Oxaziridines: New Perspectives and Insights

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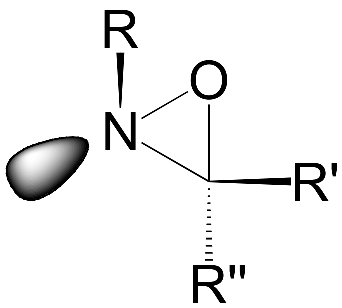
Michigan State University
11/26/2003

Oxaziridines



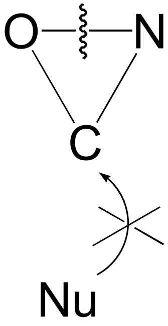
First discovered by Emmons in 1957

(Emmons, W. D. *J. Am. Chem. Soc*. **1957**, *79*, 5739)

Strained three-membered ring
Weak N-O bond

→ Unusual Reactivity

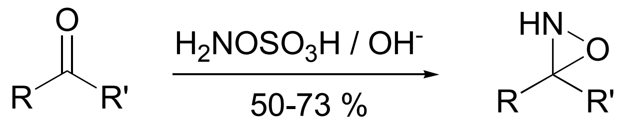
Summary of Oxaziridines' Reactivity



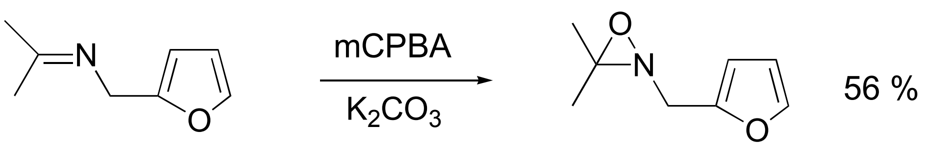
Outline

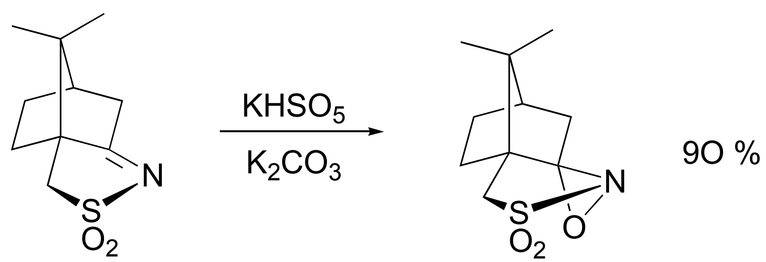
- Introduction
- Heteroatom Transfer Reactions
    - N vs O Transfer: Mechanistic Considerations
    - O Transfer Reactions
    - N Transfer Reactions
- Photochemical Rearrangement Reactions
- Conclusion

Oxaziridines: Common Methods of Preparation



(method prefered for N-H oxaziridines)





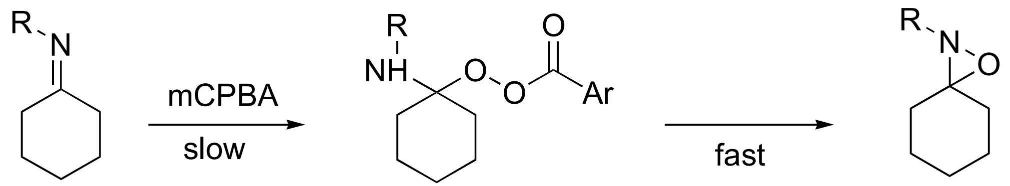
Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327-341

Widmer, J.; Schierlein, W. K. *Helv. Chim.Acta* **1974**, *57,* 657-664

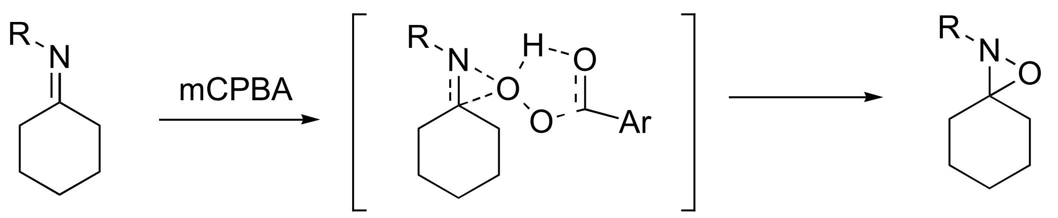
Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110,* 8477-8482

Mechanism of Imine Oxidation by Peroxy Acids

Two-stage mechanism (Baeyer-Villiger type)



Concerted mechanism



The two-stage mechanism is generally accepted for the reaction

Ogata,Y.; Sawaki, ,Y. *J. Am. Chem. Soc.* **1973**, *95*, 4687

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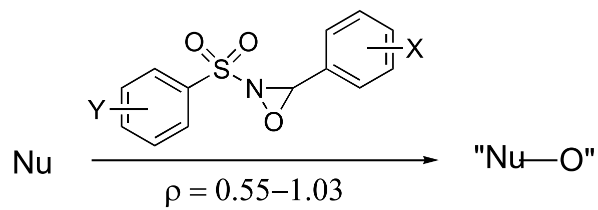
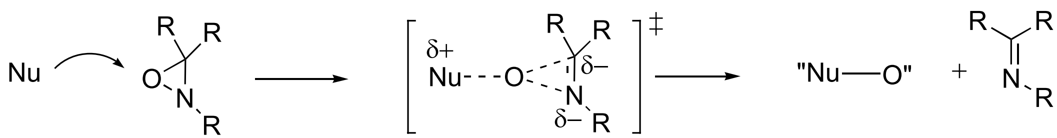
O-Transfer: Mechanistic Considerations

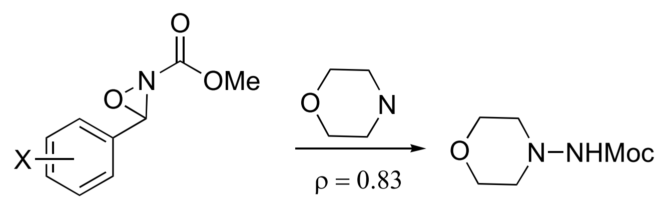


Mechanism for Oxygen Transfer to various Nucleophiles:



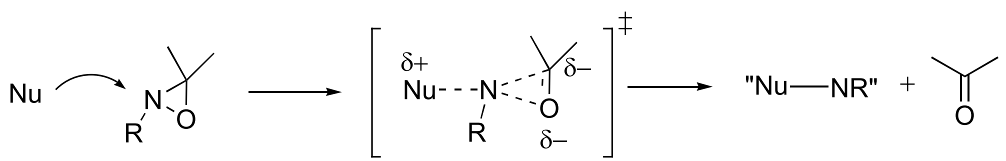
Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C. *J. Org. Chem*. **1986**, *51*, 4240-4245

N-Transfer: Mechanistic Considerations



First stable N - transfer oxaziridine

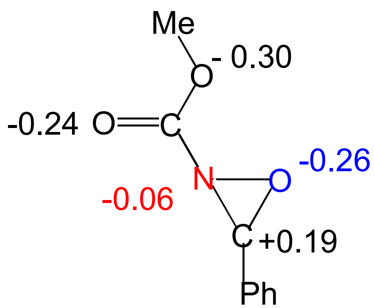
__Mechanism for Nitrogen Transfer to various Nucleophiles:__



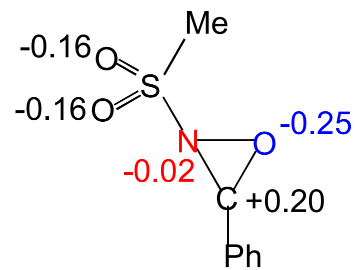
Vidal J.; Damestoy S.; Guy L.; Hanachi J,; Aubry A.; Collet A. *Chem. Eur J.* **1997**, *3*, 1691-1709

Rationalizing N vs O transfer: A Balance Between Electronics and Sterics

Electronics: Nitrogen is more electron deficient than Oxygen



(N-transfer reagent)



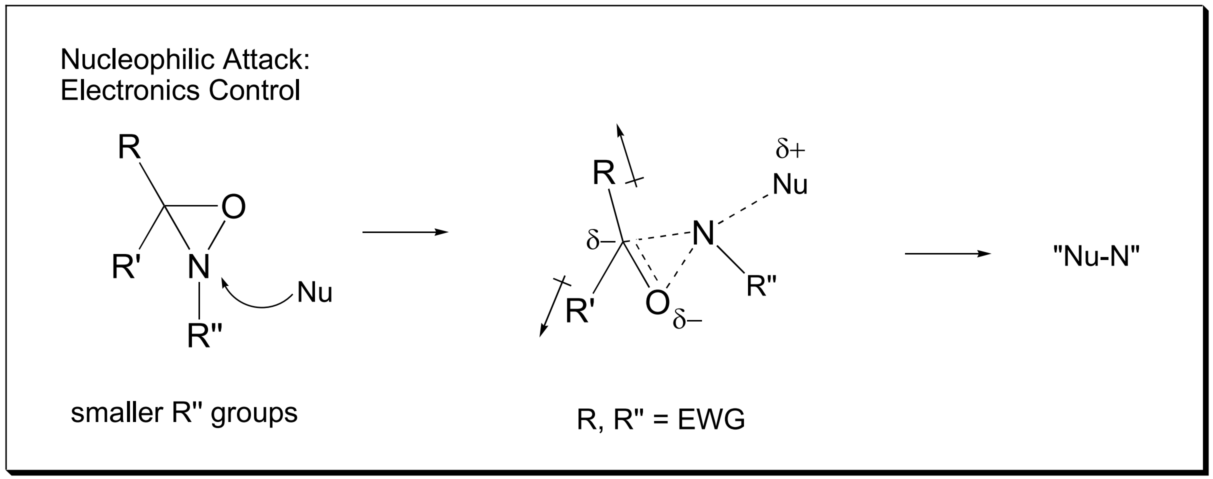
(O-transfer reagent)

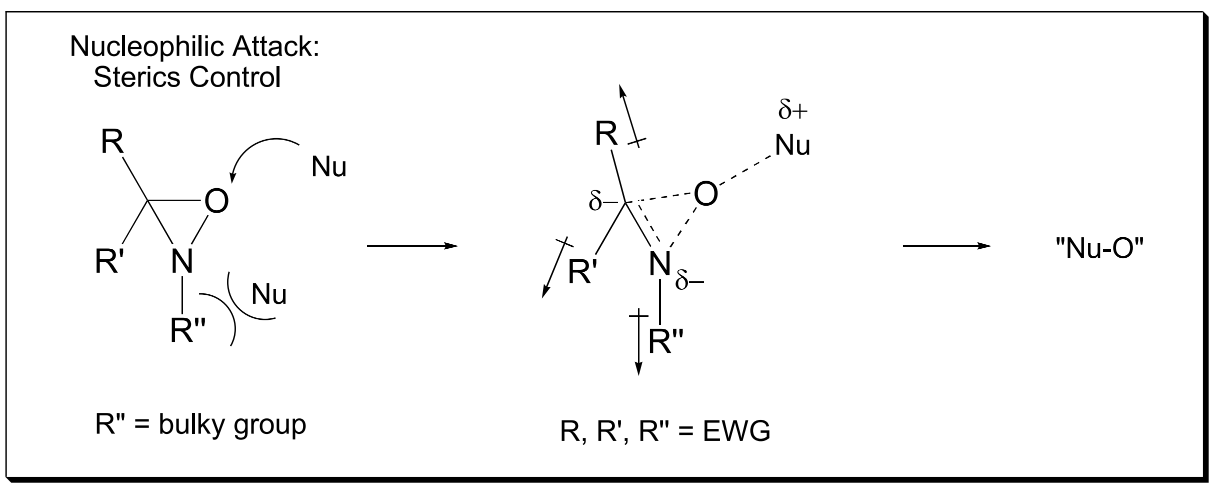
Sterics: Nucleophilic attack to Nitrogen can be hindered

