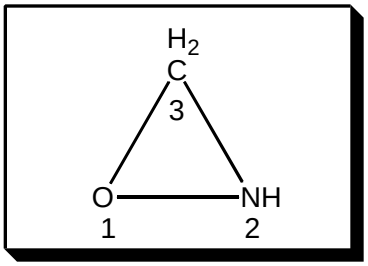
Chemistry of Oxaziridines

An Evans Group Afternoon Seminar

Nabi Magomedov

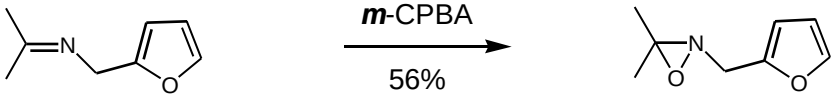
December 1, 2000



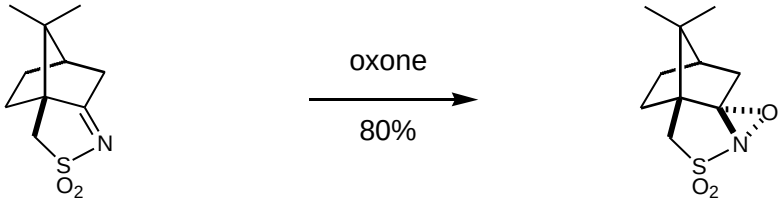
1. Preparation
2. Configurational stability
3. Acid- and base-catalyzed reactions of oxaziridines
4. Heteroatom transfer reactions: 4.1 ***O***-transfer reactions
   4.2 ***N***-transfer reactions
5. Rearrangements
6. Single electron transfer chemistry

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

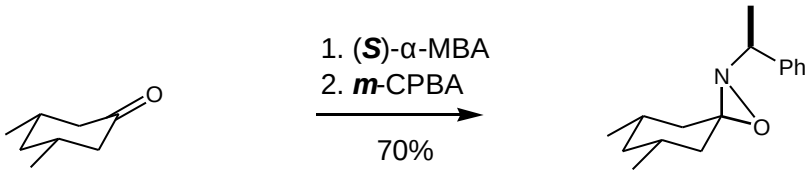
Preparation: Imine Oxidation with Peroxy Compounds



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



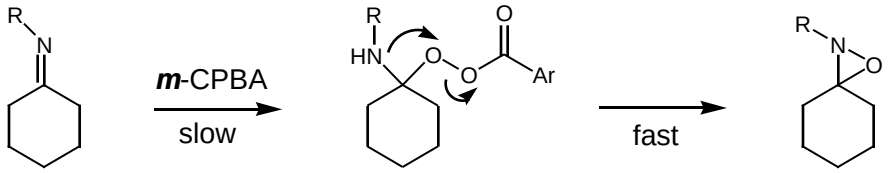
Davis ***J. Am. Chem. Soc***. **1988**, ***110***, 8477



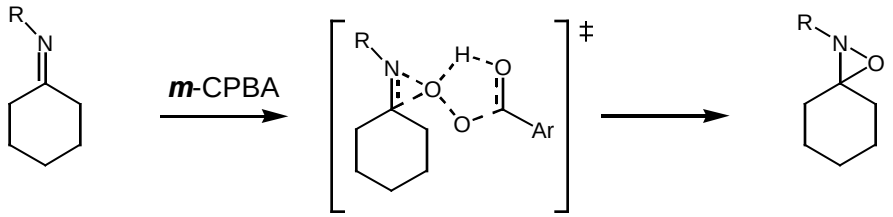
Aube ***J. Am. Chem. Soc***. **1995**, ***117***, 5169

Mechanism of Peroxy Acid Oxidation of Imines

Two-step mechanism



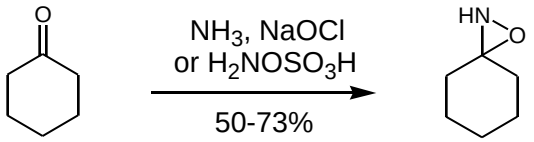
Concerted mechanism



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

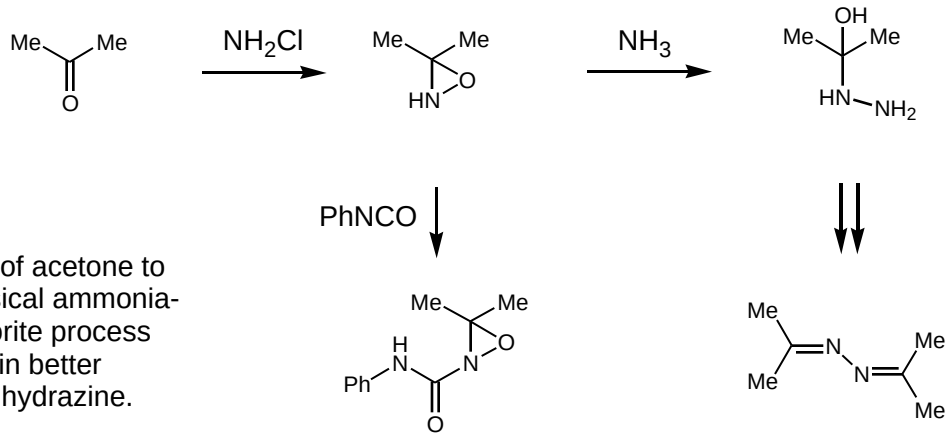
Aube ***J. Org. Chem***. **2000**, ***65***, 5120

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

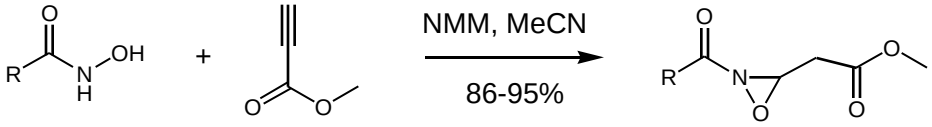


Addition of acetone to the classical ammonia-hypochlorite process resulted in better yields of hydrazine.

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

Other Methods of Preparation

Conjugate addition of hydroxamic acids to propiolates

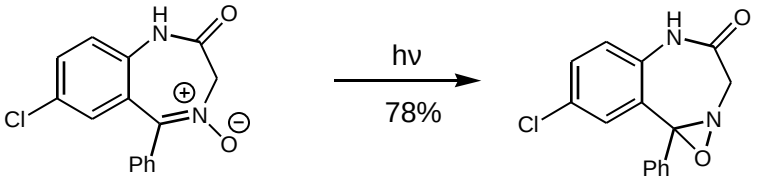


R = aryl, alkyl, alkenyl

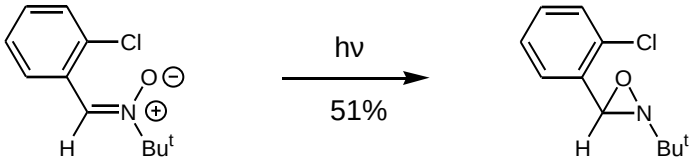
NMM = ***N***-methylmorpholine

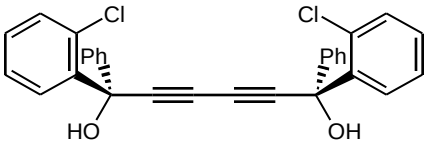
Ryu ***Tetrahedron Lett.*** **1998**, ***39***, 6227

Photolysis of nitrones



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





1:1 inclusion complex with diol

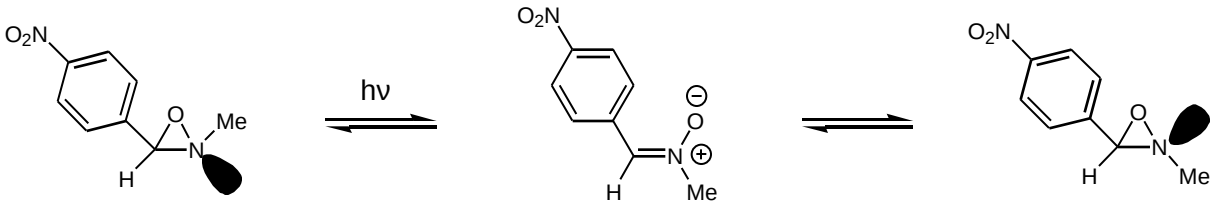
100% ***ee***

(-)-diol

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

Configurational Stability and Mechanisms of Epimerization at Nitrogen

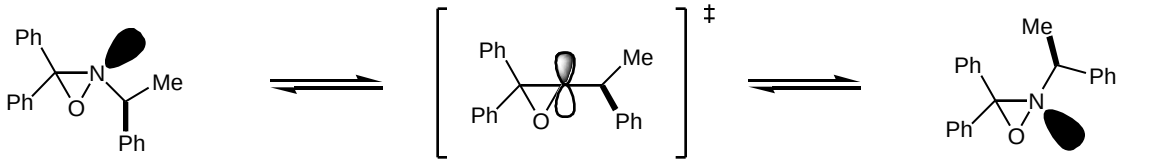
Photochemical epimerization



chiral non-racemic racemic

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

Thermal epimerization

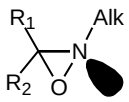


chiral non-racemic ΔG_i 31.9 kcal/mol chiral non-racemic

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

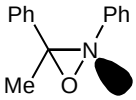
Barriers for Nitrogen Inversion in Oxaziridines

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.

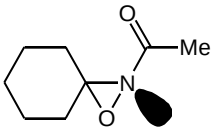


ΔG_i 25-32 kcal/mol
The bigger ***N***-alkyl group the smaller the inversion barrier:
Alk = ***i***-Pr 32 kcal/mol but Alk = ***t***-Bu 26 kcal/mol.
Boyd ***JCS, Perkin II*** **1973**, 1575

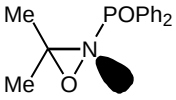
When N atom is connected to substituents capable of π-conjugation or hyperconjugation, the inversion barriers are smaller.



