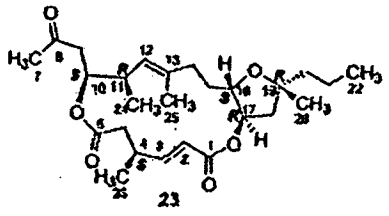
Total Synthesis of Amphidinolide

Yamaguchi. A (B4) 2005. 1. 12

Introduction

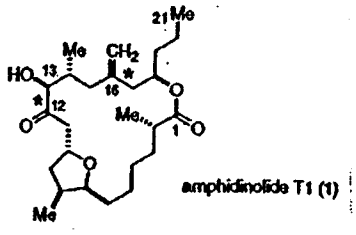
- Amphidinolides are secondary metabolites from symbiotic marine dinoflagellates *Amphidinium* sp, which were separated from inside cells of Okinawan marine flatworms. Up to now, 35 kinds of Amphidinolide have been isolated and investigated about bioactivity. The results show that Amphidinolides have cytotoxicity.

Rather complicated macrocyclic structure of these compounds is a good synthetic target, and many total syntheses have been achieved. I will introduce especially interesting ones, which are total synthesis of Amphidinolide X and T1.



X

- isolation and structure determination
  → Kobayashi, J. et. al. J. Org. Chem. 2003, 68, 5339
- cytotoxicity
  → IC_{50} 0.6 μg/ml (Murine lymphoma cell, L1210)
  9.5 μg/ml (Human epidermoid carcinoma cells, KB)
- total synthesis
  ◎ Fürstner, A. et. al. J. Am. Chem. Soc. 2004, 126, 15970



T1

- isolation and structure determination
  → Kobayashi, J. et. al. J. Org. Chem. 2000, 65, 1349
- cytotoxicity
  → IC_{50} 18 μg/ml (Murine lymphoma cell, L1210)
  >20 μg/ml (Human epidermoid carcinoma cells, KB)
- total synthesis
  Ghosh, A. K. et. al. J. Am. Chem. Soc, 2003, 125, 2374
  Fürstner, A. et. al. J. Am. Chem. Soc. 2003, 125, 15512
  ◎ Jamison, T. F. et. al. J. Am. Chem. Soc, 2004, 126, 998

Review: Kobayashi, J. et. al. Nat. Prod. Rep. 2004, 21, 77

Amphidinolide X

Total Synthesis of Amphidinolide X

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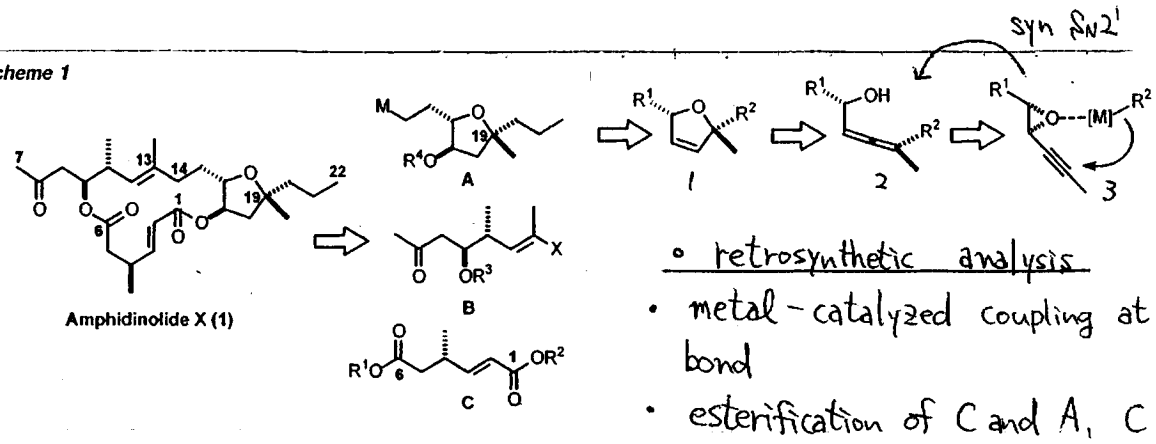
J. Am. Chem. Soc. 2004, 126, 15970

Scheme 1



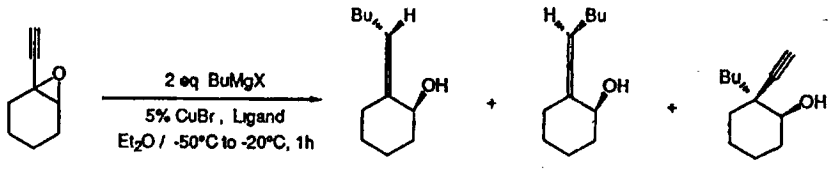
∘ retrosynthetic analysis

- metal-catalyzed coupling at the C13-C14 bond
- esterification of C and A, C and B
- A is an important fragment, which is retrosynthesized to epoxide 3
- epoxide opening have to be syn process for the desired stereochemistry
- dihydrofurane derivative 1 can be synthesized by transition metal-catalyzed cyclization of 2

∘ allene formation

epoxide opening via syn process is required

Table I: Optimization of the *anti* process



Entry	RMgX	Ligand	*Anti / Syn*[a]	yield[b] %	By-products
1	BuMgBr	$2P(OEt)_3$	46/54	95%	
2	BuMgBr	$P(NMe_2)_3$	99/1	52%	5 (30%)
3	BuMgBr	$2P(NMe_2)_3$	100/0	75%	5 (10%) + 2 (5%)
4	BuMgBr	PBu_3	88/12	50%	5 (25%) + 2 (10%)
5	BuMgBr	$2PBu_3$	100/0	74%	5 (18%)
6	BuMgCl	$2PBu_3$	94/6	45%	several
7	BuMgI	$2PBu_3$	90/10	31%	several

a) the *syn/anti* ratio was determined by ^{13}C NMR spectroscopy It is also possible to distinguish the two corresponding acetates on capillary glass GC (OV 101 column, 25 m)
b) Yield of isolated material, by column chromatography on SiO_2

- anti product is major when Cu reagent is used

Alexakis, A. et al
Tetrahedron 1991, 47, 1677

Iron-Catalyzed Cross-Coupling Reactions: Efficient Synthesis of 2,3-Allenol Derivatives**

Alois Fürstner and María Méndez*

Angew. Chem., Int. Ed. 2003, 42, 5355

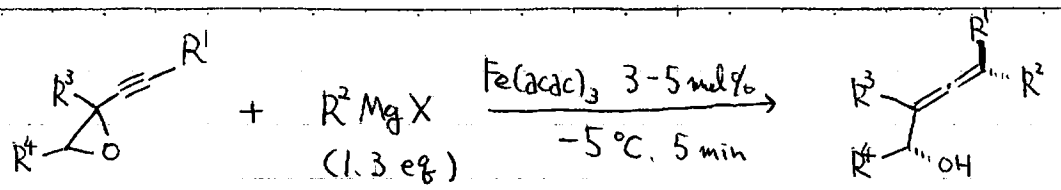
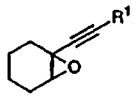
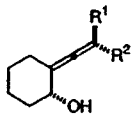
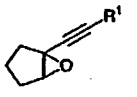
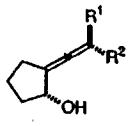
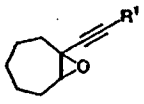
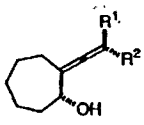
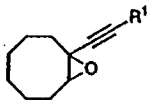
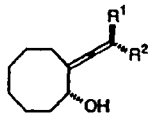
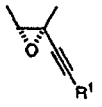
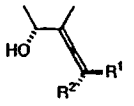
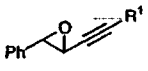
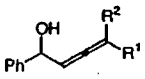


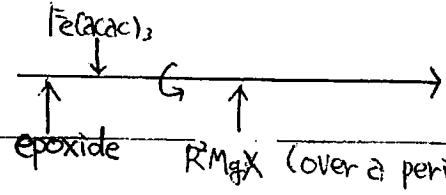
Table 1: Iron-catalyzed synthesis of 2,3-allenols from propargyl epoxides.[a]

