Kanemasa hydroxy-directed nitrile cycloaddition

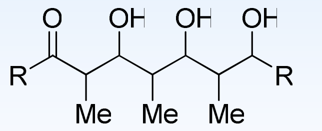
Towards synthesis of polyketides by a non-aldol approach

Christophe Allais

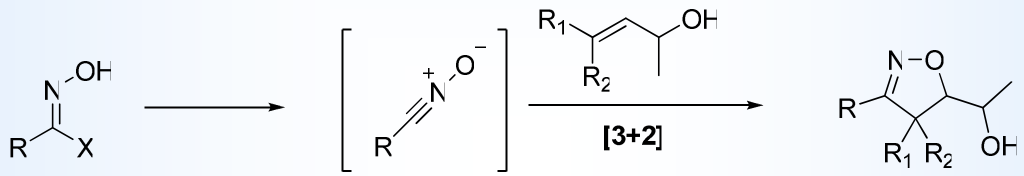
Bibliographic seminar, 20.10.2009

Outline

History: some non-aldol approaches to the synthesis of polypropionates

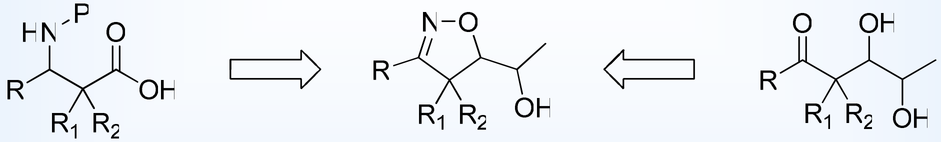


Development: discovery, stereoselectivity and scope of the cycloaddition with allylic alcohols

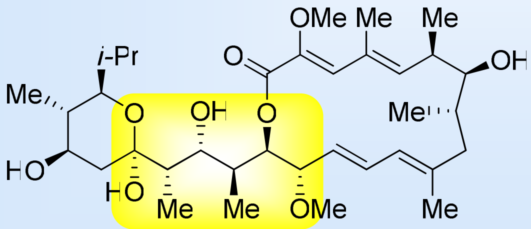


nitrile oxide

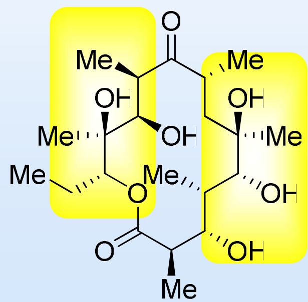
Reactivity: from oxazolines to β-amino acids and polypropionates



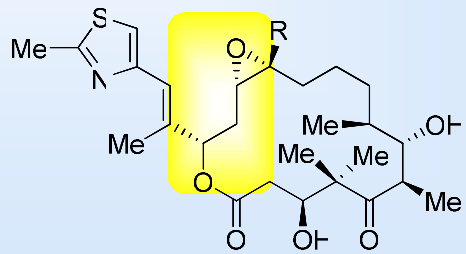
Applications in total synthesis: Bafilomycin A_1, Erythronolide A, Epothilones A and B...



Bafilomycin A_1

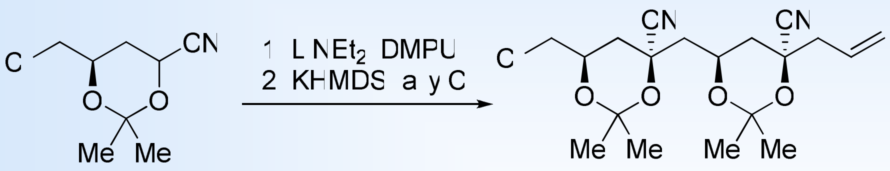


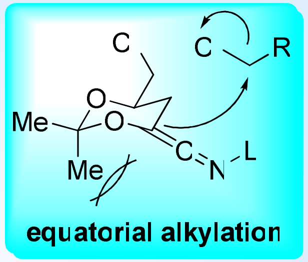
Erythronolide A



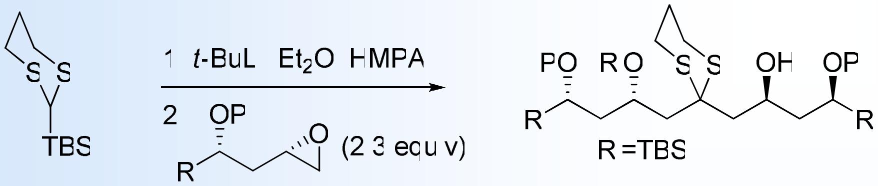
R=H, Epothilone A
R=Me, Epothilone B

Rychnovsky: cyanohydrin acetonide alkylation[1]



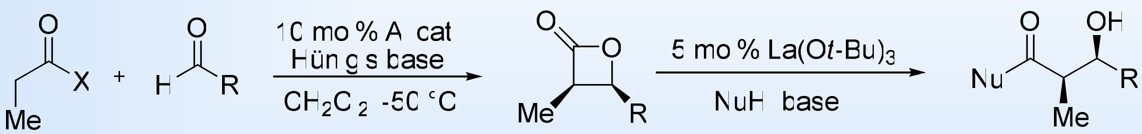


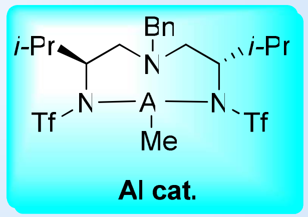
Smith III: Anion Relay Chemistry via dithiane linchpin and Brook rearrangment[2]



⇨ See Marc's seminar

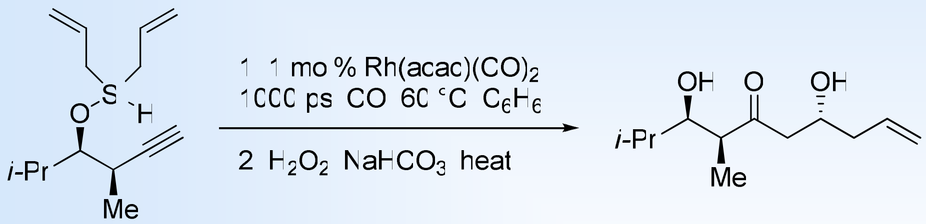
Nelson: acyl halide / aldehyde [2+2] cyclocondensation[3]

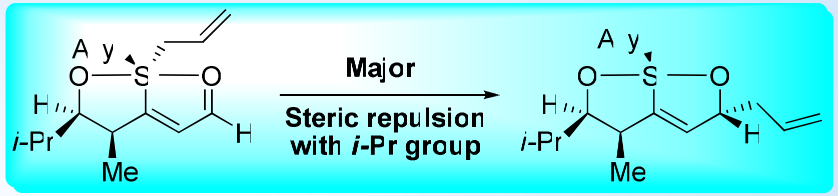




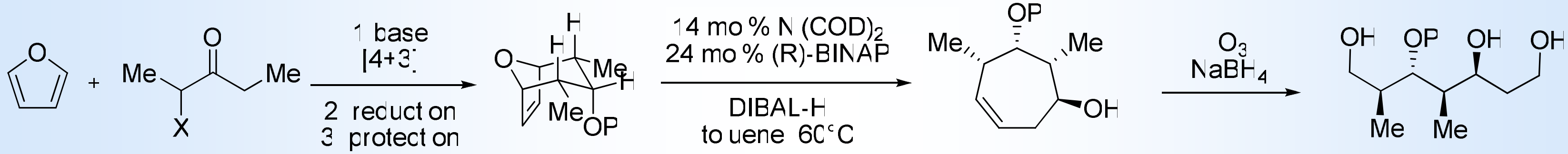
1. Rychnovsky *et al., J. Org. Chem.* **1990**, *55*, 5550.
2. Smith III *et al., J. Am. Chem. Soc*. **1997**, *119*, 6925.
3. Nelson et al., *J. Am. Chem. Soc*. **1999**, *121*, 9742.

Leighton: Alkyne silylformylation / allylation[4]





Lautens: enantioselective seven-membered ring opening[5]

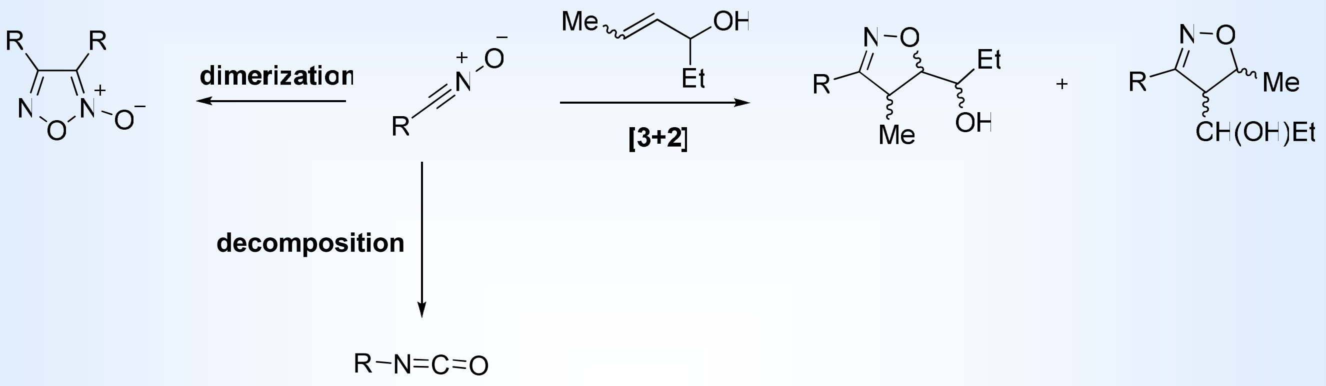


And also[6]:

- *Meso* tetrahydropyranyl diols desymmetrization (Bressy)
- Hemiacetal oxymercuration (Leighton)
- Asymmetric methylketene dimerization (Calter)
- Hydroformylation (Breit)
- Non-aldol aldol (Jung)
- Conjugate addition / Enolate oxidation (Hanessian)
- Silirane ring opening (Woerpel)
- Nitrile oxide 1,3-dipolar cycloaddition (Kanemasa)

4. Leighton *et al., Angew. Chem. Int. Ed.* **2001**, *40*, 2915.
5. Lautens *et al., J. Am. Chem. Soc*. **1997**, *119*, 11090.
6. On line Evans group seminar, by Travis Dunn (2001-2002).

