



Alternatives to Tin-Mediated Radical Reactions

Ischia Advanced School of Organic Chemistry
IASOC 2004 - Ischia Porto (Napoli)
September 18-23, 2004

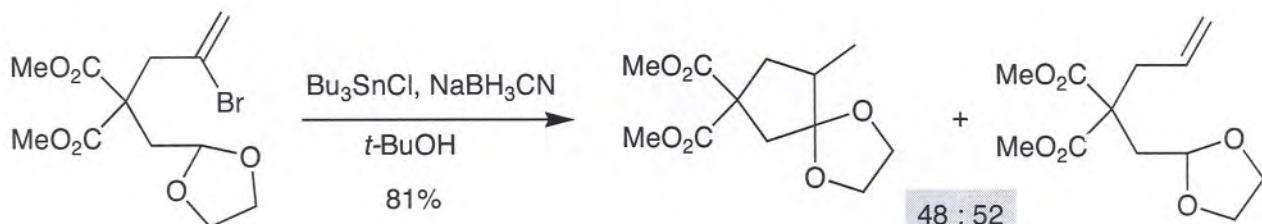
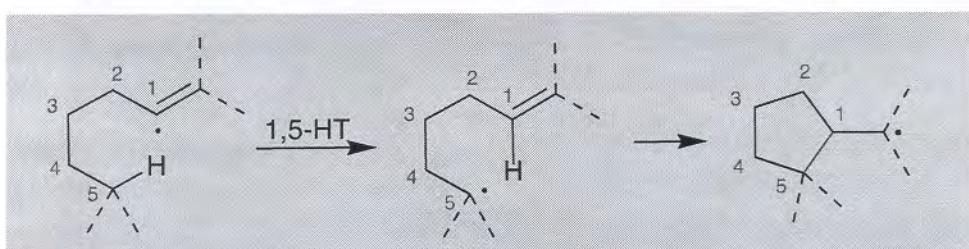


Philippe Renaud
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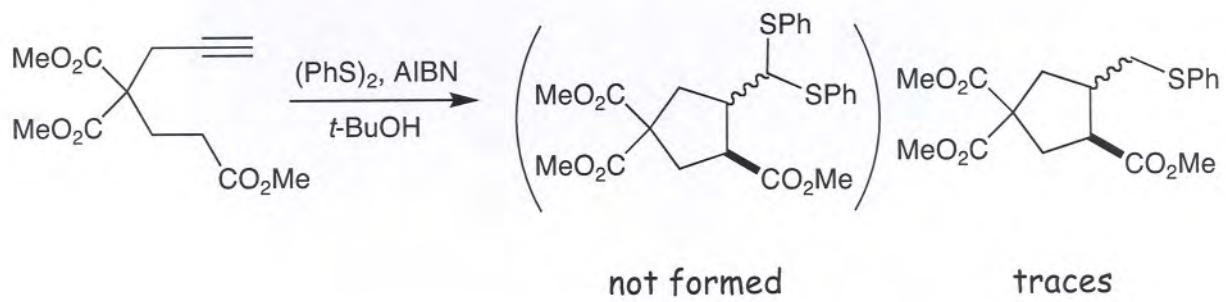
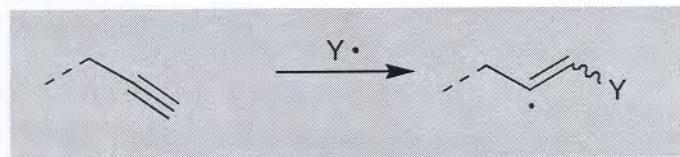
Radical Translocation: Remote Activation

D. P. Curran, W. Shen *J. Am. Chem. Soc.* 1993, 115, 6051-6059

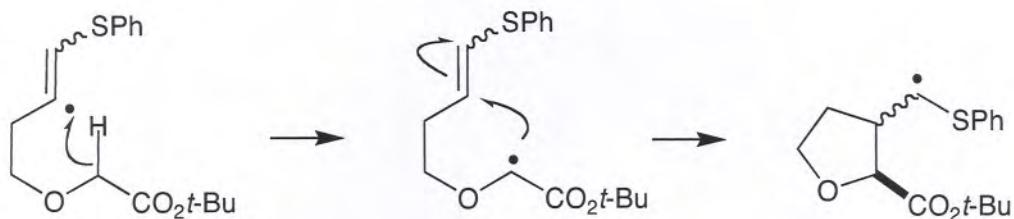
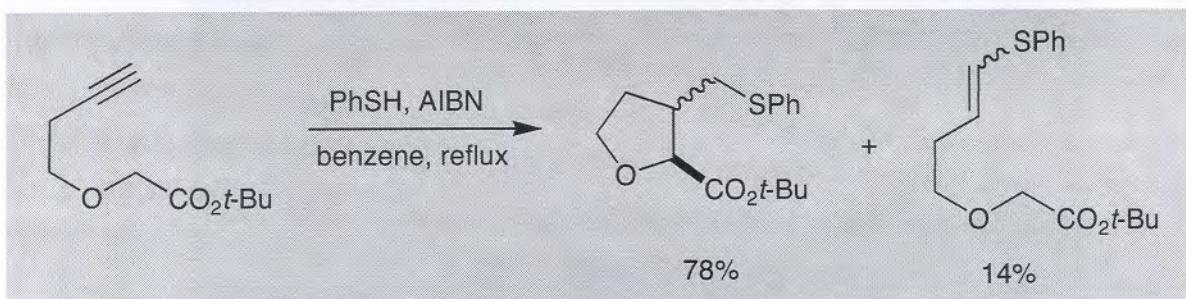




Tin-Free Procedure: PhSSPh



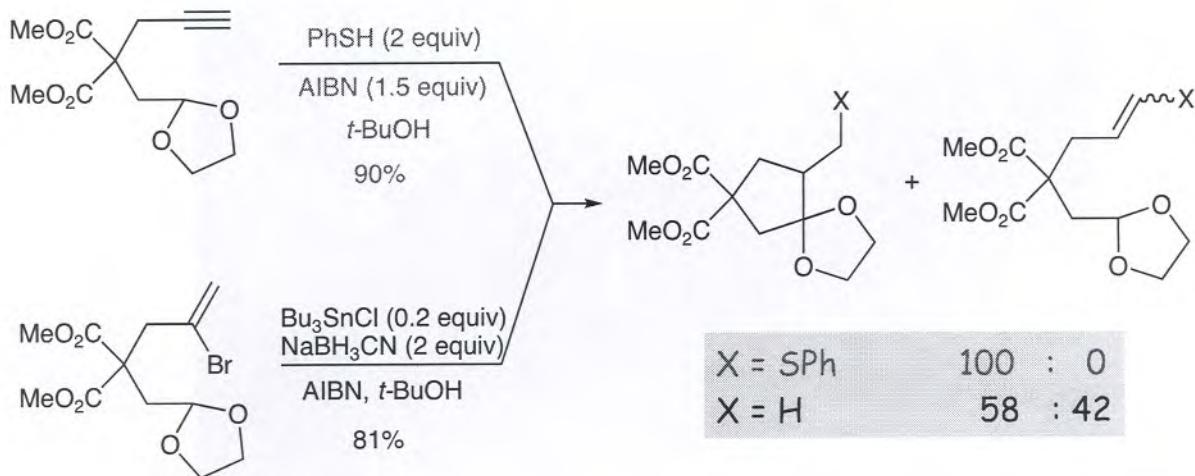
Tin-Free Procedure with Captodative Radicals



