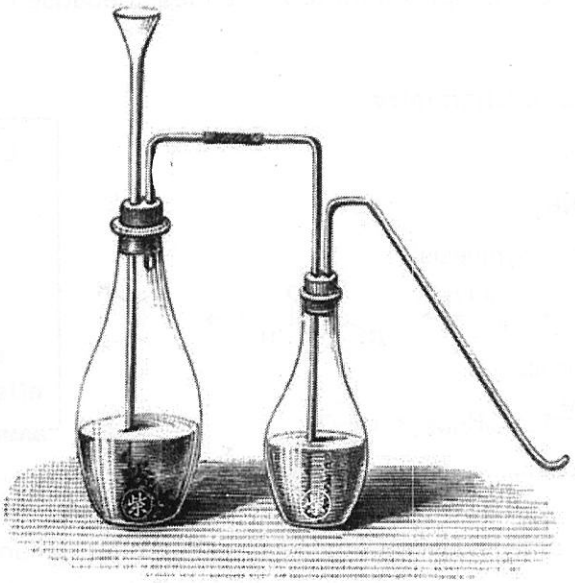
Catalytic Hydrogenative C-C Bond Formation



Preparing hydrogen.

21st / Nov. / 2009　M2 Part

Takafumi Yukawa

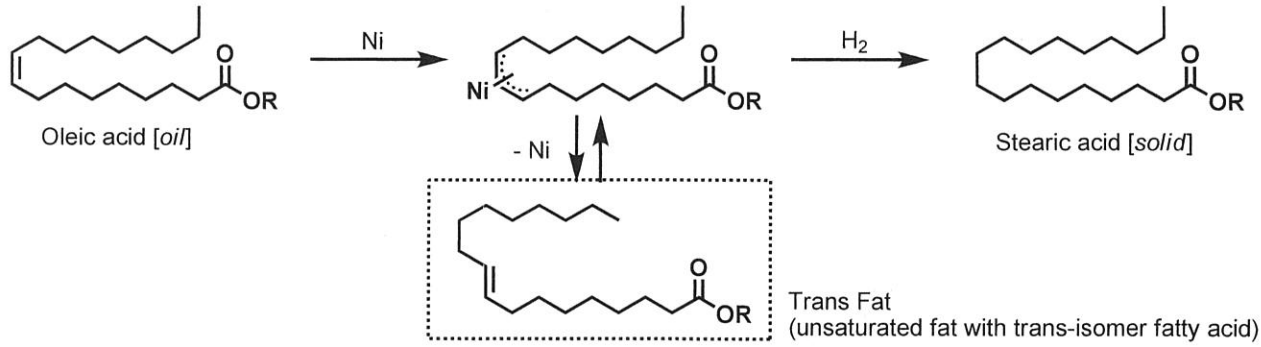
Chapter 0. Introduction

Trans Fat Problem

Trans Fat
- Substance in margarine, shortening, etc
- Byproduct made throughout the manufacturing process
- Potential risk of coronary heart desease (CHD)

☑ Hydrogenation is used in the manufacturing process of margarine.

ex) Hydrogenation of oleic acid



Oleic acid [*oil*]

Stearic acid [*solid*]

Trans Fat
(unsaturated fat with trans-isomer fatty acid)

☑ Hydrogenation has solved several problems in food market.

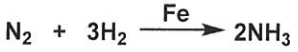
Butter		Margarine
• Unstability for supply (made from milk) • High cost • Perishable (impossible to store long time)	***improved*** ⟹	• Stability for supply (made from vegetable fat) • Low cost • Nonperishable (conservable)

Hydrogenation can be applied for food business because of its **efficiency**.

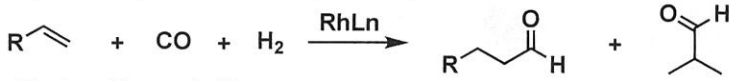
Industrial Hydrogenation

Hydrogenation is **True Green Chemistry**.

ex1) Haber-Bosch Process



ex2) Hydroformylation (Oxo Synthesis)



ex3) Fischer-Tropsch Process

Efficiency
- Excellent Atom Economy
- High Cost-Effectiveness
- Step Economy

⇓

Creating C-C bond through effective catalytic hydrogenation

T O D A Y ' S T H E M E

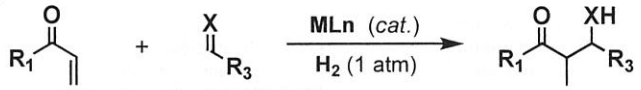
~ Catalytic Hydrogenative C-C Bond Formation ~

Chapter 1. Krische's Work

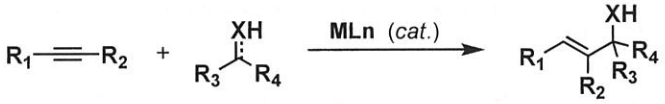
Krische group mainly focuses on **"Metal(Rh, Ir, Ru)-Catalyzed Hydrogenative C-C Bond Formation".**

Three Important Pillars in Krische group

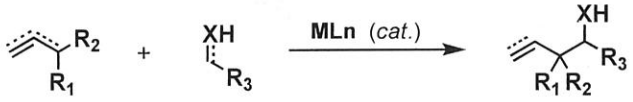
(1) Catalytic Reductive Aldol Coupling



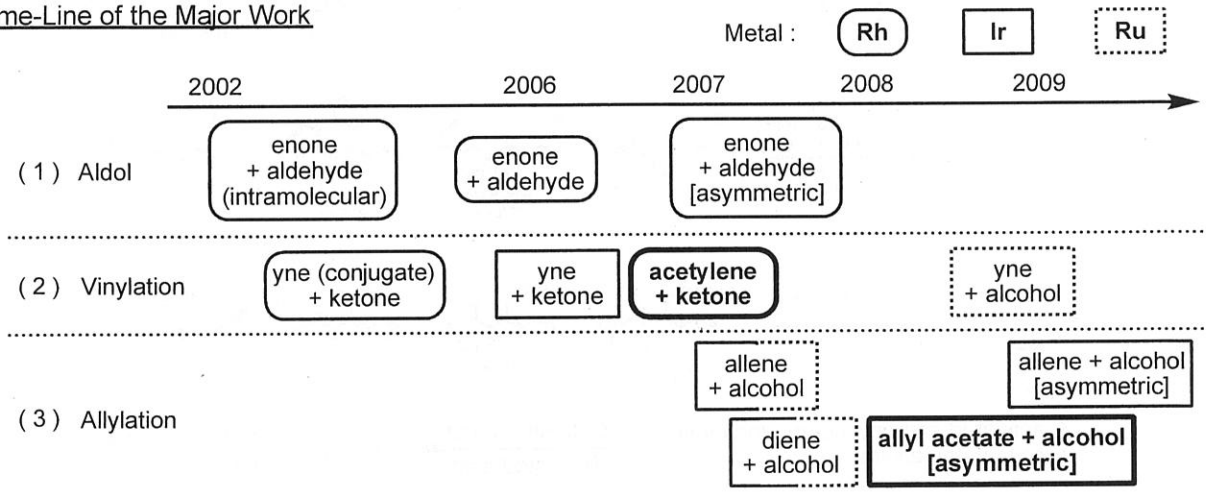
(2) Catalytic Vinylation of Carbonyl Compounds via Transfer Hydrogenation



(3) Catalytic Allylation / Propargylation from the Alcohol Oxidation Level



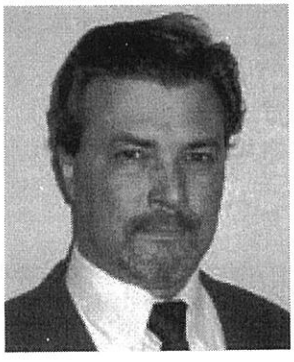
Time-Line of the Major Work



⇨ Let me focus on { H_2-Mediated Coupling of Acetylene (Chapter 2.)
Catalytic Allylation via Auto-Transfer Hydrogenation (Chapter 3.)

