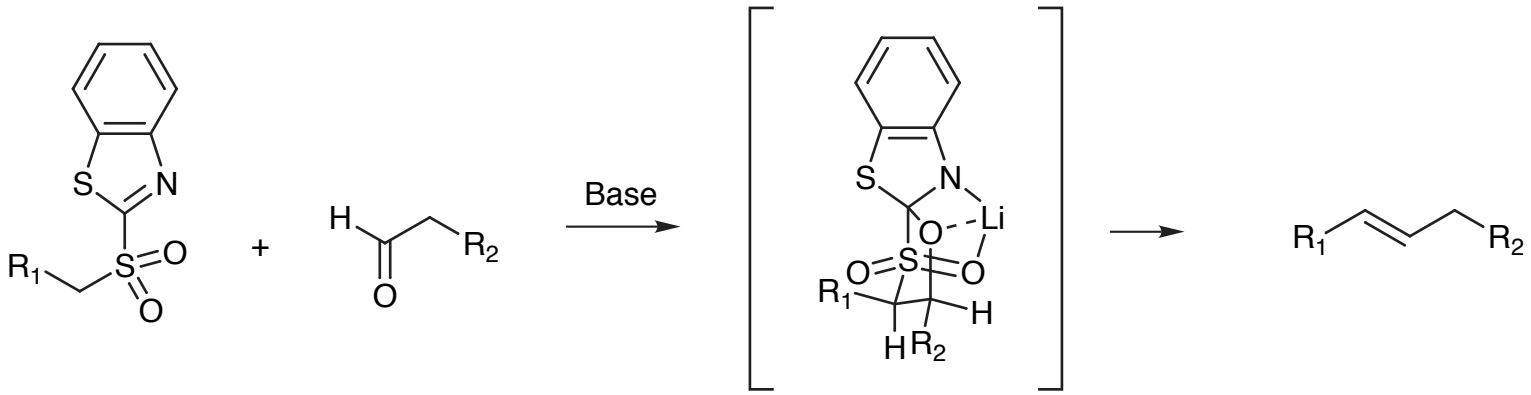


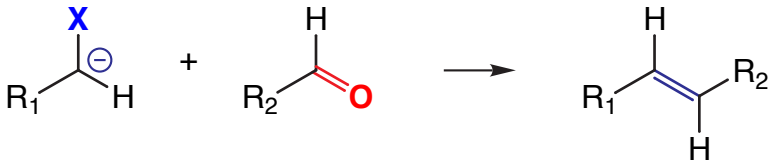
Overview of the Julia-Kocienski Olefination

Evans' Group Literature Seminar

Scott Peterson

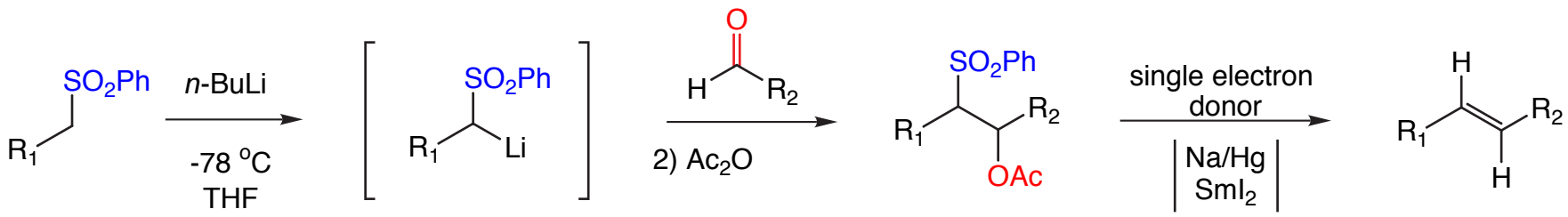
Sept. 26, 2003

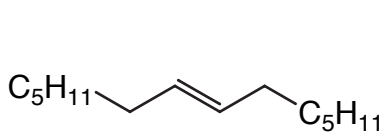
Examples of Direct Olefination from Carbonyl Compounds



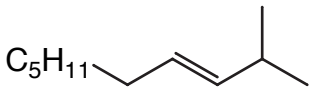
	X	Reaction
B.E Maryanoff, A.B. Reitz, *Chem. Rev.*, 1989, **89**, 863	R_3P^+	*Wittig*
	$R_2P(=O)$	*Horner-Wittig*
	$(RO)_2P(=O)$	*Horner-Wadsworth-Emmons*
L.F. van Staden, D Gravstock, D.J. Ager,*Chem. Soc. Rev.*, 2002, **31**, 195	R_3Si	*Peterson*
	ArS(=O)(=NMe)	*Johnson*
P.R. Blakemore, *J. Chem. Soc., Perkin Trans. 1,* 2002, 2563	$ArSO_2$	*classical Julia*
	$HetSO_2$	*modified Julia*

Classical Julia Olefination

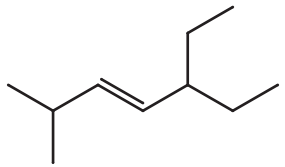




E:Z = 80:20



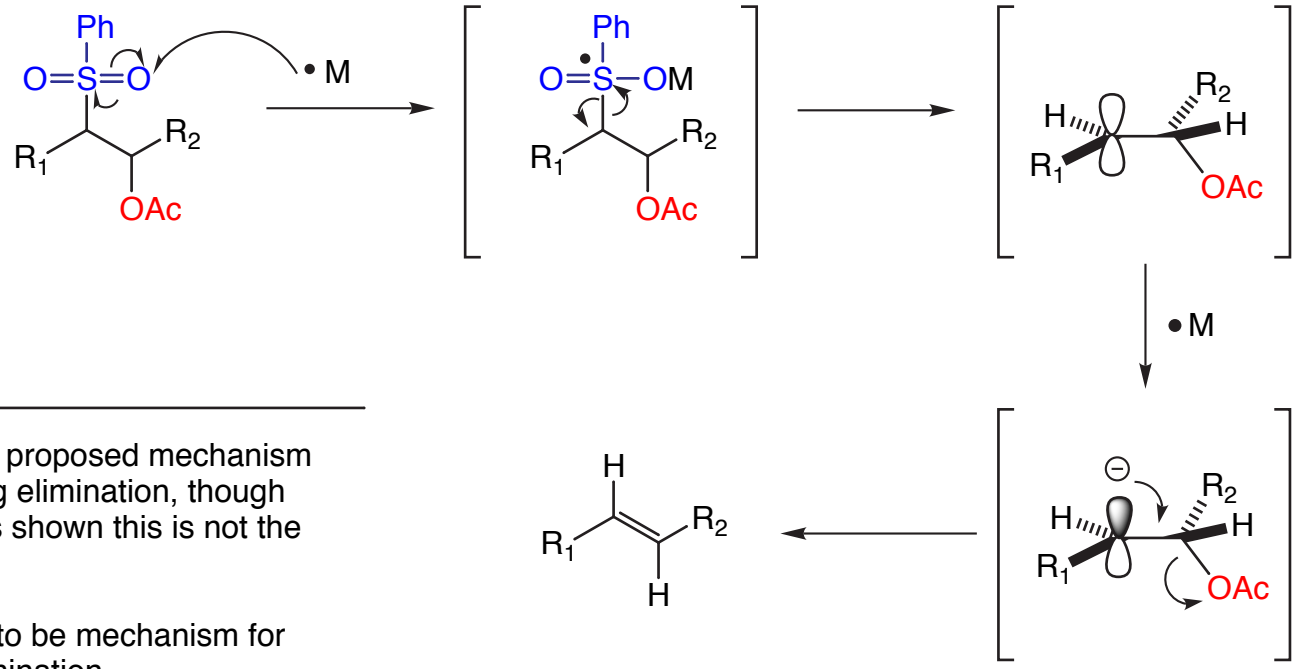
E:Z = 90:10



E:Z = >99:1

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

Mechanism of Olefin Formation

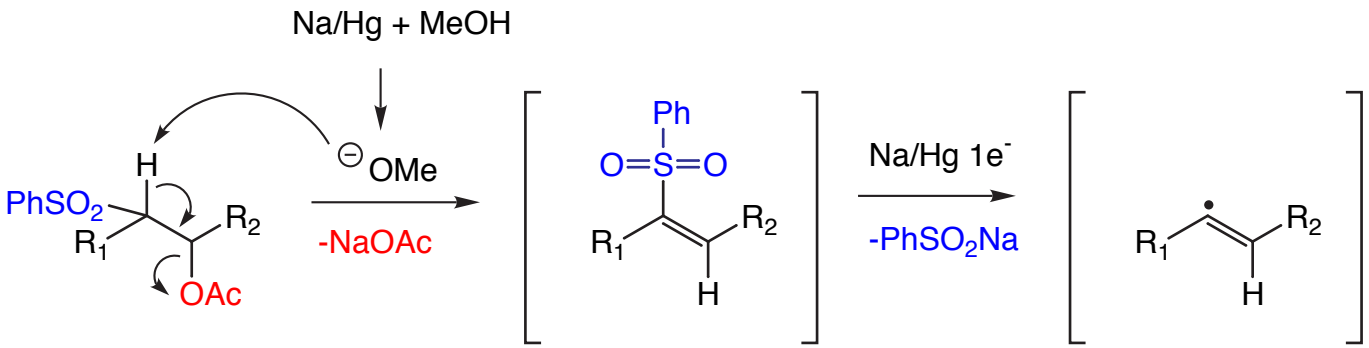


-Originally proposed mechanism for Na/Hg elimination, though Keck has shown this is not the case

-Believed to be mechanism for SmI_2 elimination

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

Mechanism of Olefin Formation

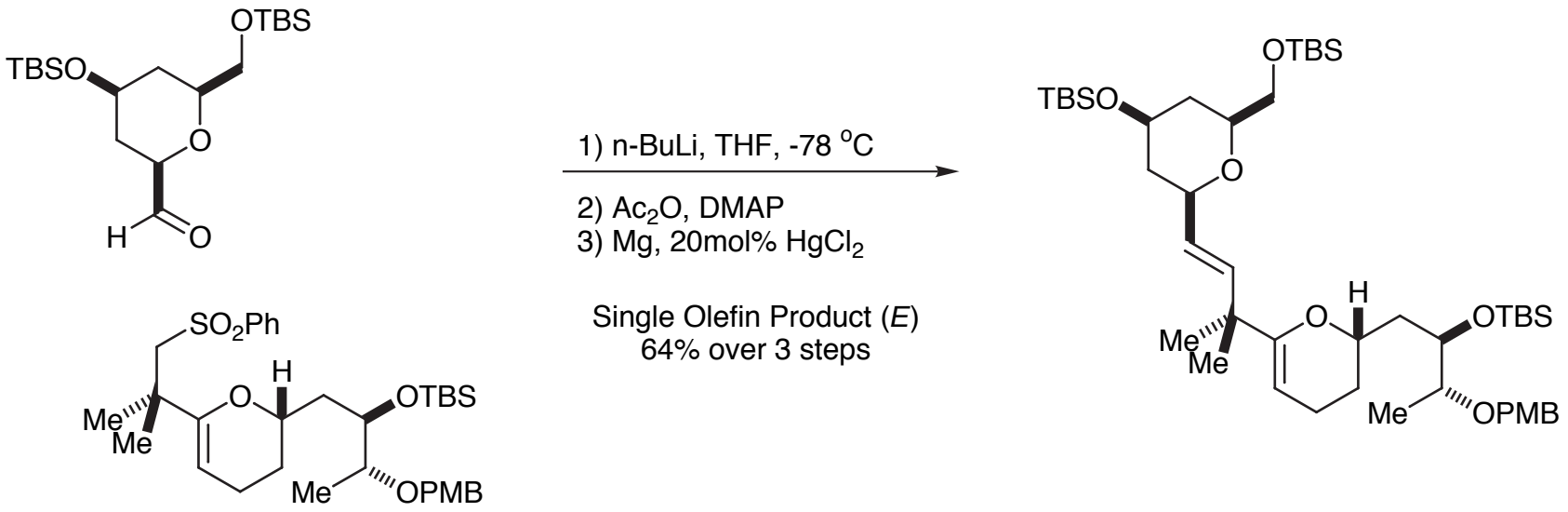


-Using MeOD results in >90% Deuterium incorpration

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

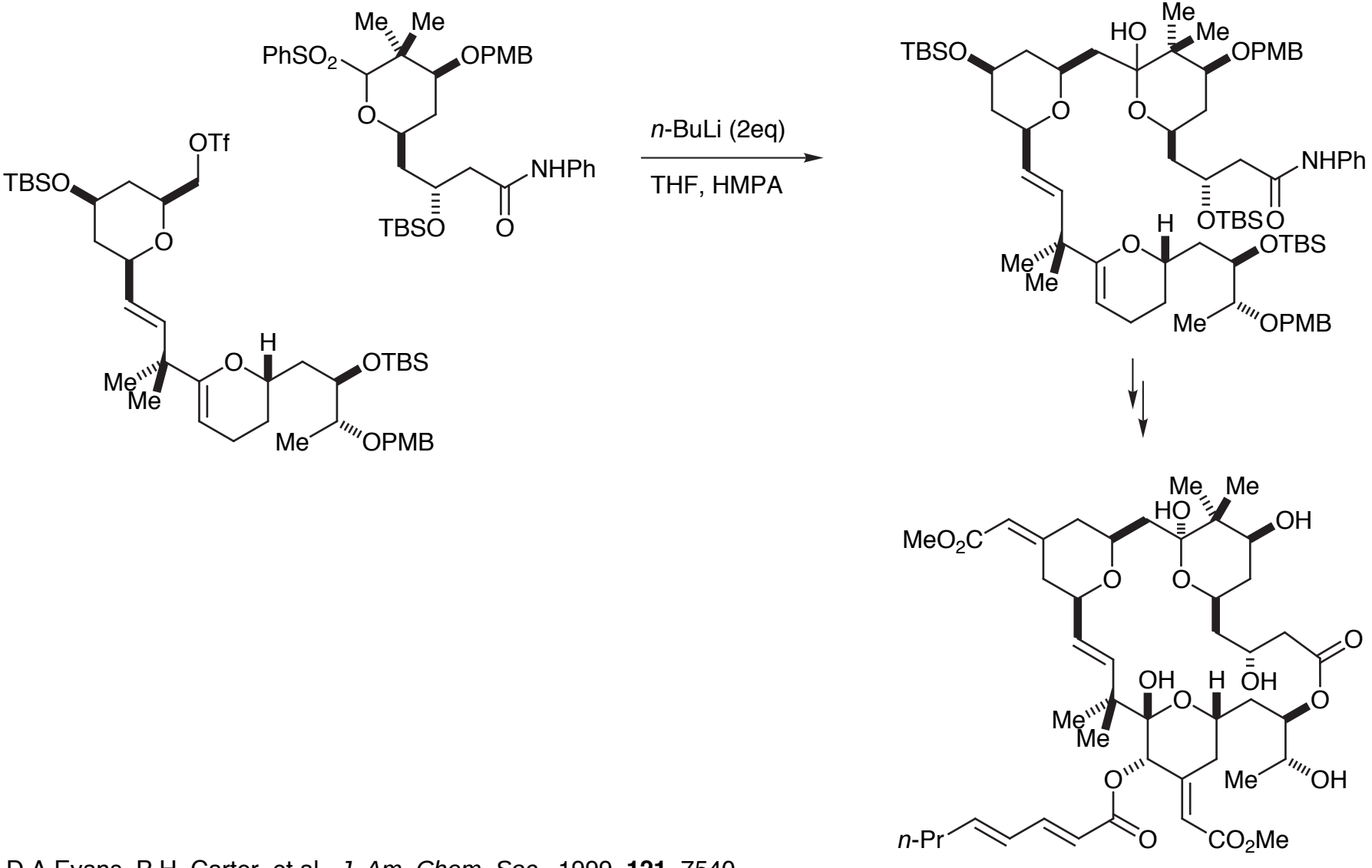
G.E. Keck et al., *J. Org. Chem.,* 1995, **60**, 3194