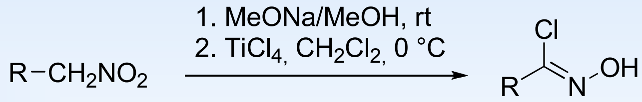
At the beginning…



Limitations

- Nitrile oxides very unstable, rapid dimerization, decomposition, synthetic method
- Poor yields
- Low regioselectivity
- Low stereoselectivity
- Internal alkenes much less reactive than terminal alkenes

Preparation of nitrile oxides

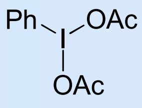


Kumaran, *Tet. Lett.* **1996,** 6407

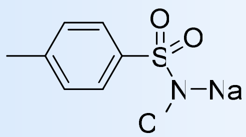
4Å MS, Et_3N (cat.), CD_3OD, rt (Kanemasa, *Tet. Lett.* **2009,** 2111)

CAN, MeCN, rt (Das, *Arkivok*, **2005** (iii), 27)

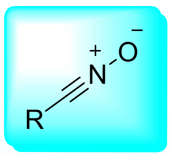
Et_3N ou RMgBr, CH_2Cl_2, rt (Kanemasa, *J. Am. Chem. Soc.* **1994,** 2324)



DIB



Chloramine T

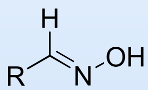


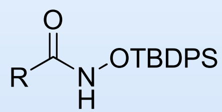
t-BuOCl, CH_2Cl_2, -78 °C (Carreira, *Angew. Chem. Int. Ed.* **2001**, 2082)

DIB, CH_2Cl_2, 0 °C to rt (Das, *Tet. Lett.* **2004**, 7347)

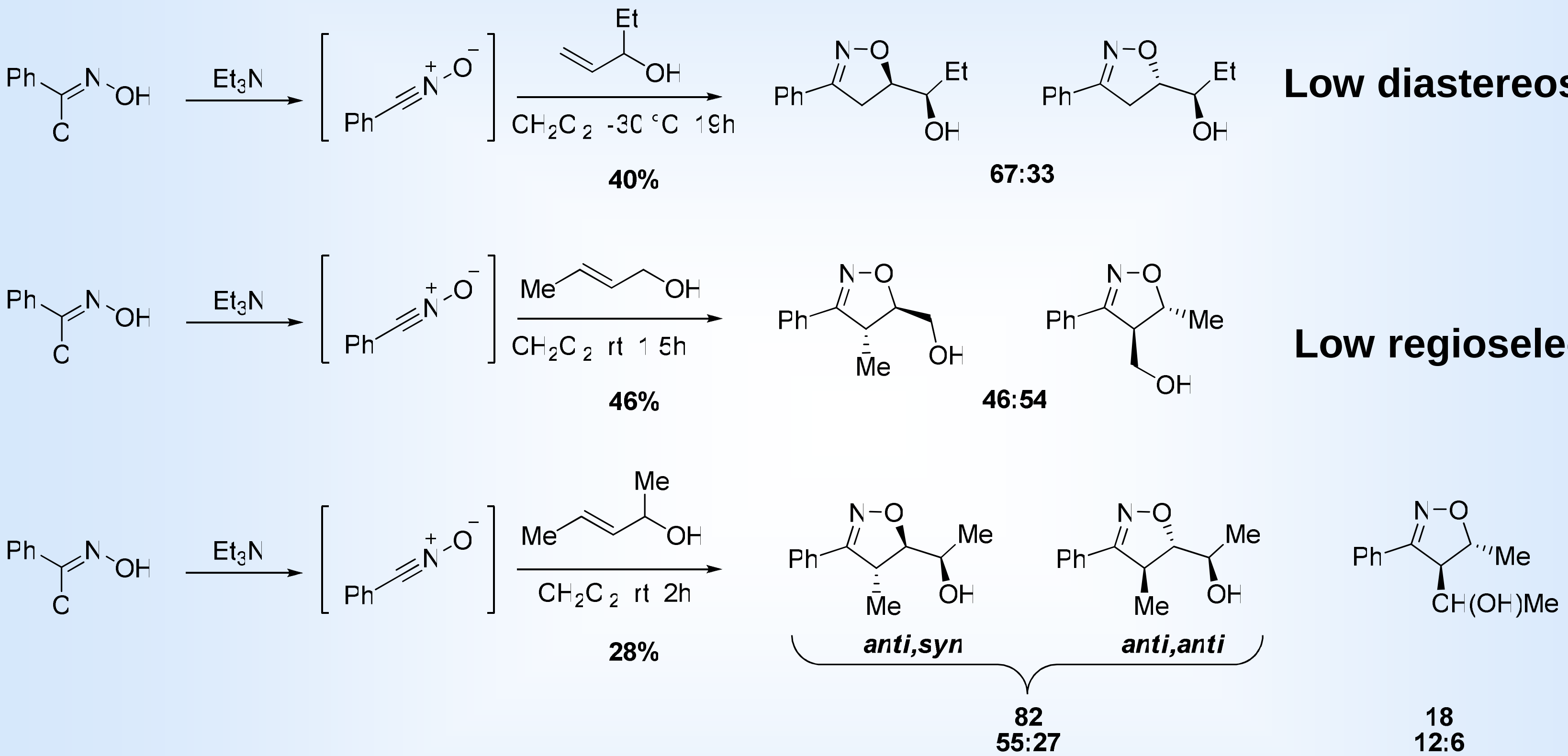
Chloramine T, EtOH, rt (Ra..., *Arkivok* **2008** (x), 75)

Tf_2O, Et_3N, -40 °C to 0 °C (Carreira, *Org. Lett.* **2000**, 539)





Shuji Kanemasa 1994: Preliminary results[7]



Low diastereoselectivity

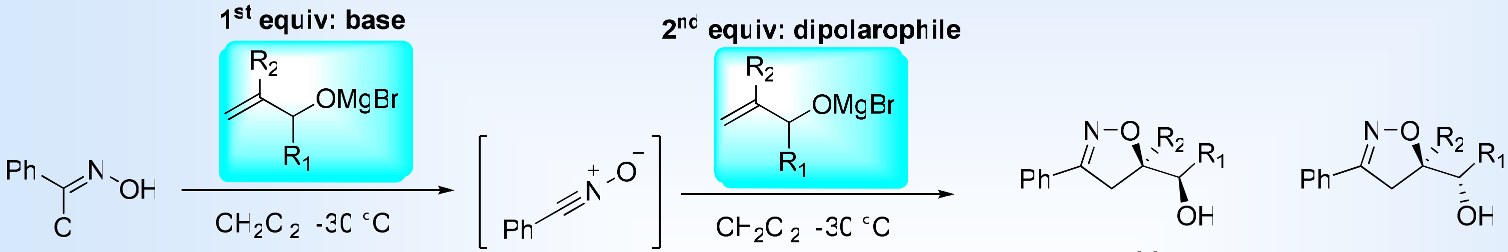
Low regioselectivity

Low yields, low selectivities, substrate-dependant reaction

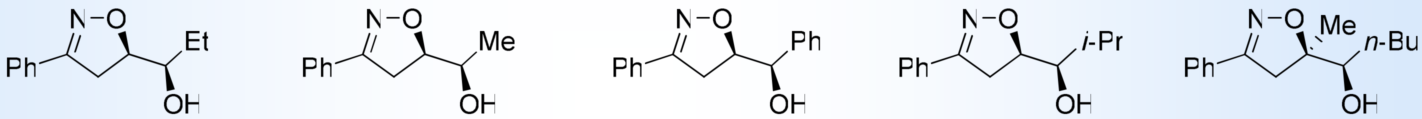
a general method is needed!

7. Kanemasa *et al.*, *J. Am. Chem. Soc*. **1994**, 2324.

First metal-assisted 1,3-cycloaddition: dramatic effect of magnesium on diastereoselectivity[7]



***syn*-adduct** ***anti*-adduct**



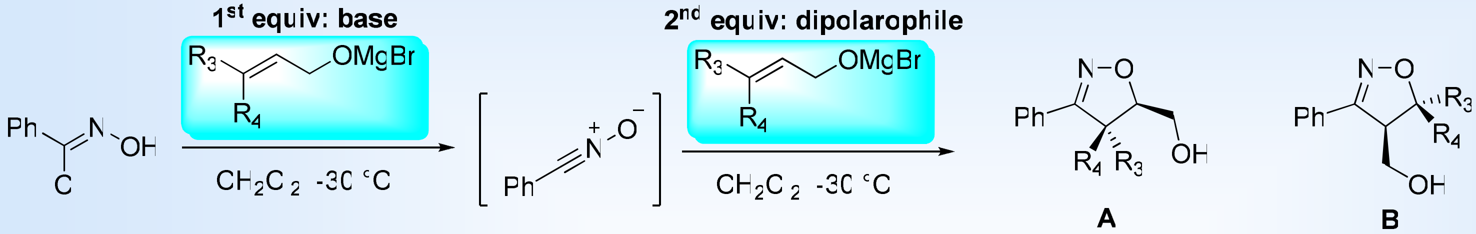
yield	**92%**	**95%**	**94%**	**95%**	**85%**
syn*/*anti	**>99:1**	**96:4**	**89:11**	**97:3**	**96:4**
(ratio without Mg)	**(67:33)**	**(61:39)**	**(56:44)**	**(65:35)**	**(60:40)**

About optimization of the reaction…

- no high *syn*-selectivity with other metal ions: Li, EtZn, Et_2Al.
- no impact on the *syn*-selectivity with small excess of THF (from EtMgBr solution)…
- …but reaction performed in THF gave in 2:1 mixture of *syn*- and *anti*- isomers.
- *i*-PrOH (2 equiv) increased yields and property with same *syn*-selectivity.

7. Kanemasa *et al., J. Am. Chem. Soc.* **1994**, 2324.

First metal-assisted 1,3-cycloaddition: dramatic effect of magnesium on regioselectivity[7]



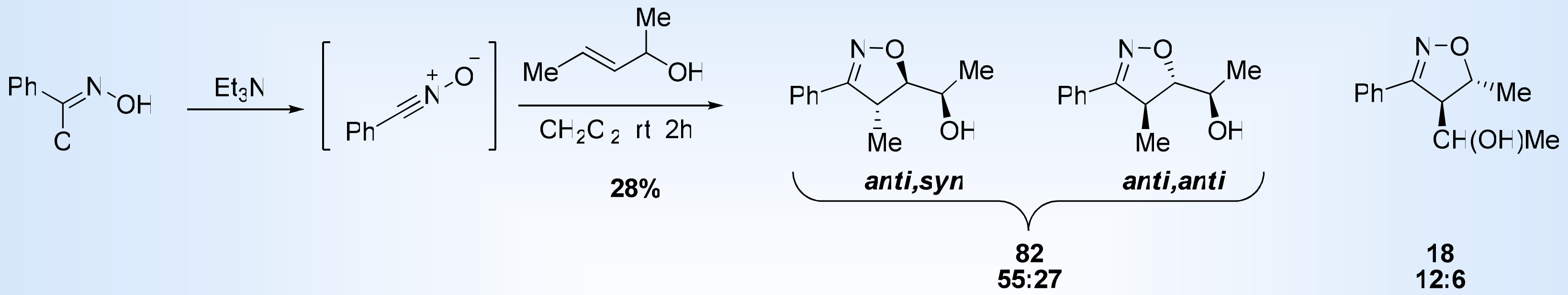
yield	**82%**	**73%**	**68%**	**14%**
(yield without Mg)	**(46%)**	**(44%)**	**(46%)**	**(19%)**
A/B	**>99:1**	**98:2**	**>99:1**	**95:5**
(ratio without Mg)	**(46:54)**	**(55:45)**	**(20:80)**	**(1:99)**