N-substituent	^{t}Bu	SO_2Me	Ph_2PO	CF_3	Me	CO_2Me	Cl	H
A value	4.8	2.5	2.5	2.5	1.8	1.2	0.6	0
RSMe	O	O	O	O	N	O/N		
RNH_2, RR'NH		O			N	N	N	N

Vidal J.; Damestoy S.; Guy L.; Hanachi J,; Aubry A.; Collet A. *Chem. Eur J.* **1997**, *3*, 1691-1709

N vs O Transfer: A suggested Model





Vidal J.; Damestoy S.; Guy L.; Hanachi J,; Aubry A.; Collet A. *Chem. Eur J.* **1997**, *3*, 1691-1709

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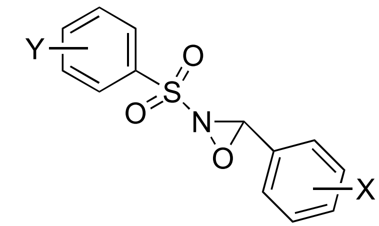
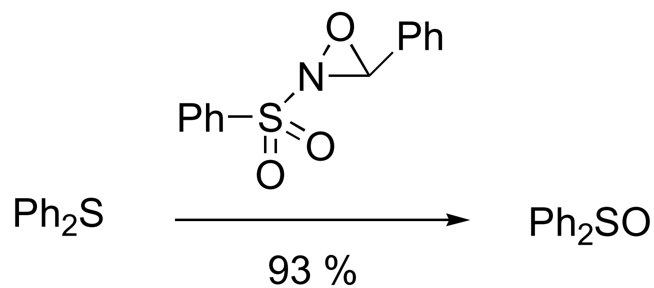
N-Sulfonyl (Davis) Oxaziridine

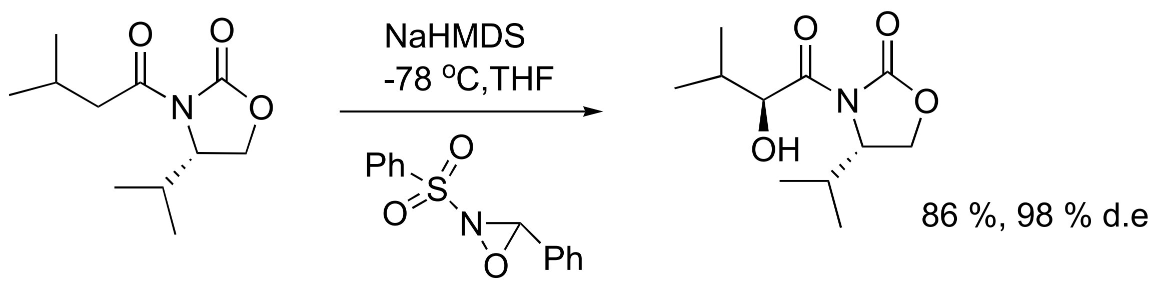


N-Sulfonyl Oxaziridines
(Davis Oxaziridines)

-Oxidation of Sulfides



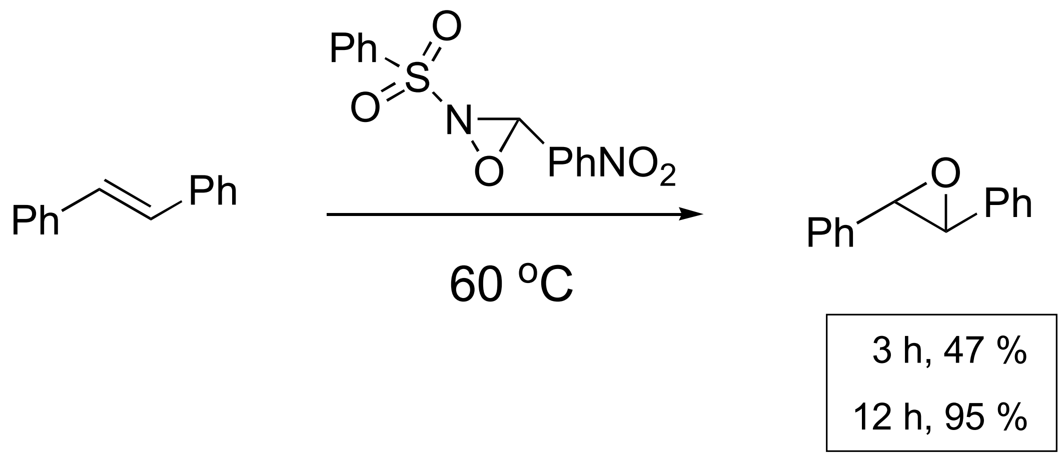
-Hydroxylation of Enolates



Davis, F. A.; Lal, S. G.; Durst, H. D. *J. Org. Chem*. **1988**, *53*, 5004.

Evans, D. A.; Morrissay, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, 107, 4346-4348

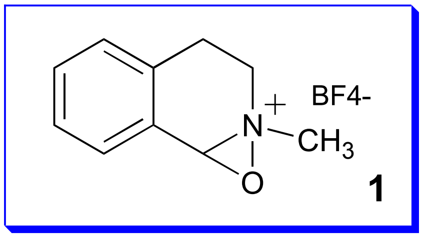
Davis Reagent: Epoxidation of Alkenes

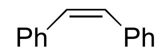
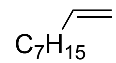
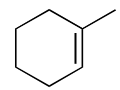


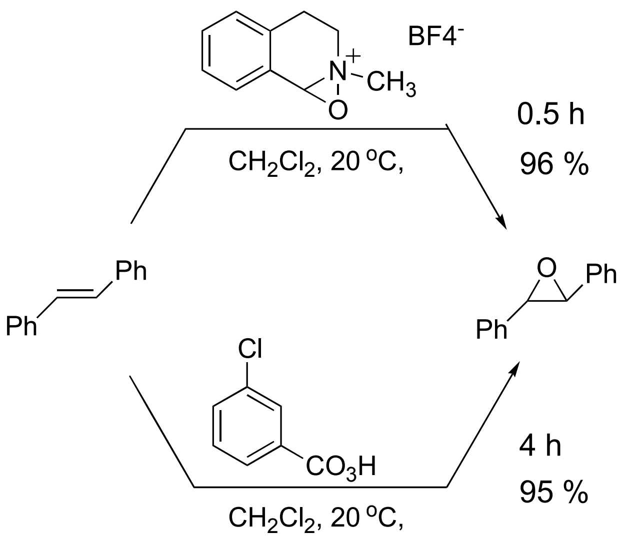
Less Efficient than mCPBA

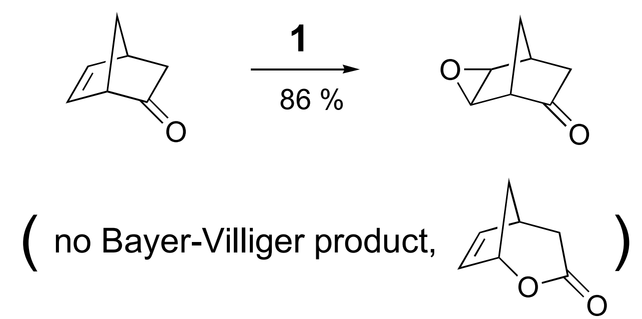
Davis, F. A.; Malik, N. F.; Award, S. B.; Harakal, M. E. *Tetrahedron Lett*. **1981**, 917

Epoxidations with Oxaziridinium Salts



Alkene	mCPBA	**1**
	3h, 92 %	1h, 89 %
	10 h, 88 %	2h, 91 %
	1h, 81 %	10 min, 84 %

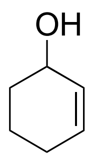
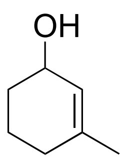
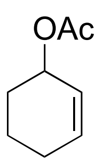
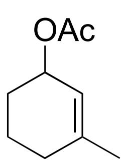


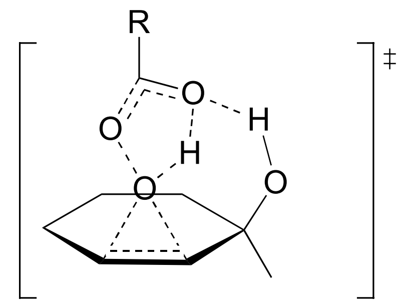


Hanquet,G.; Lusinchi, X.; Milliet, P. *Tetrahedron* **1993**, *22*, 423-438

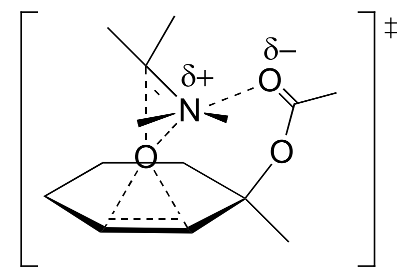
Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727-13738

Epoxidation with Oxaziridinium Salts: Directing Effects

substarate	yield	cis/trans selectivity	
		oxaziridinium salt	mCPBA
	85	60 / 40	92 / 8
	95	60 / 40	95 / 5
	92	95 / 5	50 / 50
	95	95 / 5	40 / 60



Epoxidation with peracid

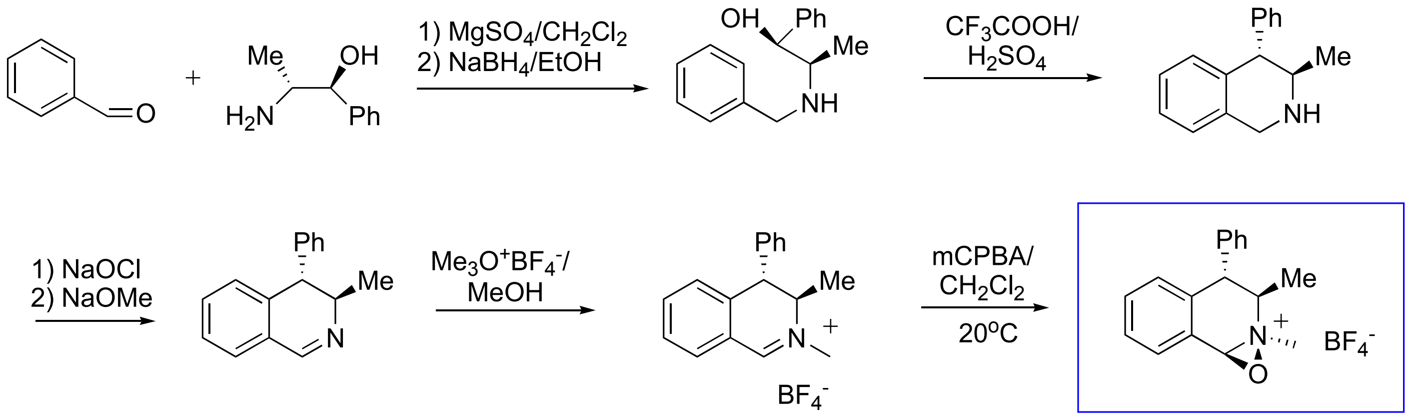


Epoxidation with oxaziridinium salt

Lusinchi, X.; Hanquet, G. *Tetrahedron* **1997**, *53*, 13727-13738

The first Chiral Oxaziridinium Salt

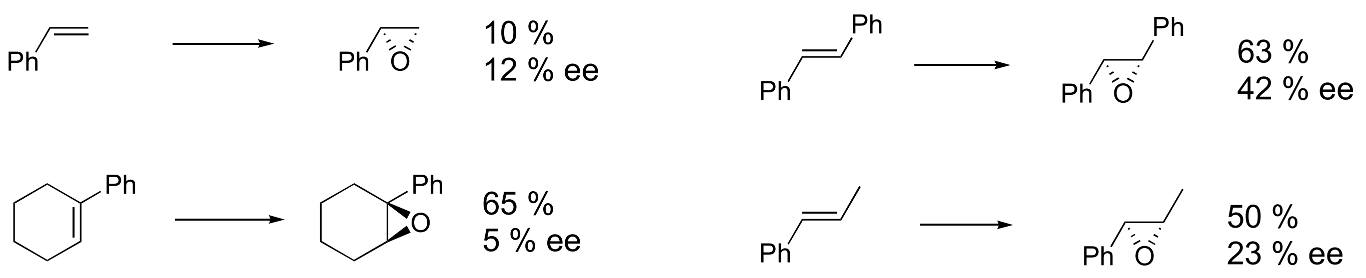
Preparation



single diastereomer

23 % overall yield

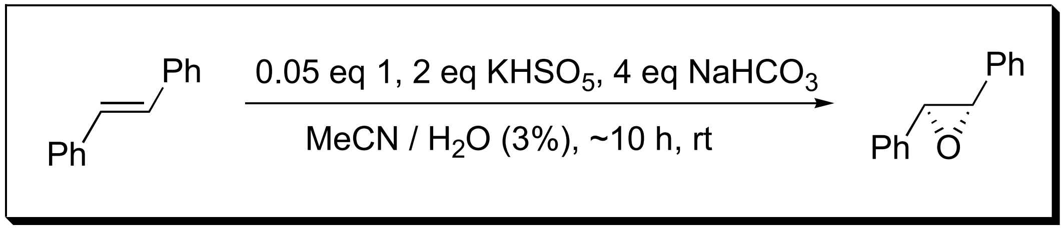
Epoxidation reactions (Stoichiometric)