S. D. Burke, K. W. Jung *Tetrahedron Lett.* 1994, 35, 5837-5840.



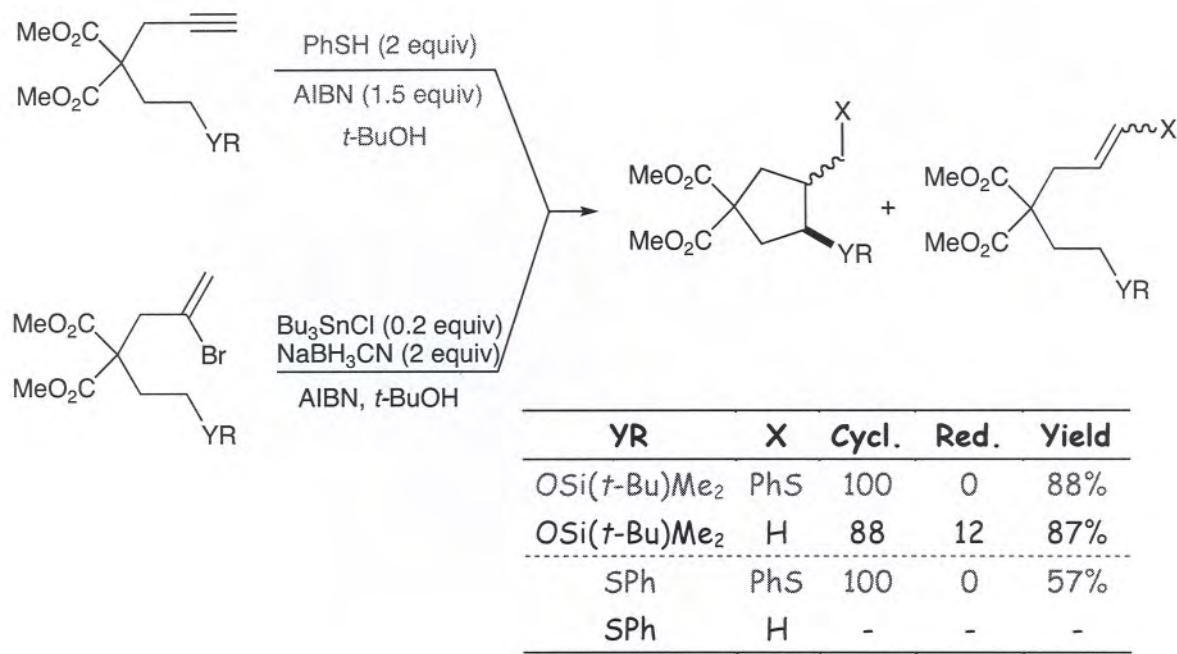
Tin Hydride versus Thiophenol



F. Beaufils, F. Dénès, P. Renaud, *Organic Lett.* 2004, 6, 2563.

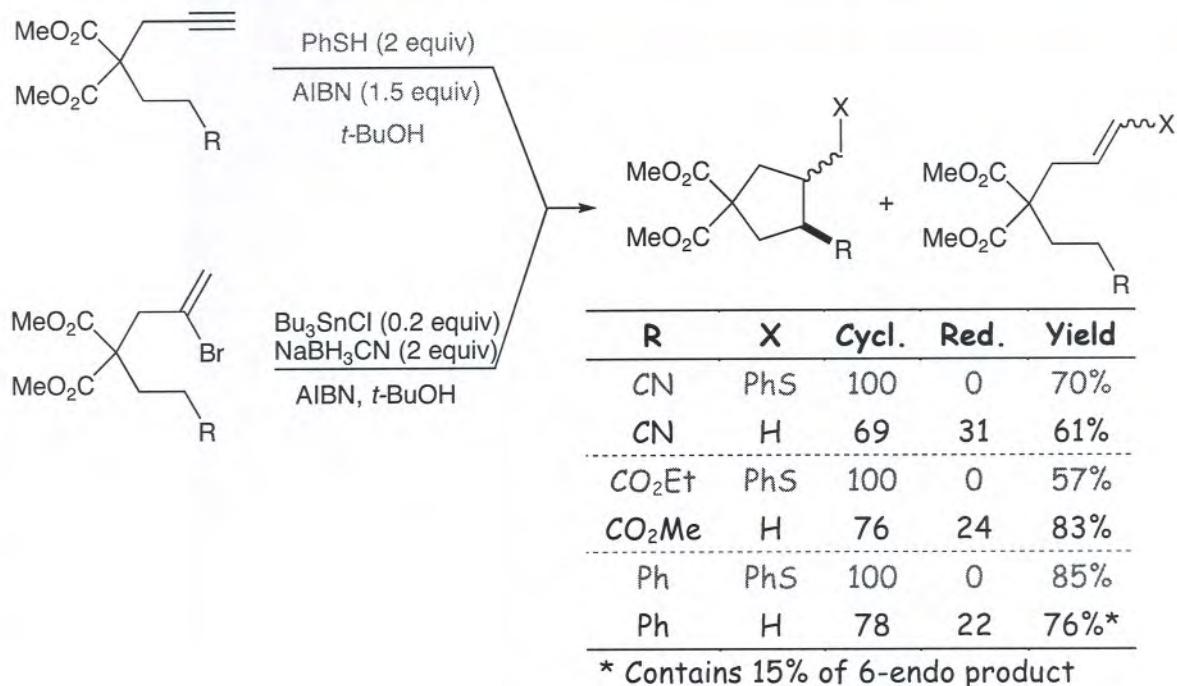


Heteroatom Substituents

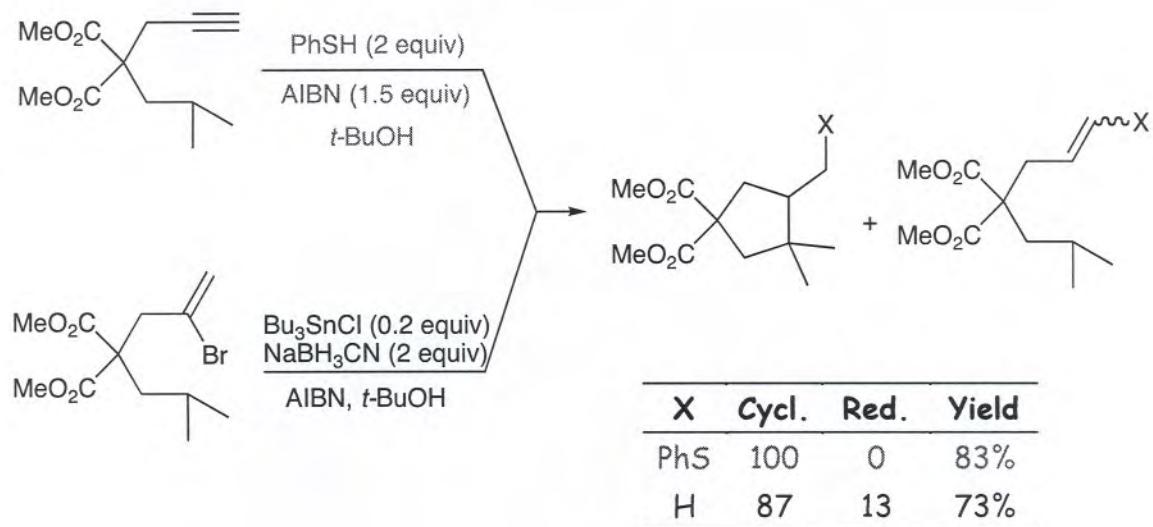




Radical Stabilizing C-Substituents

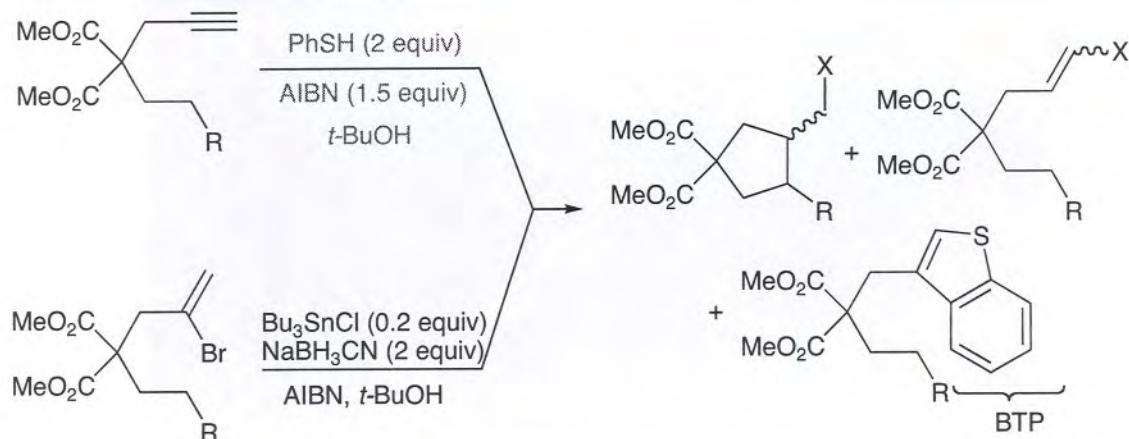


Alkyl Substituents





Alkyl Substituents

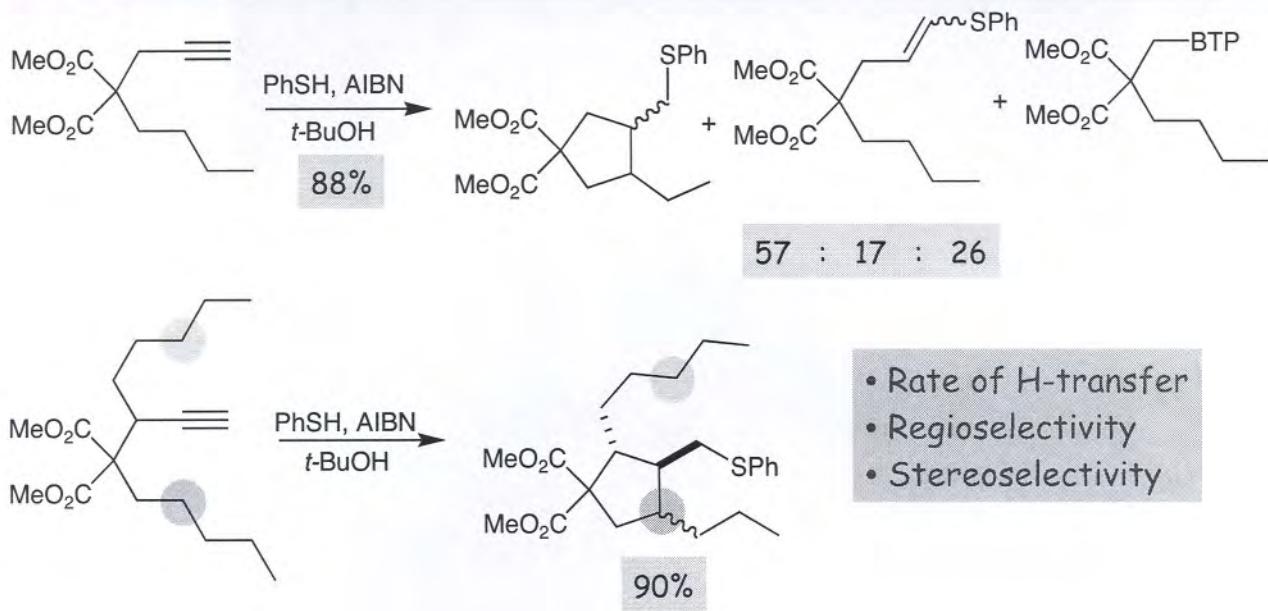


R	X	Cycl.	Red.	BTP
H	PhS	0	90	10
H	H	<4	>96	-

Et	PhS	57	17	26
Me	H	48	52	-



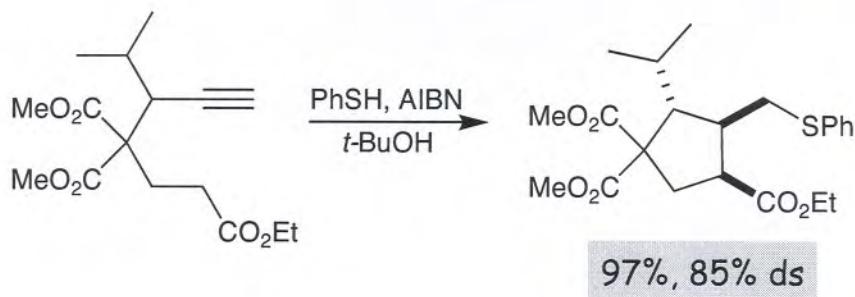
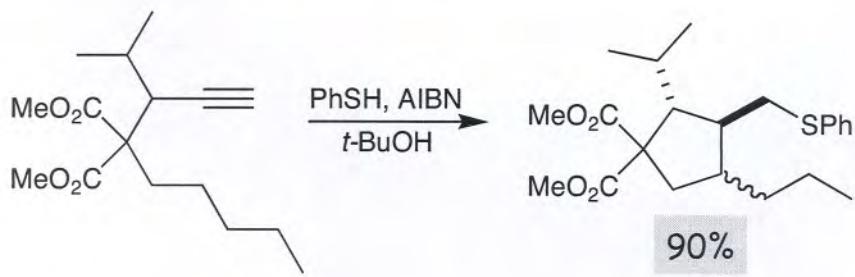
Substituents at the Propargylic Center



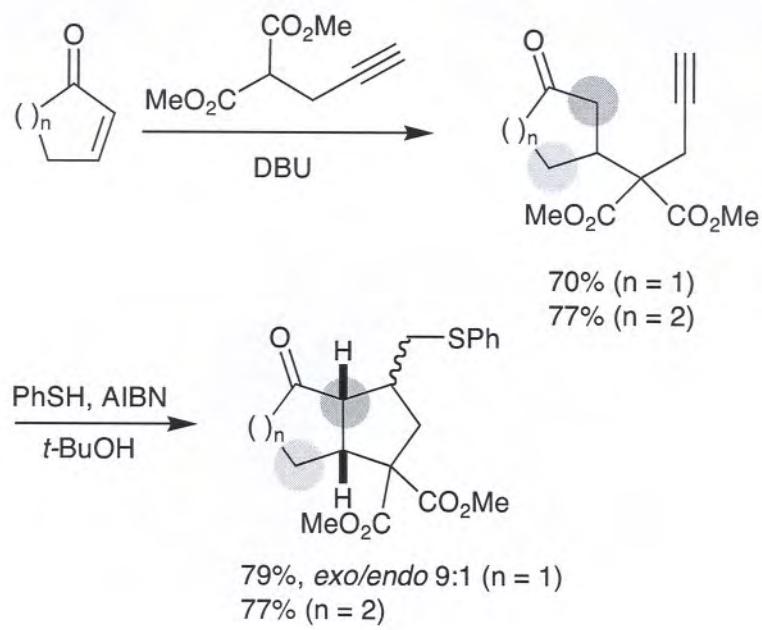
Effect of *gem*- and *vic*-disubstituents: M. E. Jung, *Synlett* 1999, 843.



