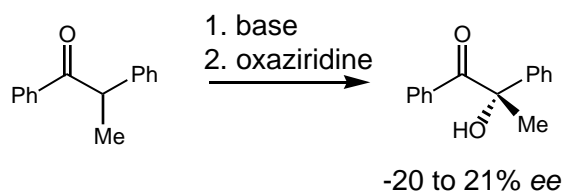
R	R'	X	yield, %	ee, %	conf.
Ph	Ph	H	84	95	S
Ph	Me	H	73	62	S
Ph	Me	Cl	61	95	S
Me	Ph	H	70	40	S
<i>t</i> -Bu	Me	H	71	89	R



Proposed model for asymmetric induction

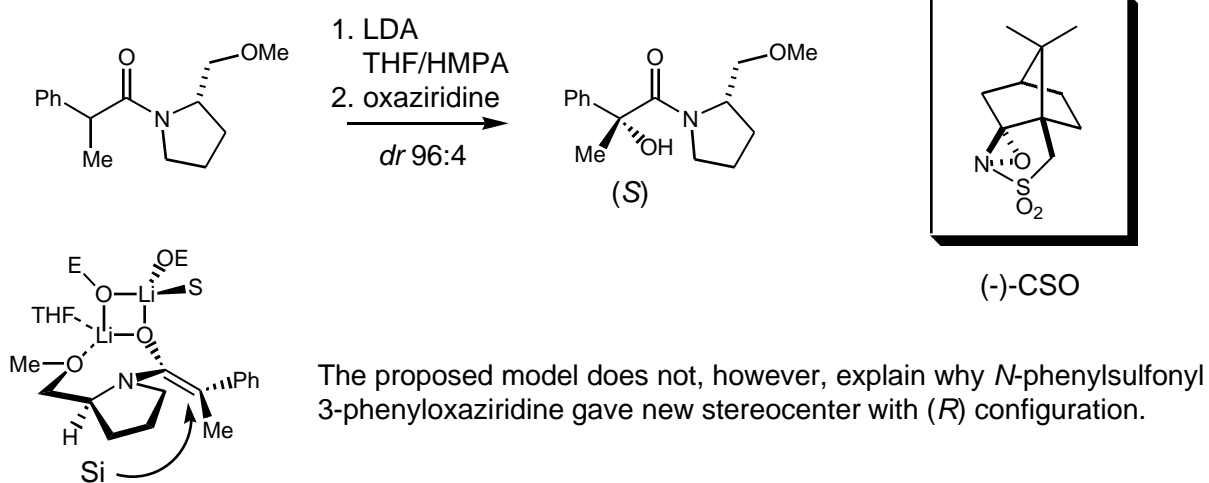
Davis *J. Am. Chem. Soc.* **1990**, 112, 6679

Oxidation of tertiary acyclic ketones gave poor enantioselectivity under a number of conditions.



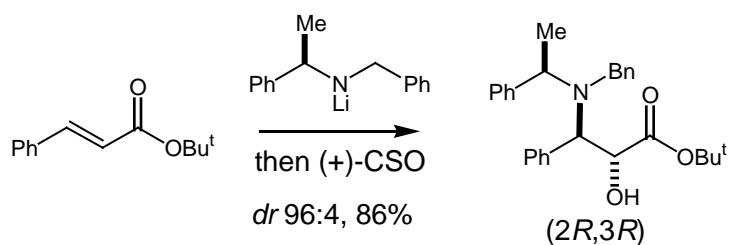
Davis *J. Org. Chem.* **1987**, 52, 5288

Double Asymmetric Induction Experiments



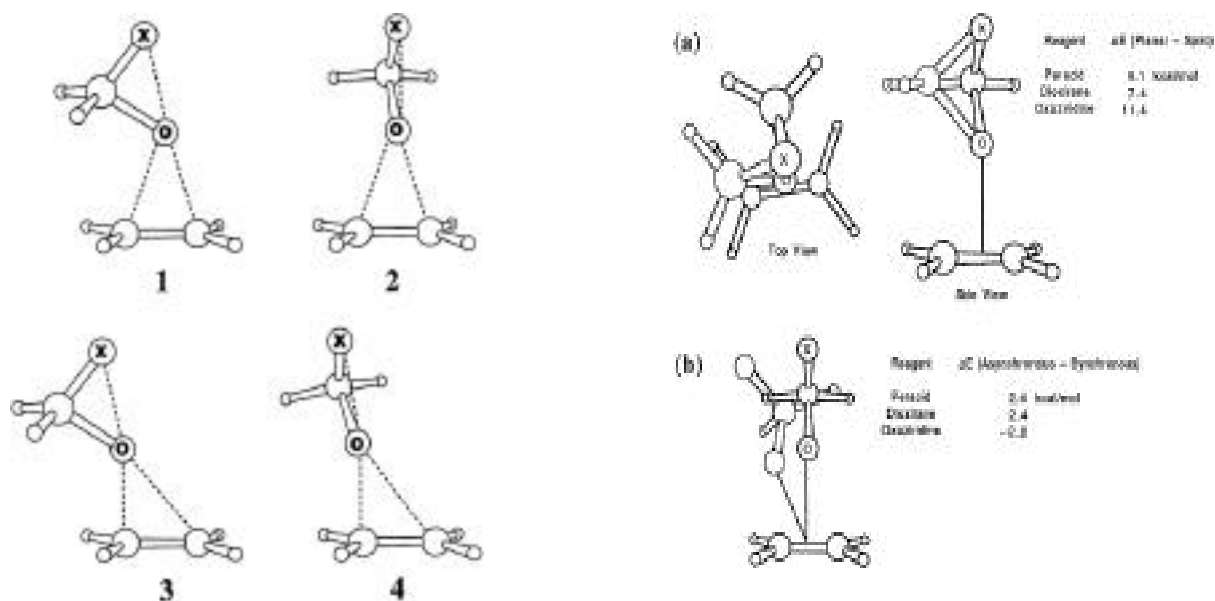
Davis *J. Org. Chem.* **1987**, 52, 5288

Asymmetric conjugate addition-oxidation cascade



Mechanism of Oxygen Transfer to Olefinic Double Bond

Questions to be addressed: 1. Planar or spiro transition state
2. Synchronous or asynchronous transition state

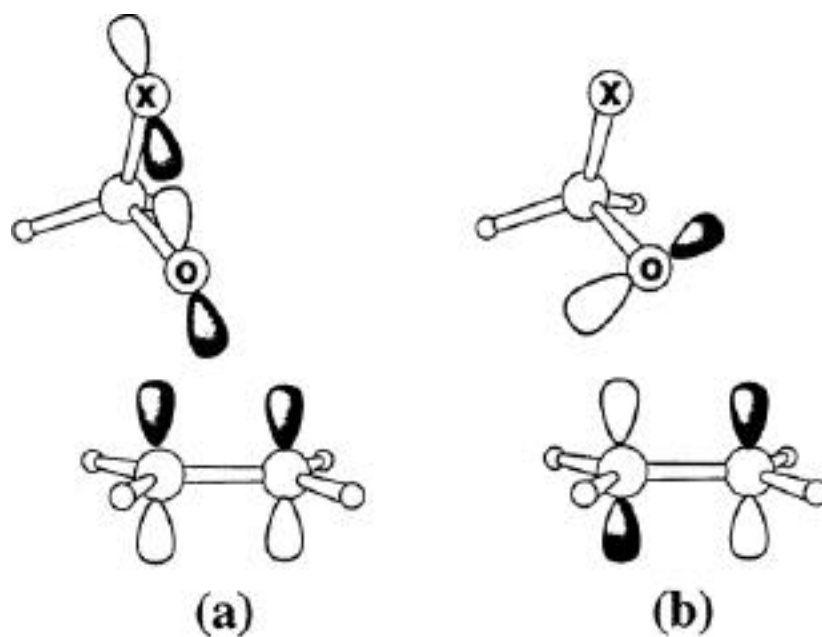


Preliminary experimental (Davis) and theoretical (Bach) studies favored structure **1**. Calculations done at more advanced level (Houk; Bach) favored spiro transition states **2** and **4**.

Transition structures (B3LYP/6-31G*) for epoxidations of ethylene by performic acid, dioxirane, peroxyxynitrous acid, and oxaziridine.