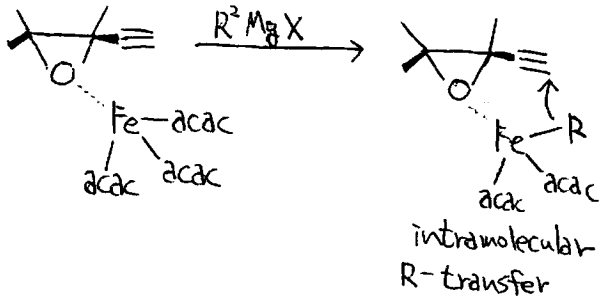
Entry	Substrate	R^1	R^2MgX	Major product	Solvent	*syn/anti*	Yield [%]
1		H	$C_6H_{13}MgBr$		toluene	78:22	72[b]
2		H	PhMgBr		toluene	75:25	83
3		H	MeMgBr		toluene	55:45	71
4		Me	$C_6H_{13}MgBr$		Et_2O	86:14	93
5		Me	$C_6H_{13}MgBr$		Et_2O	78:22	75[c]
6		Me	$C_6H_{13}MgBr$		Et_2O	50:50	54[d]
7		Me	*i*PrMgCl		Et_2O	84:16	79
8		Me	*i*PrMgCl		toluene	90:10	70
9		Me	PhMgBr		Et_2O	66:34	98
10		Ph	MeMgBr		Et_2O	65:35	69
11		CH_2OH	$C_6H_{13}MgBr$		Et_2O	92:8	65[e]
12		Me	$C_6H_{13}MgBr$		toluene	80:20	73
13		Me	$C_6H_{13}MgBr$		toluene	88:12	80
14		Me	*i*PrMgCl		toluene	84:16	79
15		Me	$C_6H_{13}MgBr$		toluene	92:8	62
16		Me	$C_6H_{13}MgBr$		Et_2O	75:25	90
17		Me	*i*PrMgCl		toluene	86:14	75[f]
18		Me	*i*PrMgCl		Et_2O	60:40	89
19		C_5H_{11}	*i*PrMgCl		toluene	91:9	94
20		C_5H_{11}	*i*PrMgCl		Et_2O	75:5	64
21		C_5H_{11}	EtMgBr		toluene	82:18	55[g]

[a] The reactions were carried out at −5 °C in the presence of $[Fe(acac)_3]$ (3–5 mol%) precatalyst and Grignard reagent (1.3 equiv), unless stated otherwise. [b] Fe–salen precatalyst. [c] −30 °C. [d] −60 °C. [e] Grignard reagent (2.3 equiv). [f] A by-product (9%) was isolated that is formed by direct attack of the Grignard at the epoxide ring of the substrate. [g] In addition to the allenol, approximately 15% of by-products were formed from direct attack of the Grignard reagent at the epoxide ring of the substrate.

- syn process is realized
- toluene is better solvent than Et_2O in the light of syn/anti selectivity
- chemical yield varies depending on the solvent, but which is better is not consistent
- diastereoselectivity decreases when reaction temperature is lowered, but the reason is not clear

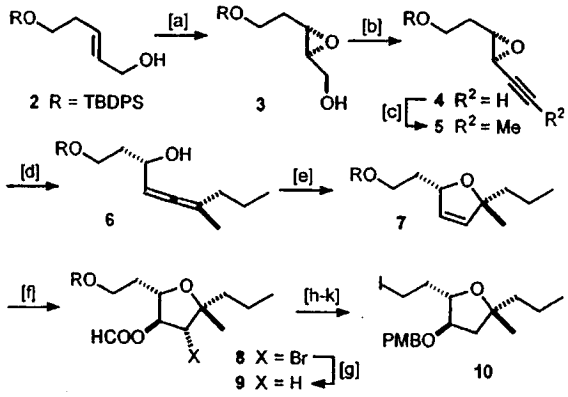
· procedure





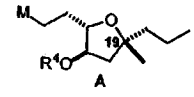
· mechanism has not been confirmed
· judging from procedure and stereoselectivit the mechanism is like the scheme written in left side (just my opinion)

Scheme 3 [a]



[a] Conditions: [a] $Ti(OiPr)_4$ cat., L-(+)-DET, tBuOOH, MS 4 Å, CH_2Cl_2, 97% (ee = 83%); [b] (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (ii) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH, 67%; [c] LiHMDS, MeOTf, THF, 95%; [d] PrMgCl, $Fe(acac)_3$ cat., toluene, 62% (syn:anti = 8:1); [e] $AgNO_3$, $CaCO_3$, aqueous acetone, 90%; [f] NBS, DMF/H_2O (15/1), 65%; [g] AIBN, $(TMS)_3SiH$, toluene; [h] $NaHCO_3$, MeOH, 90% (over both steps); [i] PMBOC(=NH)CCl_3, PPTS, CH_2Cl_2/C_6H_{12}, 76%; [j] TBAF, THF, 97%; [k] I_2, PPh_3, imidazole, MeCN/Et_2O, 92%.

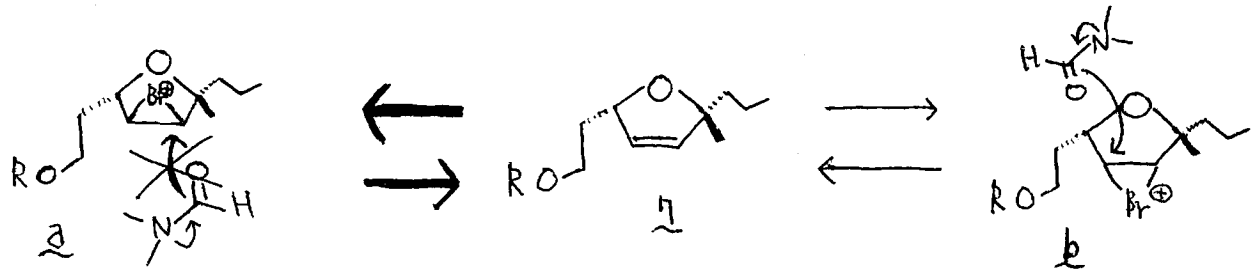
· construction of fragment A



· 5 → 6
iron-catalyzed allene formation, already described method

· 6 → 7
6 and diastereomer of 6 were not readily separable, mixture was treated with $AgNO_3/CaCO_3$ in aqueous acetone

· 7 → 8 (bromo-esterification)



downside is sterically crowded

- bromination of 7 is equilibrium step, a is more favorable
- it's hard for DMF to attack a
- DMF attacks b from less crowded side, avoiding the quaternary carbon's side

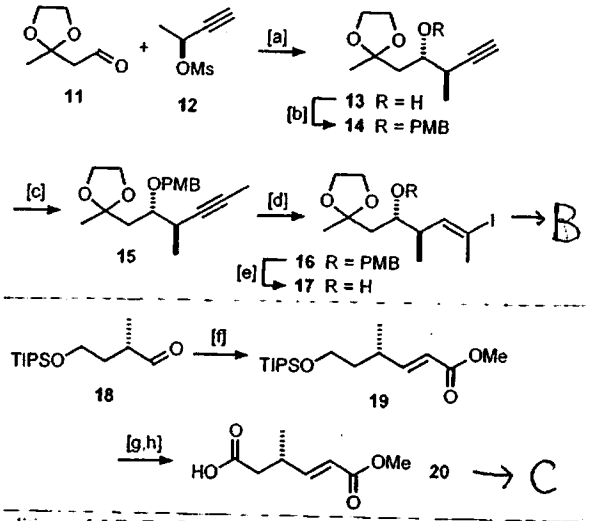
• 8 → 9 (cleavage of Br) Chatgilialoglu, C Acc. Chem. Res. 1992, 25, 188

$(Me_3Si)_3SiH$ (Tris(trimethylsilyl)silane) is rather expensive reagent, but it's less toxic than Bu_3SnH, which is often used in radicalic reaction.