Substituents at the Propargylic Center

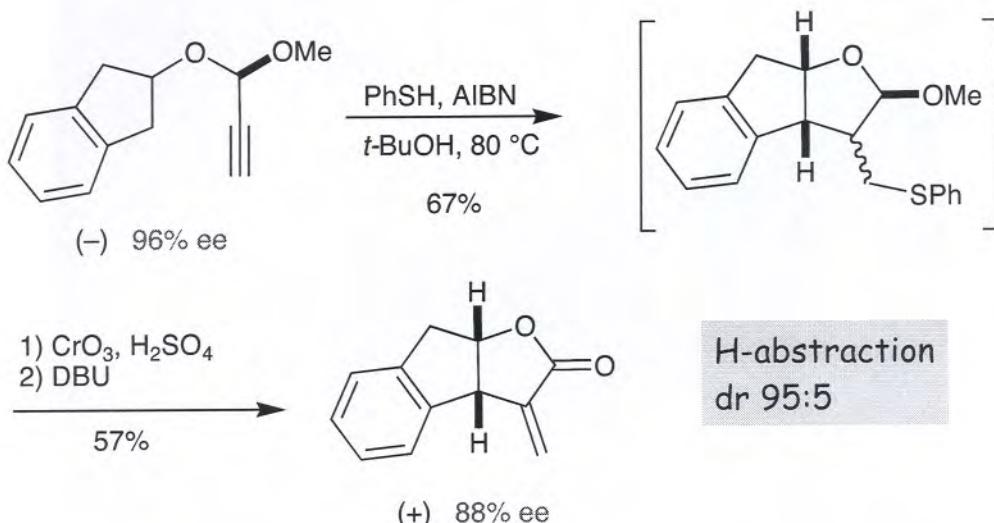


Bicyclic Systems: Activation by a Carbonyl Group





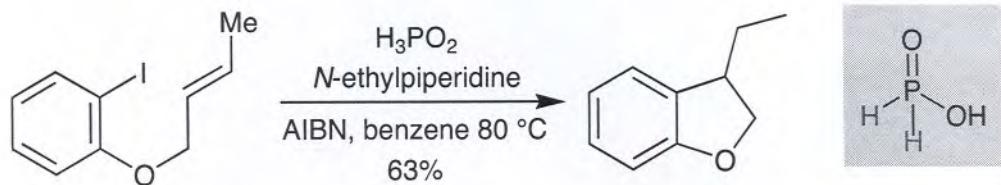
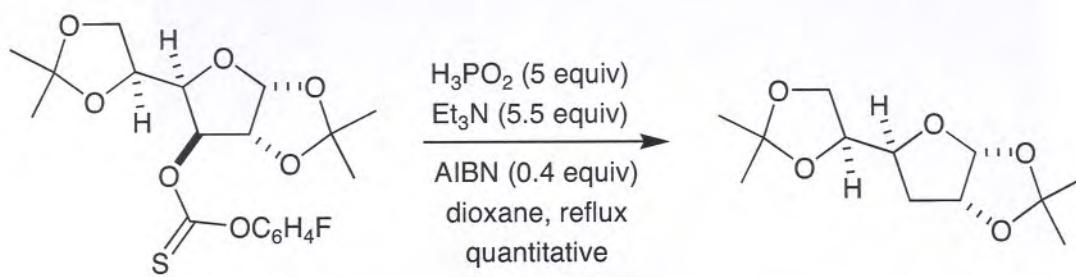
Optically active α -Methylenelactones



P. Renaud, F. Beaufils, L. Feray, K. Schenk, *Angew. Chem. Int. Ed.* 2003, 42, 4230



Hypophosphorous acid



D. H. R. Barton et al., *J. Org. Chem.* 1993, 58, 6838.

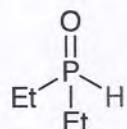
J. A. Murphy et al., *Tetrahedron Lett.* 1999, 40, 2415.

R. J. Stoodley et al., *Chem. Commun.* 1998, 2691.



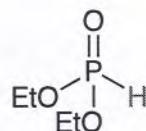
Other P-H Reagents

Diethylphosphine oxide



J. A. Murphy et al.
Organic Lett. 2003, 5,
2971.

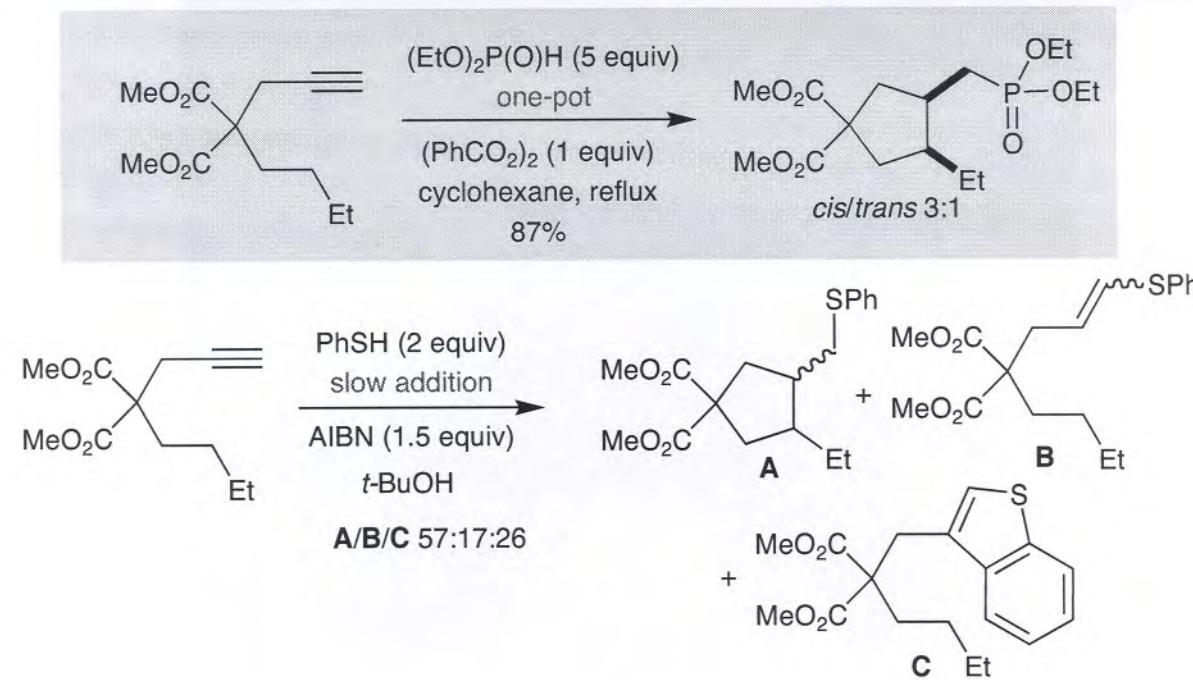
Diethylphosphite



A. F. Parsons et al.
Tetrahedron Lett. 2001, 42, 3137
and 2003, 44, 479.

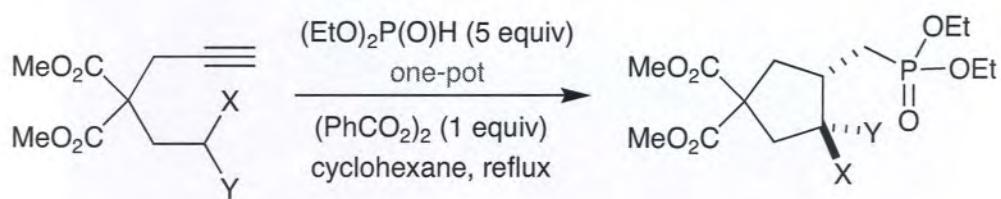


$(\text{EtO})_2\text{P}(\text{O})\text{H}$ Mediated Hydrogen Transfer





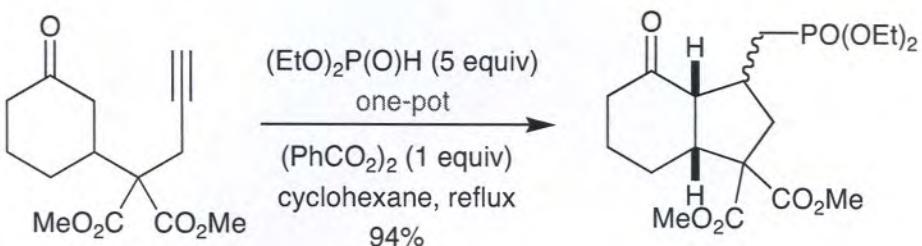
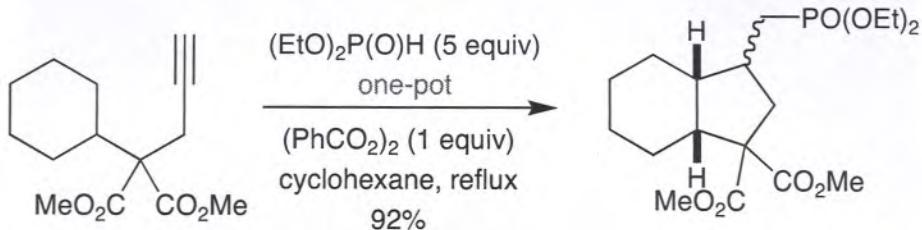
(EtO)₂P(O)H Mediated Hydrogen Transfer



Y	Z	cis/trans	yield[%]
Et	H	75:25	87
Me	Me	-	99
CO ₂ Et	H	60:40	91
Ph	H	73:27	85
OTBS	H	64:36	75

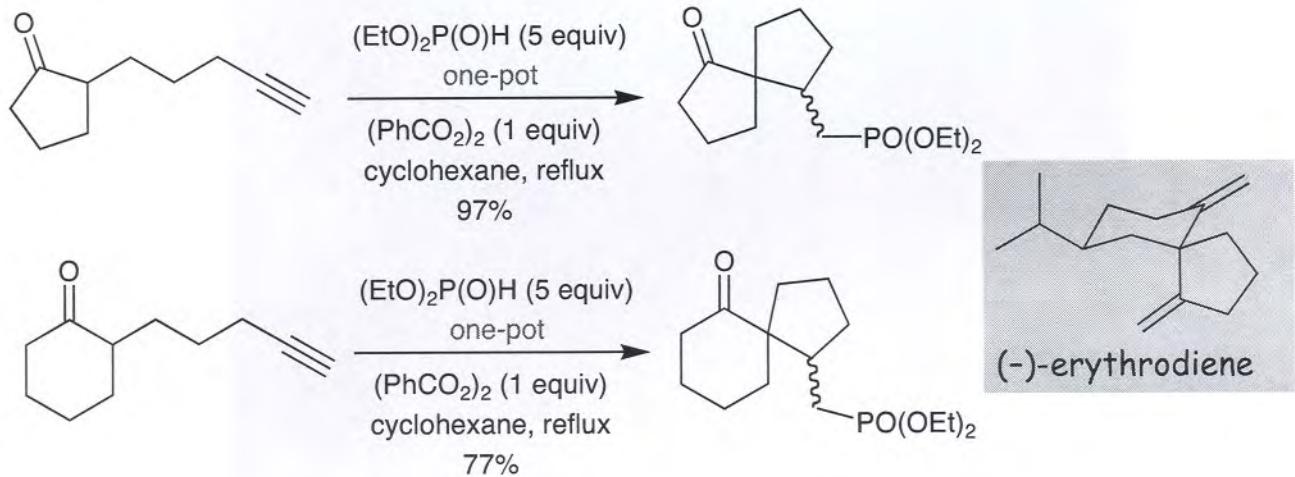


(EtO)₂P(O)H Mediated Hydrogen Transfer

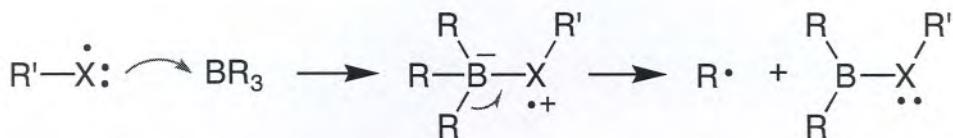
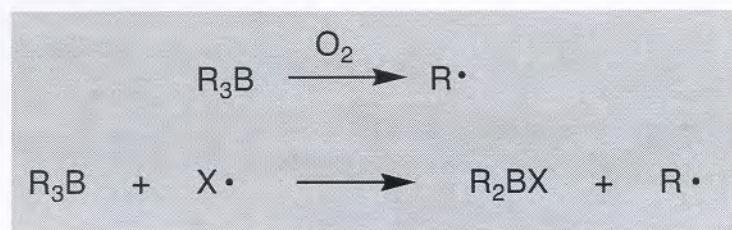




$(EtO)_2P(O)H$ Mediated Hydrogen Transfer



RADICAL REACTIONS OF ORGANOBORANES

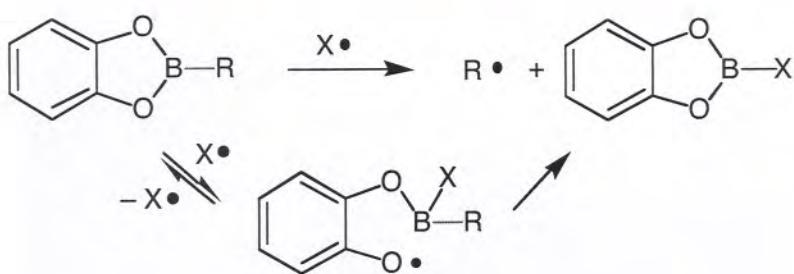


Review: H. C. Brown, M. M. Mildand, *Angew. Chem.* **1972**, *84*, 702.
C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415.