Synthesis of Bryostatin 2



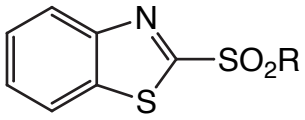
D.A.Evans, P.H. Carter, et al., *J. Am. Chem. Soc.,* 1999, **121**, 7540

Synthesis of Bryostatin 2

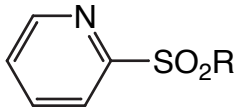


D.A.Evans, P.H. Carter, et al., *J. Am. Chem. Soc.,* 1999, **121**, 7540

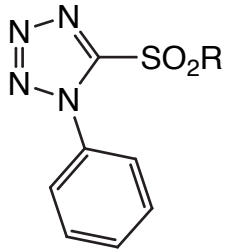
Modified Julia Olefination



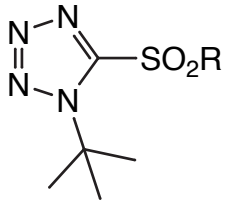
BT



PYR

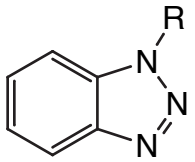


PT



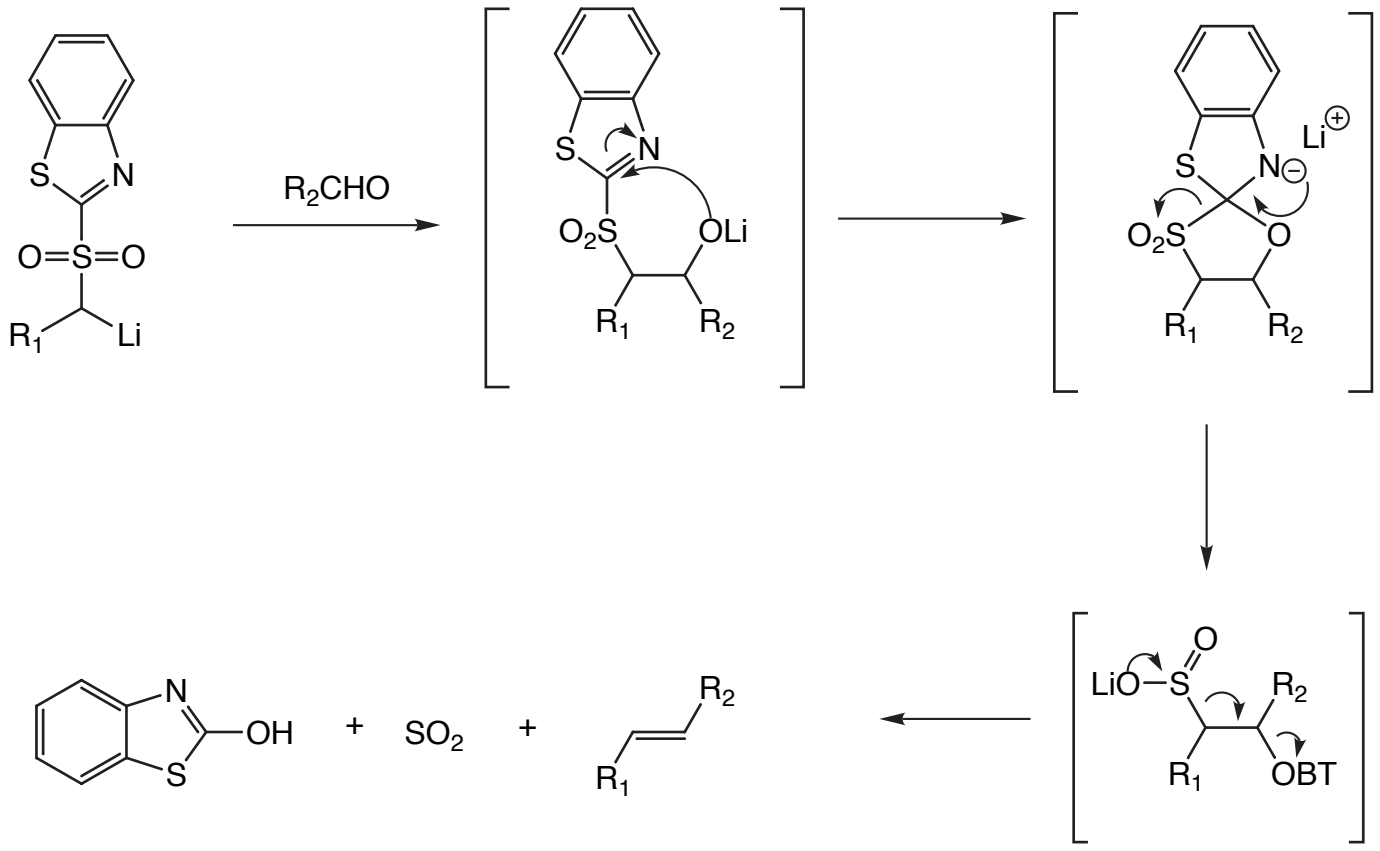
TBT

Bt =

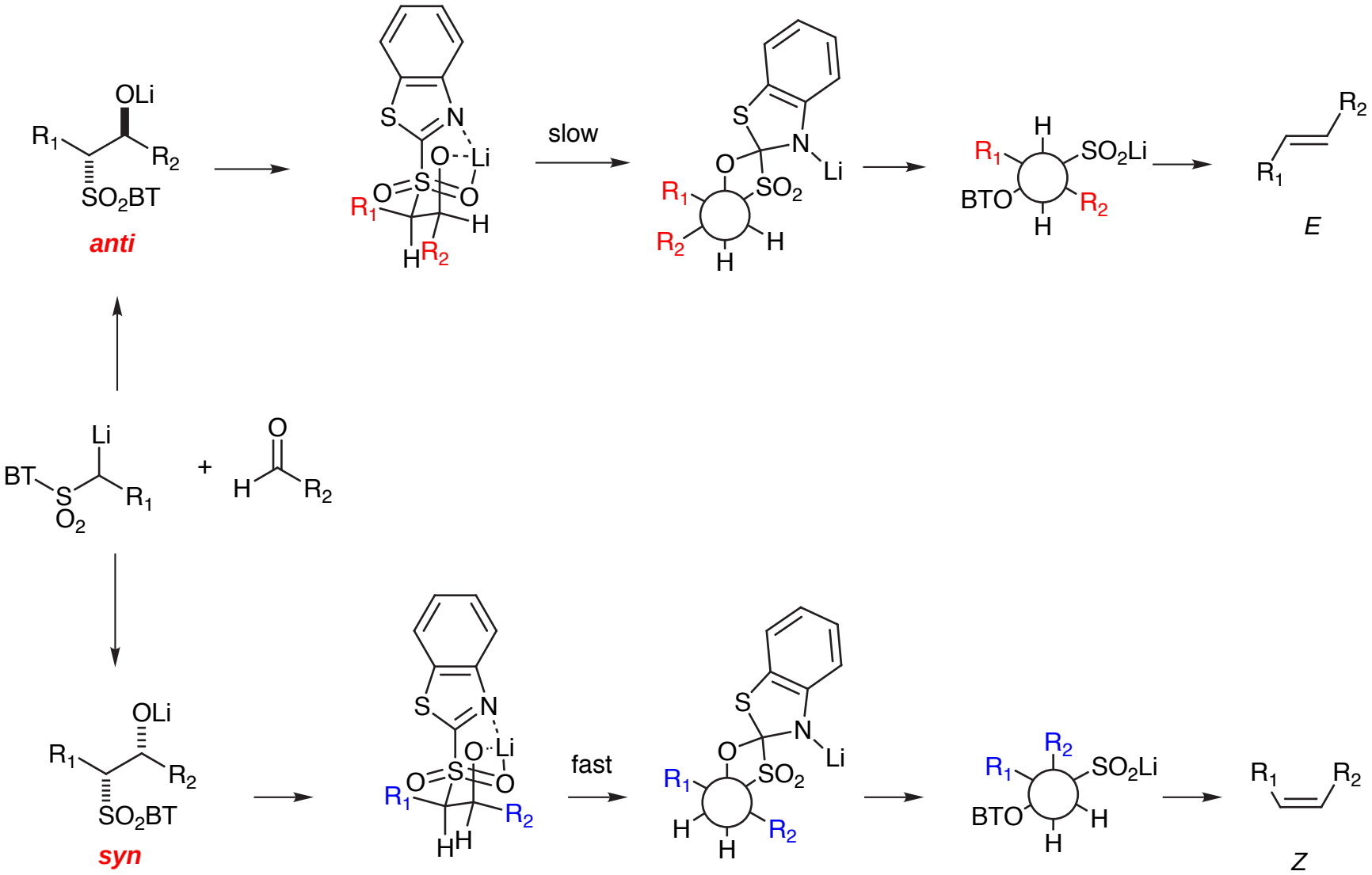


(benzotriazole)

Modified Julia Olefination - Smiles Rearrangement

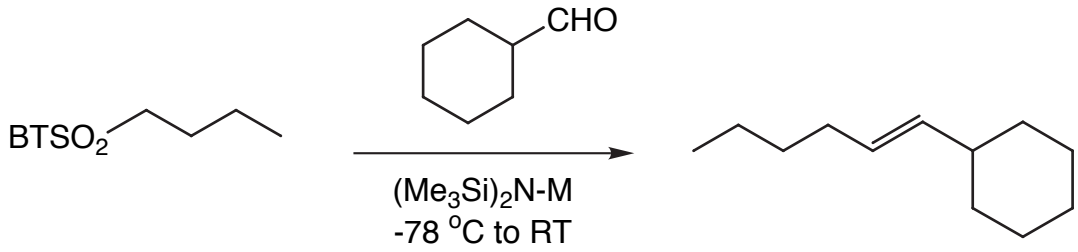


Diastereoselectivity of BT-Sulfones



J.B. Baudin, *Bull. Soc. Chim. Fr.,* 1993, **130**, 856

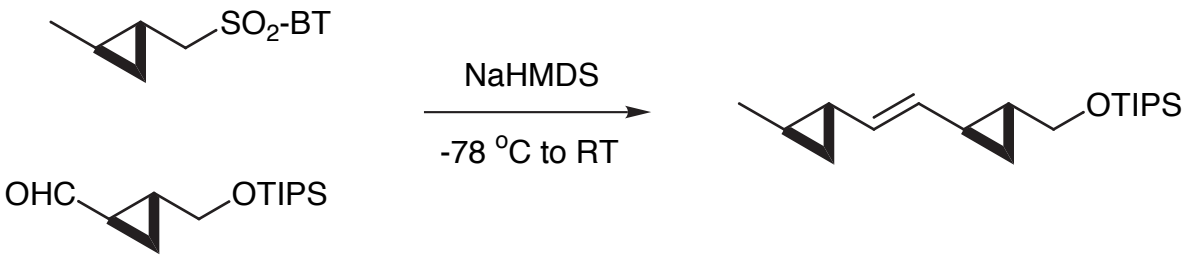
Effects of Solvent and Counterion with BT-Sulfone



M	Toluene	Et_2O	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

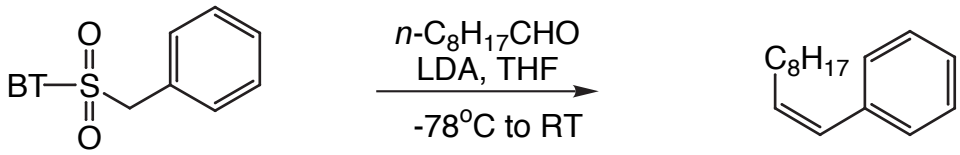
Solvent Screen in U-106305 Synthesis



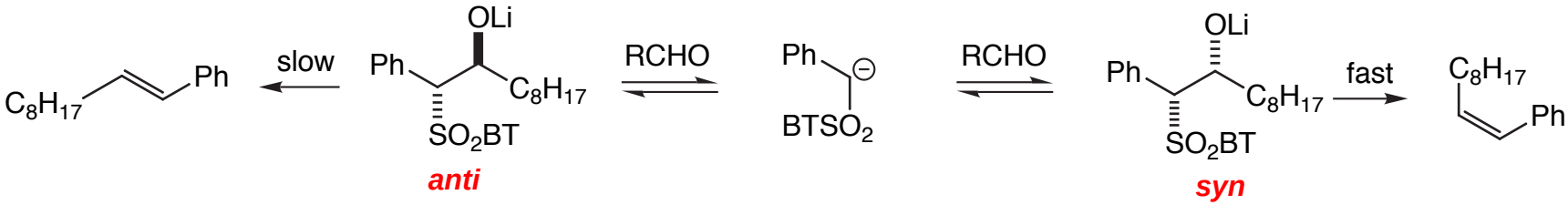
solvent	*E:Z*
toluene	9:91
CH_2Cl_2	9:91
Et_2O	11:89
THF	52:48
DME	71:29
DMF	78:22

