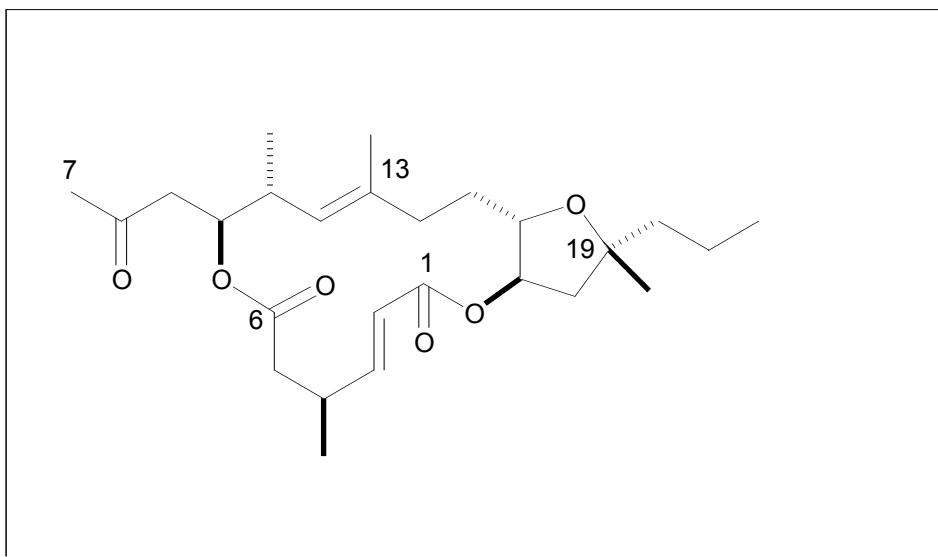


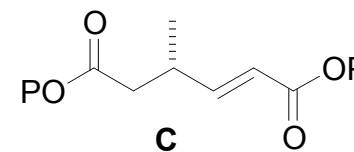
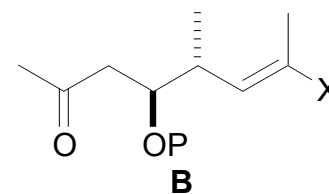
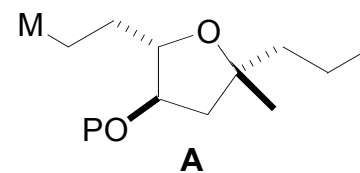
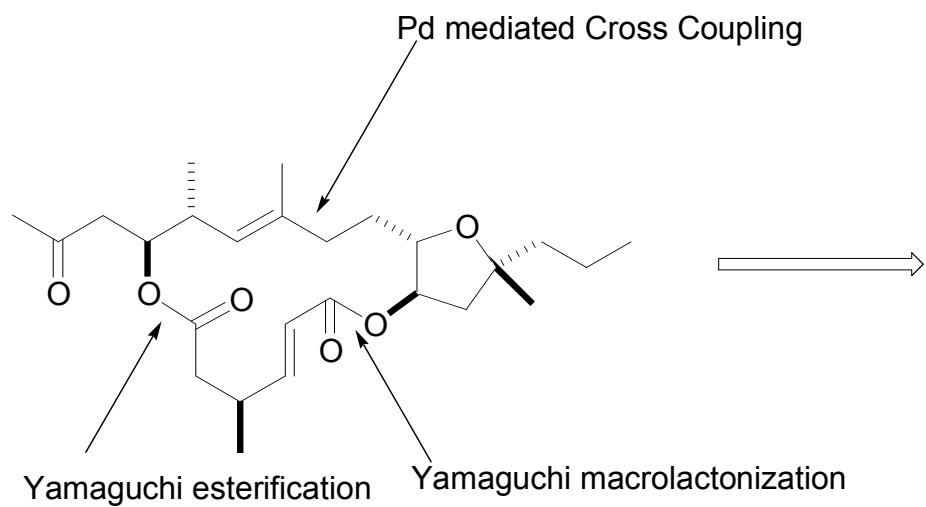
Synthesis of Amphidinolide X and an Exploration of Key Reactions

Lepage, O.; Kattinig, E.; Furstner, A. *JACS*, **2004**, *126*, 15970-15971.

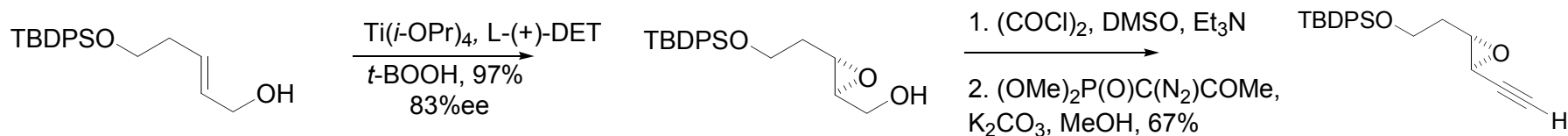


- Produced by marine dinoflagellates, *Amphidinium* sp. that live in symbiosis with a flatworm, *Amphiscolops* spp.
- Potent toxicity against various cancer cell lines, such as murine lymphoma and human epidermoid carcinoma
- Amphidinolide X is unique to class of amphidinolides in that it lacks a characteristic *exo*-methylene group, or a 1,3 diene unit
- Only naturally occurring macrolide containing a diester and a diol
- Many synthesis of other amphidinolides, first synthesis of X

Retrosynthetic Analysis



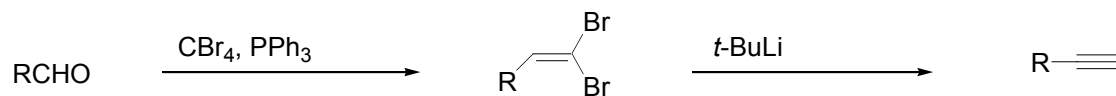
Synthesis of Fragment A of Amphidinolide X



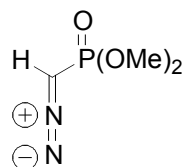
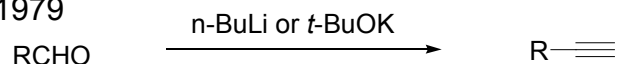
Tetrahedron, **1999**, 55, 14013.

Synthesis of Alkynes from Aldehydes:

Corey – Fuchs: 1972

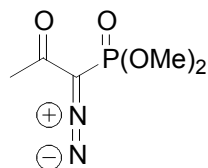
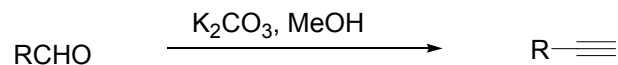


Gilbert – Seyferth: 1979



Reactions must be run at -78 C using freshly prepared reagent under inert atmosphere

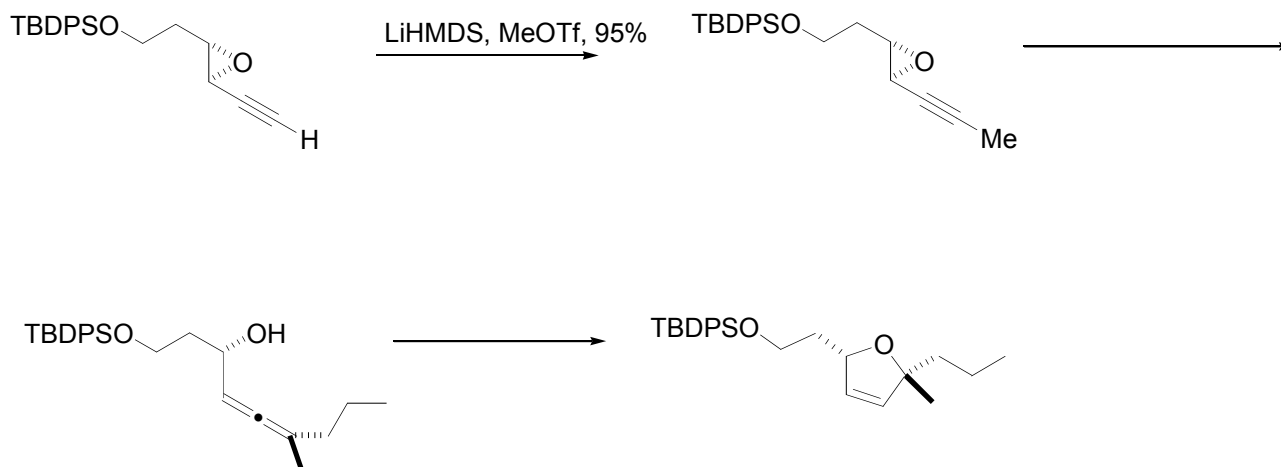
Ohira – Bestmann: 1989/1996



Reactions can be run at room temperature in a one-pot procedure w/o anhydrous conditions

Synlett, **1996**, 521.

