

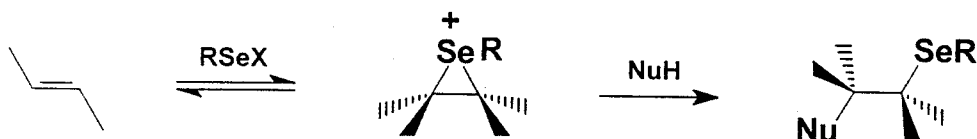
Development of Asymmetric Syntheses Promoted by Chiral Electrophilic Organoselenium Reagents



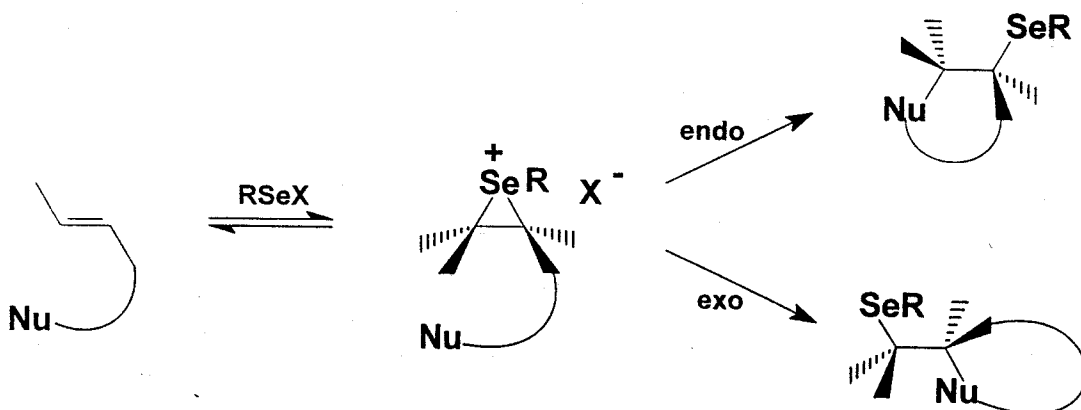
Marcello Tiecco

Department of Chemistry and Technology of Drugs
Section of Organic Chemistry
University of Perugia

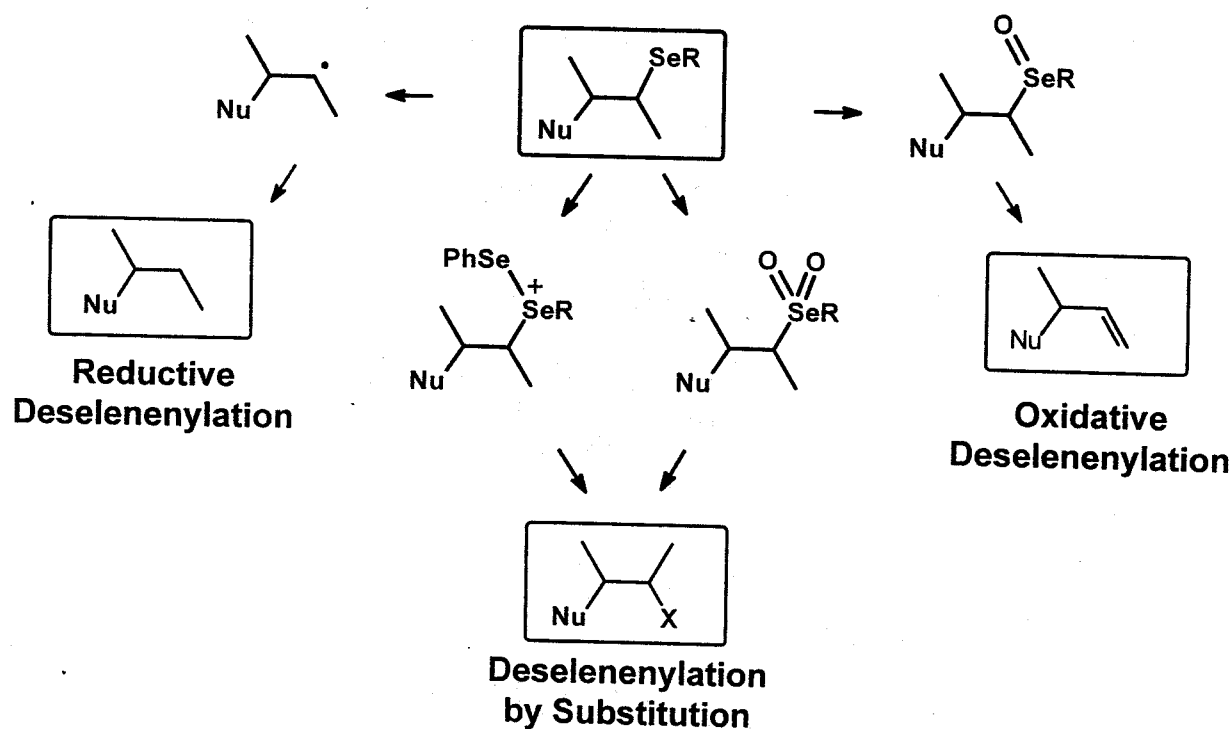
Addition of Electrophilic Organoselenium Reagents to Alkenes



Cyclofunctionalization Reactions



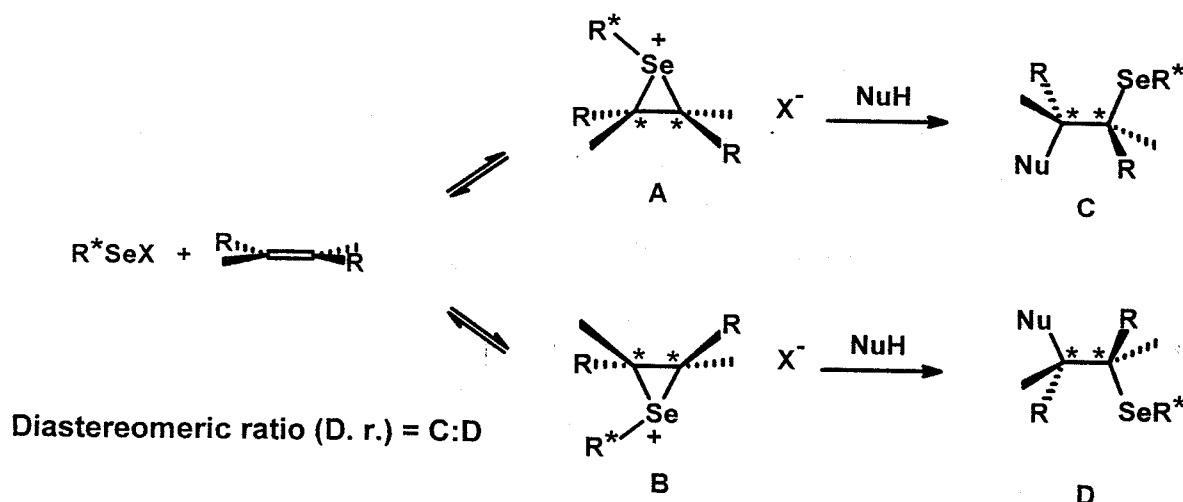
Deselenenylation Processes



Chiral Non Racemic Selenenylating Agents



Give Two Diastereomeric Seleniranium intermediates A and B
and Two Enantiomerically Pure
Diastereomeric Addition Products C and D



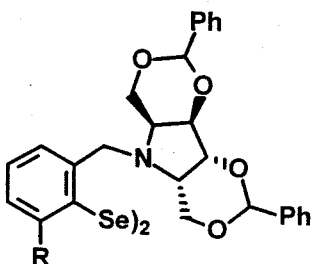
M. Tiecco, *Electrophilic Selenium, Selenocyclizations*, in *Organoselenium Chemistry, Modern Developments in Organic Synthesis*, T. Wirth Ed., Topics in Current Chemistry Vol. 208, Springer Verlag 2000, pag. 7.

R. Deziel et al., *Addition of Electrophilic Reagents to Carbon-Carbon Double Bonds*, in *Organoselenium Chemistry, A Practical Approach*, T. Back Ed., Oxford Press 2000, pag. 35.

