

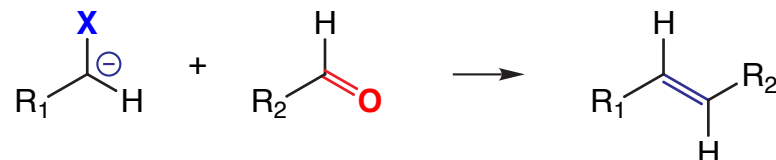
Overview of the Julia-Kocienski Olefination

Evans' Group Literature Seminar

Scott Peterson

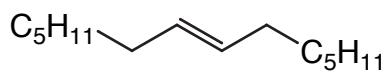
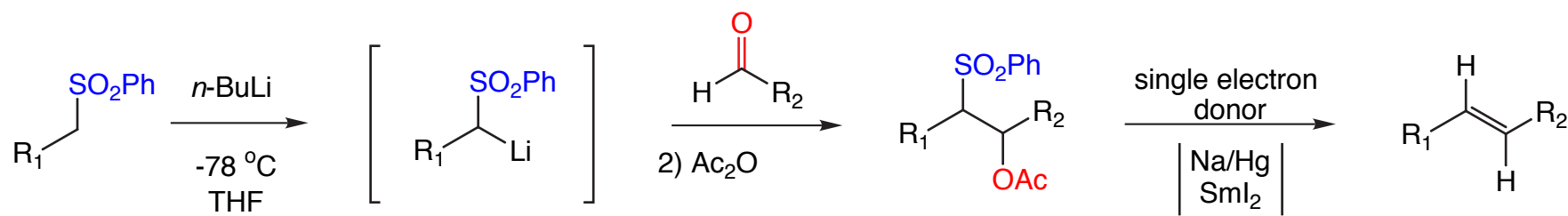
Sept. 26, 2003

Examples of Direct Olefination from Carbonyl Compounds

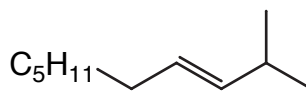


	X	<i>Reaction</i>
B.E. Maryanoff, A.B. Reitz, <i>Chem. Rev.</i> , 1989, 89 , 863	R_3P^+	<i>Wittig</i>
	$\text{R}_2\text{P}(=\text{O})$	<i>Horner-Wittig</i>
	$(\text{RO})_2\text{P}(=\text{O})$	<i>Horner-Wadsworth-Emmons</i>
L.F. van Staden, D. Gravstock, D.J. Ager, <i>Chem. Soc. Rev.</i> , 2002, 31 , 195	R_3Si	<i>Peterson</i>
	$\text{ArS}(=\text{O})(=\text{NMe})$	<i>Johnson</i>
P.R. Blakemore, <i>J. Chem. Soc.</i> , <i>Perkin Trans. 1</i> , 2002, 2563	ArSO_2	<i>classical Julia</i>
	HetSO_2	<i>modified Julia</i>

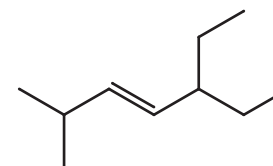
Classical Julia Olefination



E:Z = 80:20



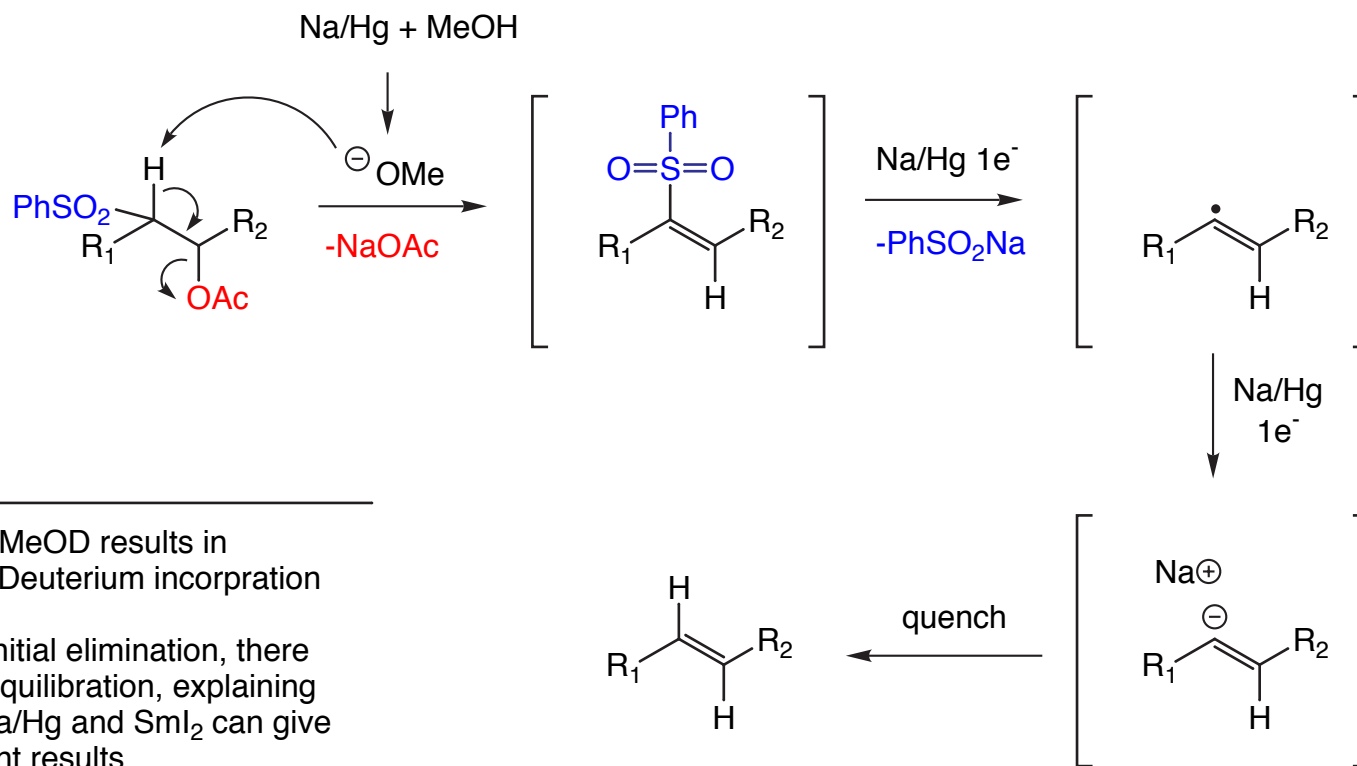
E:Z = 90:10



E:Z = >99:1

P.J. Kocienski, B. Lythgoe, *J. Chem. Soc. Perkin Trans, 1*, 1980, 1045

Mechanism of Olefin Formation

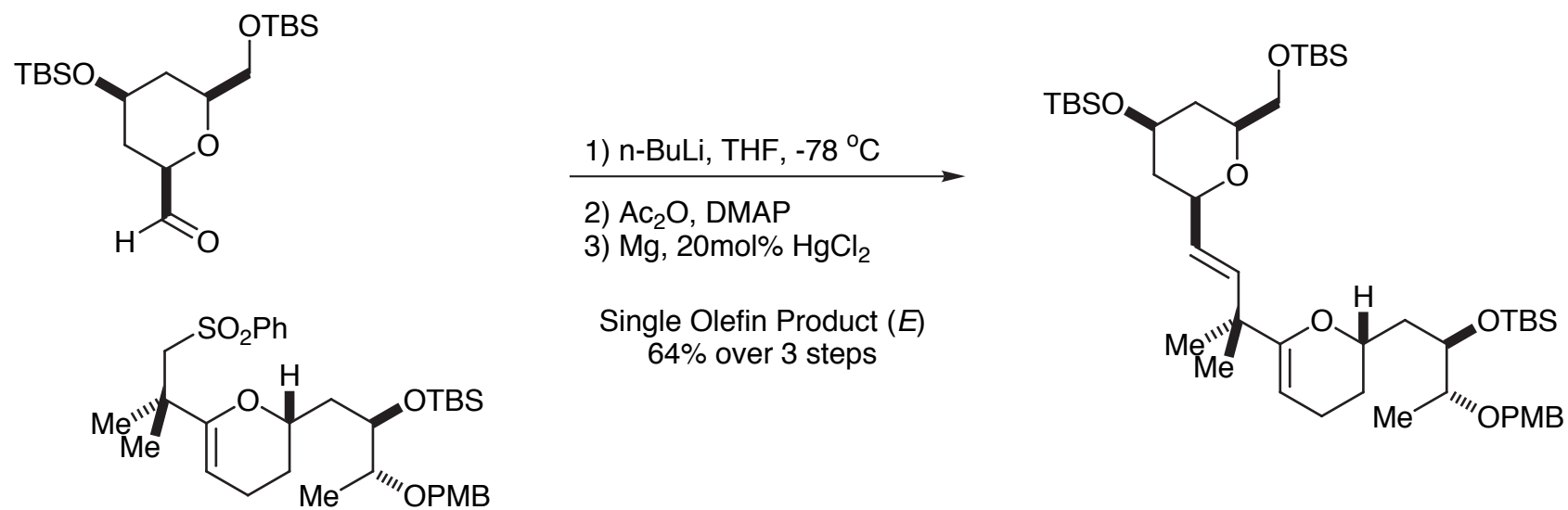


-Using MeOD results in
>90% Deuterium incorporation

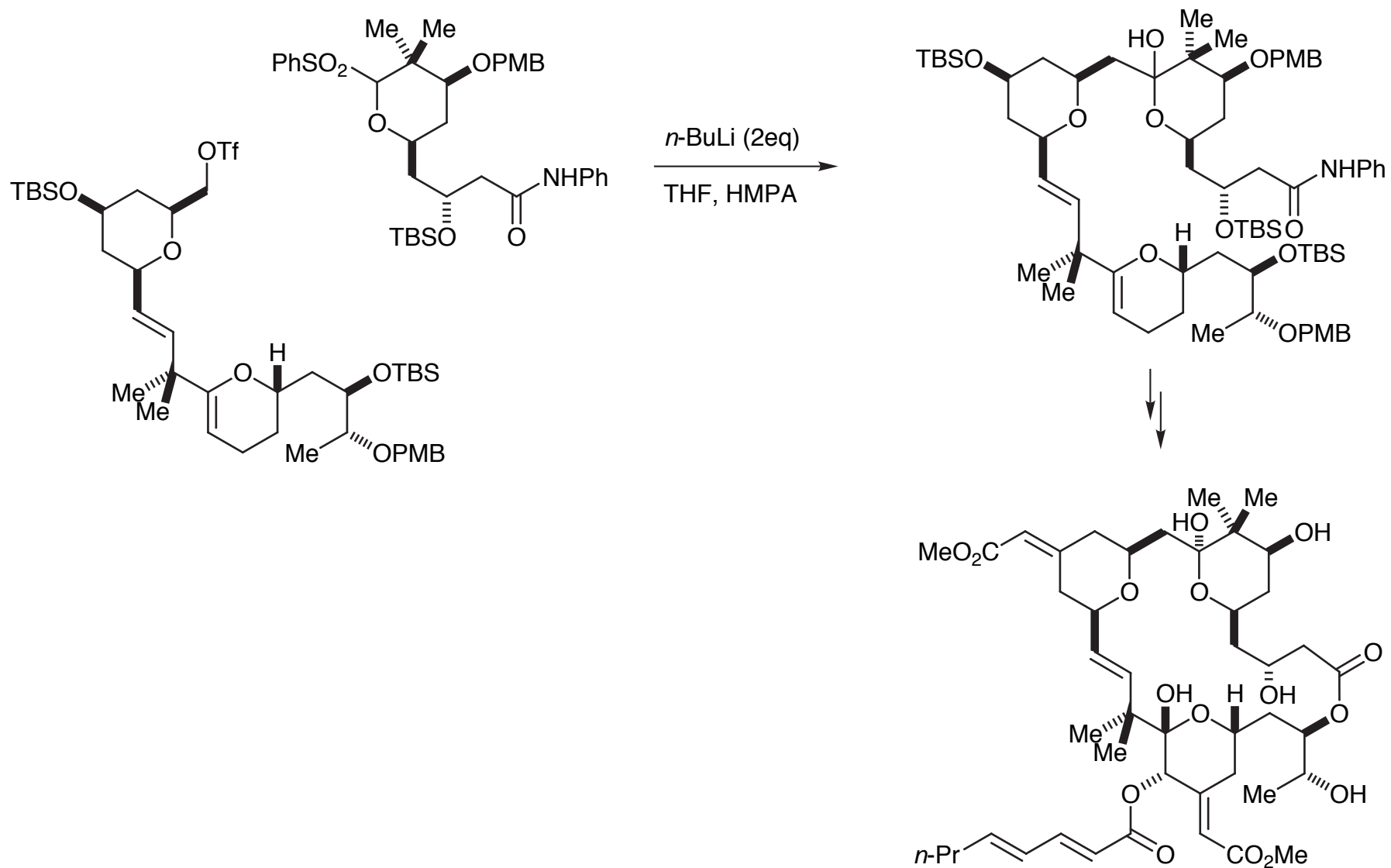
-After initial elimination, there
is no equilibration, explaining
why Na/Hg and SmI_2 can give
different results

