

Petasis-Ferrier Rearrangement

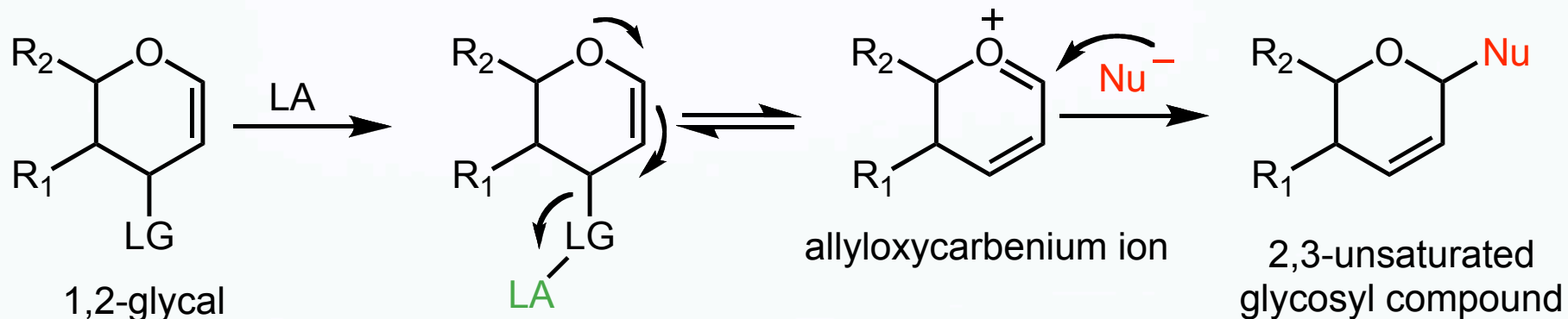
Name Reaction Presentation

Anil Kumar Gupta
Wulff Group
February 13, 2009

Ferrier Reaction

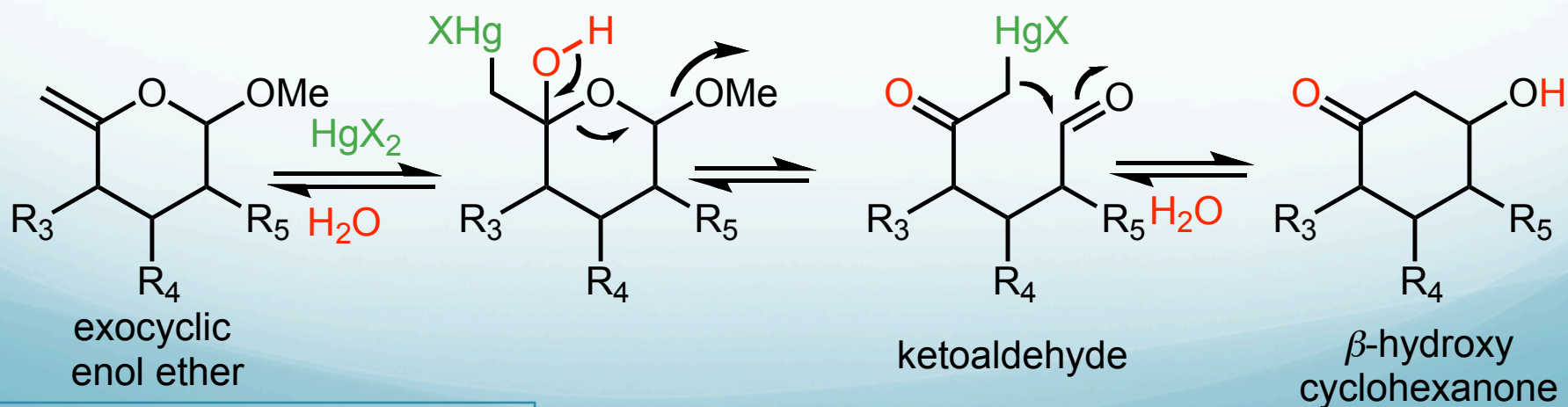
LA = $\text{BF}_3 \cdot \text{OEt}_2$, SnCl_4 , I_2 Nuc = OR, SR_2 , NR_2
 $\text{R}_1 = \text{O-acyl}$, $\text{R}_2 = \text{CH}_2\text{-O-acyl}$, LG = O-acyl, OTs

Type I Ferrier Reaction (1962)



Ferrier, R. J.; Overend, W. G.; Ryan, M. E. *J. Chem. Soc.* **1962**, 3667–3670.

Type II Ferrier Rearrangement (1979)



R_3 , R_4 , $\text{R}_5 = \text{O-acyl}$, O-alkyl

Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455–1458.

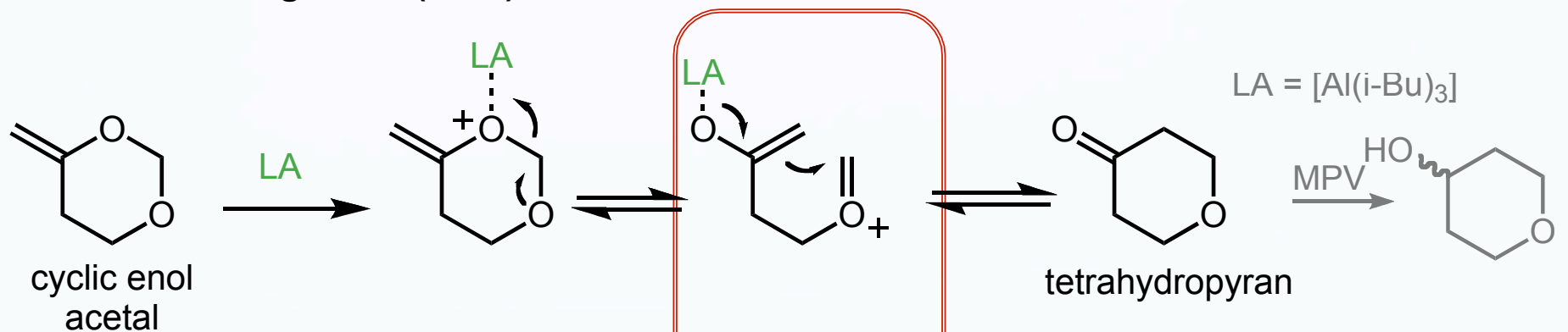
Dr. Robin J. Ferrier



- PhD, University of Edinburgh, UK, 1957, “ Synthetic and mechanistic studies of monosaccharide compounds ”
- Professor, London University, UK
- Post-doctoral, Berkeley, Professor Melvin Calvin
- Chair of Organic Chemistry, Victoria University of Wellington, New Zealand, 1970
- Consultant, GlycoSyn, Industrial Research Limited (IRL), New Zealand

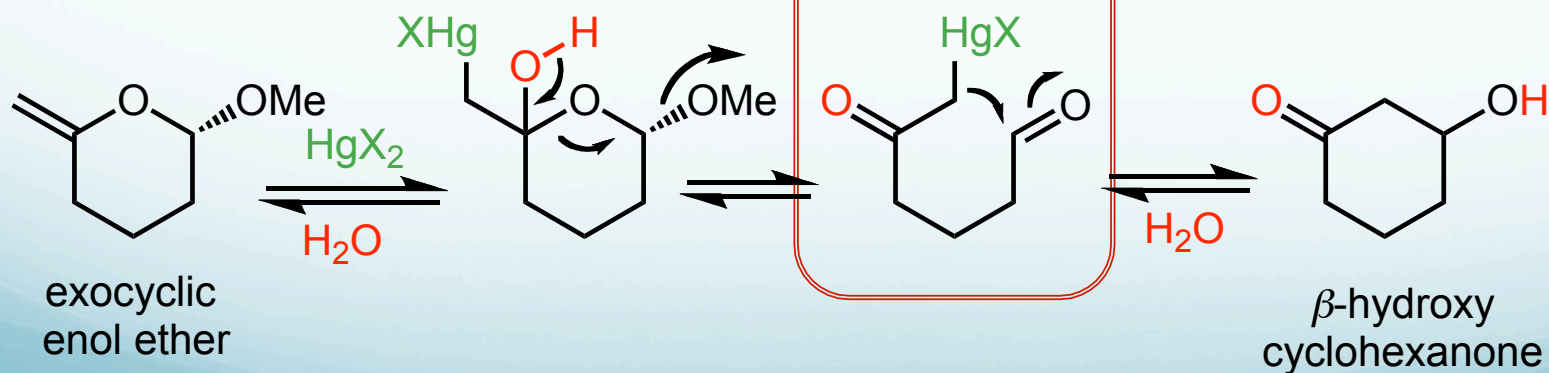
Petasis Rearrangement

Petasis Rearrangement (1996)



Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, 37, 141–144.

Ferrier Rearrangement Type II (1979)



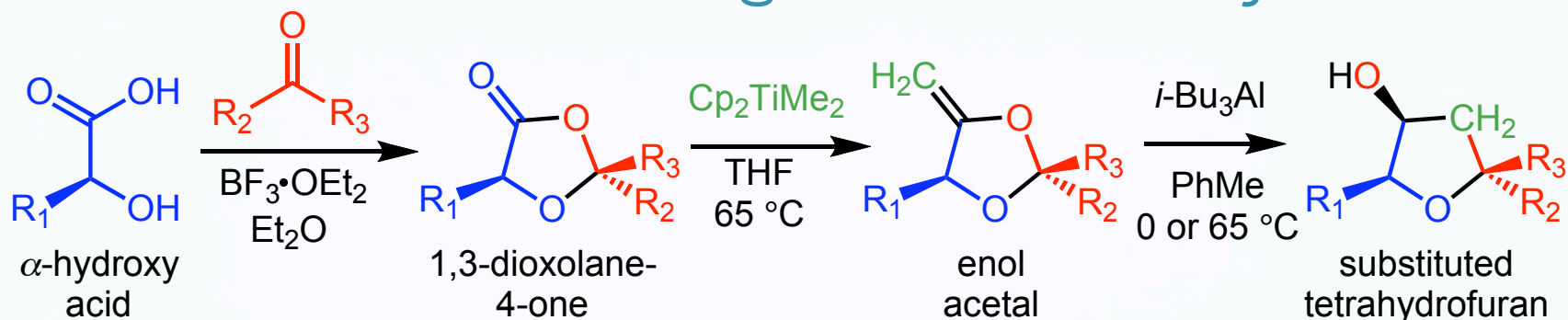
Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455–1458.