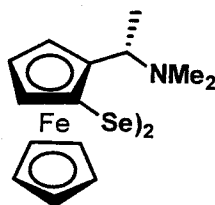
Chiral Non Racemic Diselenenides



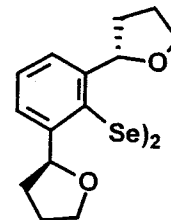
Tomoda, 1992



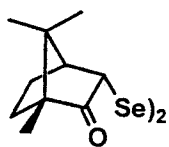
Tomoda, 1994



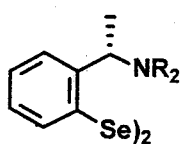
Uemura, 1994



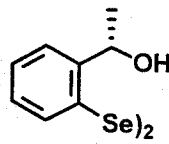
Deziel, 1994



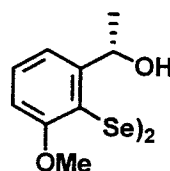
Back, 1995



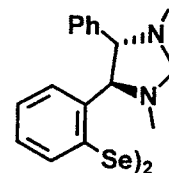
Wirth, 1995



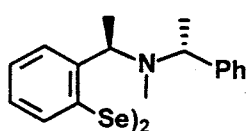
Wirth, 1995



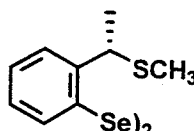
Wirth, 1998



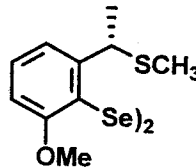
Santi, Wirth 1999



Tiecco, 2000

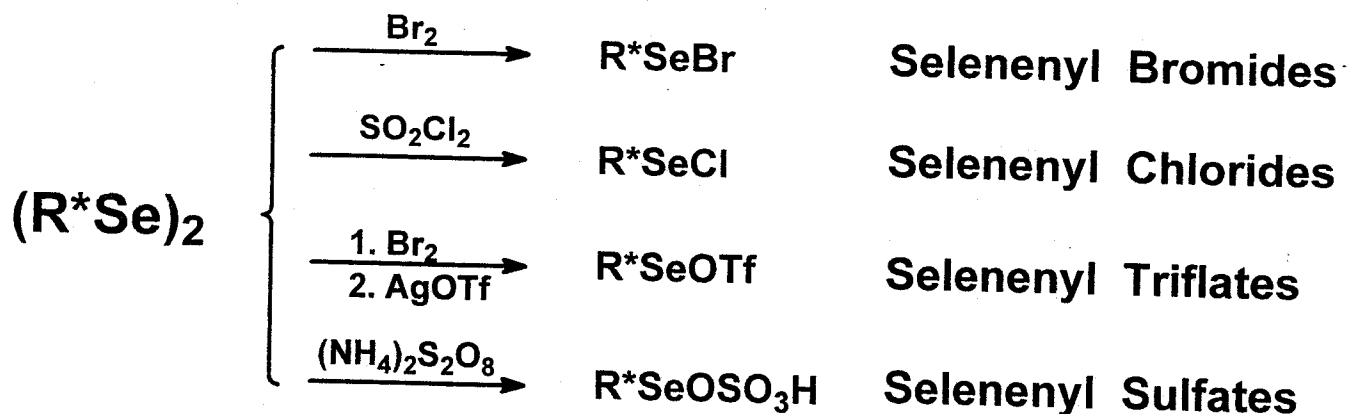


Tiecco, 2000

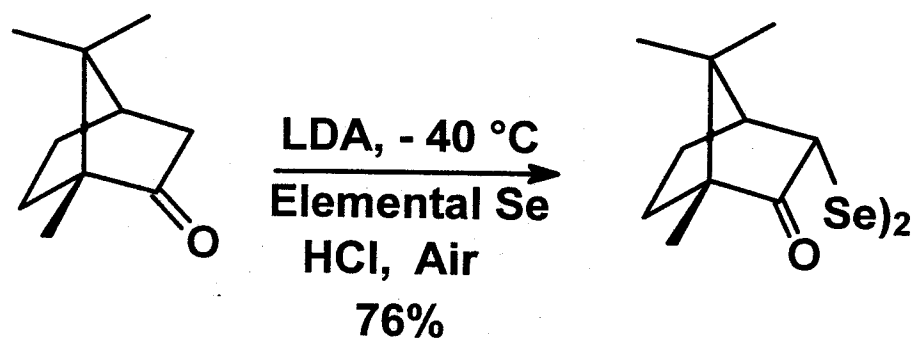


Tiecco, 2000

Production of Electrophilic Reagents from Diselenenides

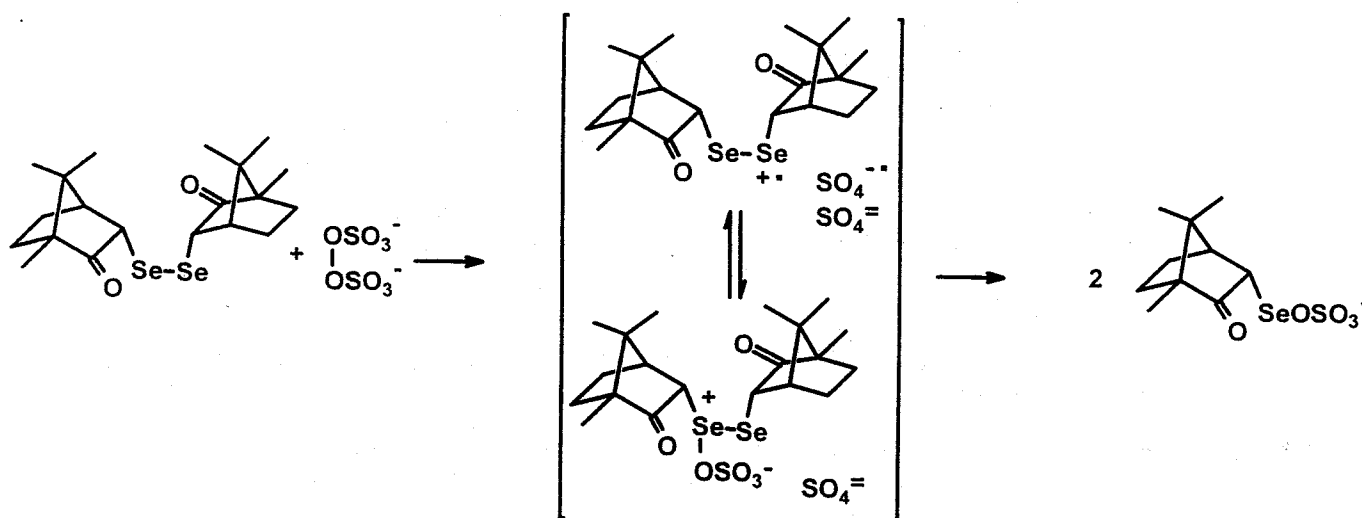


Camphor Diselenide



Back, T.G.; Dyck, B.P.; Pavez, M. *J. Org. Chem.* **1995**, *60*, 703

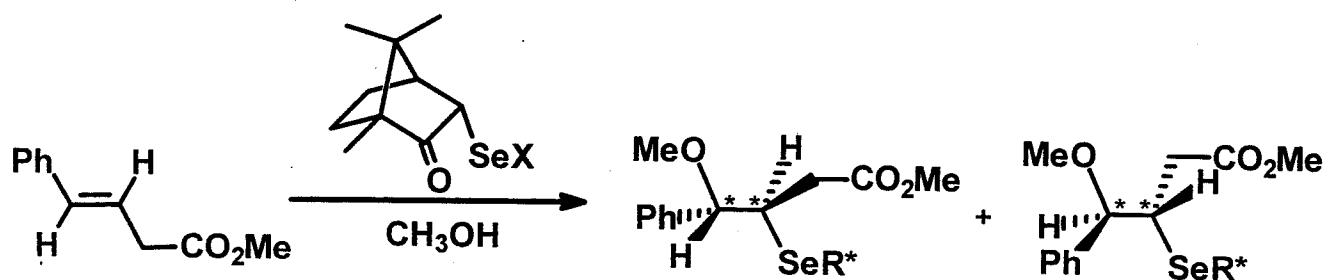
Camphorselenenyl Sulfate



In analogy with the production of phenylselenenyl sulfate from diphenyl diselenide

M. Tiecco et al. *Tetrahedron Letters*, **1989**, *30*, 1417

Methoxyselenenylation of Alkenes



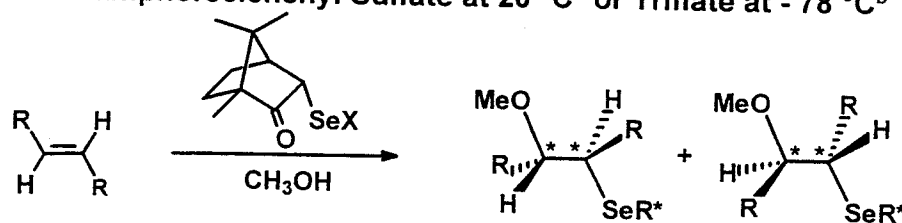
Effect of the Counteranion

X	°C	Time (hr)	Yield	D.r.
Cl	0	4	49%	40:60
Br	0	2	56%	35:65
TfO	0	5	77%	42:58
HOSO ₃	25	24	94%	85:15