G.E. Keck et al., *J. Org. Chem.*, 1995, **60**, 3194

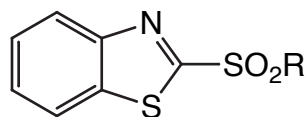
Synthesis of Bryostatin 2



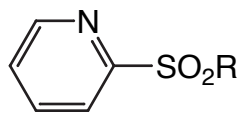
Synthesis of Bryostatin 2



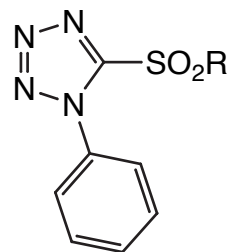
Modified Julia Olefination



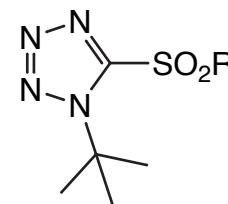
BT



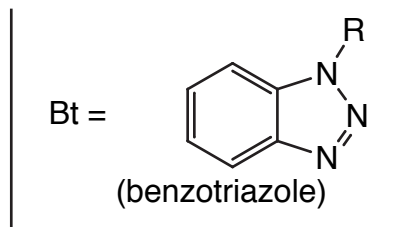
PYR



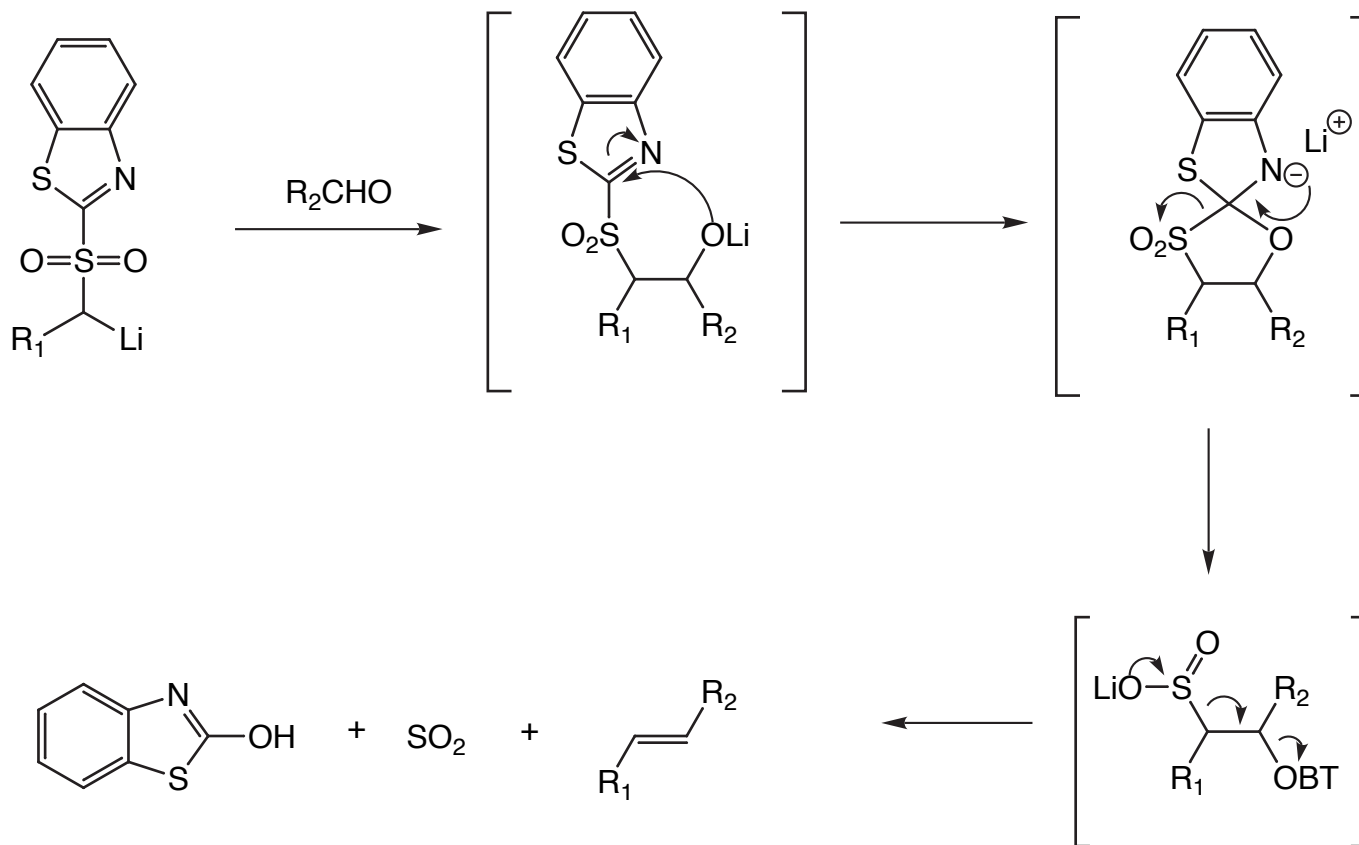
PT



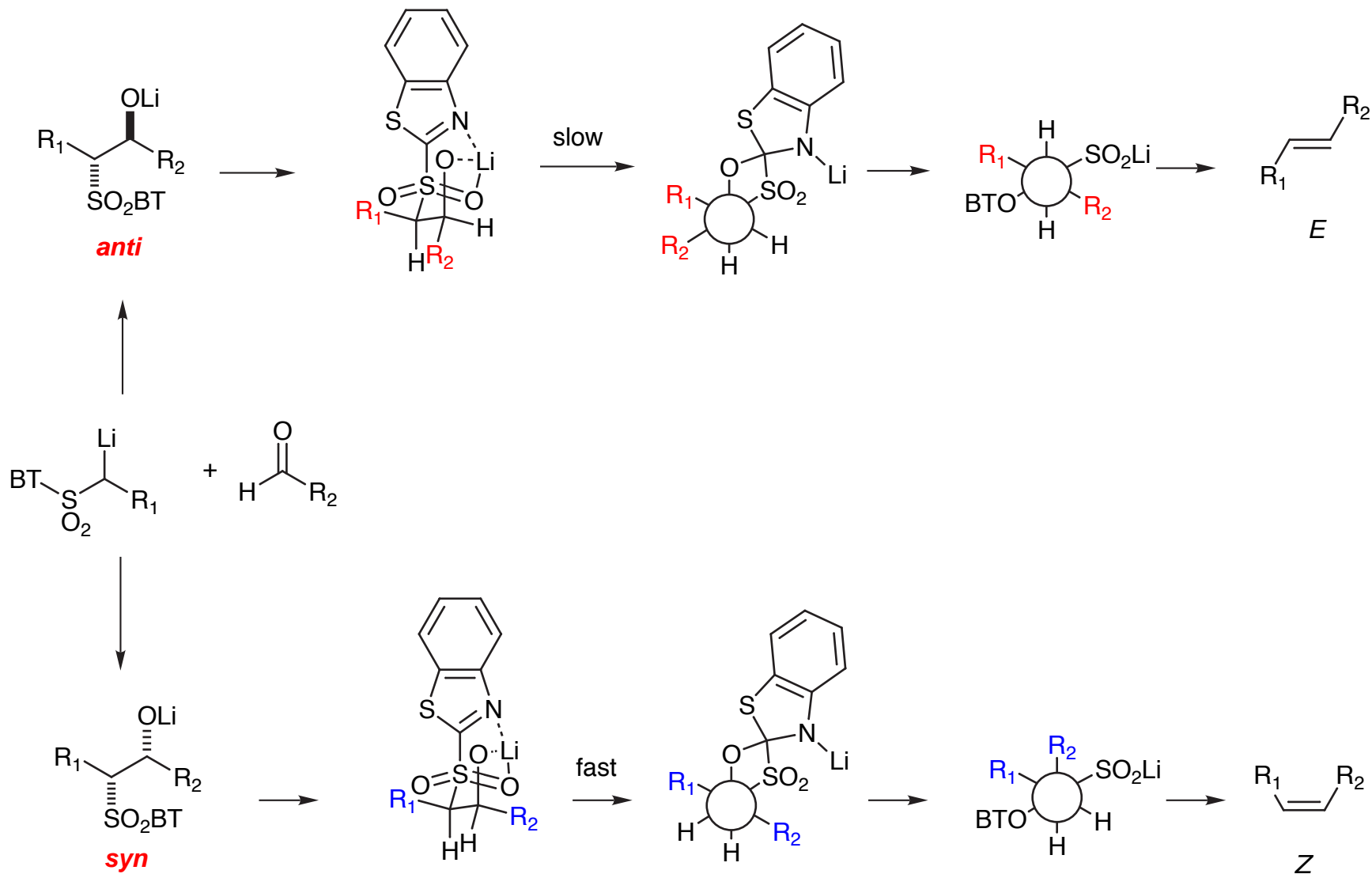
TBT



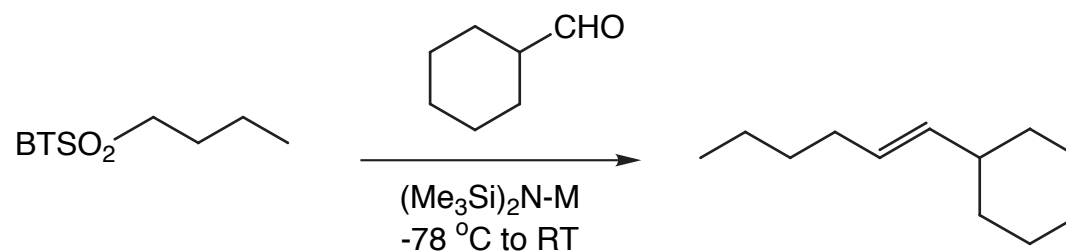
Modified Julia Olefination - Smiles Rearrangement



Diastereoselectivity of BT-Sulfones



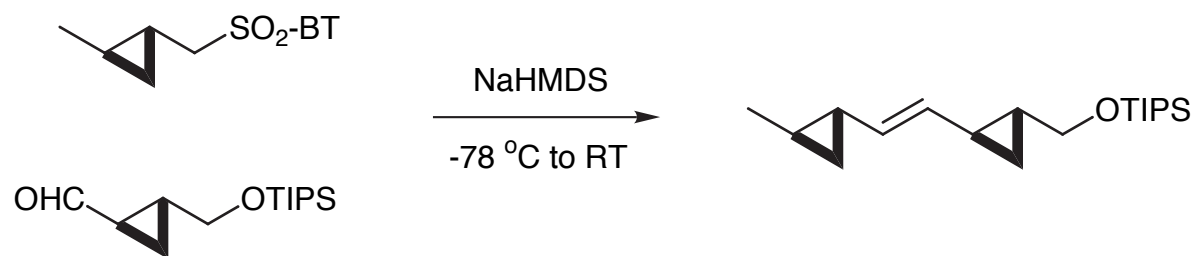
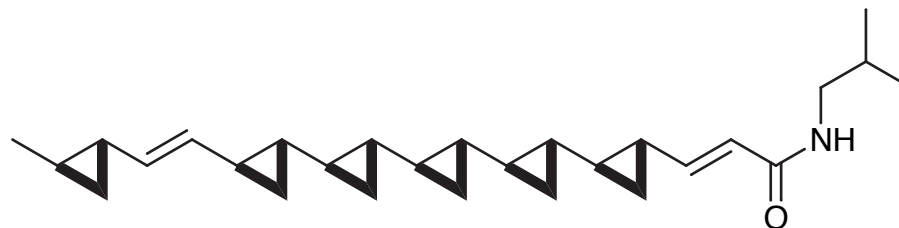
Effects of Solvent and Counterion with BT-Sulfone



M	Toluene	Et ₂ O	THF	DME
Li	50:50	49:51	66:34	70:30
Na	54:46	50:50	62:38	75:25
K	54:46	51:49	54:46	76:24

E : *Z* ratios

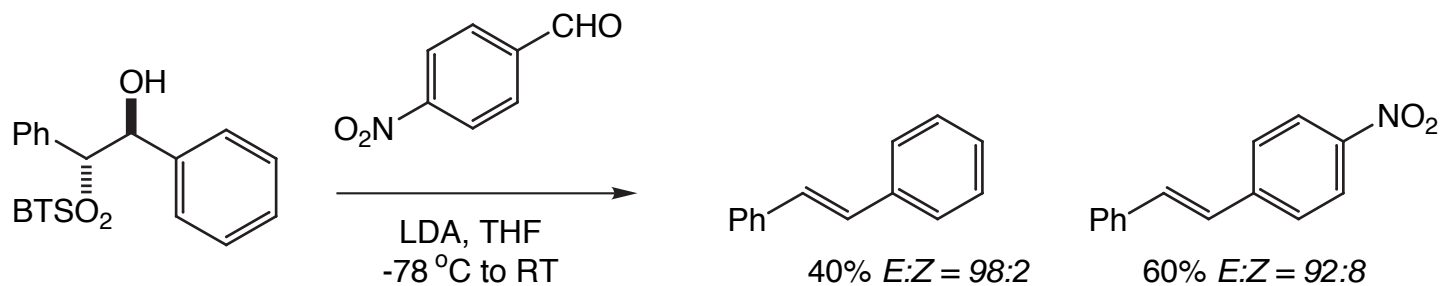
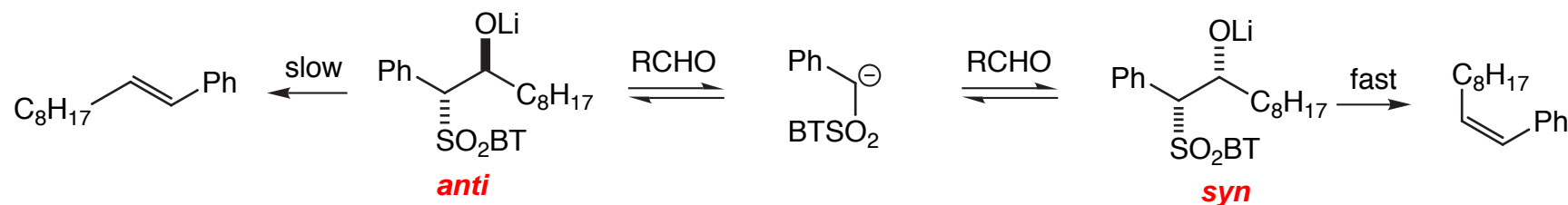
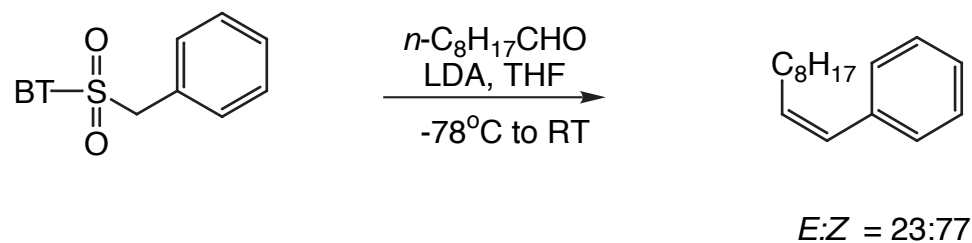
Solvent Screen in U-106305 Synthesis



