

Isomerization of allylic alcohol and its relevant reactions



Gree R. et al *Chem. Rev.* **2003**, 103, 27-51



Mazet C. et al *Chem. Lett.* **2011**, 40, 341 344

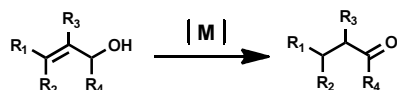
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May 10, 2011
Luqing Lin

Isomerization of allylic alcohol and its relevant reactions

1 Introduction

1.1 isomerization of allylic alcohol

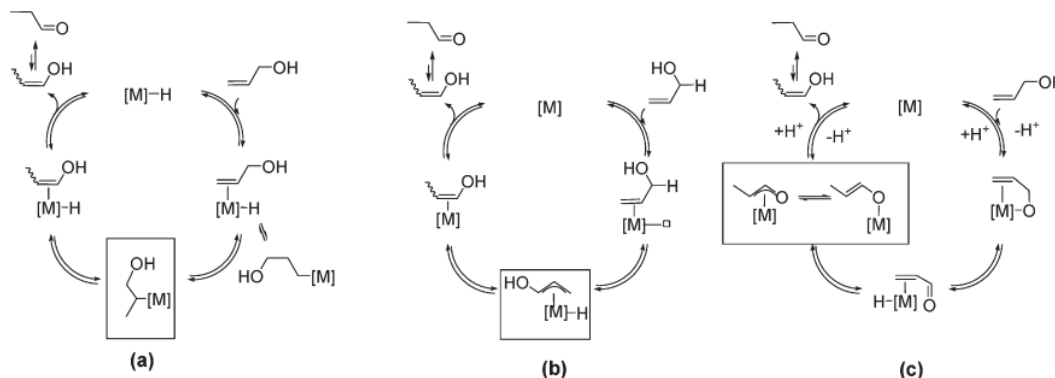


One pot internal redox reaction to synthesize carbonyl compounds.

1.2. Mechanism of isomerization of allylic alcohol

- a: Metal-hydride addition-elimination
- b: π -allyl-metal-hydride mechanism
- c: Alcoholate species mechanism

Cristina G., et al *Organometallics* **2010**, *29*, 2166-2175

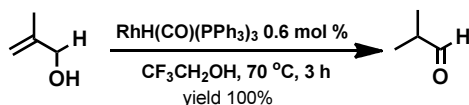


2 Isomerization Reactions

2.1 Rh complexes

RhH(CO)(PPh₃)

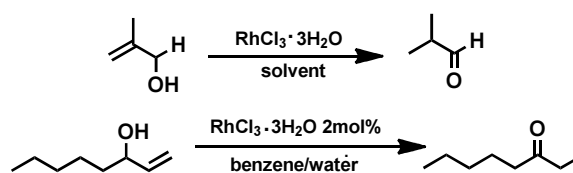
³ Scheme 1



Wietrich, M. et al. *J. Organomet. Chem.* **1975**, *86*, C17

RhCl₃ · 3H₂O

Scheme 2

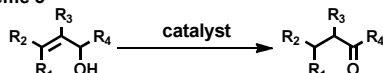


when solvent is dioxane, the yield is 30% (accompanied decarbonylation). Better result was obtained under biphasic condition in the presence of onium salts; complete conversion of 1-octen-3-ol to 3-octanone only need 2 mol % RhCl₃ · 3H₂O

Blum, J. et al *J. Mol. Cat.* **1981**, *11*, 293

RhCl₃ or Rh₂(SO₄)₃ + TPPTS(tri(m-sulphophenyl)phosphane)

Scheme 3

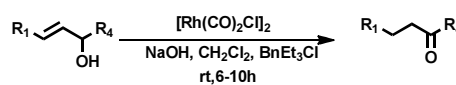


1. Biphasic(n-heptane/water) Catalysts.
2. no substitution on C-2 of allylic alcohol was investigated Except for geraniol, that gave citronellal in 44% yield, most of other reactions were quantitative.
3. This catalyst can be recycled for several times, using 1-hexene-3-ol as model
4. As extend carbon chain, reactivity decrease due to solubility of allylic alcohol

Kuntz, E. G. C. *R. Acad. Sci. Pair, Ilc, Chem.* **2000**, *3*, 607

[Rh(CO)₂Cl]₂

Scheme 4

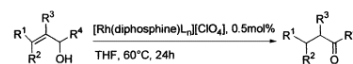


[Rh(CO)₂OH]₂ was postulated to be the true active species

Alper. H.; Hachem, K. *J. Org. Chem.* **1980**, *45*, 2269

[Rh(diphosphine)_nClO₄]

Table 1



R ¹	R ²	R ³	R ⁴	diphosphine	conversion	selectivity
Me	Me	H	H	BINAP ^a	64	80
Me	Me	H	H	BINAP ^b	88	61
Me	Me	H	H	DPPB ^b	50	24
Me	Me	H	H	DIPB ^b	42	20
H	H	Me	H	BINAP ^b	99	90
Me	H	H	H	BINAP ^b	87	93
Me	Me	H	Me	BINAP ^b	88	34
H	-CH ₂ -	H	-(CH ₂) ₂ -	BINAP ^b	82	98

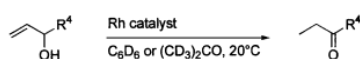
^a (COD) was used as a ligand. ^b Solvent molecules act as ligands to the metal complex. DPPB = Ph₂P(CH₂)₄PPh₂; DIPB = (*i*-Pr)₂P(CH₂)₄P(*i*-Pr)₂.

