Wataru Itano (M1の分)

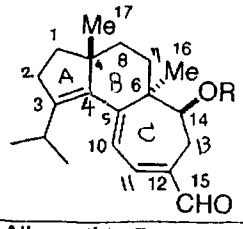
1

Literature Seminar

2005 4 6 Wed.

Total Synthesis of Allocyathin B_2

0. Introduction



(+)-Allocyathin B_2 (**1**): R = H
(+)-Erinacine A (**2**): R = 1-β-D-xylose

structual features :
* angularly fused 5-6-7 tricyclic framework
* 1,4-anti quaternary methyl group (@C17 and C16)

— a kind of cyathins, aglycon of (+)-Erinacine A (cyathane diterpenes)

Isolation & Structure determination : from bird nest fungus (family Nidulariaceae)

Cyathus earlei Lloyd's metabolite
(tropical or subtropical in Cuba, Puerto Rico, Mexico, Hawai)
by Ayer's group (1970s) (Can. J. Chem. (1979) 57, 3332-3337)

Biological activity : against actinomycetes (放線菌)
(Gram-posi & -negative bacteria (Can J. Microbiol. (1971), 17, 1401.)

especially ... (+)-Erinacine A (2) (D-xylose conjugated Allocyathin B_2)
: NGF (nerve growth factor) stimulator (TL (1999) 35, 1569.)
to treat such neurodegenerative disease (神経変性の)
as Alzheimer, Parkinson and Huntington disease

〈Contents〉

Point : How to Construct A, B, C ring?

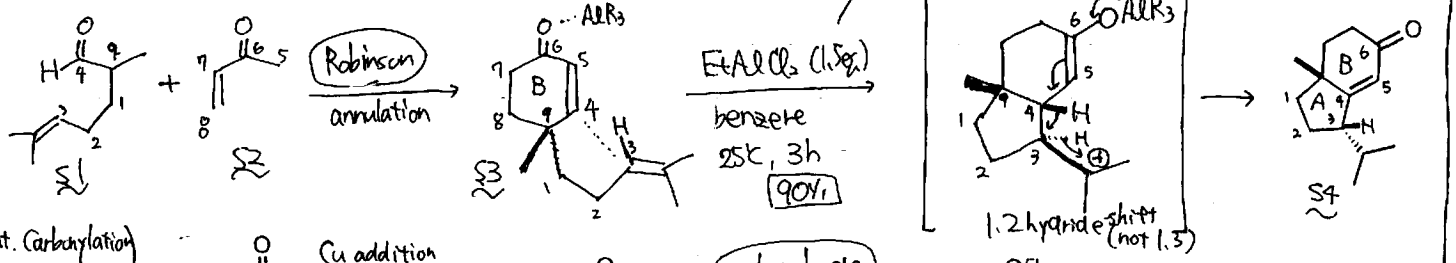
1. Outlook of the Reported Synthesis

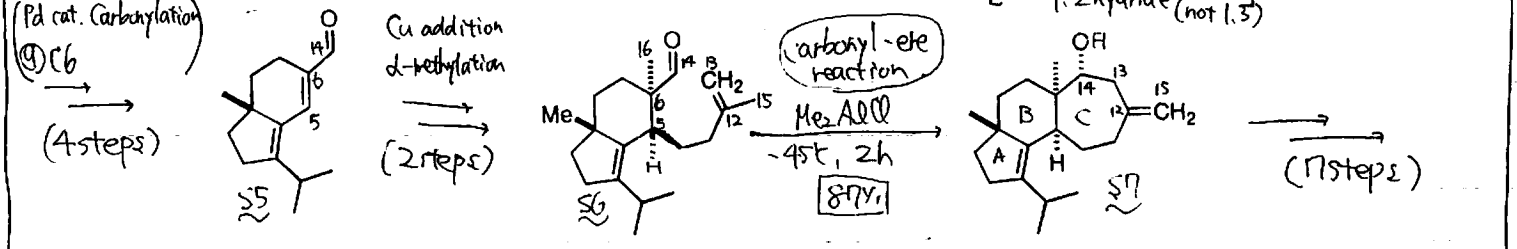
<Racemic Case>

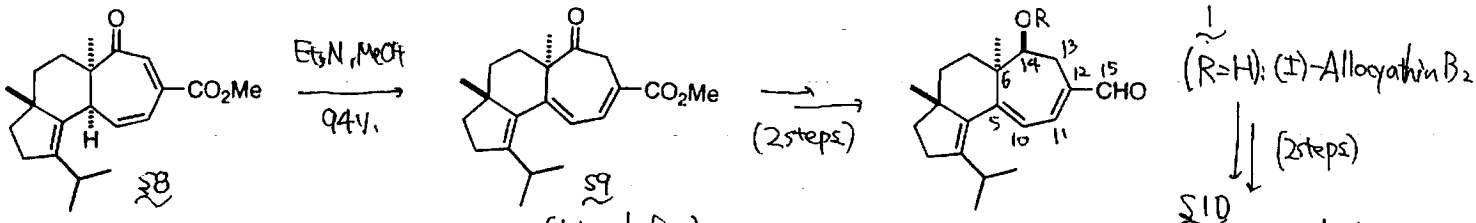
① Snider et al. (JACS, (1996), 118, 7644. / JOC, (1998), 63, 306.)

high regio and stereospecificity

Lewis Acid Induced Conjugate Addition (JACS (1980), 102, 5872.)



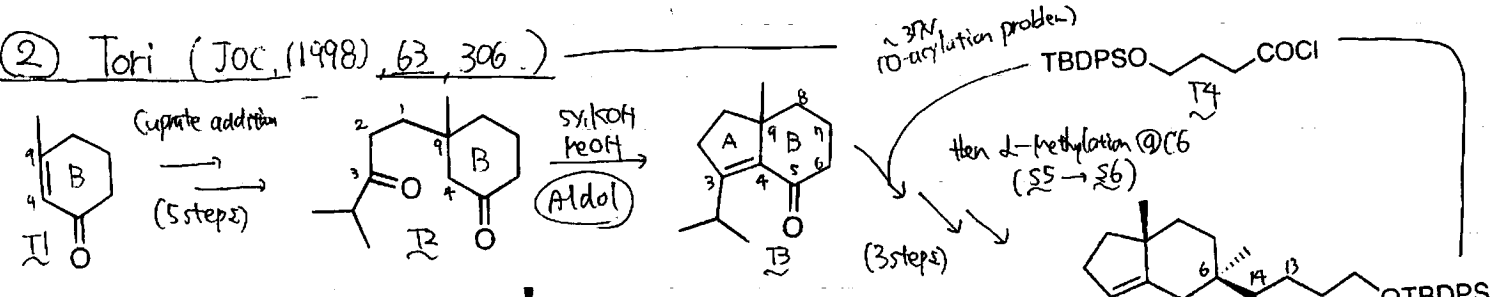


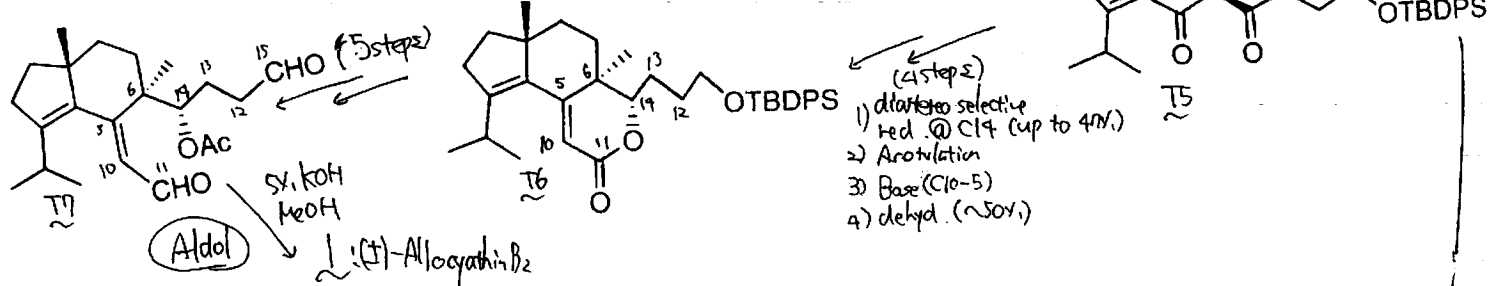


SM —1step→ A ring —1step→ B ring —7steps→ C ring —10steps→ 1

② Tori (JOC, (1998), 63, 306.)

