Literature seminar

2009.01.24

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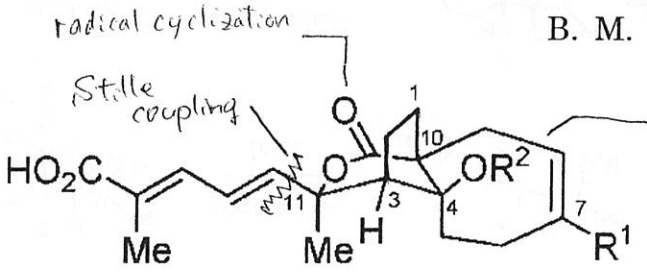
Total Synthesis of (−)-Pseudolaric Acid B



	R^1	R^2
Pseudolaric Acid B (1a)	CO_2Me	Ac
Pseudolaric Acid A	Me	Ac
Pseudolaric Acid C	CO_2Me	H

B. M. Trost et al. *J. Am. Chem. Soc.* 2007, *129*, 14556.

J. Am. Chem. Soc. 2008, *130*, 16425.

Structural features

- trans-fused hydroazulene (bicycle [5, 3, 0])
  acetoxy/hydroxy group is trans to lactone group
- 4 contiguous stereocenters

Bioactivity

- the extract of the root of *Pseudolarix Kaempferi* is Chinese herbal medicine for the treatment of dermatological fungal infections.
- contraceptive effect
- cytotoxic to several cancer cell lines in vitro
- an agonist for transcriptional activation of PPARs
- inhibits angiogenesis by diminishing the secretion of VEGF in tumor cells.
- inhibits the polymerization of tublin in multidrug-resistant cancer cell lines.

PPARs : peroxisome proliferators-activated receptors

VEGF : vascular endothelial growth factor

Pseudolaric acid A and B were isolated in 1965.

The **first** successful total synthesis is established by P. Chiu et al in **2006**. (Pseudolaric Acid A)

(Evans catalytic asymmetric aldol reaction and carbene cyclization cycloaddition cascade reaction)

Today's contents

1. Retrosynthesis

2. [5+2] cycloaddition of π-component and vinylcyclopropane

2-1 Rh catalysed [5+2] cycloaddition

(a) intramolecular reaction

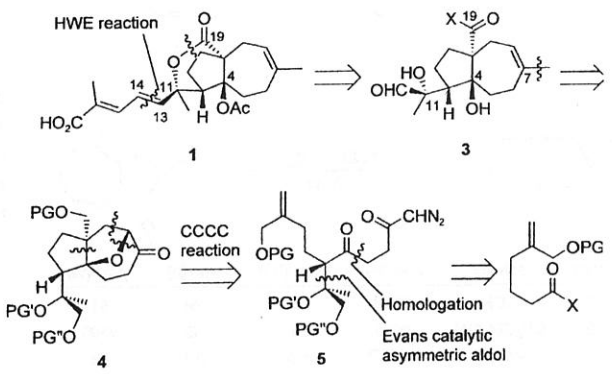
(b) intermolecular reaction

(c) recent development

2-2 Ru catalysed [5+2] cycloaddition

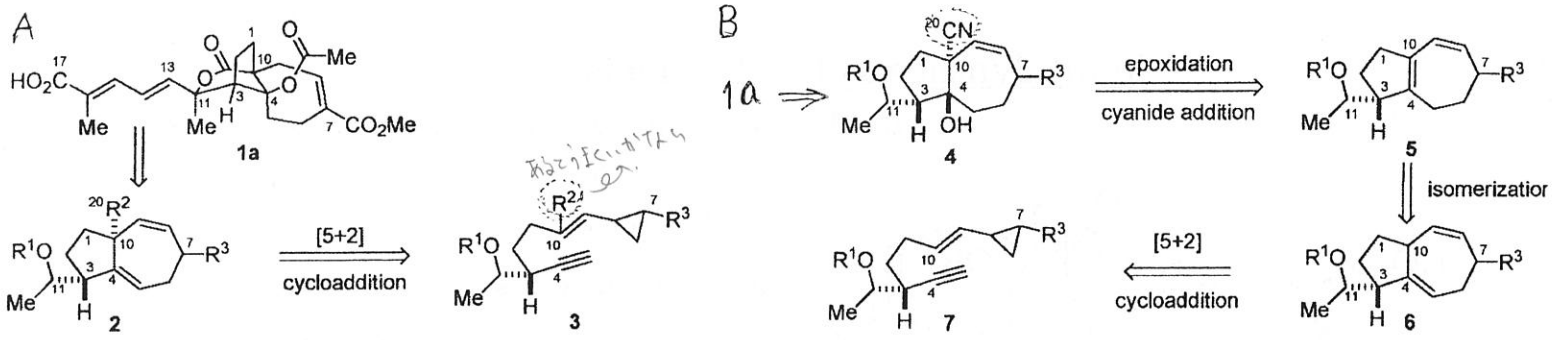
3. Total synthesis of Pseudolaric Acid B

4. Appendix (total synthesis of Pseudolaric Acid A)



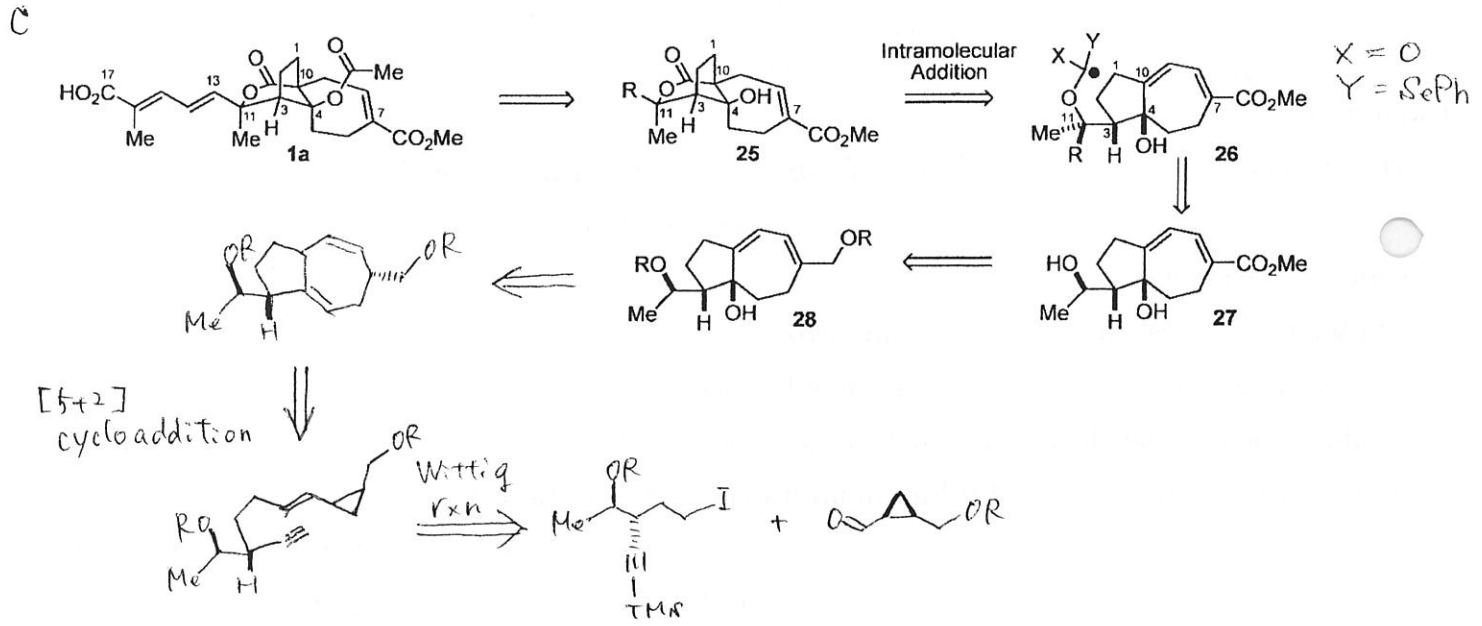
Scheme 2. Retrosynthetic analysis of pseudolaric acid A. HWE = Horner–Wadsworth–Emmons; CCCC = carbene cyclization cycloaddition cascade; PG, PG′, PG″ = protecting groups.

1. Retrosynthesis



Ru catalyst : no substitution at C10

cyanide addition turned out to be unsuccessful

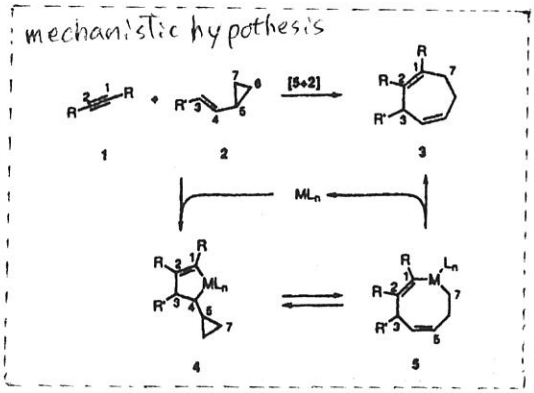


2. [5+2] cycloaddition of π-component and vinylcyclopropane

2-1 Rh catalysed [5+2] cycloaddition

(a) intramolecular reaction (π-component : alkyne, alkene, allene)

alkyne P. A. Wender et al. *J. Am. Chem. Soc.* **1995**, *117*, 4720. *Tetrahedron.* **1998**, *54*, 7203.



entry	solvent	additive	temp (°C)	time (h)	yield (%)
1	$PhCH_3$	none	110	48	84
2	CF_3CH_2OH	none	55	19	90-95
3	$PhCH_3$	AgOTf	110	0.3	83

(E = CO_2Me)

Table 1. Transition Metal Catalyzed Intramolecular [5 + 2] Cycloadditions of Vinylcyclopropanes and Alkynes

	Vinylcyclopropane-Alkyne	Cycloadduct(s), Yield	Reaction Conditions, time
	6	7	
1.		83%	A[a], 20 min.
2.		84%	B[b], 2 d
	8	9	
3.	a: R=Me	88%	B[b], 1.5 h
4.	b: R=TMS	83%	B[b], 3.5 h
5.	c: R=CO_2Me	74%	B[b], 1.25 h
6.	d: R=Ph	80%	B[b], 1.5 h
7.	e: R=H	50%[f]	C[c], 1.5 h

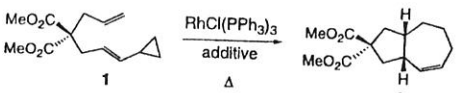
		10	11	12
8.	a: R=Me	89% (11:12=3.5:1)		B[b], 2 d
9.	a: R=Me	92% (11:12=1:2)		D[d], 2.5 h
10.	b: R=H	82% (only 11)		B[b], 2d
11.	c: R=CO_2Me	81% (only 11)		B[b], 16 h
12.	d: R=TMS	71% (only 12)		B[b], 7 d
		13	14	
13.		82%		D[d], 30 min

[a] A = 0.5 mol % $RhCl(PPh_3)_3$, 0.5 mol % AgOTf, PhMe, 110 °C. [b] B = 10 mol % $RhCl(PPh_3)_3$, PhMe, 110 °C. [c] C = 10 mol % $RhCl(PPh_3)_3$, THF, 100 °C. [d] D = 10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf, PhMe, 110 °C. [e] E = CO_2Me. [f] Lower yield in this case due to product volatility.

· entry 8, 9, 12 : isomerizarion mediated by Rh

alkene P. A. Wender et al. *J. Am. Chem. Soc.* **1998**, *120*, 1940. *Tetrahedron.* **1998**, *54*, 7203.

Table 1. Cycloaddition of Ene–Vinylcyclopropane 1[a]



1 2

entry	mol % $RhCl(PPh_3)_3$	additive[b]	concn[c] (M)	time (h)	yield[d] (%)
1	0.1	AgOTf	1.0	15	90
2[e]	0.1	AgOTf	1.0	17	86
3	0.1	AgOTf	0.4	17	88
4	1	AgOTf	0.05	5	93
5	5	AgOTf	0.01	2	91
6	10	none	0.005	2.5	91

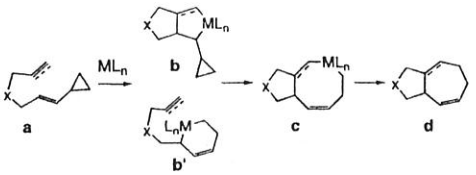
[a] Reactions were run at 110 °C in PhMe. [b] mol % AgOTf = mol % $RhCl(PPh_3)_3$. [c] Concentration of 1. [d] Isolated yield of 2. [e] Reaction run on 1 g scale.

- entry 5 : isomerization (table 2)
- entry 6 : tether = 4-atom
  → trans-fused product

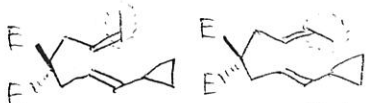
le 2. Transition Metal-Catalyzed Intramolecular [5+2] loadditions of Vinylcyclopropanes and Alkenes

Vinylcyclopropane-Alkene[a]	Cycloadduct(s)	Reaction Conditions, Time, Isolated Yield
1	2	A[b], 17 h, 86-93% (see Table 1)
3	4	B[c], 10 h, 70% (94% by GC)
5 (E:Z 5.5:1)	6	C[d], 1 h, 92%
4. 7	8	C[d], 1 h, 94%
5. 9 (E:Z 6.5:1)	10	D[e], 15 h, 78%
6. 11	12	E[f], 5 d, 77%

[a] E = CO_2Me. [b] 0.1 mol % $RhCl(PPh_3)_3$, 0.1 mol % AgOTf, $PhCH_3$, 110 °C, 1.0 M. [c] 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, THF, 65 °C, 0.01 M. [d] 10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf, $PhCH_3$, 110 °C, 0.01 M. [e] 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 110 °C, 0.01 M. [f] 10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf, $PhCH_3$, 100 °C, 0.02 M.