Dr. Nicos A. Petasis



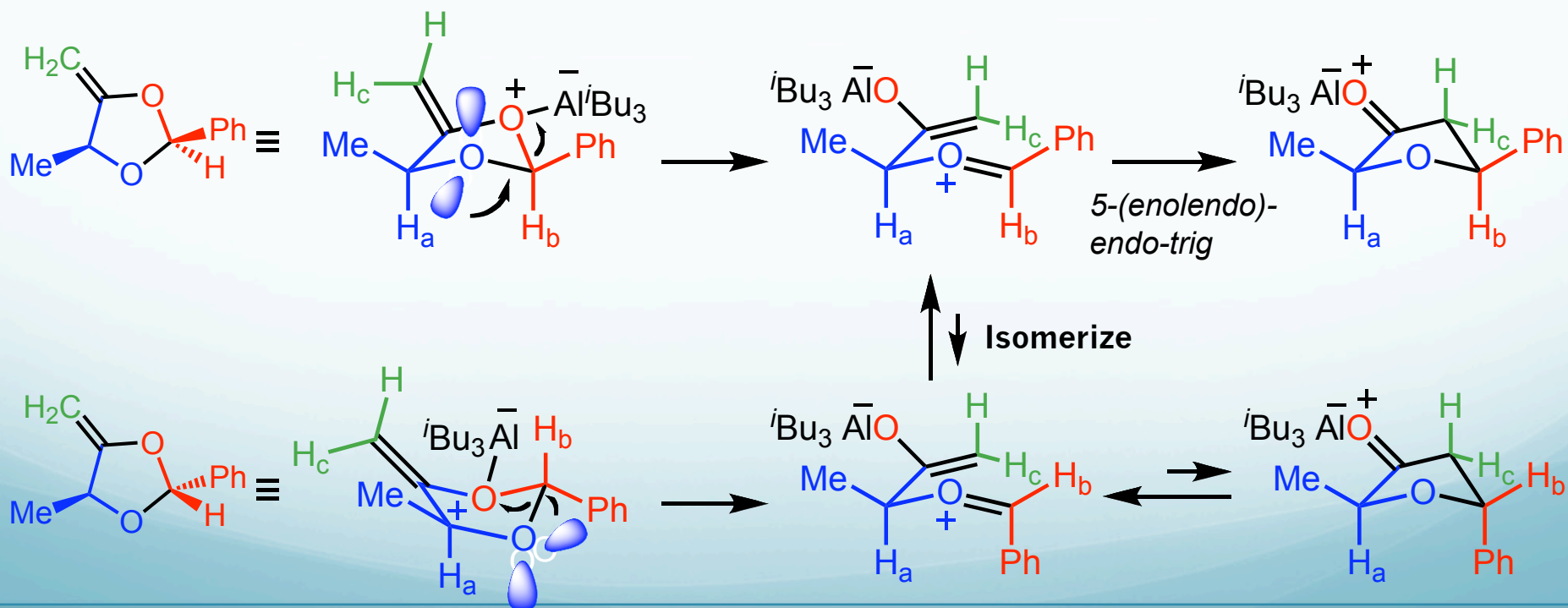
- B.S. Chemistry, Aristotle University of Thessaloniki, Greece, 1978
- Ph.D. Organic Chemistry, University of Pennsylvania, 1983
- Research Associate and Adjunct Lecturer, University of Pennsylvania, 1984-1987
- Harold and Lillian Moulton Chair and Professor in Chemistry, 2001- present
University of Southern California
- New Synthetic Methods and Strategies, organotitanium, organoboron,
combinatorial chemistry and catalysis

Petasis-Ferrier Rearrangement : Tetrahydrofuran



$\text{R}_3 = \text{Ph}, \text{R}_2 = \text{H}$ \rightarrow 90 % yield
 $\text{R}_2 = \text{Ph}, \text{R}_3 = \text{H}$ \rightarrow >99 % syn
 $\text{R}_3 = \text{Ph}, \text{R}_2 = \text{H}$ in the product

10 examples
 50-91% yield

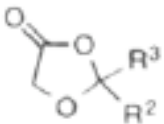
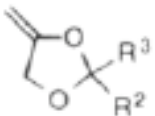
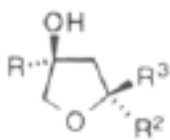


* Chiral Starting Material

Petasis, N. A.; Lu, S-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394–6395.

Substrate Scope

$R_1 = H, 65\text{ }^\circ\text{C}$

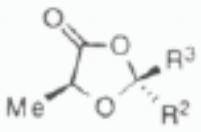
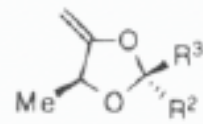
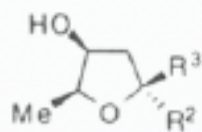
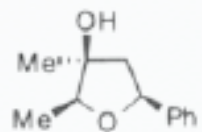
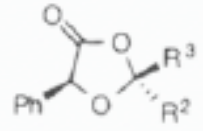
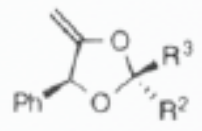
Entry	1,3-Dioxolan-4-one ^{a,b}	Vinyl acetal / ketal ^{b,c}	Conditions ^d	Tetrahydrofuran ^b
				
1	3a , $R^2, R^3 = (\text{CH}_2)_5$	5a , 88%	$i\text{Bu}_3\text{Al}, 65\text{ }^\circ\text{C}$	6a , 65% ($R = H$)
2			$\text{Me}_3\text{Al}, 65\text{ }^\circ\text{C}$	7a , 50% ($R = \text{Me}$)
3			$\text{Et}_3\text{Al}, 65\text{ }^\circ\text{C}$	8a , 55% ($R = \text{Et}$)
4	3b , $R^2 = H, R^3 = t\text{Bu}$	5b , 83%	$i\text{Bu}_3\text{Al}, 65\text{ }^\circ\text{C}$	6b , 78% (80% syn)
5	3c , $R^2 = H, R^3 = \text{CH}_2\text{Ph}$	5c , 89%	$i\text{Bu}_3\text{Al}, 65\text{ }^\circ\text{C}$	6c , 75% (61% syn)
6	3d , $R^2 = H, R^3 = (\text{CH}_2)_9\text{Me}$	5d , 88%	$i\text{Bu}_3\text{Al}, 65\text{ }^\circ\text{C}$	6d , 83% (62% syn)

^aPrepared according to literature procedures. Compound 3h was prepared via the TMSOTf-catalyzed reaction between $t\text{BuCHO}$ and the bis-TMS derivative of glycolic acid.¹¹ while compounds 3e,d were prepared from the aldehyde and glycolic acid in the presence of BF_3OEt_2

^bYields were determined following isolation by distillation or chromatography and were not optimized. ^c Prepared by the reaction of **3** with dimethyltitanocene at $65\text{ }^\circ\text{C}$ in THF, ^d All reactions were carried out with 2 equiv of the aluminum reagent in toluene at the indicated temperature.

Substrate Scope

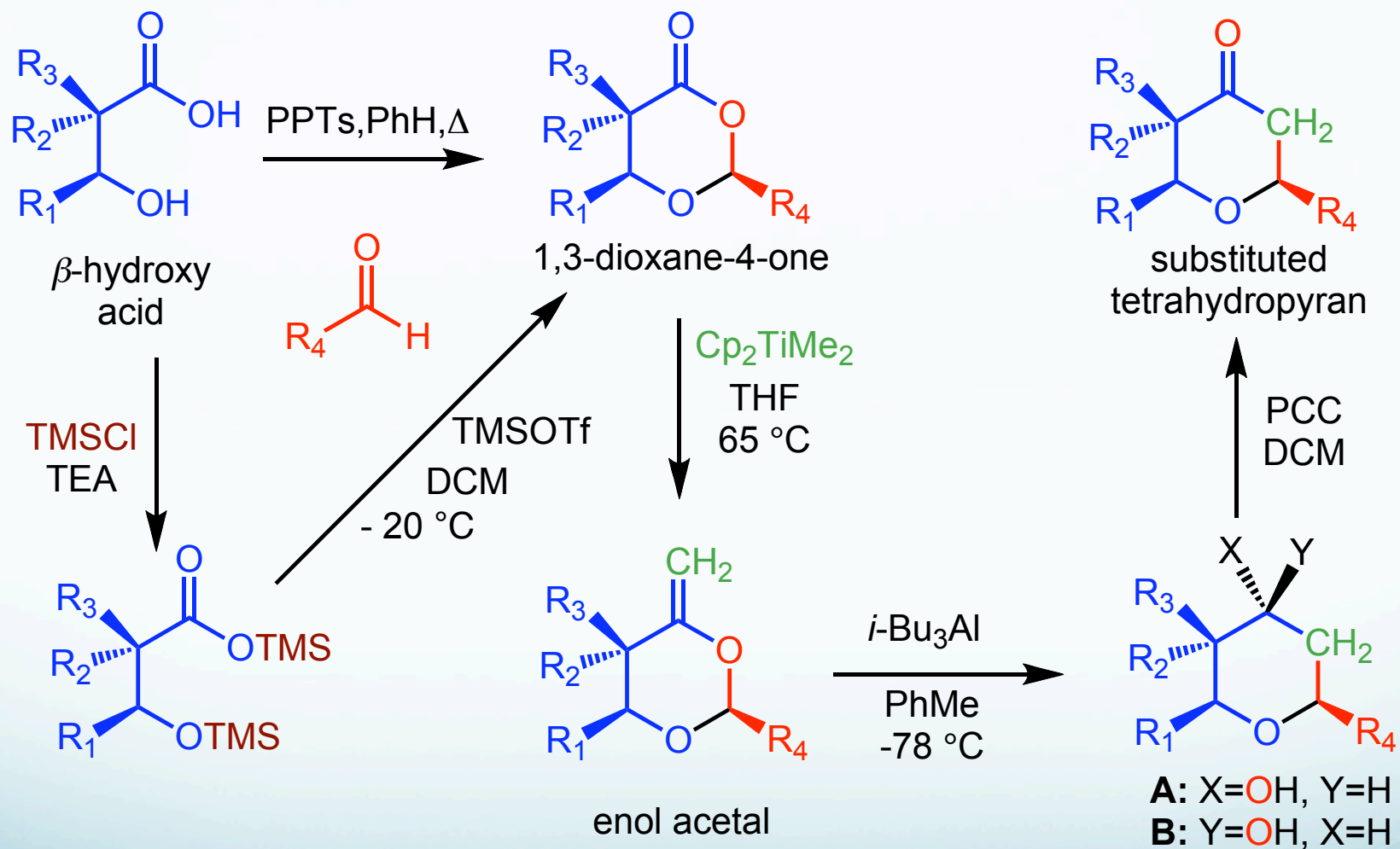
$R_1 = \text{Me}, 0\text{ }^\circ\text{C}$ or $\text{Ph}, -78\text{ }^\circ\text{C}$

Entry	1,3-Dioxolan-4-one ^{a,b}	Vinyl acetal / ketal ^{b,c}	Conditions ^d	Tetrahydrofuran ^b
				
7	3e , $R^2, R^3 = (\text{CH}_2)_5$	5e , 90%	$i\text{Bu}_3\text{Al}, 0\text{ }^\circ\text{C}$	6e , 91% (91% syn)
8	3f , $R^2 = \text{Me}, R^3 = \text{tBu}$	5f , 86%	$i\text{Bu}_3\text{Al}, 0\text{ }^\circ\text{C}$	6f , 90% (71% syn)
9	3g , $R^2 = \text{Ph}, R^3 = \text{H}$	5g , 55%	$i\text{Bu}_3\text{Al}, 0\text{ }^\circ\text{C}$	6h , 90% (> 99% syn)
10	3h , $R^2 = \text{H}, R^3 = \text{Ph}$	5h , 55%	$i\text{Bu}_3\text{Al}, 0\text{ }^\circ\text{C}$	6h , 90% (> 99% syn)
11			$\text{Me}_3\text{Al}, 0\text{ }^\circ\text{C}$	 7h , 77% (> 99% syn)
				
12	3i , $R^2 = \text{H}, R^3 = \text{tBu}$	5i , 91%	$i\text{Bu}_3\text{Al}, -78\text{ }^\circ\text{C}$	dec.
13	3j , $R^2 = \text{H}, R^3 = \text{Ph}$	5j , 74%	$i\text{Bu}_3\text{Al}, -78\text{ }^\circ\text{C}$	dec.
14	3k , $R^2 = R^3 = \text{Me}$	5k , 76%	$i\text{Bu}_3\text{Al}, -78\text{ }^\circ\text{C}$	dec.

Dec. = Decomposed

Petasis, N. A.; Lu, S-P. *J. Am. Chem. Soc.* **1995**, *117*, 6394–6395.

