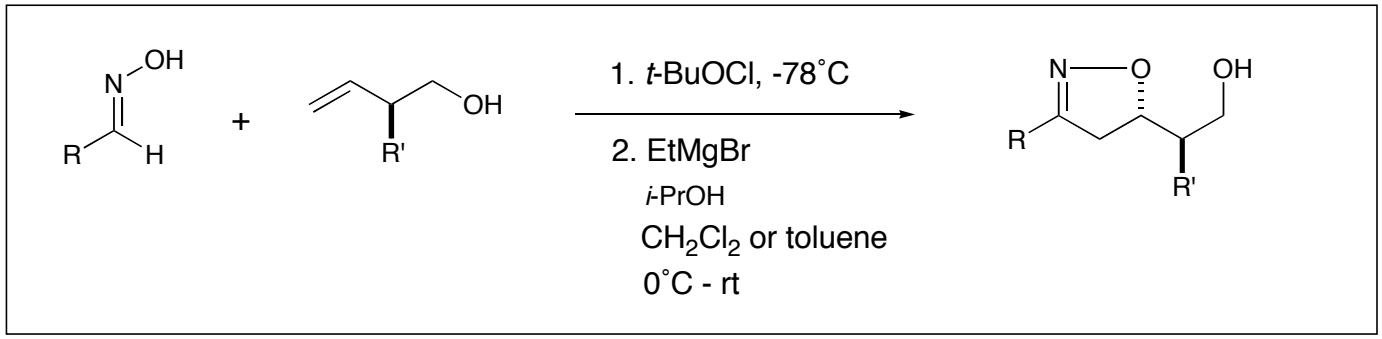
A Modular Approach to Polyketide Building Blocks: Cycloadditions of Nitrile Oxides and Homoallylic Alcohols

Organic Letters, **2005**, ASAP

Nina Lohse-Fraefel and Erick M. Carreira*



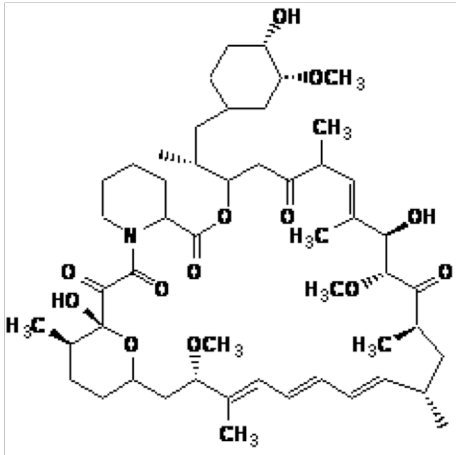
Anthony Cuzzupe
April 30, 2005

Polyketides: Natural compounds containing alternating carbonyl and methylene groups ("β-polyketones"), biogenetically derived from repeated condensations of acetyl coenzyme A

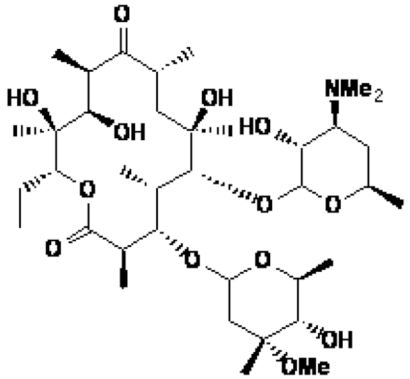
IUPAC *Pure & Appl. Chem.*, **1995**, *67*, 1307

-Usually possess potent biological activity and are structurally (stereochemically) complex.

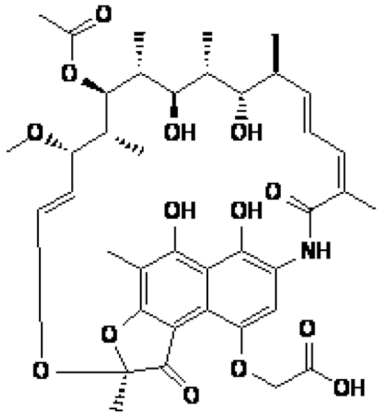
-Some examples:



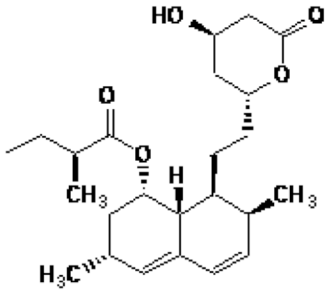
rapamycin
(immunosuppressant)



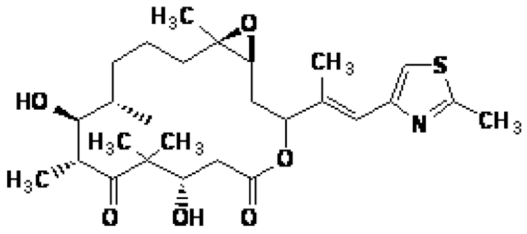
erythromycin A
(antibacterial)