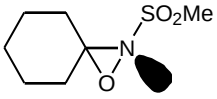
ΔG_i 23.4 kcal/mol
Ono ***Tetrahedron Lett.*** **1973**, 4107



ΔG_i 11.8 kcal/mol; $\Delta G_{r\ (N\text{-}CO)}$ 10.3 kcal/mol
Jennings ***JCS, Chem. Commun***. **1992**, 1078



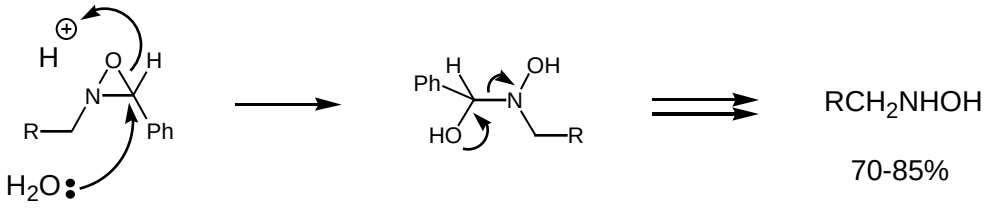
ΔG_i 13.2 kcal/mol
Jennings ***JCS, Perkin II*** **1991**, 1281



ΔG_i 20.6 kcal/mol
Jennings ***J. Am. Chem. Soc.*** **1987**, ***109***, 8099

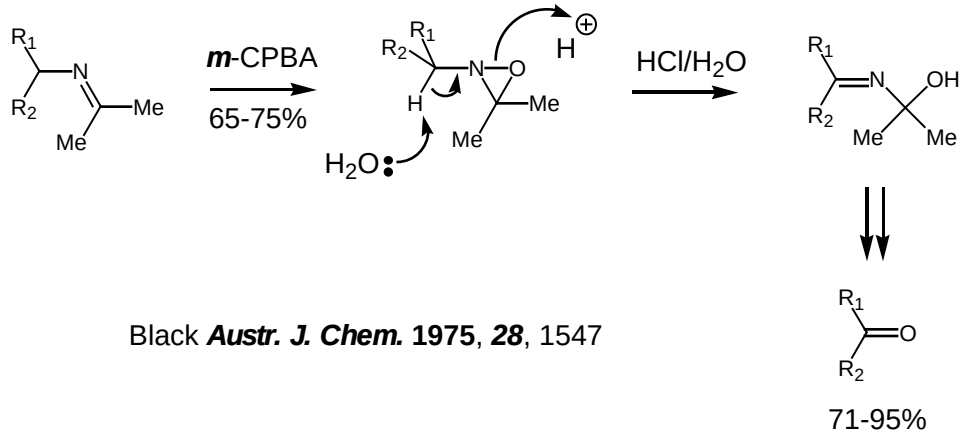
Acid-Catalyzed Ring Opening of Oxaziridines

3-Aryl-substituted oxaziridines



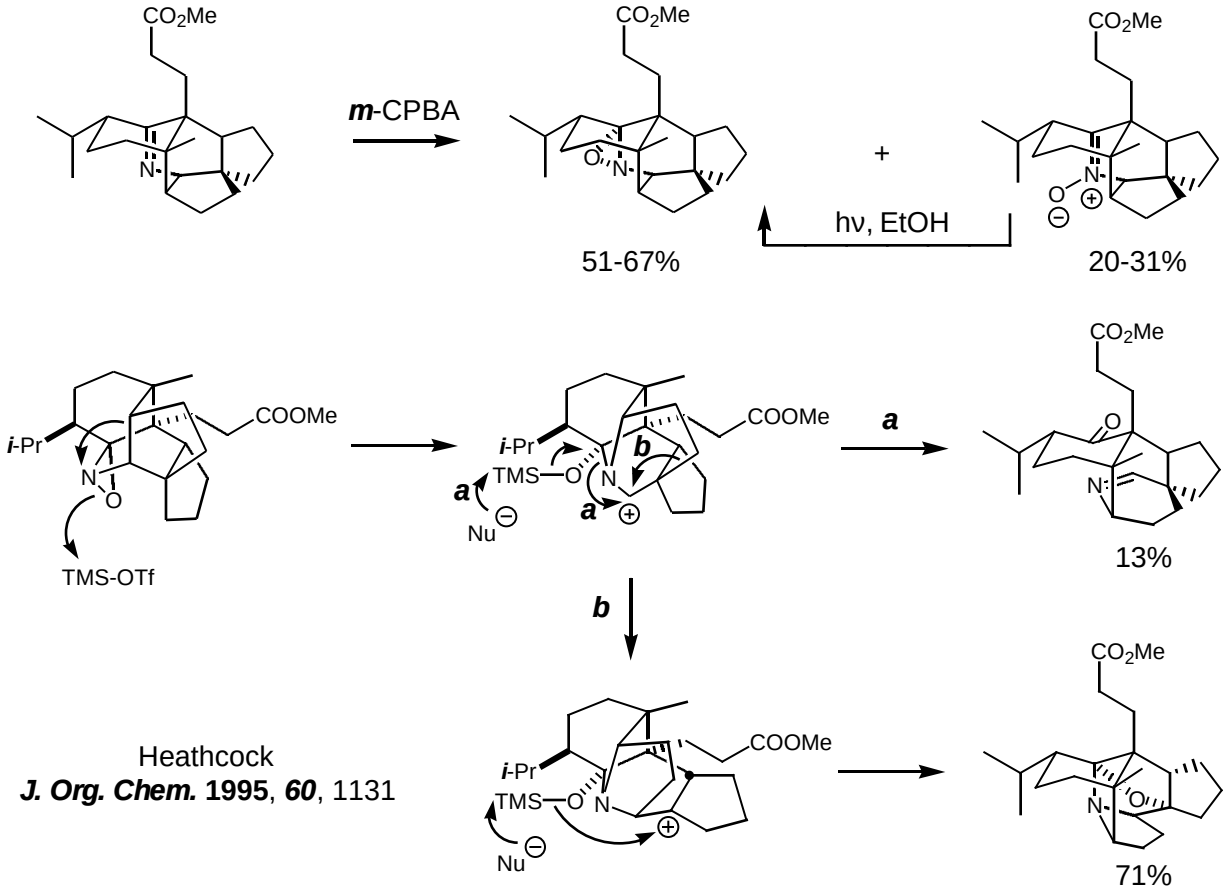
Emmons ***Chem. Heteroc. Comp.*** **1964**, ***19***, 624

3-Alkyl-substituted oxaziridines



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

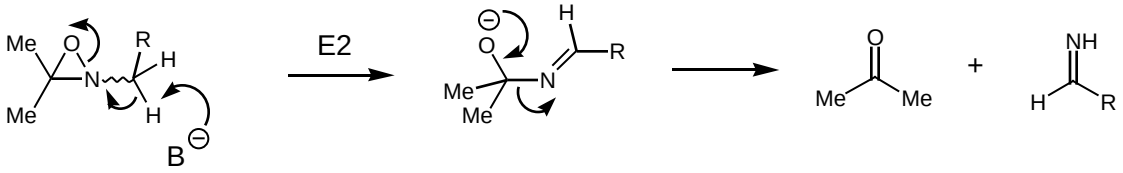
Recent Example of Acid-Catalyzed Ring Opening



Heathcock
J. Org. Chem. **1995**, ***60***, 1131

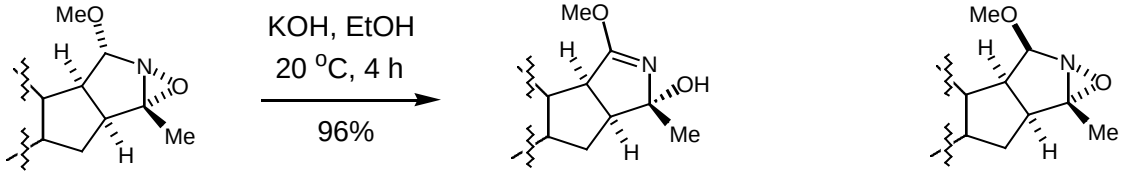
Base-Catalyzed Ring Opening of Oxaziridines

Mechanism



k_H/k_D = 4-6

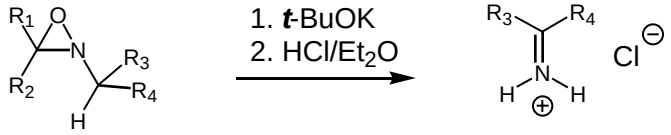
Rastetter ***J. Org. Chem.*** **1982**, ***47***, 419



unreactive

Lusinchi ***Tetrahedron*** **1974**, ***30***, 2825

Synthesis of N-H ketimines



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

R_1 = Ph; R_2 = H or Ph

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

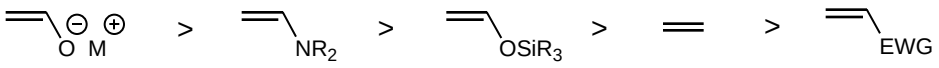
Heteroatom Transfer Reactions

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:

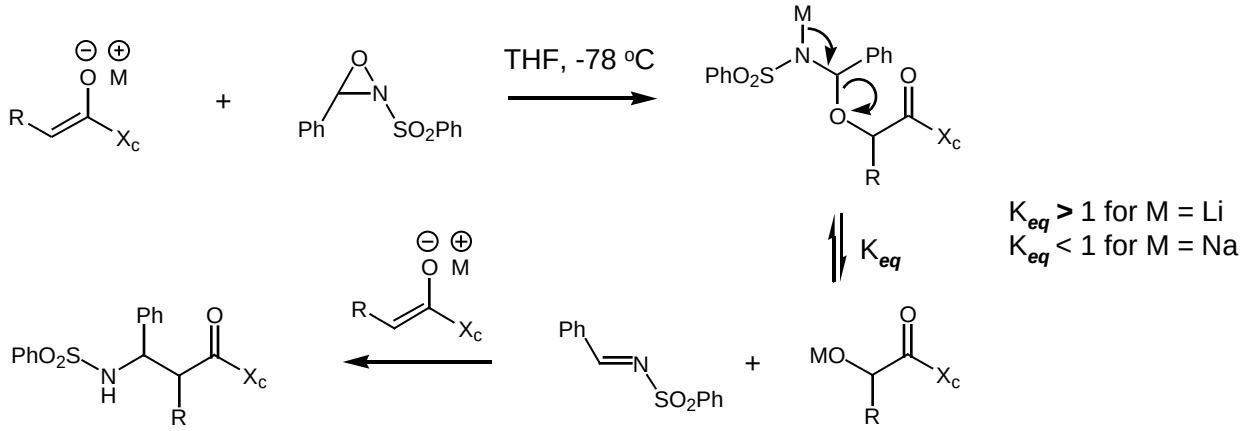


typical conditions	-78 ^{o}C, <15 min	rt, <30 min	25-60 ^{o}C	60 ^{o}C, 3-12 h	unreactive

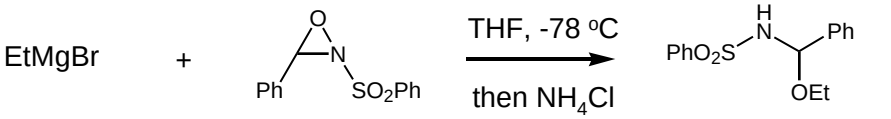
Nitrogen transfer reagents: 1. ***N***-unsubstituted oxaziridines
2. ***N***-alkyl oxaziridines
3. ***N***-acyl oxaziridines

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



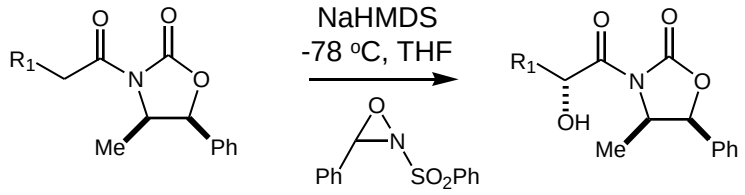
detected by NMR

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

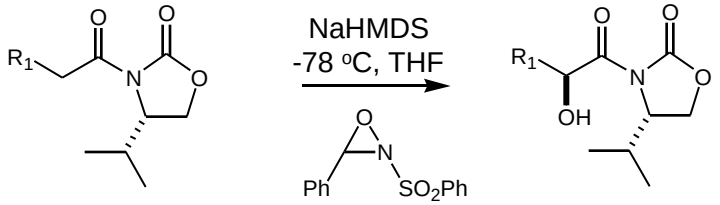
Asymmetric Enolate Oxidation with N-Sulfonyl Oxaziridines