~3% (O-acylation problem)

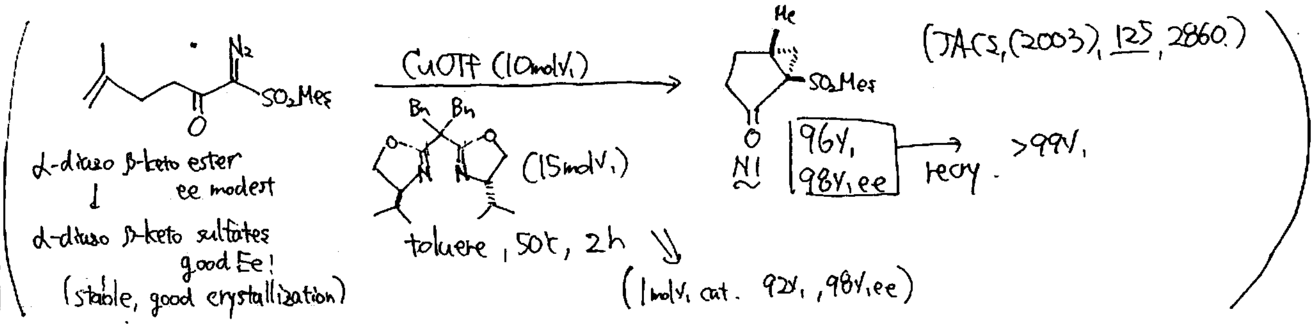


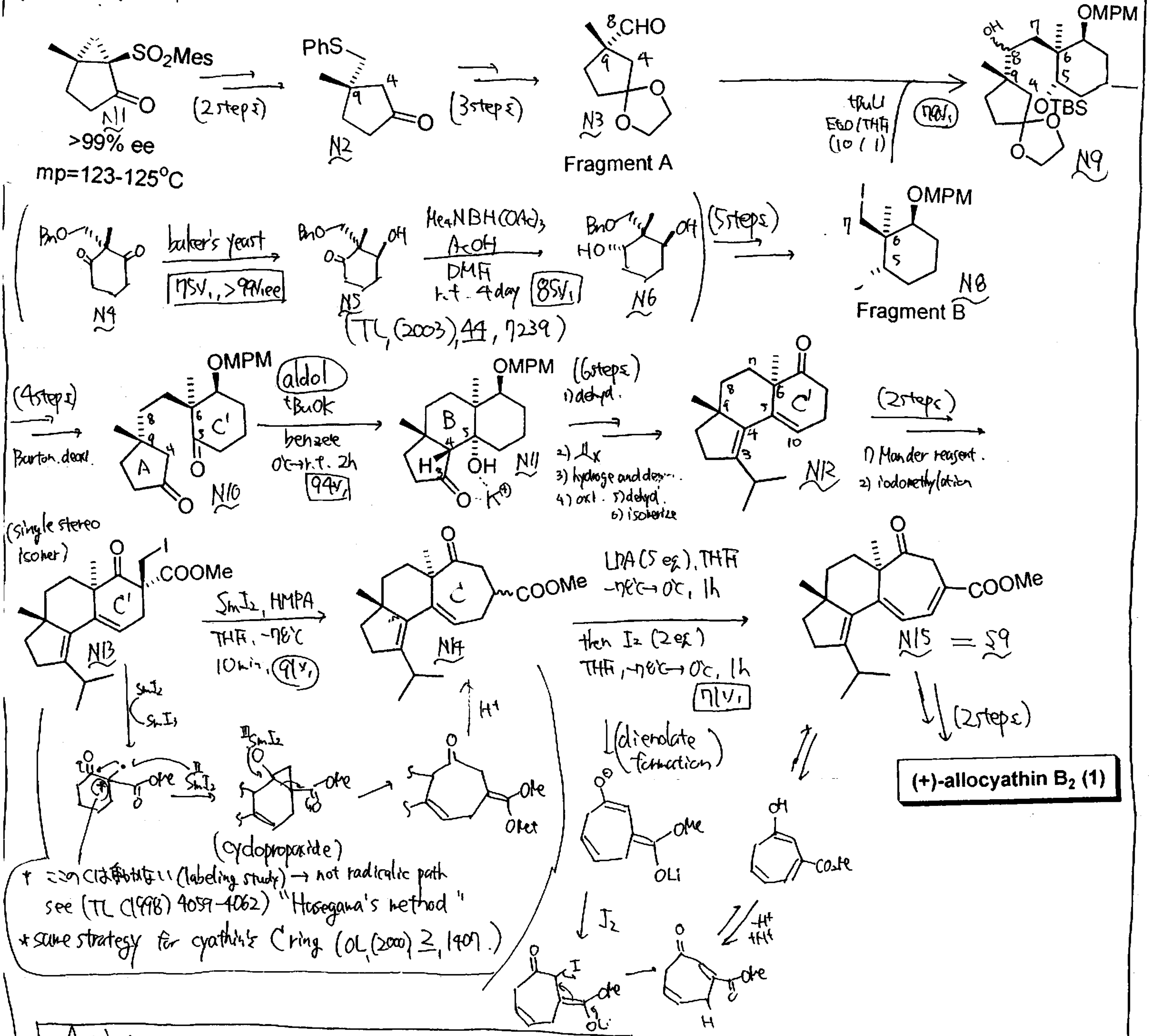


Bring (SM) —5steps→ A ring —3steps→ C ring ≠ 1

<Asymmetric Case>

③ Nakada et al. (OL (2004), 6, 4897-4900) [2004.9.29 received] "first"





SO2Mes
N1
>99% ee
mp=123-125°C
(2steps)
PhS
N2
(3steps)
CHO
N3
Fragment A
tBuLi
Et2O/THF (10/1)
OMPM
OTBS
N9
baker's yeast
75%, >99%ee
N4
N5
(TL, (2003), 44, 7239)
Me4NBH(OAc)3
AcOH
DMF
r.t. 4day 85%
N6
(5steps)
OMPM
Fragment B
N8
(4steps)
Barton deox.
OMPM
A
C'
N10
aldol
tBuOK
benzene
0℃→r.t. 2h
94%
OMPM
B
OH
N11
(6steps)
1) dehyd.
3) hydroge and deo...
4) oxi. 5) dehyd.
6) isomerize
C'
N12
(2steps)
1) Mander reagent.
2) iodomethylation
(single stereo isomer)
COOMe
N13
SmI2, HMPA
THF, -78℃
10min, 91%
COOMe
N14
LDA (5 eq), THF
-78℃→0℃, 1h
then I2 (2eq)
THF, -78℃→0℃, 1h
71%
COOMe
N15 = S9
(2steps)
(+)-allocyathin B2 (1)
H+
(cyclopropoxide)
(dienolate formation)
OMe
OLi
OH
CO2Me
I2
H+
* ここのCは動かない (labeling study) → not radicalic path
see (TL (1998) 4059-4062) "Hasegawa's method"
* same strategy for cyathin's C ring (OL, (2000) 2, 1409.)

A ring (N3), C' ring (N8) → 6steps → B ring → 9steps → C ring → 3steps → 1	(収束的合成 with ...) 7 membered ring was introduced at last stage

2. Trost's Synthesis

J|A|C|S COMMUNICATIONS

Published on Web 02/11/2005

(2005, 127, 2844-2845)

2004.10.23 received (not "first")

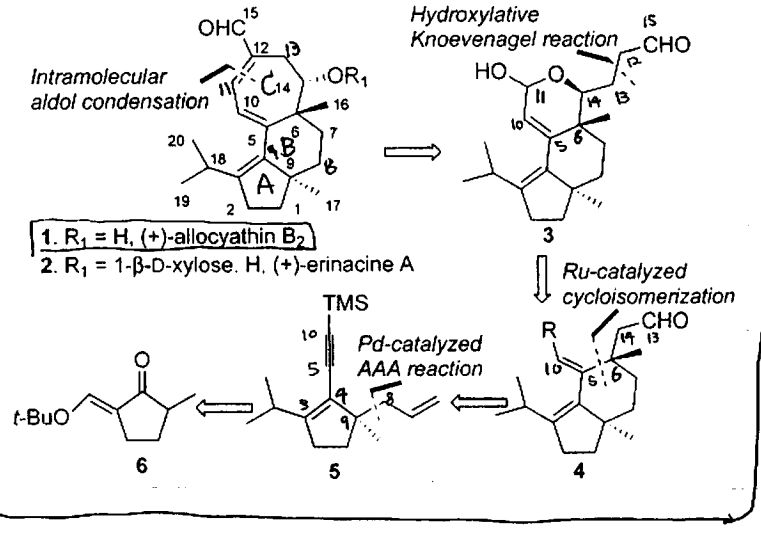
Total Synthesis of (+)-Allocyathin B_2

Barry M. Trost,* Li Dong, and Gretchen M. Schroeder

Department of Chemistry, Stanford University, Stanford, California 94301-5080

I. Retrosynthetic Analysis

[scheme 1]