Petasis-Ferrier Rearrangement : Tetrahydropyran

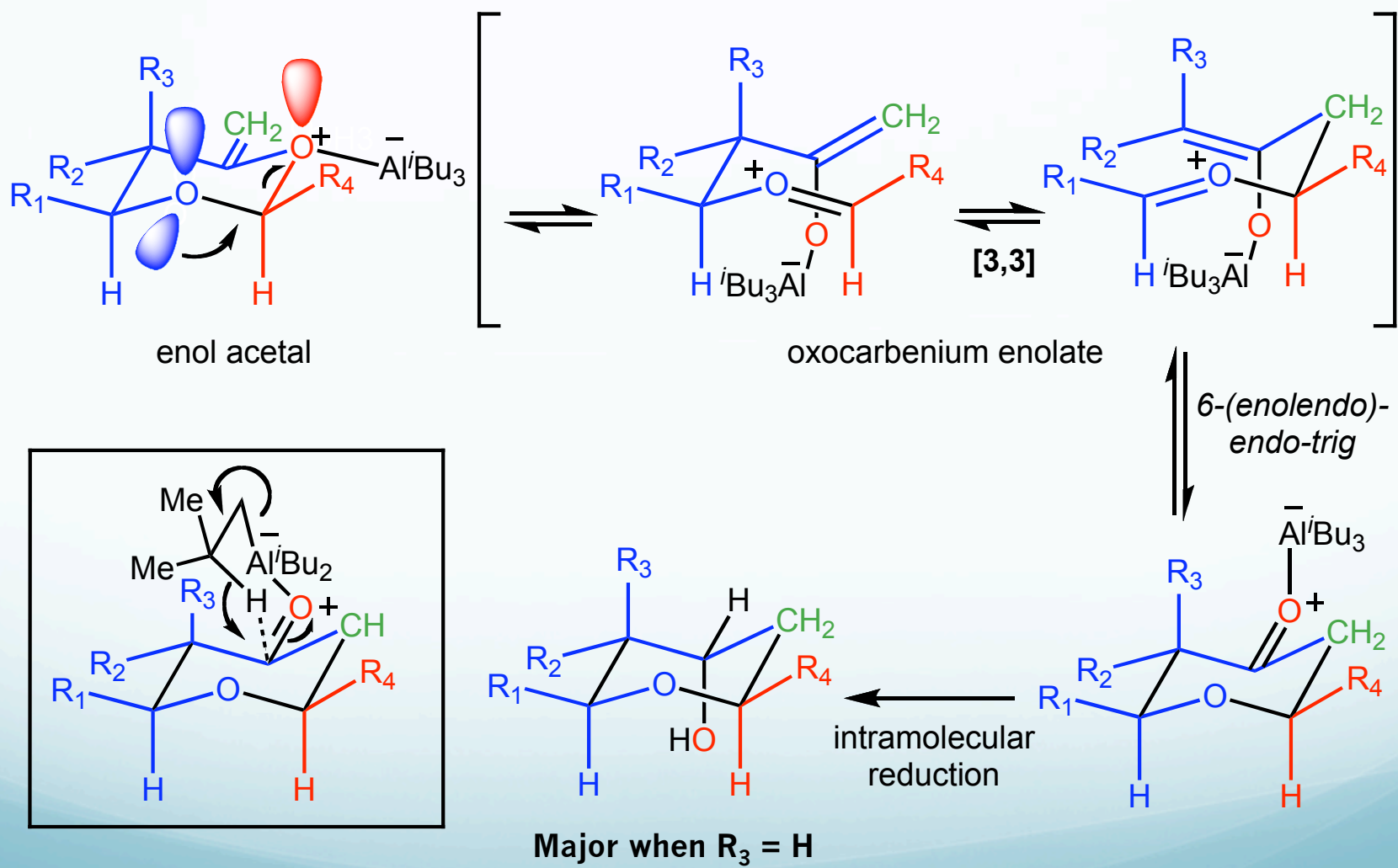


* Chiral Starting Material

Major product depends upon substitution pattern

Petasis-Ferrier Rearrangement : Tetrahydropyran

Mechanism:



Substrate Scope

Table 1. Synthesis of tetrahydropyrans from 1,3-dioxan-4-ones (4).

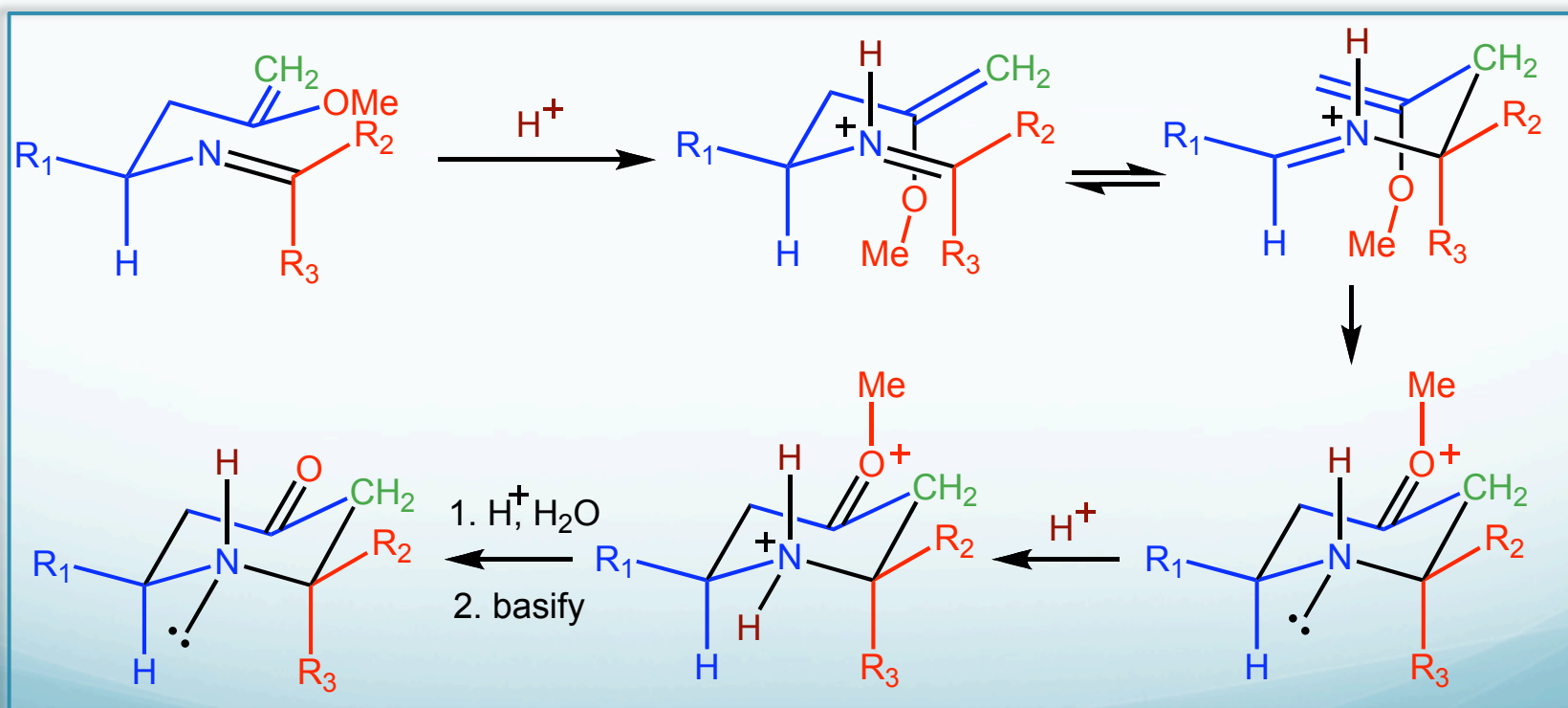
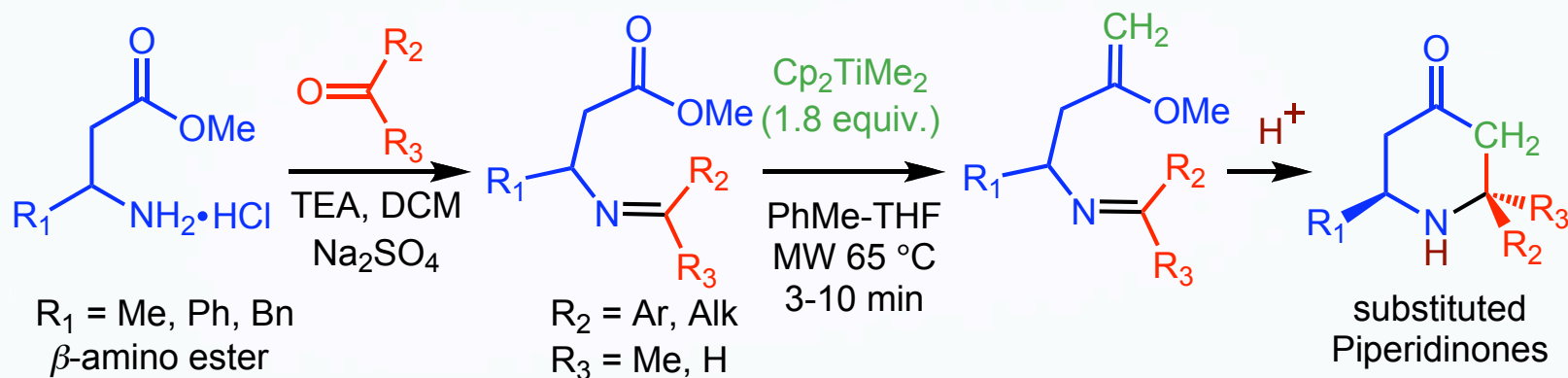
Compd	R ¹	R ²	R ³	R ⁴	Vinyl acetal (6) ^{d,e}	Alcohol ^{e,f} (7:8)	B:A Ketone (9) ^{e,g,h}
4a^a	H	Me	Me	Ph	72%	91% (1:1)	96%
4b^a	Me	H	H	^t Bu	88%	81% (1:1.5)	
4c^b	Me	H	H	(CH ₂) ₂ Ph	86%	96%	98% (86%cis)
4d^b	Me	H	H	(CH ₂) ₉ Me	80%	93%	95% (88%cis)
4e^a	Me	H	H	Ph	70%	90%	93% (93%cis)
4f^b	H	Ph	H	ⁱ Pr	67%	88% (1:8)	92% (>99%cis)
4g^b	H	H	Ph	ⁱ Pr	65%	90% (1:0)	
4h^c	Me	PhCH ₂	H	^t Bu	75%	92% (1:8)	

^aPrepared from **2** and **3**.^{4c} ^bPrepared from **1** and **3**.^{4b} ^cPrepared by the alkylation of **4b** with LDA at -78 °C and benzyl bromide.⁶ ^dVinyl acetals were prepared by the reaction of **4** with dimethyltitanocene at 65 °C in THF.⁵ ^eYields were determined followed isolation by distillation or chromatography and were not optimized. ^fObtained by the reaction of the vinyl acetal with 2 equiv. of ^tBu₃Al in toluene at -78 °C. ^gObtained by oxidation of the alcohol with PCC in CH₂Cl₂. ^hRatios of the relative stereochemistry at C₂ and C₆ were determined with NMR and are indicated in parentheses.

Petasis-Ferrier Rearrangement : Main Features

- The straightforward construction of the substrate enol acetals allows the stereocontrolled assembly of complex fragments.
- The configuration of the acetal carbon is retained or enhanced during the rearrangement.
- The rearrangement of 5-membered enol acetals takes place at a much higher temperature than for 6-membered substrates.(may be due more facile *6-(enolendo)-endo-trig* cyclization)
- Trialkylaluminum were found to be the most effective reagents (*i*-Bu₃Al, Me₃Al and Me₂AlCl)
- The stereoselective reduction (last step) depends on the substitution pattern and occur when *i*-Bu₃Al used (not occurs if Me₂AlCl used)
- Drawback: Olefination step can lead to olefin stereoisomers when applied titanocene is other than Dimethyl titanocene.