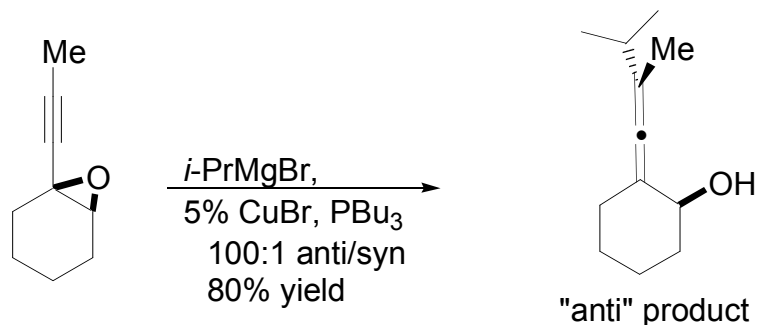
Synthesis of Fragment A of Amphidinolide X



Synthesis of Chiral 2,3-Allenols From Propargylic Epoxides

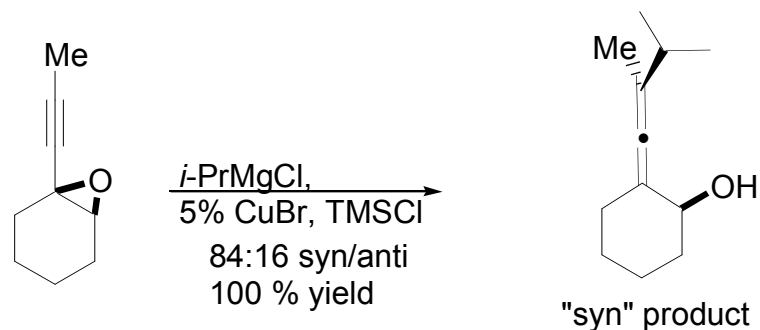
Typically use Copper catalysts and Stiochiometric Grignard reagents:

Anti diastereomer



Anti isomer predominates in organocuprate additions

Syn diastereomer



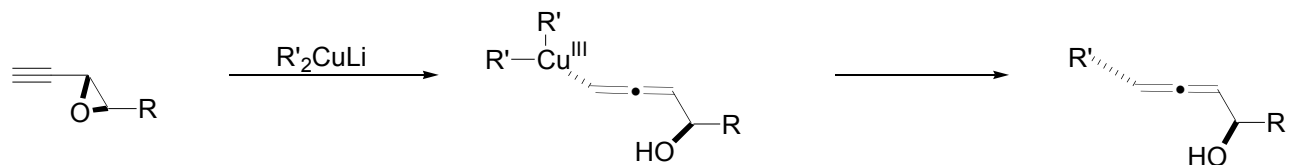
Syn diastereoselectivity dependent on presence of TMSCl and use of RMgCl

Also effective for acyclic substrates

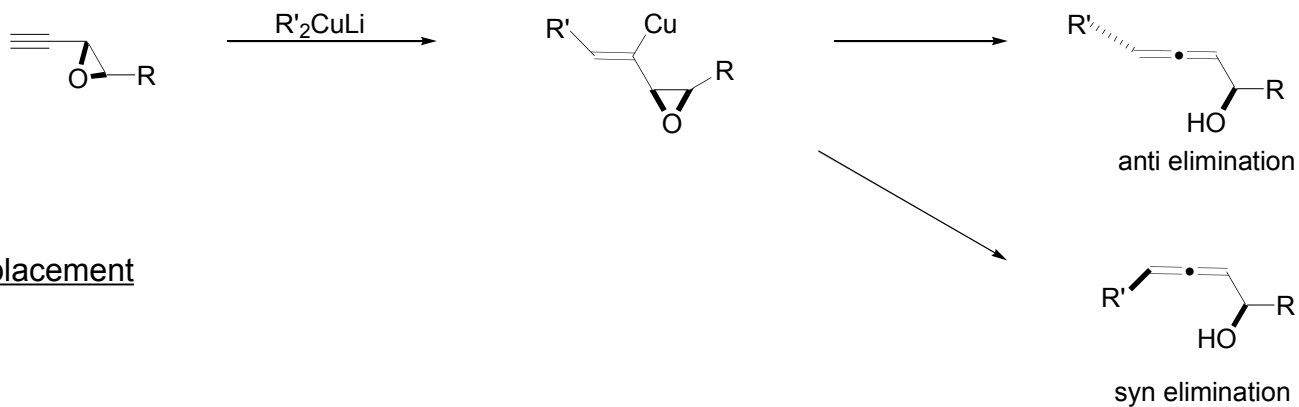
Alexakis, A.; *Tetrahedron*, **1991**, 47, 1677-1696.

Three Proposed Mechanisms

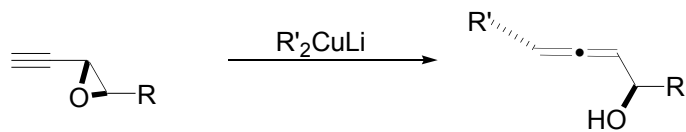
A Cu (III) intermediate



An Addition / Elimination pathway

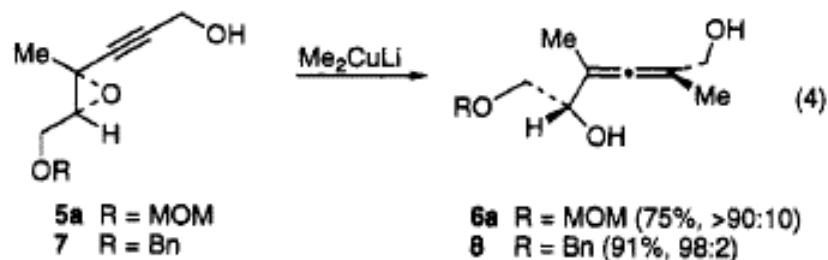


Direct S_N2' displacement

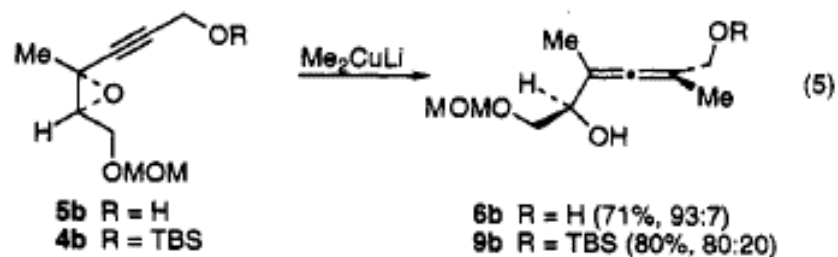


Stoichiometric Addition to Propargylic Epoxides

Stoichiometric use of organocuprates: Anti products predominate



Suspect reactions proceed via an $\text{S}_{\text{N}}2'$ pathway

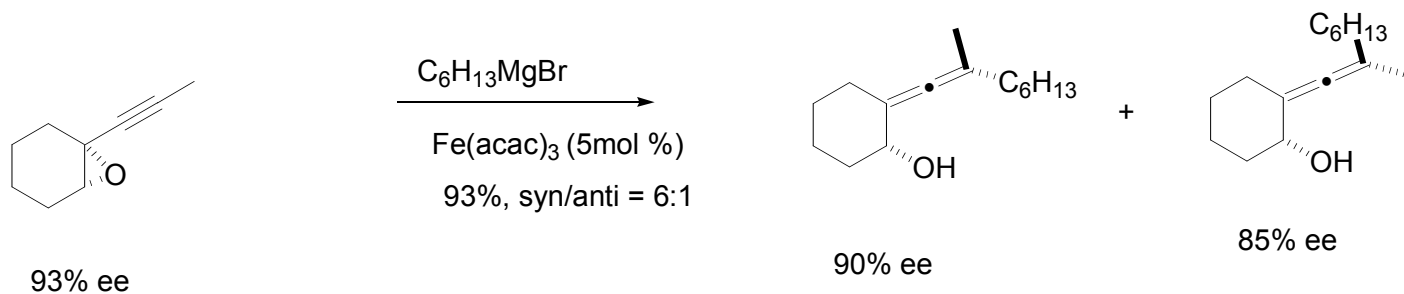
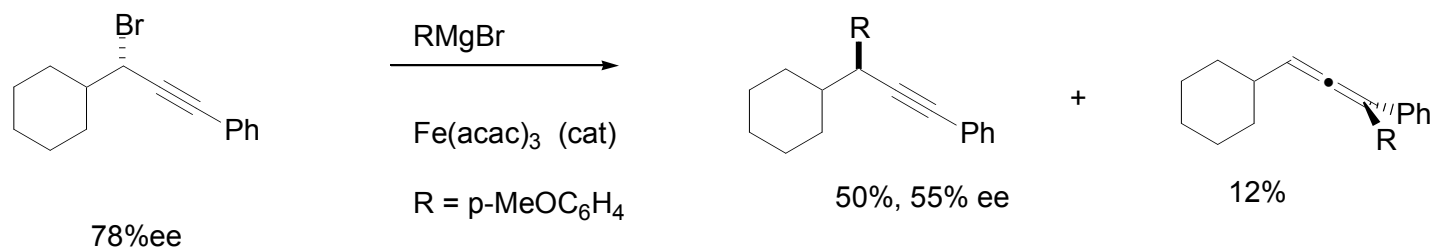


TBS ether led to decreased selectivities... unclear as to reasoning

Furstner's Catalytic Synthesis of Chiral 2,3 Allenols

Furstner, A.; Mendez, M. *Angew. Chem. Int Ed.* **2003**, *42*, 5355-5357.

