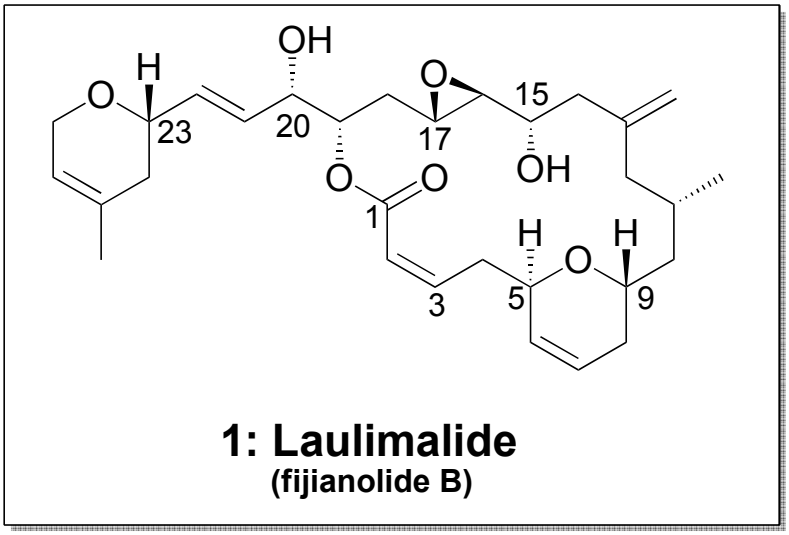
January 17, 2012
Seiko KITAHARA (B4)

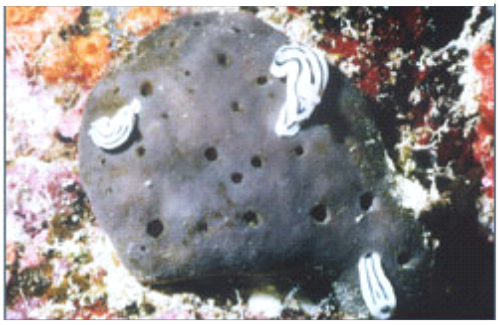
Total synthesis of Laulimalide



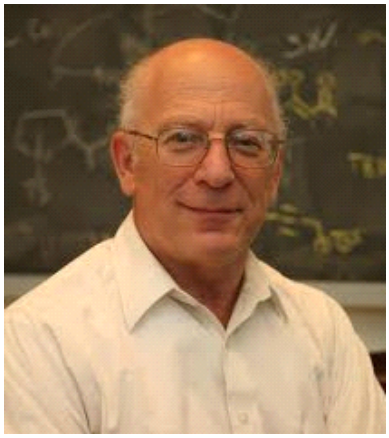
1: Laulimalide
(fijianolide B)

Contents

1. Introduction
2. Previous Total Synthesis
   2-1. Retrosynthetic Analysis
3. Trost's Total Synthesis
   -toward the atom economy-
   3-1. What is "synthetic efficiency" ??
   3-2. Retrosynthetic Analysis
   3-3. Total Synthesis
   3-4. Asymmetric Direct Aldol Reaction via a Dinuclear Zn Catalyst
   3-5. Rh-Catalyzed Cycloisomerization
   3-6. Ru-Catalyzed Alkene-Alkyne Coupling

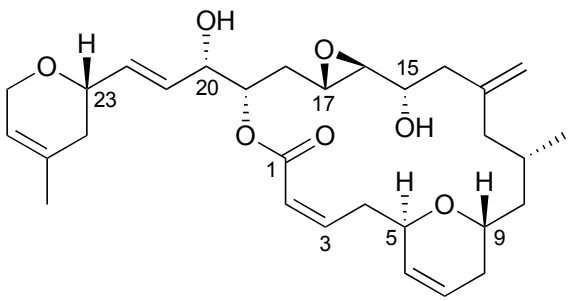


Marine Sponge,
Cacospongia mycofijiensis



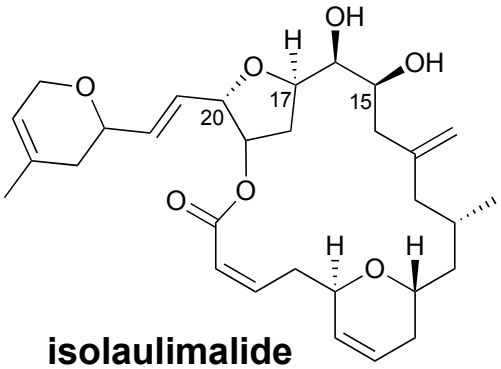
Barry M. Trost

1. Introduction



On exposure to acid

(within two hours)



1: Laulimalide : intrinsically unstable
(fijianolide B)

isolaulimalide
(fijianolide A)

<Isolation>

-From { various marine sponges such as *hyattela sp., Cacospongia mycofijiensis, fasciospongia rimosa*
a marine sponge in the genus *Dactylospongia*
a nudibranch, *Chromodoris lochi*
with its tetrahydrofuran containing isomer isolaulimalide

<Structure>

-Determined NMR analysis and X-ray crystallographic analysis
Corley, D. G *et al. J. Org. Chem*. **1988,** *53*, 3644.
Quinoa, E *et al. J. Org. Chem.* **1988,** *53*, 3642.
-20-membered macrolide

<Biological activity>

-like Taxol® (paclitaxel), induces microtubule polymerization and stabilization
-unlike Taxol® (paclitaxel), retains activity in multidrug resistant cell lines
-binds to a different site than other known microtubule stabilzers
→ suggesting new opportunities forchemotherapy ??

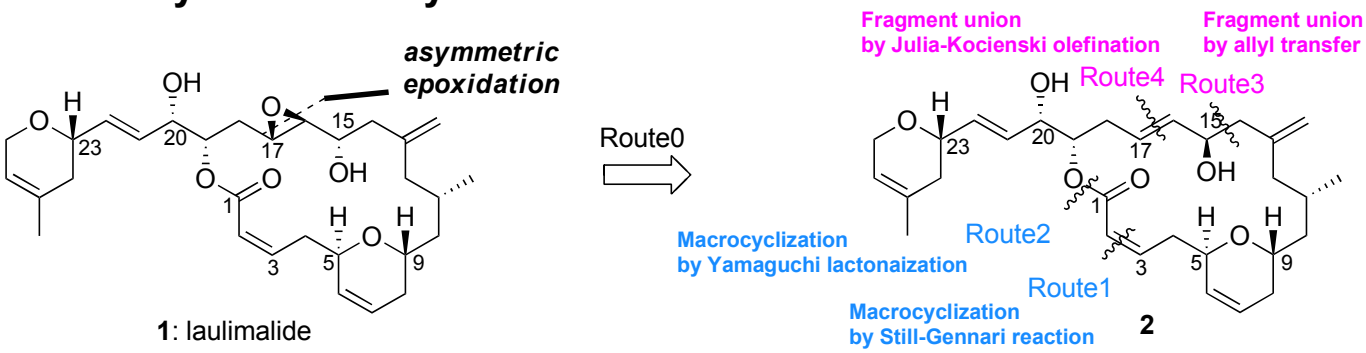
<Total synthesis>

-Hot topic for over a decade (more than 10 reports !)
due to { its significant clinical potential
its strict natural supply
unique and complex molecular architecture

Ghosh, A. K. e*t al. J. Am. Chem. Soc.* **2000,** 1*22,* 11027.
Ghosh, A. K. e*t al. J. Org. Chem.* **2001,** *66,* 8973.
Mulzer, J. *et al. Angew. Chem., Int. Ed.* **2001,** *40,* 3842.
Paterson, I. *et al. Org. Lett.* **2001,** 3*,* 3149.
Enev, V. S. *et al. J. Am. Chem. Soc.* **2001,** *123,* 10764.
Wender, P. A. e*t al. J. Am. Chem. Soc.* **2002,** 1*24,* 4956.
Crimmins, M. T. *et al. J. Am. Chem. Soc.* **2002,** 1*24,* 5958.
Williams, D. R. e*t al. Tetrahedron Lett.* **2002,** *43,* 4841.
Nelson, S. G. *et al. J. Am. Chem. Soc.* **2002,** 1*24,* 13654.
Ahmed, A. e*t al. J. Org. Chem.* **2003,** *68,* 3026.
Gallagher, B. M. e*t al.* M*ed. Chem. Lett.* **2004,** 1*4,* 475.
Uenishi, J. *et al. Angew. Chem., Int. Ed.* **2005,** 4*4,* 2756.
Gollner, A. e*t al. Chem.-Eur. J.* **2009,** *15,* 5979.
Trost, B. M. *et al. J. Am. Chem. Soc.* **2009,** 1*31,* 17089.

2. Previous Total Synthesis

2-1. Retrosynthetic Analysis



1: laulimalide

2

Although more than 10 syntheses were reported, the retrosynthetic route was limited.
(route0 → the combination of route1-4)

3. Trost's Total Synthesis

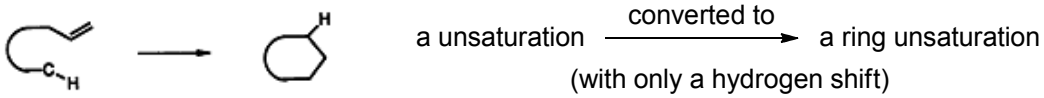
3-1. What is "synthetic efficiency"??

Trost, B. M. *et al. Science.* ***1991***. *254*, 1471.

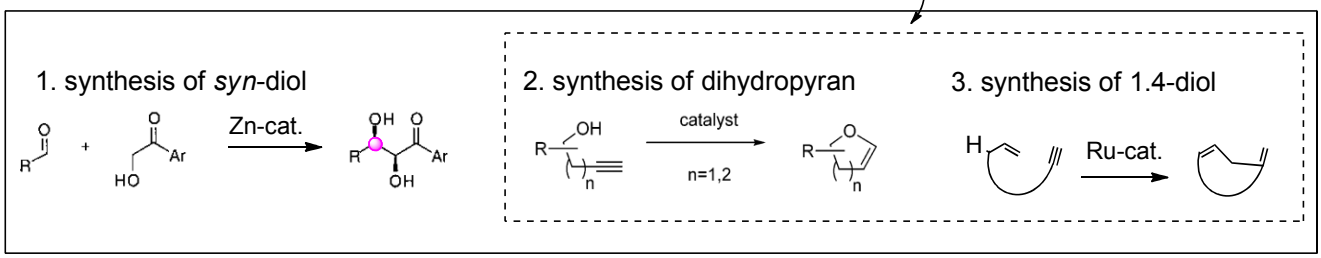
- Efficienct synthetic methods require to
  - chemo-/regio-/diastereo-/enantio-selectivity
  - atom economy = how much of the reactatns end up in the product

An process that is both selective ant atom economical remains a challenge.
Transition metal catalysis enable this ??