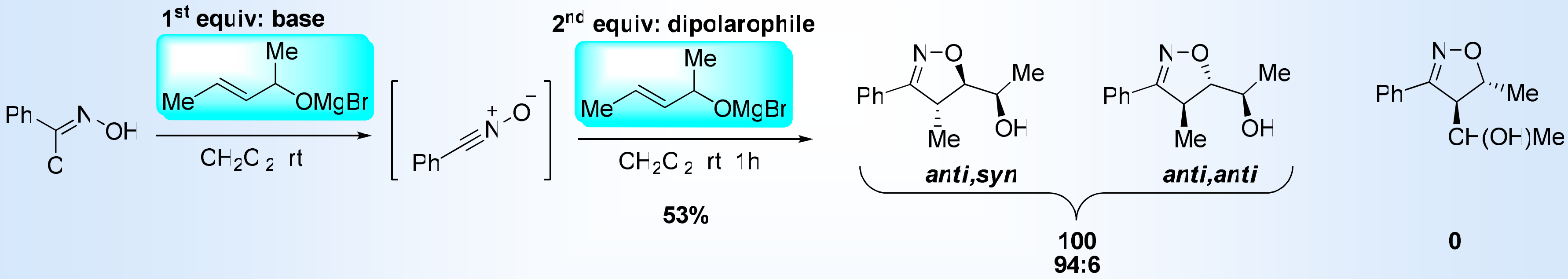
About optimization of the reaction…

- no high regioselectivity with other metal ions: Li, EtZn, Et_2Al.
- no impact on the regioselectivity with use of THF as solvent.
- *i*-PrOH (2 equiv) increased yields and property with comparable regioselectivity.

7. Kanemasa *et al., J. Am. Chem. Soc.* **1994**, 2324.

First metal-assisted 1,3-cycloaddition: dramatic effect of magnesium on both selectivities[7]



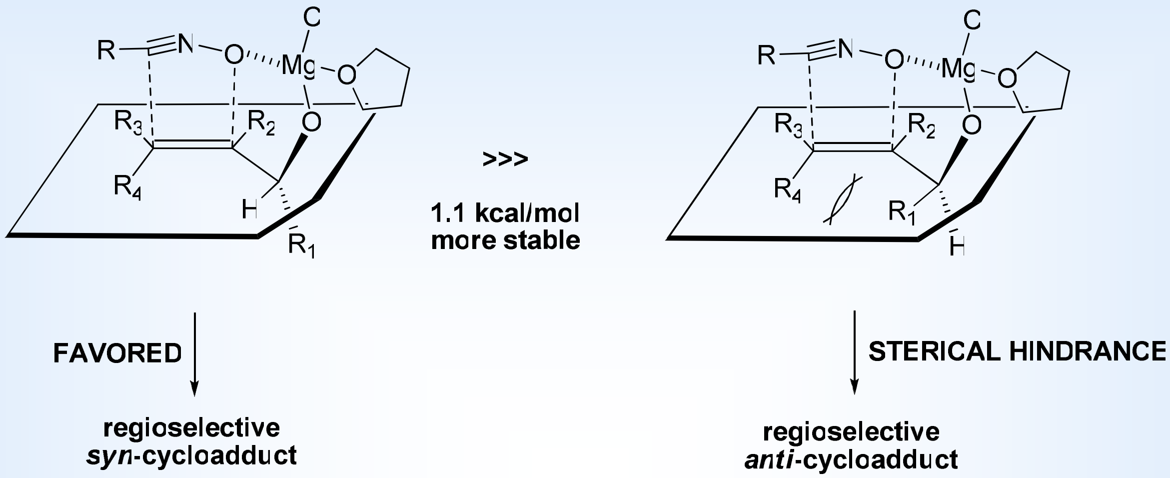


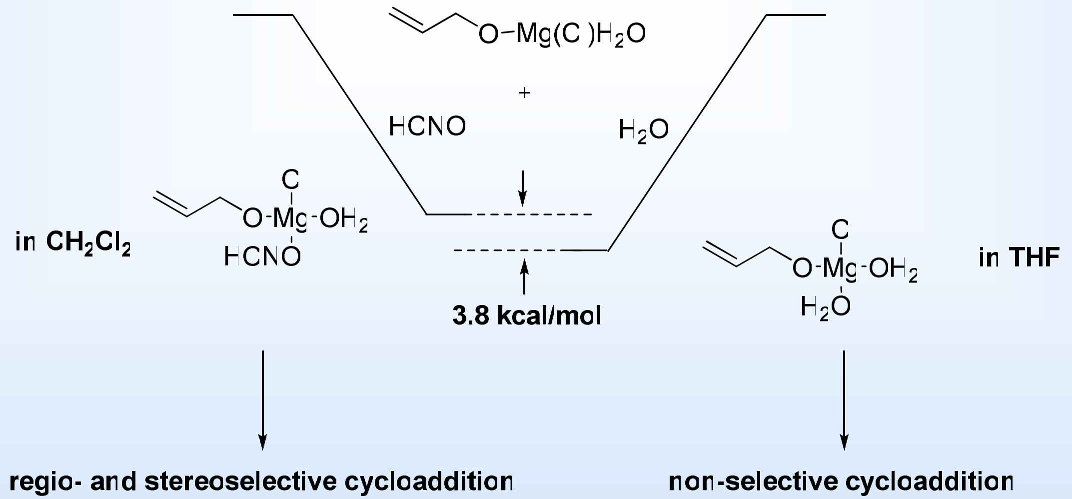
In summary…

- cycloaddition controlled in *syn*- and regio- selective manner with magnesium ions.
- allylic magnesium alkoxide much more reactive than free alcohol.
- twofold role of allylic magnesium alkoxide: base and dipolarophile.
- internal alkenes much less reactive than terminal alkenes.

7. Kanemasa *et al.*, *J. Am. Chem. Soc.* **1994**, 2324.

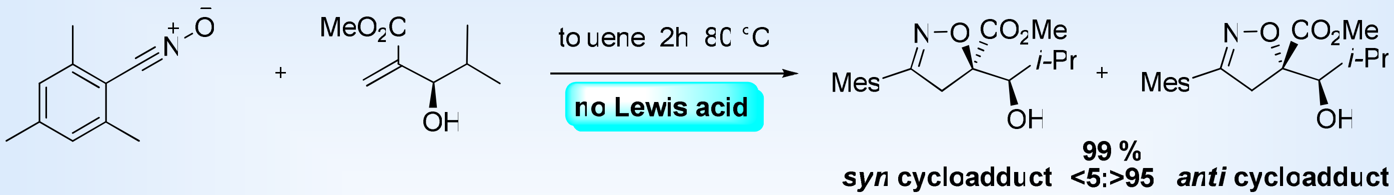
Explanation of selectivities by chelating model[7]



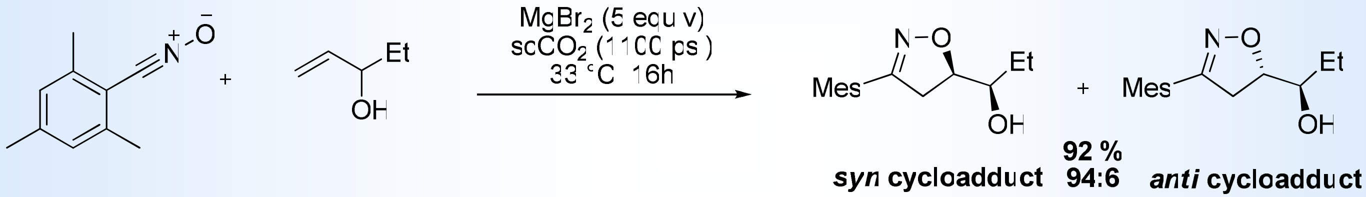


7. Kanemasa *et al.*, *J. Am. Chem. Soc.* **1994**, 2324.

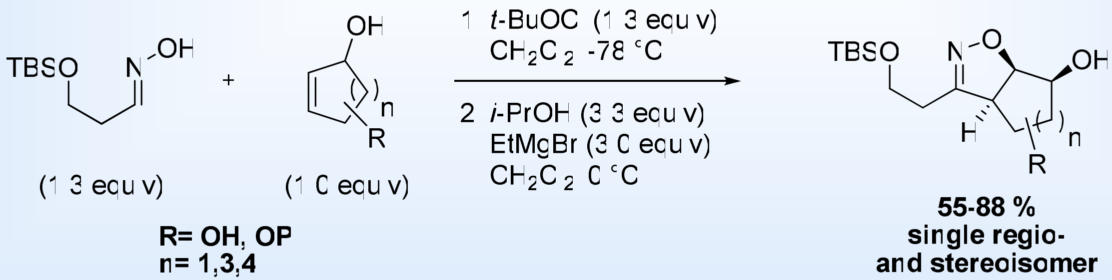
Reversal of diastereoselectivity with Baylis-Hillman adducts[8]



Nitrile oxide 1,3-dipolar cycloaddition in non-conventional solvent[9]