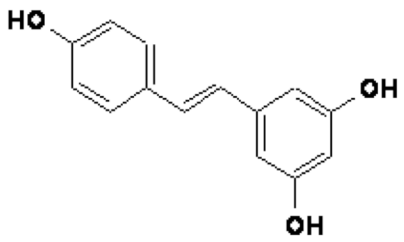
rifamycin B
(antituberculosis)



lovastatin
(anticholesterol)



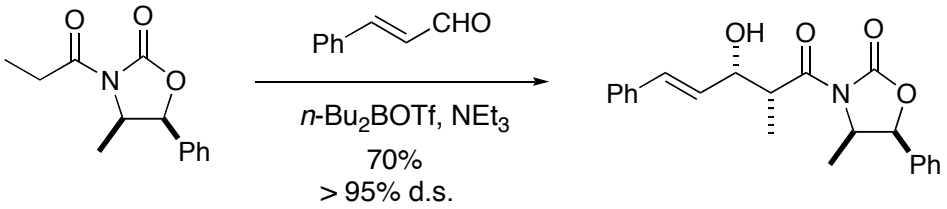
epothilone B
(anticancer)



(E)-resveratrol
(chemopreventive)

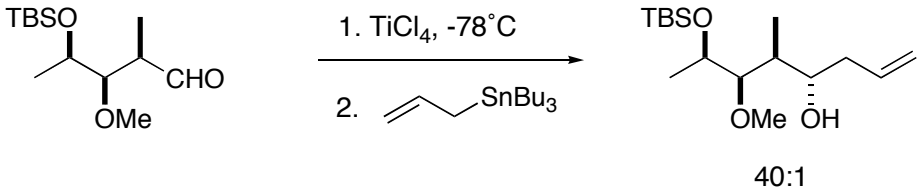
Some Common Methods for Polyketide Synthesis:

Aldol:



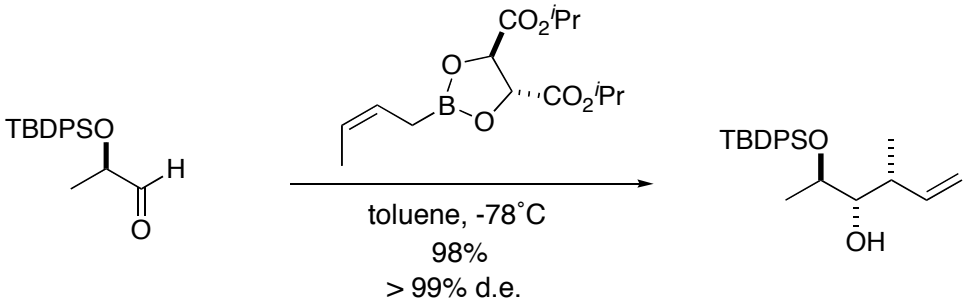
Evans, *J. Org. Chem*, **1992**, *57*, 1067
(Macbecin I)

Allylmetallation:



Keck, *Tetrahedron Lett*. **1996**, *37*, 3291
(Rhizoxins)

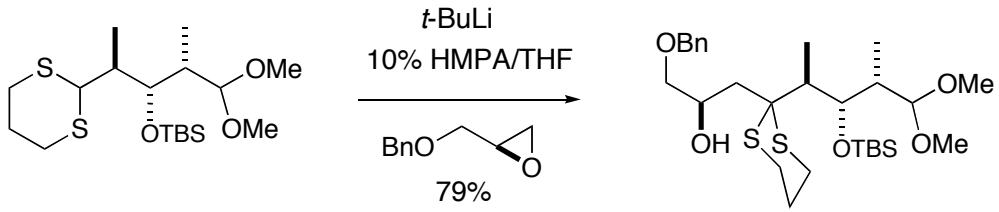
Crotylmetallation:



Roush, *J. Am. Chem. Soc*. **1996**, *118*, 7502
(Nargenicin A_1)

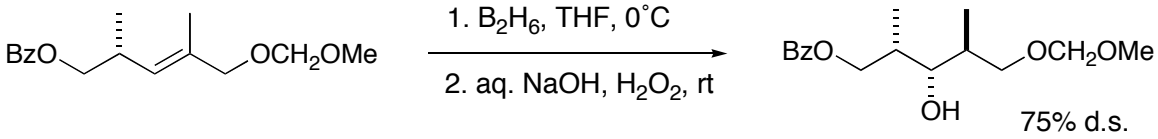
Some Alternative Methods for Polyketide Synthesis:

Dithiane coupling:



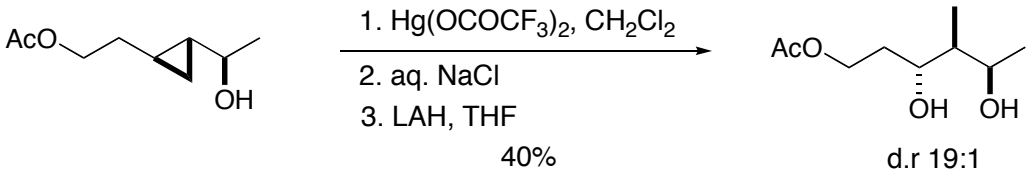
Smith, *J. Am. Chem. Soc*, **2000**, *122*, 8654
(Discodermolide)

Hydroboration:



Kishi, *Tetrahedron Lett*. **1979**, *45*, 4343

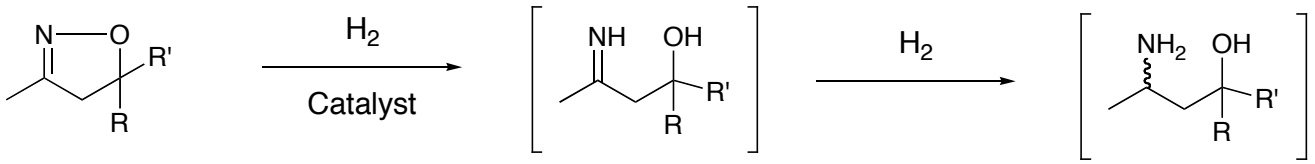
Cyclopropylcarbinol ring-opening:



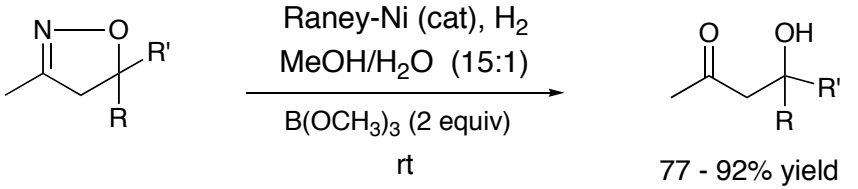
Cossy, *Acc. Chem. Res*. **2003**, *36*, 766

Isoxazolines are Latent Aldol Products

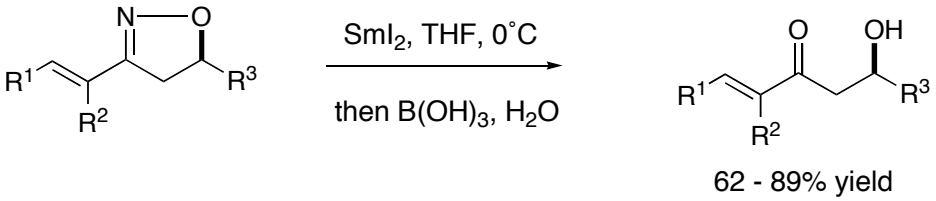
-Reduction of isoxazolines usually result in complete reduction to the amino alcohol:



Some important discoveries:



Curran, *J. Am. Chem. Soc.* **1982**, *104*, 4024



Carreira, *Org. Lett.* **2001**, *3*, 1587

Products are β-hydroxy ketones (equivalent to Aldol adducts!)

→ Isoxazolines can be used in polyketide synthesis.

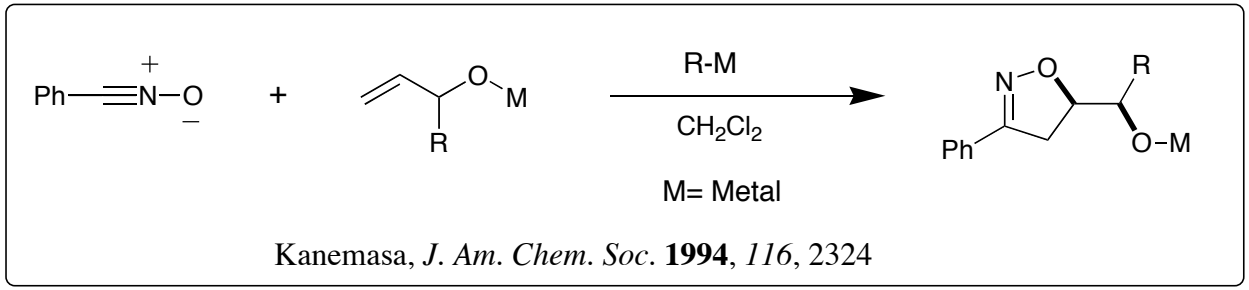
Isoxazoline Synthesis by Nitrile Oxide Cycloaddition

Problems:

> Difficult to control regio- and stereochemistry in the typical nitrile oxide cycloaddition reaction