- Cycloisomerizations offer opportunities for enhancing efficiency for construction of difficult medium and large rings

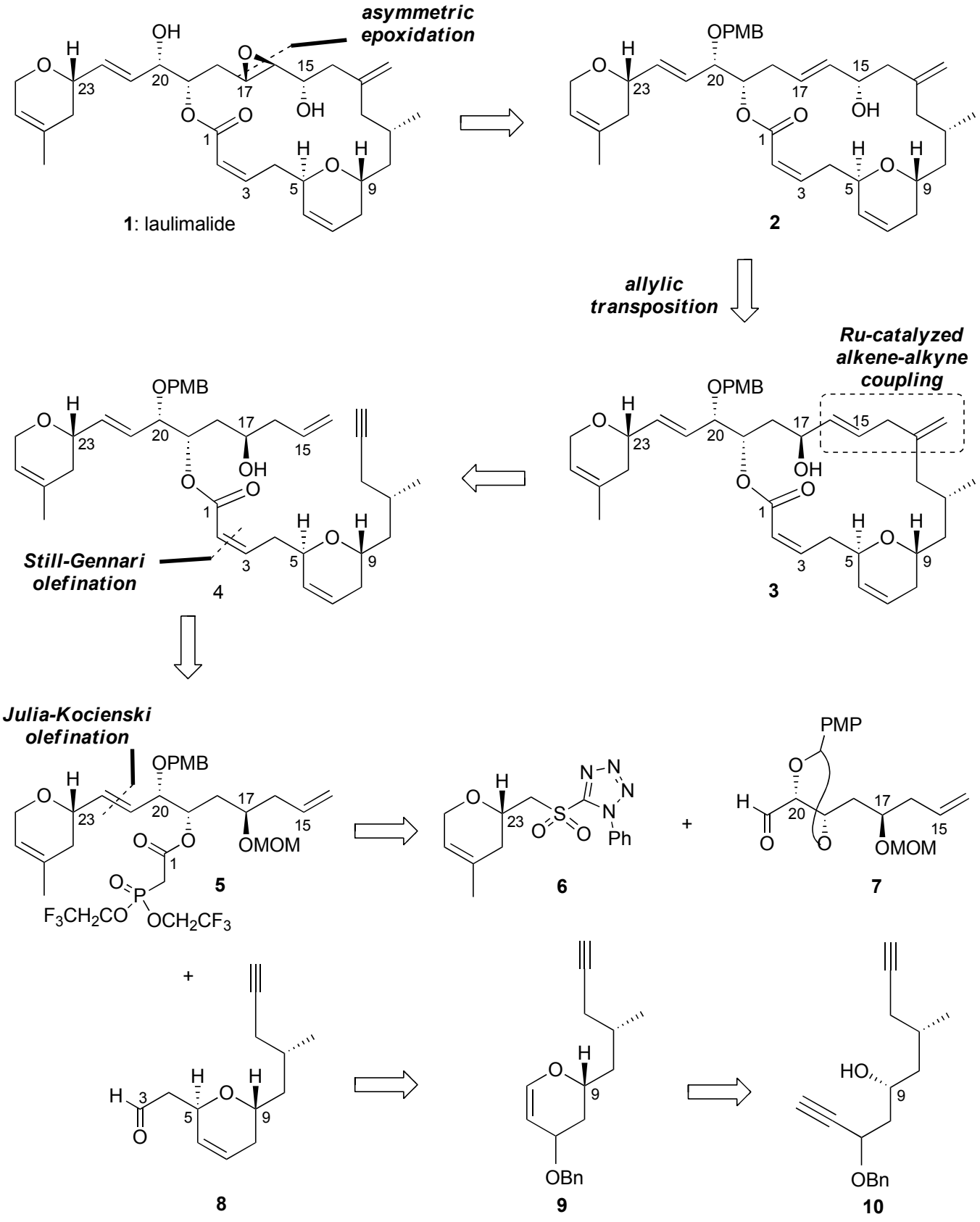


Trost used 3 atom economic reactions in total synthesis of laulimalide, and 2 of these is cycloisomerization



3-2. Retrosynthetic Analysis

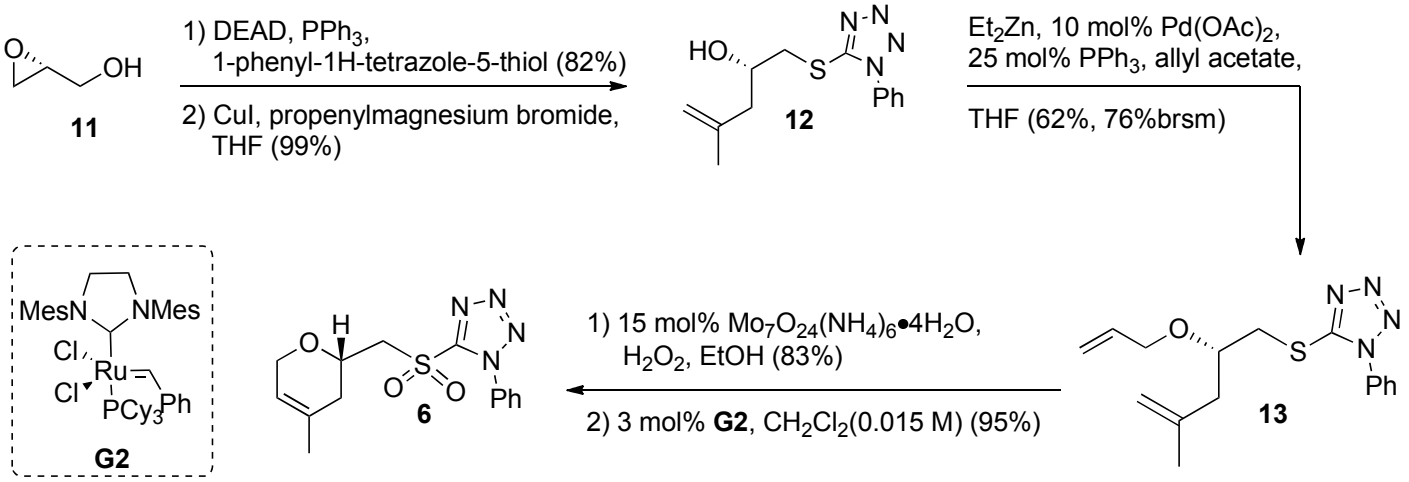
Trost's retrosynthetic anlysis is based on the notion that laulimalide **1** could be formed from 1,4-diene **3**.



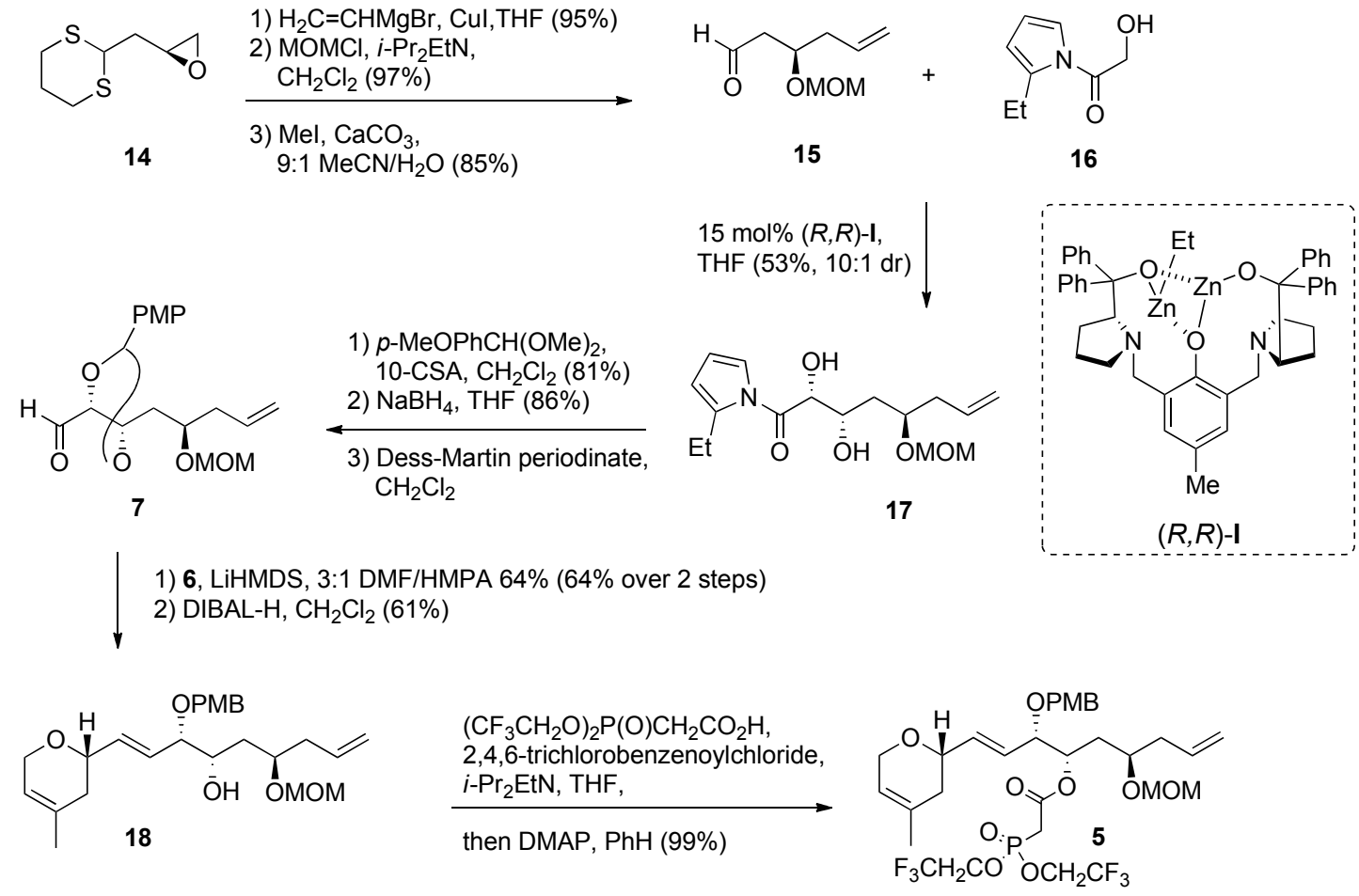
3-3. Total Synthesis

Trost, B. M. *et al. J. Am. Chem. Soc.* **2009,** *131*, 17087.

<Synthesis of 6>



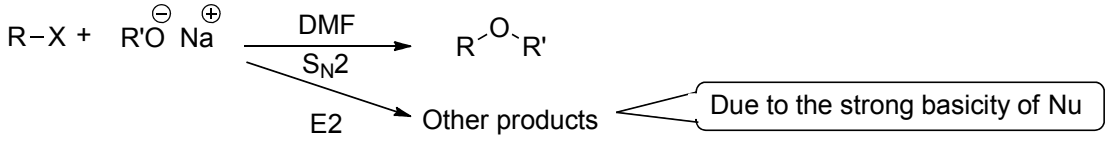
<Synthesis of 5>



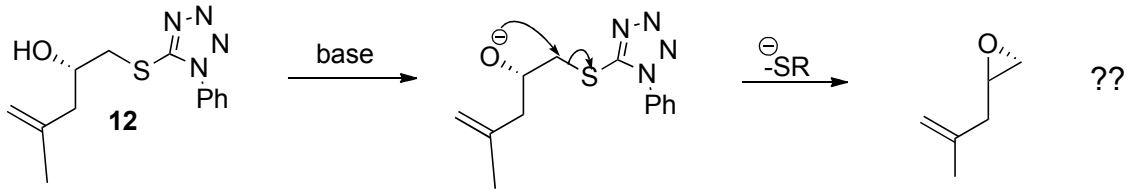
•**12** → **13**: Pd-catalyzed allylic etherification using Zn(II) alkoxides

Kim, H. *et al. Org. Lett.* **2002,** *4*, 4369.

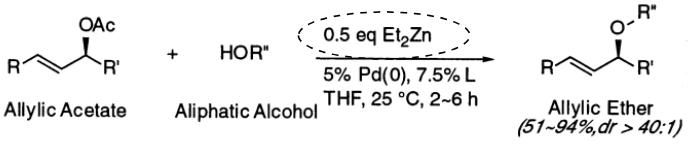
-Generally, WIlliamson ether synthesis (S_N2 type O-alkylation) is impractical.



-Also in this case, allylation under basic or acidic condition were ineffective.



Alternative approach: **Pd-catalyzed allylic etherification**

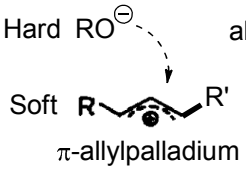


The addition of O-nucleophile to an η^3-allylmetal intermediate

↓

Mild & Stereoselective

MISMATCH !



aliphatic alcohols:
×poor nucleophilicity
×strong hardness

⟹

modulating the apparent "hardness" of $RO^{\ominus}$

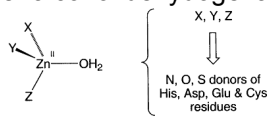
Can the **Zinc effect** lead to "softening" ??

→Zn(II)-bound alkoxides possess weakened basicity while reatining sufficient nucleophilicity !!

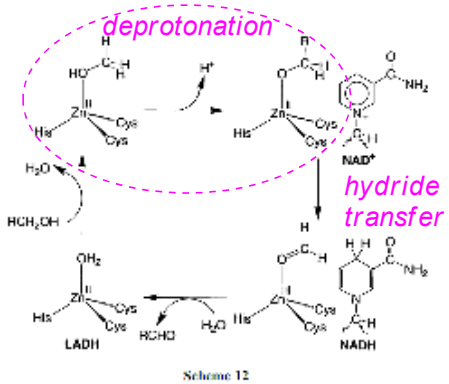
the zinc effect in biochemistry: the Zn enzyme LADH

Kimura, E. *et al. J. Am. Chem. Soc.* **1992,** *114*, 10134.
Parkin, G. *et al. Chem. Commun.* **2000,** 1971.