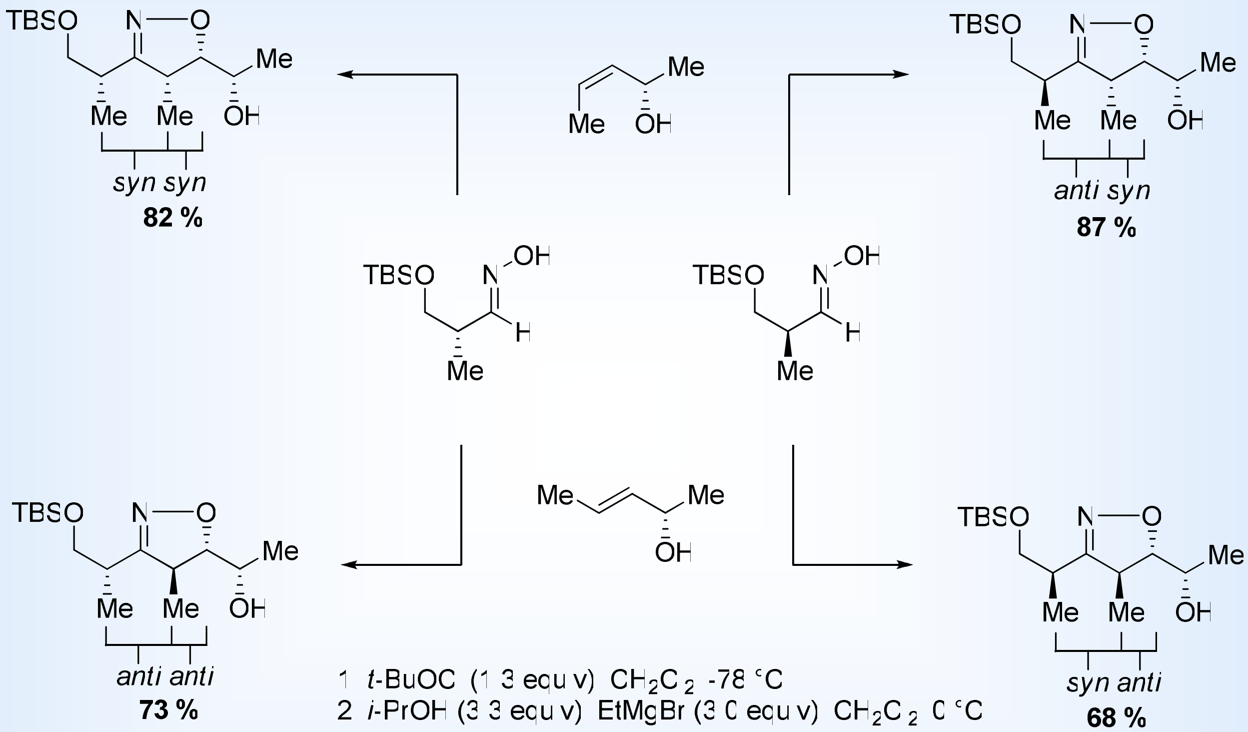


Nitrile oxide cycloaddition with cyclic allylic alcohols[10]



8. Krajčík *et al.*, *Tetrahedron* **2000**, 5465.
9. Holmes *et al.*, *Chem. Commun*. **2004**, 2622.
10. Carreira *et al.*, *Org. Lett*. **2007**, 3857.

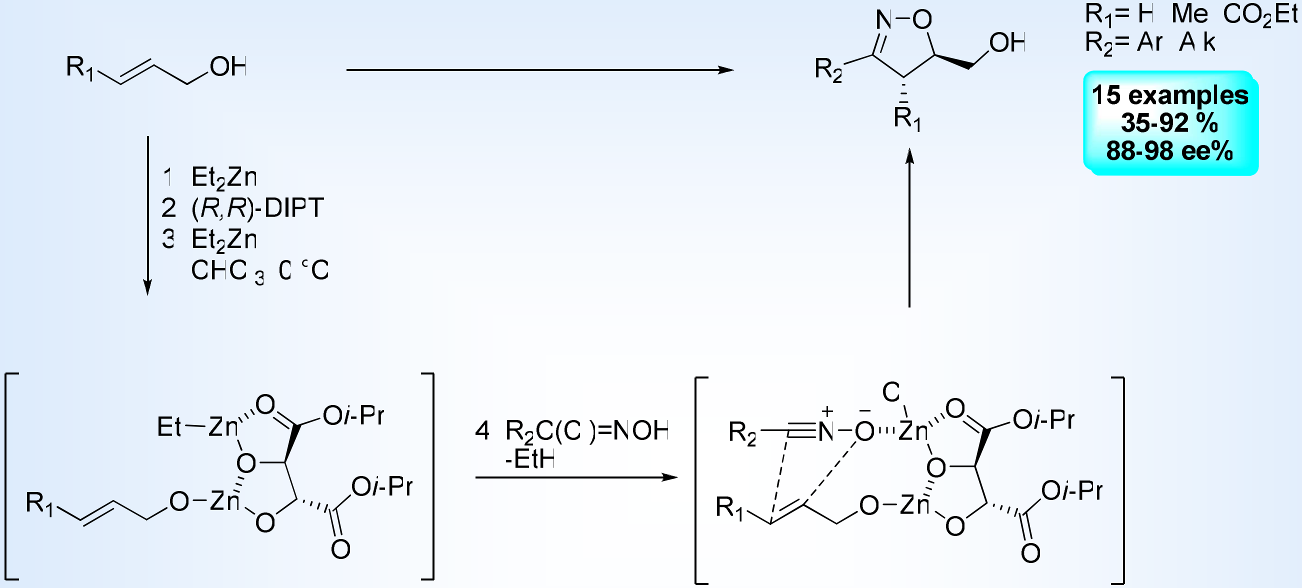
Use of chiral nitrile oxide and allylic alcohols: the Carreira's touch[11]



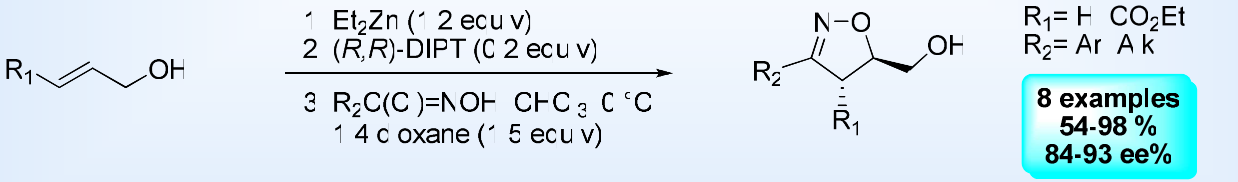
Selectively preparation of all eight possible stereoisomers

11. Carreira *et al.*, *Angew. Chem. Int. Ed.* **2001**, 2082.

Asymmetric version with DiisoPropyl Tartrate (DIPT): Inomata's work[12]



Catalytic asymmetric version[12]

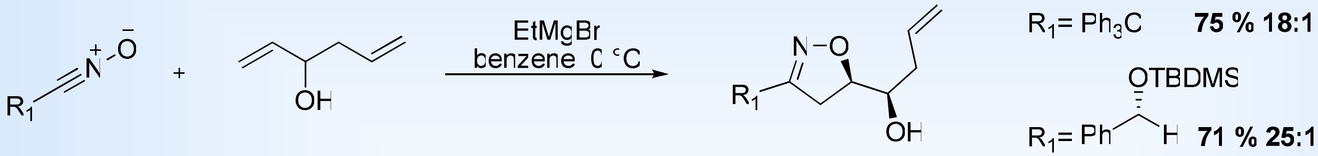


Activation by both zinc ions

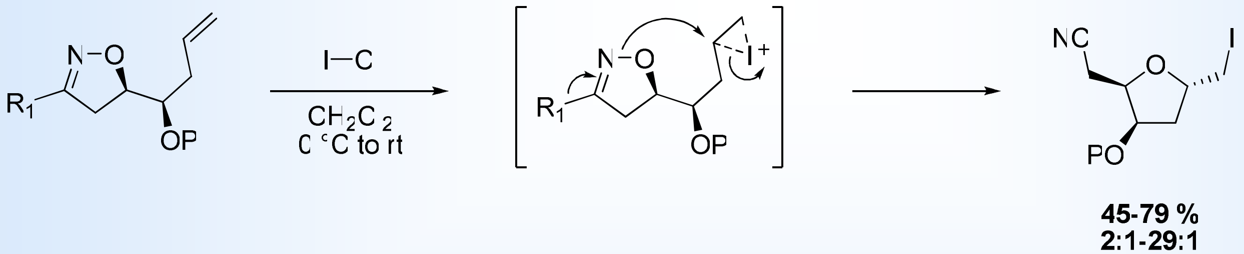
Ethereal additives to avoid formation of aggregated insoluble complex

12. Inomata *et al., Tet. Asym.* **2006**, 3075; *Synlett* **2003**, 1075.

Synthesis of tetrahydrofurans from isoxazolines[13]



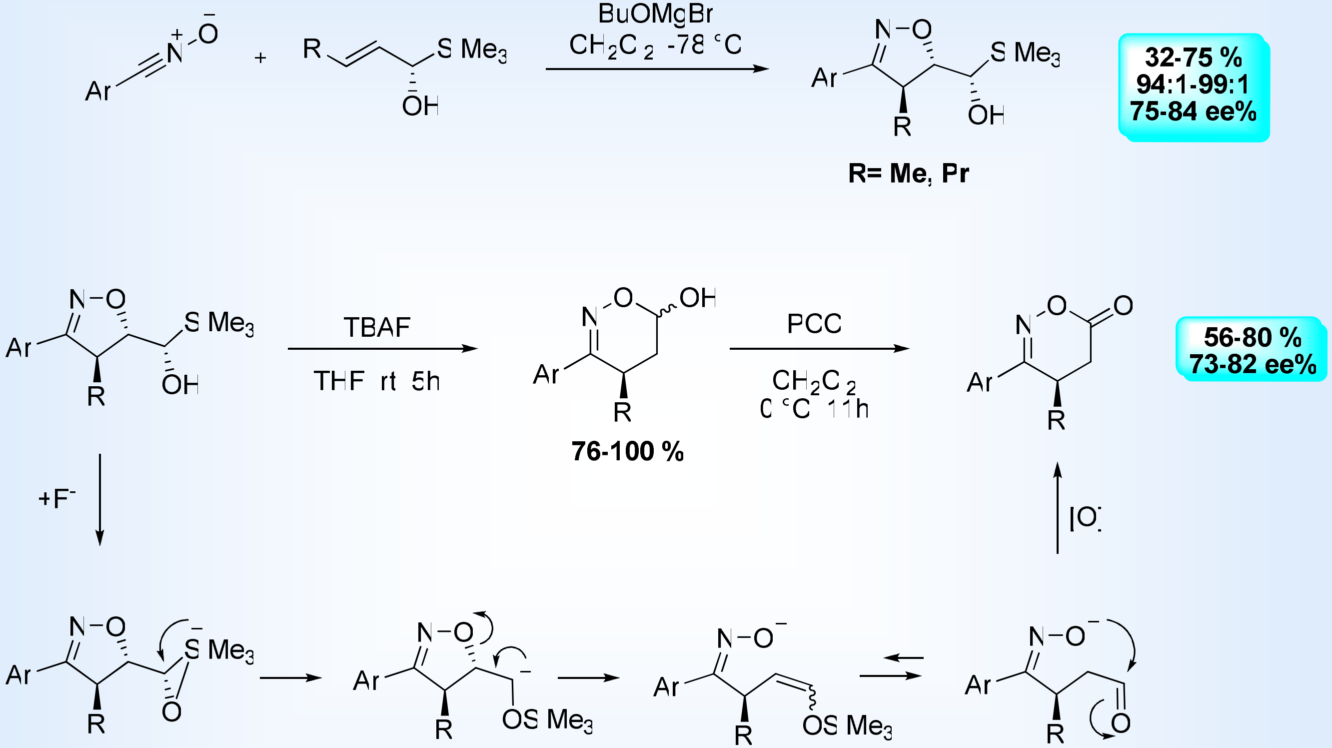
Allylic alcohols more reactive than homoallylic alcohols
Diastereoselectivity improved in benzene