Houk *J. Am. Chem. Soc.* **1997**, *119*, 10147

FMO Rational for Spiro Transition State

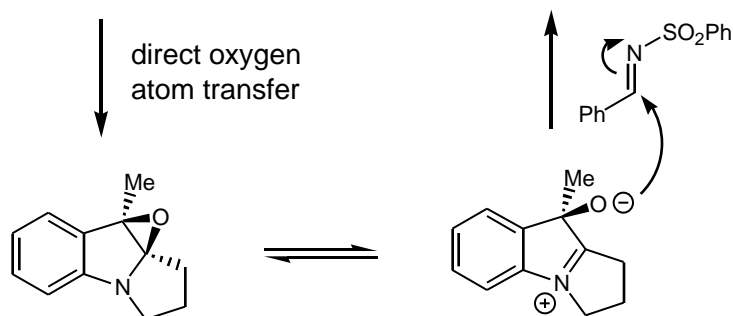
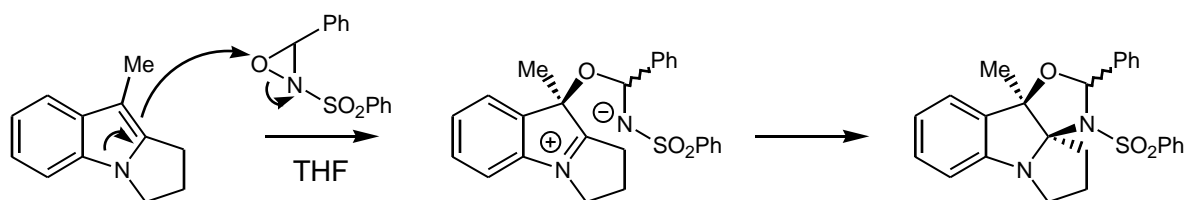


FMO interactions in the transition states of epoxidations:
(a) alkene HOMO-oxidant LUMO and (b) oxidant HOMO-alkene LUMO.

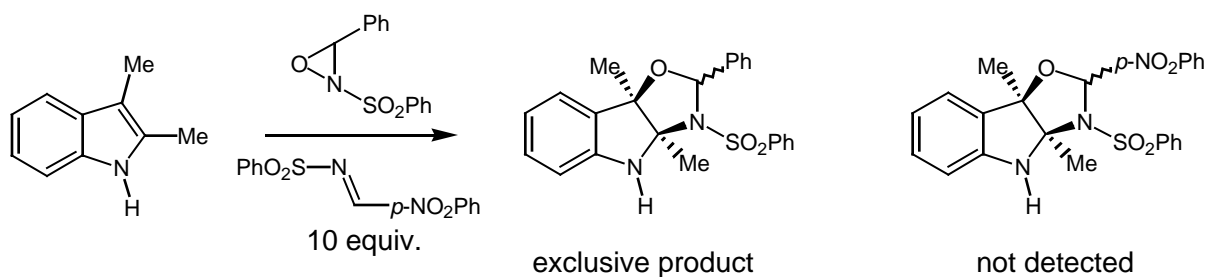
Thus, epoxidation reaction by oxaziridines has late spiro asynchronous transition state.

Houk *J. Am. Chem. Soc.* **1997**, *119*, 10147

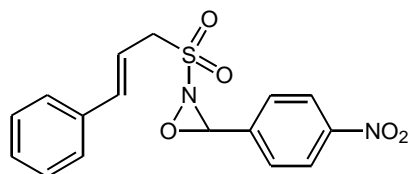
Stepwise Reaction of Neutral π -Nucleophile With Oxaziridine



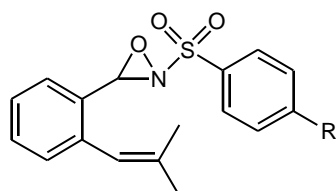
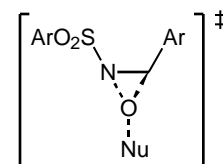
Dmitrienko
J. Am. Chem. Soc. **1997**, *119*, 1159



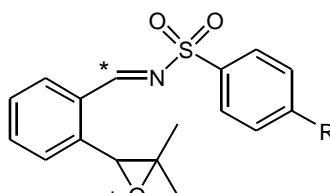
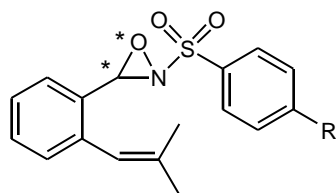
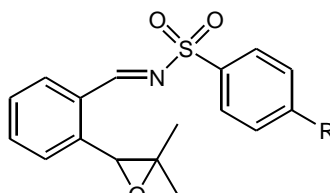
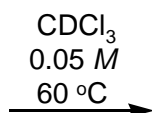
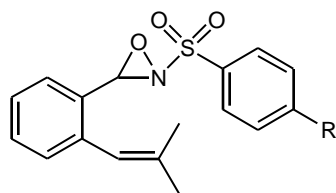
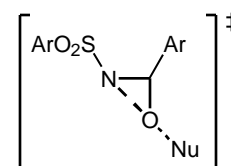
The Endocyclic Restriction Test: Asynchronous Transition State



Is capable of intramolecular epoxidation via synchronous transition state. Does not isomerize in CHCl_3 ($<0.05 \text{ M}$) at 60°C .



Is capable of intramolecular epoxidation via asynchronous transition state but *not* synchronous. Readily isomerizes at 60°C .



^{13}C , ^{18}O - substrate

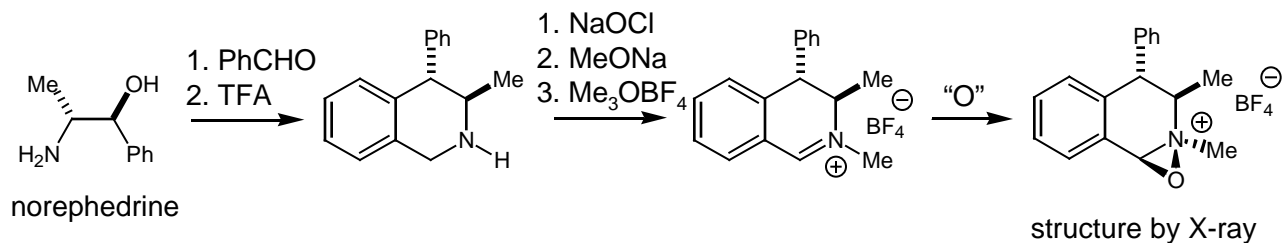
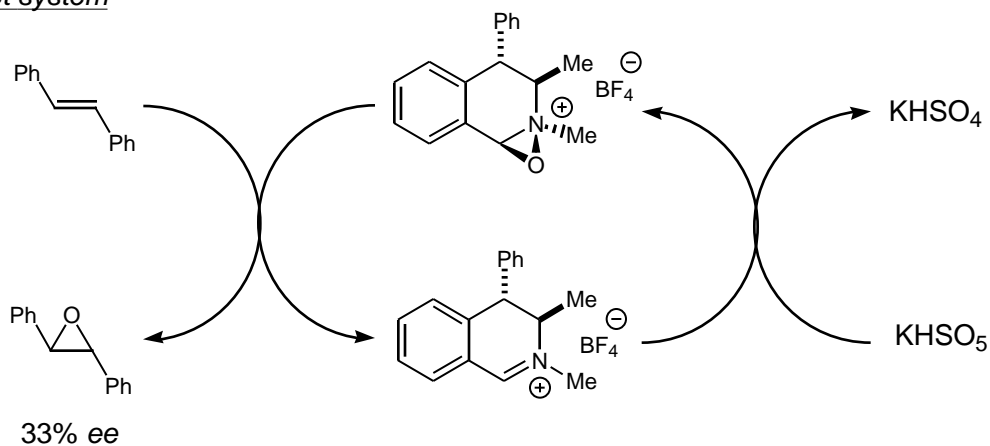
Transition state for this intramolecular reaction is electronically similar to those of intermolecular reactions as $\rho = 0.95 \pm 0.20$ and is close to the value reported by Davis.

Beak
Org. Lett. **1999**, 1, 1415

Catalytic Asymmetric Epoxidations with Oxaziridinium Salts

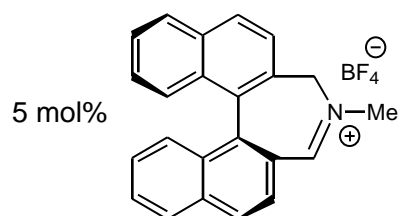
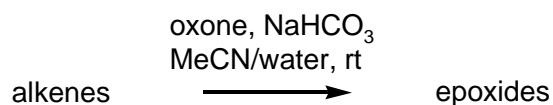
Iminium salts can be converted to oxaziridinium salts by reaction with nucleophilic oxidants which do not oxidize alkenes.

