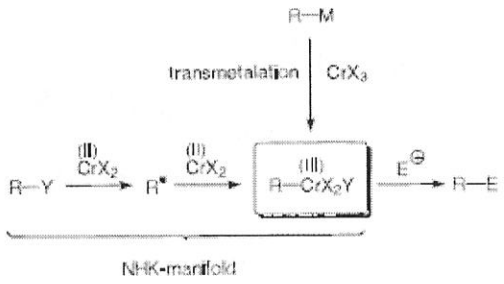
Nozaki-Hiyama-Kishi Reaction

09. 6. 3 Yazaki Ryo

Outline

1) Stoichiometric reaction
2) Catalytic reaction (Cr); Fürstner's work
3) Catalytic asymmetric reaction
4) Halichondrin synthesis; Kishi's work



・Pioneering Work; Hein (1919)

$$PhMgX + CrCl_3 \xrightarrow[Et_2O]{} PhCrCl_2 + MgXCl$$

$$PhCrCl_2 \xrightarrow{PhMgX} Ph_2CrCl + MgXCl$$

・Anet and Leblane (1957) $BnCr(ClO_4)_2(H_2O)_5$

・Kochi (1964, 68)

$$C-X + Cr(II) \xrightarrow[s.e.t.]{\text{oxidative addition } via} C-Cr(III)-X$$

・**Nozaki and Hiyama (1977)** *J. Am. Chem. Soc.* **1977**, *99*, 3179.

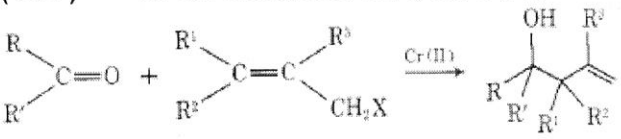
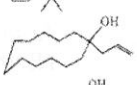
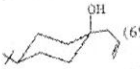
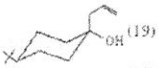
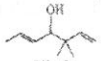
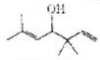
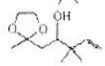
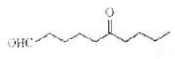
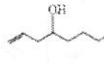


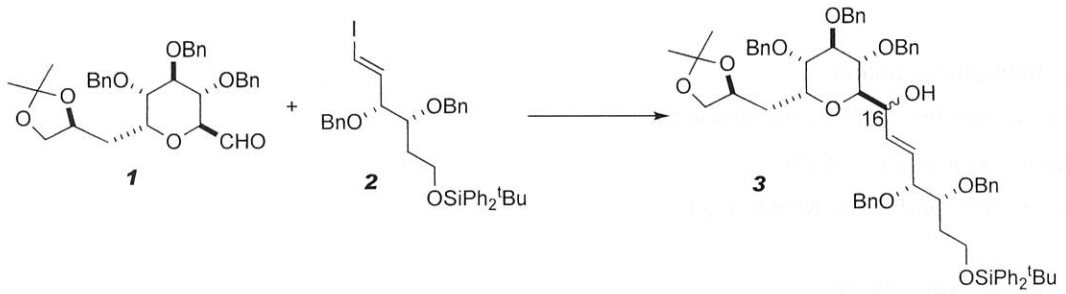
Table I. Reaction of Allyl Halides with Carbonyl Compounds

Run	RR'C=O	Allyl halide	Chromous salt[a]	Solvent	Halide/RR'C=O	Product, %[b]
1			A	THF	1	 (78)
2			B	THF	1	" (74)
3			A	DMF	4	 [74][c]
4			A	THF	2	 (82) [99][d]
5			B	THF	2	 (69)  (19)
6			A	THF	2	(77) (10)
7			A	DMF	2	(83)
8			A	THF	1.2	 (61) [82][c]
9	PhCHO		A	THF	3.5	 (94)[e]
10	PhCHO		A	THF	2	 (81)
11			A	THF	2	 (96)
12			B	DMF	2	 (54)
13			B	DMF	2	(55)
14			A	DMF	2	 [93][c]
15			A	DMF	4	 (91)[f]
16			B	THF	1.2	 (66)
17			B	THF	1.2	 (75)[g]
18			B	THF	3.7	 (66)[h]

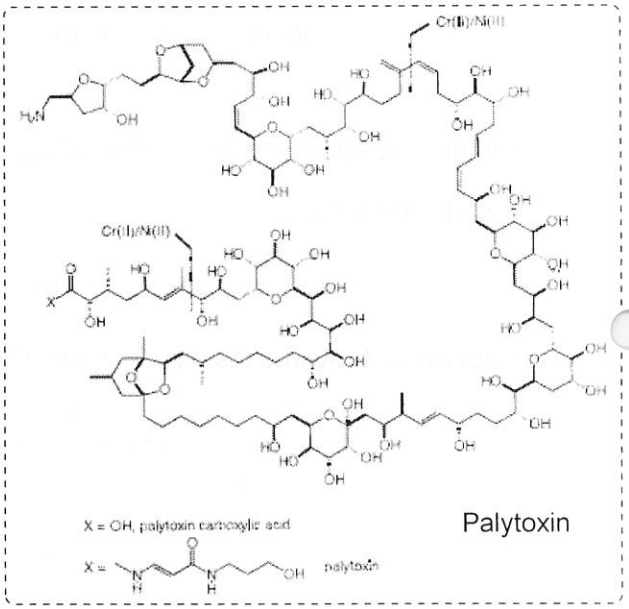
[a] Salt A signifies the one prepared from chromic chloride and lithium aluminum hydride (2:1 molar ratio). Salt B means the commercially available anhydrous chromous chloride. The ratio, chromous salt/halide, was always 2. [b] Experiments were carried out in 1–2 mmol scale of the carbonyl components and isolated yields are given unless otherwise stated. [c] Estimated by G.L.C. [d] Based on the consumed ketone. [e] 0.6-mmol scale. [f] 10-mmol scale. [g] 0.8-mmol scale. [h] 0.5-mmol scale.

aldehyde selective

· **Kishi (1986)** synthetic study on Palytoxin *J. Am. Chem.Soc. 1***986,** *108,* 5644.

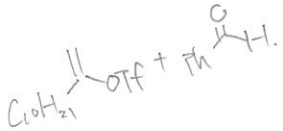


1	2	$NiCl_2$(0.1%)-$CrCl_2$/DMSO	Σ (ratio of 16a:16b stereoisomers)
1.0 eq	1.5 eq	ca. 1.5 eq	55% (1.3:1)
1.0 eq	1.5 eq	ca. 3 eq	60% (1.3:1)
1.0 eq	3.0 eq	ca. 6 eq	71% (1.3:1)
1.0 eq	10 eq	ca. 10 eq	80% (1.3:1)
1.0 eq	1.5 eq	3 eq of $Pd(OAc)_2$ (1%)-$CrCl_2$/DMSO	54% (1:1)
1.0 eq	3.0 eq	$CrCl_2$ (excess) with no added $NiCl_2$	0 ~ 80% (1.3:1)



· **Nozaki (1986)** *J. Am. Chem.Soc. 1***986,** *108,* 6048.

Success of the reaction heavily depended on the nature of the $CrCl_2$



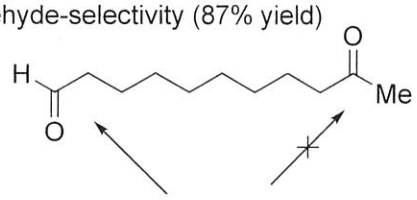
⇨ Analysis of fluorescent X-rays of the special lots revealed that **Ni was the major contaminant.**

5 mol % of $CrCl_2$ in DMF at 25 °C for 12 h are as follows: **$NiCl_2$ 83%** $MnCl_2$, < 1 %; $FeCl_3$, 9%; $CoCl_2$, 16%; CuCl, <I%; $PdCl_2$, <I%.

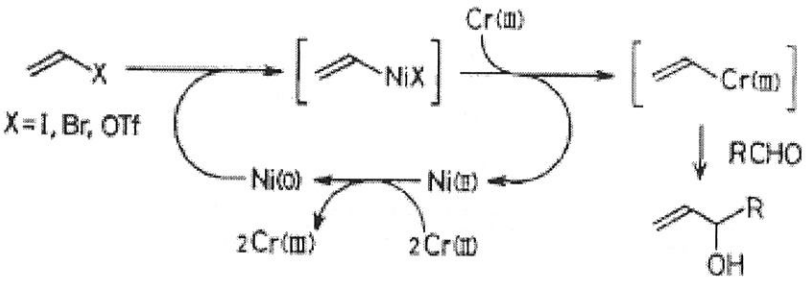
Ether or THF; Little or no reaction occurs (low solubility) ⟹ DMF is most effective.

Substrate scope · α,β-unsaturated aldehyde; 1,2-product

· aldehyde-selectivity (87% yield)



Mechanism



Feature of this reaction (Nozaki-Hiyama-Kishi reaction)

- the broad range of substrates amenable to insertion of Cr(II) under mild conditions, accounting for the remarkably wide scope of this methodology;
- the chemoselectivity of organochromium intermediates for reactions with aldehydes as the electrophilic reaction partners
- the strong driving force for such additions, which stems from the formation of highly stable O-Cr(III) bonds. This chemical incentive can be exploited to build up strain in the organic products
- a low basicity of organochromium(III) reagents
- distinct stereochemical preferences, particularly in reactions of crotylchromium reagents
- a simple setup and an excellent reliability even if applied to sensitive and polyfunctional compounds.

Chem. Rev. **1999,** *99,* 991.

Chromium reagent

$CrCl_2$ air-sensitive and hygroscopic pale gray powder
(greenish lots may result in poor results)

can be purchased or prepared from cheap $CrCl_3$ ($LiAlH_4$; Nozaki Hiyama method, Zn, Na(Hg), Mn)

$Cr(THF)_nCl_2$ **$Cr(THF)Cl_2$.** A suspension of anhydrous $CrCl_3$ (249 g, 1.57 mol) and Cr powder (44 g, 0.846 mol) in THF (2 L) was heated under reflux for 1 week, during which period a color change from violet to pale green occurred. The reaction mixture was filtered and the pale green product separated from excess Cr powder by Soxhlet extraction with THF. The product was washed with pentane (5 × 100 mL) and dried in vacuo. Yield: 370 g (1.9 mol, 81%). Depending upon the drying conditions, compounds can be obtained which have the composition $Cr(THF)_2Cl_2$ (pale green), $Cr(THF)Cl_2$, (bright blue) or $CrCl_2$ (gray). $Cr(THF)Cl_2$ was used in the following reactions.

