



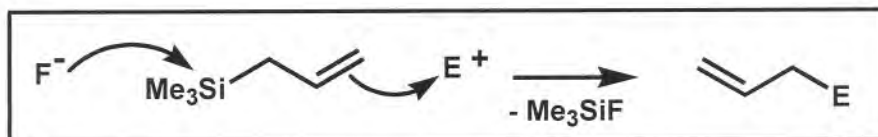
Fluoride ion induced stereoselective functionalization of heterosubstituted silyl derivatives

Dipartimento di Chimica Organica, Polo Scientifico, Via della Lastruccia, 13
50019 Sesto Fiorentino (Firenze)

C-C bond formation through organosilanes

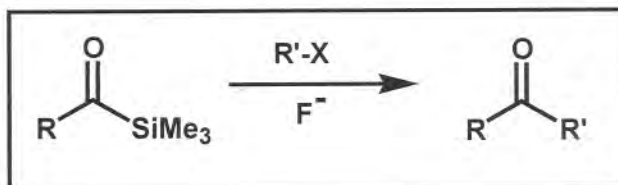
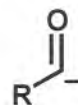
⇒ Conventional carbanions

ArCH_2^- , R-CH=CH-CH_2^-



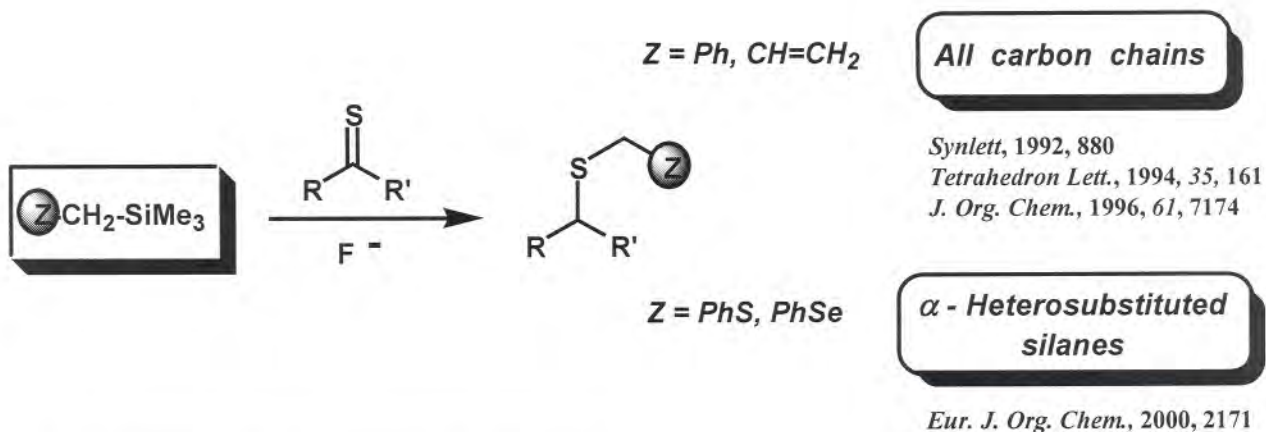
I. Fleming, J. Dunogues, R. Smithers *Org. Reactions*, 37, 57 (1989)

⇒ Non conventional carbanions
(Umpolung)



Synthesis, 647 (1989)

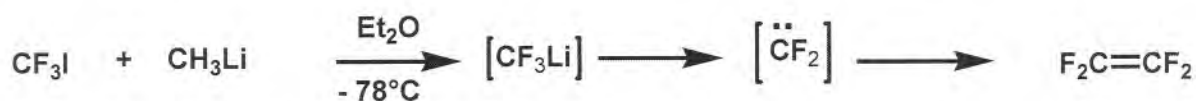
Easy transfer of silylated nucleophiles onto thiocarbonyl compounds



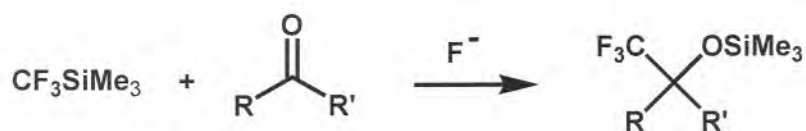
Inversion of the regiochemistry

Easy access to more versatile intermediates

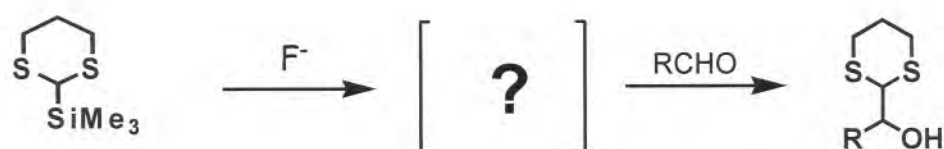
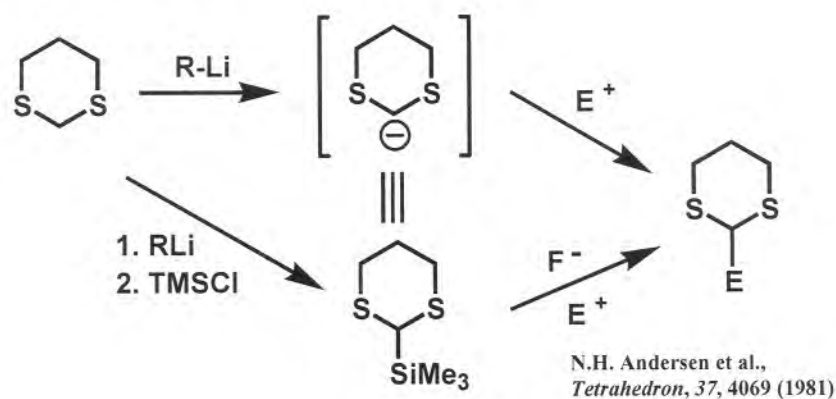
Reactivity of the C-Si bond



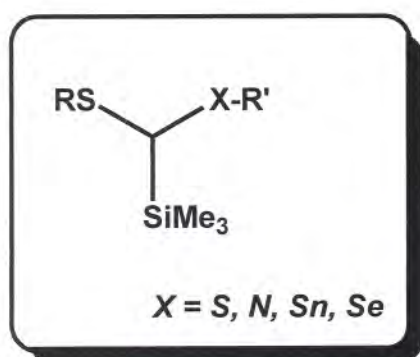
Burton, D.J., Yang, Z.-Y., *Tetrahedron*, 1992, 48, 1897



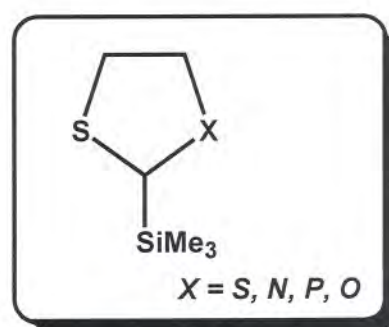
Surya Prakash, G.H., Yudin, A.K. *Chem Rev.* 1997, 97, 757



Possible use of different heterosubstituted silylated nucleophiles ?

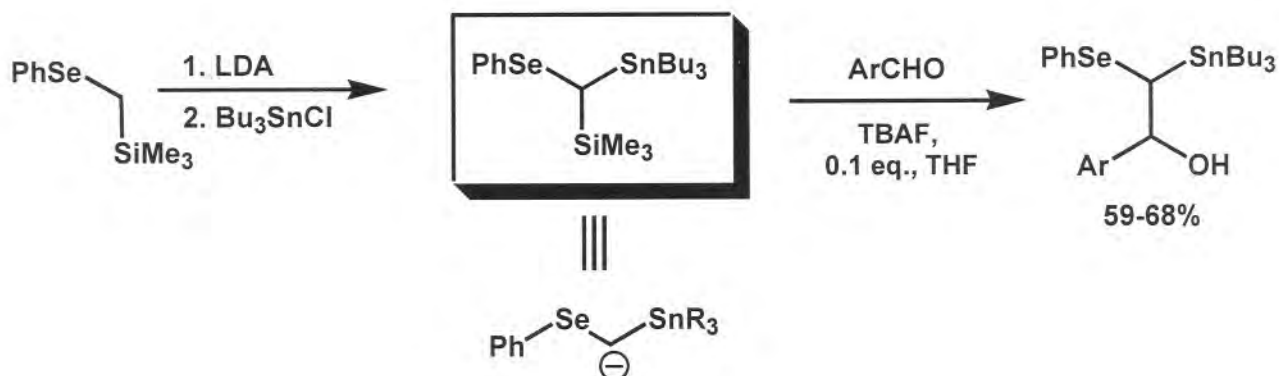
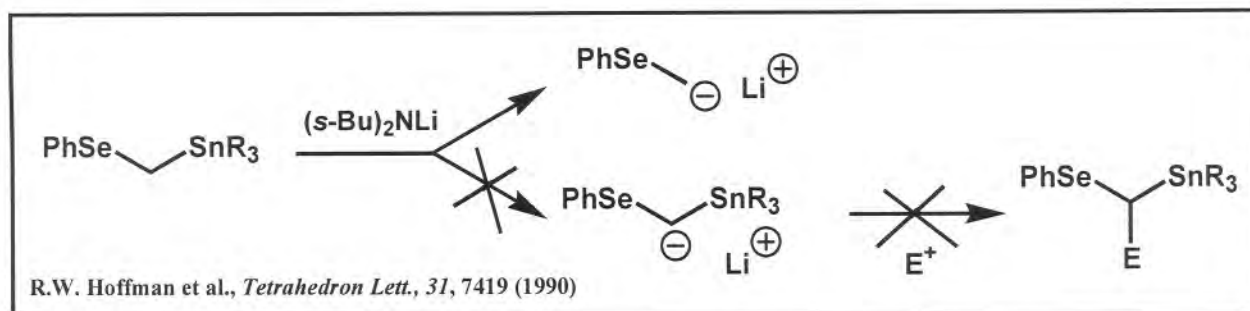


Acyclic α - heterodisubstituted organosilanes



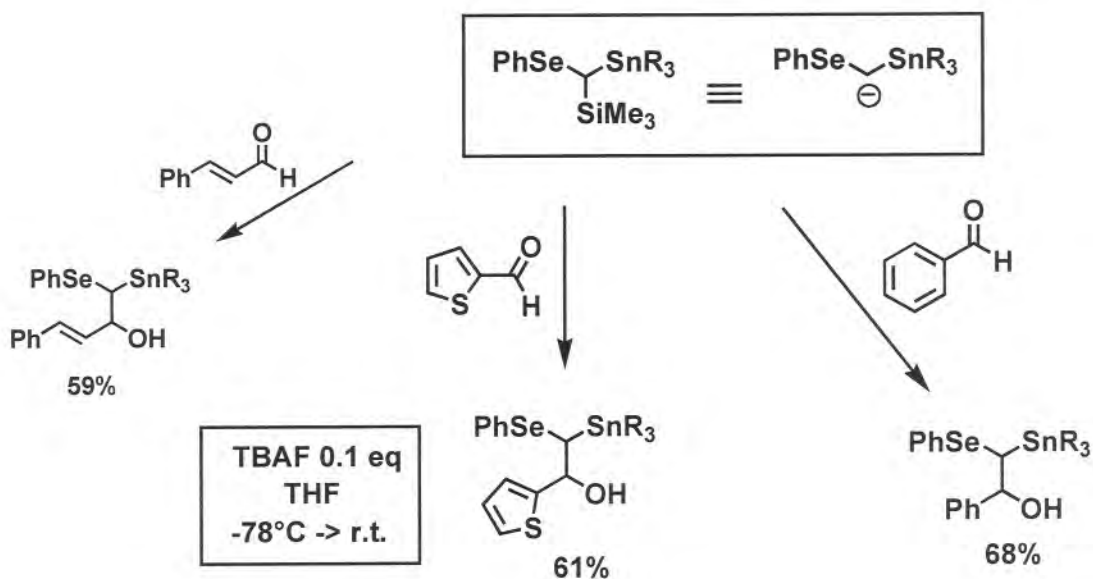
2-Trimethylsilyl-1,3-disubstituted heterocycles