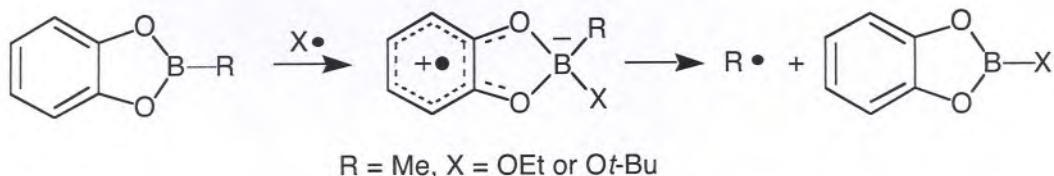
B-ALKYLCATECHOLBORANES

A. Schaffner, P. Renaud, *Eur. J. Org. Chem.* 2004, 2291.

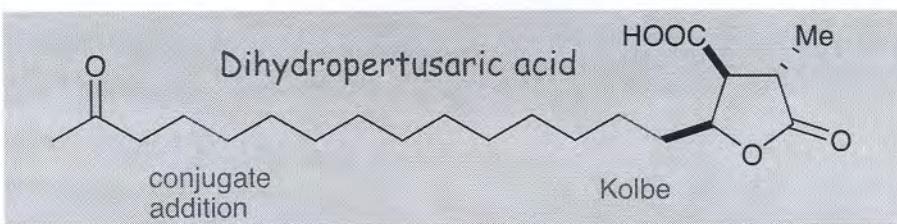
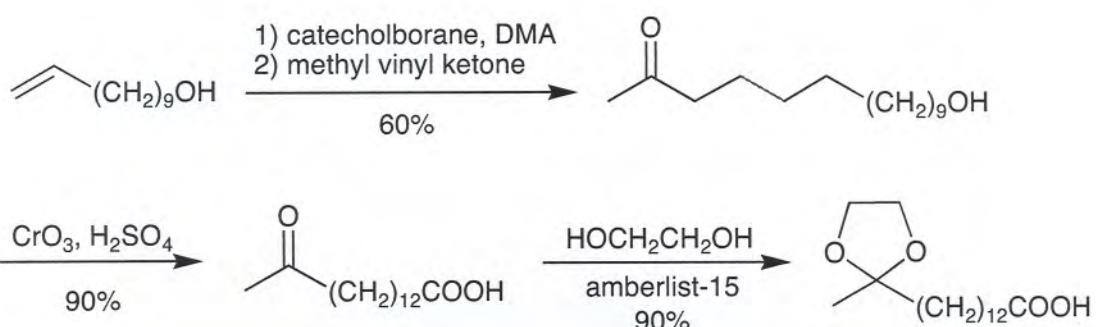


A perboryl radical intermediate

B. P. Roberts, *J. Chem. Soc. Perkin Trans. 2*, 1986, 157.



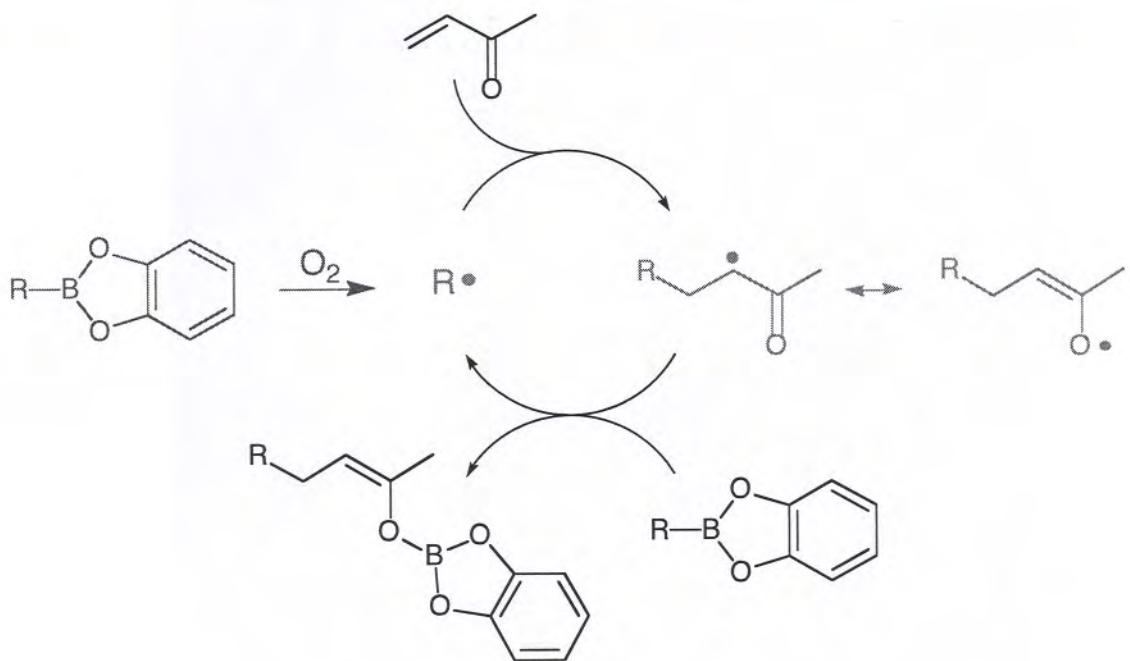
PREPARATION OF 14-OXOPENTADECANOIC ACID



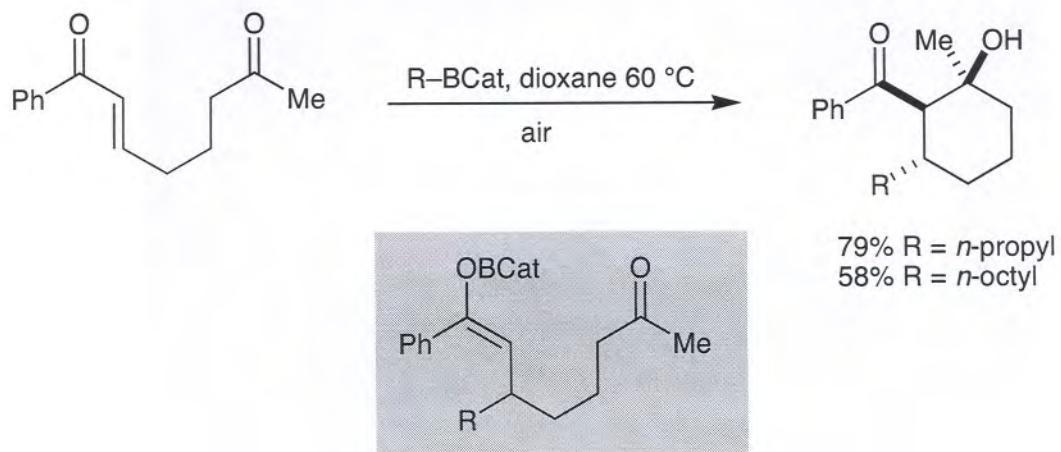
A. Brecht-Forster, J. Fitremann, P. Renaud, *Helv. Chim. Acta* 2002, 85, 3965.



OXYGEN INITIATED CONJUGATE ADDITION



RADICAL CONJUGATE ADDITION - ALDOL REACTION



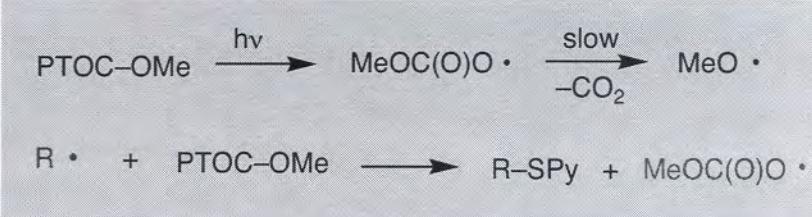
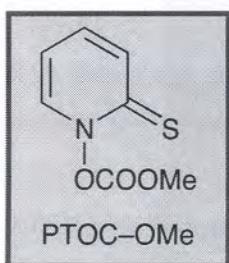
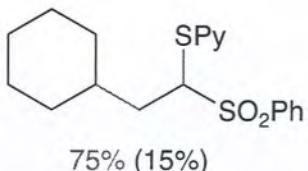


CONJUGATE ADDITION TO ACTIVATED OLEFINS

1) Catecholborane, DMA



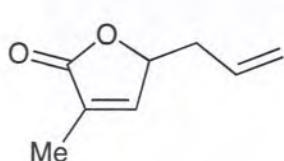
2) $\text{CH}_2=\text{CH}-\text{SO}_2\text{Ph}$ (5 equiv)
PTOC-OMe (3 equiv)
150 W lamp



C. Ollivier, P. Renaud, *Angew. Chem.* 2000, 925-928

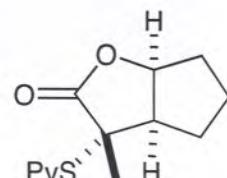


α -METHYLENELACTONES



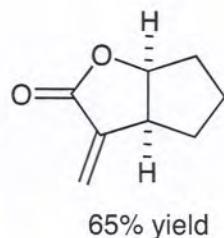
1) Catecholborane (1.2 eq)
[Rh(COD)Cl]₂ 1 mol%
PPh₃ 2 mol%