> Use of substituted olefins usually unsuccessful

Kanemasa's work on the first metal coordinated control of 1,3-dipolar cycloadditions:



Kanemasa, *J. Am. Chem. Soc.* **1994**, *116*, 2324

> Works best with allylic alcohols (terminal, di-substituted and tri-substituted alkenes) with yields up to and above 90%

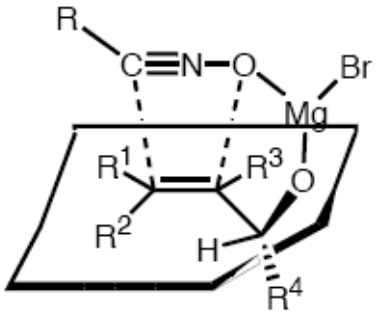
> High *syn* selectivity, up to 99:1 *syn:anti*

> Grignard Reagents work best, but amines, alkyllithiums, alkylaluminums and alkylzincs also work with lower selectivity

> Use of homoallylic alcohols led to diminished regio- and diastereoselectivity and lower yields

Isoxazoline Synthesis by Nitrile Oxide Cycloadditions

Why such high *syn* selectivity?



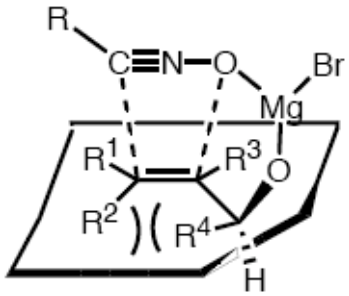
TS-A

Regioselective

Syn-cycloadducts

MAJOR

>>



TS-B

Anti-cycloadducts

Kanemasa, *J. Am. Chem. Soc.* **1994**, *116*, 2324

> Stereochemical outcome governed by TS-A being favoured due to less steric hindrance from allylic strain between R_2 and R_4

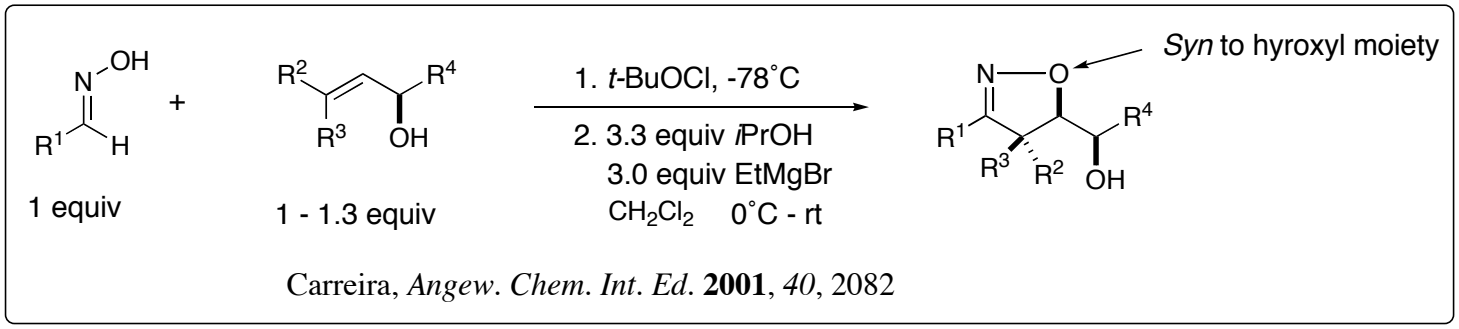
Reaction Scope:

> Although a number of allylic alcohols were used successfully, this study was limited to the use of benzonitrile oxide

Isoxazoline Synthesis by Nitrile Oxide Cycloadditions

Extension to Kanemasa's work:

> Conditions developed by Carreira and co-workers for the use of functionalised, aliphatic nitrile oxides in the hydroxy-directed nitrile oxide cycloaddition:



Carreira, *Angew. Chem. Int. Ed.* **2001**, *40*, 2082

> Nitrile oxides prepared in situ by preparation of the corresponding hyroximinoyl chloride with *t*-BuOCl and reacted directly with the allylic magnesium alkoxide