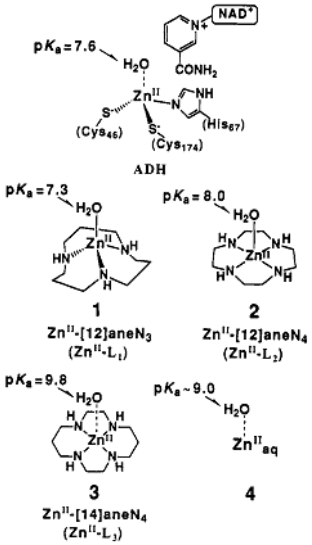
Zn^{II}-containing
liver alcohol dehydrogenases (LADH)



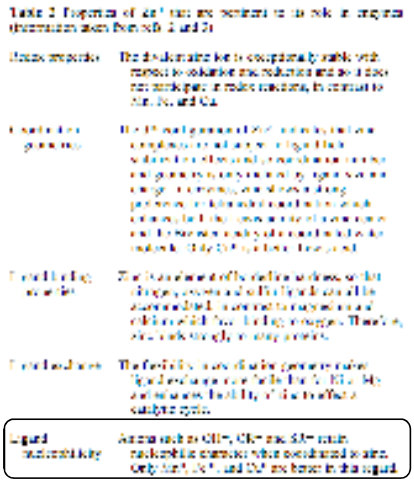
LADH catalyze the hydride transfer from alcohol to NAD^+



The pKa of alcohols(normally ~16) can be reduced by about 9 units upon coordination to Zn^{II} ??



Nucleophilicity is reatined.



•**13** → **6**: oxidation of the sulfide into the corresponding sulfone using H_2O_2 and Mo(VI)catalyst

-Altough sulfoxides and sulfones are important in synthetic oranic chemistry,
only a few reports are available for selective oxidation of sulfides to sulfoxides and sulfones

The oxidation of sulfides to sulfoxides with H_2O_2 — Kaczorowska, K. *et al. Tetrahedron.* **2005,** *61,* 8315.

Several disadvantages of sulfide oxidation:
- ×long reaction times
- ×inconvenient reaction conditions
- ×expensive oxidants
- ×undesired reactions at other FGs
- ×low yield

→

H_2O_2 is the most attractive oxidant :
- ○selectivesulfide oxidation
- ○relative mild conditions
- ○an ideal waste-avoiding oxidant: water is only byproduct !
- ○only a small excess of H_2O_2
- ○high yield
- ○liquid-phase reactions
  - ↥good solubility in water and many organic solvents

Moreover,aqueous H_2O_2 has further advantages:
- ○safty in storage, operation, and transportion
- ○commercially available
- ○reatively cheap

However, H_2O_2 alone has possibility of an over-oxidation reaction.

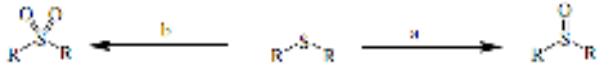
⇩

The oxidation of sulfides to sulfoxides with H_2O_2 & catalyst

Controlled oxidation of sulfides to sulfoxides and sulfones
Chiral oxidation
} is possible !

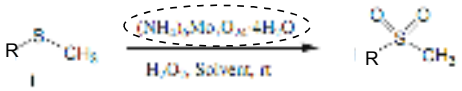
Mo(VI) catalyst/H_2O_2 system at room temperature — Jeyakumar, K. *et al. Tetrahedron. Lett.* **2006,** *47,* 4573.
Jeyakumar, K. *et al. Catalysis. communications.* **2009,** *10,* 1948.

MoO_2Cl_2/H_2O_2 system



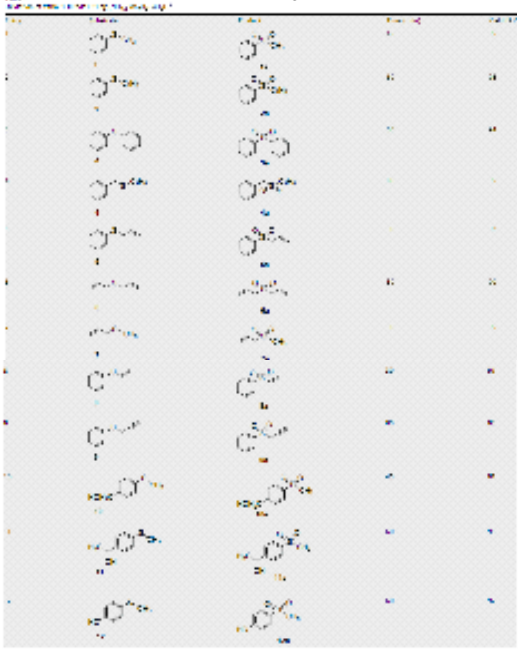
Scheme 1. Optimized reaction conditions for 4 mmol of substrate. Reagents and conditions: (a) MoO_2Cl_2 (1.5 mol %), 30% H_2O_2 (1.05 equiv), acetone/water (1.5:1), rt; (b) MoO_2Cl_2 (15 mol %), 30% H_2O_2 (4 equiv), acetonitrile, rt.

New system ←used in this time



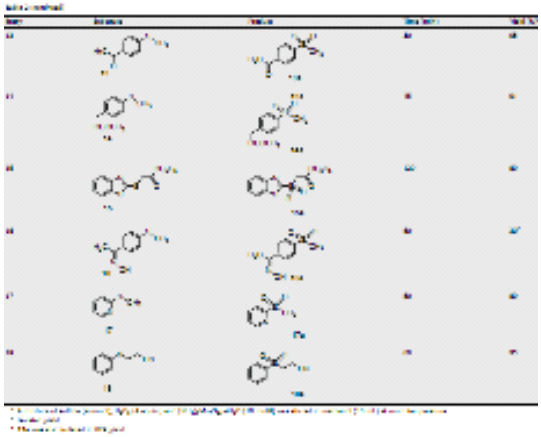
$(NH_4)_6Mo_7O_{24}•4H_2O$ is
- commercially available
- cheap
- air stable

Substrate Scope of $(NH_4)_6Mo_7O_{24}•4H_2O/H_2O_2$ System

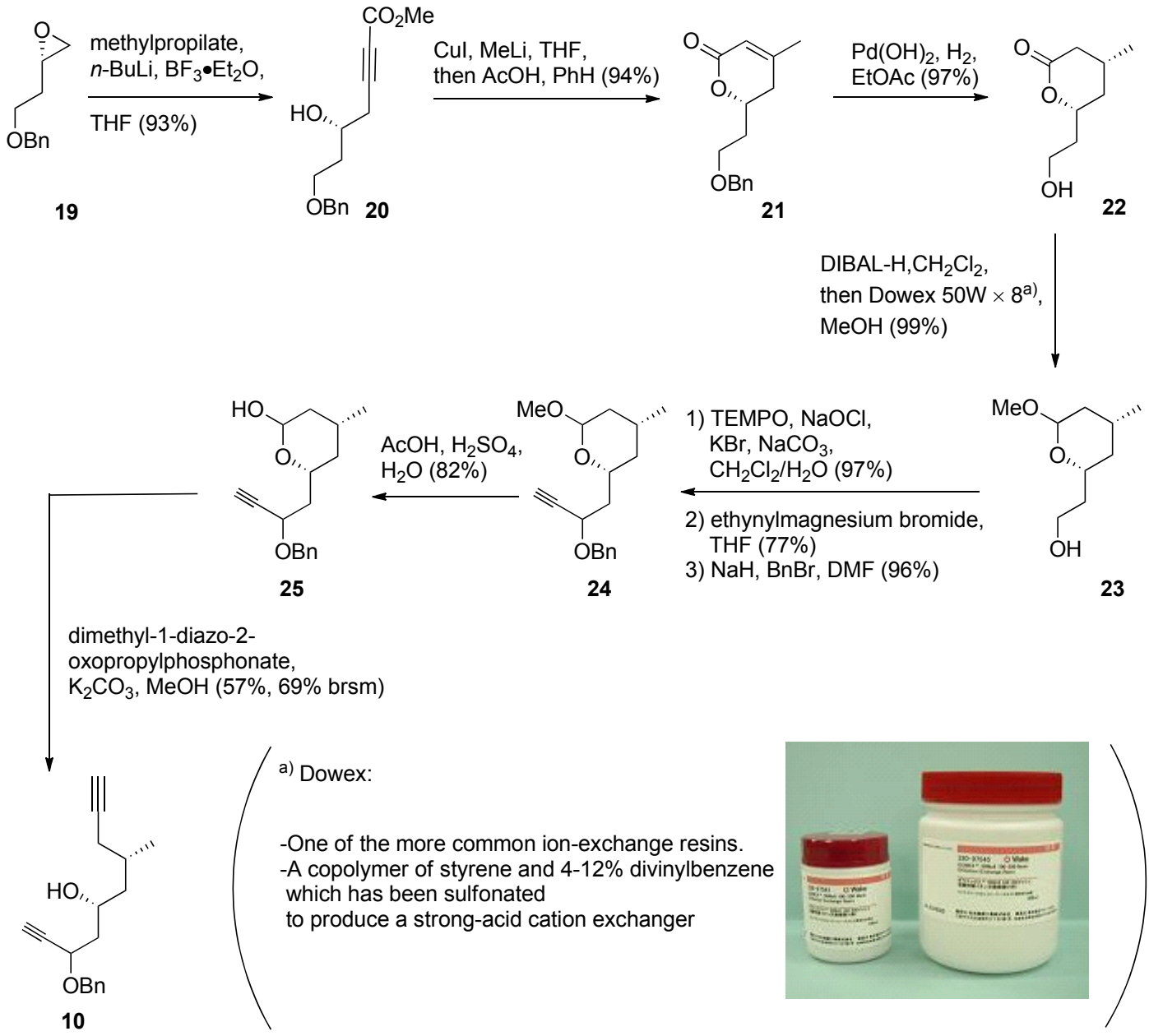


-Both systems provide excellent yield with short time.

-In both systems, various sensitive functional groups are tolerated such as alkyl, allyl, vinyl, propargyl, alcohol, ketone, ester, and remarkably oxime !



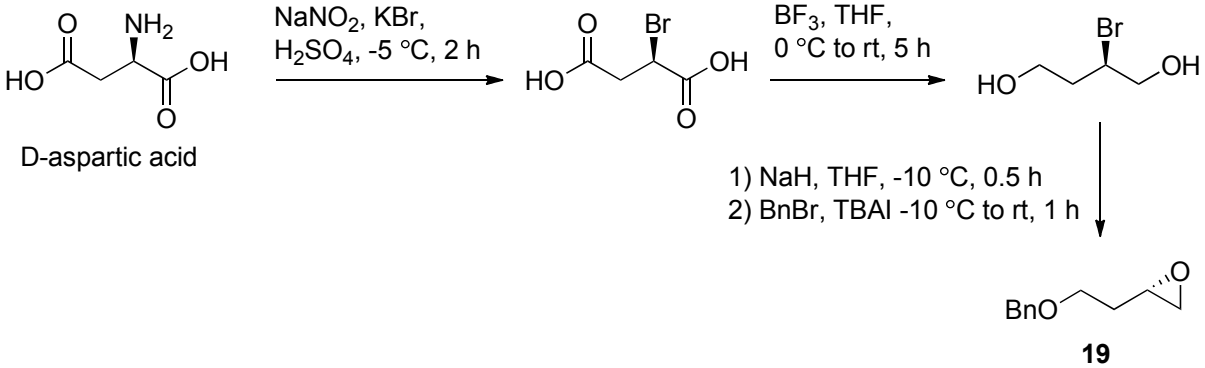
<Synthesis of 10>



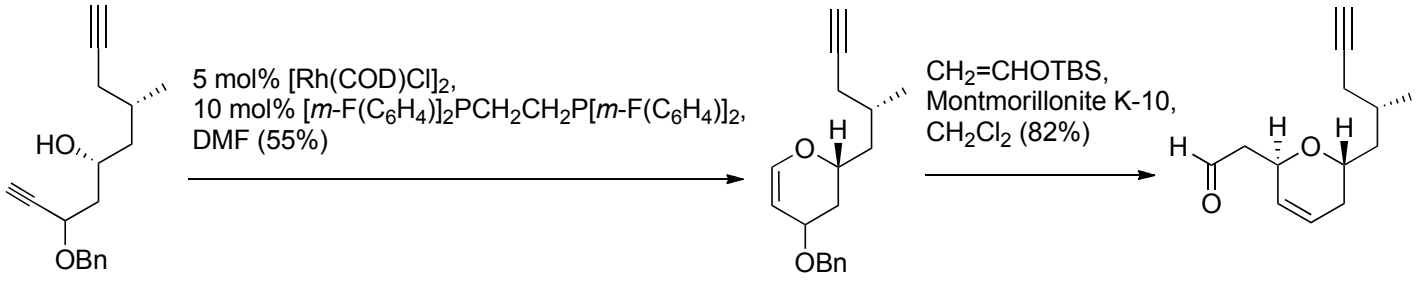
a) Dowex:

-One of the more common ion-exchange resins.
-A copolymer of styrene and 4-12% divinylbenzene which has been sulfonated to produce a strong-acid cation exchanger

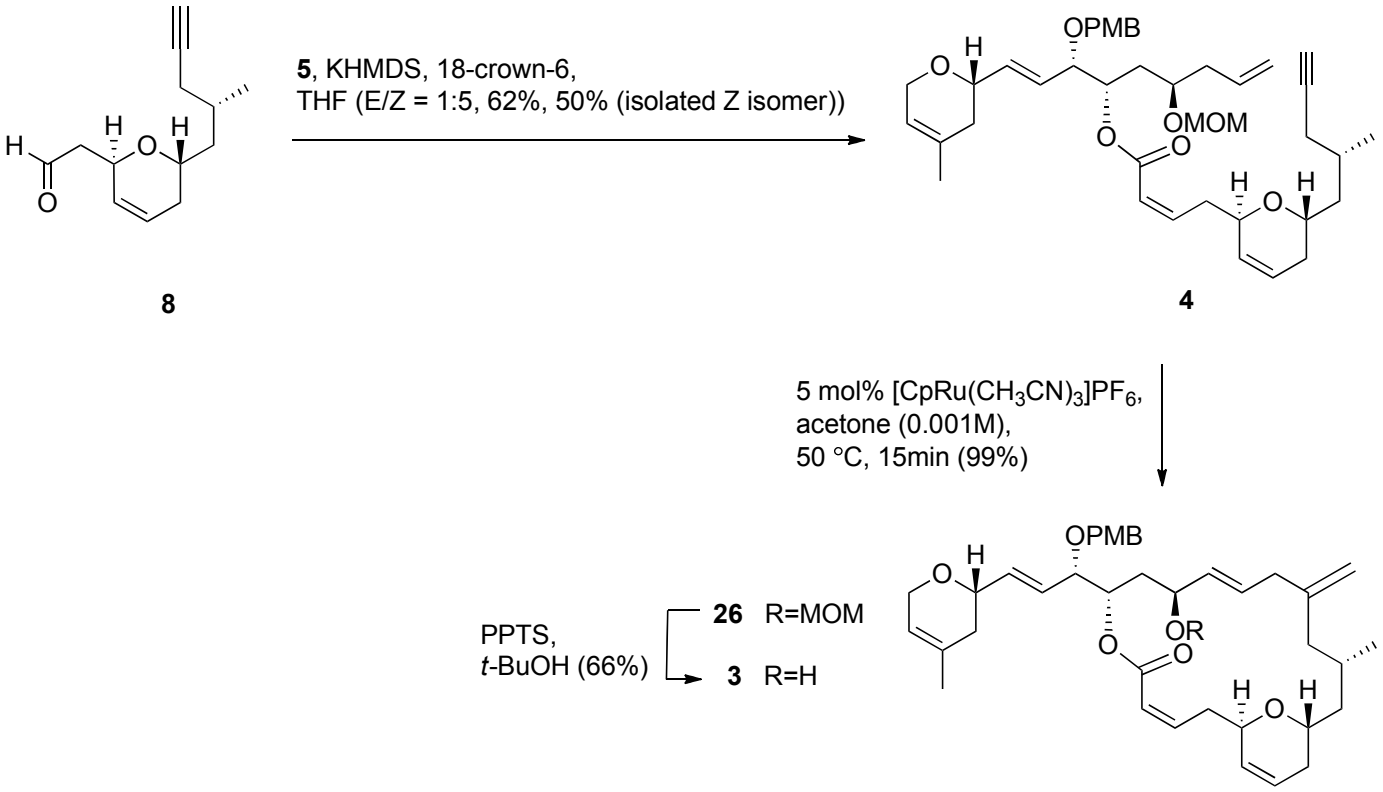
•preparation of **19**



<Synthesis of 8>

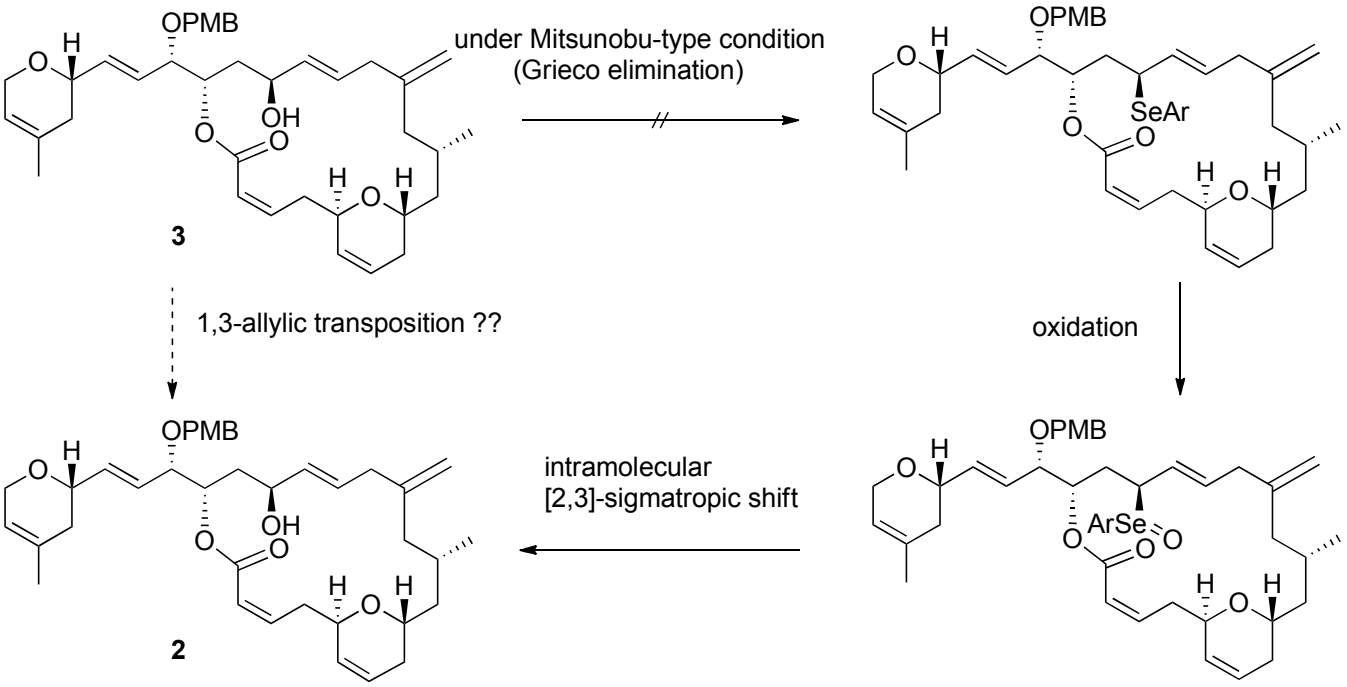


<Synthesis of 3: Intramolecular Ru-Catalyzed Alkene-Alkyne Coupling>

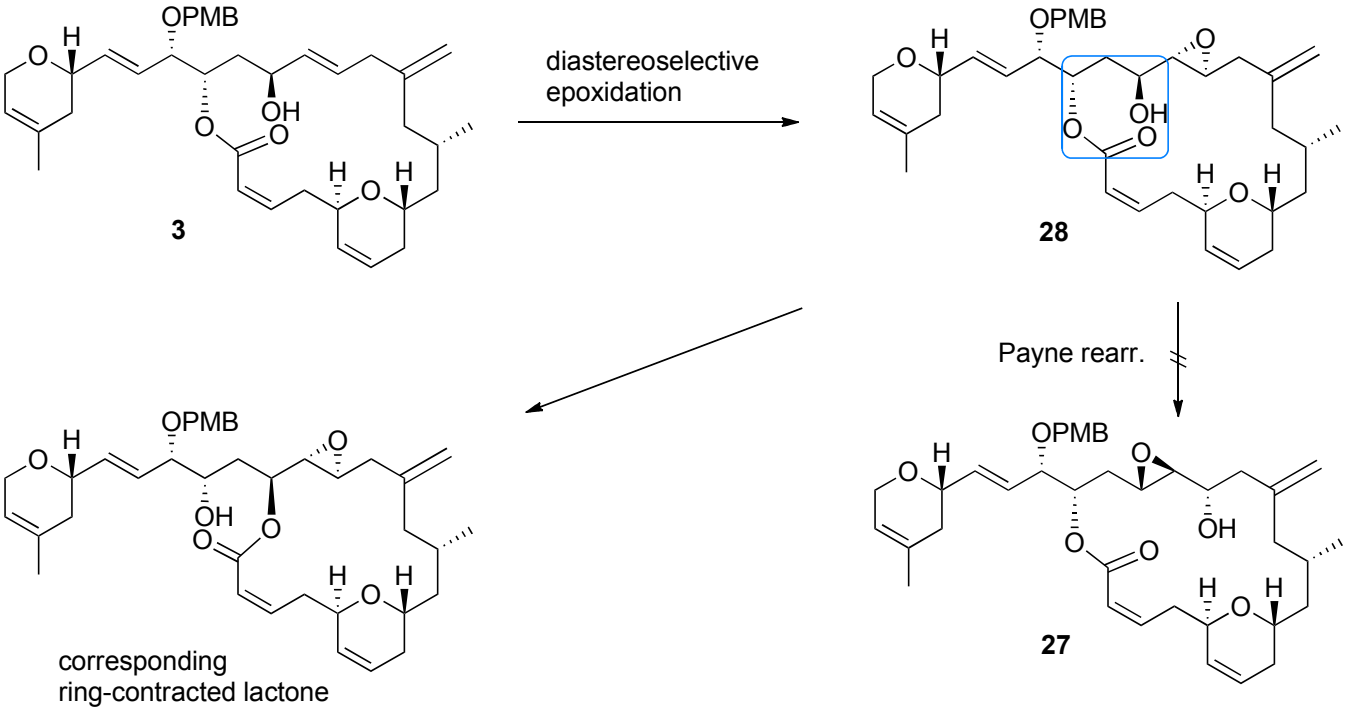


<Two failures in the step 3 → 1>

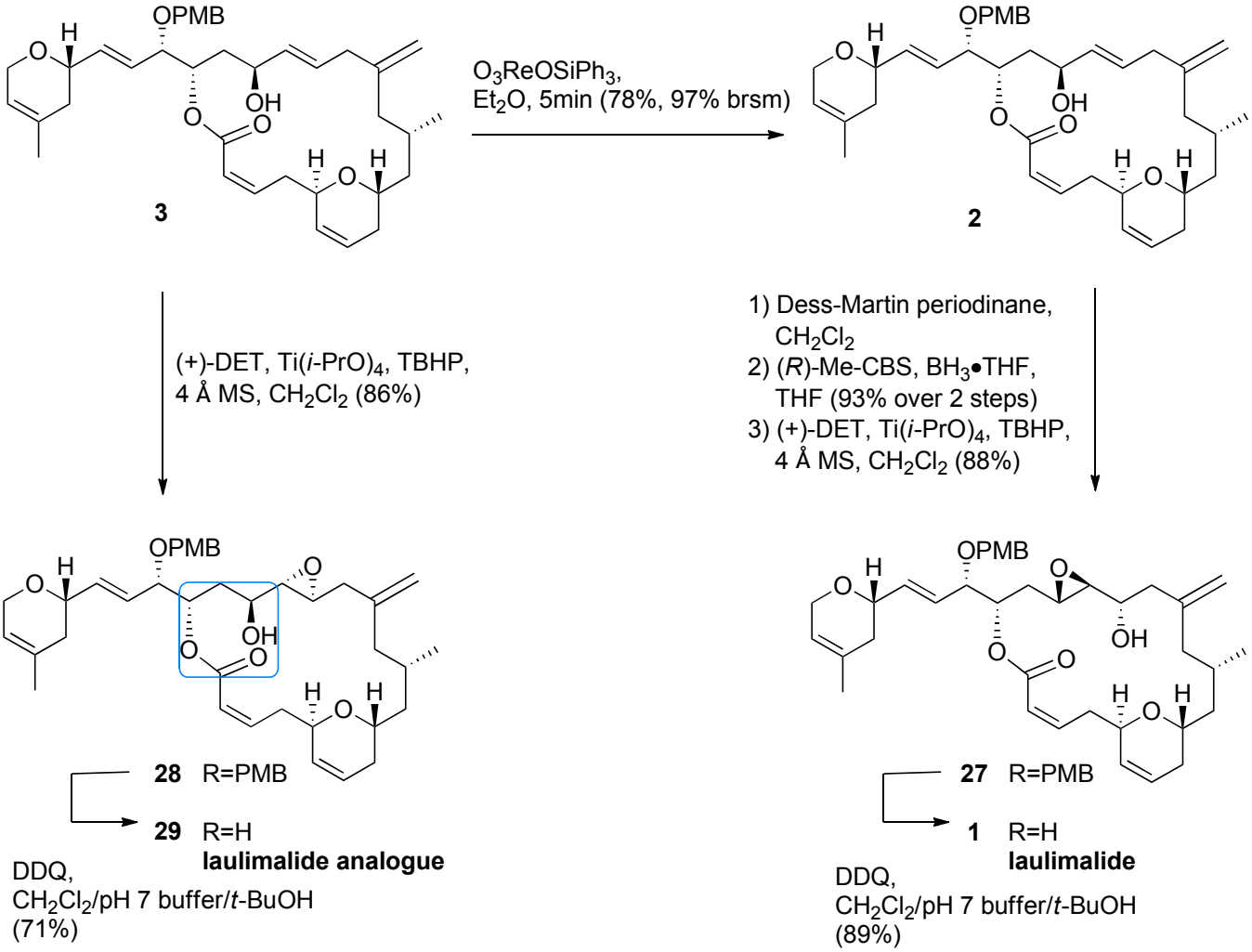
1. 1,3-allylc transposition using [2,3]-sigmatropic shift