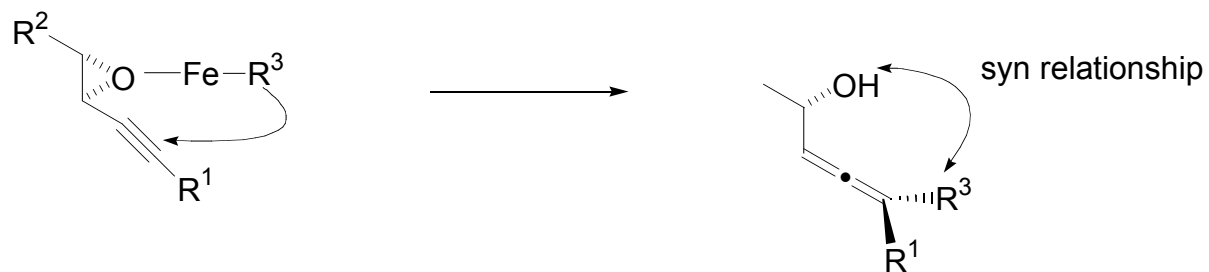
Early reports: 1976



- very fast reactions
- low catalyst loading (3-5 mol%)
- insignificant attack of Grignard to epoxide

Use of Fe(acac)₃ in cross-coupling reactions: *Angew. Chem. Int. Ed.* **2003**, *42*, 308.

Syn Selectivity



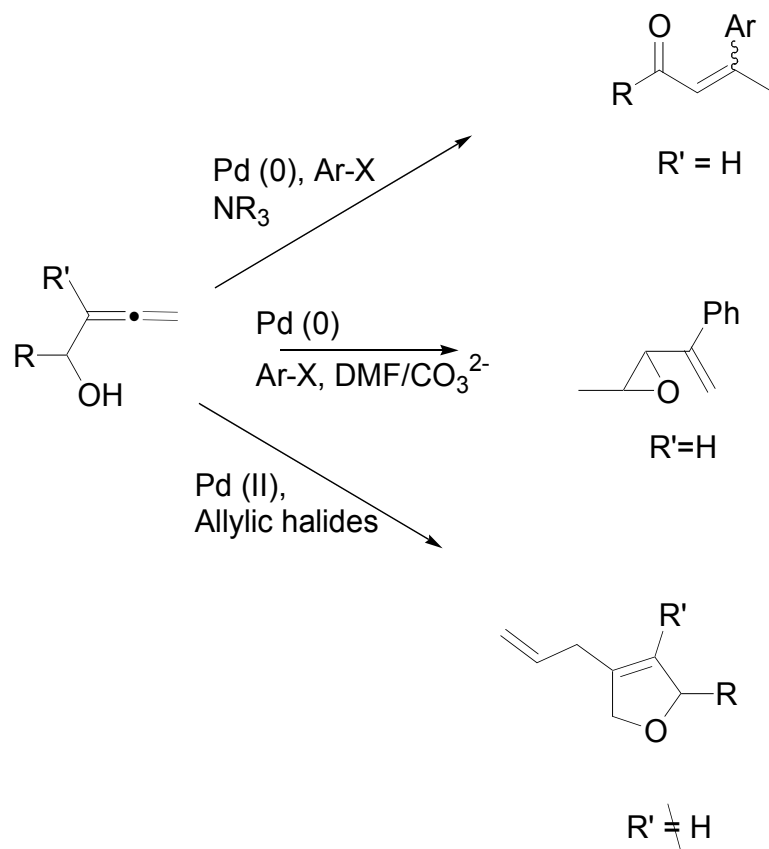
Complementary to organocuprate additions

Substrate Variability

Table 1: Iron-catalyzed synthesis of 2,3-allenols from propargyl epoxides.^[4]

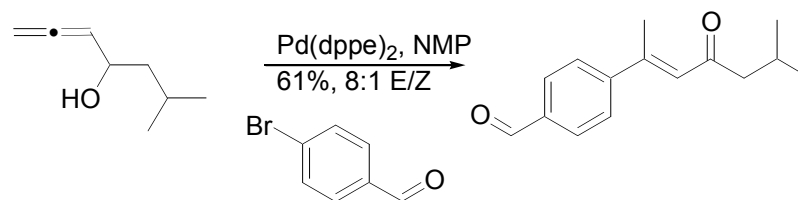
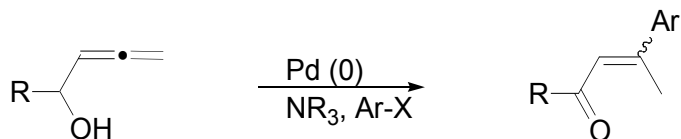
Entry	Substrate	R ¹	R ² MgX	Major product	Solvent	syn/anti	Yield [%]
1		H	C ₆ H ₁₃ MgBr		toluene	78:22	72 ^[6]
2		H	PhMgBr		toluene	75:25	83
3		H	MeMgBr		toluene	55:45	71
4		Me	C ₆ H ₁₃ MgBr		Et ₂ O	86:14	93
5		Me	C ₆ H ₁₃ MgBr		Et ₂ O	78:22	75 ^[6]
6		Me	C ₆ H ₁₃ MgBr		Et ₂ O	50:50	54 ^[6]
7		Me	<i>i</i> PrMgCl		Et ₂ O	84:16	79
8		Me	<i>i</i> PrMgCl		toluene	90:10	70
9		Me	PhMgBr		Et ₂ O	66:34	98
10		Ph	MeMgBr		Et ₂ O	65:35	69
11		CH ₂ OH	C ₆ H ₁₃ MgBr		Et ₂ O	92:8	65 ^[6]
12		Me	C ₆ H ₁₃ MgBr		toluene	80:20	73
13		Me	C ₆ H ₁₃ MgBr		toluene	88:12	80
14		Me	<i>i</i> PrMgCl		toluene	84:16	79
15		Me	C ₆ H ₁₃ MgBr		toluene	92:8	62
16		Me	C ₆ H ₁₃ MgBr		Et ₂ O	75:25	90
17		Me	<i>i</i> PrMgCl		toluene	86:14	75 ^[7]
18		Me	<i>i</i> PrMgCl		Et ₂ O	60:40	89
19		C ₃ H ₁₁	<i>i</i> PrMgCl		toluene	91:9	94
20		C ₃ H ₁₁	<i>i</i> PrMgCl		Et ₂ O	75:5	64
21		C ₃ H ₁₁	EtMgBr		toluene	82:18	55 ^[6]

