A Novel Method of Pyrrolidine Synthesis

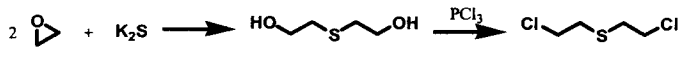
Martin D. Eastgate

Supervisor: Dr S. Warren

University of Cambridge

Episulfonium or Thiiranium ions

- Mustard gas - Meyer 1886

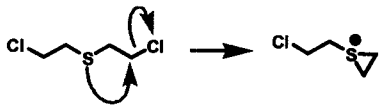


- First used in the great War during 1917
- Takes ~12h to take effect
- Only a small amount required in a shell as it can survive in the earth for up to four weeks
- Takes, on average, four to five weeks to die
- Attacks - Bronchial tubes
  - Mucus membranes
  - Cross links DNA

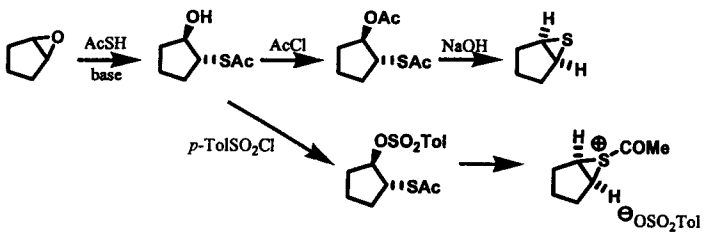
V. Meyer, *Ber. Deutsche chem.*, 1886, **19**, 3260

Episulfonium or Thiiranium ions

- Mustard gas - Meyer 1886



- Halonium ions first proposed in 1937 by Roberts
- First spectroscopically observed episulfonium ion by Goodman in 1958 (first halonium ion 1968)

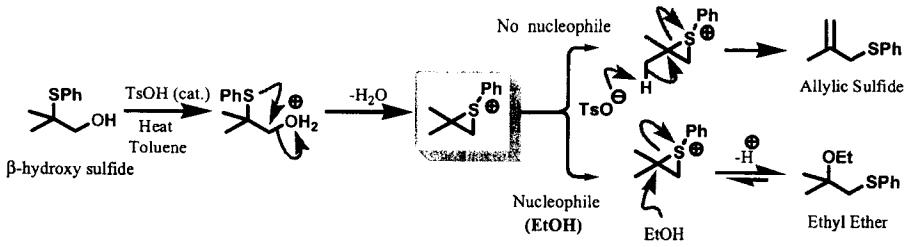


V. Meyer, *Ber. Deutsche chem.*, 1886, **19**, 3260

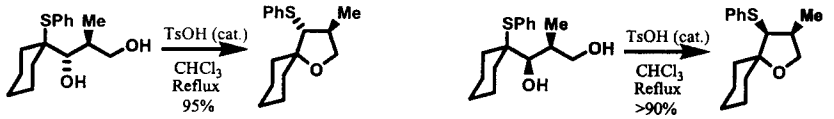
I. Roberts, G. E. Kimbal, *J. Am. Chem. Soc.*, 1937, **59**, 947

L. Goodman, A. Benitez, B. R. Baker, *J. Am. Chem. Soc.*, 1958, **80**, 1680

Episulfonium ions and THFs



P. Brownbridge

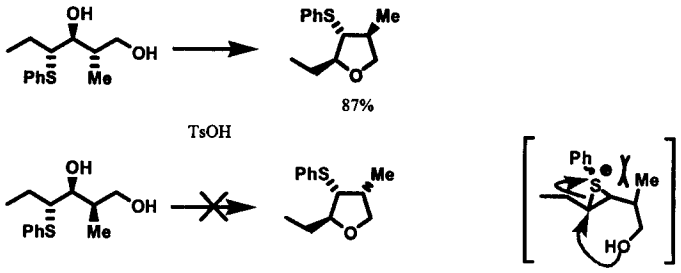


V. Aggarwal

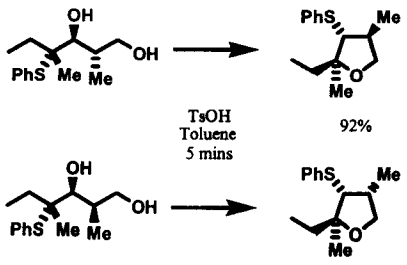
P. Brownbridge and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, 1977, 2272

V. Aggarwal, S. Warren *et al.*, *Tetrahedron Lett.*, 1988, **29**, 4885

Episulfonium ions and THFs



Chibale

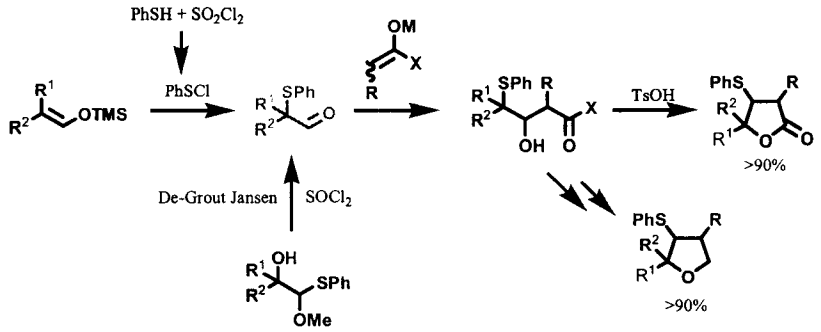


Aggarwal

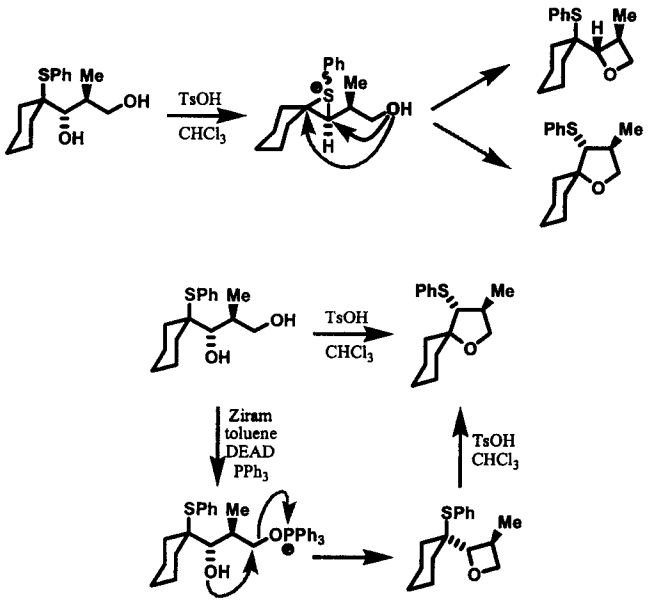
K. Chibale and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, 1996, 1935

Aggarwal *et al.*, *J. Chem. Soc. Perkin Trans 1.*, 2000, 533

Episulfonium ions, THFs and lactones

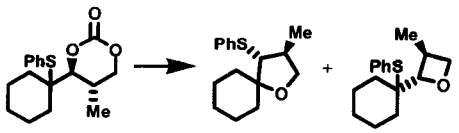


Episulfonium ions and THFs - Thermodynamic Control



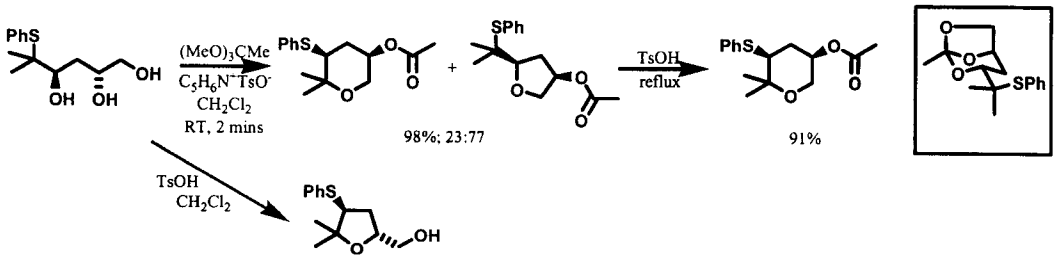
J. Eames and S. Warren, *Tet Lett*, 1996, 3525

