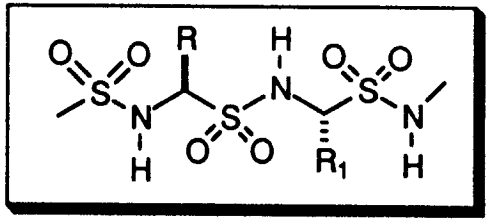
Rational Design

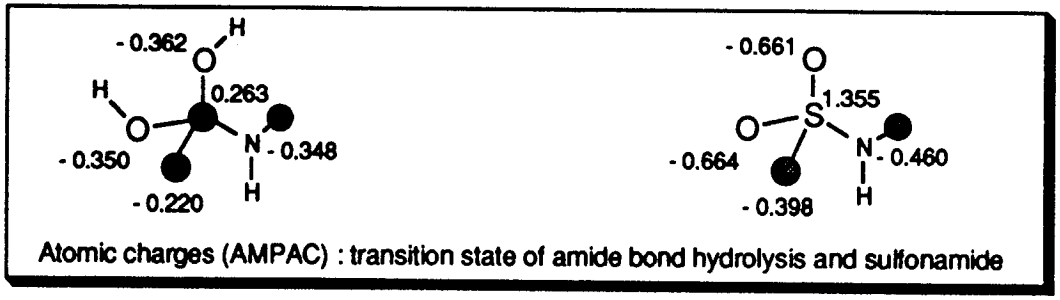
→ Sulfonamido pseudo-peptides



→ Significant changes in polarity, H-bonding capability, acid-base character (RSO_2-NHR', pKa = 10-11)

→ Enhanced metabolic stability

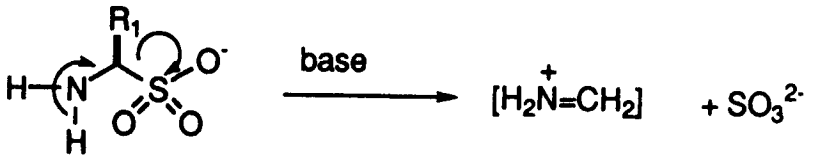
→ Structural similarity to the tetrahedral transition state involved in the amide bond enzymatic hydrolysis

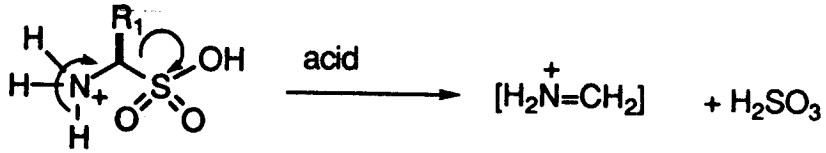


Atomic charges (AMPAC) : transition state of amide bond hydrolysis and sulfonamide

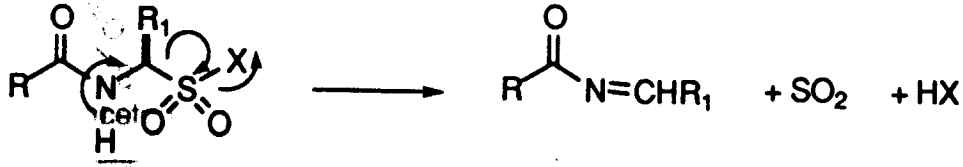
→ The oligomers and the polymers should also be interesting molecular scaffolds, with specific pseudopeptide backbone conformations based on the hydrogen-bonding network.

→ This makes sulfonamidopeptides interesting candidates in the development of protease inhibitors and new drugs



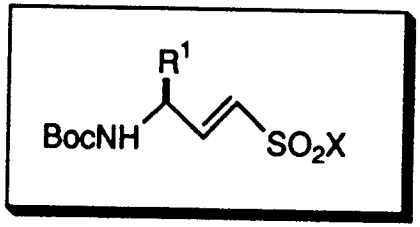


M. Frankel and P. Moses *Tetrahedron* **1960**, *9*, 289.



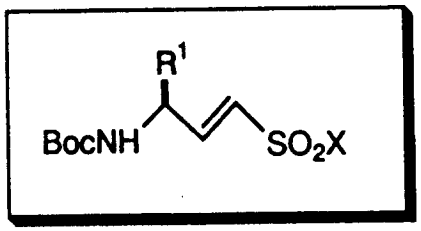
P.S. Portoghese et al. *Tetrahedron Lett.* **1981**, *22*, 537.

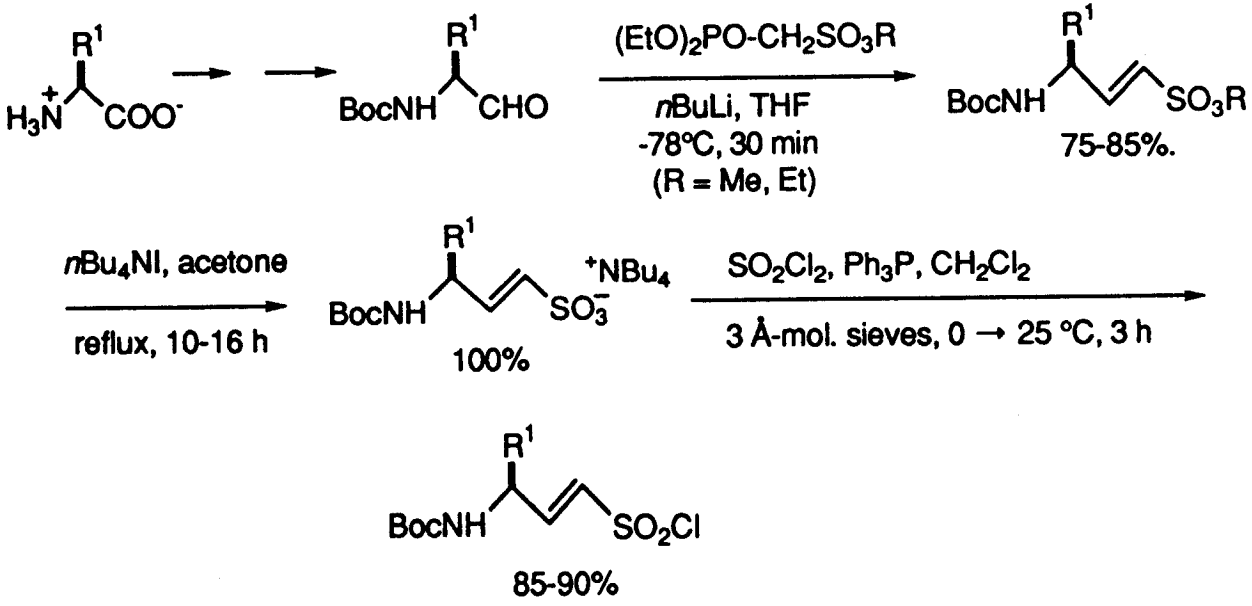
Vinylogous amino sulfonic acids (γ-amino-α,β-unsaturated)



C. Gennari, B. Salom, D. Potenza, A. Williams *Angew. Chem.* **1994**, 0000.
Università di Milano, Patent application N. MI94 A 000989; May 17, 1994.

X = Cl, stable chromatographable monomer



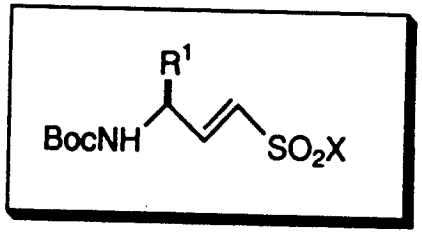


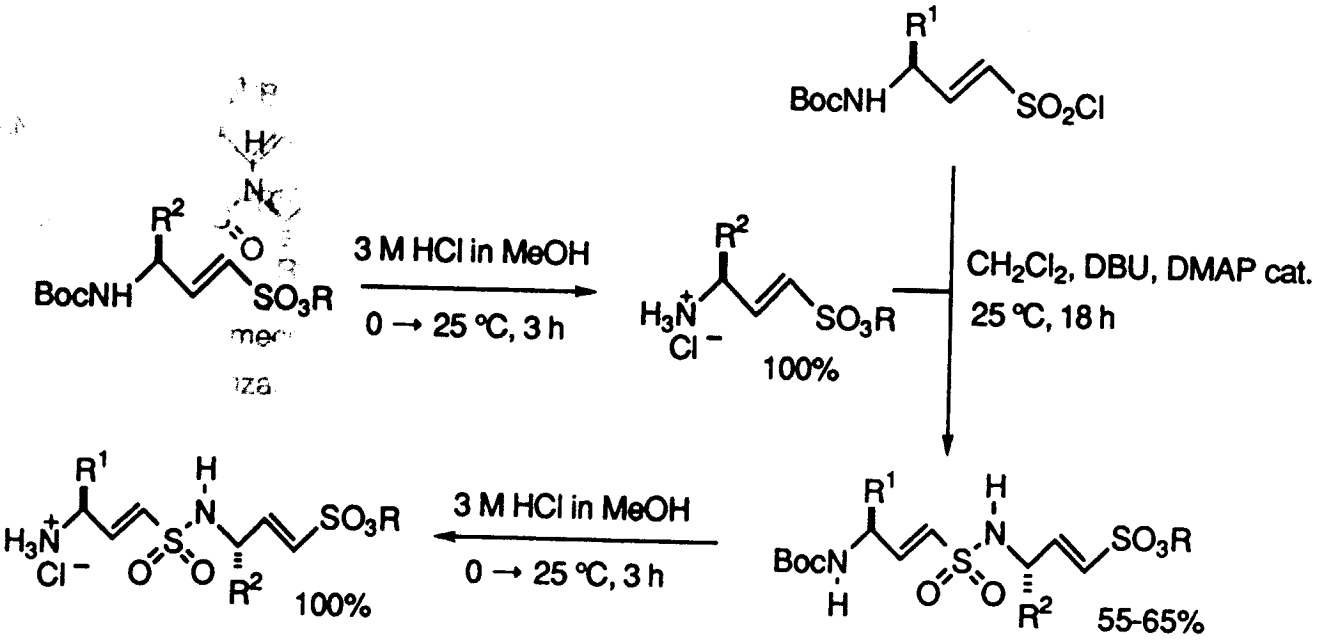
→ Wittig-Horner : complete E stereoselectivity

→ Bu_4N^+ salts : easily handleable and soluble in organic solvents, superior to Na^+, NH_4^+, $NHEt_3^+$

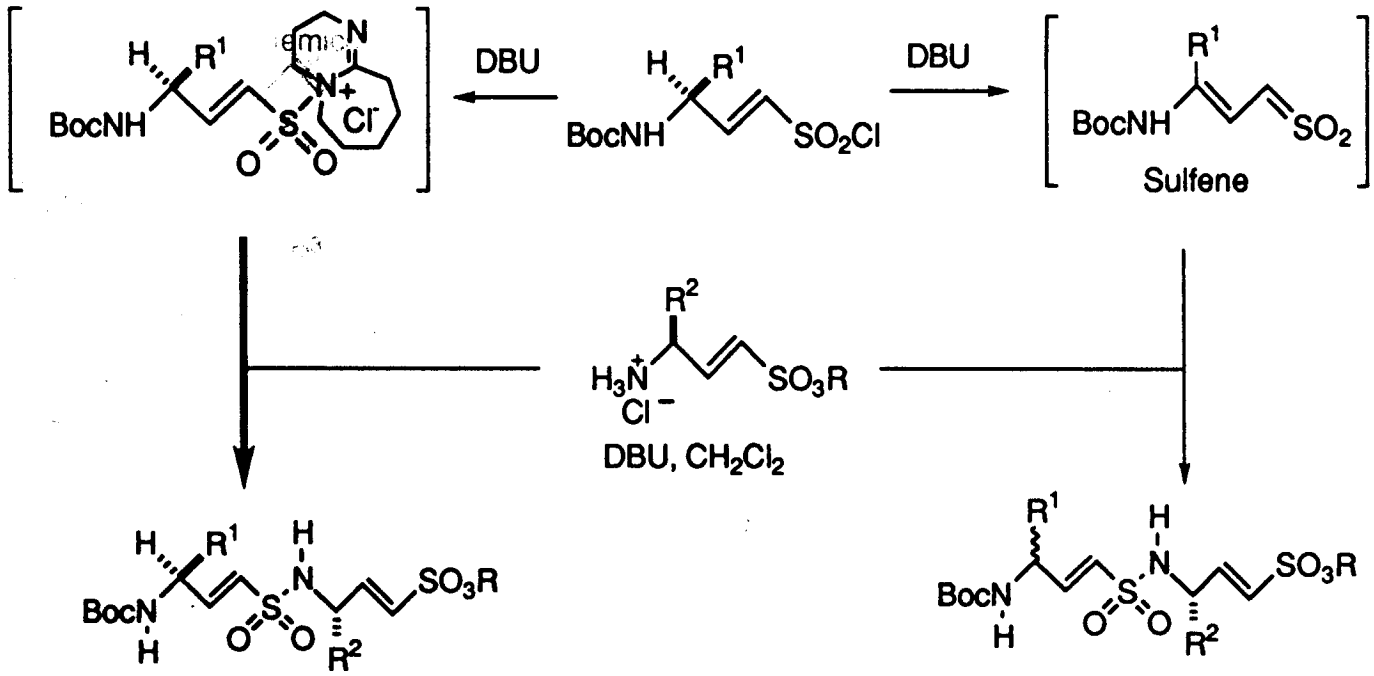
→ $SO_2Cl_2/Ph_3P/CH_2Cl_2$ superior to $(Cl_3C\text{-}O)C{=}O$/cat.DMF/CH_2Cl_2, $PCl_5/CHCl_3$