Synthesis of mixed organometallic silylated nucleophiles



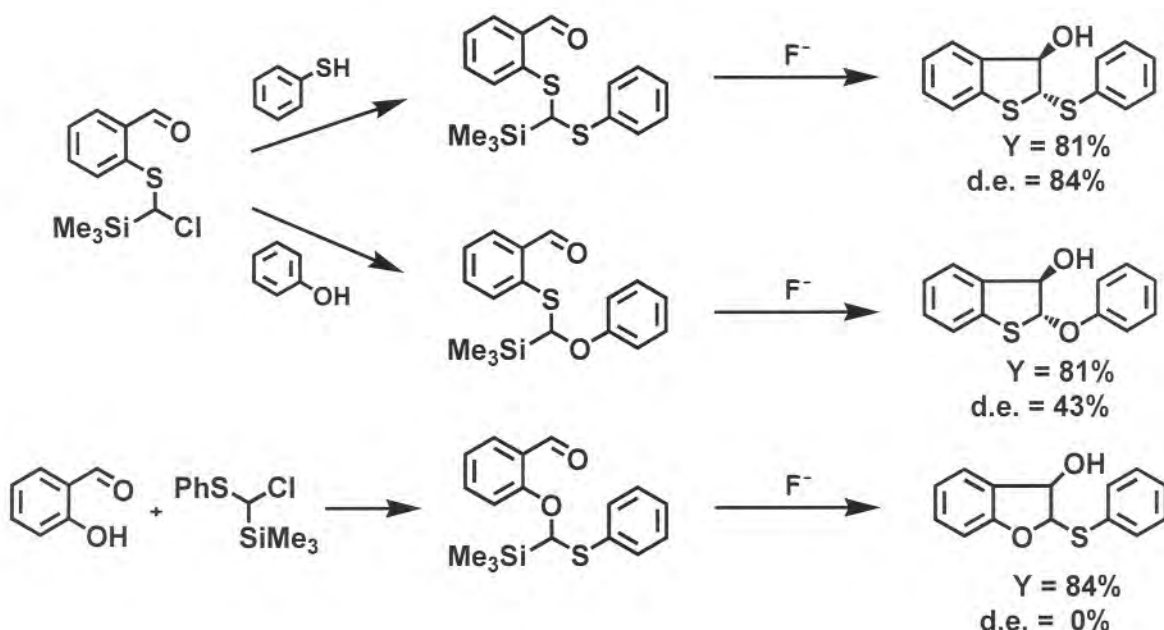
A. Degl'Innocenti, A. Capperucci, T. Nocentini, *Tetrahedron*, in press

Synthetic equivalent of not easily obtainable carbanions

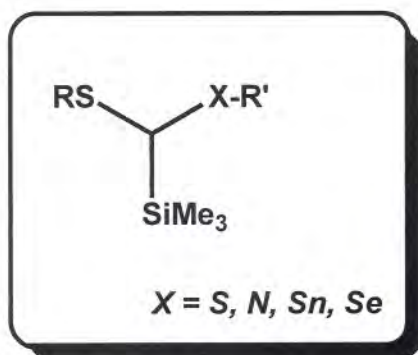


A. Degl'Innocenti, A. Capperucci, T. Nocentini, *Tetrahedron*, in press

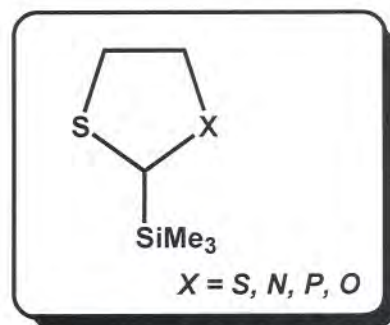
**Fluoride ion induced intramolecular functionalization:
synthesis of dihydrobenzothiophen- and dihydrobenzofuran
systems**



**Possible use of different heterosubstituted silylated
nucleophiles ?**

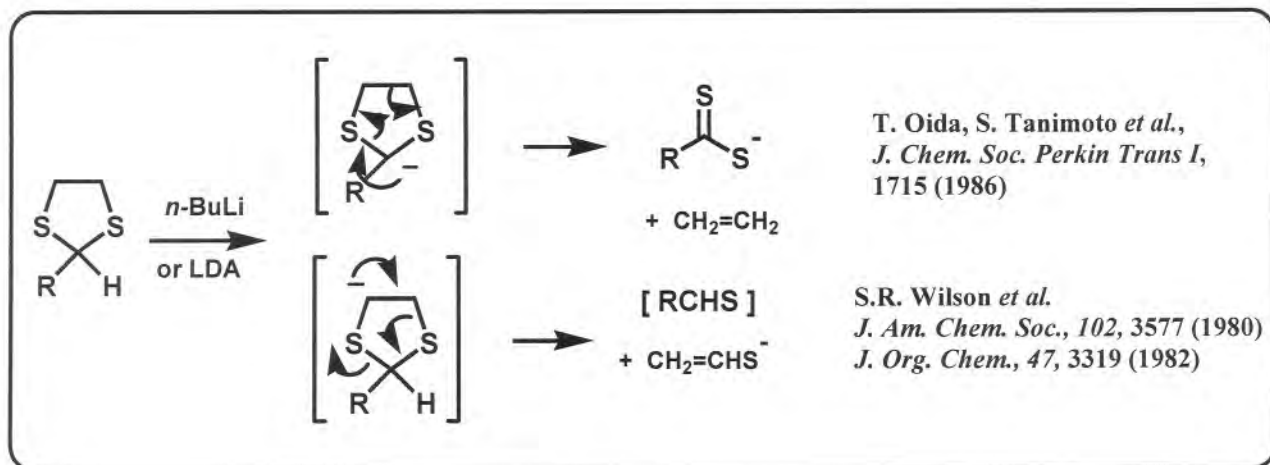
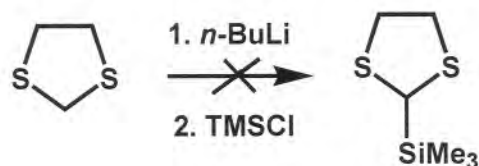


**Acyclic α -heterodisubstituted
organosilanes**

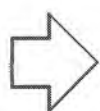
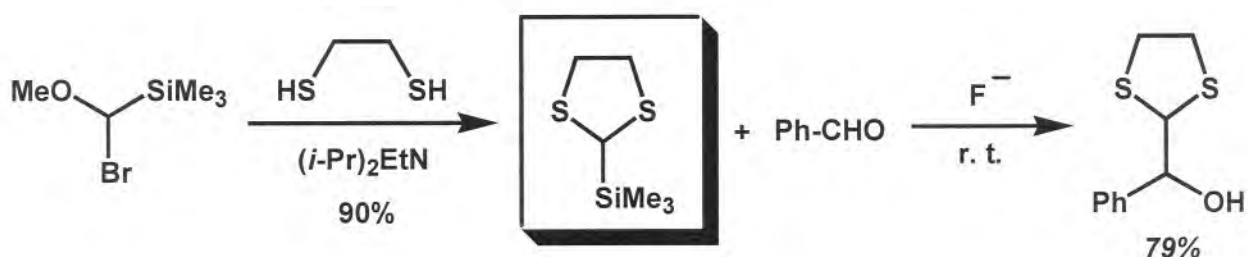


**2-Trimethylsilyl-1,3-disubstituted
heterocycles**

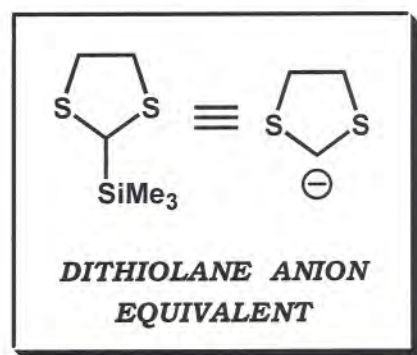
Synthesis of 2-trimethylsilyl-1,3-dithiolanes

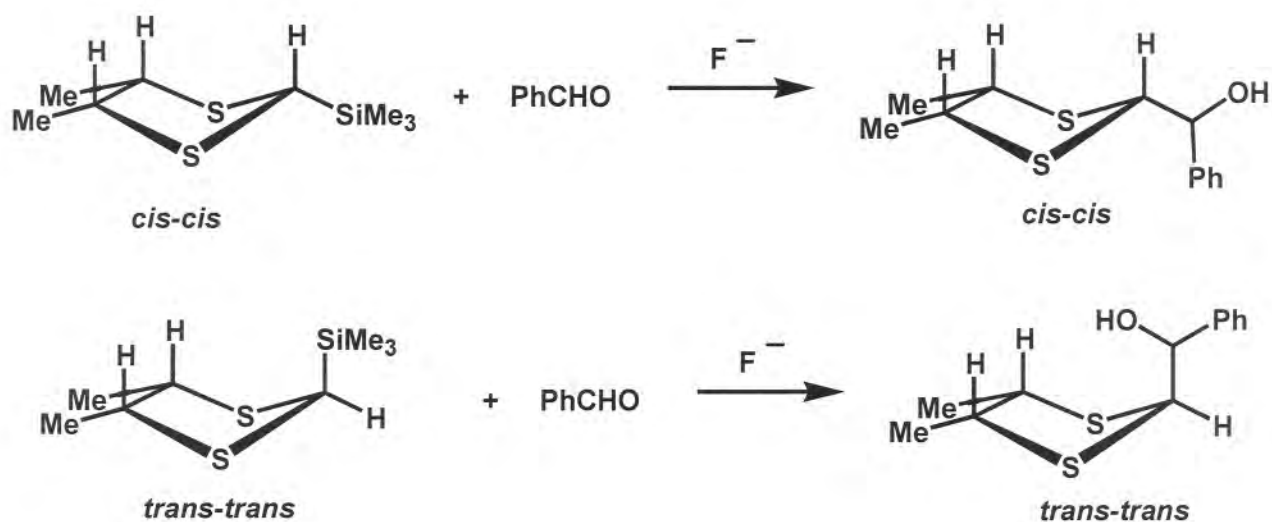
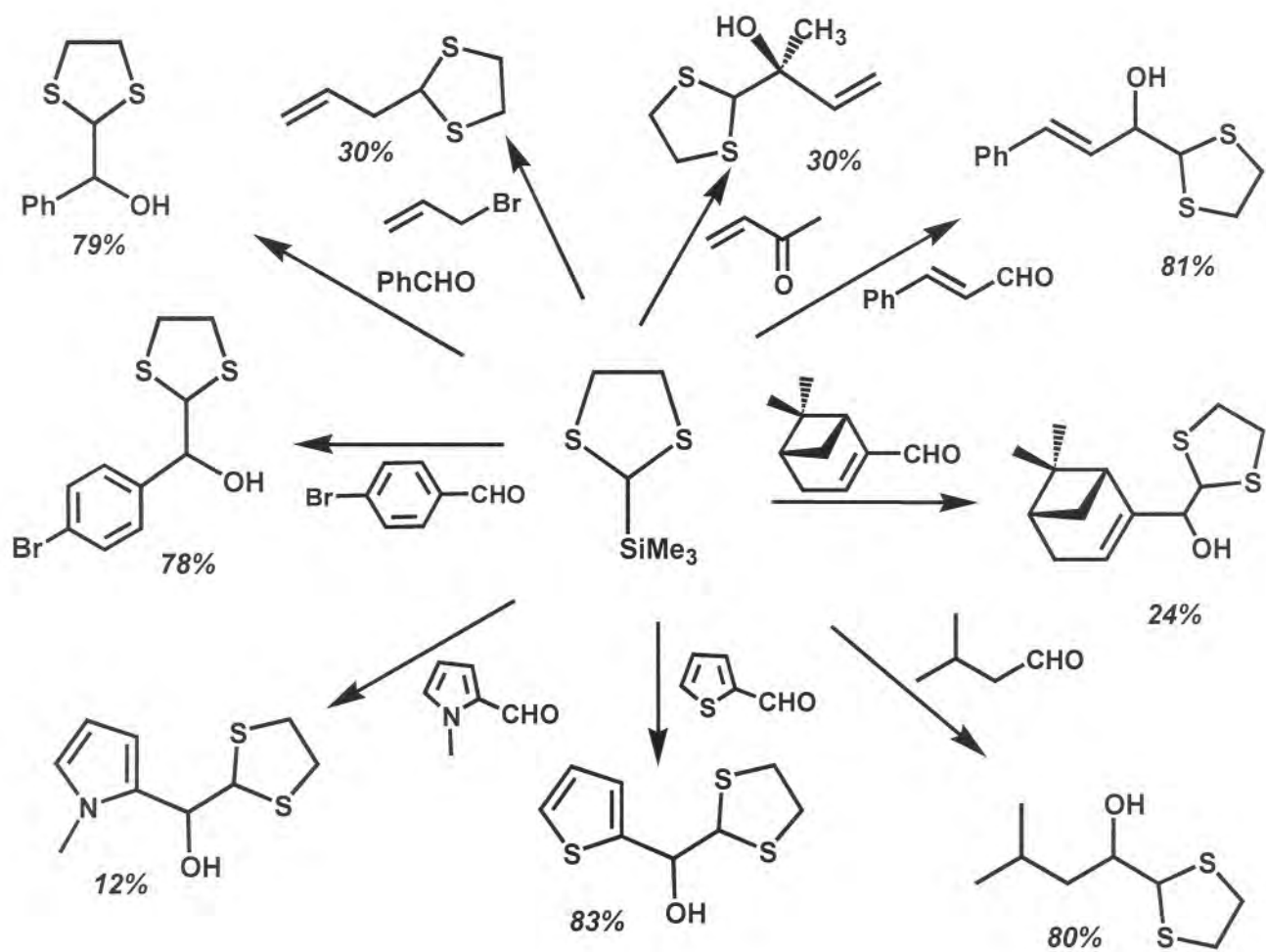