Organometallics **1991**, *10*, 3520.

$CrBr_2$ and CrI_2 No significant benefits

Catalytic Reaction

Stoichiometric NHK reactions require 2 mol of Cr(II) per 1 mol of organic halide (triflate, etc.) for the formation of the nucleophile

Cr(II) is generally used in (huge) excess for high yield.

⇩

Development of catalytic version of NHK reaction (cat. Cr) is highly desired.

Pioneering Work by Fürstner (1996) *J. Am. Chem. Soc.* **1996**, *118*, 12349 and 2533.

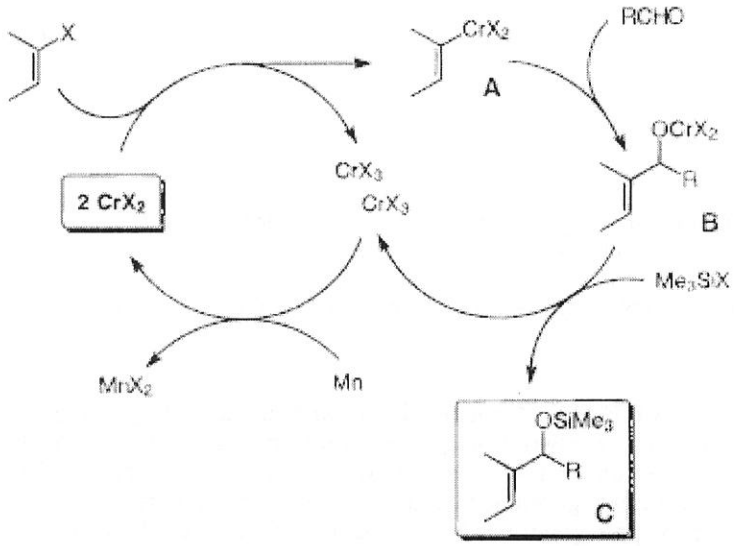
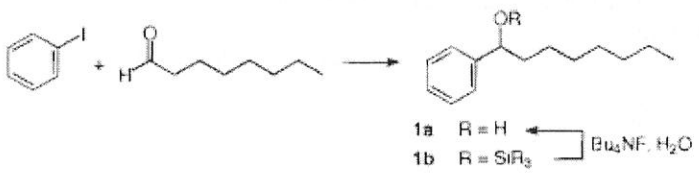


Table 1. Control Experiments: Cr^{2+}-Mediated Reaction of Iodobenzene with Octanal[a]



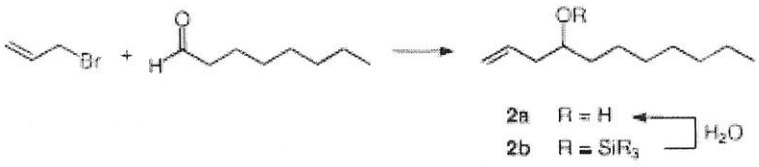
entry	$CrCl_2$ (mol %)	additives	T (°C)	isolated yield 1a (%)[b]
1	400		20	78[c]
2	400		50	65
3	30	Zn, TMSCl	70	30–40[d]
4	**15**	**Mn, TMSCl**	**50**	**67**
5	**15**	**Mn, $ClMe_2Si(CH_2)_3CN$**	**50**	**72**
6	9	Mn, $ClMe_2Si(CH_2)_3CN$	50	58
7	0	Mn, $ClMe_2Si(CH_2)_3CN$	50	0[e]
8	0	Mn, $ClMe_2Si(CH_2)_3CN$, $NiCl_2$(cat.)	50	0[e]

[a] The reactions were carried out in DME/DMF (20/3) unless stated otherwise, using $CrCl_2$ doped with $NiCl_2$ (~15%). [b] After desilylation of the admixed 1b. [c] In pure DMF. [d] Formation of 1-[(trimethylsilyl)oxy]-1-octene as side reaction; *cf.* text. [e] GC yield < 3%.

Zn, TMSCl system
- Activated Zn insert into substrate (leave the desired Cr path)
- Silyl enol formation

Mn, TMSCl system
- Mn cheap
- Low Lewis acidity (pK_h =10.59(Mn^{2+}), 8.96(Zn^{2+}))
- Electrochemical redox potentials:
  $Cr^{3+} + e^- \rightleftharpoons Cr^{2+}$ (-0.41 V)
  $Zn^{2+} + 2e^- \rightleftharpoons Zn$ (-0.76 V)
  $Mn^{2+} + 2e^- \rightleftharpoons Mn$ (-1.03 V)

Table 2. Control Experiments: Cr^{2+}-Mediated Reaction of Allyl Bromide with Octanal[a]



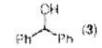
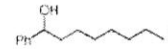
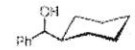
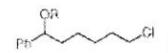
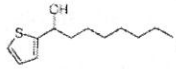
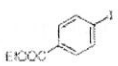
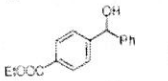
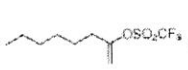
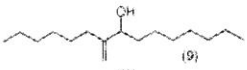
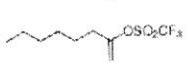
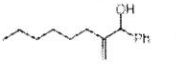
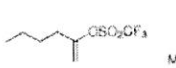
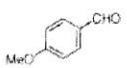
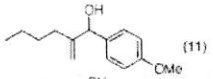
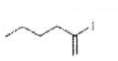
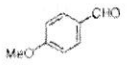
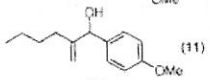
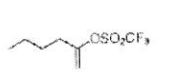
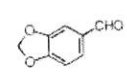
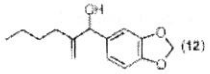
entry	$CrCl_2$ (mol %)	additives	T (°C)	isolated yield (%)[b]
1	400		rt	81
2	7	Mn, TMSCl	rt	78
3	0	Mn, TMSCl	rt	<19 (GC)[c]

[a] All reactions were carried out with undoped $CrCl_2$ in THF; reaction time 6 h. [b] Refers to the yield of the unprotected alcohol **2a** obtained after desilylation of the crude product. [c] After 90 h reaction time.

A combination of catalytic amounts of $CrCl_2$, Mn powder, and a chlorosilane rapidly and cleanly conVerts these substrates into the desired products

Aryl, Alkenyl Iodides

Table 3. Chromium-Catalyzed Reactions of Aryl Iodides, Alkenyl Iodides, and Alkenyl Triflates with Different Aldehydes[a]

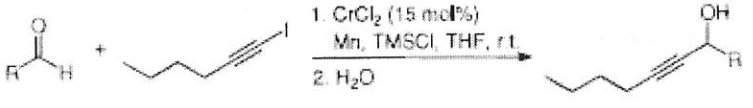
Entry	R-X	Aldehyde	Product	$ClMe_2Si(CH_2)_3CN$ Yield (%)[b]	Me_3SiCl Yield (%)[b]
1	PhI	PhCHO	 (3)	88	62
2	PhI	$CH_3(CH_2)_6CHO$	 (1a)	72	67
3	PhI	$C_6H_{11}CHO$	 (4)	71	
4	PhI	$Cl(CH_2)_5CHO$	 (5) R = Ac (6) R = H		66[c]
5		$CH_3(CH_2)_6CHO$	 (7)	57	
6		PhCHO	 (8)		57[d]
7		$CH_3(CH_2)_6CHO$	 (9)		61
8		PhCHO	 (10)		67
9			 (11)		76
10			 (11)		75
11			 (12)		80

[a] All reactions were carried out with $CrCl_2$ (15 mol %, doped with $NiCl_2$ cat.), Mn powder (4.2 mmol), aldehyde (2.5 mmol), R-X (5 mmol), chlorosilane (6 mmol) in DMF/DME (20/3) at 50 °C. [b] Refers to the product obtained after desilylation (aqueous Bu_4NF) of the crude mixture. [c] Isolated as the *O*-acetate after acetylation of the crude product. [d] 4,4′-Bis(ethoxycarbonyl)diphenyl as byproduct (20% based on I-C_6H_4COOEt).

ClMe2Si～CN
使われないのはなぜ？
trapできてない？

Alkynyl Halides

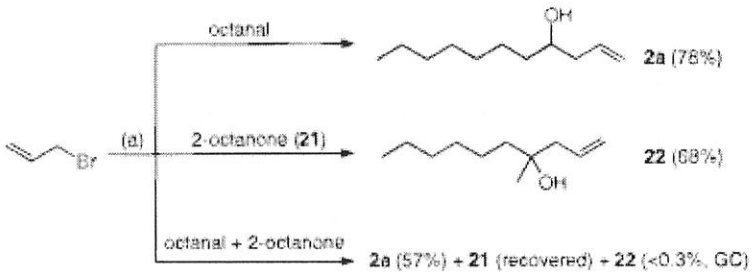
Scheme 4



17 R = n-C_5H_{11}, 79%

18 R = Ph, 62%

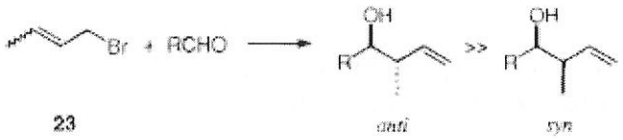
Allyl Halides



[a] Key: (a) (i) $CrCl_2$ (7 mo %), Mn, TMSCl, THF, room temperature; (ii) H_2O.