X = Cl, stable chromatographable monomer

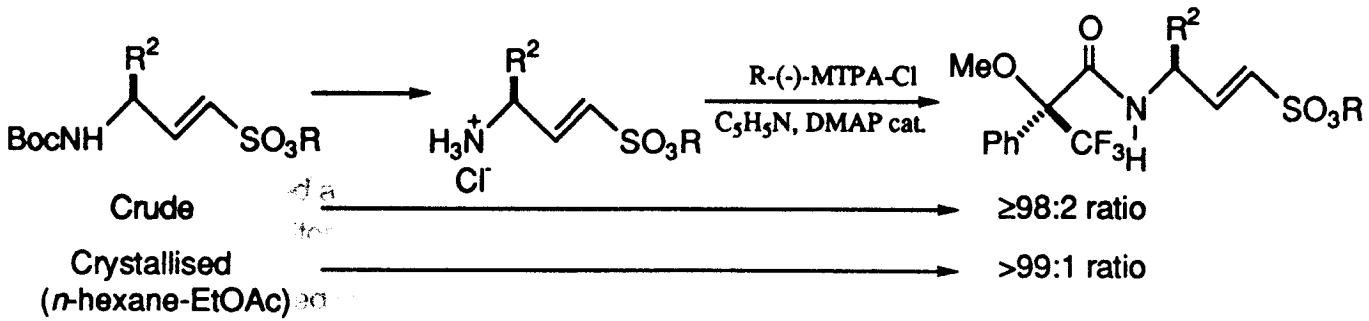




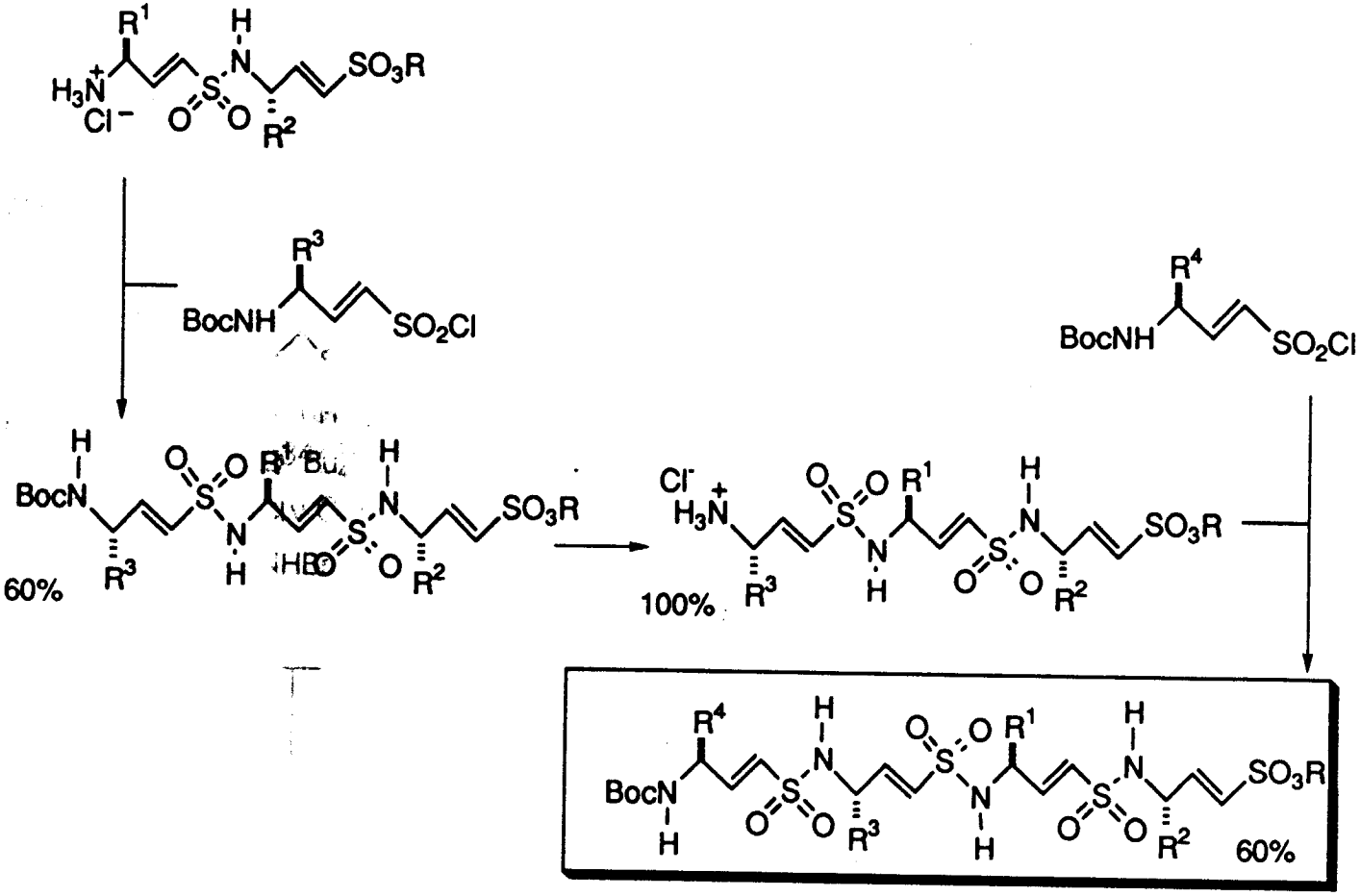
→ Dimers were obtained as single diastereoisomers (^{13}C-NMR): no epimerization during the coupling



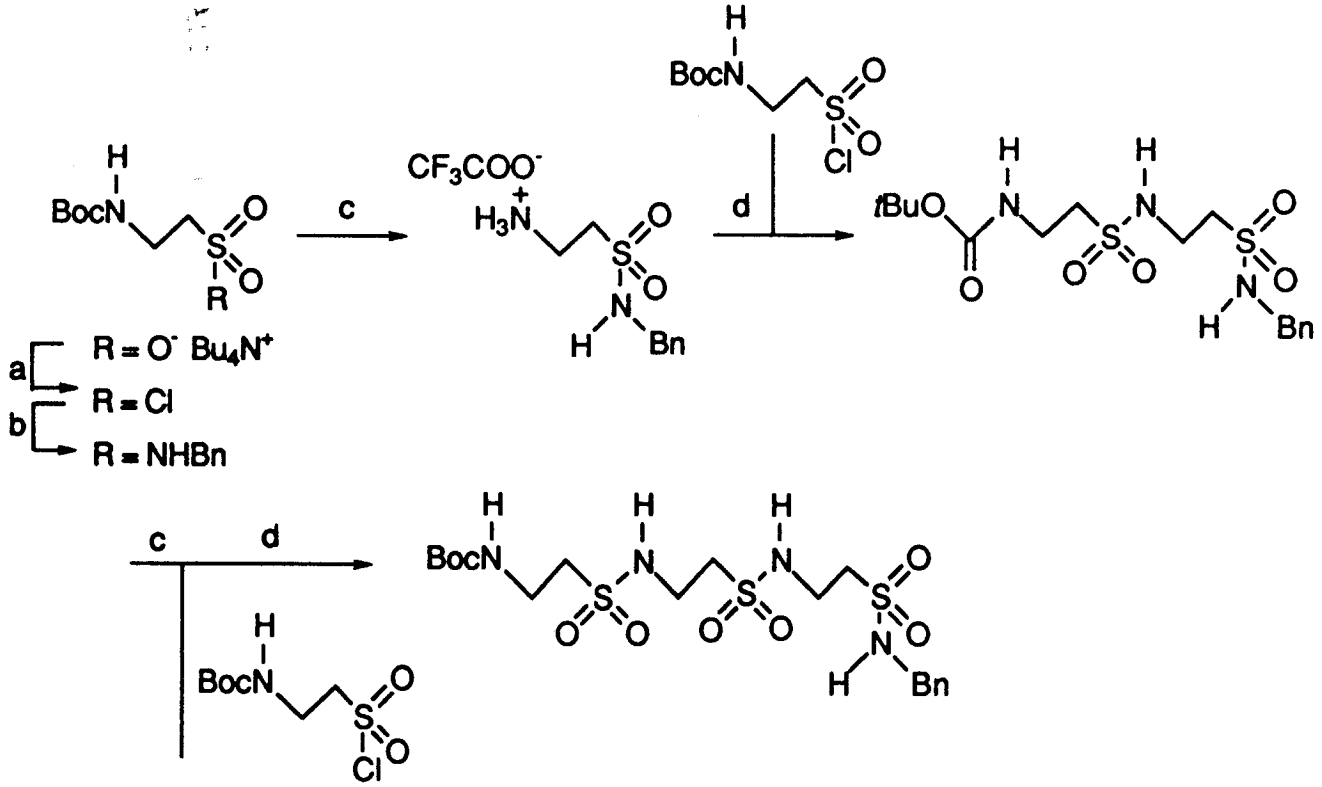
→ Coupling mechanism. Dimers were obtained as single diastereoisomers (^{13}C-NMR): no epimerization during the coupling



→ Stereochemical integrity checked via NMR analysis (^{1}H, ^{13}C, ^{19}F)


R = Et, NHBn
R1 = Me; R2 = i-Pr; R3 = CH2Ph; R4 = CH2CHMe2
60%
100%
60%
Developed a straightforward protection-deprotection-coupling chemistry for the sulfonamido bond
Synthesized sulfonamido-pseudopeptides via an iterative process

→ Sulfonamido-pseudopeptides derived from taurine.

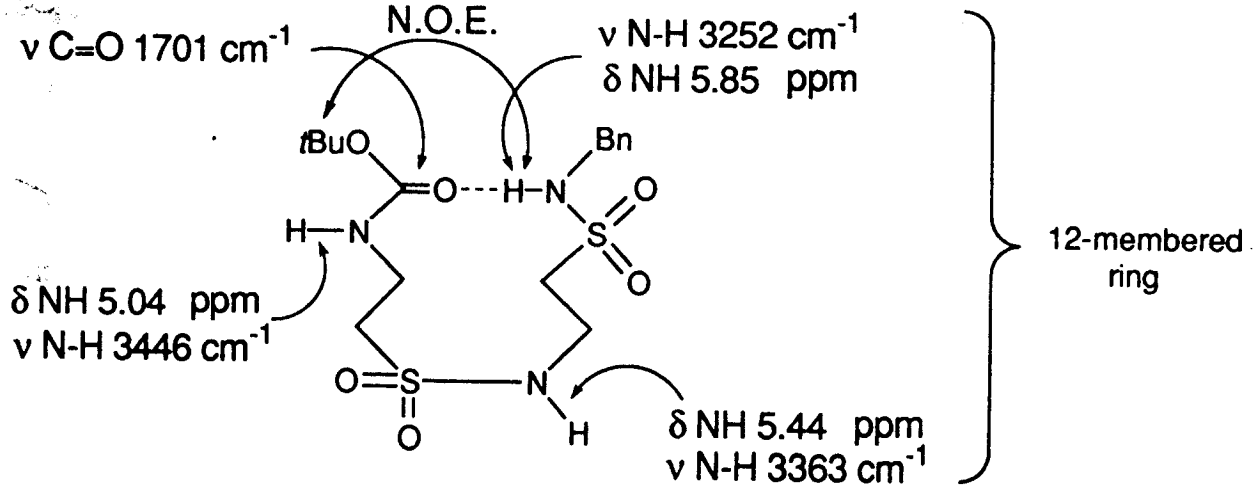


a) CH_2Cl_2, DMF, triphosgene, 25°C, 30 min. b) CH_2Cl_2 $PhCH_2NH_2$, DBU, 0 → + 25°C, 15 h (a+b = 82%). c) TFA/CH_2Cl_2 (1:1), 0°C, 20 min, 100%. d) CH_2Cl_2, DBU, 0 → + 25°C, 15 h, 55-65%.