Synthesis and reactivity of 2-trimethylsilyl-1,3-dithiolane



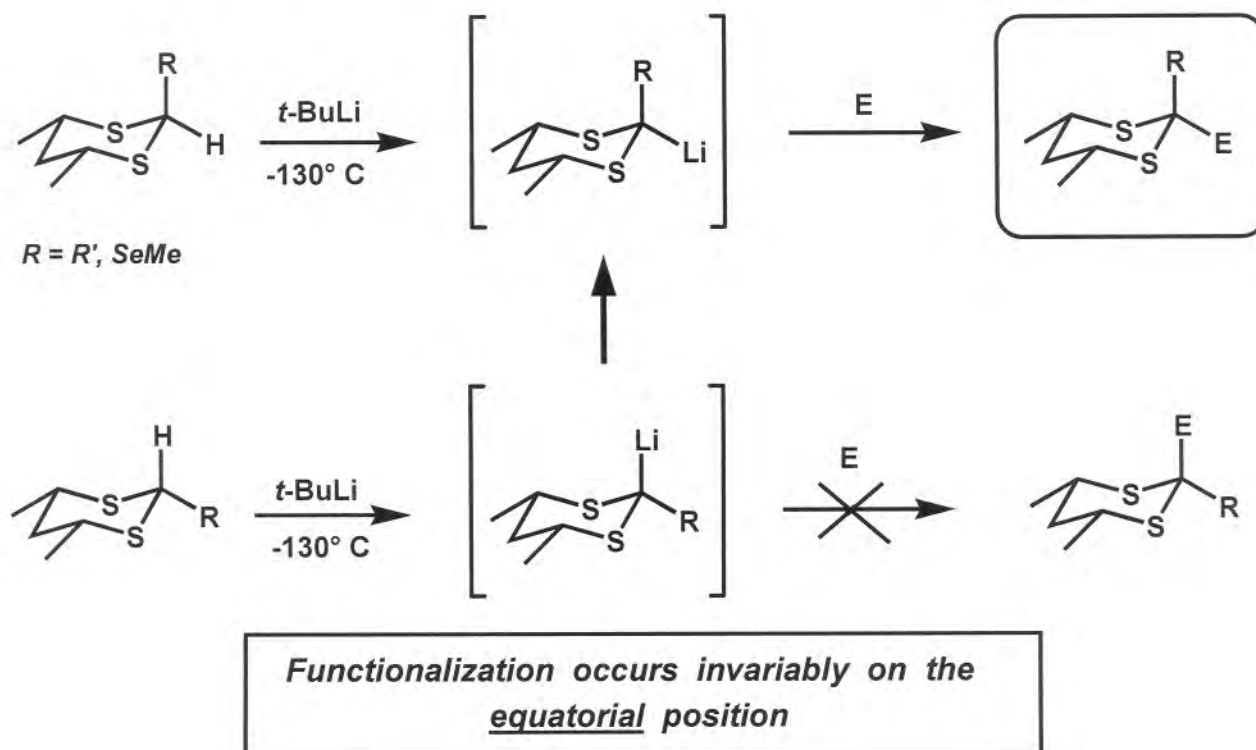
First example of silyl mediated
dithiolane transfer



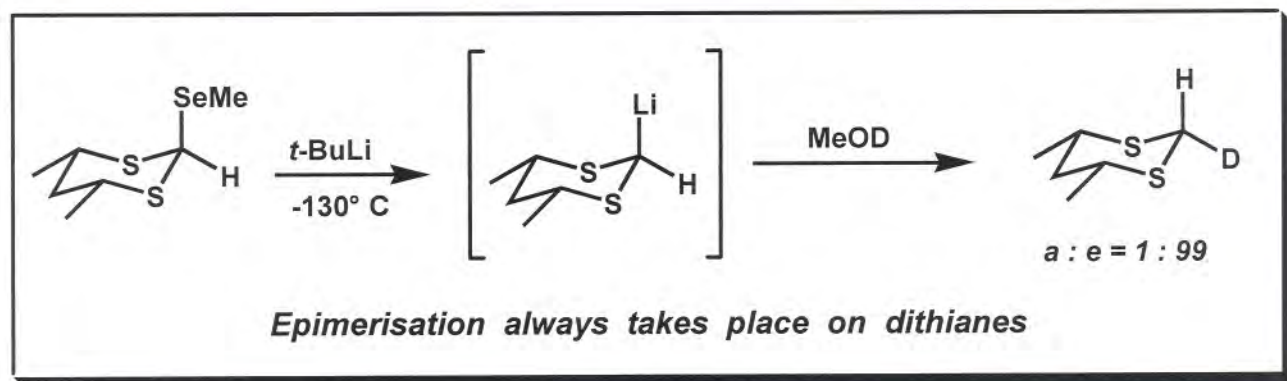
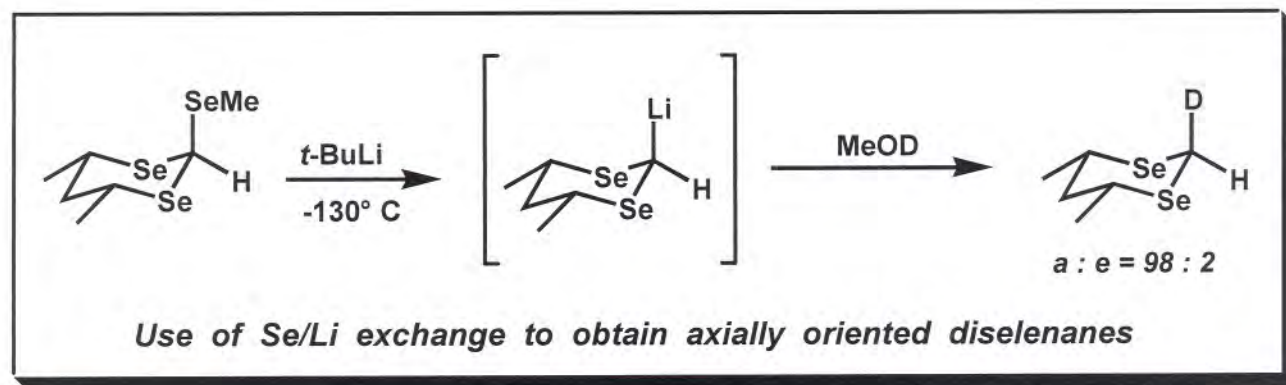


Retention of configuration at C-2 on substituted dithiolanes

Metalation of substituted dithianes

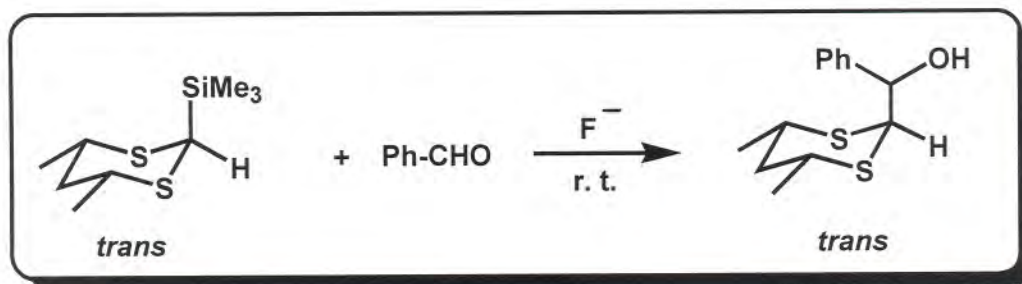
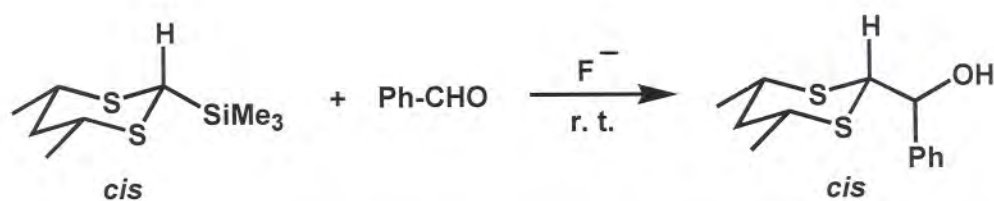


A. Krief, L. Defrère *Tetrahedron Lett.* 1996, 37, 8015.



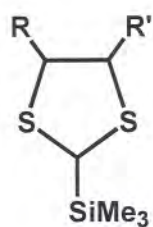
A. Krief, L. Defrère *Tetrahedron Lett.* 1996, 37, 8015.

2-Trimethylsilyl-4,6-dimethyl-1,3-dithiane transfer

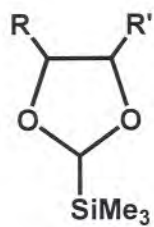


Stereoselective synthesis of C-2 substituted dithianes

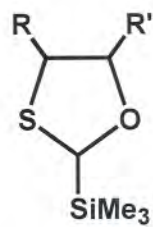
A. Capperucci, V. Ceré, A. Degl'Innocenti, T. Nocentini, S. Pollicino *Synlett*, 2002, 1447