- Ni salt; Wurtz-type coupling
- Aldehyde-selective

Diastereoselective reaction



23 — *anti* — *syn*

24 R = Ph
25 R = n-C_5H_{11}
26 R = n-C_7H_{15}
27 R = $(CH_2)_5COOMe$

- (*E*), (*Z*) *anti*-selective
  typical characteristics of a crotyl chromium intermediate

⇩

Not manganese intermediate

Table 4. Chromium-Catalyzed Reactions of Crotyl Bromide with Different Aldehydes

entry	crotyl bromide	R	chromium salt	additives	product (% yield)	*anti*:*syn*
1	(*E*)-23	Ph	$CrCl_2$ (400 mol %)		24 (100)	90:10 [1d]
2	(*E*)-23	Ph	$CrCl_2$ (7 mol %)	Mn, TMSCl	24 (79)	94:6
3	(*Z*)-23	Ph	$CrCl_2$ (7 mol %)	Mn, TMSCl	24 (64)	90:10
4	(*E*)-23	Ph	$CrCl_3$ (7 mol %)	Mn, TMSCl	24 (85)	91:9
5	(*Z*)-23	Ph	$CrCl_3$ (7 mol %)	Mn, TMSCl	24 (74)	90:10
6	(*E*)-23	n-C_5H_{11}	$CrCl_2$ (400 mol %)		25 (97)	96:4 [1c]
7	(*E*)-23	n-C_5H_{11}	$CrCl_2$ (7 mol %)	Mn, TMSCl	25 (84)	92:8
8	(*E*)-23	$(CH_2)_5COOMe$	$CrCl_3$ (7 mol %)	Mn, TMSCl	27 (83)	92:8

- $CrCl_3$ work as a precatalyst ($CrCl_3$; cheap, stable) entries 4, 5, 8
- Cp_2CrCl or $CpCrCl_2(THF)$ show higher catalytic turnover number (<1 mol%)

promote the concomitant pinacol coupling of aromatic aldehydes

1) Alkenyl Halides

Cr/Ni system

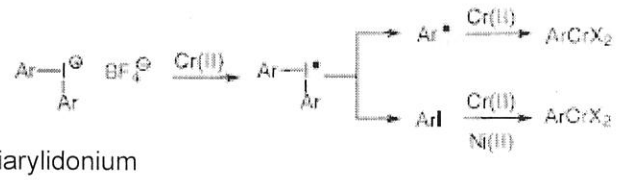
Iodoalkenes were found to be significantly more reactive than the corresponding bromoalkenes. Triflate can be employ.

The configuration of the double bond is retained

2) Aryl Halides

Low reactivity (Br, TfO limitations)

Cr/Ni system



diarylidonium

Tetrahedron lett. **1997**, *38*, 8211.

3) Alkynyl Halides

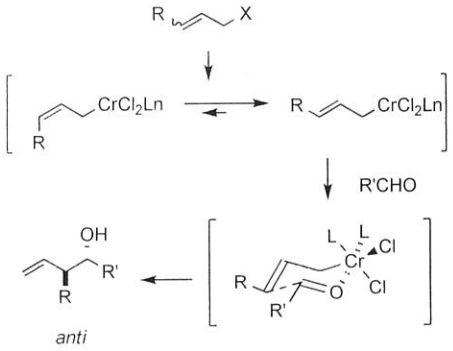
Cr/Ni system

Iodide

4) Allyl Halides

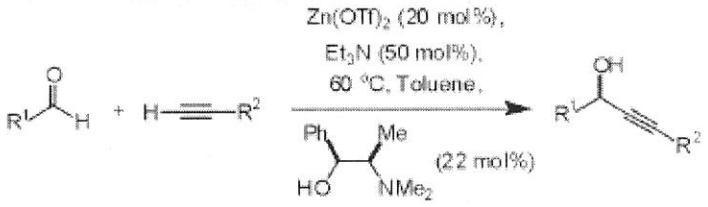
Cr (Ni; Wurzt coupling)

crotyl (*E*), (*Z*); *anti* selective

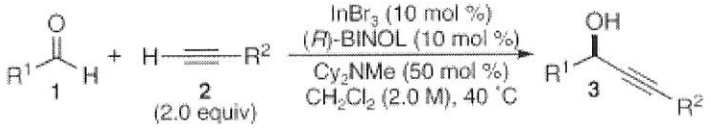


Direct Catalytiv Asymmetric Alkynylation

Carreira *J. Am. Chem. Soc.* **2001**, *123*, 9687



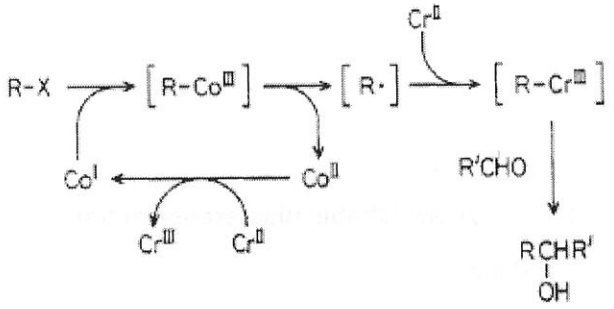
Shibasaki *J. Am. Chem. Soc.* **2005**, *127*, 13760



Mild Simple condition, Atom economical

5) Alkyl Halides

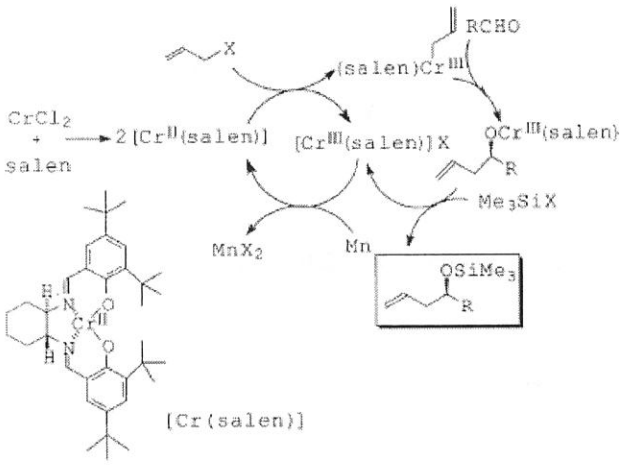
Cr/Co system Utimoto and Takai *J. Org. Chem.* **1989**, *54*, 4732

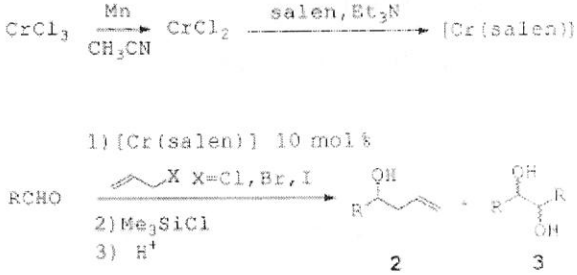


Catalytic asymmetric reaction

First catalytic asymmetric reaction

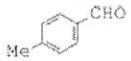
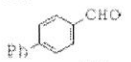
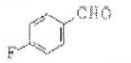
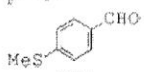
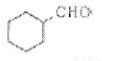
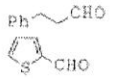
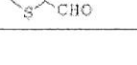
Cozzi and Umani-Ronchi *Angew. Chem., Int. Ed.* **1999**, *38*, 3357





Scheme 3. Enantioselective allylation of aldehydes mediated by [Cr(salen)] complex, prepared by the in situ reduction of $CrCl_3$.

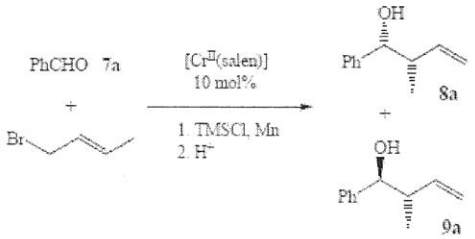
Table 3. Enantioselective addition of allyl chloride to aldehydes catalyzed by [Cr(salen)] complex.

Entry	R'CHO	Yield of 2 [%][a]	Yield of 3 [%][b]	*ee* of 2 [%][c]
1		67	16	78 (*R*)[d]
2		54	35	82 (*R*)[d]
3		41	40	77 (*R*)[d]
4		46	40	78 (*R*)[d]
5		42[e]	0[e]	89 (*R*)[d]
6		45[e]	13	77 (*S*)[d]
7		40	40	65 (*R*)[d]

- BINOL, TADDOL, sulfonamide, amino alchol, phosphane

⟹ racemic

Angew. Chem., Int. Ed. **2000**, *39*, 2327 *anti vs syn* **switchable diastereoselection**



first trial

37 (78% ee)

50% yield

67 (5 % ee)

The amount of salen ligand used is important

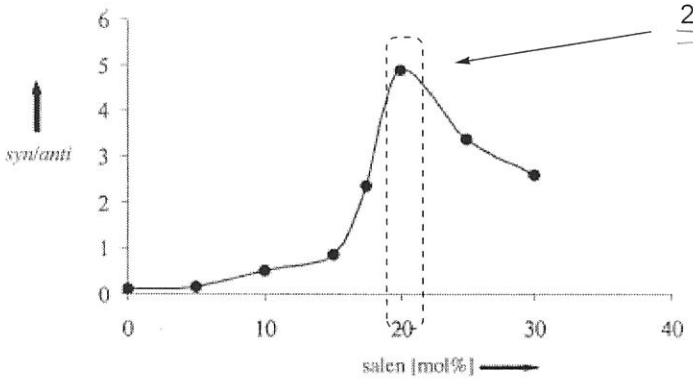
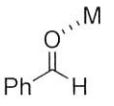


Figure 1. Influence of the amount of salen on the diastereoselectivity of the chromium-catalyzed addition of crotyl bromide to PhCHO.

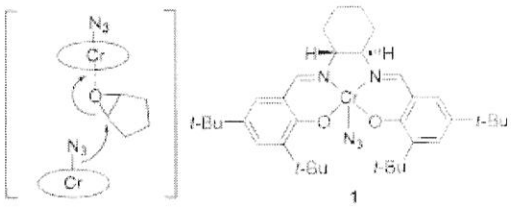
20 mol% salen (Cr 10 mol%); highest ***syn*** selectivity

83;17, 89% ee

⟹ acyclic T.S.



M; Cr-complex or Mn ??



cooperative catalysis??