→ CONFORMATIONAL PREFERENCES OF THE OLIGOMERS

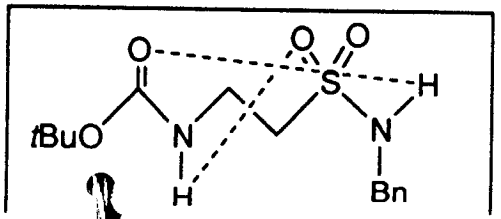
- → Variable-temperature ^{1}H-NMR spectroscopy
- → FT-IR spectroscopy
- → N.O.E. experiments
- → Computer modelling
- → X-Ray crystallography

^{1}H-NMR ($CDCl_3$, 10^{-3} M, RT) and FT-IR ($CHCl_3$, 10^{-3} M, RT)

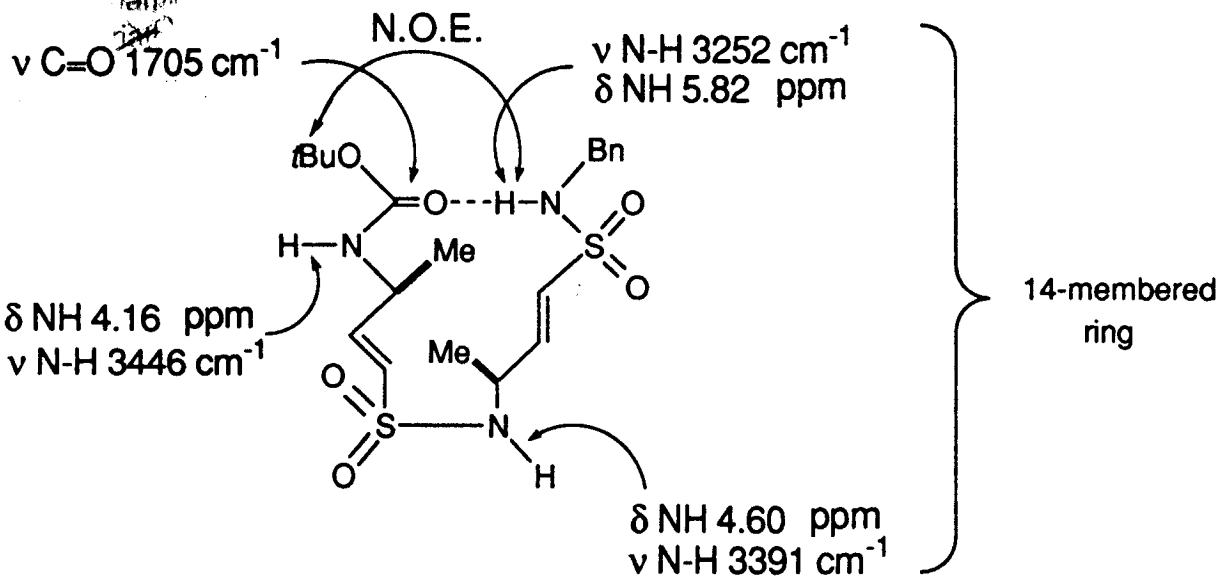


→ N-H--O angles are more linear in twelve membered rings, thus strengthening the hydrogen bonds

→ **No** 6- or 8-membered ring hydrogen bonding in monomers



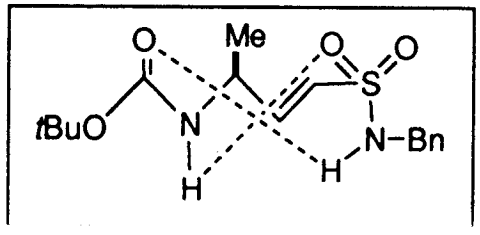
^{1}H-NMR ($CDCl_3$, 10^{-3} M, RT) and FT-IR ($CHCl_3$, 10^{-3} M, RT)



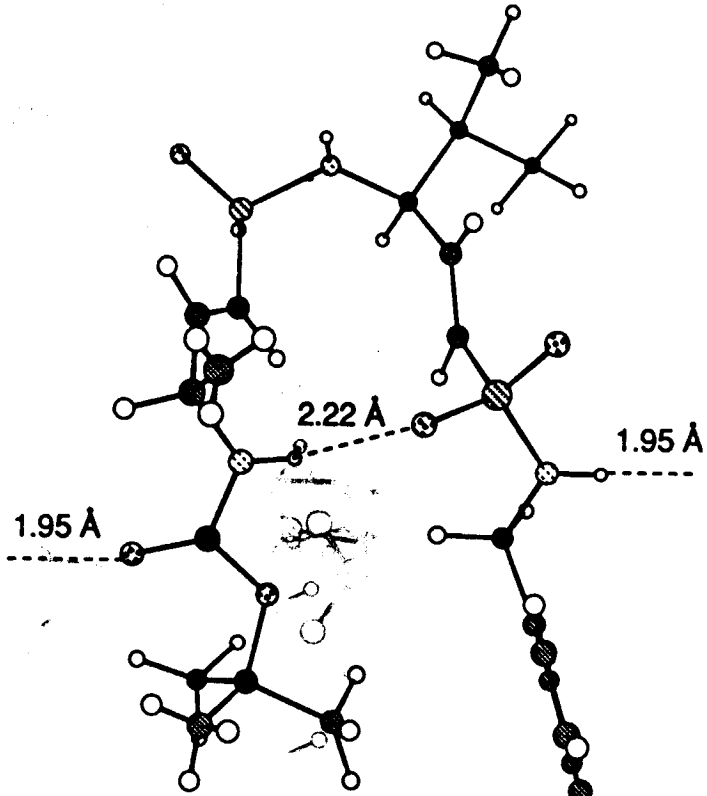
→ N.O.E. at the SO_2N-H involved in the hydrogen bonding upon irradiation of the t-Bu of the Boc group. Shift to lower frequencies of both the ν C=O (-20/-25 cm-1) and the ν N-H (-135/-140 cm-1) involved in the hydrogen bonding. Shift to lower field (1.4-1.6 ppm) for the hydrogen involved in the H-bonding.

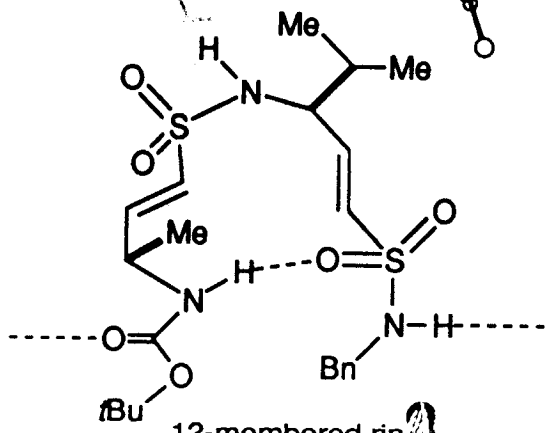
→ N-H--O angles are more linear in fourteen-membered rings, thus strengthening the H-bonds

→ **No** 7- or 9-membered ring hydrogen bonding in monomers



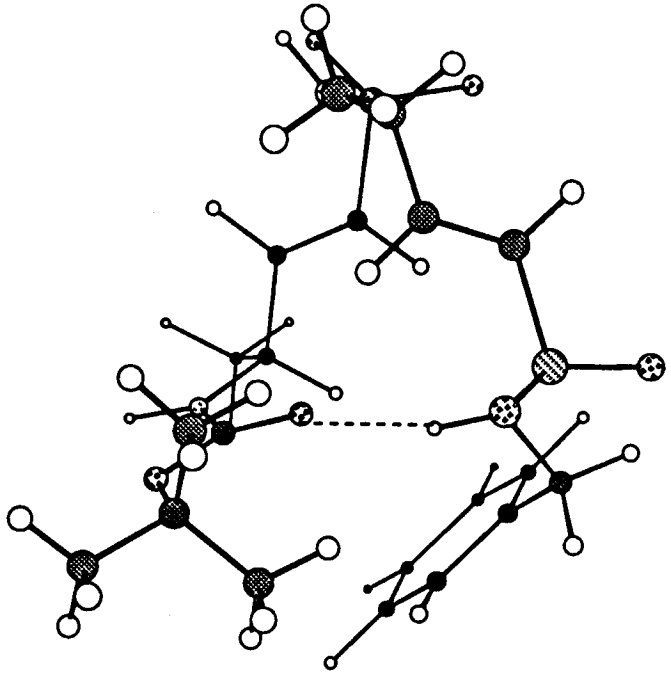
Single crystal X ray structure (O. Carugo, Univ. Pavia)

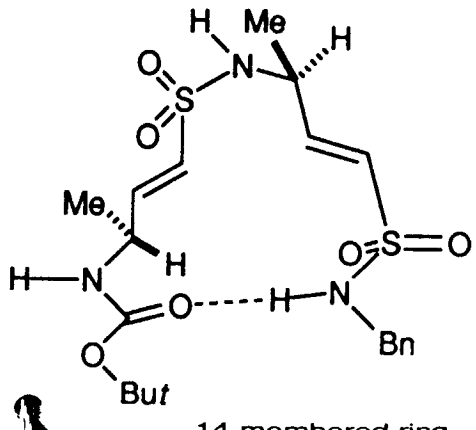




12-membered rin

Solution structure ($CHCl_3$)





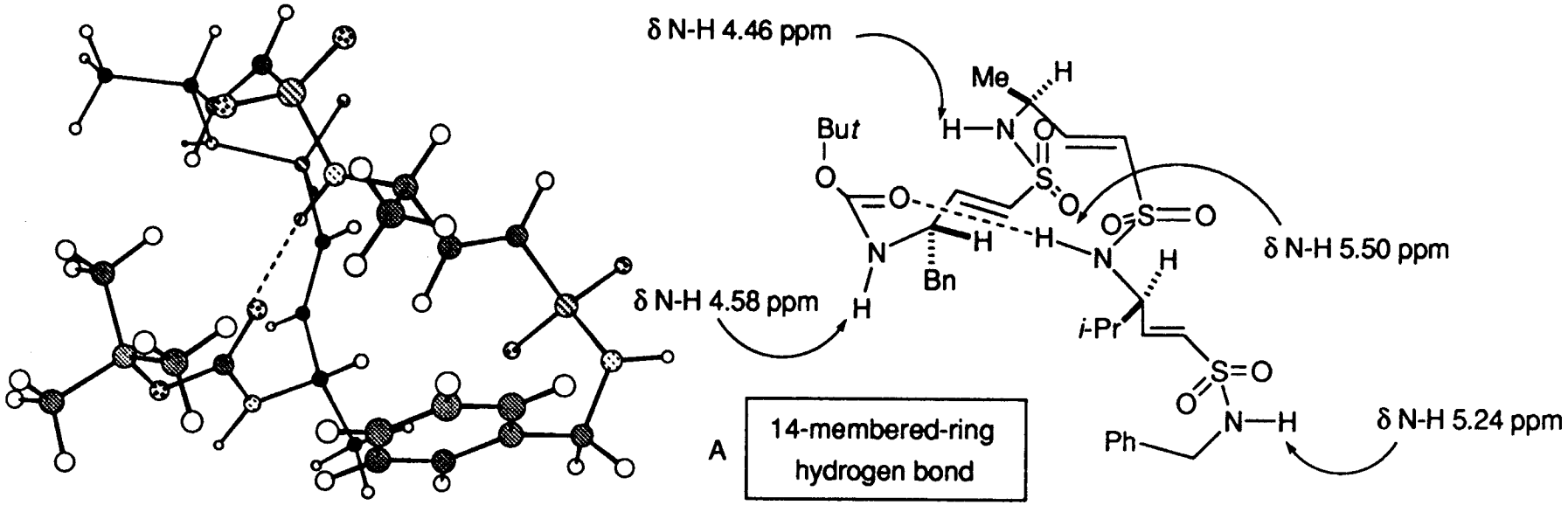
14-membered ring

12-membered ring

14-membered ring

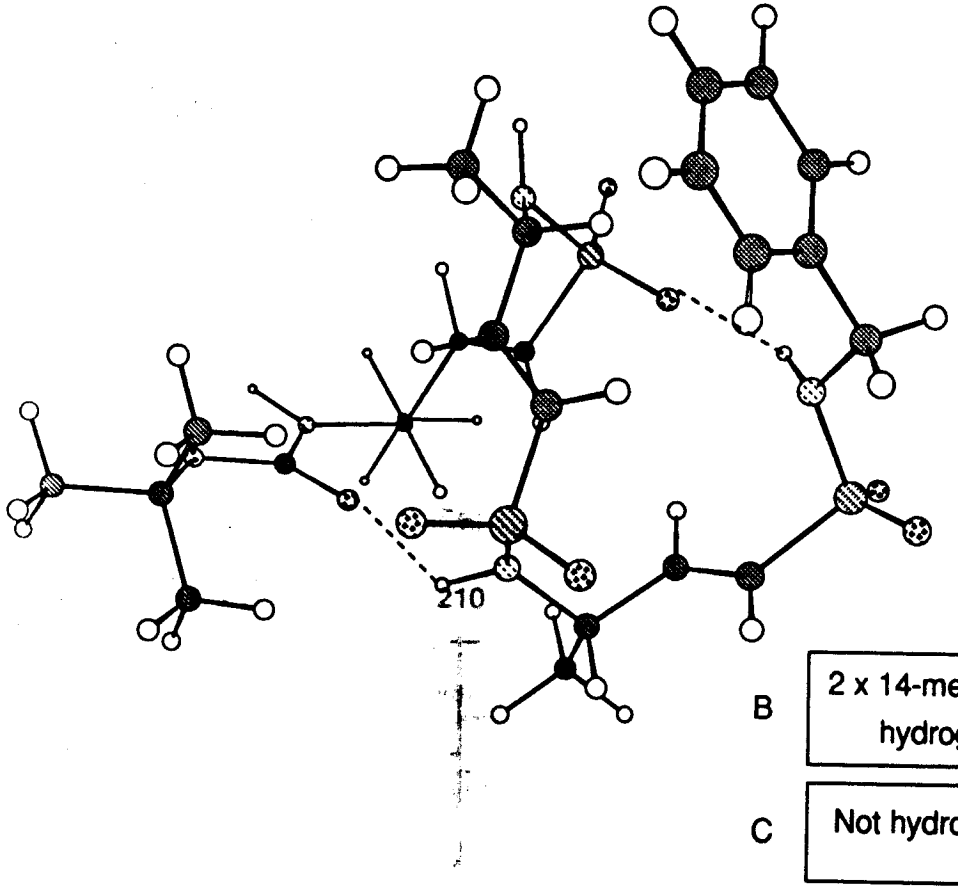
Modelling more complex cases

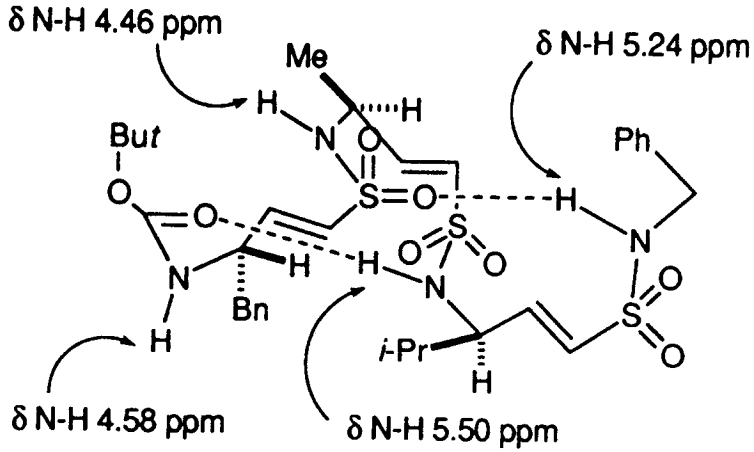
- Usage-directed Still-Chang-Guida torsional Monte Carlo method, as a part of BATCHMIN-MacroModel 3.1 molecular mechanics program, was used for the conformational search on a Silicon Graphics Iris workstation. The conformers were minimized in chloroform using the GB/SA model included in BATCHMIN. (Still, W.C. et al. J.Am.Chem. Soc. 1990,112,6127)
- The parameters for the sulfonamide group were developed at Milano University (Belvisi, L. et al. J.Mol.Struct. 1994, 318, 189-202) by the appropriate combination ab initio data with specific geometric features extracted from crystal structures.