1 ⇒ 3

Intramolecular aldol for C11-12

acetal between C11 aldehyde – C14 hydroxy

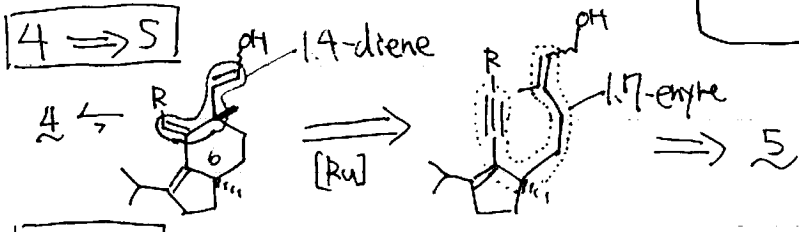
→ same strategy as Tori's case

3 ⇒ 4

introduction of 2-carbon unit and C14 hydroxy group at one stage.

stereoselectively?

4 ⇒ 5

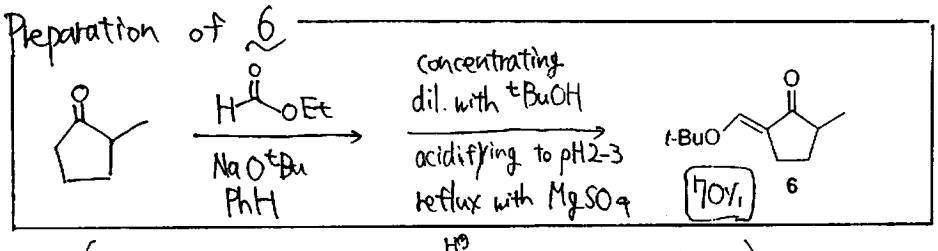


5 ⇒ 6

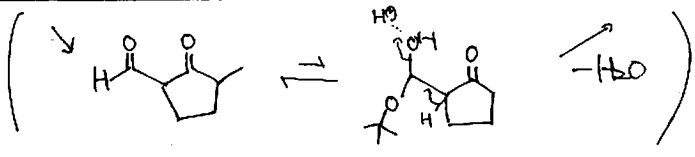
Asymetric Allylic Alkylation (AAA) of prochiral ketone (6), Sonogashira coupling.

II. Synthesis of Enyne 5

* Preparation of 6

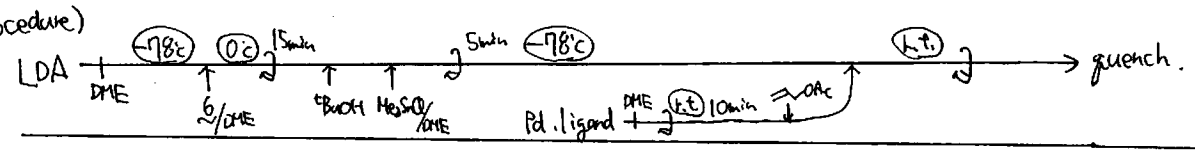


(JACS, (2004), 126, 4480-4481. Trost's Hamigeran B synthesis)

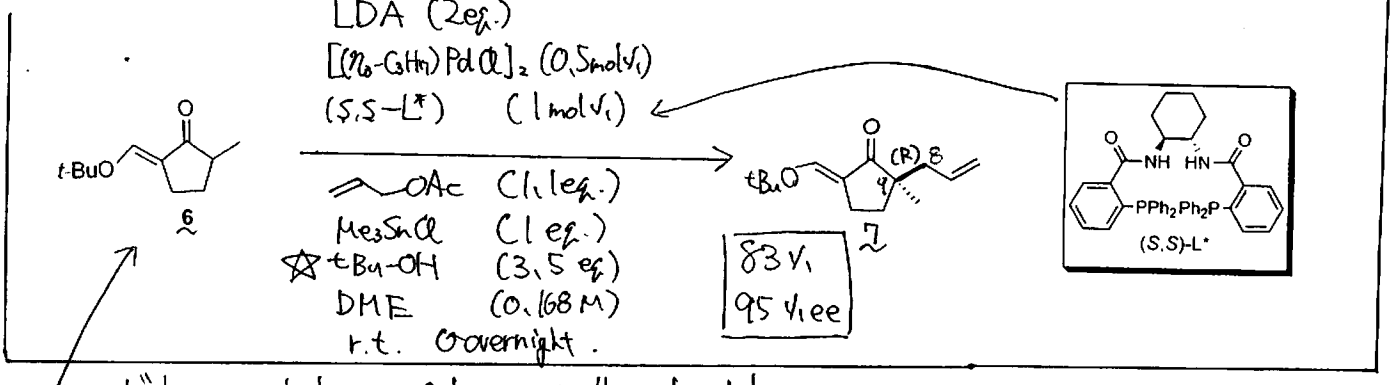


(more detail : see Harada san's lit. seminar (2002.5.15))

(procedure)



* AAA



Q prochiral "less stabilized (pka ≲20)" nucleophiles
that can only form a single enolate under base mediated reaction condition

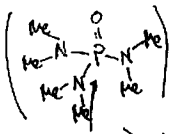
⇓

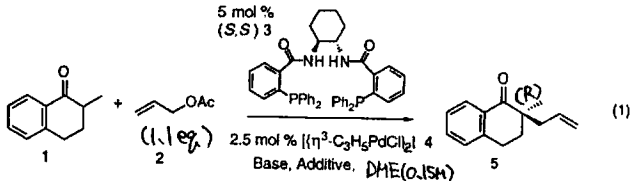
① initial work

(JACS, (1999), 121, 6759-6760)

Palladium-Catalyzed Asymmetric Alkylation of Ketone Enolates

Barry M. Trost* and Gretchen M. Schroeder





entry	base (eq no.)	additive(1eq.)	time (h)	% yield	% ee
1	LDA (1)	$(C_4H_9)_3SnOSO_2CF_3$	3	21	32
2	LDA (1)	$(C_4H_9)_3SnCl$	2	53	65
3	LDA (1)	$(CH_3)_3SnCl$	3	65	69
4	LDA (1.25)	$(CH_3)_3SnCl$	2.5	78	78
5	LDA (1.5)	$(CH_3)_3SnCl$	2.5	99	80
☆ 6	LDA (2)	$(CH_3)_3SnCl$	0.5	99	88
7	LDA (3)	$(CH_3)_3SnCl$	1.75	61	84
8	LiHMDS (2)	$(CH_3)_3SnCl$	2	94	71
9	LiTMP (2)	$(CH_3)_3SnCl$	0.5	99	86
10	LDA (2)	none	1	96	85

Solvent : DME best (THF, CH_2Cl_2, tol. dioxane, HMPA/~~THF~~ (10v%))
→ the state of aggregation of the enolate may change.

additive : stannanes better (than boranes and borates)
poor leaving group good (Nu may be ate complex?)
smaller LA good
⇒ standard condition
Sn effect "small but very reproducible"

base : Only Li base (Na, K base X)

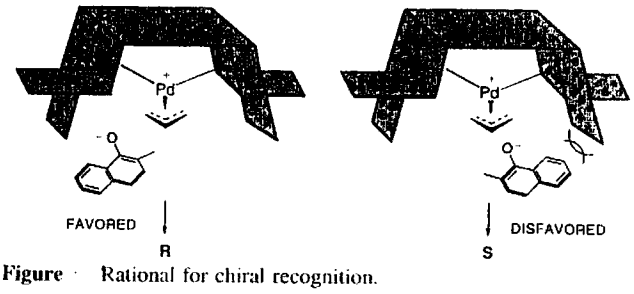


Figure Rational for chiral recognition.

"bond making and breaking occur outside the coordination sphere of the metal : so, must transmit stereochemical information through space."