$(Me_3Si)_3SiH$ ¥13100/5g
Bu_3SnH ¥3000/10g (Aldrich)

• construction of fragment B and C

Scheme 4 [a]



[a] Conditions: [a] Et_2Zn, $Pd(OAc)_2$ cat., PPh_3 cat., THF, 65% (anti:syn = 4.5:1); [b] PMBCl, NaH, TBAI, DMF, 94%; [c] LiHMDS, MeI, THF, 95%; [d] (i) Cp_2ZrHCl, C_6H_6; (ii) I_2, CH_2Cl_2, 61%; [e] DDQ, CH_2Cl_2, pH 7 buffer, 89%; [f] $(EtO)_2P(O)CH_2COOMe$, LiCl, DBU, MeCN, 94%; [g] HF·pyridine, MeCN, quant.; [h] (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (ii) $NaClO_2$, NaH_2PO_4, $(CH_3)_2C{=}CHCH_3$, tBuOH, 92%.

• 11 + 12 → 13
Pd-catalyzed Et_2Zn-mediated additic of mesylate 12 to aldehyde 11

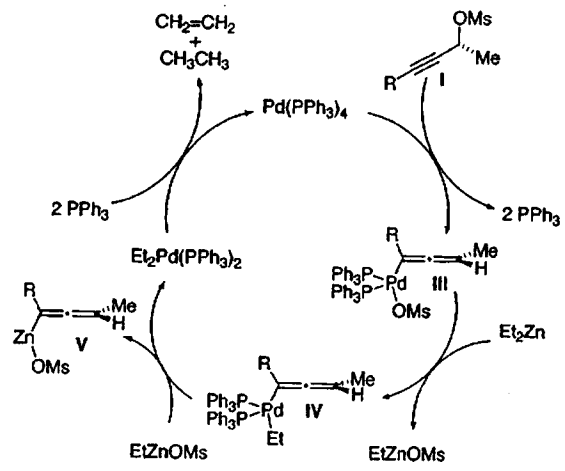
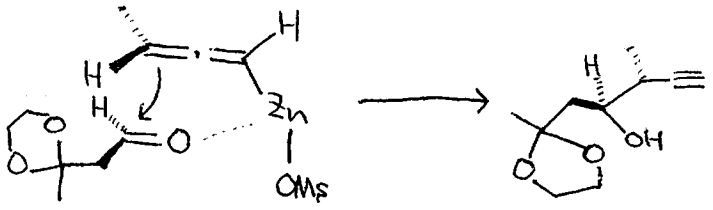


Figure 1. Possible catalytic cycle for Pd(0) catalyzed zincation of propargylic mesylates.

Marshall, J.A. et.al. J. Org. Chem. 1999, 64, 5201

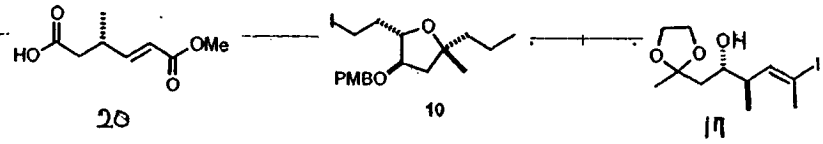
- Pd(0) attacks from anti side (S_N2')
- after transmetallation, allenylzinc species generate



cyclic TS

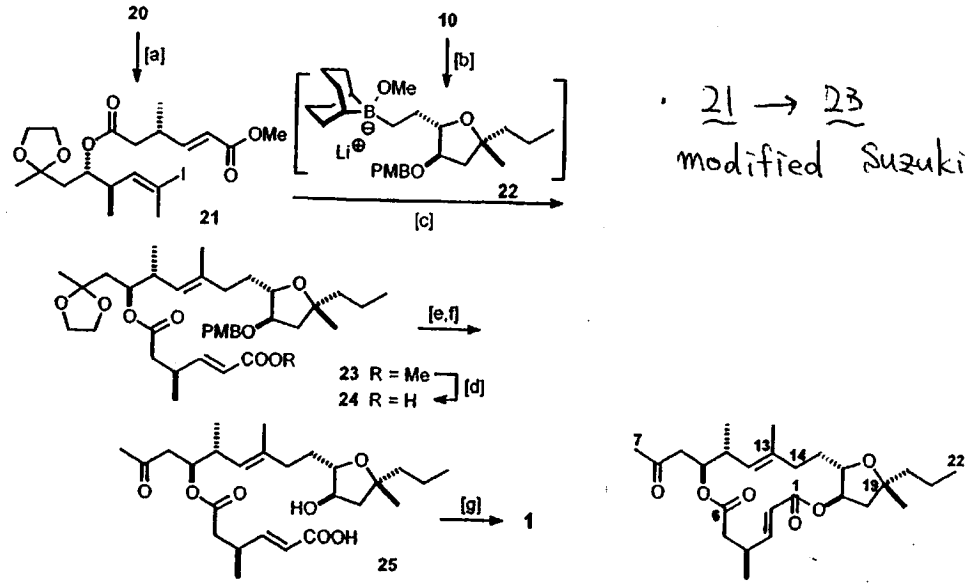
- enantiopure mesylate 12 gave 93% ee 13
- dr = 4.5/1

o linking the fragments



20 10 11

Scheme 5 [a]

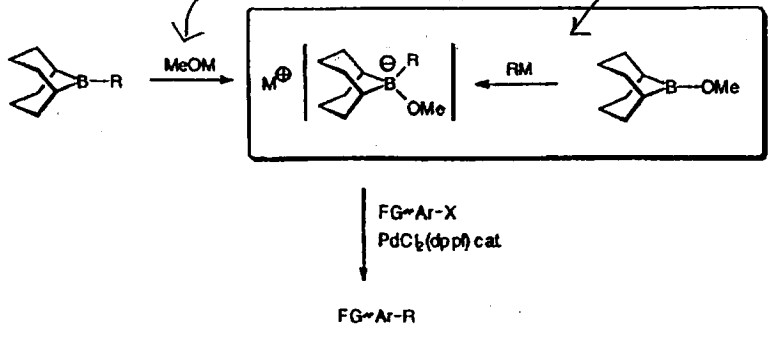


[a] Conditions: [a] 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene; then 17, DMAP, 96%; [b] tBuLi, Et_2O/THF; then 9-MeO-9-BBN; [c] (dppf)$PdCl_2$, Ph_3As, K_3PO_4, aqueous DMF, 74%; [d] LiI, pyridine, 125 °C; [e] aqueous HOAc, 53% (over both steps); [f] DDQ, CH_2Cl_2, pH 7 buffer, 84%; [g] 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, toluene, 62%.

Amphidinolide X (1)

· 21 → 23
modified Suzuki-coupling is utilized

original Suzuki-coupling — modified Suzuki-coupling

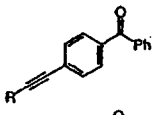
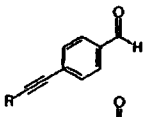
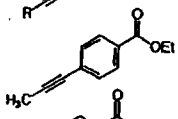
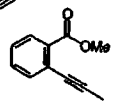
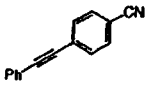
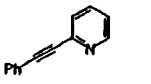
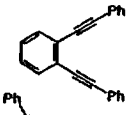
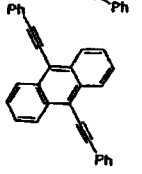


Scheme 1. Two complementary ways for performing Suzuki reactions; FG = functional group

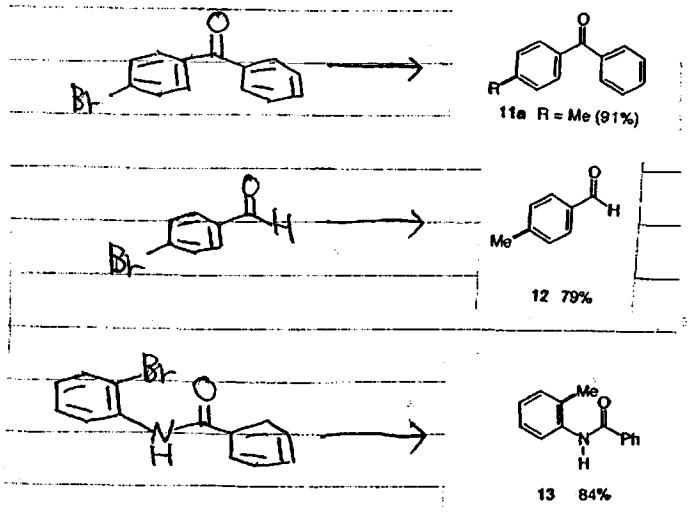
Fürstner, A. et al.
Tetrahedron, 1995, 51, 11165
Soderquist, J. A. et al.
Tetrahedron Lett, 1995, 36, 2401

advantage of
modified Suzuki-coupling →
- reagent preparation doesn't depend on hydroboration.
- applicable to alkynyl, methyl group