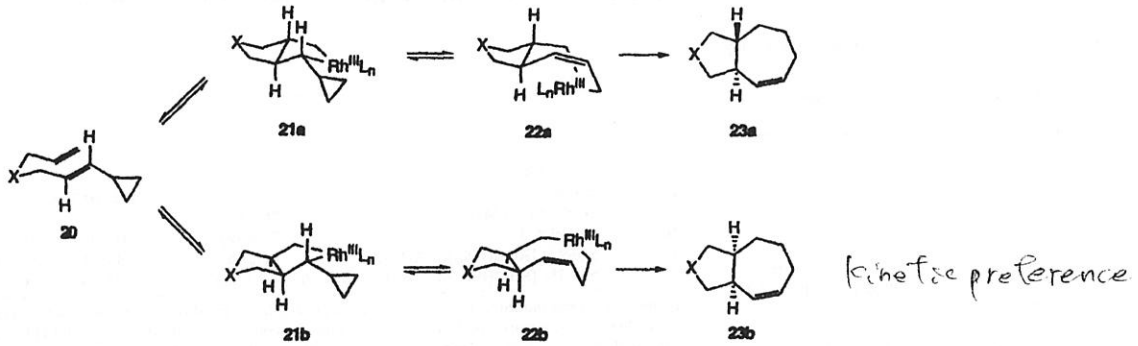


proposed mechanism



unsuccessful

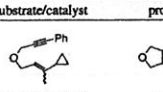
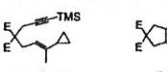
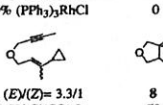
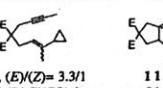
Scheme 3. Analysis of Stereoselectivity in the [5+2] Cycloaddition



kinetic preference

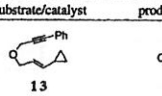
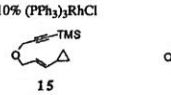
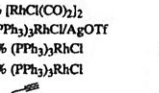
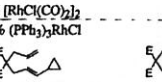
different Rh catalyst : $[Rh(CO)_2Cl]_2$ P. A. Wender et al. *J. Org. Chem.* **1998**, *63*, 4164.

Table 1. Performance of $[Rh(CO)_2Cl]_2$ vs $(PPh_3)_3RhCl$ in [5 + 2] Cycloadditions of Substituted Alkyne–Vinylcyclopropanes

substrate/catalyst	products/yields (%)		conditions[a]
	 2	 3	
1, (*E*)/(*Z*)= 3.3/1			
5% $[RhCl(CO)_2]_2$	80	0	110 °C, 20 min,
10% $(PPh_3)_3RhCl/AgOTf$	0[b]	0	110 °C
	 5	 6	
4			
5% $[RhCl(CO)_2]_2$	81	0	30 °C, 2 d, $CDCl_3$
10% $(PPh_3)_3RhCl$	0	71	110 °C, 7 d,[c]
	 8	 9	
7, (*E*)/(*Z*)= 3.3/1			
5% $[RhCl(CO)_2]_2$	78	0	110 °C, 20 min
10% $(PPh_3)_3RhCl/AgOTf$	65	13	100 °C, 17 h, THF,[c]
	 11	 12	
10, (*E*)/(*Z*)= 3.3/1			
5% $[RhCl(CO)_2]_2$	84	0	2 M, 110 °C, 3 h,[c]
10% $(PPh_3)_3RhCl$	69	20	110 °C, 2 d,[d]

[a] Unless otherwise noted, toluene is used as solvent. [b] Formation of a complex mixture of products. [c] See ref 2. [d] Slow addition of substrate.

Table 2. Performance of $[Rh(CO)_2Cl]_2$ vs $(PPh_3)_3RhCl$ in [5 + 2] Cycloadditions of Unsubstituted Alkyne–Vinylcyclopropanes

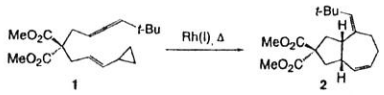
substrate/catalyst	product/yield (%)	conditions[a]
		
13	14	
5% $[RhCl(CO)_2]_2$	78	65 °C, 15 min, $CDCl_3$
5% $[RhCl(CO)_2]_2$	80	30 °C, 14 h, $CDCl_3$
10% $(PPh_3)_3RhCl$	80	110 °C, 1.5 h,[b]
		
15	16	
5% $[RhCl(CO)_2]_2$	78	30 °C, 14 h, $CDCl_3$
10% $(PPh_3)_3RhCl$	83	110 °C, 3.5 h,[b]
		
17	18	
1% $[RhCl(CO)_2]_2$	89	2 M, 110 °C, 3 h,[c]
5% $[RhCl(CO)_2]_2$	79	30 °C, 16 h, $CDCl_3$
5% $[RhCl(CO)_2]_2$	82	110 °C, 20 min
0.5% $(PPh_3)_3RhCl/AgOTf$	83	1 M, 110 °C, 20 min,[b]
10% $(PPh_3)_3RhCl$	90-95	65 °C, 19 h, CF_3CH_2OH,[b]
10% $(PPh_3)_3RhCl$	84	110 °C, 2 d,[b]
		
19	20	
5% $[RhCl(CO)_2]_2$	0	30 °C
10% $(PPh_3)_3RhCl$	50[d]	110 °C, 2 d,[b]
		
21	22	
5% $[RhCl(CO)_2]_2$	0	110 °C, 48 h
0.1% $(PPh_3)_3RhCl/AgOTf$	90	110 °C, 15 h,[e]

[a] Unless otherwise noted, toluene is used as solvent. [b] See ref 2. [c] Slow addition of substrate. [d] The low yield is due to product volatility. [e] See ref 3.

- more reactive than $(PPh_3)_3RhCl$
  (no isomerization, milder condition)
- substrate 19 : no cycloadduct
  ← because of terminal alkyne.
- substrate 20 : no reaction
  ← reductive elimination is difficult

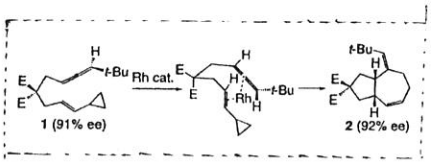
allene P. A. Wender et al. *J. Am. Chem. Soc.* **1999**, *121*, 5348.

Table 1. Cycloaddition of Allene−Vinylcyclopropane **1**



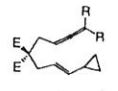
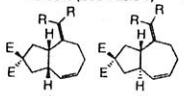
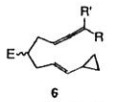
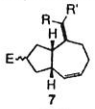
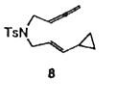
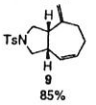
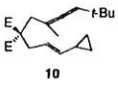
entry	catalyst	mol % Rh	solv	concn[a]	yield[b]
1	$RhCl(PPh_3)_3$	1	$PhCH_3$	0.1 M	96%
2	$RhCl(PPh_3)_3$	0.2	$PhCH_3$	1.0 M	90%
3	$[Rh(CO)_2Cl]_2$	1	DCE[c]	0.1 M	89%

[a] Concentration of **1**. [b] Isolated yield of **2**. [c] DCE = $ClCH_2CH_2Cl$.



- mono-, di-, tri-substituted allene in good to excellent yields
- ring fusion selectivity can be controlled by changing catalyst (entry 2-5)
- chirality is conserved in reaction

Table 2. Transition Metal-Catalyzed Intramolecular [5 + 2] Cycloadditions of Vinylcyclopropanes and Allenes

	Vinylcyclopropane-Allene[a] 1	Cycloadduct(s), Yield 2	Conditions, Time
1.		 89-96% (See Table 1)	A, 5 h
2.	**a**: R = H	68% (**4a** : **5a** = 1.1 : 1)	B, 10 h
3.	**a**: R = H	83% (**4a** : **5a** = >20 : 1)	C, 3.5 h
4.	**b**: R = Me	92% (**4b** : **5b** = 2 : 1)	D, 1 h
5.	**b**: R = Me	90% (**4b** : **5b** = >10 : 1)	E, 0.75 h
6.	 **a**: R = R' = Me	 93%	F, 2 h
7.	**b**: R = *t*-Bu, R' = H	91%	F, 1 h
8.	**b**: R = *t*-Bu, R' = H	88%	D, 1 h
9.		 85%	D, 0.5 h
10.		 90%	F, 0.75 h
11.		70%	G, 16 h

[a] E = CO_2Me. A: 0.2 mol % $RhCl(PPh_3)_3$, $PhCH_3$, 100 °C, 1.0 M. B: 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 100 °C, 0.01 M. C: 5 mol % $[Rh(CO)_2Cl]_2$, DCE, 90 °C, 0.003−0.01 M. D: 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 0.01 M. E. 10 mol % $Rh(CO)_2Cl$, $PhCH_3$, 110 °C, 0.01 M. F: 5 mol % $[Rh(CO)_2Cl]_2$, $PhCH_3$, 100 °C, 0.01 M. G: 5 mol % $RhCl(PPh_3)_3$, 5 mol % AgOTf, $PhCH_3$, 100 °C, 0.01 M.

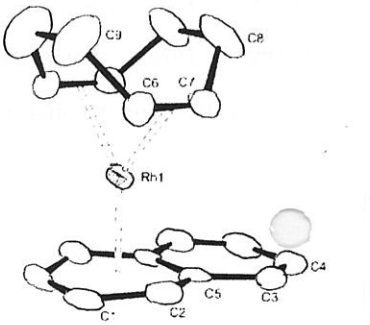
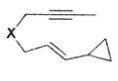
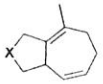


Figure 1. ORTEP diagram of $[(C_{10}H_8)Rh(cod)]^+SbF_6^-$ (**1**

Ellipsoids drawn at 50% probability level.

new Rh catalyst : $[(C_{10}H_8)Rh(cod)]^+SbF_6^-$ P. A. Wender et al. *Angew. Chem. Int. Ed.* **2002**, *41*, 4550.

Table 1. Performance of complex **1** with a variety of alkyne vinylcyclopropanes and alkene vinylcyclopropanes.

Entry	Substrate, Catalyst	Cycloadduct, Yield	Conditions[a]
	 **2** X = $C(CO_2Me)_2$	 **3**	
1	2 mol % **1**	> 99 %[b]	15 min, RT, 0.15 M
2	1 mol % $[[RhCl(CO)_2]_2]$	89 %	PhMe, 3 h, 110 °C, 2.0 M
3	10 mol % $[RhCl(PPh_3)_3]$	90–95 %	TFE,[c] 19 h, 55 °C, 0.01 M
	4 X = NTs	**5**	
4	5 mol % **1**[d]	90 %	65 min, RT, 0.20 M

	18 X = NTs	**19**	
15	5 mol % **1**	76 %	19 h, 60 °C, 0.03 M
	20 X = $C(CO_2Me)_2$	**21a**, **21b**	
16	10 mol % **1**	75 % (**a**)	10 h, 70 °C, 0.03 M
17	5 mol % $[RhCl(PPh_3)_3]$, AgOTf	78 % (**b**)	PhMe, 15 h, 110 °C, 0.01 M
18	5 mol % $[RhCl(PPh_3)_3]$, AgOTf	67 %, 2.3:1 (**a**:**b**)	PhMe, 66 h, 85 °C, 0.01 M

[a] Unless otherwise indicated, each reaction was run in a tightly capped vial at the indicated temperature, catalyst load, and concentration in 1,2-dichloroethane. [b] Found 85 % with BF_4^- anion. [c] TFE = 2,2,2-trifluoroethanol. [d] Catalyst added in four aliquots. [e] 1-g scale, found 96 % with BF_4^- anion.

streo- and regioselectivity of cycloadditions of 2-substituted-1-vinylcyclopropanes

P. A. Wender et al. *Org. Lett.* **1999**, *1*, 2089.

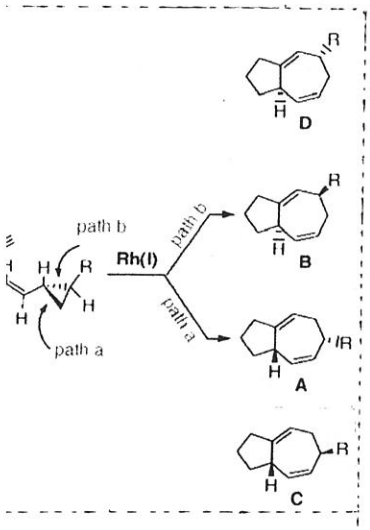
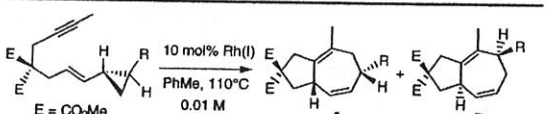


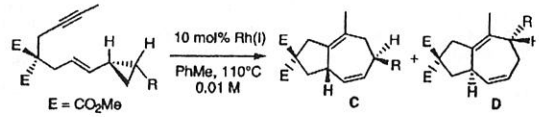
Table 1. *trans*-2-Substituted-1-vinylcyclopropanes