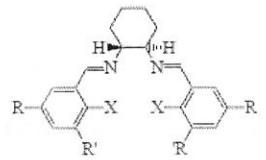
Jacobsen *J. Am. Chem. Soc.* **1998**, *120*, 10780.

8a = *syn*
9a = *anti*

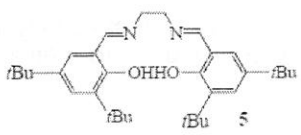
Table 1. Different additives used for modifying the simple diastreoselection in the addition of crotyl bromide to the PhCHO.[a]

Entry	Additive (10 mol%)	Yield [%][b]	8a:9a[c]	*ee* of 8a [%][d]	*ee* of 9a [%][d]
1	1	56	83:17	89(1*R*,2*S*)	36(1*S*,2*S*)
2	2	40	76:24	88(1*R*,2*S*)	30(1*S*,2*S*)
3	3	41	81:19	77(1*R*,2*S*)	22(1*S*,2*S*)
4	4	29	56:44	73(1*R*,2*S*)	12(1*S*,2*S*)
5	5	20	31:69	48(1*R*,2*S*)	3(1*S*,2*S*)
6	6	46	49:51	80(1*R*,2*S*)	11(1*S*,2*S*)
7	DMF	30	59:41	82(1*R*,2*S*)	10(1*S*,2*S*)
8	DMPU	39	53:47	82(1*R*,2*S*)	10(1*S*,2*S*)
9	Ph_3PO	35	62:38	68(1*R*,2*S*)	20(1*S*,2*S*)
10	Ph_3P[e]	39	52:48	90(1*R*,2*S*)	10(1*S*,2*S*)
11	4-PPNO	17	38:62	80(1*R*,2*S*)	0

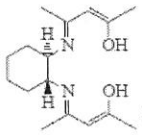
[a] All the reactions were carried out in anhydrous CH_3CN at room temperature. [b] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. The by-product derived from the pinacol coupling was observed. [c] The ratio between **8a** and **9a** was determined by GC analysis of the crude reaction mixture and ^1H NMR analysis after chromatographic purification. [d] Determined by chiral GC analysis of the corresponding *O*-methyl ether. See the Supporting Information for details. The absolute configurations of **8a** and **9a** were assigned by ^1H NMR analysis of the (*R*)-Mosher's esters derivatives (300 MHz, C_6D_6, δ OMe: (1*R*,2*S*) = 3.32, (1*S*,2*R*) = 3.39, (1*R*,2*R*) = 3.22, (1*S*,2*S*) = 3.43); see reference [9]. [e] The reaction was performed employing anhydrous $CrCl_2$ as the chromium source.



1: X = OH, R = *t*Bu, R' = *t*Bu;
2: X = OMe, R = *t*Bu, R' = *t*Bu;
3: X = OH, R = *t*Bu, R' = H;
4: X = OH, R = *t*Bu, R' = Br;



5

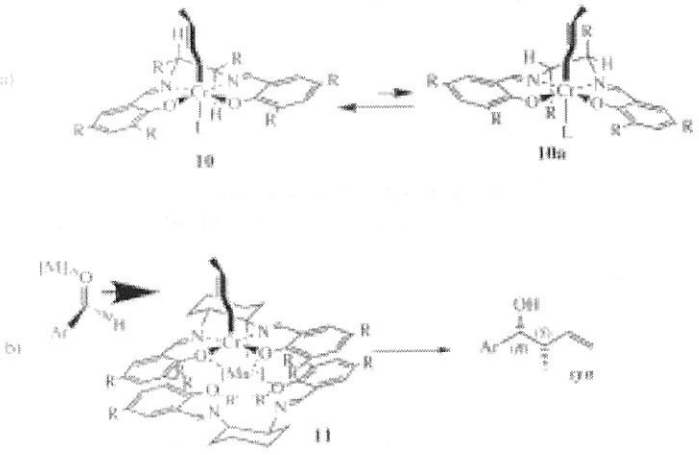


6

- Diastereoselection appears to be strongly correlated to the nature of the additve
- Facial diastereoselection is less affected.

A specific noncovalent binding of chiral Cr-comples with another molecule of salen affords this peculiar behavor

First *syn*-selective catalytic asymmetric reaction (Cr)



10 10a 11

[M] = MnX_2 (Cr-salen)
R = H, Me

Scheme 1. a) Equilibrium mixture of the stepped conformational crotyl(salen)-Cr(III) isomers. b) Plausible approach of an aldehyde to the chiral organochromium complex giving the observed diastereoisomer.

Table 2. Results of the diastereo- and enantioselective addition of organohalides to aromatic aldehydes using chiral [Cr(salen)] catalyst [Eq. (2)].[a]

RCHO	R'X	Yield [%][b]	Product (*syn*:*anti*)[c]	*ee* of *syn* [%][d]	*ee* of *anti* [%][d]
7a		72[e]	75:25[d]	86[g]	26[g]
7a		25[e,f]	75:25[d]	62[g]	25[g]
7b		48	74:26	85(1*R*,2*S*)	26(1*S*,2*S*)
7c	"	53	74:26	90(1*R*,2*S*)	27(1*S*,2*S*)
7d	"	46	61:39	82(1*R*,2*S*)	24(1*S*,2*S*)
7e	"	43	72:28	82(1*R*,2*S*)	28(1*S*,2*S*)
7f	"	49	66:34	70[h]	43[h]
7g	"	52	60:40	58(1*R*,2*S*)	15(1*S*,2*S*)
7h	"	47	71:29[d]	84(1*R*,2*S*)	16(1*S*,2*S*)

[a] Performing the reaction in the presence of $CrCl_2$ as the catalyst (10 mol%), we obtained the *anti* homoallylic alcohols as the major isomer; see Supporting Information. [b] Isolated yield after desilylation (HCl/THF) and flash chromatography. By-products derived from the pinacol coupling reaction were detected by GC analysis. [c] Determined by GC analysis of the crude reaction mixture and ^1H NMR analysis after chromatographic purification. [d] Determined by chiral GC analysis of the corresponding *O*-methyl ether. See the Supporting Information for details. The absolute configurations of 8 and 9 were assigned by analogy to the chiral GC analysis of the 8a/9a mixture. [e] Isolated yield after desilylation (Bu_4NF/THF) and flash chromatography. [f] The low yield obtained was derived from the high instability of the chiral organochromium intermediate. In fact, a large amount of bicyclohexyl-2,2'-diene (coupling product) was detected from the MS-GC analysis. [g] Determined by chiral HPLC analysis (Chiralcel OD column). [h] Determined by ^1H NMR analysis of the (*S*)-(+)-*O*-acetyl-mandelic ester. See the Supporting Information for details.

Further mechanistic study *Tetrahedron* **2001,** *57,* 835.

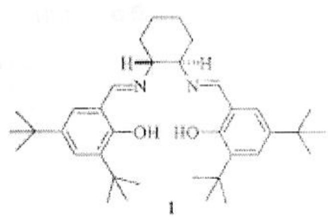
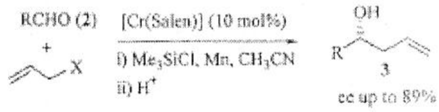


Figure 1. Salen Schiff base ligand.

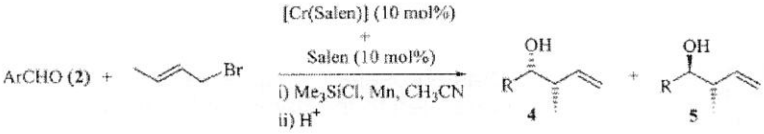
The motivation to start kinetic and mechanistic studies

(a) The TMSCl is not essential in the stereodifferentiating step stoichiometric amount of chiral [Cr(Salen)allyl] complex (yield.56%, ee.80%)

(b) The MnX_2 salts generated in the catalytic cycle play a crucial role in determining the formation of the catalytically active species.



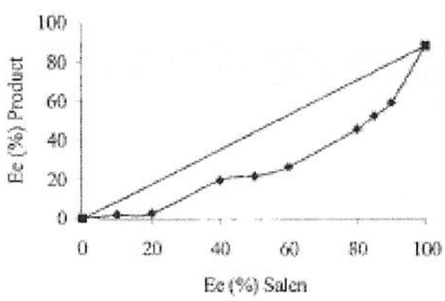
Scheme 1. Asymmetric allylation reaction of aldehydes promoted by [Cr(Salen)] complex.



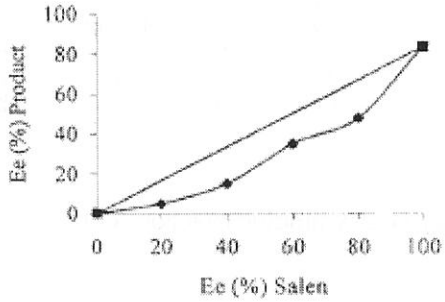
conc. ↑ することで salen ligand を additional に加えなくても syn 選択性でる。

aggregation?

(-)-NLE Crotylation Reaction

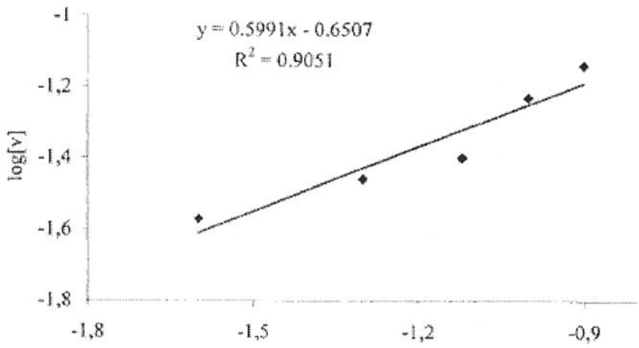


(-)-NLE Allylation Reaction



ee (syn)

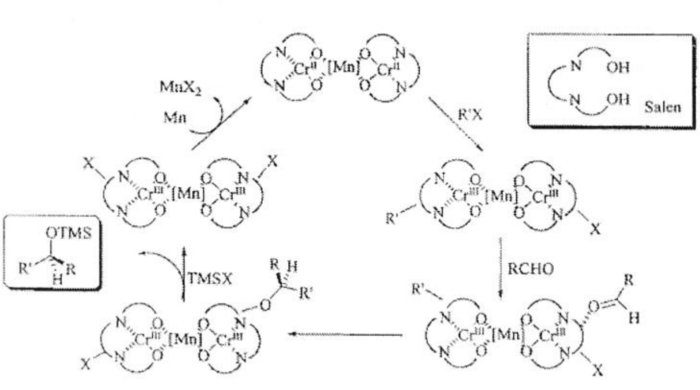
The nature of the organo halide does not signifcantly infuence the NLE.
An aggregation phenomena is involved in the enantio-differentiating step.