Diastereoselective synthesis of tetrahydrofuran by iodoetheration
Functionalization useful in organic synthesis

13. Kim *et al., Synlett* **2002**, 1691.

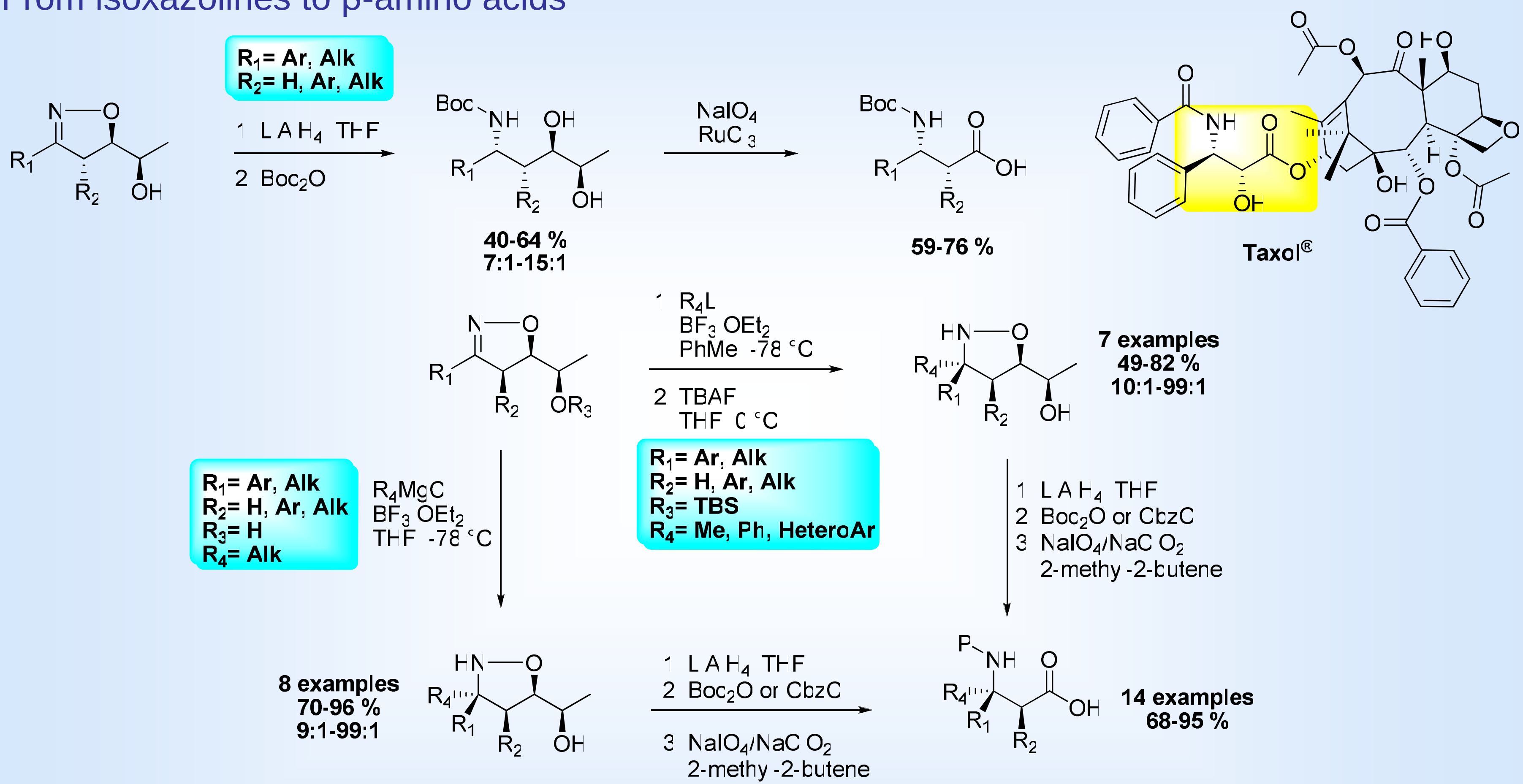
Formation of oxazinones from isoxazolines[14]



Mild conversion of isoxazolines to oxazinones *via* Brook rearrangment
No significant loss of optical purity

14. Kanemasa *et al.*, *Tetrahedron* **2002**, 9613.

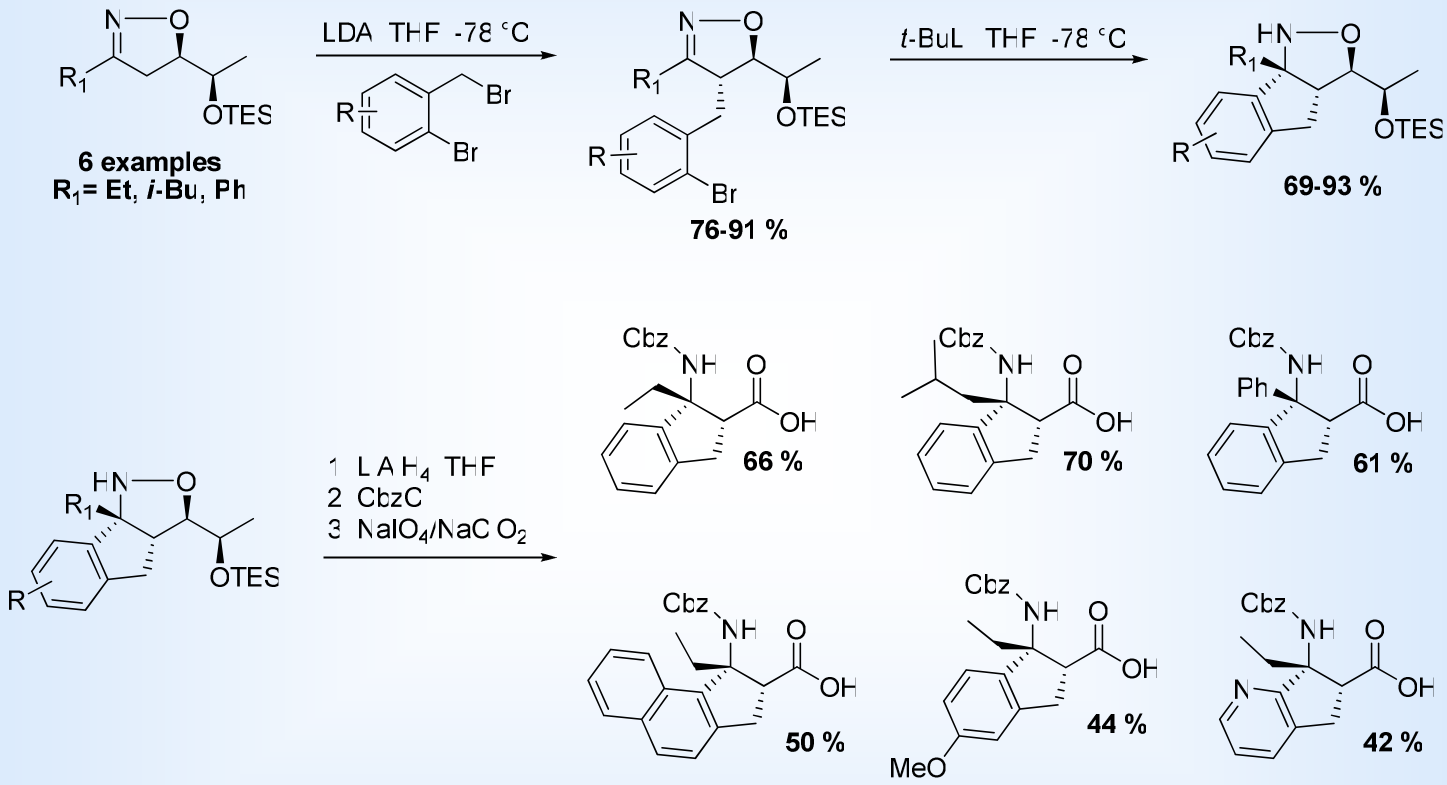
From isoxazolines to β-amino acids[15]



Versatile and efficient approach for the synthesis of β–amino acids
Installation of a challenging amine-bearing quaternary stereocenter

15. Mapp *et al.*, *J. Am. Chem. Soc.* **2003**, 6846; *Synlett* **2004**, 1409; *J. Am. Chem. Soc.* **2005**, 5376.

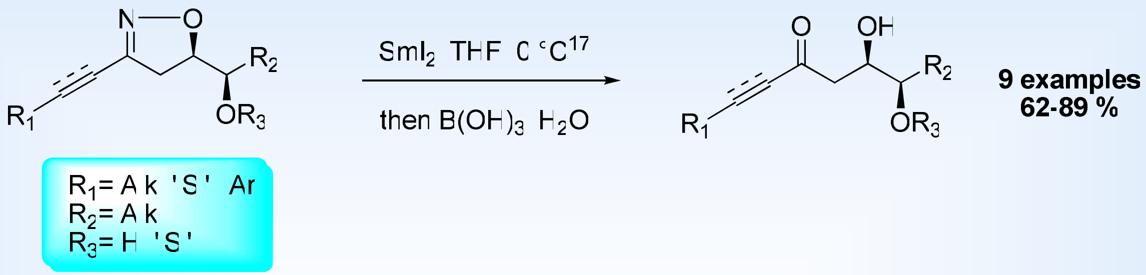
From isoxazolines to cyclic β-amino acids[15]

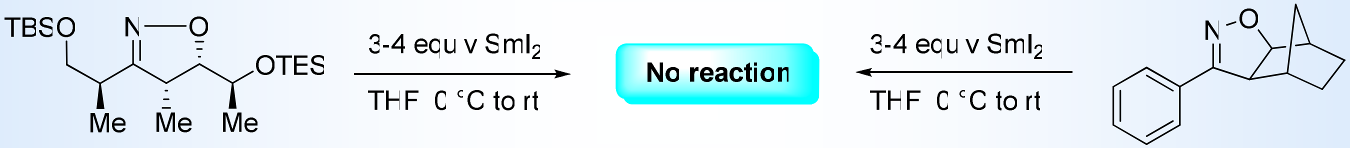


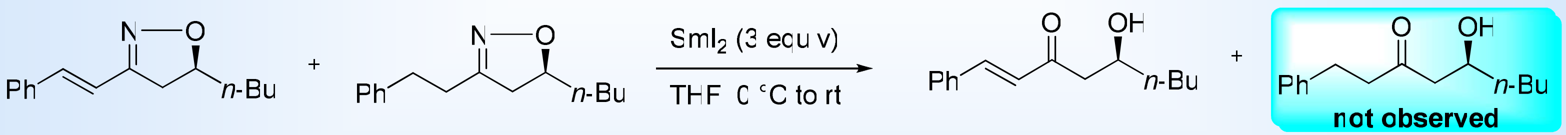
Preparation of *cis*-β-proline derivatives