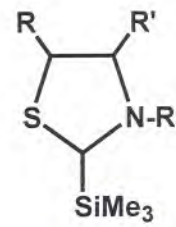
Dithiolanes



Dioxolanes

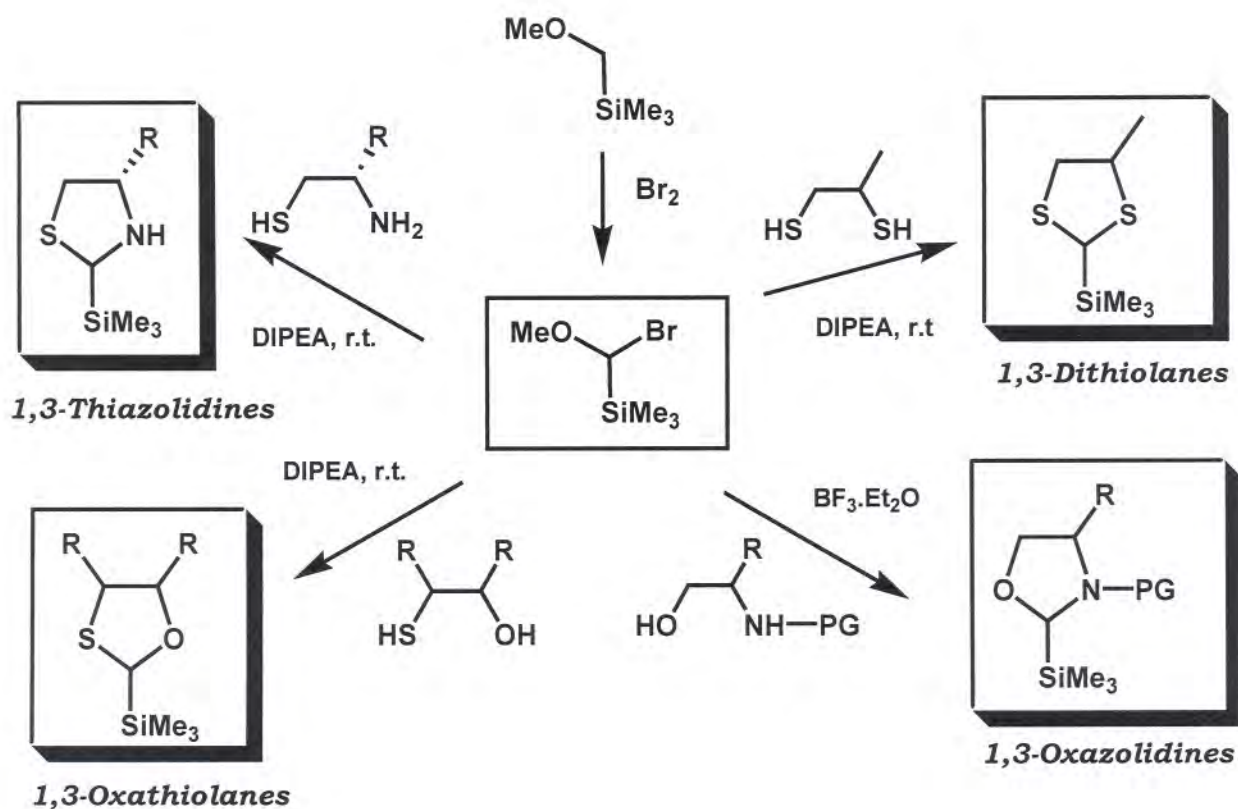


Oxathiolanes

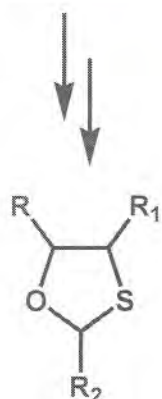
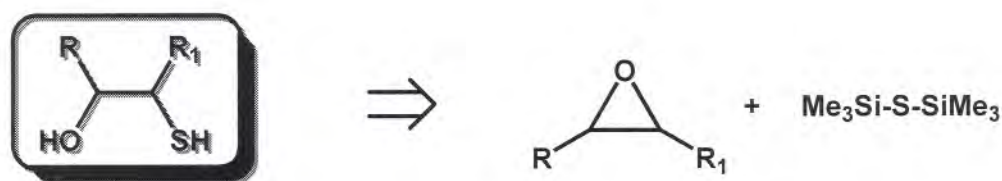


Thiazolidines

Synthesis of 2-silylated heterocycles

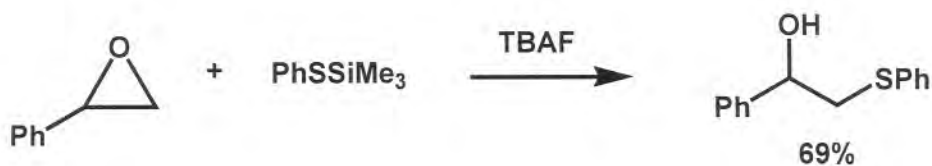


HMDST: ring opening of epoxides ?

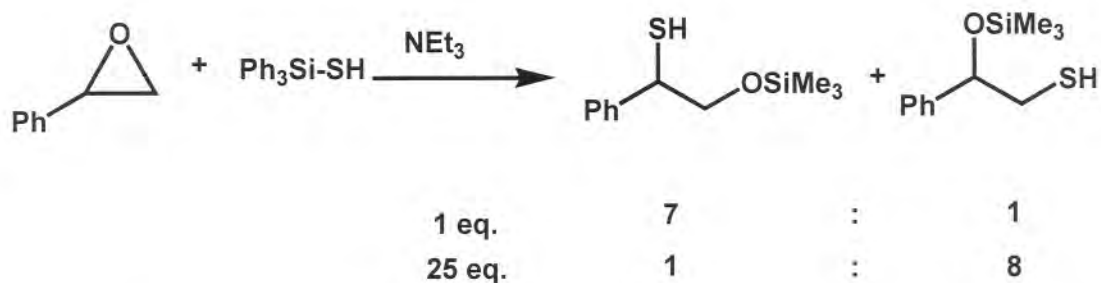


⇒ **1,3-Oxathiolanes as useful molecules in different synthetic processes**

E. Dunach *et al.*, *Tetrahedron Lett.*, 2003, 44, 853
M.J. Porter *et al.*, *Chem. Commun.*, 2002, 346
L.E. Overman *et al.*, *J. Am. Chem. Soc.*, 2000, 122, 8672.

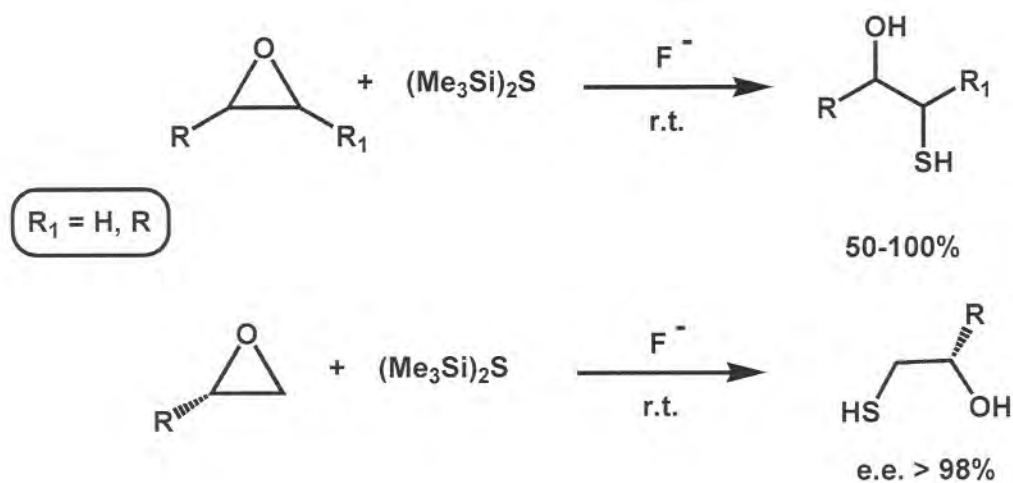


Tanabe, Y., Mori, K., Yoshida, Y. *J. Chem. Soc, Perkin 1*, 1997, 671



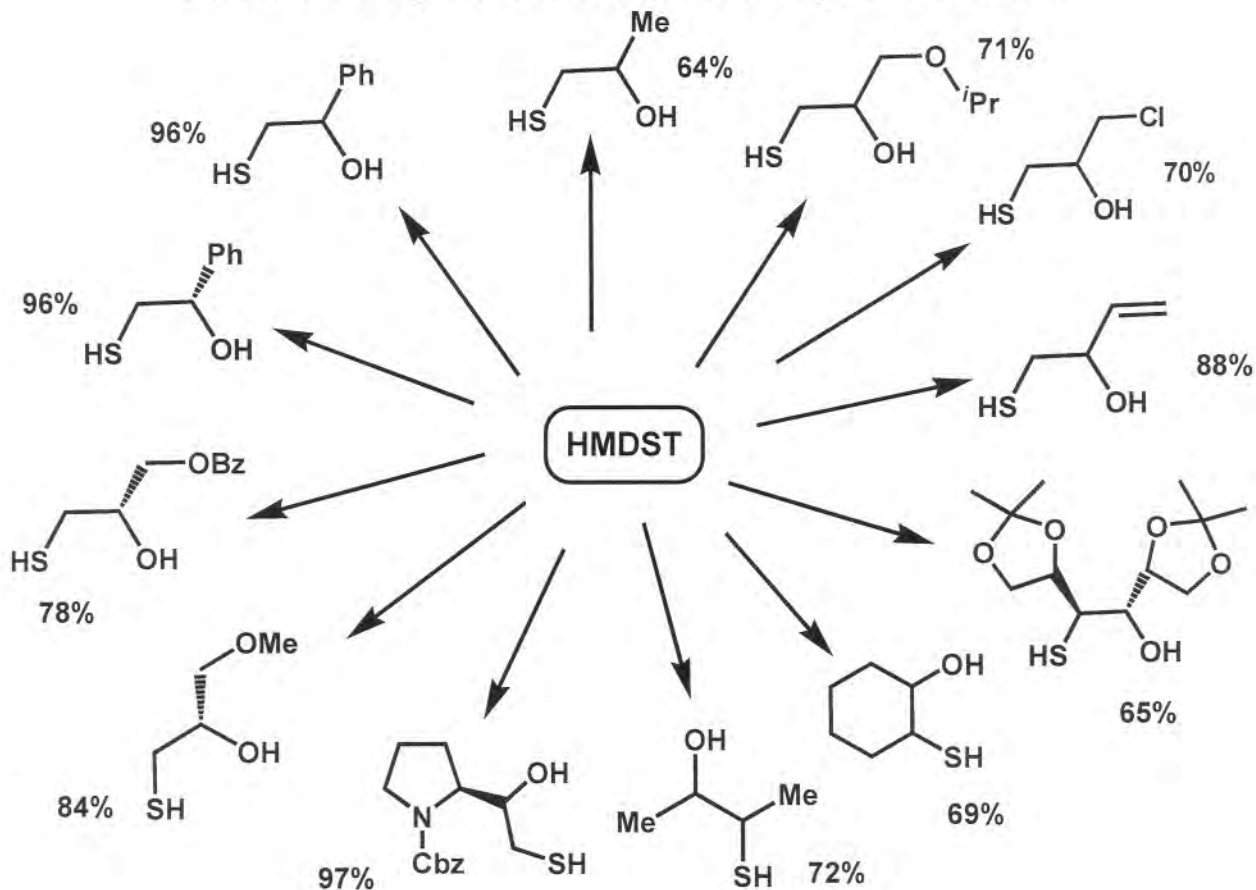
Brittain, J., Gareau, Y. *Tetrahedron Lett.*, 1993, 34, 3363.

HMDST: ring opening of epoxides

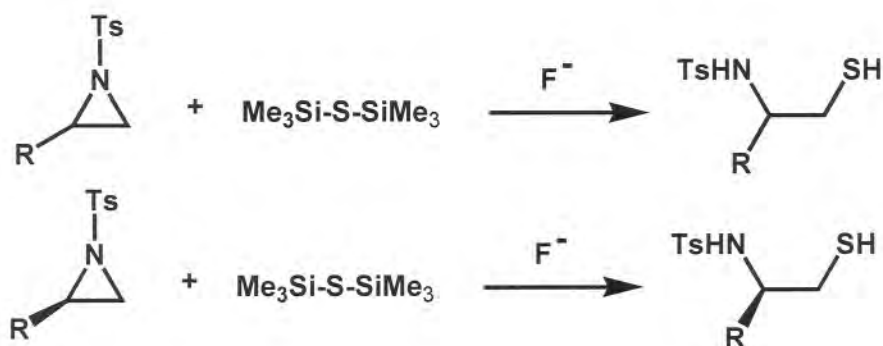


Regioselective and enantioselective ring opening

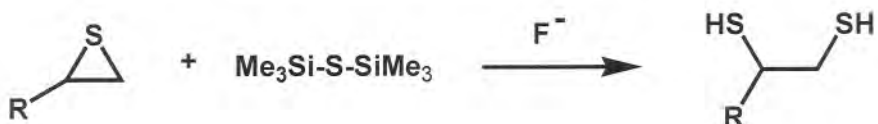
General way to obtain β -mercapto alcohols



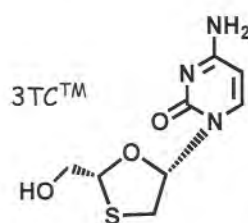
Extension to aziridines: synthesis of amino thiols



and thiiranes ...