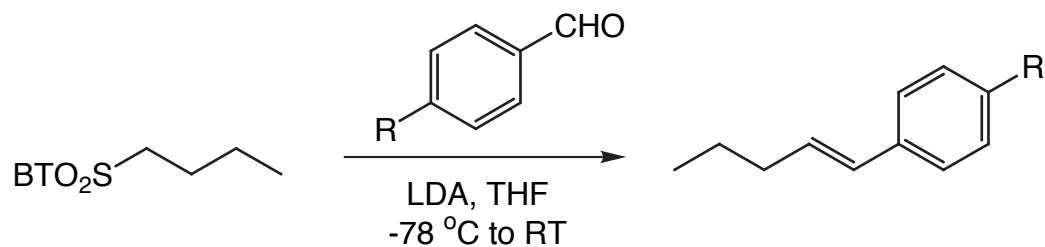
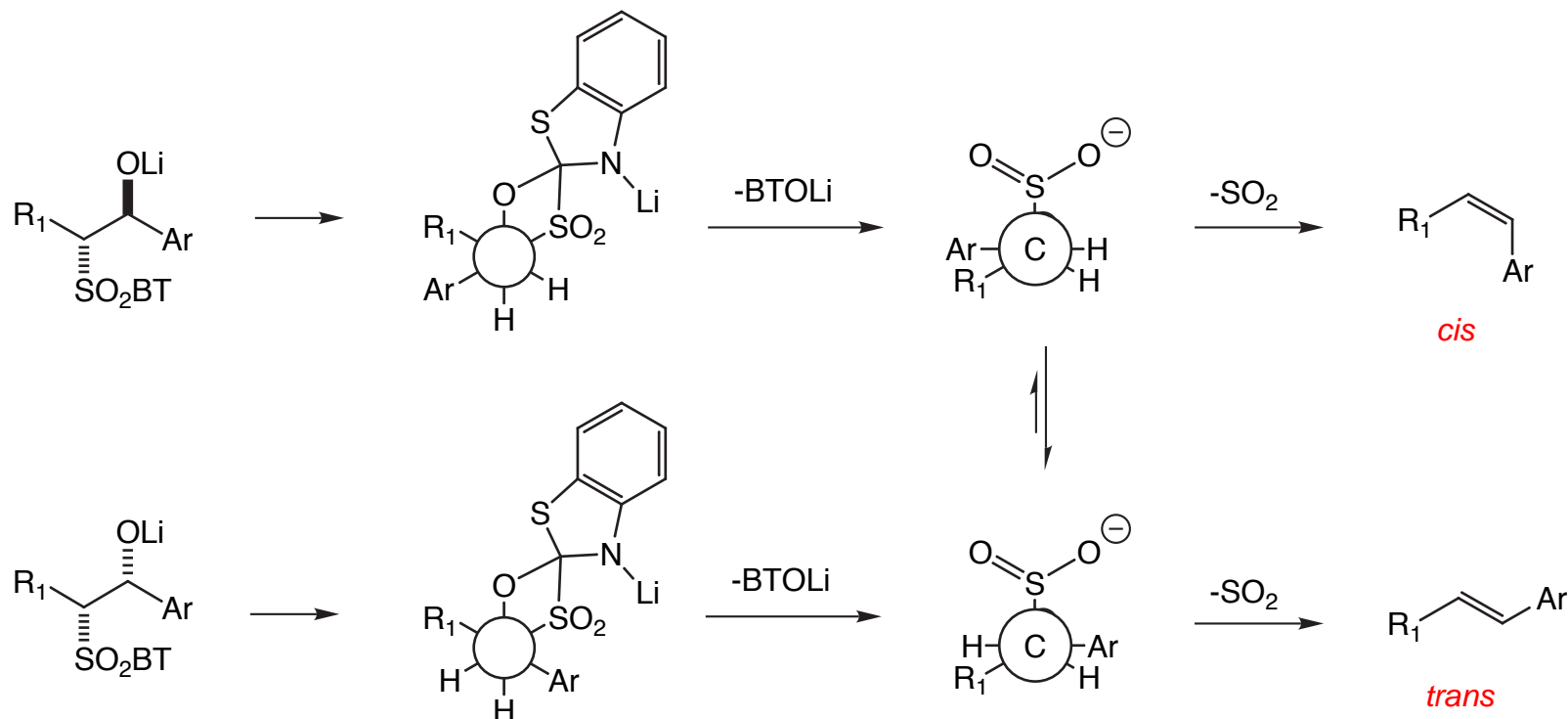
solvent	<i>E:Z</i>
toluene	9:91
CH ₂ Cl ₂	9:91
Et ₂ O	11:89
THF	52:48
DME	71:29
DMF	78:22



Retroaddition - Addition with BT-Sulfone

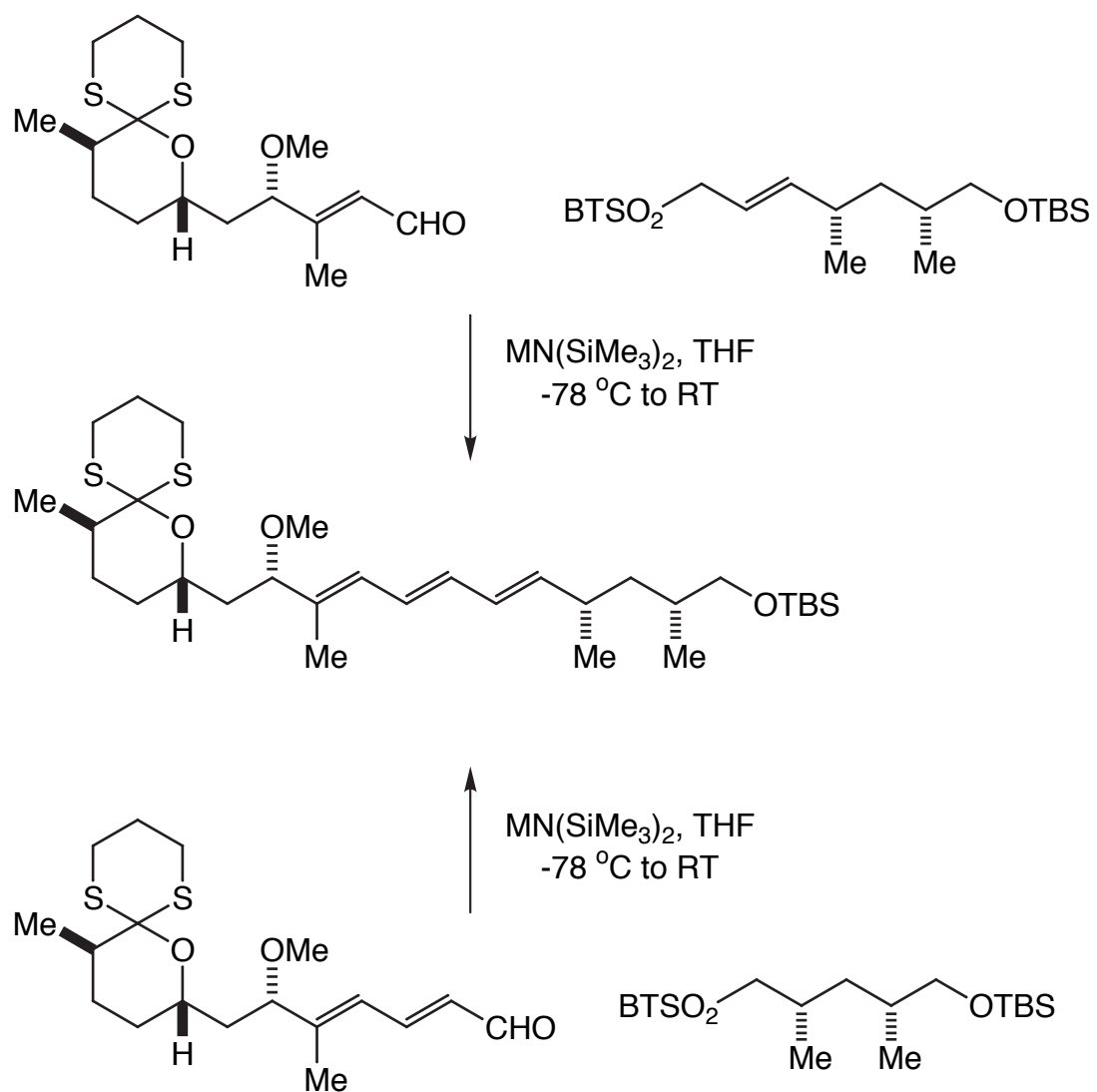


Aromatic Aldehydes with BT-Sulfones



R	yield	E:Z
OMe	95%	99:1
H	68%	94:6
Cl	51%	77:23

Reversibility in Rapamycin Synthesis



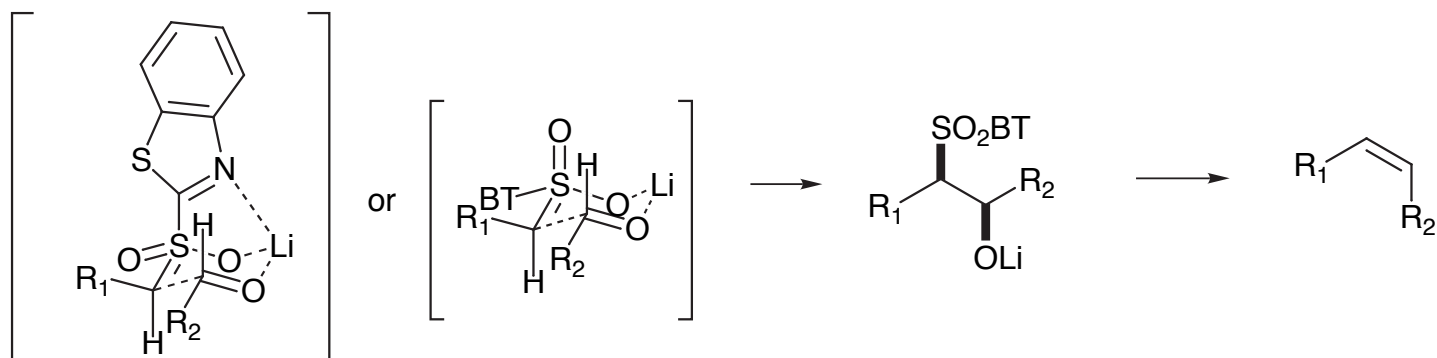
M	yield	<i>E</i> : <i>Z</i>
Li	75%	29:71
Na	79%	43:57
K	--	18:82