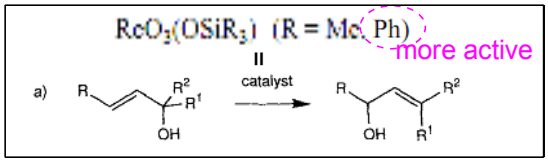
1. Payne rearrangement under basic condition



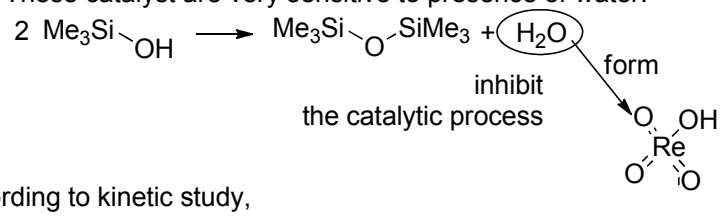
<Synthesis of laulimalide and its analogue>



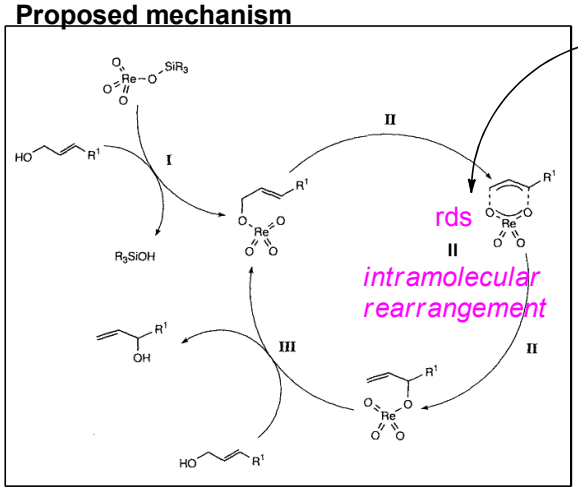
•**3** → **2**: 1,3-allylic transposition utilizing Re oxo catalysis



These catalyst are very sensitive to presence of water.



Proposed mechanism



According to kinetic study,

$v_i = k\,[\text{cat.}]^x\,[\text{substrate}]^y$

Some calculations confirm the involvement of a cyclic transition state.

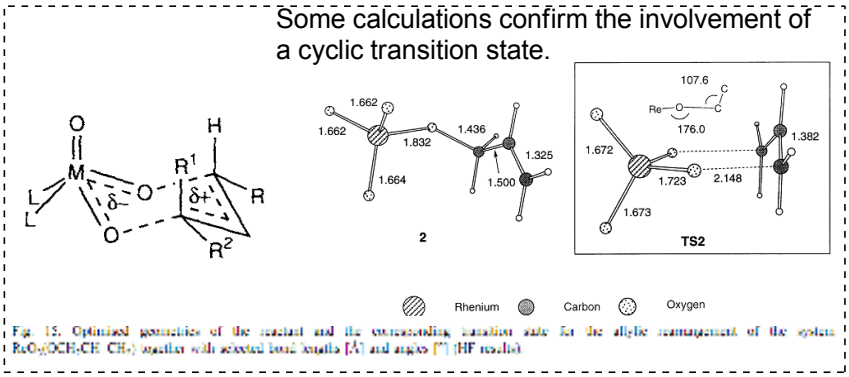


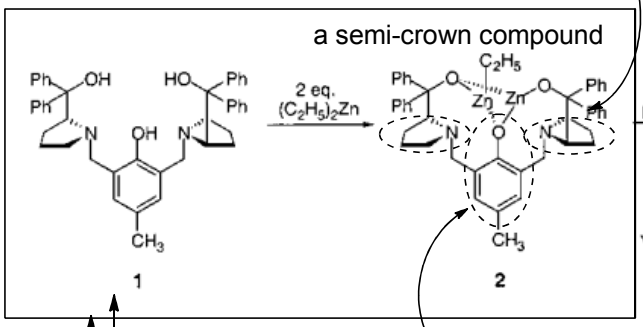
Fig. 15. Optimised geometries of the reactant and the corresponding transition state for the allylic rearrangement of the system $ReO_3(OCH_2CH{=}CH_2)$ together with selected bond lengths [Å] and angles [°] (HF results)

3-4. Asymmetric Direct Aldol Reaction via a Dinuclear Zinc Catalyst

<A Dinuclear Zinc Catalyst Design>

Trost, B. M. *et al. J. Am. Chem. Soc.* ***2000***. *122*, 12003.
Trost, B. M. *et al. J. Am. Chem. Soc.* ***2001***. *123*, 3367.

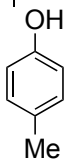
two nitrogens
The strong coordinating elements for some metals



•High binding affinity vs. Catalysis
Too high binding affinity inhibit an exchange of products for others.

a semi-crown design meets both requirement:
-good chiral recognition
-turnover at reasonable rates

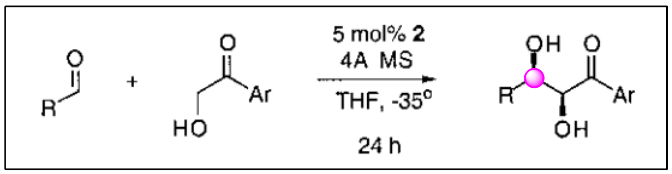
4 steps



a phenoxide moiety(as a base)
1. The alkoxide generated in the aldol reaction would be rapidly protonated by this.
2. The phenoxide might still be adequate to form the enolate.

<Substrate scope and Proposed cataltic cycle>

•α-hydroxyketones as donors



c.f. simple ketones as donors

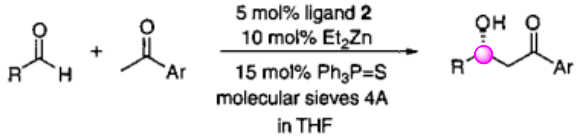
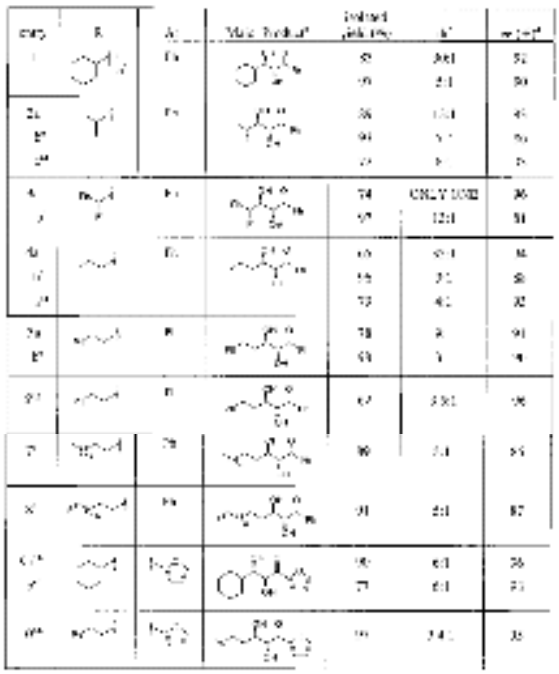
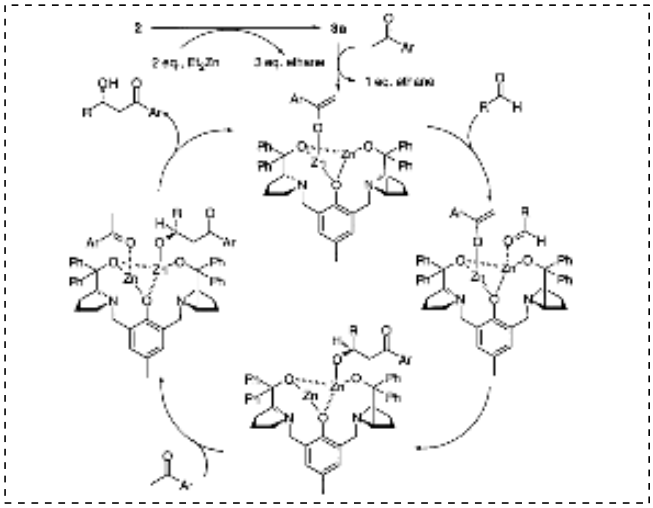


Table 2. Asymmetric Aldol Reaction[a]

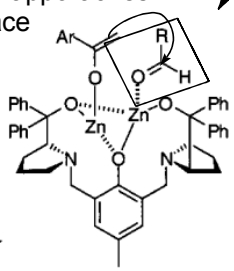


[a] All reactions as in eq 3 using a 1.5:1.0 ratio of hydroxyketone to aldehyde using 2.5 mol % catalyst unless noted otherwise. [b] See ref 7. [c] Determined by ^{1}H NMR spectroscopy on the crude mixture. [d] Determined by chiral HPLC on a Chiracel OD or OJ column. [e] For this run, 5.0 mol % catalyst was employed. [f] Reaction performed using a 3:1:1.0 ratio of hydroxyketone to aldehyde. [g] Reaction performed at −55 °C. [h] Reaction performed using 1.4:1.0 ratio of hydroxyketone to aldehyde.



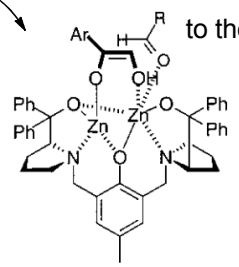
•simple ketone

the enolate apporaches to the *re* face



•α-hydroxyketone

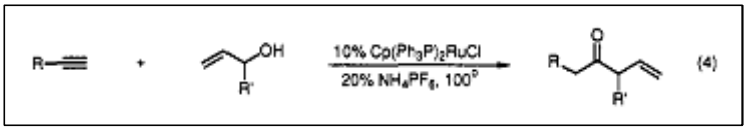
to the *si* face



α-hydroxyketone serves as a bidentate ligand.

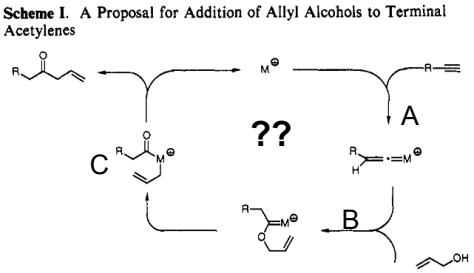
3-5. Rh(I)-Catalyzed Cycloisomerization of Homo- and Bis-homopropargylic Alcohols

<Ru-Catalyzed Reconstitutive Condensation of Allylic Alcohols and Terminal Alkynes>



Trost, B. M. *et al. J. Am. Chem. Soc.* **1992**, *114*, 5579.