Episulfonium ions and THFs - Kinetic Methods



82 : 18

Eames

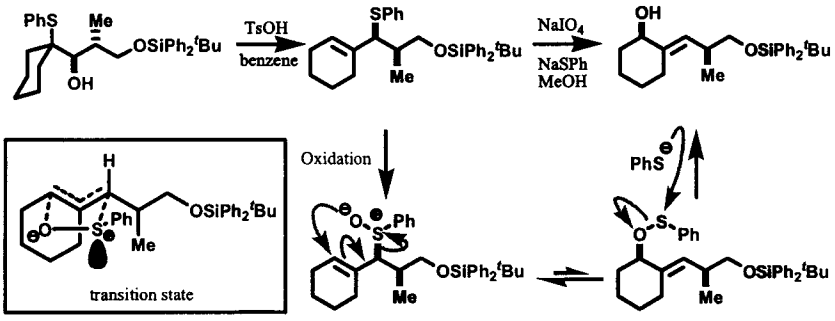


House

J. Eames and S. Warren, Unpublished work

D. House *et. al., Chem Commun.*, 2000, 1781

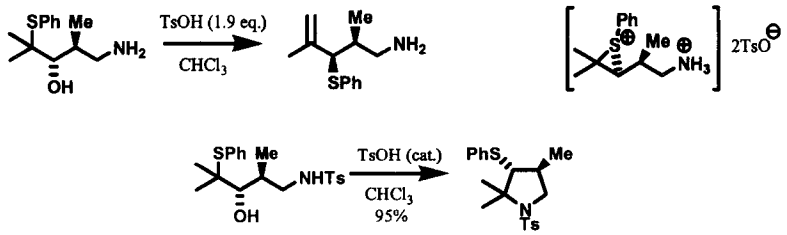
Episulfonium ions and the Evans-Mislow Rearrangement



V. Aggarwal

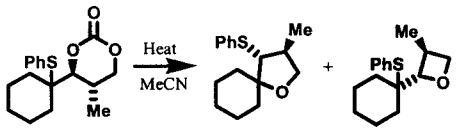
V. Aggarwal, S. Warren *et al.*, *Tetrahedron Lett.*, 1988, *29*, 4885

Pyrrolidines



Coldham

• **Is it possible to have *N*-protection with simultaneous *O*-activation ?**



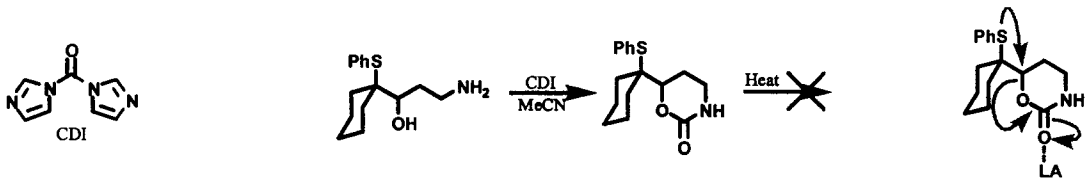
82 : 18

Eames

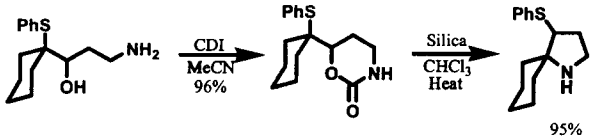
I. Coldham and S. Warren, *J. Chem. Soc. Perkin Trans. 1.*, 1993, 1637

J. Eames and S. Warren, Unpublished results

Pyrrolidines



Coldham



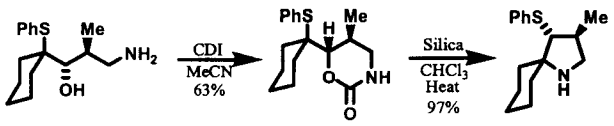
95%

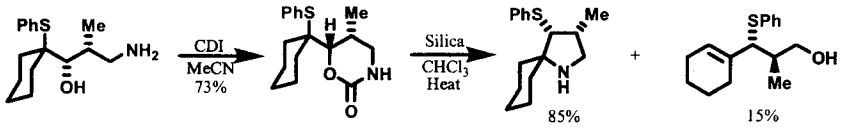
Caggiano

I. Coldham, *Unpublished Results*

L. Caggiano, D. J. Fox and S. Warren, *Chem. Commun.*, 2002, 2528

Pyrrolidines



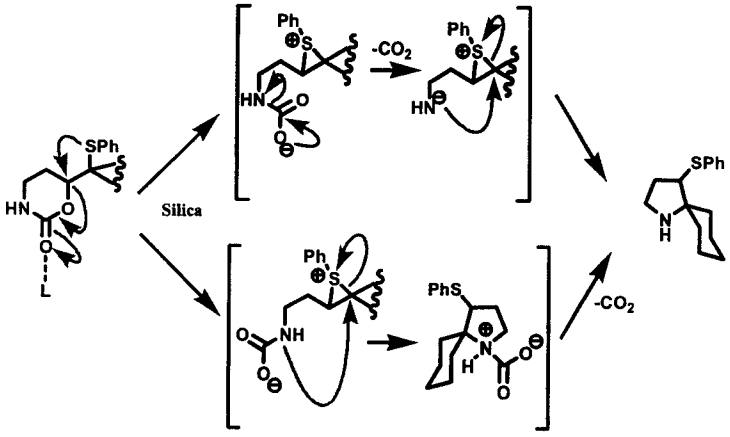


Caggiano

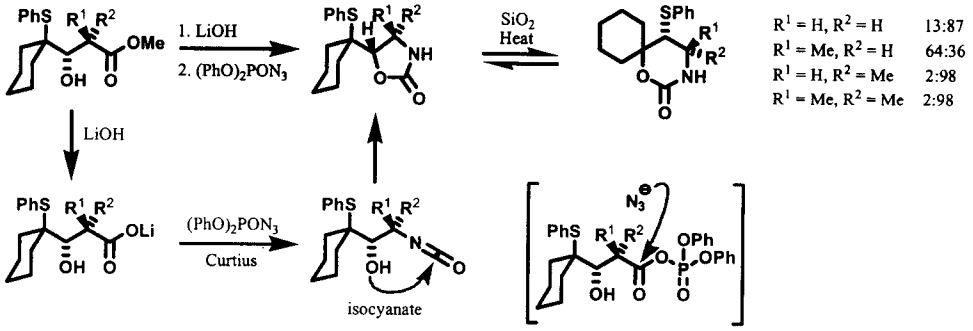
L. Caggiano, D. J. Fox and S. Warren, *Chem. Commun.*, 2002, 2528

L. Caggiano, *In Press*

Pyrrolidines

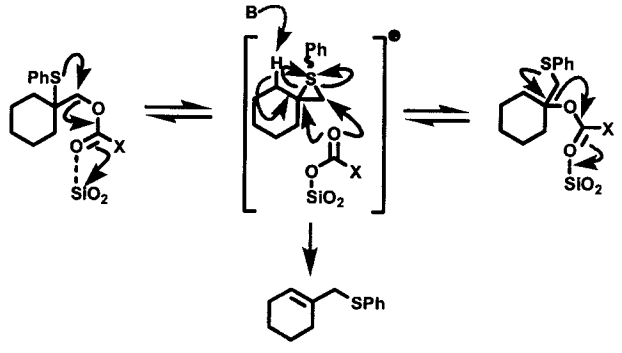


Pyrrolidines



L. Caggiano, J. Davies, D. Fox, D. Moody, S. Warren, *Chem. Commun.*, In Press

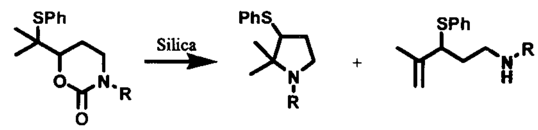
Pyrrolidines



- **X = Ph, NMe_2, OMe**

L. Caggiano, D. Fox, S. Warren, *Chem. Commun.*, 2002, 2528

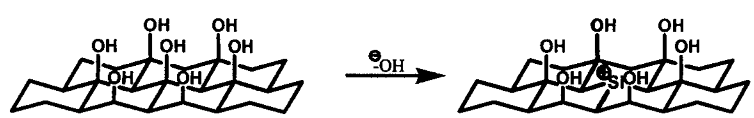
Pyrrolidines



R-Group	Pyrrolidine (yield, %)	Allylic Sufide (yield, %)
H	>95	0
Me	77	14
Bn	54	30
^{i}Pr	0	88