Palladium Catalyzed Insertion Reactions of Allenols



Palladium Catalyzed Insertion Reactions of Allenols

Synthesis of α , β -unsaturated ketones: path a

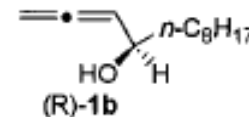
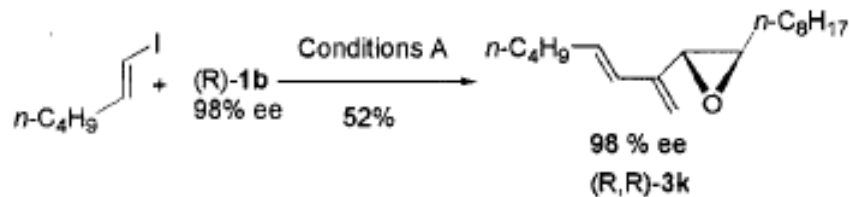
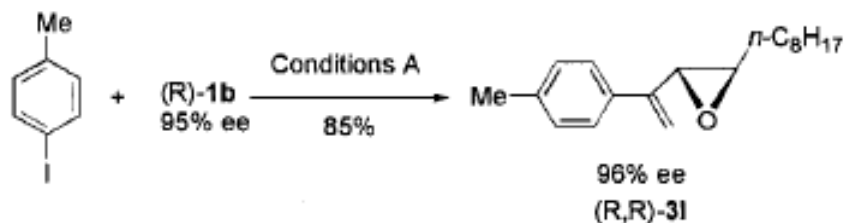
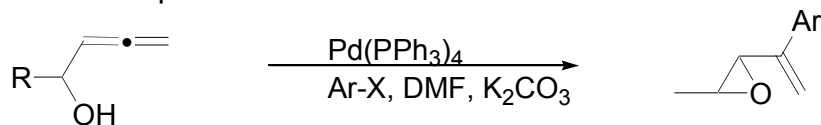


typically saw moderate E/Z ratios favoring E isomer

Palladium Catalyzed Insertion Reactions of Allenols

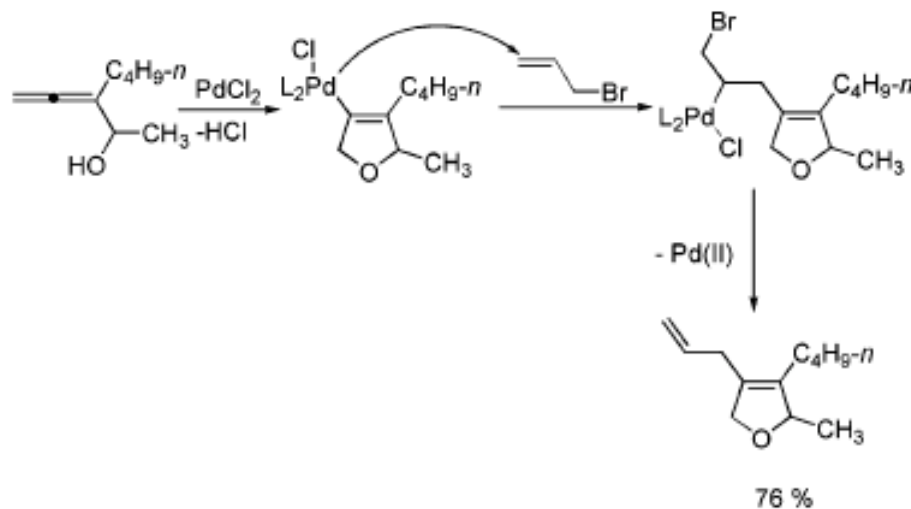
Insertion – Cyclization Reaction: path c

Very high selectivities for the trans epoxides



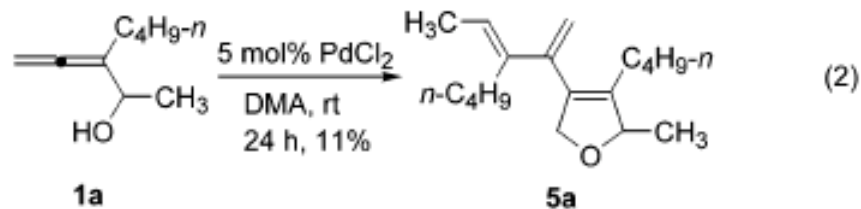
Palladium Catalyzed Insertion Reactions of Allenols

Formation of 2,5 Dihydropyrans: path b

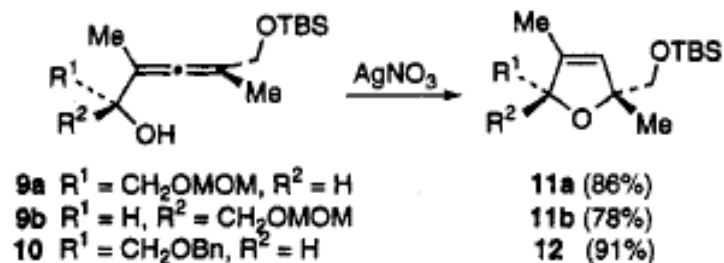


Only works with
2,2-disubstituted allenols

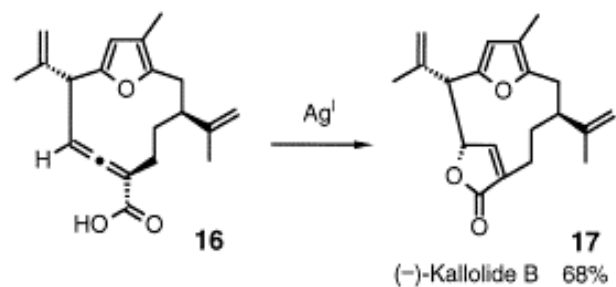
In the absence of allylic halides....



Silver Catalyzed Cyclization of Chiral 2,3 Allenols

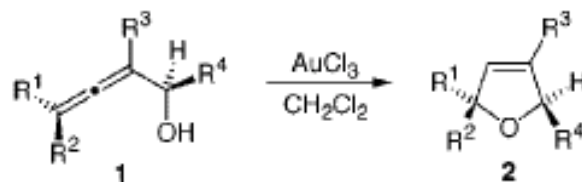


JOC, 1993, 58, 7180.



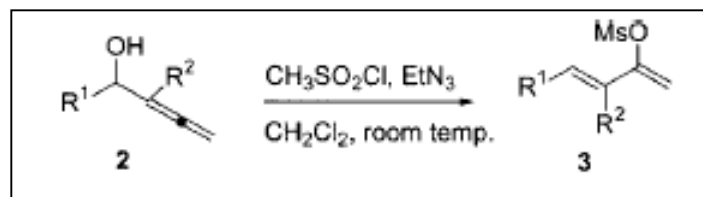
JOC, 1996, 61, 5729.

Can also use gold catalysis....

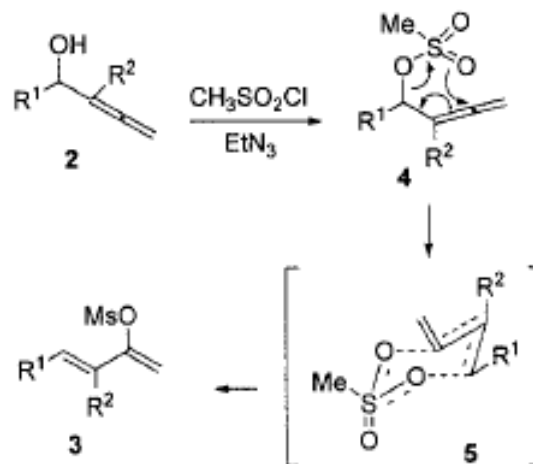


Org. Lett. 2001, 3, 2537.

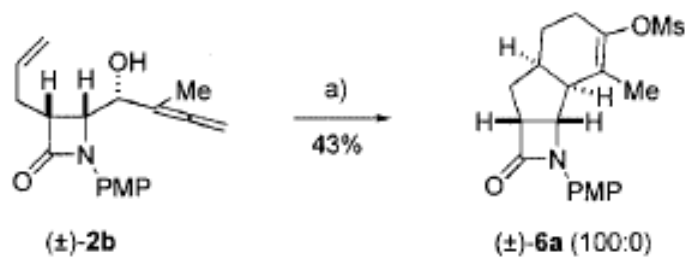
Rearrangement of Allenols w/ Mesyl Chloride



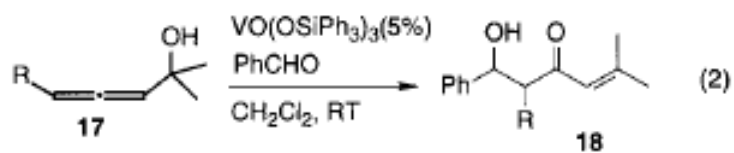
Proposed Mechanism



Application to fused ring systems

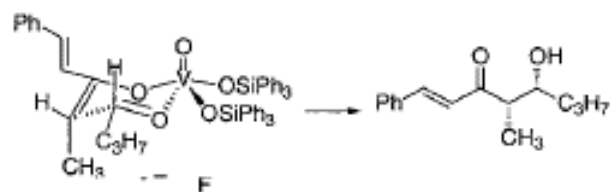
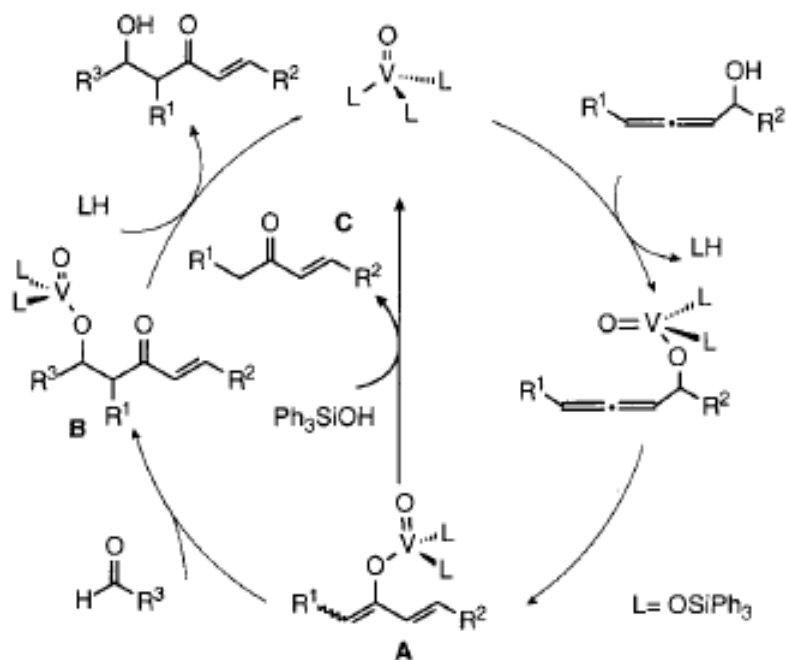