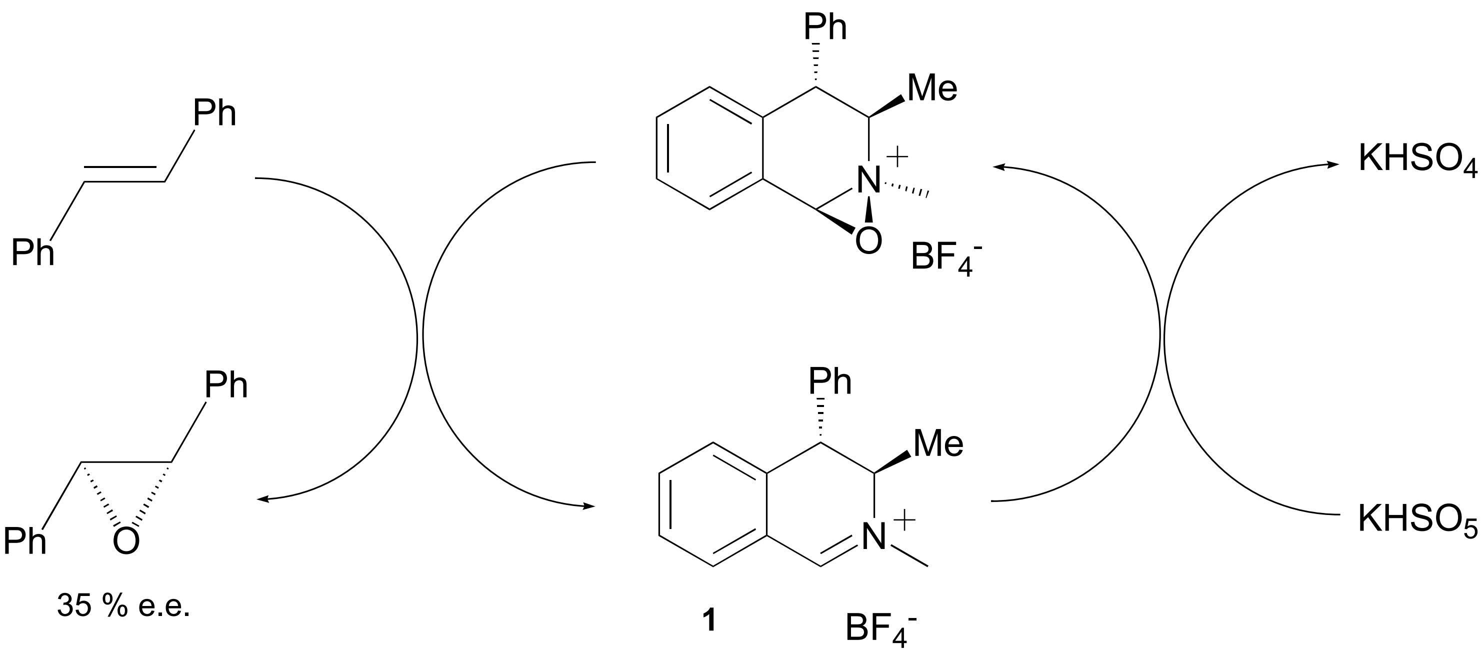


Bohe, L.; Hanquet, G.; Lusinchi, M.; Lusinchi, X. *Tetrahedron Lett.* **1993**, *34*, 7271-7274

Bohe, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141-154

Catalytic Asymmetric Epoxidation using a Chiral Iminium Salt

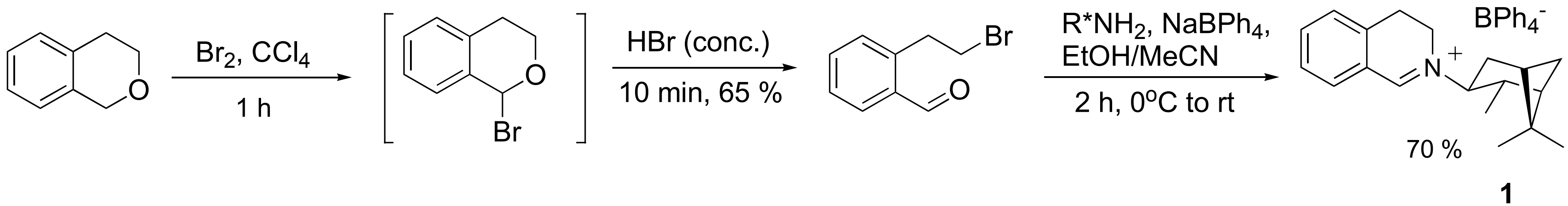




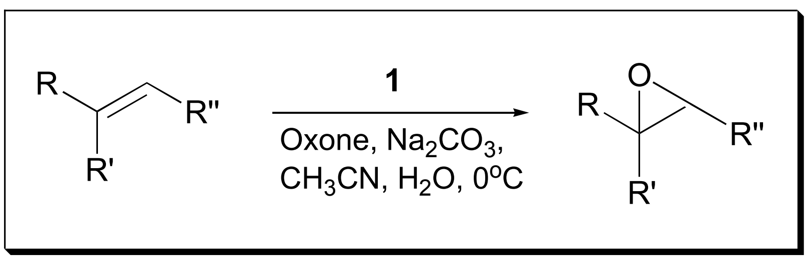
Bohe, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 141-154

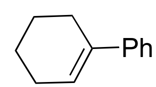
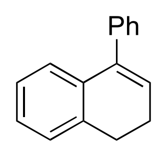
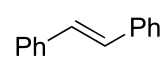
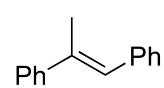
Iminium Salts with “Exocyclic Chirality”

Preparation:



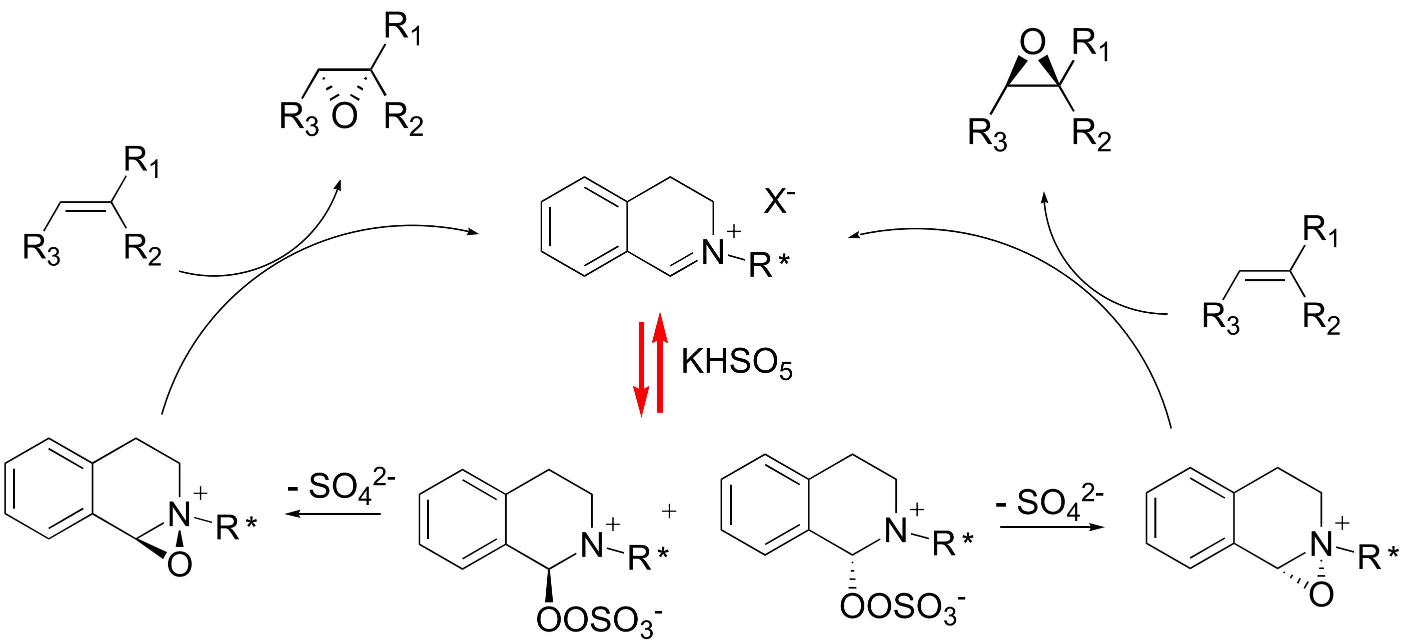
Epoxidation Reactions:



Alkene	cat..load. (mol %)	yield (%)	ee (%)	major enantiomer
	0.5	68	27	(R,R)
	5	68	40	(R,R)
	5	73	63	(S,S)
	5	75	68	(R,R)
	10	78	73	(R,R)
	5	72	15	(R,R)