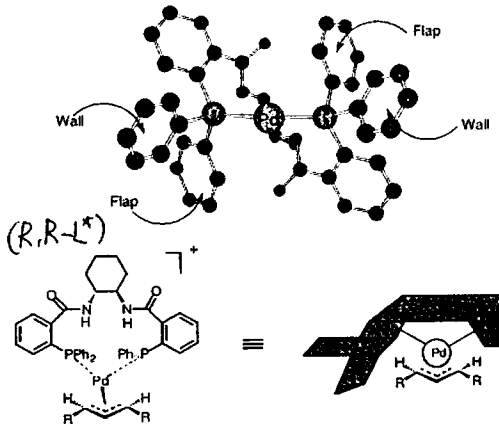


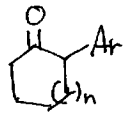
Figure model of chiral pocket and cartoon representation of complex derived from *R,R*-ligand

(JACS, (1999), 121, 4545-4554)

Palladium-Catalyzed Asymmetric Allylic Alkylation of α-Aryl Ketones**

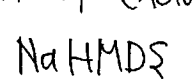
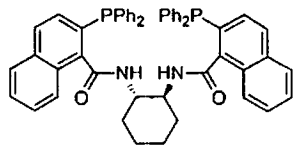
Barry M. Trost,* Gretchen M. Schroeder, and Jesper Kristensen

(Angew. Chem., Int. Ed. (2002), 41, 3492-3495.)

② α-Aryl ketone case 

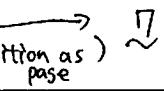
standard condition ⟶ X

counterion of enolate ⟶ big effect (Na best.)

base : NaHMDS (), ligand  , were choiced.

(S,S)-L_N

③ ^{t}BuOH effect (JACS, (2004), 126, 4480-4481)



entry	t-butanol	temp (°C)	yield (%)	ee (%)
1	none	0	93	12
2	none	−60	80	29
3	1 equiv	rt	85	15
4	3 equiv	rt	86	79
5	7 equiv	rt	87	91
6[b]	7 equiv	rt	83	95

[a] All reactions were performed with 1.1 equiv of allyl acetate 1 equiv of trimethyltin chloride, 2 equiv of LDA, 2.5 mol % of $[\eta^3\text{-}C_3H_5PdCl]_2$, and 5 mol % (S,S)-ligand. [b] For this run, 1 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$ and 2 mol % (S,S)-ligand were used.

- with old bottle of ^{n}BuLi ~60%, 92-96% ee
- but ...
- ⟶ fresh bottle of ^{n}BuLi (for LDA) used
  ?? higher level of lithium alkoxide in old bottle??
- So... ^{t}BuOH was added (LDA ⟶ ^{t}BuOLi ~ non-nucleophilic alkoxide)

☆ change the state of enolate aggregation??

(cf) for Li enolate aggregation in THF 大有機, I, p321
JACS, (1993), 115, 3380-3381)

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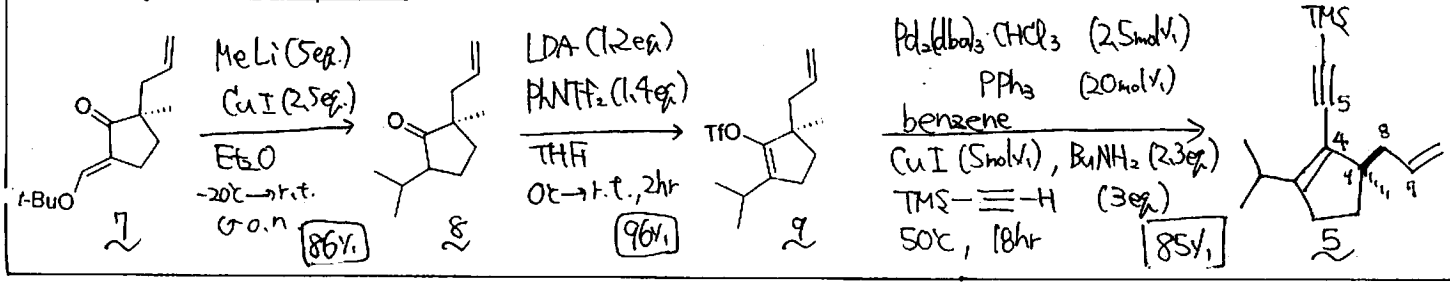
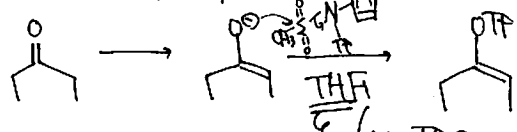
* Sonogashira Coupling



7 ⟶ 8 CuI ... freshly purified, in situ generation of Me_2CuLi 「Gillman reagent」

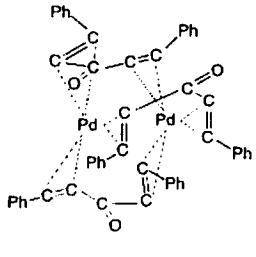
⟶ 9 Mc Murry's protocol (TL, (1983), 24, 979.)



good yield.

(if TfO used ... TfO⟋⟍⟋⟍OTf or polymerized)

⟶ 5

$Pd^0_2(dba)_3$ ⇒ 

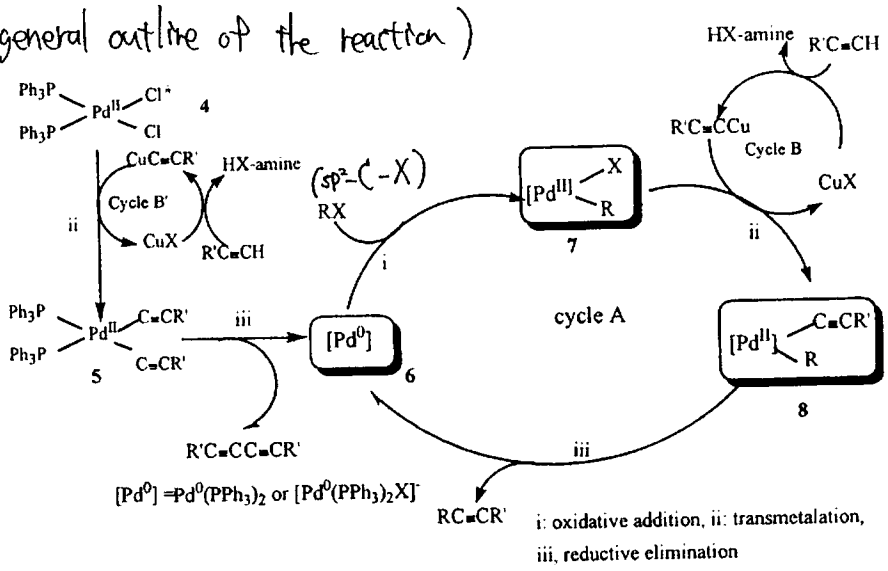
relatively stable to oxygen (compared with $Pd^0(PPh_3)_4$)

(strem catalog 2004-2006)

薗頭-(萩原)

カップリング → coupling reaction of terminal acetyleres with aryl and vinyl halides
sp^2-C

(general outline of the reaction)



original:
(TL, (1975), 50, 4467-4470)

Review:
(J. Organomet. Chem, (2002), 653, 46-49)
(有機合成, (2004), 62, 355-362)

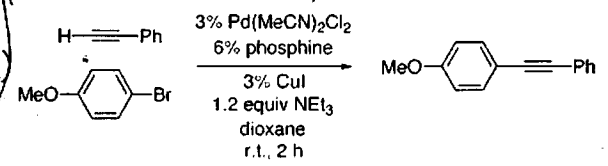
sp_2-C-OTf case
((Corey's (±)-Ginkgolide B synthesis)
⇒ this time condition

(recent progress)

Reactivity : vinyl-I ≈ vinyl-Br > Ar-I > vinyl-Cl ≫ Ar-Br > Ar-Cl

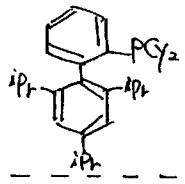
- With Ar-Br → generally heating required ~80°C
  But, bulky, electron-rich phosphines such as $P(^tBu)_3$ → rxn proceed at r.t.

best condition ($Pd(PhCN)_2Cl_2$ (3 mol%)
$P(^tBu)_3$ (6 mol%)
CuI (2 mol%), $HN(iPr)_2$ (1.2 eq.)
dioxane, r.t.) (Buchwald, Fu et al., OL, (2000), 2, 1729-1731)



phosphine	% yield (GC)
PPh_3	<2
P(o-tolyl)$_3$	<2
dppf	<2
PCy_3	<2
$P(t\text{-}Bu)_3$	96