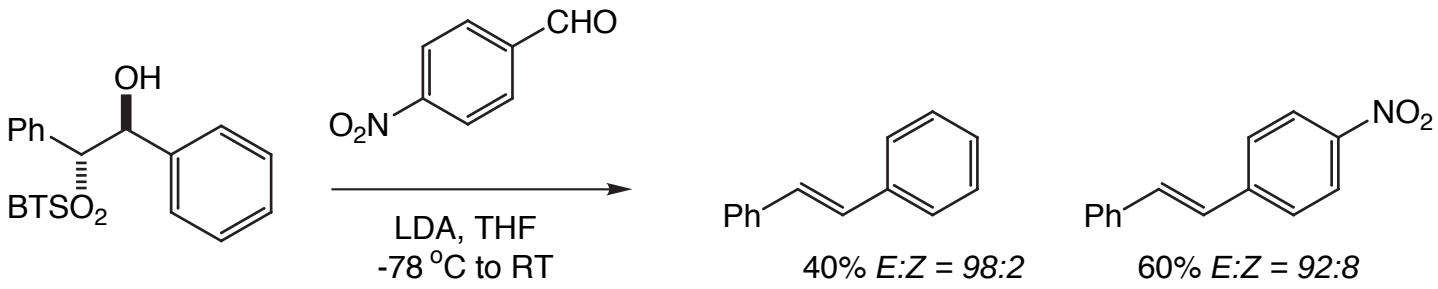
A.B. Charette, et al., *J. Am. Chem. Soc.*, 1996, **118**, 10327

Retroaddition - Addition with BT-Sulfone



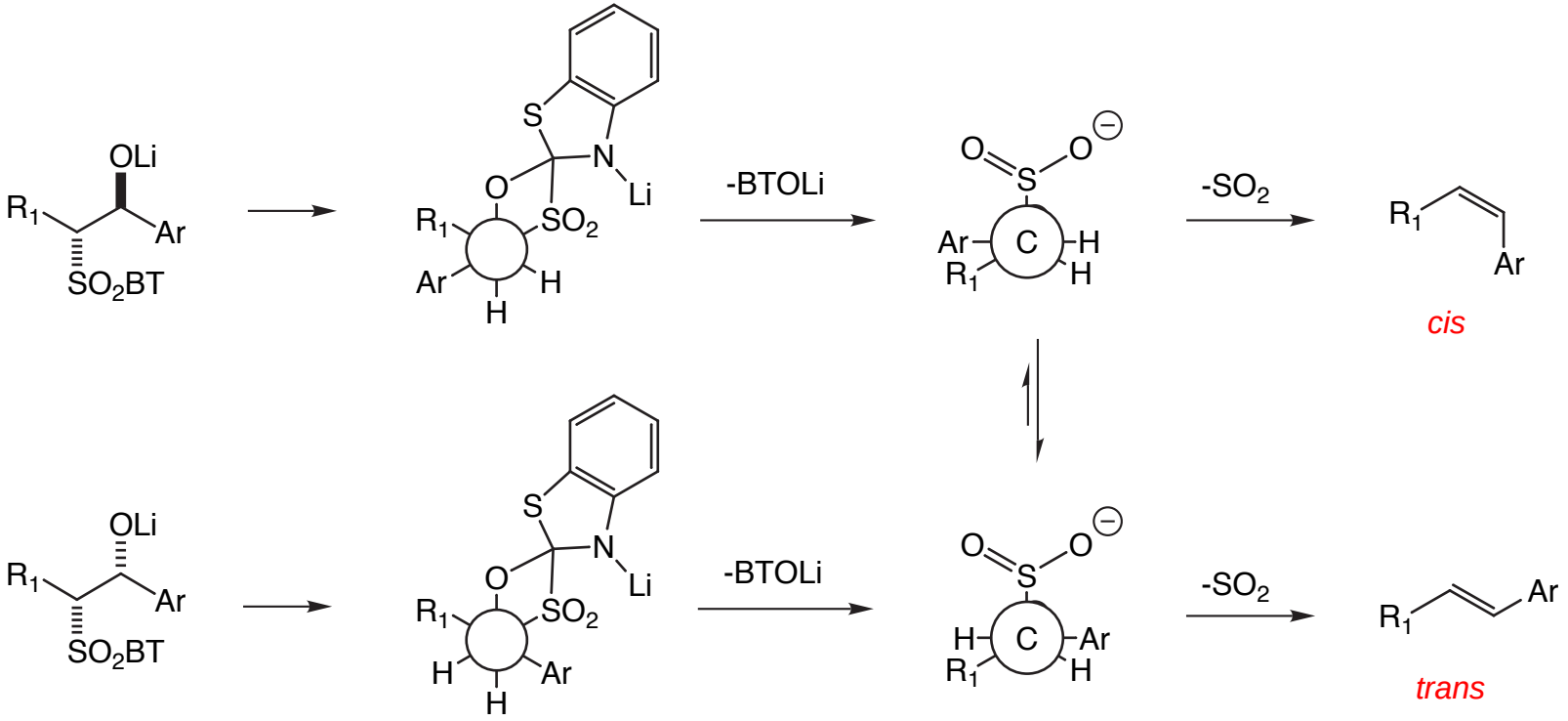
E:Z = 23:77

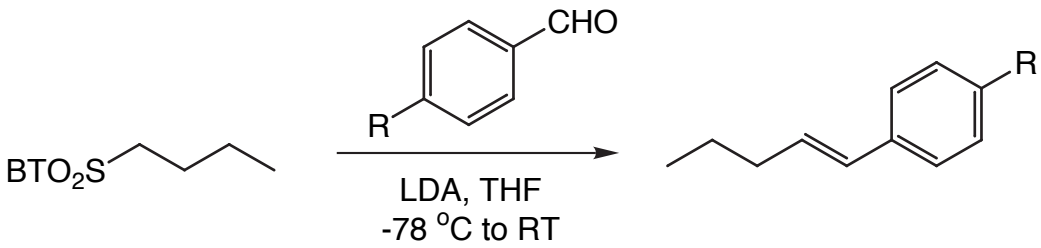




P.R. Blakemore, Ph.D. Thesis, University of Glasgow, Glasgow, 1999

Aromatic Aldehydes with BT-Sulfones

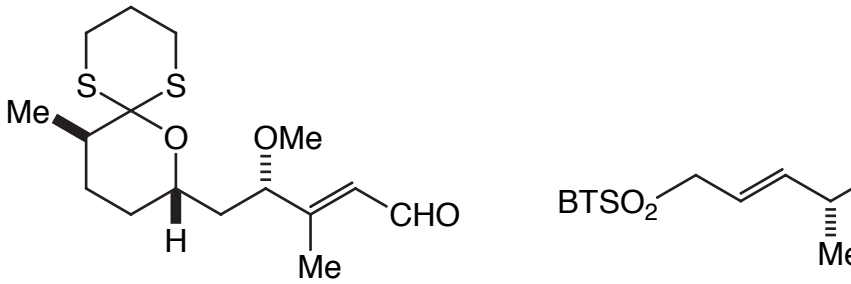




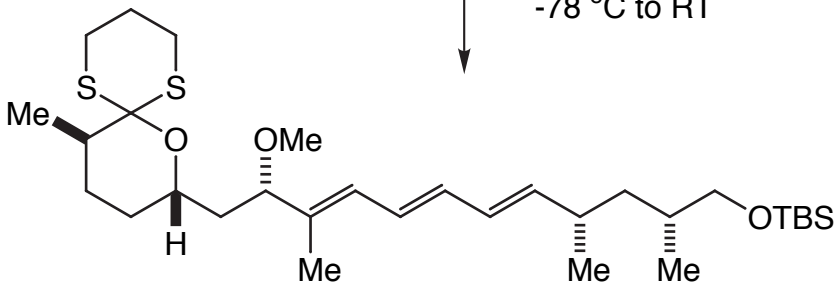
R	yield	E:Z
OMe	95%	99:1
H	68%	94:6
Cl	51%	77:23

J.B. Baudin, et al. *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

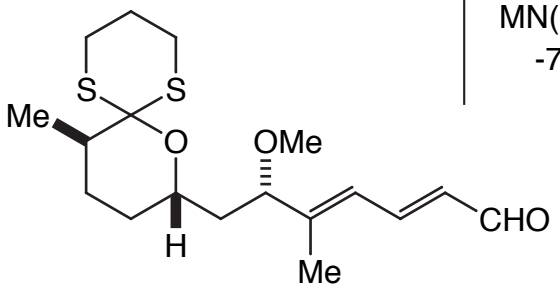
Reversibility in Rapamycin Synthesis

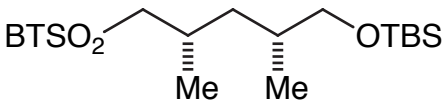


$MN(SiMe_3)_2$, THF
-78 °C to RT



$MN(SiMe_3)_2$, THF
-78 °C to RT



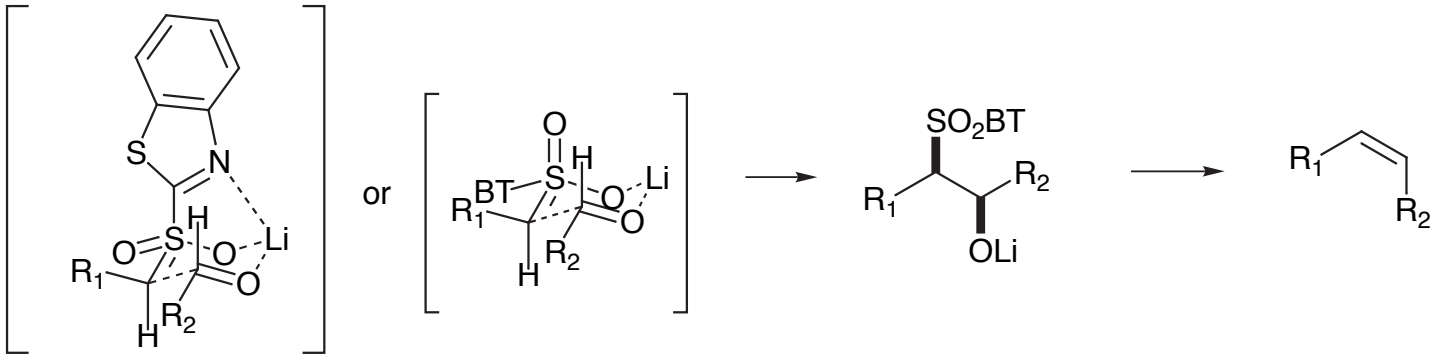


M	yield	*E:Z*
Li	75%	29:71
Na	79%	43:57
K	--	18:82

M	yield	*E:Z*
Li	68%	95:5
Na	21%	78:22

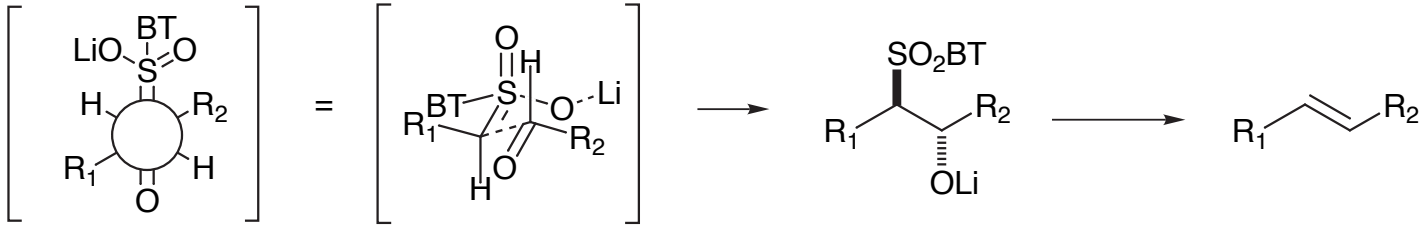
P. Kocienski, et al., *Synthesis*, 1996, 285