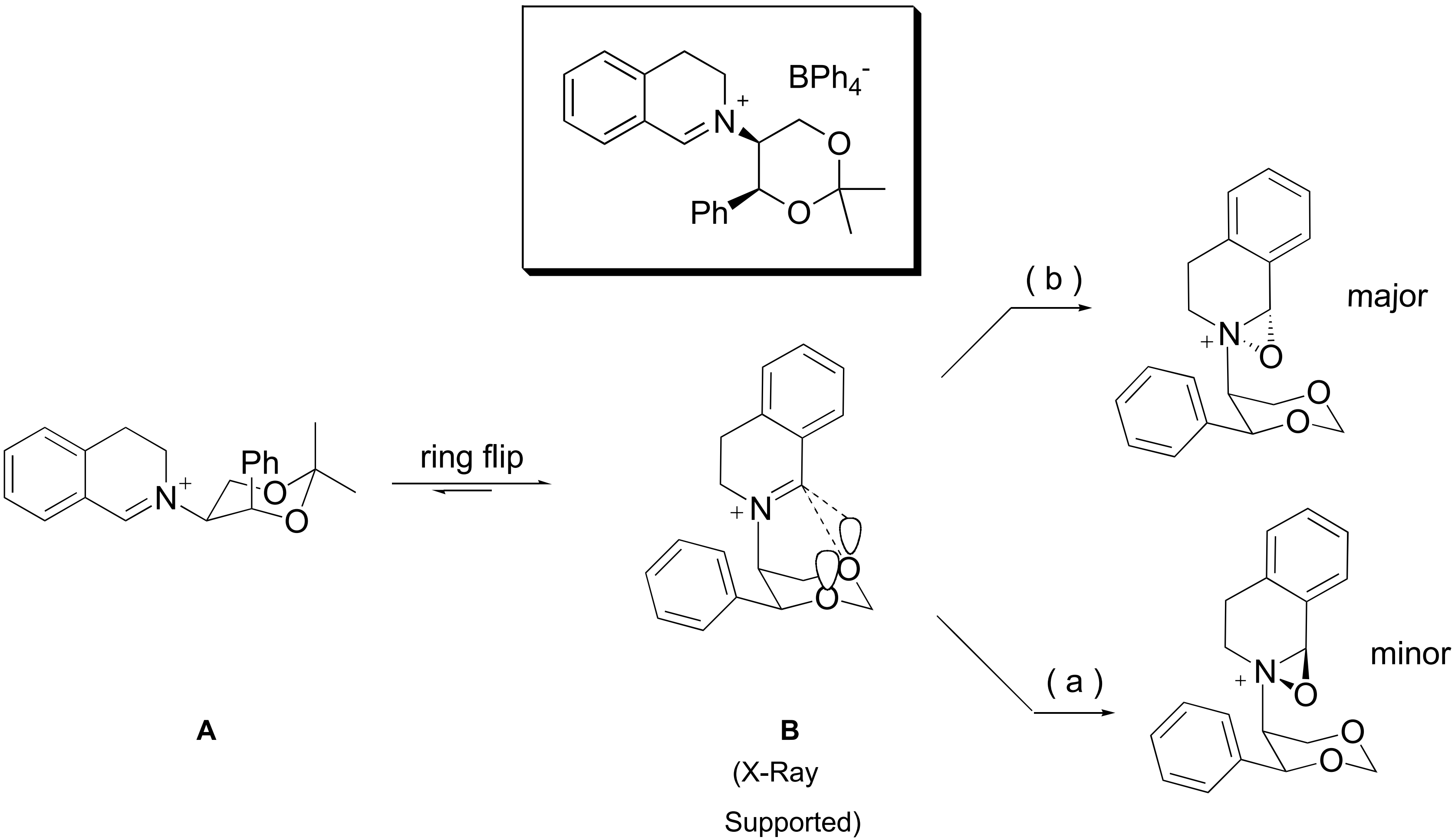
Page, P. B.; Rassias, G.; Bethel, D. Schilling, M. B. *J. Org.Chem.* **1998**, *63,* 2774-2777

Stereocontrol of Oxaziridination is a possible problem



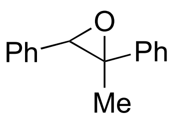
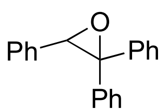
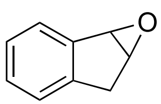
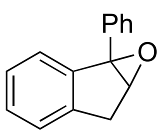
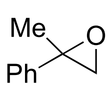
Page, P. B.; Rassias, G.; Barros, D. Ardakani, A.; Slawin A*. J. Org. Chem.* **2001**, *66*, 6926-6931

Can Functionalized Iminium Salts Solve the Problem of Stereocontrol ?

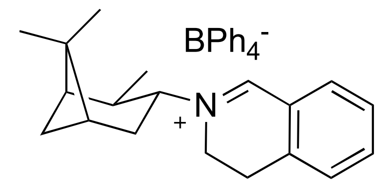


Page, P. B.; Rassias, G.; Barros, D. Ardakani, A.; Slawin A. *J. Org. Chem.* **2001**, *66*, 6926-6931

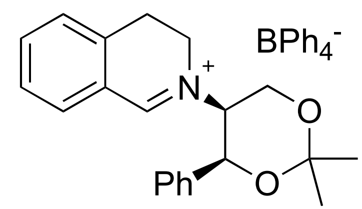
Catalytic Asymmetric Epoxidation Using a Functionalized Iminium Salt

Epoxide	Catalyst 1	Catalyst 2
	72%, **15% ee** (R,R)	52%, **52% ee** (1S,2S)
	43%, **5% ee** (S)	54%, **59% ee** (S)
	34%, **3% ee** (1S,2R)	52%, **17% ee** (1S,2R)
	73%, **20% ee** (1S,2R)	64%, **49% ee** (1S,2R)
	68%, **8% ee** (R)	64%, **20% ee** (R)

(Conditions: Oxone (2eq), Na_2CO_3 (4eq), H_2O/MeCN (1:1), 0ºC, 5 mol% catalyst)



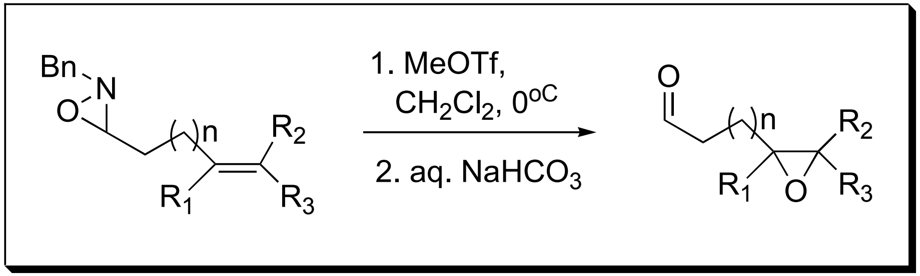
1



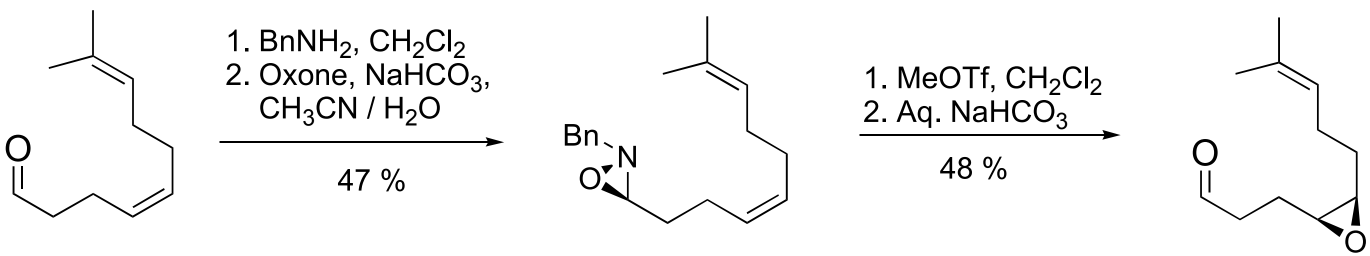
2

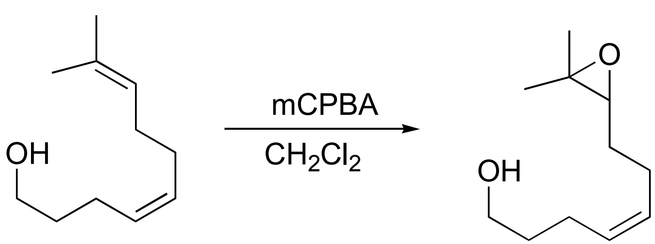
Page, P. B.; Rassias, G.; Barros, D. Ardakani, A.; Slawin A. *J. Org. Chem.* **2001**, *66*, 6926-6931

Intramolecular Epoxidation of Unsaturated Oxaziridines



R_1	R_2	R_3	n	Yield
H	Me	Me	1	39%
H	Me	Me	2	41%
nBu	H	H	1	39%

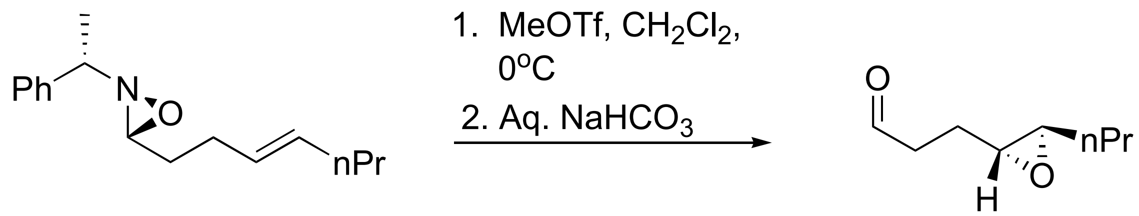




Regioselectivity can be complementary to that of mCPBA

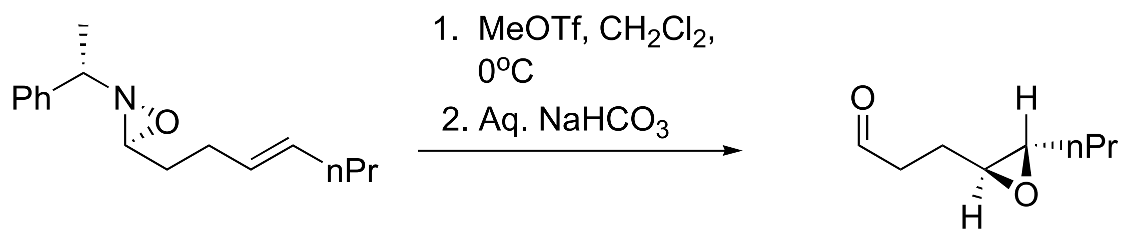
Armstrong, A.; Draffan, A. G. *J. Chem. Soc., Perkin Trans. I* **2001**, 2861-2873

Stereoselective Intramolecular Epoxidation in Unsaturated Oxaziridines



90 % de

93 % ee



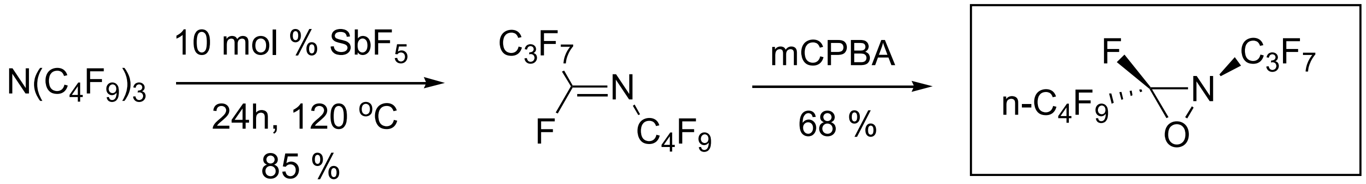
90 % de

92 % ee

Armstrong, A.; Draffan, A. G. *J. Chem. Soc., Perkin Trans. I* **2001**, 2861-2873

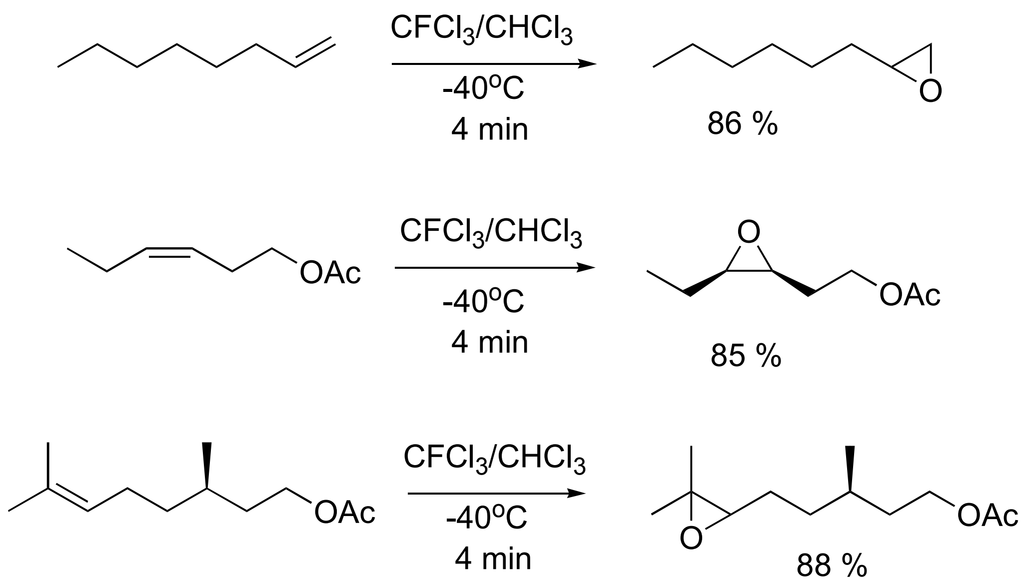
Epoxidations with Perfluorinated Oxaziridines