M. Tiecco, L. Testaferri, C. Santi, F. Marini, L. Bagnoli, A. Temperini *Tetrahedron Lett.* **1998**, 39, 2809

Methoxyselenenylation of Alkenes

with Camphorselenenyl Sulfate at 20 °C^a or Triflate at -78 °C^b

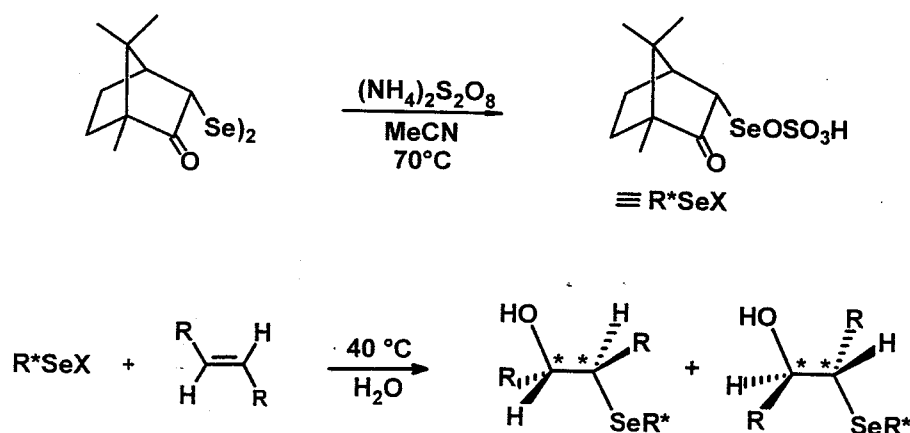


Alkene	With Sulfate at 20 °C		With Triflate at -78 °C	
	%Yield	D. r.	%Yield	D. r.
Methyl styrylacetate	94	85:15		
Methyl <i>E</i> -3-hexenoate	79	90:10		
<i>E</i> -3-Pentenitrile	76	88:12		
<i>E</i> -4-Octene	78	86:14		
<i>E</i> -5-Decene			88	94:6
Cyclohexene	73	75:25	71	75:25
Ciclooctene	82	83:17		
Styrene	91	65:35	77	74:26
α -Methylstyrene	86	75:25	88	83:17

a) M. Tiecco, L. Testaferri, C. Santi, F. Marini, L. Bagnoli, A. Temperini, *Tetrahedron Lett.* **1998**, 39, 2809
 b) T. G. Back, B. P. Dyck, S. Nan, *Tetrahedron*, **1999**, 55, 3191

Hydroxyselenenylation of Alkenes

with Camphorselenenyl Sulfate at 40 °C



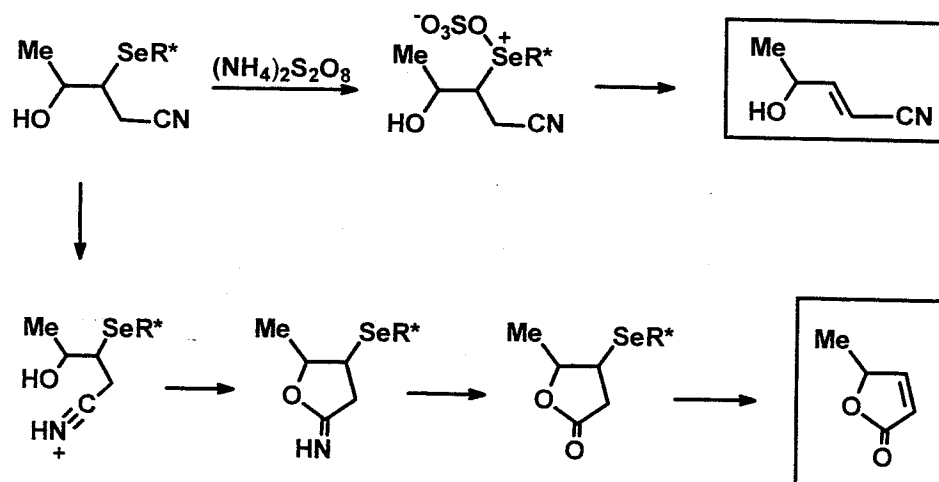
M. Tiecco, L. Testaferri, C. Santi, F. Marini, L. Bagnoli, A. Temperini, C. Tomassini,
Eur. J. Org. Chem **1998**, 2275-2277

Entry	Alkenes	Reaction Time (h)	Addition Products	%Yield	D. r.
1		36		80	91:9 ^{a,d}
2		39		89	94:6 ^{b,d}
3		60		60	90:10 ^{b,e}
4		37		68	78:22 ^{a,d}
5		31		75	90:10 ^{a,d}
6		45		50	81:19 ^{c,d}
7		28		68	65:35 ^{a,d}
8		40		62	65:35 ^{c,d}

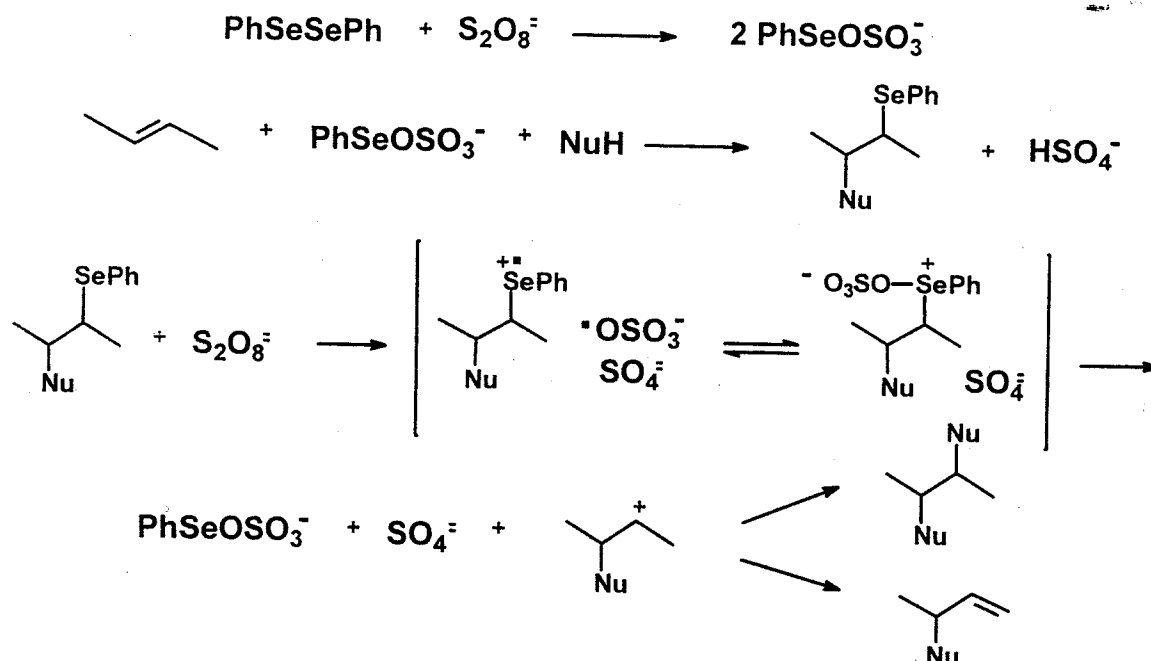
- a) The two diastereomers were separated.
 b) The minor isomer was not obtained in a pure form.
 c) The two diastereomers were detected by GC-MS.
 d) Determined by GC-MS.
 e) Determined by proton NMR.