Scheme I. A Proposal for Addition of Allyl Alcohols to Terminal Acetylenes

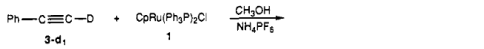


The close examination of the mechanism
- -Ligand subsitution
- -Kinetic and deuterium experiments
- -Identity of the reactive profile

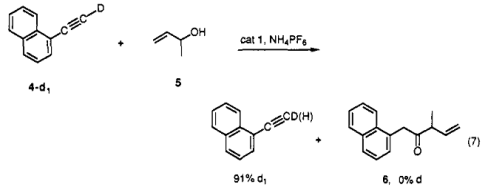
A. Vinylidene Formation

Deutrium labeling

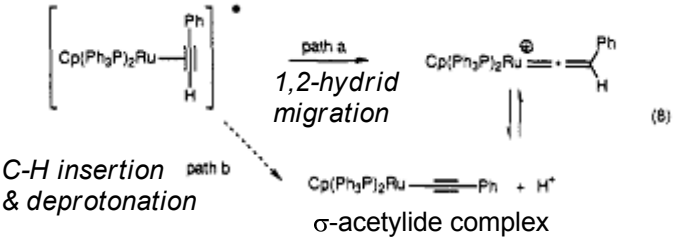
stoichiometric condition



catalytic condition



π-alkyne complex



(1) the NMR spectrum of **2** in CDO_3D containing of $NDPF_4$

the absense of the vinylic hydrogen
&
the disappearance of ^{13}C signal for the vinylidene carbon
(with all the other ^{13}C siganls remaining)

(2) deutrium loss of **3** in eq 6

→ reversibility of vinylidene formation

(3) litte deutrium loss of **3** in eq7

→ β-protonation of σ-acetylide > reversal to π-alkyne complex
faster

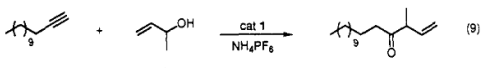
summary:
-Vinylidene complex is formed.
-The equiliration of the vinylidene complex with starting alkyne is more slow then its further reaction.

B. Addition of Allylic Alcohols

(1) the extremely facile loss of PPh_3 from cat.**1**

(2) addition of PPh_3

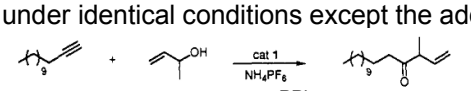
retardation or the rate of the condensation reaction



within 1 h

addition of PPh_3 ⟹

under identical conditions except the addition

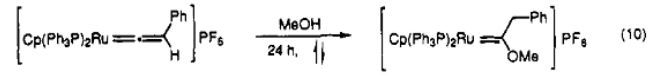


4 h

(3) comparison of the reactivity of 3-buten-2-ol **5** with other alcohols

5, starically equivalent to IPA, reacted much mroe rapidly than MaOH.

MeOH



(10)

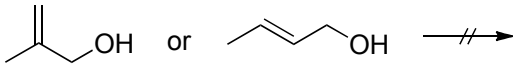
2

EtOH, IPA

NO addition (for steric reasons)

→ precoordination of the olefinic group of **5**

(4) placing Me directly on the double bond of the allylic alcohols

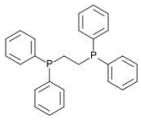


→ condensation products

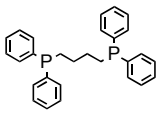
→ steric inhibition of olefin coordination

(5) replacing PPh_3 with the chelating ligands dppe and dppb

inhibition of the condensation reaction
→ preclusion of preccordination of the olefinic group of the allylic alcohols
(due to relactance of the ligands to dissociate a phosphine)



dppe



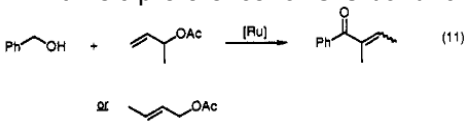
dppb

summary:
-Precoordination of the olefinic goup is required and actually takes place.

C. The Nature of the Allyl Intermediate : evidence regarding the role of σ- vs. π-allyl complexes

(0) precedents of Ru-catalyzed coupling

→ intrinsic preference for C-C bond formation to the more substituted allyl terminus

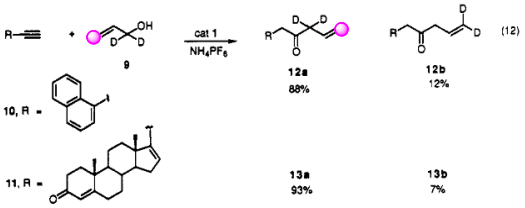


(11)

Tsuji, Y. *et al. J. Organomet. Chem.* **1989**, *369*, C51.

(1) regiochemical outcome from eq 12

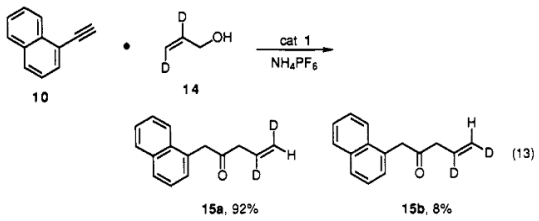
retaining the positional identity of the allylic alcohol



(12)

(2) geometrical outcome from eq 13

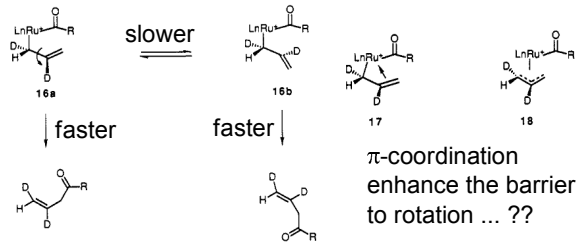
retaining olefin geometry



(13)

→ little intervention of σ-complex
(See the right column.)

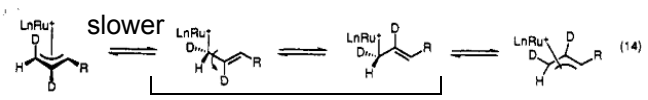
a) Slower C-C bond rotation than reductive elimination



π-coordination enhance the barrier to rotation ... ??

NOT reasnable

b) Slower η^3 to η^1 allyl slippage than reductive elimination



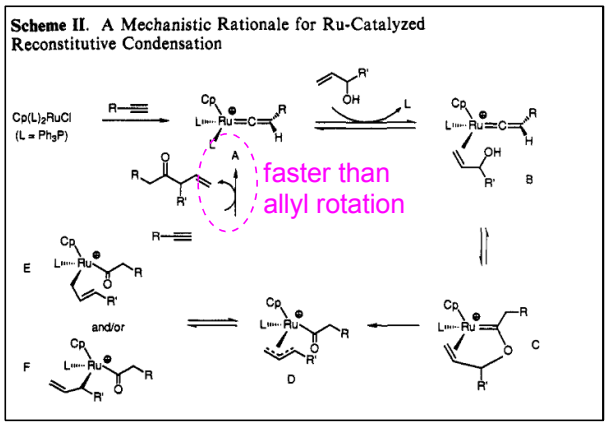
(14)

scramble the olefin geometry

summary:
-Judging from almost no scramble of both regimochemistry and olefin geometry,
η^3-π-allyl complex undergos reductive elimination much faster than borh allyl rotation and η^3 to η^1 allyl slippage .

➤This scheme accommodates all of the preceding observations.

Scheme II. A Mechanistic Rationale for Ru-Catalyzed Reconstitutive Condensation



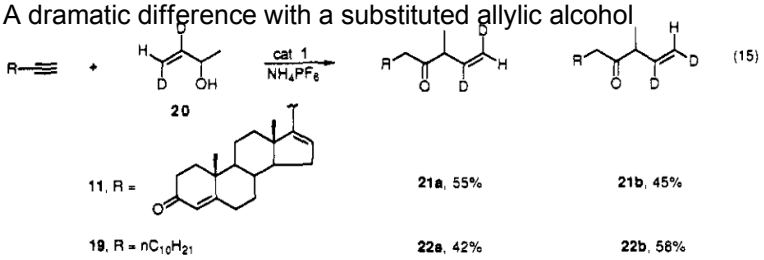
If R=H (unsubstituted allyl alcohol),
D should be sufficiently destabilized
to ensure rapid reductive elimination

(Due to the presence of the acyl group
on an already electron-poor Ru(IV) species)

→ relatively slow η^3 to η^1 allyl slippage

But if R≠H(substituted allyl alcohol),
the competition between the rate
for reductive elimination and η^3 to η^1 allyl slippage
is changed ! (See below.)

A dramatic difference with a substituted allylic alcohol

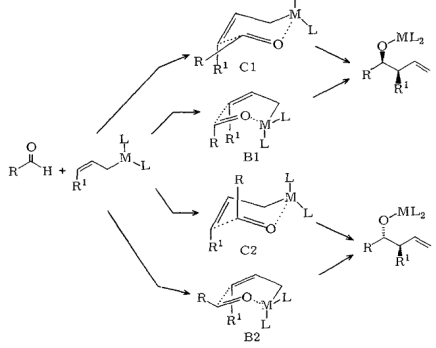


The high regioselectivity
&
The loss of olefin geometry

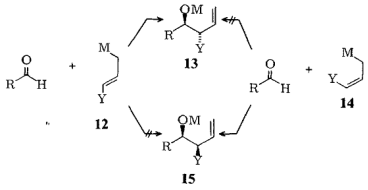
-Scrambling of olefin geometry → σ-complex E as an obligatory intermediate or a species in dynamic equilibrium
-The high regioselectivity → reminiscent of eq11 (the reaction of monosubstituted allyl organomethallics at the more substituted allyl terminus)

Why C-C bond formation the more substituted allyl terminus is favored ??

Precedents: 6-membered transition state



Scheme 5. C1, C2 = chair-like, B1, B2 = boat-like transition states.



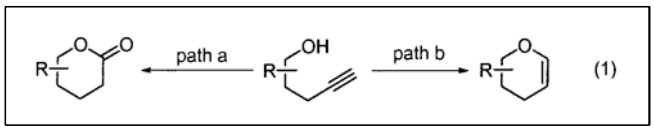
Scheme 2. Y = alkyl or a heteroatom-bonded group, M = metal.

An allylic rearrangement is always observed in reactions between allylmetal compounds such as **12** or **14** and aldehydes under kinetically controlled conditions (Scheme 2). Thus, it is reasonable to propose a six-membered cyclic transition state, especially when the metal can coordinate to the carbonyl group of the aldehyde as a Lewis acid due

Trost, B. M. *et al. J. Am. Chem. Soc.* **2002**, *124*, 2528.

Like such a reaction, the metal itself prefers the less substituted allyl terminus
and cyclic transition state invokes allyl inversion ??

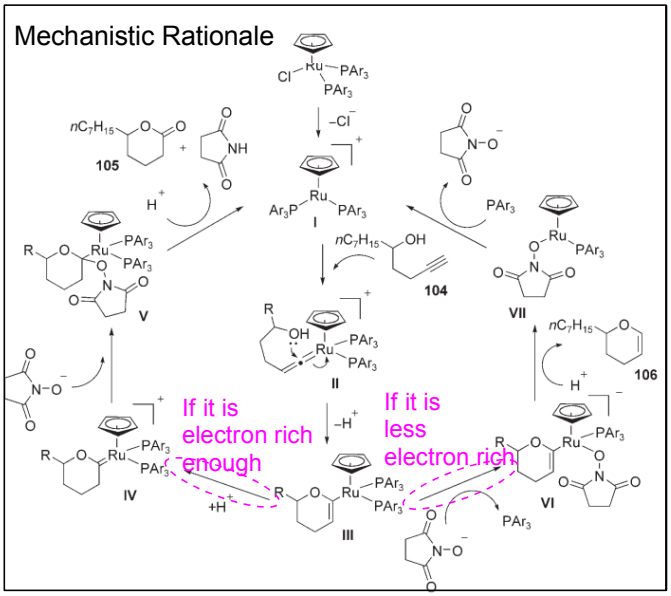
<Ru-Catalyzed Oxidative Cyclization vs Cycleisomerization of Bis-homopropargylic Alcohols>



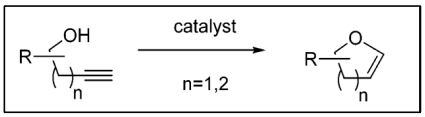
Trost, B. M. *et al. J. Am. Chem. Soc.* **2002**, *124*, 2528.