Preparation:



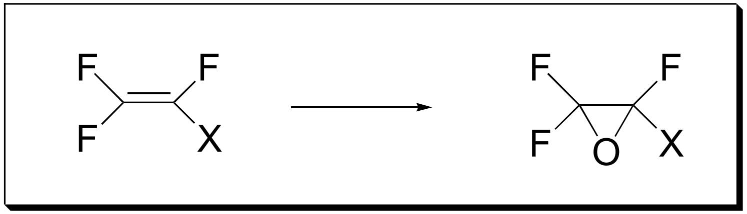
1

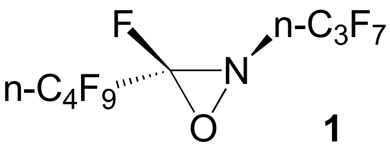
Epoxidation reactions:



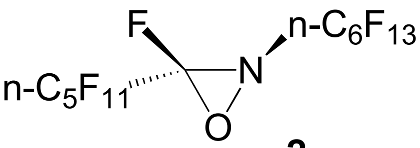
Arnone, A.; Marteau, D.; Novo, B.; Petrov, V.; Pregnolato, M.; Resnati, G.; *J.Org. Chem*. **1996**, *61*, 8805

Epoxidations of Electron Poor Olefins





1

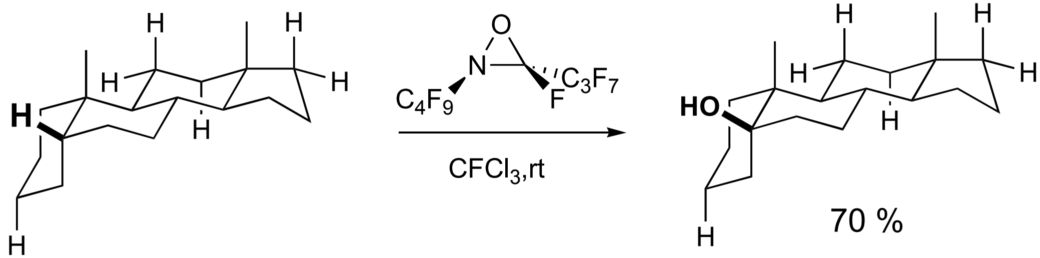


2

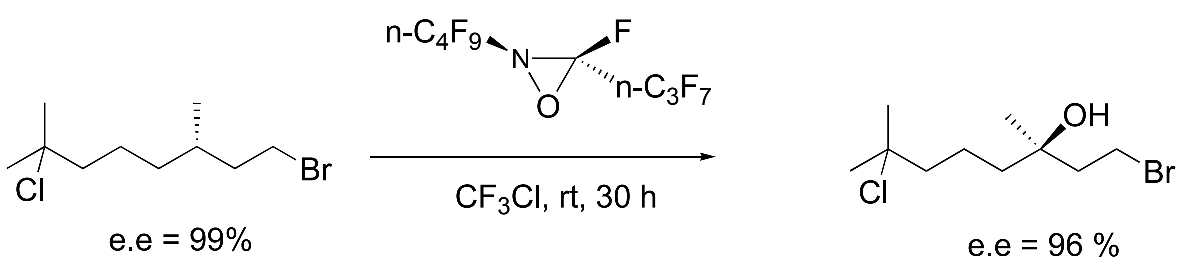
X	Oxaziridine	Conditons	Yield
$(CH_3)_3Si$	2	neat / rt / 20 min	82 %
Cl	1	neat / 100^{o}C / 16 h	60 %

Arnone, A.; Marteau, D.; Novo, B.; Petrov, V.; Pregnolato, M.; Resnati, G.; *J.Org. Chem*. **1996**, *61*, 8805

Oxyfunctionalization of Unactivated C-H Bonds by Perfluorinated Oxaziridines



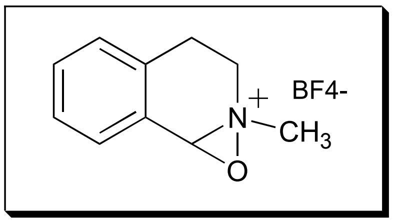
- Enantiospecific
- 3º C-H > 2º C-H > 1º C-H
- Equatorial C-H > Axial C-H
- Oxenoid Atom Insertion (?)



Resnati, G.; Arnone, A.; Cavicchioli, M.; *J. Org. Chem*. **1994**, *59,* 5511-5513

Arnone, A.; Foletto, S.;Metrangolo, P.; Pregnolato, M. Resnati, G. *J.Org. Chem*. **1999**, *1*, 281-284

Summary for O-Transfer Reactions

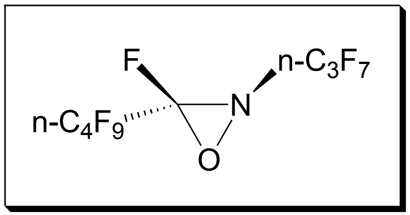


Oxaziridinium Salts:

•Very reactive for epoxidation of alkenes.

•Syn selectivity for epoxidation of allylic acetates.

•Capabe for catalytic asymmetric epoxidation.



Perfluorinated Oxaziridines :

• Very reactive O-donors.

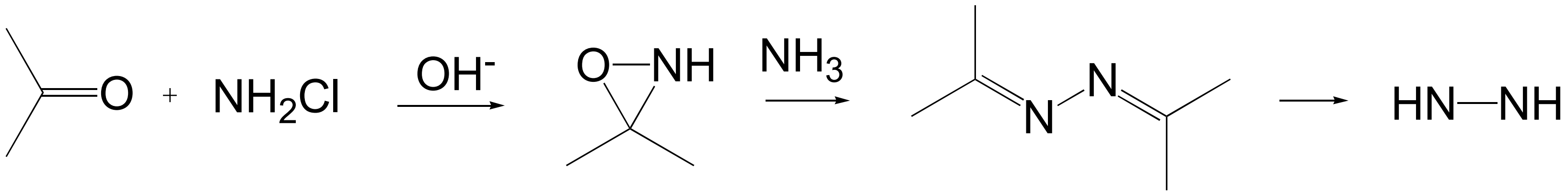
•Epoxidation of e^- poor alkenes efficient.

•Capable for C-H activation.

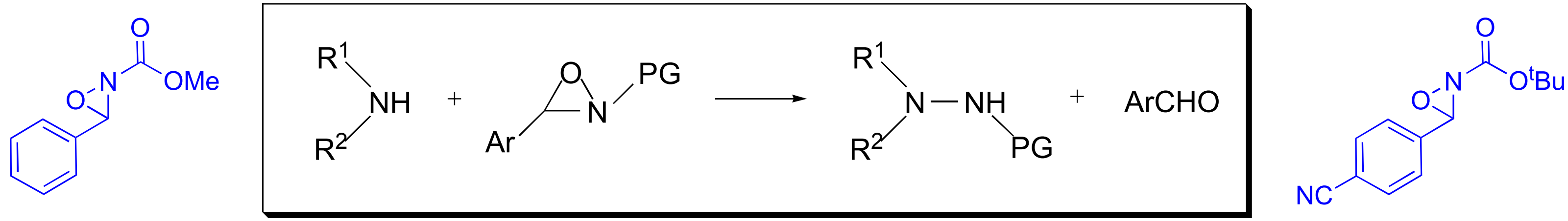
Outline

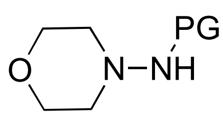
- Introduction
- HeteroatomTransfer Reactions
  - N vs O Transfer: Mechanistic Considerations
  - O Transfer Reactions
  - N Transfer Reactions
- Photocemical Rearrangement Reactions
- Conclusion

Amination of Ammonia:
A large Scale Industrial Process

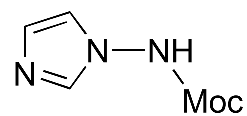


The First Stable N-Transfer Oxaziridines: N-N Bond Formation

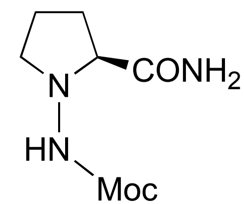




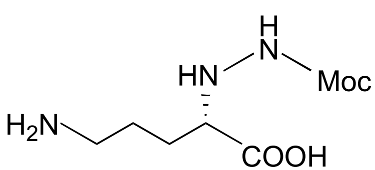
PG = Moc, 91 %
PG = Boc, 92%



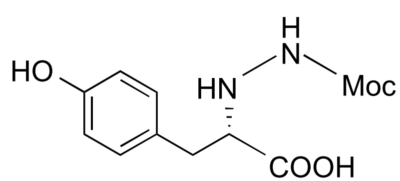
76%



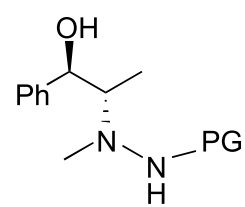
58 %



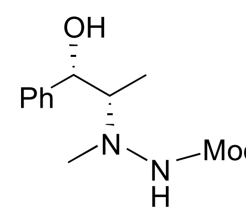
85 %



67 %



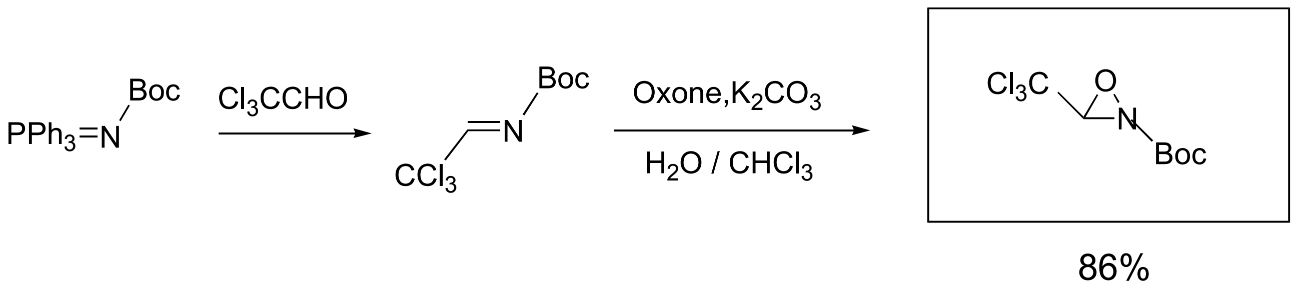
PG = Moc, 77%
PG = Boc, 70%

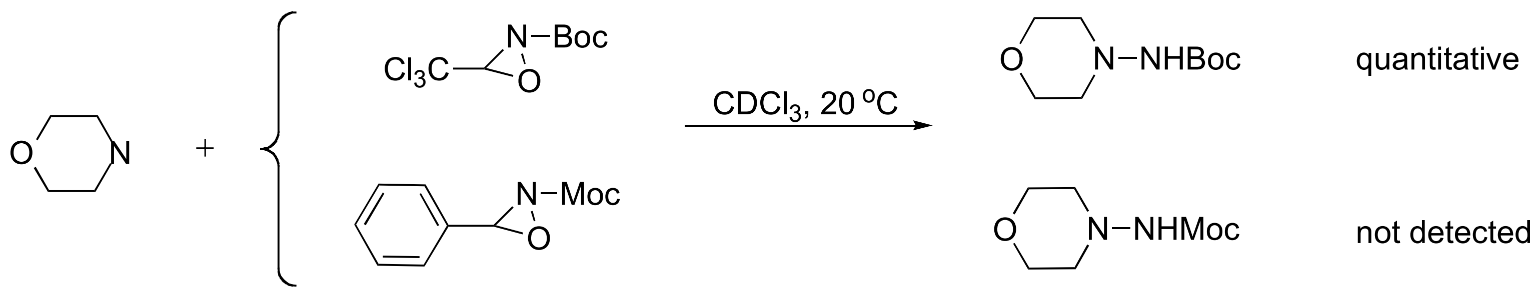


76 %

Vidal, J.; Guy, L.; Sterin, S.; Collet, A. *J. Org. Chem.* **1993,** *58, 4791-4793*
Vidal J.; Damestoy S.; Guy L.; Hanachi J,; Aubry A.; Collet A. *Chem. Eur J.* **1997**, *3*, 1691-1709