Allenol Addition to Aldehydes

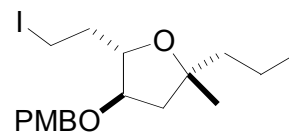
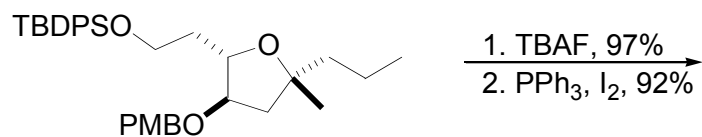
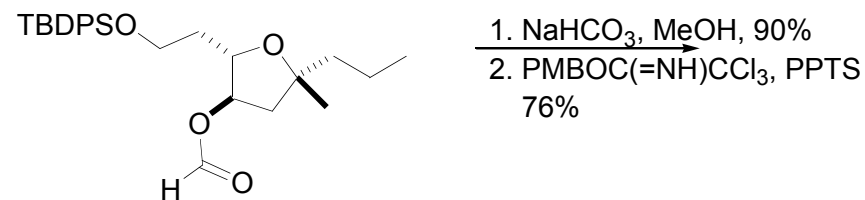
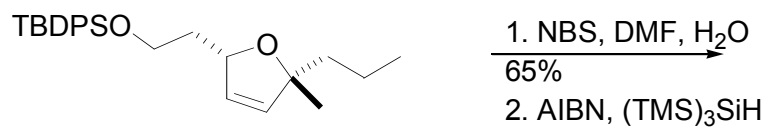
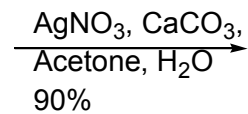
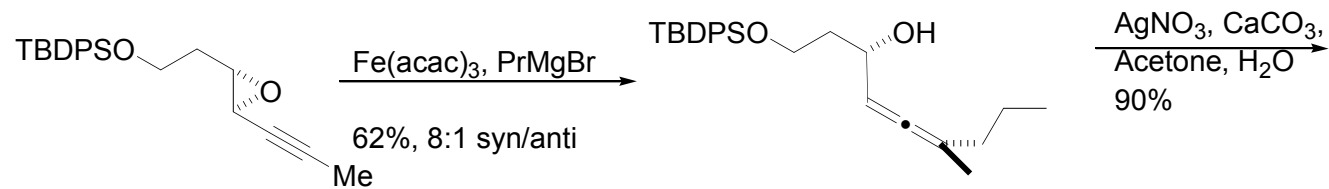


a: R=CH₃, 86% yield, *syn/anti* = 77/23

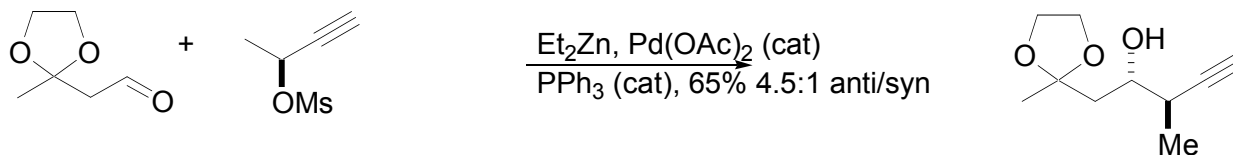
b: R=*i*-C₃H₇, 57% yield, *syn/anti* = 88/12



Fragment A cont.



Synthesis of Fragment B



Early work: Marshall

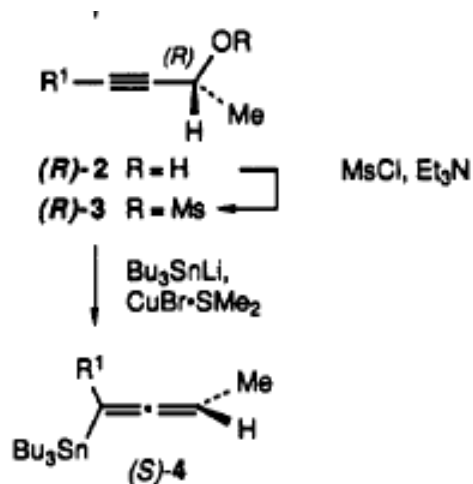
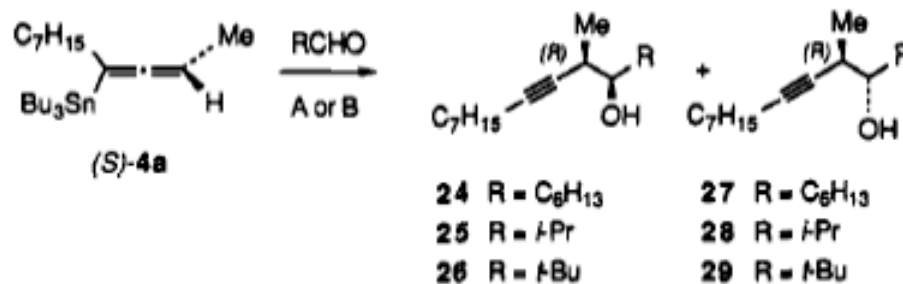


Table I. Additions of Allenylstannane (*S*)-4a to Achiral Aldehydes



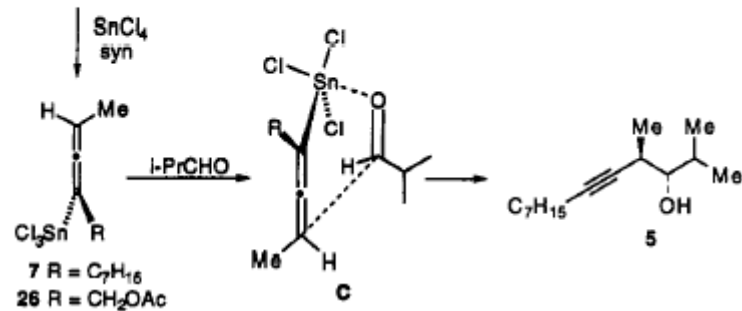
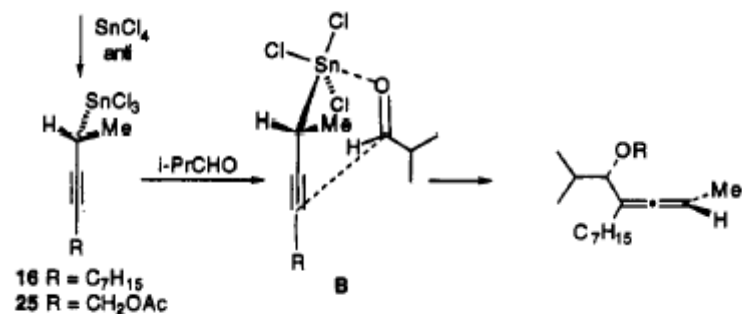
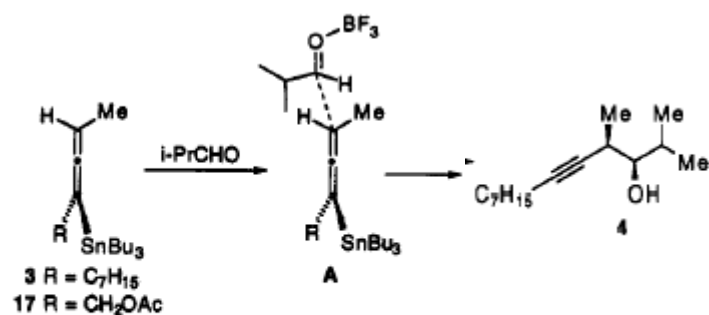
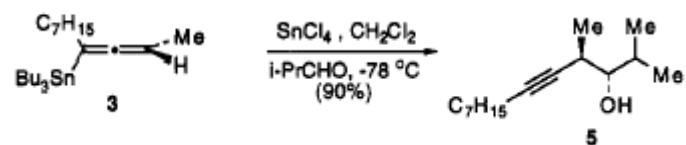
entry	R	condns ^a	yield, %	syn:anti
1 ^b	C ₆ H ₁₃	A	83	39:61
2 ^b	C ₆ H ₁₃	B	56	66:34
3	<i>i</i> -Pr	A	80	99:1
4	<i>i</i> -Pr	B	68	88:12
5	<i>t</i> -Bu	A	92	99:1

^a A = BF₃·OEt₂, CH₂Cl₂, -78 °C, 0.5 h; B = MgBr₂·OEt₂, CH₂Cl₂, -23 to 0 °C, 24–36 h. ^b Racemic 4a was employed.