Hanquet system

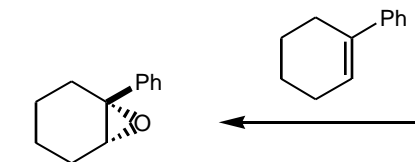
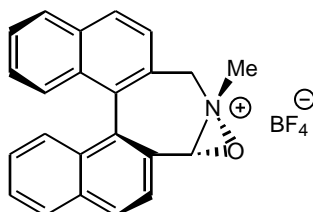
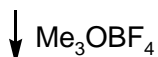
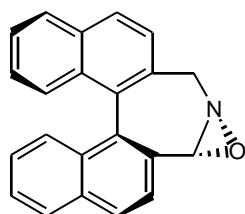
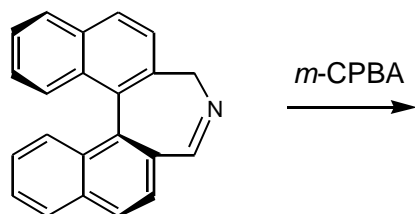


Hanquet *Tetrahedron Lett.* **1993**, *34*, 7271

Catalytic Epoxidation with Binaphthyl-derived Oxaziridinium



alkene	time, h	yield, %	ee, %
<i>trans</i> -stilbene	3	71	31 (<i>R,R</i>)
<i>trans</i> - α -methylstilbene	2	60	45 (<i>R,R</i>)
1-phenylcyclohexane	2	80	71 (<i>R,R</i>)
1-methylcyclohexane	1	80	39 (1 <i>S</i> ,2 <i>R</i>)
styrene	12	66	8 (ND)

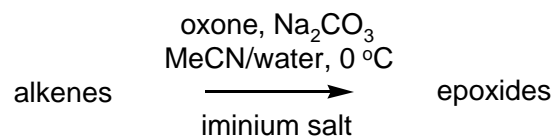
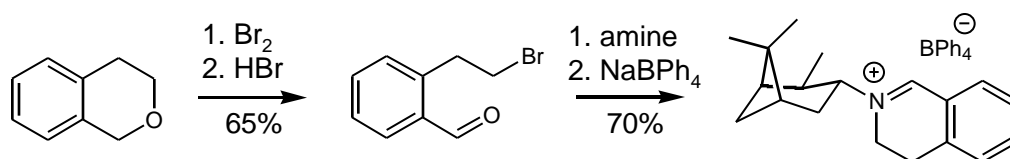


72% ee (*R,R*)

- reaction is stereospecific with respect to alkene geometry.
- more substituted alkenes are more reactive.
- the corresponding oxaziridine did not provide the epoxide under the reaction conditions.

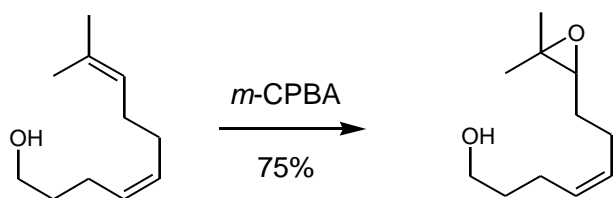
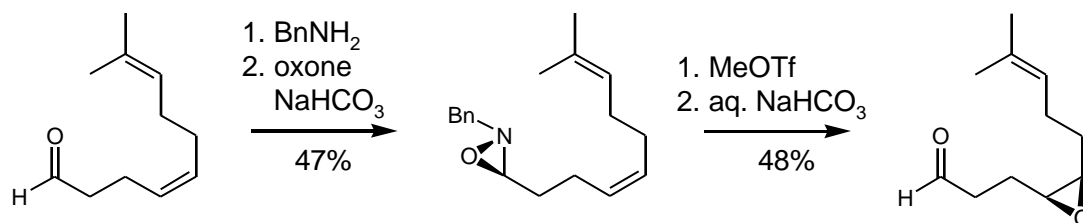
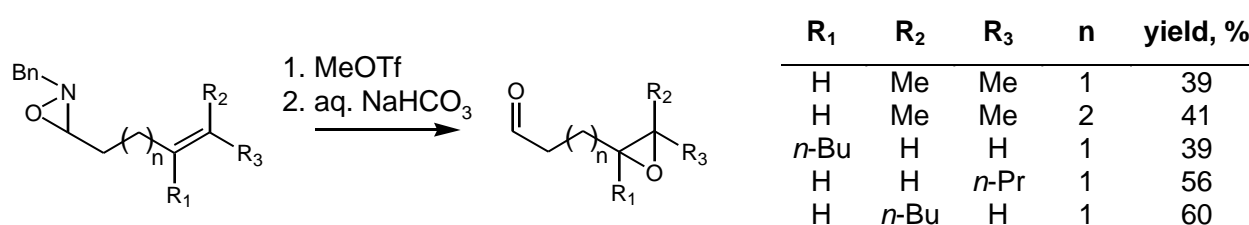
Aggarwal
JCS, Chem. Commun. **1996**, 191

Page's System for Catalytic Asymmetric Epoxidation



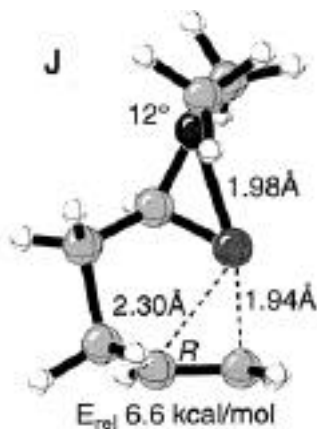
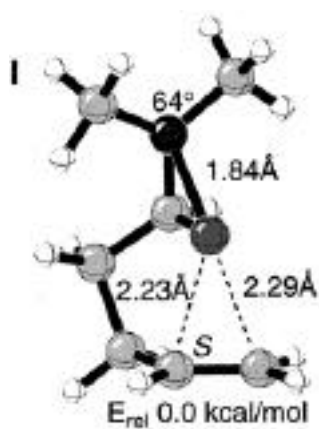
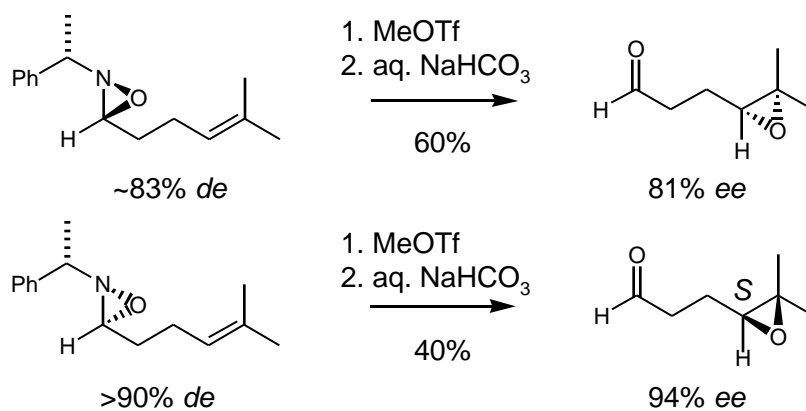
alkene	mol%	yield, %	ee, %	conf.
1-Ph-cyclohexene	0.5	68	27	(<i>R,R</i>)
1-Ph-cyclohexene	5	68	40	(<i>R,R</i>)
<i>trans</i> -stilbene	10	78	73	(<i>R,R</i>)
<i>trans</i> - <i>trans</i> -methylstilbene	5	72	15	(<i>R,R</i>)