Possible Explanation for Diastereoselctivity



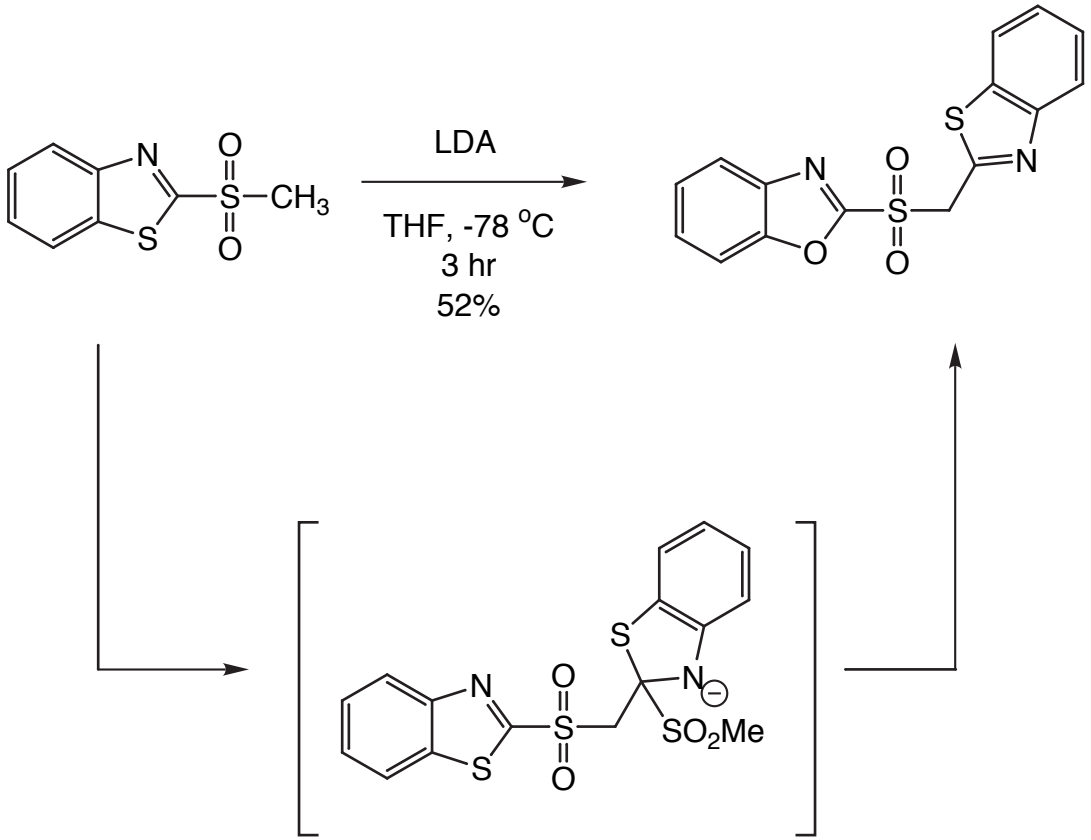
Chelate (closed) Transition State favored for non-polar solvents, small counter-ions (Li)

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



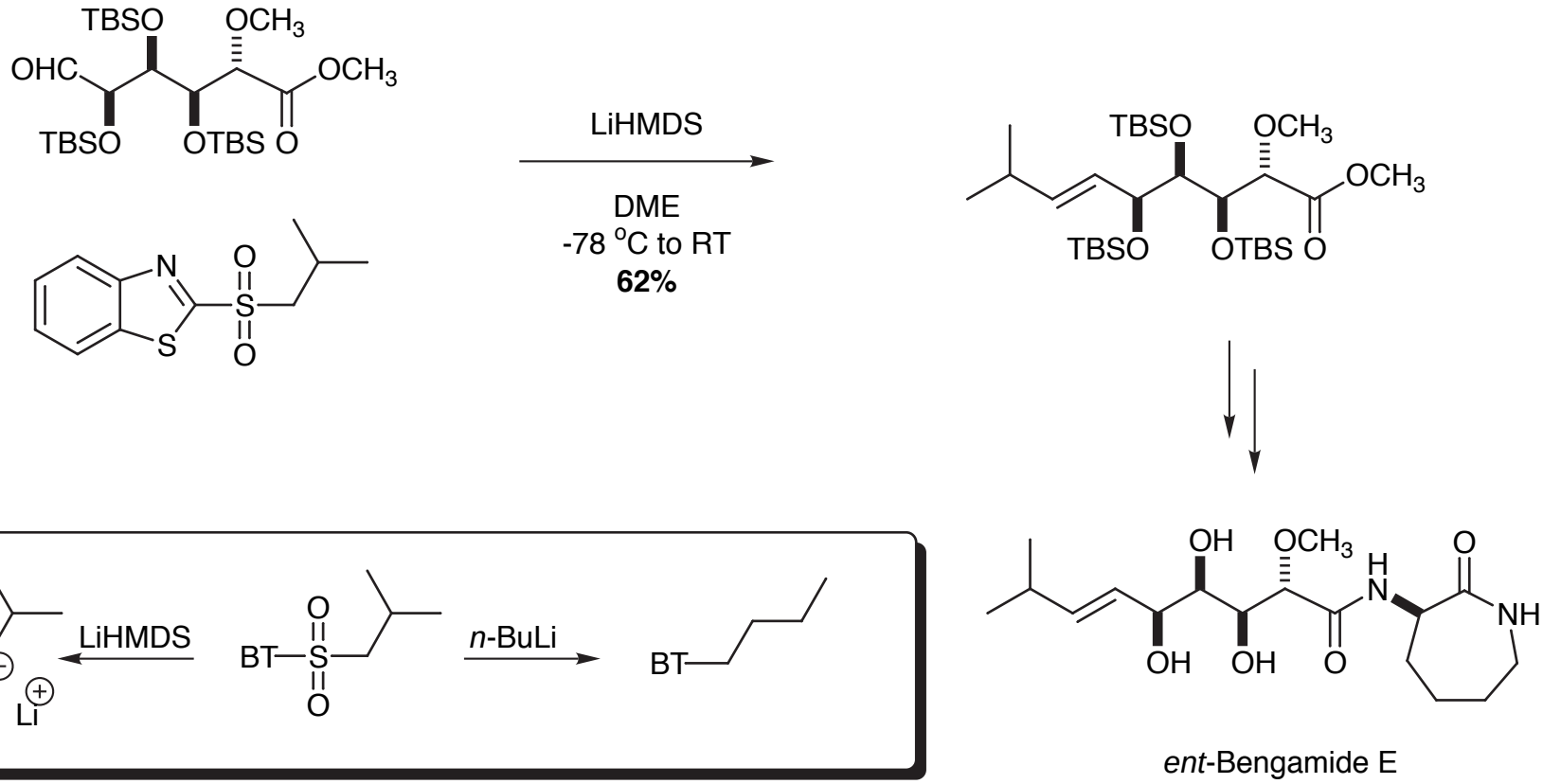
S. Peterson, *Meandering Thoughts,* 2003

Ipso Substitution with BT-Sulfones



J.B.Baudin, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

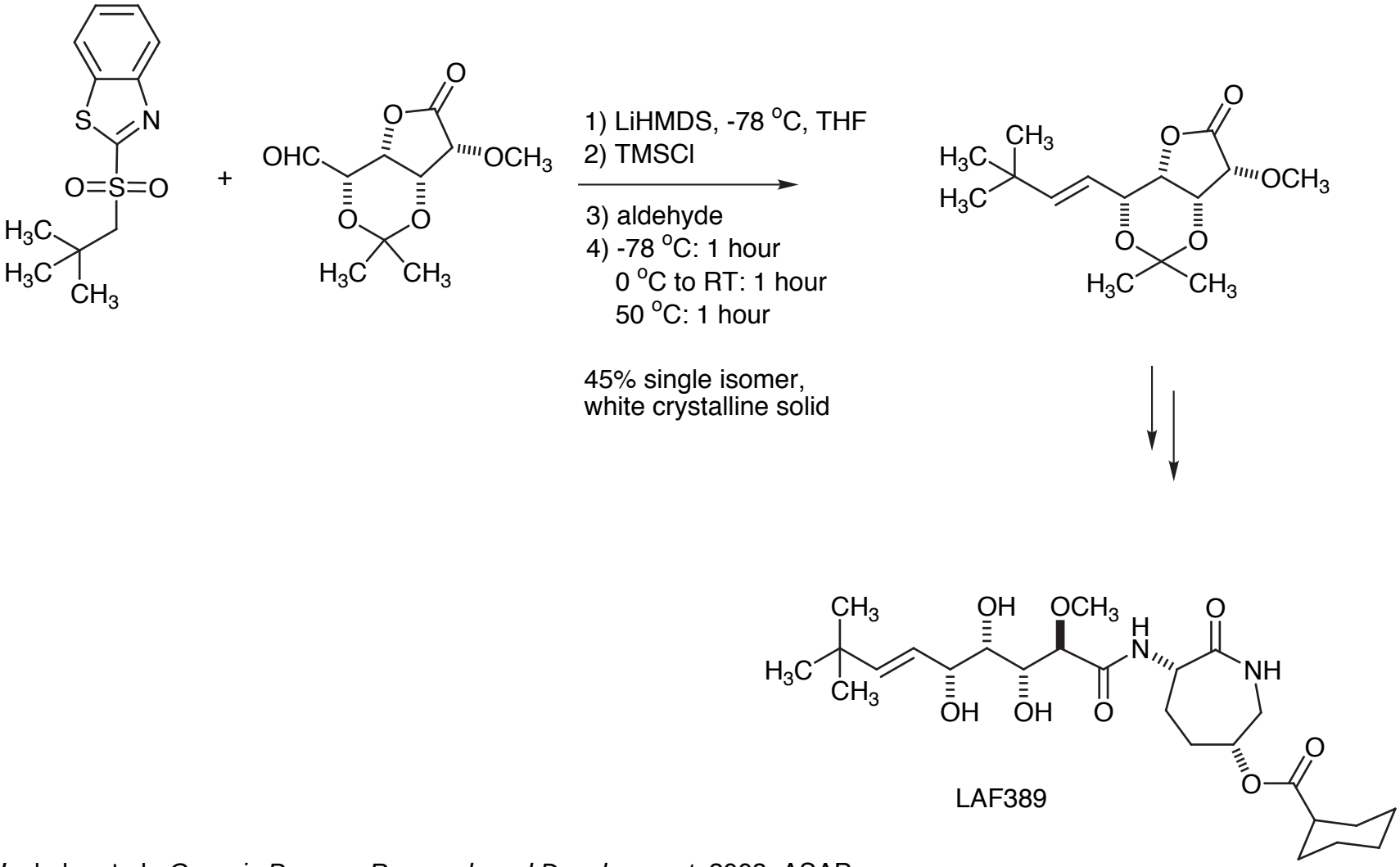
Synthesis of ent-*Bengamide E*



ent-Bengamide E

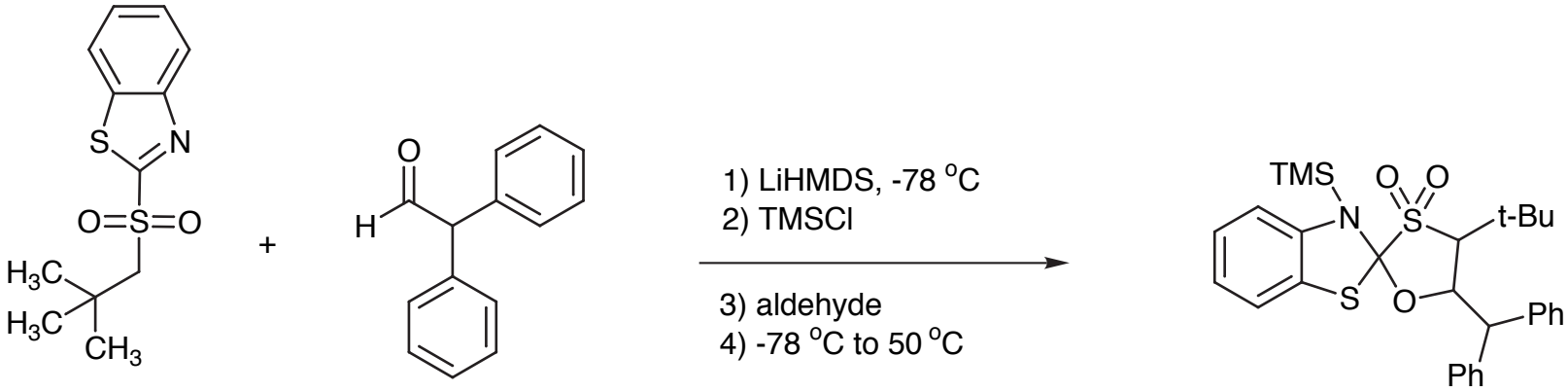
K.J.McRae, PhD Thesis, Research School of Chemistry, Canberra, 2001
J.B.Baudin, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 856