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

Evans' auxiliary method



R_1	*dr*	yield, %
CH_2Ph	94:6	86
Ph	90:10	77
$CH_2CH{=}CH_2$	95:5	91

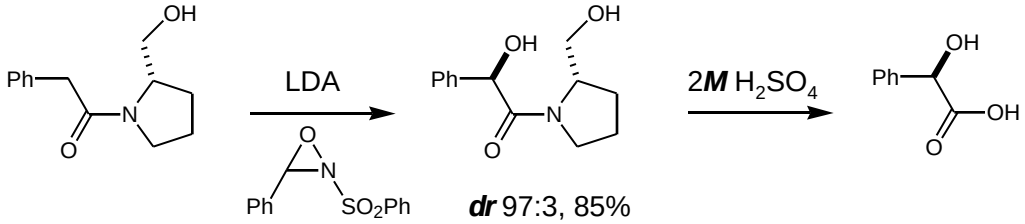


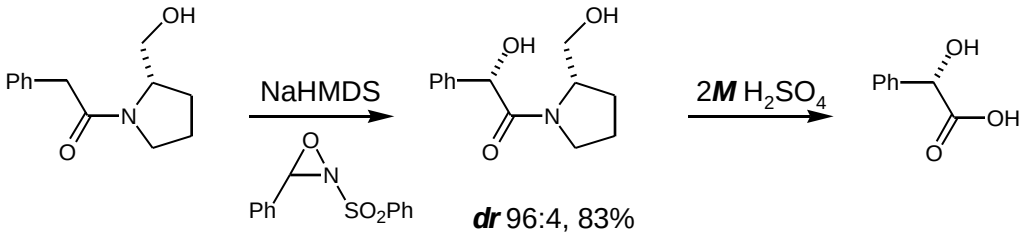
R_1	*dr*	yield, %
CH_2Ph	95:5	85
i-Pr	99:1	86

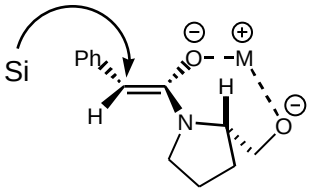
Evans ***J. Am. Chem. Soc.*** **1985**, ***107***, 4346

Oxidation of Chiral Amide Enolates with N-Sulfonyl Oxaziridines

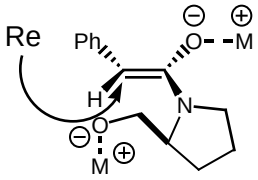
2-Pyrrolidinemethanol auxiliary







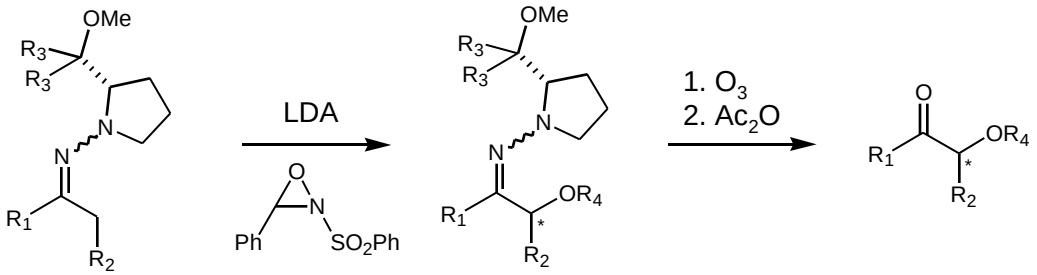
Li as a counterion



Na as a counterion

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

Oxidation of Enders' Hydrazones with N-Sulfonyl Oxaziridines

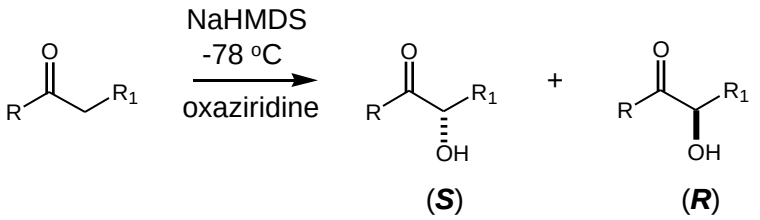


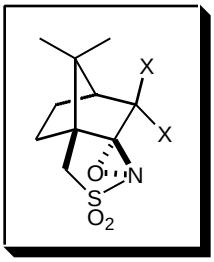
For R_1=H ***O***-benzylation (NaH/DMF then BnCl) was required before the oxidative cleavage of the auxiliary.

R_1	R_2	R_3	R_4	overall yield, %	*ee*, %	conf.
Ph	Me	H	COMe	51	93	***R***
Ph	Me	Me	COMe	73	88	***R***
Ph	Ph	H	COMe	74	>96	***S***
H	***n***-Hex	H	Bn	63	56	***R***
H	***n***-Hex	Et	Bn	55	>96	***S***

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

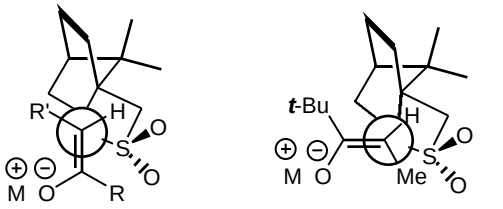
Oxidation of Prochiral Enolates with Non-racemic Oxaziridines





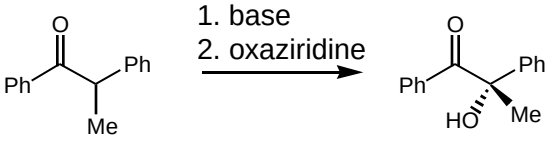
R	R'	X	yield, %	*ee*, %	conf.
Ph	Ph	H	84	95	***S***
Ph	Me	H	73	62	***S***
Ph	Me	Cl	61	95	***S***
Me	Ph	H	70	40	***S***
***t*-Bu**	Me	H	71	89	***R***

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



Proposed model for asymmetric induction

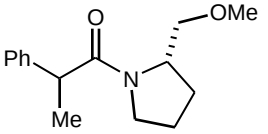
Oxidation of tertiary acyclic ketones gave poor enantioselectivity under a number of conditions.



-20 to 21% ***ee***

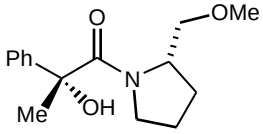
Davis ***J. Org. Chem.*** **1987**, ***52***, 5288

Double Asymmetric Induction Experiments

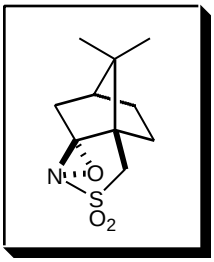


1. LDA
   THF/HMPA
2. oxaziridine

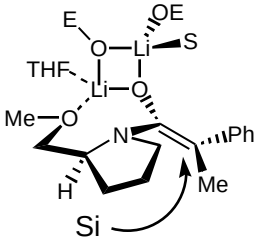
dr 96:4



(***S***)



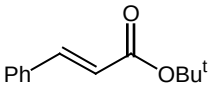
(-)-CSO

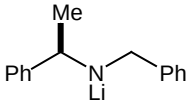


The proposed model does not, however, explain why ***N***-phenylsulfonyl 3-phenyloxaziridine gave new stereocenter with (***R***) configuration.

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

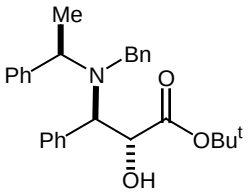
Asymmetric conjugate addition-oxidation cascade





then (+)-CSO

dr 96:4, 86%



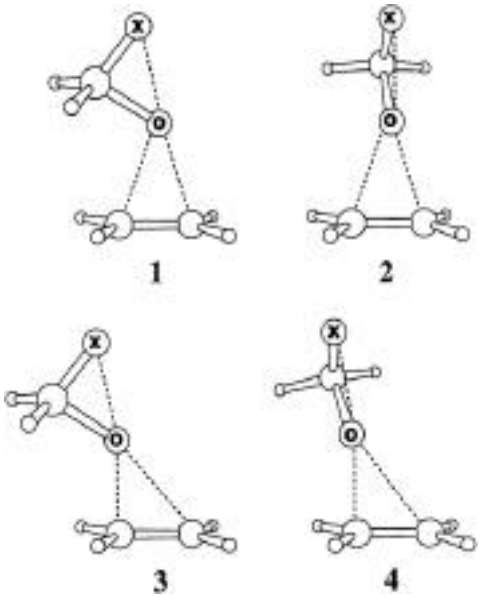
(2***R***,3***R***)

However, if substrate contains benzyl group instead of phenyl, ***dr*** 40:60 is observed in favor of (2***S***,3***R***) diastereomer.

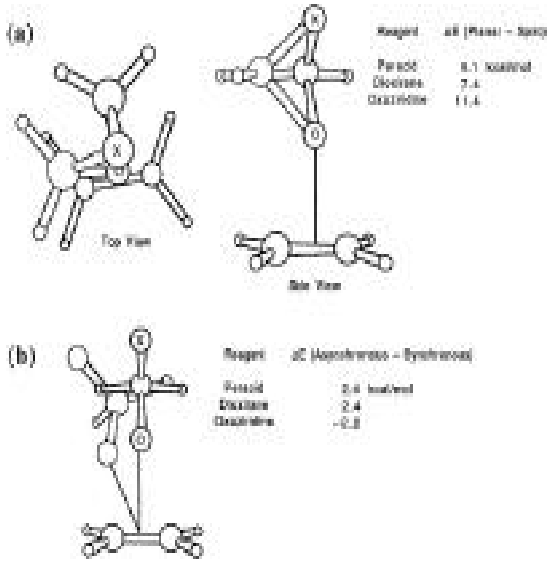
Davis
Tetrahedron **1994**, ***50***, 3975

Mechanism of Oxygen Transfer to Olefinic Double Bond

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



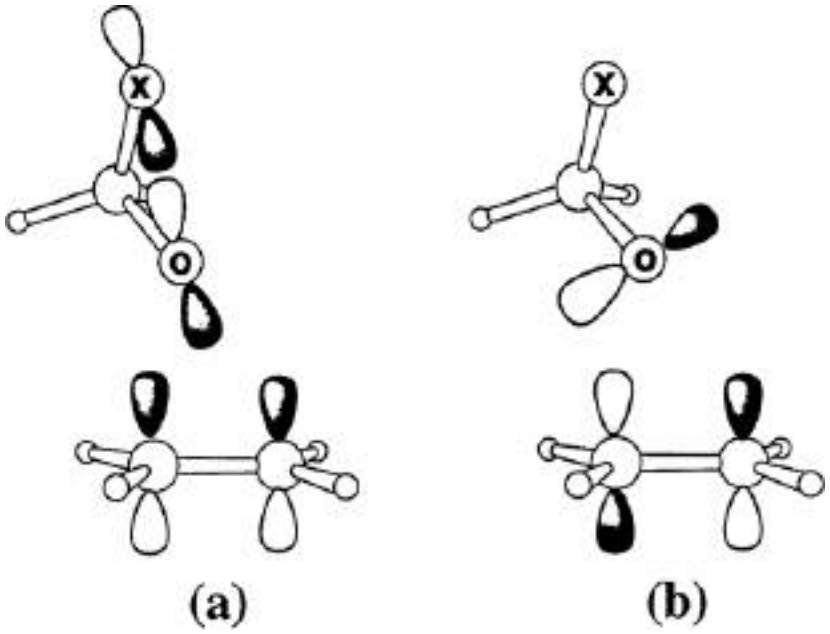
Preliminary experimental (Davis) and theoretical (Bach) studies favored structure **1**. Calculations done at more advanced level (Houk; Bach) favored spiro transition states **2** and **4**.