Intramolecular Epoxidation of Unsaturated Oxaziridiniums



Armstrong *SynLett* **1998**, 646

Asymmetric Intramolecular Epoxidation: Spiro Transition State

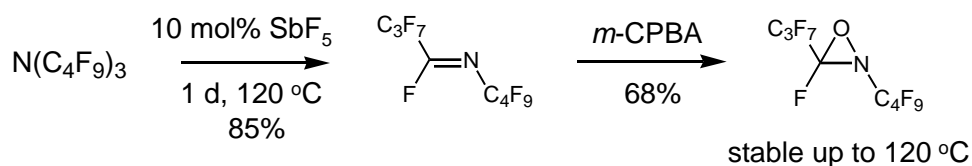


Armstrong
Tetrahedron Lett. **1999**, 40, 4453

Houk
J. Am. Chem. Soc. **2000**, 122, 2948

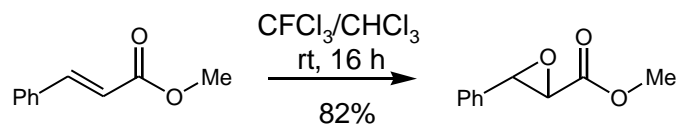
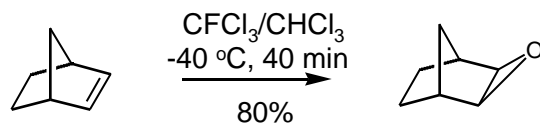
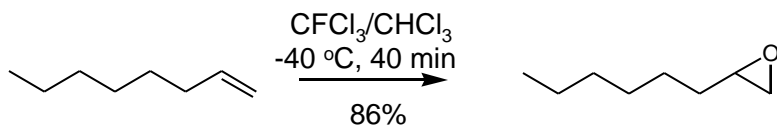
Epoxidations with Perfluorinated Oxaziridines

Preparation



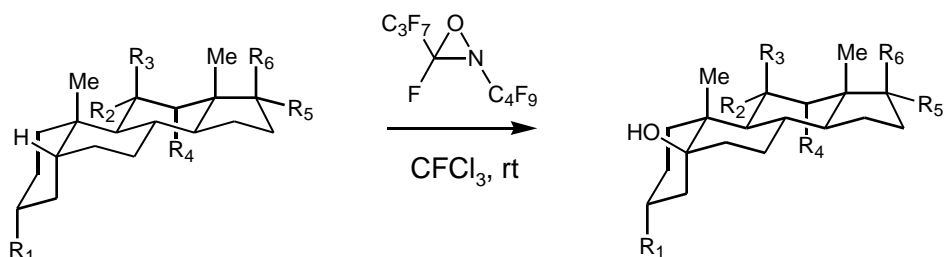
Resnati *Chem. Rev.* **1996**, *96*, 1809

Epoxidation reactions



Resnati *J. Org. Chem.* **1996**, *61*, 8805

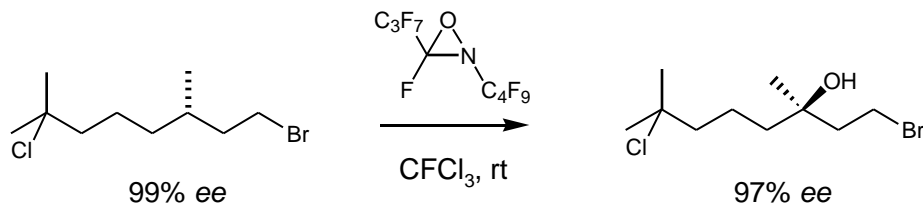
Oxidation of Unactivated C-H Bonds



R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	yield, %
H	H	H	H	H	H	70
OAc	H	H	H	O	O	68
H	H	H	H	H	CH(CH ₃)(CH ₂) ₂ COOMe	79
OAc	H	H	OAc	H	CH(CH ₃)(CH ₂) ₂ COOMe	66
OAc	O	O	Br	H	COCH ₂ OAc	58

- oxidation is enantiospecific.
- 3° C-H > 2° C-H >> 1° C-H
- equatorial C-H > axial C-H
- groups with -I effect increase the reaction time.
- compatible with COOH, ester, Hal, and ketone functionalities.
- oxidizes 2° OH and OMe to ketones.

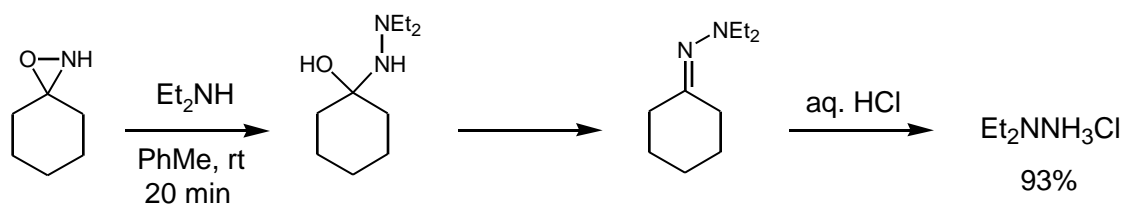
Resnati *J. Org. Chem.* **1994**, *59*, 5511



Resnati *Org. Lett.* **1999**, *1*, 281

N-Amination with N-H Oxaziridines

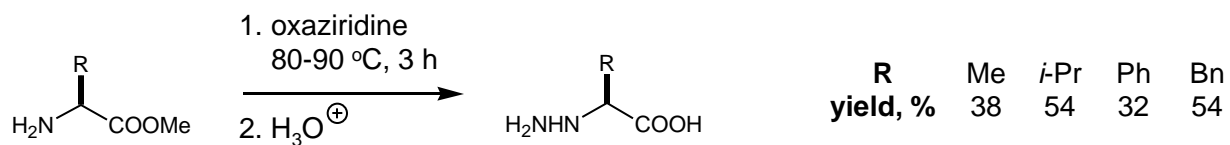
Amination of secondary amines



substrate	product	yield, %
Bu ₂ NH	Bu ₂ NNH ₃ Cl	75
(NCCH ₂ CH ₂) ₂ NH	(NCCH ₂ CH ₂) ₂ N=C-C ₆ H ₁₀	71
		80

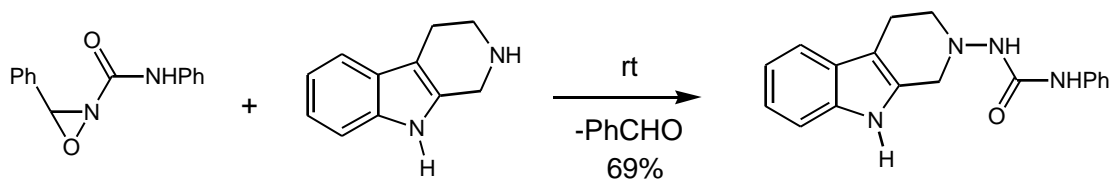
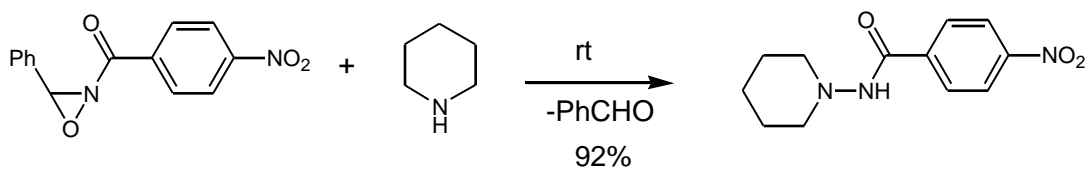
Schmitz
J. Prakt. Chem. **1985**, 327, 445

Amination of primary amines

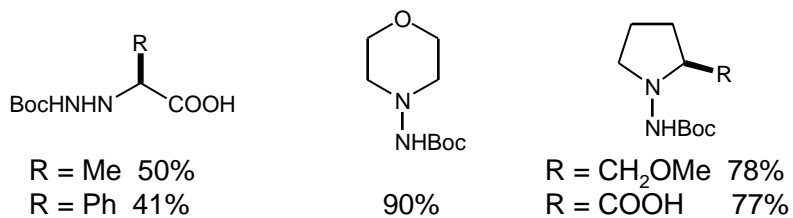
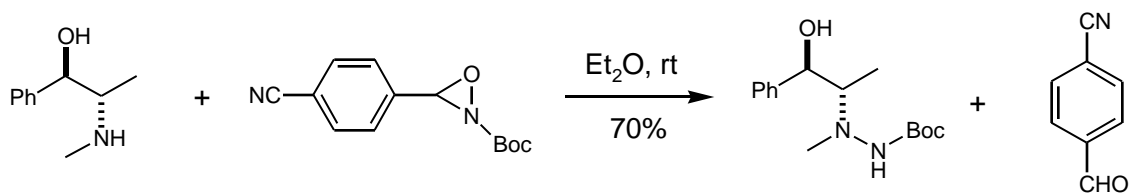