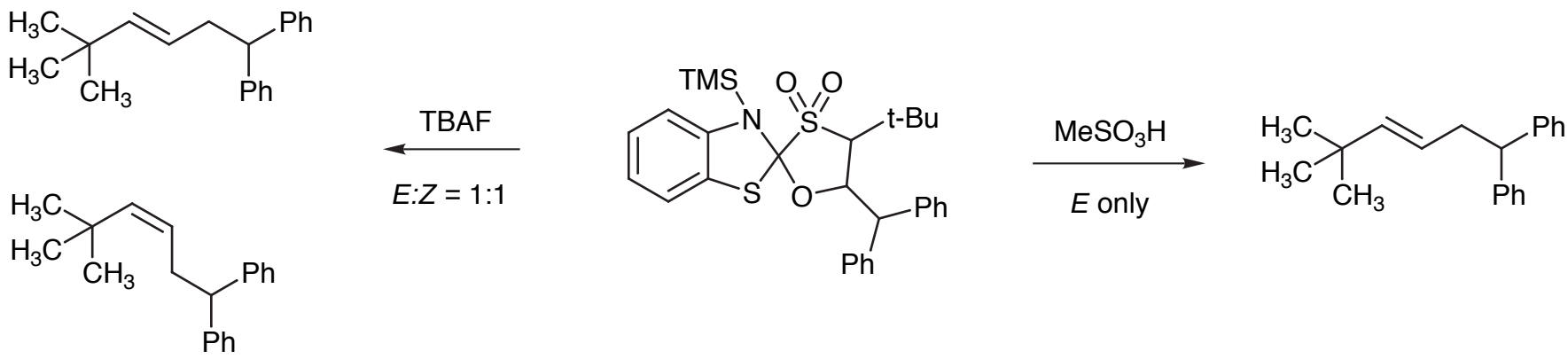
Synthesis of LAF389



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

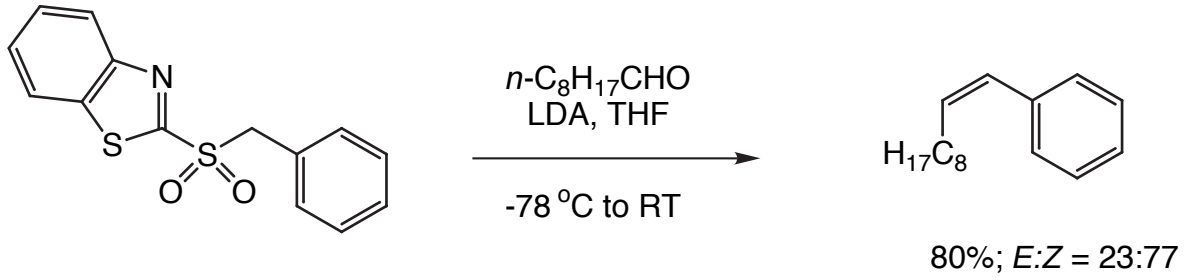
Synthesis of LAF389

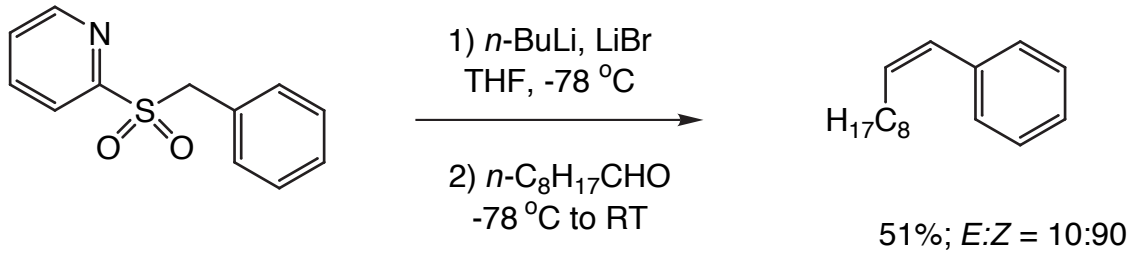




L. Waykole, et al., *Organic Process Research and Development*, 2003, ASAP
(Novartis Process Group)

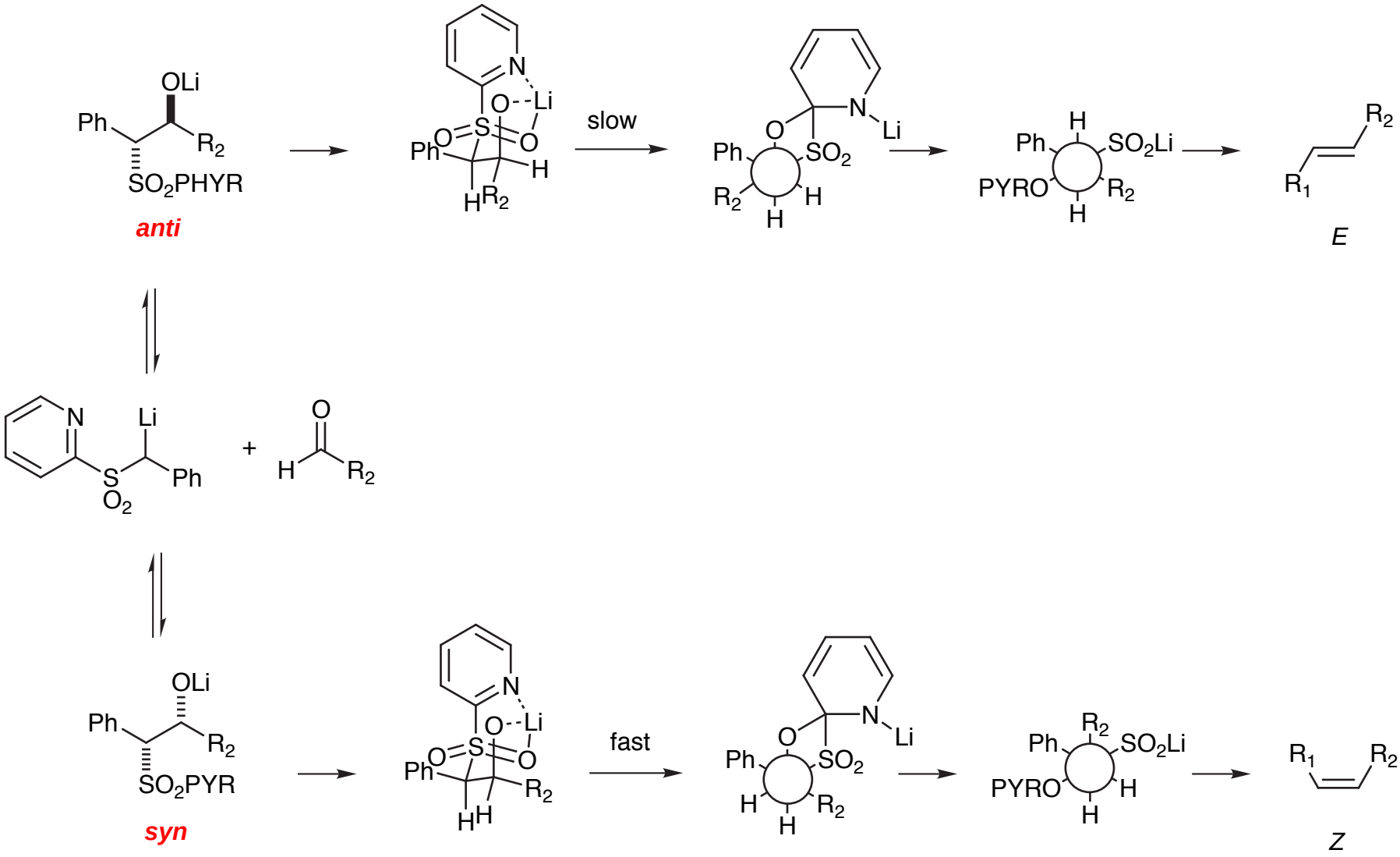
Pyridinyl (PYR) Sulfones - Higher cis Selectivities



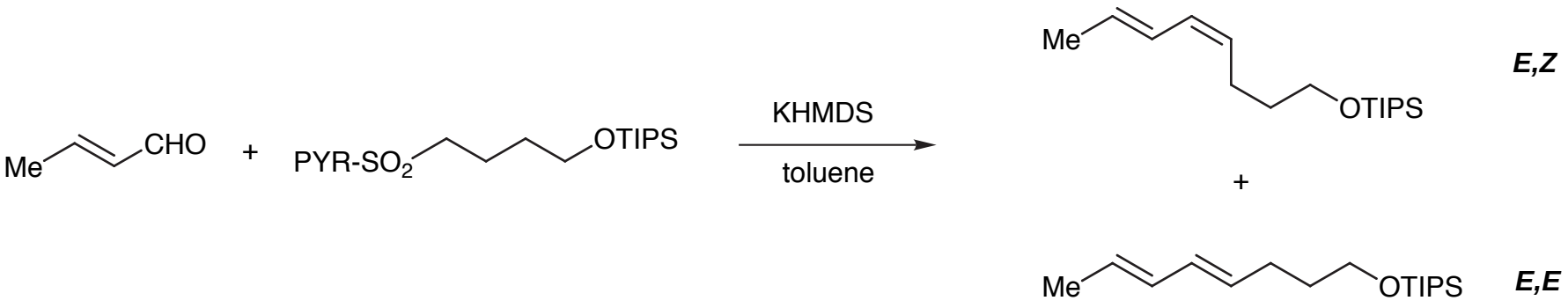


S. A. Julia, et al., *Bull. Soc. Chim. Fr.*, 1993, **130**, 336

Diastereoselectivity of PYR-Sulfones



Pyridinyl (PYR) Sulfones Examples

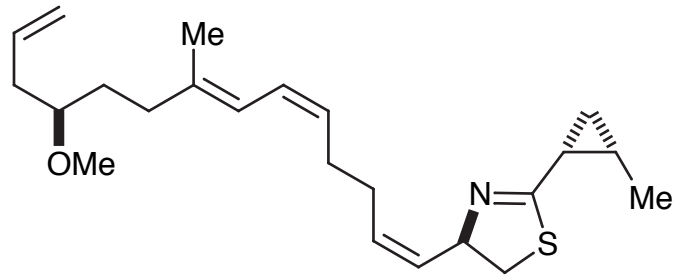


temp	yield	Ratio *E,Z : E,E*
-78 °C	35%	84:16
0 °C	53%	90:10
25 °C	67%	91:9

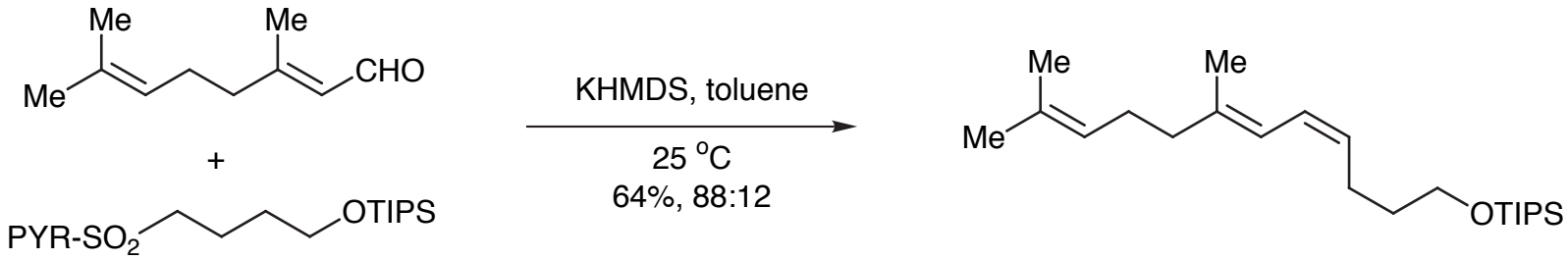
Potassium metallate is stable at RT for 5 min!

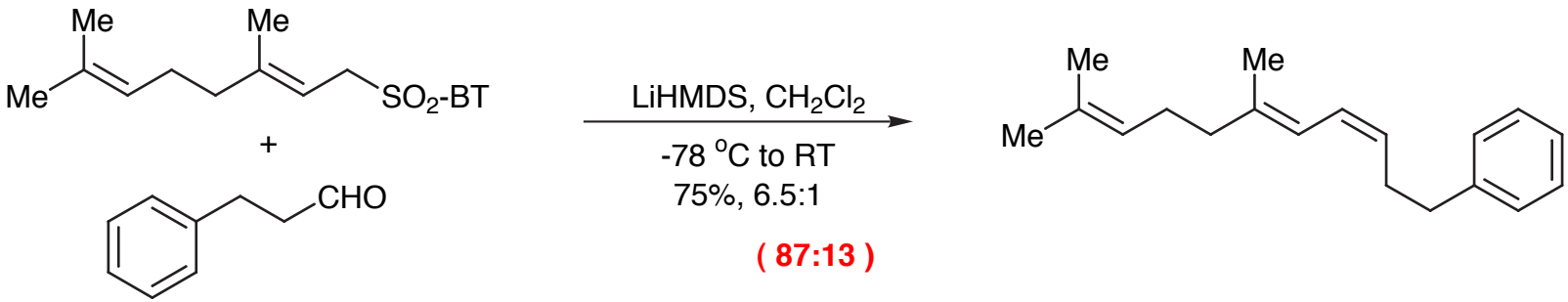
A. B. Charette, et al., *Tet Lett*, 2001, **42**, 5149

Pyridinyl (PYR) Sulfones Examples



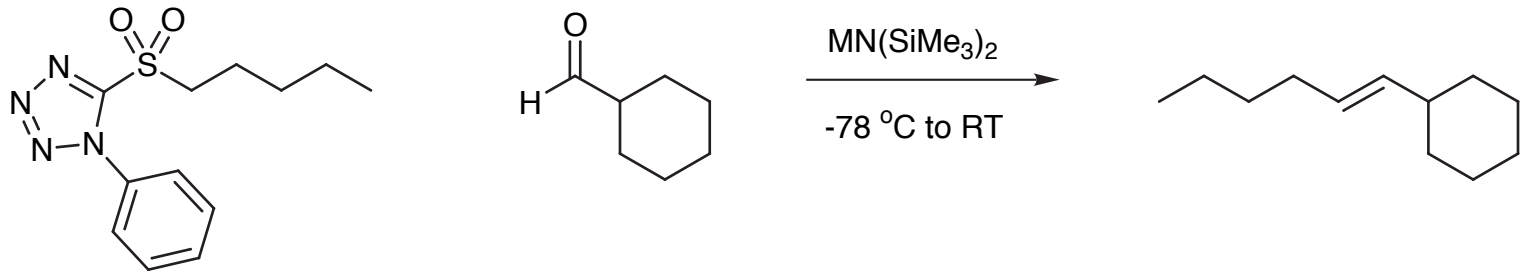
Curacin B



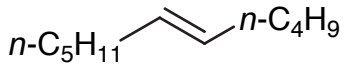


A. B. Charette, et al., *Tet Lett*, 2001, **42**, 5149

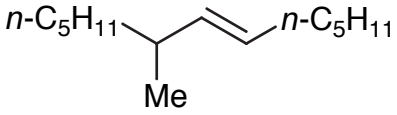
1-Phenyl-1H-tetrazol-5-yl Sulfones



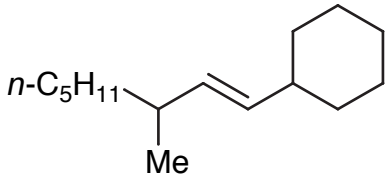
M	toluene	Et_2O	THF	DME
Li	51:49	61:39	69:31	72:28
Na	65:35	65:35	73:27	89:11
K	77:23	89:11	97:3	99:1