Nitrogen Analogue to Petasis-Ferrier Rearrangement



Substrate Scope

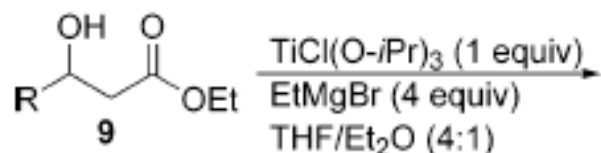
TABLE 1. Summary of Reaction Conditions and Yields for the Synthesis of Piperidinones

entry	compd	yield ^a of imine 19, %	piperidinones 21			cyclization conditions				yield ^b from 19, %	
			R ¹	R ²	R ³	acid	solvent	temp, °C	time, h		hydrolysis
1	A	75 ^c	Me	Ph	H	7 M HCl	H ₂ O	20	0.5		61 ^d
2	B	89	Ph	Ph	H	7 M HCl	H ₂ O	20	0.5		62 ^d
3	C	94	Ph	2,4-MeOC ₆ H ₃	H	7 M HCl	H ₂ O	20	17		12 ^d
4	D	74 ^e	Me	Ph	Me	7 M HCl	H ₂ O	20	17		trace
5	A	75 ^c	Me	Ph	H	2 equiv of TsOH	CH ₂ Cl ₂	20	17	1 M HCl (0.5 h)	61
6	E	83	PhCH ₂	Ph	H	2 equiv of TsOH	CH ₂ Cl ₂	40	17	1 M HCl (0.5 h)	61
7	C	94	Ph	2,4-MeOC ₆ H ₃	H	2 equiv of TsOH	CH ₂ Cl ₂	20	17	1 M HCl (0.5 h)	40
8	F	87 ^c	Me	(<i>E</i>)-4-MeOC ₆ H ₄ CH=CH	H	2 equiv of TsOH	CHCl ₃	60	17	1 M HCl (0.5 h)	37
9	C	94	Ph	2,4-MeOC ₆ H ₃	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	51
10	G	61	Me	2,4-MeOC ₆ H ₃	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	58
11	H	58	Me	3-Br C ₆ H ₄	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	48
12	I	90	Ph	^t Bu	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	58
13	J	91 ^f	Ph	Et	H	2 equiv of TsOH	DME	20	17	1 M HCl (0.5 h)	34
14	B	72	Ph	Ph	H	2 equiv of TsOH	DMSO	28	17	1 M HCl (0.5 h)	61
15	A	75 ^c	Me	Ph	H	2 equiv of Al(ⁱ Bu) ₃	DMSO	28	17	1 M HCl (0.5 h)	68
16	B	72	Ph	Ph	H	2 equiv of Al(ⁱ Bu) ₃	DMSO	28	17	1 M HCl (0.5 h)	70
17	C	94	Ph	2,4-MeOC ₆ H ₃	H	2 equiv of Al(ⁱ Bu) ₃	DMSO	28	17	1 M HCl (0.5 h)	66
18	K	55	Me	2-F C ₆ H ₄	H	2 equiv of Al(ⁱ Bu) ₃	DMSO	28	17	1 M HCl (0.5 h)	64
19	F	87 ^c	Me	(<i>E</i>)-4-MeOC ₆ H ₄ CH=CH	H	2 equiv of Al(ⁱ Bu) ₃	DMSO	28	17	1 M HCl (0.5 h)	51
20	D	74 ^e	Me	Ph	Me	2 equiv of Al(ⁱ Bu) ₃	DMSO	28	17	1 M HCl (0.5 h)	69 ^g
21	L	73	Ph	-(CH ₂) ₅ -		2 equiv of Al(ⁱ Bu) ₃	DMSO	28	17	1 M HCl (0.5 h)	52

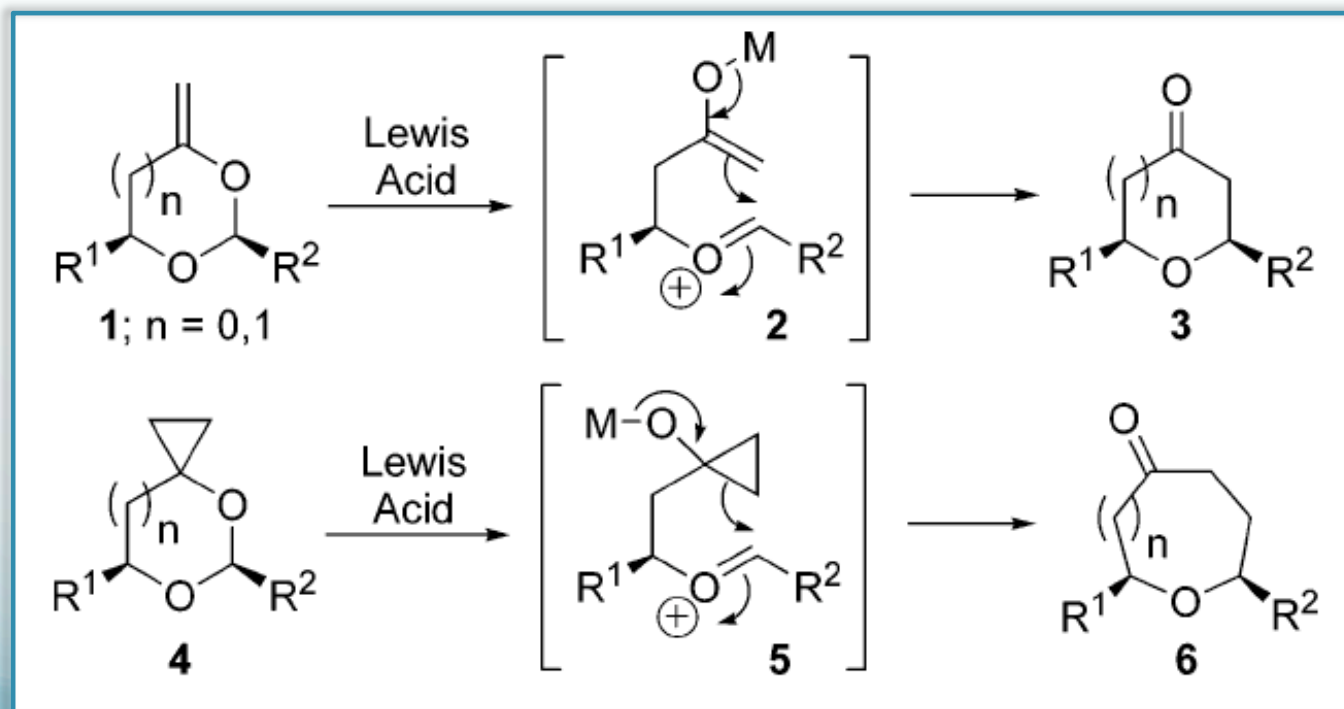
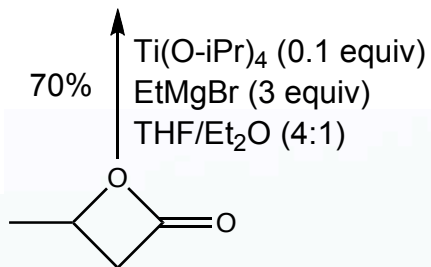
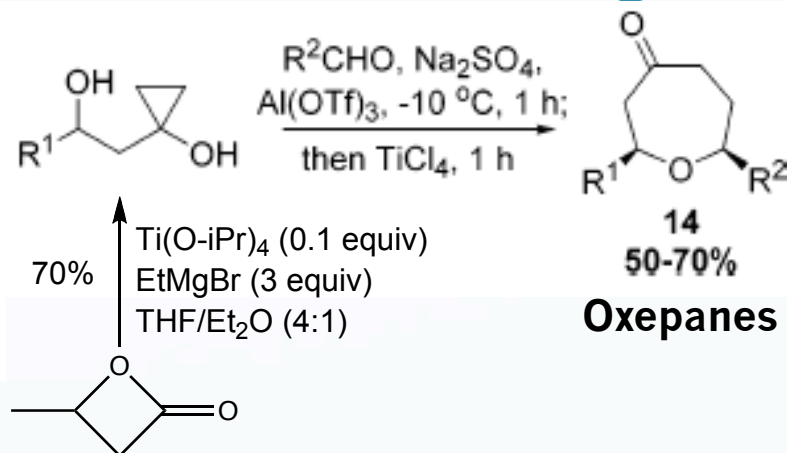
^a Isolated yield from amines 18 after purification. ^b Isolated yield after purification; except where otherwise indicated, only the 2,6-*syn* isomer was detected by NMR of the crude mixture and only this isomer was isolated; relative stereochemistry was assigned by NOE, except for 21B, which was assigned by comparison with the literature. ^c Yield based on aldehyde. ^d Isolated as HCl salt. ^e *E*:*Z* ratio was 93:7. ^f 19:18:propionaldehyde 80:13:7. ^g dr (2,6-*syn*:2,6-*anti*) = 89:11 in both crude mixture and isolated material.

Variant of Petasis-Ferrier Rearrangement

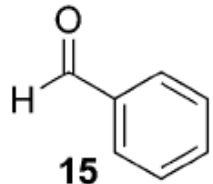
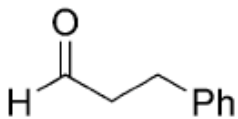
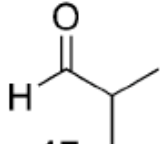
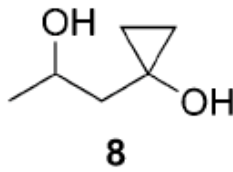
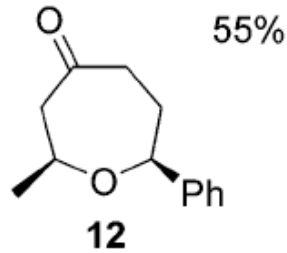
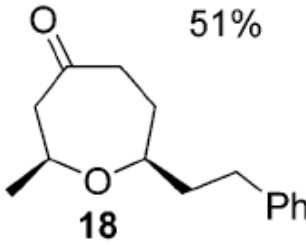
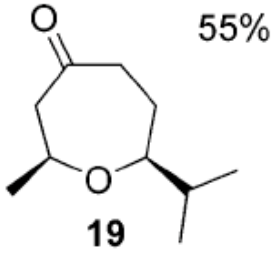
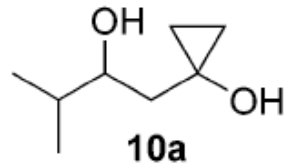
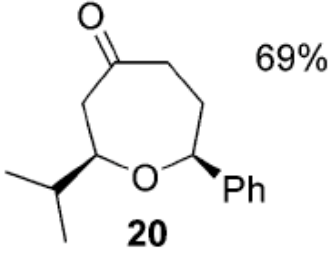
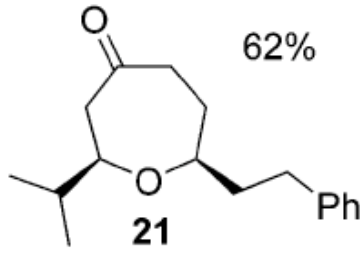
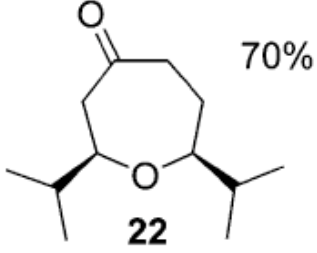
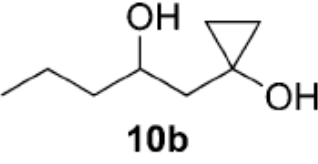
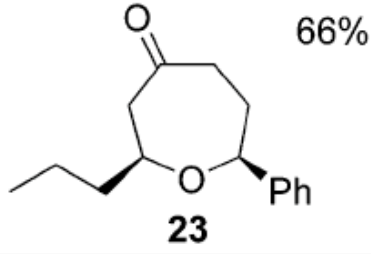
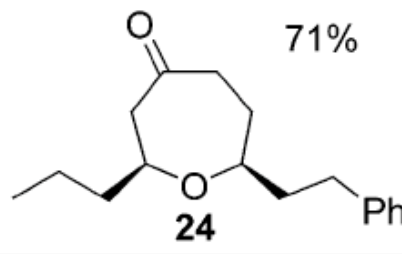
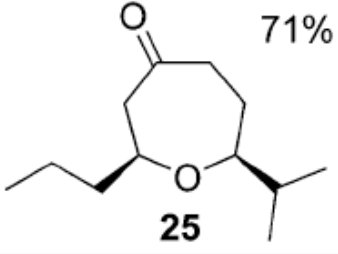
**Kulinkovich
Reaction**