M	yield	<i>E</i> : <i>Z</i>
Li	68%	95:5
Na	21%	78:22

P. Kocienski, et al., *Synthesis*, 1996, 285

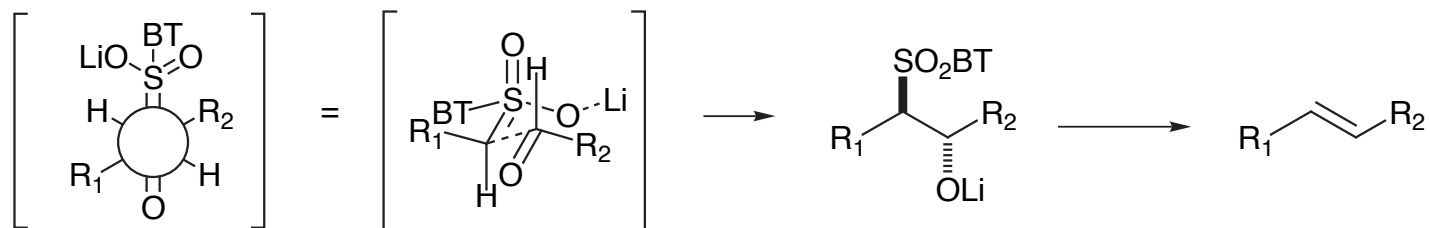
14-counterexample 9/25/03 10:21 AM

Possible Explanation for Diastereoselectivity

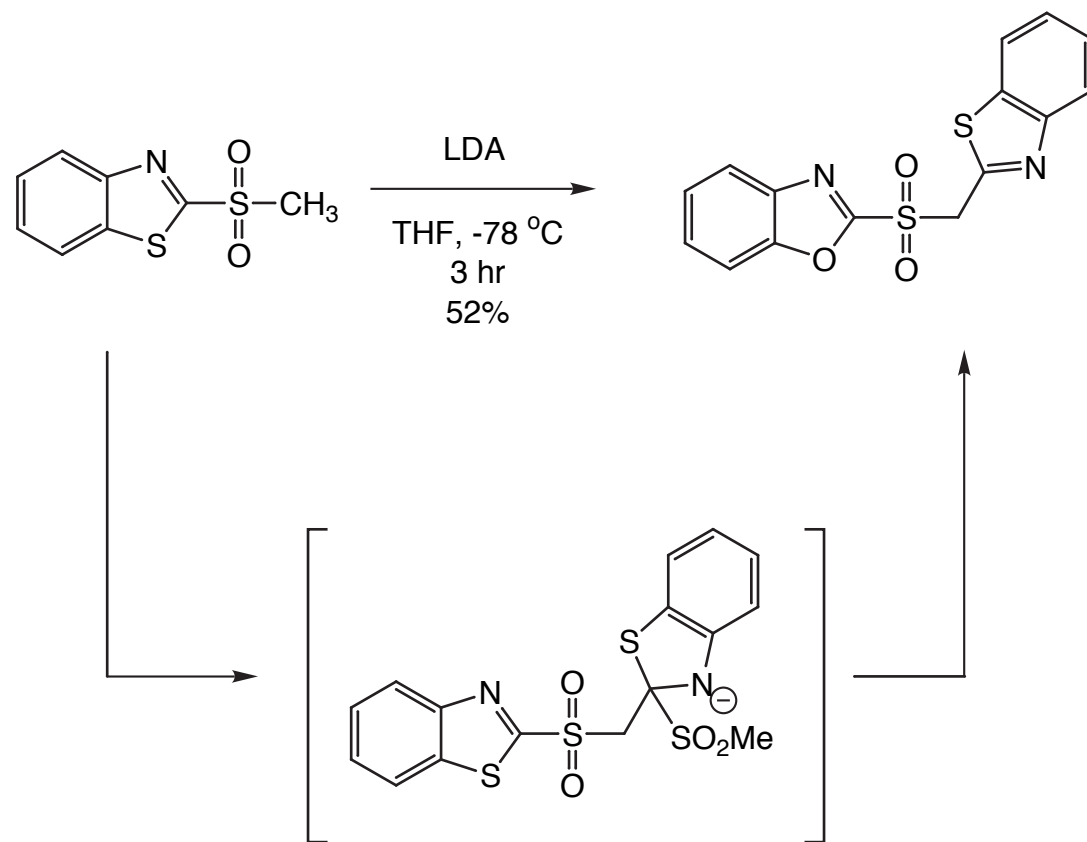


Chelate (closed) Transition State favored for **non-polar solvents**, **small counter-ions** (Li)

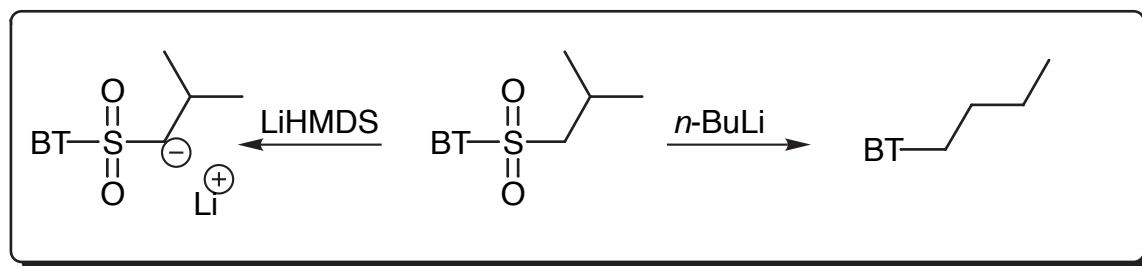
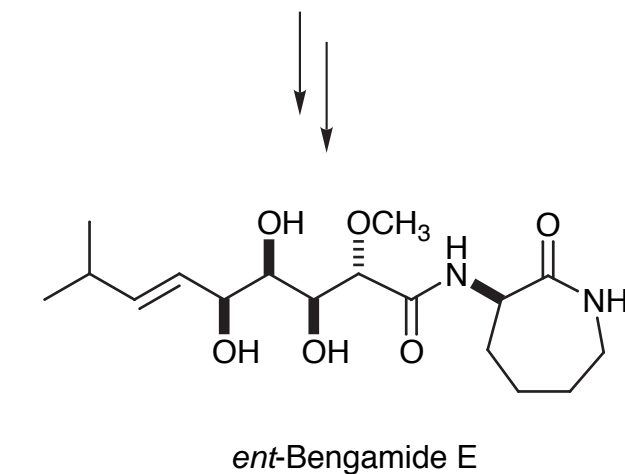
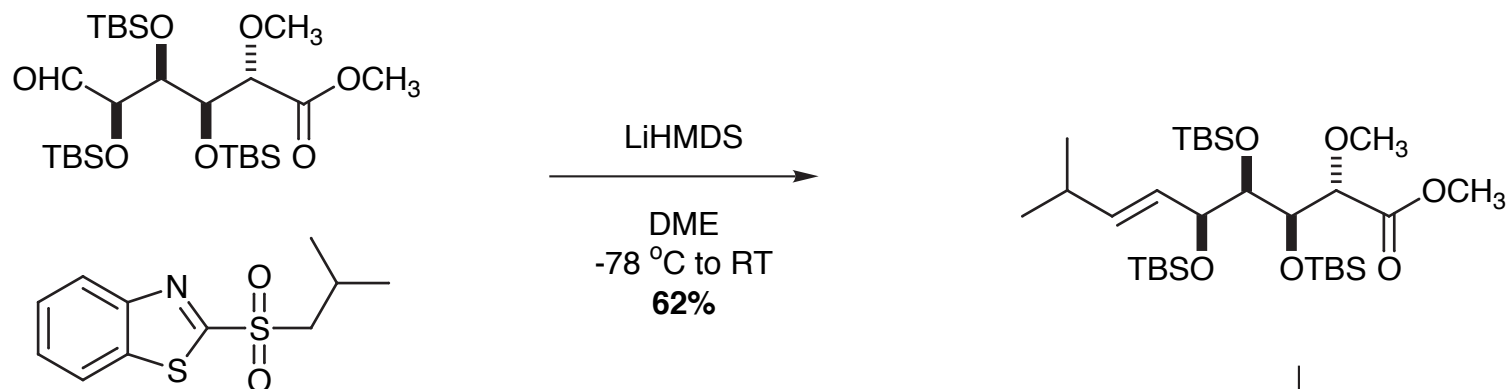
Non-chelate (opened) Transition State favored for **polar solvents**, **large counter-ions** (K)



*Ips*o Substitution with *BT*-Sulfones

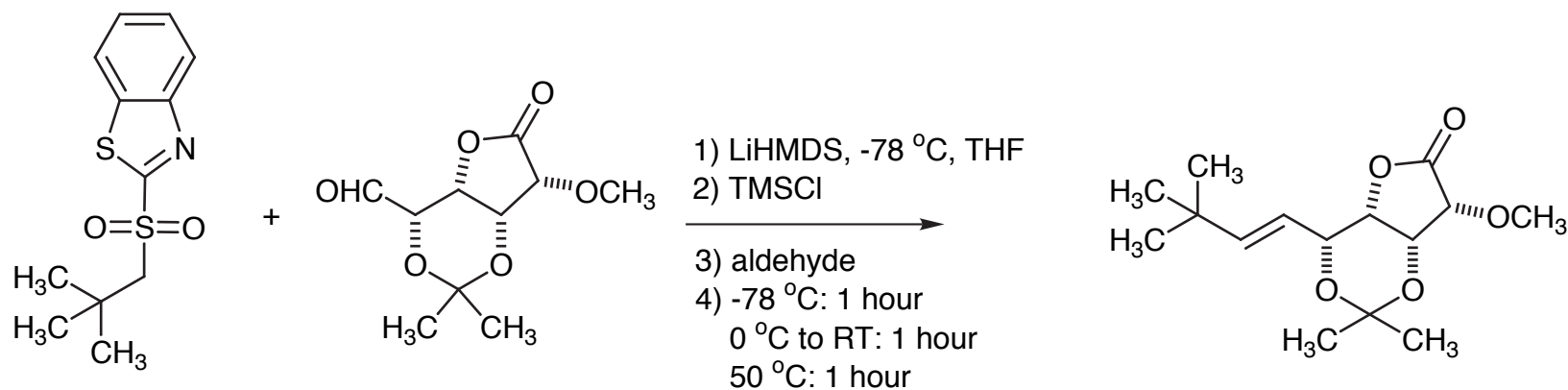


Synthesis of ent-Bengamide E

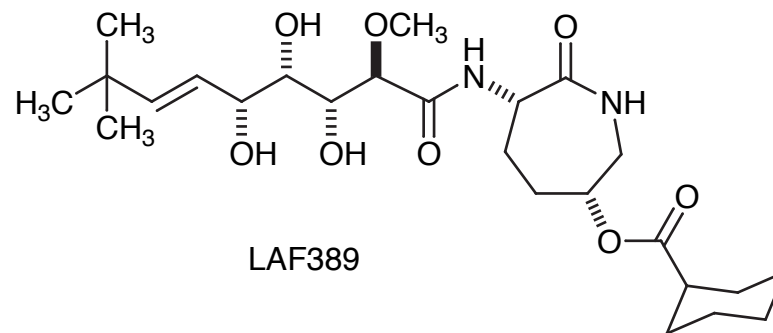


K.J.McRae, PhD Thesis, Research School of Chemistry, Canberra, 2001
 J.B.Baudin, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

Synthesis of LAF389

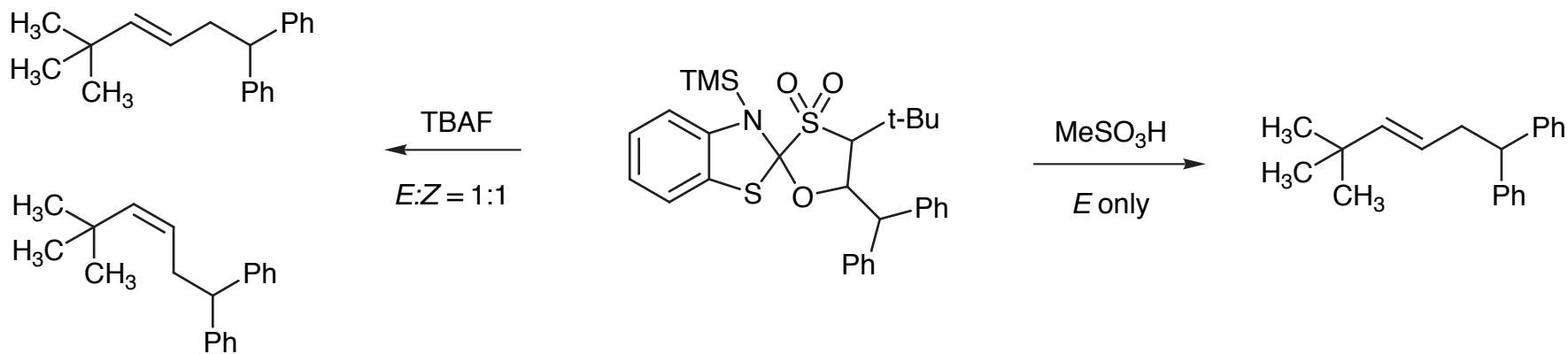
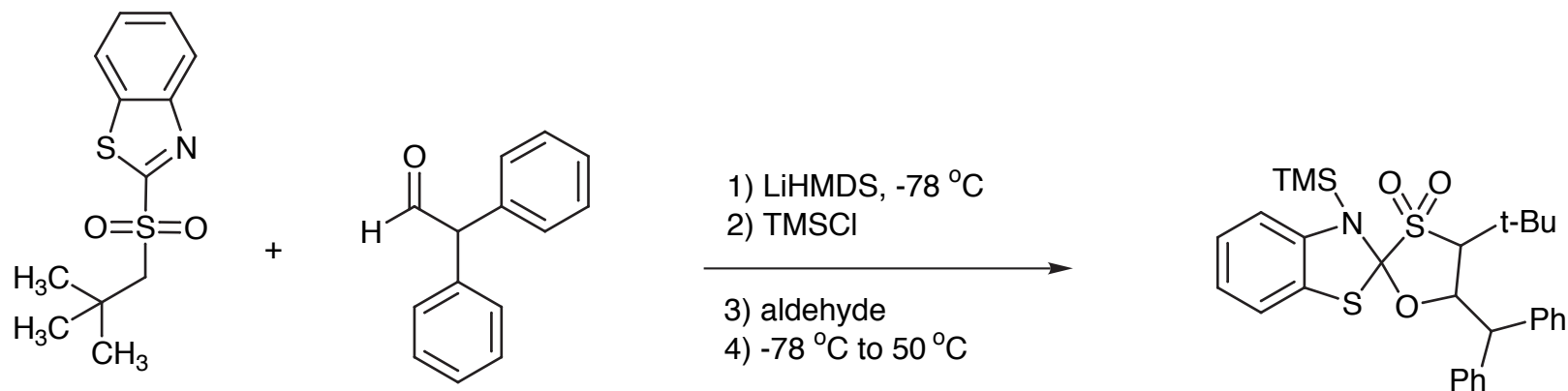