E:Z = 94:6



E:Z = 96:4

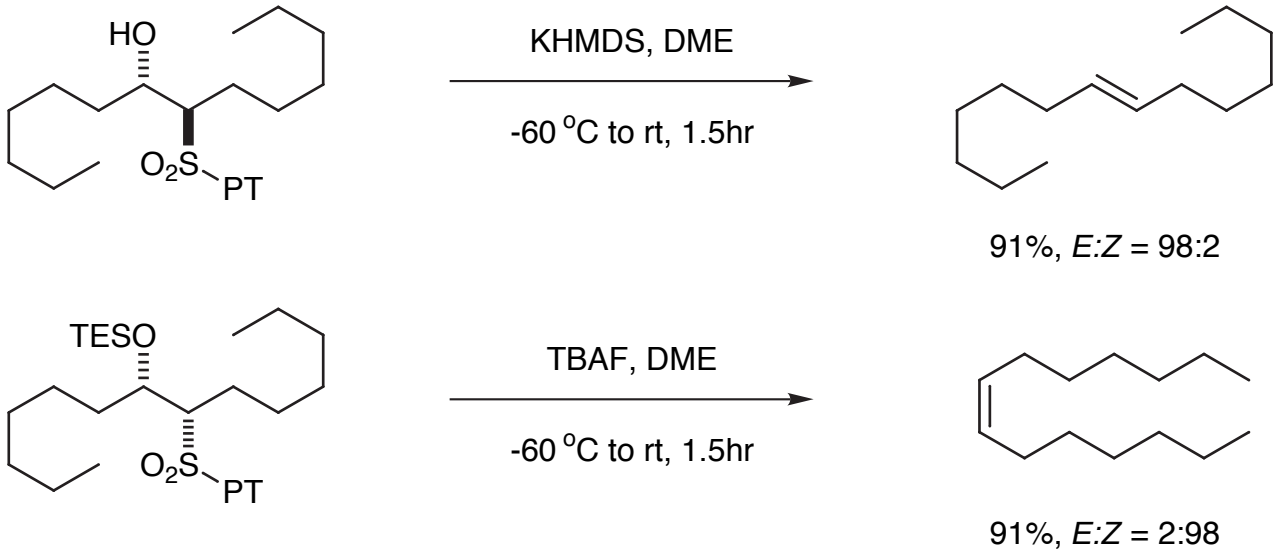


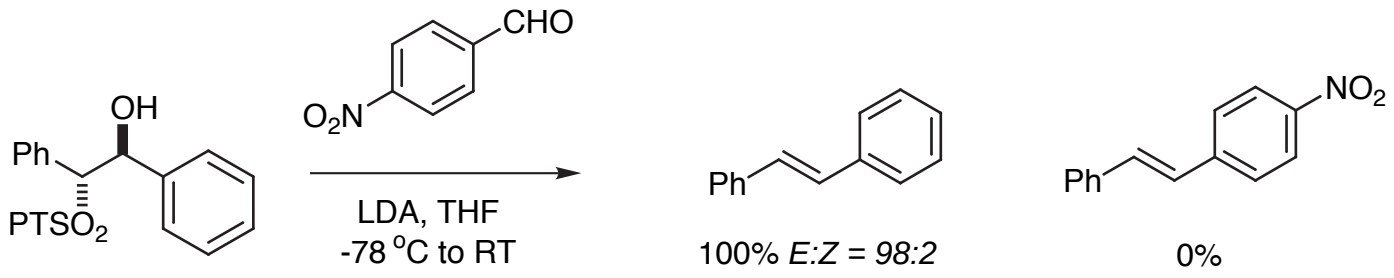
E:Z = 99:1

1.5eq aldehyde
KHMDS, DME -78 °C to RT

P.J. Kocienski, et al., *Synlett*, 1998, 26

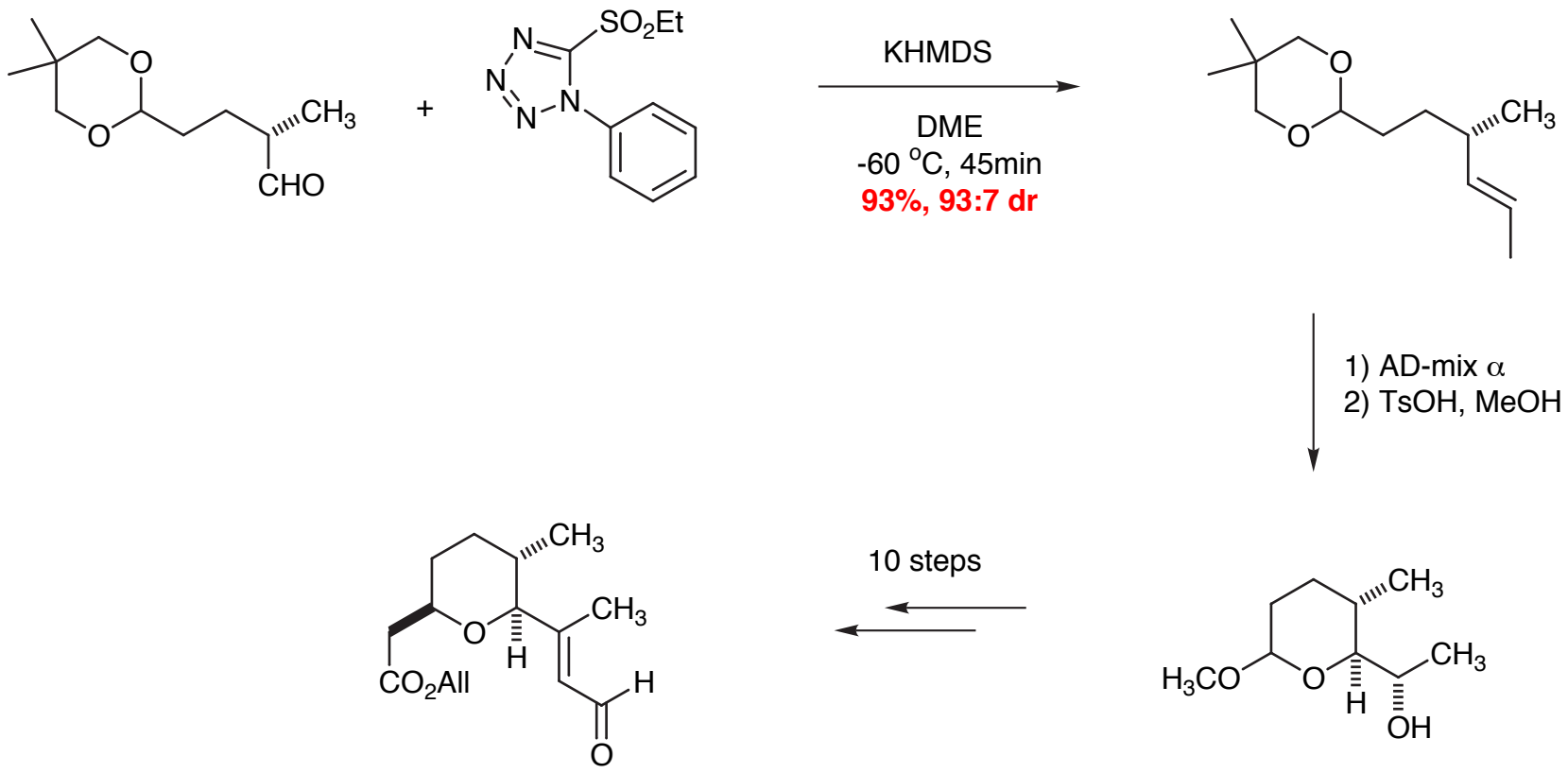
Kinetically Controlled Diastereoselectivity - Irreversible





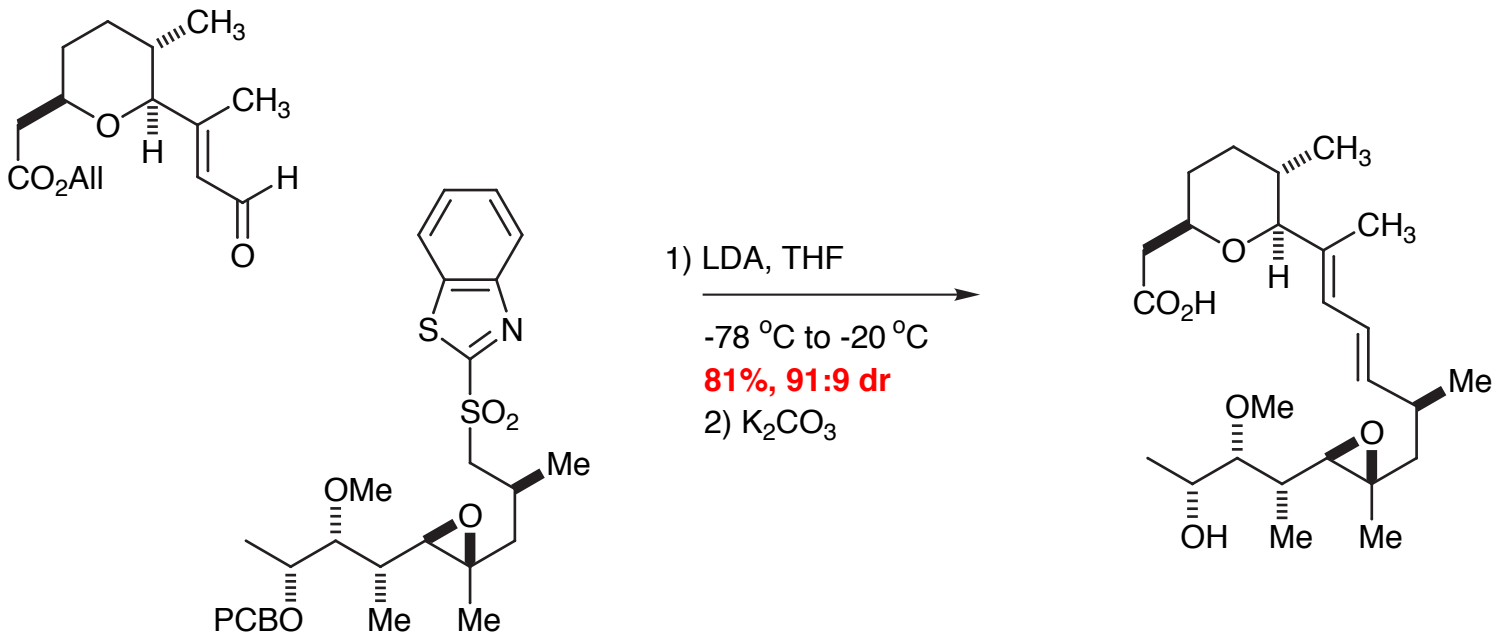
P.R. Blakemore, Ph.D. Thesis, University of Glasgow, Glasglow, 1999

Synthesis of Herboxidine



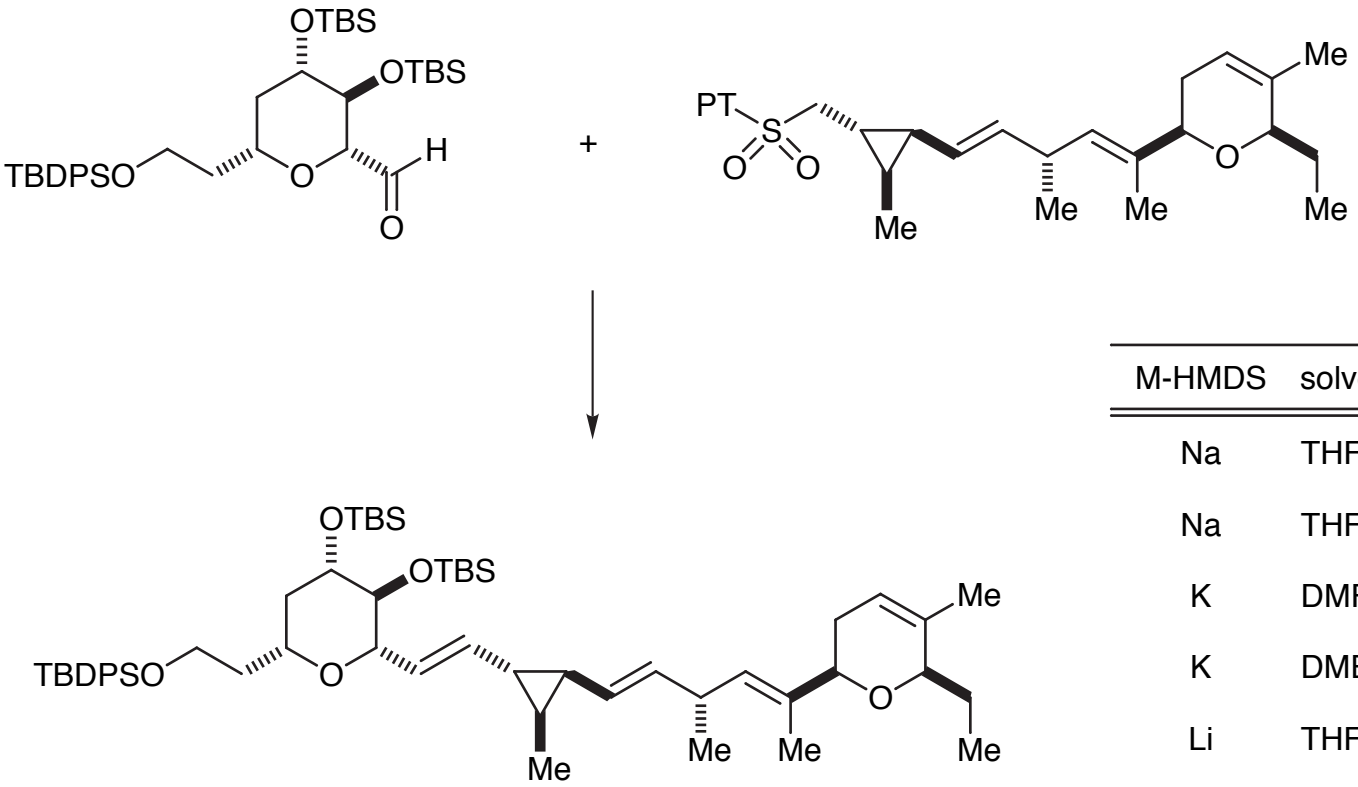
P.J.Kocienski, et al., *J. Chem. Soc., Perkin Trans. 1,* 1999, 955