Entry	R	Catalyst[a]	Time	Product	Yield[b]	A : B : (X)[c]
1	CH_2OH (**3**)	$Rh(PPh_3)_3OTf$	1.5 h	**4**	96%	1 : 0
2	"	$[Rh(CO)_2Cl]_2$	0.5 h	**4**	86%	2.3 : 1
3	CH_2OAc (**5**)	$Rh(PPh_3)_3OTf$	2 h	**6**	92%	1 : 0
4	"	$[Rh(CO)_2Cl]_2$	1.5 h	**6**	85%	2.5 : 1
5	CH_2OTBS (**7**)	$Rh(PPh_3)_3OTf$	1 h	**8**	95%	1 : 0
6	"	$[Rh(CO)_2Cl]_2$	1 h	**8**	86%	3.5 : 1
7	CHO (**9**)	$Rh(PPh_3)_3OTf$	16 h	–	decomp.	-----
8	"	$[Rh(CO)_2Cl]_2$	0.5 h	**10**	68%	0 : 1 : (1.4)
9[d]	"	$[Rh(CO)_2Cl]_2$	8 h	**10**	98%	0 : 1
10	CO_2H (**11**)	$Rh(PPh_3)_3OTf$	2 h	**12**	69%	4 : 1 : (1)
11	"	$[Rh(CO)_2Cl]_2$	2 h	**12**	73%	1 : 22
12	CO_2Me (**13**)	$Rh(PPh_3)_3OTf$	1 h	**14**	81%	20 : 1
13	"	$[Rh(CO)_2Cl]_2$	1 h	**14**	93%	1 : 11

[a] $Rh(PPh_3)_3OTf$ = $Rh(PPh_3)_3Cl$ + AgOTf (1:1). [b] isolated yields. [c] ratios determined by g.c. analysis, (X) refers to isomerized byproducts. [d] reaction at 55°C

Table 2. *cis*-2-Substituted-1-vinylcyclopropanes



Entry	R	Catalyst[a]	Time	Product	Yield[b]	C : D[c]
1	CH_2OH (**15**)	$Rh(PPh_3)_3OTf$	1 h	**16**	84%	3.5 : 1
2	"	$[Rh(CO)_2Cl]_2$	1 h	**16**	93%	9.0 : 1
3	CH_2OTBS (**17**)	$Rh(PPh_3)_3OTf$	2 h	**18**	81%	1 : 0
4	"	$[Rh(CO)_2Cl]_2$	1 h	**18**	96%	1 : 0
5	CHO (**19**)	$Rh(PPh_3)_3OTf$	4 h	–	decomp.	-----
6[d]	"	$[Rh(CO)_2Cl]_2$	15 h	**20**	92%	0 : 1
7	CO_2Me (**21**)	$Rh(PPh_3)_3OTf$	2 h	**22**	95%	6.4 : 1
8	"	$[Rh(CO)_2Cl]_2$	2 h	**22**	98%	1.5 : 1

[a] $Rh(PPh_3)_3OTf$ = $Rh(PPh_3)_3Cl$ + AgOTf (1:1). [b] isolated yields. [c] ratios determined by g.c. analysis. [d] reaction at 55°C

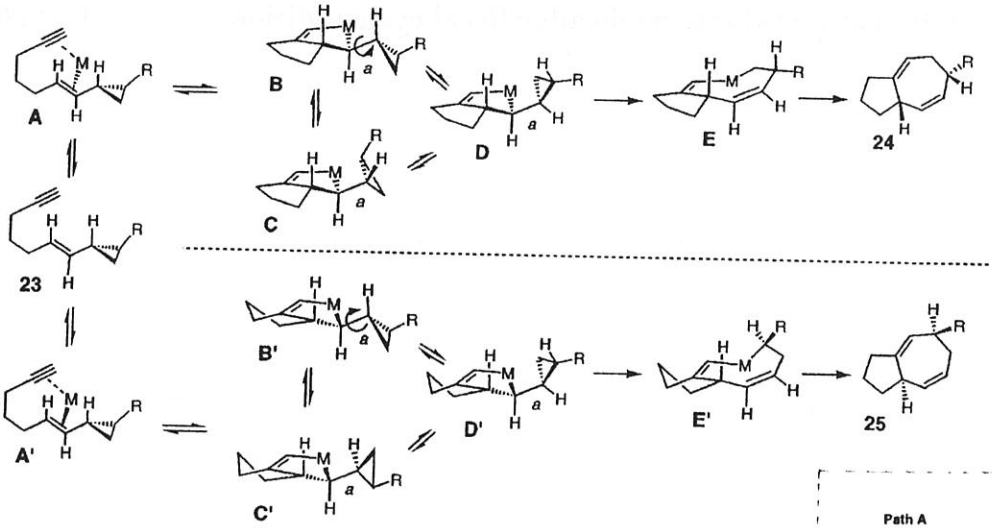
path a

path b

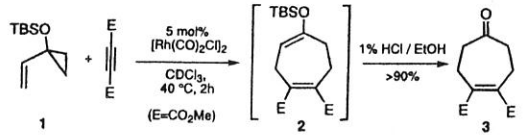
$Rh(PPh_3)_3Cl$: path a

$[Rh(CO)_2Cl]_2$: path b

Scheme 3

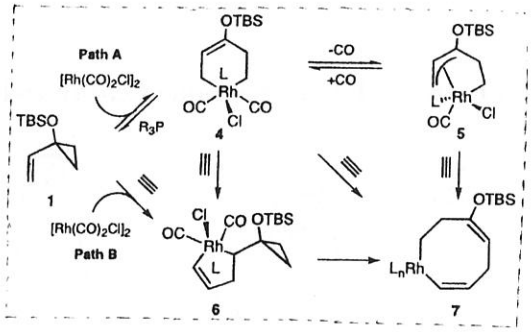


(b) intermolecular reaction (π -component : alkyne, allene)

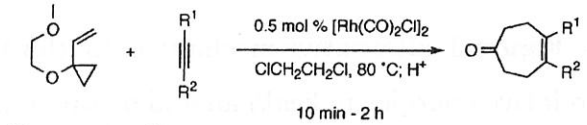


P. A. Wender et al. *J. Am. Chem. Soc.* **1998**, *120*, 10976.

proposed mechanism



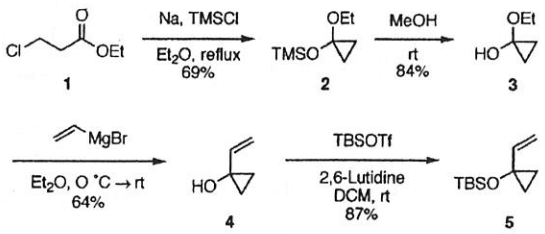
new and pracrical 5C component



5C component up to 100 mmol | 2C component 1.2-1.3 equiv | 75-97%

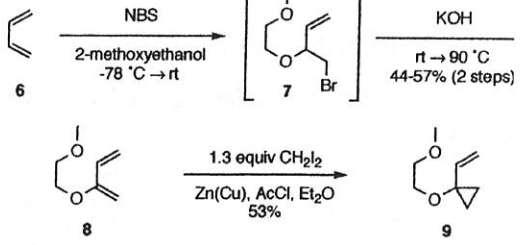
P. A. Wender et al. *Org. Lett.* **2000**, *2*, 1609.

Scheme 1



- no decomposition (temp : 40 to 80 ℃)
- 6-fold increase in reaction rate using 10-fold decrease in catalyst loading
- reactive functionarity are tolerated, it can be conducted on large scale

Scheme 2



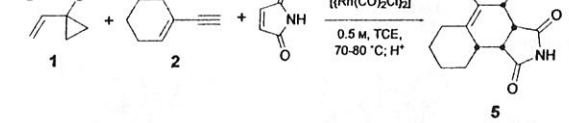
further studies for application of this new 5C component

(1) Serial [5+2]/[4+2] cycloadditions

P. A. Wender et al

Angew. Chem. Int. Ed. **2001**, *40*, 3895.

Table 3. Scale-up study of the [5+2]/[4+2] cycloadditions.



Entry	Mol % Catalyst	t [h]	Scale	Yield [%][a]
1	2 mol %	1 h	1 mmol	92
2	1 mol %	4 h	1 mmol	90
3	1 mol %	6 h	10 mmol	92
4	1 mol %	6 h	100 mmol	91

a] Yields of isolated products.

(2) [5+2] cycloadditions of allene and vinylcyclopropane

P. A. Wender et al. *J. Am. Chem. Soc.* **2005**, *127*, 6530.

Scheme 1. For Details See Tables 1 and 2

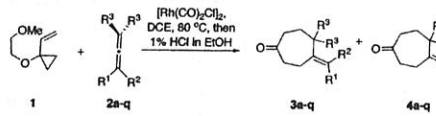


Table 1. Cycloadditions of VCP 1 with Various Alkynyl-Substituted Allenes

Entry	R^1	R^2	R^3	T/h	Yield(%)[c] (3a-k:4a-k)
1	≡—TMS	H	Me	1	95 (1:1.8)
2	≡—Ph	H	Me	1	83 (1:1.6)
3	≡—Ph	CH_2CO_2Et	Me	1	92 (1:2)
4	≡—Ph	C_4H_9	Me	3	80 (2:3)[b]
5	≡—TMS	C_4H_9	Me	1	80 (2:5)
6	≡—CH_2CH_2OH	C_4H_9	Me	1	65 (1:1.2)
7	≡—CH_2OMe	H	Me	5	45 (1:1.3)
8	≡—CH_2NBn_2	C_4H_9	Me	1	22 (1:2.2)
9	≡—H	CH_2CO_2Et	Me	24	n. r.[a]
10	≡—H	C_4H_9	Me	36	n. r.[a]
11	≡—Ph	H	H	36	n. r.[a]

[a] n.r. = no reaction. [b] Diastereomers could not be separated by column chromatography. [c] Isolated yields.

Table 2. Cycloadditions of VCP 1 with Other Functionally Substituted Allenes 2

entry	R^1	R^2	R^3, R^3	t/h	yield (%)[c] (3l-q:4l-q
1	≡—Ph	H	Me	1	69 (2:1)[b]
2	CO_2Et	Me	Me	36	n. r.[a]
3	CN	H	Me	1	99 (2:3)
4	CN	H	H	36	n. r.[a]
5	CN	H		1	99 (5:2)
6	CN	H	H/Me	1	52 (1:2)[b]

[a] n.r. = no reaction. [b] Diastereomers could not be separated by colu chromatography. [c] Isolated yields.

- additional coordinating group
- not react with alkynyl group

Mechanism of $[Rh(CO)_2Cl]_2$–catalysed intermolecular [5+2] cycloaddition

JACS. **2004**, *126*, 9154.

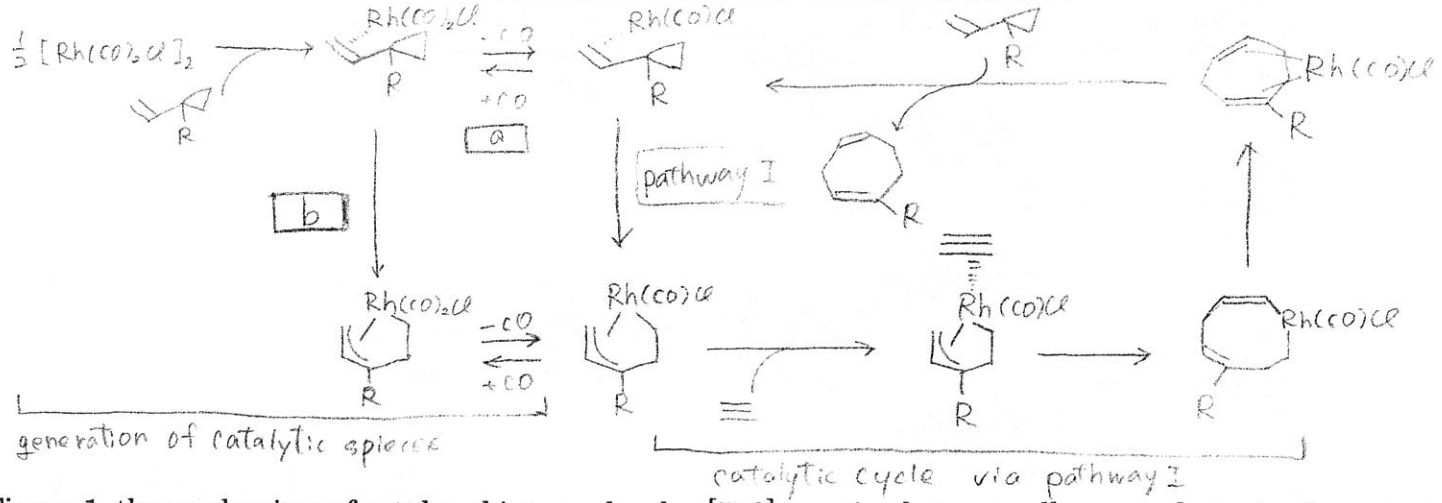


Figure 1. the mechanism of catalyzed intermolecular [5+2] reaction between alkynes and vinylcyclopropane

