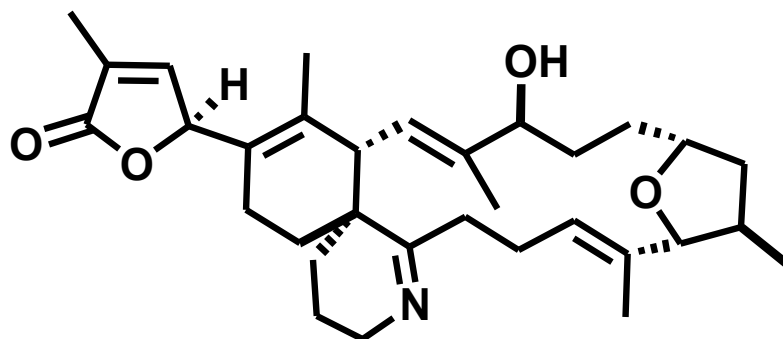


# Studien zur Totalsynthese von (-)-Gymnodimin

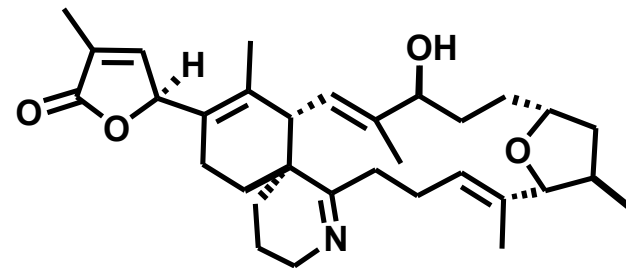


**James D. White, Laura Quaranta & Guoqiang Wang**

*J. Org. Chem.* **2007**, 72, 1717-1728

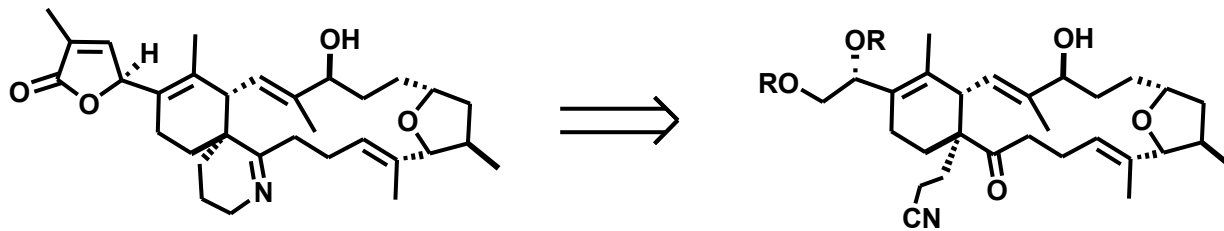
## Einleitung

- 1994 in Neuseeland von Seki et. al entdeckt
- produziertes Neurotoxin von Dinoflagellates *Gymnodinium sp.* (Karenia Selliforme)
- orale Aufnahme wenig toxisch ( $LD_{50}$  755  $\mu\text{g}/\text{kg}$ )
- bei Injektion stark toxisch ( $LD_{50}$  96  $\mu\text{g}/\text{kg}$ )
- bioaktives Spiroimin
- ähnliche Struktur wie Pinnatoxine, Spirolide und Pteriatoxine

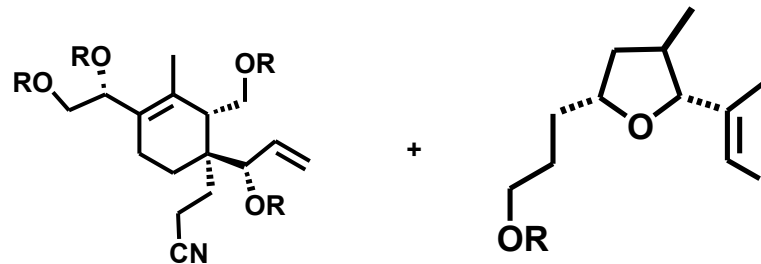


Seki, Satake, Mackenzie *Tetrahedron Lett.* 1995, 36, 7093-7096

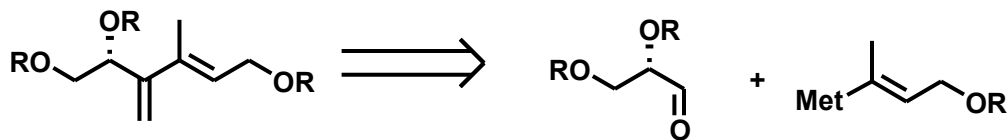
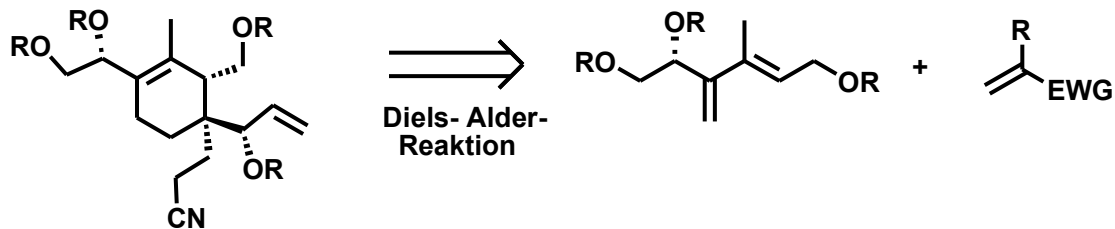
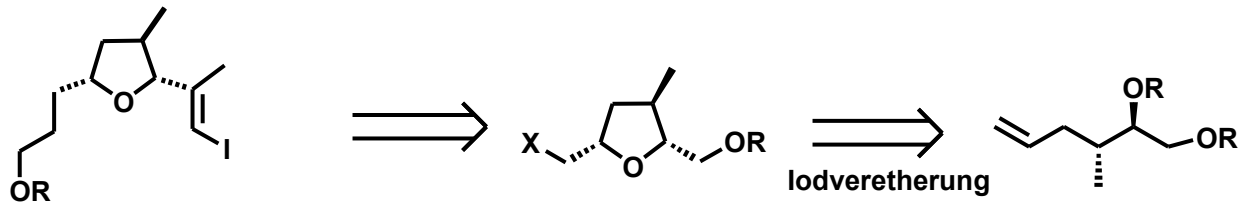
**Retrosynthese:**



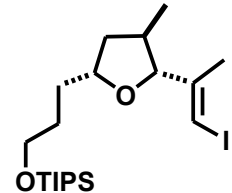
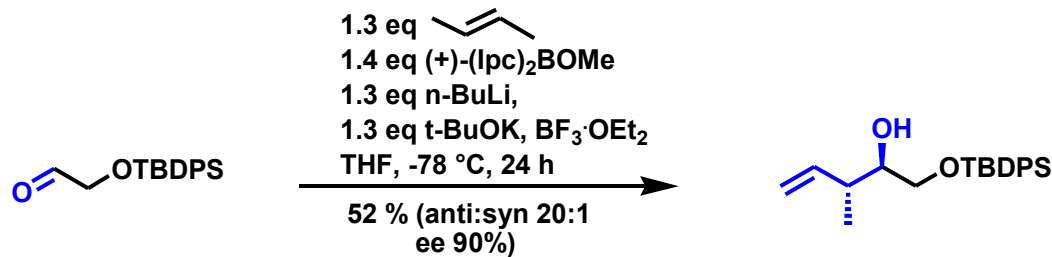
  
**B-Alkyl Suzuki-Miyaura-  
Kupplung**



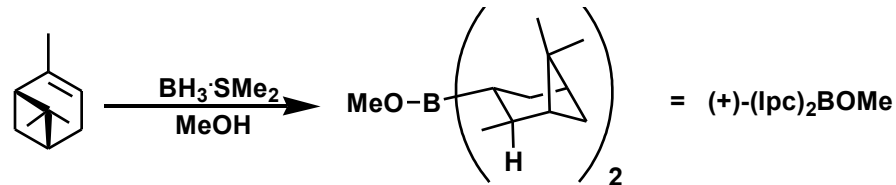
**Retrosynthese:**



**Brown – Crotonylierung:**



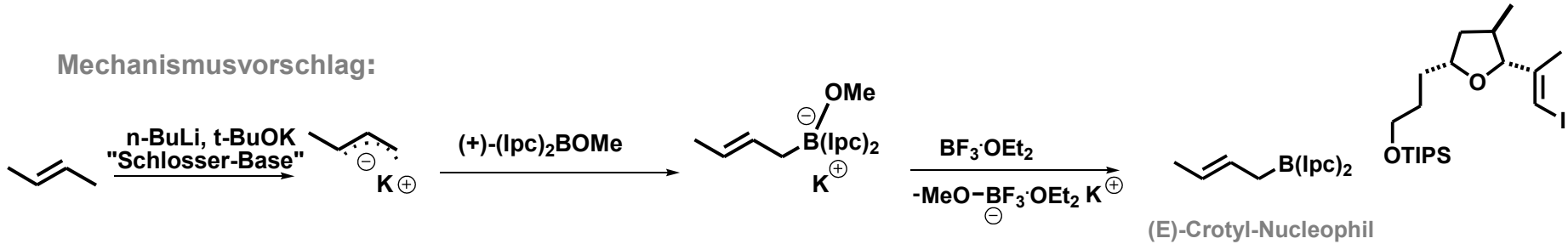
→ Darstellung des chiralen Reagens:



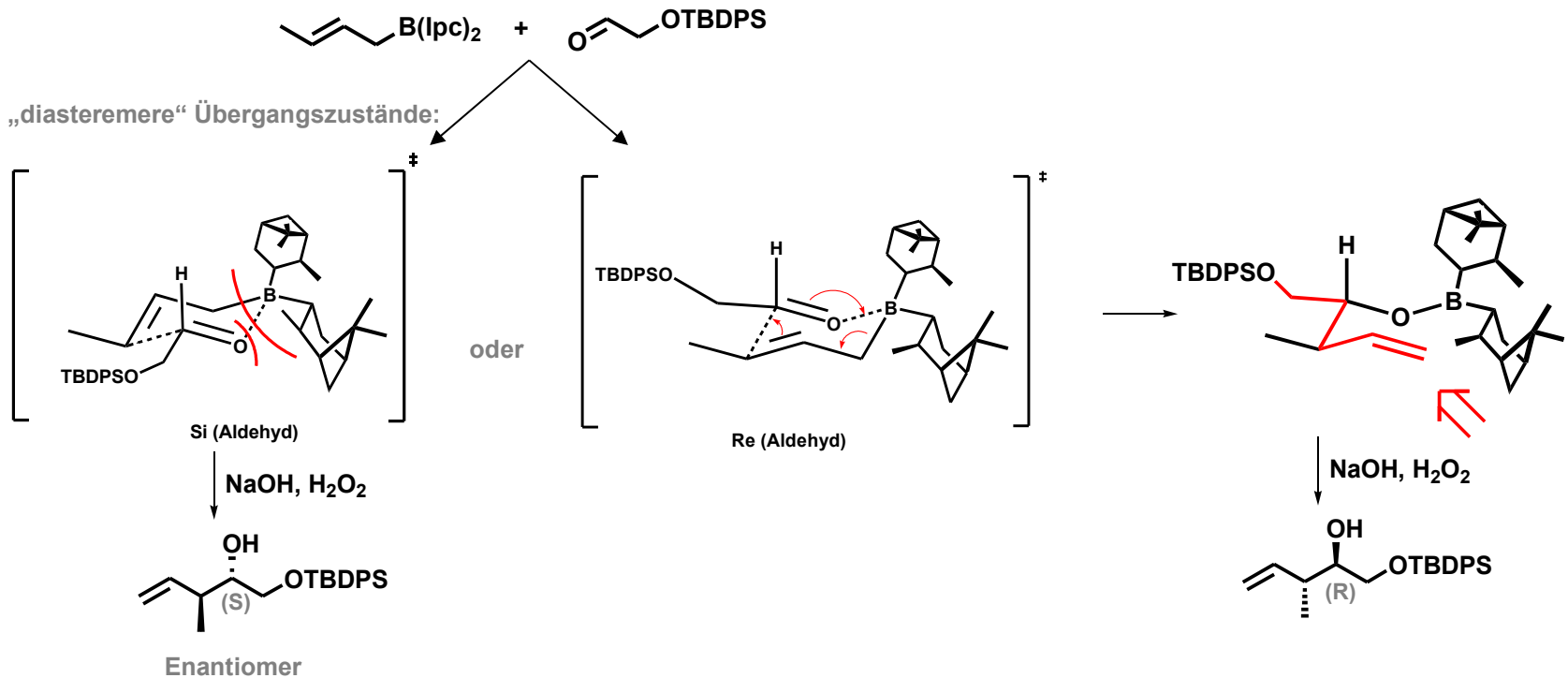
→ (E) - But-2-en als Alkylierungsmittel

H. C. Brown, K. S. Bhat; *J. Am. Chem. Soc.* **1986**, *108*, 293-294

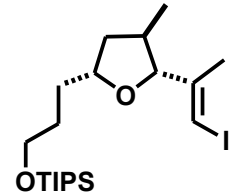
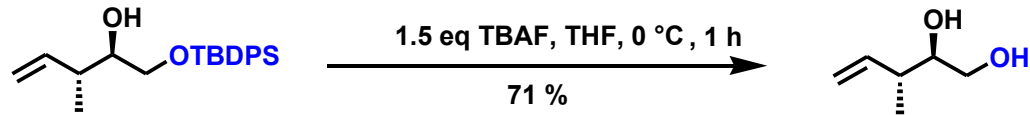
Mechanismusvorschlag:



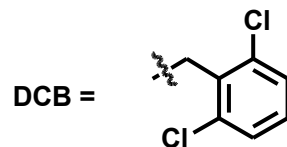
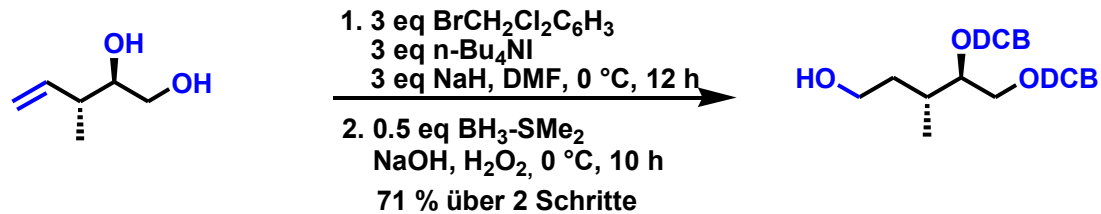
Zwei „diastereomere“ Übergangszustände:



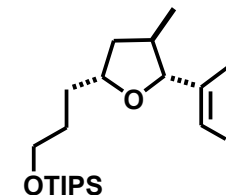
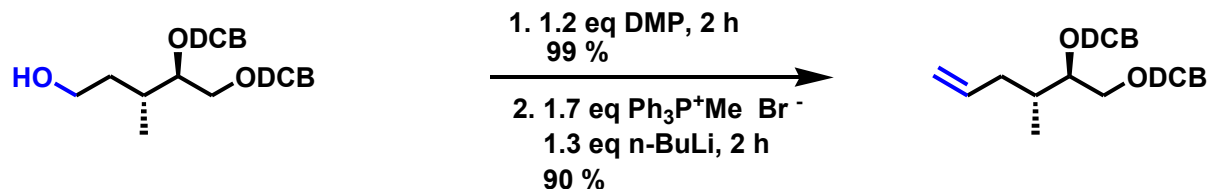
Entschützung:



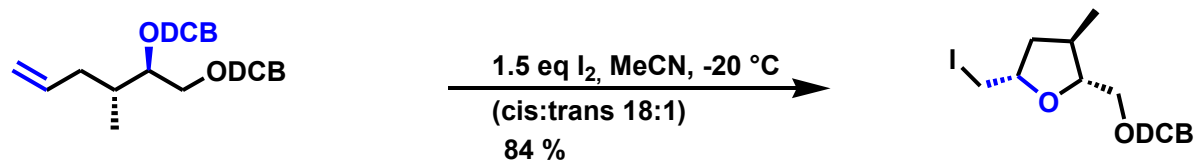
Schützung mit DCB & Hydroborierung:



**Oxidation mit DMP & Wittig-Olefinierung:**

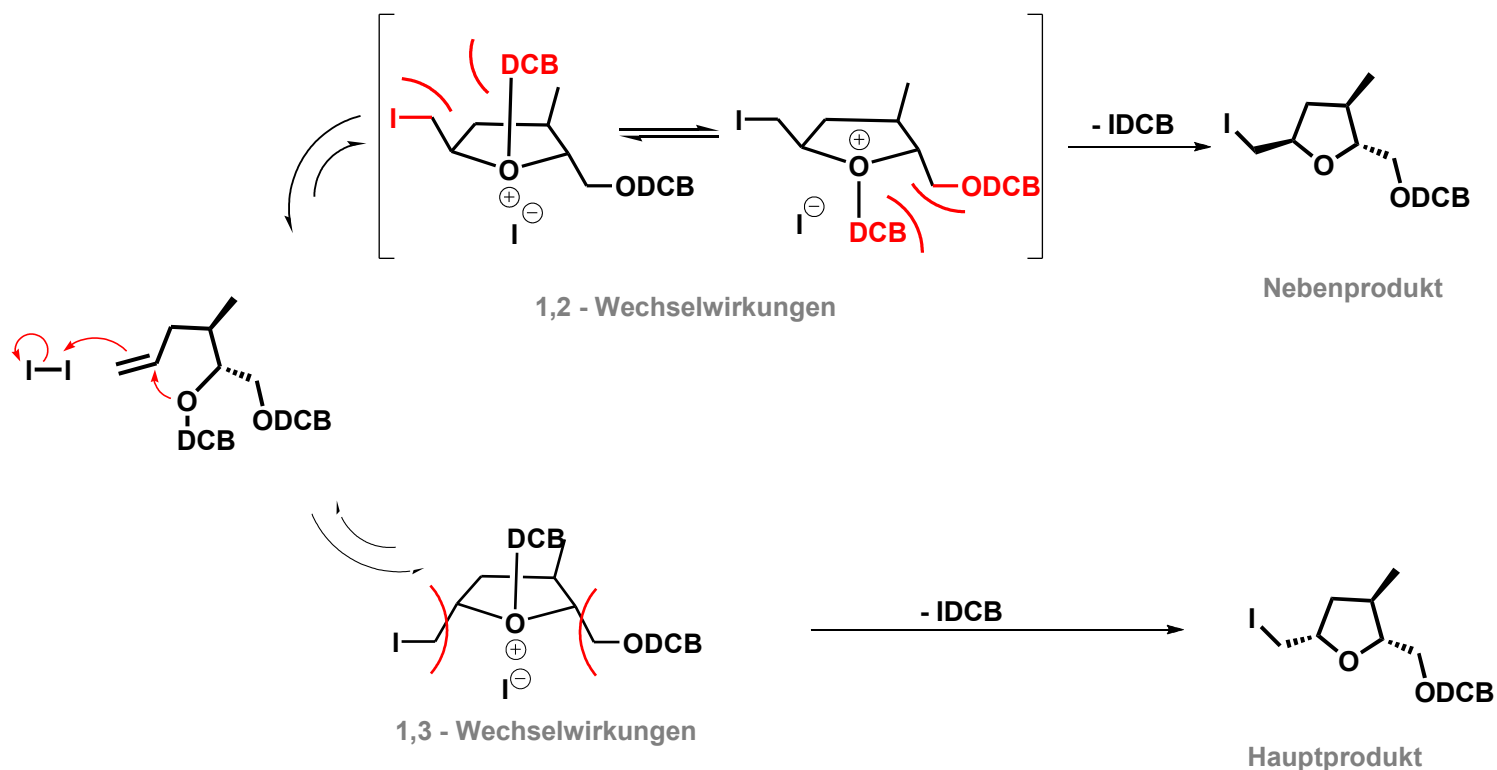


**Jodveretherung:**



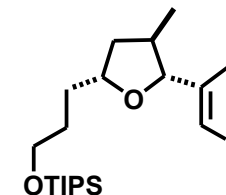
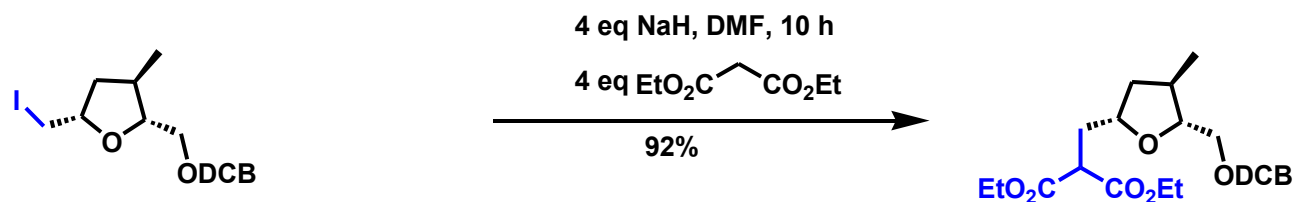


Mechanismusvorschlag:

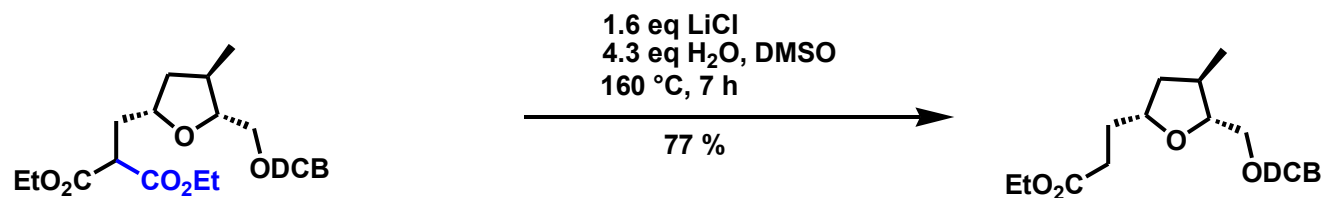


J. D. White, L. Quaranta, G. Wang; *Org. Lett.*, 2003, 5, 4109  
S. D. Rychnovsky, P. A. Barlett; *J. Am. Chem. Soc.* 1981, 103, 3963

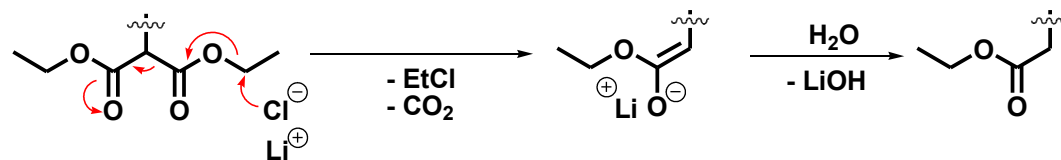
Umsetzung mit Diethylmalonat:



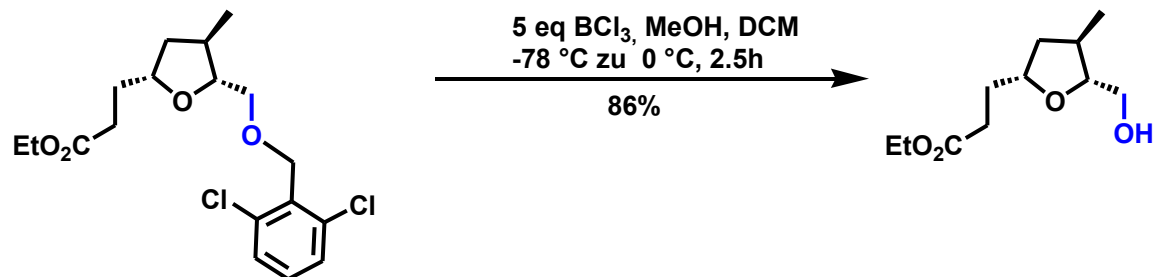
Decarboxylierung:



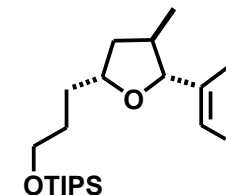
Mechanismusvorschlag:



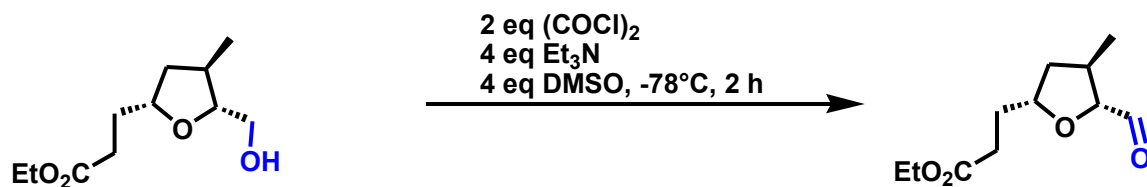
### Entschützung mittels $\text{BCl}_3$ :



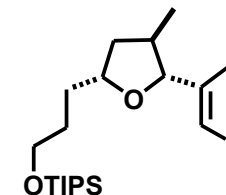
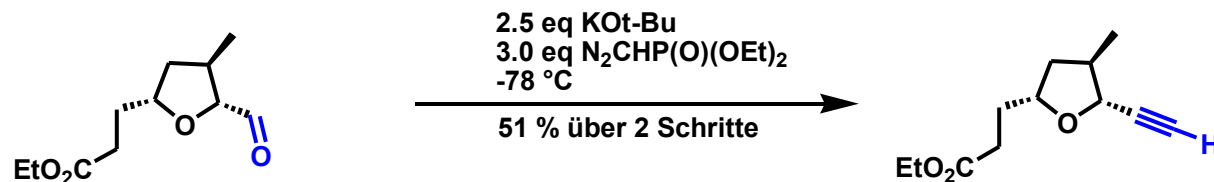
Reaktion verläuft nach einem  $\text{S}_{\text{N}}2$  Mechanismus



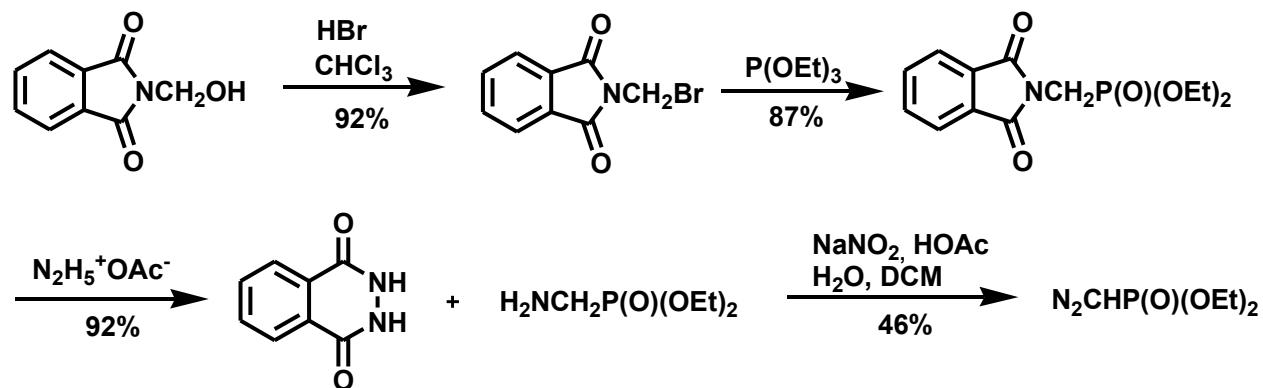
### SWERN - Oxidation:



### Alkinylierung mit Gilbert-Seyferth-Reagens:

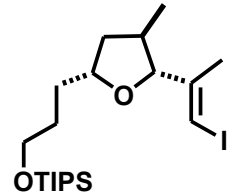
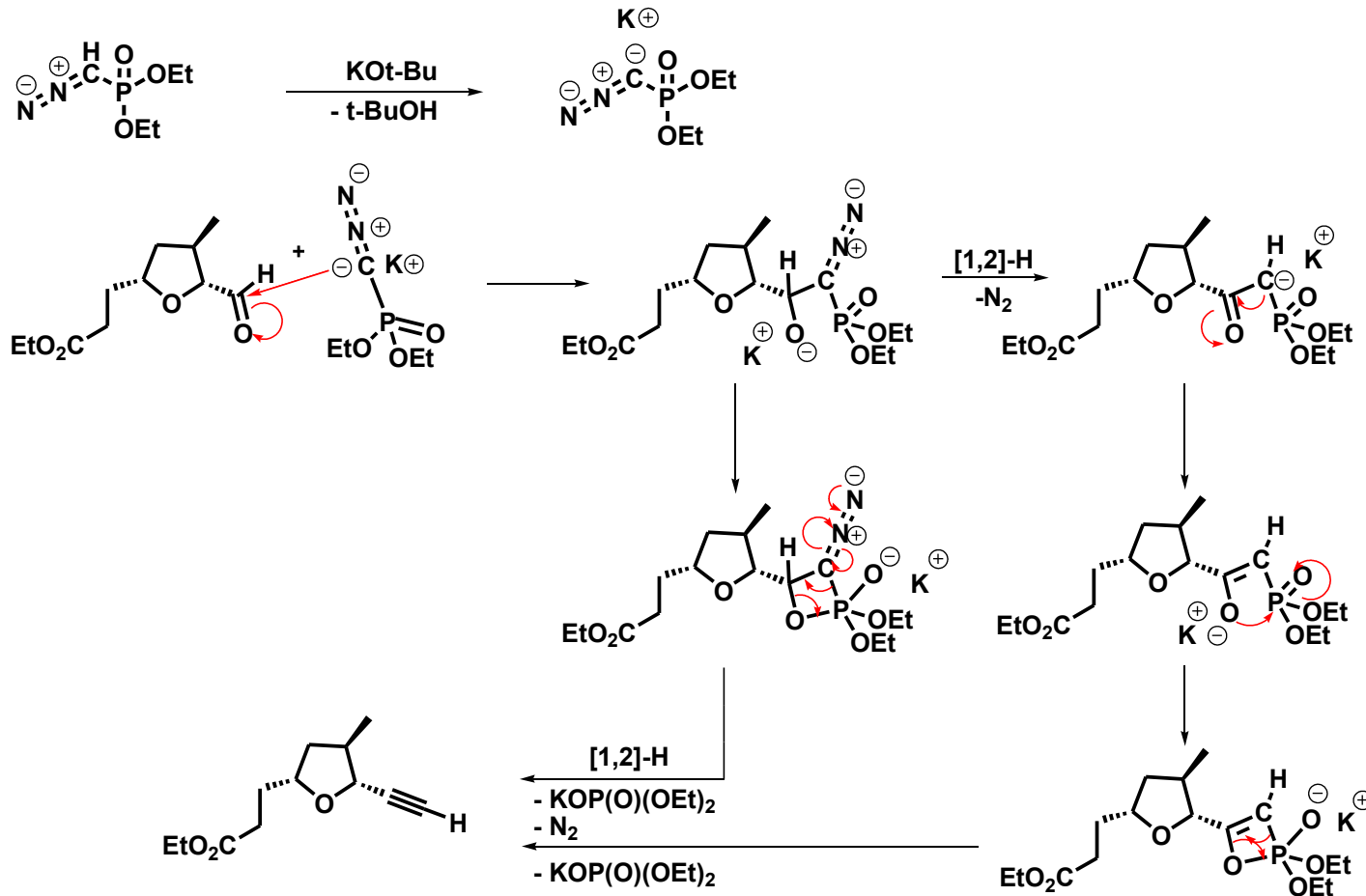


### Vorschlag zur Darstellung des Gilbert – Seyferth – Reagens:

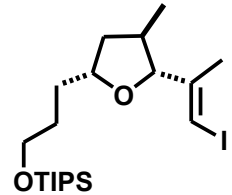
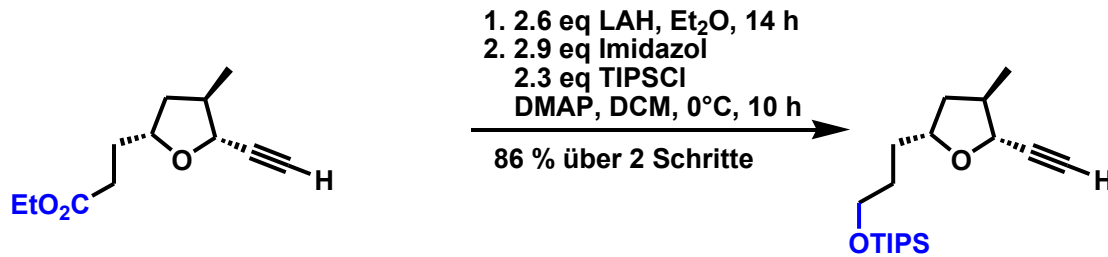


D. Seyferth, R. S. Marmor; *Tetrahedron Lett.* 1970, 11, 2493  
J. C. Gilbert, U. J. Weerasooriya; *J. Org. Chem.* 1979, 44, 4997

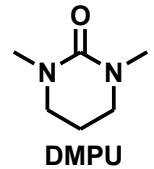
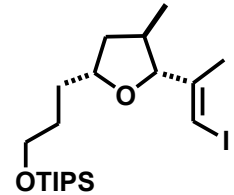
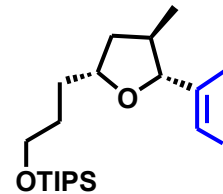
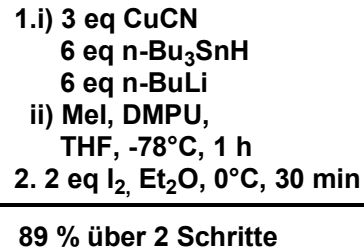
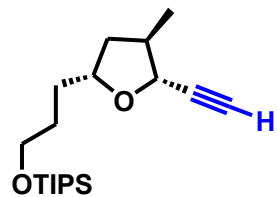
Mechanismusvorschlag:



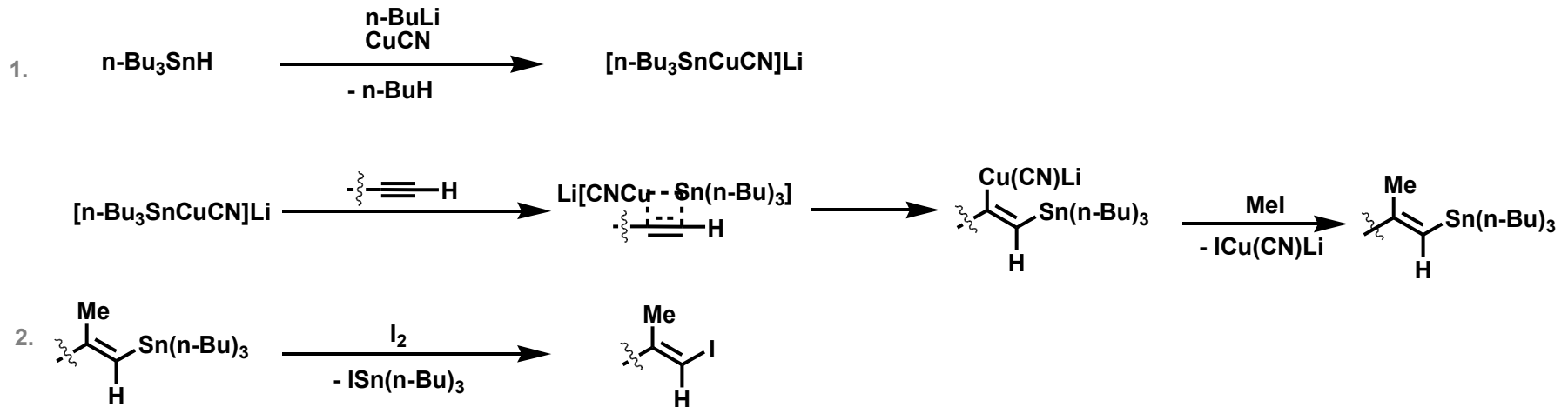
**Reduktion zum Alkohol & Schützung mit TIPSCI:**



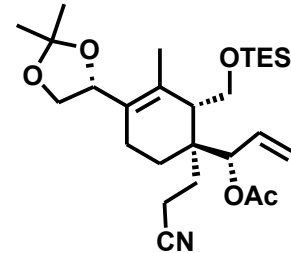
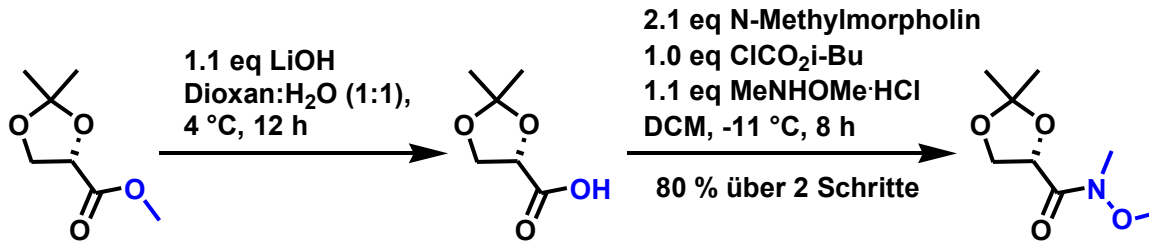
Stannylcuprierung:



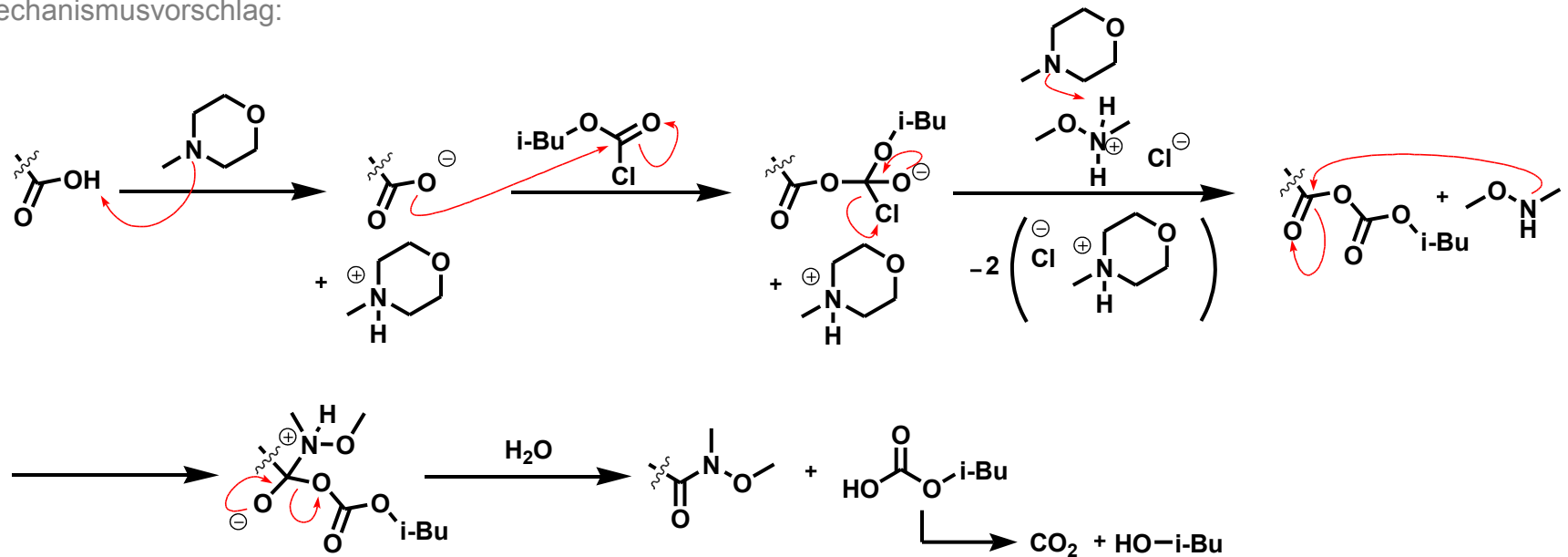
Mechanismusvorschlag:



**Esterverseifung mit anschließender Weinrebamidbildung:**



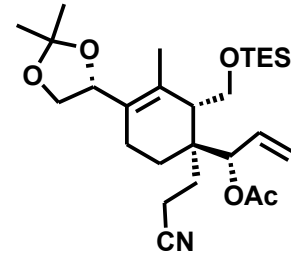
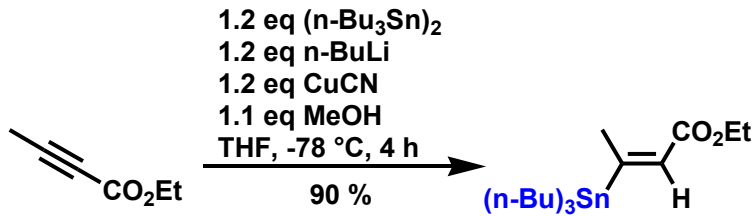
Mechanismusvorschlag:



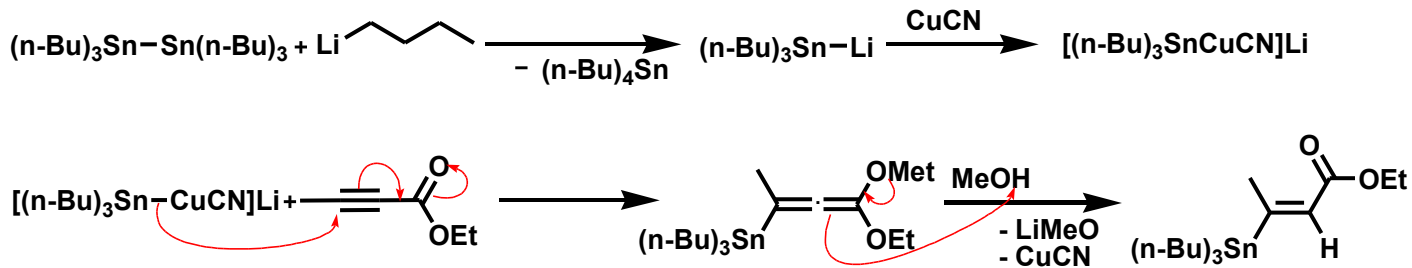
Brückner R. *Reaktionsmechanismen*; 3. Auflage; Spektrum-Verlag: München, D, 2004, pp 288



Stannylcuprierung:

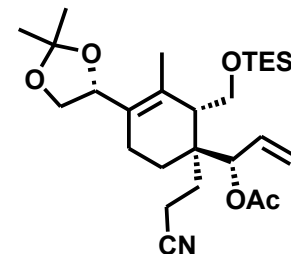
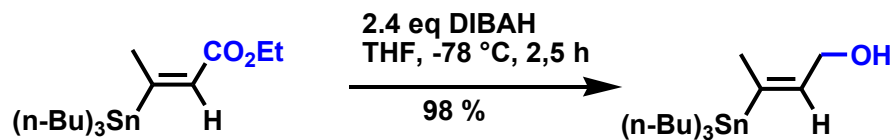


Mechanismusvorschlag:

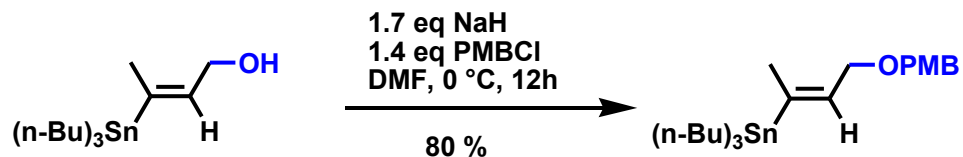


Lee, C. E.; Kick, E. K. *J. Am. Chem. Soc.* 1998, 120, 9735-9747

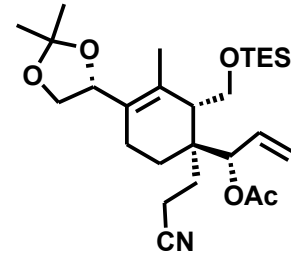
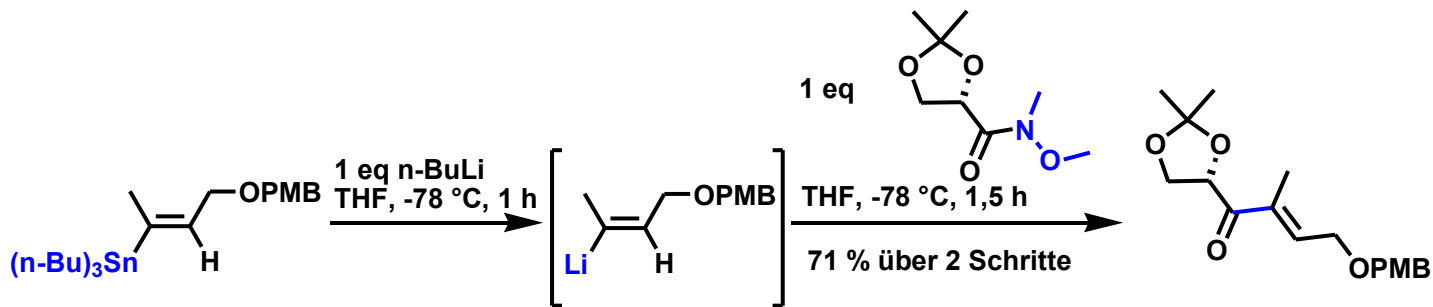
Reduktion mit DIBAH:



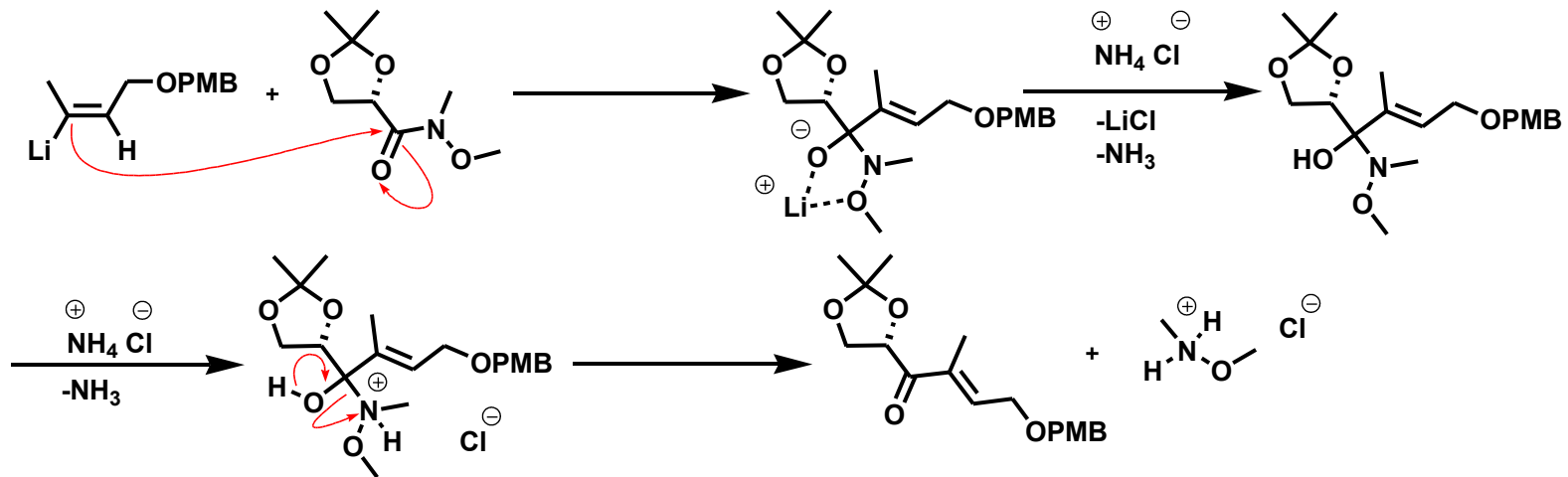
Schützung mit PMBCl:



Transmetallierung mit anschließender Weinreb-Keton-Synthese:

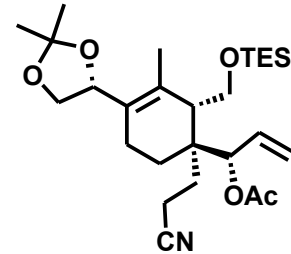
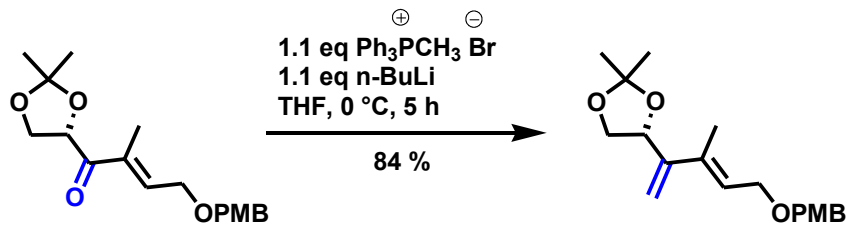


Mechanismusvorschlag:

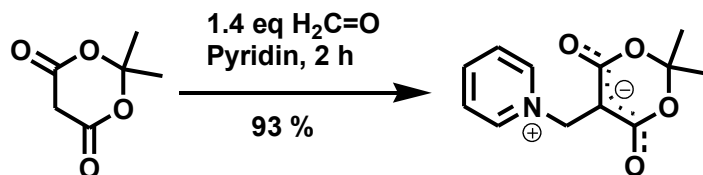


Brückner R. *Reaktionsmechanismen*; 3. Auflage; Spektrum-Verlag: München, D, 2004, pp 313f

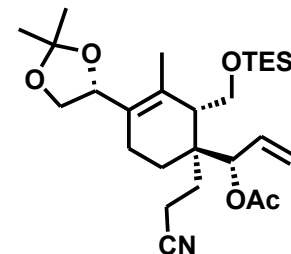
**Wittig-Olefinierung:**



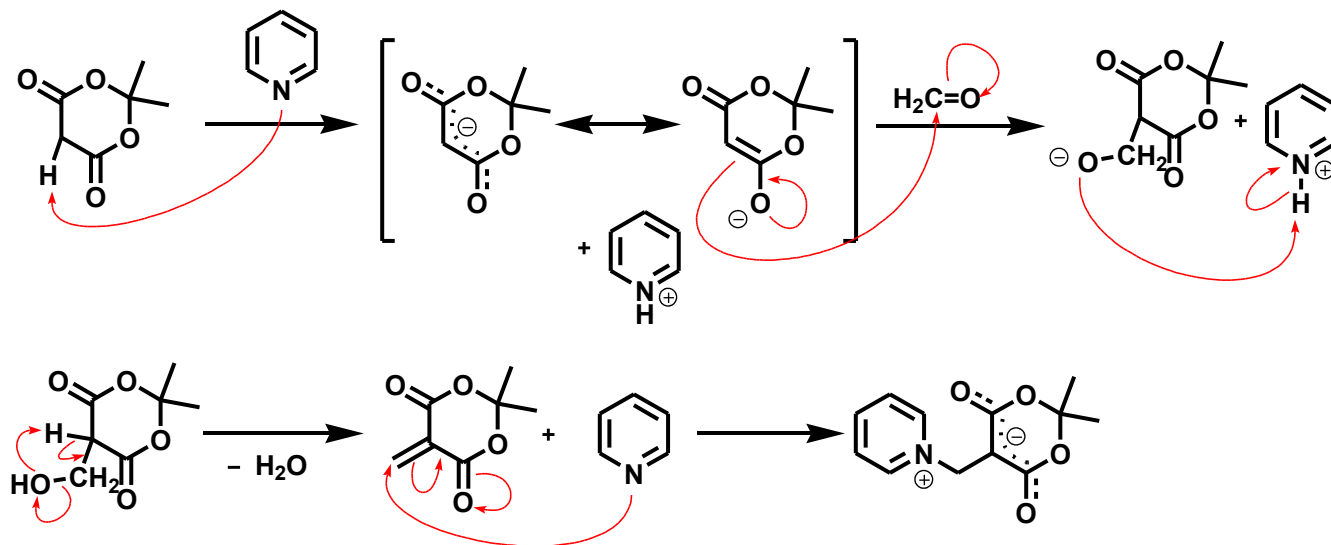
**Dienophil-Synthese:**



Meldrums Säure

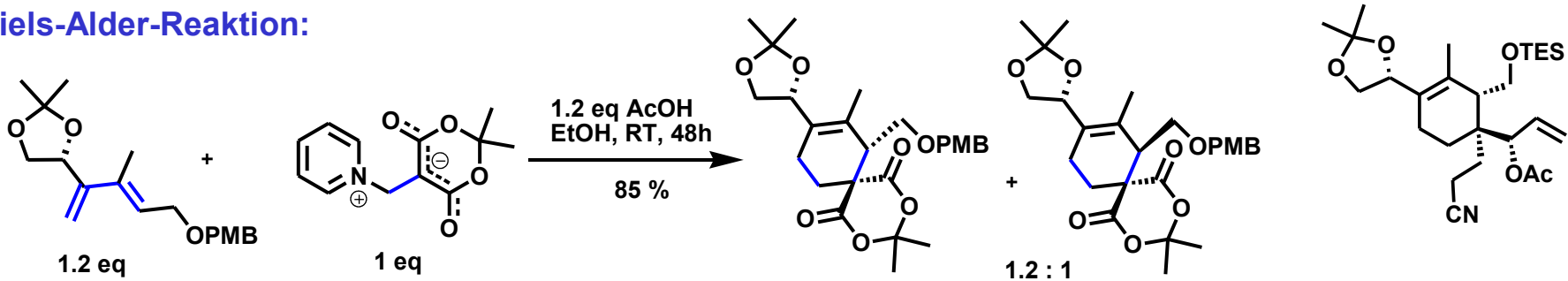


Mechanismusvorschlag:

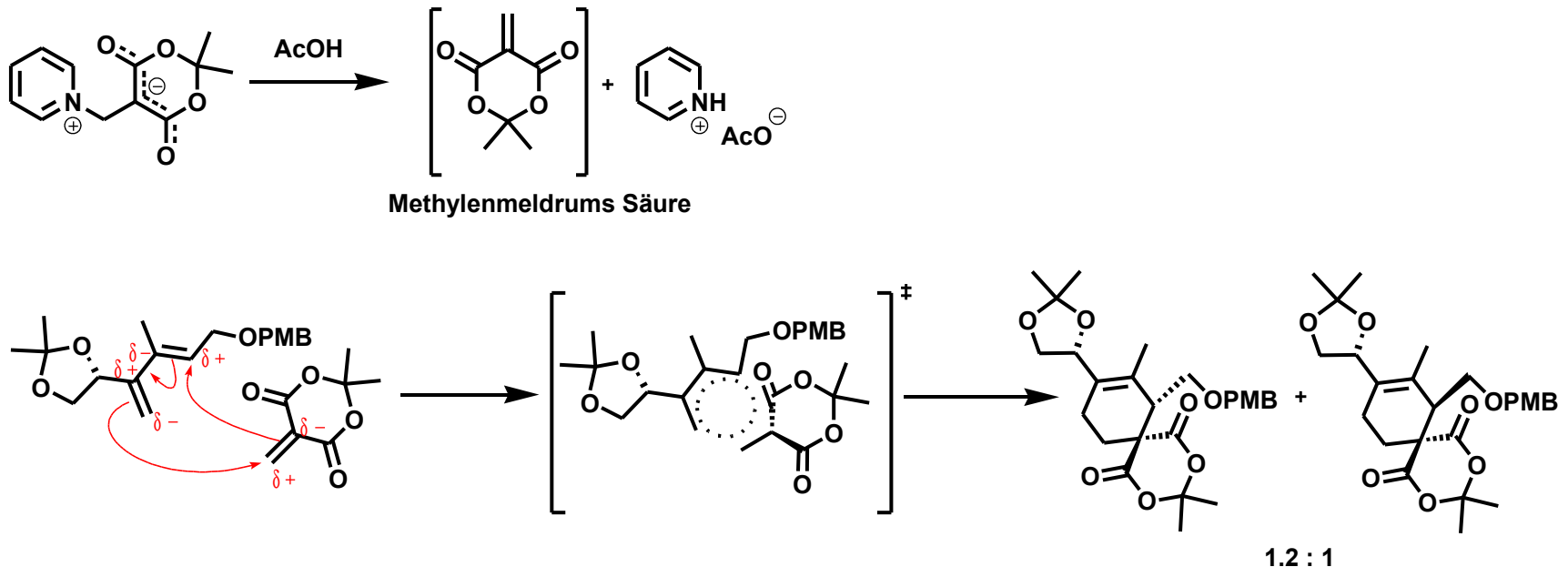


Zia-Ebrahimi, M.; Huffman, G. W. *Synthesis* 1996, 215-218

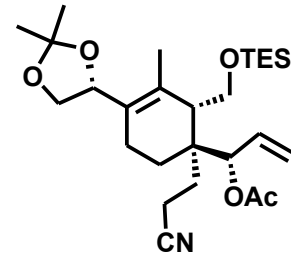
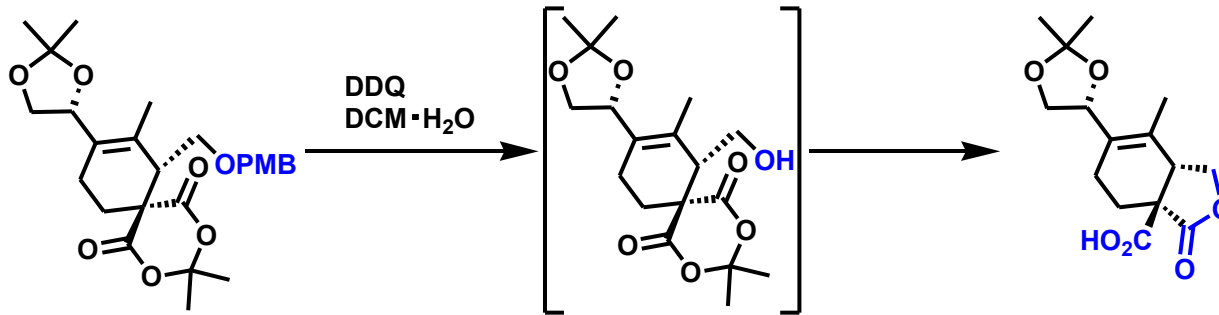
**Diels-Alder-Reaktion:**



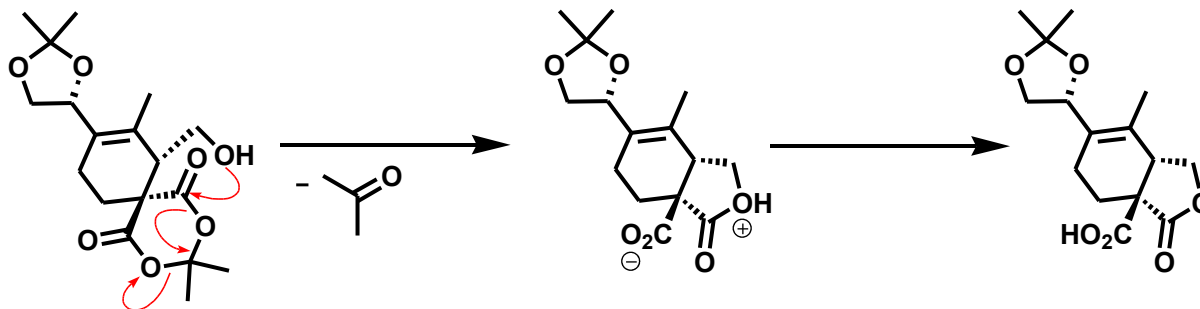
Mechanismusvorschlag:



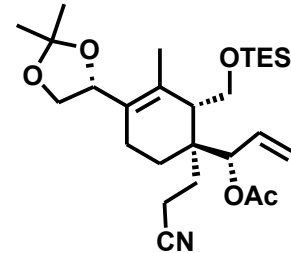
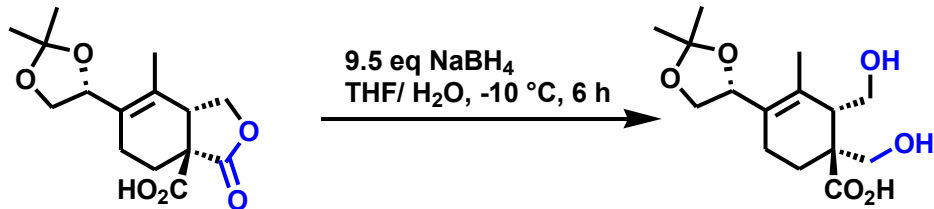
Entschützung mit DDQ mit anschließender spontaner Umesterung:



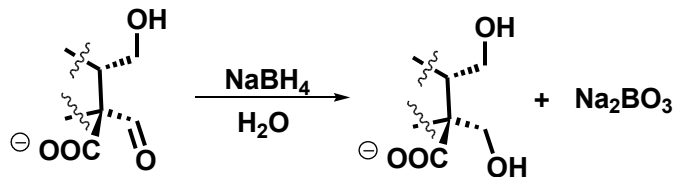
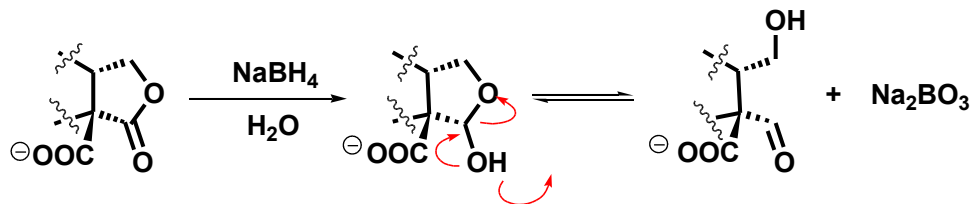
Mechanismusvorschlag:



### Reduktion mit Natriumborhydrid:



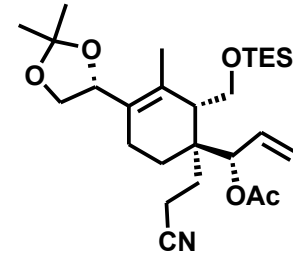
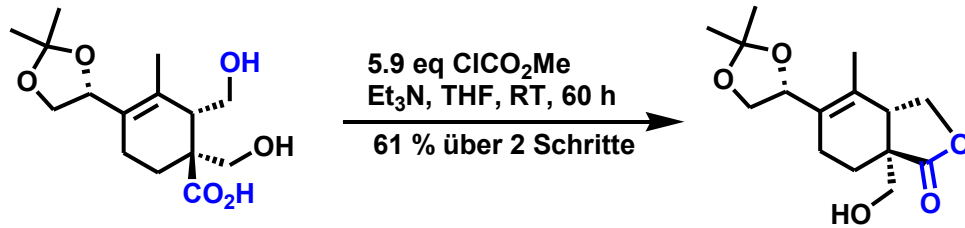
### Mechanismusvorschlag:



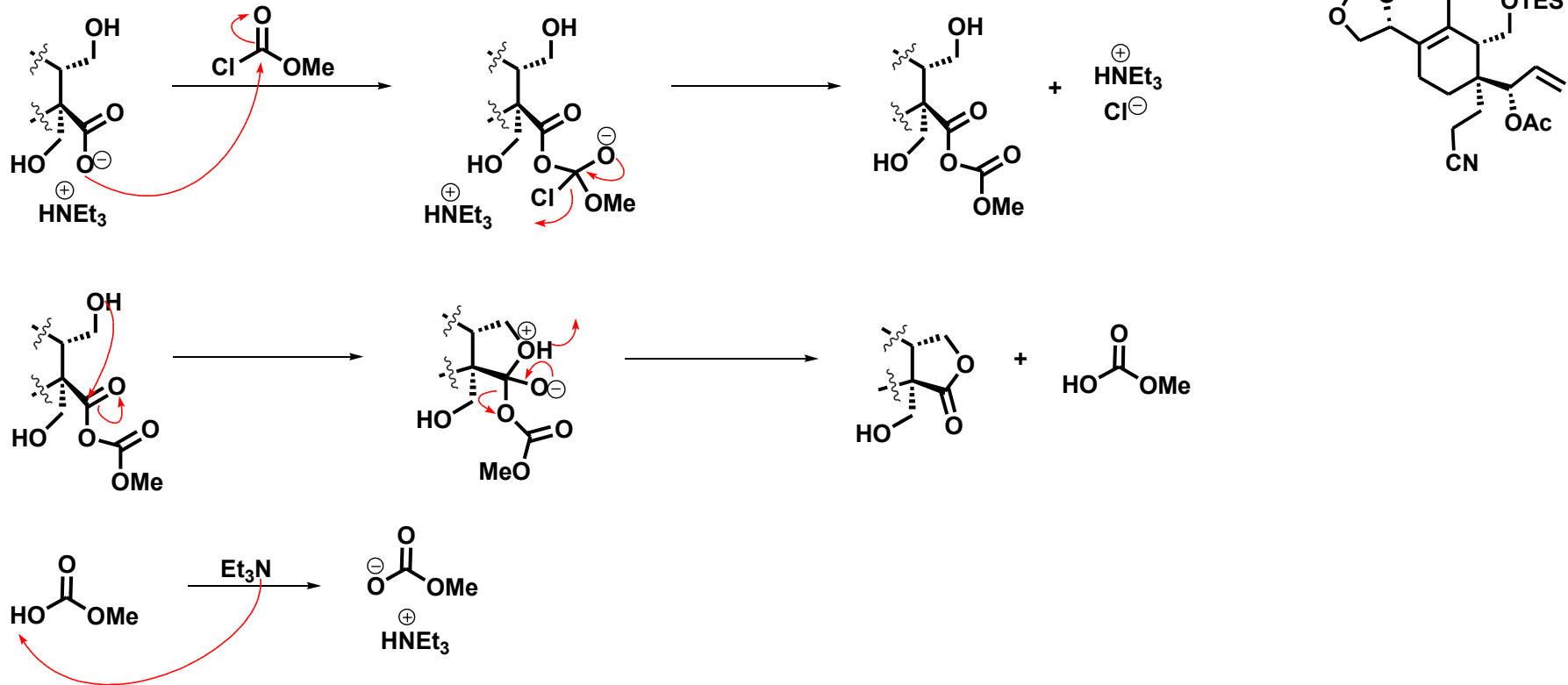
Brückner R., Reaktionsmechanismen, *Spektrum-Verlag*, 3. Auflage 2004 S.788



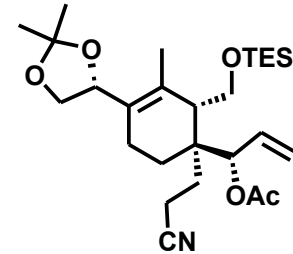
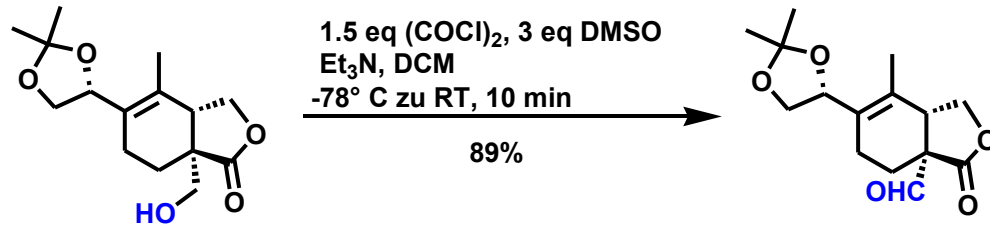
**trans-Lactonbildung:**