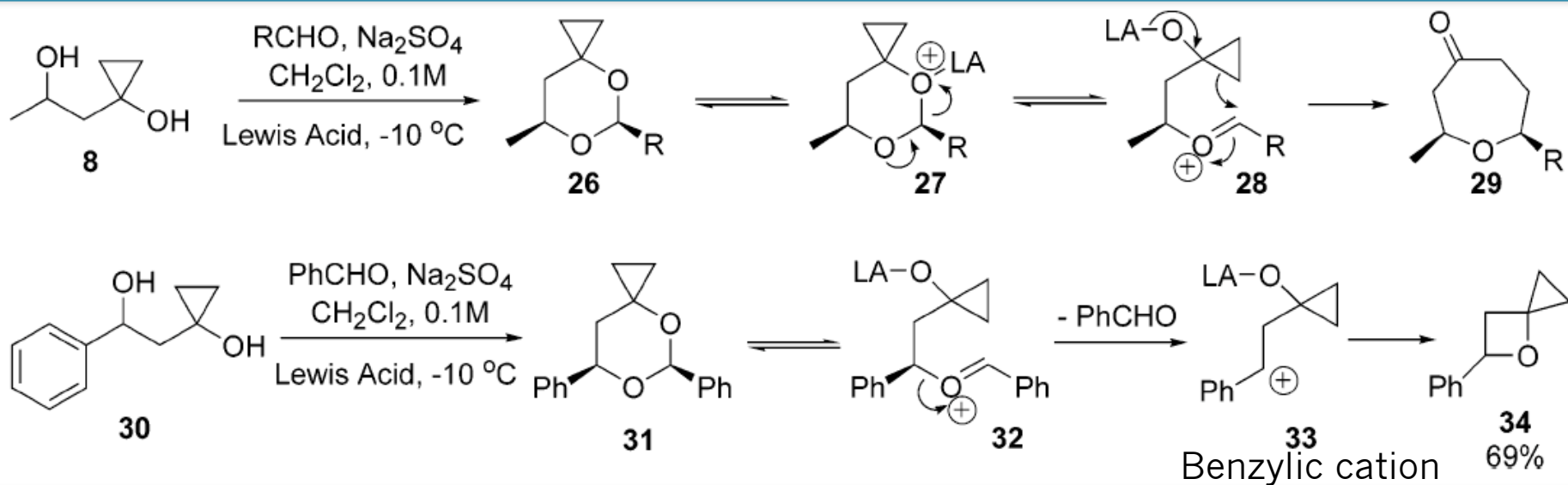
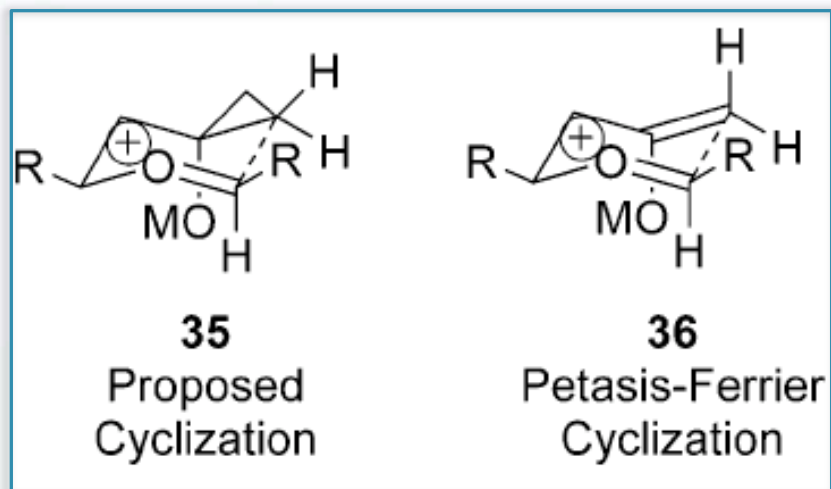
R	Yield
CH(CH ₃) ₂ (10a)	51%
(CH ₂) ₂ CH ₃ (10b)	51%



Substrate Scope

RCHO diol	 15	 16	 17
 8	 12 55%	 18 51%	 19 55%
 10a	 20 69%	 21 62%	 22 70%
 10b	 23 66%	 24 71%	 25 71%

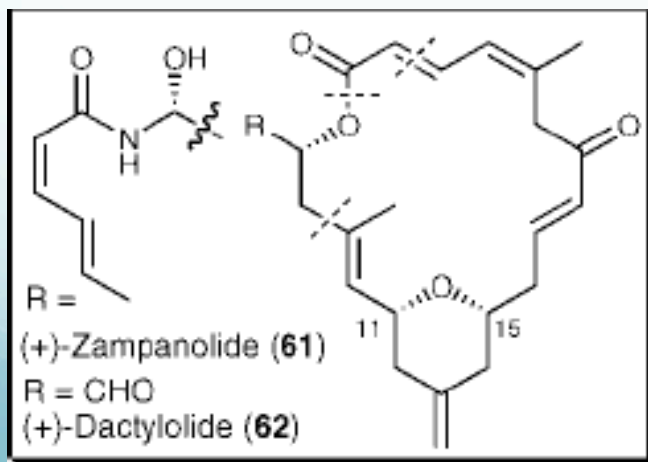
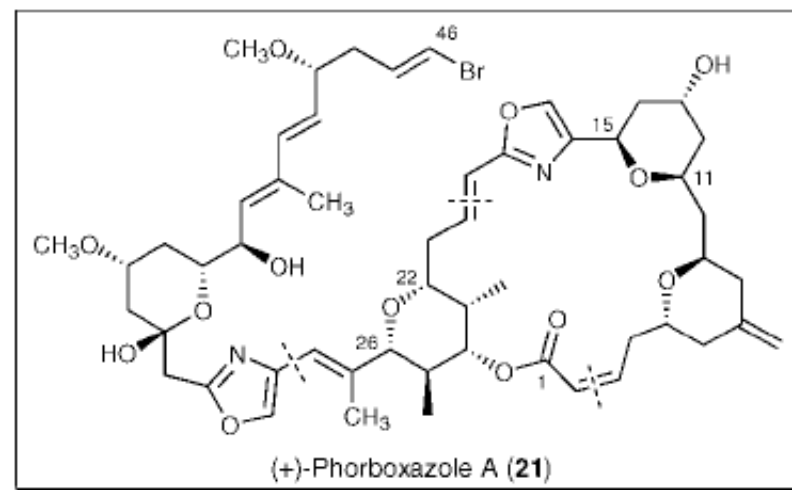
Mechanism



Application to Total Synthesis

(+)-Phorboxazole A

Smith, A. B., III; Verhoest, P. R.; Minbiole, Kevin P.; Lim, J. J. *Org Lett* **1999**, *1*, 909-912. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org Lett* **1999**, *1*, 913-916. (c) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834-4836. (d) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942-10953. (e) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005**, *7*, 4399-4402. (f) Smith, A. B.; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T.; Meis, R. *J. Org. Chem.* **2008**, *73*, 1192-1200. (g) Smith, A. B., III; Razler, T. M.; Meis, R.; Pettit, G. R. *J. Org. Chem.* **2008**, *73*, 1201-1208.



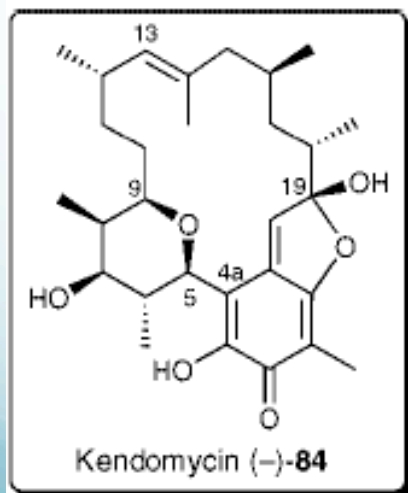
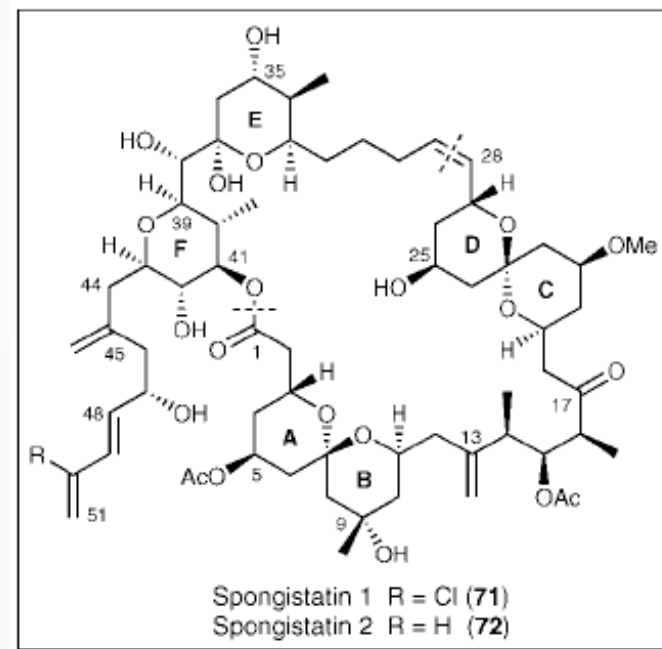
(+)-Zampanolide and (+)-Dactylolide

(a) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426-12427. (b) Smith, A. B., III; Safonov, I. G. *Org. Lett.* **2002**, *4*, 635-637. (c) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102-11113.

Application to Total Synthesis

(+)-Spongistatin 1

(a) Smith, A. B., III; Zhu, W.; Shirakami, S.; Sfougatakis, C.; Doughty, V. A.; Bennett, C. S.; Sakamoto, Y. *Org. Lett.* **2003**, *5*, 761–764. (b) Smith, A. B., III; Sfougatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637–3640.



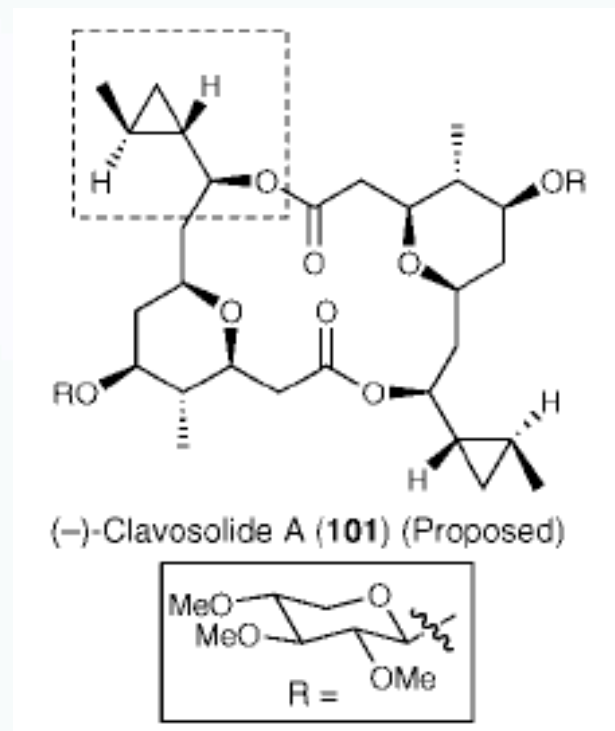
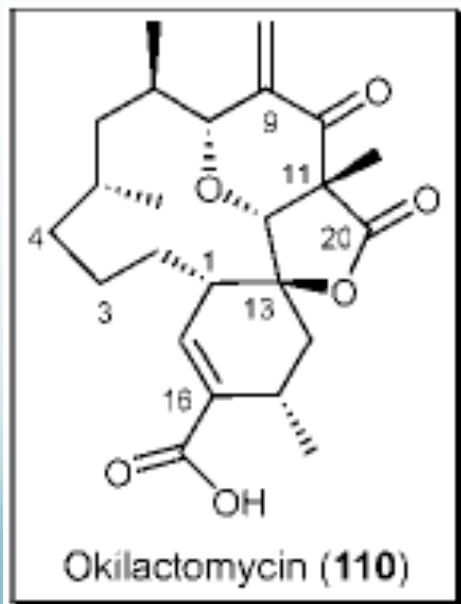
(-)-Kendomycin

(a) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949. (b) Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299.

Application to Total Synthesis

(-)-Clavosolide A

Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315–3318.



(-)-Okilactomycin

(a) Smith, A. B., III; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872–14874. (b) Smith, A. B., III; Bosanac, T.; Basu, K. *J. Am. Chem. Soc.* **2009**, *131*, 2348–2358.