45% single isomer,
white crystalline solid



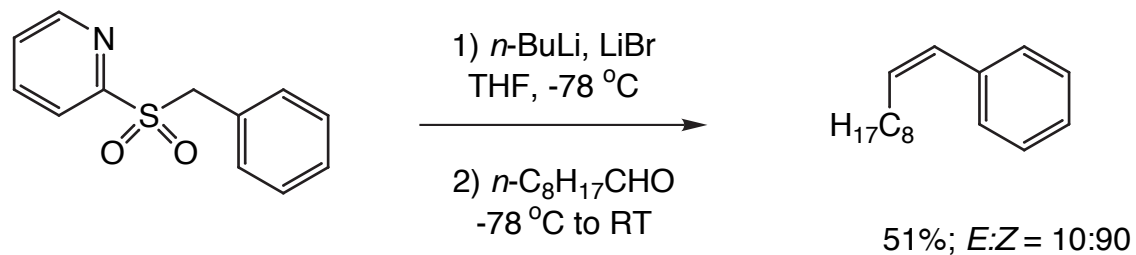
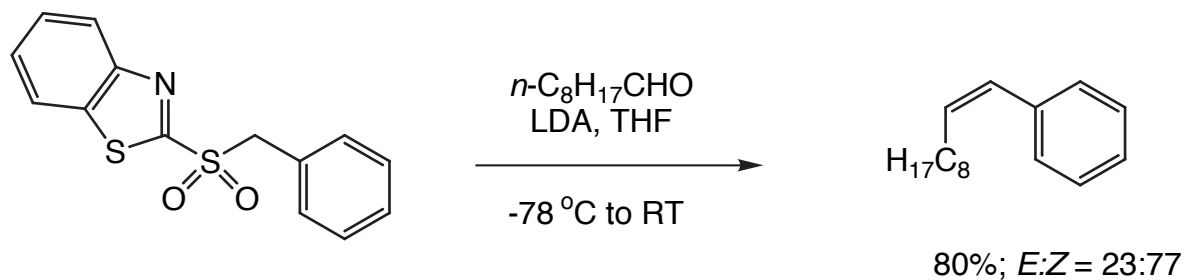
L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

Synthesis of LAF389

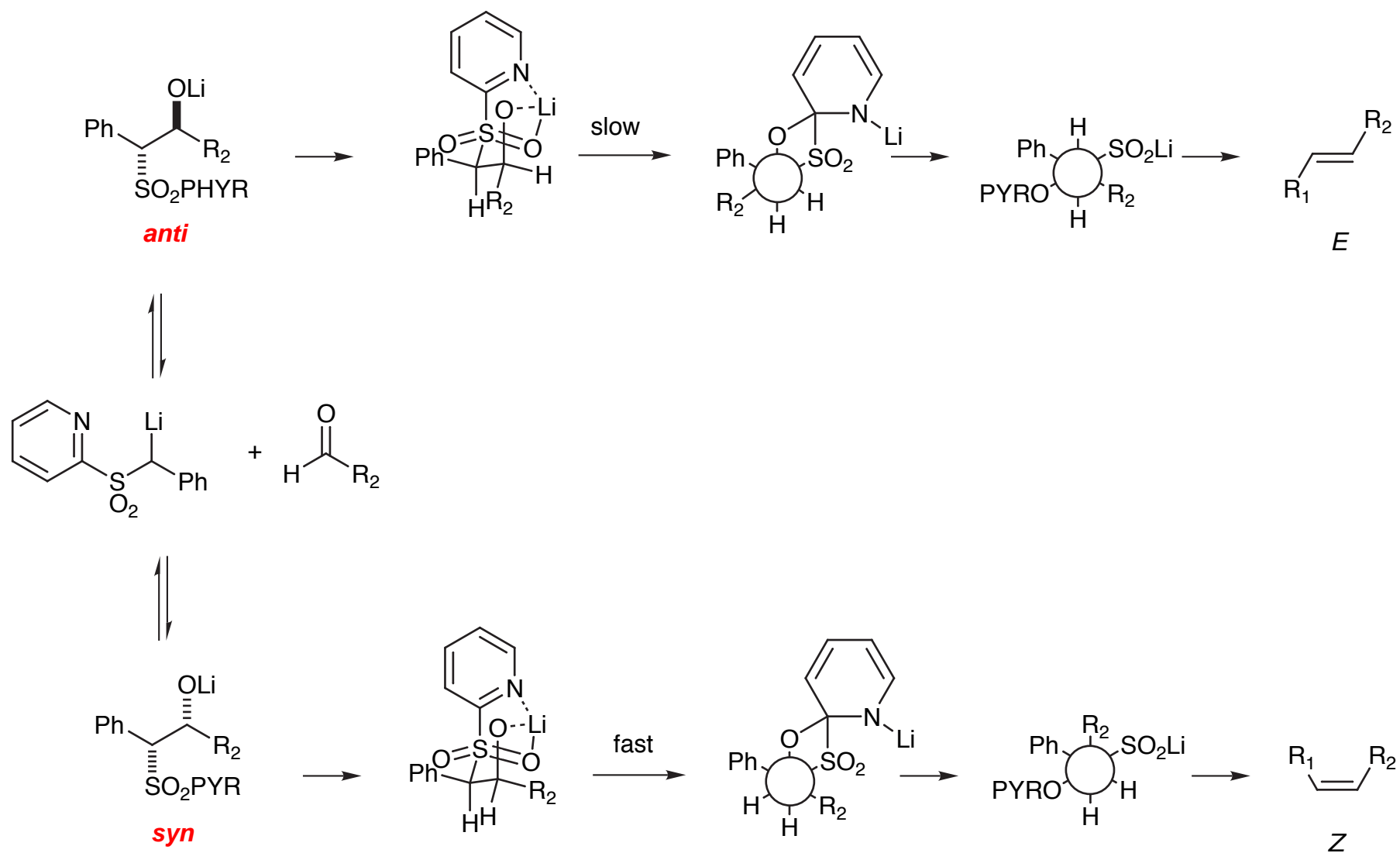


L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

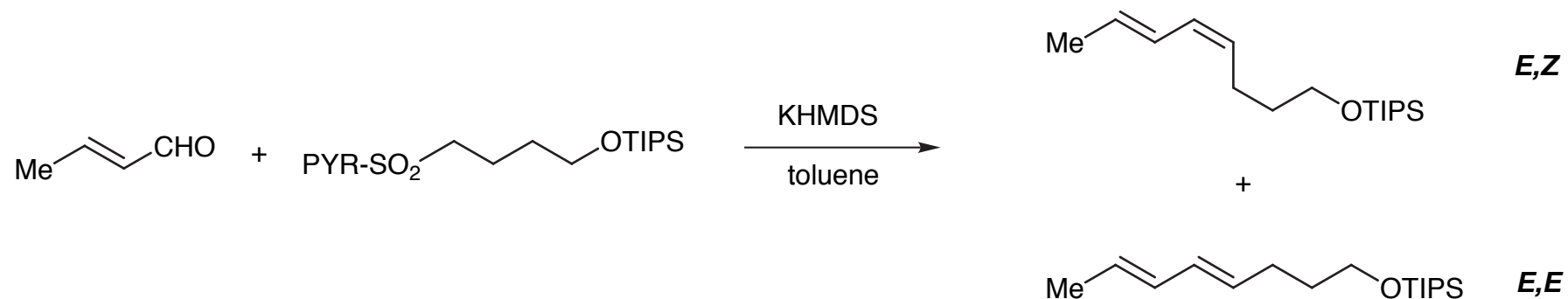
Pyridinyl (PYR) Sulfones - Higher cis Selectivities



Diastereoselectivity of *PYR*-Sulfones



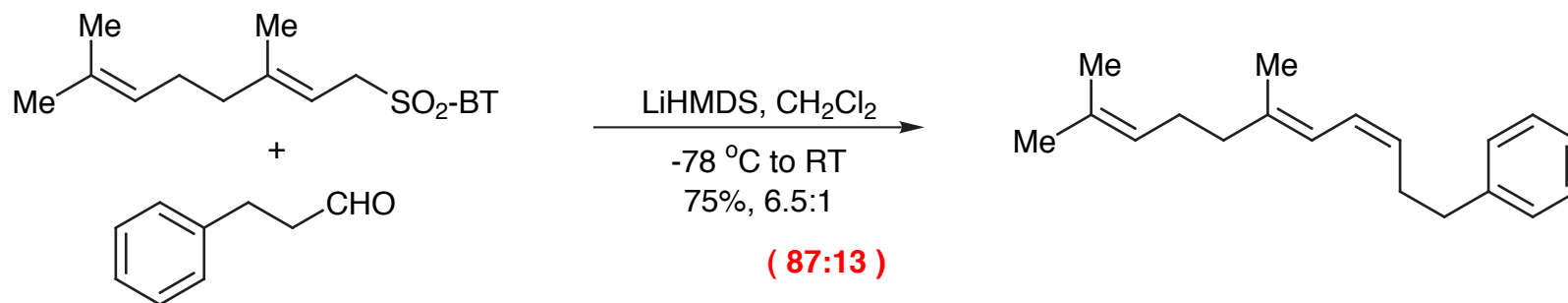
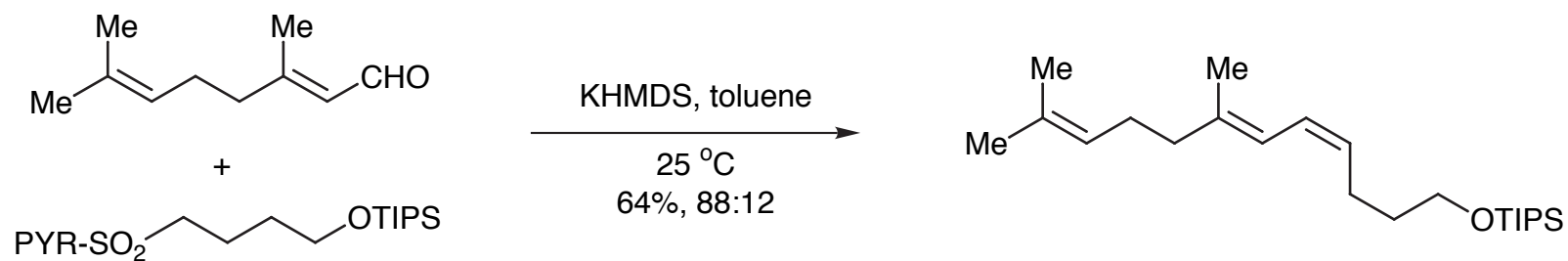
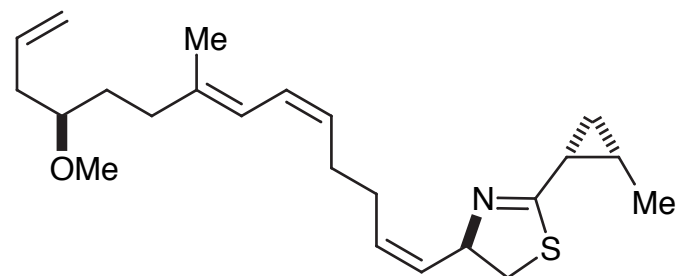
Pyridinyl (PYR) Sulfones Examples



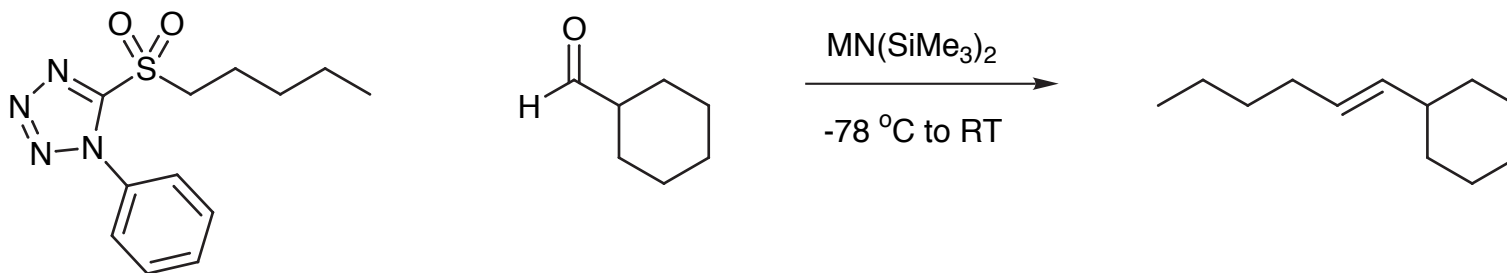
temp	yield	Ratio <i>E,Z</i> : <i>E,E</i>
-78 °C	35%	84:16
0 °C	53%	90:10
25 °C	67%	91:9

← Potassium metallate is stable at RT for 5 min!