L. Caggiano, J. Davies, D. Fox, D. Moody, S. Warren, *Chem. Commun.,* In Press

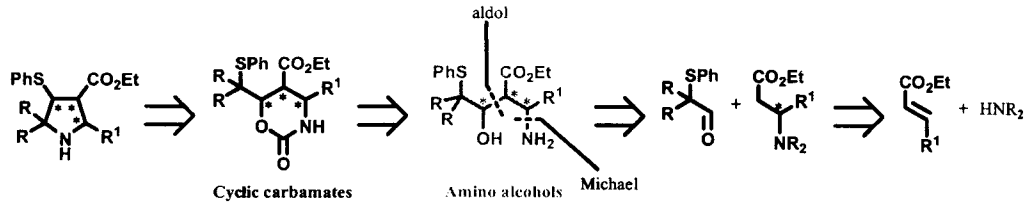
Pyrrolidines



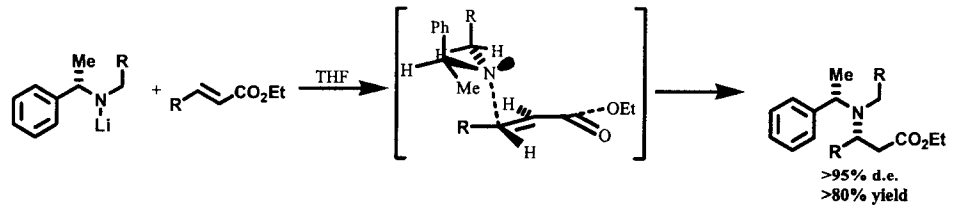
C. Brinker *et al., J. Non-Crystalline Solids*, 1990, 120, 26

H. Kamiya *et al., J. Am. Ceramic Soc.*, 2000, 83, 287

Disconnection



• **Davies style Michael additions of lithium α-methylbenzyl amides proceed with high diastereoselectivity**

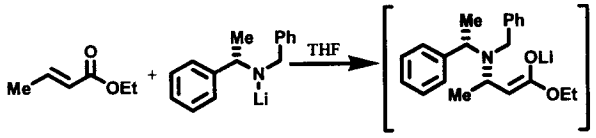


S. G. Davies

S. G. Davies and D. R. Fenwick, *J. Chem. Soc. Chem. Commun.*, 1995, 1109

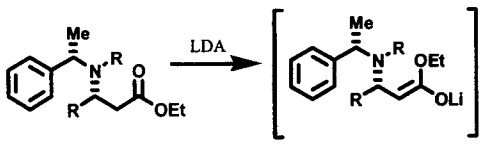
Aldol Chemistry

Tandem Procedure



***Z*-Enolate**

Step-wise Procedure

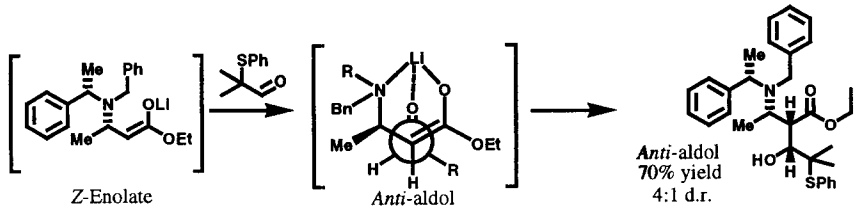


***E*-Enolate**

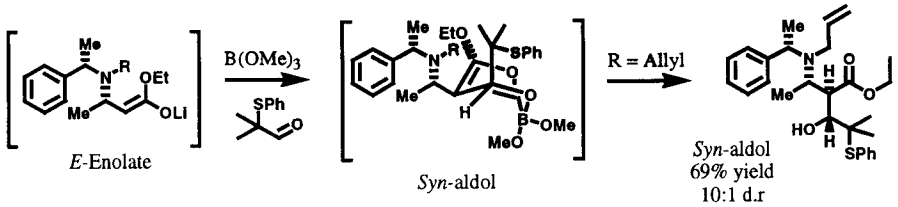
N. Asao, T. Uyehara and Y. Yamamoto, *Tetrahedron*, 1990, 46, 4563

Aldol Chemistry

Tandem Procedure



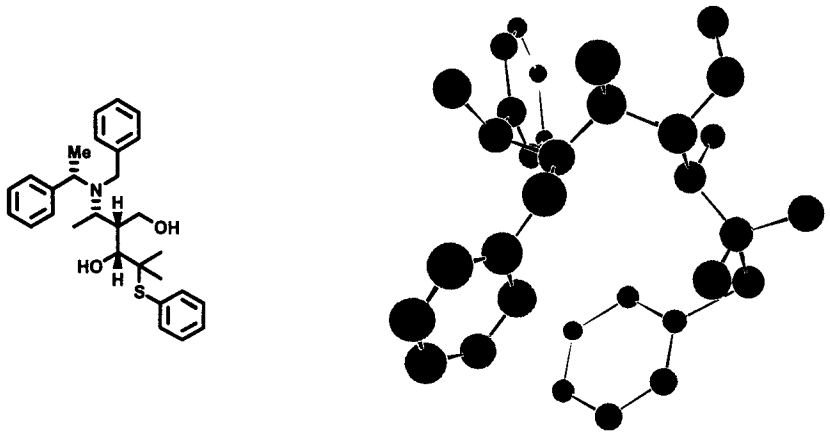
Step-wise Procedure



I. C. Baldwin, P. Briner, M. D. Eastgate, D. J. Fox and S. Warren, *Organic Letters,* 2002, **4**, 4381

N. Asao, T. Uyehara and Y. Yamamoto, *Tetrahedron,* 1990, **46**, 4563

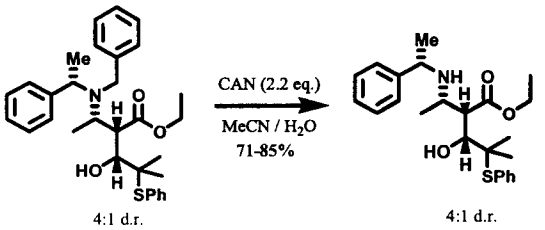
Aldol Chemistry



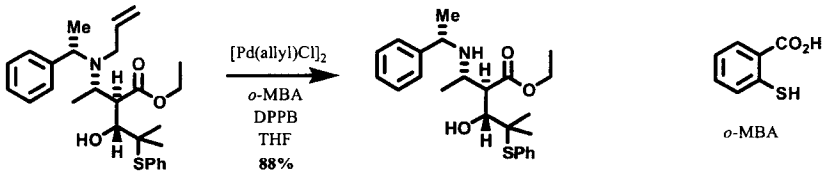
I. C. Baldwin, P. Briner, M. D. Eastgate, D. J. Fox and S. Warren, *Organic Letters,* 2002, **4**, 4381

Amino Alcohol Synthesis

• **Mono-debenzylation by ceric ammonium nitrate (CAN) (S. G. Davies)**



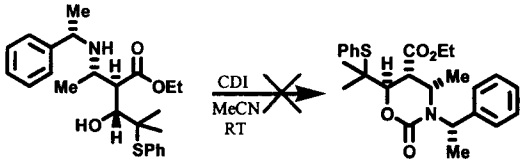
• **Deallylation (J. P. Genet)**

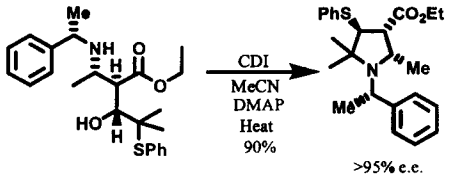


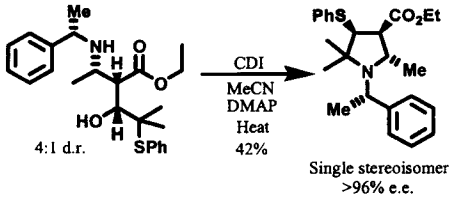
S. G. Davies *et al, Chem. Commun.*, 2000, 337