Review

1. *Acc. Chem. Res.* **2007**, *40,* 1394
2. *J. Org. Chem.* **2007**, *72*, 1063
3 *Synthesis* **2008**, *17*, 2669
4. *Chem. Lett.* **2008**, *37*, 1102
5. *Aldrichimica Acta* **2008**, *41*, 95
6. *Angew. Chem., Int. Ed.* **2009**, *48*, 34
7. *Chem. Commun.* **2009**, *ASAP*

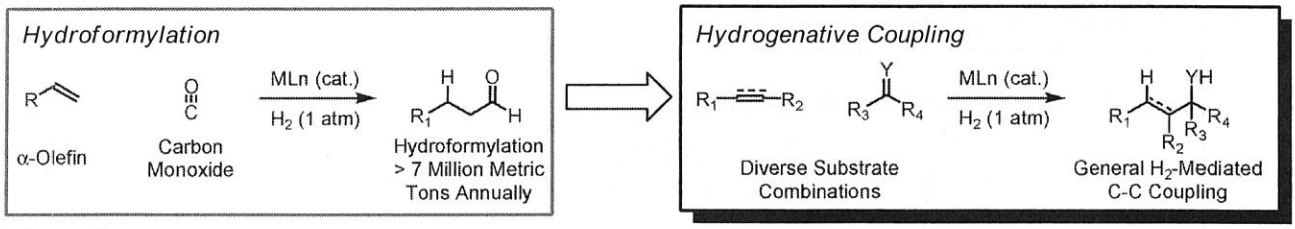


Michael J. Krische obtained a B.S. degree in chemistry from the University of California at Berkeley, where he performed research under the guidance of Professor Henry Rapoport as a President's Undergraduate Fellow. After one year of study abroad as a Fulbright Fellow, he initiated graduate research at Stanford University under the mentorship of Professor Barry Trost as a Veatch Graduate Fellow. Following receipt of his Ph.D. degree, he worked with Jean-Marie Lehn at the Université Louis Pasteur as an NIH Post-Doctoral Fellow. In the fall of 1999, he was appointed Assistant Professor at the University of Texas at Austin. He was promoted directly to Full Professor in 2004 and in 2007 he received the Robert A. Welch Chair in Science.

Chapter 2. H_2-Mediated Coupling of Acetylene (*J. Am. Chem. Soc.* **2009**, *131*, 16054)

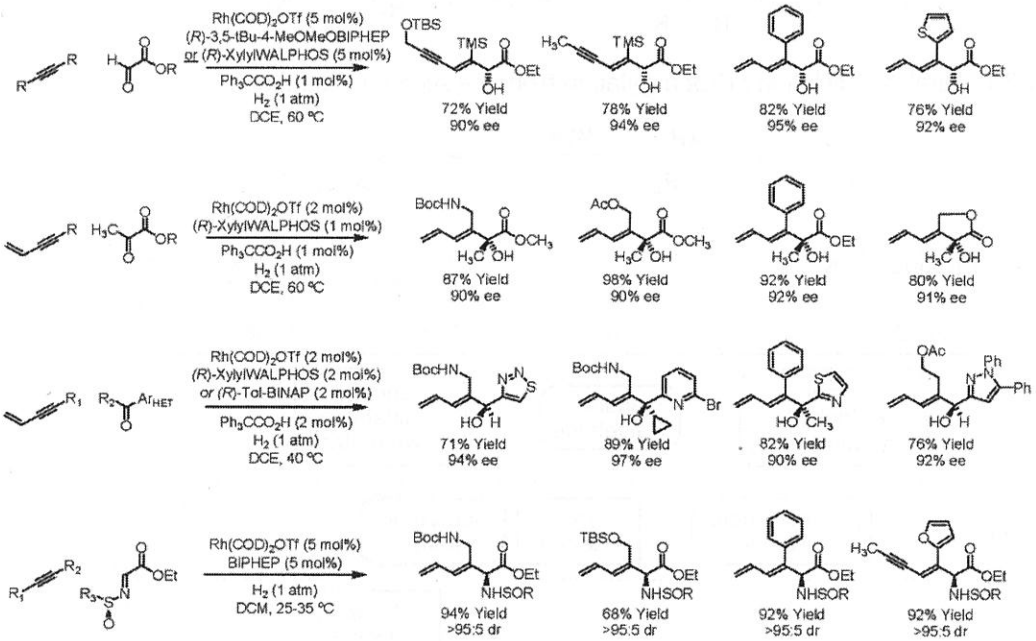
2-1. Background

Idea



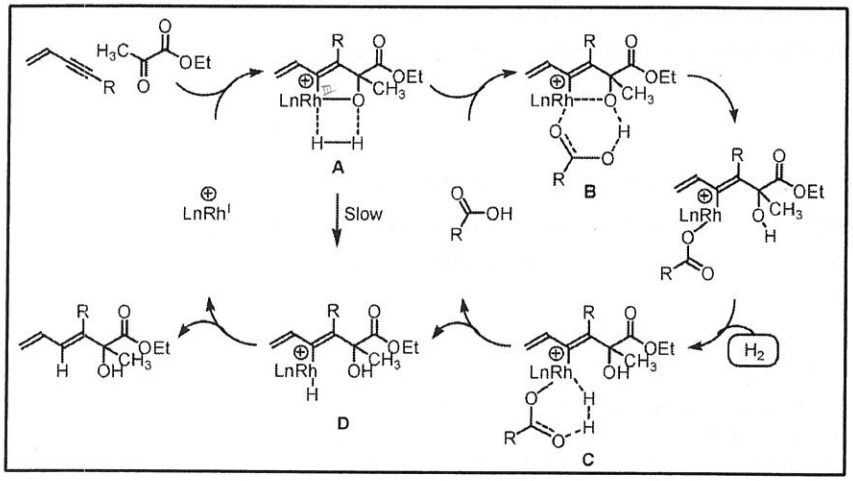
Data so far

SCHEME 7. Asymmetric Hydrogenative Coupling of Conjugated Alkynes to Activated Carbonyl Compounds and Imines: A Step toward Hydrogenative Reactions Involving α-Olefins and Styrenes



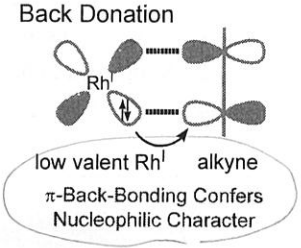
Substrate : { activated carbonyl compound / imine, conjugated alkyne } —Cationic Rh cat., Brønsted acid→ Result : { moderate yield, high ee }

Proposed Mechanism



Rh catalyst coordinated to alkyne

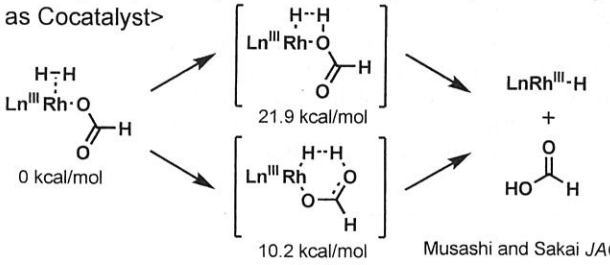
Back Donation



A - D : H_2 oxidative addition through high energetic four-centered transition state

A - B - C - D : metallacycle protonolysis with carboxylic acid, followed by hydrogenolysis of rhodium carboxylate

<Brønsted Acid as Cocatalyst>



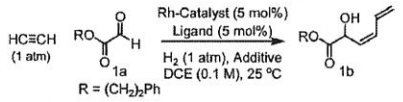
Six-centered TS (**C**) is favorable and rhodium hydride is formed.

Musashi and Sakai *JACS*, **2002**, *124*, 7588

2-2. Hydrogenative (*Z*)-Butadienylation Using Acetylene

Optimization

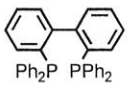
Table 1. Optimization of the Hydrogen-Mediated Reductive Coupling of Acetylene and Phenethyl Glyoxalate[a]



entry	Rh catalyst	ligand	additive	**1b** yield%
1	$Rh(cod)_2OTf$	BIPHEP	TPAA (Ph_3CCO_2H)	32
2	$Rh(cod)_2OTf$	BIPHEP		17
3	$[RhCl(cod)]_2$	BIPHEP	TPAA	not observed
4	$Rh(cod)_2BF_4$	BIPHEP	TPAA	41
5	$Rh(cod)_2SbF_6$	BIPHEP	TPAA	51
6	$Rh(cod)_2BARF$	BIPHEP	TPAA	52
7	$Rh(cod)_2SbF_6$	PPh_3	TPAA	not observed
8	$Rh(cod)_2SbF_6$	DPPE	TPAA	not observed
9	$Rh(cod)_2SbF_6$	*rac*-BINAP	TPAA	29
10	$Rh(cod)_2SbF_6$	BIPHEP	TPAA–Na_2SO_4[b]	59
11	$Rh(cod)_2SbF_6$	BIPHEP	TPAA–Na_2SO_4[b,c]	68

[a] Cited yields are of pure isolated material. TPPA = triphenylacetic acid. For entry 7, 10 mol % of Ph_3P was used. See Supporting Information for detailed experimental procedures. [b] Two equivalents of Na_2SO_4 were added. [c] Loading of TPAA is 7.5 mol %.