2) PTOC-OMe (3eq)
 $h\nu$, 10 °C



63% yield

1) *m*-CPBA (1 eq),
 CH_2Cl_2 , -10 °C
2) EtOH, reflux 2h



65% yield



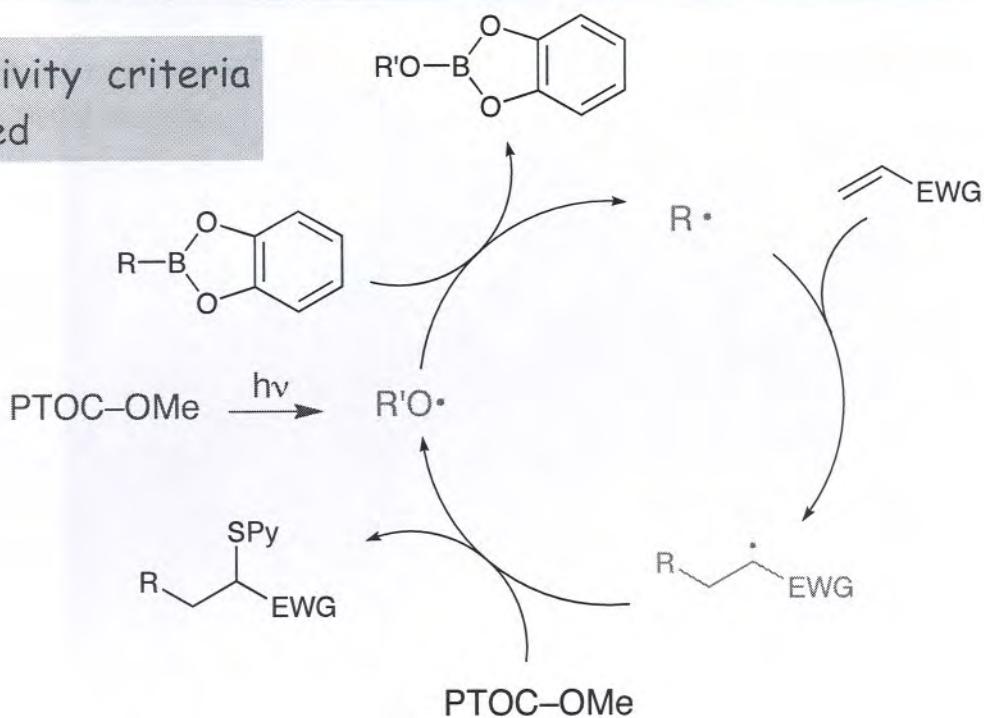
Mirabolide

B. Becattini, C. Ollivier, P. Renaud, *Synlett* 2003, 1485.

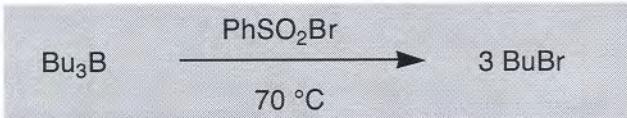


MECHANISM

Selectivity criteria
fulfilled



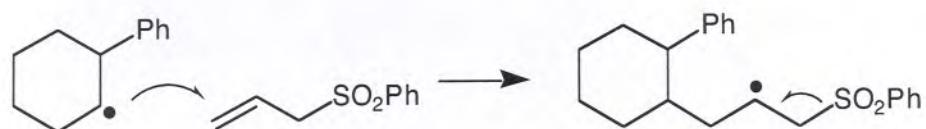
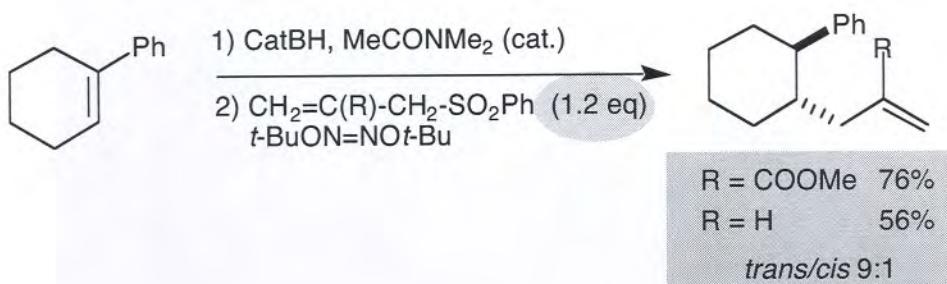
BROMINATION OF ORGANOBORANES



A. G. Davies, B. P. Roberts, *Acc. Chem. Res.* 1972, 5, 387



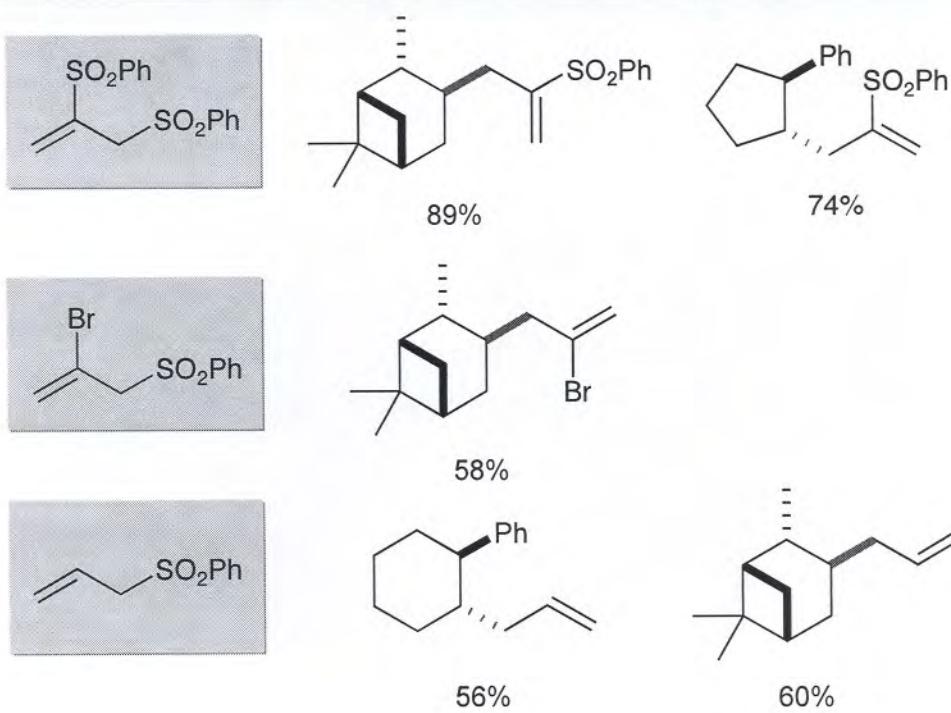
ALLYLATION OF ORGANOBORANES WITH SULFONES



A. Schaffner, P. Renaud, *Angew. Chemie Int. Ed.* 2003, 42, 2658.

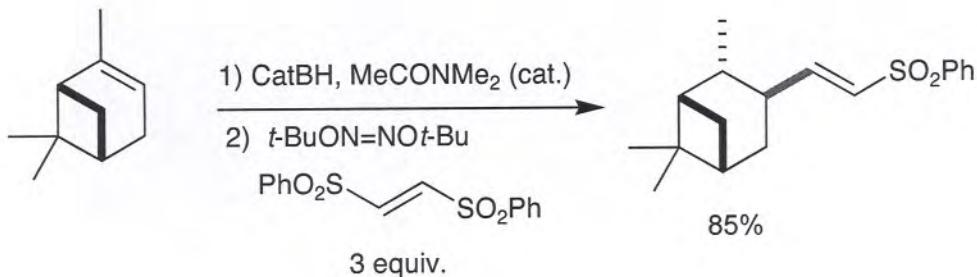
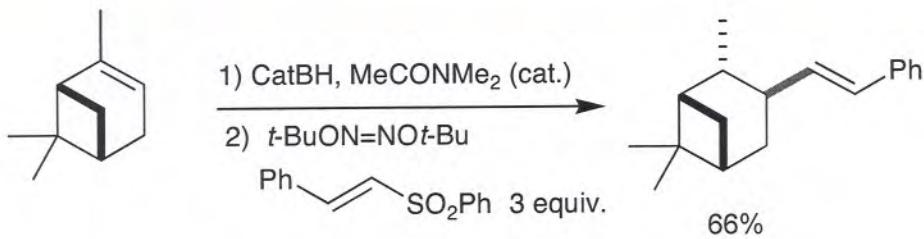


ALLYLATION OF ORGANOBORANES WITH SULFONES

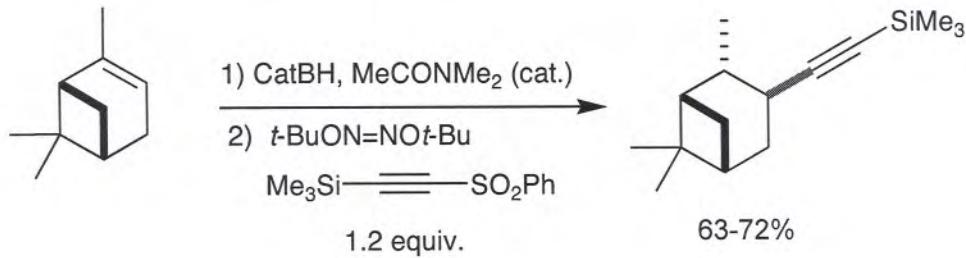
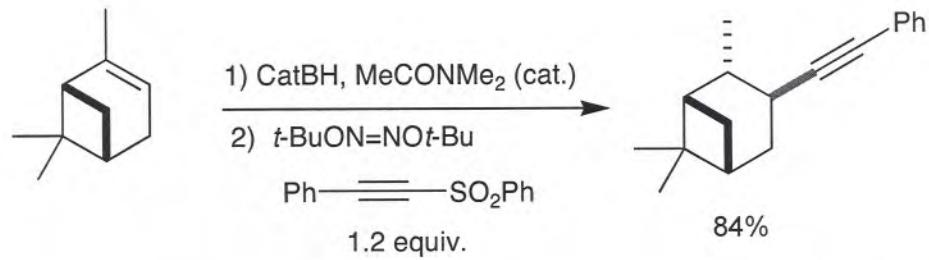