The rate determining step of the reaction dimetic molecule is involved

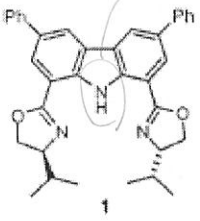
Figure 5. Plotting of log[rate] vs log[Cr]. Determination of the order dependence on total chromium concentration.

求電子付加が 律速?



Weak Lewis acd $Zn(OTf)_2$ (10mol%); syn:anti = 66:34 71% ee (syn)
Strong Lewis acid $Sc(OTf)_3$ or BF_3OEt_2; racemic

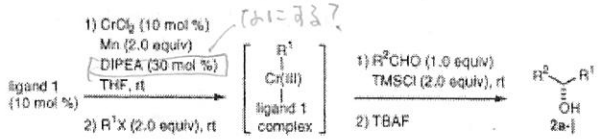
Nakada *J. Am. Chem. Soc.* **2003**, *125*, 1140.



1

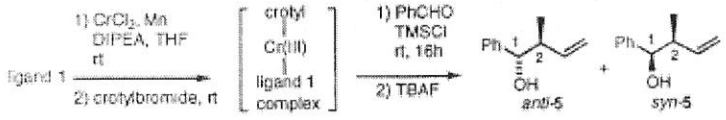
- DBFOX; not satisfactory
- No pinacol product was observed.

Table 1. Enantioselective Allylations of Aldehydes



entry	product	R^1	X	R^2	ee(%)[a,b]	yield(%)[c]	time(h)
1	2a	allyl	Br	Ph	90(*S*)[f]	93	12
2[d]	2a	allyl	Br	Ph	93(*S*)[f]	89	12
3	2a	allyl	Cl	Ph	89(*S*)[f]	95	16
4	2a	allyl	I	Ph	64(*S*)[f]	52	12
5	2b	allyl	Br	*p*-BrPh	92(*S*)[g]	87	12
6	2c	allyl	Br	PhCH=CH	95(*S*)[h]	87	12
7[e]	2d	allyl	Br	$PhCH_2CH_2$	86(*R*)[i]	91	12
8	2e	allyl	Br	*c*-C_6H_{11}	94(*S*)[f]	95	12
9	2e	allyl	Cl	*c*-C_6H_{11}	93(*S*)[f]	88	12
10	2f	allyl	Br	*n*-C_5H_{11}	92(*R*)[j]	83	12
11	2g	methallyl	Br	Ph	46(*S*)[k]	77	16
12	2g	methallyl	Cl	Ph	95(*S*)[k]	96	16
13	2h	methallyl	Cl	PhCH=CH	90(*S*)[l]	50	16
14	2i	methallyl	Br	*c*-C_6H_{11}	96(*S*)[m]	96	16
15	2i	methallyl	Cl	*c*-C_6H_{11}	95(*S*)[m]	98	16
16	2j	methallyl	Br	*n*-C_5H_{11}	79(*R*)[e,n]	65	16
17	2j	methallyl	Cl	*n*-C_5H_{11}	96(*R*)[e,n]	83	16

Scheme 1. Enantioselective Crotylation of Benzaldehyde



anti, 75% ee (1*S*,2*S*)[17]; *syn*, 21% ee (1*R*, 2*S*)[17] (without ligand 1 *anti* / *syn* = 86 / 14, 48%)
anti / *syn* = 73 / 27, 38%

Berkessel *Angew. Chem., Int. Ed.* **2003**, *42*, 1032

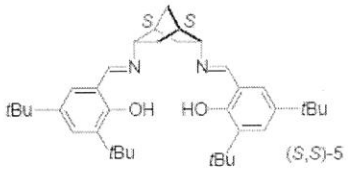
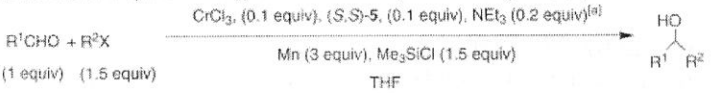
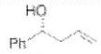
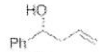
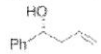
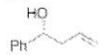
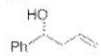
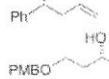
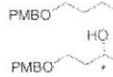
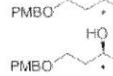


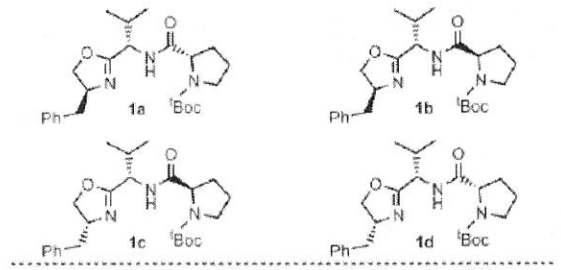
Table 1: Catalytic, enantioselective Nozaki–Hiyama–Kishi-type additions in the presence of ligand (*S,S*)-**5**.

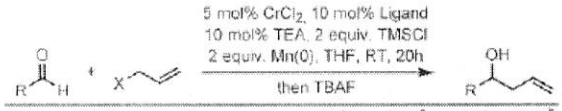


Entry	Aldehyde	Halide	Product	ee [%]	Yield [%][b]	Reaction temperature[c]
1				90[d,e]	72	5 °C
2				31[d,f]	[g]	RT
3				79[d,e]	76	RT
4				54[e,h]	78	RT
5				64[f,h]	[g]	RT
6				92[e,h]	69[i]	10 °C
7				75[h,j]	59[i]	15 °C
8				61[h,k,l]	54[i]	20 °C

[a] For entries 7 and 8, the reaction was run in the presence of 0.02 equiv of $NiCl_2$. [b] Yield after flash chromatography. [c] Reaction temperature was optimized for entries 1, 2, 5, 6, 7, and 8. [d] Enantiomeric excess was determined by gas chromatography (GC) of the corresponding TMS ethers on a chiral stationary phase (Macherey–Nagel: Lipodex A, 95 °C). [e] Absolute configurations were assigned by comparison of optical rotations with literature data.[d, 11, 12] [f] Absolute configuration based on GC/HPLC data (that is, comparison of the products of entries 2 and 1 and of the products of entries 3 and 5 on an analytical scale). [g] Not determined. [h] Enantiomeric excess determined by HPLC on a chiral phase (Daicel: Chiralcel OD-H). [i] Some debenzylation occured as a side reaction. [j] Absolute configuration determined by 1) oxidative cleavage (ozonolysis), 2) reduction to 1,2,4-butanetriol, 3) GC co-injection with a sample of known absolute configuration.[13] [k] Reaction was performed with (*R,R*)-**5**. [l] Assignment of absolute configuration in analogy to entry 7.

Sigman *Org. Lett.* **2005**, *7*, 1837 (Aldehyde)

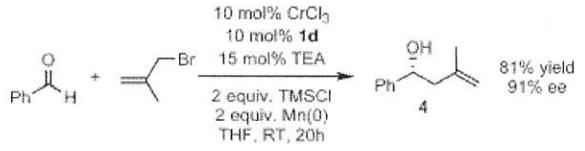


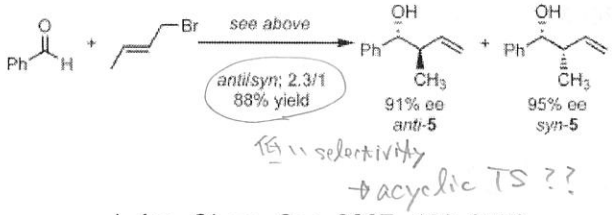


entry	ligand	R	X	yield(%)	%ee[a]	configuration[b]
1	**1a**	Ph	Br	75	76	*S*
2	**1b**	Ph	Br	88	36	*R*
3	**1c**	Ph	Br	22	89	*S*
4	**1d**	Ph	Br	95	92	*R*
5	**1d**	Ph	I	85	84	*R*
6	**1d**	Ph	Cl	15	83	*R*

(a) ee determined by HPLC equipped with a chiral stationary phase (b) see supporting information for details.

Figure 2. Identification and optimization of oxazoline-amide ligands.

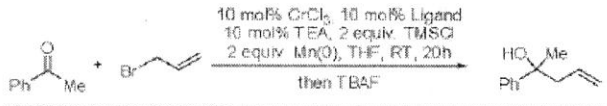


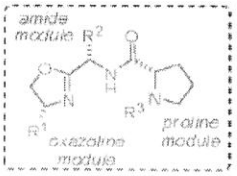


TS = selectivity

→ acyclic TS ??

J. Am. Chem. Soc. **2007**, *129*, 2752
(Ketone; first example using allyl halides)





Ligand	ER	yield (%)	configuration
1a	68:32	40	*R*
1b	79:21	32	*R*
1c	80:20	65	*S*
1d	66:34	38	*R*
2a	91:9	69	*R*
2b	63.5:36.5	56	*R*

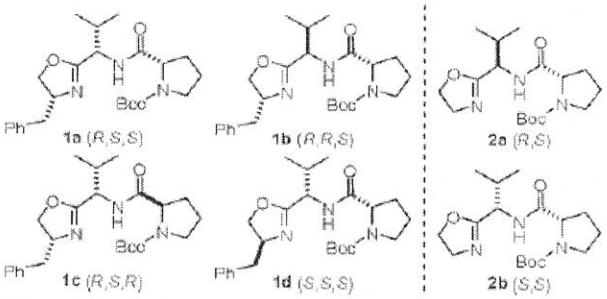
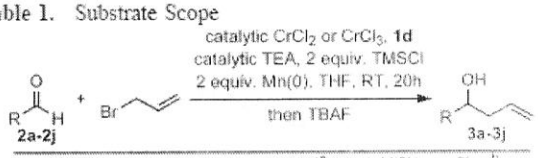


Figure 1. Evaluation of ligand diastereomers and truncation of the ligand structure in the enantioselective allylation of acetophenone.