A 14-membered-ring hydrogen bond

Modelling more complex cases





B — 2 x 14-membered-ring hydrogen bonds

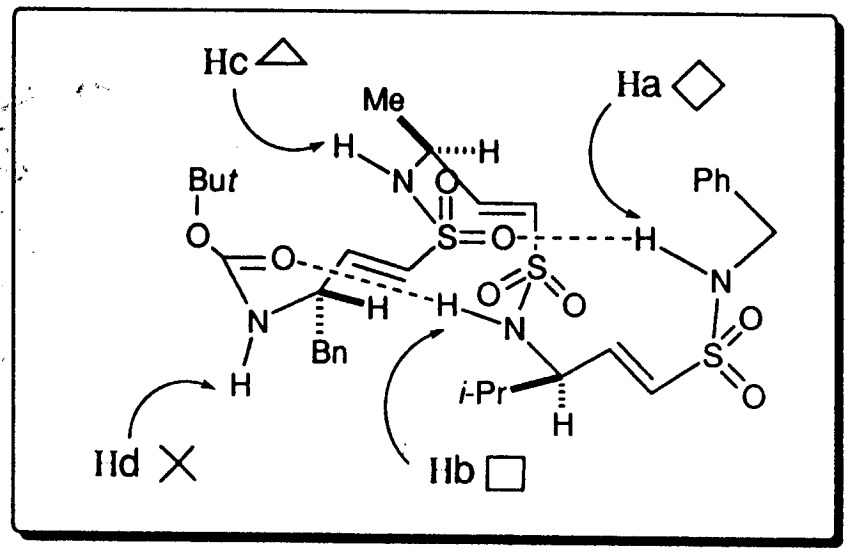
C — Not hydrogen-bound

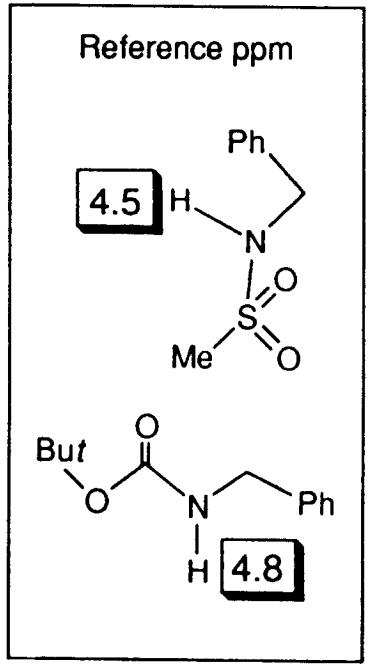
ν C=O 1698 (bound)
1719 (free)[shoulder]

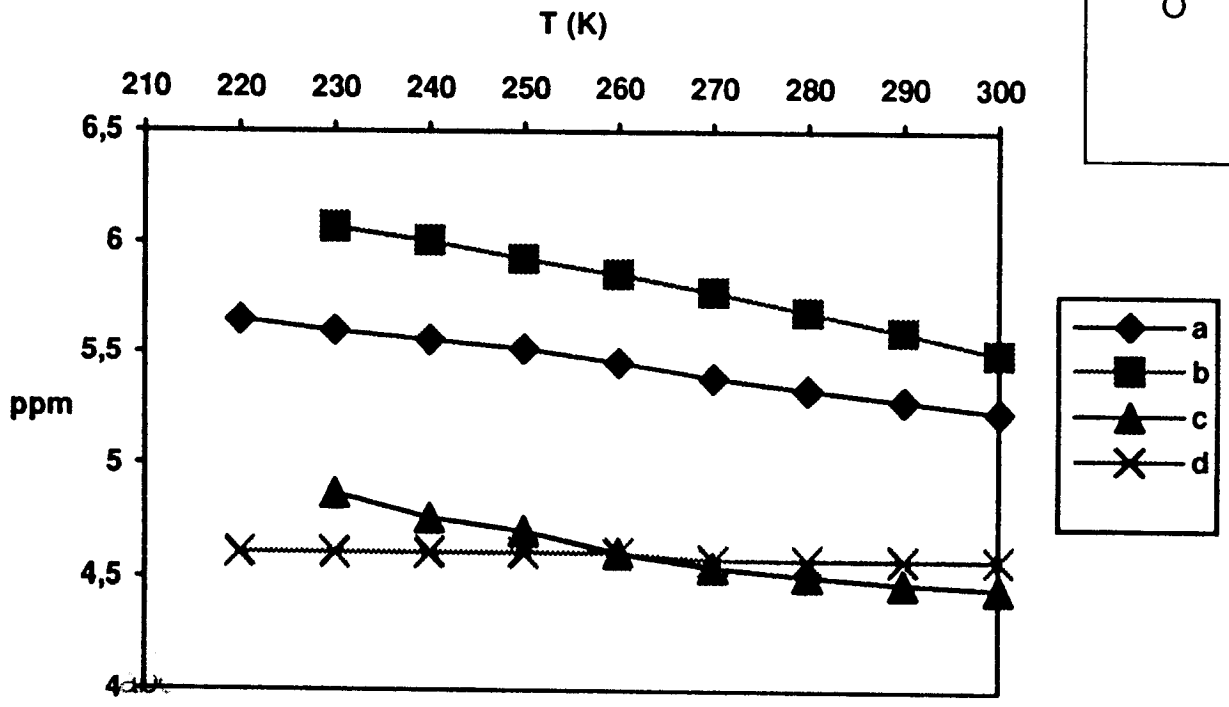
ν N-H (CONH) 3444 (free)

ν N-H (SO_2NH) 3389 (free)

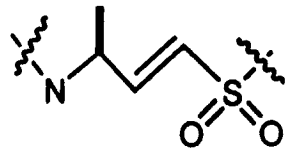
ν N-H (SO_2NH) 3249 (bound)[broad]


Hc
Ha
Me
But
Ph
Bn
i-Pr
Hd
Hb

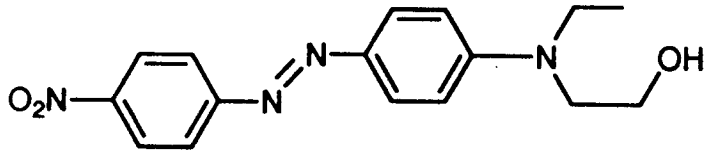

Reference ppm
4.5
Ph
Me
But
Ph
4.8


T (K)
210
220
230
240
250
260
270
280
290
300
6,5
6
5,5
5
4,5
4
ppm
a
b
c
d

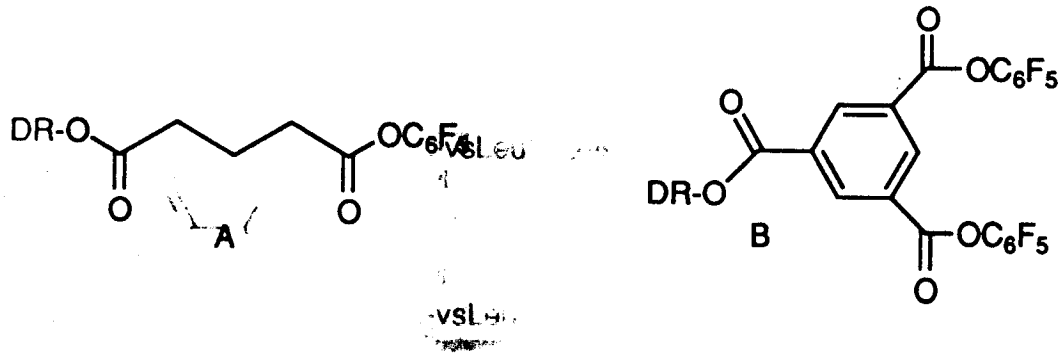
→ Collaboration with W. Clark Still and Peter Nestler, Columbia University, New York, N.Y. 10027, USA
assisted by a NATO Collaborative Research Grant 1992-1994



≡ L-vsAla (vinylogous sulfonoalanine)

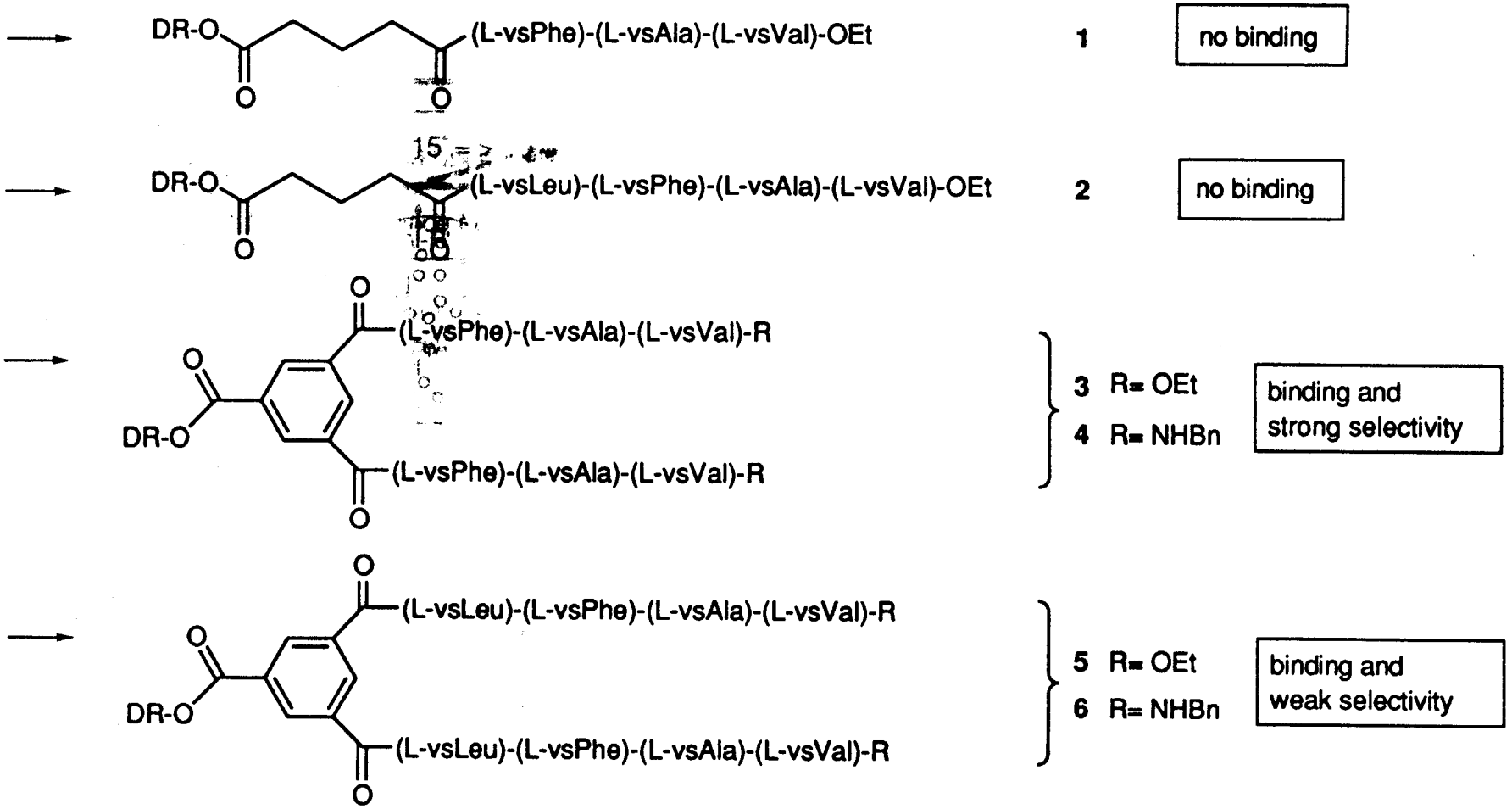


≡ Disperse Red 1 (**DR**-OH)