Rh source, phosphine ligand and additive are examined.

BIPHEP : 

Entry 1, 2 : Acid is essential.

Entry 1, 3 - 6 : The rhodium(I) counterion plays a decisive role.

Entry 7 - 9 : Screening of standard phosphine ligands

Entry 10, 11 : Adding Na_2SO_4 as a dehydrating reagent

Afterward, Rh counteranion is changed.

$[Rh(cod)_2]SbF_6 \longrightarrow [Rh(cod)_2]BARF$

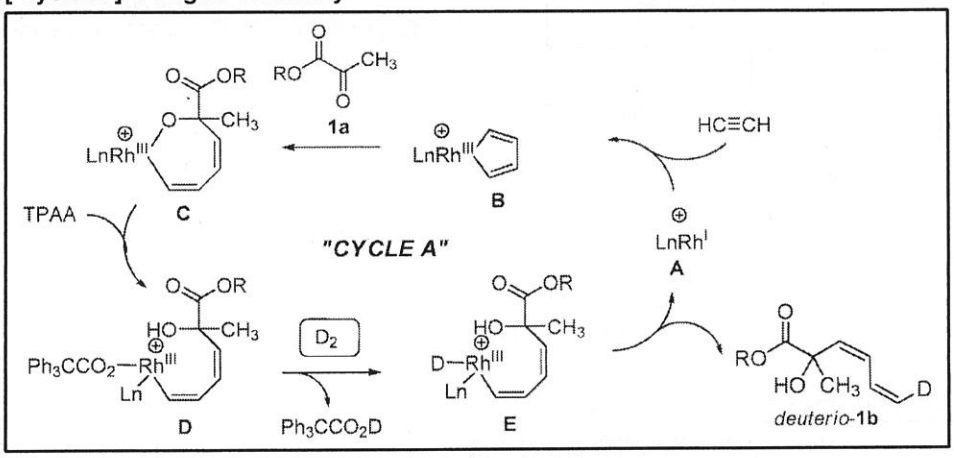
solubility small < large

Proposed Two Catalytic Cycles

There seem to be two possible catalytic mechanisms shown below.

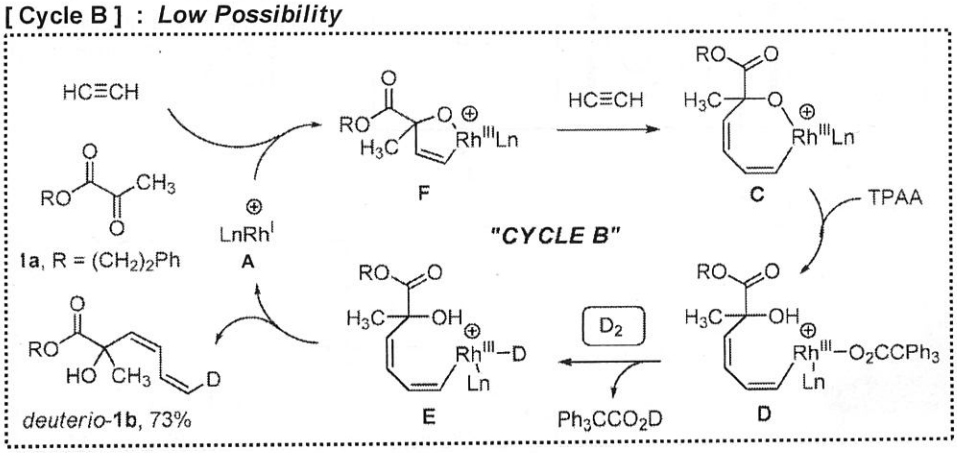
Scheme 1. Hydrogen-Mediated Coupling of Acetylene to Pyruvate **1a** (TPAA = Ph_3CCO_2H) and Plausible Catalytic Cycles A and B Consistent with the Results of Deuterium Labeling

[Cycle A] : *High Possibility*



A - B - C : acetylene dimerization to form a cationic rhodacyclopentadien, then carbonyl insertion

[Cycle B] : *Low Possibility*



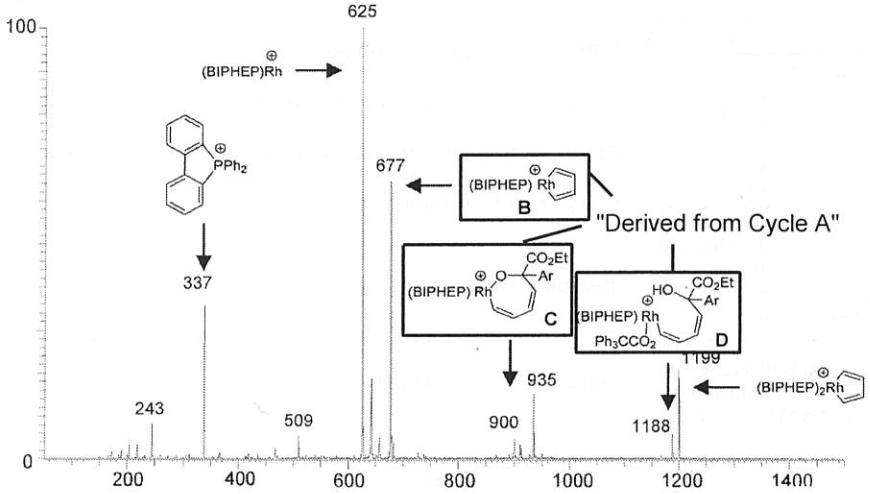
A - F - C : acetylene - carbonyl oxidative coupling, then insertion of a second acetylene

Mechanistic Study

Purpose { Support for Cycle A / Excluding the Possibility of Cycle B } ⇨ *Analysis* { (a) ESI-MS / ESI-CAD-MS; (b) Computational Modeling (based on DFT); (c) Experiments of Putative Intermediate }

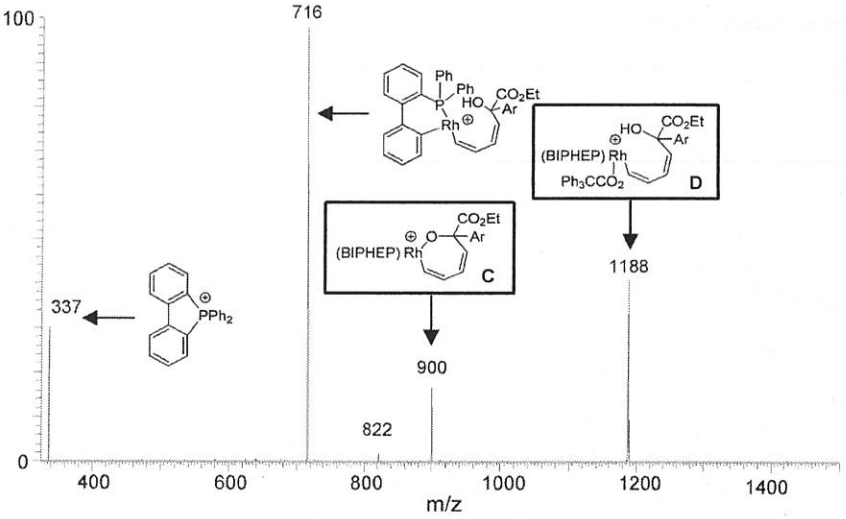
(a) ESI-MS / ESI-CAD-MS Analysis

[ESI-MS]



1. Key MS of Cycle A are observed. (m/z 677, 900, 1188)
2. Key MS of Cycle B are NOT observed.
3. MS of intermediate E is not obeserved, due to rapid reductive elimination.

[ESI-CAD-MS (MS/MS/MS) of the ion of m/z 1188 (intermediate D)]

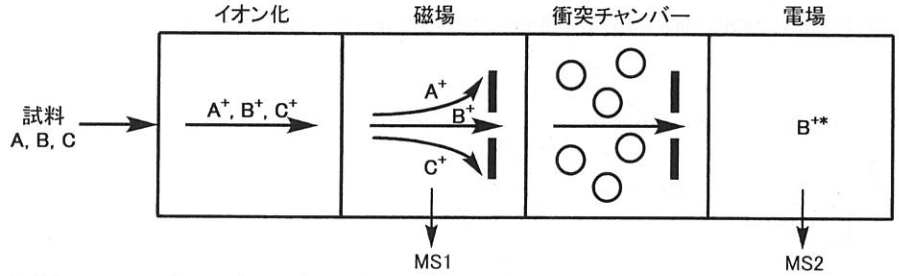


MS of intermidiate C is also observed.