J. P. Genet *et al, Tetrahedron Lett.*, 1995, 1267

Pyrrolidine Synthesis

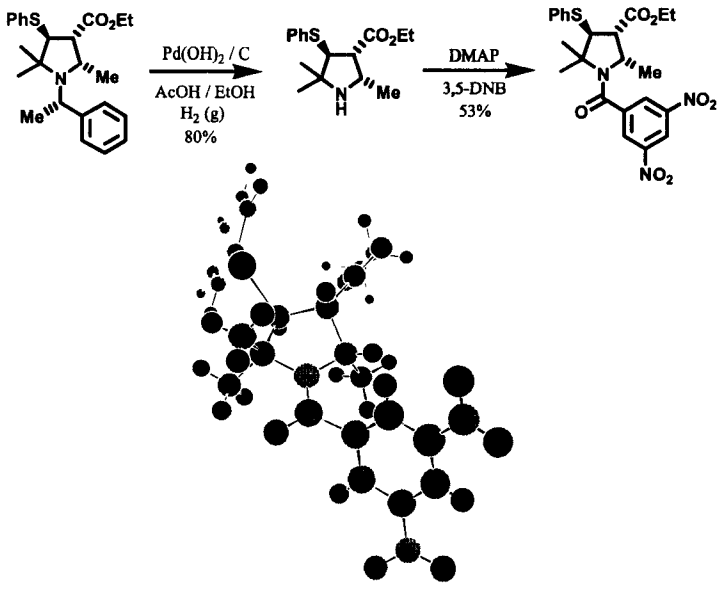




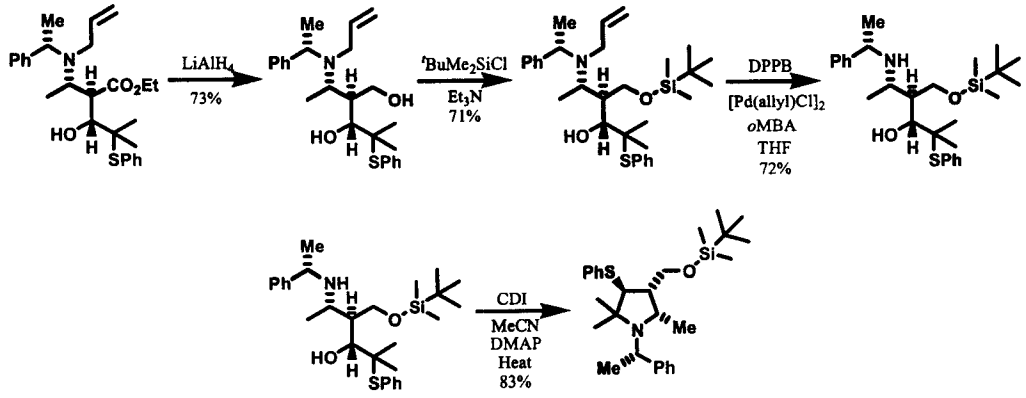


I. C. Baldwin, P. Briner, M. D. Eastgate, D. J. Fox and S. Warren, *Organic Letters*, 2002, 4, 4381

Pyrrolidine Synthesis

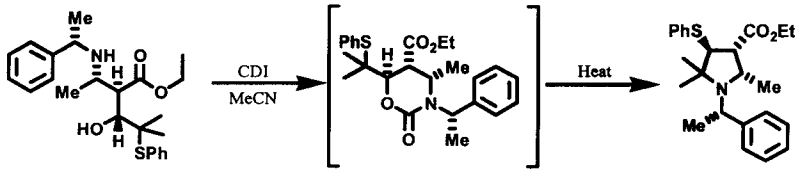


Pyrrolidine Synthesis



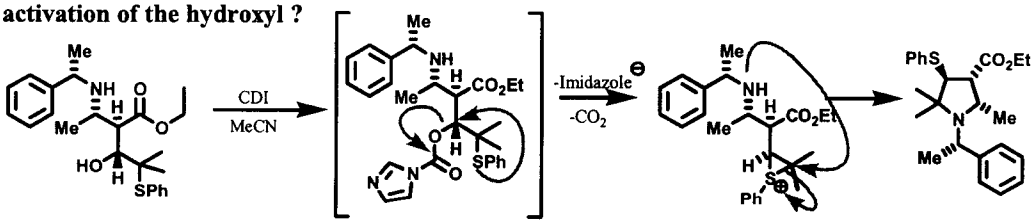
Mechanism

• **Thermal instability of the cyclic carbamate ?**



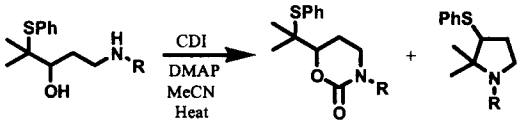
not observed

• **Selective activation of the hydroxyl ?**



Imidazolide

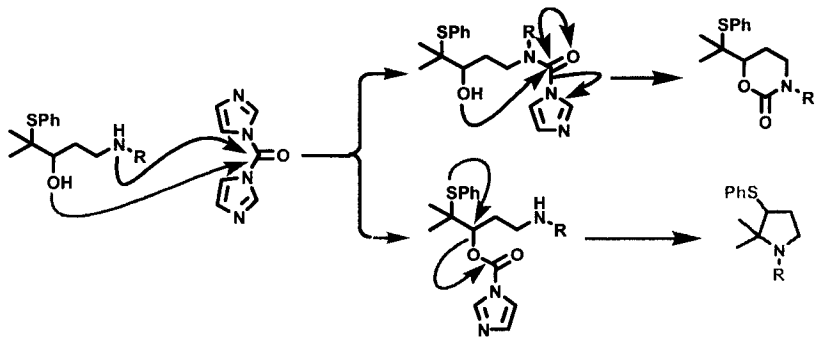
Mechanism



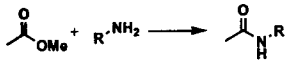
R-Group	Carbamate	Pyrrolidine
Me	**>99**	**<1**
Et	**>99**	**<1**
Benzyl	**80**	**20**
^{i}Pr	**20**	**80**
α-Methyl benzyl	**<1**	**>99**
Benzhydryl (Ph_2CH)	**<1**	**>99**