> Magnesium alkoxides also generated in situ

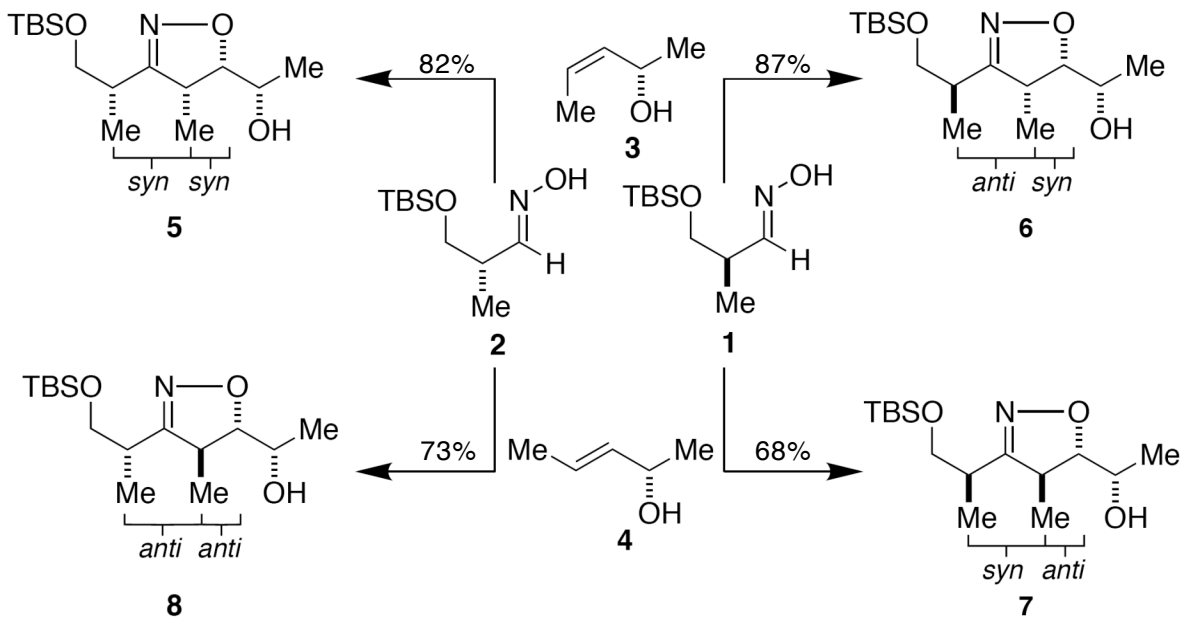
> Use of *i*-PrOH as additive improved reaction time and yields

> Procedure is tolerant of a wide range of functionality and olefin substitution

> Desired cycloadducts obtained in good yields and high diastereoselectivities

Isoxazoline Synthesis by Nitrile Oxide Cycloadditions

> Single-step preparation of all possible diastereomers of latent propionates:



> All adducts regio- and stereochemically pure by ^{1}H and ^{13}C NMR

> Structure of a derivative of adduct **6** confirmed by X-ray crystallography

Carreira, *Angew. Chem. Int. Ed.* **2001**, *40*, 2082

A Modular Approach to Polyketide Building Blocks: Cycloadditions of Nitrile Oxides and Homoallylic Alcohols

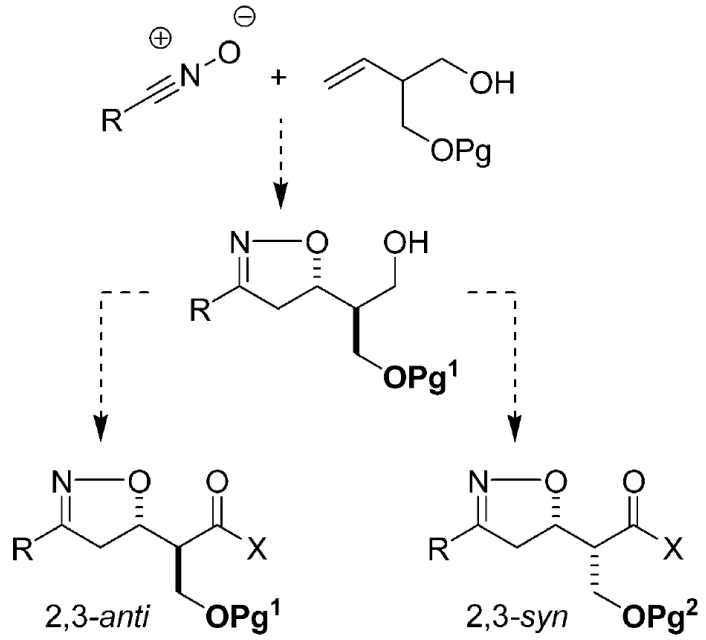
Problems anticipated:

> Homoallylic alkoxides less reactive than allylic alkoxides

> In absence of a highly reactive alkene, aliphatic nitrile oxides might undergo dimerization

Aim:

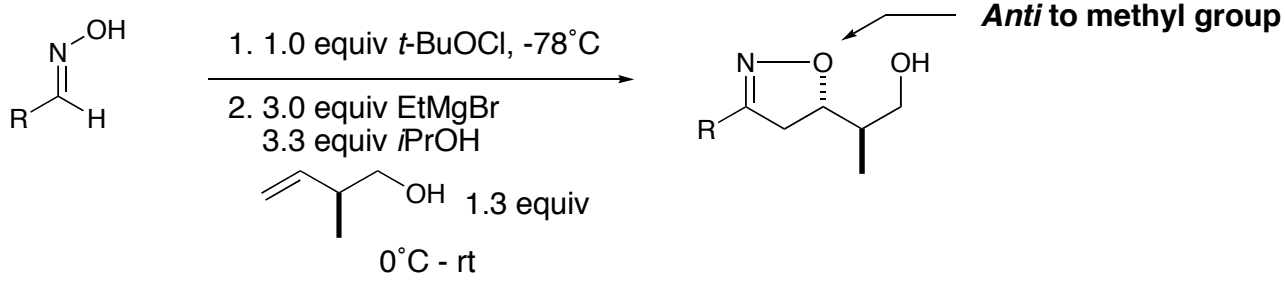
> Devolop strategies to provide access to the stereochemical permutations of dipropionate subunits, allowing divergent asymmetric synthesis from a single diastereoselective cycloaddition reaction

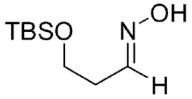
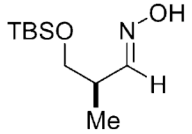
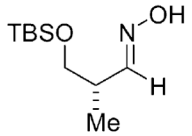
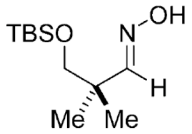
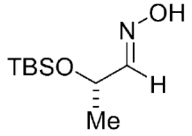
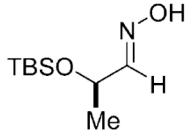


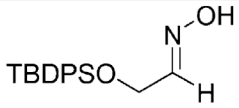
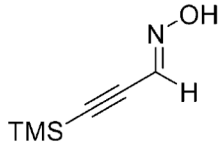
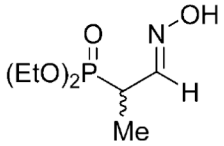
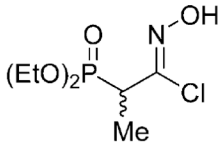
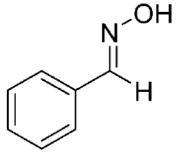
Carreira, *Org. Lett.* **2005**, ASAP

Results:

> A broad range of nitrile oxides react smoothly with (*s*)-2-methyl-3-butenol under the conditions previously optimised for allylic alcohols.



entry	substrate	solvent	d.r.[a]	yield
1		CH_2Cl_2	8:1[b]	67%
2		CH_2Cl_2	7:1	83%
3		CH_2Cl_2	9:1	85%
4		toluene	4:1[b]	89%
5		toluene	6:1[c]	82%
6		toluene	5:1[c]	83%

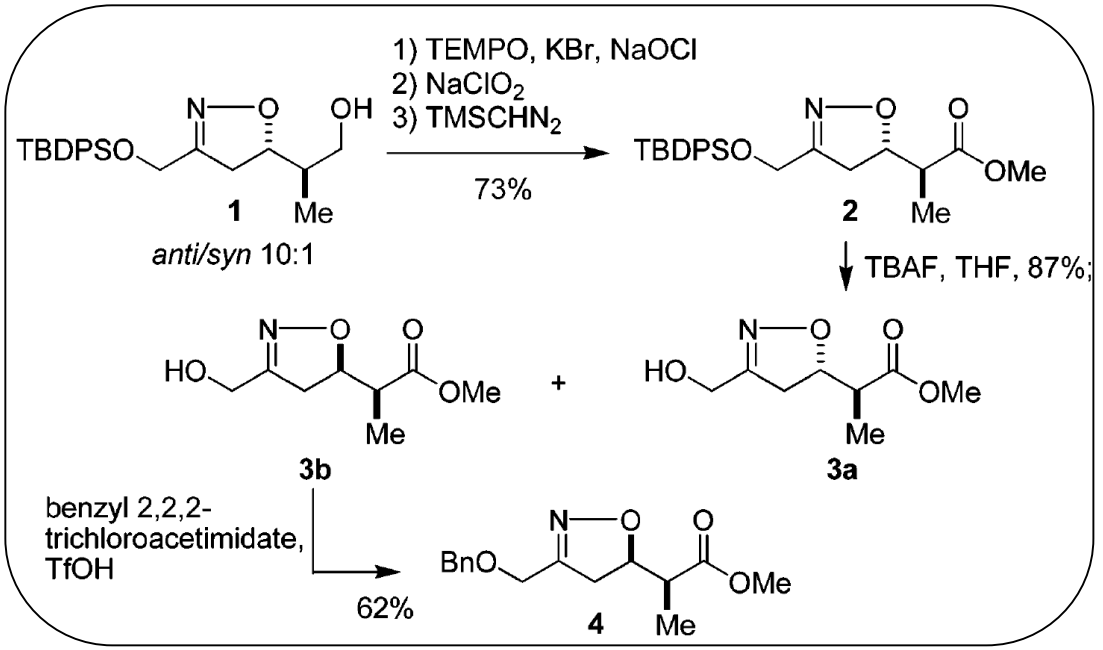
entry	substrate	solvent	d.r.[a]	yield
7		toluene	10:1[c]	87%
8		toluene	5:1[b]	66%[d,e]
9		CH_2Cl_2	11:1[f]	36%
10		CH_2Cl_2	13:1[f]	71%[g]
11		CH_2Cl_2	7:1	87%[e,h]