Boc-vsPhe-vsAla-vsVal-OEt (Trimer-OEt)
Boc-vsPhe-vsAla-vsVal-NHBn (Trimer-NHBn)
Boc-vsLeu-vsPhe-vsAla-vsVal-OEt (Tetramer-OEt)
Boc-vsLeu-vsPhe-vsAla-vsVal-NHBn (Tetramer-NHBn)

$\xrightarrow{25\%\ TFA/CH_2Cl_2}$ $\xrightarrow[i\text{-}Pr_2NEt/CH_2Cl_2/RT]{\textbf{A or B}}$



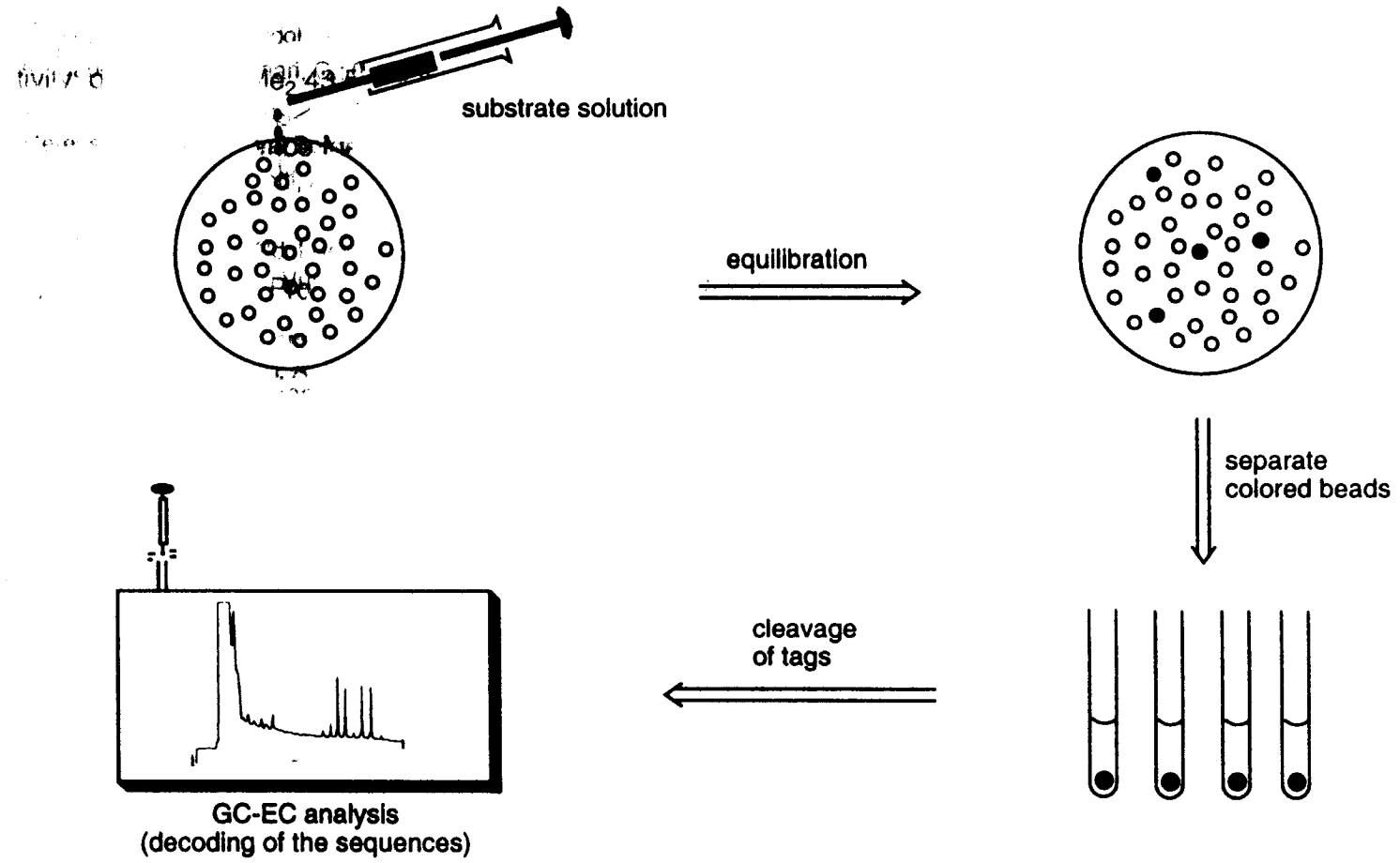
Derivatives **1-6** were screened for binding and selectivity with an encoded tripeptide combinatorial library using a solid-phase color assay in $CHCl_3$

$R^1(C{=}O)$-AA3-AA2-AA1-$NH(CH_2)_5CONH$-Polystyrene Bead

15^4 = > 50 000 Different members (50 625)

	N-terminal-R'	AA3	AA2	AA1
1	methyl	Gly	Gly	Gly
2	ethyl	D-Ala	D-Ala	D-Ala
3	isopropyl	L-Ala	L-Ala	L-Ala
4	*tert*-butyl	D-Ser-O-*t*-Bu	D-Ser-O-*t*-Bu	D-Ser-O-*t*-Bu
5	*tert*-amyl	L-Ser-O-*t*-Bu	L-Ser-O-*t*-Bu	L-Ser-O-*t*-Bu
6	CF_3	D-Val	D-Val	D-Val
7	isobutyl	L-Val	L-Val	L-Val
8	$MeOCH_2$—	D-Pro	D-Pro	D-Pro
9	cyclopropyl	L-Pro	L-Pro	L-Pro
10	cyclobutyl	D-Asn N-trilyl	D-Asn N-trilyl	D-Asn N-trilyl
11	cyclopentyl	L-Asn N-trilyl	L-Asn N-trilyl	L-Asn N-trilyl
12	$AcOCH_2$	D-Gln N-trityl	D-Gln N-trityl	D-Gln N-trityl
13	Ph	L-Gln N-trityl	L-Gln N-trityl	L-Gln N-trityl
14	Me_2N	D-Lys N-Boc	D-Lys N-Boc	D-Lys N-Boc
15	morpholino	L-Lys N-Boc	L-Lys N-Boc	L-Lys N-Boc

W. C. Still, et al. J.Am.Chem.Soc. 1994, 116, 373; J.Am.Chem.Soc. 1994, 116, 7467



Binding Assay on Resin-supported Encoded Combinatorial Libraries

The most deeply colored beads were picked and decoded using gas chromatography:

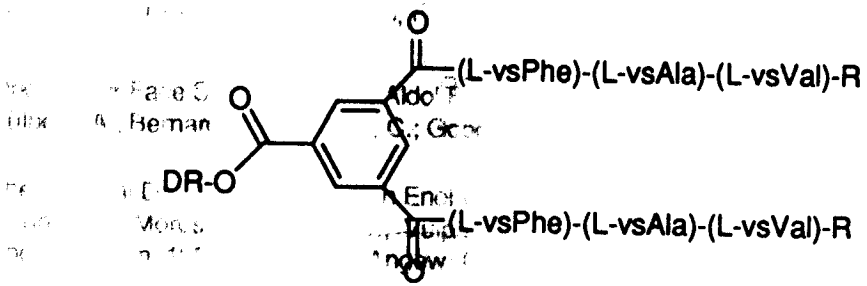
Selectivity for **3** : $R^1 = NMe_2$ 43.5%; AA1 = L-Gln N-trityl 70.0% (23 decoded beads).

Sequence Me_2N-CO-AA3-AA2-L-Gln-N-Trityl 26%

Selectivity for **4** : AA3 = L-Pro (25%); AA2 = L-Gln N-trityl (22%); AA1 = L-Gln N-trityl 53% (32 decoded beads).

AA2 = D-Val (19%) AA1 = D-Pro 19%.

Sequence R^1-CO-L-Pro-D-Val-D-Pro 10%



3 R= OEt

4 R= NHBn

Rational Design of Stereoselective Boron Enolates

E.C. Milano (C. Gennari) -Cambridge (I. Paterson) Laboratory Twinning grant 1990-1993
E.C. Human Capital and Mobility Network grant 1993-1996
N.A.T.O. Travel award 1988-1990 and 1990-1992 (Milano U.-Cambridge U., England)
C.N.R., M.U.R.S.T. Rome

Transition State Modelling of the Aldol Reaction of Boron Enolates: a Force Field Approach.
Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J.M.; Paterson, I. J.Org.Chem. **1990**, 55, 3576

Origins of Stereoselectivity in Chiral Boron Enolate Aldol Reactions: a Computational Study using Transition State Modelling.
Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J.M.; Paterson, I.Tetrahedron **1991**, 47, 3471

Diastereofacial Selectivity in the Aldol Reactions of Chiral α-Methyl Aldehydes: a Computer Modelling Approach.
Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J.; Paterson, I. Tetrahedron **1992**, 48, 4439-4458.

Developing a Force Field for the Transition State of the Aldol Reaction of Enolborinates: Evaluation of the Use of Fixed Point Charges.
Bernardi, A.; Cassinari, A.; Comotti, A.; Gardner, M.; Gennari, C.; Goodman, J.; Paterson, I.
Tetrahedron **1992**, 48, 4183-4192.

The Rational Design of Highly Stereoselective Boron Enolates Using Transition State Computer Modeling : a Novel, Asymmetric Anti-Aldol Reaction for Ketones.
Gennari, C.; Hewkin, C.T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J.; Paterson, I. J.Org.Chem. **1992**, 57, 5173-5177.

Origins of π-Face Selectivity in the Aldol Reactions of Chiral *E*-Enol Borinates: a Computational Study Using Transition State Modelling.
Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J.M.; Paterson, I. Tetrahedron **1993**, 49, 685.

The Rational Design of Chiral Boron Enolates: a Novel , Highly Enantioselective Aldol Reaction for Thioacetates and Thiopropionates.
Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A.
Angew. Chem. **1993**,105, 1717. Angew. Chem. Int. Ed. Engl. **1993**, 32, 1618.

Computer-Assisted Design of Chiral Boron Enolates: The Role of Ate Complexes in Determining Aldol Stereoselectivity.
Bernardi, A.; Comotti, A.; Gennari, C.; Hewkin, C.T.; Goodman, J.; Schlapbach, A.; Paterson, I.
Tetrahedron **1994**, 50, 1227-1242.

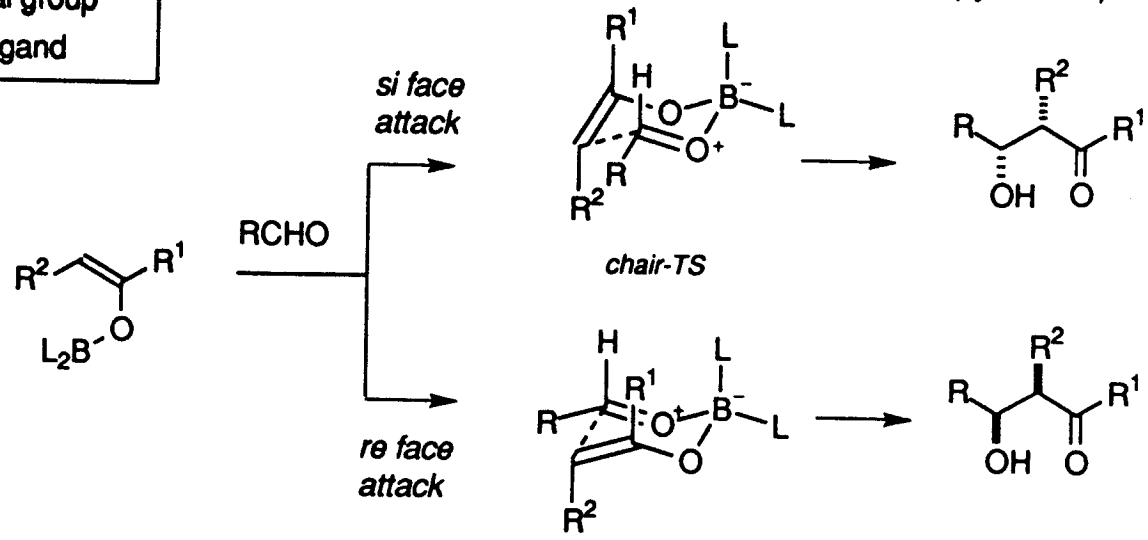
Reagent Control in the Aldol Addition Reaction of Chiral Boron Enolates with Chiral Aldehydes.
Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. Tetrahedron Letters **1994**, 35, 4623-4626.

A highly enantio- and diastereoselective aldol reaction for α-heterosubstituted thioacetates.
Gennari, C.; Vulpetti, A.; Moresca, D. Tetrahedron Letters 1994, 35, 4857-4860.