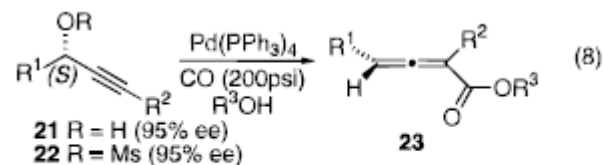
Best results with BF₃-OEt and bulky aldehydes

Marshall; *JOC*, **1995**, *60*, 5556.

Transmetalation to Allenyl Tin Chlorides



Pd-catalysed Formation of Allenic Esters

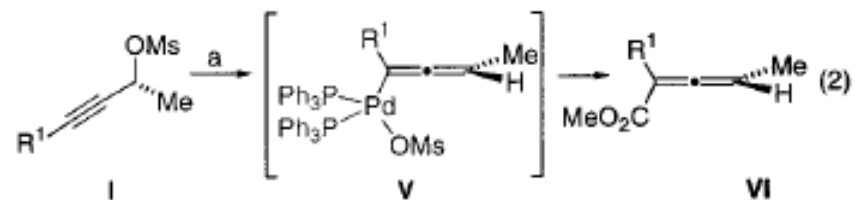


22	R ¹	R ²	23	R ³	yield, %	ee, % ^a
22a	CH ₃	<i>n</i> -C ₇ H ₁₅	23a	Bn	84	80
22a	CH ₃	<i>n</i> -C ₇ H ₁₅	23b	TMSE ^b	80	84
22a	CH ₃	<i>n</i> -C ₇ H ₁₅	23c	CH ₃	86	84
22b	<i>n</i> -C ₅ H ₁₁	H	23d	TMSE	80	95
22b	<i>n</i> -C ₅ H ₁₁	H	23e	Bn	80	93
22c	H	<i>n</i> -C ₄ H ₉	23f	Bn	76	–

^a determined by HPLC analysis of **23** or the derived iodobutenolides **24**

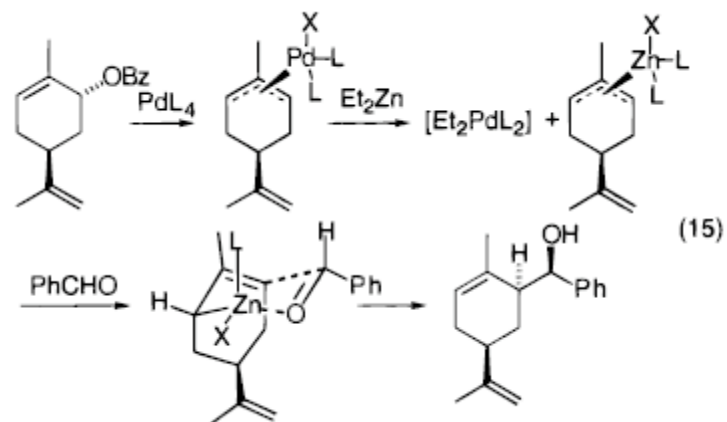
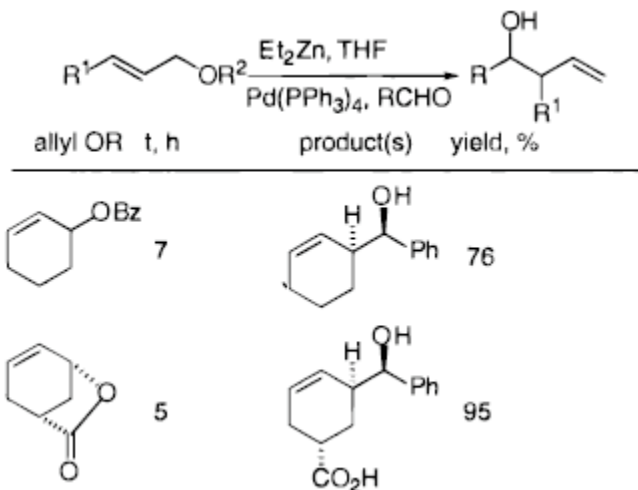
^b TMSE = Me₃SiCH₂CH₂OH

Proposed mechanism:



a. (Ph₃P)₄Pd, CO, MeOH, THF

Synthesis of Allylic Zinc Intermediates via Transient Organopalladium Species

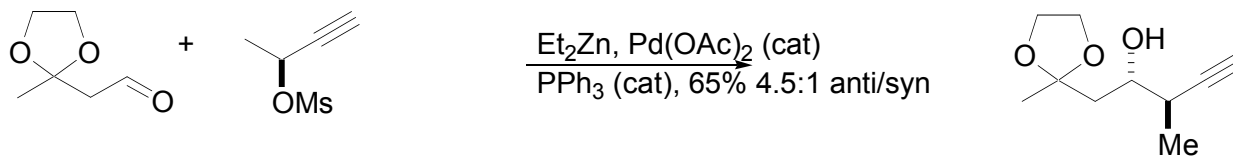


Decent selectivity only with cyclic or secondary allylic benzoates

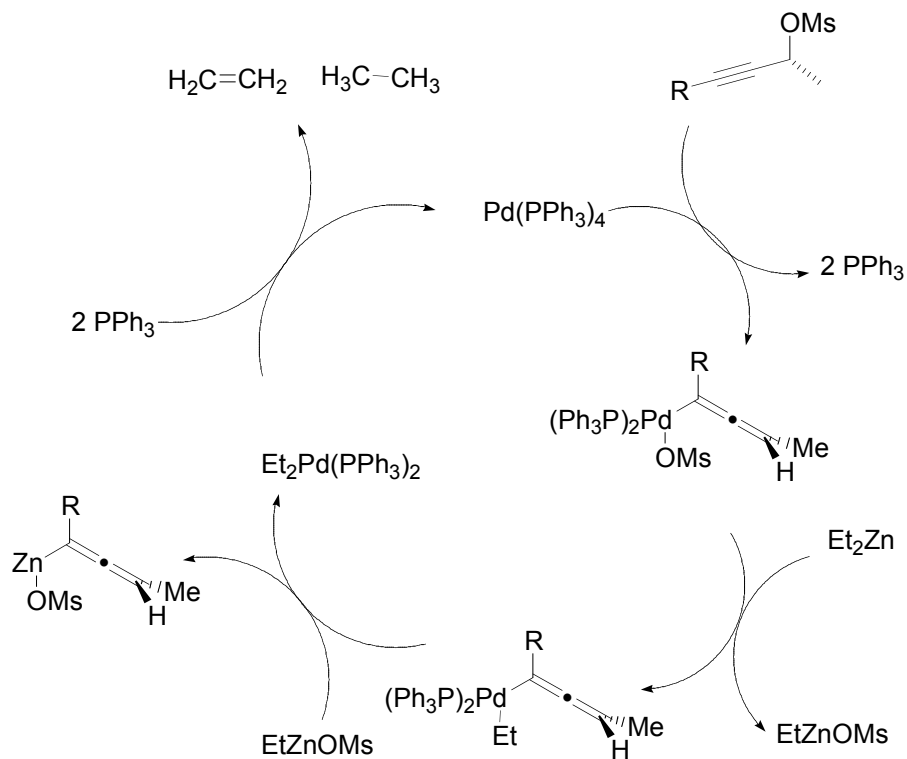
Tamaru; *ACIEE*, **1995**, 34, 787

Review of transient Pd intermediates: Marshall, J. A. *Chem. Rev.* **2000**, 100, 3163-3185.