Entry	Substrate	Method[a]	Time	Conversion	Lactone Isolated yield		Dihydropyran Isolated yield	
1a		A	23h	>99%		69%		7%
1b		C	25h	99%		4%		64%
2a		A	24h	97%		63%		6%
2b		B	18h	100%		70%		5%
2c		C	24h	100%		5%		72%
3a		A	24h	93%		58%		8%
3b		B	18h	100%		67%		7%
3c		C	24h	100%		6%		67%
4a		A	26h	100%		65%		7%
4b		C	26h	99%		5%		68%
5a		A	22h	100%		51%		6%
5b		C	19h	100%		6%		70%
6a		A	24h	70%		48%		9%
6b		B	25h	98%		64%		8%
6c		C	25h	94%		5%		62%
6d		D	22h	100%		6%		65%
7a		A	24h	No Rxn[b]		----		----
7b		C	22h	75%[c]		----		46% (61%)[d]
8a		A	25h	No Rxn		----		----
8b		E	25h	75%		----		44% (59%)[d]

∗**3** = $(C_4H_9)_4NPH_6$, **4** = *N*-hydroxysuccinimide

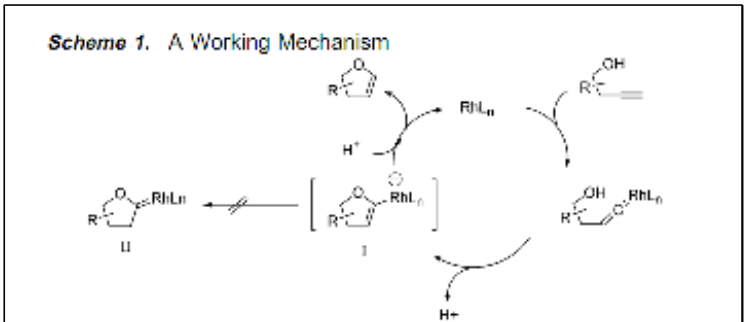


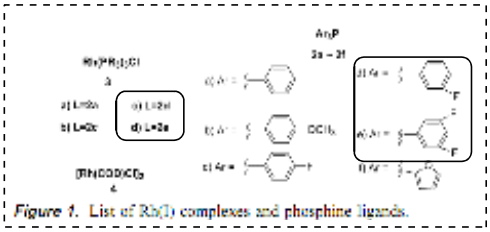
<Rh-Catalyzed Cycloisomerization of Homo- and Bis-homopropargylic Alcohols>



Trost, B. M. *et al. J. Am. Chem. Soc.* **2003**, *125*, 7482.

5	9	17	A	100%	61%	
6	10	18	C	100%	61%	
7	11	19	C D	100% >98%	58% 70%	
8	12	20	C D	>95% >95%	54% 67%	
9	13	21	A	94%	52%	





3-6. Ru-Catalyzed Alkene-Alkyne Coupling

➤To maximize the atom economy ...

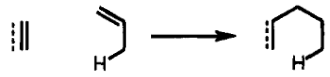
A+B → C+D ⟹ A+B → C+ D

a waste product

Trost, B. M. *et al. J. Am. Chem. Soc.* ***1995***. *117*, 615.
Trost, B. M. *et al. Chem. Rev.* ***2001***. *101*, 2067.

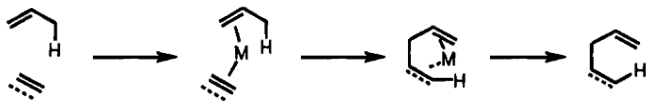
➤Diels-Alder type reactions are ideal: They incorporate all of the atoms of the reactants

●Ideal catalysis of the Alder en reaction



-the simplest form
-catalysis : only TS energy ↓
-one-step process

●Alternative catalytic concept



-catalysis : precoordination of two reactant partners
-one or more steps

<Cross coupling of alkynes with alkenes>

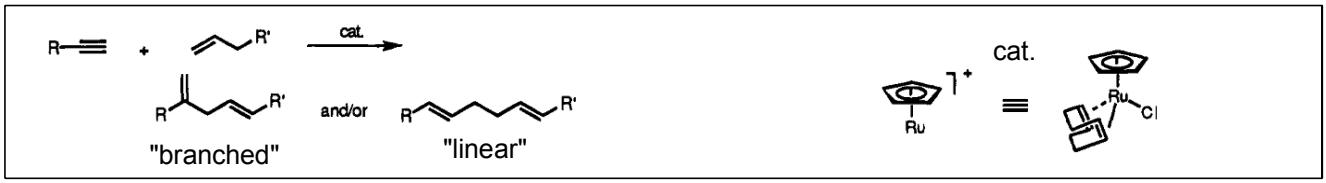
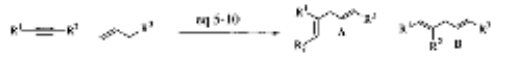


Table 2. Ruthenium-Catalyzed Alder-ene Reaction[a]

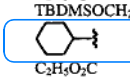
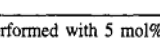


R^1	R^2	R^3	catalyst	Ratio A:B	Yield
$CH_3(CH_2)_2$-	H	-CH_2OCH_3	1	5.2:1	56%
$CH_3(CH_2)_2$-	H	-CH_2OH	1	4:1	57%
$CH_3(CH_2)_2$-	H	-$COCH_3$	1	3.8:1	50%
$Cl_3C(CH_2)_2$-	H	-$CH_2CH_2CO_2CH_3$	1	3.8:1	71%
$CH_3(CH_2)_2$-	H	-CH_2CH_2CH=CH_2	1	6.4:1	52%
BnO_2C-	H	-CH_2CH_3	1	5.6:1	90%
TBDMSOCH$_2$-	H	-CH_2CH_3	1	5.0:1	56%
$CH_3(CH_2)_2$-	H	-CH_2CH=$CHCO_2Et$	1	5.3:1	46%
$CH_3(CH_2)_4CH(OBn)$-	H	-CH_2CH_3	1	1:2.0	53%
	H	-CH_2CH_3	1	1.9:9	65%
$BnO(CH_2)_2$-	CH_2	-$CH_2CH_2CO_2CH_3$	1	1:2.6	38%
MOMOCH$_2$-	CH_2CH_2-	-$CH_2CO_2CH_3$	1	1:1.8	54%
$NC(CH_2)_2$-	H	-$CH_2CO_2CH_3$	2	8:1	65%
PhCH(NHBoc)$(CH_2)_2$-	H	-$CH_2CO_2CH_3$	2	>20:1	84%
$CH_3COCH_2CH_2$-	H	-$CH_2CO_2CH_3$	2	5:1	86%
	H	-$CH_2CO_2CH_3$	2	10:1	75%
$(CH_3)_2C(OH)(CH_2)_2$-	H	-$CH_2CH_2CH_3$	2	1:32	91%
$NC(CH_2)_2$-	CH_2CH_2	-$CH_2CH_2CH_3$	2	3.3:1	73%
PhCH(NHBoc)$(CH_2)_2$-	-CO_2Et	-$CH_2CH_2CH_3$	2	1:5	62%
			1	1:3.5	61%
TsNHCH$_2$CH$_2$-	-TMS	-$CH_2CO_2CH_3$	2	>98:2	78%
HOCH$_2$CH$_2$-	-TMS	-CH_2CH_3	2	>98:2	79%
CH_3OCH_2-	-TMS	-CH_2OCH_3	2	>98:2	61%
			1	>98:2	31%
$CH_3CH_2CH_2$-	TBS	-$CH_2CH_2CH_3$	2	>98:2	88%

[a] Catalyst: **1** = $CpRu(COD)Cl$, **2** = $CpRu(CH_3CN)_3PF_6$.

Table 3. Chemoselectivity[a]

the same as the above

entry	R	R′	solvent	conversion[c]	isolated yield %[f]	ratio[c] branched:linear
1	n-C_3H_7	n-C_4H_9	4:1 DMF−H_2O	80	56(69)	5.2:1
2	n-C_3H_7	CH_2CH_2OH	1:1 DMF-H_2O	95	57(60)	4.0:1
3	n-C_3H_7	$COCH_3$	1:1 DMF-H_2O	100[d]	50(−)	3.8:1
4	n-C_3H_7	$CH_2CH_2CH_2CO_2CH_3$	1:1 DMF-H_2O	95	71(75)	3.8:1
5	n-C_3H_7	CH_2CH_2CH=CH_2	CH_3OH[b]	99	52(−)	6.4:1
6	$C_2H_5O_2C$	n-C_4H_9	3:1 DMF-H_2O	100	90(−)	5.6:1
7	TBDMSOCH$_2$	n-C_4H_9	3:1 DMF-H_2O	100	86(−)	5.0:1
8		n-C_4H_9	3:1 DMF-H_2O	100	85(−)	1.7:1
9	$C_2H_5O_2C$		3:1 DMF-H_2O	65	46(70)	5.3:1

[a] All reactions were performed with 5 mol% **3** at 100 °C for 2 h unless otherwise stated.
[c] Determined by gas chromatography. [d] Reaction performed for 16 h.
[f] Numbers in parentheses represent isolated yields based upon unreacted starting material.

➤Extremely high chemoselectivity & control of olefin geometry

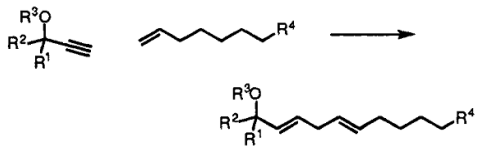
free OH, TBS ehters, ketones, and esters
in either the alkene or alkyne

➤Generally, the major produt is the branched one.

➤Branching at propargylic position has significant effect on regio selectivity. (the linear product ↑)

➤Replacing an alkyl branch by an oxygen inverts the regioselectivity.

= the more reactive cationic complex



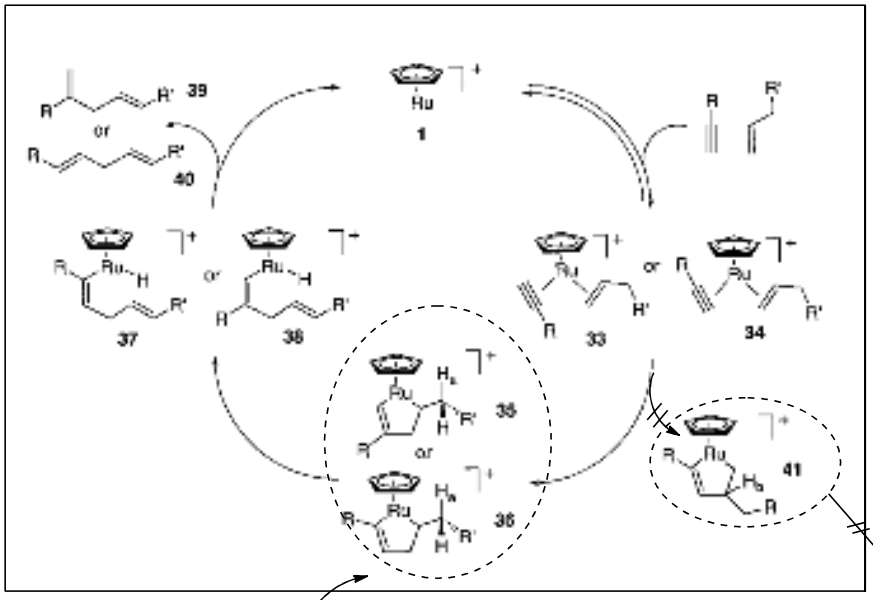
➤As the size of R3 ↑, then the linear ↑

Table 4. Reaction of Progargylic Ethers and Analogues with Terminal Alkenes[a]

entry	R^1	R^2	R^3	R^4	solvent ratio DMF−H_2O	conversion[c]	isolated[e] yield	ratio[c] branched:linear
1	n-C_5H_{11}	H	$PhCH_2$	CH_3	3:1	65	53(82)	1:2.0
2	n-C_5H_{11}	H	TBDMS	CH_3	3:1	100	88(- -)	1:2.4
3	n-C_5H_{11}	H	TIPS	CH_3	3:1	60[b]	41(68)	1:3.7
4	$-(CH_2)_5-$		H	CH_3	3:1	85	65(76)	1:9.9
5	CH_3		$-O(CH_2)_3O-$	CH_3	3:1	60	41(68)	1:5.6
6	CH_3		$-O(CH_2)_3O-$	CO_2CH_3	1:1	90	59(65)	1:5.6

[a] All reactions were performed with 5 mol% **3** at 100 °C for 2 h unless stated otherwise.
[b] Reaction time = 16 h. [c] Determined by gas chromatography.
[e] Numbers in parentheses represent isolated yields based upon unreacted starting material.

<Proposed catalytic cycle>



➤This model may explain the effect of a propargylic oxygen substituent .

Ru coordinates the oxygen.

If the alkyne coordinates with the opposite orientation ... (possible in principle)

Syn-β-hydrogen elimination of H_b

Electronic effect vs. Steric effect

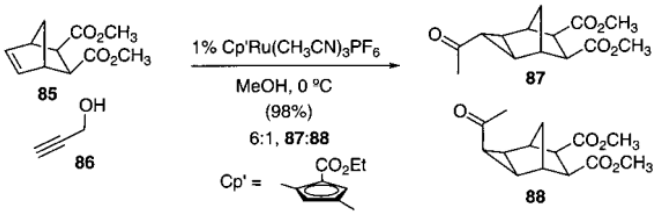
- Electronically, **35** is favored. Carbametalations normally prefer to attach the less substitued terminus of the alkyne.
- Sterically, **36** is favored.