Secondary Products from the Hydroxyselenenylation of *E*-3-Pentenitrile

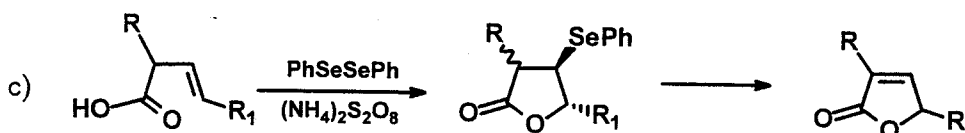
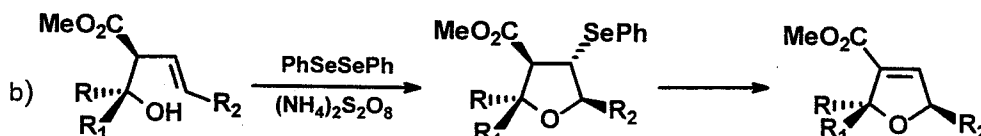
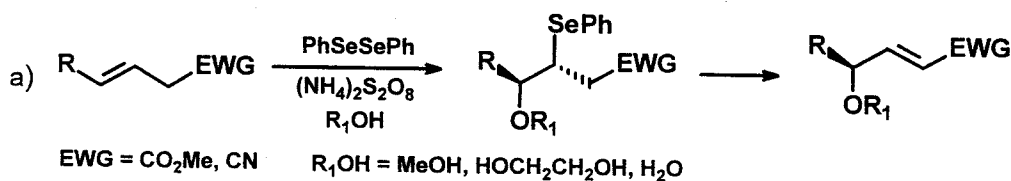


One-Pot Sequential Selenenylation - Deselenenylation Reactions Catalyzed by Phenylselenenyl Sulfate





Examples of One - Pot Sequential Oxyselenenylation - Elimination Reactions Catalyzed by Phenylselenenyl Sulfate



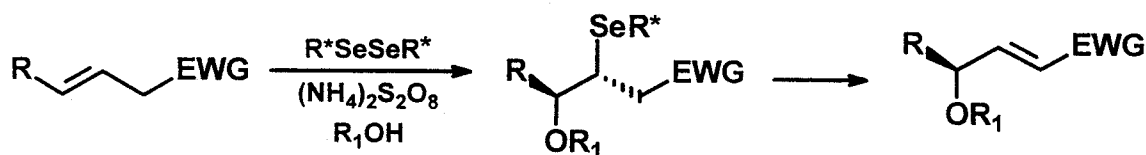
a) M. Tiecco *et al.*, *J.C.S. Chem Commun.*, **1993**, 632.

b) M. Tiecco *et al.*, *Pure Appl. Chem.* **1993**, 65, 722; M. Tiecco *et al.*, *Eur. J. O. C.* **1999**, 797

c) M. Tiecco *et al.*, *Synlett*, **1993**, 798.



One - Pot Sequential Oxyselenenylation - Elimination Reactions of β,γ - Unsaturated Esters and Nitriles Promoted by Camphorselenenyl Sulfate



EWG = CO₂Me, CN

R₁OH = MeOH, HOCH₂CH₂OH, H₂O

Alkoxyseleenylation - Elimination in Methanol



Entry	Alkenes	Time (h)	Products	% Yield	% ee	R/S
1	<chem>Ph-CH=CH-CH2-CO2Me</chem>	36	<chem>Ph-CH(OMe)-CH=CH-CO2Me</chem>	72	65	R
2	<chem>Et-CH=CH-CH2-CO2Me</chem>	24	<chem>Et-CH(OMe)-CH=CH-CO2Me</chem>	71	86	S
3	<chem>Me-CH=CH-CH2-CO2Me</chem>	72	<chem>Me-CH(OMe)-CH=CH-CO2Me</chem>	60	70	S
4	<chem>Me-CH=CH-CH2-CN</chem>	27	<chem>Me-CH(OMe)-CH=CH-CN</chem>	66	70	S

Tetrahedron: Asymmetry, 1999, 10, 747

Alkoxyseleenylation - Elimination in Ethylene Glycol



Entry	Alkenes	Time (h)	Products	% Yield	% ee	R/S
1	<chem>Ph-CH=CH-CH2-CO2Me</chem>	20	<chem>Ph-CH(OCH2CH2OH)-CH=CH-CO2Me</chem>	87	40	R
2	<chem>Et-CH=CH-CH2-CO2Me</chem>	46	<chem>Et-CH(OCH2CH2OH)-CH=CH-CO2Me</chem>	46	46	S
3	<chem>Me-CH=CH-CH2-CN</chem>	30	<chem>Me-CH(OCH2CH2OH)-CH=CH-CN</chem>	57	64	S

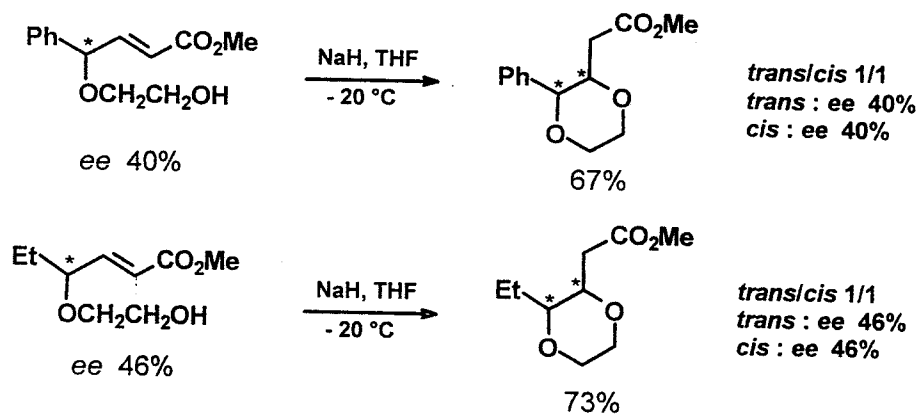
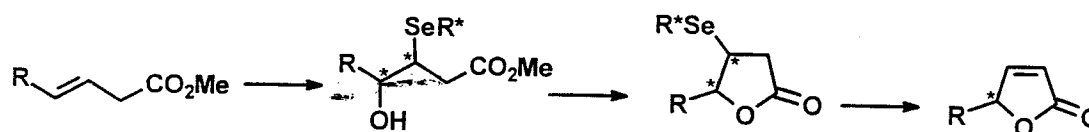
Tetrahedron: Asymmetry, 1999, 10, 747



Hydroxyselenenylation - Elimination in Acetonitrile and Water

Entry	Alkenes	Time (h)	Products	% Yield	% ee	R/S
1		22		55	60	R
				33	40	R
2		26		33	60	S
				31	50	S
3		45		70	46	S

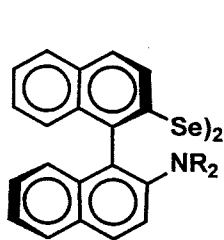
Tetrahedron: Asymmetry, 1999, 10, 747



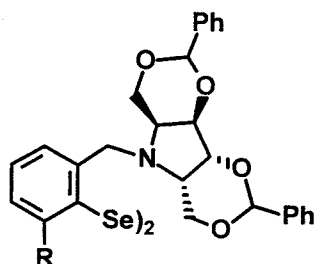
Tetrahedron: Asymmetry, 1999, 10, 747



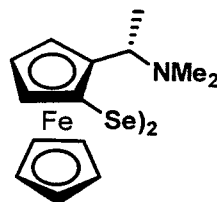
Chiral Non Racemic Diselenides



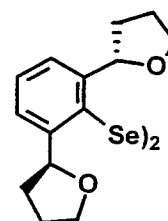
Tomoda, 1992



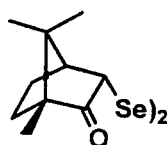
Tomoda, 1994



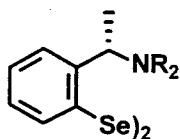
Uemura, 1994



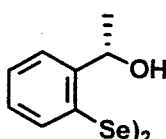
Deziel, 1994



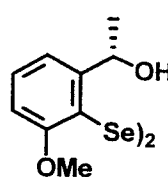
Back, 1995



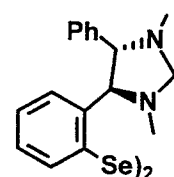
Wirth, 1995



Wirth, 1995



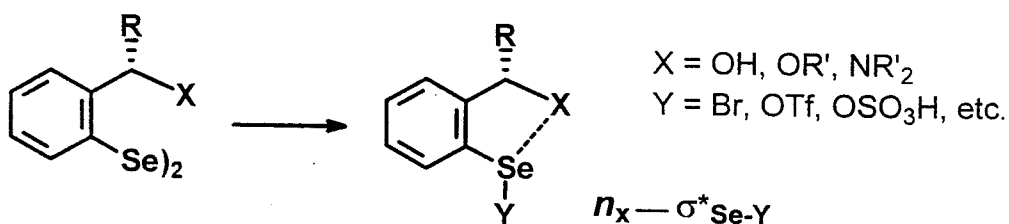
Wirth, 1998



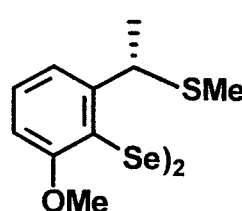
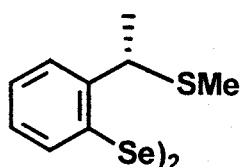
Santi, Wirth 1999

Orbital Interaction Between the Heteroatom Lone Pair and the Low-Lying SeY Antibonding Orbital