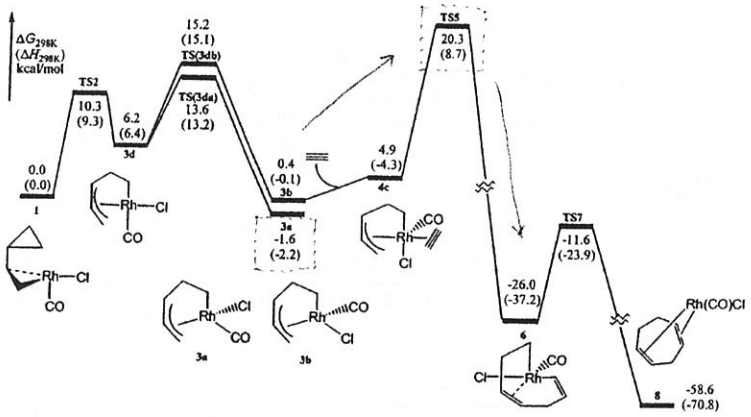


Figure 2. The energy surface of the catalytic cycle of (5 + 2) reaction.[4]

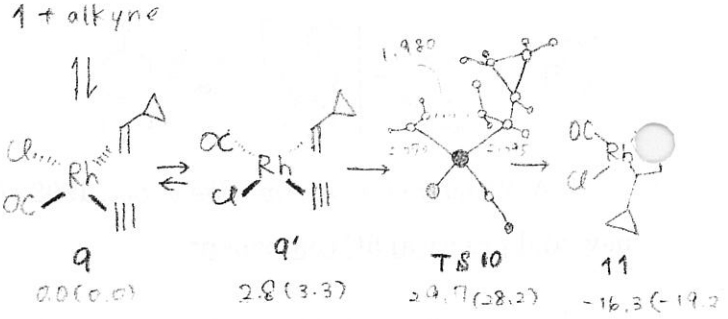


Figure 3. alternative mechanism (pathway II)
(relative energies in kcal/mol and distanaces in Å)

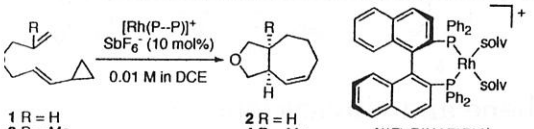
activation free energy of oxidative coupling step pathway I 21.9 kcal/mol pathway II 29.7 kcal/mol

(c) recent developmemt

(i) asymmetric catalysis of [5+2] cycloaddition of vinylcyclopropanes and π-systems

P. A. Wender et al. *J. Am. Chem. Soc.* **2006**, *128*, 6302.

able 1. Screening of Ligands[d]



entry	substrate, ligand (P—P)	temperature	conversion	ee
1	1, (*S,S*)-DIOP	rt	80%	28%
2	1, (*R,R*)-CARBOPHOS	70 °C	>99%	-51%[a]
3	1, (*R,R*)–Et,Et-DUPHOS	70 °C	>99%	-23%[a]
4	1, (*S,S*)-BDPP	70 °C	>99%	-44%[a]
5	1, (*R*)-BINAP[b]	rt	5%	69%
6	1, (*R*)-BINAP	50 °C	>99% (96%)[c]	60%
7	1, (*R*)-*tol*-BINAP[b]	rt	15%	66%

[a] Opposite sense of induction. [b] 10 mol % excess ligand was used [c] enthetical value is GC yield. [d] DCE = 1,2-dichloroethane. Conversior ee were measured by GC.

heme 1. Proposed Model for Stereocontrol

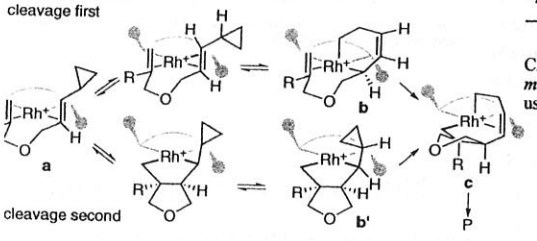
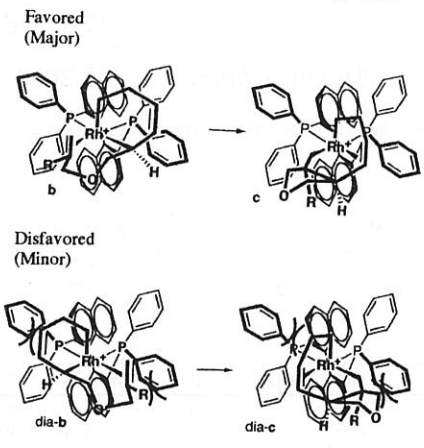


Table 2. Asymmetric [5 + 2] Cycloaddition Reactions[e]

entry	substrate	cycloadduct	conditions	yield, ee
1	**7** R = Me	**8** R = Me	70 °C, 2 d, 0.05 M	72%, >95%[a]
2	**9** R = CH_2OBn	**10** R = CH_2OBn	70 °C, 2 d, 0.01 M	80%, >99%[b]
3	**11** R = H	**12** R = H	50 °C, 1.5 d, 0.03 M	73%, 52%[c]
4	**13**	**14**	40-60 °C, 8 d, 0.01 M	90%, 96%[c]
5	**15**	**16**	70 °C, 6 d, 0.01 M	92%, 95%[c]
6	**17**	**18** X = TsN	rt, 2 d, 0.01 M	87%, 56%[b]
7	**19**	**20** X = O	70 °C, 2 d, 0.01 M	95%,[d] 22%[a]

[a] Determined by GC. [b] Determined by HPLC, *i*-PrOH/hexane eluent, CHIRALPAK AD column. [c] Determined by GC following treatment with *m*-CPBA. [d] Conversion determined by GC; 10 mol % excess BINAP was used. [e] Conditions: 10 mol % [Rh((*R*)-BINAP)]+ SbF_6^-. E = CO_2Me.

Scheme 2. Stereochemistry-Determining Steps



(ii) computationally designed two component [5+2+1] cycloaddition of ene-vinylcyclopropane and CO

P. A. Wender et al. *J. Am. Chem. Soc.* **2007**, *129*, 10060.

Scheme 1. Rationale for the Two-Component [5+2+1] Reaction

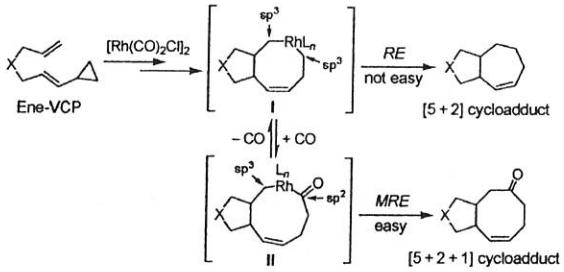
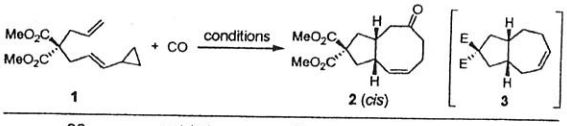


Table 1. Optimization Studies of the [5+2+1] Cycloadditions



entry	CO [atm]	catalyst [mol %]	T [°C]	solvent	concn [M]	t [h]	yield [%]
1	0	10% $[Rh(CO)_2Cl]_2$	110	toluene	0.05	24	10[a]
2	1	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	5	44[b]
3	4	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	24	8
4	0.2[c]	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	5	70[d]
5	0.2	5% $[Rh(CO)_2Cl]_2$	60	dioxane	0.05	48	17
6	0.2	5% $[Rh(CO)_2Cl]_2$	90	dioxane	0.05	5	70
7	0.2	5% $[Rh(CO)_2Cl]_2$	100	dioxane	0.05	5	61
8	0.2	5% $[Rh(CO)_2Cl]_2$	80	DCE	0.05	5	62[e]
9	0.2	5% $[Rh(CO)_2Cl]_2$	80	toluene	0.05	12	14
10	0.2	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.01	5	68
11	0.2	5% $[Rh(CO)_2Cl]_2$	80	dioxane	0.20	5	34
12	0.2	10% $[Rh(CO)_2Cl]_2$	80	dioxane	0.05	5	72
13	1	10% $RhCl(PPh_3)_3$	80	dioxane	0.05	17	N.R.
14	1	10% $RhCl(PPh_3)_3$ + 10% AgOTf	80	dioxane	0.05	18	23[f]
15	1	5% $[Rh(CO)_2Cl]_2$ + 10% AgOTf	80	dioxane	0.05	13	7

[a] Accompanied with a [5+2] cycloadduct **3** (59%); see Supporting Information for details. [b] Cis/trans = 5:1. [c] Conditions: 0.2 atm CO + 0.8 atm N_2. [d] Cis/trans > 20:1. [e] Cis/trans = 4:1. [f] Cis/trans = 1:1.

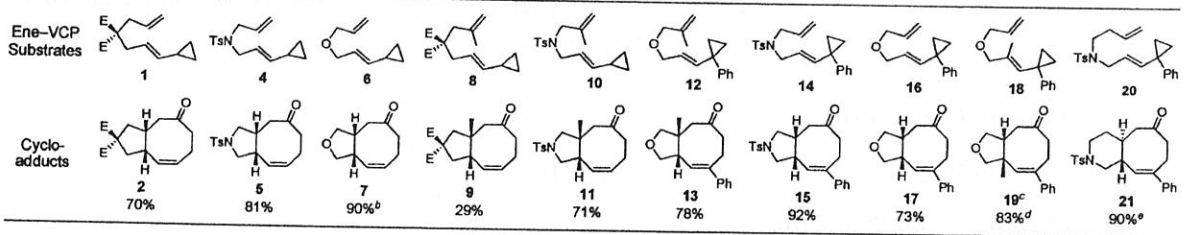
computed energy (X = CH_2)

RE (reductive elimination) : 25 ~ 30 kcal/mol

CO insertion step : 13 ~ 14 kcal/mol

MRE (migratory RE) : 23 ~ 24 kcal/mol

Table 2. Rh(I)-Catalyzed [5+2+1] Cycloaddition Reactions of Ene-vinylcyclopropane Substrates and CO[a]



[a] E = CO_2Me. Isolated yields were reported unless otherwise indicated. [b] GC yield. Isolated yield is 44% owing to the volatility of the product. [c] Confirmed by X-ray analysis. [d] A [5+2] product was obtained in 11% yield. [e] Combined yield of diastereomers (trans/cis = 5:1).

(iii) origins of differences in reactivities of alkenes, alkynes, and allenes

P. A. Wender et al. *J. Am. Chem. Soc.* **2008**, *130*, 2378.

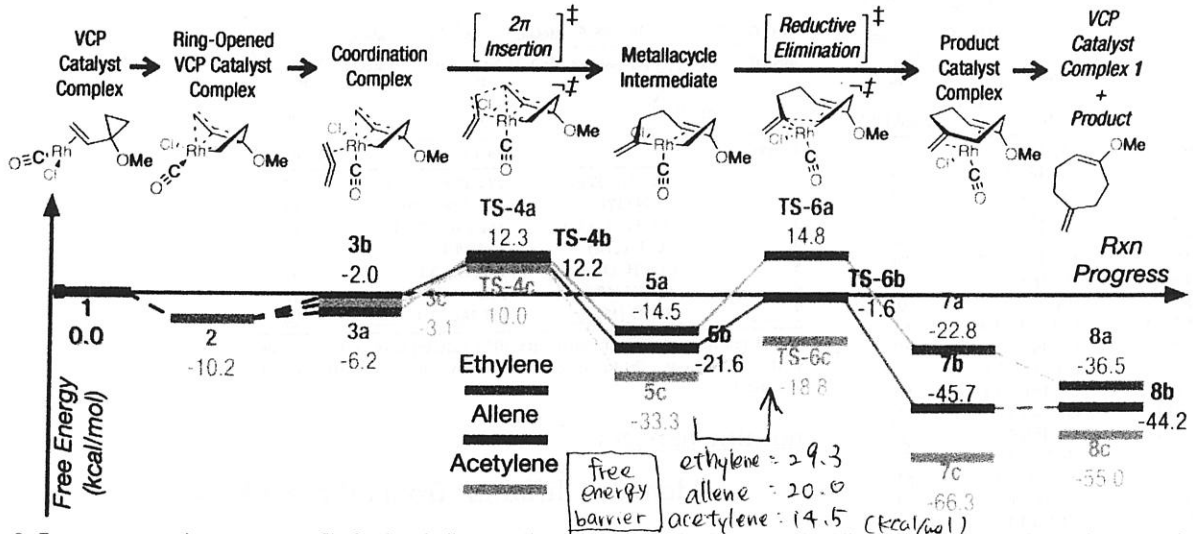


Figure 2. Free energy reaction progress profile for the Rh-dimer-catalyzed intermolecular (5 + 2) cycloadditions involving acetylene, ethylene, and allene.

: highest energy transition state
allene, acetylene : 2π-insertion
ethylene : reductive elimination

- allene and acetylene

  RE step was assisted by developing ligand π-Rh coordination.

- ethylene

  RE step is unassisted because of the lack of π-system.