Table 1. Palladium-catalyzed arylations of alkynyl metal reagents mediated by 9-OMe-9-BBN.[a]

Entry	Substrate	RM	Product			Yield(%)
1	4-bromobenzophenone	PhC≡CK		1a	R = Ph	89
2		MeC≡CNa		b	R = Me	89
3	4-bromobenzaldehyde	MeC≡CNa		2a	R = Me	67
4		PhC≡CK		b	R = Ph	77
5	ethyl 4-bromobenzoate	MeC≡CNa		3		86
6	methyl 2-bromobenzoate	MeC≡CNa		4		87
7	4-bromobenzonitrile	PhC≡CK		5		93
8	2-bromopyridine	PhC≡CK		6		82
9	1,2-dibromobenzene	PhC≡CK		7		87
10	9,10-dibromoanthracene	PhC≡CK		8		85[b]
11	9,10-dibromoanthracene	PhC≡CLi				84[b]

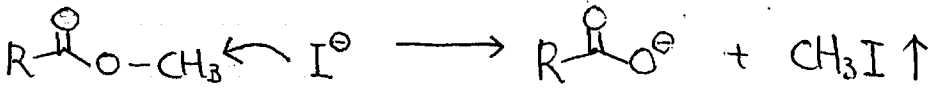
[a] Reaction conditions: ArBr (1 equiv.), 9-OMe-9-BBN (1.2 equiv.), RM (1.2 equiv.), $PdCl_2(dppf)$ (3 mol%), THF, reflux unless stated otherwise. [b] with 6 mol% of $PdCl_2(dppf)$.



KOKUYO

• 23 → 24

selective cleavage of methyl ester (LiI, pyridine, 125 °C)



Org. React. 1976, 24, 187

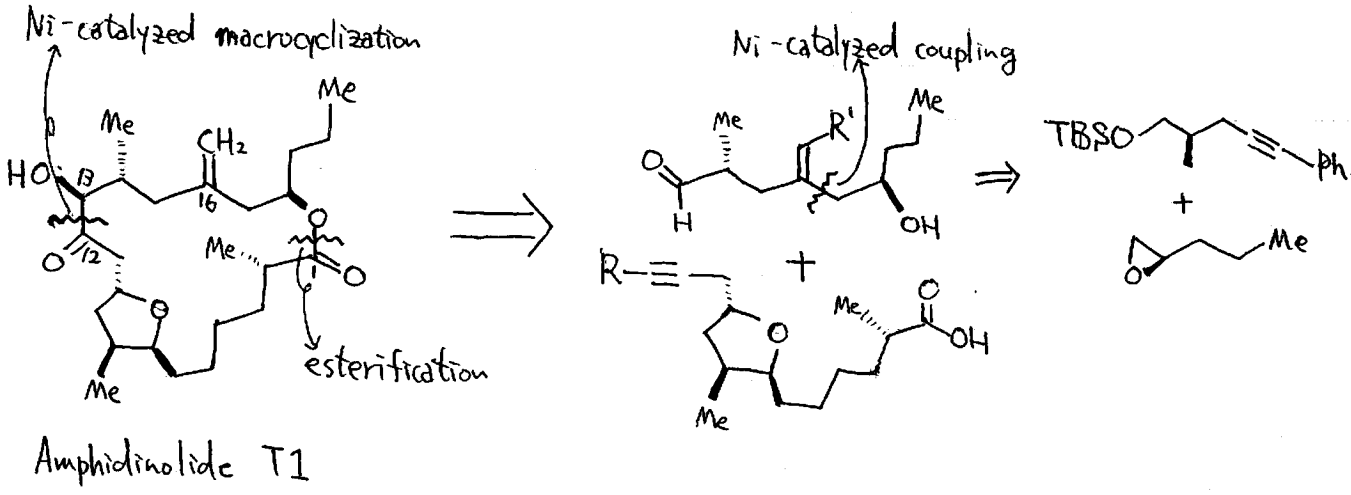
Amphidinolide T1

Synthesis of Amphidinolide T1 via Catalytic, Stereoselective Macrocyclization

Elizabeth A. Colby, Karen C. O'Brien, and Timothy F. Jamison*
Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

J. Am. Chem. Soc. 2004, 126, 998

° Retrosynthetic analysis



Amphidinolide T1

° Ni-catalyzed coupling of alkyne with various electrophiles

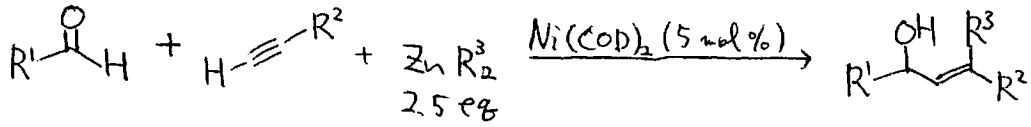
Prof. Montgomery, Prof. Mori, Prof. Tamaru, and others have developed Ni-catalyzed efficient junction of two π-electron systems such as alkyne-aldehyde, alkyne-enone, 1,3-diene-aldehyde and other combinations. (Review: Tamaru, Y. J. Organomet. Chem. 1999, 576, 215, Montgomery, J. Acc. Chem. Res. 2000, 33, 467, Houpis, I. N. et. al. Tetrahedron 2000, 56, 817) When alkyne is used, it is regarded as vinylanion synthon.

• example (alkyne-aldehyde coupling)

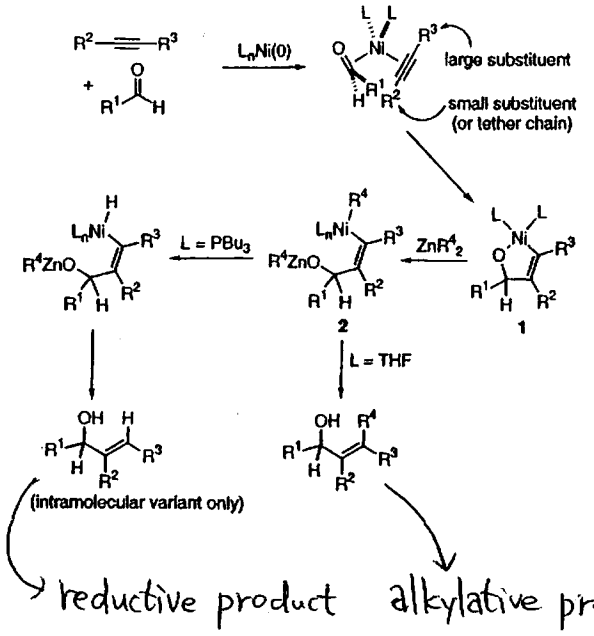
A New Stereoselective Method for the Preparation of Allylic Alcohols

Eric Oblinger and John Montgomery*
Department of Chemistry, Wayne State University Detroit, Michigan 48202-3489

J. Am. Chem. Soc. 1997, 119, 9065



Scheme 1. Proposed Mechanism for Ynal Cyclizations and Three-Component Couplings



reductive product alkylative product

proposed mechanism is show in left side

when phosphine ligand is added, reductive product is obtained only in intramolecular case

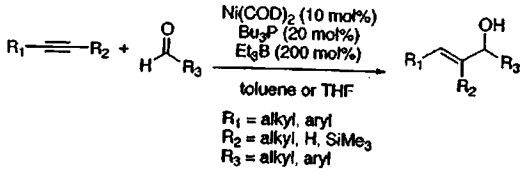
Highly Selective Catalytic Intermolecular Reductive Coupling of Alkynes and Aldehydes

Org. Lett. 2000, 2, 4221

Wei-Sheng Huang, Johann Chan, and Timothy F. Jamison*

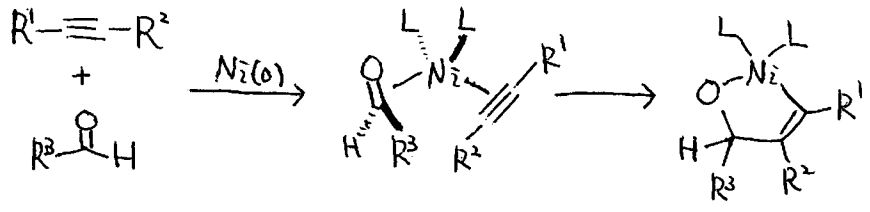
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Jamison's group studied related reaction intensively and achieved first catalytic and intermolecular reductive coupling of alkyne and aldehyde.