⇨ intermidiate **C** ⇌ (*reversible*) intermidiate **D**

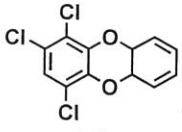
「CAD-MS」及び「タンデム質量分析法」について

CAD-MS（Collisional Activated Dissociation Mass）：衝突活性化開裂 質量分析法

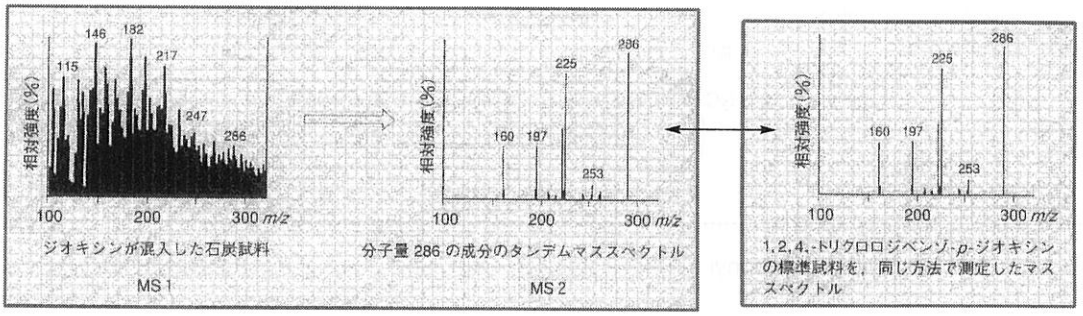


タンデム質量分析法（MS/MS）
質量分析計を直列に置き、特定の（フラグメント）イオンのみを選択的に分離分析する。

応用例：1,2,4-トリクロロジベンゾ-*p*-ジオキシンの同定

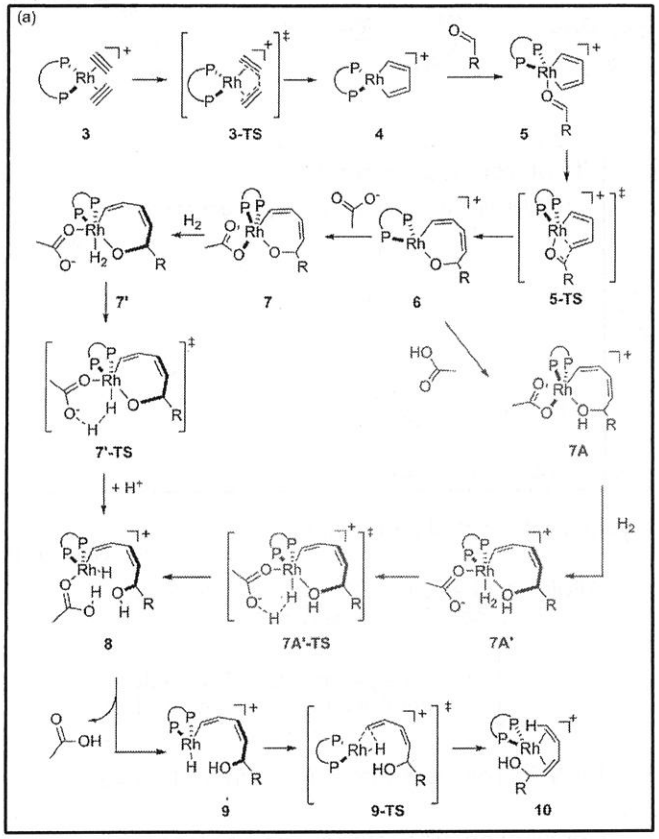


1,2,4-トリクロロジベンゾ-*p*-ジオキシン



(b) Computational Modeling (based on DFT) Analysis

[Cycle A]



[Cycle B]

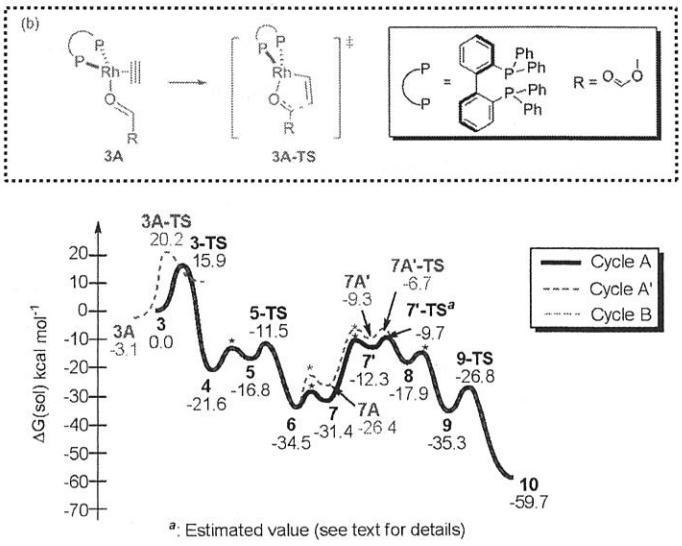


Figure 2. Computed reaction energy profile.

Reaction cycle should be determined by the barrier of the first TS (3-TS and 3A-TS).

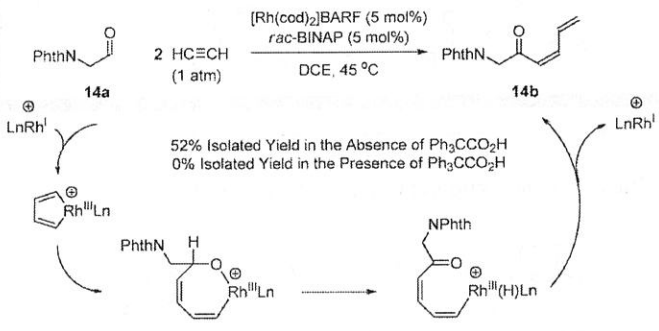
{ Cycle A : 15.9 kcal/mol **(3 - 3-TS)**
{ Cycle B : 23.3 kcal/mol **(3A - 3A-TS)**

⟹ Cycle A has a priority.

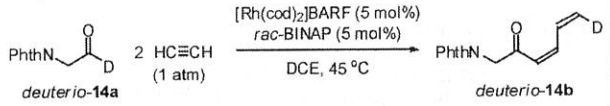
(c) Experiments of Putative Intermediate Analysis

< Experiment 1 >

Scheme 3. Rhodium-Catalyzed Coupling of Acetylene to Aldehyde **14a** in the Absence of Hydrogen and Brønsted Acid Cocatalyst Delivers Ketone **14b**, Corroborating Intervention of the Proposed Oxarhodacycloheptadiene Intermediate



Isotope Check



Coupling of acetylene to aldehyde **14a** is performed in the absence of both hydrogen and carboxylic acid.

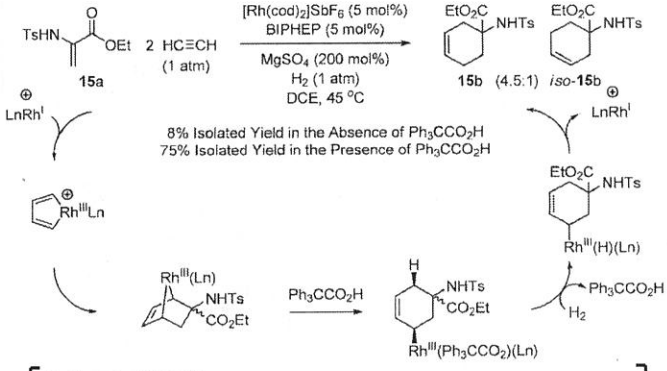
⇓

β-hydride eliminated **14b** is obatained. (supported by isotope check)

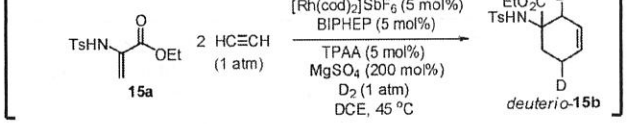
corroboration of the proposed "oxarhodacycloheptadiene intermediate"

< Experiment 2 >

Scheme 4. Rhodium-Catalyzed Hydrogenation of Acetylene in the Presence of Dehydroalanine **15a** Delivers the Product of Reductive [2 + 2 + 2] Cycloaddition **15b**, Corroborating Intervention of the Proposed Rhodacyclopentadiene Intermediate



Isotope Check



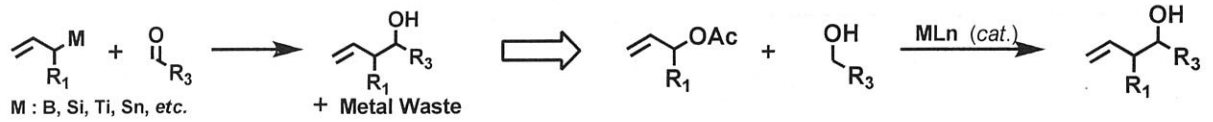
Coupling of acetylene to dehydroalanine **15a** is performed under the standard condition.