Carreira, *Org. Lett.* **2005**, ASAP

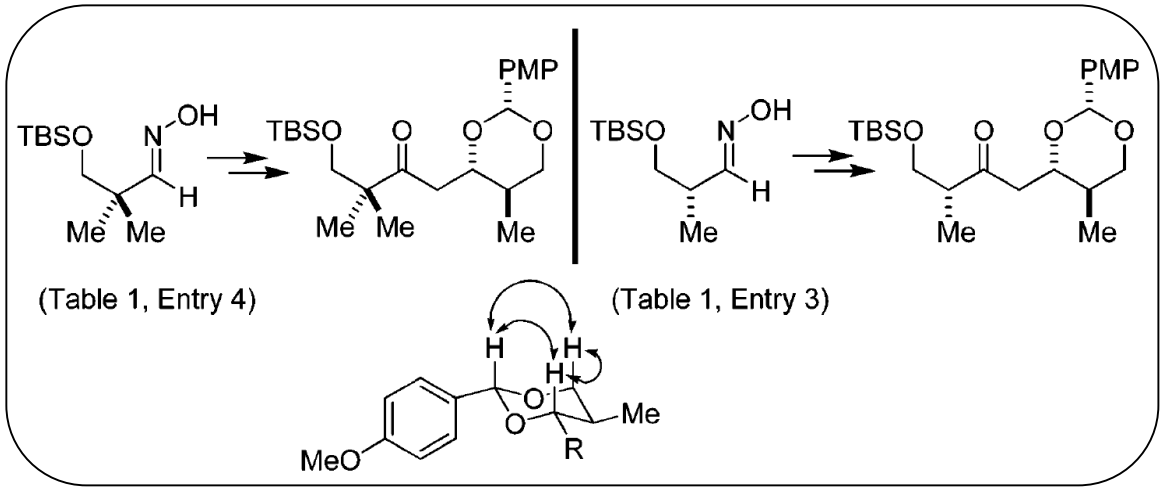
> Diastereomeric ratios generally determined by NMR spectroscopy

> Relative stereochemistry determined by conversion of cycloadduct **1** into known isoxazoline **4**

Panek, *J. Am. Chem. Soc.* **1993**, *115*, 7898

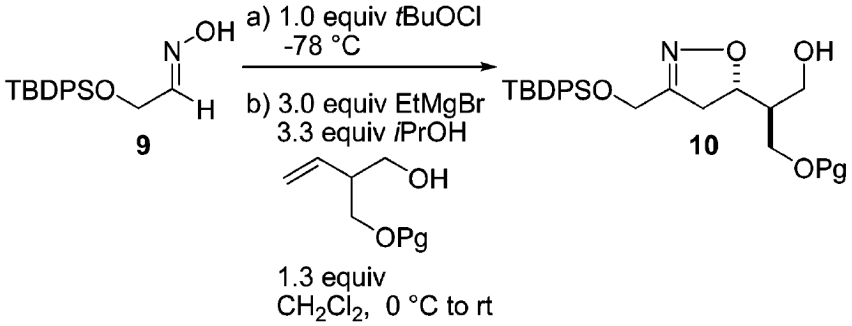


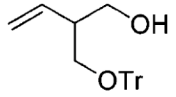
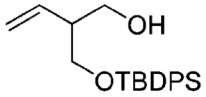
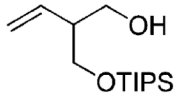
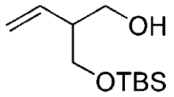
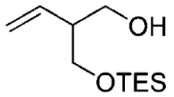
.... and further confirmed by derivatisation of two additional adducts and subsequent NOE experiments



Carreira, *Org. Lett.* **2005**, ASAP

Scope of cycloaddition extended to include monoprotected homoallylic diols:



entry	monoprotected homoallylic diol	d.r.	yield
1		19:1[a]	82%
2		21:1[b]	85%
3		14:1[b]	73%
4		10:1[b]	78%
5		6:1[b]	53%