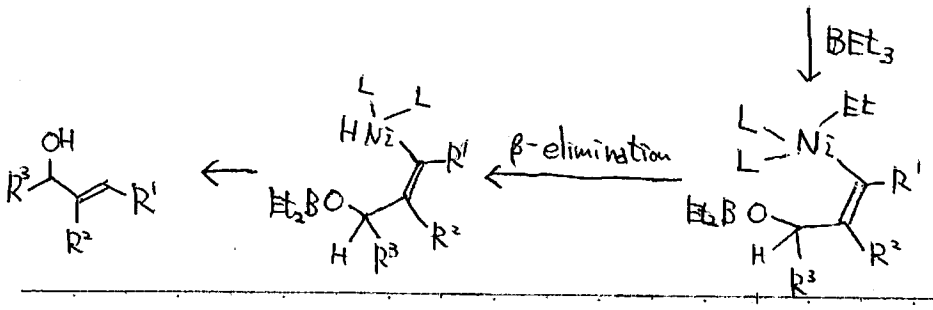


200 mol % of BEt_3 is employed

$Ni(cod)_2$ / Bu_3P = 1/2



mechanism is supposed to be like shown in left side



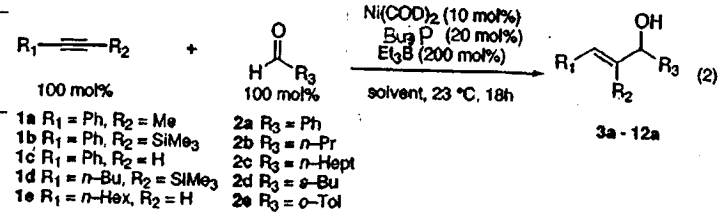
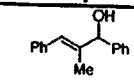
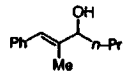
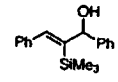
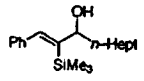
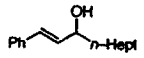
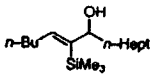
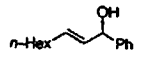
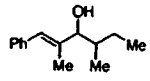
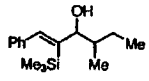
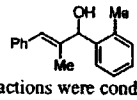
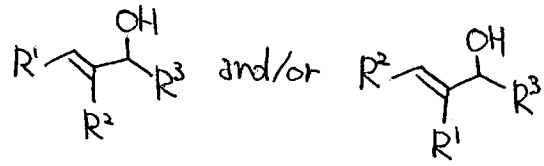


Table 2. Intermolecular Catalytic Reductive Couplings of Internal and Terminal Alkynes with Aromatic and Aliphatic Aldehydes[a]

entry	alkyne	aldehyde	major product		yield,[b] regioselectivity[c]
1[d]	1a	2a		3a	77% (92:8)
2	1a	2b[e]		4a	85% (92:8)
3[d,f]	1b[e]	2a		5a	49% (>98:2)
4	1b	2c		6a	89% (>98:2)
5[g]	1c[e]	2c		7a	45% (>98:2)
6	1d	2c		8a	58% (>98:2)
7[d]	1e[e]	2a		9a	76% (96:4)
8[f]	1a	2d		10a	41% (94:6) (66:34 dr)
9[f]	1b	2d		11a	31% (>98:2) (58:42 dr)
10	1a	2e		12a	83% (93:7)

[a] Except where noted, all reactions were conducted using the conditions indicated in eq 2 (1 mmol of alkyne, 1 mmol of aldehyde, toluene, Ar atmosphere). [b] Combined isolated yield of regioisomers. [c] Minor regioisomers (3b–12b) not shown. Regioselectivity (a:b) was determined either by separation of regioisomers (silica gel chromatography) or with a ^{1}H NMR spectrum of the product mixture. [d] THF used as solvent. [e] 200 mol % used. [f] Reaction conducted under reflux. [g] Reaction conducted at 0 °C.

- two isomer can generate



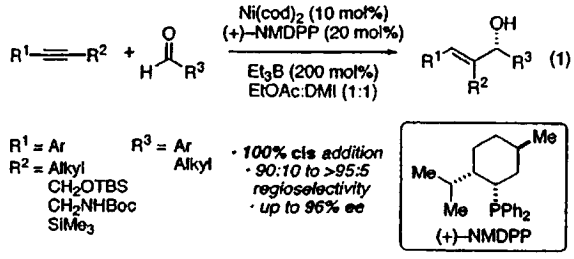
- regioselectivity is up to >98/2
- yield is up to 89%
- adopted in total synthesis of Amphidinolide T1

Catalytic Asymmetric Reductive Coupling of Alkynes and Aldehydes: Enantioselective Synthesis of Allylic Alcohols and α-Hydroxy Ketones

Karen M. Miller, Wei-Sheng Huang, and Timothy F. Jamison*

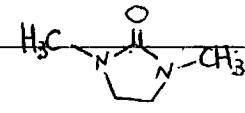
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

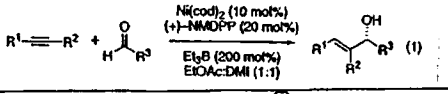
J. Am. Chem. Soc. 2003, 125, 3442



Jamison succeeded in asymmetric reaction, utilizing chiral phosphine ligand.

DMI : 1,3-dimethylimidazolidinone

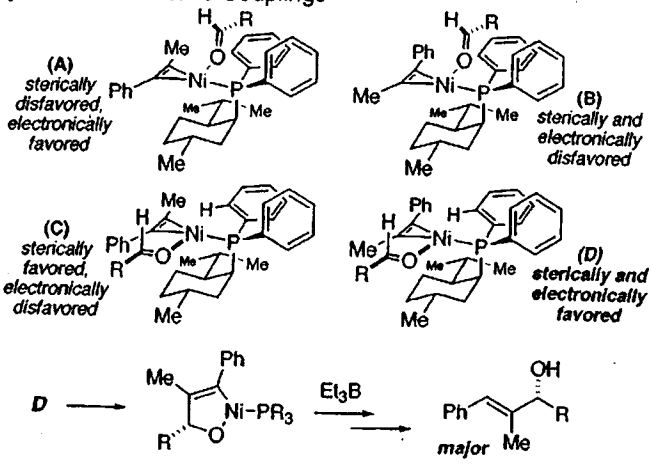




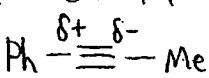
entry/ product	R^1	R^2	R^3	yield (%), regioselectivity	ee (%)
1	Ph	Me	*i*-Pr	95 (>95:5)	90
2	Ph	Me	*c*-C_6H_{11}	97 (>95:5)	90
3	Ph	Me	Ph	79 (91:9)	73
4	Ph	Me	*n*-Pr	82 (>95:5)	65
5	(*p*-MeO)Ph	Me	*i*-Pr	80 (>95:5)	88
6	(*p*-Cl)Ph	Me	*i*-Pr	75 (>95:5)	83
7	1-naphthyl	Me	*i*-Pr	93 (>95:5)	90
8	Ph	Et	*i*-Pr	81 (>95:5)	93
9[b]	Ph	Et	*c*-C_6H_{11}	78 (>95:5)	89
10	Ph	*n*-Pr	*i*-Pr	74 (>95:5)	92
11	Ph	*i*-Pr	*i*-Pr	58[c] (>95:5)	92
12	Ph	CH_2OTBS	*i*-Pr	59 (>95:5)	85
13	Ph	CH_2NHBoc	*i*-Pr	60 (>95:5)	96
14	Ph	$SiMe_3$	*n*-Pr	43[c] (>95:5)	92
15	*n*-Pr	*n*-Pr	*i*-Pr	35[c] (−)	42

[a] See eq 1. Experimental procedure (see Supporting Information): A solution of $Ni(cod)_2$ (0.05 mmol), (+)-NMDPP (0.10 mmol), and Et_3B (1.0 mmol) in EtOAc/DMI (1:1, total volume 0.50 mL) was cooled to −25 °C. An alkyne (0.50 mmol) was added via syringe, and then an aldehyde (1.0 mmol) was added via syringe over 8 h. The solution was allowed to stir 36 h, and silica gel chromatography afforded allylic alcohols **1**−**15**. Regioselectivity was determined by ^1H NMR; enantioselectivity was determined by chiral GC or HPLC analysis. [b] Performed on 5.0 mmol scale. [c] Some alkylative coupling was observed (transfer of Et group (instead of H) from Et_3B).