(crystal structure determinations, nmr spectroscopy and theoretical calculations)

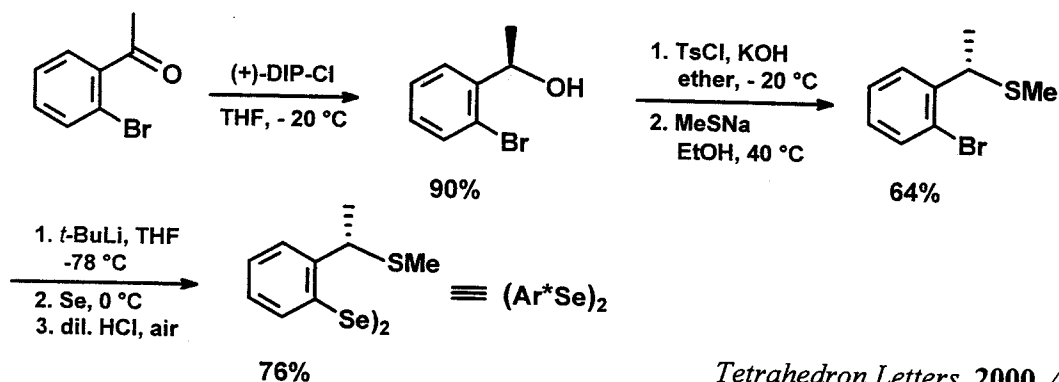


Two New Sulfur Containing Chiral Diselenides



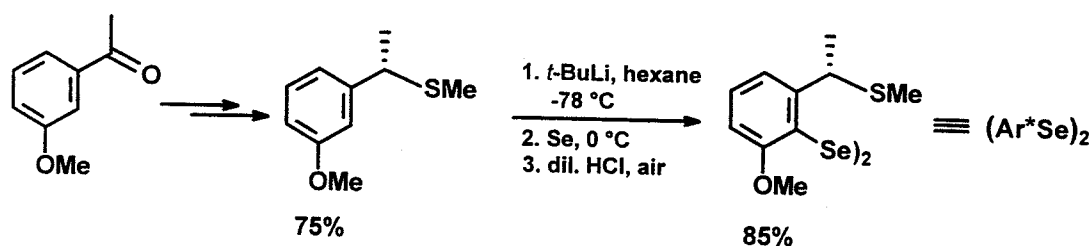
Syntheses

2-[(1S)-1-(Methylthio)ethyl]phenyl Diselenide (SD)



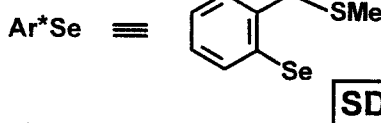
Tetrahedron Letters, 2000, 41, 3241

6-Methoxy- 2-[(1S)-1-(methylthio)ethyl]phenyl Diselenide (MSD)



Seleno Methoxylation and Hydroxylation Reactions with the Triflate of the Sulfur Diselenide SD

Starting Alkenes	Seleno Methoxylation (at -78 °C)	Time h	D. r. (Yield)	Seleno Hydroxylation (at 20 °C)	Time h	D. r. (Yield)
Styrene		9	96:4 (80%)		6	95:5 (75%)
β -Methylstyrene		6	96:4 (78%)		6	96:4 (72%)
α -Methylstyrene		6	90:10 (80%)		4	90:10 (80%)
<i>E</i> -5-Decene		9	90:10 (76%)		6	88:12 (79%)
Cyclohexene		7	82:18 (75%)			
Methyl styrylacetate		17	90:10 (87%)			
Methyl 3-hexenoate		24	90:10 (73%)			

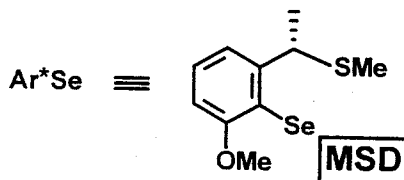


Tetrahedron Letters, 2000, 41, 3241

Seleno Methoxylation and Hydroxylation Reactions at -30 °C with the Sulfate of the Sulfur Diselenide MSD



Starting Alkenes	Seleno Methoxylation	Time h	D. r. (Yield)	Seleno Hydroxylation	Time h	D. r. (Yield)
Styrene		24	98:2 (72%)		24	98:2 (65%)
β -Methylstyrene		19	98:2 (76%)		20	98:2 (70%)
α -Methylstyrene		24	95:5 (58%)		24	98:2 (73%)
2,4,6-Trimethylstyrene		24	99:1 (60%)		25	99:1 (75%)
<i>E</i> -5-Decene (Triflate at -78 °C)		4	96:4 (70%)		3	97:3 (79%)
Cyclohexene (Triflate at -78 °C)		5	91:9 (77%)			
Phenyl cyclohexene		24	98:2 (60%)			



Diastereomeric Ratios in the Methoxyselenenylation Reactions with Different Diselenides

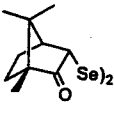
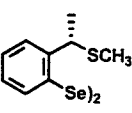
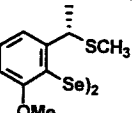
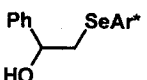
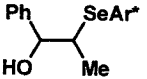
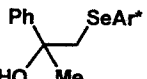
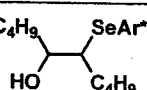
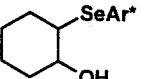


Starting Alkenes	Seleno Methoxylation Products	 Sulfate ^a At 20 °C	 Triflate ^b At -78 °C	 Sulfate ^c At -30 °C	 Triflate ^d At -78 °C
Styrene		65:35 (91%)	96:4 (80%)	98:2 (72%)	98:2 (55%)
β -Methylstyrene			96:4 (78%)	98:2 (75%)	92:8 (51%)
α -Methylstyrene		75:25 (86%)	90:10 (80%)	95:5 (58%)	
<i>E</i> -5-Decene		86:14 (78%)	90:10 (76%)	96:4 (70%)	
Cyclohexene		75:25 (73%)	82:18 (75%)	91:9 (77%)	

a) M. Tiecco *et al.*, *Tetrahedron Lett.* **1998**, 39, 2809; b) *ibid.*, **2000**, 41, 3241;
c) Present work; d) T. Wirth *et al.*, *J. C. S. Chem. Commun.*, **1998**, 1867.

Diastereomeric Ratios in the Hydroxyselenenylation Reactions with Different Diselenides



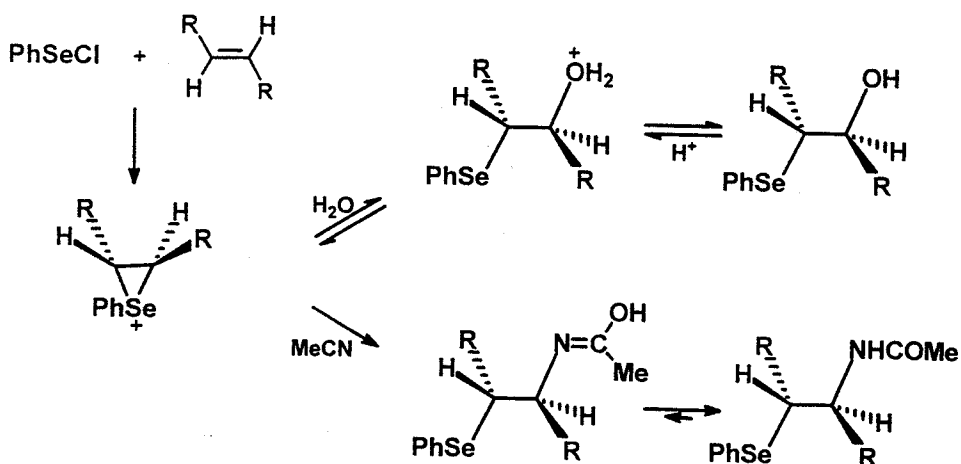
Starting Alkenes	Seleno Hydroxylation Products	 Sulfate ^a At 40 °C	 Triflate ^b At 20 °C	 Sulfate ^c At - 30 °C
Styrene		65:35 (68%)	95:5 (75%)	98:2 (65%)
β -Methylstyrene		65:35 (62%)	96:4 (72%)	98:2 (70%)
α -Methylstyrene			90:10 (80%)	98:2 (73%)
<i>E</i> -5-Decene		94:6 (78%)		97:3 (70%)
Cyclohexene		78:22 (68%)		72:28 (85%)

a) M. Tiecco *et al.*, *Eur. J. O. C.* 1998, 2275; b) *Tetrahedron Lett.* 2000, 41, 3241; c) Present work.