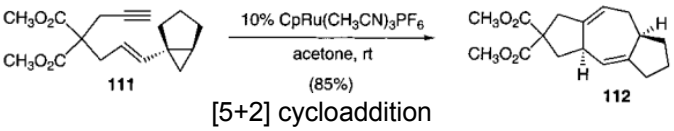
Which effect is dominant ??

Normally,electronic rather than steric effects dominate leading via **35** to the branched **39**.

On the other hand, as R increases in size, steric effects bacome more important:
17 → **19** should be disfavored relative to **16** → **18**.

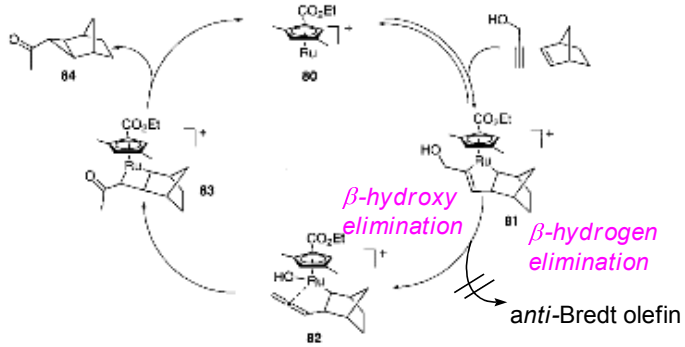
When β-hydrogen elimination is inhibited ...





[5+2] cycloaddition

Scheme 5

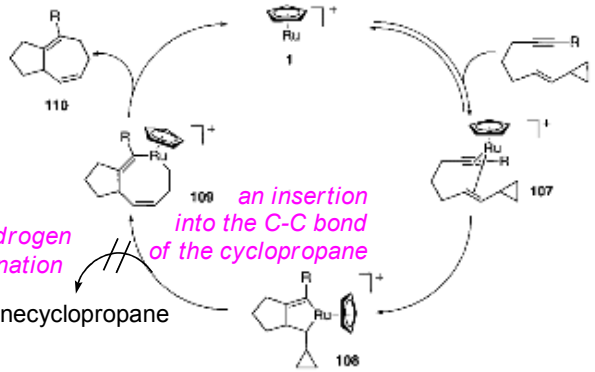


β-hydroxy elimination

β-hydrogen elimination

anti-Bredt olefin

Scheme 7



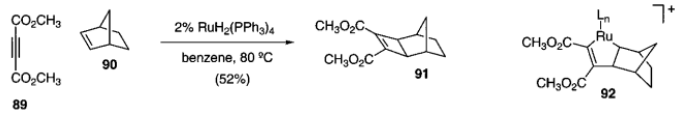
an insertion into the C-C bond of the cyclopropane

β-hydrogen elimination

methylenecyclopropane

- The ruthecycle **81** cannot achieve the required geometry.
- β-hydrogen elimination would generate *anti*-Bredt olefin.

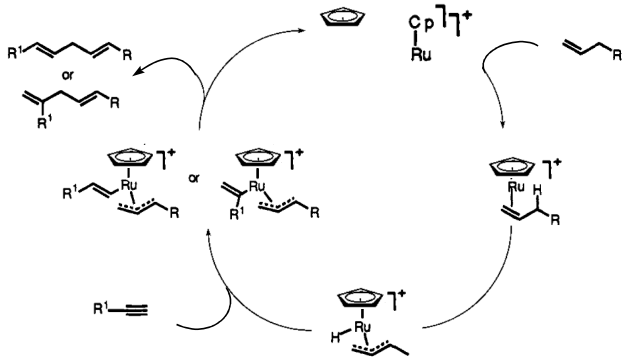
→Then, if even β-hydroxy elimination is impssible, what occurs ??



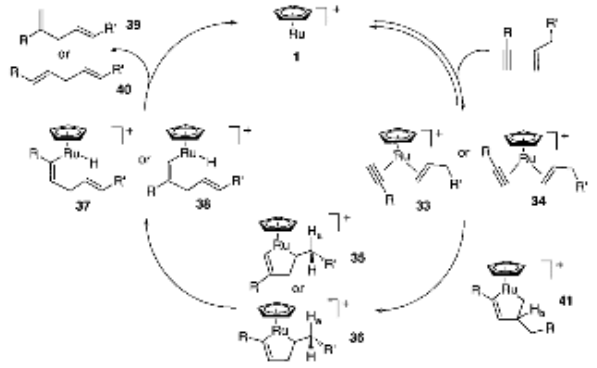
<How the reaction mechanism was confirmed ??>

➤This Ru-catalyzed reaction proceeds without complications arising from self-condensation of either partner.
→How does this practical reaction occurs ??

Path **1**: allyl mechanism



Path **2**: Ruthenacycle mechanism



➤Initially, path **1** seemed more possible than path **2** due to absence of homo-coupling product.

-If Path **2** operates, the formation of a ruthenacyclopentadiene should be preferred to that of a ruthenacyclopentene.

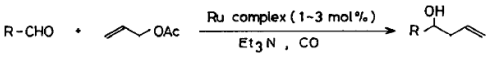
lead to homo-coupling products

lead to cross-coupling products

➤However, the validity of path **1** was questioned, because the regioselectivity about alkene was disrurbing.

-In light of other work, the formation of a π-allylruthenium complex should undergo reductive elimination with formation of the new C-C bond to the more substitued allyl terminus.

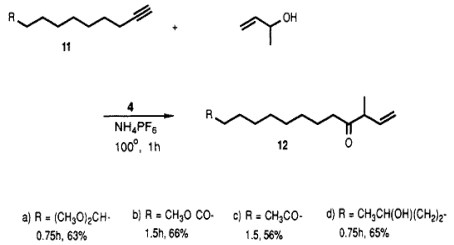
precedents of reductive elimination



Ruthenium complex catalyzed allylation of aldehydes with allylic compounds [a]

Run	Aldehyde	Allylic compound	Product	Yield (%) [b]
1	C_6H_5CHO	CH_2=$CHCH_2OAc$	$C_6H_5CH(OH)CH_2CH$=CH_2	87
2	$CH_3(CH_2)_5CHO$	CH_2=$CHCH_2OAc$	$CH_3(CH_2)_5CH(OH)CH_2CH$=CH_2	57
3	C_6H_5CH=$CHCHO$	CH_2=$CHCH_2OAc$	C_6H_5CH=$CHCH(OH)CH_2CH$=CH_2	48
4	C_6H_5CHO	CH_2=$CHCH(CH_3)OAc$	$C_6H_5CH(OH)CH(CH_3)CH$=CH_2	84
5 [c]	C_6H_5CHO	CH_3CH=$CHCH_2OAc$	$C_6H_5CH(OH)CH(CH_3)CH$=CH_2	64
6	C_6H_5CHO	CH_2=$CHCH_2OCO_2CH_3$	$C_6H_5CH(OH)CH_2CH$=CH_2	39
7	C_6H_5CHO	CH_2=$CHCH_2Br$	$C_6H_5CH(OH)CH_2CH$=CH_2	38
8	C_6H_5CHO	CH_2=$CHCH_2OH$	–	0
9 [d]	C_6H_5CHO	CH_2=$CHCH_2OAc$	$C_6H_5CH(OH)CH_2CH$=CH_2	91

[a] Aldehyde (10 mmol), allylic compound (3.3 mmol), triethylamine (10 mmol), $Ru_3(CO)_{12}$ (0.033 mmol) and THF (8.0 ml) at 120°C for 24 h under 10 kg cm^{-2} of initial carbon monoxide pressure. [b] Determined by GLC based on the amount of allylic acetate charged. [c] At 140°C. [d] $RuCl_3 \cdot nH_2O$ (0.10 mmol) in place of $Ru_3(CO)_{12}$.



Left: Tsuji, Y. *et al. J. Organomet. Chem.* ***1989***. *369*, C51.
Reight: Trost, B. M. *et al. J. Am. Chem. Soc.* ***1990***. *112*, 7809.

➤Path **1** was abondoned by the experimental support.

-To probe the involvment of a π-allylruthenium chemistry, the reaction of (E)-2 butene was explored.

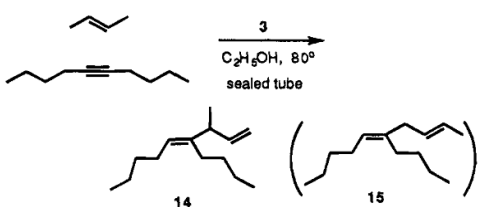
If path 1 operates, this reaction should result in
the same regioisomer as a 1-alkene: obtaining **15** as the product.

↓

Spectral data clearly show the adduct is **14** and not **15**.

↓

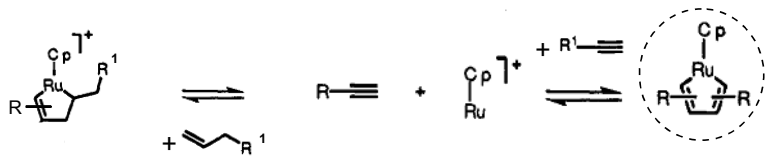
This experiment suggests NOT involving π-allylruthenium mechanism
and supports path 2, which, furthermore, more consistently rationalizes the regioselectivity.



<Why self-coupling of alkyne does not dominate ??>

If the ruthenacyclopentene and ruthenacyclopentadiene are in dynamic equilibrium,
the products then depend upon the rate of further reactions.

Fsst reversible formation



The unimolecular
β-hydrogen elimination

the Alder ene type product

NOT observed

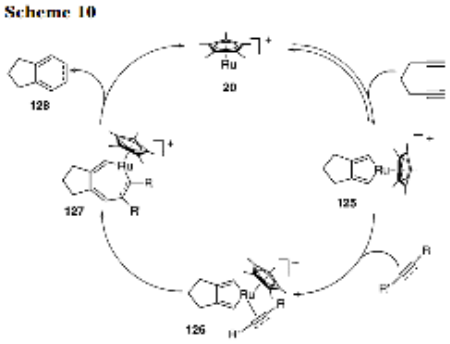
The bimoledcular paths
for the further reaction

numerous side product
such as arenes of cyclopentadienes

(formed via the same mechanism as "scheme 10")

The unimolecula reaction rmay dominate over
the bimoledcular reaction.

So, although the rethenacyclopendadiene spiecies was formed,
only the cross-coupling product was obtained.

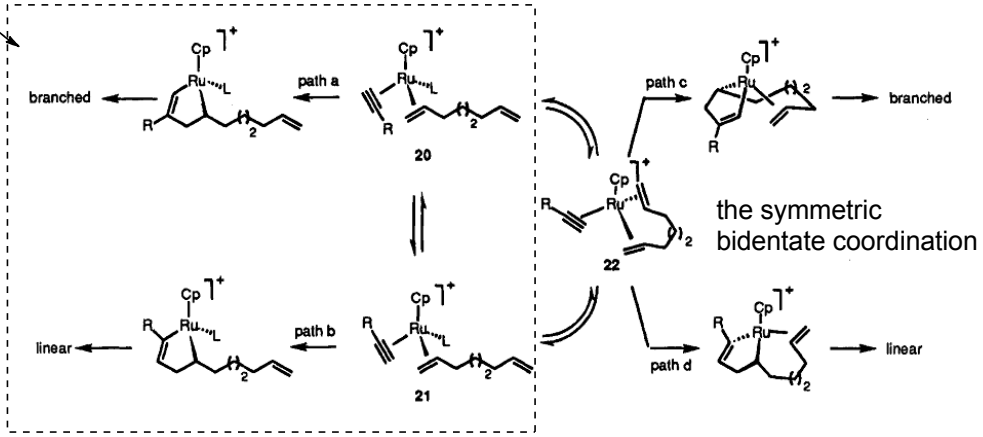


<the unique ability of a remote olefin>

➤The reaction of 1,7-octadiene proceeds with the enhanced selectivity for branched product.

If the reaction followed paths a and b exclusively...
The branched to linear ration should be the same as for 1-octene, which is not the case.

→Other paths should be involved !



If **22** was formed, steric factors arising from interaction of R and the olefin are eliminated from consideration.

The bias for branched vs linear product may simply reflect the intrinsic steric and electronic factors
associated with the tautomerization to the metallacycle (paths c and d)