⇓

Product of reductive [2 + 2 + 2] cycloaddition **15b** is obatained. (supported by isotope check)

corroboration of the proposed "rhodacyclopentadiene intermediate"

Chapter 3. Catalytic Allylation via Auto-Transfer Hydrogenation (*J. Am. Chem. Soc.* **2008**, *130*, 14891)

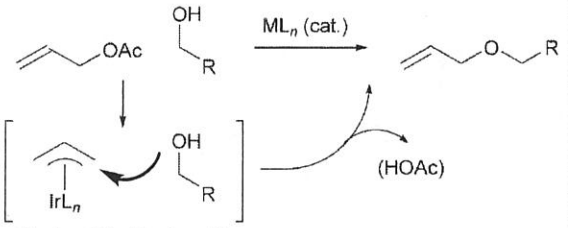


M : B, Si, Ti, Sn, *etc.* + Metal Waste

Idea

Tsuji-Trost type Reaction

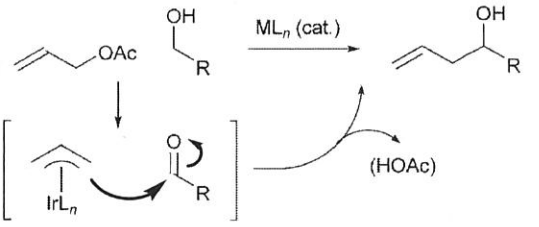
O-Allylation through conventional allylic substitution:



Electrophile–Nucleophile

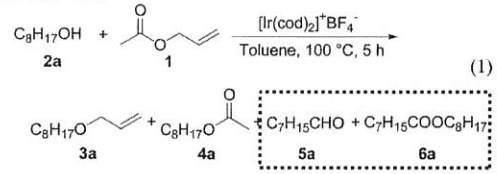
Transfer Hydrogenation

C-Allylation through transfer hydrogenative coupling:



Nucleophile–Electrophile

TABLE 1. Reaction of 2a with 1 Catalyzed by $Ir(cod)_2^+BF_4^-$ [a]



A stoichiomeric reaction of **1** with **2a** afforded ally octyl ether (**3a**) (23%), octyl acetate (**4a**) (1%), octanal (**5a**)

		conv (%)		yield (%)			
run	**1** (equiv)	**2a**	**1**	**3a**	**4a**	**5a**	**6a**
1	1	84	76	23	1	1	16
2	2	87	50	56	1	1	11
3	5	96	24	86	4	4	2
4	10	>99	27	99	n.d.	n.d.	n.d.
5[b]	10	5	3	trace	n.d.	n.d.	n.d.
6[c]	10	3	1	n.d.	1	n.d.	n.d.
7[d]	10	19	11	7	11	n.d.	n.d.
8[e]	10	99	21	4	13	n.d.	74
9[f]	10	49	15	27	trace	n.d.	n.d.

[a] **2a** (1 mmol) was allowed to react with **1** in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol) in toluene (1 mL) at 100 °C for 5 h. [b] $[IrCl(cod)]_2$ (0.01 mmol) was used as a catalyst. [c] $[IrCl(CO)(P\text{-}Ph_3)_2]$ (0.01 mmol) was used as a catalyst. [d] $[Rh(cod)_2]^+BF_4^-$ (0.01 mmol) was used as a catalyst. [e] Na_2CO_3 (0.03 mmol) was added. [f] At 90 °C.

< Allylation of Alcohol by Ir Catalyst >

Ishii et al *JOC* **2004**, *69*, 3474

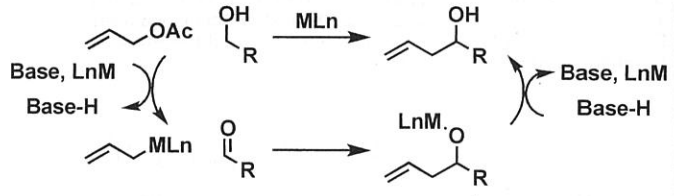
Allyllation of alcohol is difficult to be achieved by simple Tsuji-Trost type reaction

- Ir catalyst instead of Pd catalyst
- Optimization to lessen byproduct

Entry 8 : Transfer hydrogenative product is major.

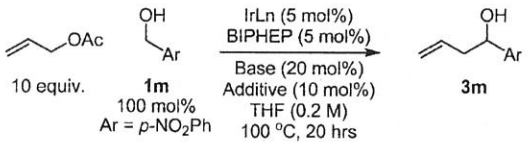
⇒ Conbination of Ir catalyst and base can enhance "Transfer hydrogenation reaction" !?

Transfer Hydrogenation Under Basic Condition



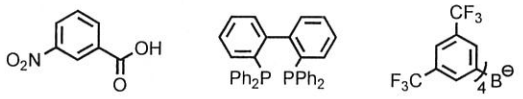
Optimization

Table 1. Selected Optimization Experiments Illustrating the Effect of Basic and Acidic Additives and Iridium Source in the Transfer Hydrogenative Allylation of *p*-Nitrobenzyl Alcohol **1m**[a]



	Entry	Base	Additive	Iridium Source	Yield (%)
⇨	**1**	**Cs_2CO_3**	***m*-NO_2BzOH**	**$[Ir(cod)Cl]_2$**	**80**
	2	K_2CO_3	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	21
	3	Na_2CO_3	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	15
	4	Li_2CO_3	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	12
	5	---	*m*-NO_2BzOH	$[Ir(cod)Cl]_2$	< 5
Additive-Base	6	Cs_2CO_3	---	$[Ir(cod)Cl]_2$	47
	7	---	---	$[Ir(cod)Cl]_2$	10
	8	---	*m*-NO_2BzOCs	$[Ir(cod)Cl]_2$	72
	9	Cs_2CO_3	*m*-NO_2BzOCs	$[Ir(cod)Cl]_2$	79
	10	Cs_2CO_3	*o*-NO_2BzOH	$[Ir(cod)Cl]_2$	39
	11	Cs_2CO_3	*p*-NO_2BzOH	$[Ir(cod)Cl]_2$	49
	12	Cs_2CO_3	BzOH	$[Ir(cod)Cl]_2$	39
	13	Cs_2CO_3	*p*-MeOBzOH	$[Ir(cod)Cl]_2$	42
	14	Cs_2CO_3	*m*-FBzOH	$[Ir(cod)Cl]_2$	41
	15	Cs_2CO_3	*m*-NO_2BzOMe	$[Ir(cod)Cl]_2$	47
IrLn	16	Cs_2CO_3	---	$[Ir(cod)(BIPHEP)]BARF$	41
	17	Cs_2CO_3	*m*-NO_2BzOH	$[Ir(cod)(BIPHEP)]BARF$	72

Base, additive and iridium source are examined.



m-NO_2BzOH BIPHEP BARF

Entry 1 - 5 : Cs_2CO_3 is best.

Other carbonate bases / No bases added } far less effective

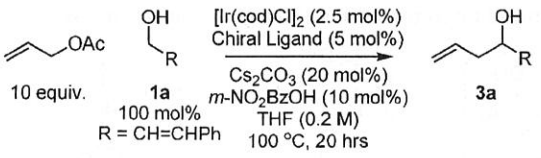
Entry 6 - 9 : Base is essential, Acid promotes the reaction.

Entry 6, 10 - 15 : *m*-NO_2BzOH is also crucial.