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

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

FMO Rational for Spiro Transition State

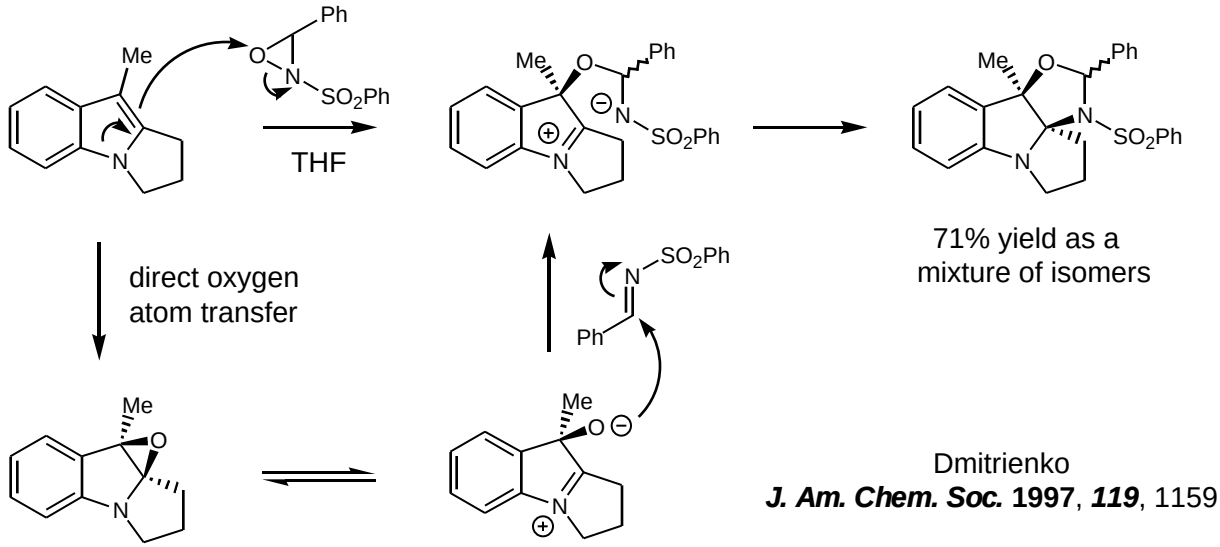


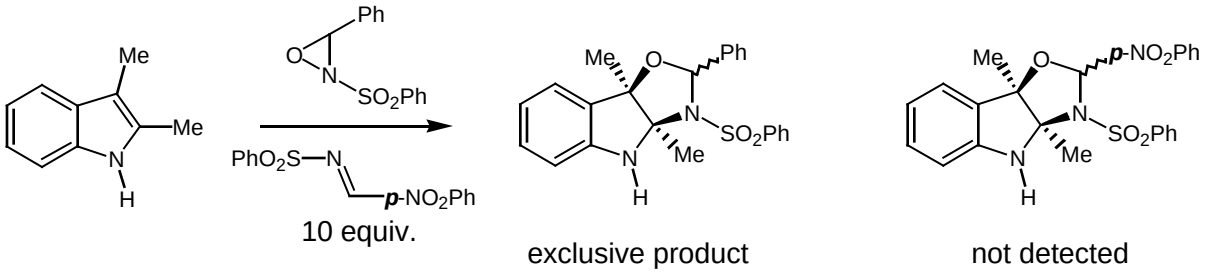
FMO interactions in the transition states of epoxidations:
(a) alkene HOMO-oxidant LUMO and (b) oxidant HOMO-alkene LUMO.

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

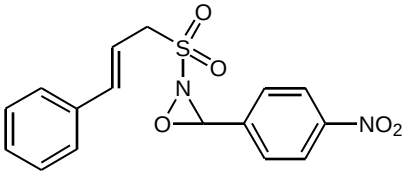
Houk ***J. Am. Chem. Soc.*** **1997**, ***119***, 10147

Stepwise Reaction of Neutral π-Nucleophile With Oxaziridine

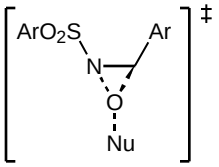


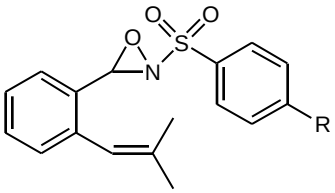


The Endocyclic Restriction Test: Asynchronous Transition State

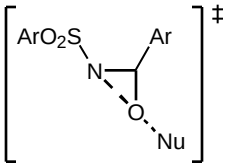


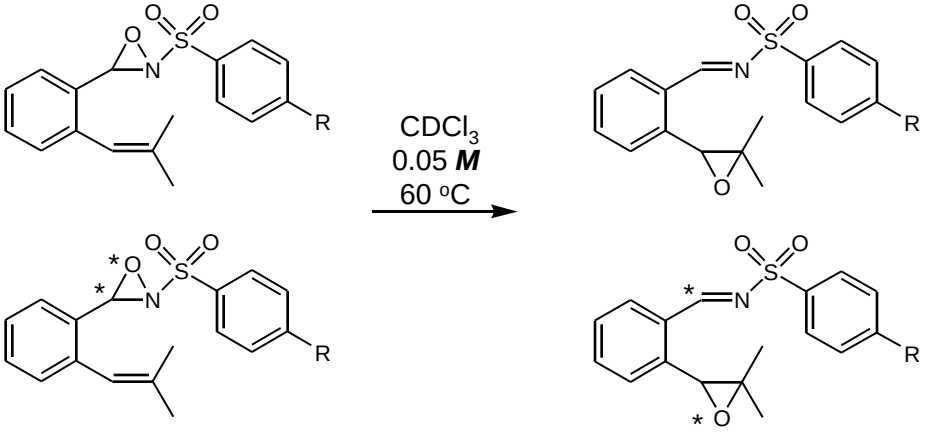
Is capable of intramolecular epoxidation via synchronous transition state. Does not isomerize in $CHCl_3$ (<0.05 ***M***) at 60 °C.





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





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

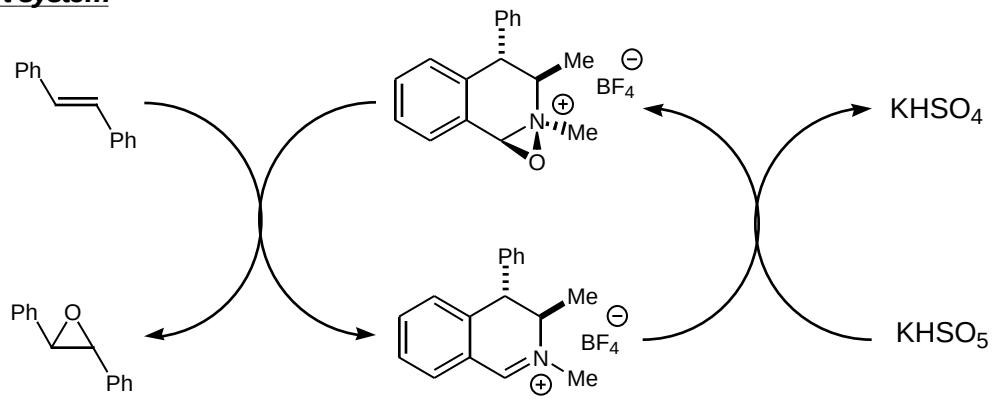
Transition state for this intramolecular reaction is electronically similar to those of intermolecular reactions as ρ = 0.95±0.20 and is close to the value reported by Davis.

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

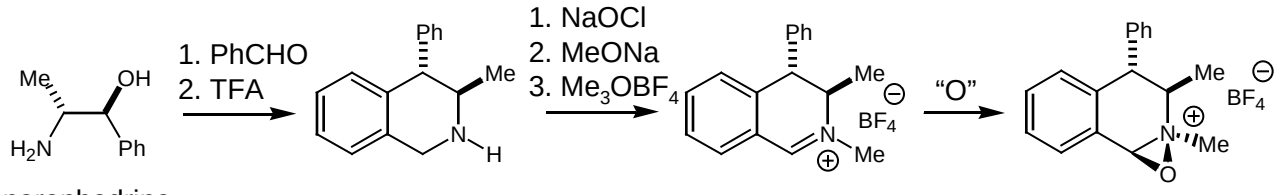
Catalytic Asymmetric Epoxidations with Oxaziridinium Salts

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

Hanquet system



33% ***ee***

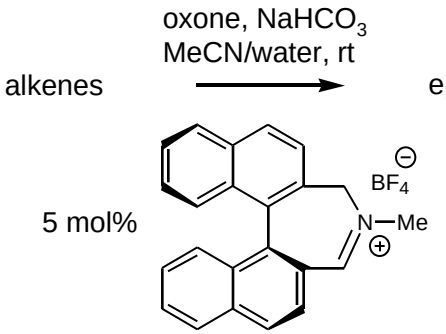


norephedrine

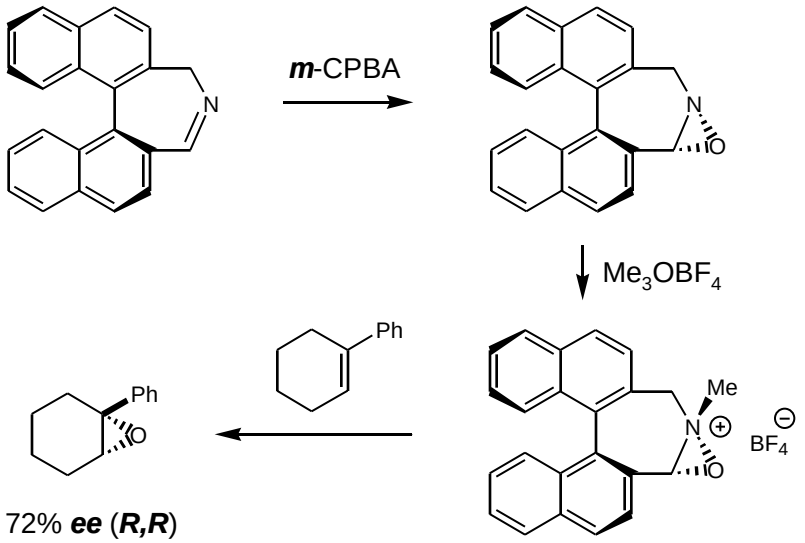
structure by X-ray

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

Catalytic Epoxidation with Binaphtyl-derived Oxaziridinium



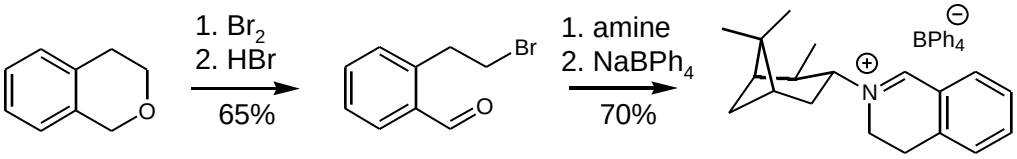
alkene	**time, h**	**yield, %**	***ee*, %**
***trans*-stilbene**	3	71	31 (***R,R***)
***trans*-α-methylstilbene**	2	60	45 (***R,R***)
1-phenylcyclohexane	2	80	71 (***R,R***)
1-methylcyclohexane	1	80	39 (1***S,2R***)
styrene	12	66	8 (ND)

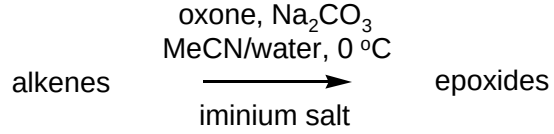


- reaction is stereospecific with respect to alkene geometry.
- more substituted alkenes are more reactive.
- the corresponding oxaziridine did not provide the epoxide under the reaction conditions.