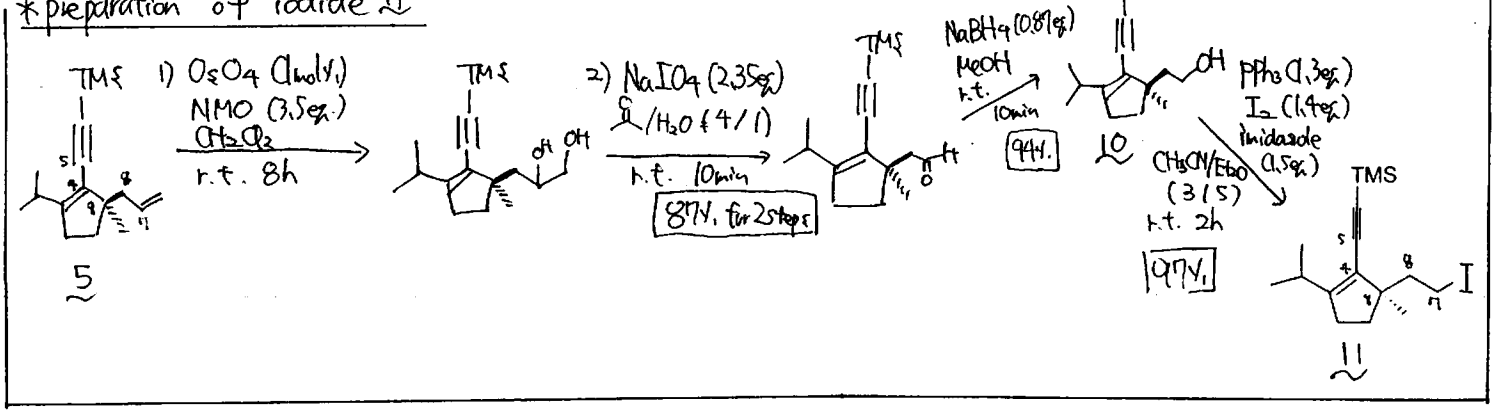
- with Ar-Cl
  $P(^tBu)_3$ or $(1\text{-Ad})_2PBn$ → ~100°C rxn. proceed (Plenio et al. Angew. Chem Int. Ed. (2003), 42, 1058



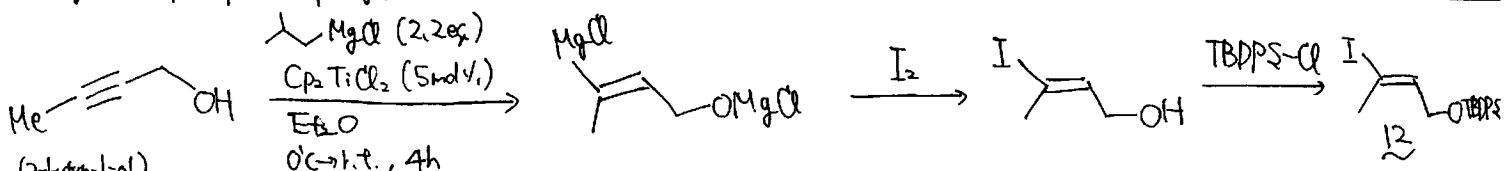
→ 70-95°C rxn. proceed well (Buchwald et al, Angew. Chem, Int. Ed. (2003), 42, 5993.)

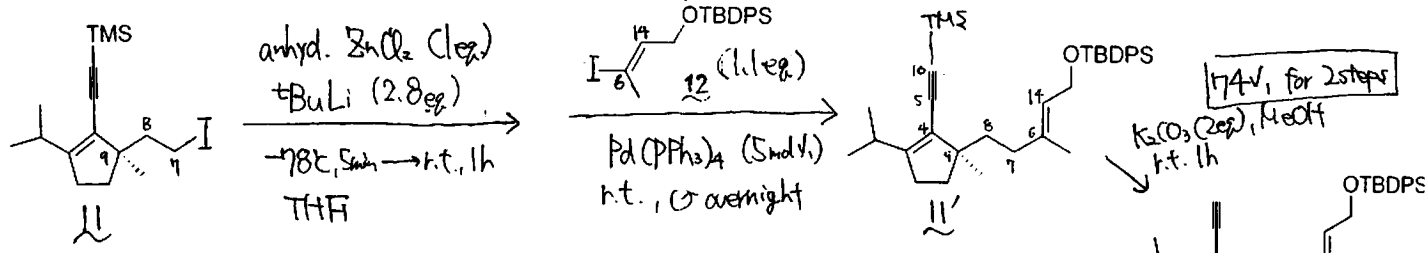
III. Synthesis of 1,7-Enyne 14

*preparation of iodide 11



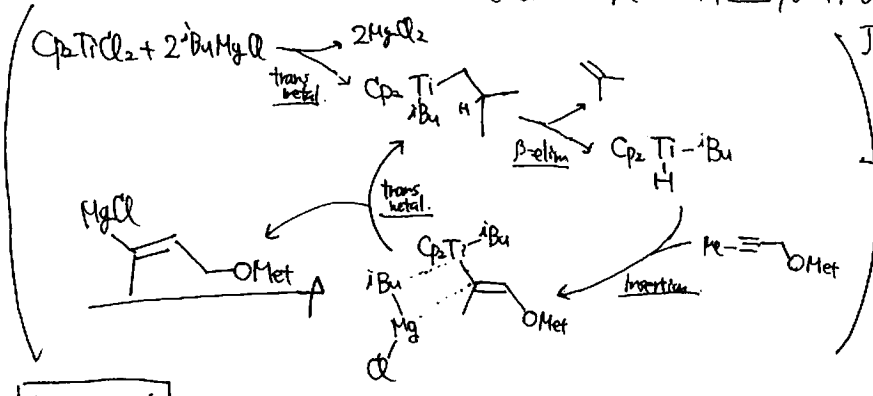
* Negishi sp_3–sp_2 coupling





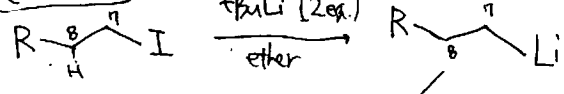
preparation of 12 syn-hydromagnesiation catalyzed by Ti(IV), then quenched by I_2

(Tetrahedron, (2002), 58, 6577-6584, Org. Synth., (1990), 69, 106-113
J. Chem. Soc., Chem. Commun (1981), 718-721)



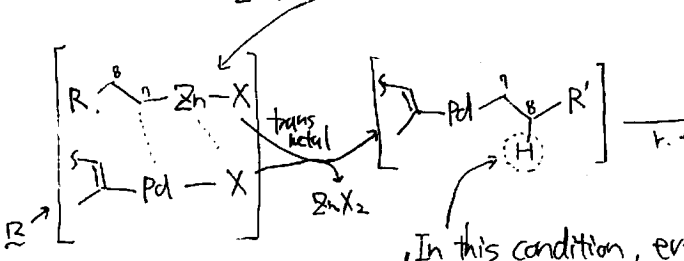
proposed mechanism (F. Sato et al., T.L. (1981), 22, 85-88)

11 → 11'



(J.O.C. (1990), 55, 5406-5409.)

Li–I exchange method. no elimination occurs with ^tBuLi (even though allylic proton exists (@C8))



12

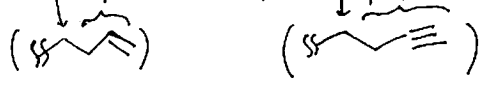
(JACS, (1980), 3298-3299)

In this condition, even when this proton is allylic or propargylic one, no β-elimination occurs. reductive elim dominantes.

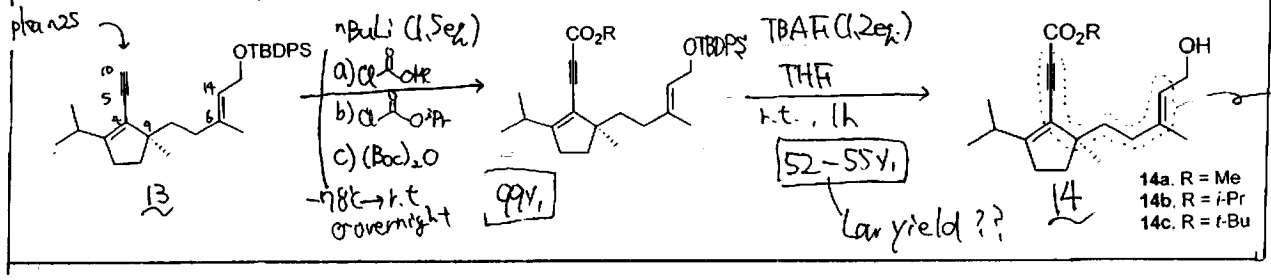
Zn-assisted Pd-coupling ⇓ Negishi coupling

merit of alkyl zinc

⇓ alkenyl–homoallyl or alkenyl–homopropargyl coupling OK!