VINYLATION

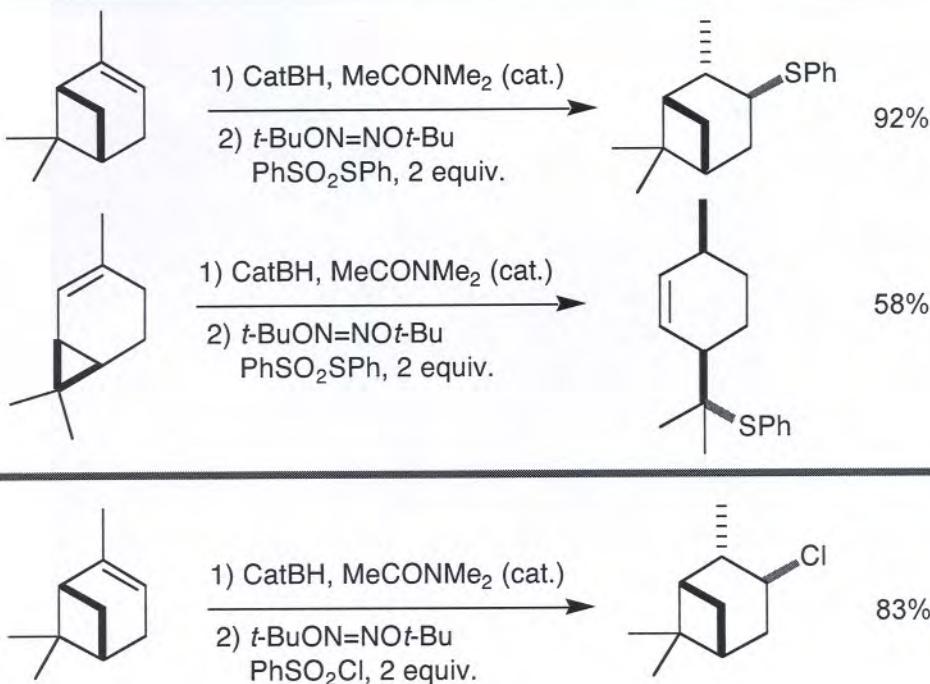


ALKYNYLATION

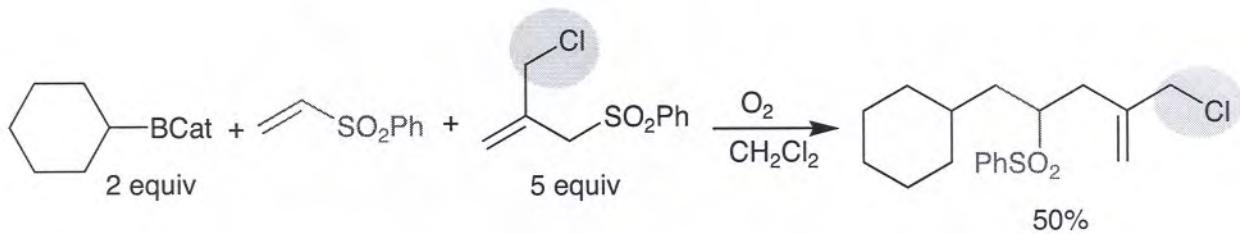




SULFURIZATION, CHLORINATION

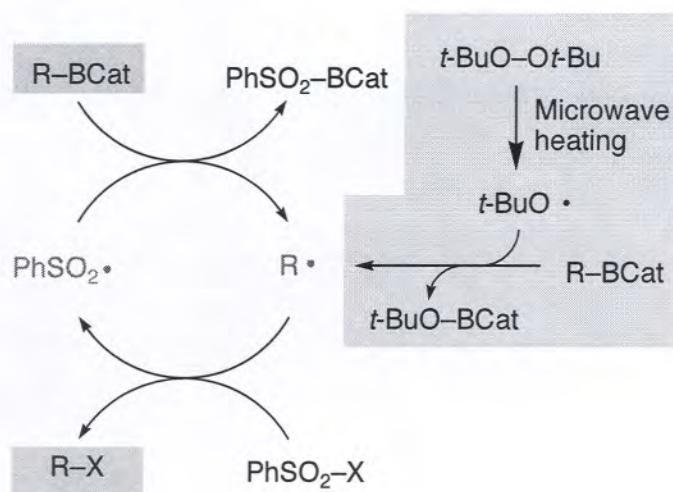


THREE-COMPONENT REACTIONS

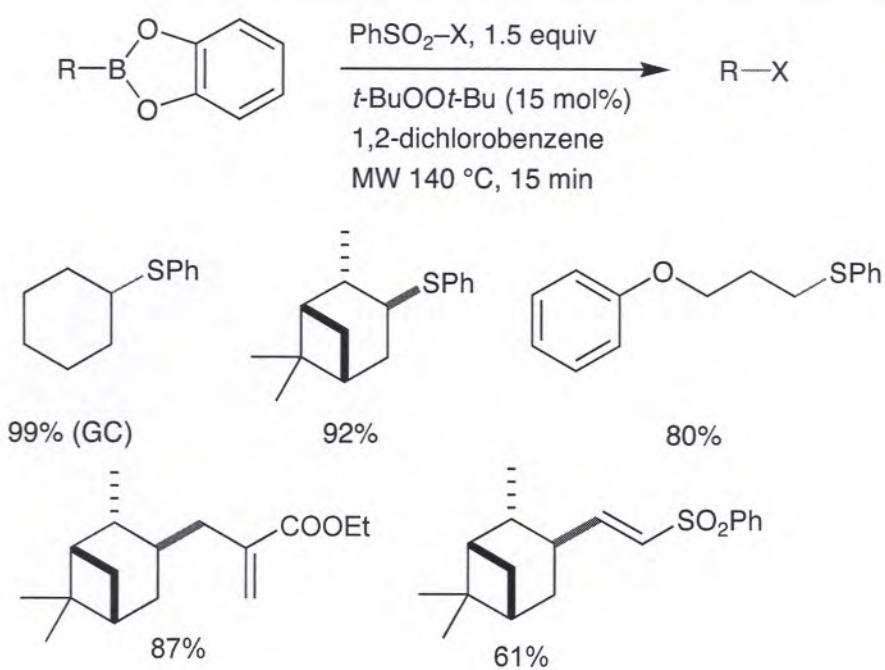




Microwaves-Assisted Reactions

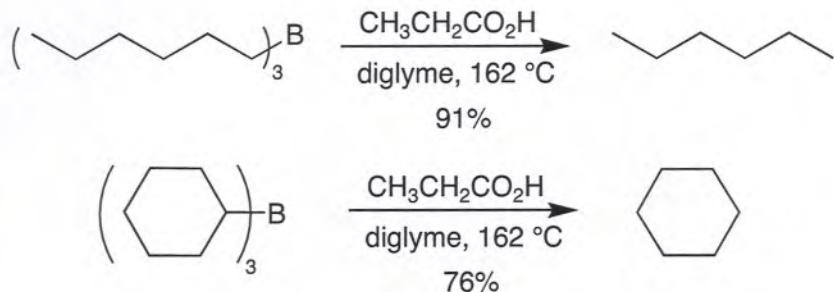


Microwaves-Assisted Reactions





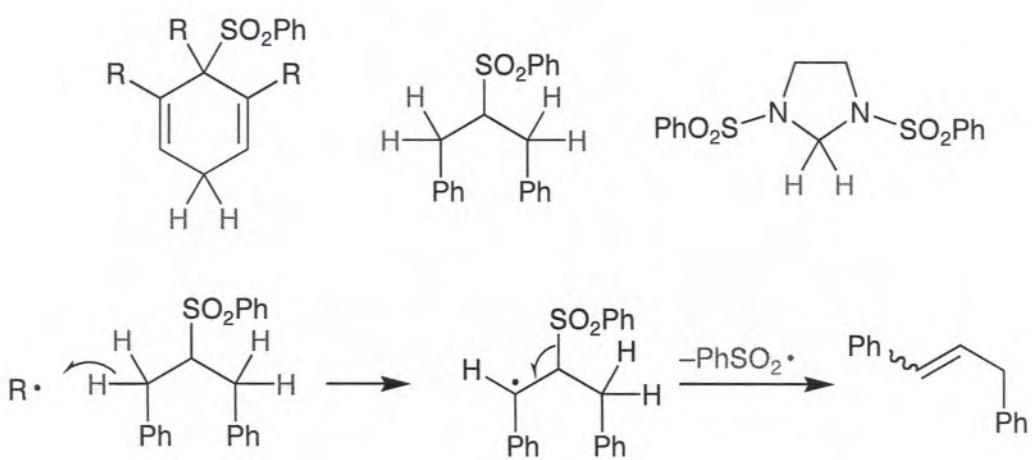
Protonation of Organoboranes



H. C. Brown, *J. Am. Chem. Soc.* 1959, 81, 4109

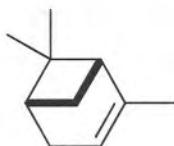


Radical Reduction of Organoboranes

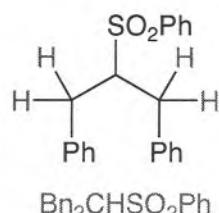
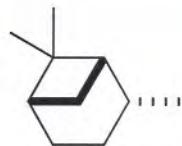




Radical Reduction of Organoboranes



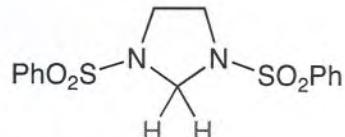
1) CatBH, MeCONMe₂ (cat.)
2) Initiator, reducing agent



O₂, Bn₂CHSO₂Ph (1.2 eq) **99% (GC)**
CH₂Cl₂, reflux 3 h, rt 8 h

t-BuOOt-Bu (15 mol%) **99% (GC)**
Bn₂CHSO₂Ph (1.2 eq)
1,2-Cl₂Ph, MW 140 °C, 15 min

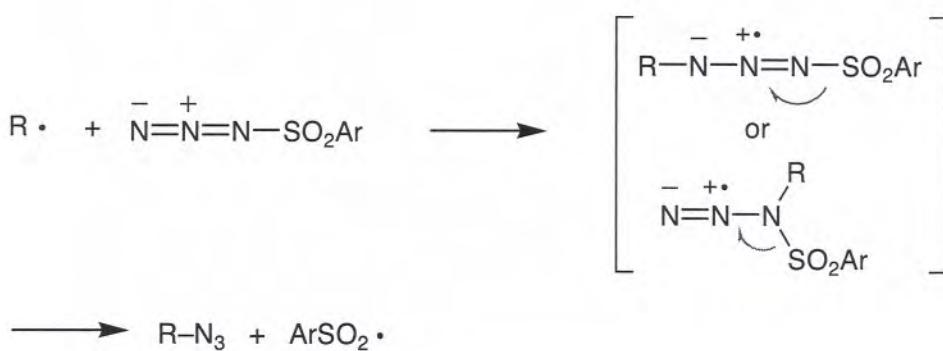
t-BuOOt-Bu (15 mol%) **84% (GC)**
BPSI (1.2 eq)
1,2-Cl₂Ph, MW 140 °C, 15 min



1,2-bis(phenylsulfonyl)-
imidazolidine = BPSI



A RADICAL AZIDATION

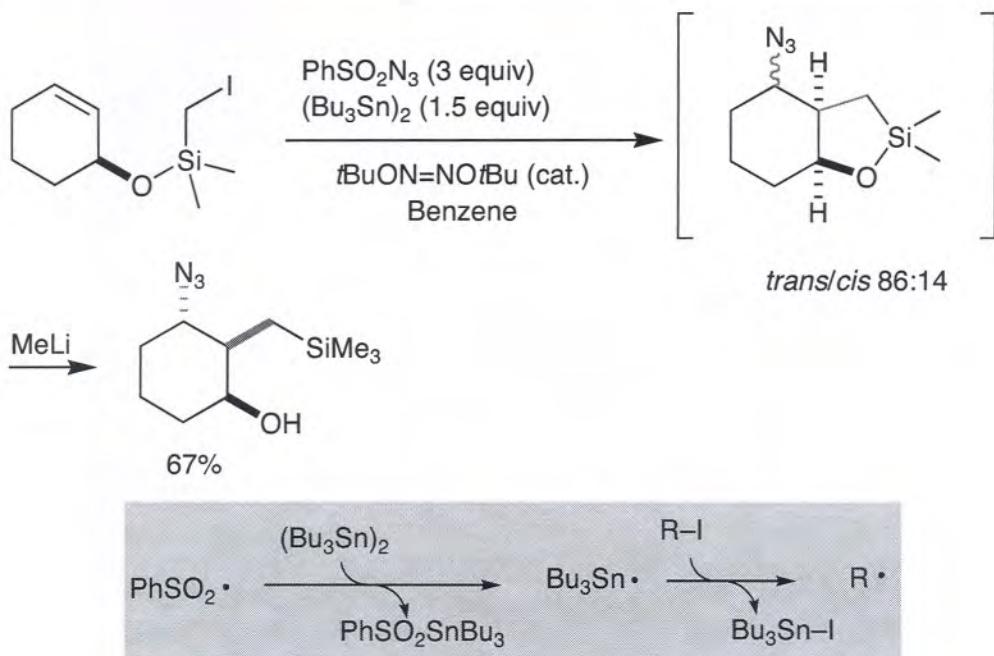


Ollivier, P. Renaud, *J. Am. Chem. Soc.* 2000, 122, 6496 and *J. Am. Chem. Soc.* 2001, 123, 4717.

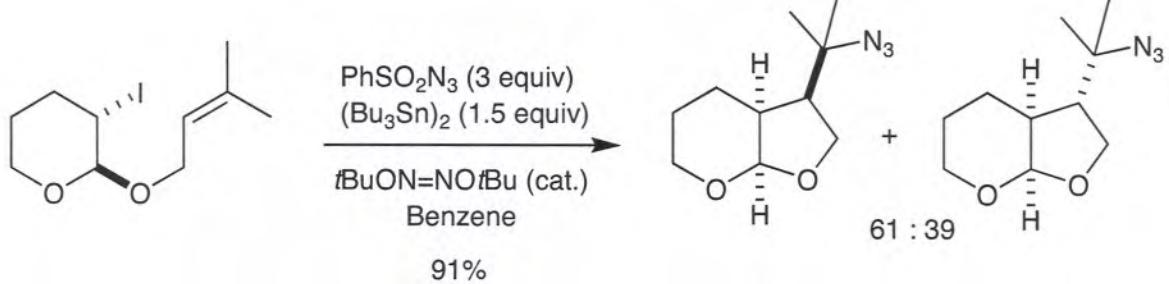
Review: P. Panchaud, L. Chabaud, Y. Landais, C. Ollivier, P. Renaud, S. Zigmantas, *Chem. Eur. J.* 2004, 10, 3606.