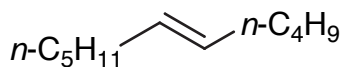
Pyridinyl (PYR) Sulfones Examples



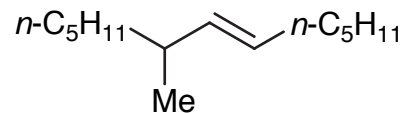
1-Phenyl-1H-tetrazol-5-yl Sulfones



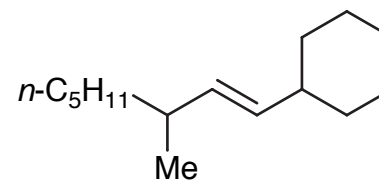
M	toluene	Et ₂ O	THF	DME
Li	51:49	61:39	69:31	72:28
Na	65:35	65:35	73:27	89:11
K	77:23	89:11	97:3	99:1



$E:Z = 94:6$



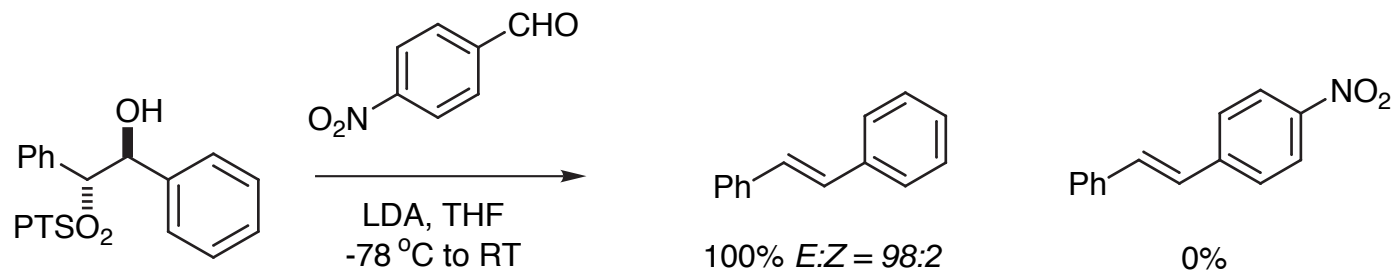
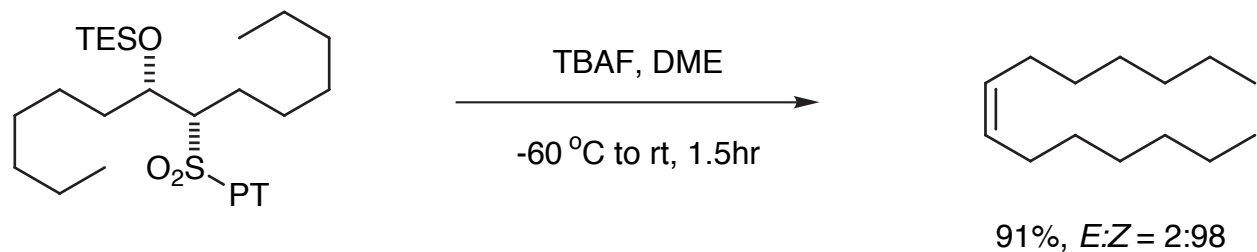
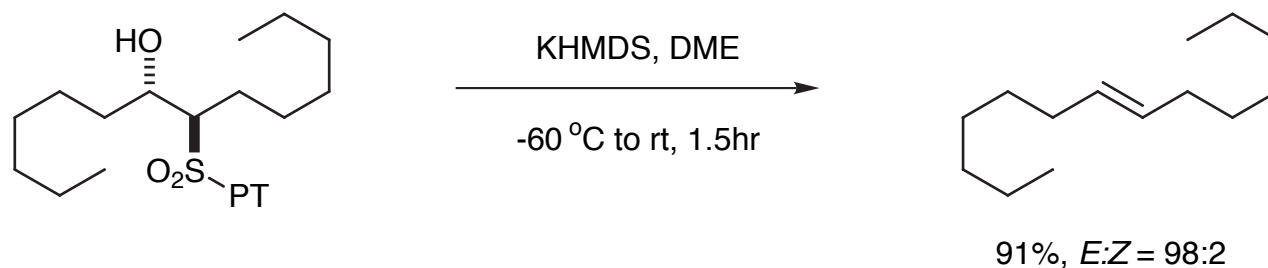
$E:Z = 96:4$



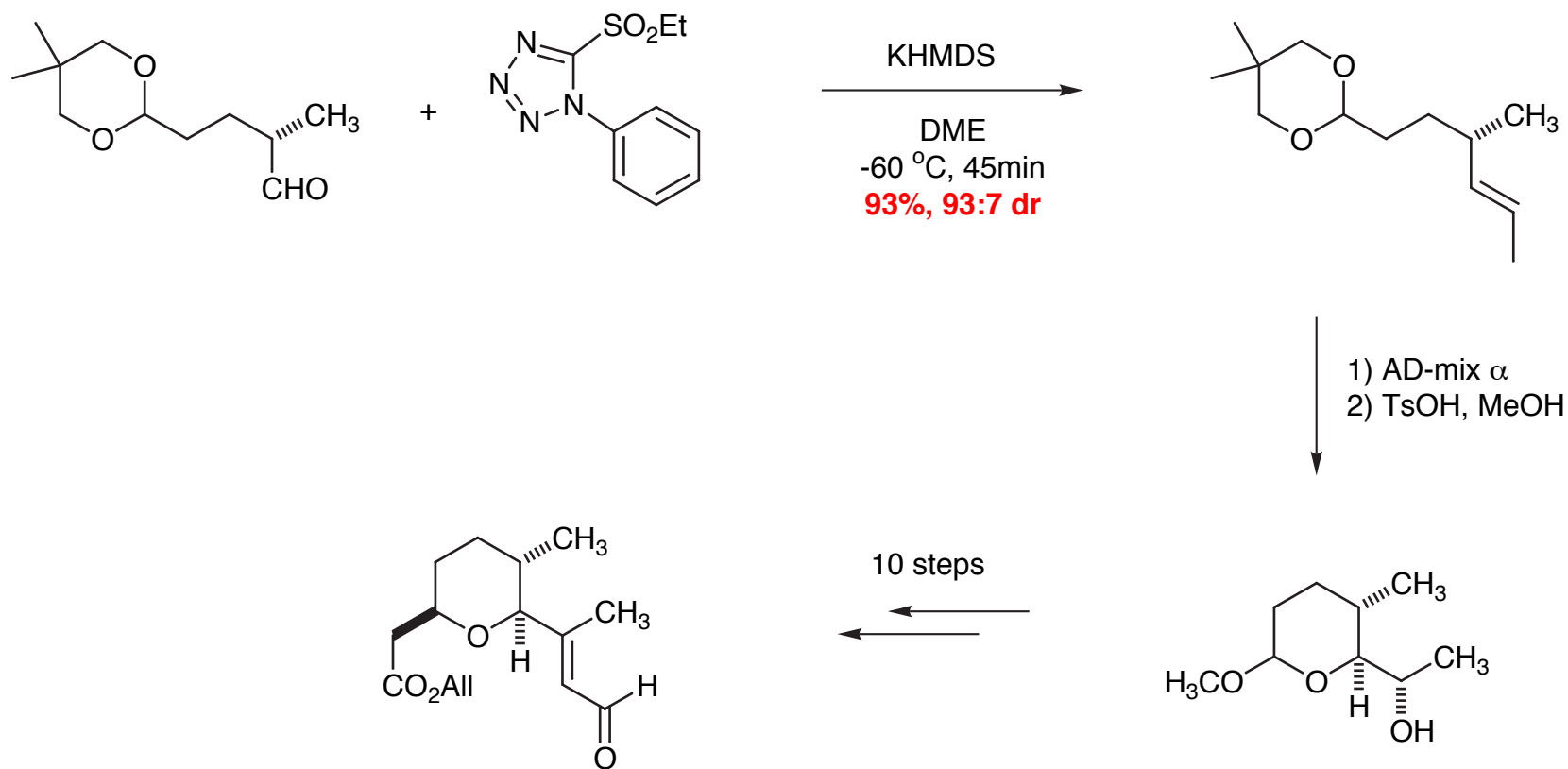
$E:Z = 99:1$

1.5eq aldehyde
 KHMDS, DME $-78\text{ }^\circ\text{C}$ to RT

Kinetically Controlled Diastereoselectivity - Irreversible



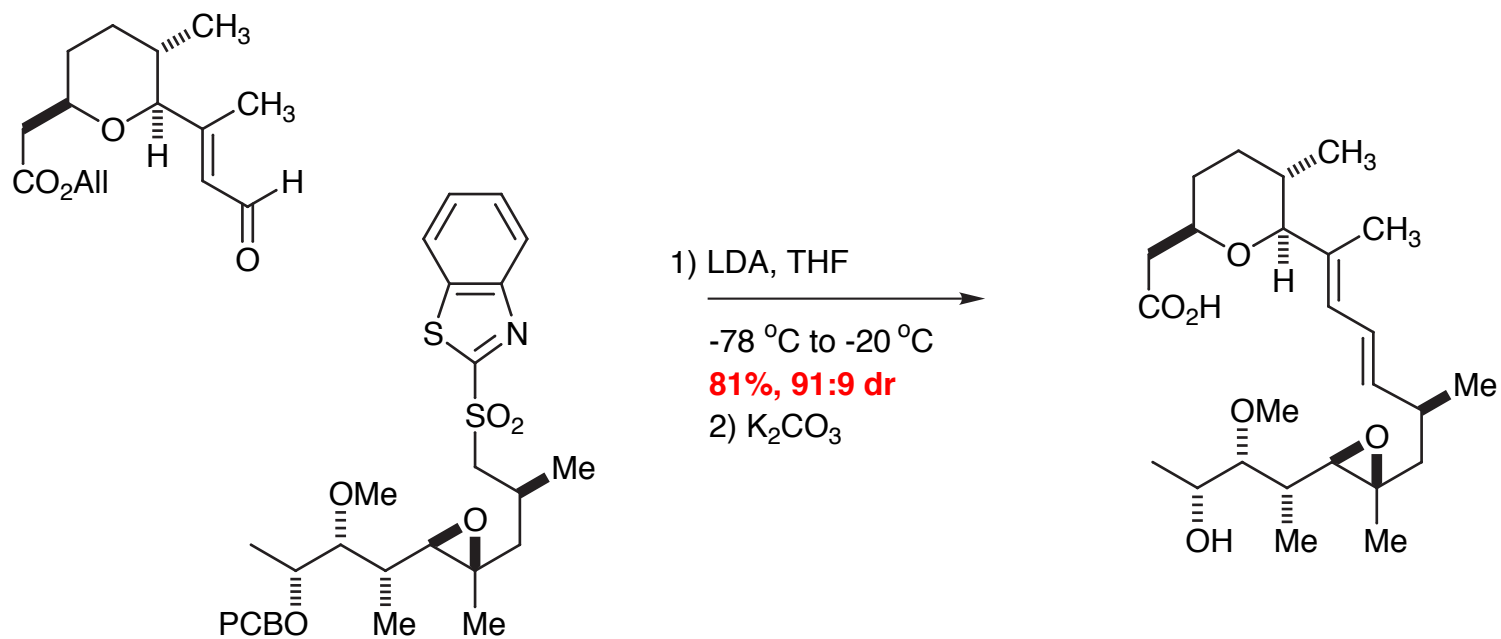
Synthesis of Herboxidine



P.J.Kocienski, et al., *J. Chem. Soc., Perkin Trans. 1*, 1999, 955

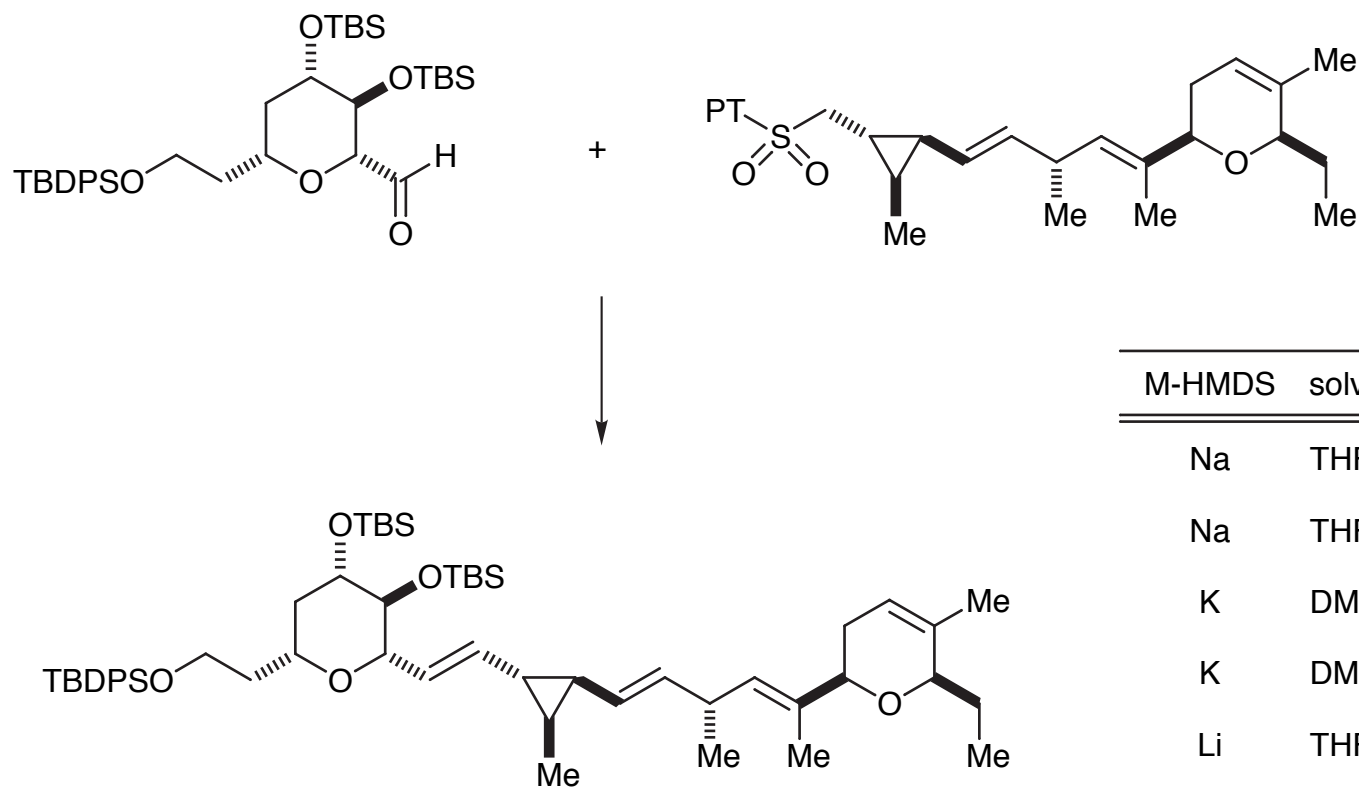
24-herbo pt 1 9/25/03 1:34 PM

Synthesis of Herboxidine



P.J.Kocienski, et al., *J. Chem. Soc., Perkin Trans. 1*, 1999, 955

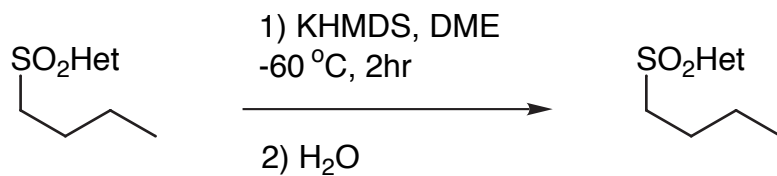
Synthesis of (+)-Ambruticin



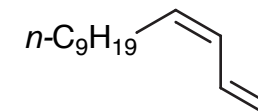
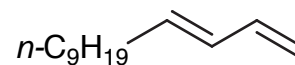
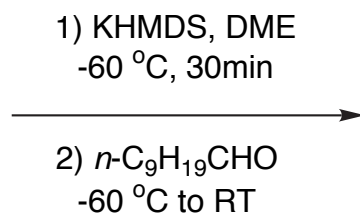
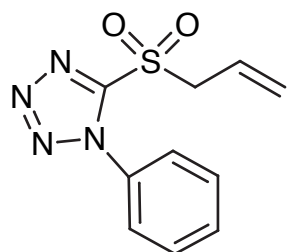
M-HMDS	solvent	temp	<i>E</i> : <i>Z</i>
Na	THF	-78 °C	1:8
Na	THF	-35 °C	1:6
K	DMF	-60 °C	1:1
K	DME/18-c-6	-60 °C	1:3
Li	THF/HMPA	-60 °C	3:1
Li	DMF/HMPA	-35 °C	>30:1
Li	DMF/HMPU	-35 °C	>30:1