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

Page's System for Catalytic Asymmetric Epoxidation

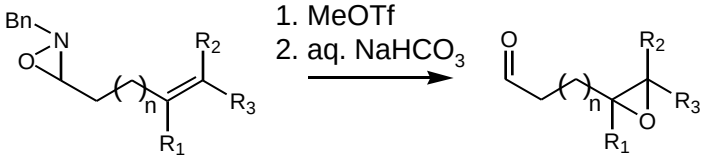




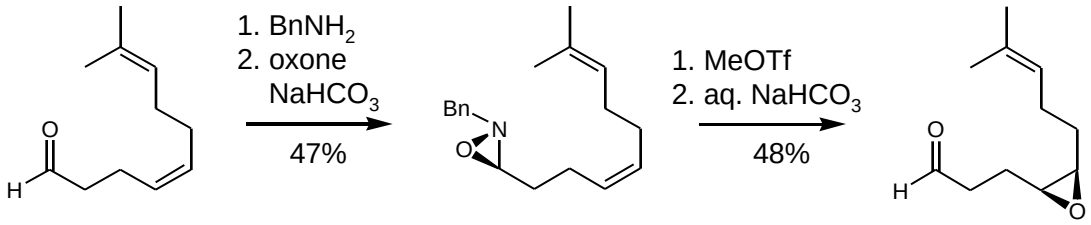
alkene	mol%	yield, %	*ee*, %	conf.
1-Ph-cyclohexene	0.5	68	27	***(R,R)***
1-Ph-cyclohexene	5	68	40	***(R,R)***
***trans*-stilbene**	10	78	73	***(R,R)***
trans-α-methylstilbene	5	72	15	***(R,R)***

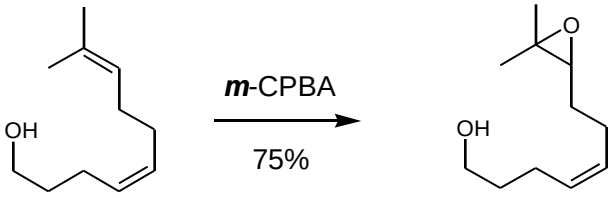
Page ***J. Org. Chem.*** **1998**, ***63***, 2774

Intramolecular Epoxidation of Unsaturated Oxaziridiniums



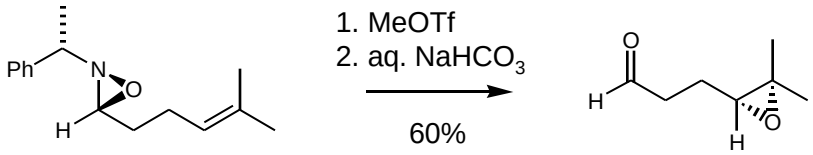
R_1	R_2	R_3	n	yield, %
H	Me	Me	1	39
H	Me	Me	2	41
n-Bu	H	H	1	39
H	H	***n***-Pr	1	56
H	***n***-Bu	H	1	60



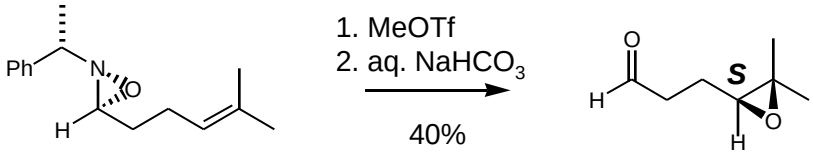


Armstrong ***SynLett*** **1998**, 646

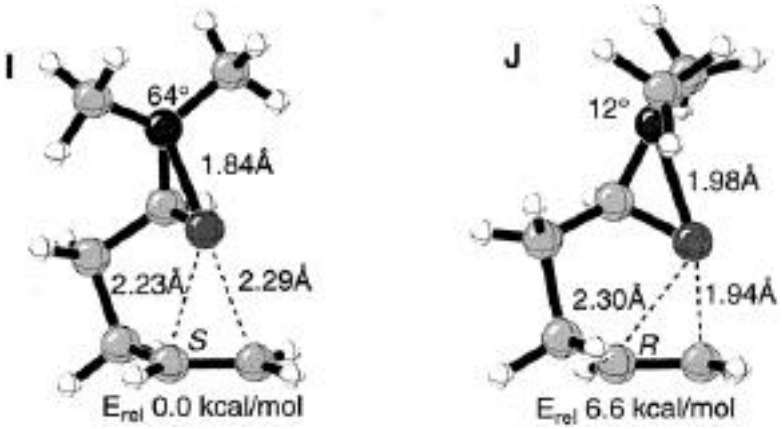
Asymmetric Intramolecular Epoxidation: Spiro Transition State



~83% ***de*** 81% ***ee***



>90% ***de*** 94% ***ee***

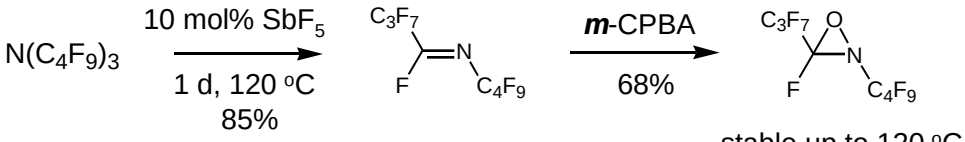


Armstrong
Tetrahedron Lett. **1999**, ***40***, 4453

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

Epoxidations with Perfluorinated Oxaziridines

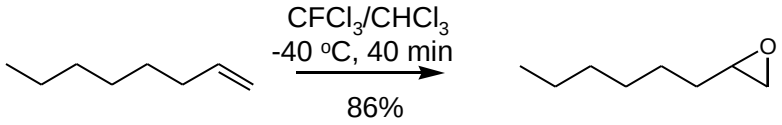
Preparation

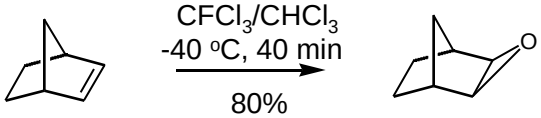


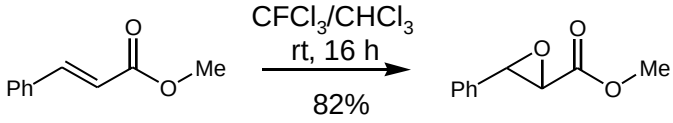
stable up to 120 °C

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

Epoxidation reactions

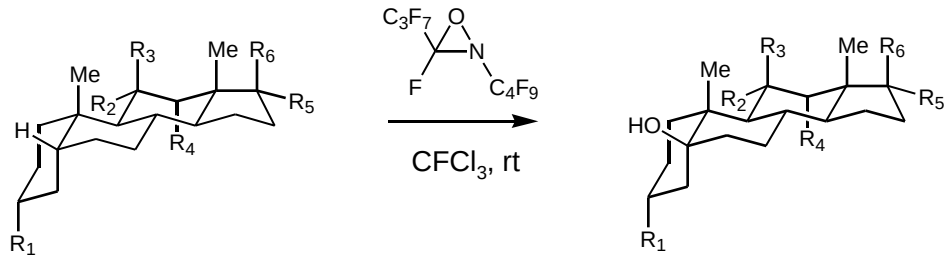






Resnati ***J. Org. Chem.*** **1996**, ***61***, 8805

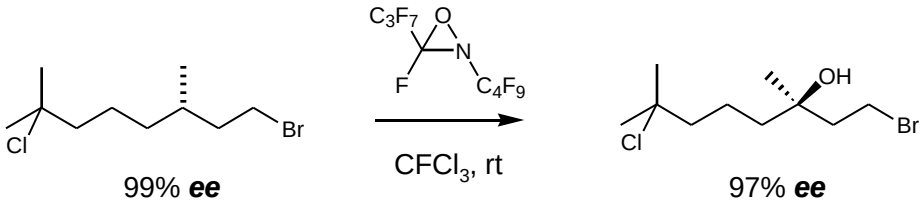
Oxidation of Unactivated C-H Bonds



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	$CH(CH_3)(CH_2)_2COOMe$	79
OAc	H	H	OAc	H	$CH(CH_3)(CH_2)_2COOMe$	66
OAc	O	O	Br	H	$COCH_2OAc$	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

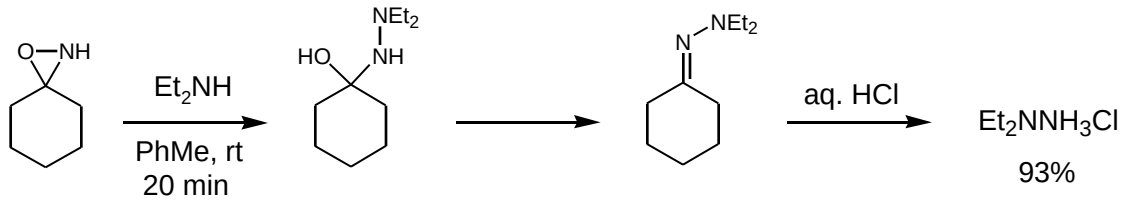


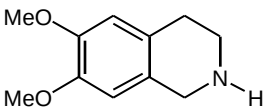
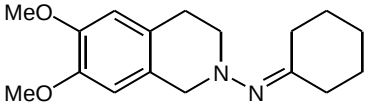
99% ***ee*** 97% ***ee***

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

N-Amination with N-H Oxaziridines

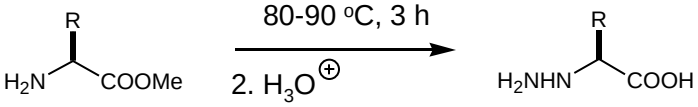
Amination of secondary amines



substrate	product	yield, %
Bu_2NH	Bu_2NNH_3Cl	75
$(NCCH_2CH_2)_2NH$	$(NCCH_2CH_2)_2N$=***c***-C_6H_{10}	71
		80