* 1,7-Enyne 14 synthesis



VI. Intramolecular Ru catalyzed Enyne Cycloisomerization

Review (for Transition Metal Catalyzed : Chem. Rev. (2002), 102, 813-834.
for Ru Catalyzed : Chem. Rev. (2001), 101, 2067-2096.
for Asymetric version : Angew. Chem., Int. Ed., (2004), 43, 1048-1052)

* Definition of Intramolecular Cycloisomerization

"direct transformation of a linear precursor to a cyclic product without additional reactant and typically producing few byproducts"

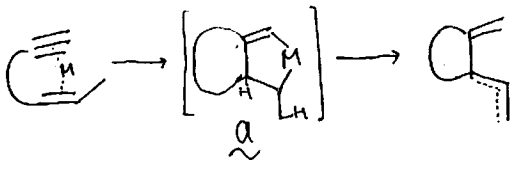
such as  Alder-ene reactions normally required harsh conditions but Transion metal can proceed(catalyzed) this type rxn.

* Classification of transion-metal-catalyzed I. C. of 1.6 or 1.7 Enynes

generally, complexation of the metal to alkene or alkyne.

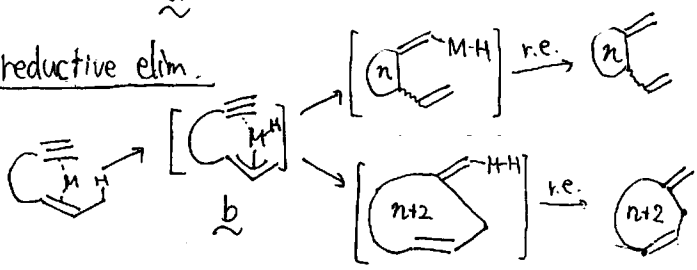
then...

① metallacycle(a) → β-hydrogen elim.
(almost all of transition metal)



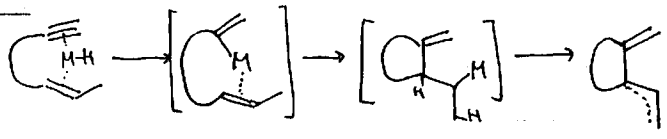
a

② π-allyl complex(b) → carbometallation → reductive elim.
need for allylic C-H activation
(n=5, with Ru (Trost et al, JACS (1999) 121, 9728.))

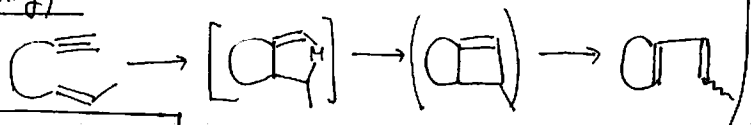


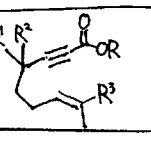
b

③ hydrometallation → carbometallation → β-elim.
metal source — metal hydride
(Pd → 1,3 or 1,4 diene, Ru → 1,3 diene)

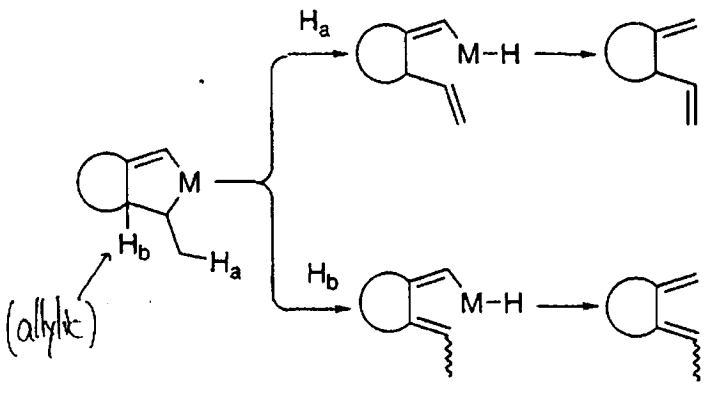


④ metallacycle (a) → reductive elim (→ ring opening)
Enyne metathesis, [2+2]
(Pd, Ru, Pt...)



☆ Trost's Ru case ⇒ ① (exception:  ⇒ ②)

* Tendency of Product by metal source (mechanistically ①'s case)



1,4-diene ("normal ene product")
- Pd (depend on substrate)
- Ti (exclusively, but toluene ~100°C)
- Rh (selectivity good, mild, but expensive)
- Ru (← Trost) ⇒ Asymmetric (Pd, Rh)

1,3-diene (Diels Alder)
- Pd (mainly)
- Co

* Ni-Cr, Pt, Ni

β-elimination required { a vacant coordination site on the metal
cis relationship between the carbon-metal and carbon-hydrogen bond for good orbital overlap

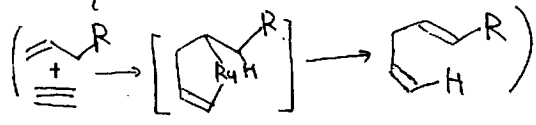
(Ha ⟶ C-Ha bond energy is higher, but geometrically favor for β-elim. ⟶ 1,4-diene
Hb ⟶ C-Hb lower bond strength, but geometrically unfavor ⟶ 1,3-diene.

* Trost's Ru catalyzed Cycloisomerization

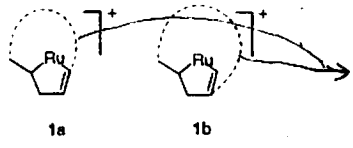
① mild condition, good selectivity for 1,4-diene (r.t., ⌀ or DMF)

(histrical) intermolecular ⇒ only mono substituted olefin participated

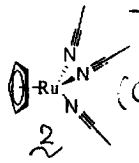
- with  1 (CpRuII(cod)Cl)

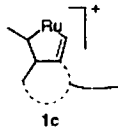


if only mono substituted olefin can be applied ...



⟶ tethers would not be short.

-  2 (CpRu(CH3CN)3PF6) allowed for the participation of 1,2-disubstituted alkene (Intermolecular : TL, (1999), 40, 7739.)

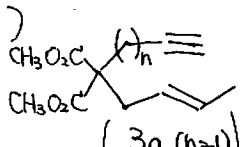


⟶ this time, short tethers ok.

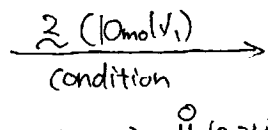
Ruthenium-Catalyzed Cycloisomerizations of 1,6- and 1,7-Enynes (JACS, (2000), 122, 714-715) (JACS (2002), 124, 5025-5026)

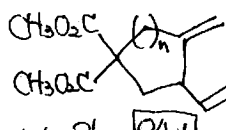
Barry M. Trost* and F. Dean Toste

1)



3a (n=1), 3b (n=2)



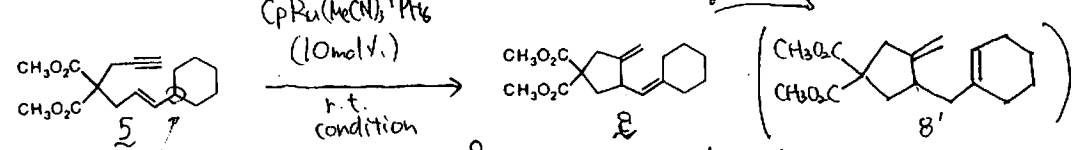


4a (n=1), 4b (n=2)

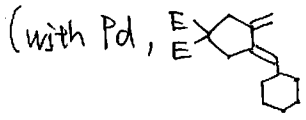
(n=1) ⌀ (0.2M), r.t., 2h 84%

(n=2) ⌀ (0.2M), 60°C, 10h 67%

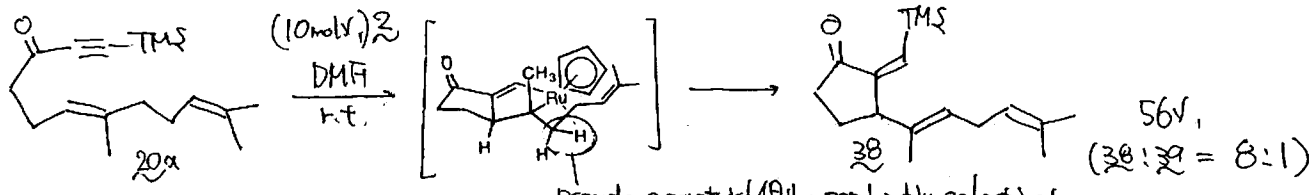
⇒ 1,4-diene only. 5 and 6 ring OK.