E.N. Jacobsen, P. Liu, *J. Am. Chem. Soc.*, 2001, **123**, 10772

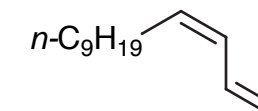
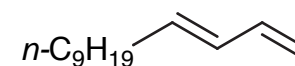
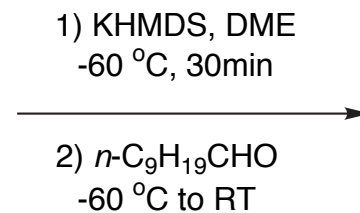
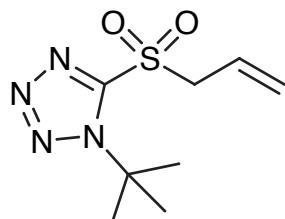
tert-Butyl-1H-tetrazol-5-yl Sulfones



Het	yield
BT	0%
PT	20%
TBT	91%

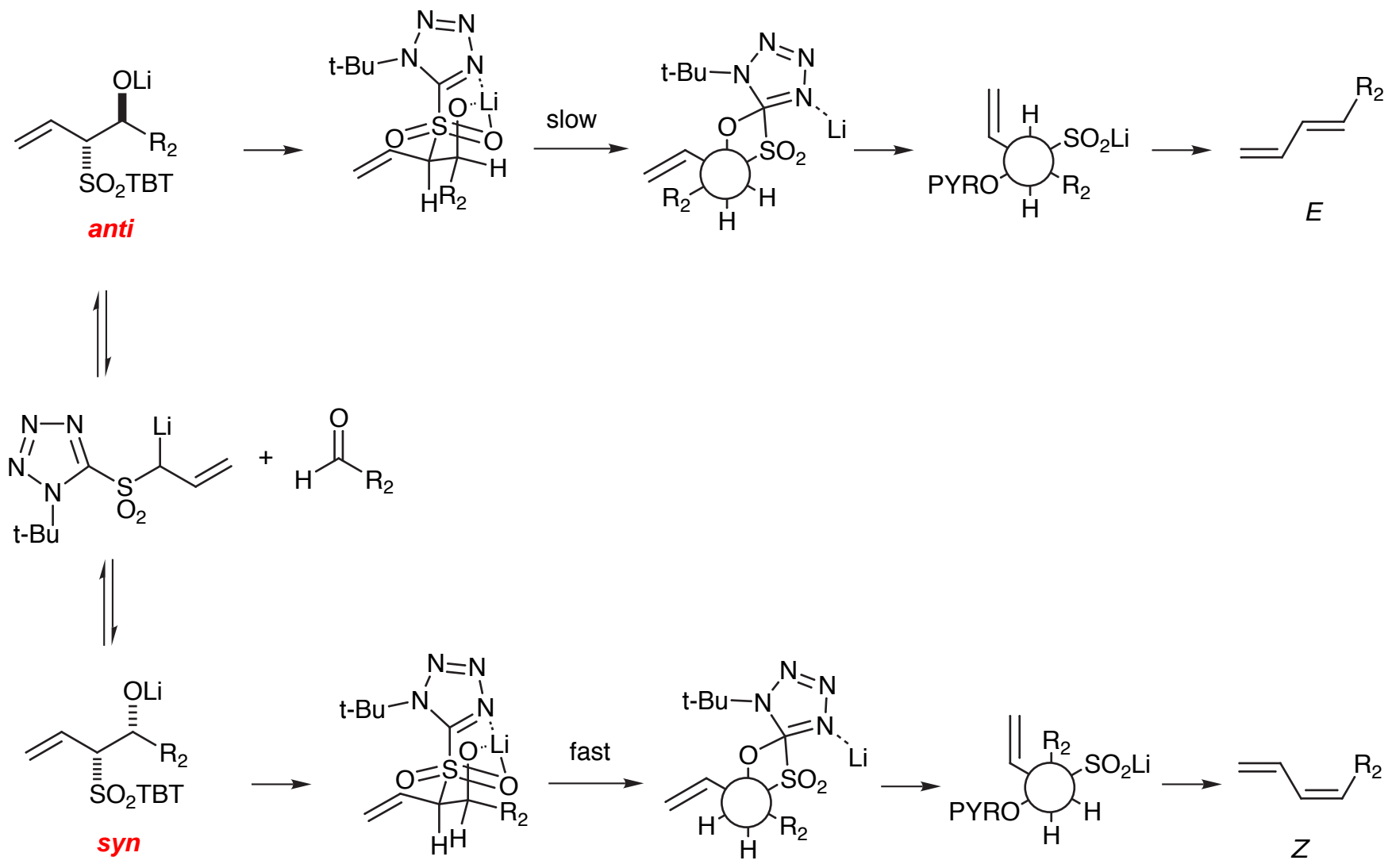


39% **67:33**

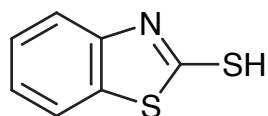
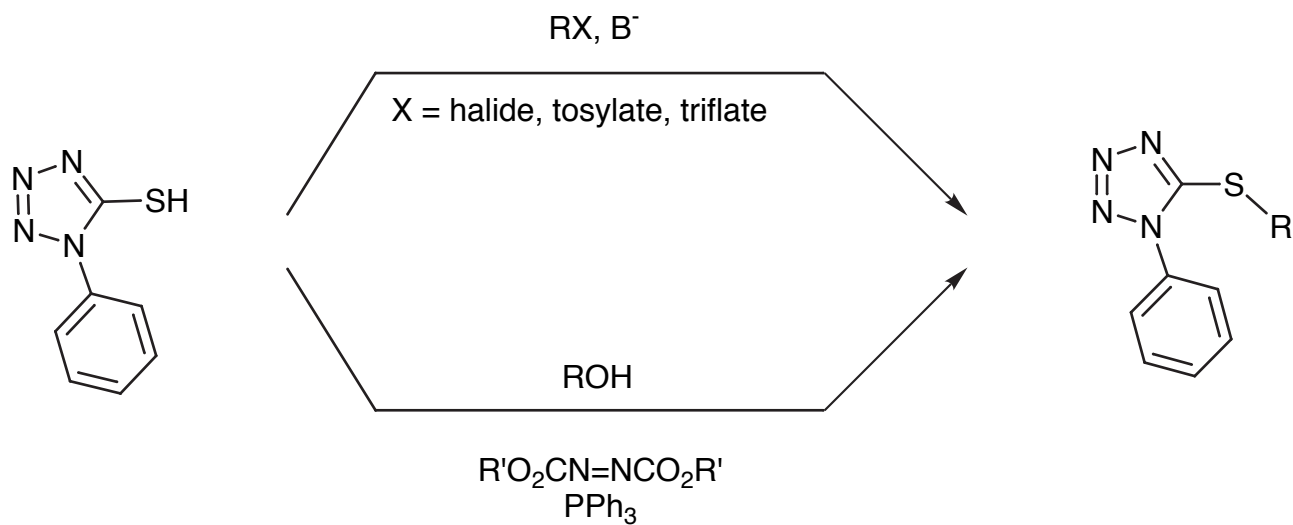


60% **4:96**

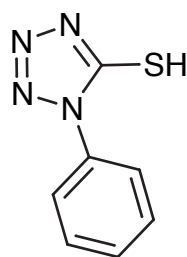
Diastereoselectivity of TBT-Sulfones



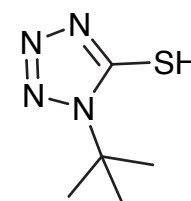
Sulfone Synthesis



2-mercaptobenzothiazole
100g = \$18.00

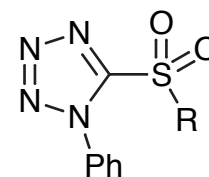
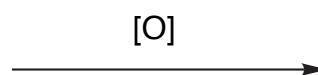
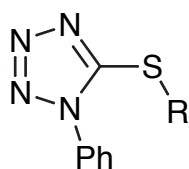


1-phenyl-1-*H*-tetrazole-5-thiol
25g = \$22.60



tert-butyl isothiocyanate; 25g = \$57.80
Sodium azide; 25g = \$51.90

Sulfone Synthesis



MCPBA

$(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O} / \text{H}_2\text{O}_2$ Mo(VI)

$\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O} / \text{H}_2\text{O}_2$ W(VI)

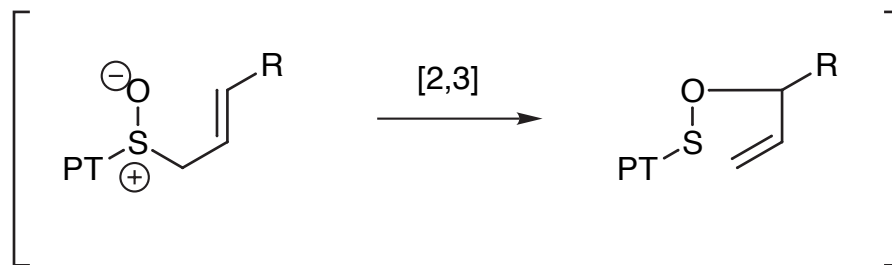
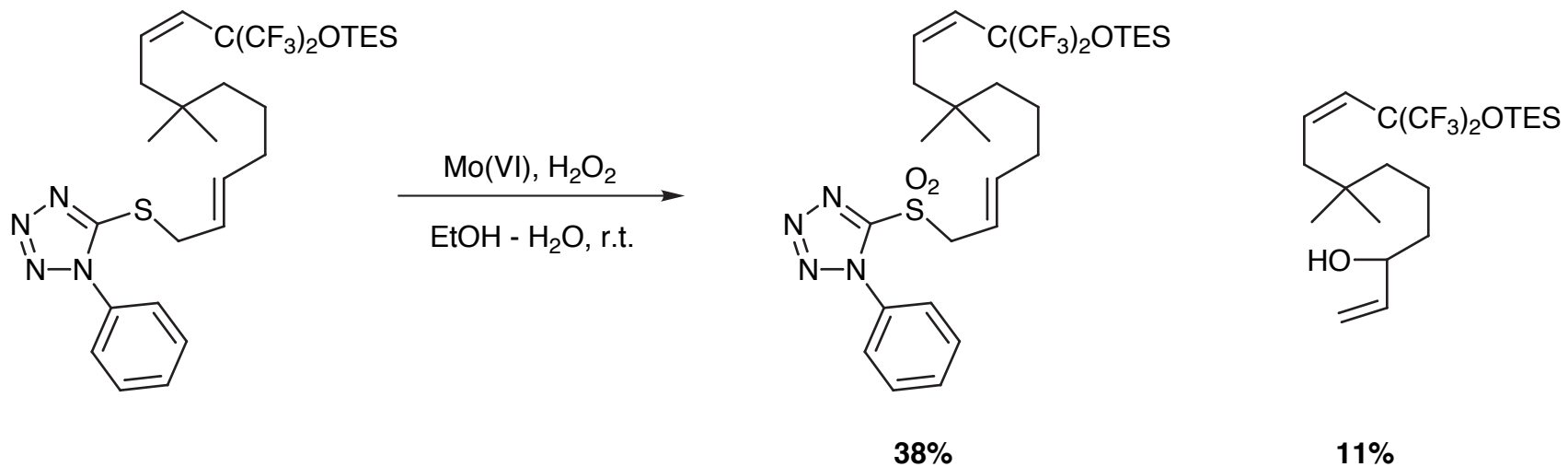
Oxone