CYCLIZATION-AZIDATION

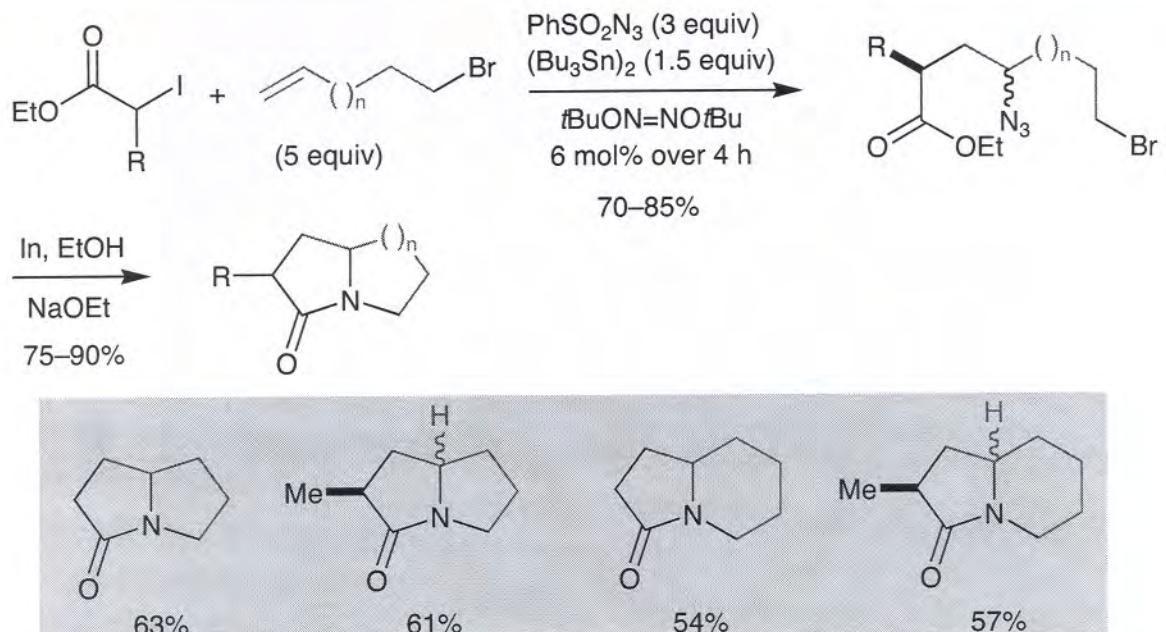


CYCLIZATION-AZIDATION





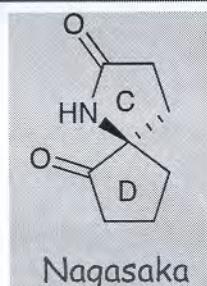
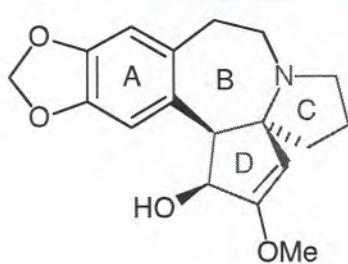
PYRROLIZIDINONES AND INDOLIZIDINONES



Renaud, P; Ollivier, C.; Panchaud, P. *Angew. Chem. Int. Ed.* 2002, 3460.



CEPHALOTAXINE (*Cephalotaxus fortunei*)

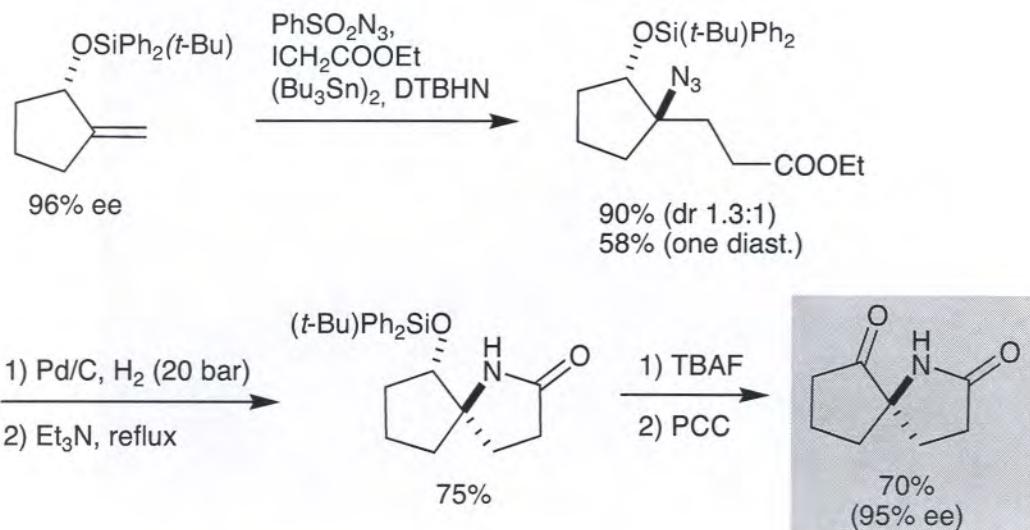


- Isolation:** Paudler et al 1963
- Structure:** Abraham et al 1969 (X-ray)
- Activity:** ester derivatives show antileukemic activity
- Synthesis:** Weinreb 1972 (\pm)
Semmelhack 1972 (\pm)
Mori 1995 (-)
Nagasaki 1997 (-)
Tietze 1999 (-)

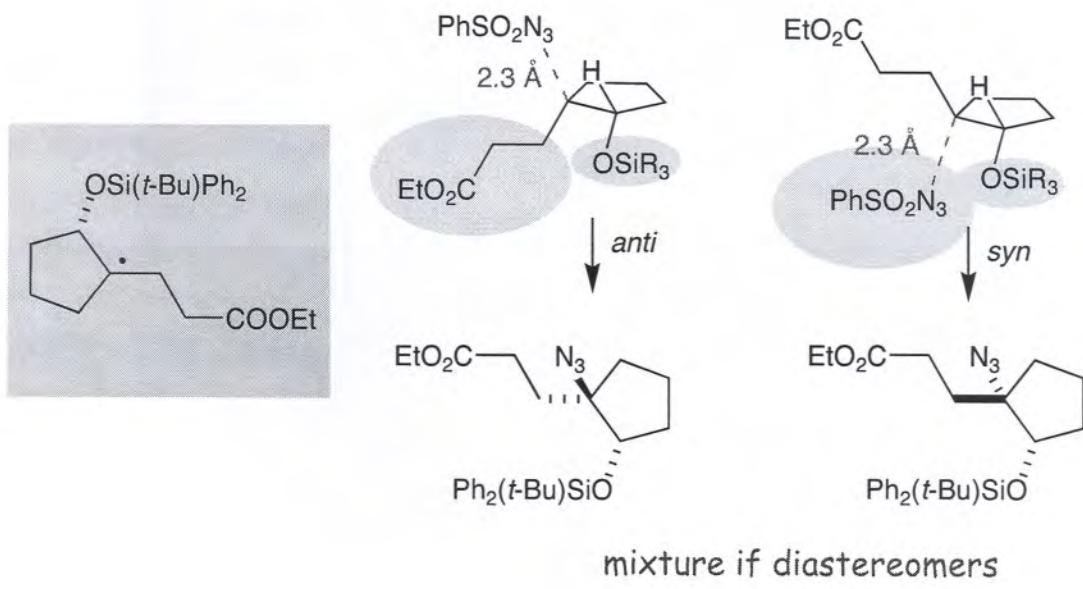
Chinese plum yew



SYNTHESIS OF NAGASAKA INTERMEDIATE

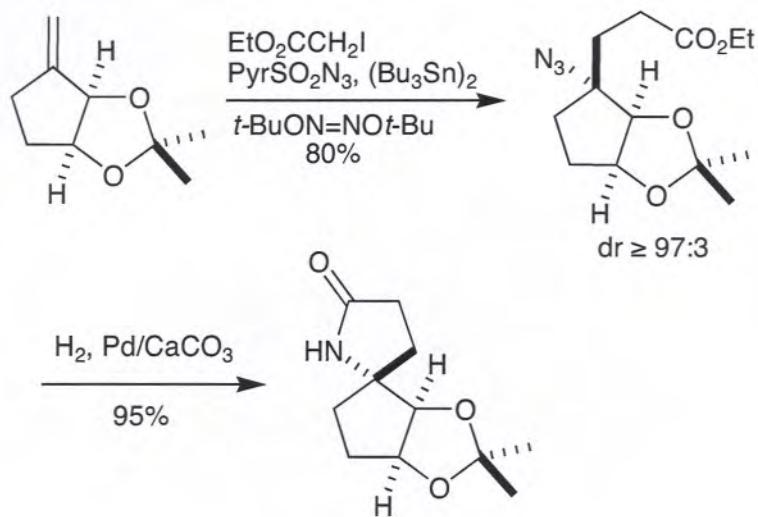


STEREORESELECTIVITY WITH 1,2-DISUBSTITUTED CYCLOALKYL RADICALS

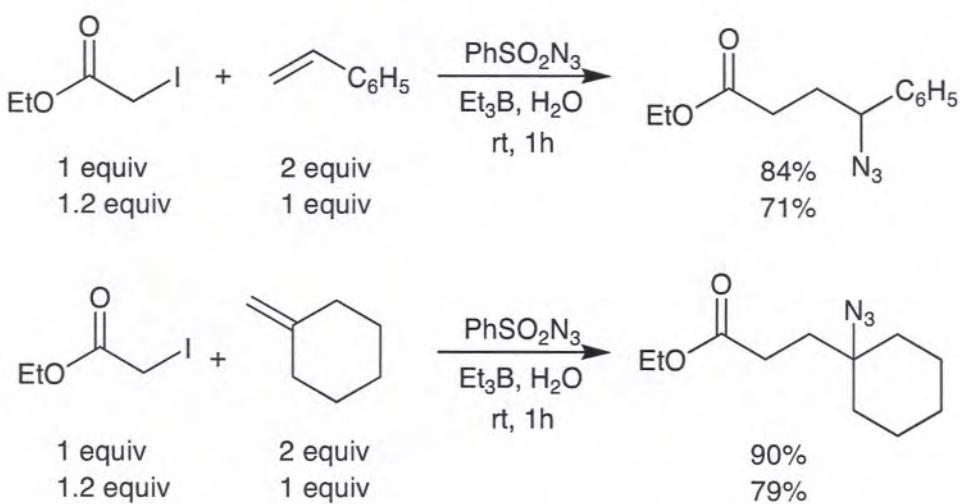




STEREORESELECTIVITY WITH 1,2-DISUBSTITUTED CYCLOALKYL RADICALS



TIN-FREE CARBOZIDATION



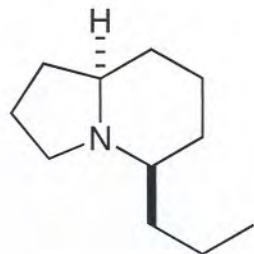
Et₃B in water: K. Oshima and coll. *Synlett* 2002, 674.
P. Panchaud, P. Renaud, *J. Org. Chem.* 2004, 69, 3205.



(-)-INDOLIZIDINE 167B



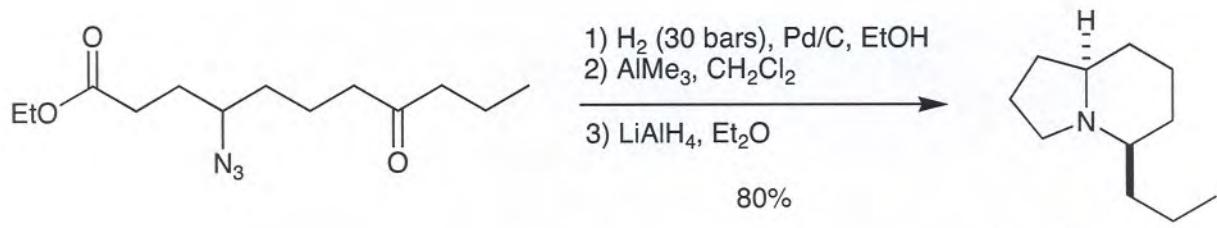
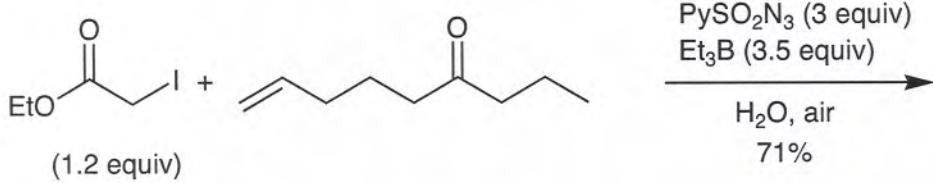
Dendrobates Leucomelas
Poison dart frogs
Symptoms similar to curare.