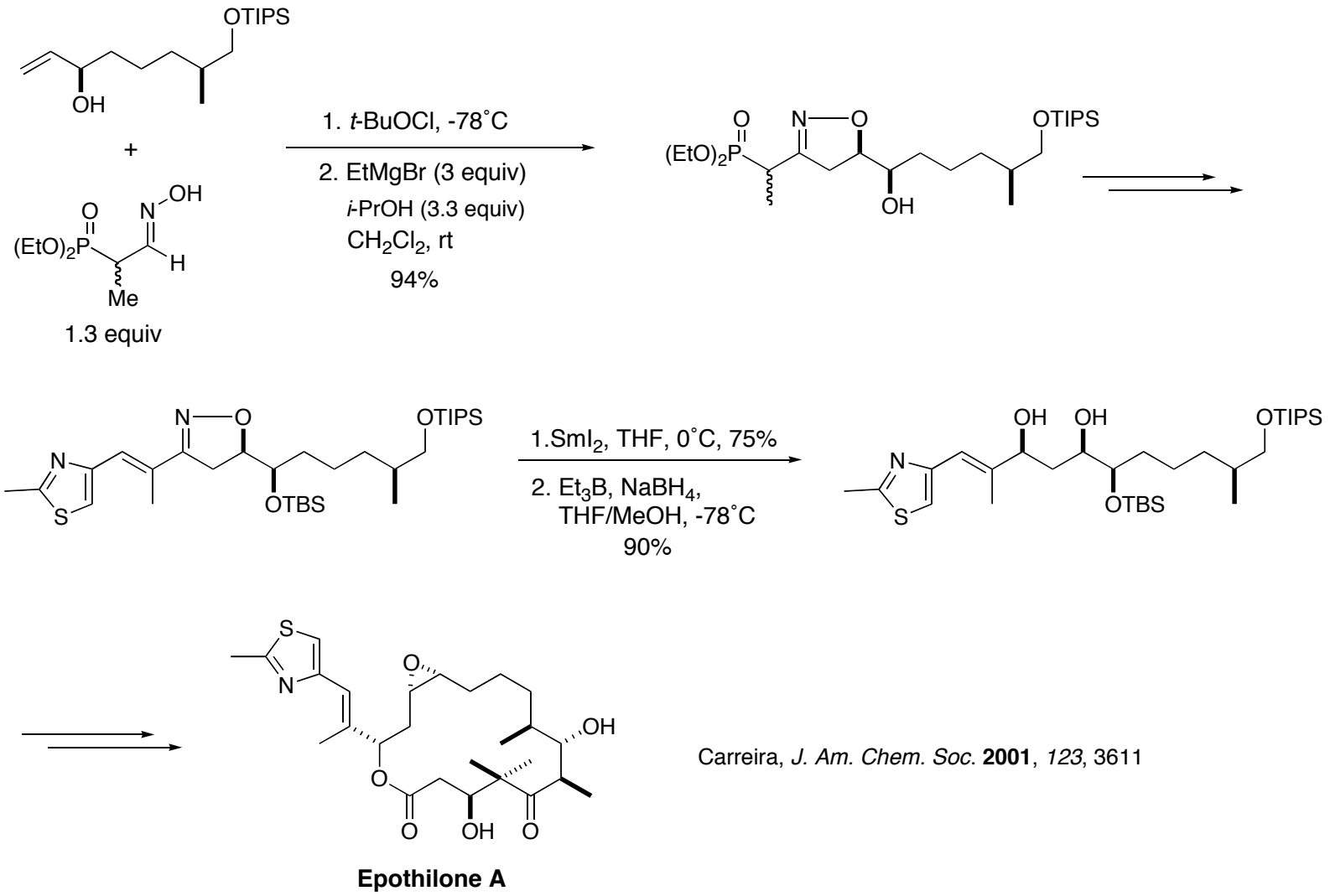
> Yield and diastereoselectivity increases as steric demand of protecting group increases

> Immediate cycloadducts are *anti*, but the corresponding *syn* derivatives can be accessed by a simple orthogonal protection-deprotection protocol

> Therefore access to both *syn* and *anti* diastereoisomers is possible using same set of starting materials

Carreira, *Org. Lett.* **2005**, ASAP

Example of use in Total Synthesis:
Directed Nitrile Oxide Cycloaddition for the Synthesis of Epothilone A



Epothilone A

Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611

Conclusions

> The Mg-mediated, hydroxyl-directed nitrile oxide cycloaddition is highly stereoselective

> Procedure is operationally simple and versatile and is tolerable of a wide range of functionality and olefin substitution

> The methodolgy considerably expands the range of protected polyketide subunits that can be accessed

> Using isoxazolines as masked aldol adducts:
- Enables convergent syntheses with the use of complex olefin and nitrile oxide coupling partners
- Avoids the need for subsequent protection steps

> The cycloaddition with and allylic alcohol has been used successfully in total synthesis

> Use of the extended methodolgy involving homoallylic alcohols in total synthesis is pending