Done in collaboration with B. Oelze

Mechanism



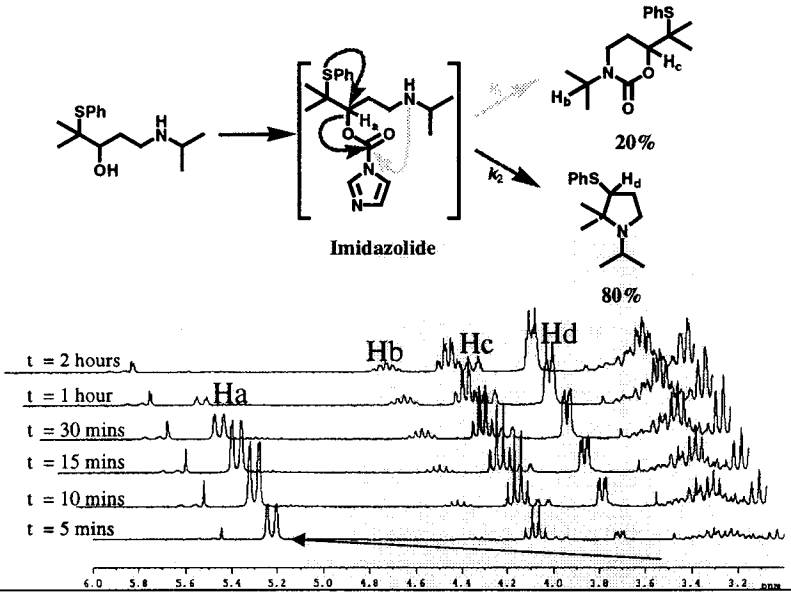
Mechanism

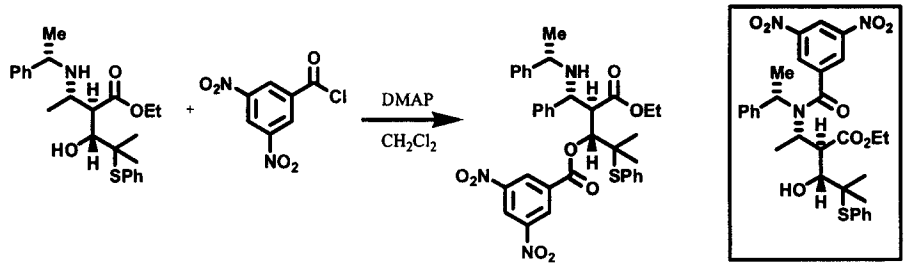


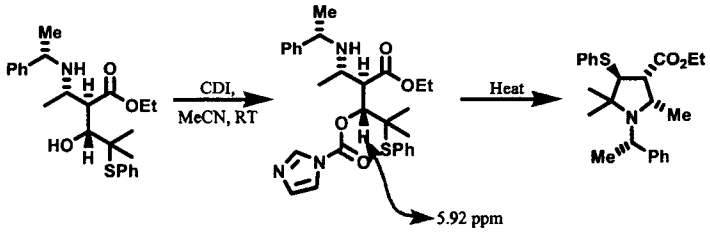
R-Group	pK_a	Relative Rate
Methyl	10.64	100
Ethyl	10.67	13.0
^{n}Propyl	10.58	10.3
^{n}Butyl	10.58	12.4
Allyl	9.49	2.42
Benzyl	9.34	1.93
^{t}Butyl	10.42	5.10
^{i}Propyl	10.63	0.495

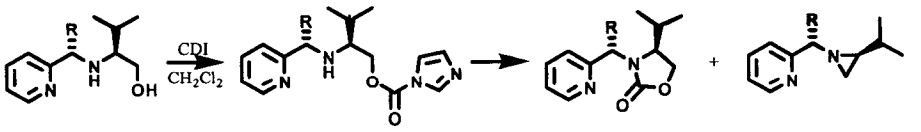
E. Arnet, J. G. Miller, A. R. Day, *J. Am. Chem. Soc.*, 1950, **72**, 5635

Mechanism: NMR Kinetics





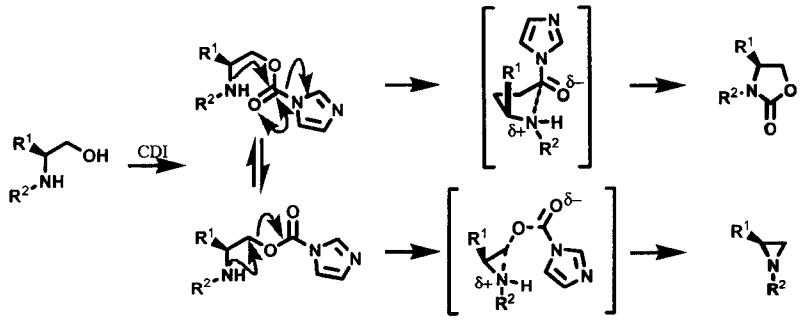




R = allyl
R = ^{i}Pr
R = $EtMe_2C$

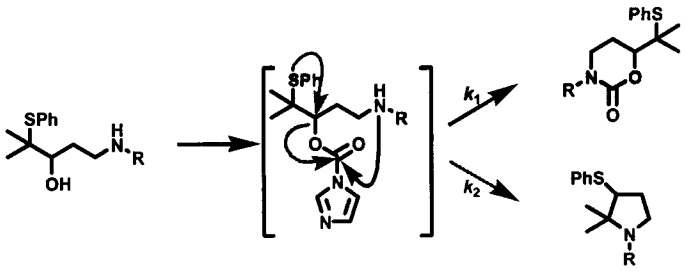
R = allyl, 35% yield
R = ^{i}Pr, 0% yield
R = $EtMe_2C$, 25% yield

R = allyl, 52% yield
R = ^{i}Pr, 65% yield
R = $EtMe_2C$, 31% yield



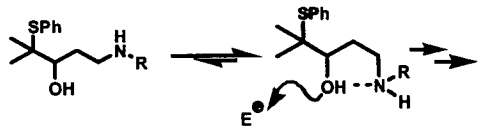
D. Savoia *et al., Eur. J. Org. Chem.*, 2001, 517

Mechanism



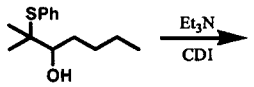
R = benzyl, isopropyl, α-methylbenzyl and benzhydryl

- **There is a kinetic isotope effect, for the formation of imidazolide, of $k_H / k_D = 2$**
- **[Imidazole] affects only the rate of carbamate formation**
- **This is consistent with *internal general base catalysis***

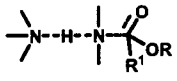


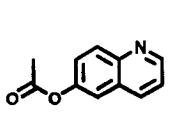
Internal general base catalysis

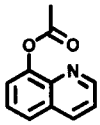
- **E.M. = ~15**



Mechanism

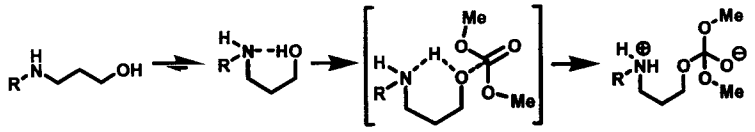




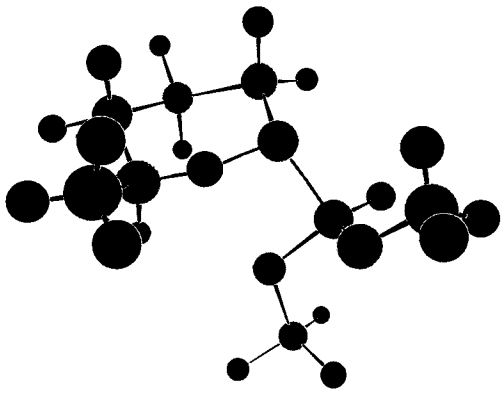


T. C. Bruice, S. M. Felton, *J. Am. Chem. Soc.*, 1969, **91**, 2799

Molecular Modelling



Derivative	ΔH_{act} / kJmol^{-1}
N-Me	201.23
N-^{i}Pr	196.80

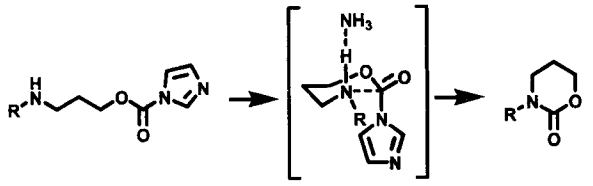


*p*Ka - $MeNH_2$ 10.64

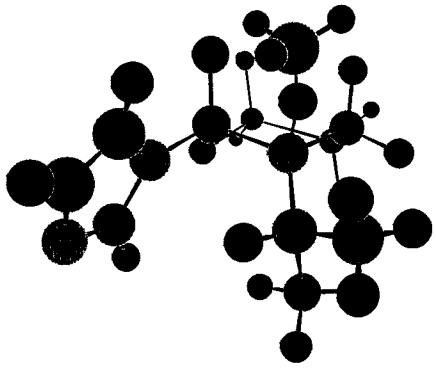
*p*Ka - $^{i}PrNH_2$ 10.63

at the 6-31(d,p)++ level

Molecular Modelling



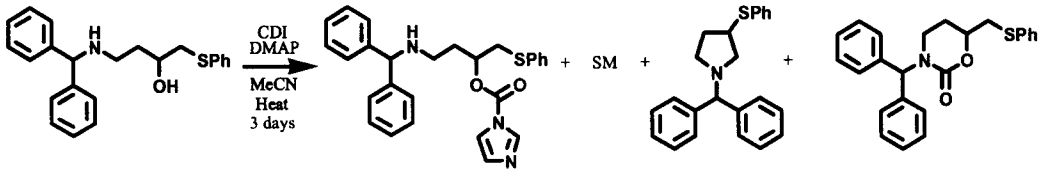
Derivative	ΔH_{act} /kJmol^{-1}
N-Me	205.17
N-^{i}Pr	220.71