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

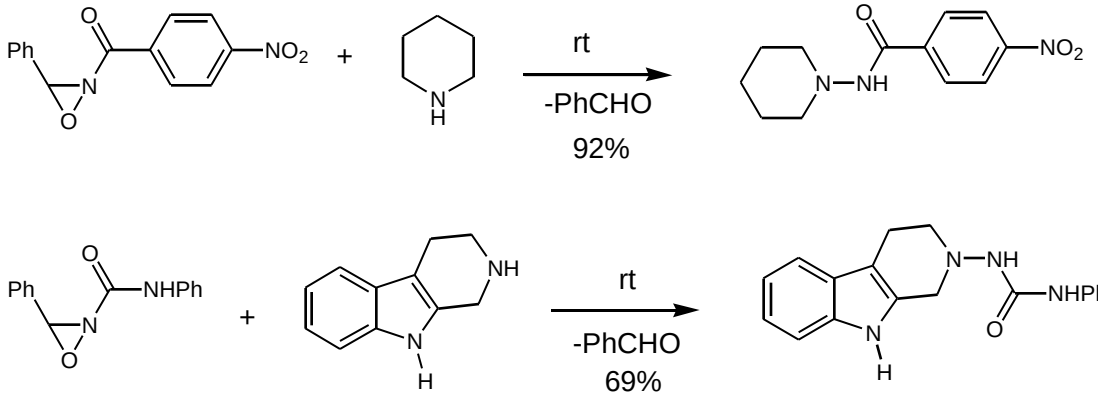
Amination of primary amines



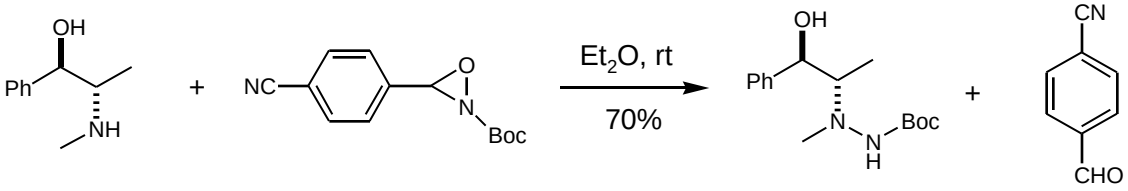
R	Me	***i***-Pr	Ph	Bn
yield, %	38	54	32	54

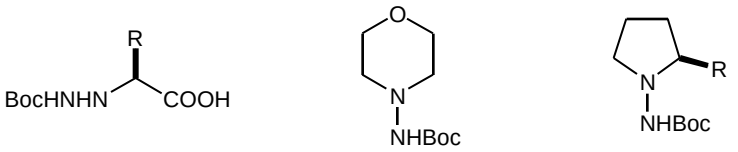
Schmitz ***Synthesis***, **1991**, 327

N-Acylamidation with Oxaziridines



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





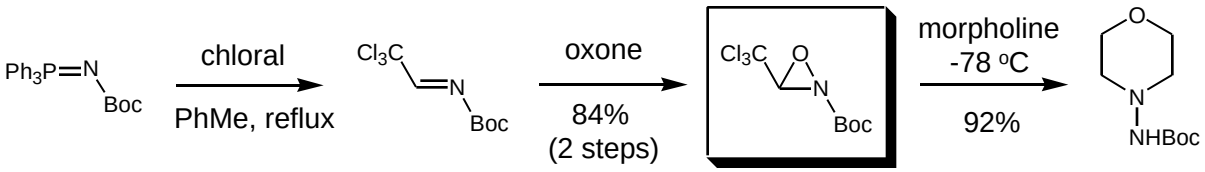
R = Me 50%
R = Ph 41%

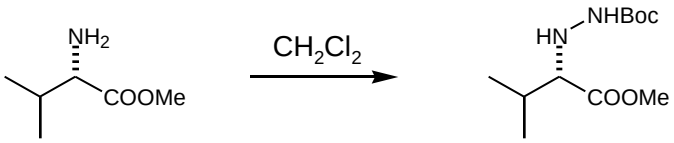
90%

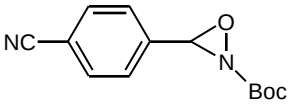
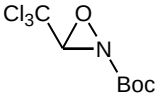
R = CH_2OMe 78%
R = COOH 77%

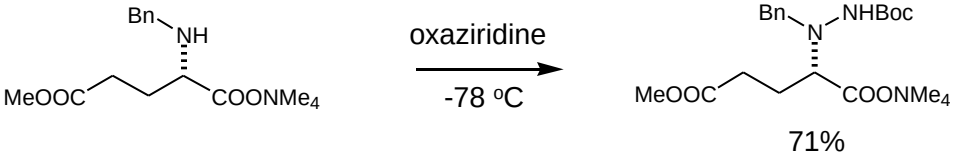
Collet
J. Org. Chem. **1993**, ***58***, 4791

More Efficient Reagent for N-Acylamidation





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

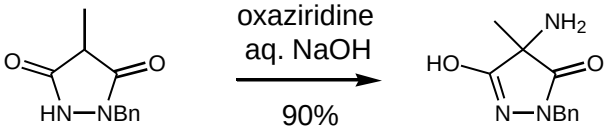


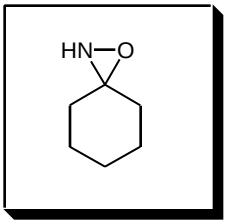
71%

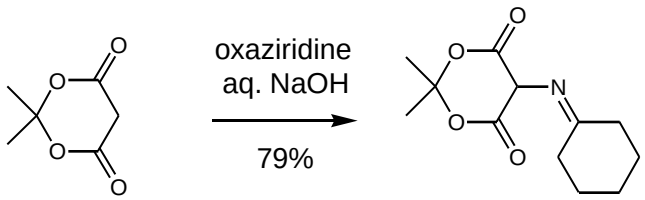
Collet ***Tetrahedron Lett.*** **1998**, ***39***, 8845

Amination of Carbon Nucleophiles

Amination of C-H acidic compounds

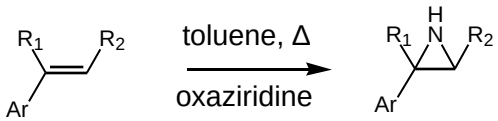






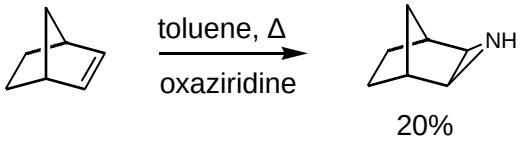
Schmitz ***Synthesis*** **1991**, 327

Epamination of alkenes



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

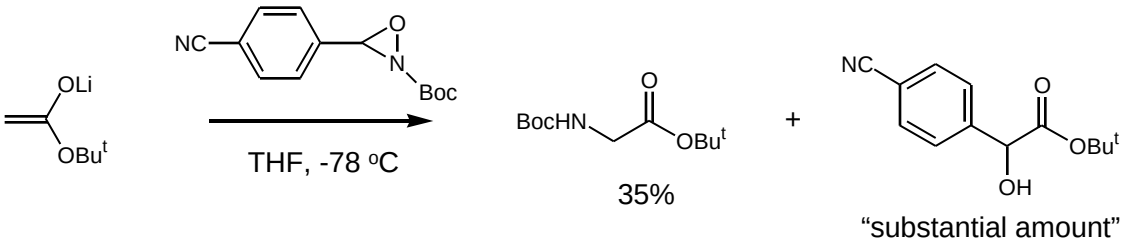
Ar	**R_1**	**R_2**	**yield, %**
4-ClC_6H_4	H	H	58
4-$NO_2C_6H_4$	H	H	49
Ph	Me	H	46
4-$MeOC_6H_4$	H	Me	36

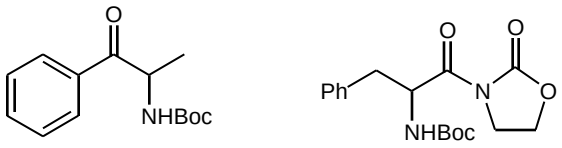


20%

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

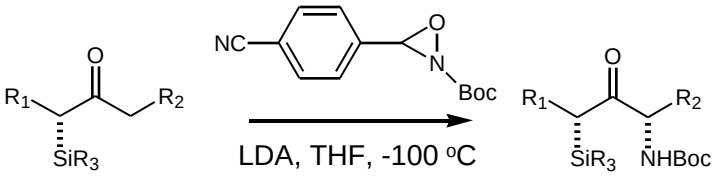
Amination of Enolates





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

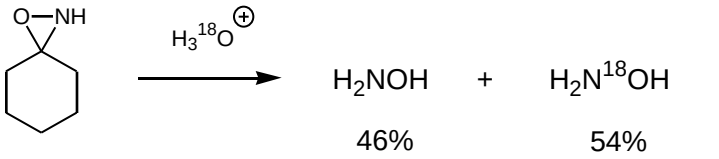
Collet ***J. Org. Chem***. **1993**, ***58***, 4791

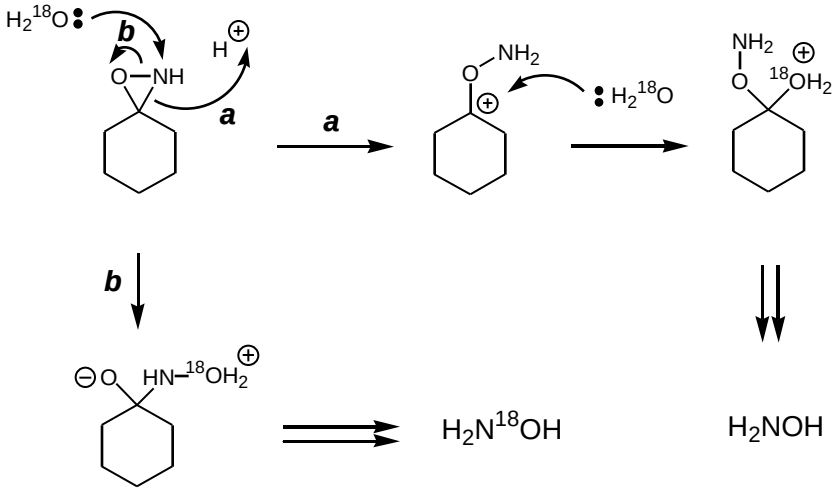


R_1	R_2	R_3	yield, %	*dr*
Me	Me	Me_2Bu^t	27	90:10
Et	Et	Me_2Bu^t	37	93:7
n-Pr	***n***-Pr	Me_2Bu^t	29	94:6

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

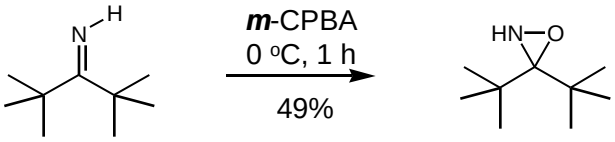
O-Amination Reactions

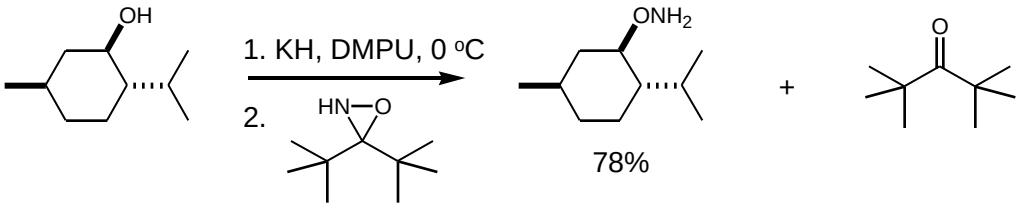


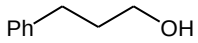
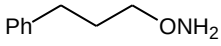
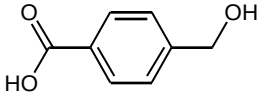
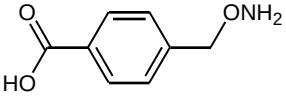
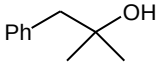
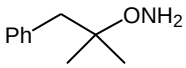