2) 

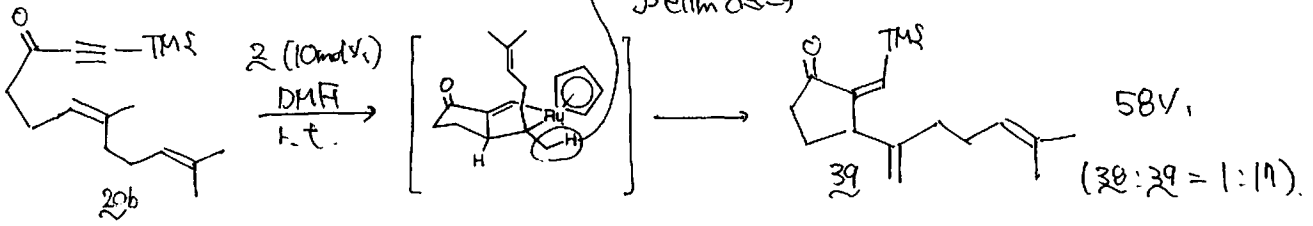
(in acetone, 74%, (8:8' = 1:1) ⇒ solvent effect
in DMF, 82%, (8 only))

⇒ branch at allylic position OK (intermolecular version failed)
(with Pd,  only obtained)

3) Regioselectivity can be rationalized by Ruthenacycle mechanism.



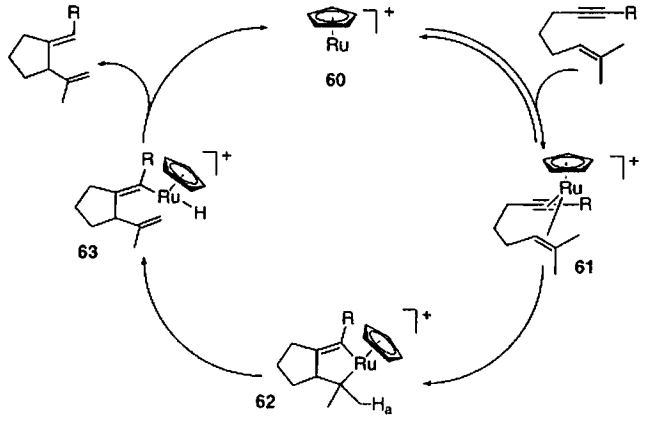
pseudo equatorial 位置のアルケンが selective に β-elim を受ける



4) trans-olefins participate more readily in cycloisomerization than the corresponding cis-olefins.
⇒ also rationalized by ruthenacycle

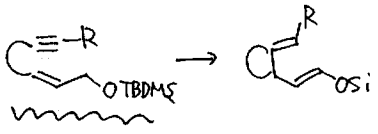
3)※4) ⇒

Scheme Proposed Mechanism for the Ruthenium-Catalyzed Cycloisomerization of Enynes



※ In several examples,
regio and diastereo selectivity was accounted by this model

(JACS, (2002), 124, 5025-5036
JACS, (2004), 126, 15592-15602)

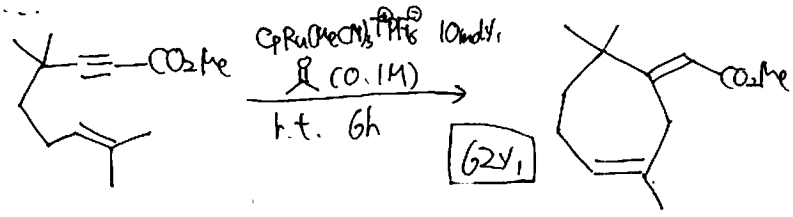


Ruthenium-Catalyzed Cycloisomerization of 1,6-Enynes Initiated by C–H Activation (JACS, (1999), 121, 9728-9729) 12

Barry M. Trost* and F. Dean Toste (JACS, (2002), 124, 5025.)

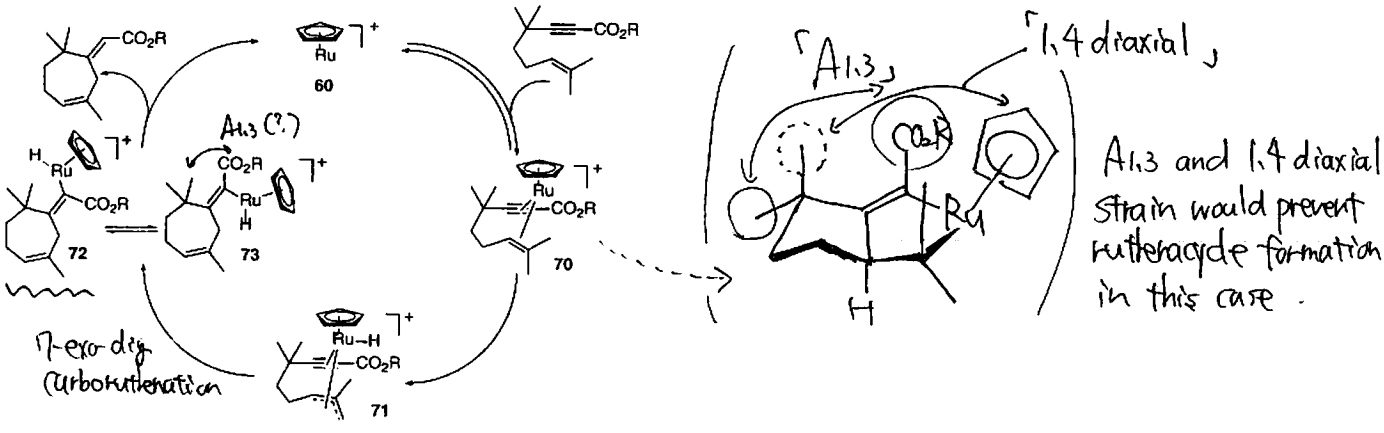
When the enyne is { 1,6-enyne; quaternary center at propargylic position; cis-di or trisubstituted alkenes } → 7-exo-dig cyclization occurred.

such as ...



This fact may be rationalized by C-H activation at allylic proton.

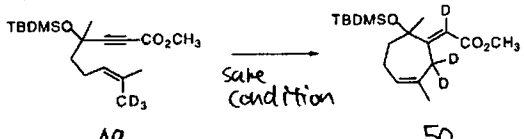
Scheme 3. Proposed Mechanism for the Ruthenium-Catalyzed Formation of Cycloheptenes



(remarks)

geometry of enoate is opposite that obtained in the previous case ⇒ A1,3 (?)
(72 should reductive elim.)

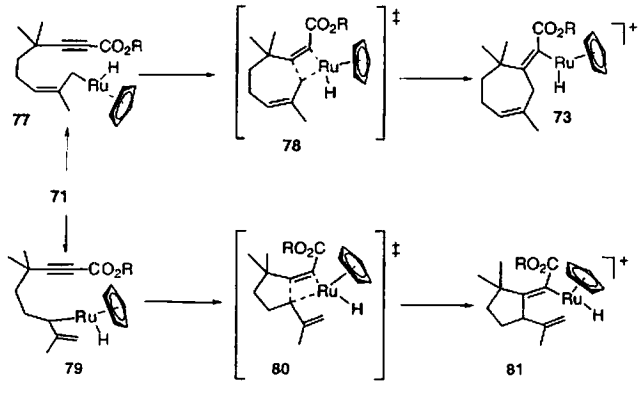
(support for C-H activation)



49 50

⇒ this result support C-H activation mechanism and selective insertion into C-H bond of a cis substituent was observed (override the kinetic isotope effect)

(rationale for 7-exo-dig carboruthenation)



① 77 maybe more stable than 79 (by steric factor (?))