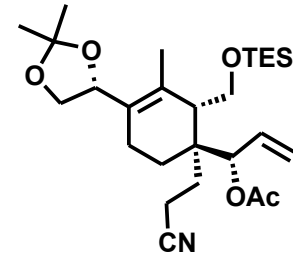
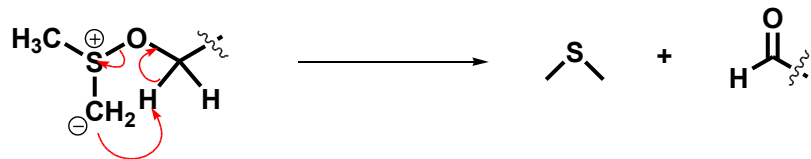
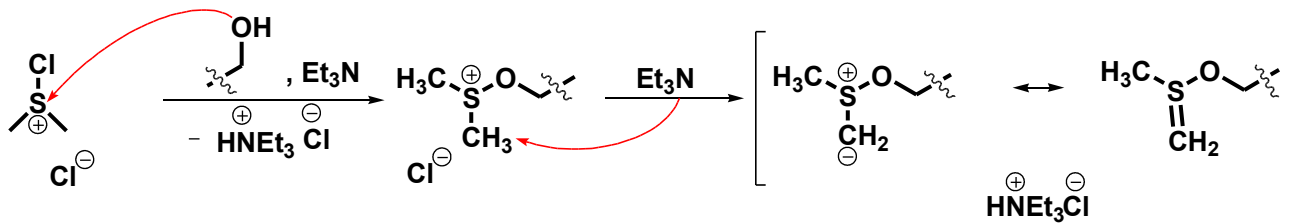
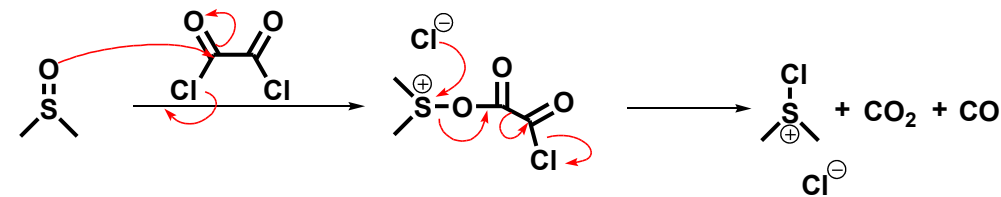
Mechanismusvorschlag:



**Swern- Oxidation:**

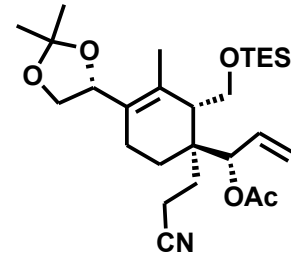
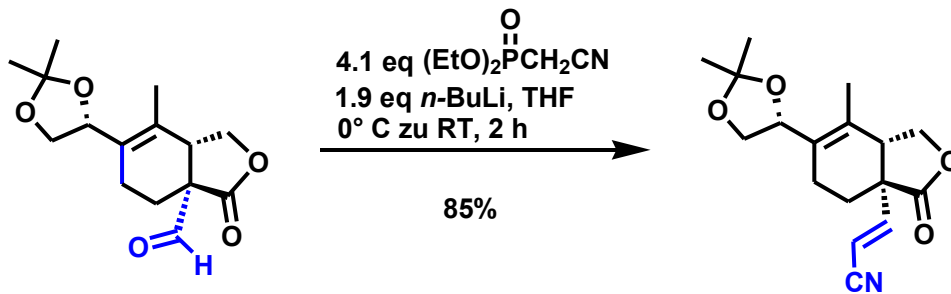


Mechanismusvorschlag:



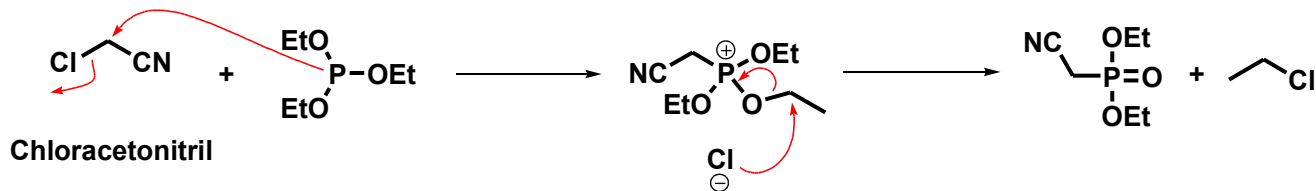
Brückner R., Reaktionsmechanismen, Spektrum-Verlag, 3. Auflage 2004 S.745

Alkenylierung (HWE-Mechanismus):



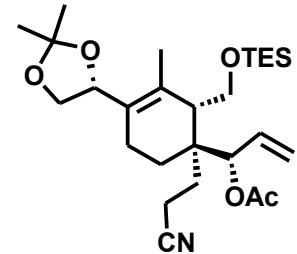
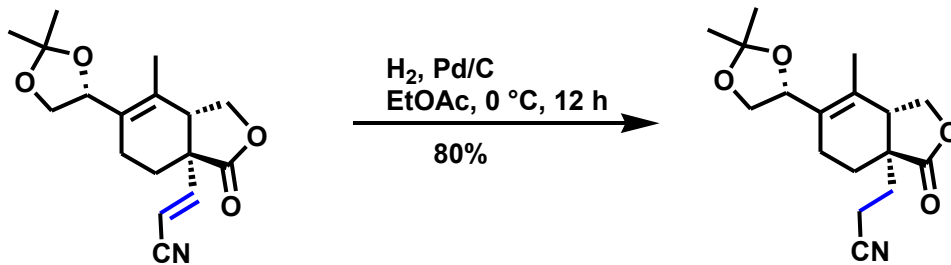
Vorschlag zur Darstellung von Cyanmethylphosphonsäurediethylester:

→ Michaelis- Arbuzov- Reaktion

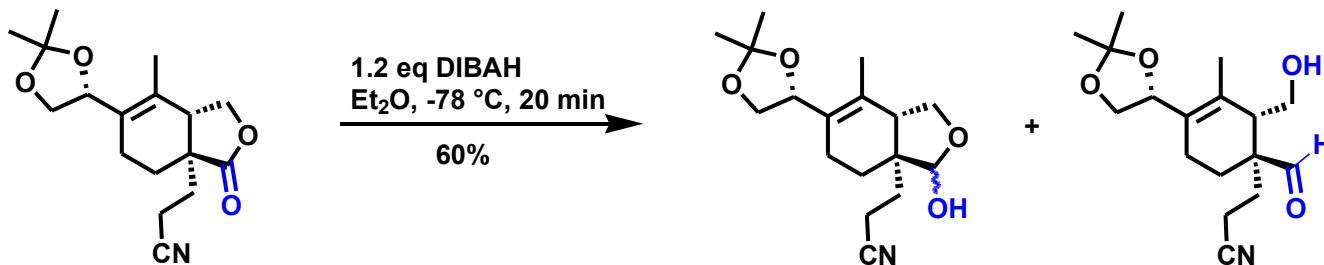


Beckert, R.; Fanghangel, E.; *Organikum*, Wiley- VCH Verlag GmbH, Weinheim 2004 S. 245

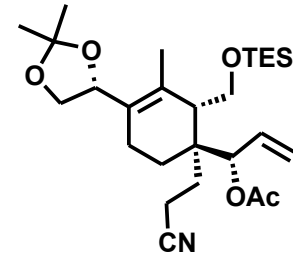
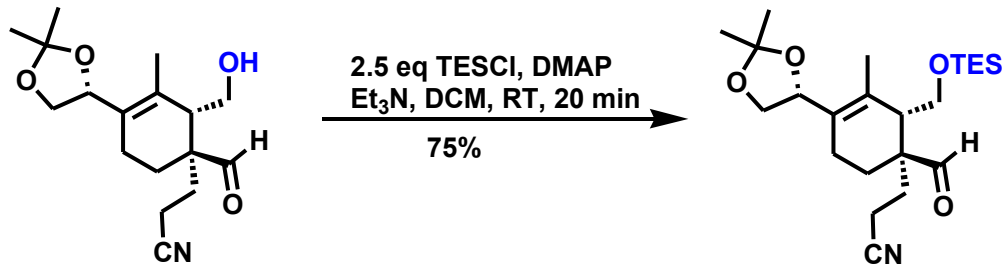
**Pd- katalysierte Hydrierung:**



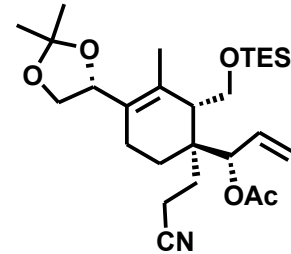
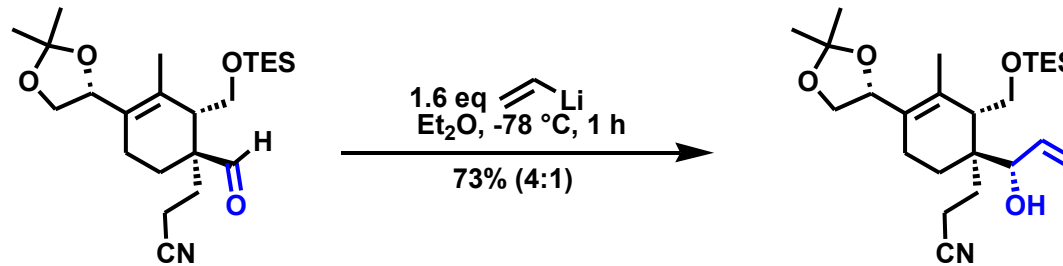
**Reduktion mit DIBALH:**



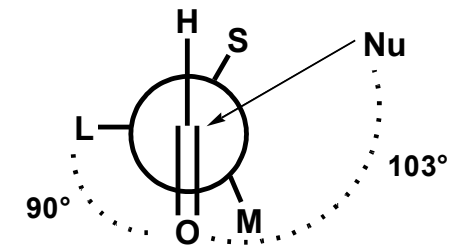
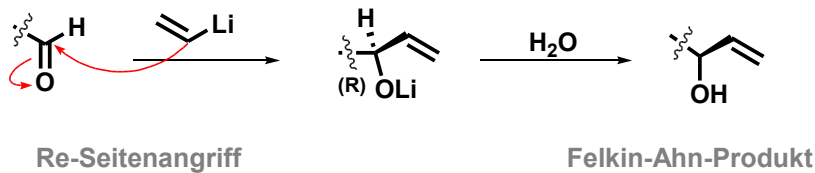
Schützung mit TESCI:



Alkenylierung des Aldehyds:



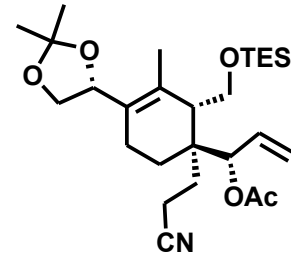
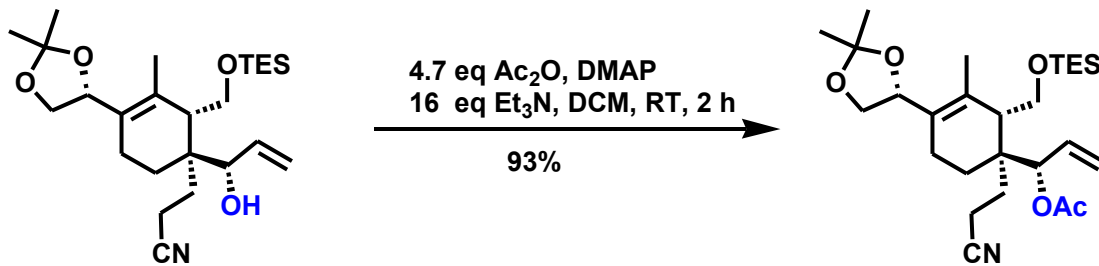
Mechanismusvorschlag:



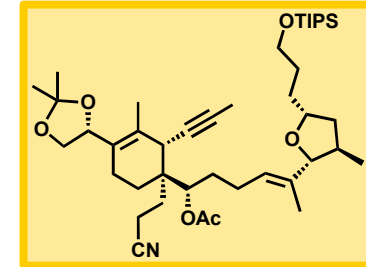
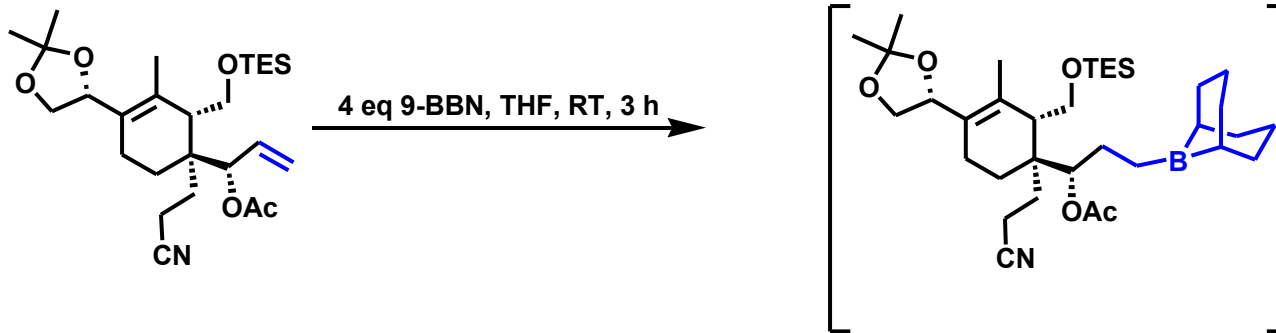
- S  $\text{CH}_2\text{-CH}_2\text{-CN}$
- M  $\text{CH}_2\text{-CH}_2\text{-R}$
- L  $\text{CH}(\text{CH}_2\text{-OTES})\text{R}$