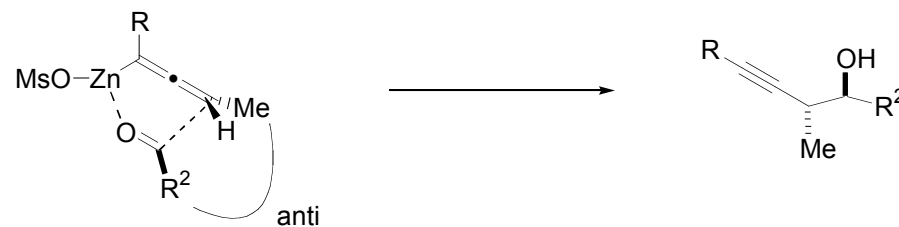
Proposed Mechanism



Proposed Mechanism of Organozinc reagent

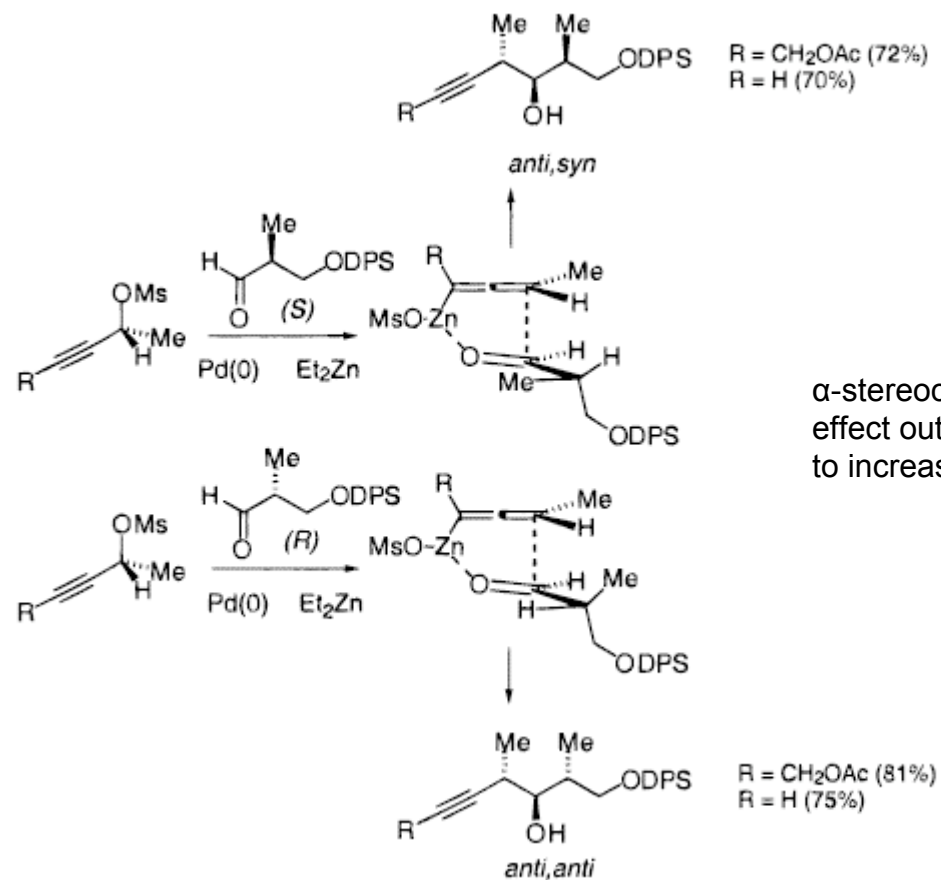


Proposed Mechanism cont.



typical selectivities are
3:1 – 7:1 favoring anti
product

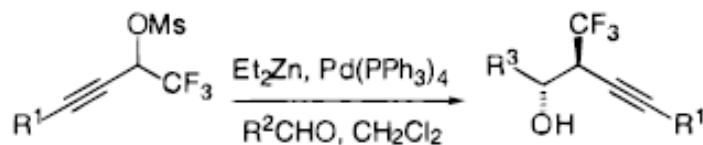
Aldehyde w/ α -stereocenter



α -stereocenter does not
effect outcome, but does lead
to increased diastereoselectivity

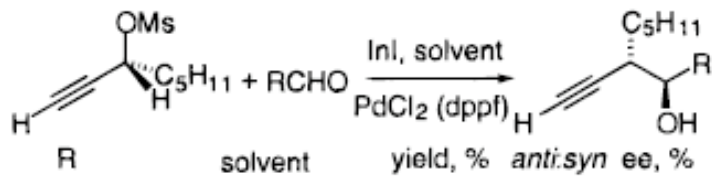
Other Examples

Can get very high selectivity with trifluoromethyl propargylic mesylates:



R ¹	R ²	yield, %	<i>anti: syn</i>
CH ₂ OBn	Bu	76	91:9
CH ₂ OBn	<i>t</i> -Bu	60	> 99:1
CH ₂ OBn	Ph	55	87:13
Ph	Bu	56 ^a	93:7
Pr	Bu	33 ^b	93:7
<i>t</i> -Bu	Bu	70	95:5

Can also form organoindium reagents:

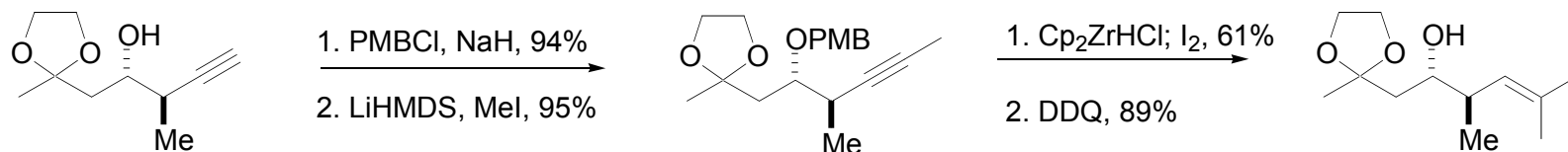


R	solvent	yield, %	<i>anti: syn</i>	ee, %
<i>c</i> -C ₆ H ₁₁	3:1 THF-HMPA	74	97:3	86
<i>c</i> -C ₆ H ₁₁	3:1 THF-HMPA	79 ^a	95:5	89
<i>c</i> -C ₆ H ₁₁	1:1 THF-DMSO	73	95:5	89
C ₆ H ₁₃	3:1 THF-HMPA	77	84:16	95
C ₆ H ₁₃	1:1 THF-DMSO	83	86:14	96
<i>i</i> -Pr	3:1 THF-HMPA	74	94:6	93
<i>i</i> -Pr	1:1 THF-DMSO	64	96:4	95

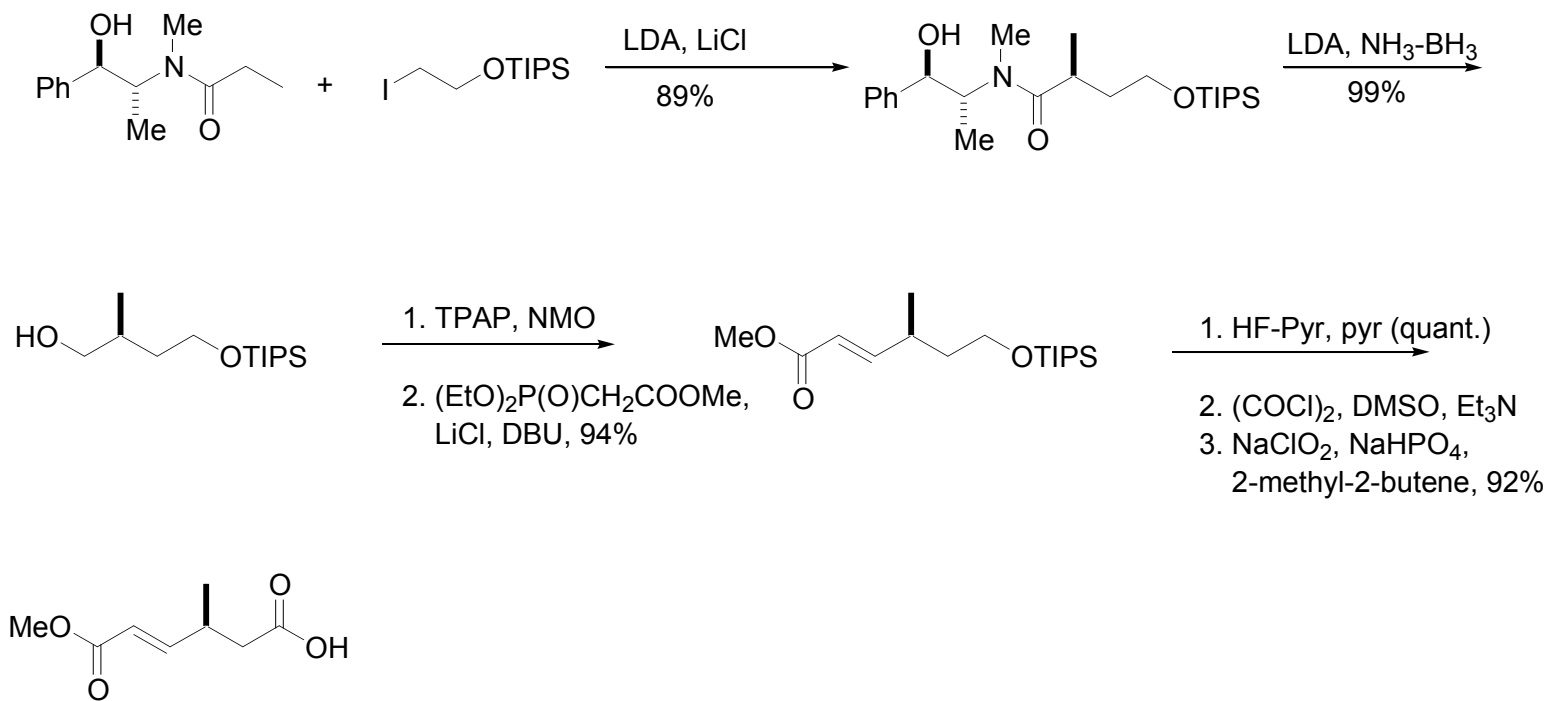
^a InI was prepared from In and I₂.