Entry 16, 17 : neutral Ir complex ≥ cationic Ir complex

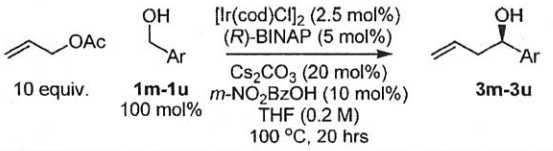
$[Ir(cod)Cl]_2$ $[Ir(cod)(BIPHEP)]^+$

Table 3. Selected Results from an Assay of Chiral Ligand in the Transfer Hydrogenative Allylation of Cinnamyl Alcohol **1a** and Effect of Temperature on Enantiomeric Excess[a]



	Entry	T °C	Chiral Ligand	Yield (%)	ee (%)
⇨ T °C	**1**	**100**	**(*R*)-Cl,MeO-BIPHEP**	**71**	**91 (*R*)**
T °C	2	80	(*R*)-Cl,MeO-BIPHEP	61	93 (*R*)
T °C	3	120	(*R*)-Cl,MeO-BIPHEP	59	90 (*R*)
Chiral Ligand	4	100	(*R*)-MeO-BIPHEP	69	80 (*R*)
Chiral Ligand	5	100	(*R*)-BINAP	64	90 (*R*)
Chiral Ligand	6	100	(*R*)-tol-BINAP	51	88 (*R*)
Chiral Ligand	7	100	(-)-TMBTP	59	82 (*R*)
Chiral Ligand	8	100	(*S*)-C1-TUNEPHOS	80	70 (*S*)
Chiral Ligand	9	100	(*R*)-C2-TUNEPHOS	77	77 (*R*)
Chiral Ligand	10	100	(*S*)-C3-TUNEPHOS	72	78 (*S*)
Chiral Ligand	11	100	(*S*)-C4-TUNEPHOS	57	80 (*S*)
Chiral Ligand	12	100	(*R*)-H8-BINAP	68	85 (*R*)
Chiral Ligand	13	100	(*S*)-BIPHEMP	68	80 (*R*)
Chiral Ligand	14	100	CTH-(*S*)-P-PHOS	71	86 (*S*)
Chiral Ligand	15	100	(*R*)-SOLPHOS	41	40 (*R*)
Chiral Ligand	16	100	(*S*)-SEGPHOS	69	78 (*S*)
Chiral Ligand	17	100	(*R*)-SYNPHOS	69	83 (*R*)

Table 7. Ir-Catalyzed Transfer Hydrogenative Allylation of Benzylic Alcohols **1m–u**[a]



Entry	Aryl Moiety	Alcohol	Product	Yield (%)	ee (%)
1	*p*-NO_2Ph	**1m**	**3m**	72	91
2	*p*-(CO_2Me)Ph	**1n**	**3n**	77	93
3	piperonyl	**1o**	**3o**	76	91
4	Ph	**1p**	**3p**	62	93
5	*p*-BrPh	**1q**	**3q**	74	93
6	*o*-MeOPh	**1r**	**3r**	80	92
7	*p*-MeOPh	**1s**	**3s**	73	93
8	3,5-Cl_2Ph	**1t**	**3t**	61	92
9	2-(*N*-Me-indolyl)	**1u**	**3u**	55	90

Table 3.

Ligand : 

(R)-Cl,MeO-BIPHEP

Temp. : 100°C

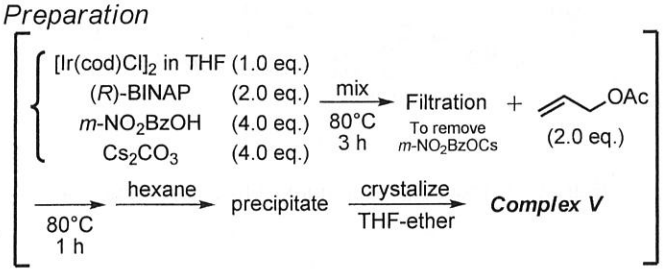
Table 7.

Aromatic substrate scope ⟶ { moderate yield / high ee

Mechanistic Study

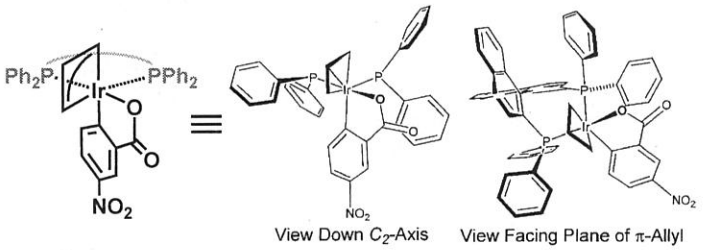
< X-ray Diffraction Analysis >

Preparation



"*ortho*-cyclometalated iridium(III)–π-allyl complex"

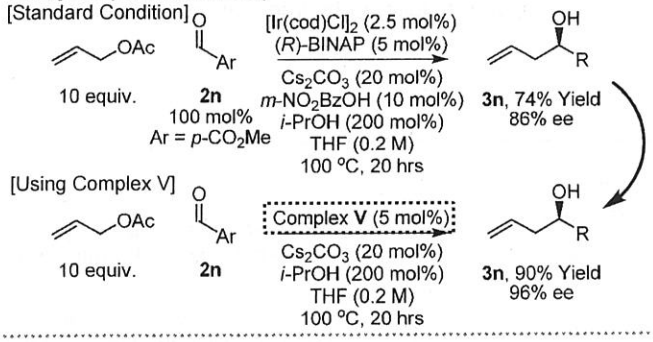
Structure determined by single-crystal X-ray diffraction



⟹ Does *Complex V* serve as an active catalyst?

Confirming the Activity of Complex V

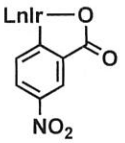
☑ ***Scheme 1.*** Experiments Corroborating Intervention of *Ortho*-Cyclometalated Iridium(III)–π-Allyl Complex **V** as a Catalytically Relevant Entity[a]



Check 1 : Reactivity / Selectivity of *Complex V*

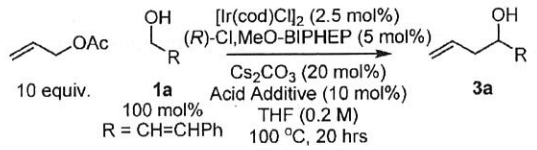
When using *complex V*,

{ Superior Conversion / Optical Enrichment } are observed.

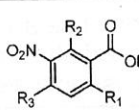
⟹ Structure of 

is important in reactivity and selectivity ?

☑ ***Table 4.*** Selected Optimization Experiments Illustrating the Effects of Substitution of *m*-Nitrobenzoic Acid on Conversion and Enantiomeric Excess in the Transfer Hydrogenative Allylation of Cinnamyl Alcohol **1a**[a]



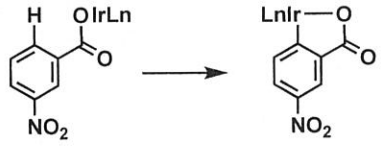
	Entry	Carboxylic Acid	Yield (%)	ee (%)
⇨	**1**	**R_1 = R_2 = R_3 = H**	**71**	**91 (*R*)**
	2	No Acid Additive	8	47 (*S*)
	3	R_1 = Me, R_2 = R_3 = H	18	65 (*S*)
	4	R_2 = Me, R_1 = R_3 = H	50	67 (*R*)
	5	R_3 = Me, R_1 = R_2 = H	69	91 (*R*)



Check 2 : Effect of Substitution of *m*-NO_2BzOH

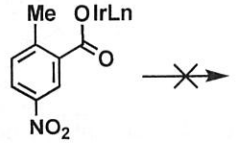
Entry 1, 4, 5 : (*R*)-isomer

The preferred site of cyclometalation remains free.

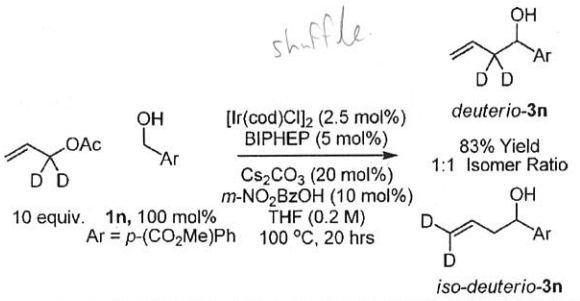


Entry 3 : (*S*)-isomer

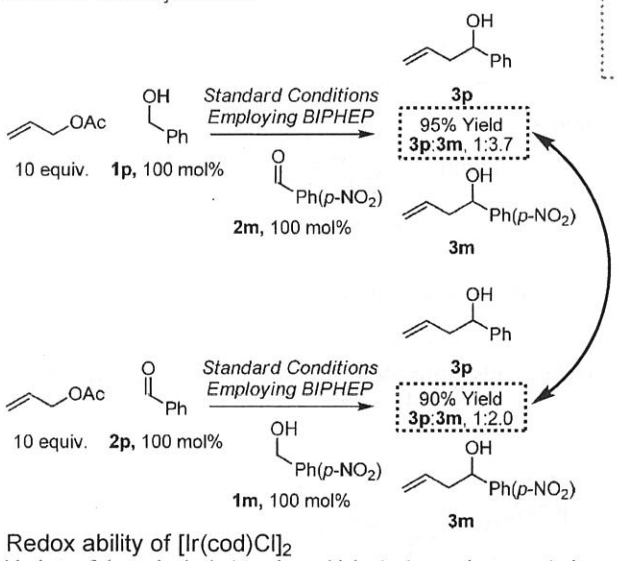
Methyl group blocks the preferred site of cyclometalation.