Schmitz *Synthesis*, **1991**, 327

N-Acylation with Oxaziridines

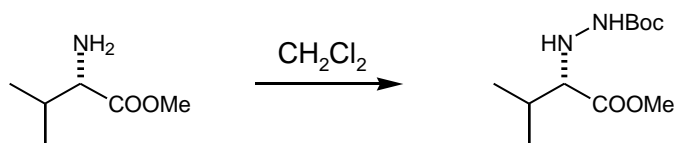
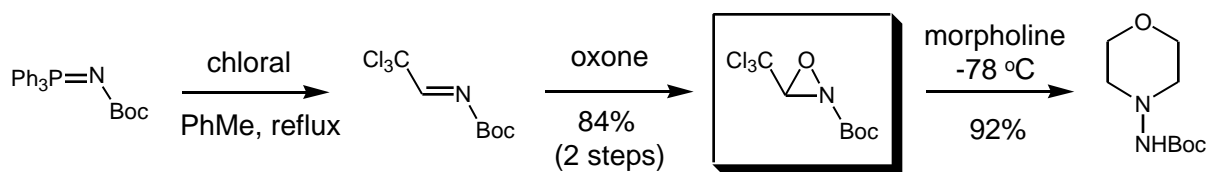


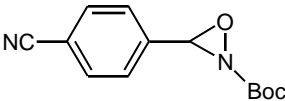
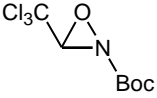
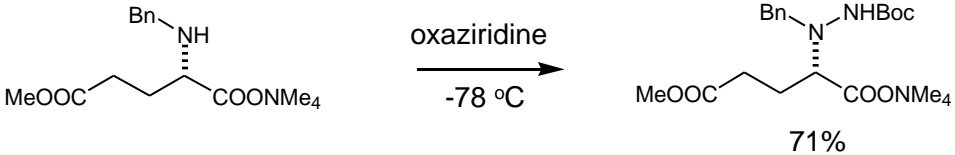
Schmitz *Liebigs Ann. Chem.* **1969**, 725, 1



Collet
J. Org. Chem. **1993**, 58, 4791

More Efficient Reagent for N-Acylation

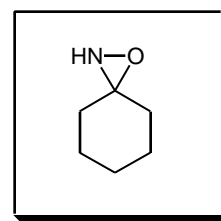
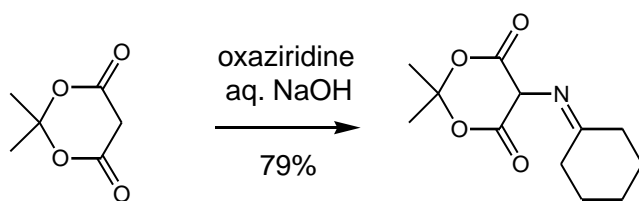
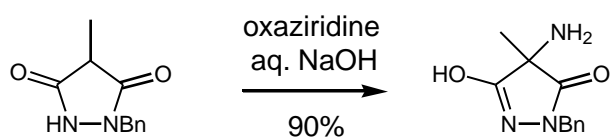


oxaziridine	conditions	yield, %
	24 h, rt	44%
	3 h, 0 °C	56%
	oxaziridine -78 °C	71%

Collet *Tetrahedron Lett.* **1998**, 39, 8845

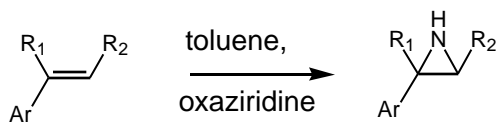
Amination of Carbon Nucleophiles

Amination of C-H acidic compounds



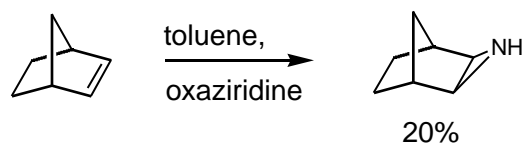
Schmitz *Synthesis* **1991**, 327

Epamination of alkenes



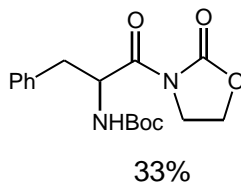
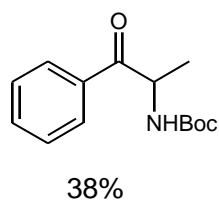
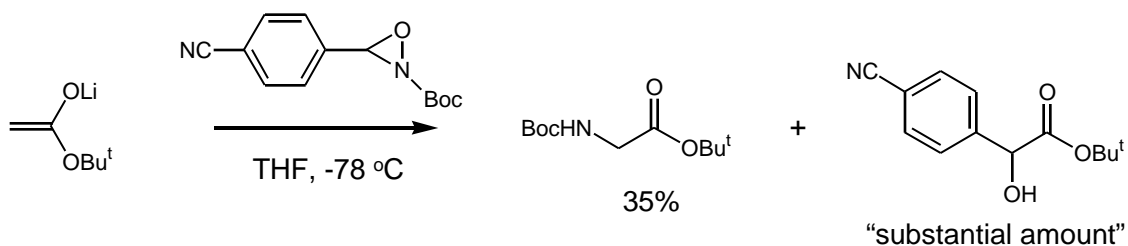
Ar	R ₁	R ₂	yield, %
4-ClC ₆ H ₄	H	H	58
4-NO ₂ C ₆ H ₄	H	H	49
Ph	Me	H	46
4-MeOC ₆ H ₄	H	Me	36

- temperatures above 100 °C are required.
- reaction is stereoselective.
- with a few exceptions, only aromatic alkenes react.



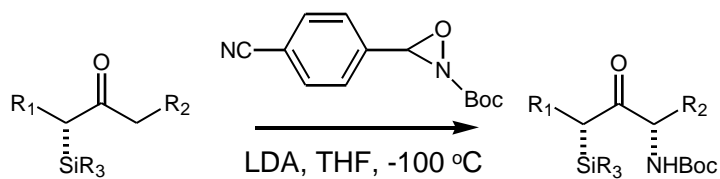
Schmitz *J. Geterozickl. Soedin.* **1974**, 12, 1629

Amination of Enolates



Aldol addition is a problem. Could *ortho*-substituted oxaziridines be used to slower the aldol addition?

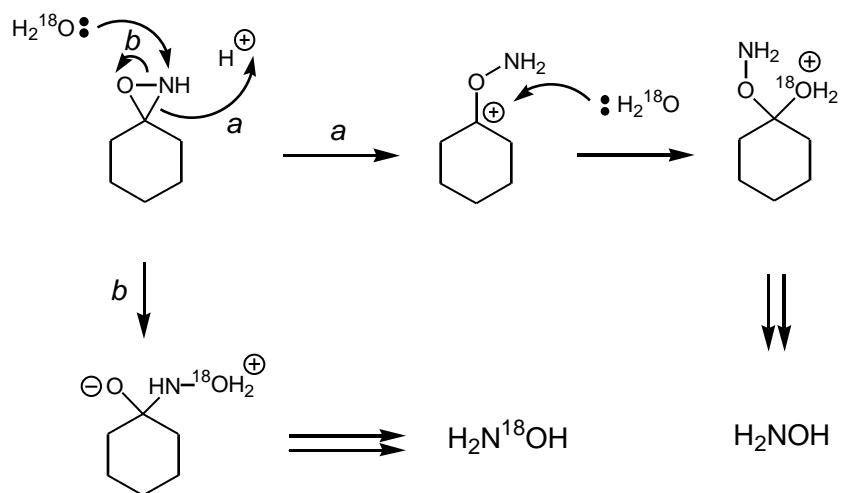
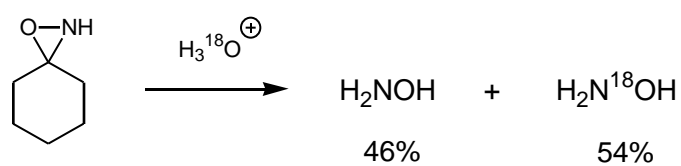
Collet *J. Org. Chem.* **1993**, *58*, 4791



R ₁	R ₂	R ₃	yield, %	<i>dr</i>
Me	Me	Me ₂ Bu ^t	27	90:10
Et	Et	Me ₂ Bu ^t	37	93:7
<i>n</i> -Pr	<i>n</i> -Pr	Me ₂ Bu ^t	29	94:6