15. Mapp *et al.*, *J. Am. Chem. Soc.* **2003**, 6846..

From isoxazolines to β-hydroxy ketones[16]



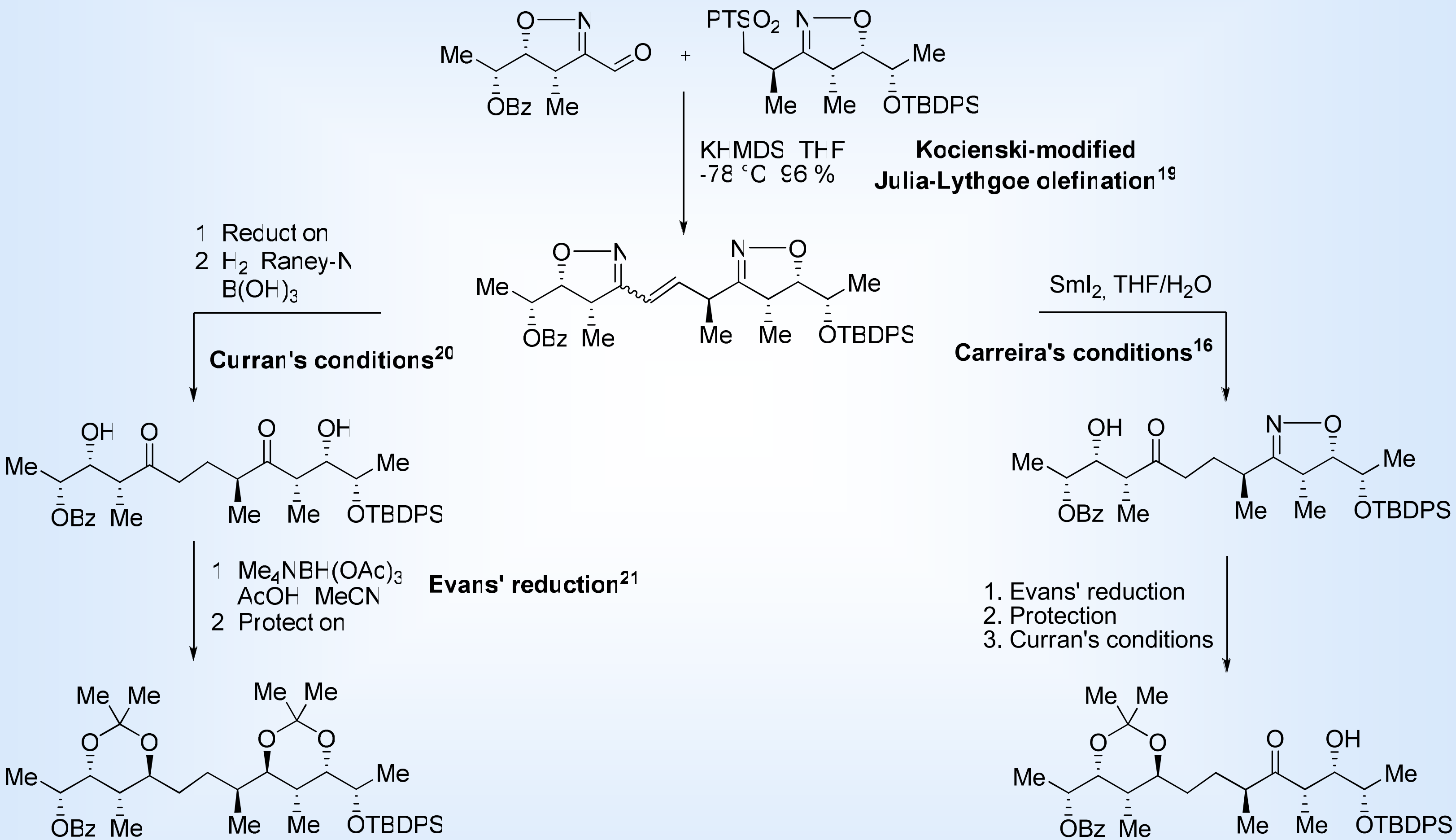




Mild, efficient, tolerant and chemoselective reduction of unsaturated isoxazolines

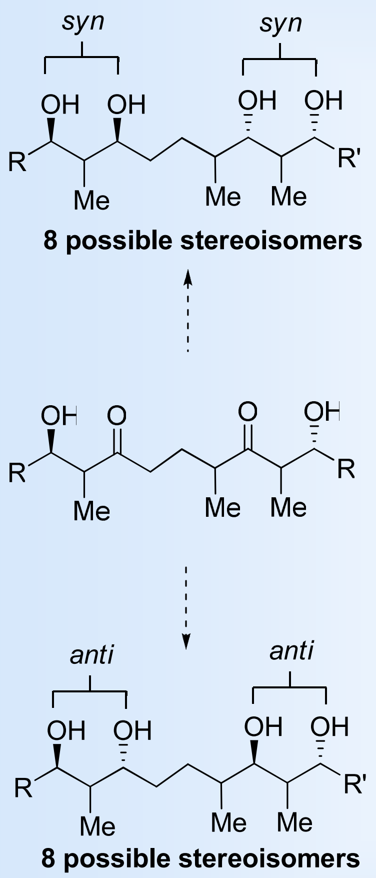
16. Carreira *et al., Org. Lett.* **2001**, 1587.
17. Keck *et al., Tet. Lett.* **1995**, 7419; Marco-Contelles *et al., J. Org. Chem.* **1996**, 359.

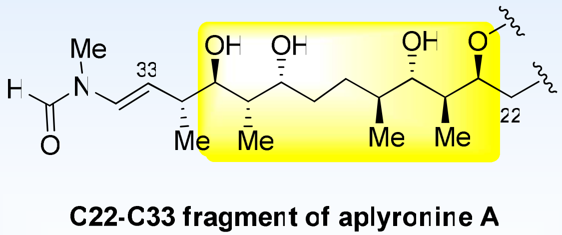
From isoxazolines to polypropionates[18]

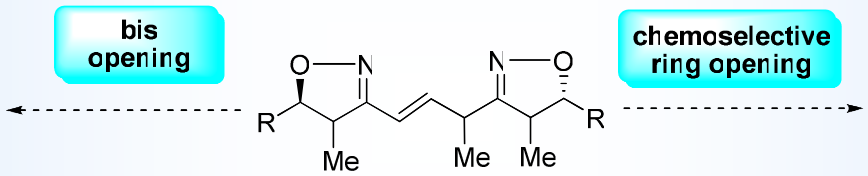


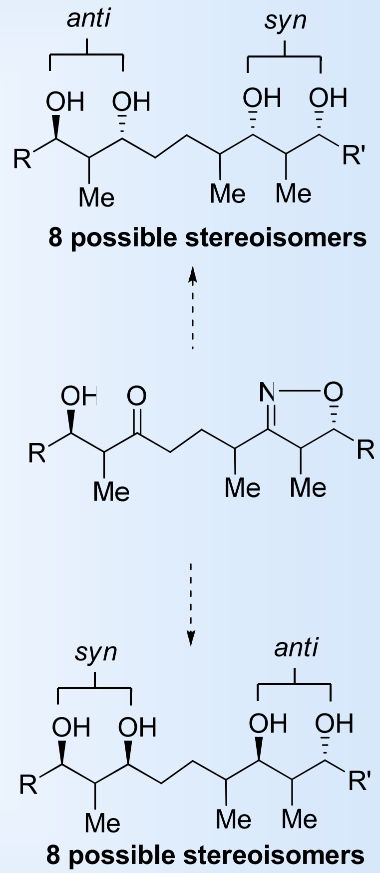
18. Carreira *et al.*, *Org. Lett.* **2004**, 2485.
19. Kocienski *et al.*, *Synlett* **2000**, 365.
20. Curran *et al.*, *J. Am. Chem. Soc.* **1983**, 5826.
21. Evans *et al.*, *J. Am. Chem. Soc.* **1988**, 3560.

From bis(isoxazolines) to polypropionates[18]









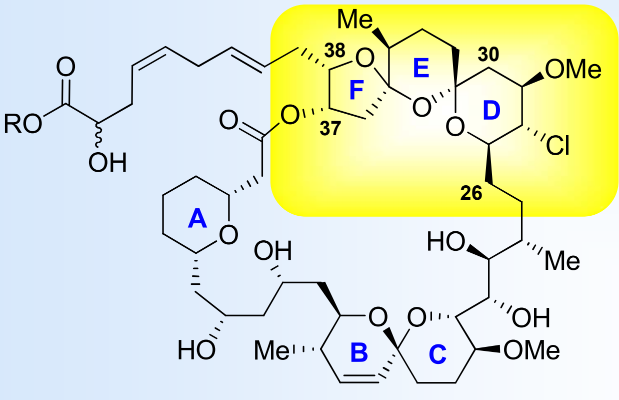
All 128 stereoisomers of this skeleton could be easily accessible

Extremely versatile methodology

Modular non-aldol strategy for efficient polypropionates synthesis

18. Carreira *et al.*, *Org. Lett.* **2004**, 2485.

Spirastrellolide A: Fürstner[22]

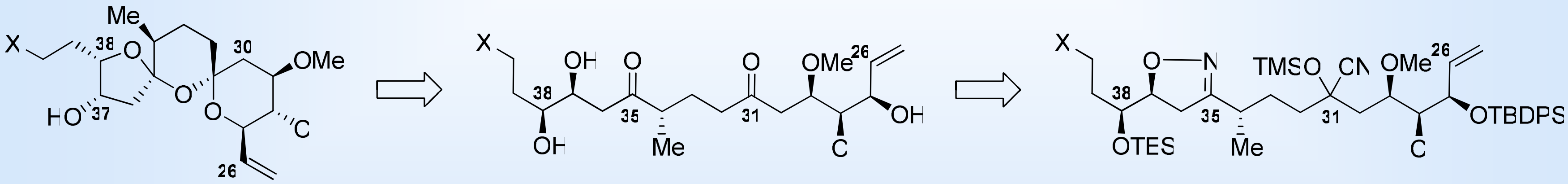


Spirastrellolide A

Isolated from Carribean sponge *Spirastrella coccinea* by Andersen[23] in 2003.