Synthesis of Herboxidine



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

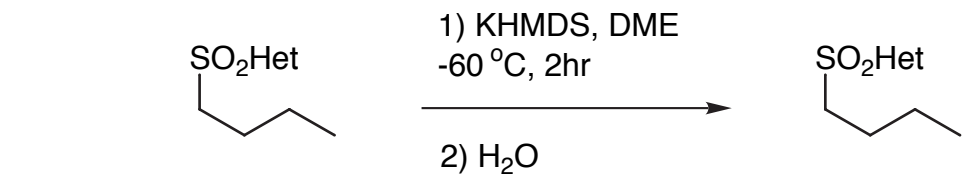
Synthesis of (+)-Ambruticin



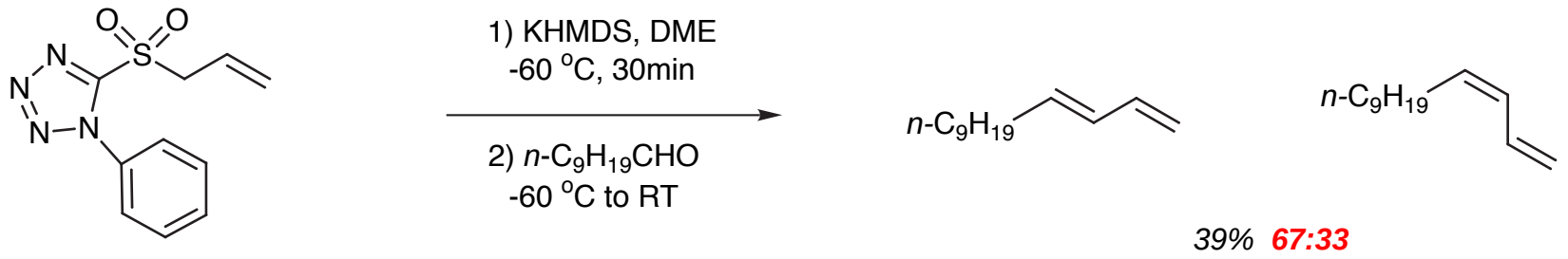
M-HMDS	solvent	temp	*E : Z*
Na	THF	-78 °C	1:8
Na	THF	-35 °C	1:6
K	DMF	-60 °C	1:1
K	DME/18-c-6	-60 °C	1:3
Li	THF/HMPA	-60 °C	3:1
Li	DMF/HMPA	-35 °C	>30:1
Li	DMF/HMPU	-35 °C	>30:1

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

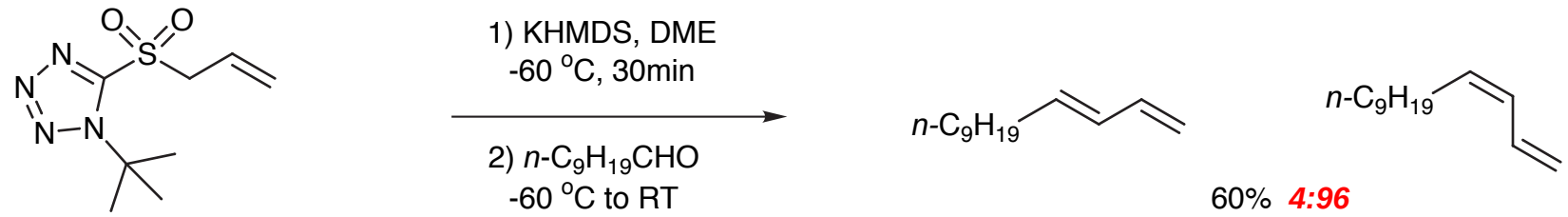
tert-*Butyl-1H-tetrazol-5-yl Sulfones*



Het	yield
BT	0%
PT	20%
TBT	91%

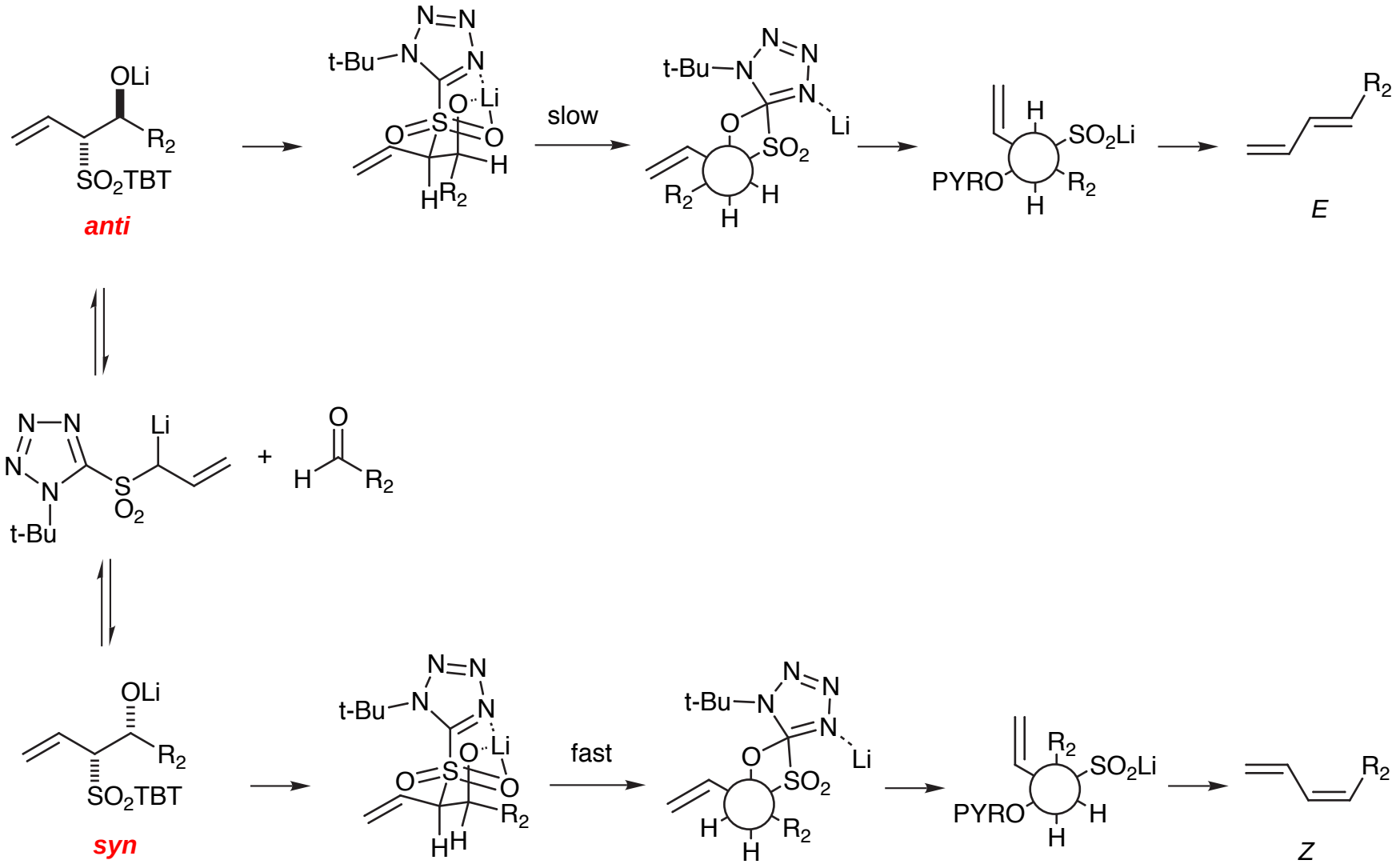


39% ***67:33***

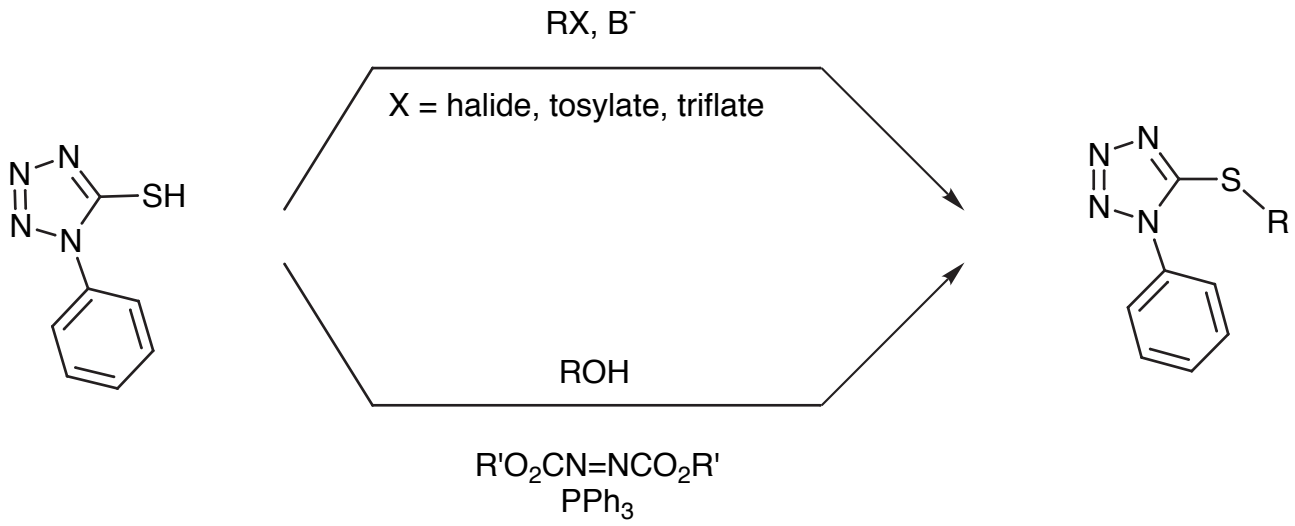


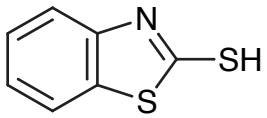
60% ***4:96***

Diastereoselectivity of TBT-Sulfones

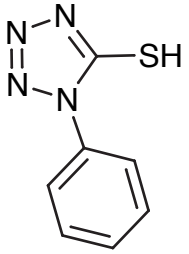


Sulfone Synthesis

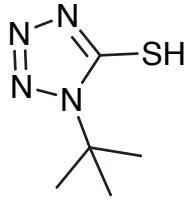




2-mercaptobenzothiazole
100g = $18.00



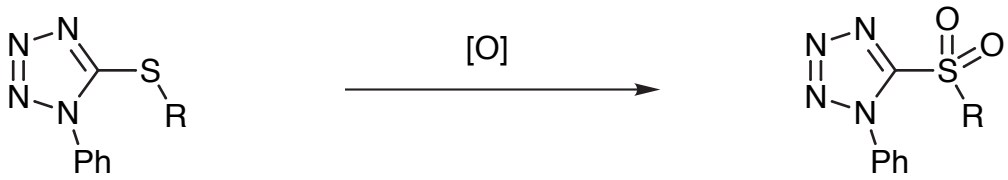
1-phenyl-1-*H*-tetrazole-5-thiol
25g = $22.60



t-Bu—N=C=S + NaN_3

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

Sulfone Synthesis



MCPBA

$(NH_4)_6Mo_7O_{24}$-$4H_2O$ / H_2O_2 Mo(VI)

Na_2WO_4-$2H_2O$ / H_2O_2 W(VI)

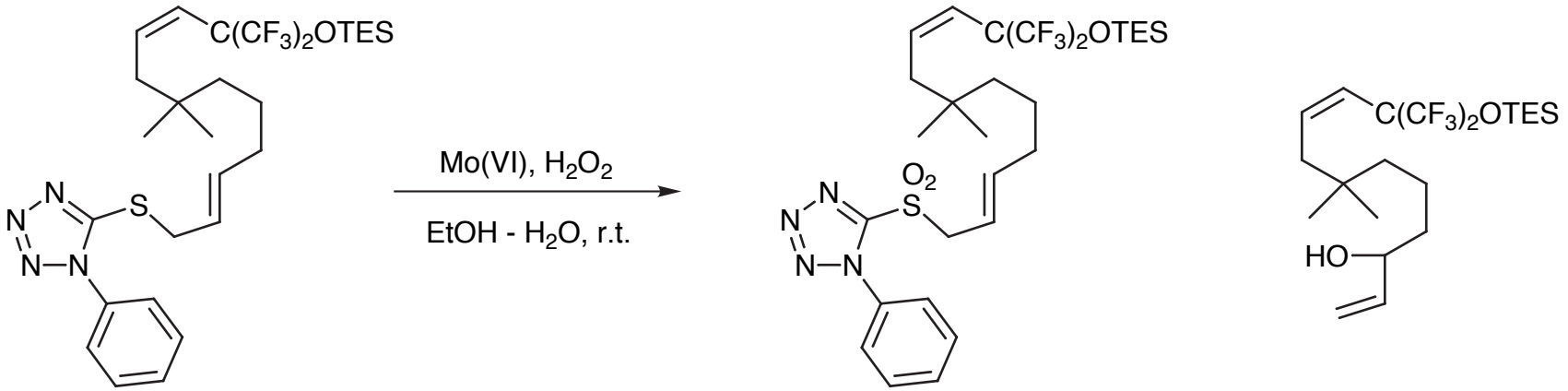
Oxone

CH_3CO_3H

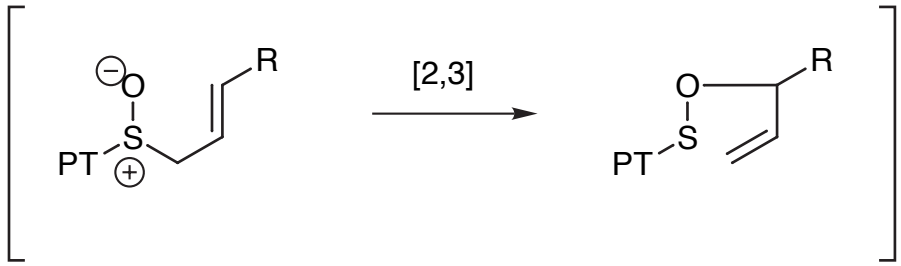
$KMnO_4$

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

Oxidation Problems - Allylic Sulfones

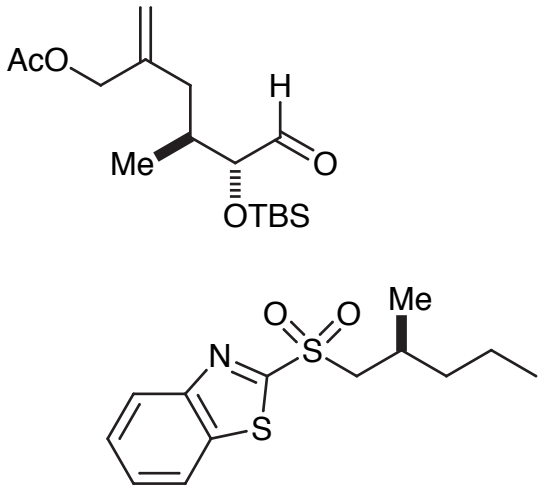


38% **11%**



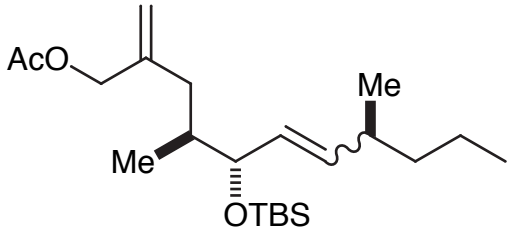
H. Hilpert, B. Wirz, *Tetrahedron*, 2001, **57**, 681
D.A. Evans, G.C. Andrews, *Acc. Chem. Res.*, 1974, **7**, 147