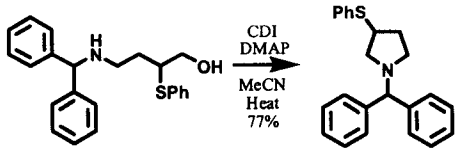
This represents an ~400 fold decrease in rate

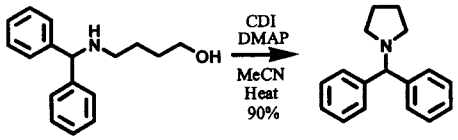
at the 6-31(d,p)++ level

Structural Modifications

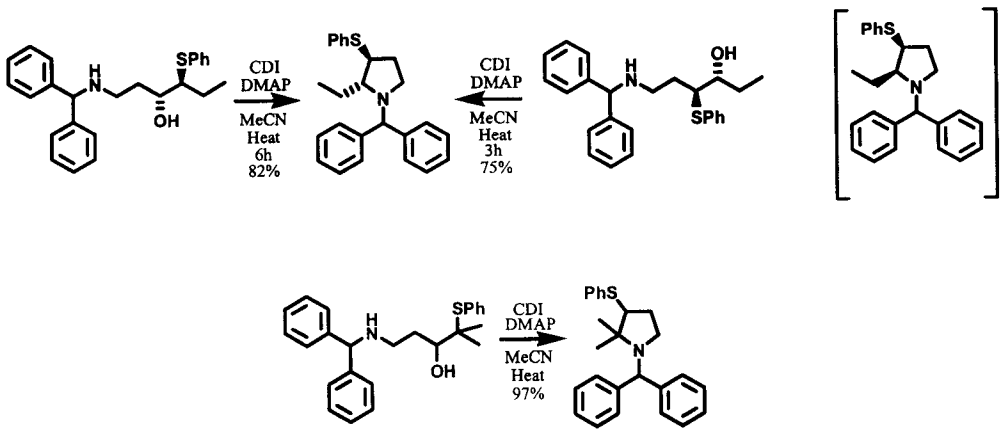


8 : 4 : 2 : 1 ratio from the ^{1}H-NMR spectrum of the crude reaction product.

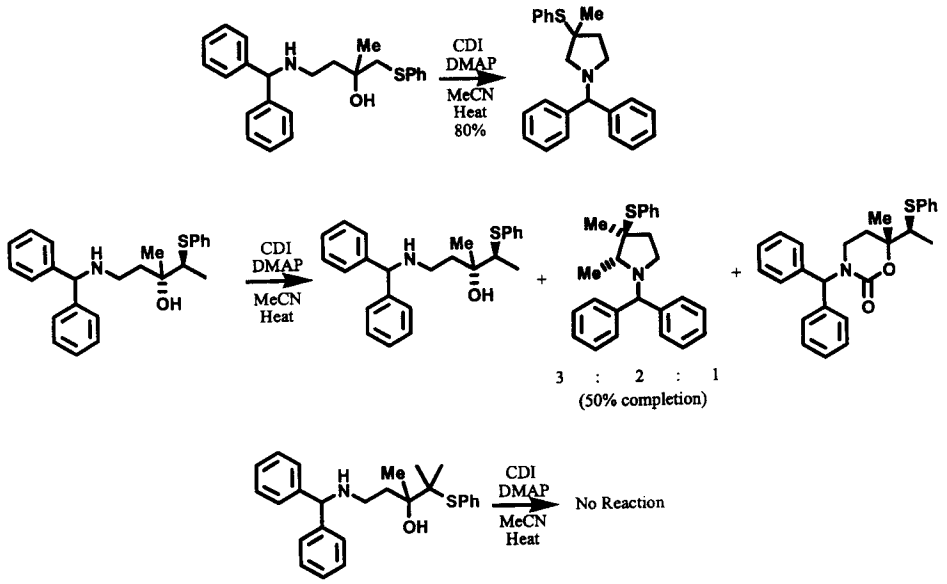




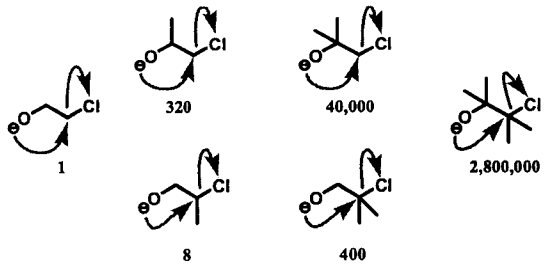
Structural Modifications



Structural Modifications

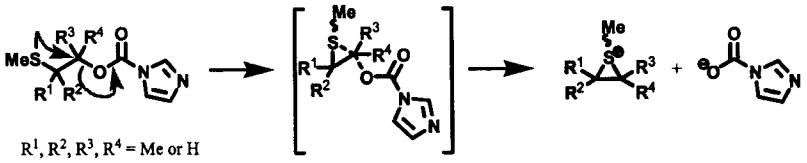


Thorpe-Ingold Effects



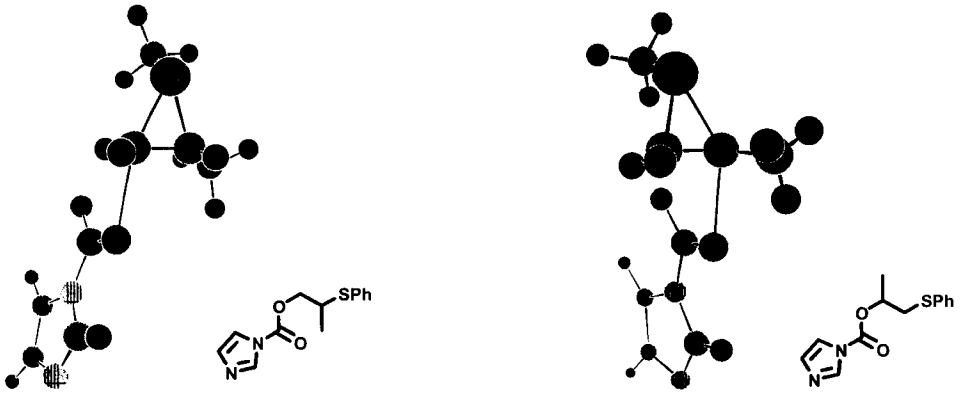
A. J. Kirby, *Adv. Phys. Org. Chem.*, 1980, 185

Molecular Modelling



Substrate	Δ H_{act} /kJmol^{-1}			Imaginary Vibrational mode
	PM3	STO-3G(d)+	6-31G(d,p)++	cm^{-1}
1°O, 1°S	267	247	-	-
1°O, 2°S	244	208	201	237 (6_31)
1°O, 3°S	212	181	177	310 (6_31)
2°O, 1°S	215	191	187	197 (6_31)
2°O, 2°S syn	203	174	167	227 (6_31)
2°O, 2°S anti	205	176	175	201 (6_31)
2°O, 3°S	194	167	157	234 (6_31)

Molecular Modelling



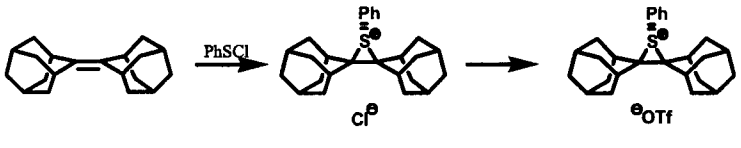
Substrate	C–S Bond / Å	C–O Bond / Å
1°O, 2°S	2.029	2.372
2°O, 1°S	2.129	2.472
1°O, 2°S Starting material	2.746	1.437