*Smith, A. B., III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675–687

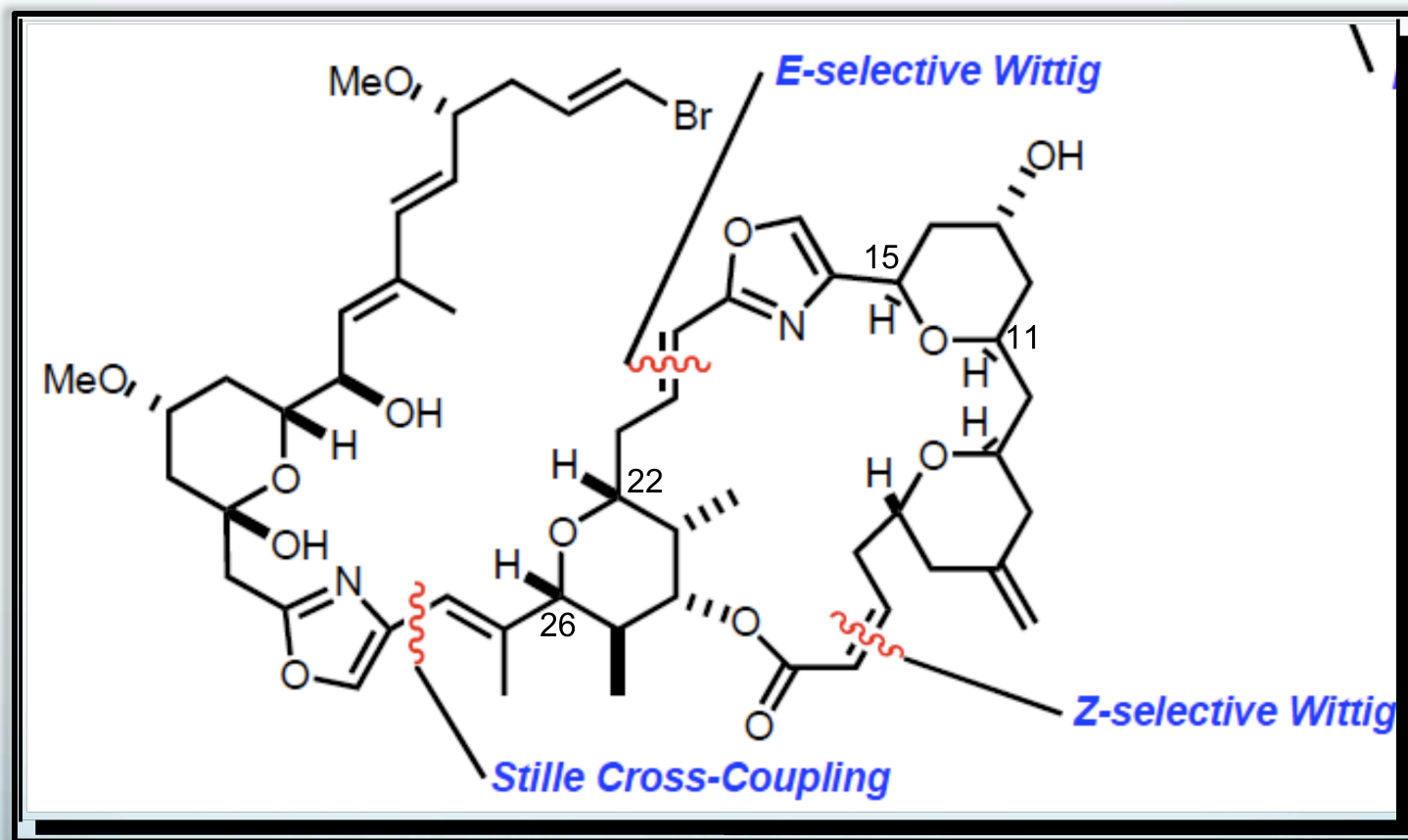
Dr. Amos B. Smith



- Bucknell University's first combined four-year B.S.- M.S. degree in Chemistry, 1966
- PhD, 1972 & Research Associate at Rockefeller University.
- Professor, Department of Chemistry at the University of Pennsylvania, 1973
- Currently, Rhodes-Thompson Professor of Chemistry, a Member of the Monell Chemical Senses Center, the Associate Director of the Penn Center for Molecular Discovery (PCMD),
- First Editor-in-Chief of the new American Chemical Society journal, Organic Letters, 1998

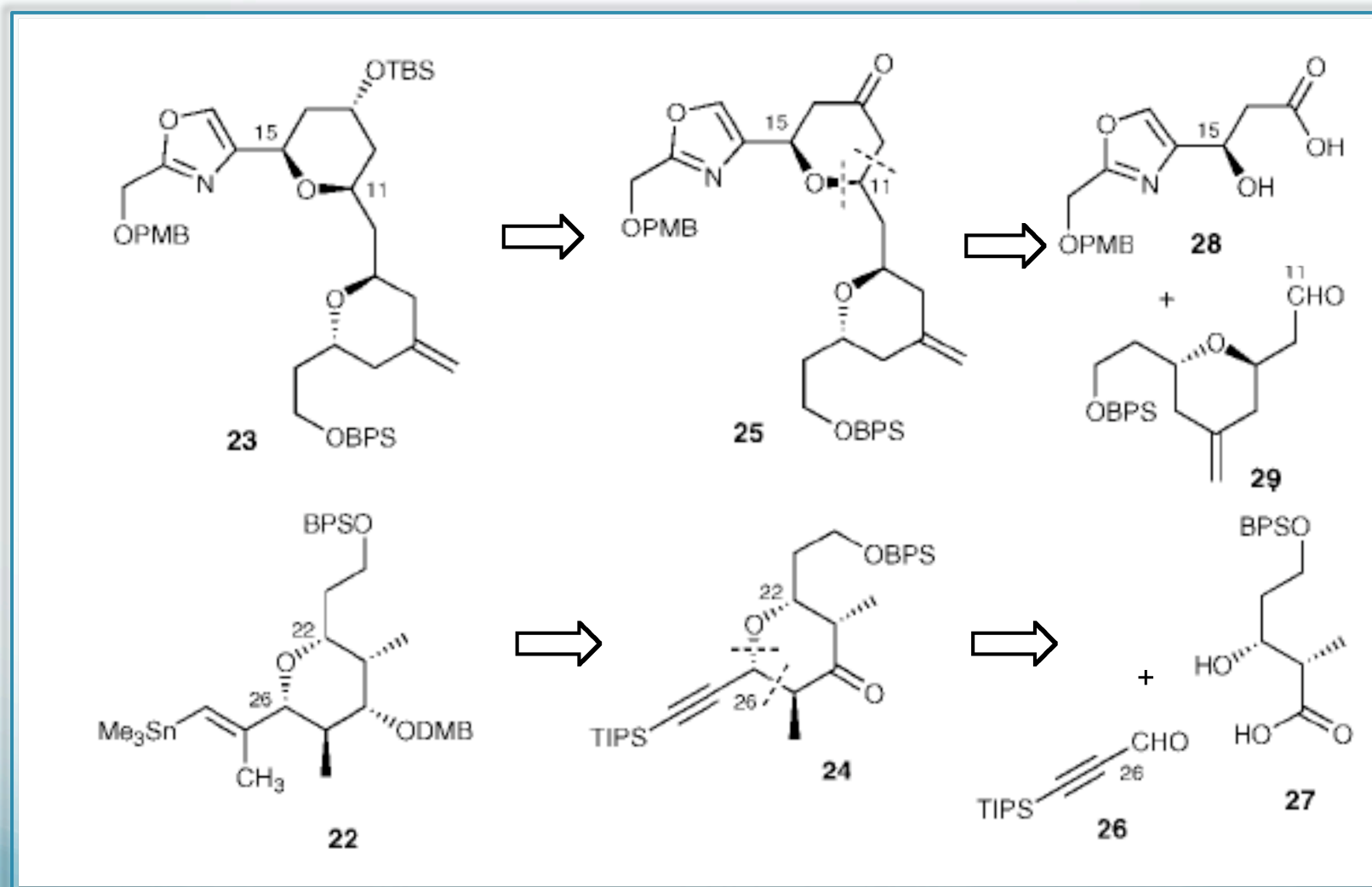


Phorboxazole A



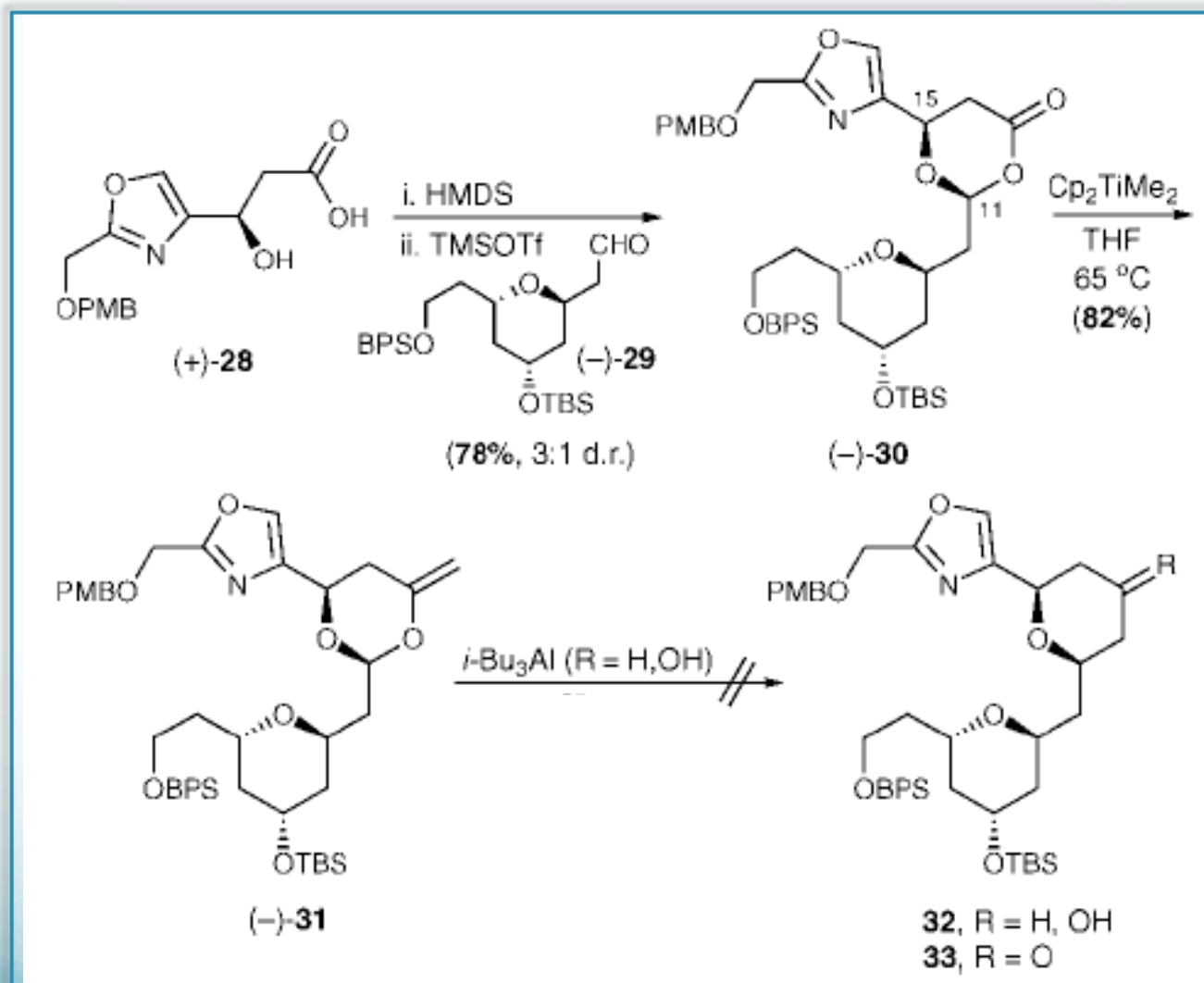
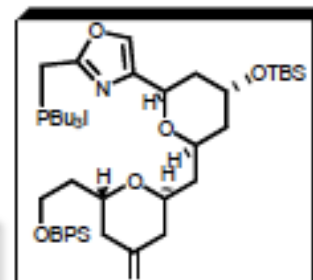
Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953.