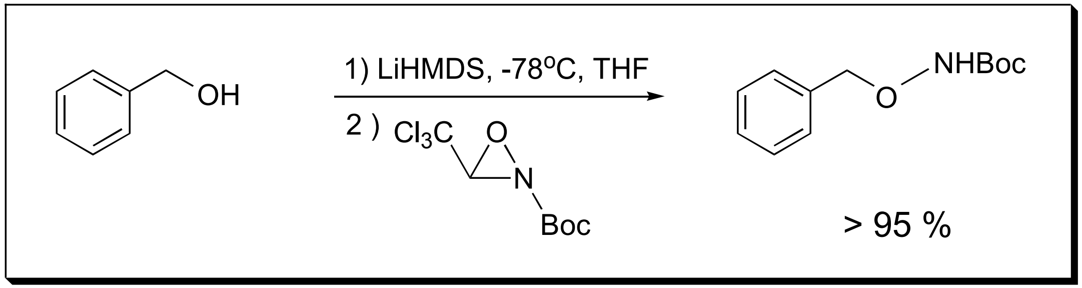
A More Powerful Reagent For Electrophilic Amination

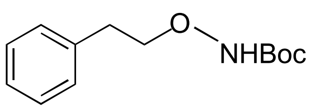




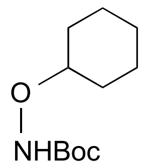
Vidal, J; Hannachi, J. C.; Hourdin, G.; Mulatier, J. C.; Collet, A. *Tetrahedron Lett.* **1998**, *39,* 8845-8848

O-Amination of Alcohols: Synthesis of Hydroxylamines

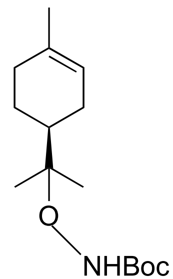




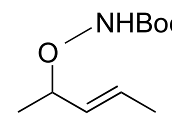
80 %



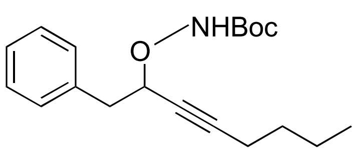
85 %



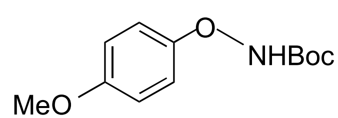
50 %



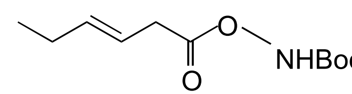
96 %



80 %



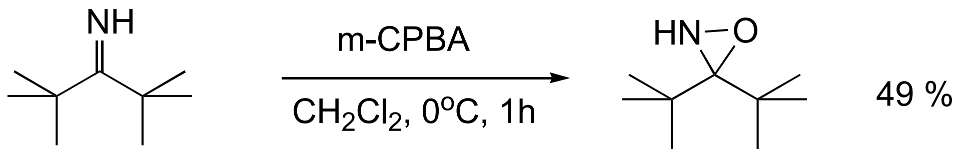
87 %

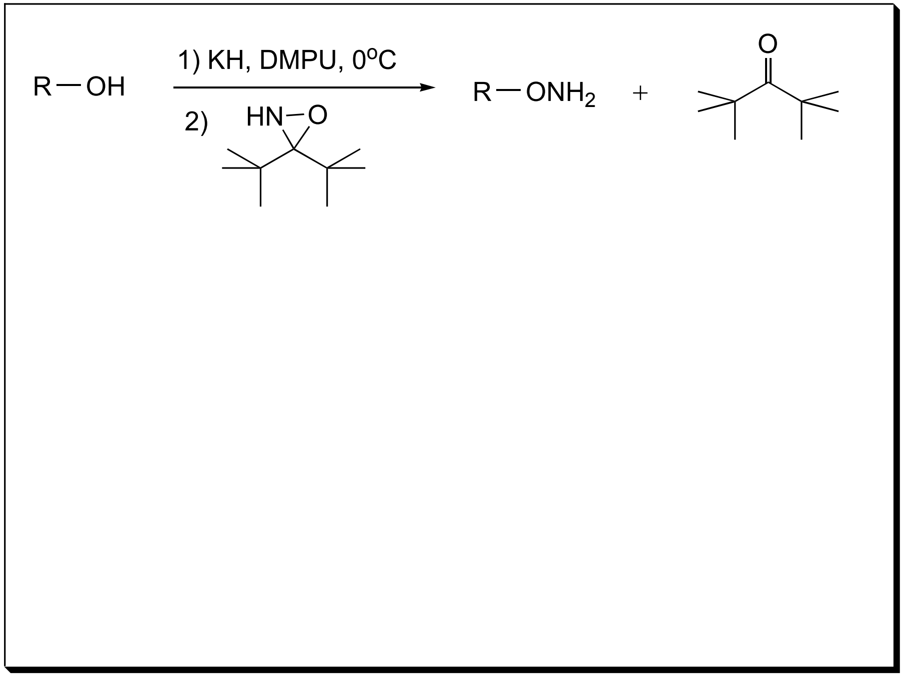


80 %

Foot, O. F.; Knight, W. *Chem. Comm.* **2000**, 975-976

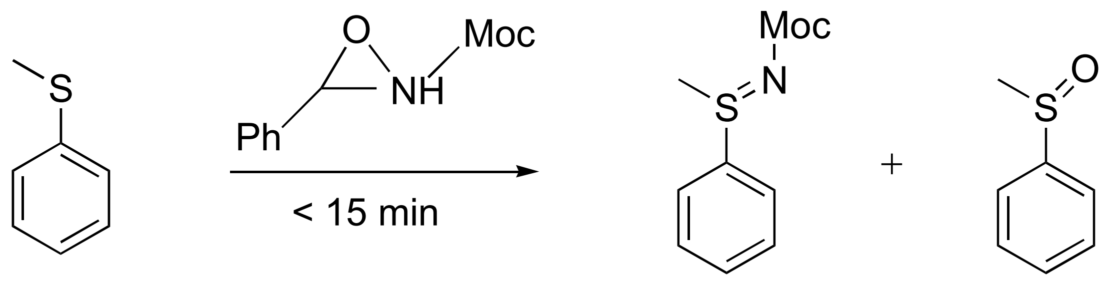
O-Amination of Alcohols: One-pot Preparation of Oximes





Choong, I. C.; Ellman, J. A. *J. Org. Chem.* **1999**, *64,* 6528-6529

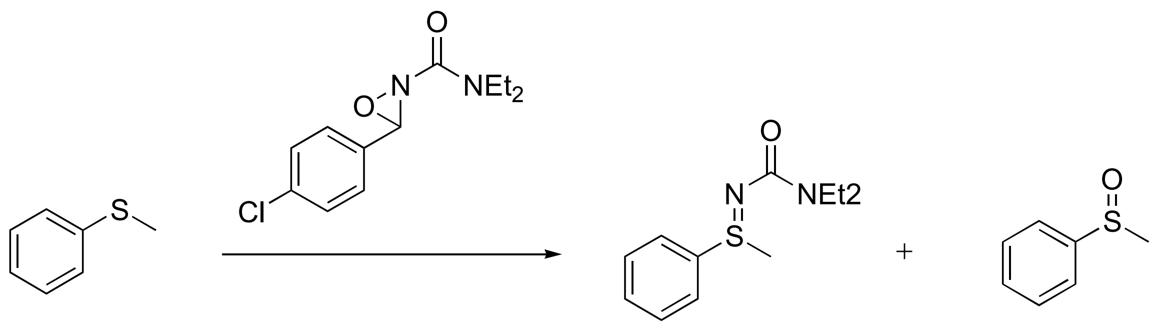
S-Amination : O-Transfer is a Problem



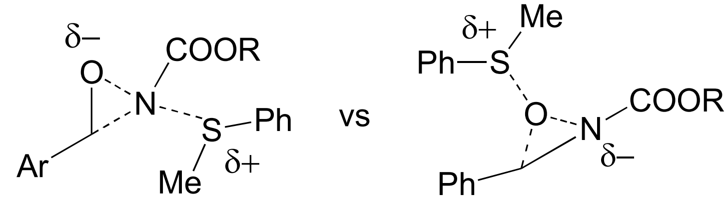
Solvent	T (°C)	Amination/ Oxidation
$CDCl_3$	19	34 / 66
$CDCl_3$	0	45 / 55
$CDCl_3$	-34	52 / 48
CH_3CN	19	48 / 52
CH_3CN	0	58 / 42
CH_3CN	-35	67 / 33

Vidal J.; Damestoy S.; Guy L.; Hanachi J,; Aubry A.; Collet A. *Chem. Eur J.* **1997**, *3*, 1691-1709

Improved Control of N vs O Transfer to S-Nucleophiles



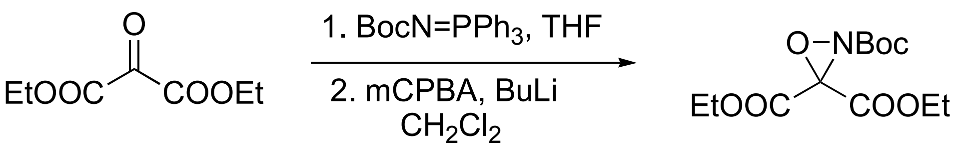
Solvent	Temp. °C	N/O
Toluene	19	<1/10
Toluene	-40	1/3
THF	19	1/4
THF	-40	2/3
MeOH	19	3/1
MeOH	-30	7/1
CF_3CH_2OH	19	10/1
CF_3CH_2OH	-40	>10/1



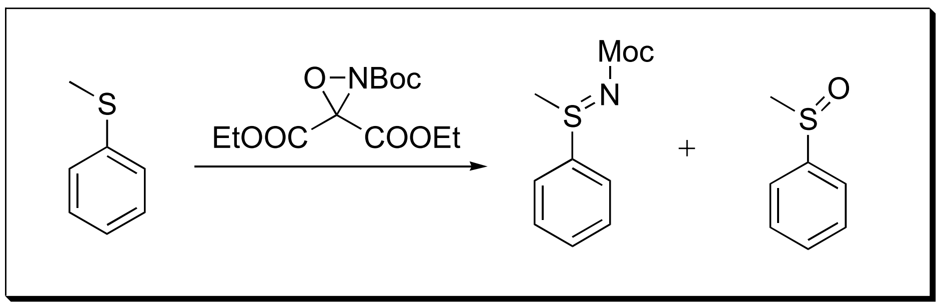
(more polar TS)

Armstrong, A.; Edmonds, I. D.; Swarbrick, M. E. *Tetrahedron Lett.* **2003**, *44*, 5335-5338

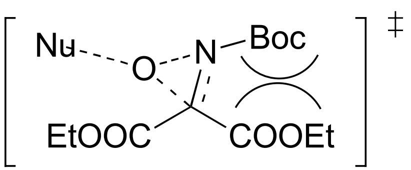
High Degree of N-Transfer with a Novel Oxaziridine



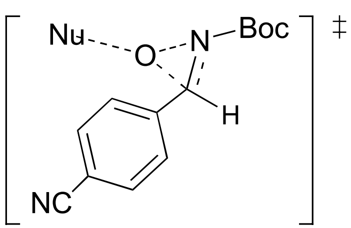
50 %



Transition States for Byproduct's Formation:



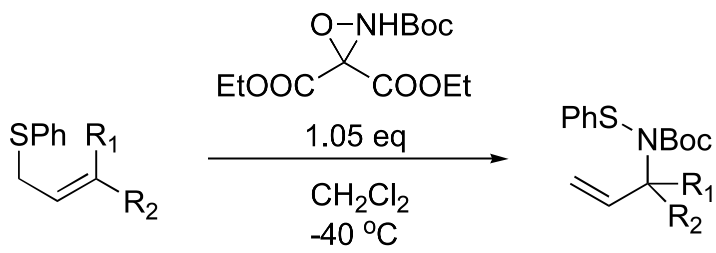
(less favored)

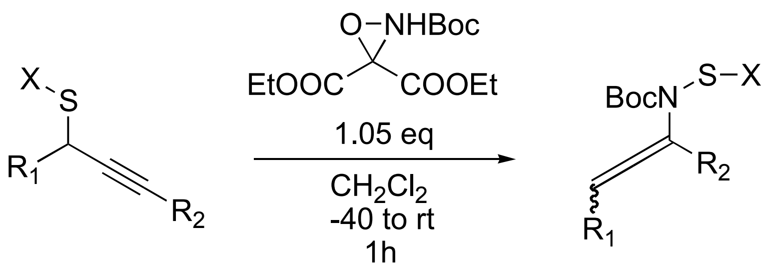


Solvent	T (°C)	N/O
$CDCl_3$	10	90/10
$CDCl_3$	0	95/5
$CDCl_3$	-40	>98/2

Armstrong, A.; Cooke, R. S. *Chem. Comm*. **2002**, 904-905

Tandem Amination of Sulfides / [2,3]-sigmatropic rearrangement





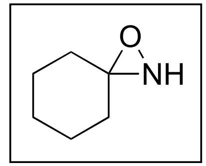
R_1	R_2	Yield (%)
H	Me	94
Me	Me	93
H	Ph	73
H	COOMe	85

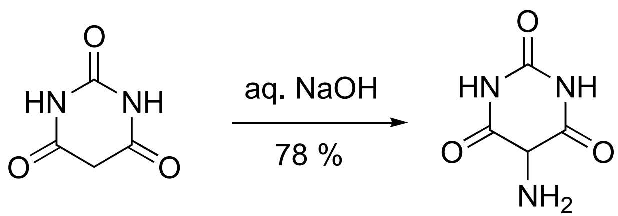
X	R_1	R_2	Yield (%)
Ph	H	I	85
Ph	H	COOtBu	66
Ph	H	Ph	88
N-hexyl	Me	Me	13

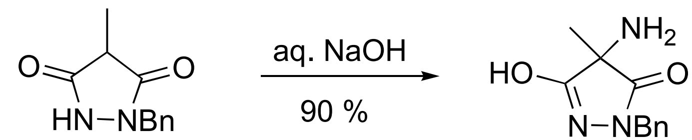
Armstrong, A.; Cooke, R. S. *Chem. Comm*. **2002**, 904-905

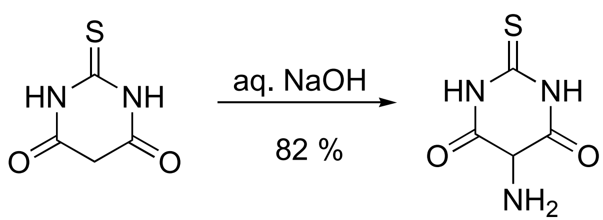
Armstrong, A.; Cooke, R. S.; Shanahan, S. E. *Org. Biomol. Chem*. **2003**, *1*, 3142-3143

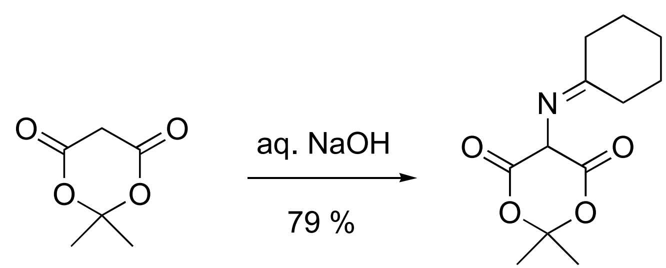
C-Amination of Enolates with N-H Oxaziridines





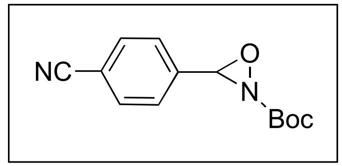




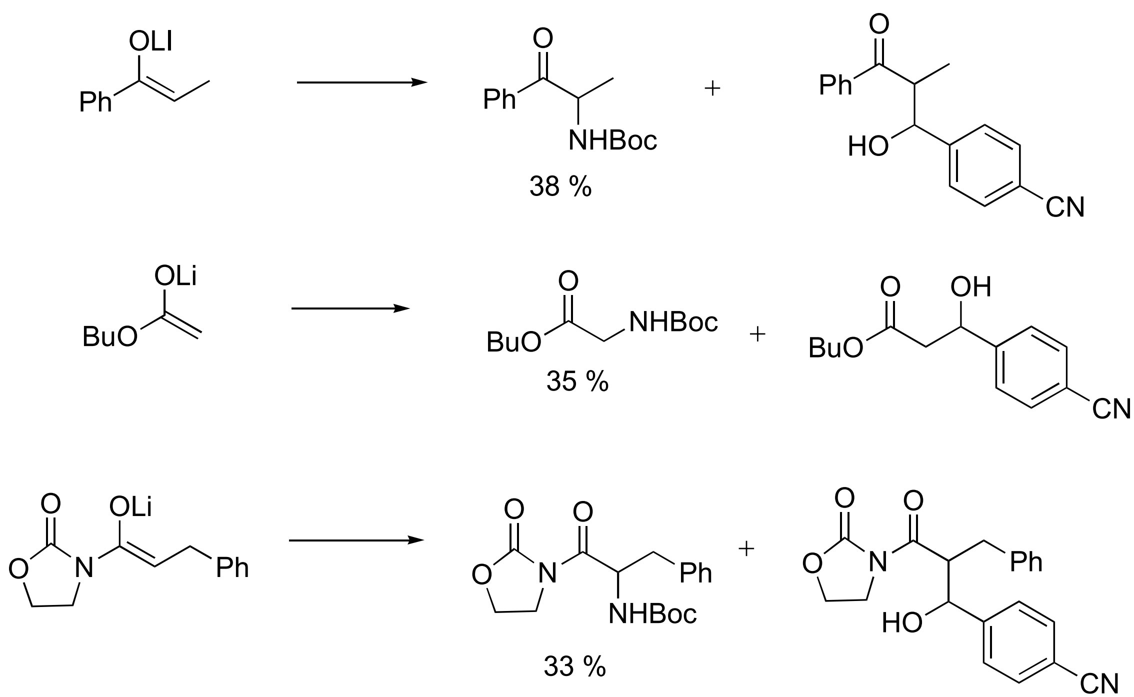


Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327-341

Amination of Enolates: Aldol Addition is Competing



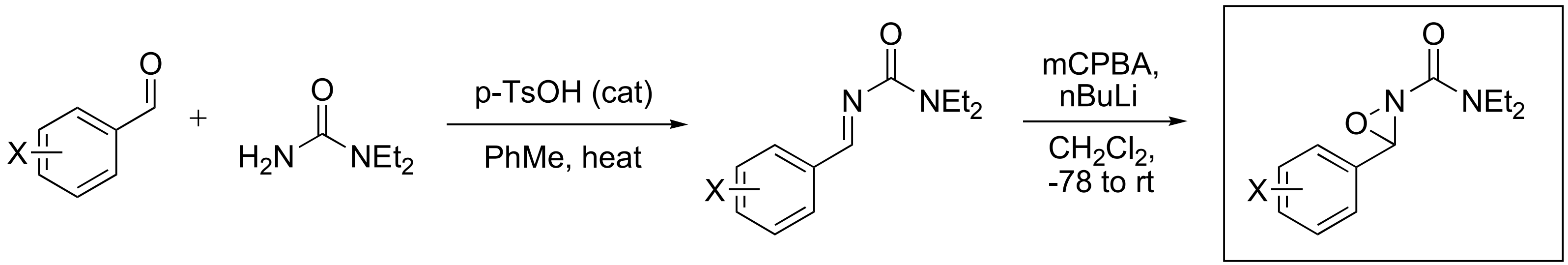
major problem: aldol addition



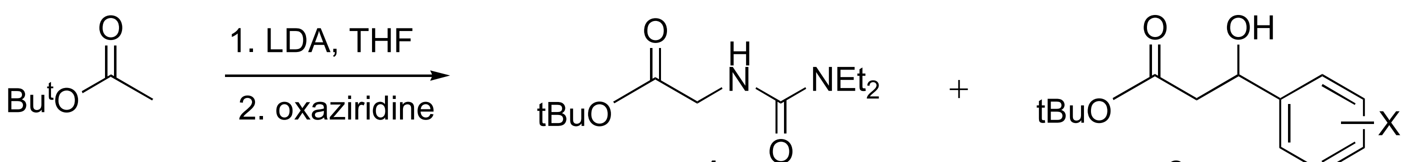
“significant amounts”

Vidal, J.; Guy, L.; Sterin, S.; Collet, A. *J. Org. Chem.* **1993**, *58,* 4791-4793

Can *ortho*-substituted Oxaziridines Slow Down the Aldol Addition ?



> 92 % trans

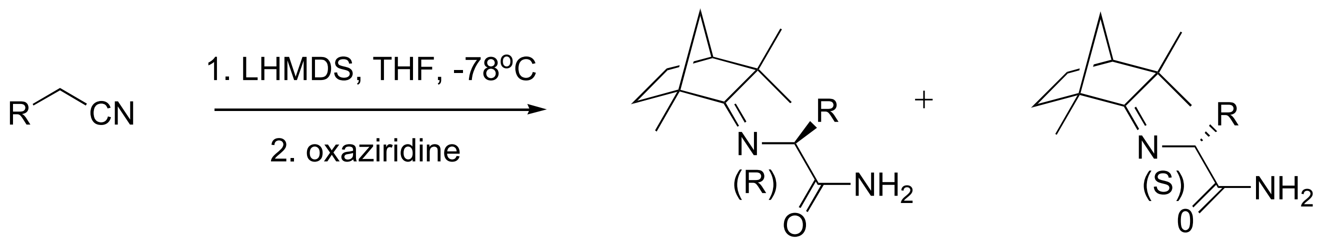


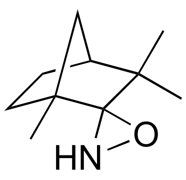
1 2

X	**1**	**2**
4-CN	39	20
2-Cl	-	-
2,6-diCl	-	-
4-Cl	31	10
2-CN	55	7

Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron Lett.* **2000**, *41*, 2247-2251

Asymmetric Amination of Carbanions

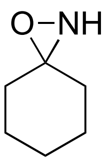




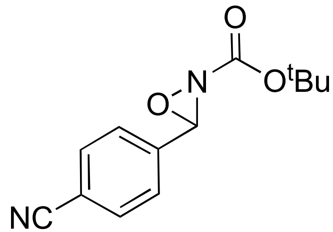
R	Time (h)	Yield (%)	de (%)
Ph	5	55	50
2-naphthyl	9	31	52
1-naphthyl	4	48	33
CN	7	57	23

Page, P. B.; Limousin, C.; Murrell, V. L. *J. Org. Chem.* **2002**, *67*, 7787-7796