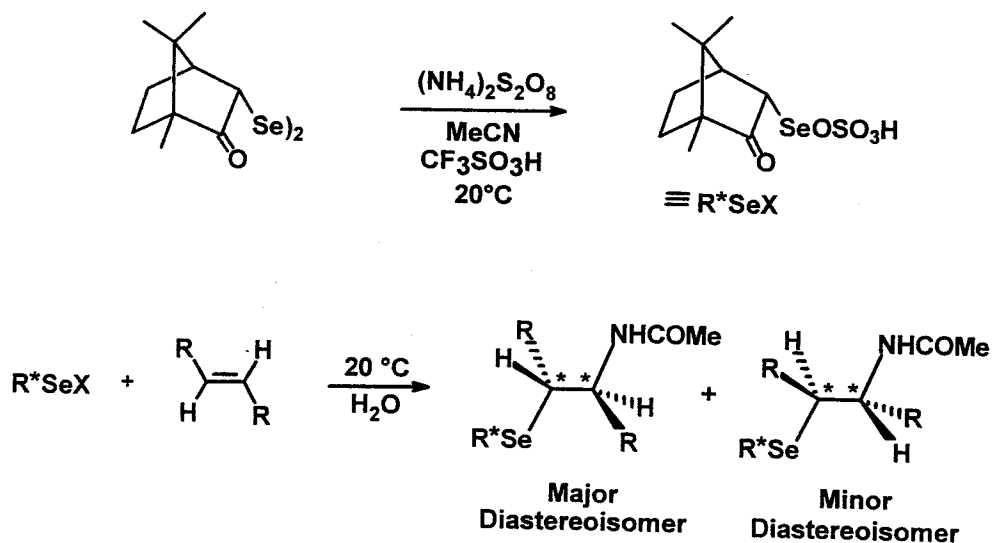
Acetamidosenenylation of Alkenes with Phenylselenenyl Chloride



In MeCN and H₂O in the presence of CF₃SO₃H



Asymmetric Acetamidosenenylation of Alkenes with Camphorselenenyl Sulfate



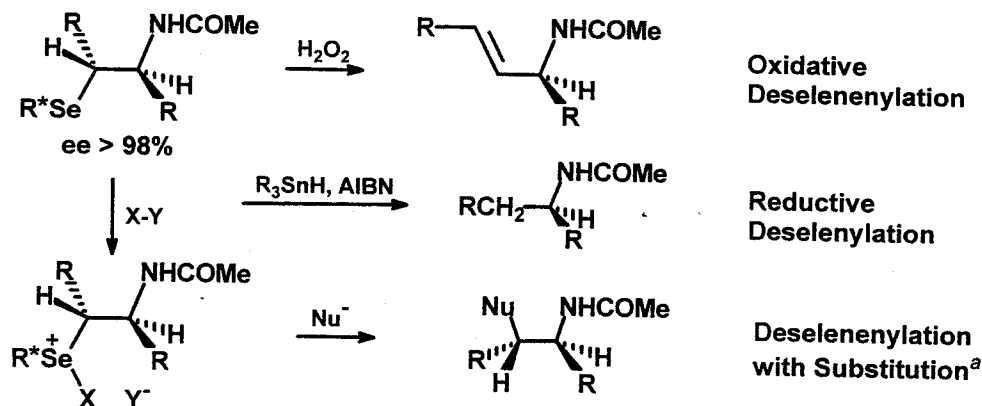
Acetamidosenenylation of Alkenes with Camphorselenenyl Sulfate at 20 °C.



Entry	Alkenes	Time (h)	Addition Products	Yield (%)	D.r.
1	<i>E</i> -3-Hexene	23		82	73:27
2	<i>E</i> -4-Octene	24		78	75:25
3	<i>E</i> -5-Decene	24		80	80:20
4	Styrene	30		50	53:47
5	Cyclohexene	26		61	65:45
6	Cyclooctene	25		86	60:40

The acetamidosenenylation of alkenes occurs with moderate to poor facial selectivity. However, the two diastereomeric addition products can be easily separated by column chromatography and can be converted into enantiomerically pure derivatives by deselenenylation.

From the Optically Pure **Major** Diastereomers

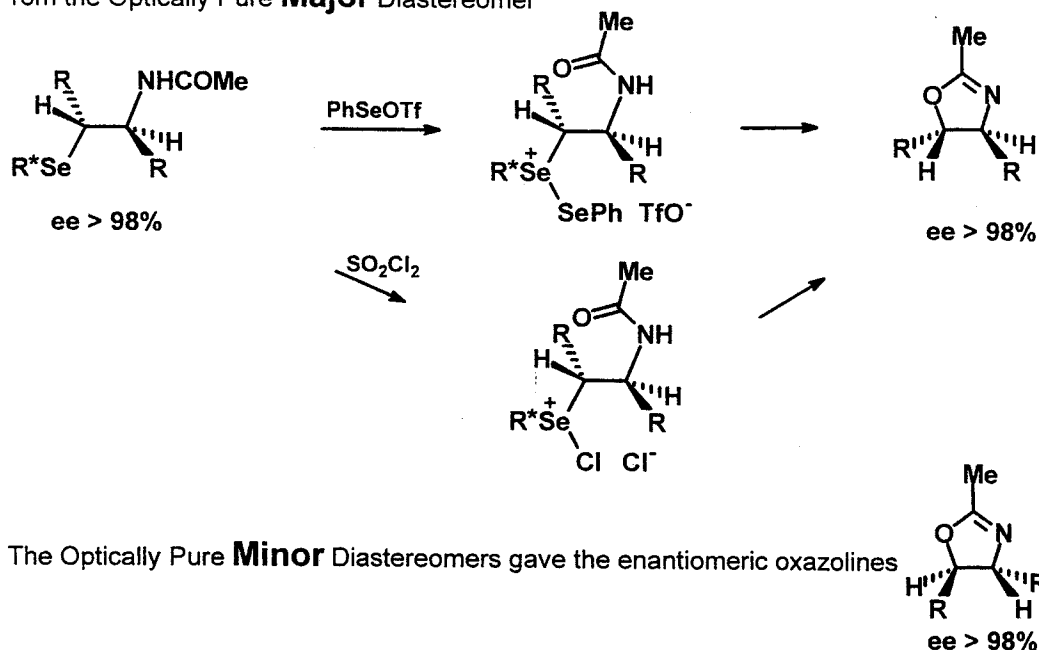


The Optically Pure **Minor** Diastereomers gave the enantiomeric compounds

a) M. Tiecco *et al.*, *J.C.S. Chem. Commun.*, **1994**, 1883; *J.Org. Chem.*, **1996**, 61, 7085.

Stereospecific Conversions of Acetamido Selenides into 4,5-Disubstituted Oxazolines

From the Optically Pure **Major** Diastereomer

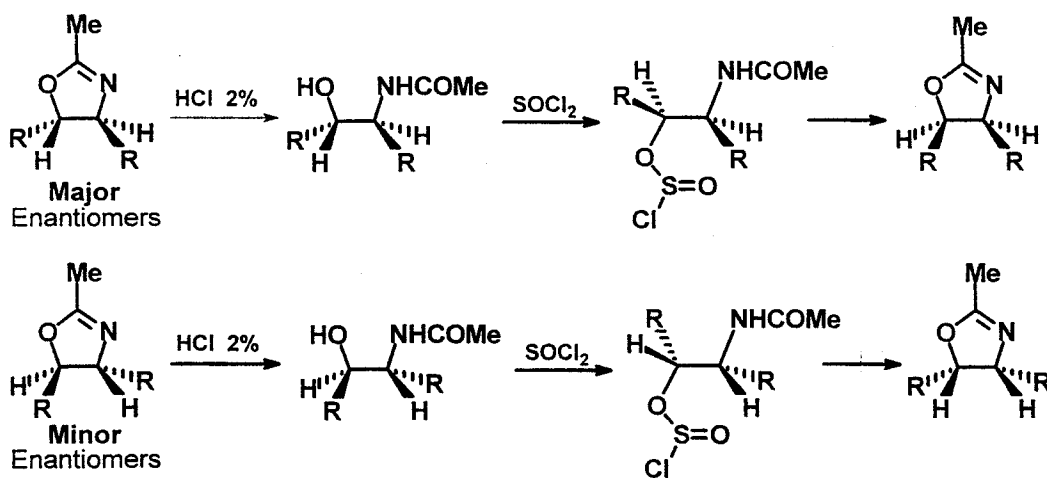


The Optically Pure **Minor** Diastereomers gave the enantiomeric oxazolines

4,5 - Disubstituted Oxazolines

Major Isomers						
%Yield: PhSeX	75	60	72	70	55	72
SO ₂ Cl ₂	98	95	93	85		81
[α]	- 49°	- 24°	- 63°	- 16°	+ 32°	+ 28°
Minor Isomers						
%Yield: PhSeX	84	68	70	75	55	45
SO ₂ Cl ₂	95	90	97	82		78
[α]	+ 49°	+ 24°	+ 63°	+ 16°	- 32°	- 28°