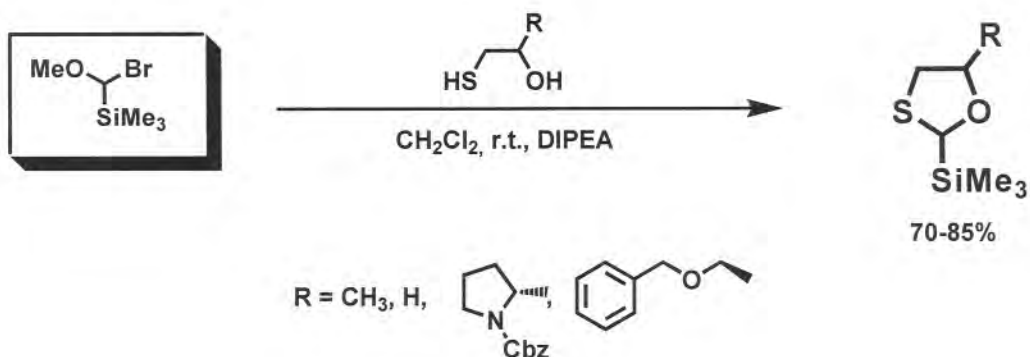


1,3-Oxathiolanes

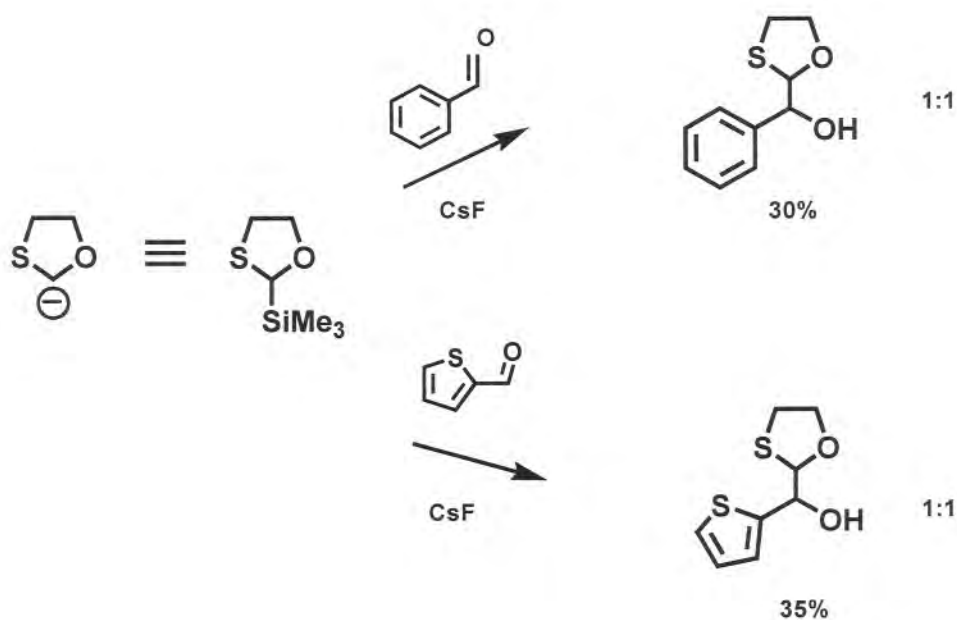


- cytosine nucleoside analogue
- high antiviral activity

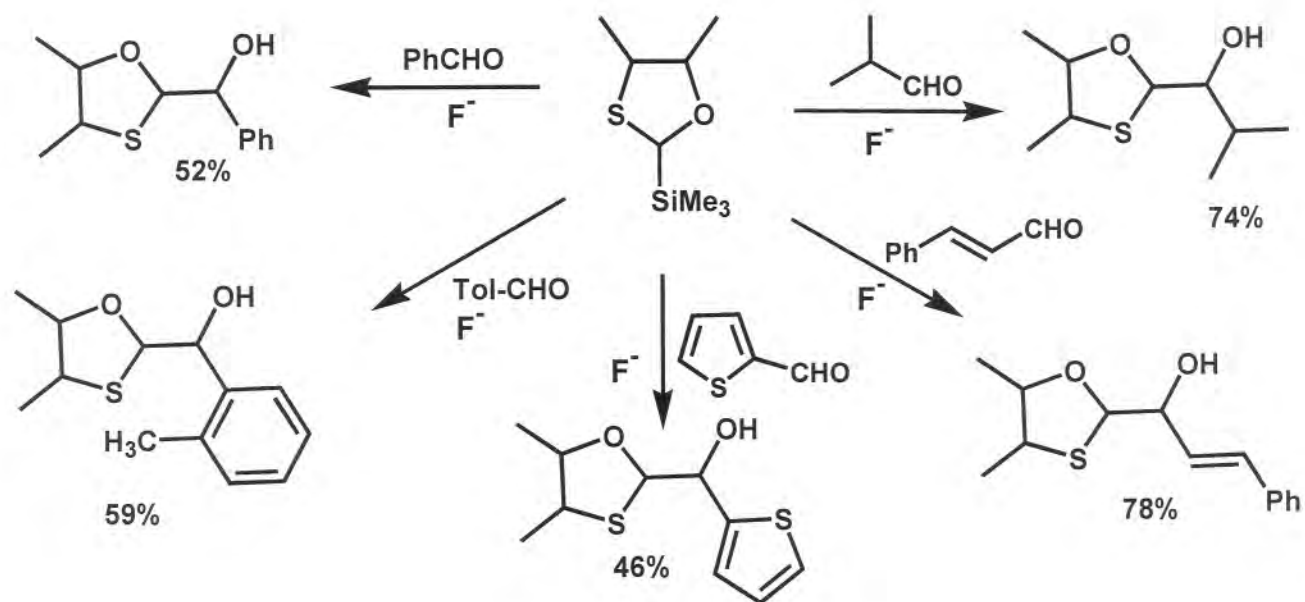
O. Dwyer, *Synlett*, 1995, 1163



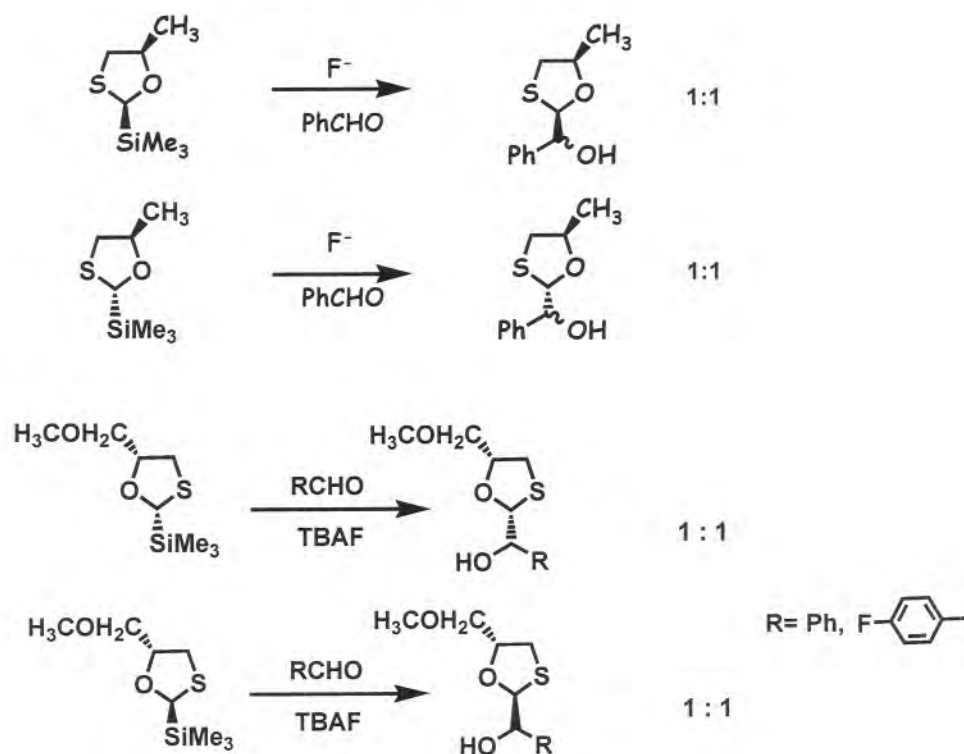
Functionalization of 1,3-oxathiolanes



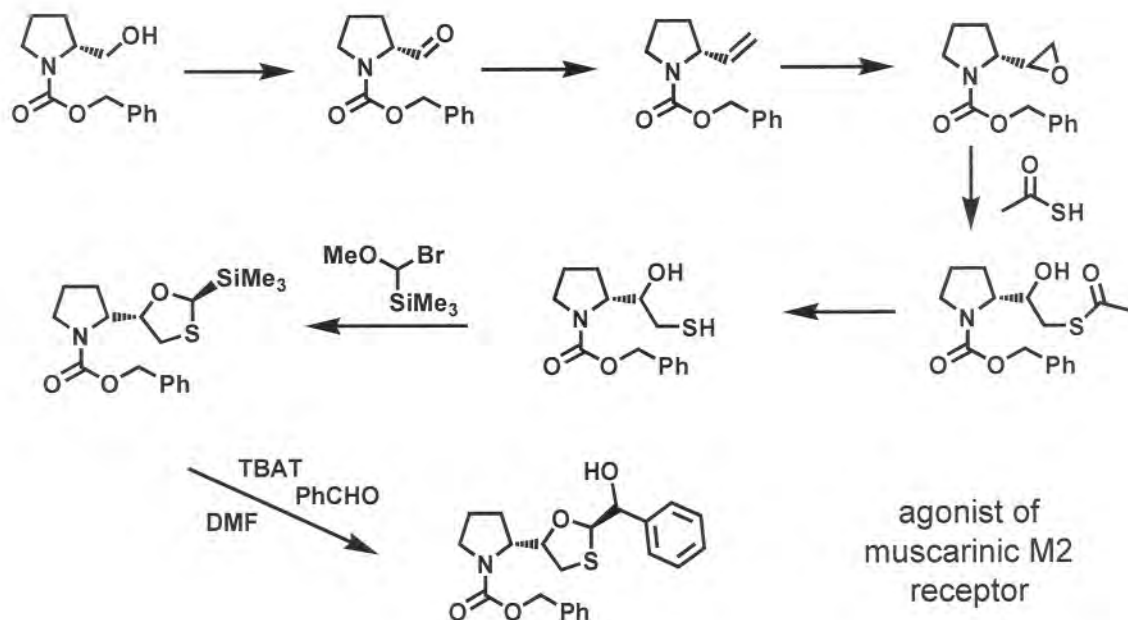
Easy transfer of 2-trimethylsilyl-oxathiolanes



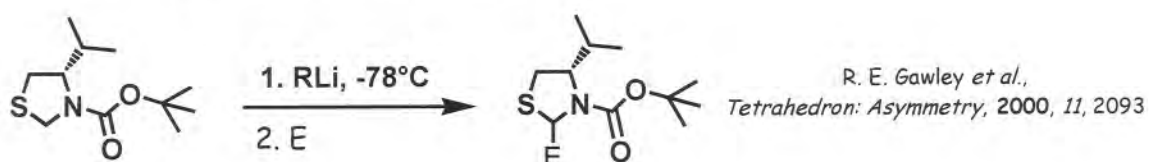
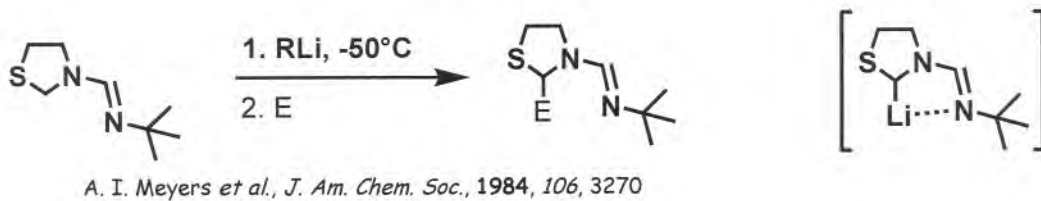
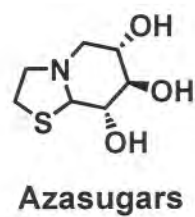
Stereoconservative functionalization of 1,3-oxathiolanes