C-S bond lengths in X-ray structures of episulfonium ions ~1.9Å

A. J. Bennet *et al., J. Org. Chem.,* 1994, **59**, 7108

V. Lucchini *et al., J. Org. Chem.,* 2000, **65**, 3367

Episulfonium ion X-ray structures

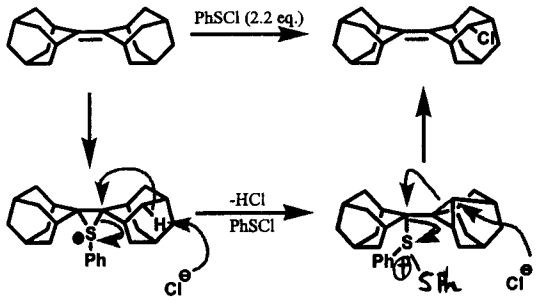


S-C 1.909 Å

C-C 1.500 Å

C-S-C 46.1°

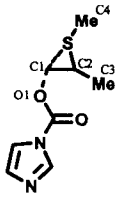
C-C-S 67.9 °



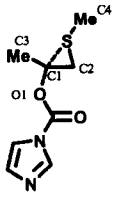
A. J. Bennet *et al., J. Org. Chem.,* 1994, **59**, 7108

Molecular Modelling

Electron density differences between the ground state and the transition state



1°O, 2°S



2°O, 1°S

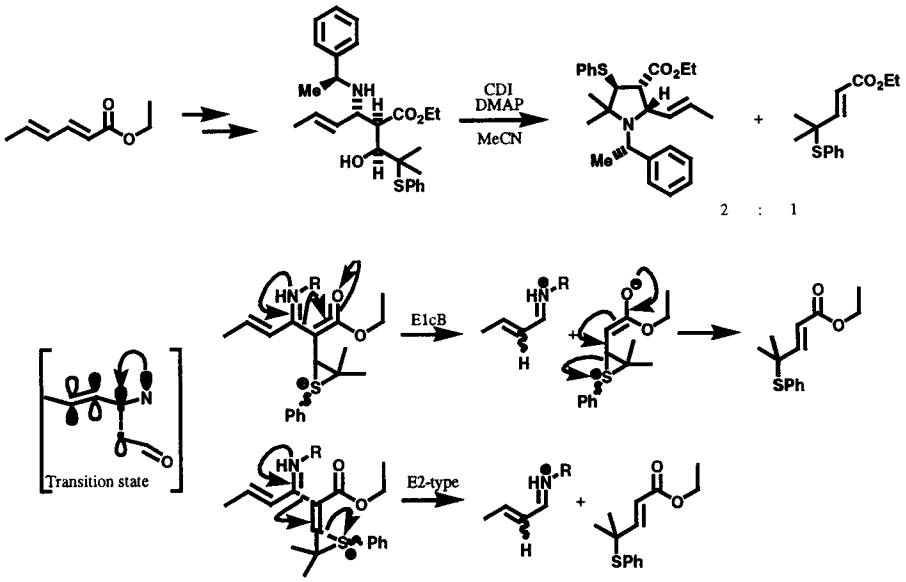
	C1	C2	C3	C4	S	O1
1°O, 2°S	-0.233	-0.162	0.115	-0.008	0.276	-0.234
2°O, 1°S	0.083	-0.022	-0.252	0.017	0.130	-0.303

enthalpy

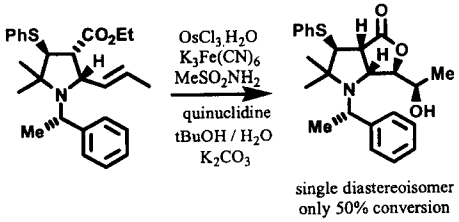
Activation energy - 1°O, 2°S = 201 kJmol^{-1}

- 2°O, 1°S = 187 kJmol^{-1}

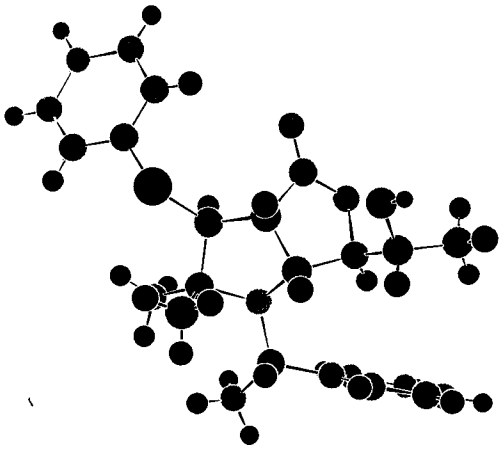
Structural Modifications



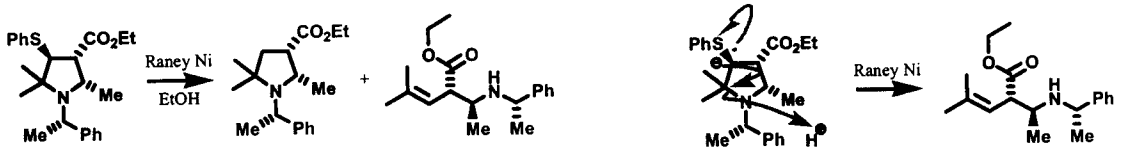
Structural Modifications

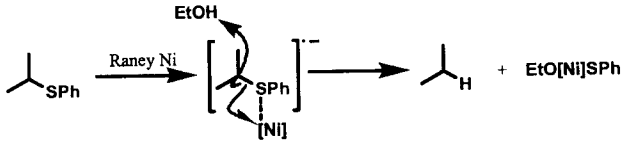


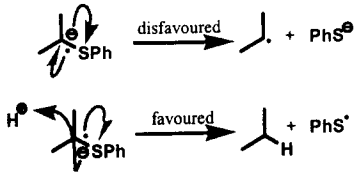
single diastereoisomer
only 50% conversion