Scheme 1. Proposed Steric and Electronic Control in Catalytic Asymmetric Reductive Couplings



- up to 97% yield, up to 96% ee
- proposed TS (Scheme 1)
  - phenyl ring of phosphine avoids interaction with isopropyl group
  - aldehyde coordinates to less crowded side (C, D) by way of the electron pair cis to aldehyde H and placement of the aldehyde R group away from the metal center
  - more electron-rich carbon of alkyne attacks aldehyde

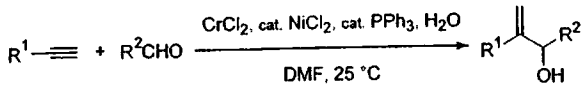


- $R^1 = R^2 = n\text{-Pr}$ (entry 15) → bad result

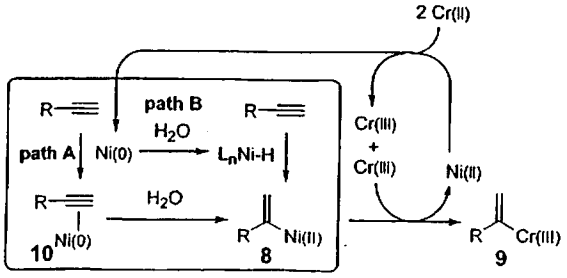
Regioselective Reductive Coupling of Alkynes and Aldehydes Leading to Allylic Alcohols

Org. Lett. 2003, 5, 653

Kazuhiko Takai,* Shuji Sakamoto, and Takahiko Isshiki

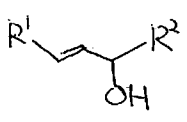


Scheme 4



- reductive coupling using $CrCl_2$ and $NiCl_2$ gave opposite regioselectivity (up to >99 / <1)

regioisomer →

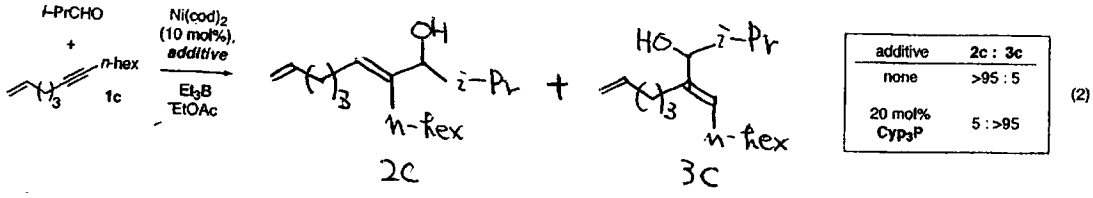


Ligand-Switchable Directing Effects of Tethered Alkenes in Nickel-Catalyzed Additions to Alkynes

Karen M. Miller and Timothy F. Jamison*

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

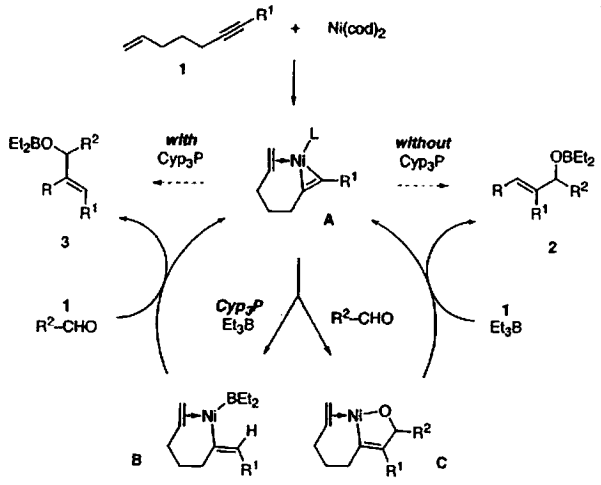
J. Am. Chem. Soc. 2004, 126, 15342



additive	2c : 3c
none	>95 : 5
20 mol% Cyp_3P	5 : >95

(2)

Scheme 1



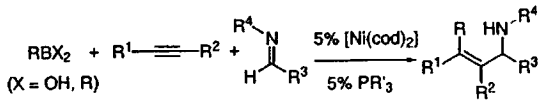
- remote C=C dictates regioselectivity
- regioselectivity is reversed with Cyp_3P
- in the absence of Cyp_3P, C–C bond formation is prior to alkenyl H introduction
- in the presence of Cyp_3P, installation of alkenyl H is prior to C–C bond formation

Catalytic Three-Component Coupling of Alkynes, Imines, and Organoboron Reagents**

Angew. Chem. Int. Ed. 2003, 42

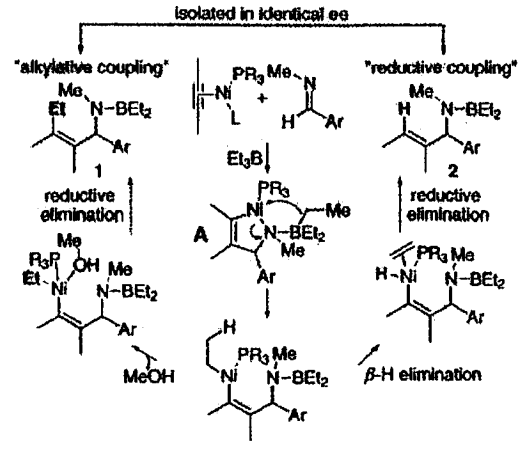
*Sejal J. Patel and Timothy F. Jamison**

Jamison also developed catalytic coupling of alkyne, imines, and organoboran



Solvent: MeOAc/MeOH, 50°C

Scheme 1. Catalytic assembly of allylic amines from alkynes, imines, and organoboron reagents.



- alkylative reaction
- CH_3OH occupies coordination site required for β-H elimination
- 1 and 2 were isolated in identical ee, which support that enantioselectivity and diastereoselectivity are determined in the same step and before a common intermediate A divide into two pathways to lead to either 1 or 2.