Schmitz ***Synthesis*** **1991**, 327

Synthetically Useful O-Amination Procedure

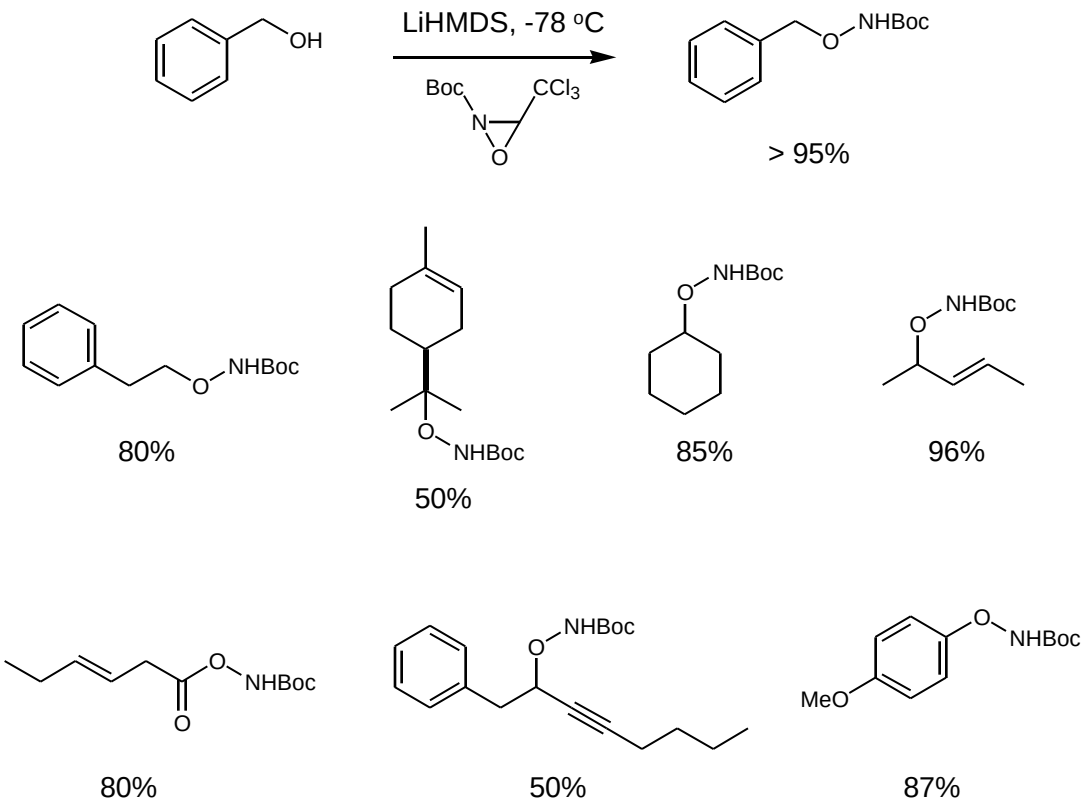




alcohol	product	yield, %
		86
		56
		10

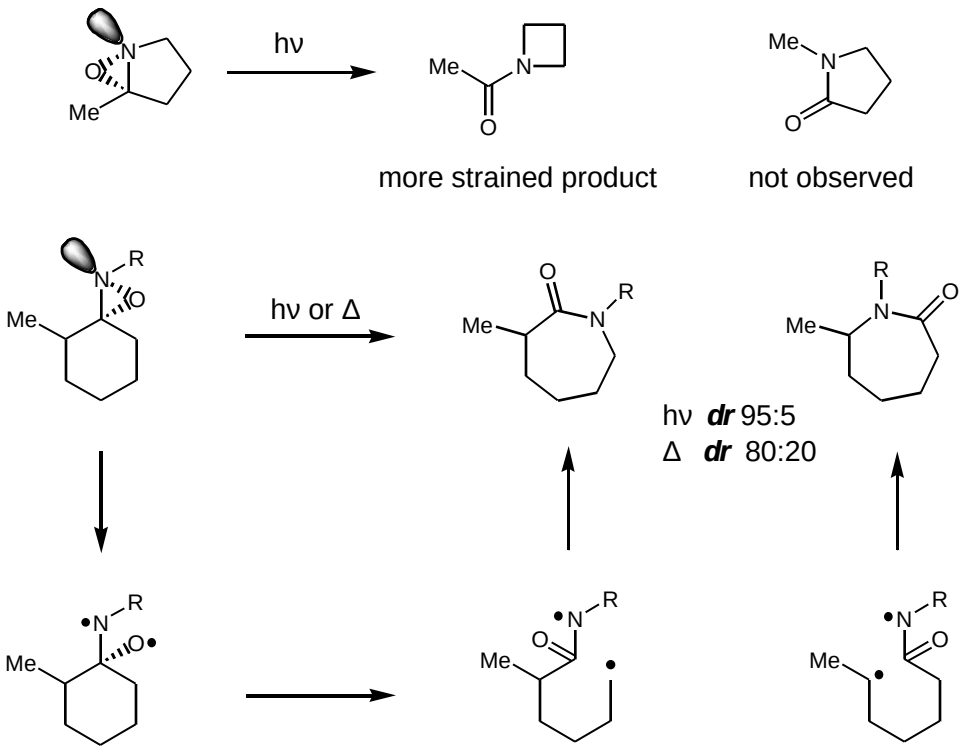
Ellman ***J. Org. Chem***. **1999**, ***64***, 6528

N-Boc-Hydroxylamines via O-Amination of Alcoholates



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

Oxaziridine to Amide Rearrangement: Puzzling Selectivity

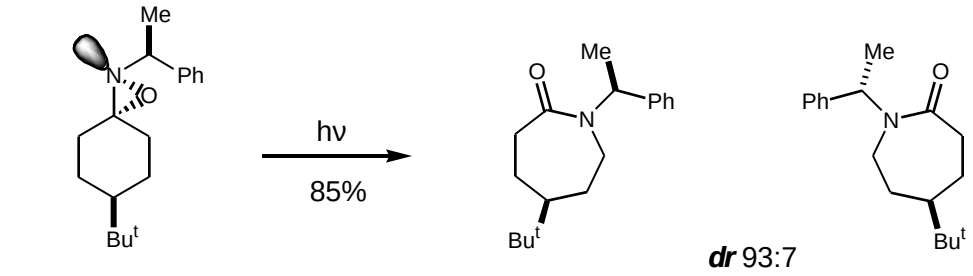


- oxaziridine did not epimerize at ***N*** during irradiation as evidenced by ^{1}H NMR.
- less stable radical leads to the product.

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.

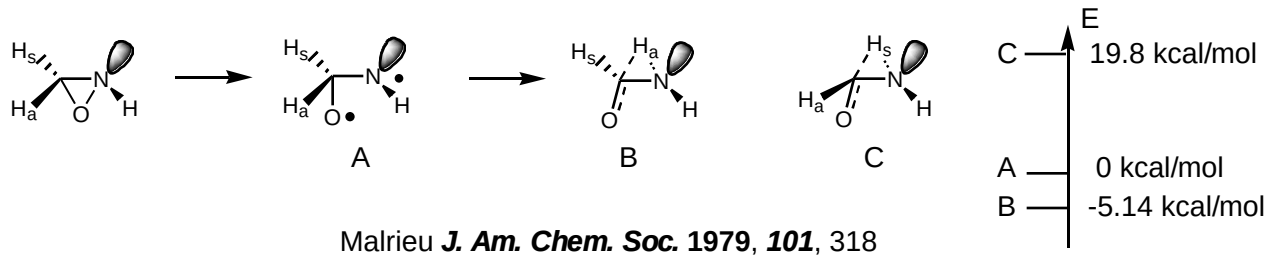


dr 93:7

structure by X-ray structure by X-ray

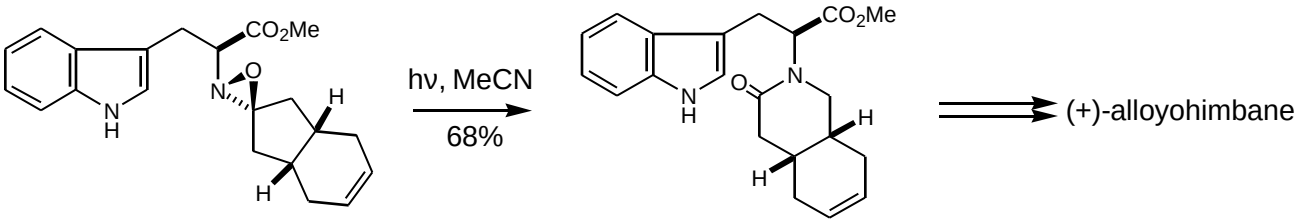
Lattes ***J. Am. Chem. Soc.*** **1982**, ***104***, 3929

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.