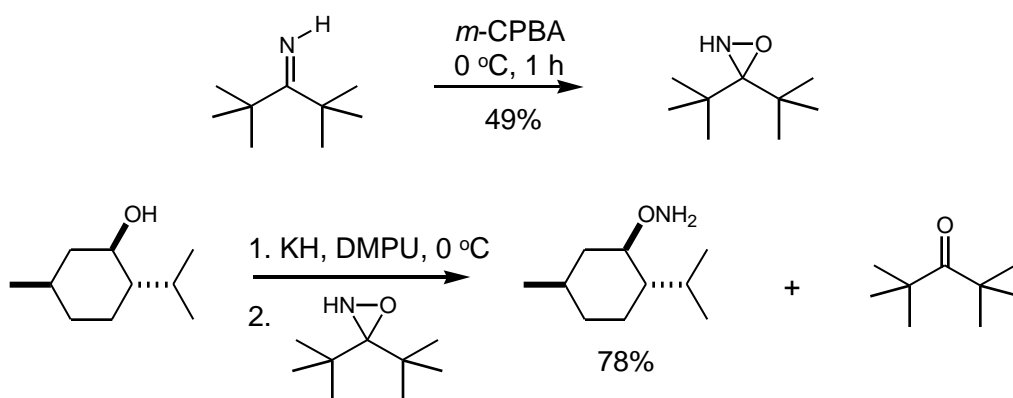
Enders *Tetrahedron: Asymmetry* **1998**, *9*, 3709

O-Amination Reactions



Schmitz *Synthesis* **1991**, 327

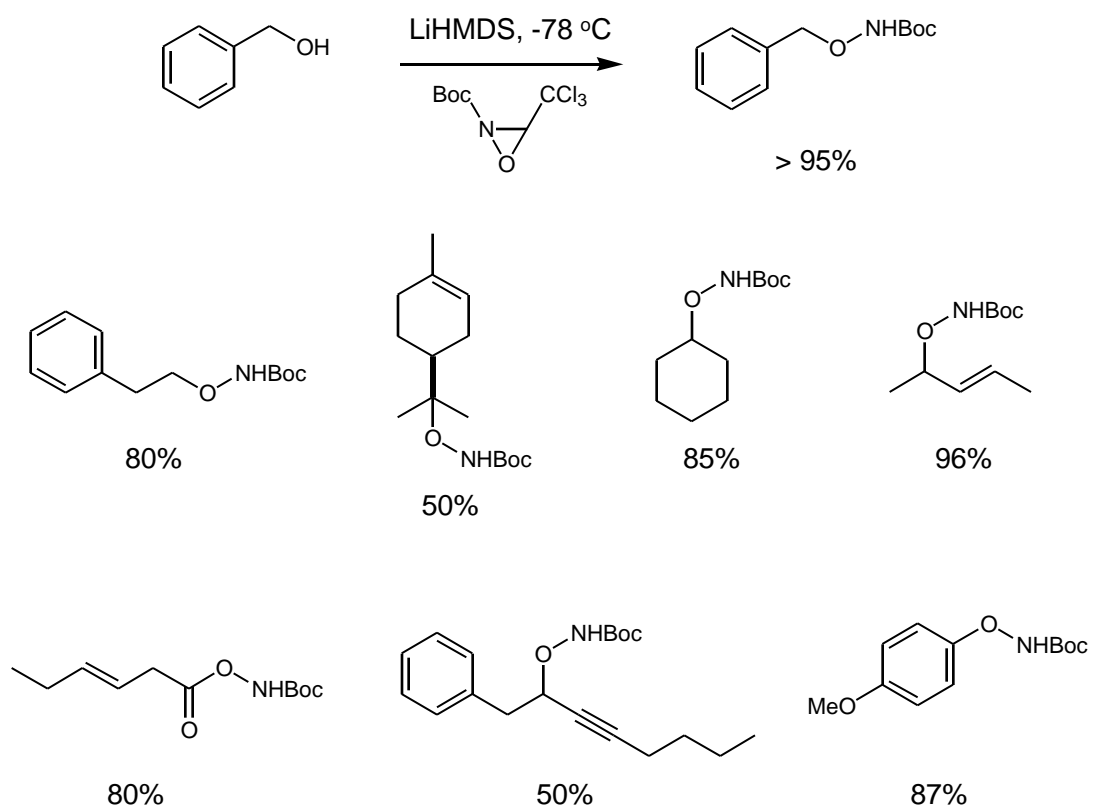
Synthetically Useful O-Amination Procedure



alcohol	product	yield, %
		86
		56
		10

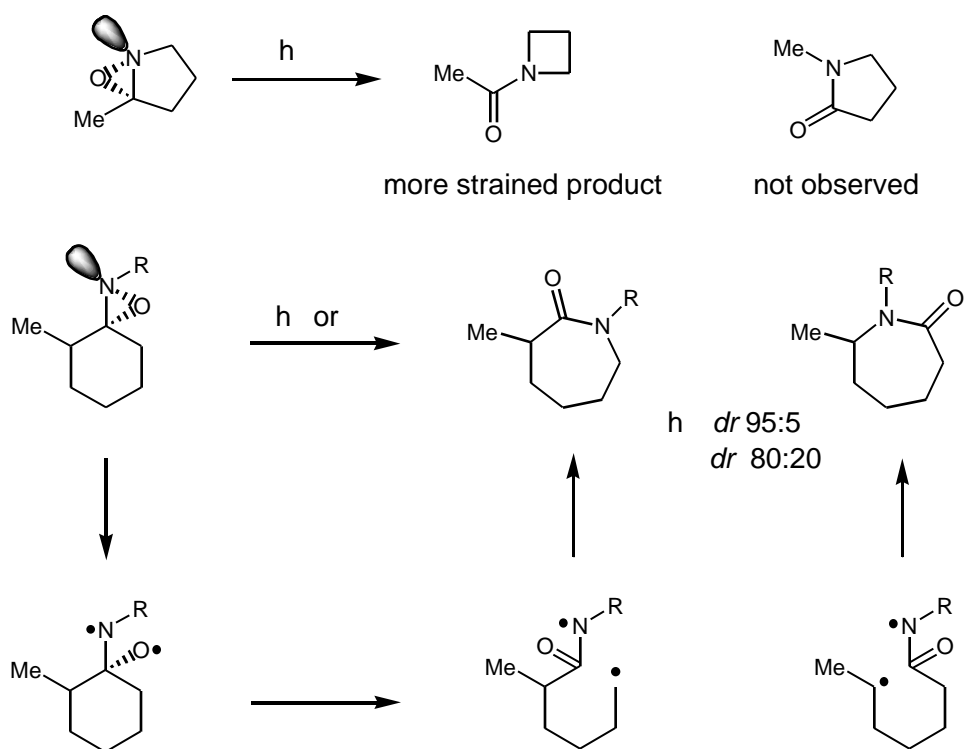
Ellman *J. Org. Chem.* **1999**, *64*, 6528

N-Boc-Hydroxylamines via *O*-Amination of Alcoholates



Knight *JCS, Chem. Commun.* **2000**, 975

Oxaziridine to Amide Rearrangement: Puzzling Selectivity

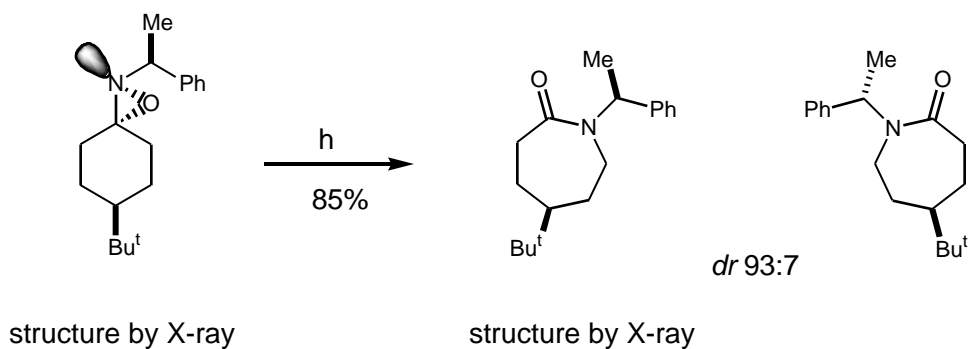


- oxaziridine did not epimerize at *N* during irradiation as evidenced by ^1H NMR.
- less stable radical leads to the product.