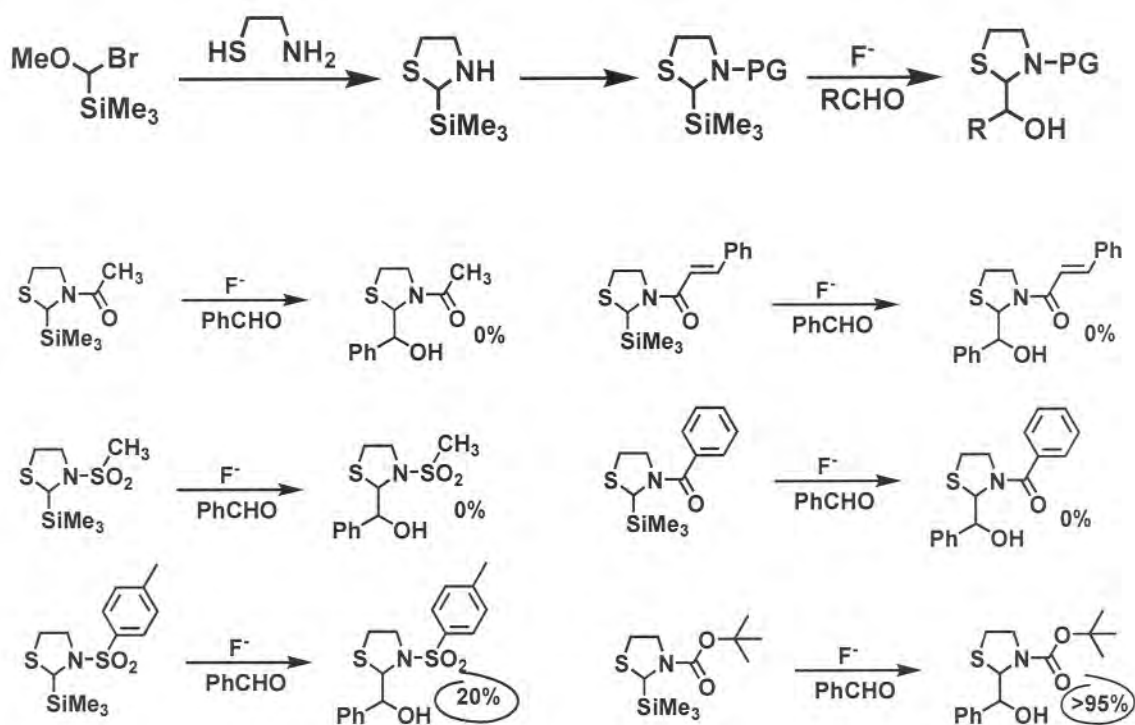
1,3-Oxathiolanes functionalization toward the synthesis of biological active molecules



1,3-Thiazolidines

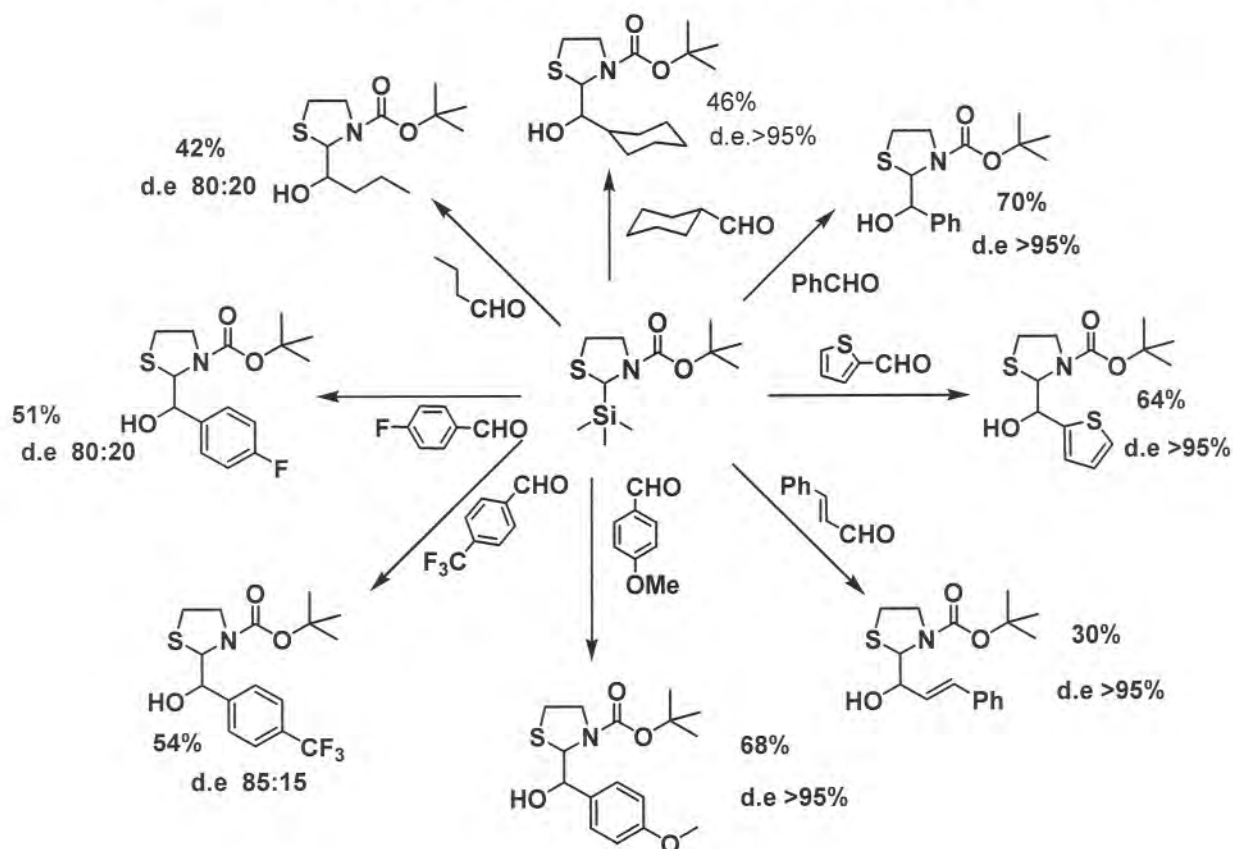


Thiazolidines functionalization

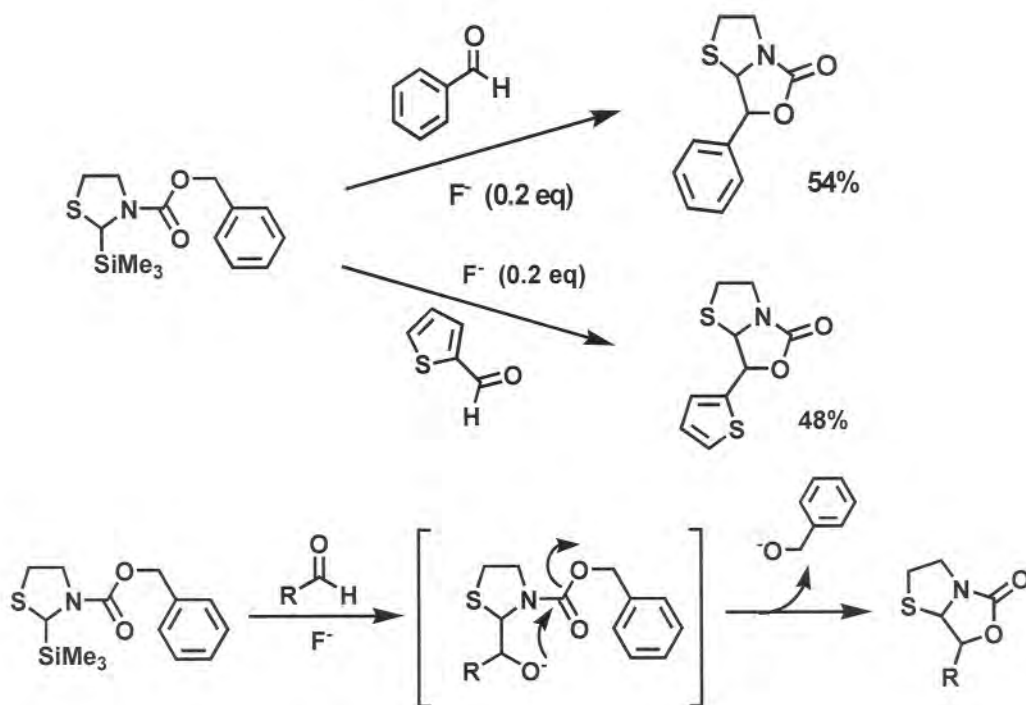


A. Degl'Innocenti, A. Capperucci, T. Nocentini
et al., *Lett. Org. Chemistry*, 2004, 1, 55

Reactivity of N-Boc protected thiazolidines

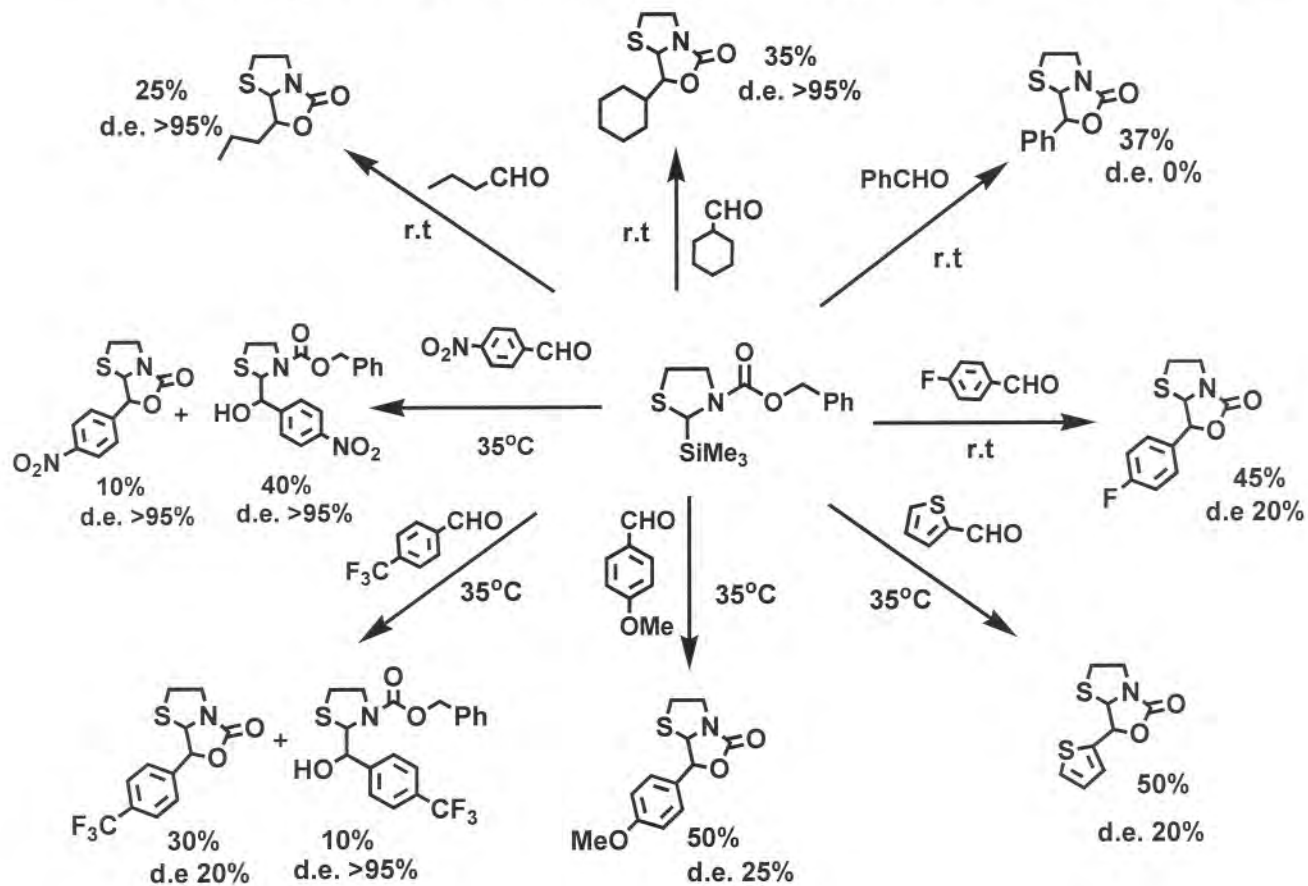


Peculiar behaviour of *N*-Cbz protected thiazolidines: synthesis of bicyclic systems