Allyl bromide; 2 equiv.

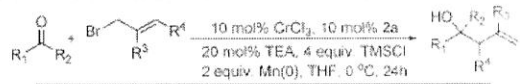
Table 1. Substrate Scope

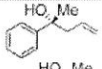
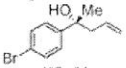
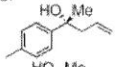
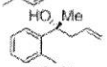
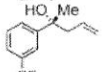
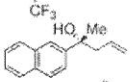
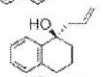
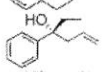
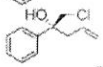
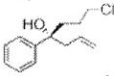
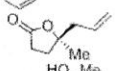
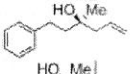
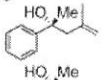
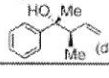


entry	R	method[a]	yield(%)	%ee[b]
1	C_6H_5 (**2a**)	A	95	92
2		B	89	94
3	4-BrC_6H_5 (**2b**)	A	87	91
4		B	73	90
5	4-$MeOC_6H_5$ (**2c**)	A	95	89
6		B	98	89
7	2-Furyl (**2d**)	A	73	92
8		B	61	92
9	2-Napthyl (**2e**)	B	93	94
10	PhCH=CH (**2f**)	A	79	89
11		B	79	87
12	$PhCH_2CH_2$ (**2g**)	A	94	46
13		B	98	48
14	C_6H_{11} (**2h**)	A	81	89
15		B	64	87
16	$BnOCH_2$ (**2i**)	A	67	53
17	2-Napthyl-O(C=O)- **2j**	B	60	77

[a] Method A: 5 mol% $CrCl_2$, 10% **1d**, 10 mol% TEA. Method B: 10 mol% $CrCl_3$, 10 mol% **1d**, 15 mol% TEA. [b] See Supporting Information for enantiomeric excess and absolute configuration determination.

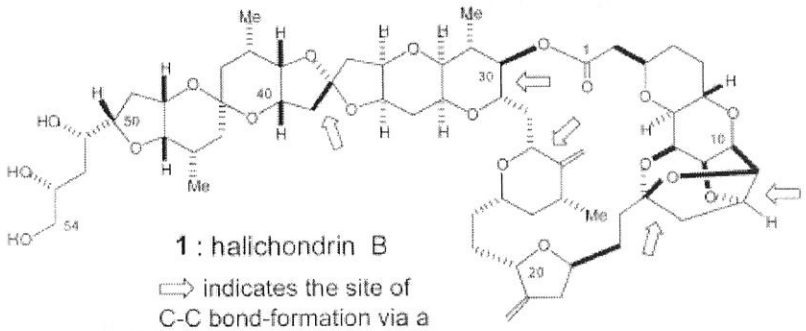
Table 1. Substrate Scope



entry	product	yield (%)[a]	ee (%)[b]	ER[b]
1		82	92	96:4
2		73	90	95:5
3		94	86	93:7
4		83	87	93.5:6.5
5		63	91	95.5:4.5
6		95	92	96:4
7		64	59	79.5:20.5
8		77	93	96.5:3.5
9		56	90	95:5
10		66	91	95.5:4.5
11[c]		75	16	58:42
12		93	33	66.5:33.5
13		73	91	95.5:4.5
14	 (dr 3.8:1)	69	88 (*anti*) 70 (*syn*)	94:6 85:15

Total synthesis of Halichondrin B (key person Kishi Yoshito)

- Isolated from the marine sponge *Halichondria okadai*
  (Uemura and Hirata *J. Am. Chem. Soc.* **1985**, *107*, 4796.)
- Exhibit extraordinary in vitro and in vivo antitumor activity

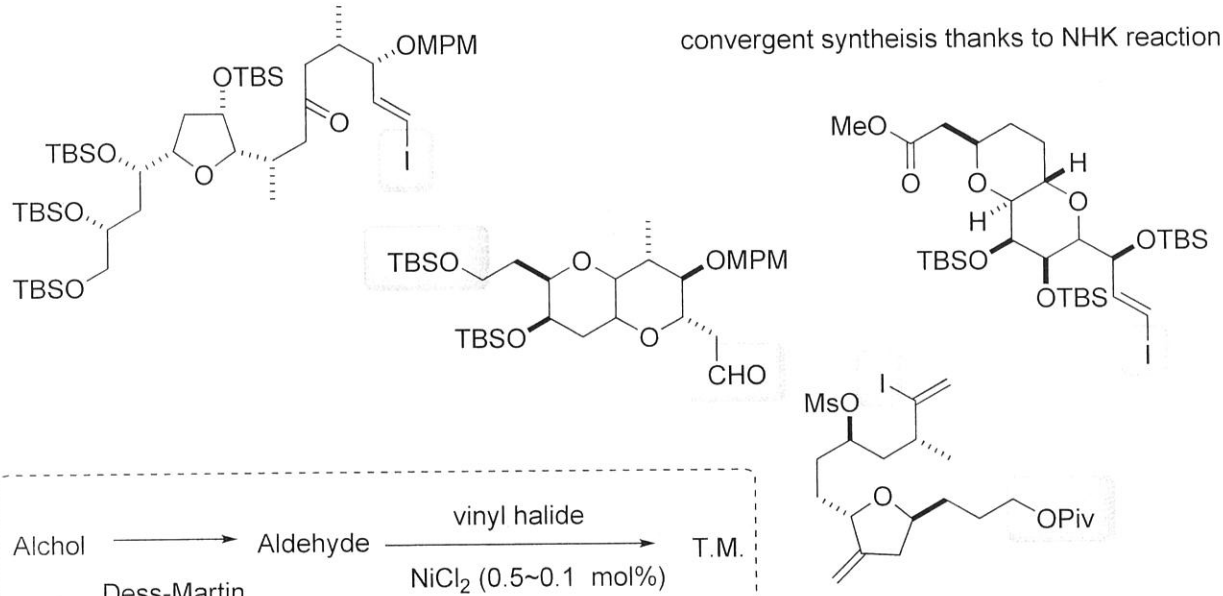


1 : halichondrin B

⇨ indicates the site of C-C bond-formation via a Ni(II)/Cr(II)-mediated coupling

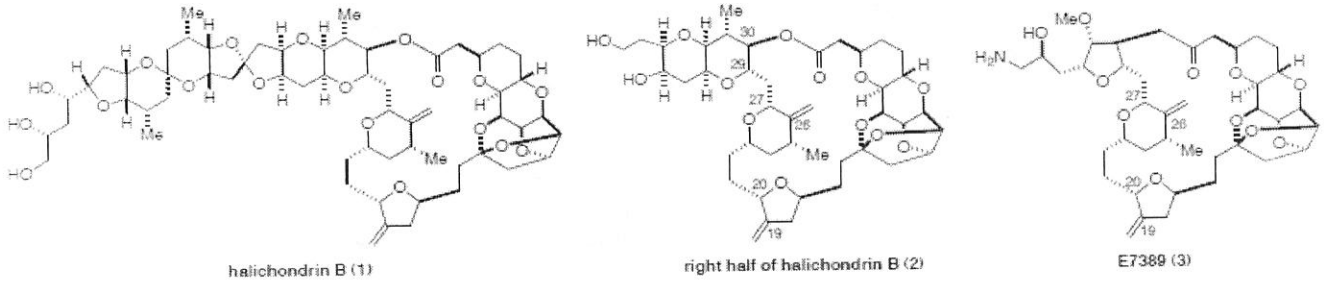
Total synthesis; Kishi *J. Am. Chem. Soc.* **1992**, *114*, 3163 (***First and Only***)

convergent syntheisis thanks to NHK reaction



Alchol → (Dess-Martin) → Aldehyde → (vinyl halide; $NiCl_2$ (0.5~0.1 mol%), $CrCl_2$, DMF/THF, rt) → T.M.

Figure 1



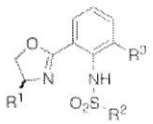
halichondrin B (1) | right half of halichondrin B (2) | E7389 (3)

function-oriented synthesis; *Acc. Chem. Res.* **2008**, *41*, 40

Application of Enantioselective NHK reaction

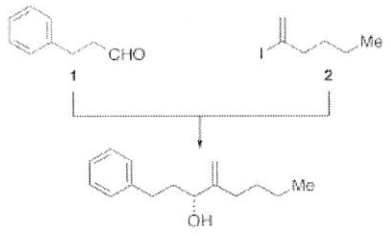
Kishi *Org. Lett.* **2002**, *4*, 4421 (stoichiometric process)

1) reduce the amout of Cr salt
2) asymmetric process

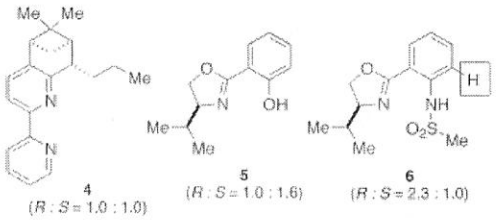


9 : R^1=*t*-Bu, R^2=2-naphthyl, R^3=Me : *R* : *S* = 12 : 1.0
10 : R^1=*i*-Pr, R^2=4-MeOPh, R^3=OMe : *R* : *S* = 7.6 : 1.0
11 : R^1=*i*-Pr, R^2=Me, R^3=OMe : *R* : *S* = 6.4 : 1.0
7 : R^1=*i*-Pr, R^2=Me, R^3=Me : *R* : *S* = 5.6 : 1.0