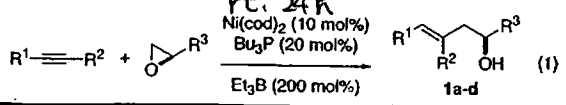
• Ni-catalyzed reaction which combines π-system and epoxide

Nickel-Catalyzed Reductive Coupling of Alkynes and Epoxides

Carmela Molinaro and Timothy F. Jamison*

J. Am. Chem. Soc. 2003. 125 8076

Table 1. Intermolecular Reductive Coupling of Alkynes and Epoxides[a]

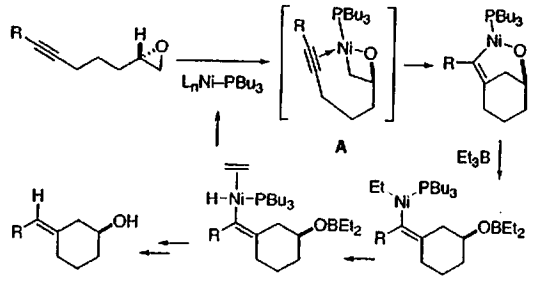


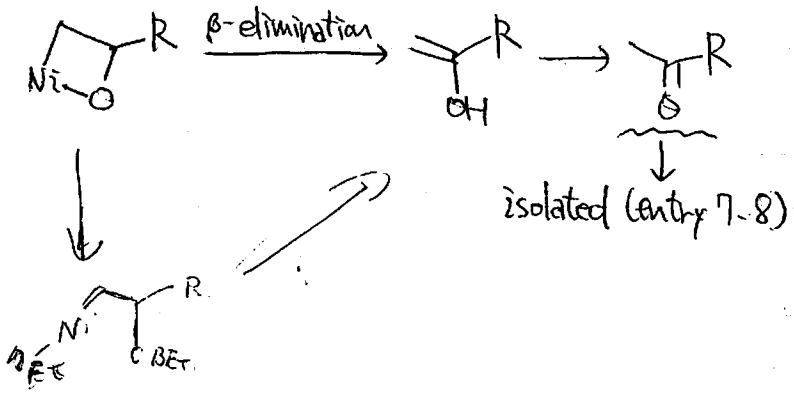
entry	R^1	R^2	R^3	additive	product	yield (%)	regioselectivity alkyne	regioselectivity epoxide
1[b]	Ph	Me	Me	Et_3P	1a	0	>95:5	>95:5
2[b]	Ph	Me	Me	Bu_3P	1a	36	>95:5	>95:5
3[b]	Ph	Me	Me	$(n\text{-Oct})_3P$	1a	35	>95:5	>95:5
4[c]	Ph	Me	Me	Bu_3P	1a	25	>95:5	>95:5
5[d]	Ph	Me	Me	Bu_3P	1a	34	>95:5	>95:5
6	Ph	Me	Me	Bu_3P	1a	71	>95:5	>95:5
7	Ph	Me	*n*-Hex	Bu_3P	1b	68	>95:5	>95:5
8	Ph	Me	Ph	Bu_3P	1c	50[e]	88:12	83:17
9	*n*-Pr	*n*-Pr	Et	Bu_3P	1d	35[e]	na	>95:5

[a] See eq 1, ref 9, and Supporting Information. [b] Ether used as solvent. [c] Toluene used as solvent. [d] Ethyl acetate used as solvent. [e] Overall yield after conversion to TBDPS ether.

- epoxide has no multiple bond
- regioselectivity is high.
- reductive product
- support for Nickella(II) oxetane structure if the isolation of epoxide's isomer

Scheme 1. Reductive Cyclization via a Proposed Nickella(II)oxetane

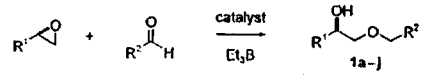




Catalytic Reductive Coupling of Epoxides and Aldehydes: Epoxide-Ring Opening Precedes Carbonyl Reduction**

*Carmela Molinaro and Timothy F. Jamison**

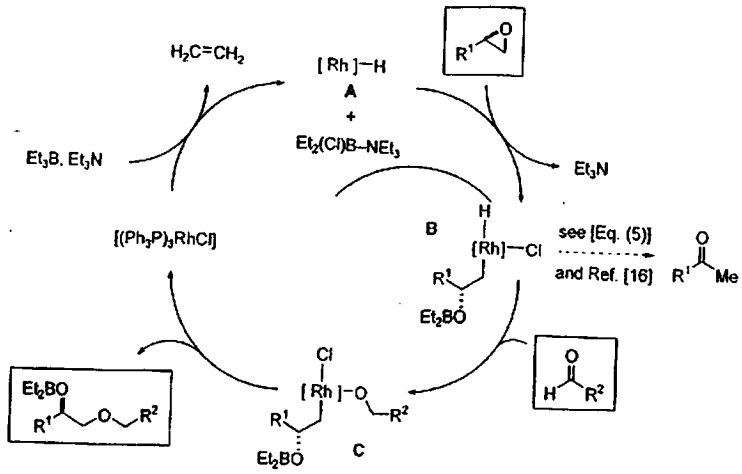
Angew. Chem. Int. Ed. 2005, 44, 129



Entry	R^1	R^2	Catalyst	Product	Yield [%]
1	Et	Ph	$[Ni(cod)_2]$, Bu_3P	1a	64
2	Et	Ph	$[(Bu_3P)_2NiCl_2]$	1a	62
3	Et	Ph	$[(Ph_3P)_3RhCl]$	1a	90
4	Ph	Ph	$[(Ph_3P)_3RhCl]$	1b	74
5	*i*Pr	Ph	$[(Ph_3P)_3RhCl]$	1c	26
6	*t*Bu	Ph	$[(Ph_3P)_3RhCl]$	1d	12
7	*i*Pr	Ph	$[(Ph_3P)_3RhCl]$, Et_3N	1c	96
8	*t*Bu	Ph	$[(Ph_3P)_3RhCl]$, Et_3N	1d	90
9	Et	2-naphthyl	$[(Ph_3P)_3RhCl]$, Et_3N	1e	70
10	*n*-hexyl	*p*-anisyl	$[(Ph_3P)_3RhCl]$, Et_3N	1f	67
11	*n*-hexyl	2-furyl	$[(Ph_3P)_3RhCl]$, Et_3N	1g	57
12	*n*-hexyl	*i*Pr	$[(Ph_3P)_3RhCl]$, Et_3N	1h	15

[a] Standard procedure: To the catalyst specified and, where indicated, Et_3N (20 mol%) at room temperature were added the epoxide, aldehyde, Et_3B (200 mol%, dropwise). The mixture was stirred for 16 h and purified by silica-gel chromatography. See Supporting Information for details. cod = cycloocta-1,5-diene.

- C-O bond forming reaction
- catalyst : 1.6 ~ 40 mol%
- aliphatic aldehyde gives low yield
- Et_3N improves chemical yield
- proposed mechanism is shown in next page



Scheme 1. Proposed mechanism for the catalytic reductive coupling of epoxides and aldehydes.

$[(Ph_3P)_3RhCl]$

↓ transmetallation, β-elimination

A

↓ epoxide opening

B

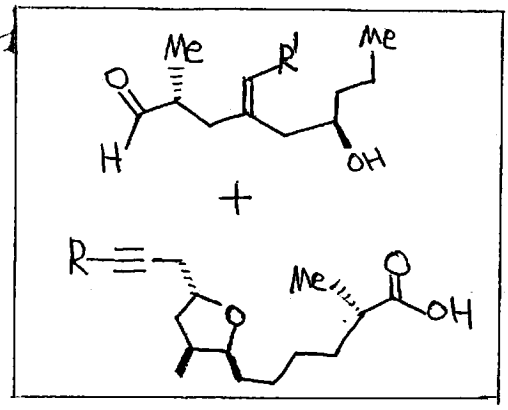
↓ insertion

C

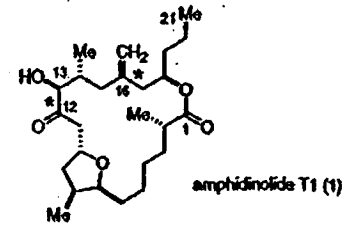
↓ reductive elimination

$[(Ph_3P)_3RhCl]$

required fragments →



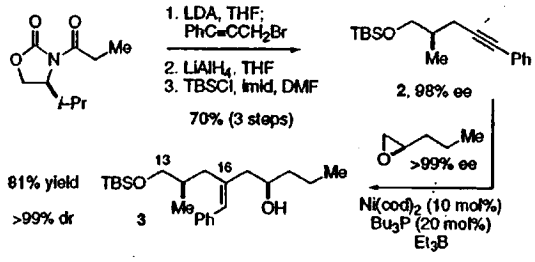
target compound ↓



amphidinolide T1 (1)

° Synthesis of fragment 3

Scheme 1. Enantioselective Synthesis of the C13–C21 (3) Fragment of **1** Using a Nickel-Catalyzed Alkyne–Epoxide Reductive Coupling



· 2 → 3

epoxide preparation → Jacobsen's kinetic resolution

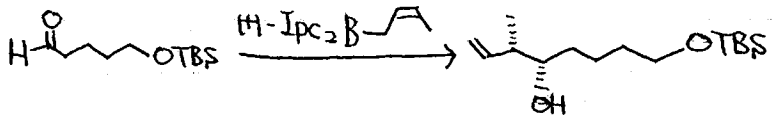
Jacobsen, E. N. et. al.