Retrosynthetic Analysis

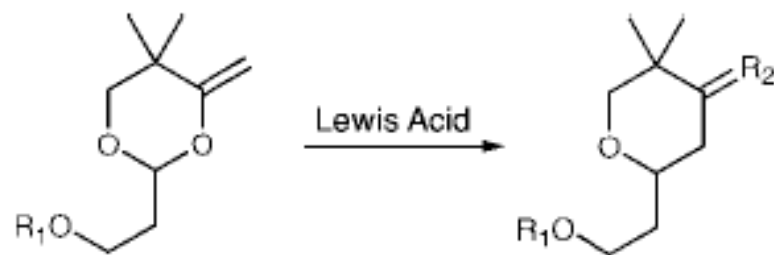
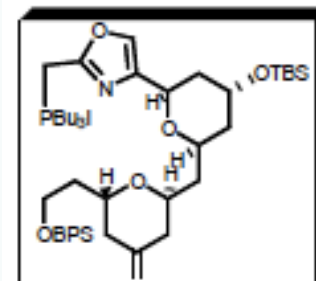


Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953.

Initial Attempts towards P-F Reaction



Optimization of P-F Reaction



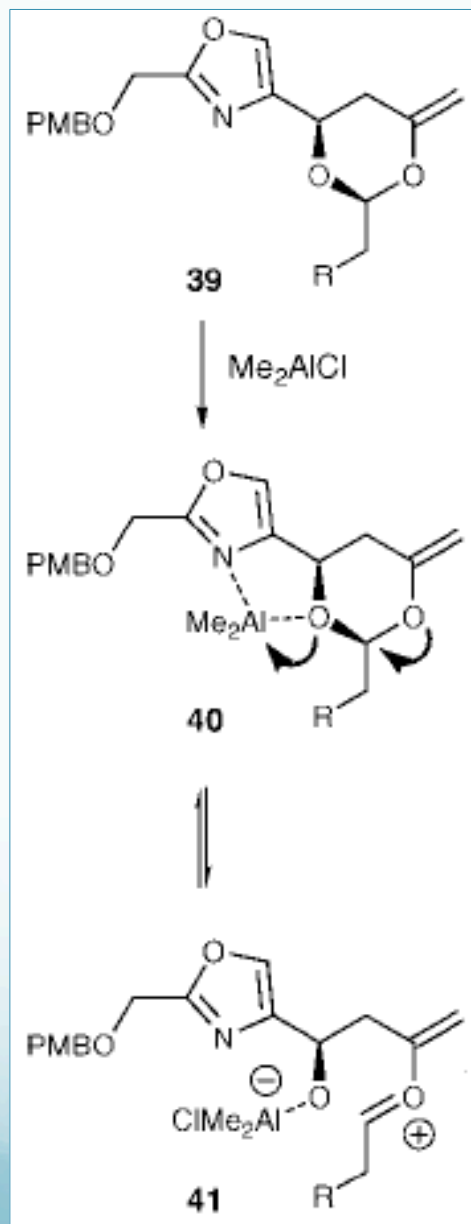
34a, R₁=Ph
34b, R₁=BPS

35, R₁=Ph, R₂=(H, OH)
36, R₁=Ph, R₂=O
37, R₁=BPS, R₂=(H, OH)
38, R₁=BPS, R₂=O

Lewis Acid	R ₁ =Ph	R ₁ =BPS
<i>i</i> -Bu ₃ Al	87% (35)	85% (37)
ZnCl ₂	25% (36)	0%
Me₂AlCl	95% (36)	92% (38)
MeAlCl ₂	60% (36)	--
BF ₃ •OEt ₂	0%	--
TiCl ₄	0%	--
TiCl ₂ (O <i>i</i> -Pr) ₂	0%	--
SnCl ₄	0%	--

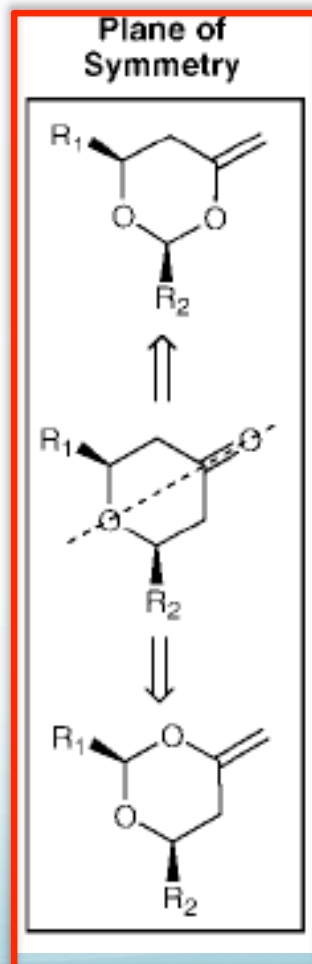
But
failed

Inherent Pseudo symmetry of P-F Reaction

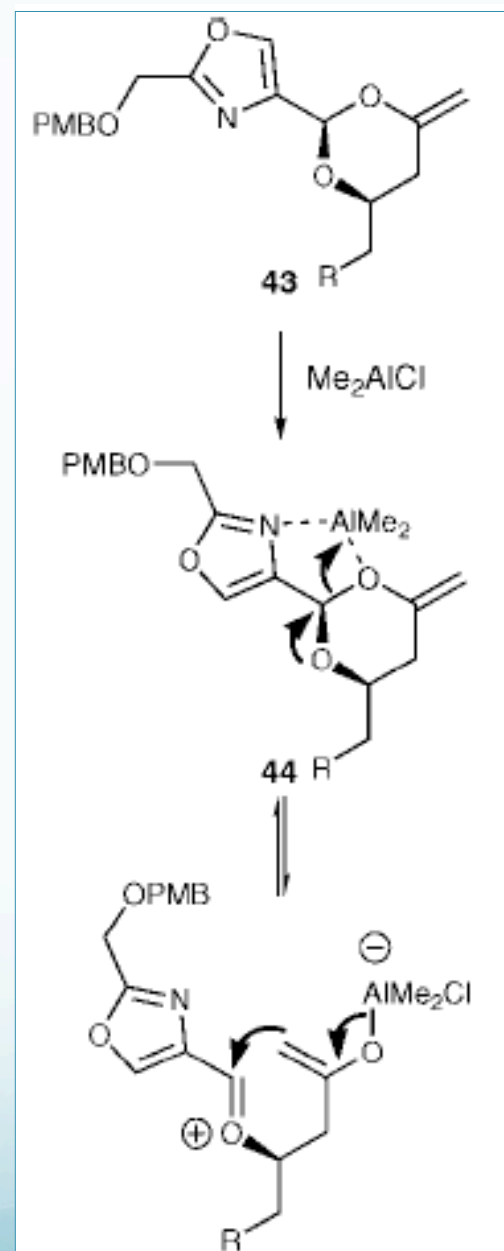


Unproductive Al coordination

Switch
Coupling
Partners
→

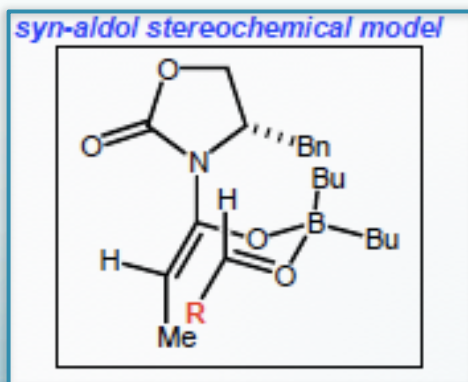
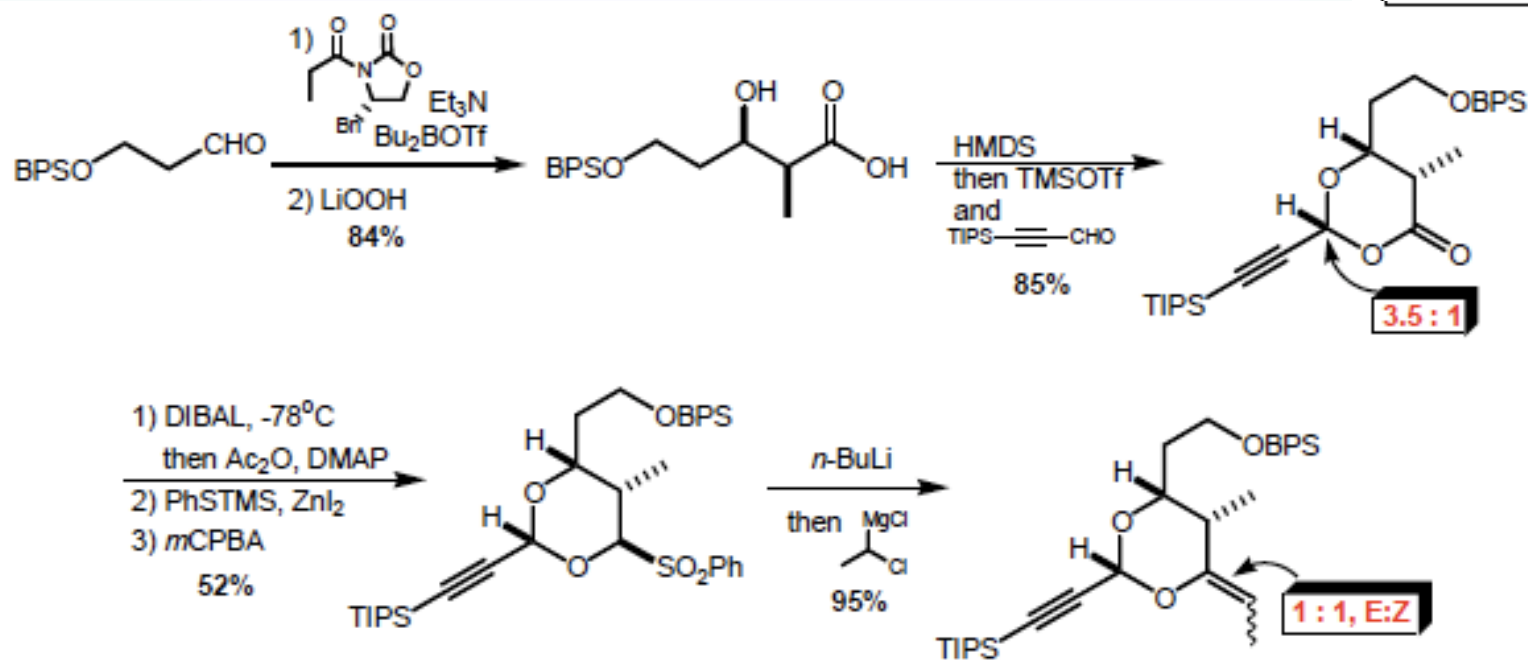
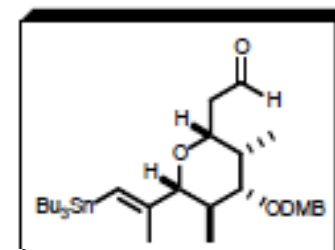