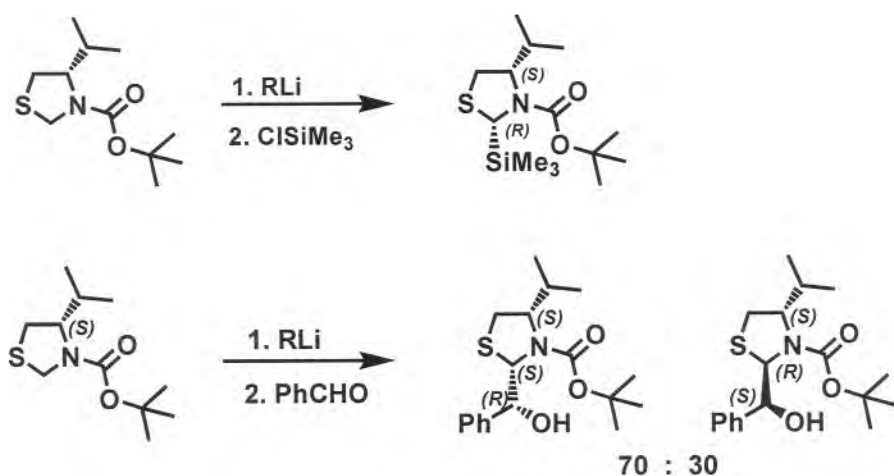


A. Degl'Innocenti, A. Capperucci, T. Nocentini, S. Biondi *et al.*, *Lett. Org. Chemistry*, 2004, 1, 55

Reactivity and stereochemistry of *N*-Cbz protected thiazolidines

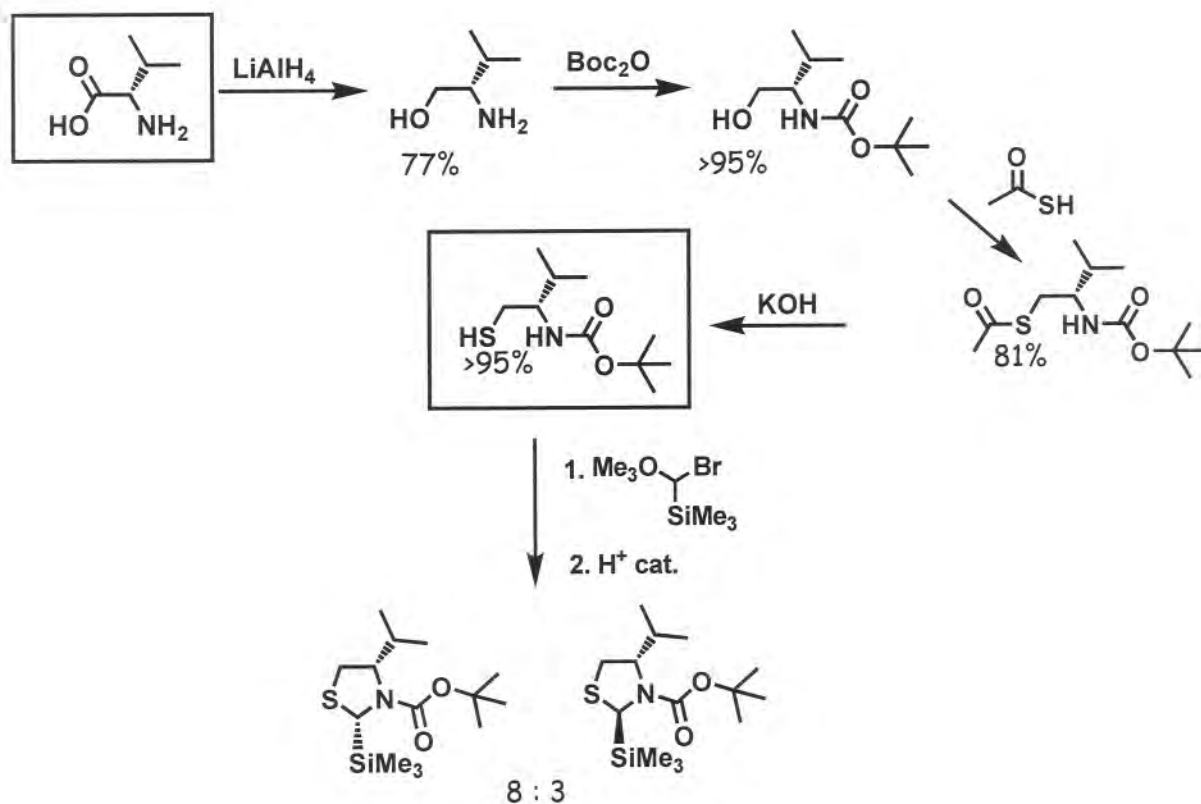


Reactivity under BuLi conditions

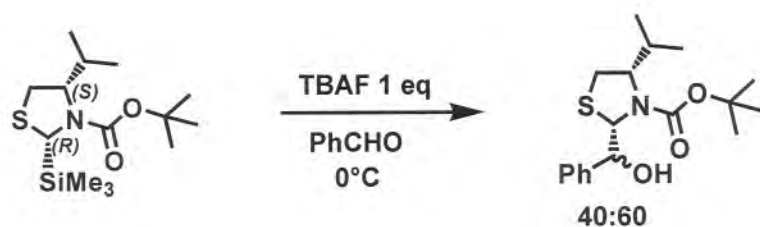
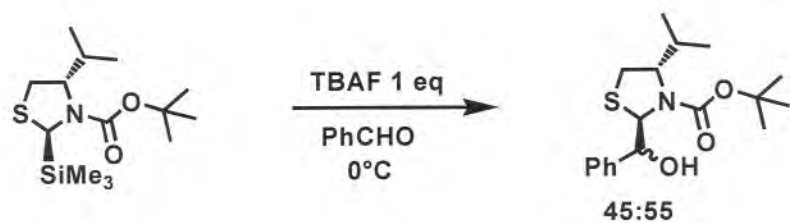


R. E. Gawley *et al.*, *Tetrahedron: Asymmetry*, 2000, 11, 2093

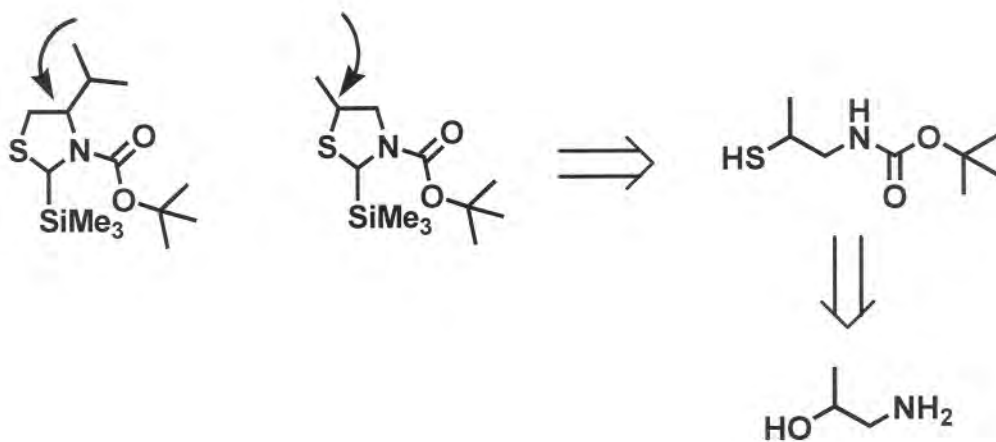
Silyl 1,3-thiazolidines



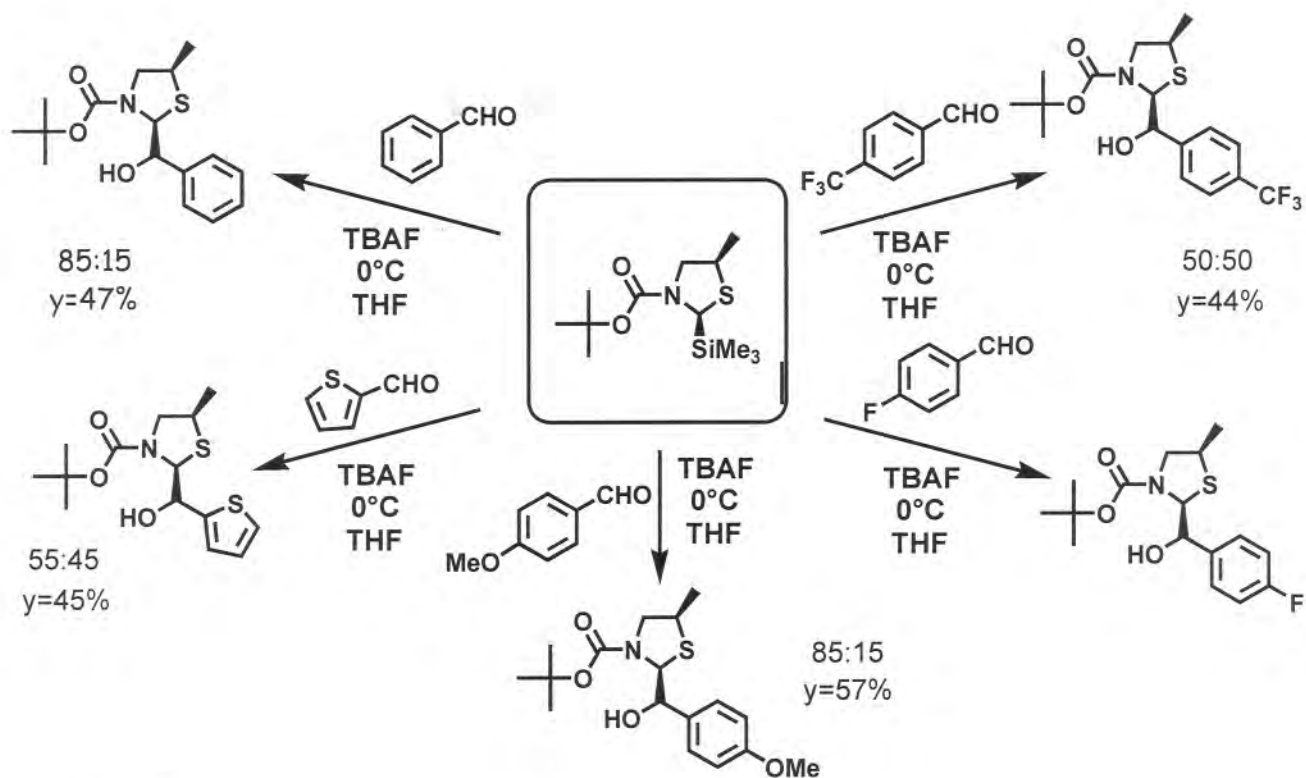
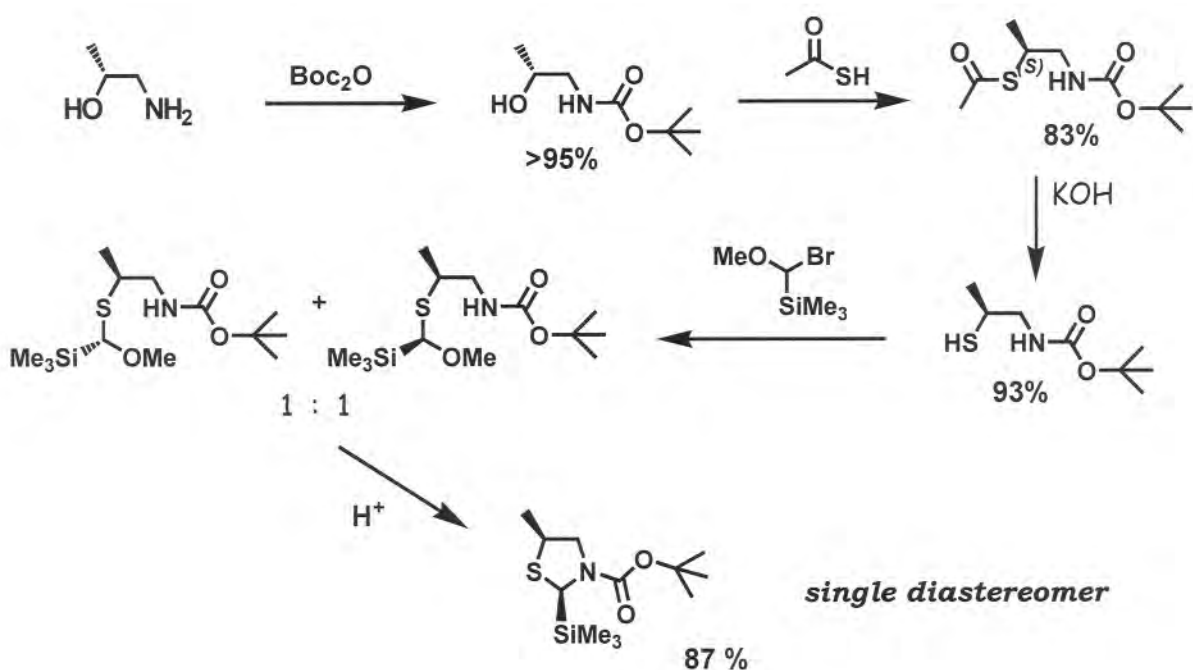
Functionalization of enantiopure thiazolidines