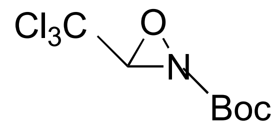
Summary for N-Transfer



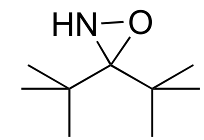
Unstable



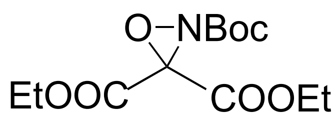
N-Amination



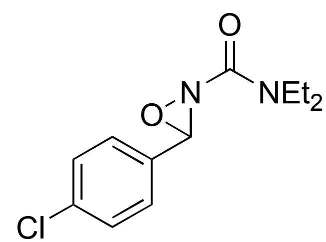
N-Amination,
O-Amination



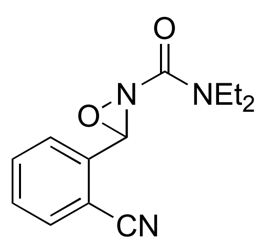
O-Amination



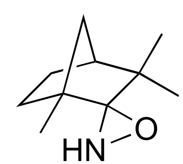
S-Amination



S-Amination



Enolate Amination



Carbanion Amination

Outline

- Introduction
- Heteroatom Transfer Reactions
  - N vs O Transfer: Mechanistic Considerations
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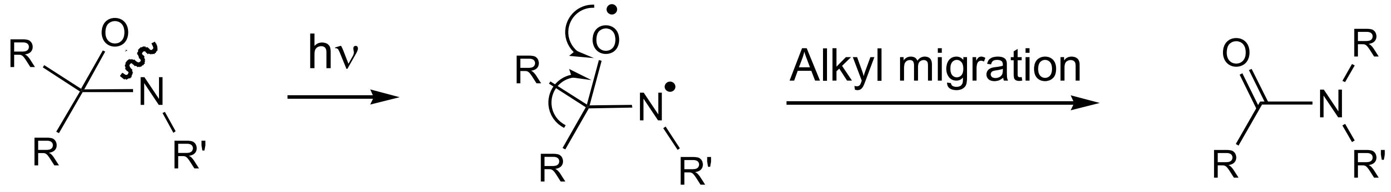
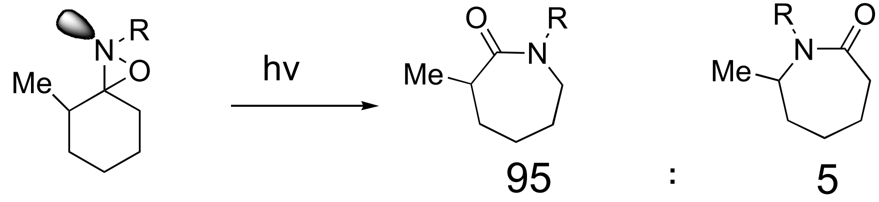
  - N Transfer Reactions
- Photochemical Rearrangement Reactions
- Conclusion

Photochemical Rearrangements: General Pattern

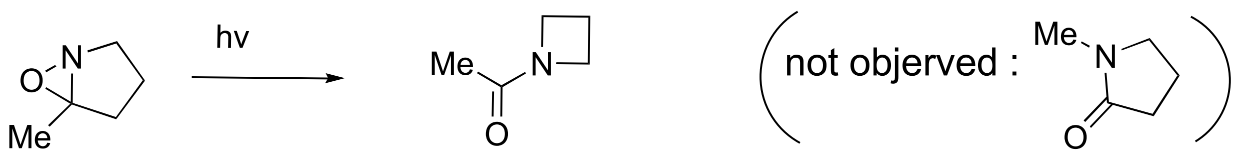


Photochemical Rearrangement of Oxaziridines: Puzzling selectivity !

1)



2)

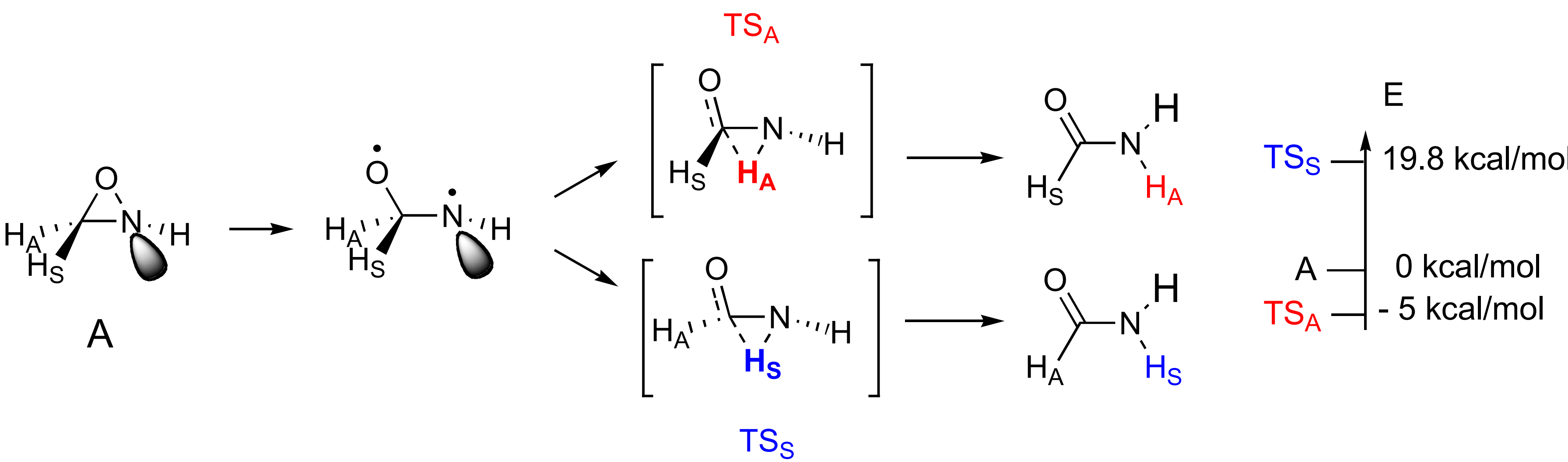


(more strained product predominates)

Oliveros, E.; Riviere, M.; Lattes, A. *Nouv. J. Chim.* **1979**, *3,* 739-753

Rarello, J.; Riviere, M.; Desherces, E.; Lattes, A. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1971**, 273, 1097-1100

Theoretical Studies Gave the Answer



Stepwise mechanism:

a) Photochemical breaking of the N-O bond

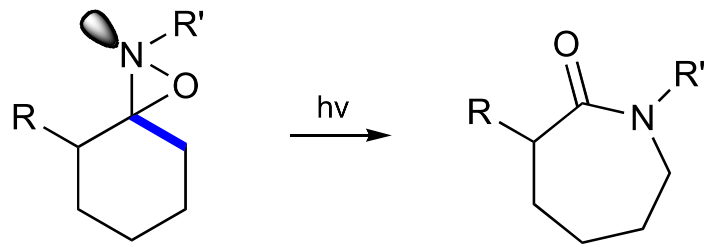
b) H (or R) migration to N

The bond anti to the N-lone pair is cleaved more easily

Oliveros, E.; Riviere, M.; Malrieu, J. P.; Teichteil, C *J. Am. Chem. Soc.* **1979**, *101*, 318-322

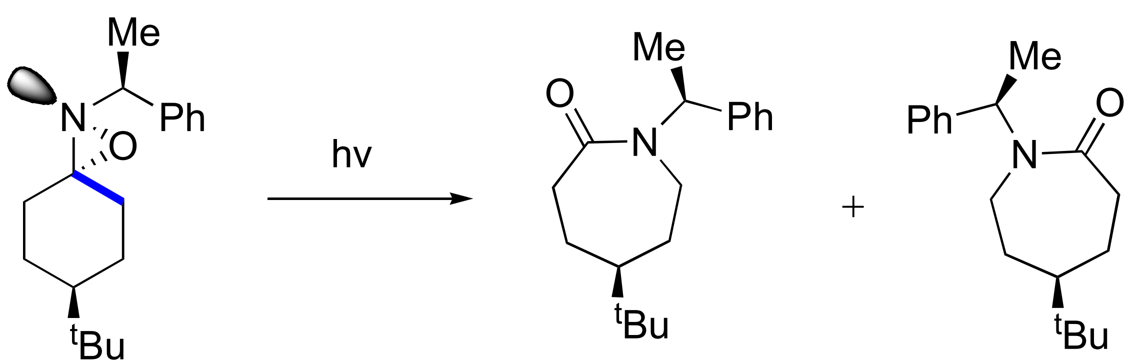
Basic Concepts that can be Exploited

a)



➡ **Migration of less substituted group**

b)

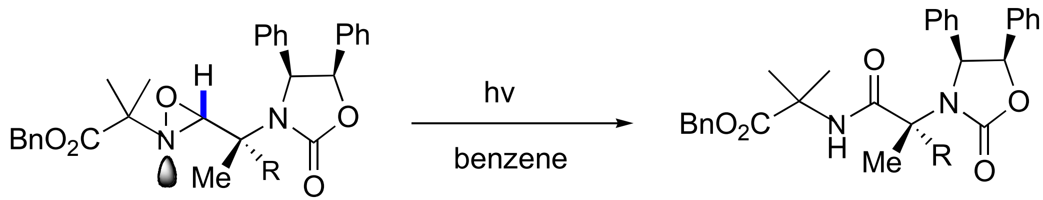


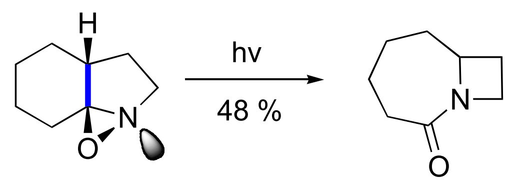
13 : 1

➡ **Asymmetric Ring Expansion**

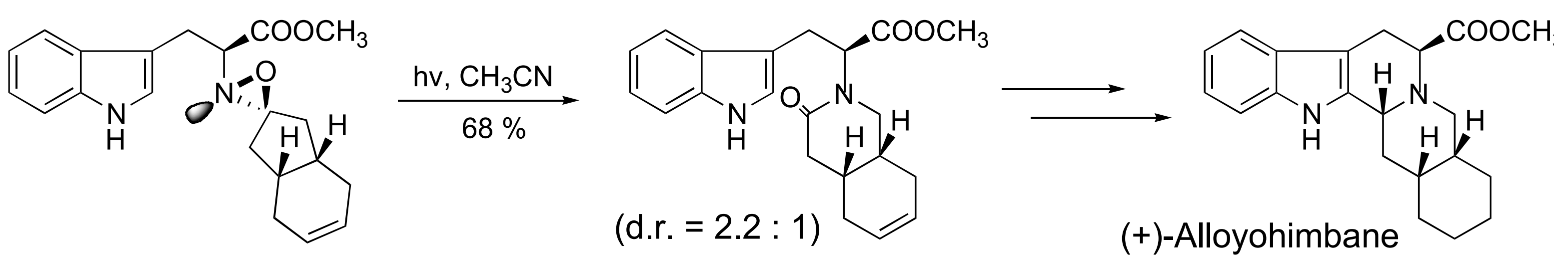
Lattes, A.; Oliveros, E. *J. Am. Chem. Soc.* **1982**, *104*, 3929-3934

Applications of Photochemical rearrangement of Oxaziridines





(rarely synthesized bicyclic skeleton)



Wenglowsky, S.; Hegedus, L. *J. Am. Chem. Soc.* **1998**, *120*, 12468-12473

Bourguet. E.; Baneres, J. L.; Girard, J. P.; Parello, J.; Vidal, J. P.; Lusinchi, S.; Declercq, J. P. *Org. Lett.* **2001**, *3*, 3067-3070

Aube, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009-9018

Conclusions

Oxaziridines show a diversity in reactivity that can be very useful in Organic Synthesis:

- Oxaziridinium salts are systems that can be further developped in catalytic asymmetric epoxidations.

- Perfluorinated oxaziridines' reactivity should be explored more, especially in C-H activation reactions.

- N-transfer oxaziridines are very useful for electrophilic amination processes.

- Oxaziridines' photochemical rearrangement is a valuable method for lactam synthesis.

Thanks-Giving To:

Proffesor W. D. Wulff

<u>Wulff's Group:</u>

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