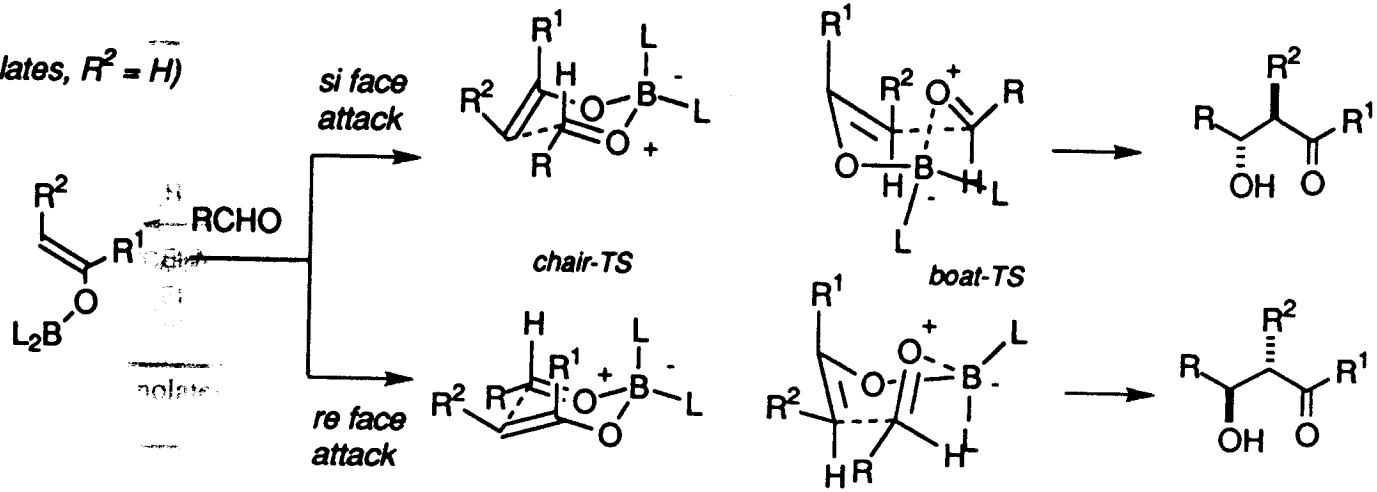
The aldol reaction of enolborinates

R^1 = achiral group
L = chiral ligand

(*Z enolates*)



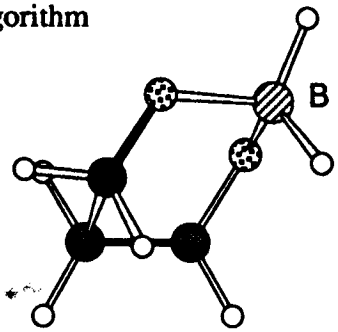
(*E enolates*)
(*Unsubstituted enolates, R^2 = H*)

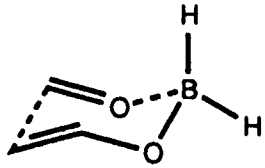


Ab initio (3-21G)
Baker's TS searching algorithm

Accessible to:

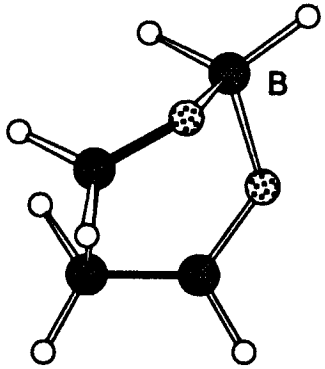
Z enolates
E enolates
Unsubstituted enolates

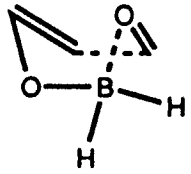




chair (1)

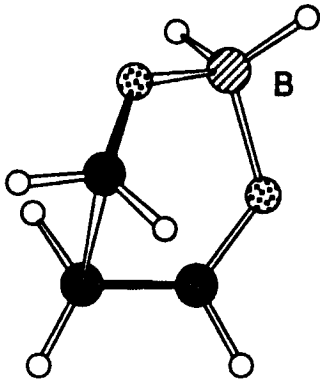
Unsubstitued enolates
(E enolates)

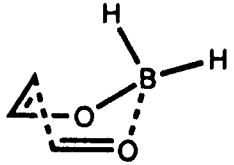




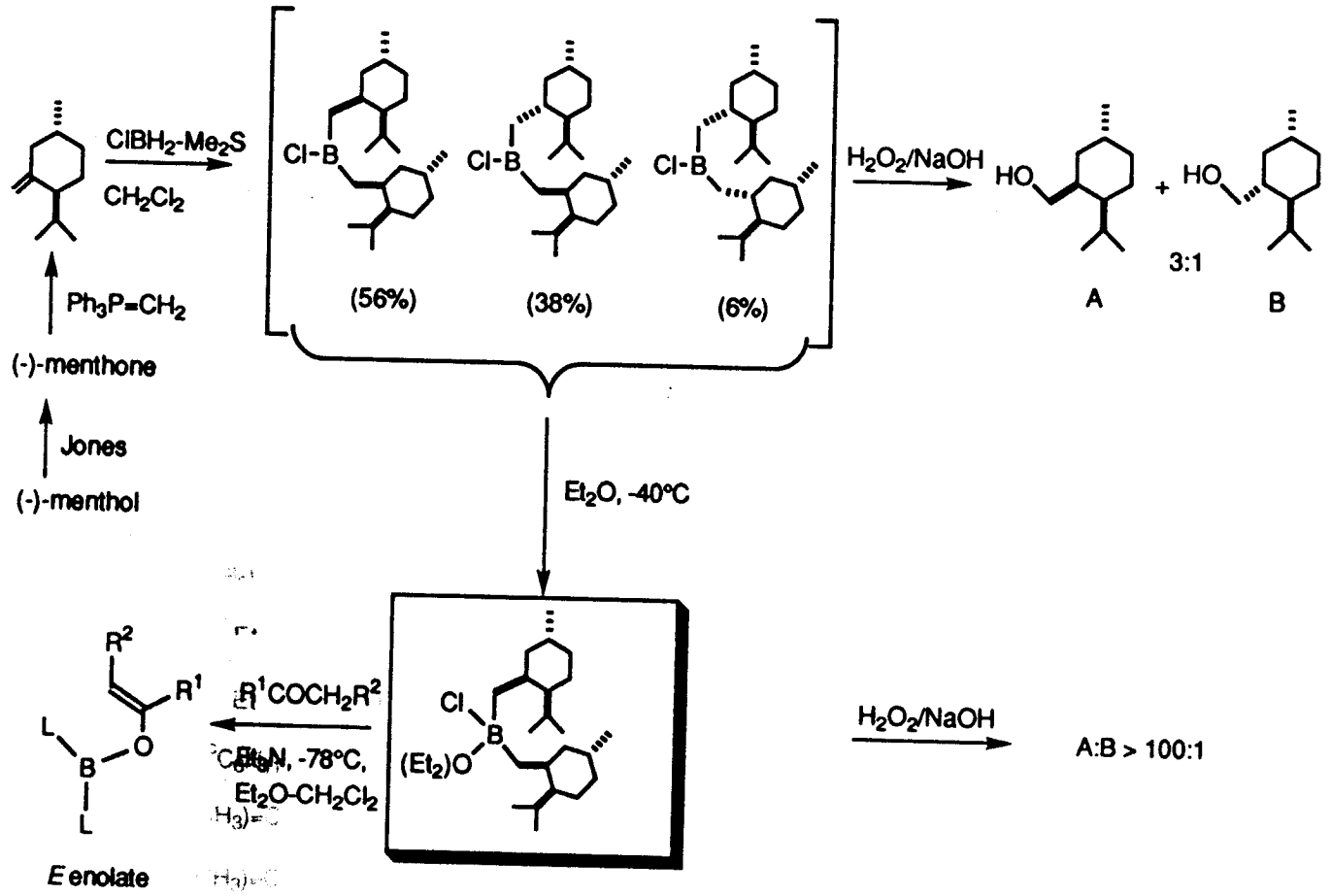
boat A (2)

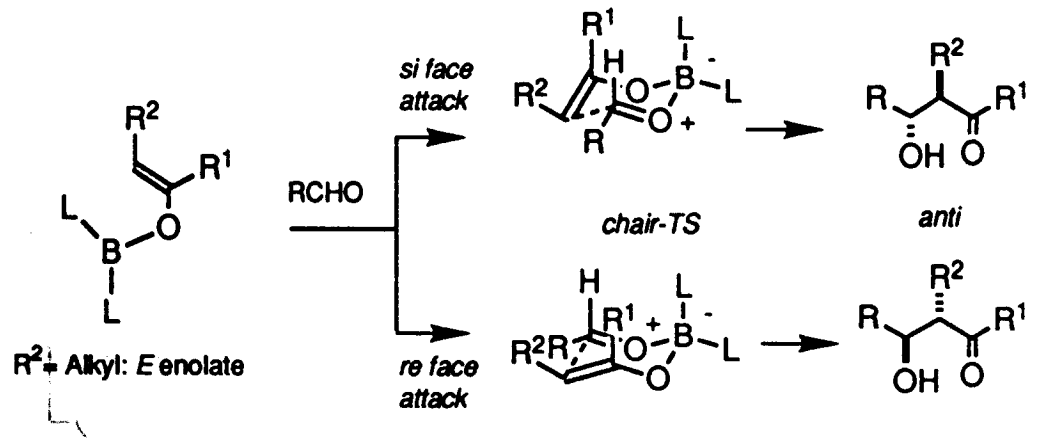
Unsubstitued enolates
(E enolates)

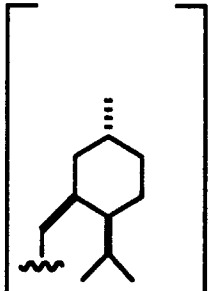


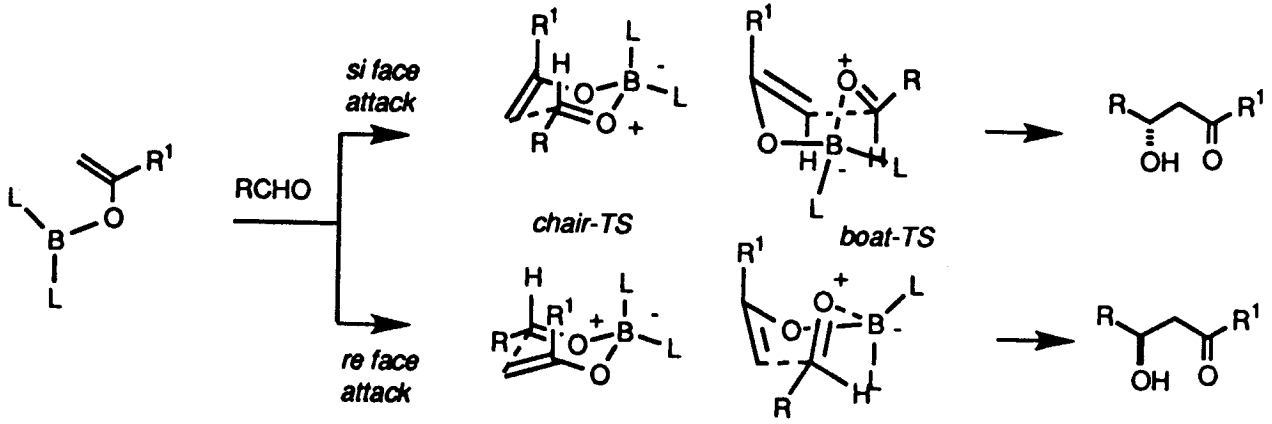


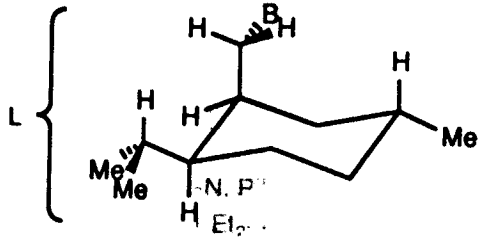
boat B (3)


ClBH2-Me2S
CH2Cl2
Ph3P=CH2
(-)-menthone
Jones
(-)-menthol
Cl-B
(56%)
(38%)
(6%)
H2O2/NaOH
HO
3:1
A
B
Et2O, -40°C
Cl
B
(Et2)O
R1COCH2R2
Et3N, -78°C,
Et2O-CH2Cl2
R2
R1
L
B
O
L
E enolate
H2O2/NaOH
A:B > 100:1