Yield = 89 %

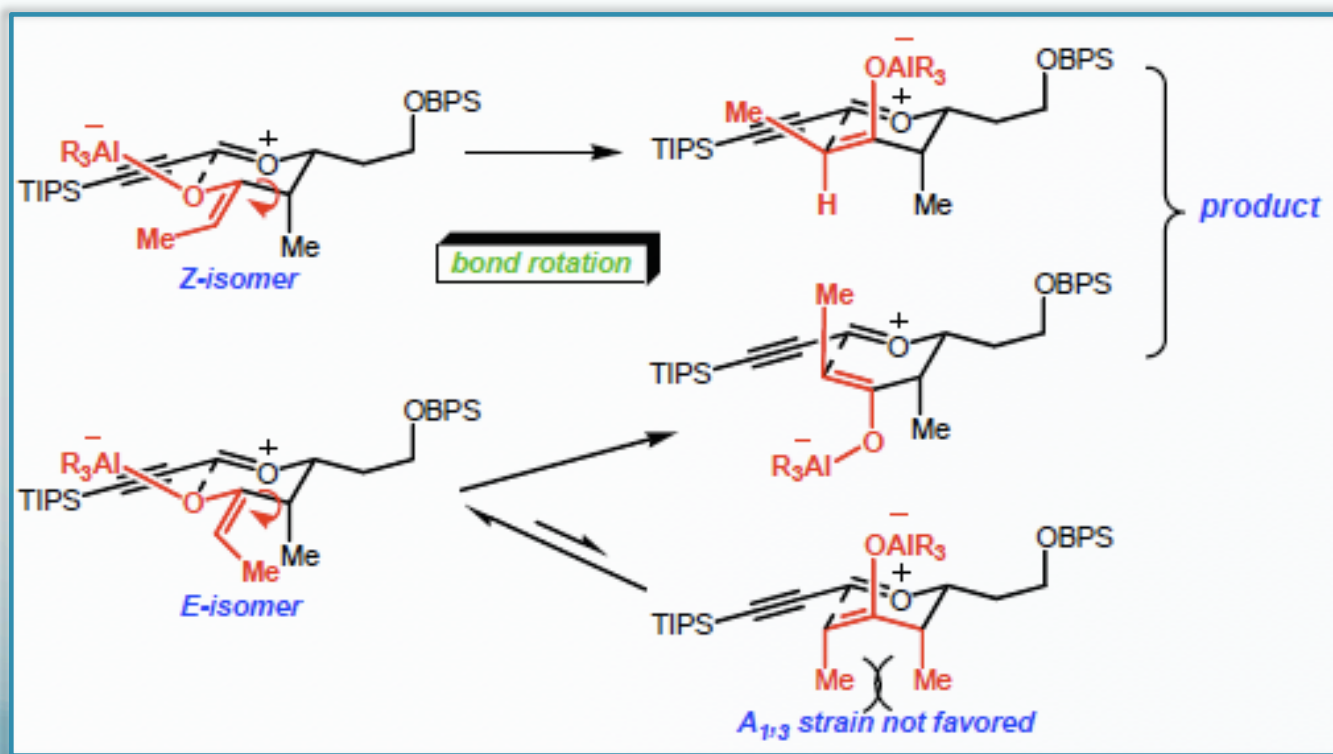
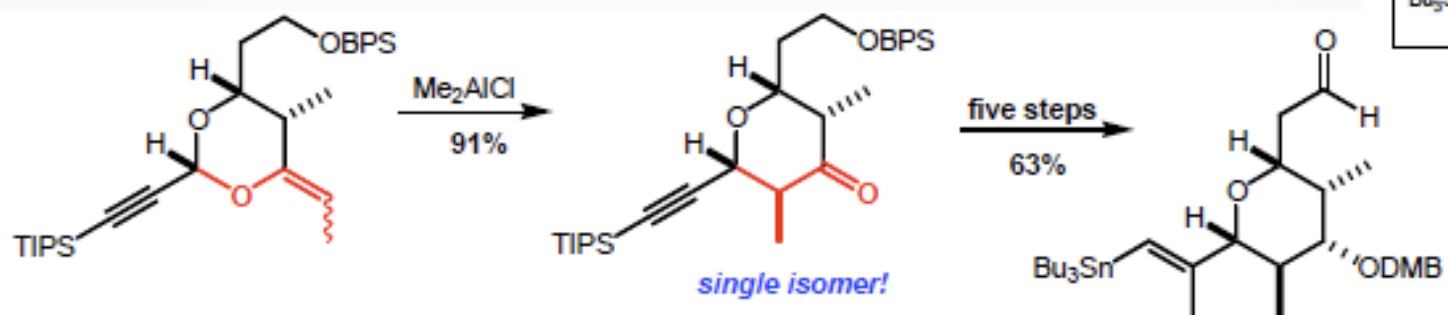
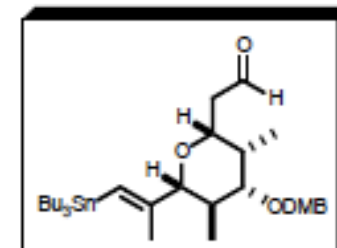


Productive Al coordination

P-F Reaction for other fragment



Mechanistic Rationale



The background features a pixelated sun in the upper center, set against a light blue sky. The bottom of the image transitions into a blue gradient with wavy, layered patterns.

Thanks

Application to Total Synthesis

- **(+)-Phorboxazole A [4]**

(a) Smith, A. B., III; Verhoest, P. R.; Minbiole, Kevin P.; Lim, J. J. *Org Lett* **1999**, *1*, 909-912. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org Lett* **1999**, *1*, 913-916. (c) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834-4836. (d) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942-10953.

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- **(+)-Spongistatin 1 [2]**

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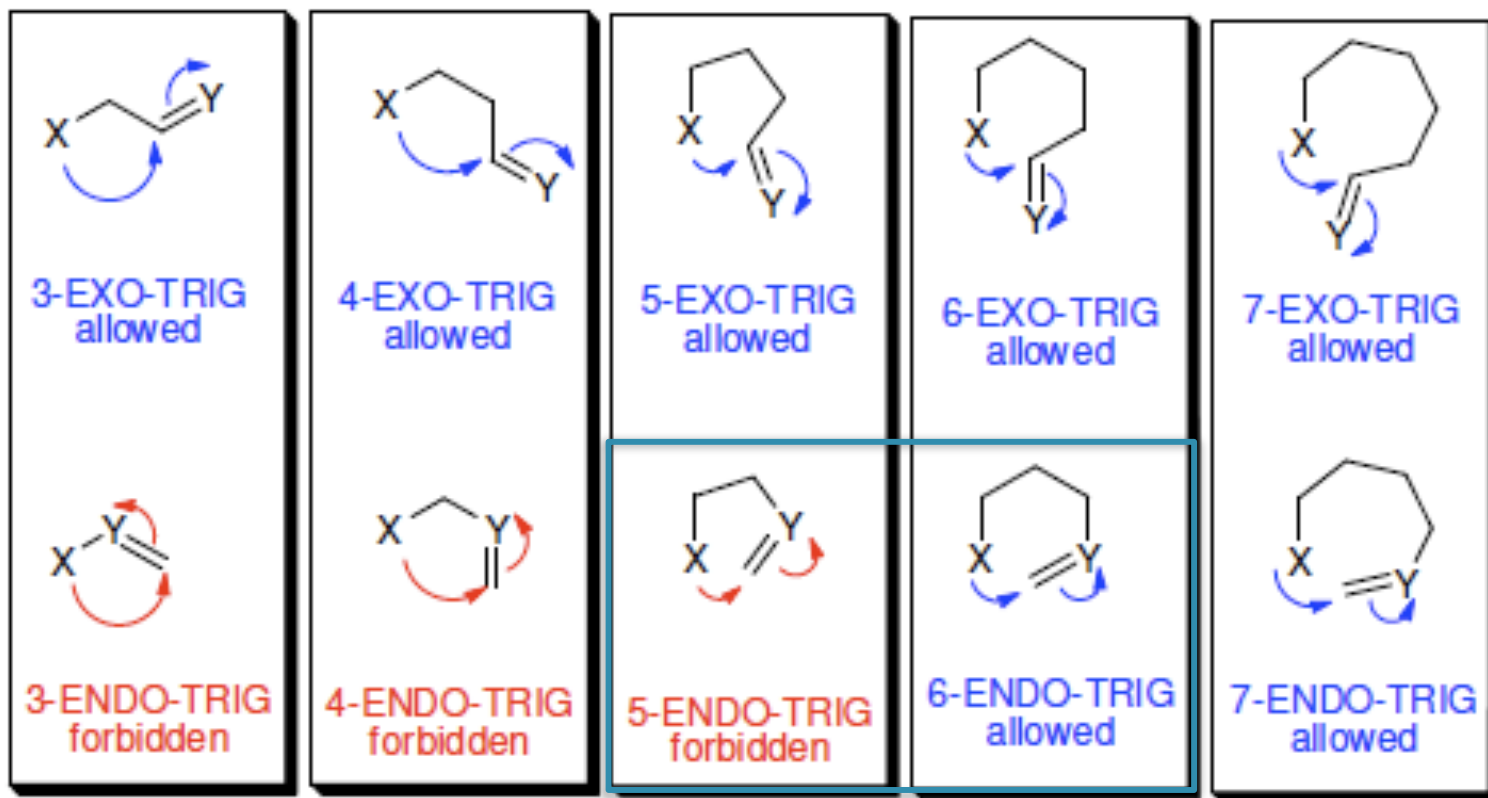
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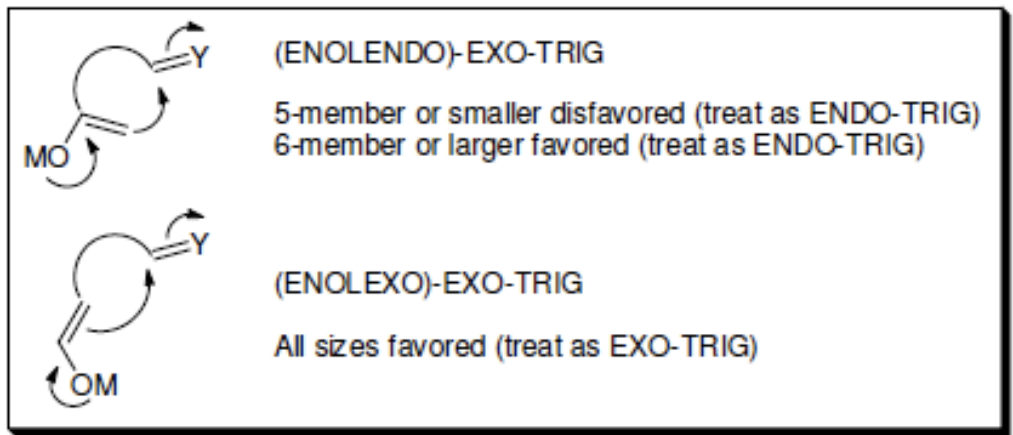
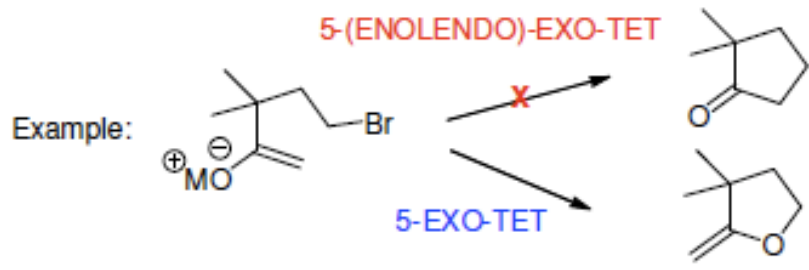
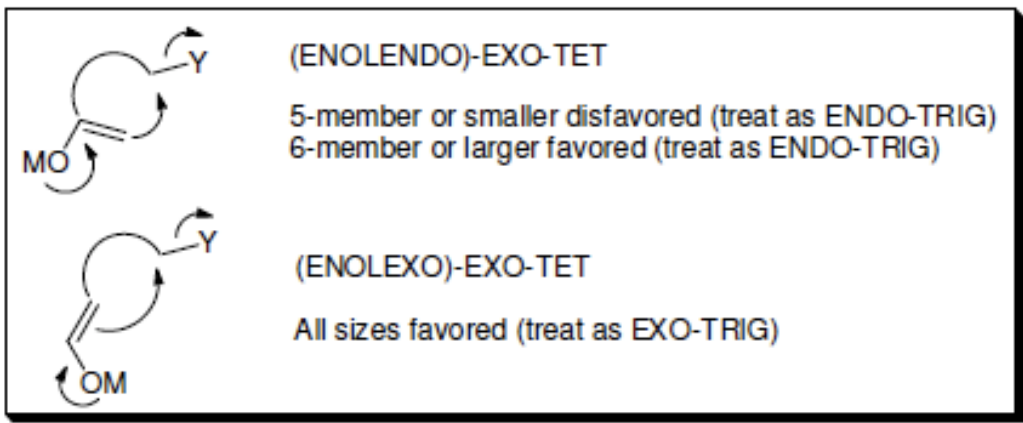
- ***Smith, A. B., III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675-687**

Baldwin Rules

>>> Trigonal Systems (TRIG)



Ring closures involving enolates



Kulinkovich Reaction: Mechanism