Influence of the substituent position on the reaction stereochemistry

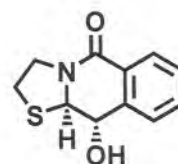
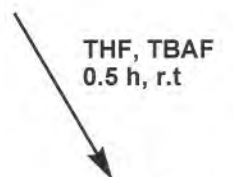
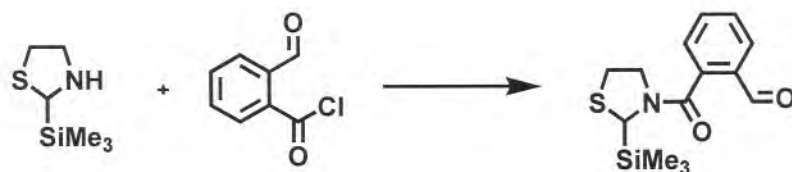


Synthesis of 5-substituted enantiopure thiazolidines



⇒ Retention of configuration

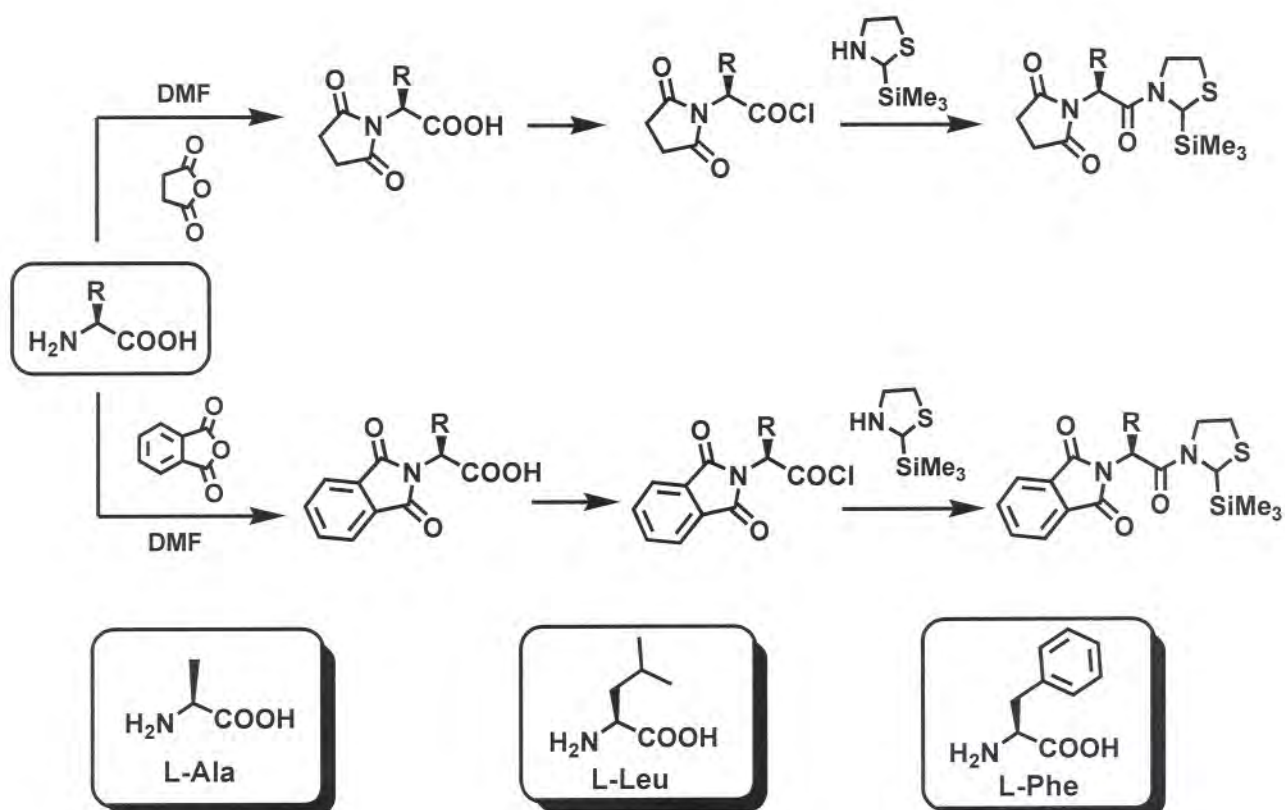
Stereoselective intramolecular functionalization of thiazolidines



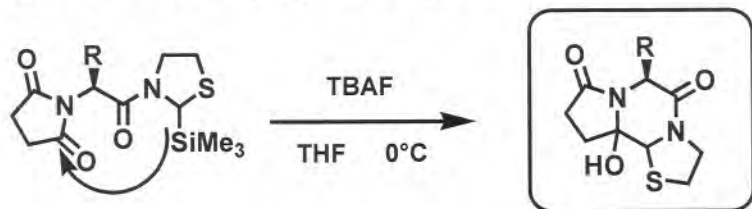
Y = 80%
d.e. = 70%

- **Fluoride ion induced intramolecular cyclization**

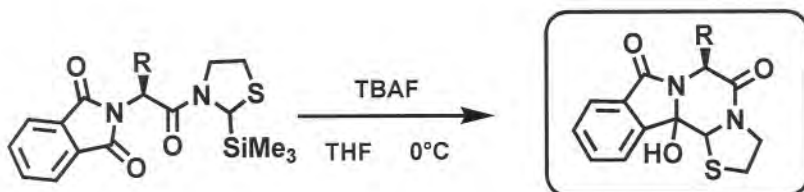
- **Biologically interesting compounds**



Synthesis of polycyclic heterocycles



single diastereomer



⇒ **Medicinal chemistry and stereoselective organic synthesis**

Tetrahedron: Asymmetry, 2002, 13, 2727

⇒ **Antimalaric activity**

J. Med. Chem., 2004, 47, 000

⇒ **Structural analogues of Tadalafil**

J. Med. Chem., 2003, 46, 4533

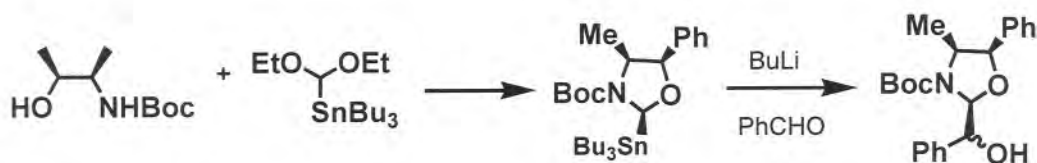
1,3-Oxazolidines



⇒ **Chiral auxiliaries in asymmetric synthesis**

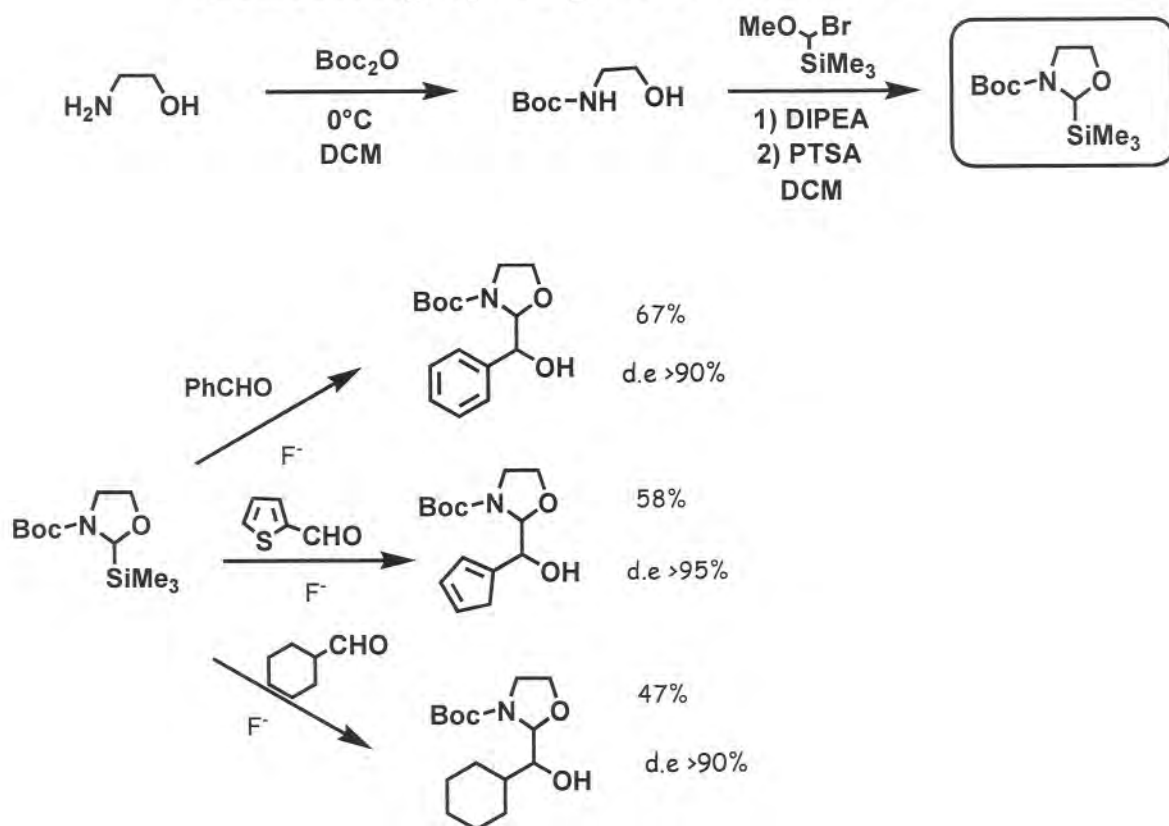
Eur. J. Org. Chem., 2004, 677-685

⇒ **Molecules with pharmaceutical activity**



Colombo, L., Di Giacomo, M., Brusotti, G., Delogu, G. *Tetrahedron Lett.* 1994, 35, 2063.

Reactivity of Silyl Oxazolidines



... in conclusion

- ✓ *Development of a general and easy approach to obtain new α -heterosubstituted silylated nucleophiles*
- ✓ *First example of transfer onto electrophiles through the C-Si bond functionalization*
- ✓ *Silylated heterocycles as masked heterocyclic anions*
- ✓ *Stereoselective synthesis of different cyclofused heterocyclic compounds*
- ✓ *Synthesis and reactivity of new α -substituted geminal stannyl silanes*

Thanks....

Antonella Capperucci

Tiziano Nocentini

Simona Biondi

Giulio Castagnoli

Irene Malesci

Arianna Cerreti