② TS 80 is significantly more congested than TS 78

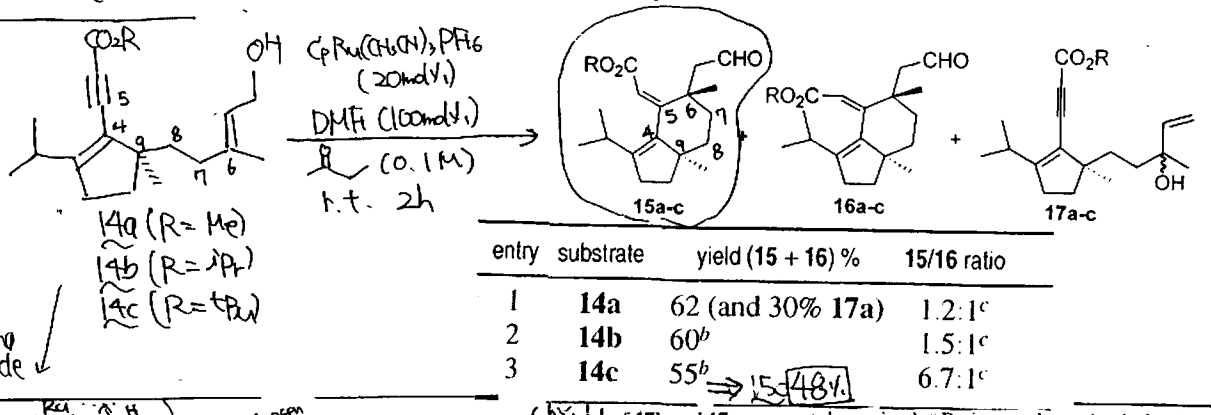
these factor may be enough to overcome the kinetic bias of 5-exo-dig cyclization.

⇓

so 7-exo cyclization occurred.

Figure 6. Proposed mechanism for carbaruthenation.

* in real case — desired one

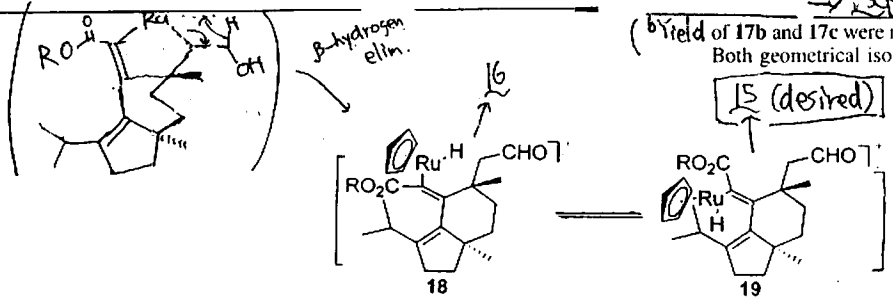


entry	substrate	yield (15 + 16) %	15/16 ratio
1	**14a**	62 (and 30% **17a**)	1.2:1[c]
2	**14b**	60[b]	1.5:1[c]
3	**14c**	55[b] ⇒ 15: 48%	6.7:1[c]

([b] Yield of **17b** and **17c** were not determined. [c] Ratio was determined after isolation. Both geometrical isomers were obtained as single diastereomers.)

ruthenacycle

β-hydrogen elim.



15 (desired)

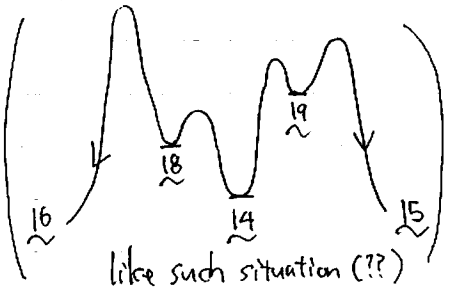
- only 1,4-anti products were detected. • ester were isomerized.
- The products are stable to the reaction condition.

① the reaction outcome reflects the stability of intermediates 18 and 19.
⇒ but considering the relative size of the ester and CpRu, that is unlikely. (大槻 I p156.)

② Curtin-Hammett situation

$$P_1 \longleftarrow A \rightleftharpoons A' \longrightarrow P_2 \qquad (14)$$

一般的に (14) 式のような反応で，反応物 A と A′ が速い平衡にあるとすると，たとえ二つの生成物がそれぞれの配座異性体から生成するにしても，生成物比 P_1/P_2 は二つの遷移状態のエネルギー差によってのみ決まっており，反応物の異性体存在比とは無関係であることが導かれる．生成物比が速度支配で決まっている限り，反応物の速い前平衡の存在には関係なく，生成物を与える二つの遷移状態のエネルギー差によってのみ生成比が決定される．これを Curtin-Hammett の原理という[3]．



like such situation (??) 「If reductive elimination is slower than olefin isomerization, ...」

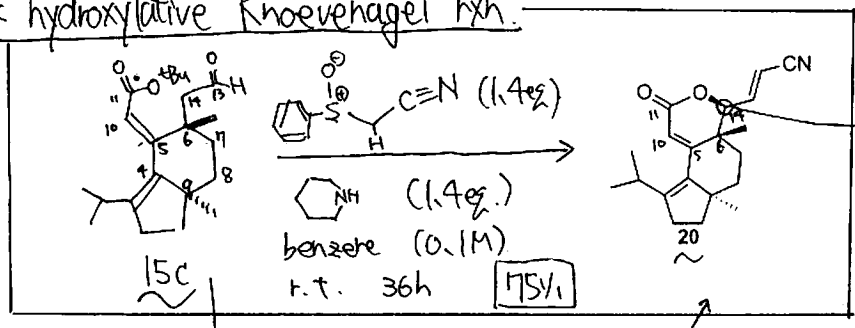
「It is imaginable that 19 undergoes faster reductive elimination than 18 to maximize relief of strain energy in the transition state」

tBu ester ⇒ 「most relief was achieved in this case」

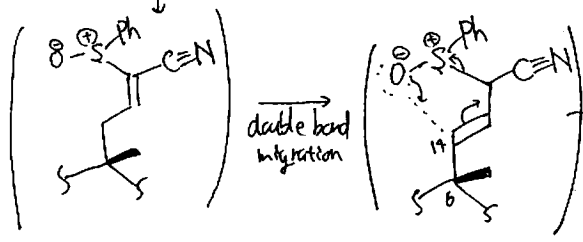
anyway ... 15c was obtained in 48% yield as a single diastereomer.

V Completion of Total Synthesis

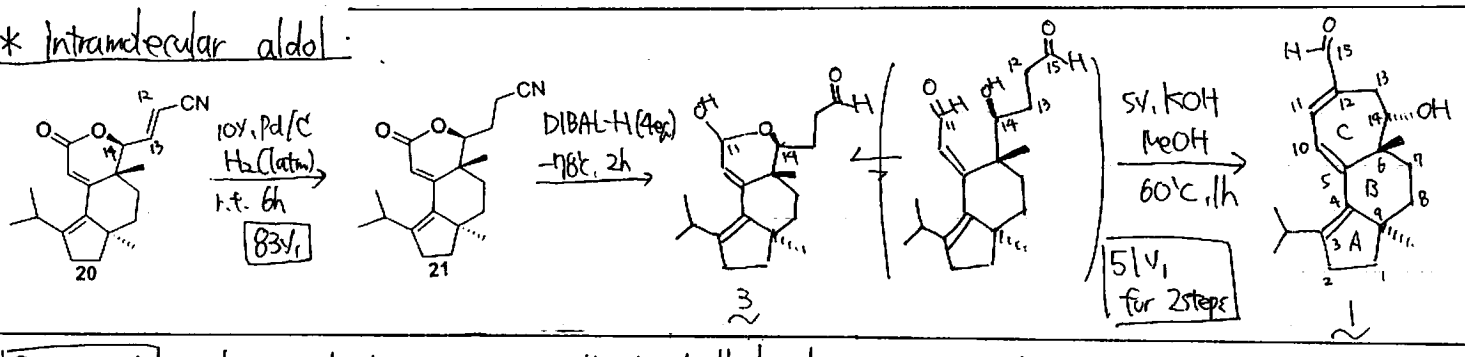
* hydroxylative Knoevenagel rxn.



(Nakami et al. T.L. (1981) 22. 4489.
JACS (1984) 106, 7890)



* Intramolecular aldol:

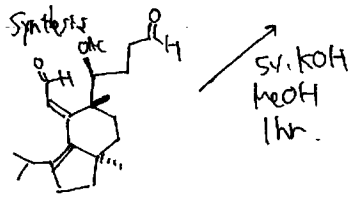


20 → 21 selective hydrogenation of C12-13 double bond.

→ 3 partially reduction to aldehyde

→ 1 from a variety of aldol conditions.
(same as Tori's case)

cf) Tori's Synthesis



(overview)

A ring $\xrightarrow{(14\text{steps})}$ B ring $\xrightarrow{(4\text{steps})}$ C ring

total (18 steps) 1.9%

* In last 5steps, B & C ring construction.