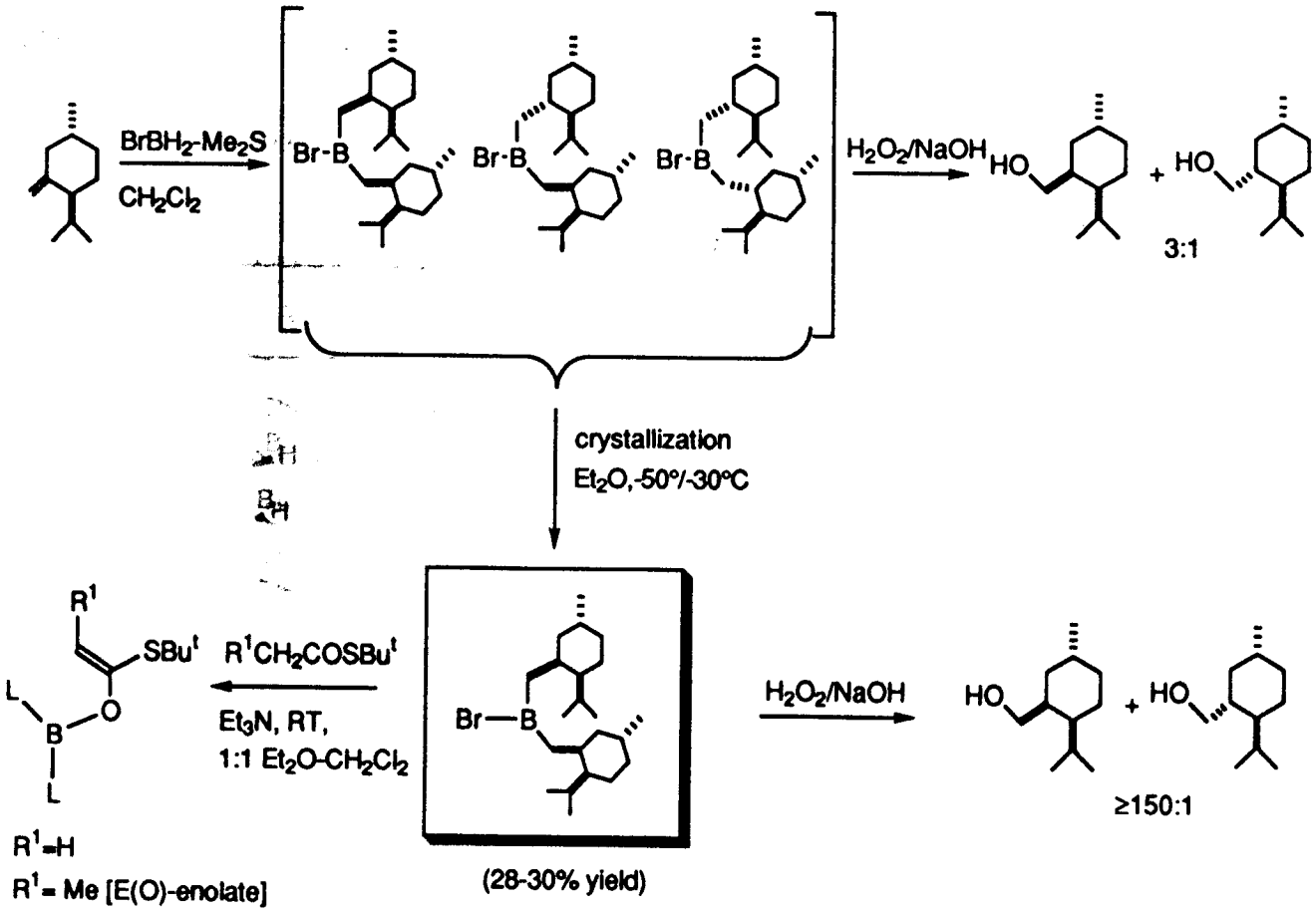


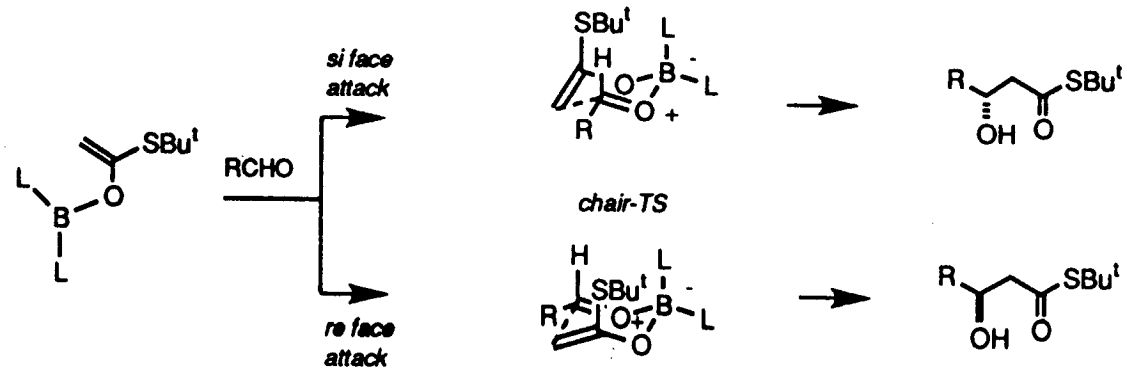
Entry	R	R^1	R^2	L	*re-si* ratio (calcd.)	*re-si* ratio (expt.)	% Yield	Anti-Syn (expt.)
1	$C(CH_3)=CH_2$	Et	Me	Ipc from (+)-α-pinene	1:2.8	1:1.0-1.5	80	80:20
2	$C(CH_3)=CH_2$	Et	Me		22:1	7.0:1	62	93:7
3	$C(CH_3)=CH_2$	^iPr	Me		59:1	15.6:1	51	100:0
4	Et	Et	Me		24:1	9.2:1	50	92:8
5	Et	^iPr	Me		-	12.1:1	50	97:3
6	$^cC_6H_{11}$	^iPr	Me		-	6.6:1	54	100:0
7	$C(CH_3)=CH_2$	$-(CH_2)_3-$		from (-)-menthone	5:1	6.7:1	60	100:0
8	$C(CH_3)=CH_2$	$-(CH_2)_4-$			-	3.5:1	59	100:0
9	$C(CH_3)=CH_2$	Ph	Me		15:1	13.0:1	60	86:14

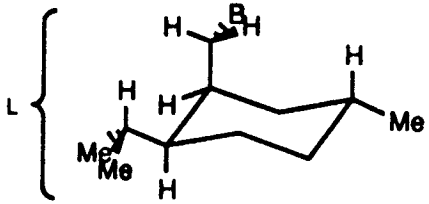




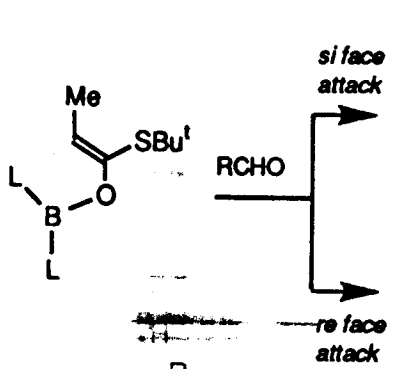
Entry	R	R^1	*Expt. re-si* ratio	% Yield
1	$C(CH_3)=CH_2$	^{i}Pr	7.3:1	66
2	$C(CH_3)=CH_2$	^{i}Bu	3.4:1	80
3	$C(CH_3)=CH_2$	^{t}Bu	7.1:1	62
4	$C(CH_3)=CH_2$	Me	3.9:1	65
5	$C(CH_3)=CH_2$	Ph	5.5:1	81
6	$CH_2CH_2CH_3$	Me	6.5:1	65
7	$C(CH_3)=CH_2$	Et	4.4:1	51

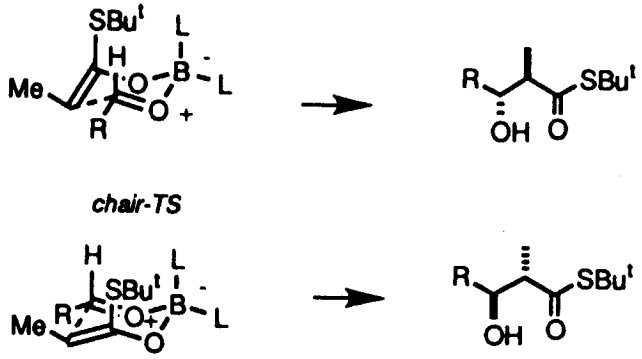

BrBH2-Me2S
CH2Cl2
Br-B
H2O2/NaOH
HO
+ HO
3:1
crystallization
Et2O,-50°/-30°C
R1
SBut
L
B
O
L
R1CH2COSBut
Et3N, RT,
1:1 Et2O-CH2Cl2
Br—B
H2O2/NaOH
HO
+ HO
≥150:1
R1=H
R1= Me [E(O)-enolate]
(28-30% yield)



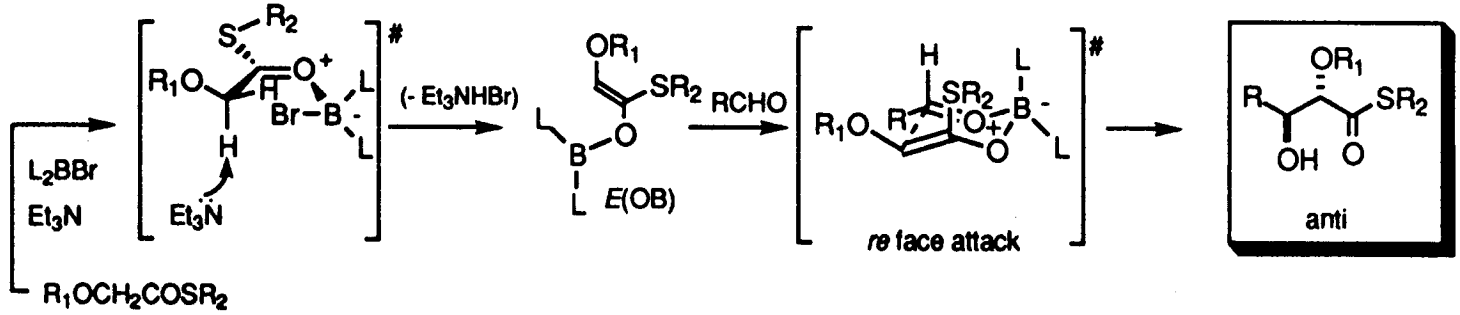


Entry	R	*re-si* ratio	*anti-syn* ratio	% yield
1	Ph	94.7:5.3	-	68
2	iPr	97.6:2.4	-	75
3	$PhCH_2CH_2$	98.3:1.7	-	79
4	CH_2=C(Me)-	93.6:6.4	-	71
5	n-C_3H_7	97.0:3.0	-	86
6	c-C_6H_{11}	96.7:3.3	-	88
7	CH_2=C(Me)-	80:20	-	60]

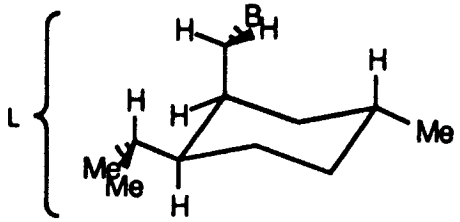


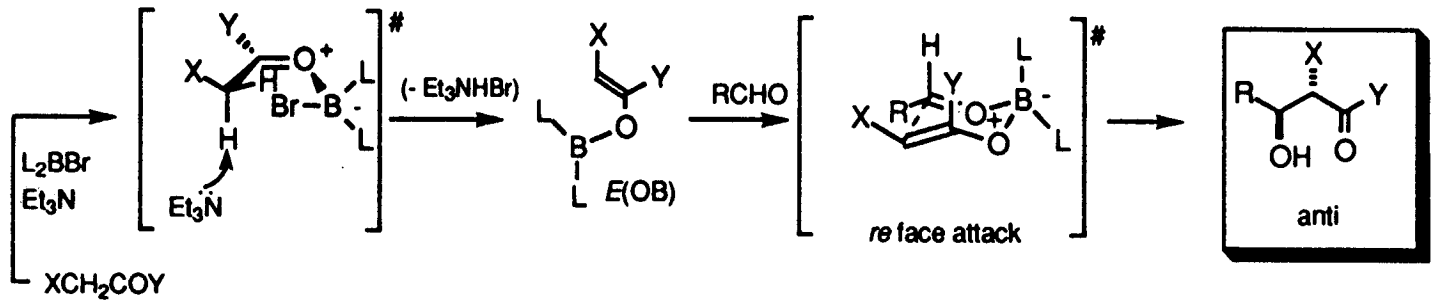


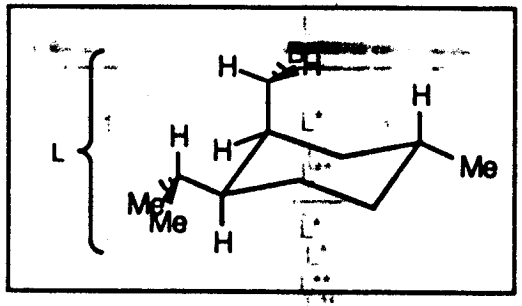
Entry	R	*re-si* ratio	*anti-syn* ratio	% yield
1	Ph	≥99:1	95:5	69
2	iPr	99:1	96:4	61
3	$PhCH_2CH_2$	≥99:1	≥97:3	57
4	CH_2=C(Me)-	≥99:1	94:6	43
5	n-C_3H_7	99:1	≥97:3	64
6	PhCH=CH	99:1	≥97:3	66
[CH_3CH_2COSPh ⟶ 7	CH_2=C(Me)-	≥99:1	80:20	68]
[CH_3CH_2COSPh ⟶ 8	Ph	≥99:1	74:26	65]



R	R_1	R_2	*Expt.* *re-si* ratio	*Expt.* *anti-syn* ratio	% Yield
Ph	Bn	Bu^t	≥97:3	≥97:3	65
CH_2=C(Me)-	Bn	Bu^t	97.8:2.2	>98:2	78
Ph	Bn	Ph	≥98:2	>99:1	40-50
Ph	TBDMS	Ph	98.5:1.5	>99:1	79
i-Pr	Bn	Bu^t	97.7:2.3	≥97:3	50-60
n-Pr	Bn	Bu^t	97.6:2.4	≥97:3	57

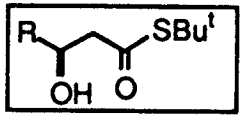




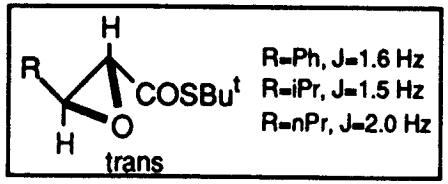


R	X	Y	*Expt.* *re-si* ratio	*Expt.* *anti-syn* ratio	% Yield
Ph	Cl	SBu^t	>99:1[a]	91:9[b]	65
Ph	Br	SBu^t	>99:1[a]	≥97:3 (97.5:2.5)[b]	40-50
i-Pr	Cl	SBu^t	97:3[a]	≥96:4[b]	70
i-Pr	Br	SBu^t	≥99:1[a]	≥97:3 (97.8:2.2)[b]	55
n-Pr	Cl	SBu^t	97.3:2.7[a]	96:4[b]	73
n-Pr	Br	SBu^t	>99:1[a]	>99:1[b]	45
Ph	Cl	OBu^t	-	-	0
Ph	Br	OBu^t	-	-	0
CH_2=C(Me)-	Cl	SPh	96.3:3.7[c]	52:48	55
CH_2=C(Me)-	Br	SPh	96:4[d]	80:20	55