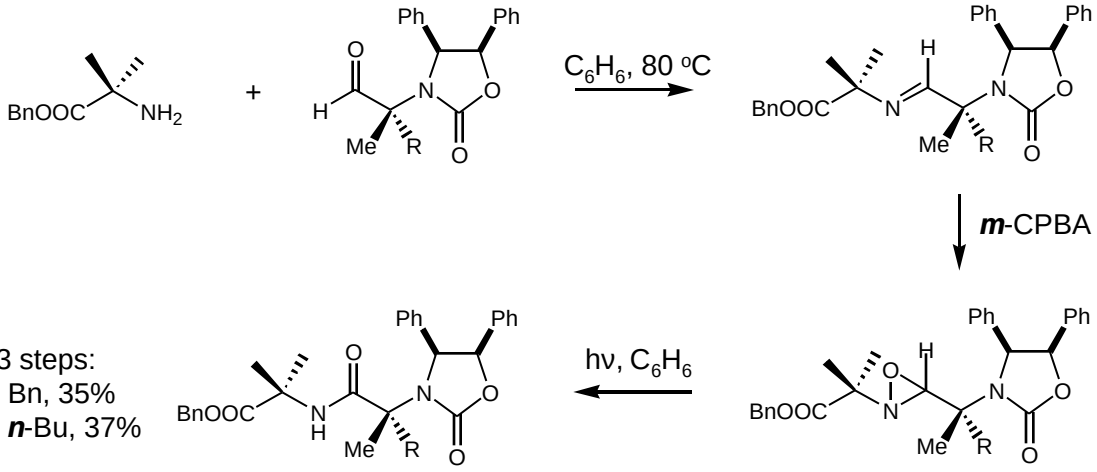


Malrieu ***J. Am. Chem. Soc.*** **1979**, ***101***, 318

Recent Applications of Photochemical Rearrangement

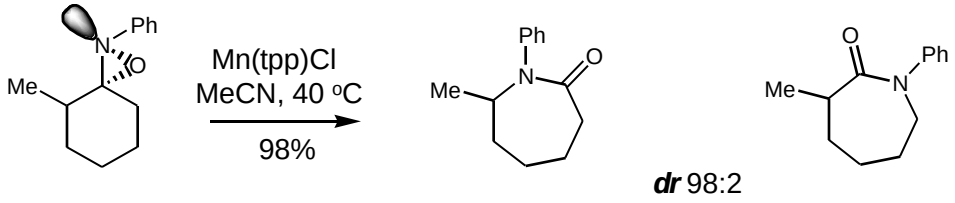


Aube ***J. Am. Chem. Soc.*** **1994**, ***116***, 9009

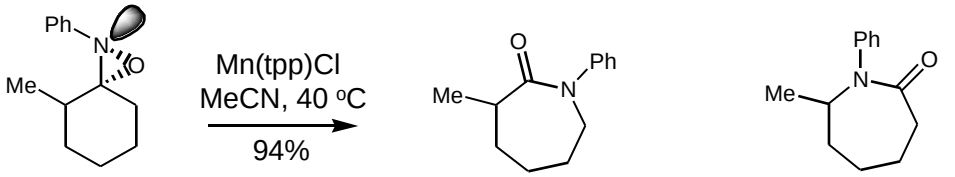


Hegedus ***J. Am. Chem. Soc***. **1998**, ***120***, 12468

Lewis Acid-Catalyzed Rearrangement: Reversal of Selectivity

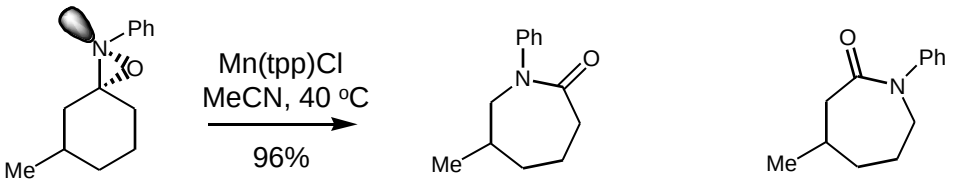


dr 98:2



dr 98:2

tpp = tetraphenylporphyrin

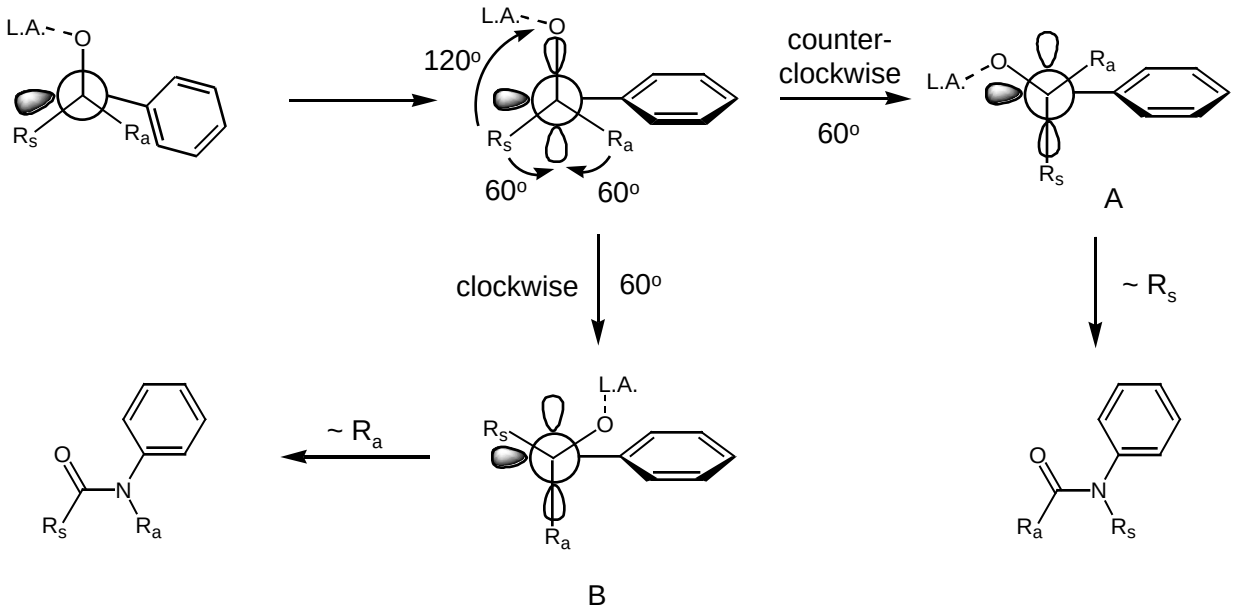


dr 94:6

- 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

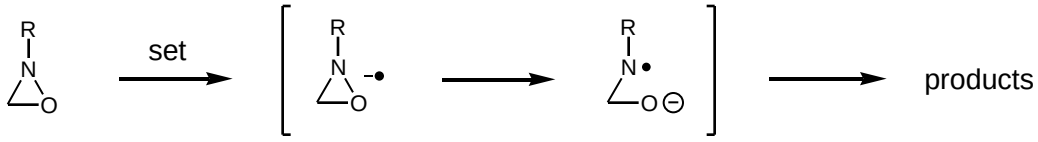
Possible Explanation of the Observed Stereospecificity



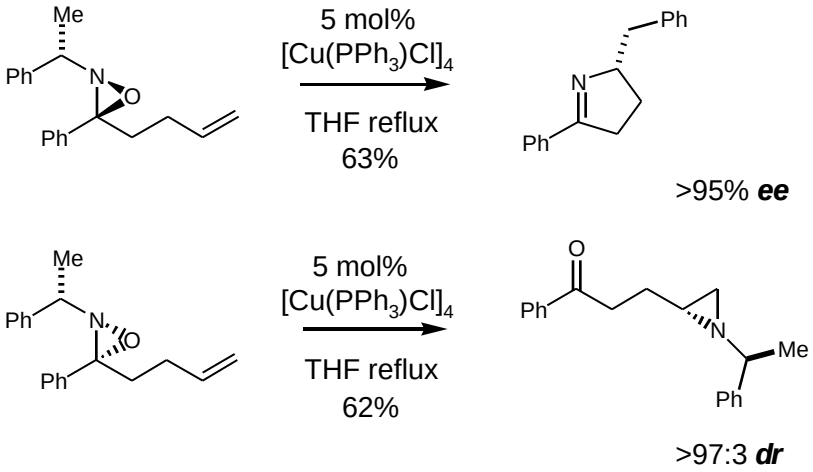
As Lewis acid is very big and anionic oxygen is highly solvated in MeCN, rotamer A looks better than B. One may argue though, that upon counterclockwise rotation to reach A, substituent R_a should ***pass*** Ph. No eclipsing of substituents is required to reach structure B upon clockwise rotation.

Single Electron Transfer Reactions of Oxaziridines

Generalized reactivity pattern:

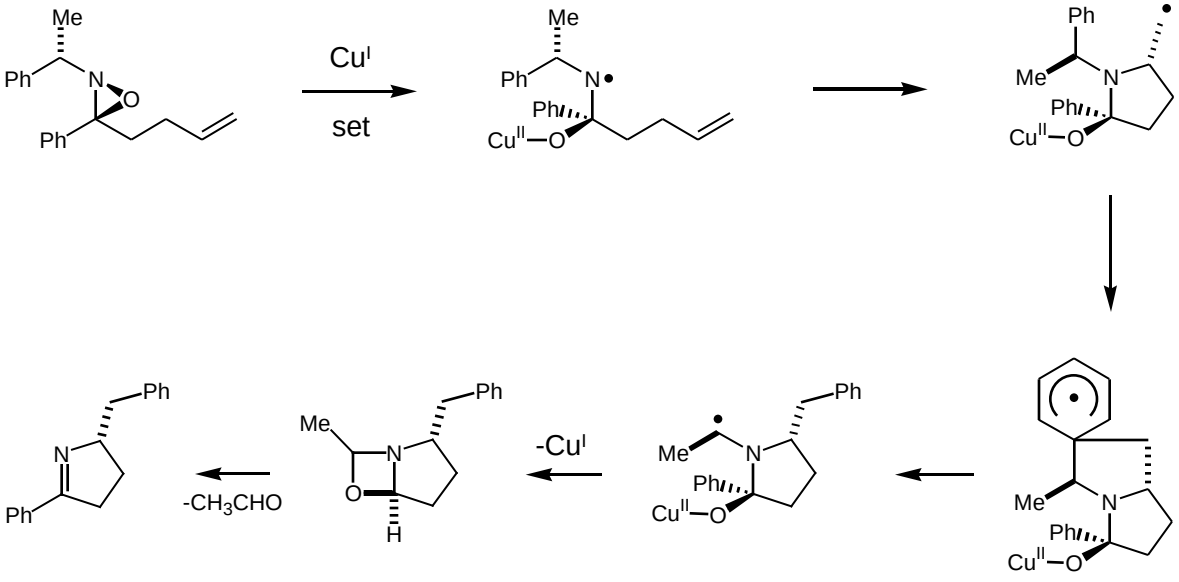


Minisci ***Tetrahedron*** **1970**, ***26***, 4083



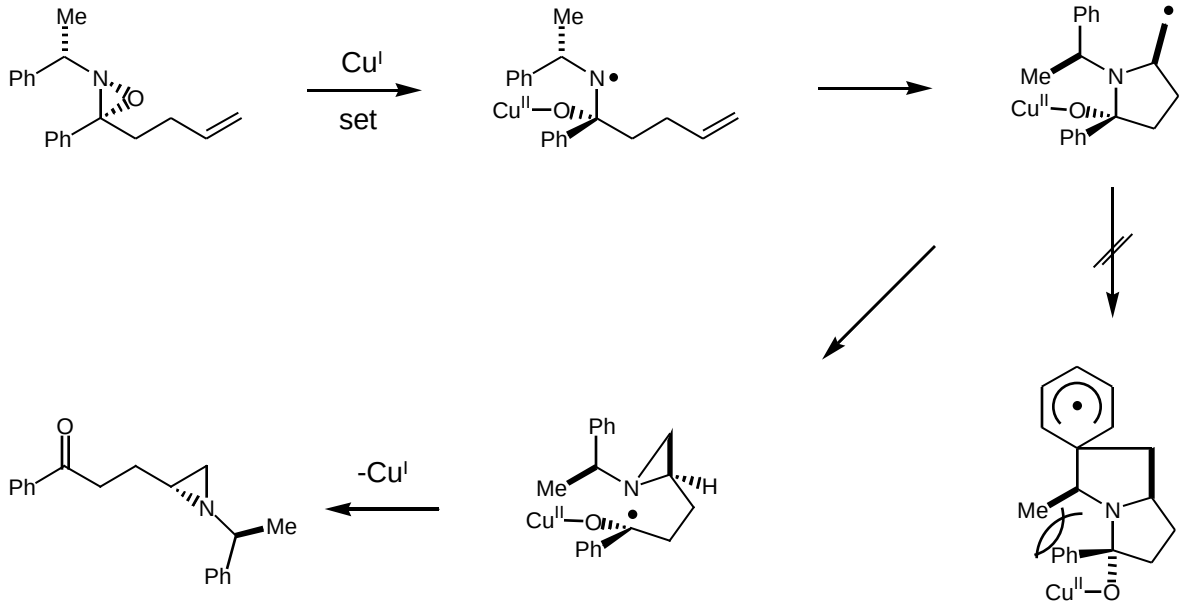
Aube ***J. Am. Chem. Soc.*** **1992**, ***114***, 5466

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.