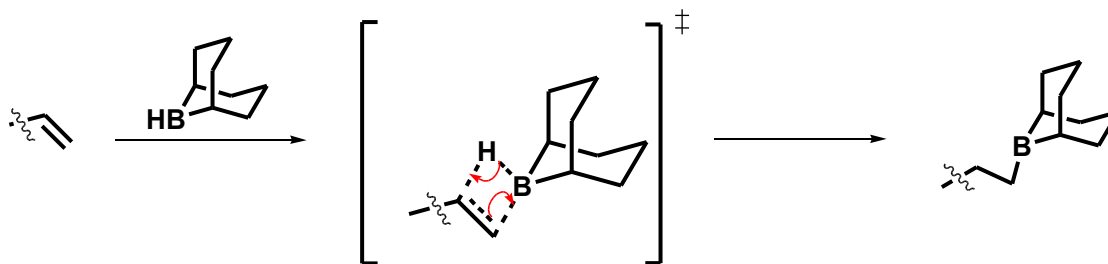
**Schützung mit Essigsäureanhydrid:**



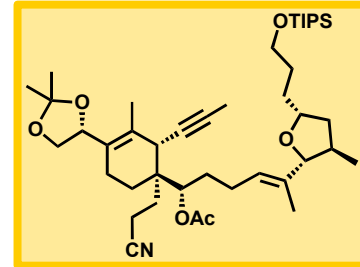
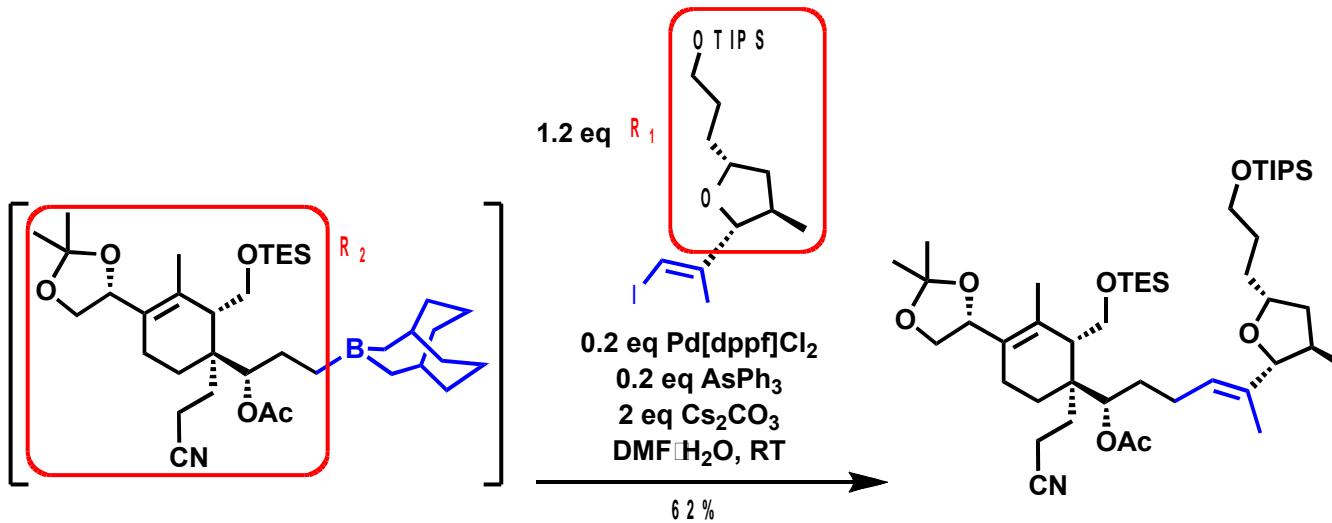
Hydroborierung:



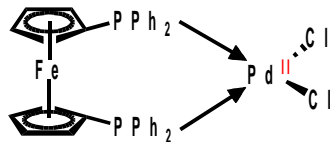
Mechanismusvorschlag:



**Suzuki-Miyaura-Kupplung:**



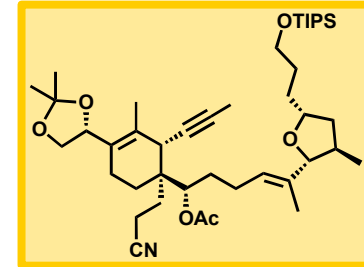
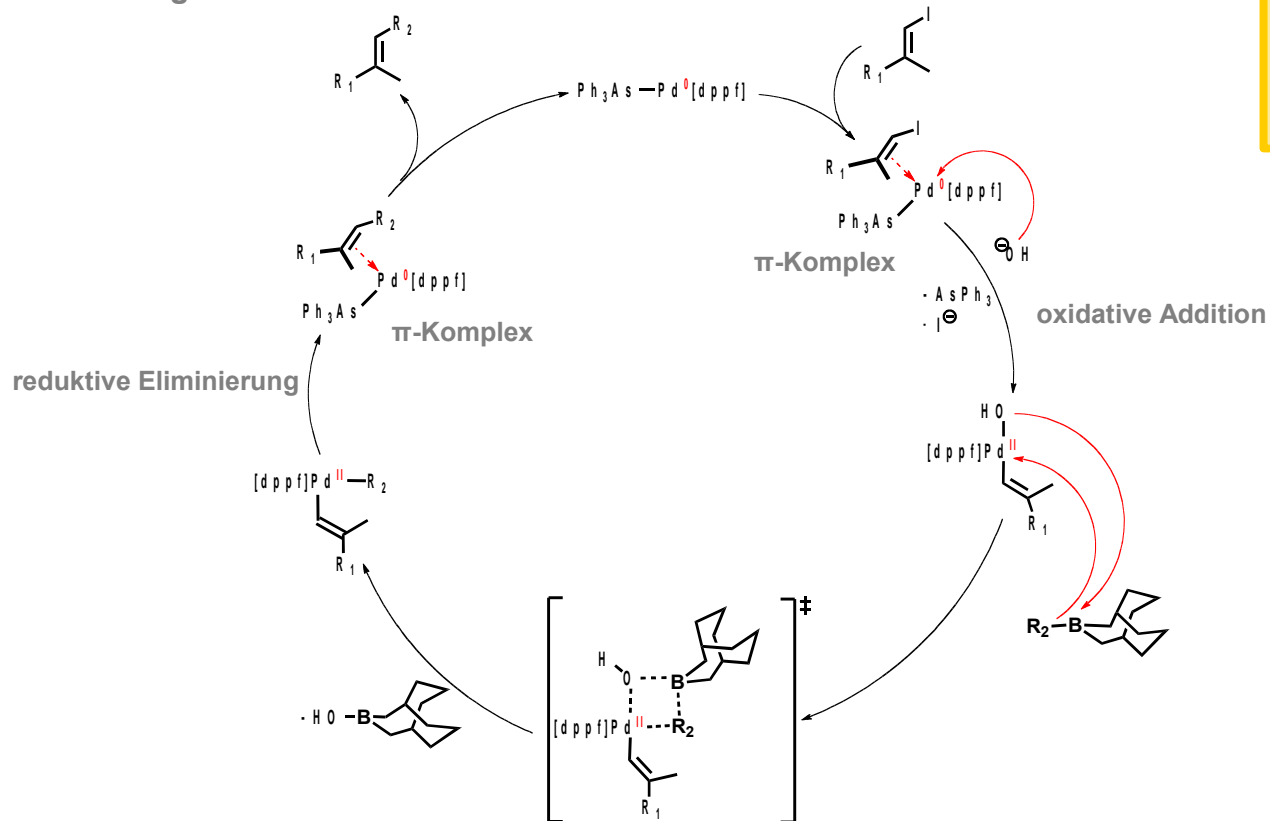
Katalysator  $\text{Pd}[\text{dppf}]\text{Cl}_2$



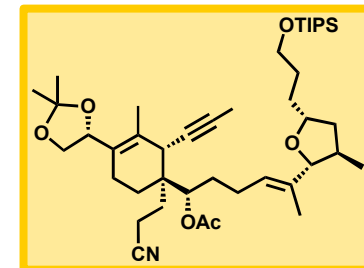
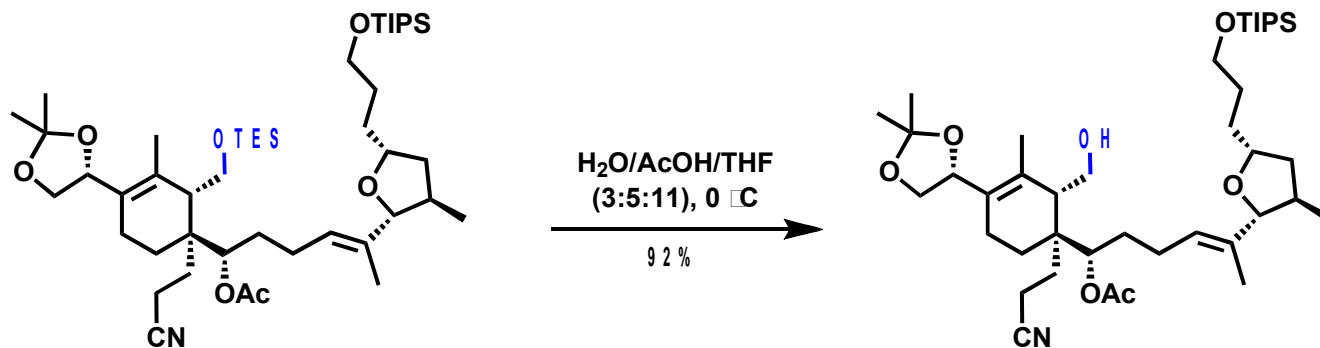
A. Suzuki, N. Miyaura, *Chem. Rev.* 1995, 95, 2457-2483

## Suzuki-Miyaura-Kupplung:

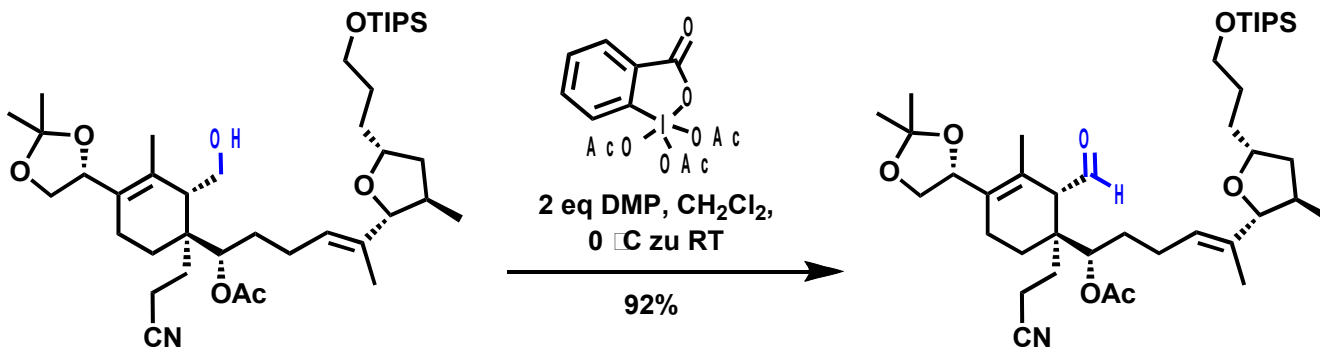
### Mechanismusvorschlag:



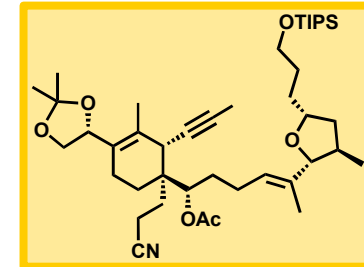
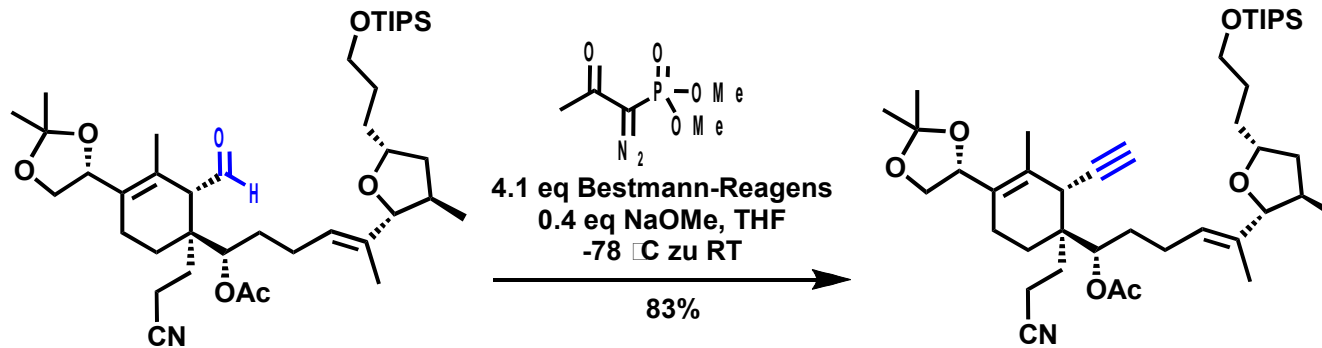
**TES-Abspaltung:**