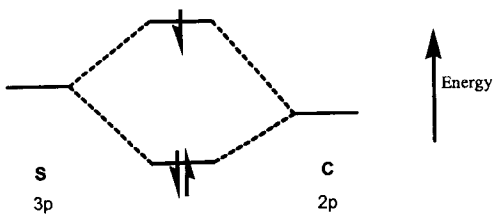


Structural Modifications

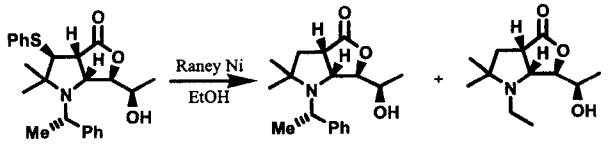


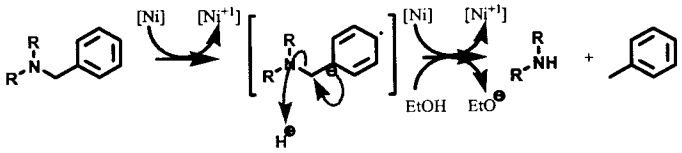


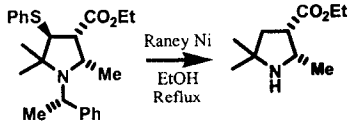




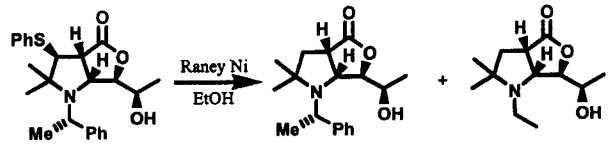
Structural Modifications

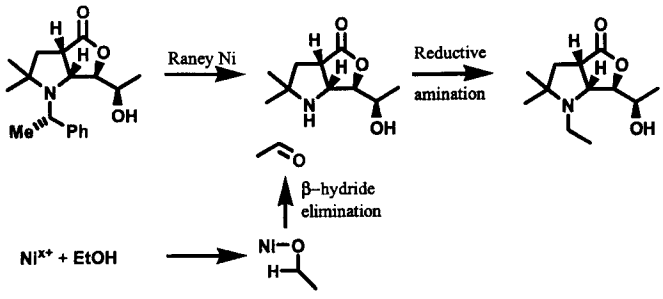




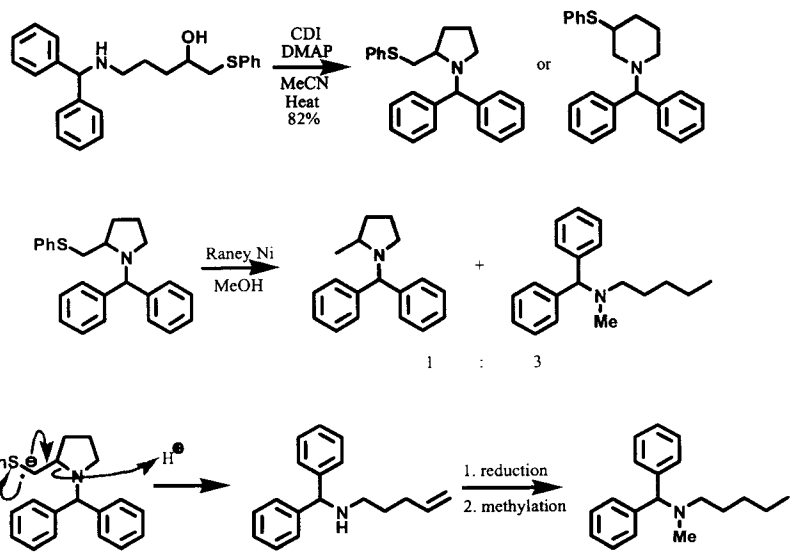


Structural Modifications

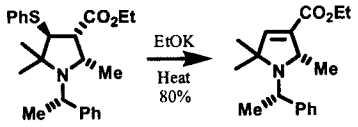




Structural Modifications

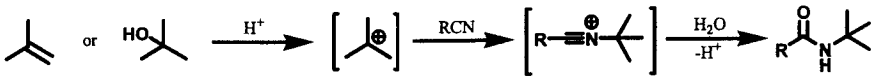


Structural Modifications

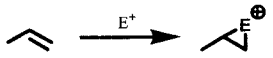


Ritter Reactions

- The Ritter reaction

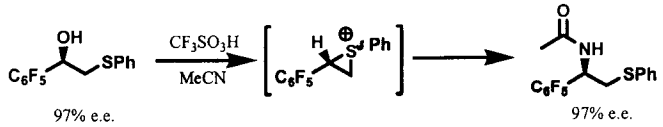


- Need to be able to form a stable carbocation intermediate



E = Cl, Br, I, RS, RSe

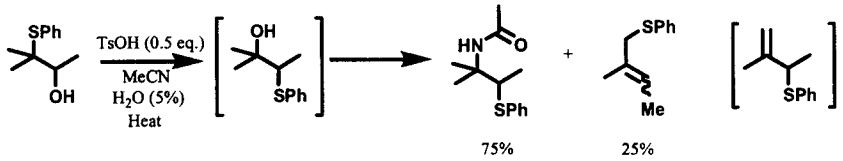
- Toshimitsu has developed a stereospecific Ritter reaction



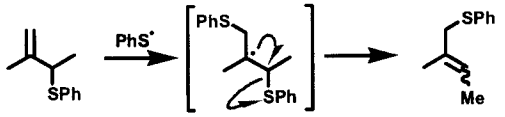
97% e.e. 97% e.e.

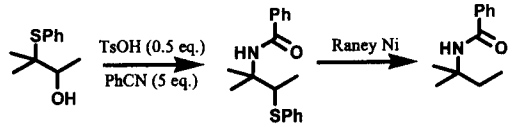
A. Toshimitsu, C. Hirosawa, K. Tamao, *Tetrahedron,* 1994, **50**, 8997

Ritter Reactions



75% 25%



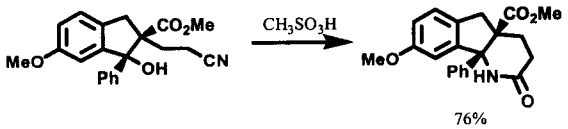


70%

M. D. Eastgate, T. J. Morley, D. J. Fox, S. Warren, *Synthesis,* 2002, 2124

Ritter Reactions

• Compernolle - intramolecular Ritter reaction

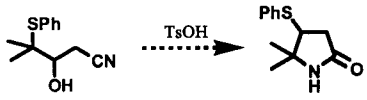


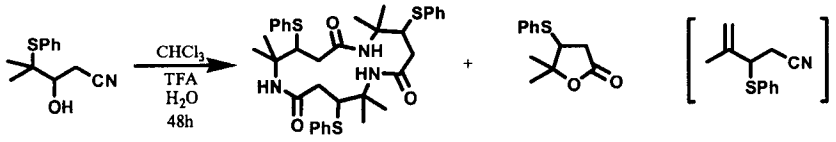
76%

• π-Cation complex ?

F. Compernolle *et al.*, *Organic Letters,* 2000, **2**, 3083

Ritter Reactions

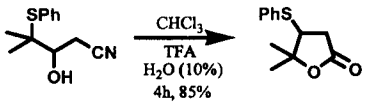


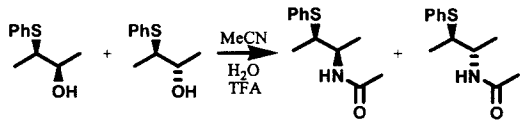


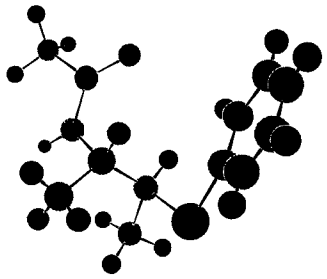
38%

M. D. Eastgate, T. J. Morley, D. J. Fox, S. Warren, *Synthesis,* 2002, 2124

Ritter Reactions



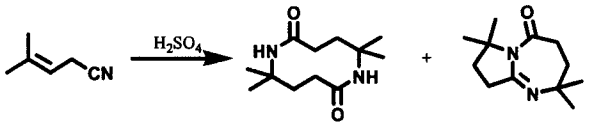




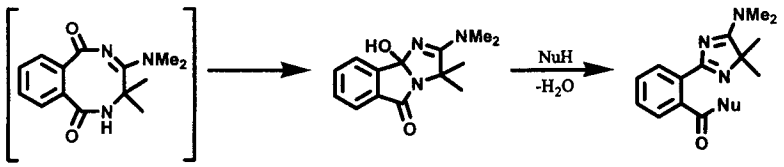
M. D. Eastgate, T. J. Morley, D. J. Fox, S. Warren, *Synthesis*, 2002, 2124

Ritter Reactions

• Duckner - inter/intramolecular Ritter reaction



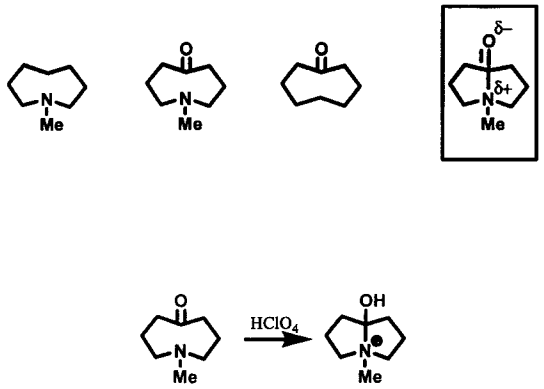
• Transannular Interactions - Germain



J. W. Duckner and M. J. Gunter, *Aust. J. Chem.*, 1968, **21**, 2809

G. Germain *et al.*, *Chimia*, 1988, **42**, 25

Transannular Interactions



P. Rademacher, *Chem. Soc. Revs.*, 1995, 143

J. N. Leonard, *Rec. Chem. Progr.*, 1956, **17**, 243

Transannular Interactions