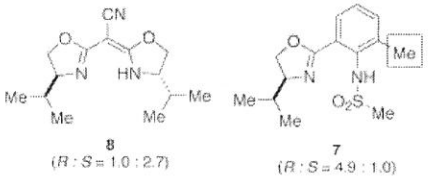
Scheme 2



R-3

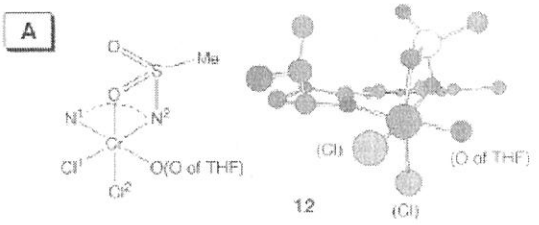


4 (*R* : *S* = 1.0 : 1.0)
5 (*R* : *S* = 1.0 : 1.6)
6 (*R* : *S* = 2.3 : 1.0)

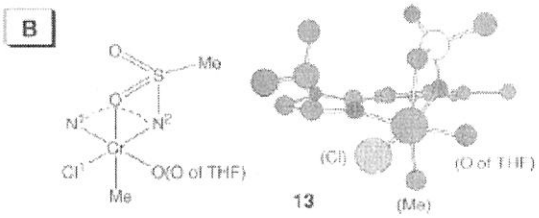


8 (*R* : *S* = 1.0 : 2.7)
7 (*R* : *S* = 4.9 : 1.0)

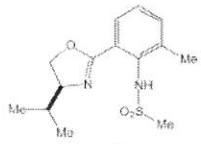
X-ray analysis



12



13



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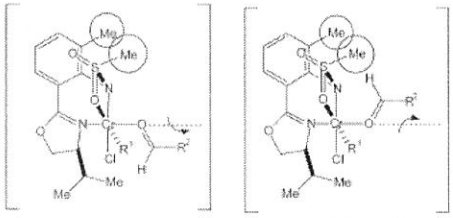
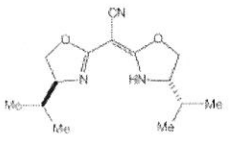


A : favored B : disfavored



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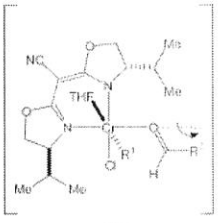
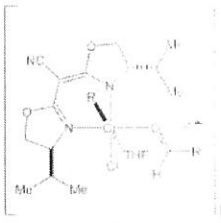
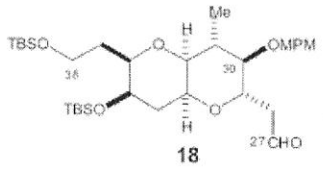


C :
This mode of coordination and rotation leads to a disfavored transition state.



D
This mode of coordination and rotation leads to a favored transition state
Note the position of R^1 and Cl.



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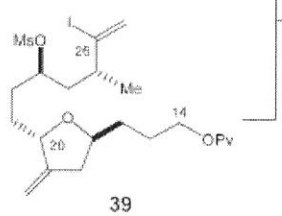
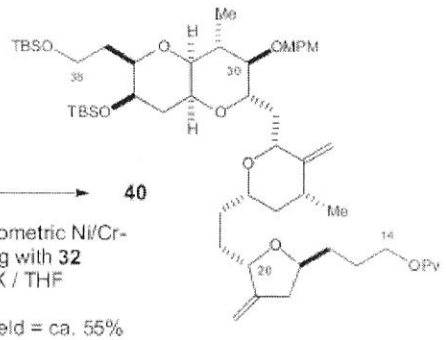


39



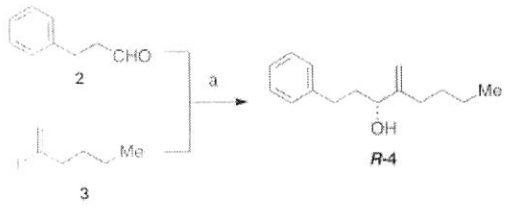
40

1. stoichiometric Ni/Cr-coupling with **32**
2. *t*-BuOK / THF

overall yield = ca. 55%
overall stereoselectivity
with **32** =ca. 20 : 1
without **32** = ca. 3.5:1

C14-C35 segment

Kishi *Org. Lett.* **2002**, *4*, 4435 (**catalytic process**)

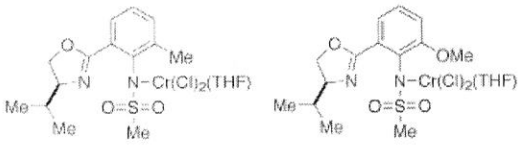


catalytic with **1a**
EtCN (*R* : *S* = 5.0 : 1.0)
THF (*R* : *S* = 4.3 : 1.0)

catalytic with **1b**
EtCN (*R* : *S* = 6.1 : 1.0)
THF (*R* : *S* = 4.0 : 1.0)

stoichiometric with **1a**
EtCN (*R* : *S* = 5.5 : 1.0)

stoichiometric with **1b**
EtCN (*R* : *S* = 6.3 : 1.0)



[a] Reagents and conditions: (a) **2** (1 equiv), **3** (2 equiv), **1** (10 mol %), $NiCl_2$ (10 mol %), Mn (2 equiv), TMSCl (2 equiv), $Et_2N{\cdot}HCl$ or $(Bn)(n\text{-}Bu)_3NCl$ (20 mol %), LiCl (2 equiv), EtCN or THF, rt.

Furstner condition using sulfoaminde ligand

(1) both complex function as effective catalysts

(2) TMSCl is the best agent to dissociate chromium-alkoxides

(3) Mn(0) is the most effective reducing agent

(4) addition of $(Bn)(n\text{-}Bu)_3NCl$ or Et_3NHCl enhances the coupling efficiency,

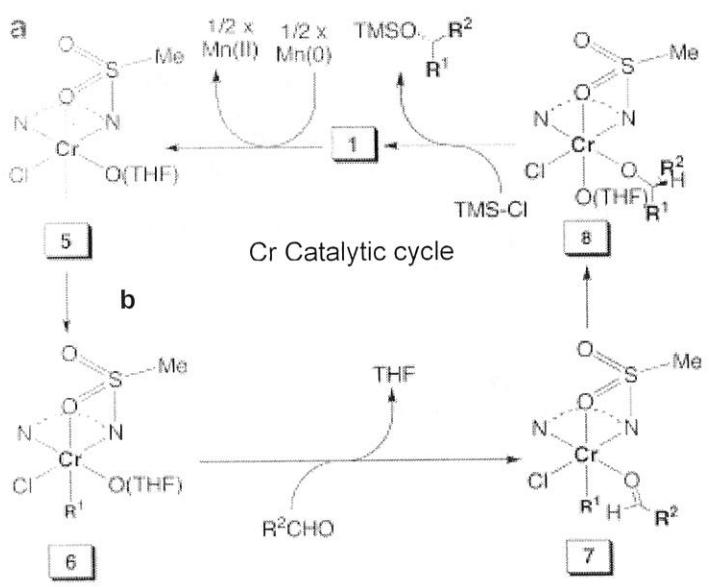
(5) addition of LiCl enhances the coupling rate

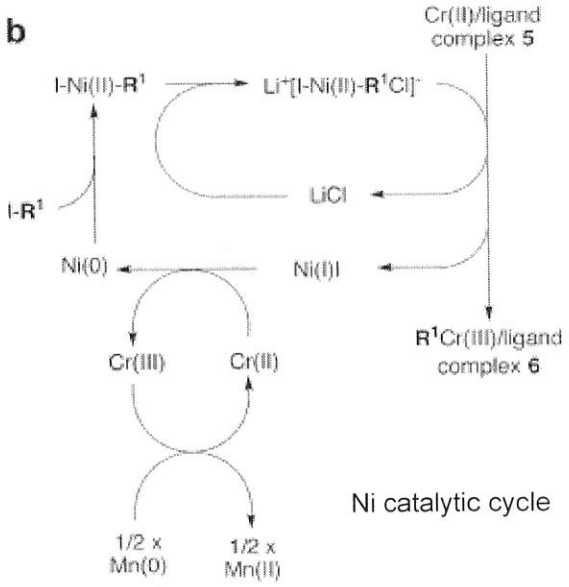
(6) EtCN and THF are good solvents

(7) 10 mol % of 1a,b is sufficient to complete the coupling within 24 h at rt

(8) the optimal temperature is around rt but the reaction proceeds at 0 °C

(9) the optimal range of concentration is 0.5 - 0.1 M



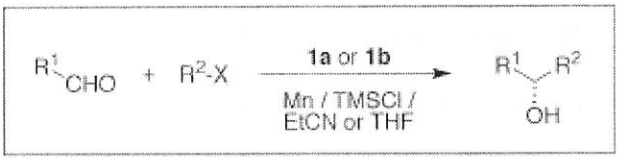


LiCl; formation of the Ni-ate complex from the alkenyl-Ni(II) complex

⟹ Enhancing the rate of transmetalation

$(Bn)(n\text{-}Bu)_3NCl$ or Et_3NHCl effect is unclear.