· exergonic at 5 → 7
ethylene : 8.3
allene : 24.1
acetylene : 33.0
(kcal/mol)

2-1 Ru catalysed [5+2] cycloaddition

scope and limitation

B. M. Trost et al. *Chem. Eur. J.* **2005**, *11*, 2577.

Table 1. (Continued)

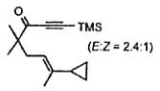
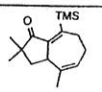
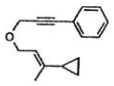
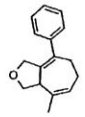
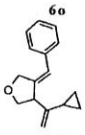
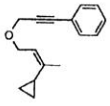
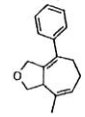
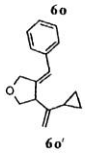
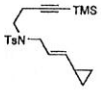
Entry	Substrate	Product	Yield [%]
13	 (*E*:*Z* = 2.4:1) **5m**	 **6m** +  **6m'**	82 (3.7:1)
15	 **5o**	 **6o** +  **6o'**	82 (6.2:1)

Table 1. (Continued)

Entry	Substrate	Product	Yield [%]
16	 **5o'**	 **6o** +  **6o'**	78 (1:14)
18[b]	 **5q**	 **6q**	67

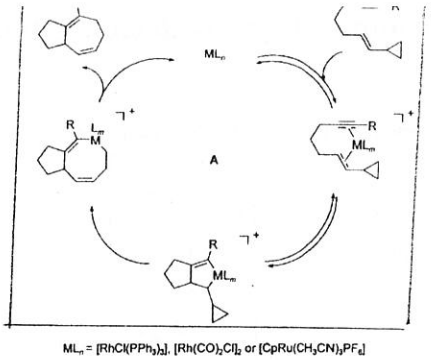
this Ru-catalysed reaction most likely proceeds according to mechanism A

- Alder-ene reaction : ruthenacyclopentene accommodates all observations
- observed in entry 13, 15, 16

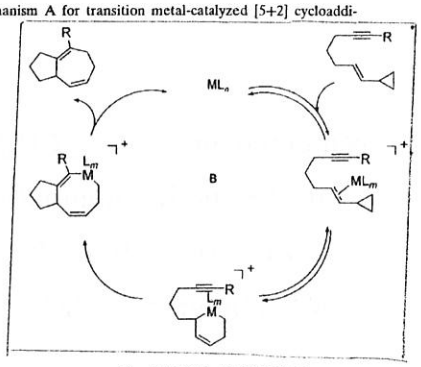
  β -hydride elimination

  Z-olefine favors β -hydride elimination

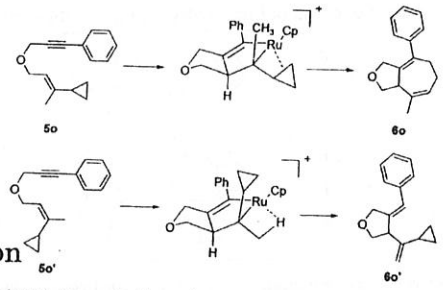
  remained cyclopropane moiety
- difference in tether length → no reaction (5w ~ 5z)



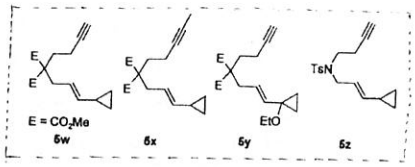
Scheme 2. Mechanism A for transition metal-catalyzed [5+2] cycloadditions.



Scheme 3. Mechanism B for transition metal-catalyzed [5+2] cycloadditions.



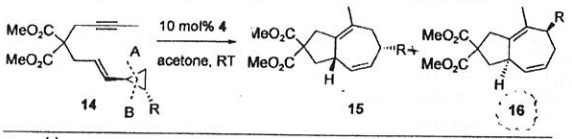
Scheme 4. Proposed ruthenacyclopentenes derived from *trans*- and *cis*-olefins **5o** and **5o'**.



streo- and regioselectivity of cycloadditions of 2-substituted-1-vinylcyclopropanes

B. M. Trost et al. *Chem. Eur. J.* **2005**, *11*, 2577.

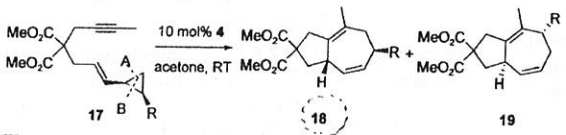
Table 3. Regioselectivity of the cycloaddition of *trans* substrates.



Entry[a]	R	15:16[b]	Yield [%]
1	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2	90
2[c]	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2.5	88
3[d]	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2.3	80
4[e]	CO_2CH_3 (**14a**)	**15a**:**16a** 1:2	78
5	$COCH_3$ (**14b**)	**15b**:**16b** 2:1	83
6[d]	$COCH_3$ (**14b**)	**15b**:**16b** 1:1.2	88
7	COOH (**14c**)	**15c**:**16c** 1:3	78
8[f]	COOH (**14c**)	NA	0
9	(*E*)-CH=CH-CHO (**14d**)	**15d**:**16d** 1:1.6	82
10	(*E*)-CH=CH-CO_2Et (**14e**)	**15e**:**16e** 1:2.5	87
11	C≡CH (**14f**)	**15f**:**16f** 1:2.5	85
12	CH_2OTBS (**14g**)	**15g**:**16g** 1.5:1	90
13	CH_2OTIPS (**14h**)	**15h**:**16h** 3:1	81
14[c]	CH_2OTIPS (**14h**)	**15h**:**16h** 2:1	88
15	CH_2O-4-Br-Bz (**14i**)	**15i**:**16i** 1.6:1	71
16	CN (**14j**)	**15j**:**16j** 1:1.9	87
17	SO_2Ph (**14k**)	**15k**:**16k** 1:1	80
18	CHO (**14l**)	**15l**:**16l** 1:15	78

[a] All reactions performed with 10% catalyst by using 0.1–0.2 M substrate in acetone unless otherwise noted. [b] Ratio determined by proton NMR. [c] Reaction performed in DMF. [d] Reaction performed in the presence of 10–15% $In(OTf)_3$. [e] Reaction performed in the presence of 10% HMPA. [f] Reaction performed in the presence of 10% Bu_4NOH.

Table 4. Regioselectivity of cycloaddition of *cis* substrates.



Entry[a]	R	18:19[b]	Yield [%]
1	CO_2CH_3 (**17a**)	**18a**:**19a** > 20:1	87
2	CN (**17b**)	**18b**:**19b** >20:1	81
3	CH_2OTIPS (**17c**)	**18c**:**19c** >20:1	85
4	CH_3 (**17d**)	**18d**:**19d** >20:1	87
5	$COCH_3$ (**17e**)	**18e**:**19e** 2:1	93
6	C≡CH (**17f**)	NA	NR
7	CHO (**17g**)	**15l**:**16l**[c] 1:12	82

[a] All reactions were performed with 10% catalyst using 0.1–0.2 M substrate in acetone. [b] Ratio determined by proton NMR. [c] See Scheme 9.

notable aspects

- aldehyde : different from all the others
- in trans : bond energy appears to be important
- in cis : steric effects dominates

comparison to Rh catalyst

- aldehyde substrate

Rh : not same product

Ru : same product

- siloxy substrate

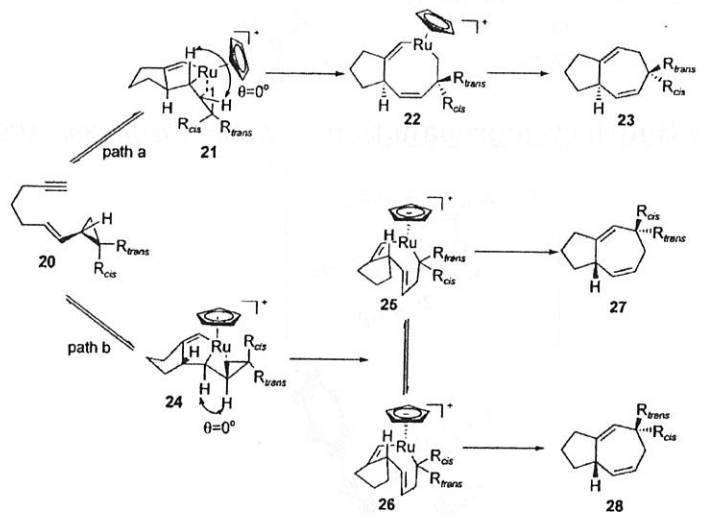
Rh : exclusively 15 ($(PPh_3)_3RhCl$)

Ru : equimolar mixture of 15,16

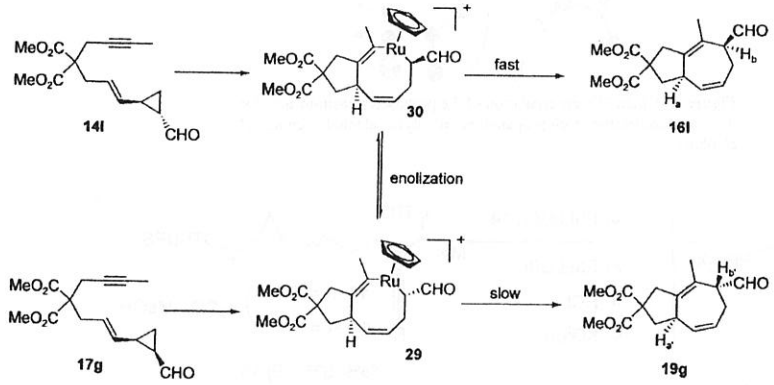
- ester substrate

Rh : effect regioselectivity

Ru : not effect regioselectivity

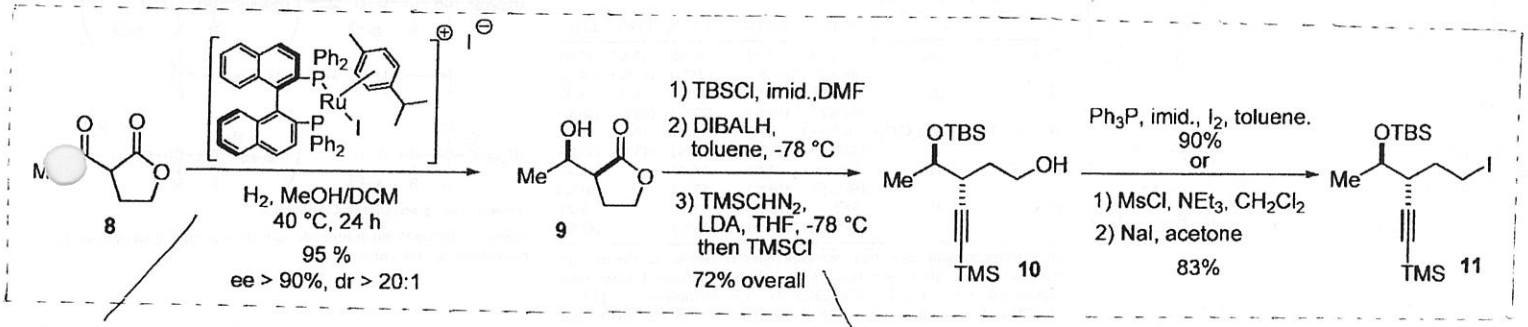


Scheme 8. Proposed mechanistic rationale for the regio- and diastereoselectivity of cyclopropane ring opening for disubstituted cyclopropanes.



Scheme 10. Proposed mechanism to account for selective formation of **16l**.

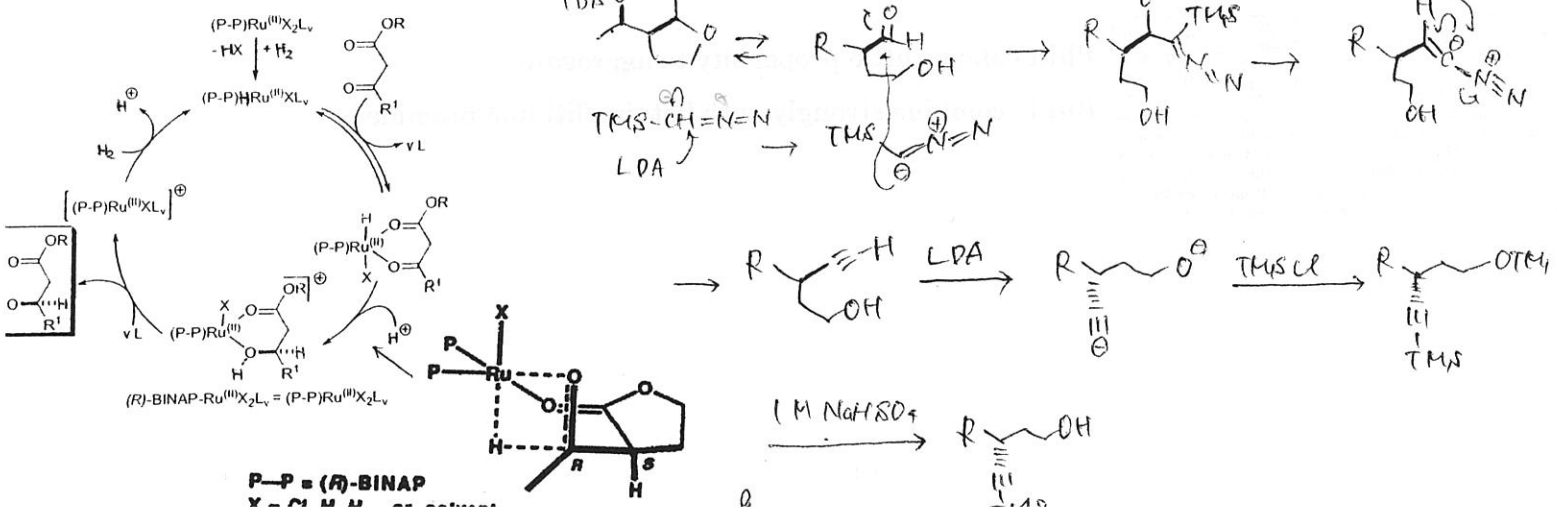
3. Total synthesis of Pseudolaric Acid B

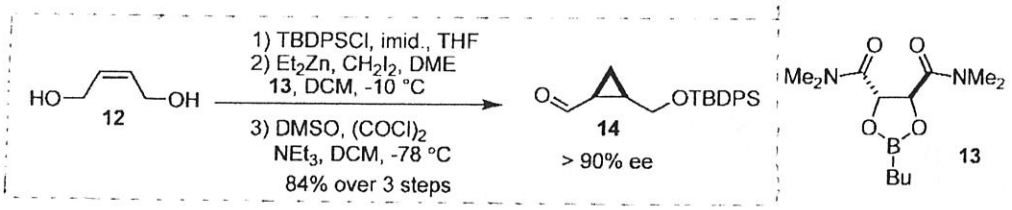


Dynamic Kinetic Resolution

Tetrahedron Asymmetry, 1990, 1, 1

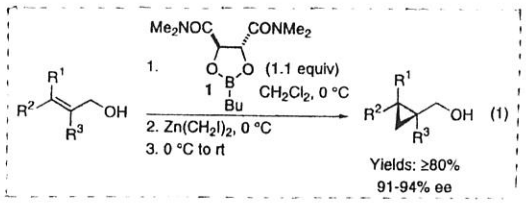
LDA = 3.5eq.
TMSCHN2 = 1.2eq.
TMSCl = 4.5eq.