J. W. Daly, *Fortschr. Chem. Org. Naturst.* 1982, 41, 205.



(-)-INDOLIZIDINE 167B



(\pm)-indolizidine 167B

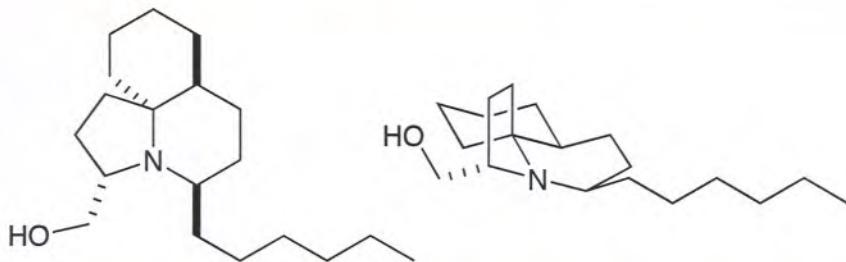


LEPADIFORMINE

Isolation
From the tunicate
Clavelina
Lepadiformis
J. F. Biard,
Tetrahedron Lett.
1994, 35, 2691.



sea squirt
(Encyclopædia Britannica)



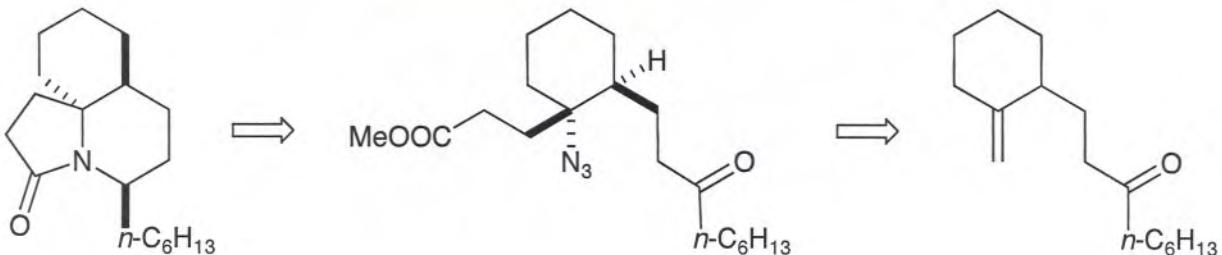
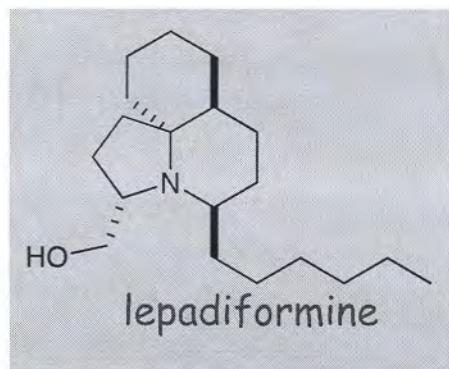
cytotoxic activity against various tumor cell lines
cardiovascular effects

Synthesis

- C. Kibayashi, *J. Am. Chem. Soc.* 2000, 122, 4583
M. Weinreb *Organic Lett.* 2001, 3, 3507.
R. L. Funk *Organic Lett.* 2001, 3, 3511.
(W. H. Pearson, *J. Org. Chem.* 1999, 64, 688).

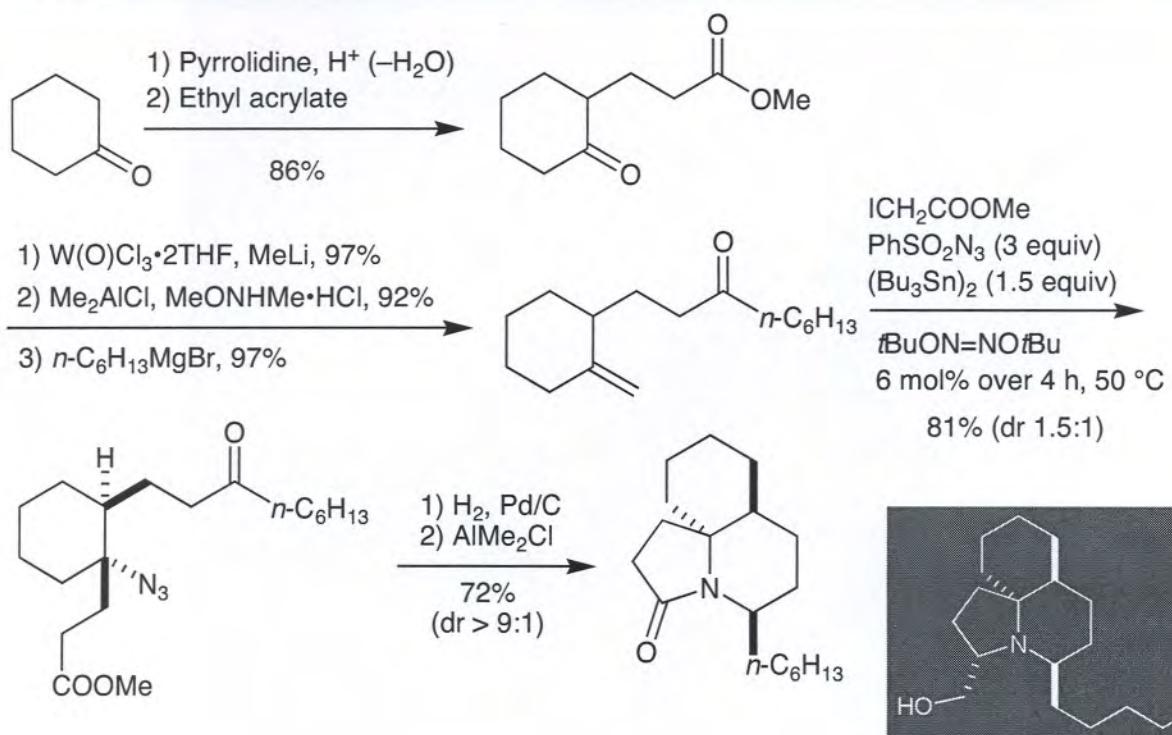


Retrosynthesis

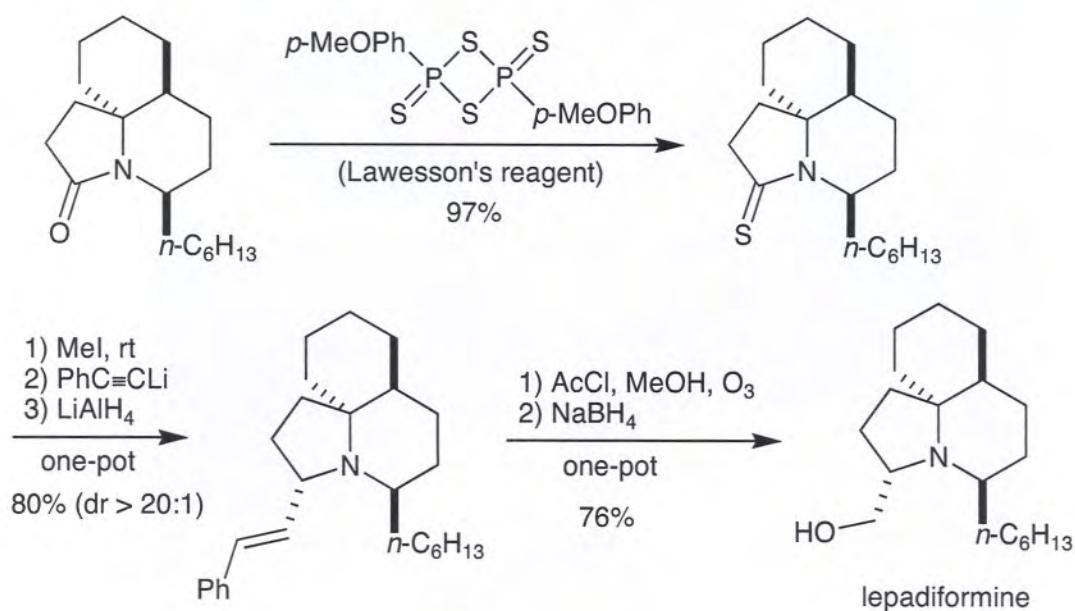




THE TRICYCLIC CORE OF LEPADIFORMINE



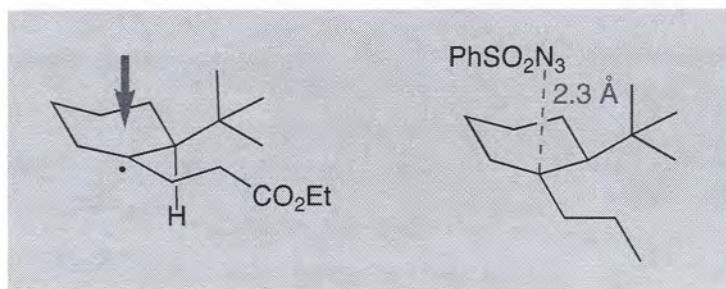
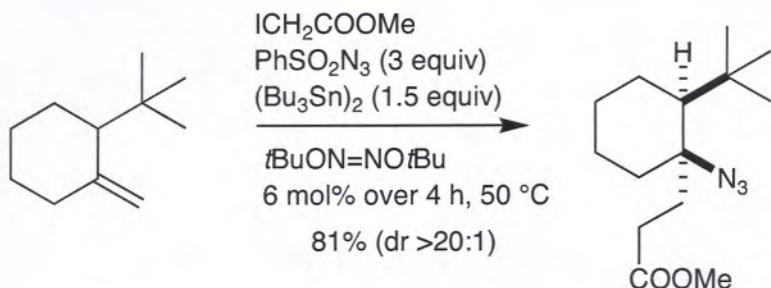
LEPADIFORMINE



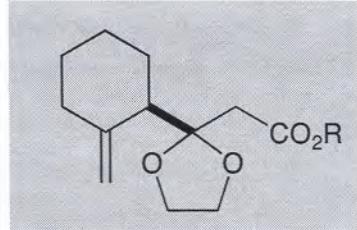
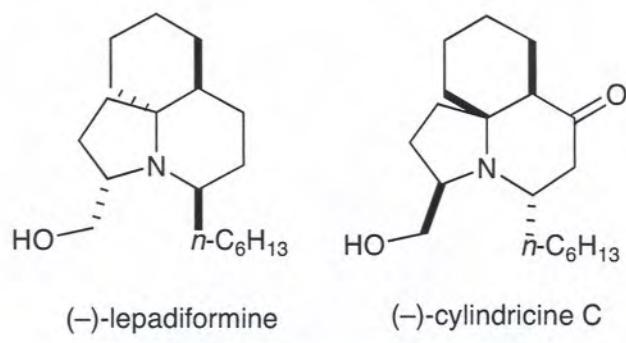
I. Takahata et al, *J.Chem. Soc., Perkin Trans. 1*, 1989, 1211.



Stereoselectivity Control



CYLINDRICINE C





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