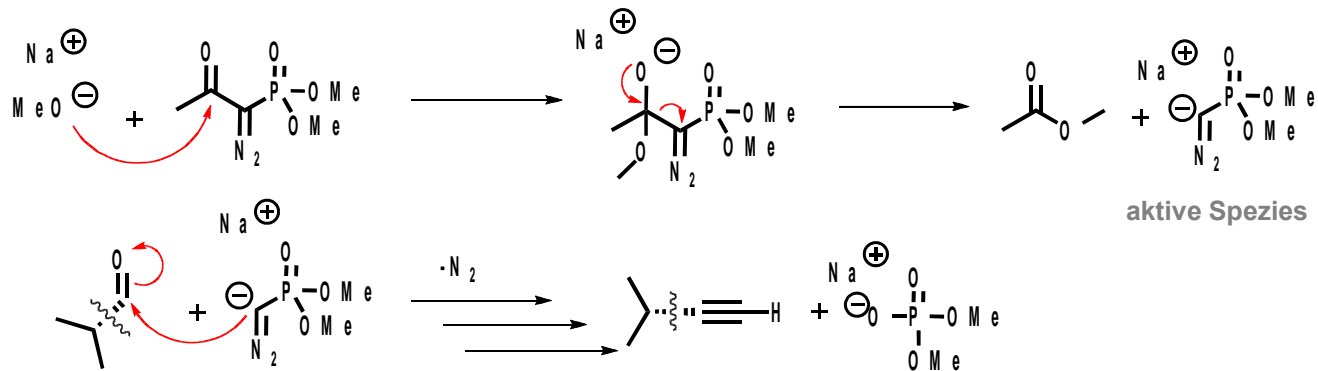
**Dess-Martin-Oxidation:**



**Gilbert-Seyferth Alkinylierung (Ohira-Bestmann Variante):**



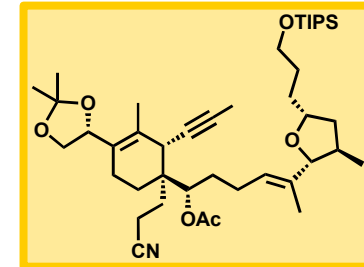
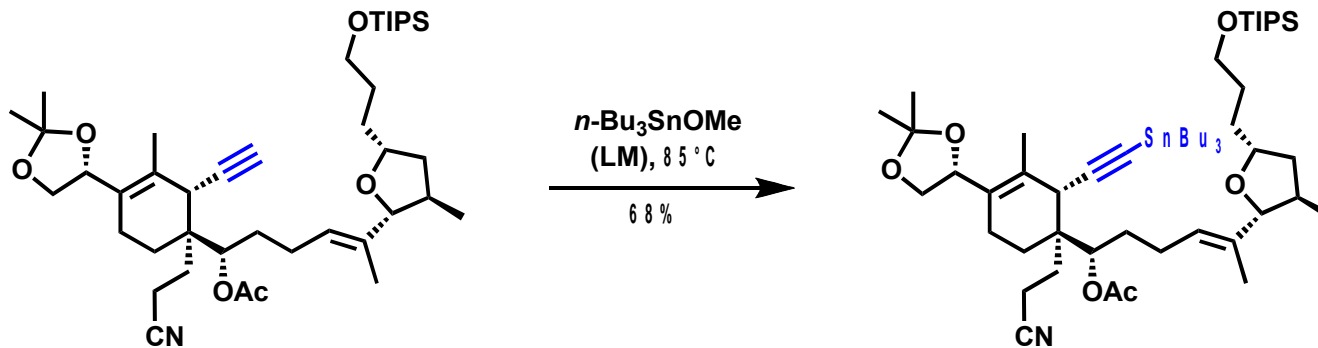
**Mechanismusvorschlag:**



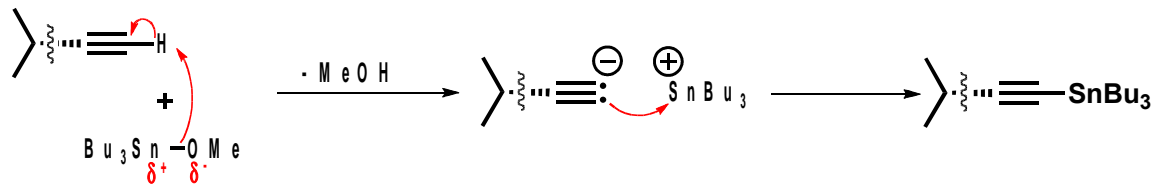
Mechanismus analog S. 13

S. Ohira, *Synt. Commun.*, 1989, 19, 561-564

Stannylierung am terminalen Alkin:

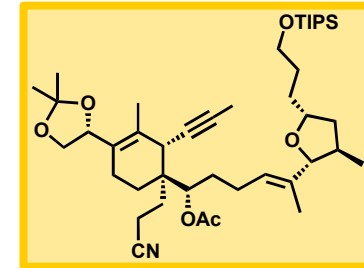
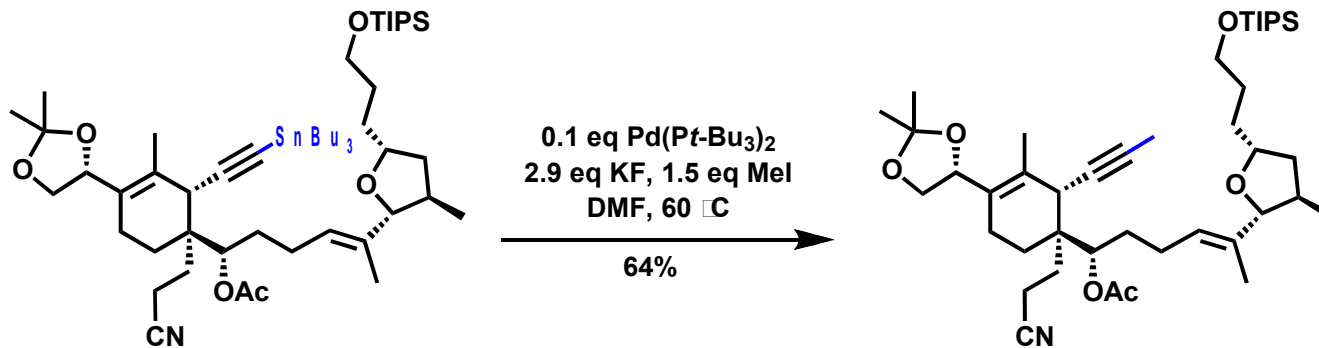


Mechanismusvorschlag:



M. W. Logue, K. Teng, *J. Org. Chem.* 1982, 47, 2549-2553

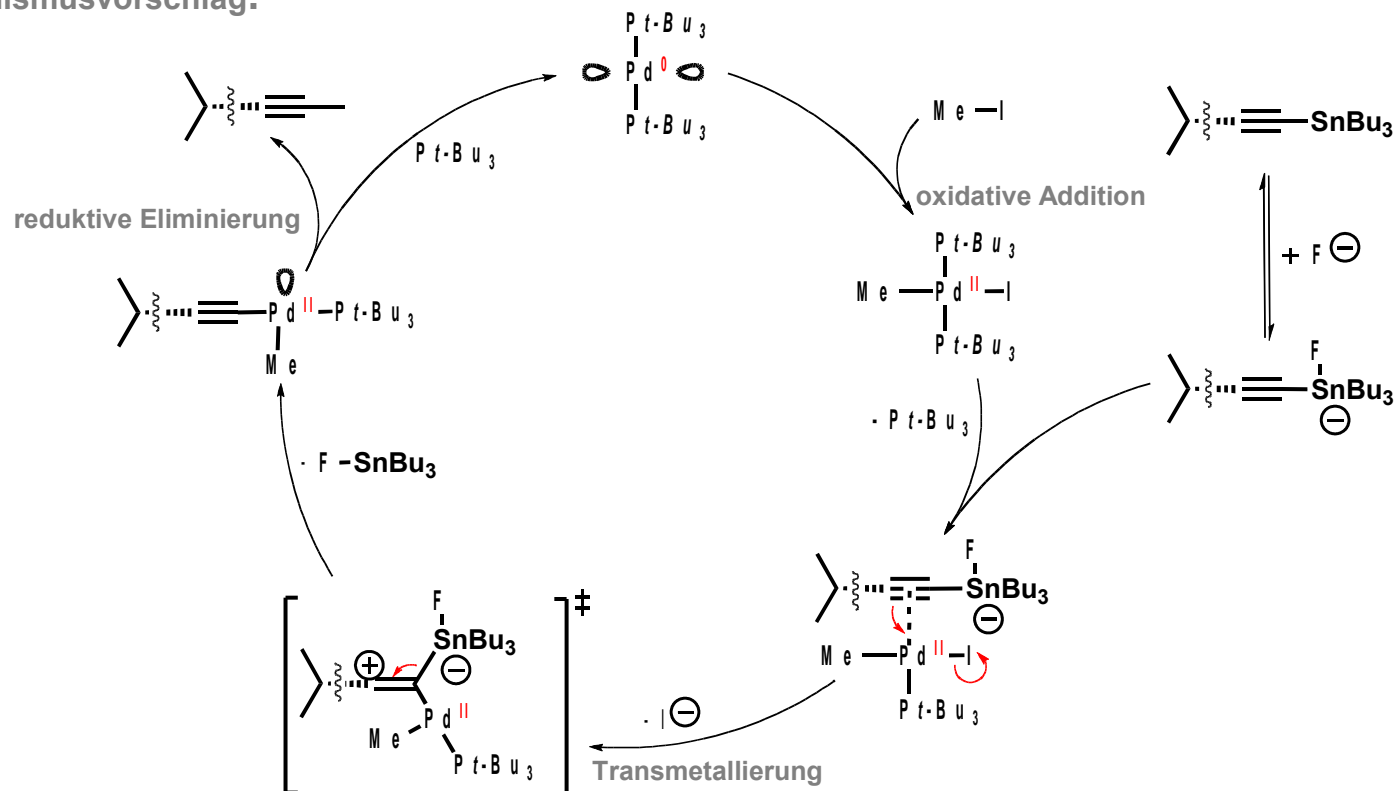
**Methylierung durch Stille Kupplung:**



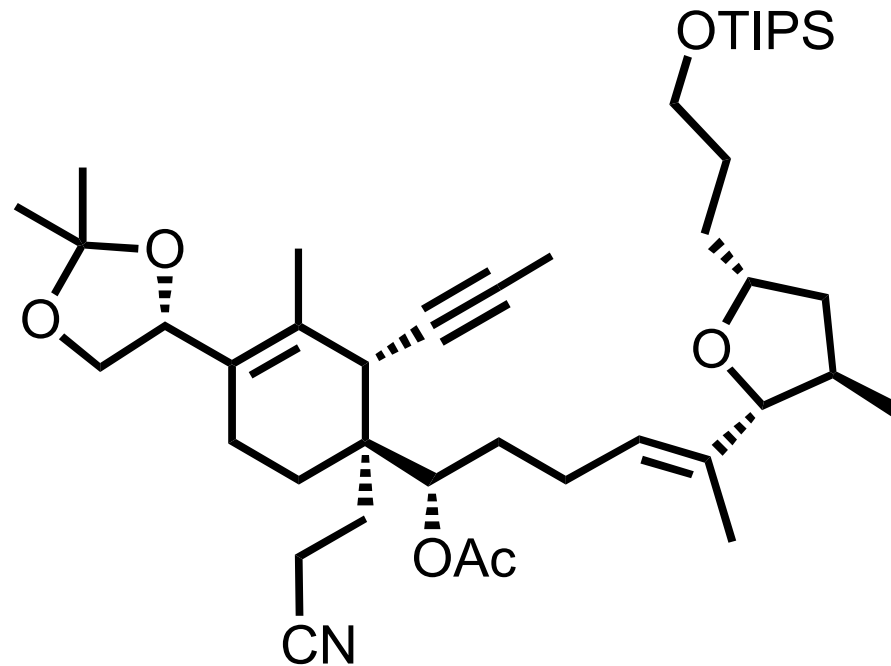


## Methylierung durch Stille-Kupplung:

Mechanismusvorschlag:



T. Hosoya, M. Wakao, Y. Kondo, H. Doi, M. Suzuki, *Org. Biomol. Chem.* 2004, 2, 24-27



<b>Abkürzung</b>	<b>Bedeutung</b>		
9-BBN	9-Borbicyclo[3.3.1]nonan	Ph	Phenyl
Ac	Acyl	PMB	para-Methoxybenzyl
DCB	2,6-Dichlorbenzyl	RT	Raumtemperatur
DCM	Dichlormethan	SG	Schutzgruppe
DDQ	2,3-Dichlor-5,6-dicyan-p-benzochinon	t-Bu	tert-Butyl
DIBAL	Diisobutylaluminiumhydrid	TBDPS	tert-butyl-diphenyl-silyl
DMAP	Dimethylaminopyridin	TES	Triethylsilyl
DMF	Dimethylformamid	THF	Tetrahydrofuran
DMP	Dess-Martin-Periodinan	TIPS	Triisopropylsilyl
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinon	ÜZ	Übergangszustand
DMSO	Dimethylsulfoxid		
dppf	Diphenylphosphinoferrocene		
eq	Äquivalent		
FG	funktionelle Gruppe		
i-Bu	Isobutyl		
lpc	Isopinocampheyl		
LD	lethal dose		
n-Bu	n-Butyl		

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Swern-O.	S. 11, 27
Dess-Martion-O.	S. 38

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Abspaltung von DCB	S. 11
Abspaltung von PMB	S. 23
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Einführung von PMB	S. 18
Einführung von TES	S. 31, 38
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