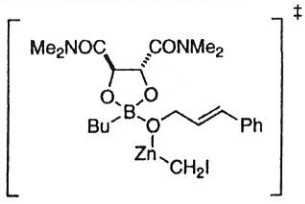




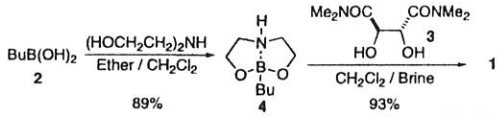
Charette modification of the Simmons-Smith cyclopropanation

J. Am. Chem. Soc. **1998**, *120*, 11943.





Scheme 1



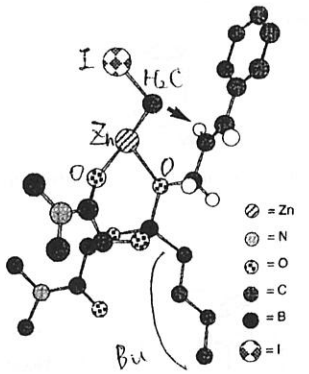
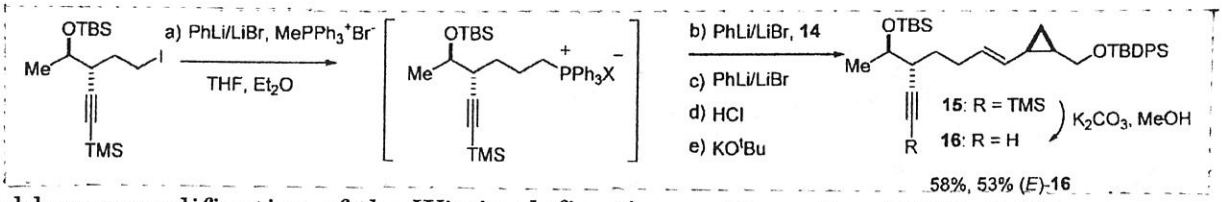
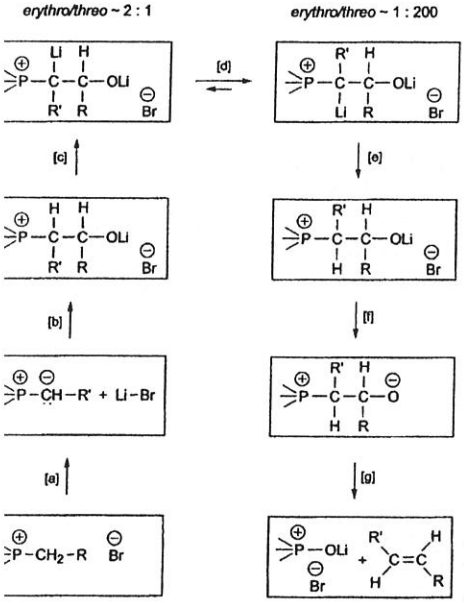


Figure 1. Chem 3D representation of the proposed transition state for the enantioselective cyclopropanation of allylic alcohols (cinnamyl alcohol).



Schlosser modification of the Wittig olefination

Chem. Eur. J. **2003**, *9*, 570.

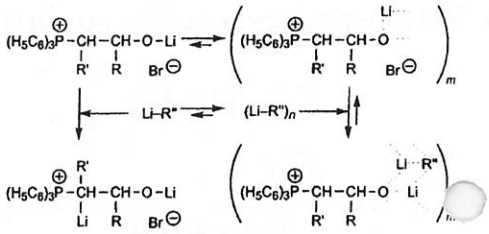


me 2. The multistep, if one-pot protocol for *trans*-selective olefin ation. a) Lithium bromide containing phenyllithium (or any other nolithium) in THF and diethyl ether. b) Aldehyde R–CH=O. c) Lith- bromide containing phenyllithium in diethyl ether. d) Either 1 min at or 30 min at −75 °C. e) Hydrogen chloride (1.0 equiv) in diethyl ether 75 °C. f) Potassium *tert*-butoxide. g) Some 15 min at −25 °C.

Table 1. *trans*-Selective Wittig reactions involving betaine-ylides prepared from ylides $(H_5C_6)_3P^{\oplus}-^{\ominus}CH-R'$ and aldehydes R–CH=O: *Z*/*E* ratios and, in parentheses, yields of olefins.[a]

R	R′	LiC_4H_5	$LiCH_3$	LiC_4H_9	LIS[b]	LIT[c]
$H_{13}C_6$	C_4H_9	< 0.5:99.5	3:97	50:50	33:67	17:83
		(88 %)[d]	(87 %)	(92 %)	(86 %)	(84 %)
H_5C_6	C_3H_7	< 0.5:99.5	1.5:98.5	12:88	6:94	23:77
		(88 %)[d]	(92 %)	(77 %)	(63 %)	(60 %)
$H_2C=C-CH_3$[e]	$(CH_2)_2C_6H_5$	< 0.5:99.5	2:98	16:84	12:88	36:64
		(58 %)[d]	(59 %)	(57 %)	(45 %)	(42 %)
$(H_3C)_2CH$	C_5H_{11}	< 0.5:99.5	2:98	16:84	–	13:87
		(66 %)[f]	(59 %)	(57 %)		(62 %)
$(H_3C)_3C$	C_5H_{11}	94:6	98:2	97:3	–	76:24
		(59 %)	(63 %)	(56 %)		(42 %)

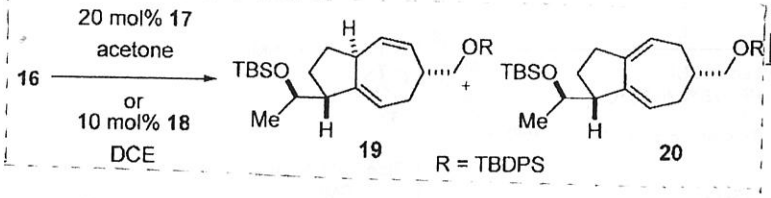
[a] Standard working procedure: see Experimental Section. At the decisive stage of betaine ylide formation, the tetrahydrofuran/diethyl ether ratio approached 1:1. [b] LIS = $LiCH(CH_3)C_2H_5$ (*sec*-butyllithium). [c] LIT = $LiC(CH_3)_3$ (*tert*-butyllithium). [d] The same limit of stereoselectivity and virtually the same yields were attained when the reaction was performed in an approximate 7:1:2 (*v*/*v*/*v*) mixture of tetrahydrofuran, diethyl ether, and cyclohexane, respectively. [e] 2-Methyl-2-propenal (methacroleine). [f] A *Z*/*E* ratio of 3:97 and a yield of 65 % were found when the reaction was performed in an approximate 7:1:2 (*v*/*v*/*v*) mixture of tetrahydrofuran, diethyl ether, and cyclohexane, respectively.

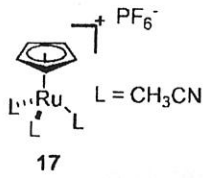


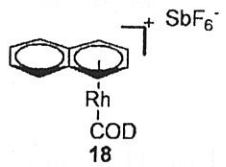
Scheme 4. Betaine/lithium bromide adducts sequestering alkyllithium by heteroaggregate formation.

PhLi : shows little propensity to aggregate

BuLi : combine strongly with betaine/lithium bromide







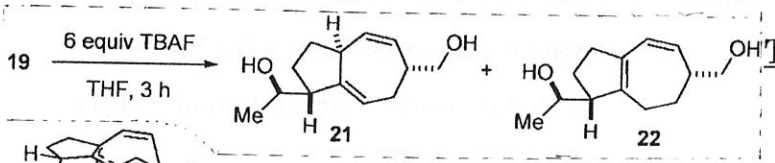
With **17**: 48% **19**, 15% **20**
With **18**: 88% **19**, < 5% **20**

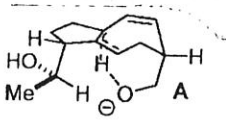
[5+2] cycloaddition

- cannot identify additive for modulating selectivity
- weak ligands : no effect
- stronger ligands : low turnover numbers

20 comes from C-H activation of Ru

using Rh catalyst, 19 was obtained exclusively

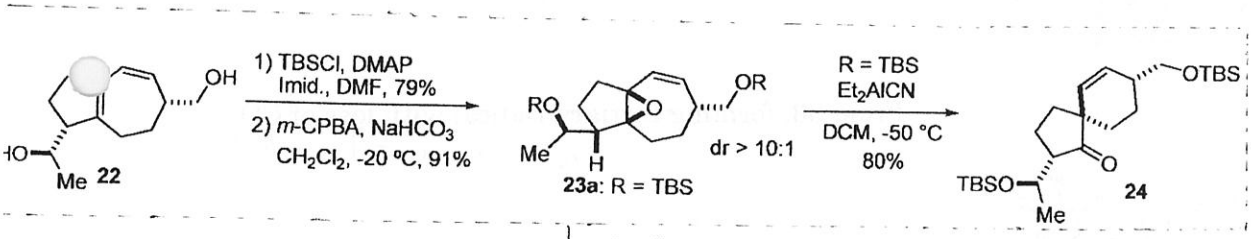


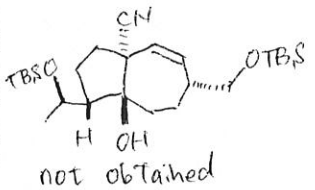


With 0.5 g MS 3Å/mmol TBAF: 80%, **21**:**22** = 1:1
With 1.0 g MS 3Å/mmol TBAF: 90%, **21**:**22** < 1:20

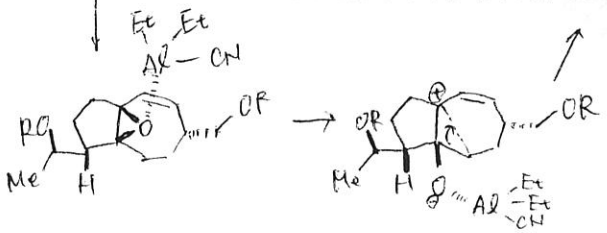
TBAF mediated isomerization

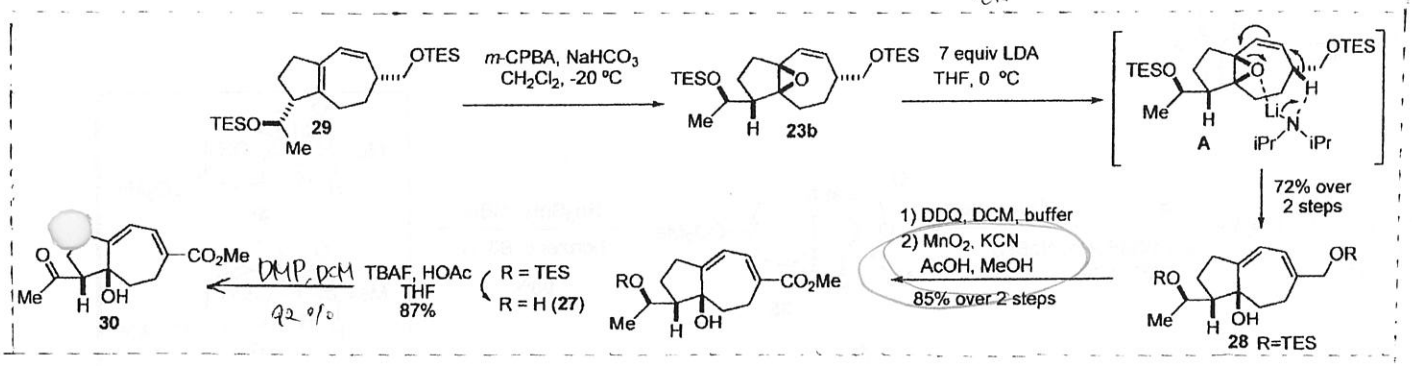
- acidic / basic condition : unsuccessful (no reaction or decomposition)
- activate diene system with Pd : no reaction
- in attempting deprotection of silylether group, isomerization occurred