$\text{CH}_3\text{CO}_3\text{H}$

KMnO_4

P.R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2563

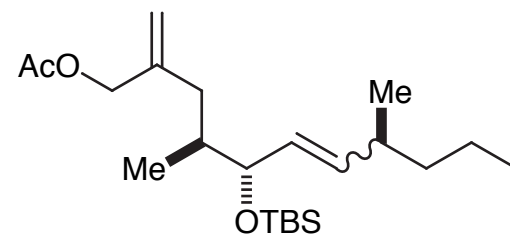
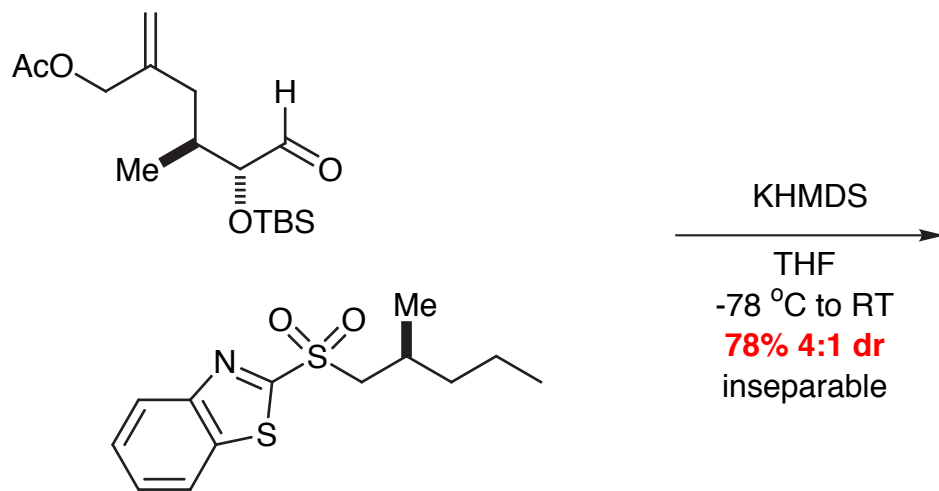
Oxidation Problems - Allylic Sulfones



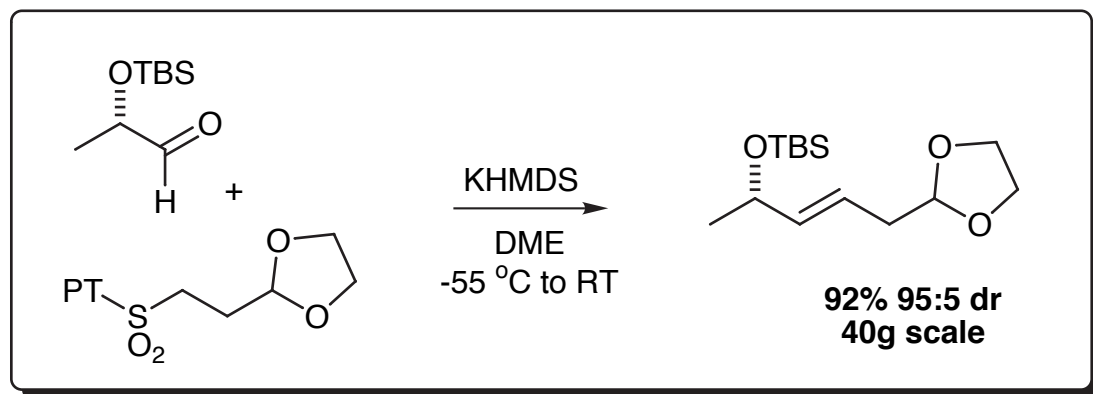
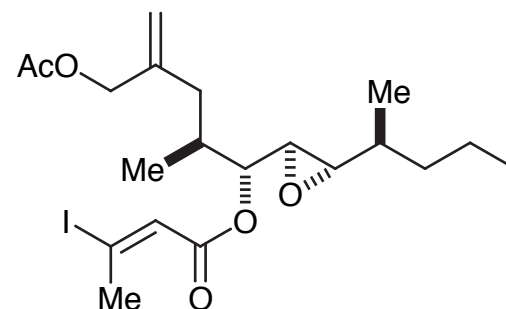
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Synthesis of the Proposed Structure of Amphidinolide-A

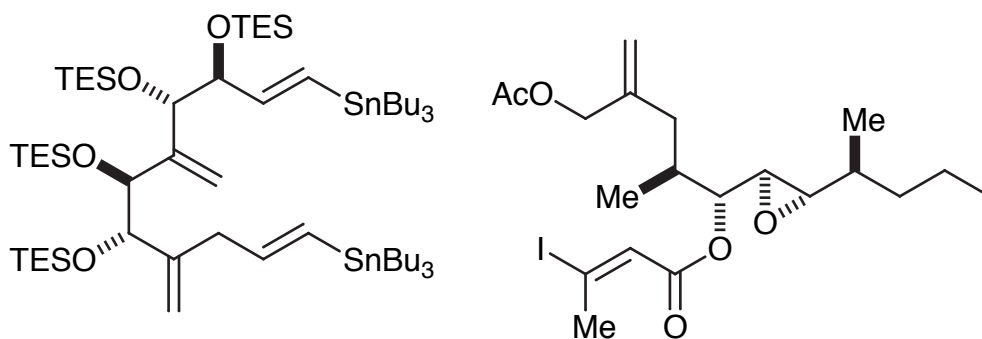


- 1) HF-pyr (separate isomers)
- 2) *t*-BuOOH, Ti(O*i*Pr)₄
- 3) EDC, DMAP, CH₂Cl₂, (*E*)-iodobut-2-enoic acid

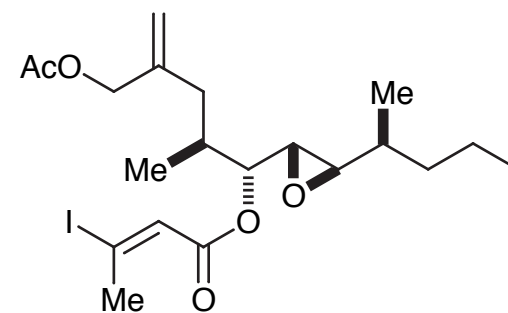
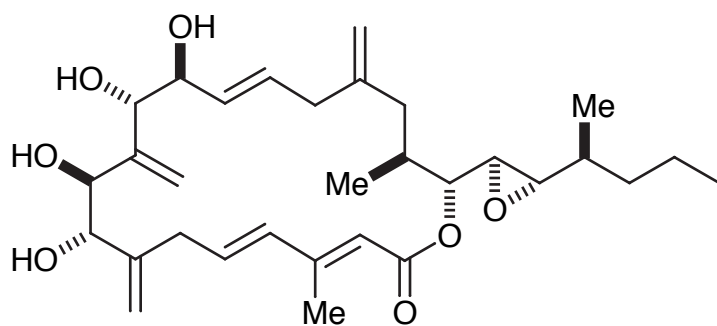


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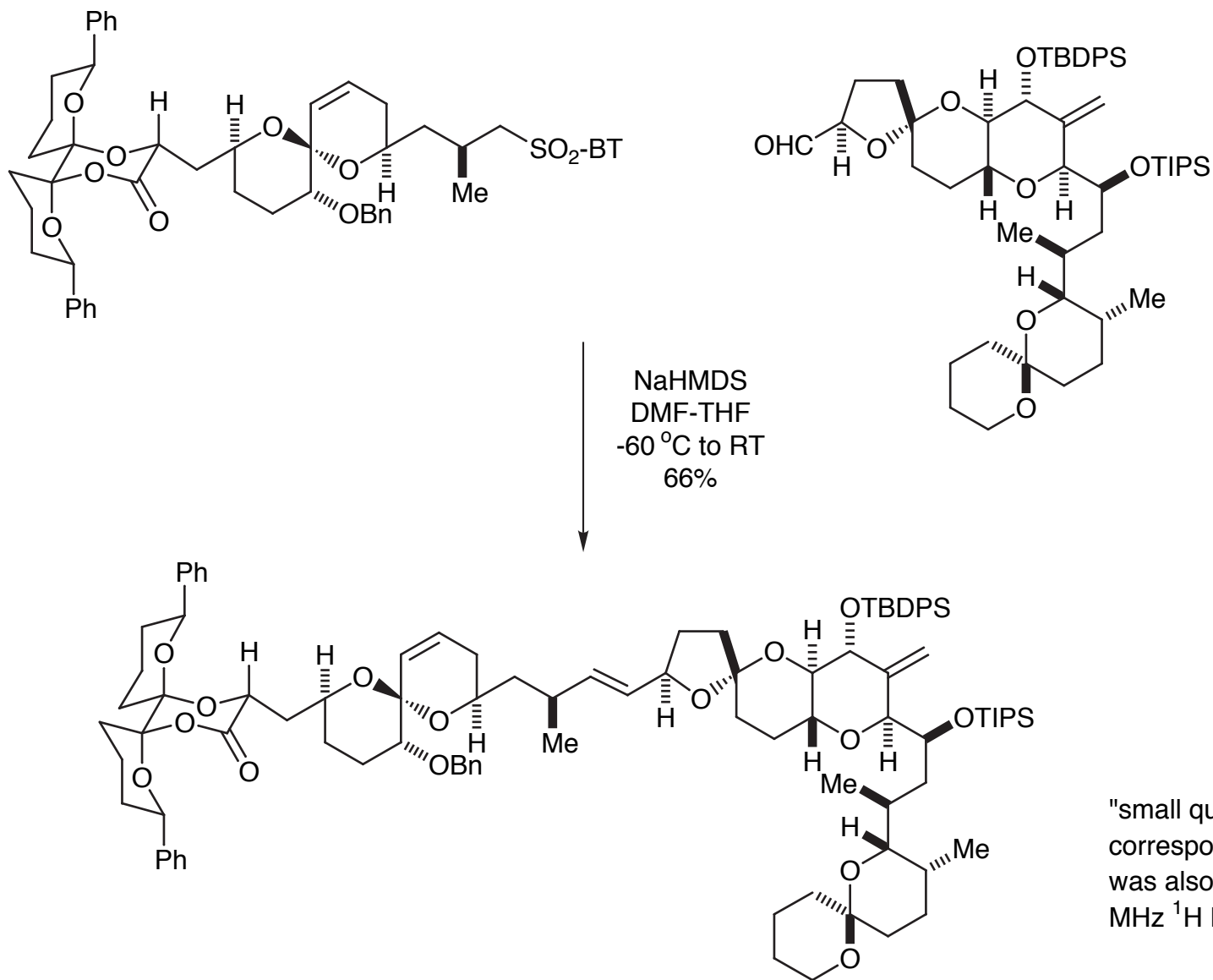
Synthesis of Proposed Structure of Amphidinolide-A



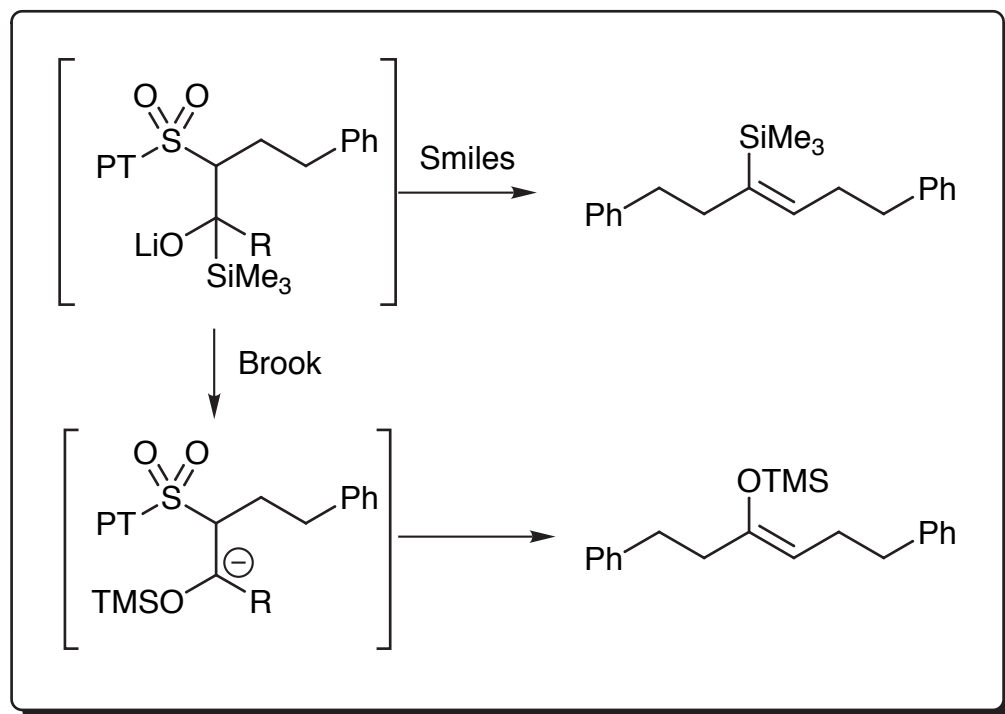
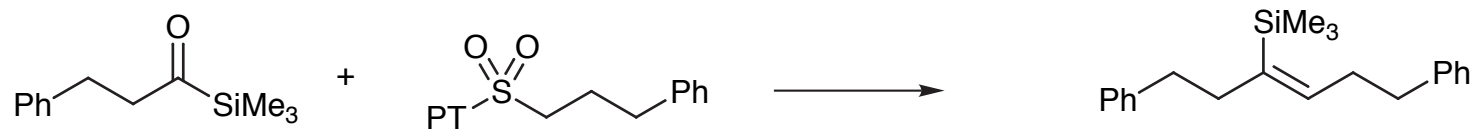
- 1) $\text{Pd}_2(\text{dba})_3$, Ph_3As
- 2) PPTS
- 3) $\text{Pd}_2(\text{dba})_3$, Ph_3As , LiCl



Synthesis of Okadaic Acid



Synthesis of Vinylsilanes



M-HMDS	temp	yield	<i>E</i> : <i>Z</i>
Li	-78 °C	93%	64:36
Li	-85 °C	89%	74:26
Li	-95 °C	84%	75:25
Na	-78 °C	50%	59:41
K	-78 °C	NA	NA

J. Wicha, et al., *Org. Lett.*, 2003, 5, 2789

35-vinylsilanes.cdx 9/25/03 11:37 AM