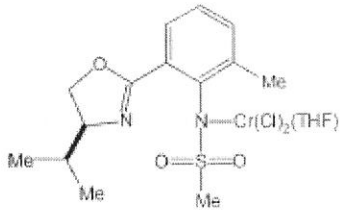
Apply this Cr-complex to several Cr-mediated coupling reactions



Cr-Mediated Coupling

Ni/Cr-Mediated Coupling

Co/Cr-Mediated Coupling



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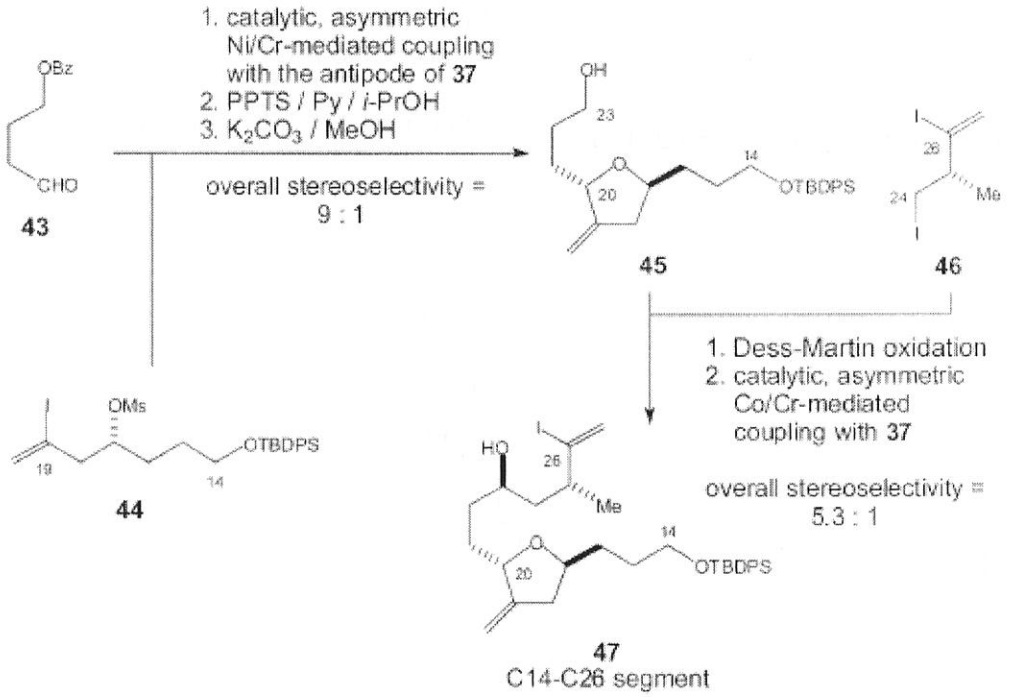
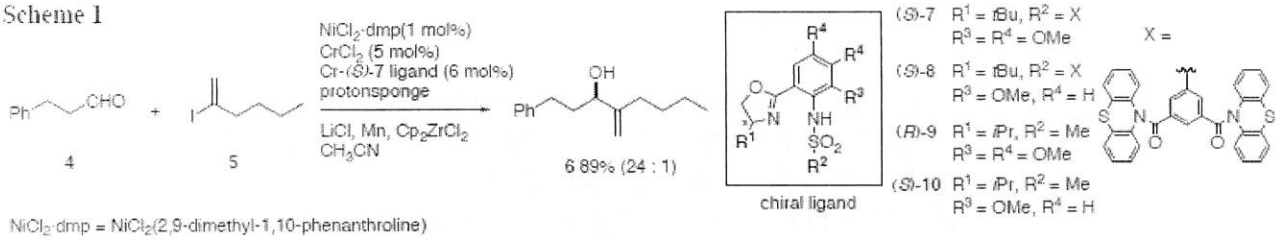


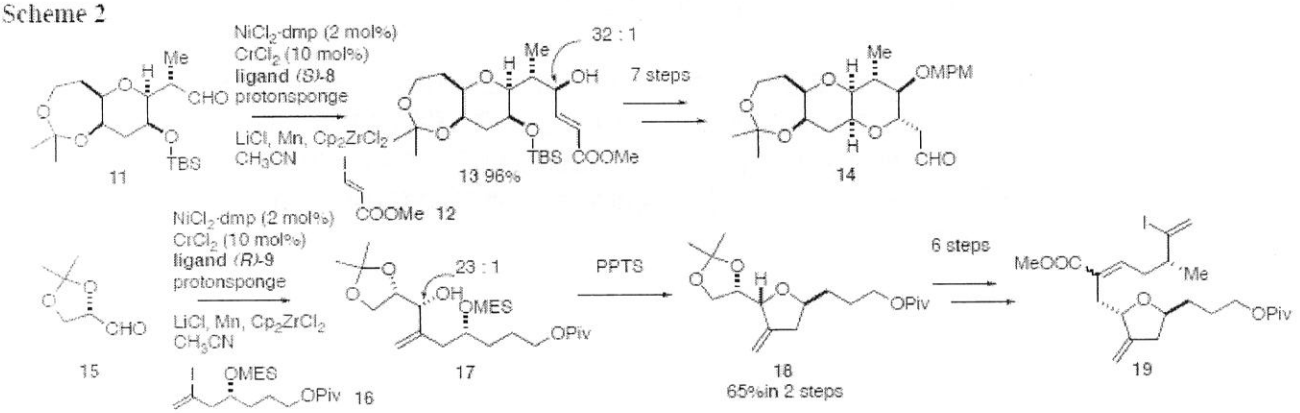
Recent work; 第６回次世代シンポジウム要旨　１－０１より引用

Scheme 1

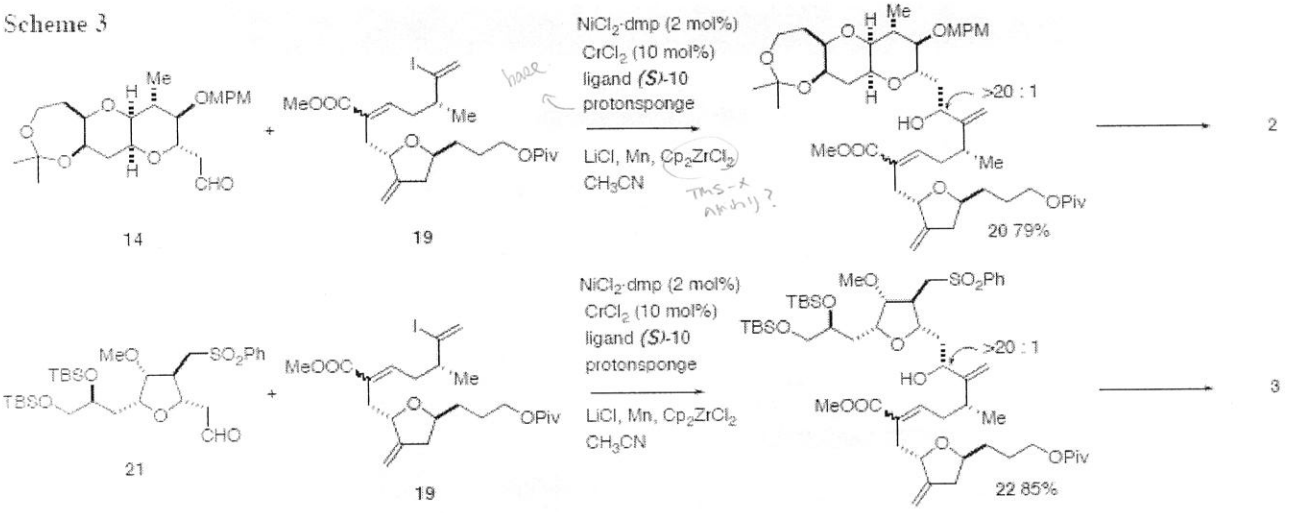


$NiCl_2$·dmp = $NiCl_2$(2,9-dimethyl-1,10-phenanthroline)

Scheme 2



Scheme 3



Summary

Target-oriented synthesis

Development new reaction (stoichiometric reaction) ⇒ catalytic reaction ⇒ catalytic asymmetric reaction ⇒

↓

Total synthesis
Halichondrin B

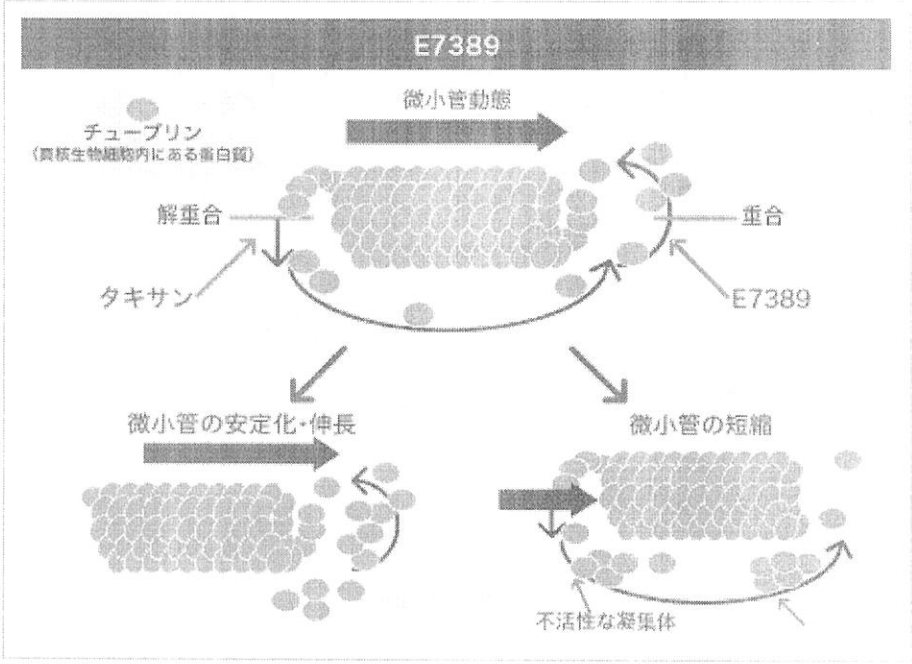
Function-oriented synthesis
structure optimization

↓

Pratical synthesis
E7389
⇒ Drug??

「E7389」(一般名・エリブリン)は、がん領域における期待の新規化合物です。クロイソカイメン由来の海洋天然物ハリコンドリンBに類似した合成化合物で、細胞分裂で重要な役割を果たす微小管の構成成分であるチューブリンの重合を阻害して細胞分裂を抑制する強力な抗腫瘍活性が確認されています。
「E7389」は、現在フェーズⅢ進行中の難治性の乳がんをはじめ、非小細胞肺がん、前立腺がん、肉腫などのがん種を対象に進めています。難治性の乳がんは2009年度に日・米・欧同時申請を目指します。

このほか、がんの増殖阻止をめざした「E7080」、「E7820」がフェーズⅡ、がん縮小をめざした「E7070」「E6201」がそれぞれフェーズⅠの段階にあり、これらにモルフォテックで創出され、現在フェーズⅡ/Ⅲ準備中の「MORAb-003」やフェーズⅡの「MORAb-009」などのがん抗体治療を加え、臨床試験段階に充実したパイプラインを築いています。



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