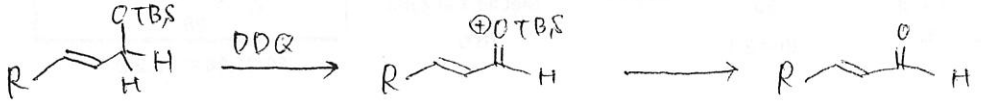


not obtained

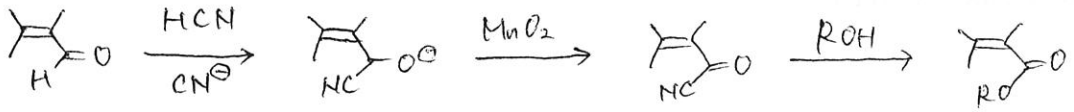


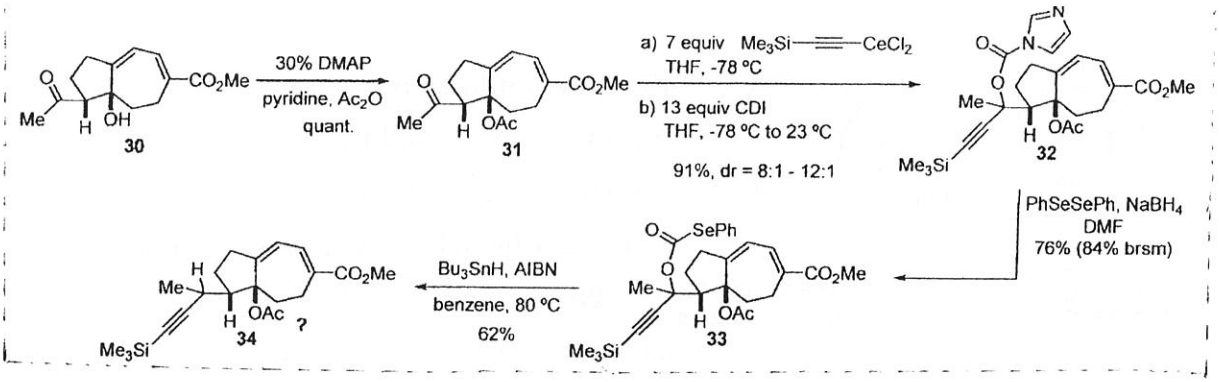


A Facile Oxidation/Deprotection of Electron Rich Silyl Ethers Using DDQ *Synlett*, **1998**, 915.



Oxidation of α,β-unsaturated aldehyde to ester *J. Am. Chem. Soc.* **1968**, *90*, 5616.

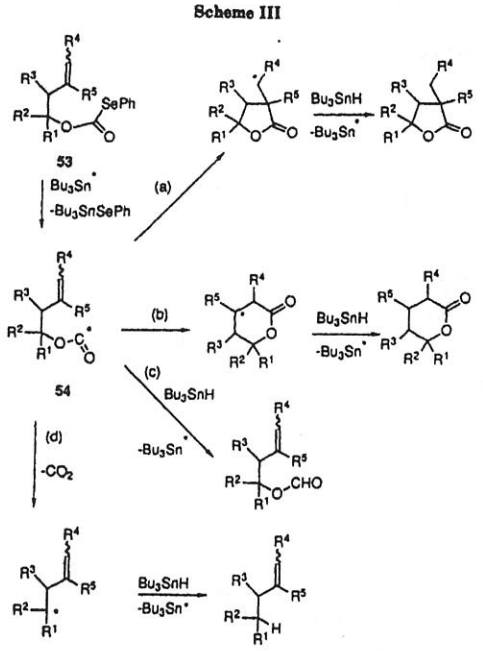




other conditions • initiate with BEt_3/O_2 : complex mixture

• activate conjugate system with $Yb(OTf)_3$: triene products (elimination of HOAc)

radical lactonization by *Se*-phenyl selenocarbonate *J. Org. Chem.* **1992**, *57*, 4696.

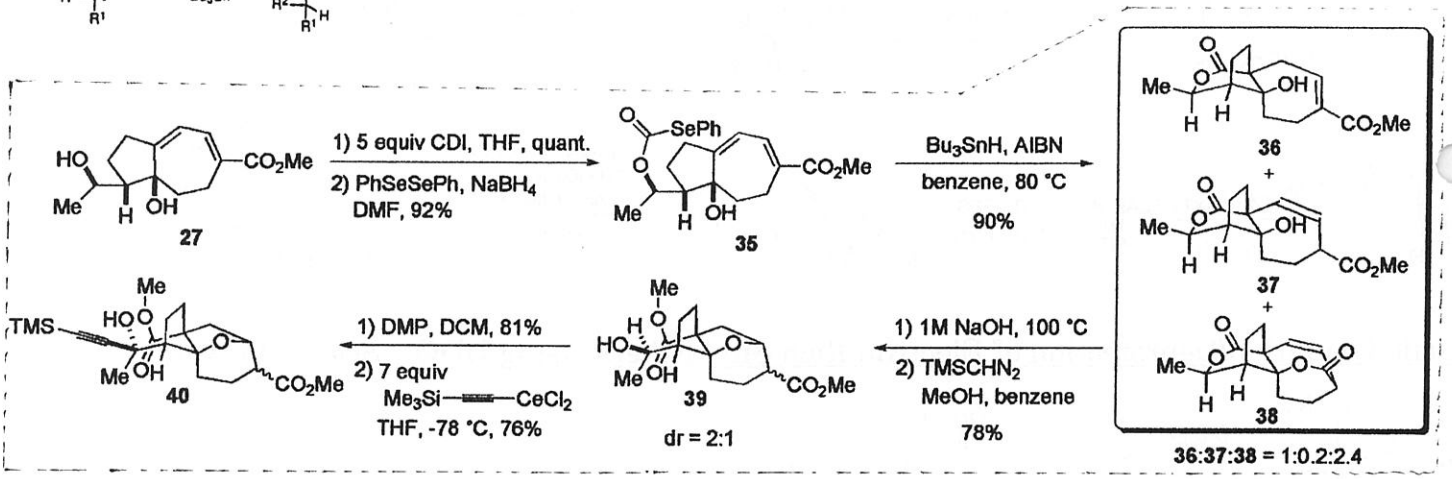


high regioselectivity favoring **exo addition**

(path (a) in scheme III)

From 33, forming tertiary radical with loss of CO

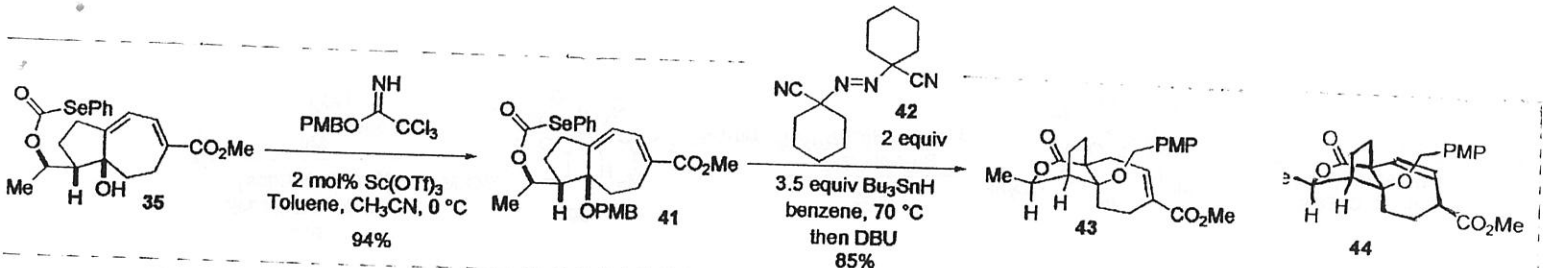
(path (d) in scheme III)



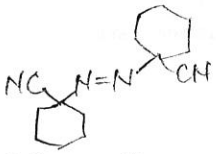
• opening of oxo bridge was unsuccessful.

• lactonization using Otera's catalyst did't occurred.
(because the formation of oxo brige pulls away the ester at C10 and the alcohol at C11.)

hoping that the mixture (36,37,38) could be transformed to single compound



entry	conditions	products
1	2.2 equiv Bu_3SnH, 0.6 equiv AIBN, benzene, 80 °C	<20% conversion
2	3 equiv Bu_3SnH, 1.2 equiv AIBN, benzene, 80 °C	5−15% **43**, 30−50% **44**, several impurities
3	3 equiv Bu_3SnH, 1.2 equiv AIBN, benzene, 80 °C, then DBU	56% **43**, several impurities
4	1.4 equiv Bu_3SnH, 0.2 equiv **42**, toluene, 110 °C	5−15% **43**, 30−50% **44**, 20−30% impurity
5	3.5 equiv Bu_3SnH, 2.0 equiv **42**, benzene, 70 °C, then DBU	85% **43**, 92% purity



42 : thermally more stable and cleaner continuous generation of radicals

TABLE IV

RATES OF DECOMPOSITION OF AZO NITRILES IN TOLUENE AT 80.2°

R-group	Concn. range, moles/liter	k (sec.$^{-1}$ × 10^4) range	No. of runs	Average deviation
CH_3-[a]	0.137–0.0463	1.72–1.60	3	0.06
C_2H_5-	.0274– .0154	0.94–0.80	4	.06
n-C_3H_7	.0181– .0143	1.74–1.65	2	.05
iso-C_3H_7	.0183– .0135	1.03–1.02	2	.01
n-C_4H_9	.0142	1.58	1	..
iso-C_4H_9	.0193– .0163	7.1	2	.00
C_6H_{11}[b]	.0165	0.083	1	..

[a] Not flushed with nitrogen. [b] Cyclohexanone.

Decomposition rates of cyclo-R(CN)C-N=N-C(CN)R-cyclo

cyclo-R	k_d (sec^{-1} × 10^4) at 80.0°C, in toluene
butyl	0.00173
pentyl	0.726
hexyl	0.063
heptyl	12.22
octyl	83.5
decyl	18.42

J. Am. Chem. Soc. **1949**, *71*, 2661.

J. Am. Chem. Soc. **1953**, *75*, 2078.

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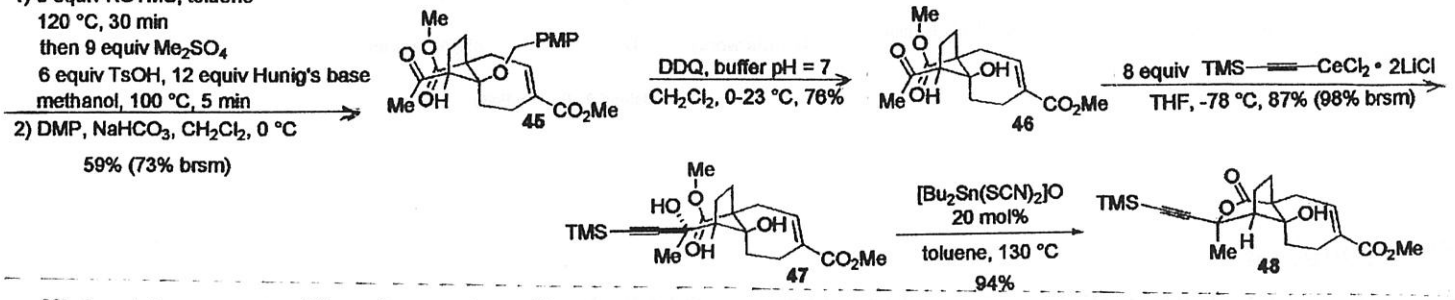
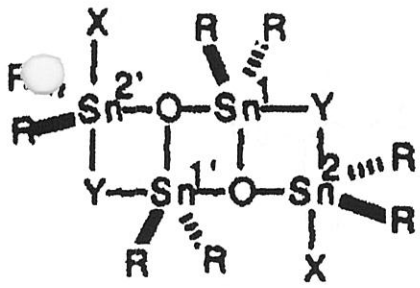


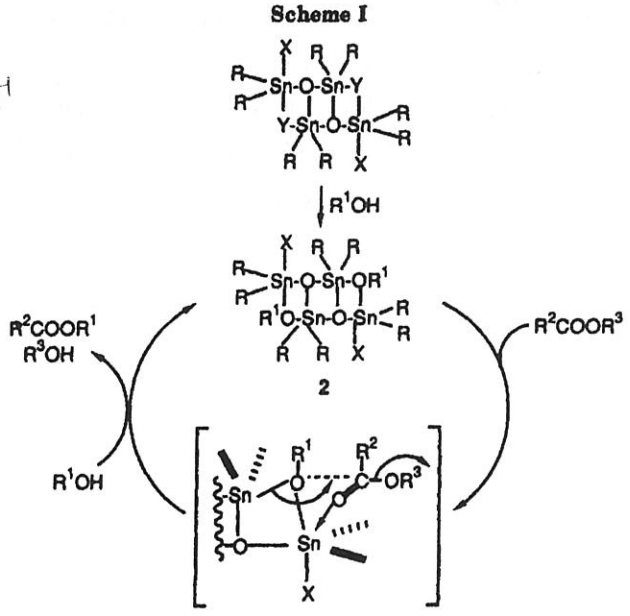
highly efficient transesterification using distannoxane catalyst

J. Org. Chem. **1991**, *56*, 5307.



1a : R=Bu, X=Y=-NCS
1b : R=Bu, X=-NCS, Y=OH
1c : R=Bu, X=Y=Cl
1d : R=Bu, X=Cl, Y=OH
1e : R=Me, X=Y=-NCS