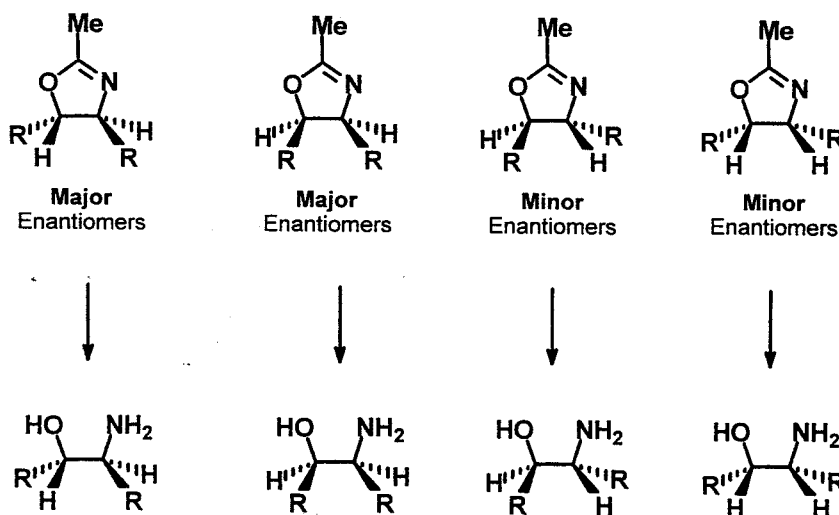
Conversion of *Trans* - 4,5 - Dialkyl Oxazolines into *Cis* - 4,5 - Dialkyl Oxazolines



R = C₂H₅, C₃H₇, C₄H₉

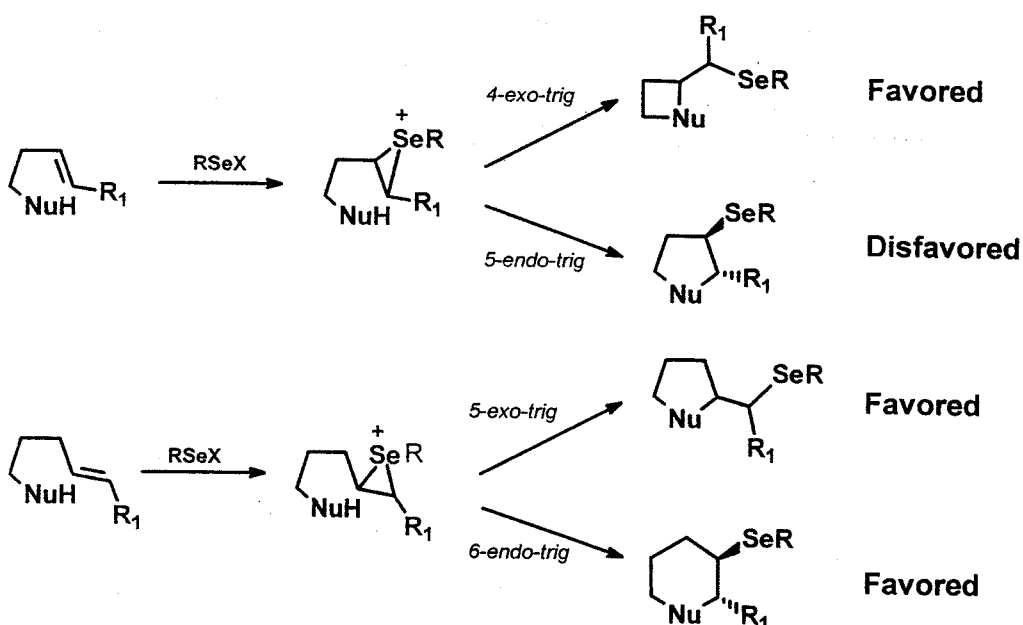
Formation of Vicinal Aminoalcohols from 4,5 - Dialkyl Oxazolines

By Treatment with HCl 25% at 50 °C



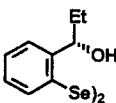
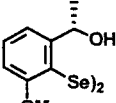
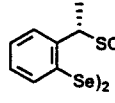
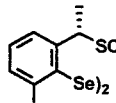
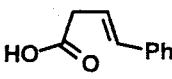
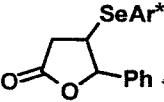
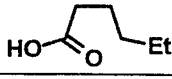
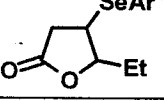
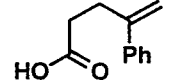
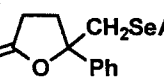
R = C₂H₅, C₃H₇, C₄H₉

Selenium Promoted Cyclization Reactions of Alkenes Containing Internal Nucleophiles (Cyclofunctionalizations)



Diastereomeric Ratios in the Selenolactonization Reactions with Different Diselenides

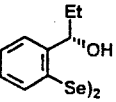
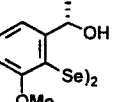
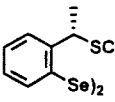
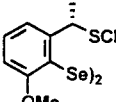
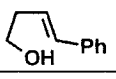
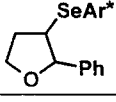
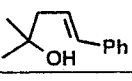
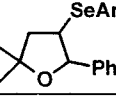
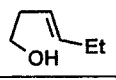
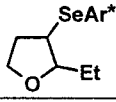
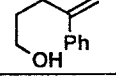
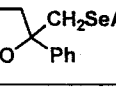
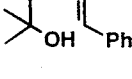
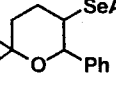


Starting Alkenes	Seleno Lactonization Products	 Triflate ^a At - 100 °C	 Triflate ^b At - 78 °C	 Triflate ^c At - 78 °C	 Sulfate ^c At - 30 °C
		71:29 (41%)	96:4 (54%)	95:5 (75%)	98:2 (72%)
				90:10 ^d (73%)	92:8 (60%)
		87:13 (54%)		90:10 (95%)	

a) T. Wirth *et al.*, *Eur. J. O. C.*, **1998**, 1361; b) T. Wirth *et al.*, *J. C. S. Chem. Commun.*, **1998**, 1867.
c) Present work; d) M. Tiecco *et al.*, *Tetrahedron Lett.* **2000**, 41, 3241.

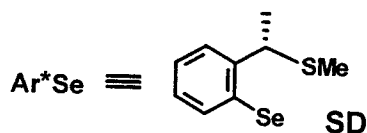
Diastereomeric Ratios in the Selenoetherification Reactions



Starting Alkenes	Seleno Etherification Products	 Triflate ^a At - 100 °C	 Triflate ^b At - 78 °C	 Triflate ^c At - 78 °C	 Sulfate ^c At - 30 °C
		84:16 (87%)		93:7 (88%)	
				93:7 ^d (88%)	96:4 (69%)
		50:50 (60%)	60:40 (42%)	80:20 (56%)	
		80:20 (45%)		91:9 (73%)	
				94:6 (79%)	

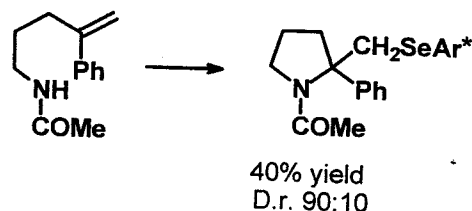
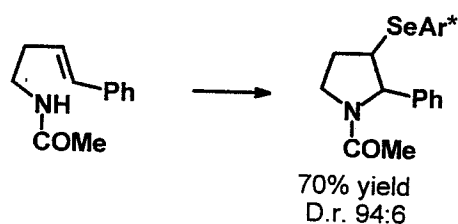
a) Wirth *et al.*, *Eur. J. O. C.*, **1998**, 1361; b) T. Wirth *et al.*, *J. C. S. Chem. Commun.*, **1998**, 1867.
c) Present work; d) M. Tiecco *et al.*, *Tetrahedron Lett.* **2000**, 41, 3241.