☑ ***Scheme 2.*** Ir-Catalyzed Transfer Hydrogenative Allylation of Benzylic Alcohol **1n** Employing Isotopically Labeled Allyl Acetate[a]



☑ ***Scheme 3.*** Experiments Establishing Rapid Redox Equilibration in Advance of Carbonyl Addition[a]



cf. Redox ability of $[Ir(cod)Cl]_2$

Oxidation of benzyl alcohol to benzaldehyde by various catalytic system [a]

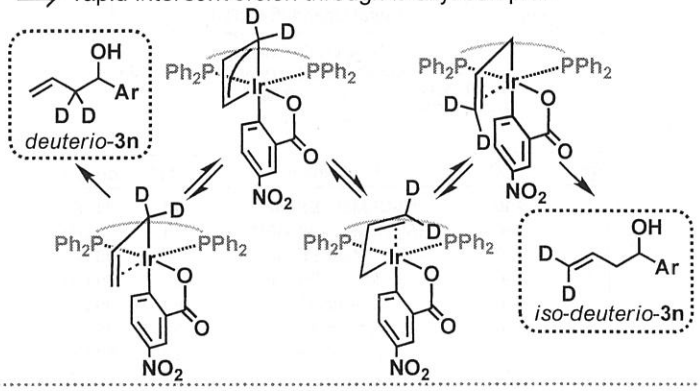
Entry	Catalyst	Acetone (ml)	Yield (%) [b,c]
1 [d]	$[Cp^*IrCl_2]_2$	10	13
2	$[Cp^*IrCl_2]_2$	10	71
3 [e]	$[Cp^*IrCl_2]_2$	10	69
4	$[Cp^*IrCl_2]_2$	30	87
5	None	10	0
6	$[IrCl(cod)]_2$	10	0
7	$[Cp^*RhCl_2]_2$	10	58
8	$RuCl_2(PPh_3)_3$	10	3

Yamaguchi et al *J. Organomet. Chem.* **2002**, *649*, 289

Check 3 : Deuterium Labeling of Allyl Acetate

Equimolar quantities of *deuterio*-**3n** and *iso-deuterio*-**3n**

⇒ rapid interconversion through π-allyl complex

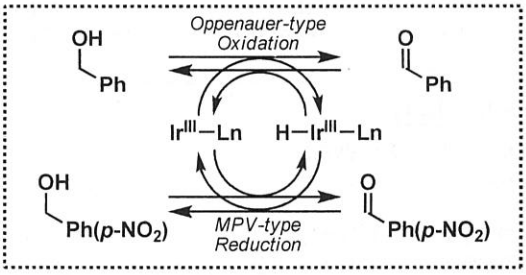


Check 4 : Competition Experiments

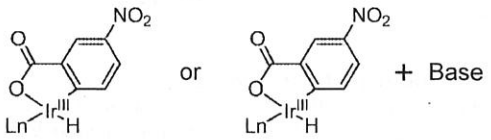
Similar product distribution is observed.

⇒ rapid redox equilibration in advance of C-C coupling

↑ Oppenauer / MPV type redox?

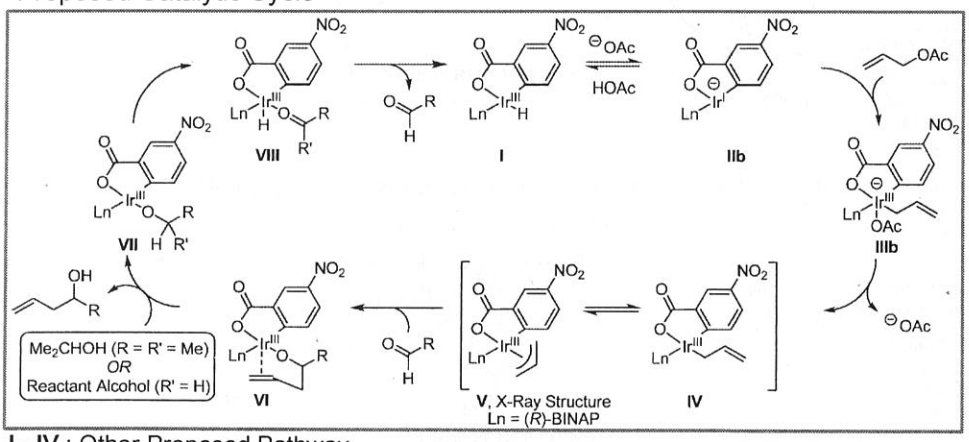


Entry 6 : $[Ir(cod)Cl]_2$ itself doesn't have redox ability.

⇒ 

have the ability of hydrogen transfer redox?

< Proposed Catalytic Cycle >



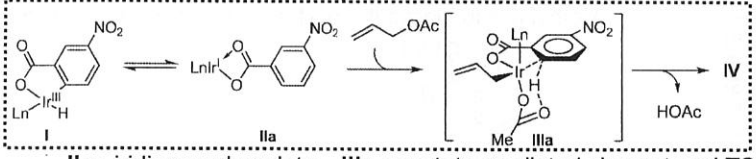
IIb : Anion is stabilized by *o*-carboxy and *p*-nitro group

IV - V : Rapid equilibration (X-ray diffraction / isotopic labeling)

VI : Homoallyl iridium alkoxide (disability of β-hydride elimination)

VI - VII : Change for reactant alcohol

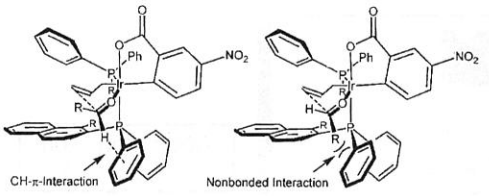
I - IV : Other Proposed Pathway



IIa : iridium carboxylate **IIIa** : acetate-mediated six-centered TS

Duration of catalytic cycle may be longer when fixed attachment of the *ortho*-C-benzoate linkage is remained.

< Model Accounting for Absolute Stereocontrol >



Favored Mode of Addition Disfavored Mode of Addition

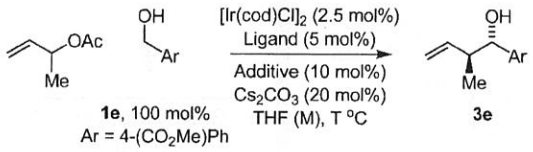
Based on single-crystal X-ray diffraction data,

Favored Mode : weakly attractive aldehyde C-H π-interaction

Disfavored Mode : severe non-bonded interaction (sterically hindered)

Allylation Using α-Methyl Allyl Acetate as Crotylmetal Reagents (*J. Am. Chem. Soc.* **2009**, *131*, 2514)

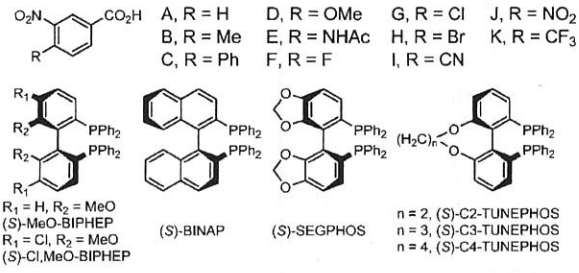
Table 1. Optimizing Relative and Absolute Stereocontrol in Transfer Hydrogenative Carbonyl Crotylation from the Alcohol Oxidation Level[a]