Scheme I



feature of Otera's catalyst

- 2 kind of pentacoordinate tin atom
- high solubility in organic solvent
- various functional groups are unaffected

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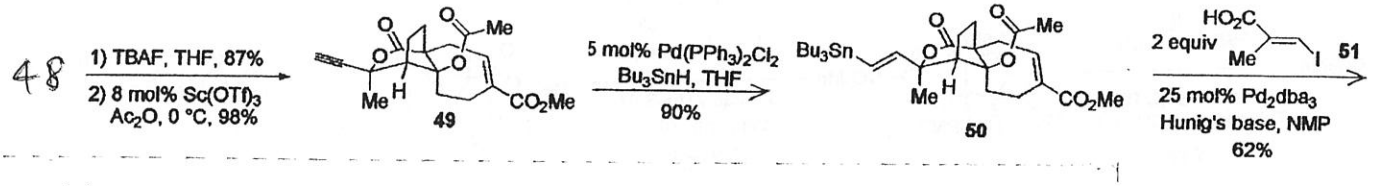
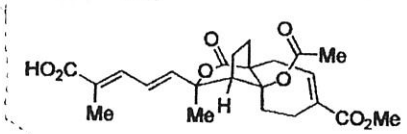
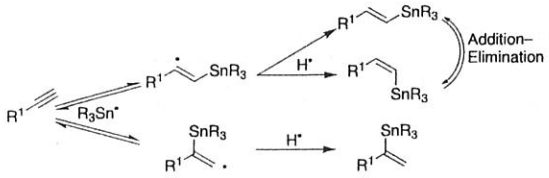




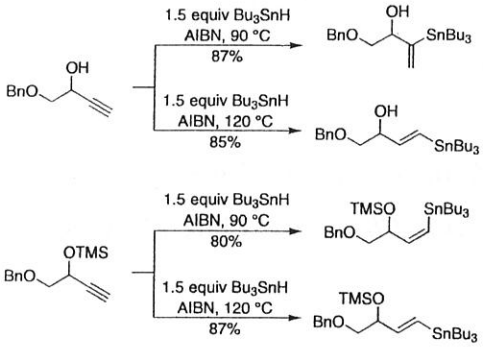
Pd(0)-catalysed hydrostannylation

J. Org. Chem. 1997, *62*, 7768.

Synthesis, 2005, 6, 853.

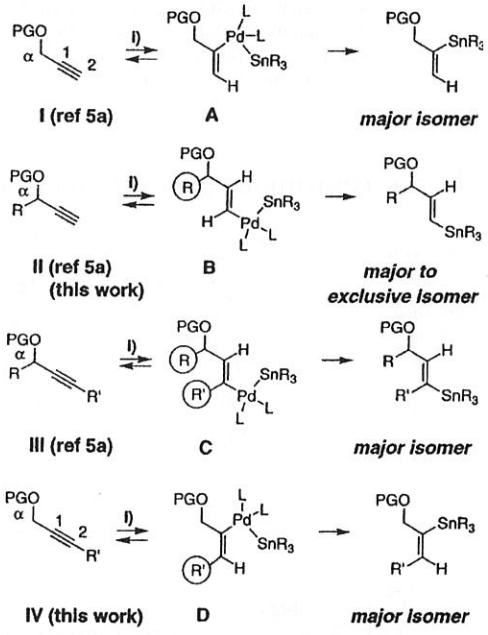


Scheme 30 Mechanism of radical alkyne hydrostannation.



Scheme 31 Altering selectivities for propargylic alcohols and ethers.

Scheme 5



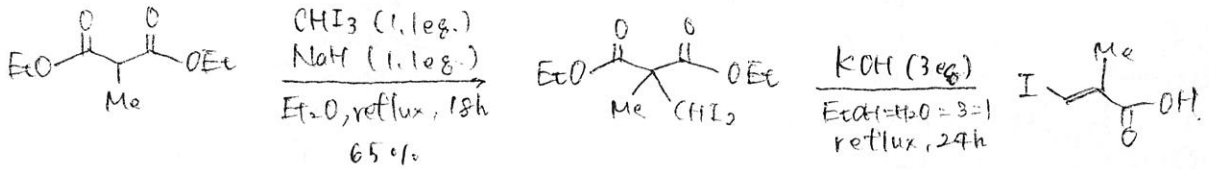
I) Method B: Bu_3SnH/Pd(0)

Stille coupling

- $Pd(CH_3CN)Cl_2$, $Pd(PhCN)_2Cl_2$: low yield (< 30 %) → $Pd_2(dba)_3$

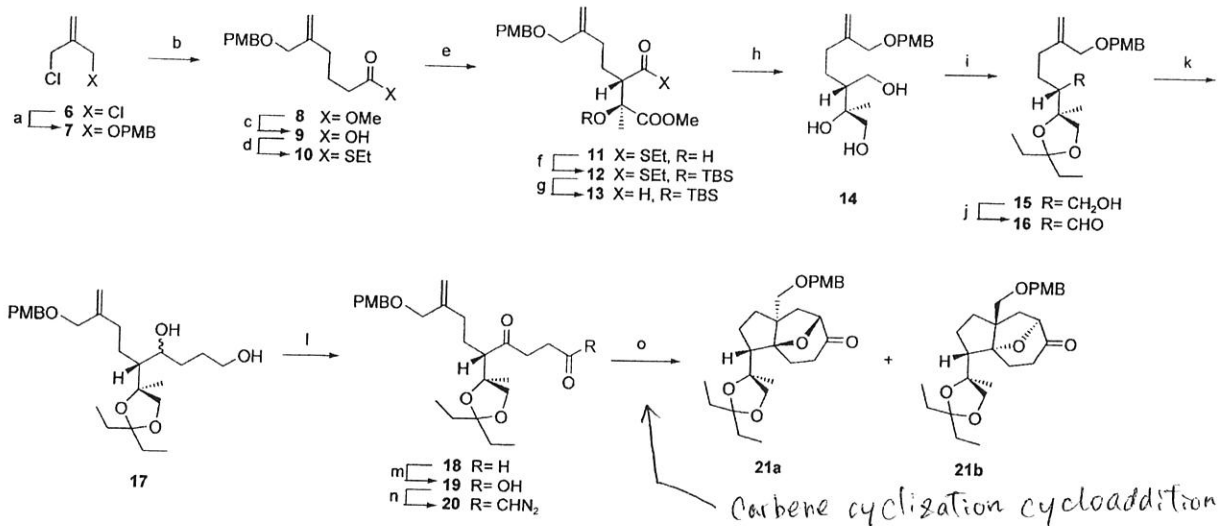
synthesis of **51**

J. Chem. Soc., Perkin Trans. 1 1990, 47.

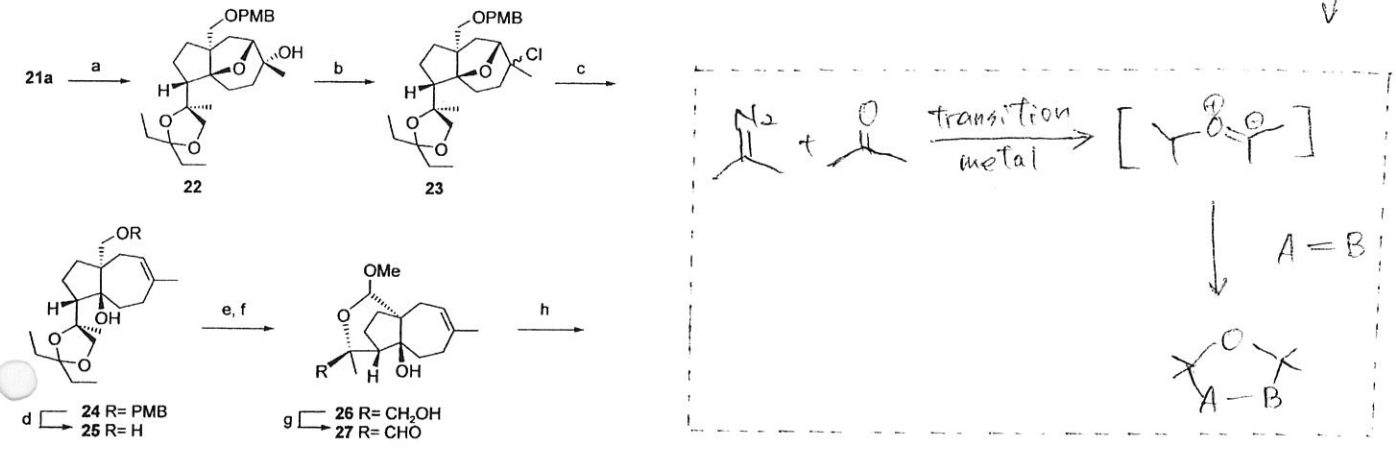


4. Appendix (total synthesis of Pseudolaric Acid A)

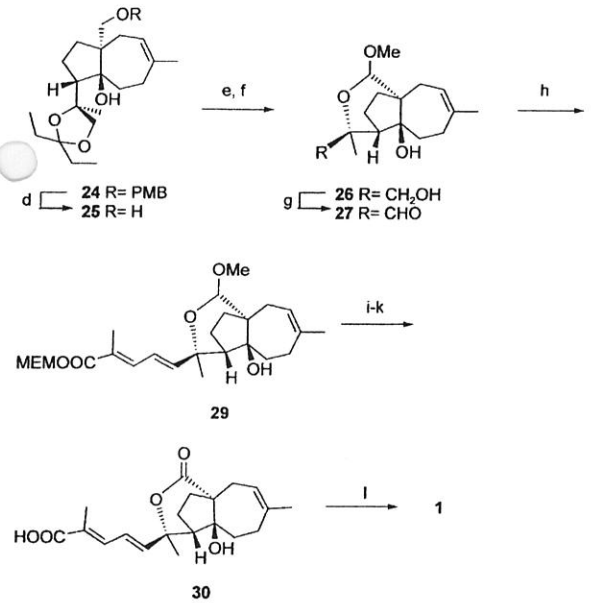
P. Chiu et al *Angew. Chem. Int. Ed.* **2006**, *45*, 6197.



Scheme 3. Reagents and conditions: a) NaH, PMBOH, THF, reflux, 61%; b) $ICH_2CH_2CO_2Me$, Zn(Cu), CuCN, DMA, THF, 60°C, 12 h, 91%; c) 20% NaOH, MeOH, RT, 4 h, 96%; d) EtSH, DCC, DMAP, CH_2Cl_2, 3 h, 97%; e) 1. LDA, TESCl, THF, −78°C-RT; 2. [Cu{(*S*,*S*)-*t*Bu-box}][OTf]$_2$, methyl pyruvate, CH_2Cl_2, −78°C, 76%, 88% *ee*; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 97%; g) Et_3SiH, Pd/C, CH_2Cl_2, 81%; h) 1. LAH, THF, 0°C, 4 h; 2. TBAF, THF, RT, 2 h; i) 3,3-dimethoxypentane, PTSA, RT, 1 h, 66% from **12**; j) Dess–Martin periodinane, CH_2Cl_2, RT, 88%; k) $ClMgO(CH_2)_3MgCl$, THF, 0°C, 90%; l) Swern oxidation, 90%; m) $NaClO_2$, NaH_2PO_4, *t*BuOH, 2-methyl-2-butene, RT, 96%; n) 1. *i*BuOCOCl, Et_3N, THF/Et_2O, −20→0°C, 0.5 h; 2. CH_2N_2, Et_2O, 0°C–RT, 3 h, 71%; o) 3% [Rh_2{(*S*)-bptv}$_4$], $PhCF_3$, −40°C, 82% yield (50% **21a**, 32% **21b**). PMB = *p*-methoxybenzyl, DMA = *N*,*N*-dimethylacetamide, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, LDA = lithium diisopropylamide, TES = triethylsilyl, box = bis(oxazoline), Tf = trifluoromethanesulfonyl, TBS = *tert*-butyldimethylsilyl, LAH = lithium aluminum hydride, TBAF = tetra-*n*-butylammonium fluoride, PTSA = *p*-toluenesulfonic acid, bptv = α-(*tert*-butyl)-1,3-dihydro-1,3-dioxo-2*H*-benz[*f*]isoindole-2-acetato.



Tetrahedron, 2002, 58, 9477.



Scheme 4. Reagents and conditions: a) MeMgCl, THF, 0°C, 96%; b) $SOCl_2$, DMPU, 0°C–RT; c) Na, Et_2O, reflux, 78% over 2 steps from **22**; d) DDQ, CH_2Cl_2/H_2O, RT, 86%; e) Dess–Martin periodinane, CH_2Cl_2, RT, 91%; f) MeOH, CSA, RT, 95%; g) Dess–Martin periodinane, CH_2Cl_2, RT, 93%; h) (*E*)-$(EtO)_2POCH_2CH{=}C(CH_3)CO_2MEM$ **28**, *n*BuLi, THF, 83%; i) 60% AcOH, 60°C, 1 h; j) Dess–Martin periodinane, CH_2Cl_2; k) 3 N HCl/THF, RT, 66% over 3 steps from **29**; l) AcCl, DMAP, 80%. DMPU = 1,3-dimethylhexahydro-2-pyrimidinone, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, CSA = camphorsulfonic acid, MEM = 2-(methoxyethoxy)methyl.