Lattes *J. Am. Chem. Soc.* **1982**, *104*, 3929

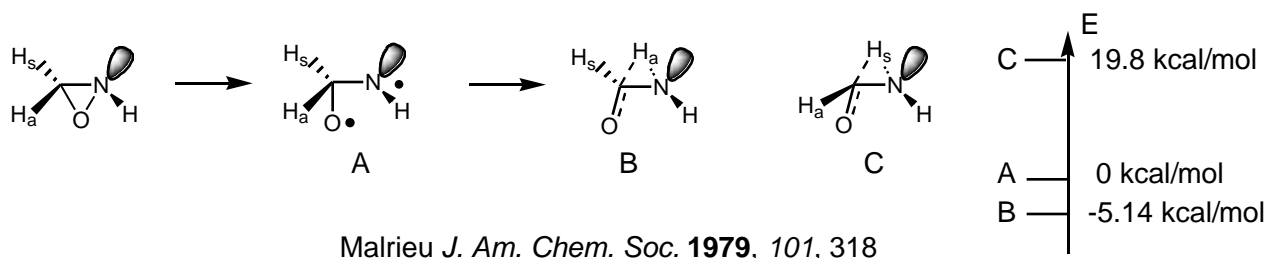
Stereoelectronic Effect

Both experimental and theoretical studies suggest that the C-C bond *anti* to the nitrogen lone pair is cleaved more easily.

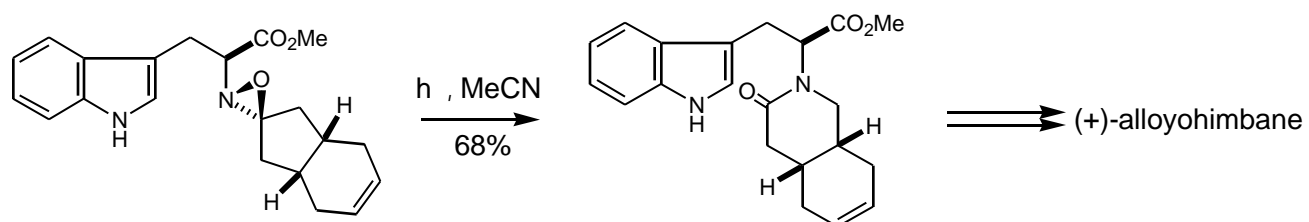


Lattes *J. Am. Chem. Soc.* **1982**, 104, 3929

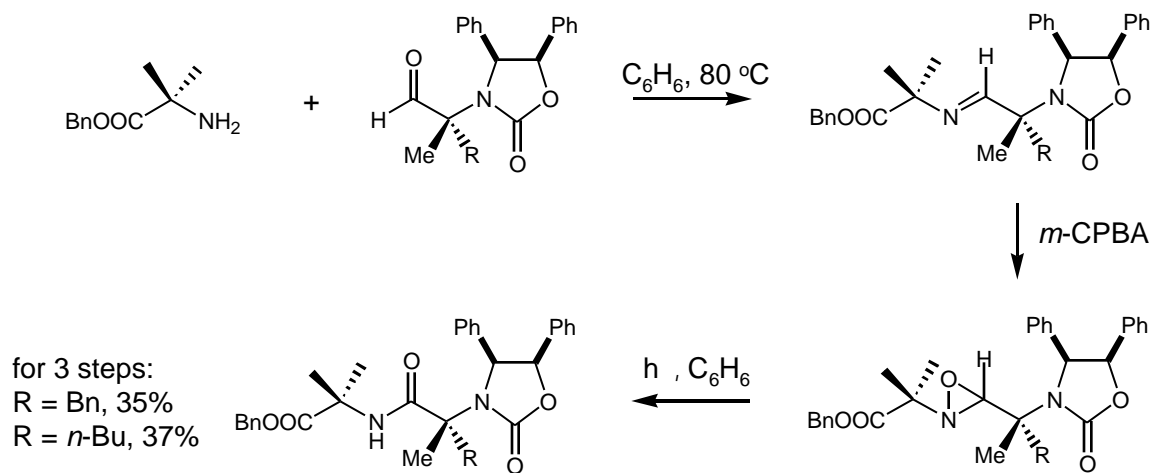
Theoretical study ruled out the concerted mechanism for the rearrangement with very high E_a and strongly supported the mechanism involving N-O bond cleavage to form biradical intermediate.



Recent Applications of Photochemical Rearrangement

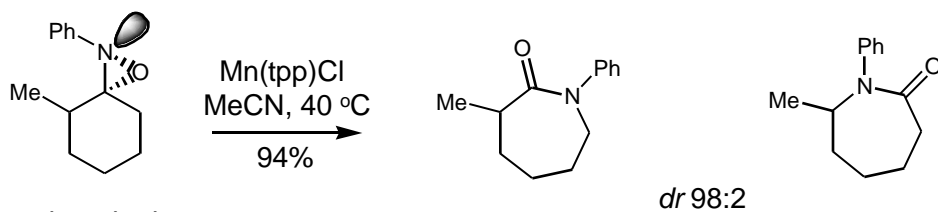
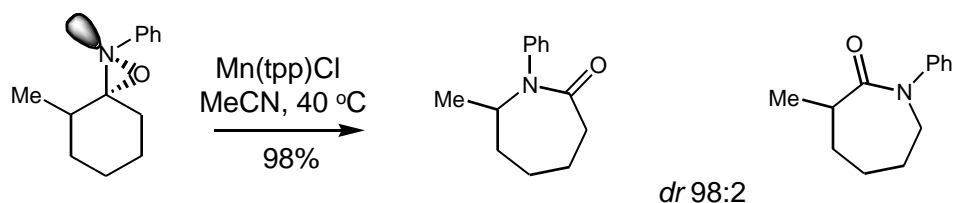


Aube *J. Am. Chem. Soc.* **1994**, *116*, 9009

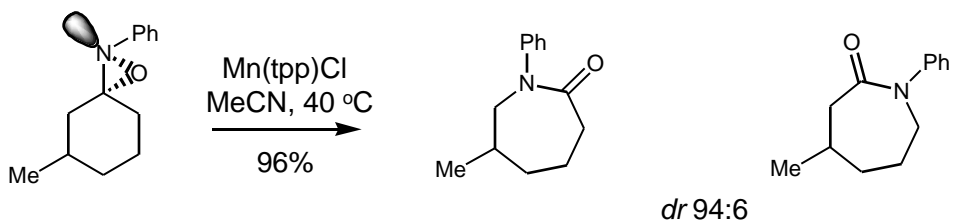


Hegedus *J. Am. Chem. Soc.* **1998**, *120*, 12468

Lewis Acid-Catalyzed Rearrangement: Reversal of Selectivity



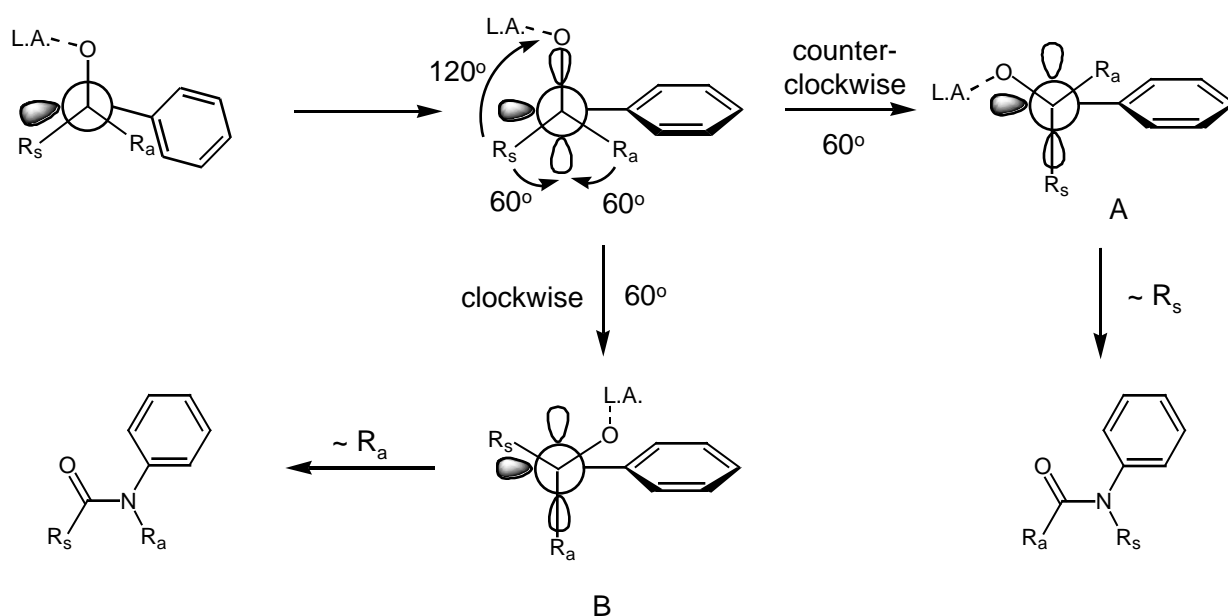
tpp = tetraphenylporphyrin



- reaction is stereospecific: substituent *syn* to the lone pair migrates.
- *e*-transfer reagents, such as Cu(tpp) , Fe(tpp) , and Co(tpp) , showed no catalytic activity.
- reactions are complete in 20-40 min with 2 mol% of the catalyst.