Synthesis of the Proposed Structure of Amphidinolide-A

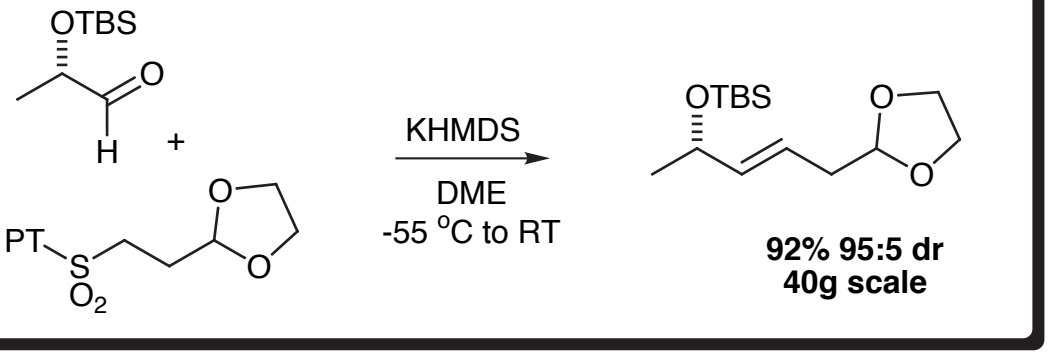


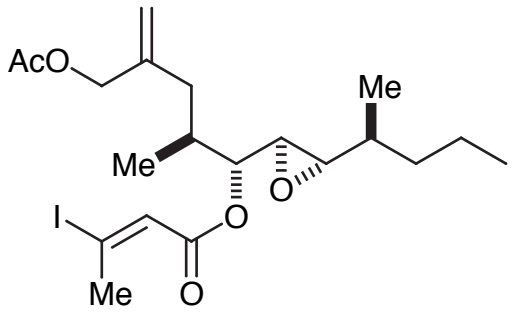
KHMDS

THF
-78 °C to RT
78% 4:1 dr
inseparable



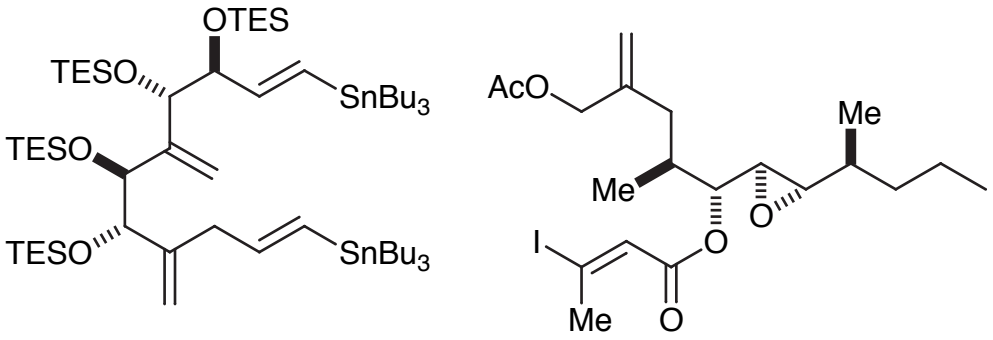
1) HF-pyr (separate isomers)
2) *t*-BuOOH, $Ti(OiPr)_4$
3) EDC, DMAP, CH_2Cl_2,
(*E*)-iodobut-2-enoic acid



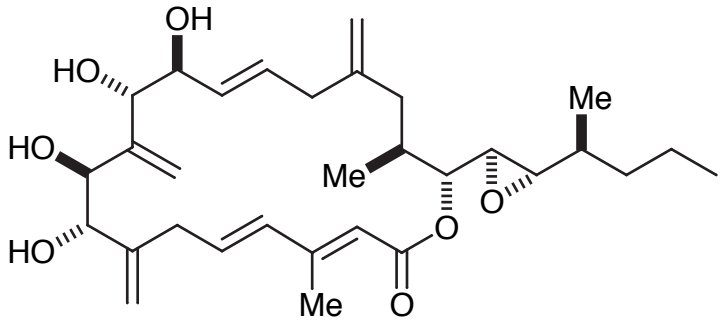


G.Pattenden, H.W.Lam, *Angew. Chem. Int. Ed.*, 2002, **41**, 508
M. Hirama, *Tet. Lett.*, 1999, **40**, 4897

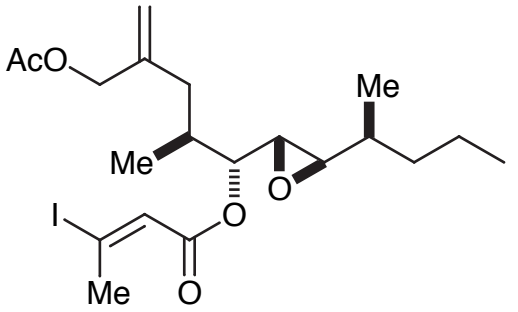
Synthesis of Proposed Structure of Amphidinolide-A

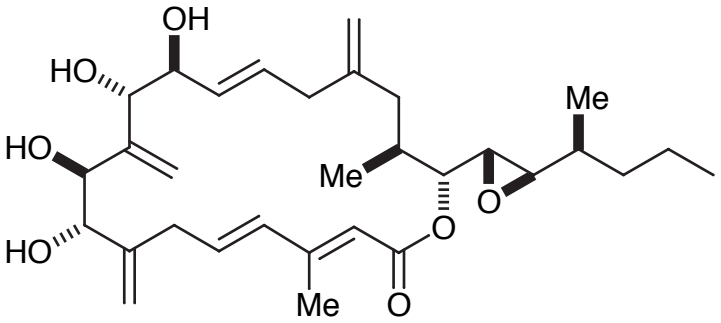


1) $Pd_2(dba)_3$, Ph_3As
2) PPTS
3) $Pd_2(dba)_3$, Ph_3As, LiCl



NOT Amphidinolide-A

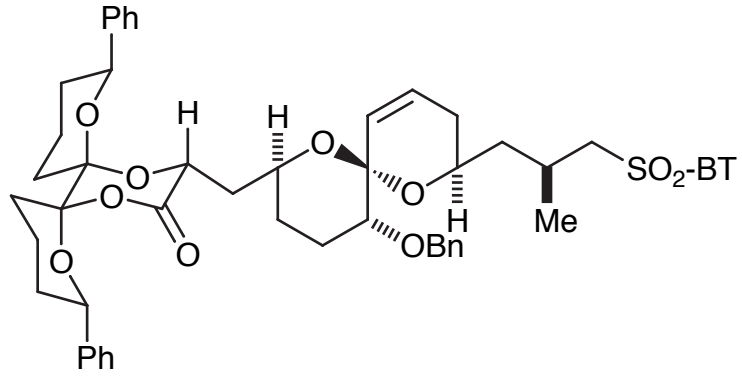


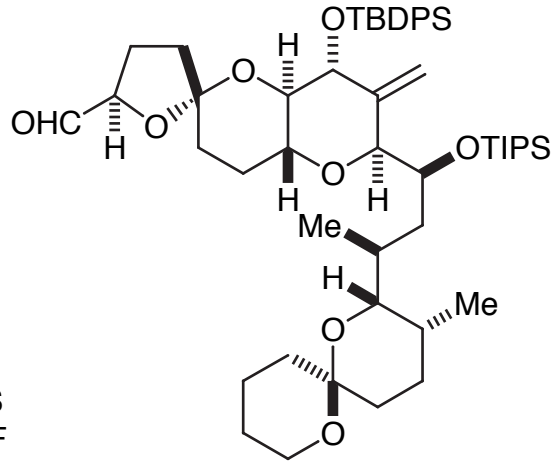


NOT Amphidinolide-A

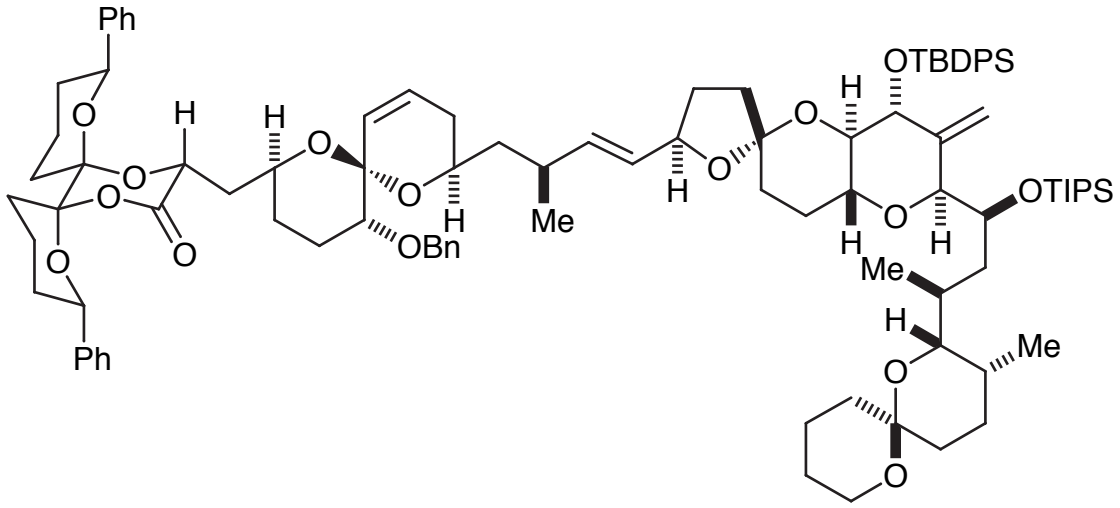
G.Pattenden, H.W.Lam, *Angew. Chem. Int. Ed.*, 2002, **41**, 508

Synthesis of Okadaic Acid





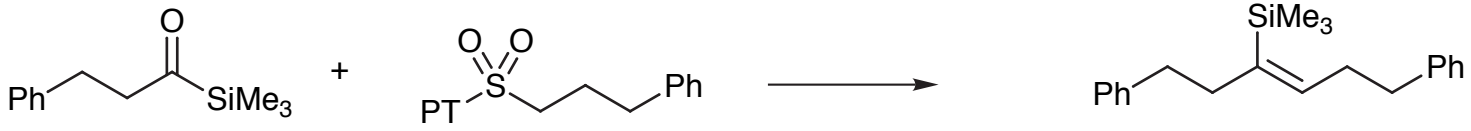
NaHMDS
DMF-THF
-60 °C to RT
66%

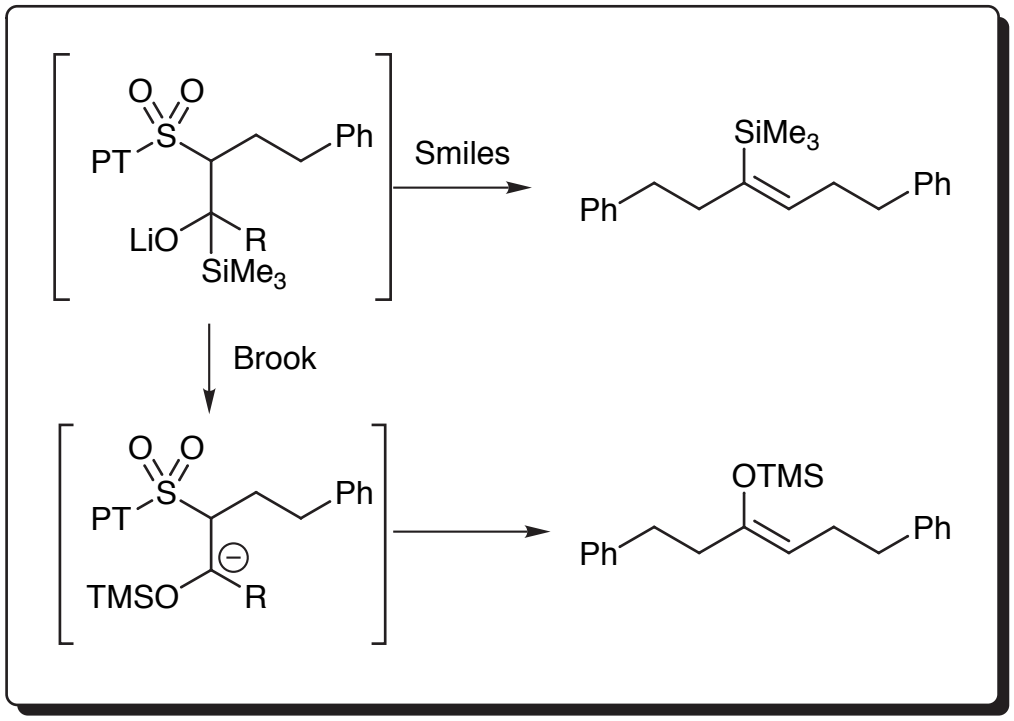


"small quantity of the corresponding (Z)-isomer was also detected by 600 MHz ^{1}H NMR"

S.V. Ley, et al., *J. Chem. Soc., Perkin Trans. 1,* 1998, 3907

Synthesis of Vinylsilanes





M-HMDS	temp	yield	*E : Z*
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