Asymmetric Syntheses of Nitrogen Heterocycles

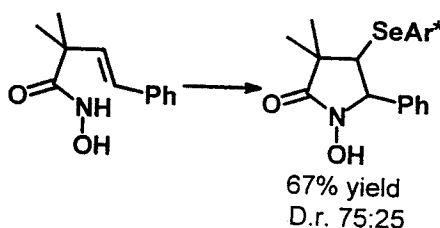
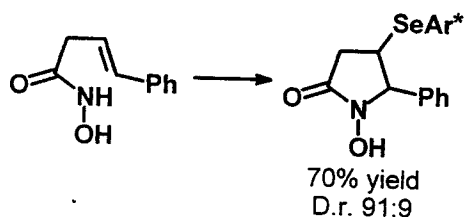


Triflate at -78 °C

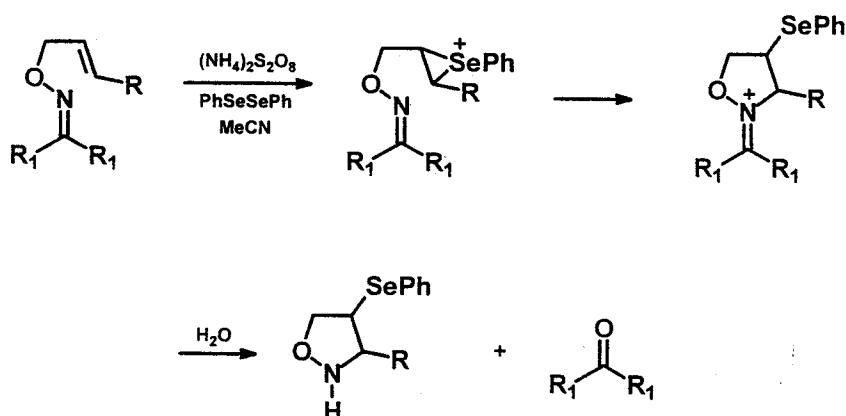
N-Acetyl Pyrrolidines



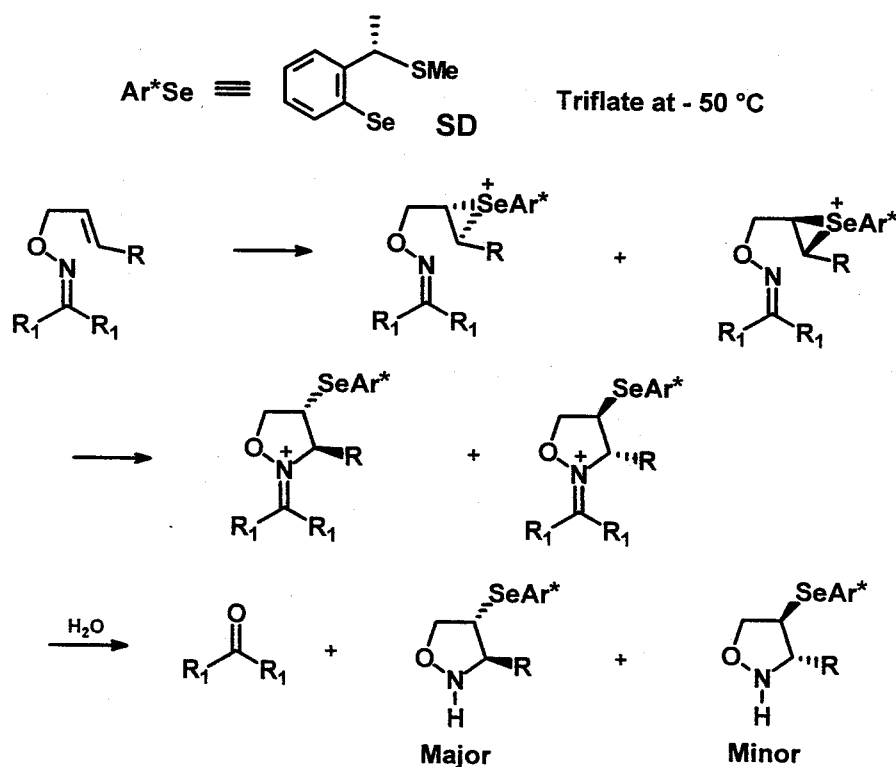
N-Hydroxy γ-Lactams



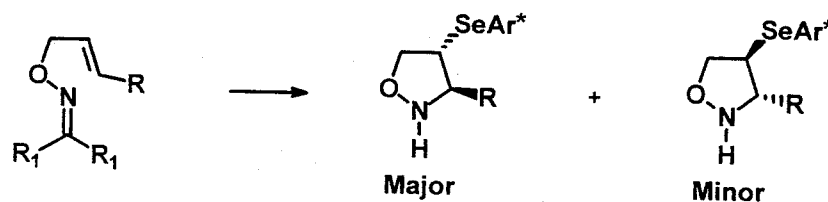
Conversion of O-Allyl Oximes into Isoxazolidines Promoted by Phenylselenenyl Sulfate



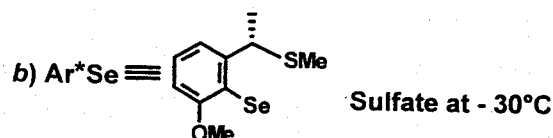
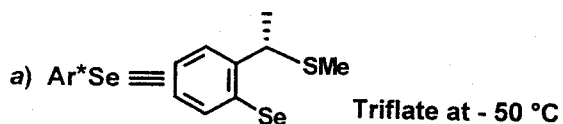
Asymmetric Synthesis of Isoxazolidines



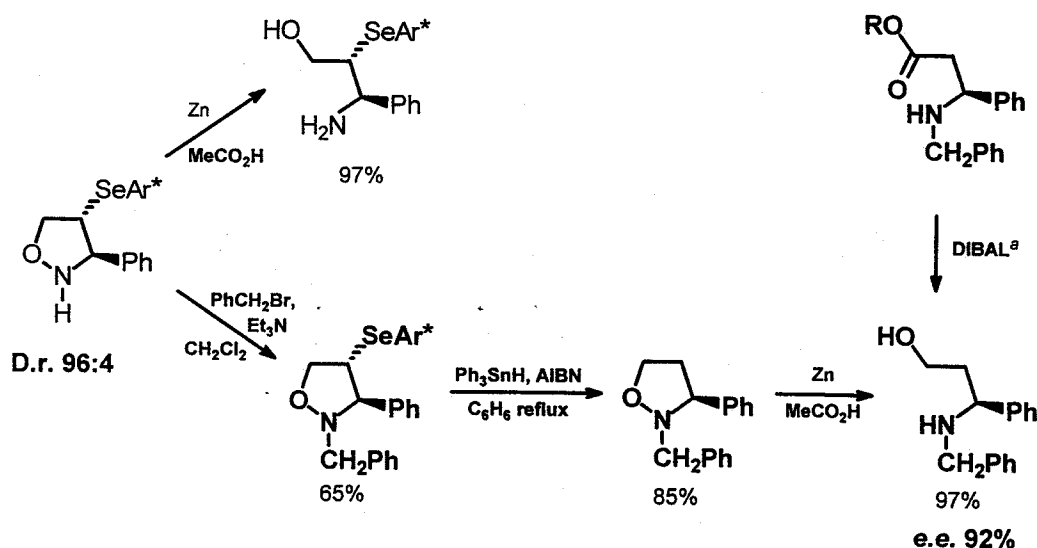
Diastereomeric Ratios of Isoxazolidines



R	R ₁	%Yield	D.r.
Me	<i>n</i> -Pr	58	90:10 ^a
Et	<i>n</i> -Pr	93	88:12 ^a
Ph	<i>n</i> -Pr	77	93:7 ^a
Ph	<i>n</i> -Pr	70	96:4 ^b



Conversion of Isoxazolidines into 1,3-Aminoalcohols



a) T. Fujisawa *et al.*, *Heterocycles*, **1997**, *45*, 1883

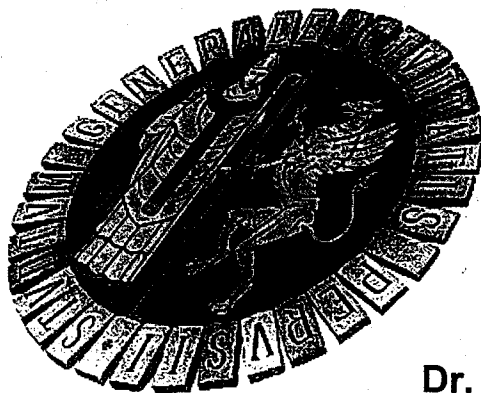
Acknowledgments

MURST - National Research Project

"Stereoselezione in Sintesi Organica. Metodologie e Applicazioni"

Università di Perugia, Progetti di Ateneo

National Research Council, Rome



Prof. Lorenzo Testaferri
Dr. Luana Bagnoli
Dr. Francesca Marini

Dr. Claudio Santi
Dr. Andea Temperini
Dr. Silvia Sternativo
Dr. Cristina Tomassini