Completion of Fragments B and C

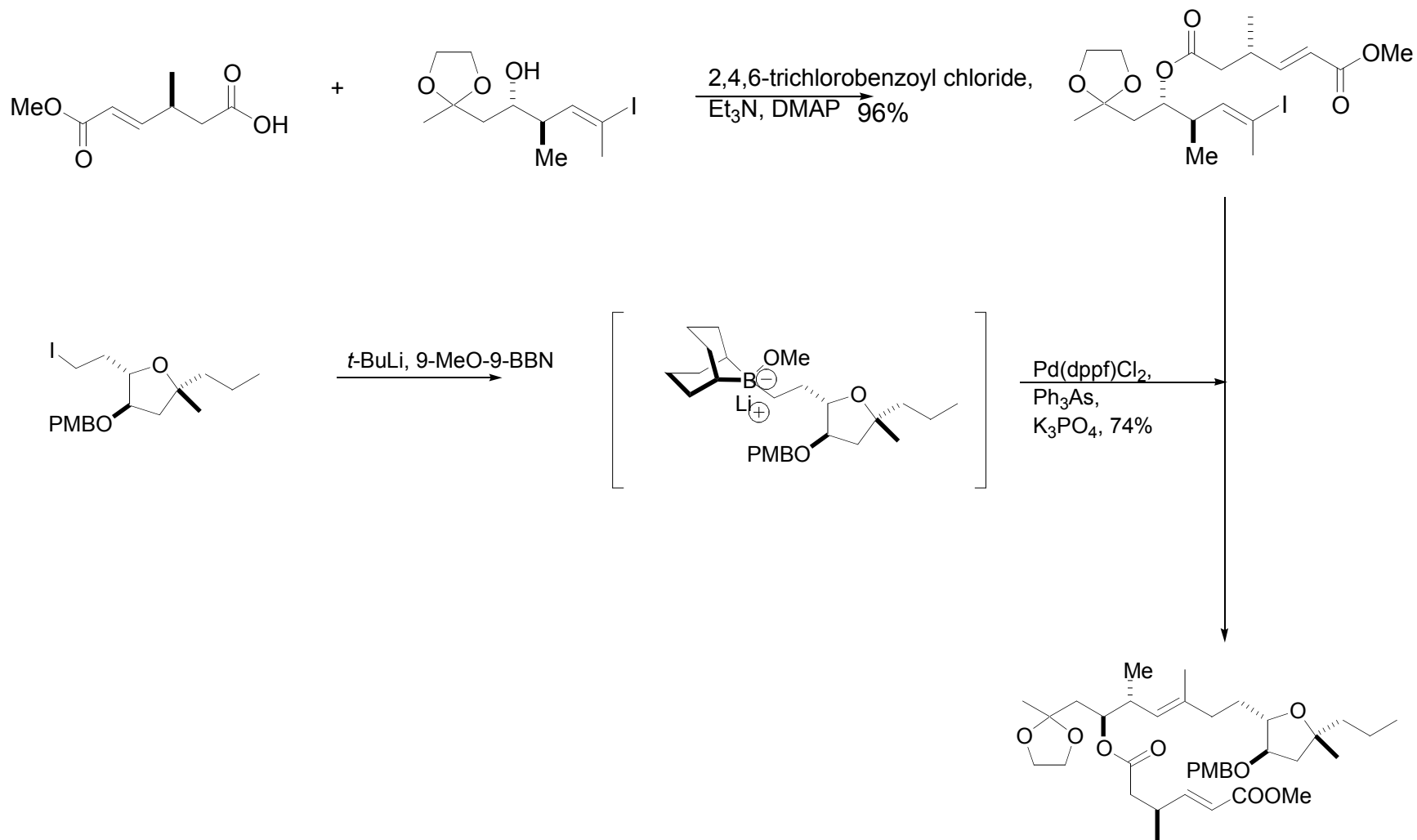
B (cont.)



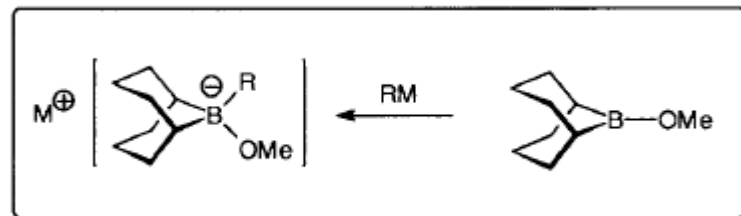
Synthesis of Fragment C



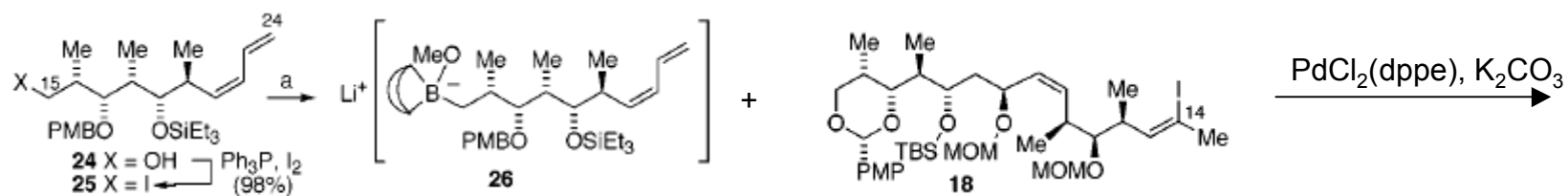
Coupling of Fragments B, C, and A



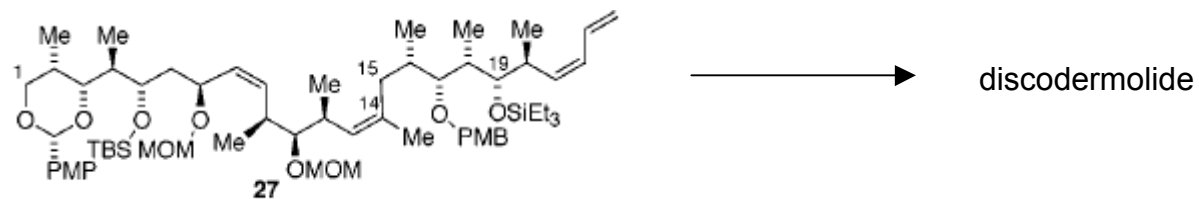
Alkyl Boronates From Organometallics



Tetrahedron, **1995**, *51*, 11165.

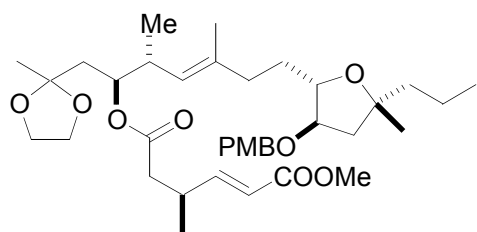


¹Key: (a) *t*-BuLi, Et₂O, -78 °C; 9-BBNOMe, THF, -78 °C to rt; I



J. Org. Chem. **1998**, *63*, 7885–7892

Completion of Amphidinolide X



1. Lil, pyr.

2. Aq. AcOH

3. DDQ

4. 2,4,6-trichlorobenzoyl chloride,
Et₃N, DMAP