Suda *JCS, Chem. Commun.* **1994**, 949

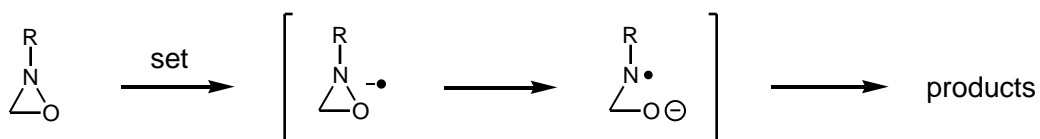
Possible Explanation of the Observed Stereospecificity



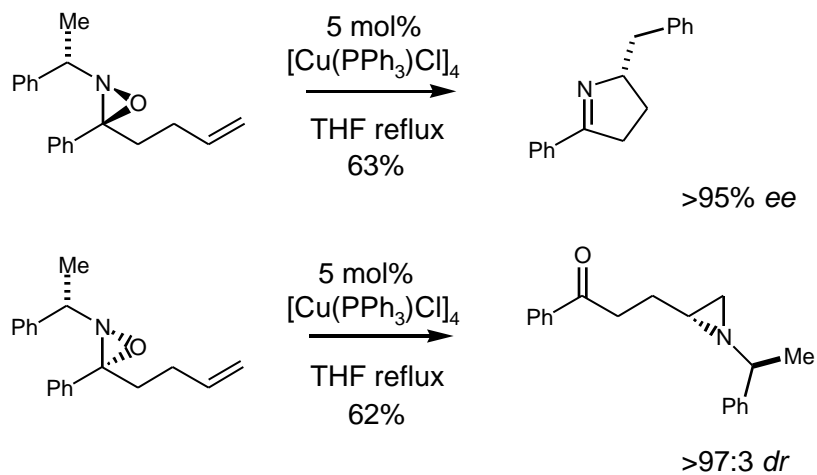
As Lewis acid is very big and anionic oxygen is highly solvated in MeCN, rotamer A looks better than B. One may argue though, that upon counterclockwise rotation to reach A, substituent R_a should pass Ph. No eclipsing of substituents is required to reach structure B upon clockwise rotation.

Single Electron Transfer Reactions of Oxaziridines

Generalized reactivity pattern:

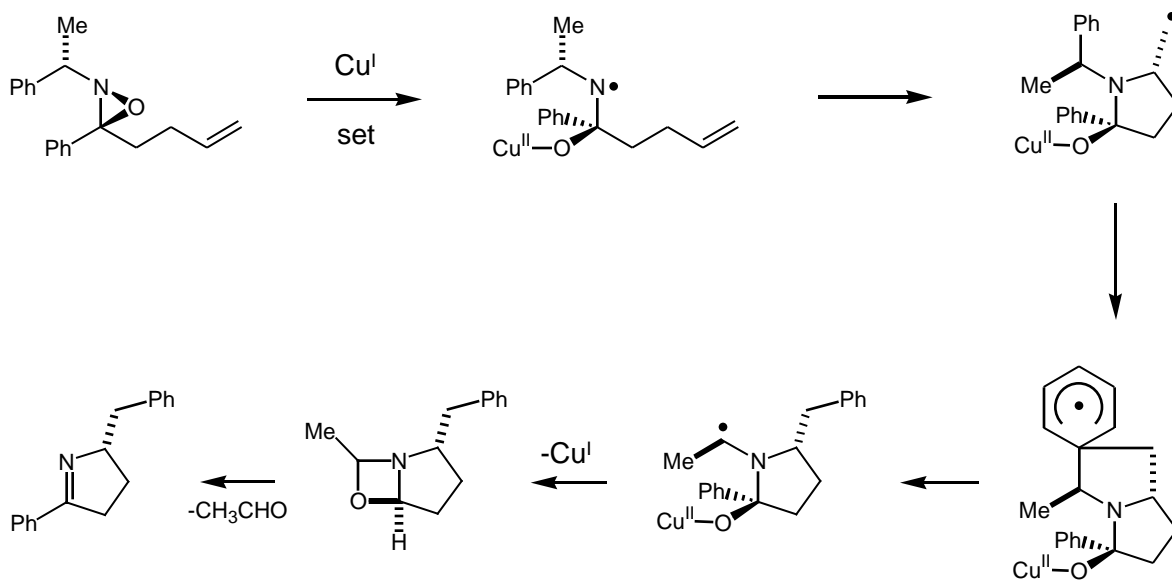


Minisci *Tetrahedron* **1970**, 26, 4083



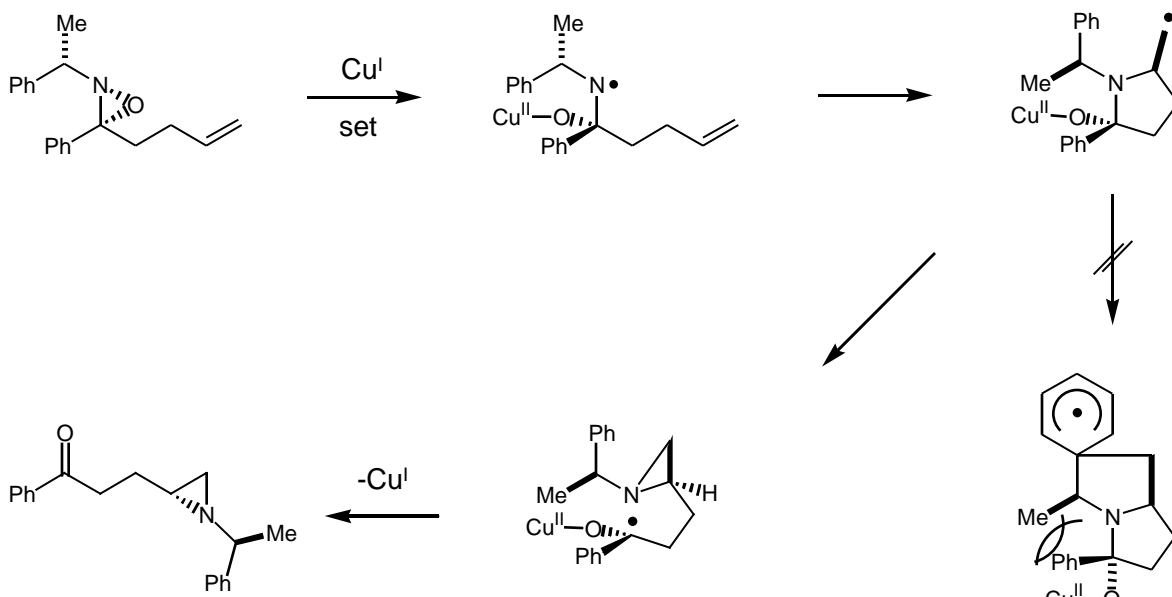
Aube *J. Am. Chem. Soc.* **1992**, 114, 5466

Proposed Mechanism



Aube *J. Am. Chem. Soc.* **1992**, *114*, 5466

Reaction Pathway for Diastereomeric Oxaziridine



Aube *J. Am. Chem. Soc.* **1992**, 114, 5466

Conclusions

- Oxaziridines are readily available by a number of synthetic methods.
- Nitrogen inversion barrier in oxaziridines is high enough to allow preparation of non-racemic compounds.
- *N*-Sulphonyl oxaziridines are widely used as reagents for the oxygenation of enolates.
- Oxaziridinium salts are very promising reagents for the catalytic asymmetric epoxidation of alkenes.
- Perfluorinated oxaziridines are powerful oxidants, and can oxidize electron deficient olefins and unactivated C-H bonds.
- *N*-H and *N*-acyl oxaziridines are useful reagents for the electrophilic amination of amines, *O*- and *C*-nucleophiles. Catalytic variants of this reaction are still to be developed.
- The stereospecific photochemical rearrangement of oxaziridines is a valuable method of lactam synthesis.
- The stereospecific Lewis acid-catalyzed rearrangement of *N*-aryl oxaziridines provides complementary selectivity to that observed in the photochemical reaction.
- Single-electron transfer to oxaziridines proceeds under mild conditions to generate nitrogen-centered radicals. This reaction may find application in a synthesis of complex molecules via cascade bond formation.