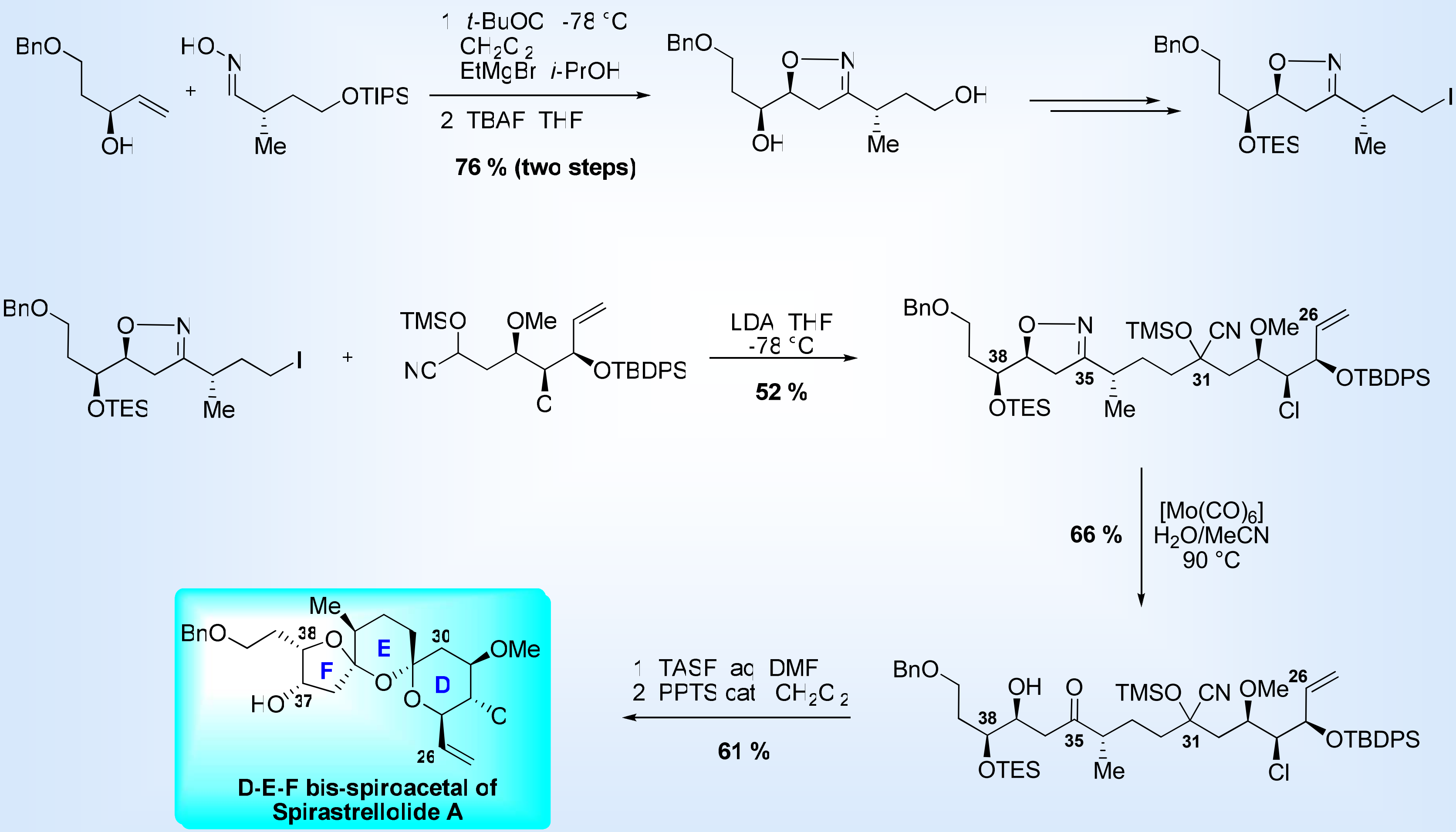
Potent and selective phosphatase inhibitory properties

Retrosynthetic pathway of northern hemisphere



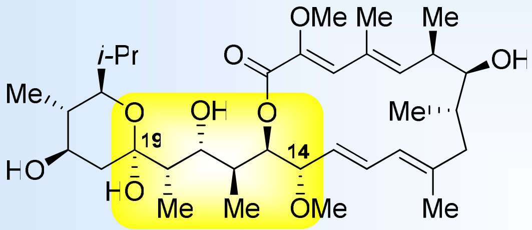
22. Fürstner *et al., Angew. Chem. Int. Ed.* **2006**, 5510.
23. Andersen *et al., J. Am. Chem. Soc*. **2003**, 5296.

Synthesis of northern fragment of Spirastrellolide A[22]



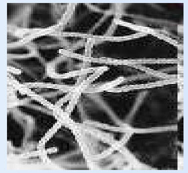
22. Fürstner *et al.*, *Angew. Chem. Int. Ed.* **2006**, 5510.

Bafilomycin A_1: Carreira[24]



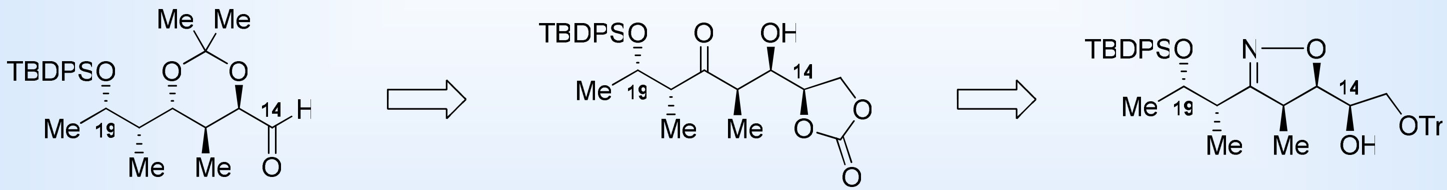
Bafilomycin A_1

Isolated from culture of *Streptomyces griseus* sp. *sulphurus* by Drautz[25] in 1983.



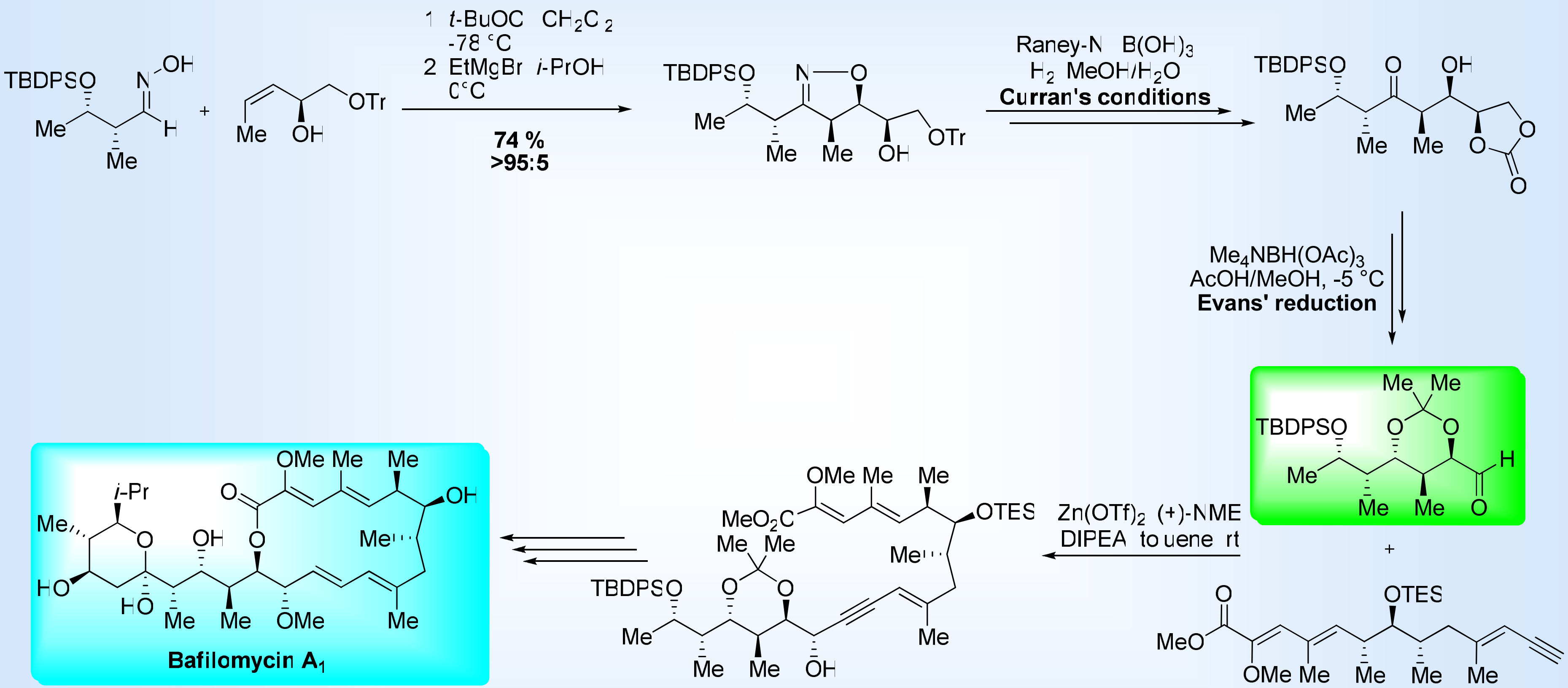
Antibacterial and antifungal activity
Inhibition of V-type ATPases

Retrosynthetic pathway of C14-C19 polypropionate fragment



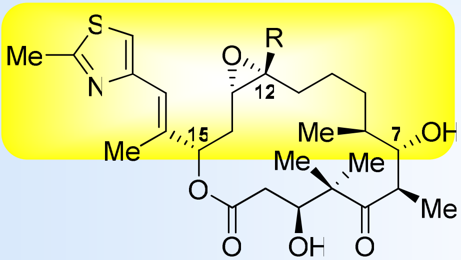
24. Carreira *et al., Angew. Chem. Int. Ed.* **2009**, 578.
25. Drautz *et al., Tet. Lett*. **1983**, 5193.

Synthesis of Bafilomycin A_1[24]



24. Carreira *et al.*, *Angew. Chem. Int. Ed.* **2009**, 578.

Epothilones A and B: Carreira[26]

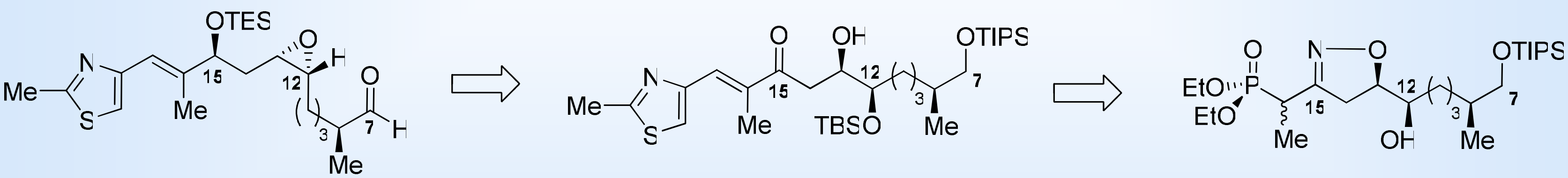


R=H, Epothilone A
R=Me, Epothilone B

Isolated from culture of *Sorangium cellulosum* by Höfle[27] in 1987.