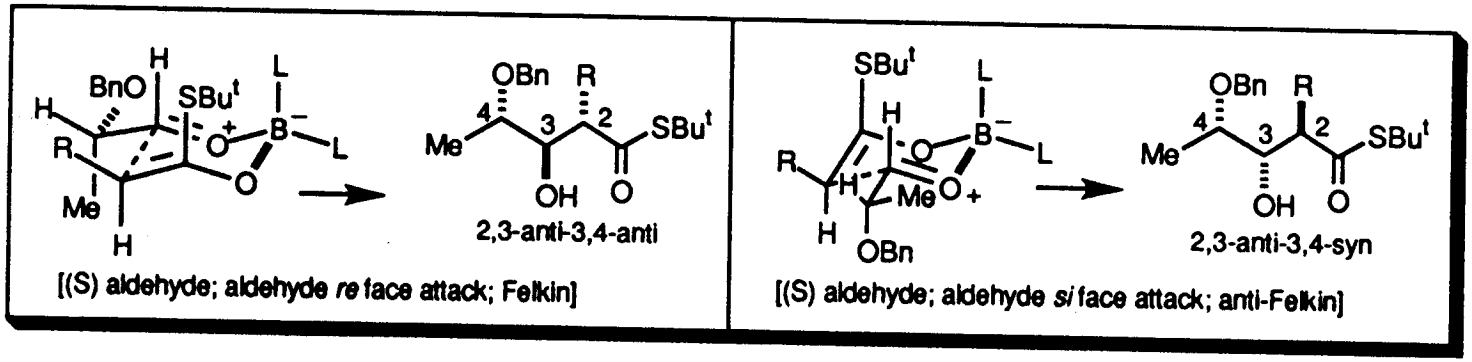
[a]Treatment with Zn/NH_4Cl/MeOH gave (known absolute configuration):



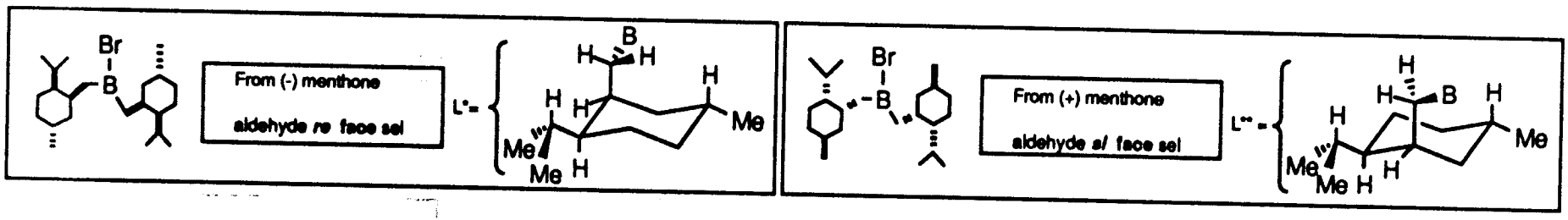
[b]Treatment with tBuOK/tBuOH gave:

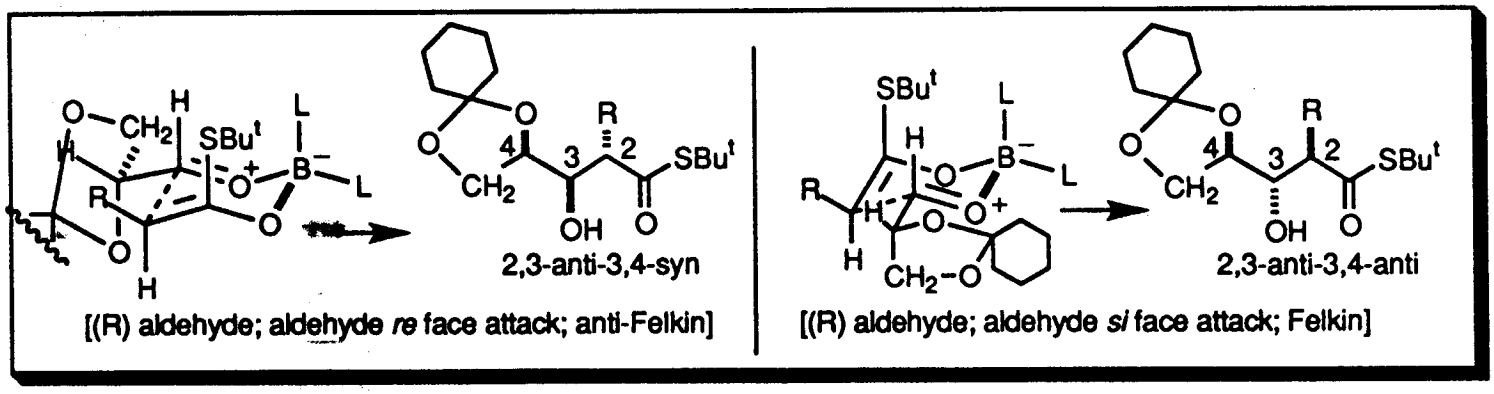


[c]95:5 for the *syn* isomer. [d] 93:7 for the *syn* isomer.

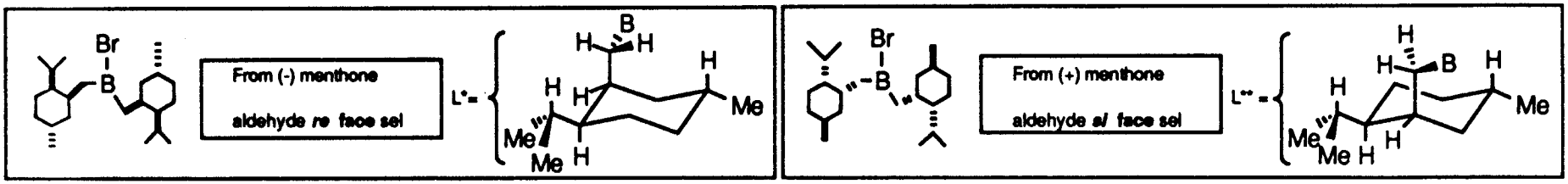


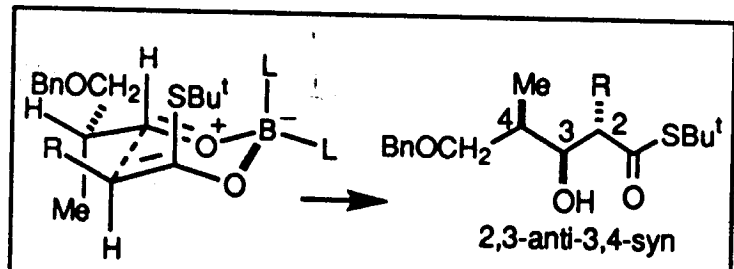
Entry	R	L	Aldehyde Abs. conf.	Enolate *E* : *Z* [2,3-Anti: 2,3-Syn]	%E.E. (major diaster.)	2,3-anti 3,4-anti (Felkin)	2,3-anti 3,4-syn	2,3-syn 3,4-anti (Felkin)	2,3-syn 3,4-syn	Yield %
1	Me	L*	S	>98:2	100	≥99	≤1	Not detected		65
2	Me	L**	S	>98:2	100	≤1	≥99	Not detected		60
3	H	L*	S	---	100	93	7	---		75
4	H	L**	S	---	100	6	94	---		65





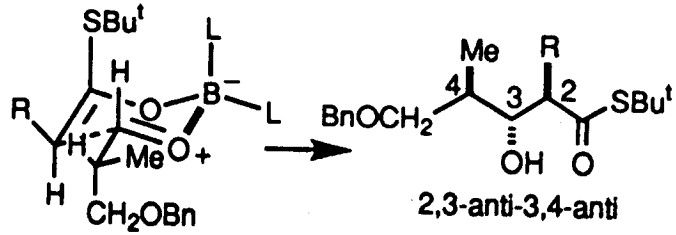
Entry	R	L	Aldehyde Abs. conf.	Enolate *E* : *Z* [2,3-Anti: 2,3-Syn]	%E.E. (major diaster.)	2,3-anti 3,4-anti (Felkin)	2,3-anti 3,4-syn	2,3-syn 3,4-anti (Felkin)	2,3-syn 3,4-syn	Yield %
1	Me	L*	R	>98:2	100	5	95	Not detected		45
2	Me	L**	R	>98:2	100	99	1	Not detected		50
3	H	L*	R	---	100	3	97	---		72
4	H	L**	R	---	100	96	4	---		75





2,3-anti-3,4-syn

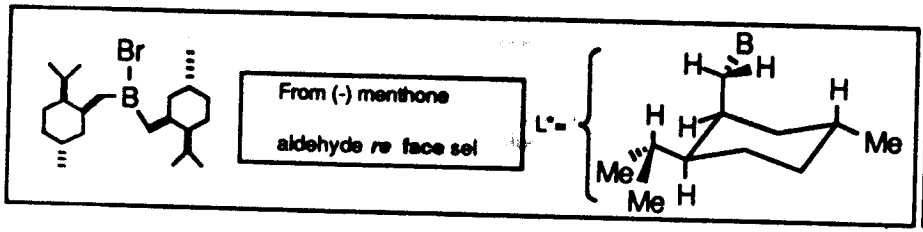
[(R) aldehyde; aldehyde *re* face attack; Felkin]

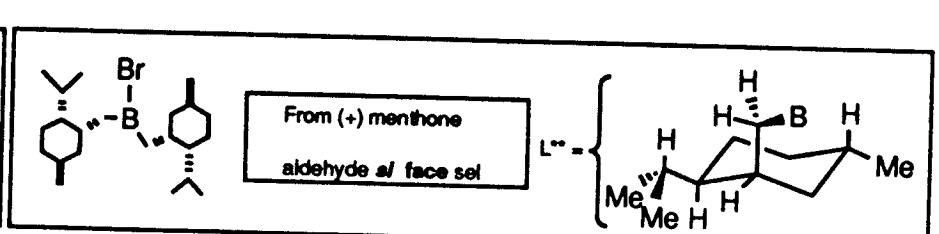


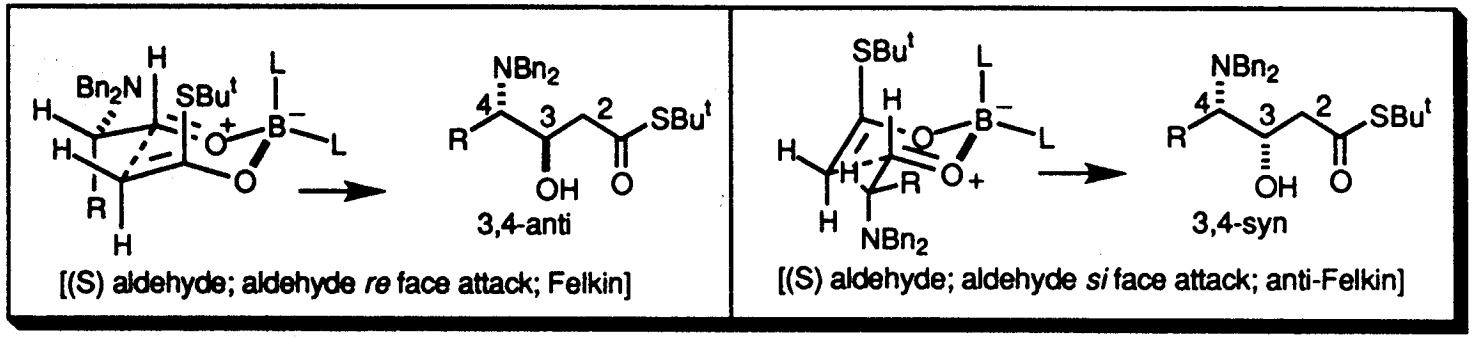
2,3-anti-3,4-anti

[(R) aldehyde; aldehyde *si* face attack; anti-Felkin]

Entry	R	L	Aldehyde Abs. conf.	Enolate *E*:*Z* [2,3-Anti: 2,3-Syn]	%E.E. (major diaster.)	2,3-anti 3,4-syn (Felkin)	2,3-anti 3,4-anti	2,3-syn 3,4-anti (Felkin)	2,3-syn 3,4-syn	Yield %
1	Me	L*	R/S	>98:2	-	51	49	Not detected		81
2	Me	L*	R	>98:2	100	95	5	Not detected		60
3	Me	L**	R	>98:2	100	35	65	Not detected		60
4	H	L*	R/S	---	-	50	50	---		70
5	H	L*	R	---	100	68	32	---		70
6	H	L**	R	---	100	4	96	---		60







Entry	R	L	Aldehyde Abs. conf.	%E.E. (major diaster.)	3,4-anti (Felkin)	3,4-syn	Yield %
1	Bn	L*	S	100	**98.6**	1.4	70
2	Bn	L**	S	100	3.2	**96.8**	60
3	Me	L*	S	100	**98.5**	1.5	66
4	Me	L**	S	100	3.7	**96.3**	61
5	*i*-Bu	L*	S	100	**>100**	<1	68
6	*i*-Bu	L**	S	100	2.5	**97.5**	62