1e, 100 mol%
Ar = 4-(CO_2Me)Ph

3e

Entry	Ligand	Acid	OAc (eq)	THF (M)	T °C	Y (%)	dr (ee%)
1	BIPHEP	A	10	0.2	100	85	2.0:1
2	BIPHEP	B	10	0.2	100	72	2.7:1
3	BIPHEP	C	10	0.2	100	10	2.0:1
4	BIPHEP	D	10	0.2	100	68	2.2:1
5	BIPHEP	E	10	0.2	100	50	1.5:1
6	BIPHEP	F	10	0.2	100	78	2.3:1
7	BIPHEP	G	10	0.2	100	93	2.6:1
8	BIPHEP	H	10	0.2	100	80	2.4:1
9	BIPHEP	I	10	0.2	100	70	3.0:1
10	BIPHEP	J	10	0.2	100	65	3.5:1
11	BIPHEP	K	10	0.2	100	86	2.4:1
15	BIPHEP	I	5	0.2	100	57	3.7:1
16	BIPHEP	I	2	0.2	100	55	4.3:1
17	BIPHEP	I	2	0.5	100	77	4.8:1
18	BIPHEP	I	2	1.0	100	75	7.1:1
19	BIPHEP	I	2	1.0	90	78	7.5:1
20	BIPHEP	J	2	1.0	90	42	7.6:1
21	(*S*)-BINAP	I	2	1.0	90	75	3.5:1 (95)
22	(*S*)-MeO-BIPHEP	I	2	1.0	90	63	5.8:1 (94)
23	(*S*)-Cl,MeO-BIPHEP	I	2	1.0	90	67	3.0:1 (96)
⇨ **24**	**(*S*)-SEGPHOS**	I	**2**	**1.0**	**90**	**70**	**7.4:1 (95)**
25	(*S*)-C2-TUNEPHOS	I	2	1.0	90	68	7.7:1 (91)
⇨ **26**	**(*S*)-C3-TUNEPHOS**	I	**2**	**1.0**	**90**	**77**	**8.0:1 (97)**
27	(*S*)-C4-TUNEPHOS	I	2	1.0	90	71	6.4:1 (92)



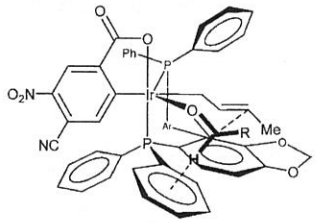
Entry 1 - 11 : **I, J** are effective as a co-catalyst.

Entry 9, 15, 16 : ~~10 eq. of α-methyl allyl acetate is necessary.~~

Entry 9, 10, 17 - 20 :
Anti-dr are increased with increasing concentration.
Co-catalyst **I** is better than **J** under 90 °C

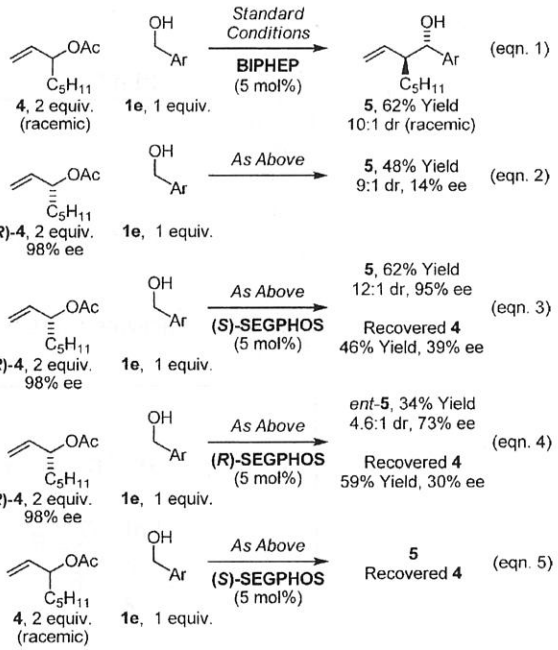
Entry 21 - 27 : High dr and ee are observed when using (*S*)-SEGPHOS or (*S*)-C_3-TUNEPHOS

<Stereocontrol>



Stereocontrol will be determined by the same mechanism as allyl acetate.

Scheme 2. Experiments Aimed at Probing the Origins of Stereoselection in Ir-Catalyzed Transfer Hydrogenative Crotylation (Ar = (4-(CO_2Me)Ph)[a]



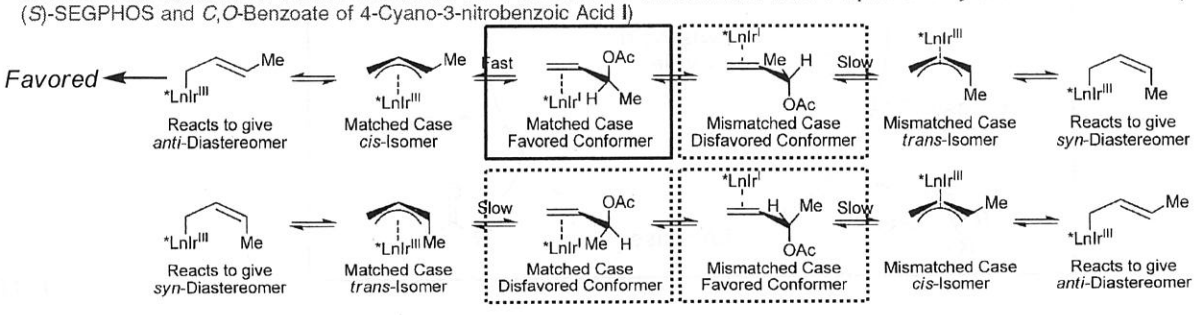
Time (h)	Recovered (*S*)-4	Compound 5
6	59% Yield, 22% ee	37% Yield, 95% ee, 11.3:1 dr
12	53% Yield, 27% ee	45% Yield, 95% ee, 12.6:1 dr
24	52% Yield, 22% ee	48% Yield, 94% ee, 11.3:1 dr
48	48% Yield, 21% ee	56% Yield, 94% ee, 10.8:1 dr

Eqn. 2 : Racemization occurs via π-facial interconversion

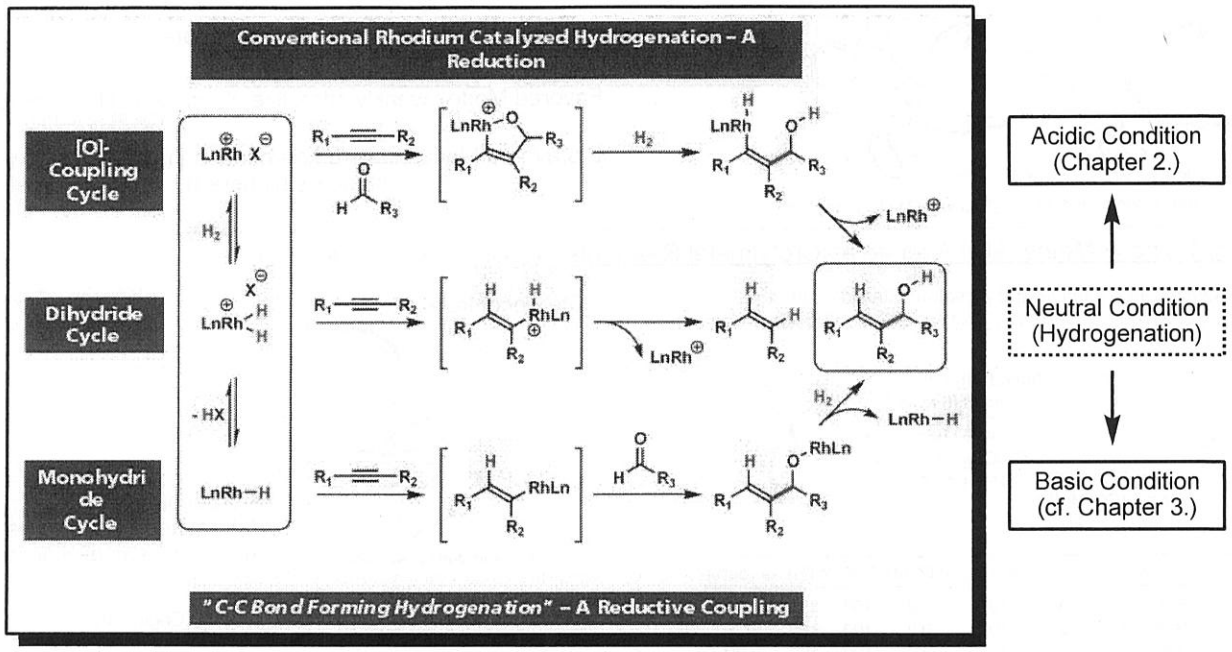
Eqn. 3, 4 : (*S*)-SEGPHOS is matched with (*R*)-substrate.
(*R*)-SEGPHOS is NOT matched with (*R*)-substrate.

Eqn. 5 : (*R*)-Allylic acetate 4 is consumed by rapid stereochemically matched reaction.

Scheme 3. Stereochemical Features Associated with Formation and Isomerization of the Purported Crotyl Iridium Intermediates (*Ln = (*S*)-SEGPHOS and *C,O*-Benzoate of 4-Cyano-3-nitrobenzoic Acid **I**)



Chapter 4. Conclusion



- Allylation (Chapter 3.)