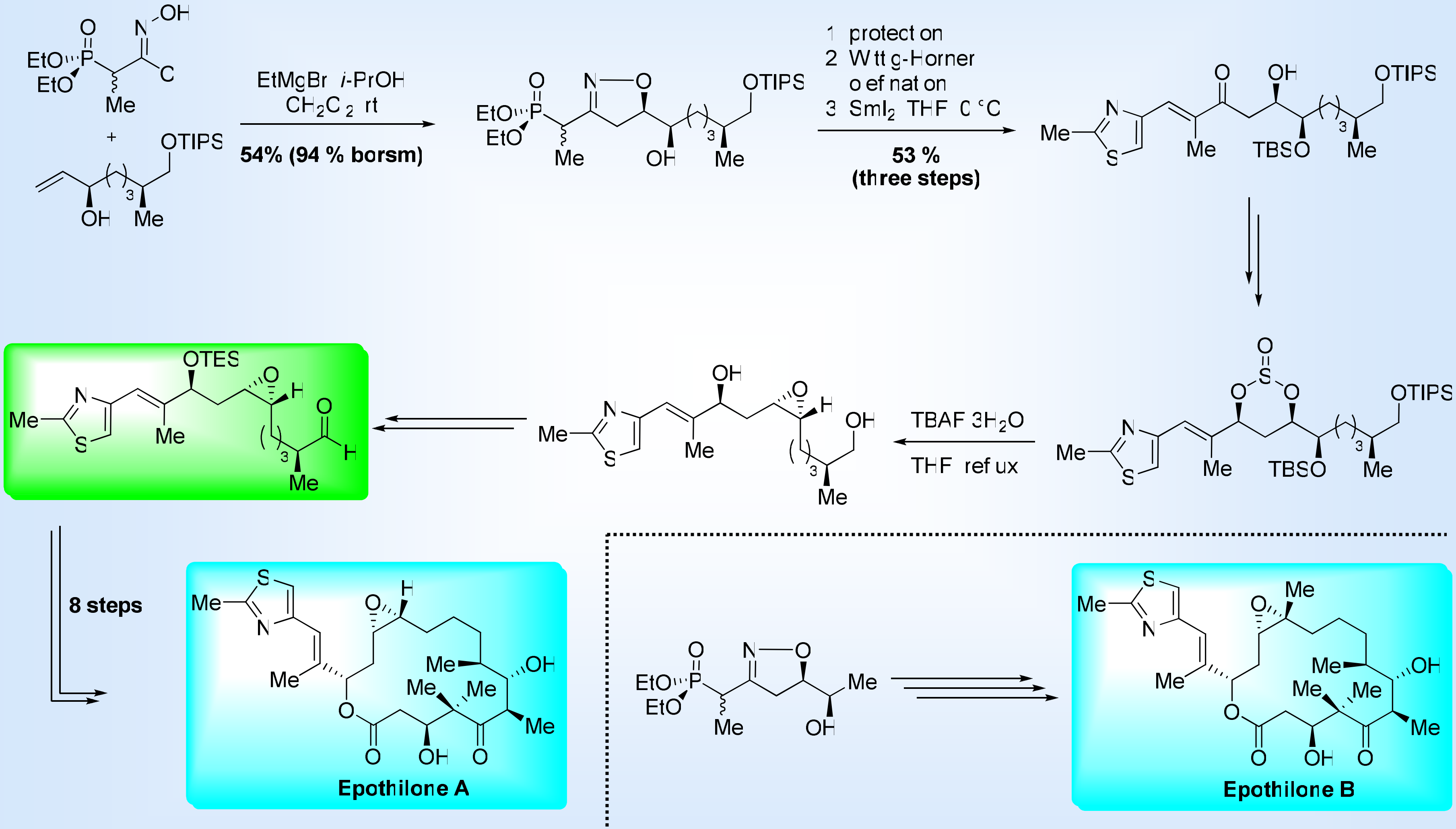
Induction of tubulin polymerization
Anticancer chemotherapeutic

Retrosynthetic pathway of C7-C15 northern fragment for Epothilone A



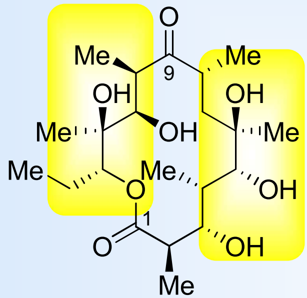
26. Carreira *et al., J. Org. Chem.* **2001**, 6410; *J. Am. Chem. Soc*. **2001**, 3611.
27. Höfle *et al., Angew. Chem. Int. Ed*. **1996**, 1567.

Synthesis of Epothilones A[26]



26. Carreira *et al., J. Org. Chem.* **2001**, 6410; *J. Am. Chem. Soc.* **2001**, 3611.

Erythronolide A: Carreira[28]

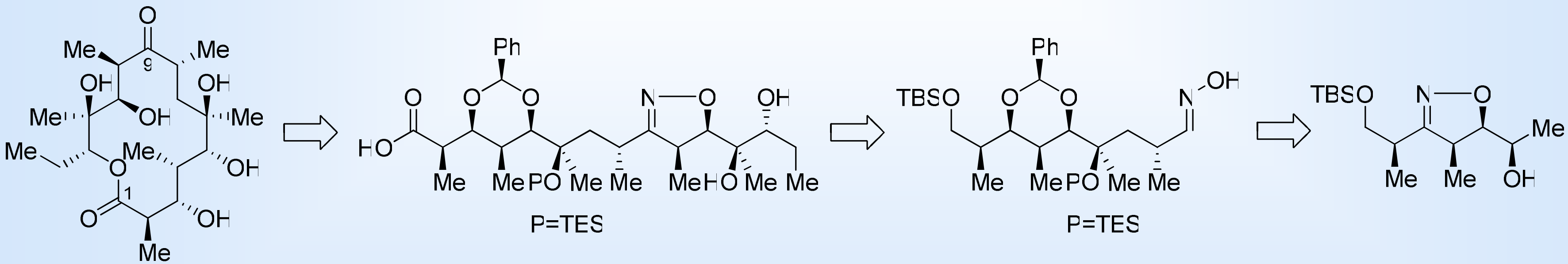


Erythronolide A

Isolated from *Streptomyces erythraeus* by Smith[29] in 1952.

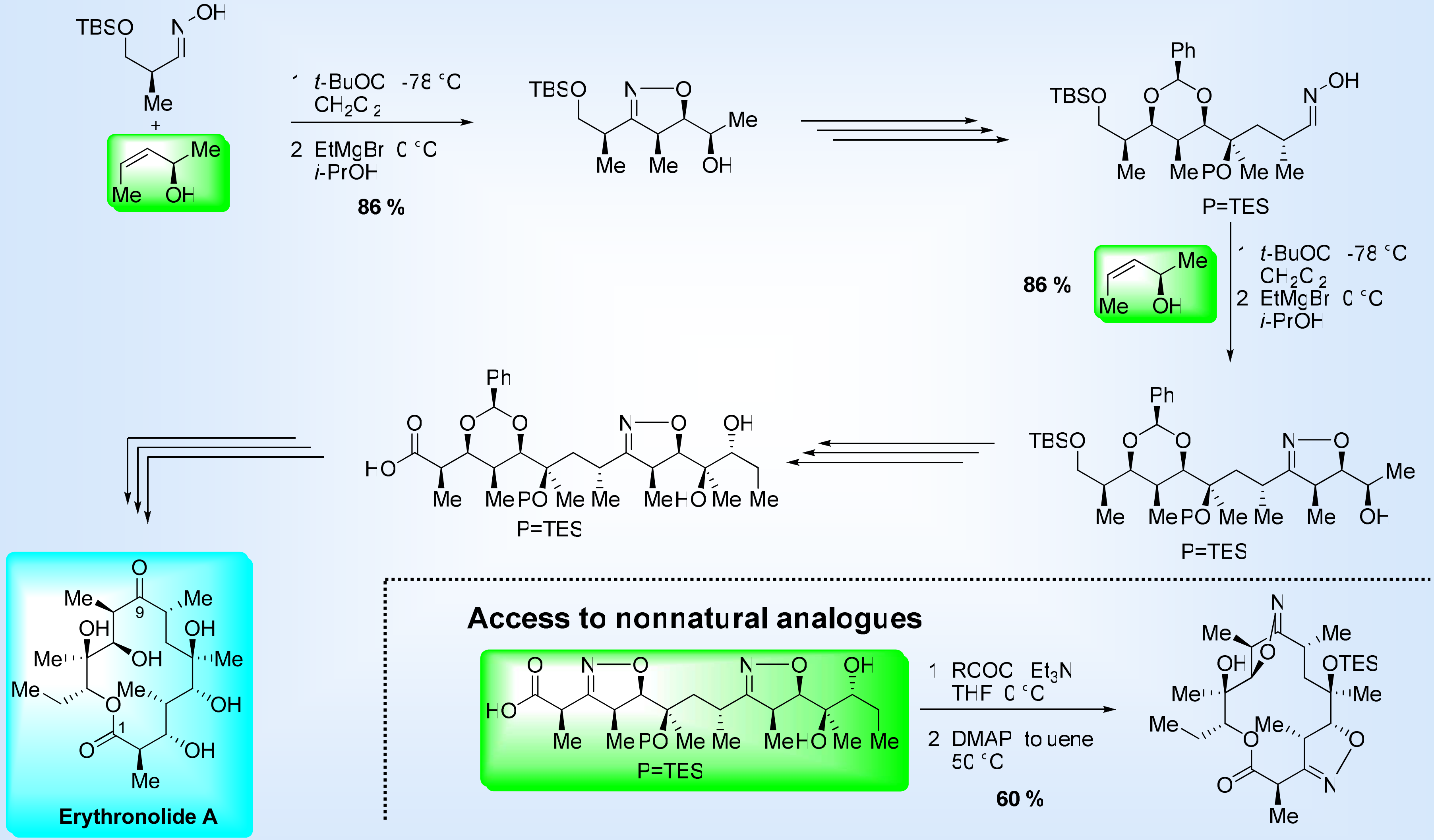
Antiinfective properties
Antibiotic activity

Retrosynthetic pathway of Erythronolide A using double cycloaddition



28. Carreira *et al., Angew. Chem. Int. Ed*. **2005**, 4036.
29. Smith *et al., Antibiot. Chemother*. **1952**, 281.

Synthesis of Erythronolide A[28]



28. Carreira *et al.*, *Angew. Chem. Int. Ed.* **2005**, 4036.

Nitrile oxides 1,3-dipolar cycloaddition with allylic alcohols

- Kanemasa: high regio- and diastereoselectivities in the presence of Mg^{2+} ions

- Inomata: development of catalytic asymmetric version with Zn/tartrate system

- Mapp: from isoxazolines to β-amino acid derivatives

- Carreira: from isoxazoline to β-hydroxy ketones, synthesis of polypropionates with high stereoselectivity, use of this non-aldol approach for several total syntheses…