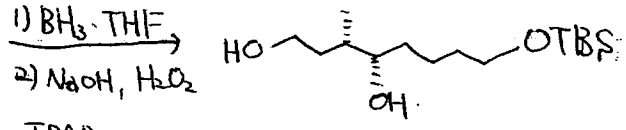
J. Am. Chem. Soc, 2002, 124, 1307

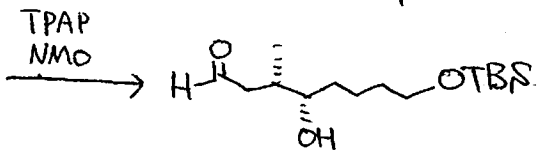
Ni-catalyzed alkyne-epoxide coupling

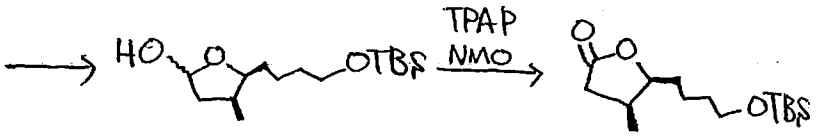
- synthesis of fragment 7

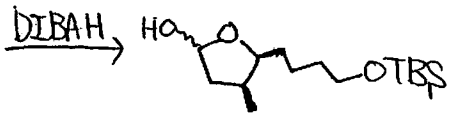
4 → 5



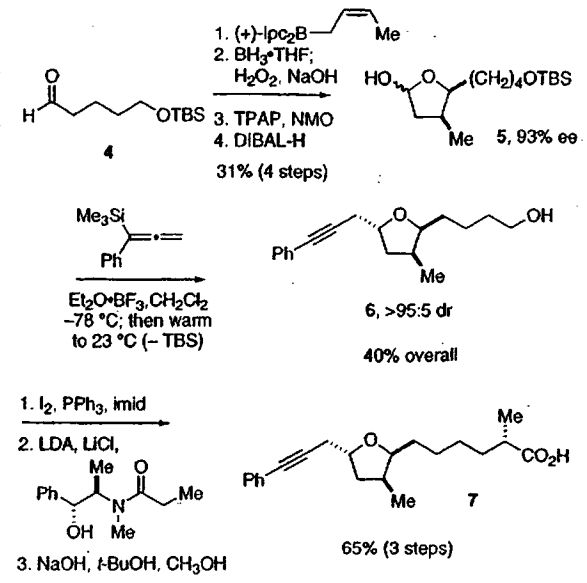








Scheme 2. Synthesis of the C1–C12 Fragment (7) of Amphidinolide T1



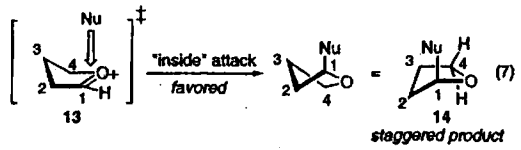
- setereoselective allenylsilane addition to oxocarbenium ion

A Stereoelectronic Model To Explain the Highly Stereoselective Reactions of Nucleophiles with Five-Membered-Ring Oxocarbenium Ions

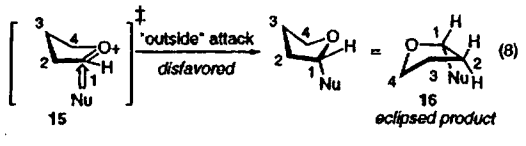
J. Am. Chem. Soc. 121, 12209

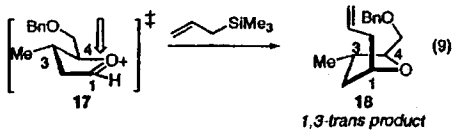
Catharine H. Larsen, Brian H. Ridgway, Jared T. Shaw, and K. A. Woerpel*

Department of Chemistry, University of California Irvine, California 92697-2025

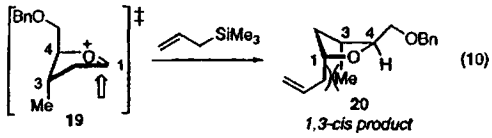


- transition state for staggered product is favored

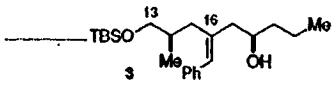


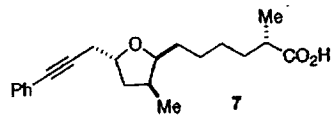


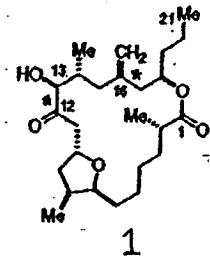
- nucleophile approaches from inside of the ring and generate 1,3-trans product



◦ Macrocyclization

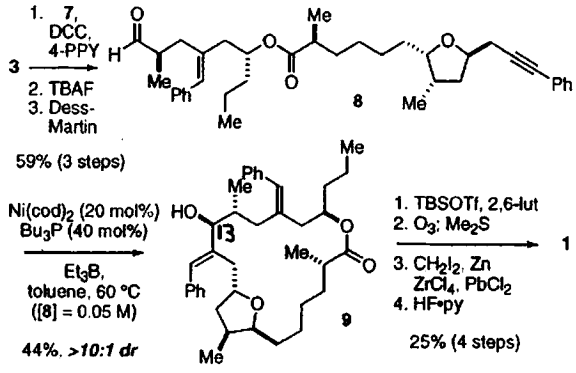






1

Scheme 3. Synthesis of Amphidinolide T1 (**1**) via Stereoselective Macrocyclization: Intramolecular, Nickel-Catalyzed Alkyne–Aldehyde Reductive Coupling



• 8 → 9

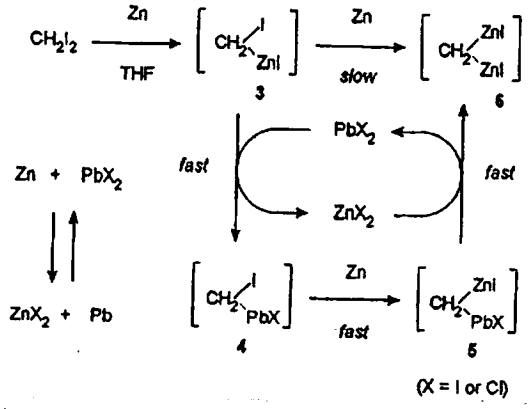
intramolecular Ni-catalyzed macrocyclization

stereochemistry at C13 is explained by Houk-model, however intermolecular coupling of closely related compound were nearly nonstereoselective (1.5/1)

→ stereoselectivity (>10:1 dr) is largely due to the stereochemistry of 8

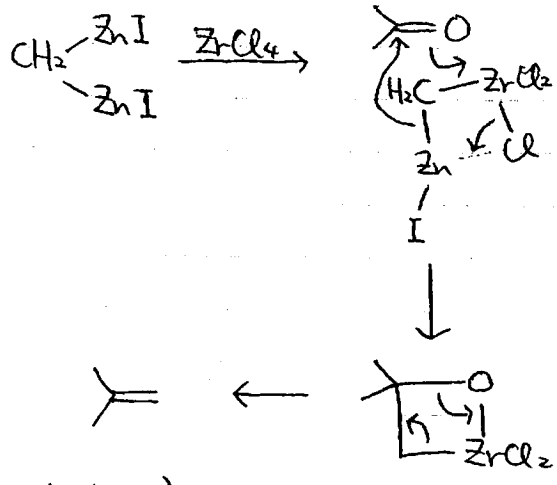
◦ selective methylenation at C16

Scheme 1



Takai, K. Utimoto, K. et. al.
J. Org. Chem. 1994, 59, 2668

catalytic amount of lead promotes geminal dizinc compound formation



- chemical yield is low (25%, 4 steps)
- carbonyl group near -OTBS group is less reactive