[Rh(diphosphine)_nClO₄]

An efficient catalysts for transposition of allyl alcohol, even for the challenging examples (two alkyl groups in terminal position and 2-cyclohexen-1-ol), also giving excellent conversion yield.

Tani. K. *Pure & Appl. Chem.* **1985**, *57*, 1845.

Triphenyl phosphite derived ligands

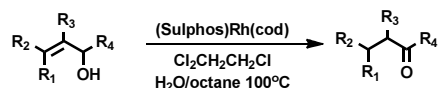


R⁴ = H, Me, *n*-Pent

Rh catalysts : HRh[P(OPh)₃]₄, Rh[P(OPh)₃]₄[ClO₄], Rh[P(OPh)₃]₃[P(OPh)₂(OC₆H₄)]

Ziolkowski J. et al *Gazz. Chim. Ital.* **1994**, *124*, 403

(Sulphos)Rh(cod)



Scope was limited to no more than two substitutions on olefin of allylic alcohol

Bianchini, C.; Oberhauser, W. *New J. Chem.* **2001**, *25*, 11

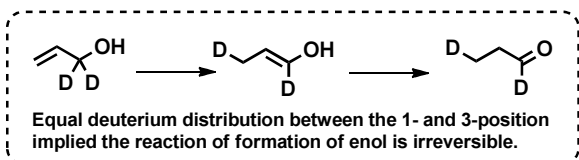
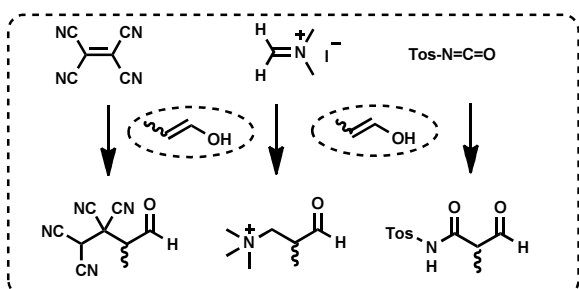
[Rh(diphosphine)_n][ClO₄]

Table 2

R ¹	R ³	R ⁴	enol production time ^a	enol isomerization time ^b
H	H	H	14 min	(Z) 120 min (E) 40 min
H	Ph	H	330 min	
H	H	Me	9 min	(Z) 180 min (E) 50 min
H	H	Ph	124 min	(Z) 5.5 h
Ph	H	H	167 min	(Z) ~8 h (E) ~6 h
H	OEt	H	50 h	
H	Me	H	16 min	8 days
-CH ₂ -	-(CH ₂) ₂ -	H	27 h	5 days

^a Time required to convert ~98% of the allylic alcohol.

^b Time required to transpose ~98% of the enol into the carbonyl compound.



Deuterated substrate decrease reaction speed.
Turnover limiting step is not sure, but suggested by author, maybe is initial hydrogen abstraction

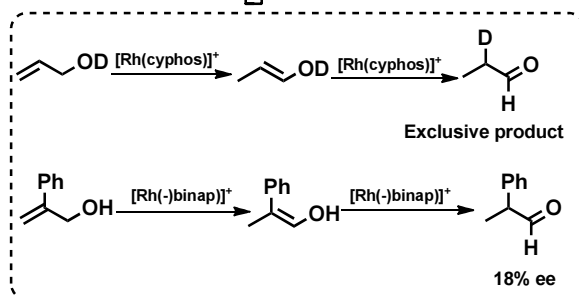
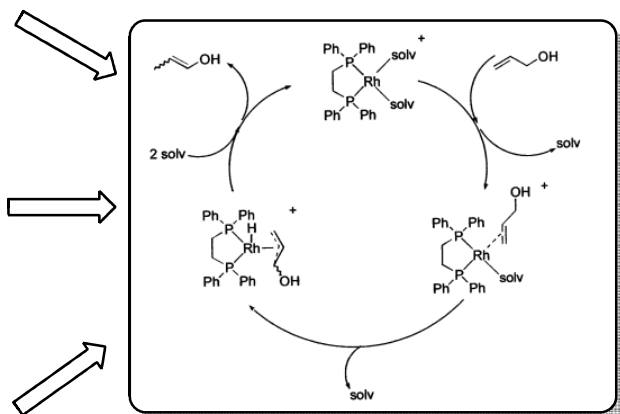


Table 3

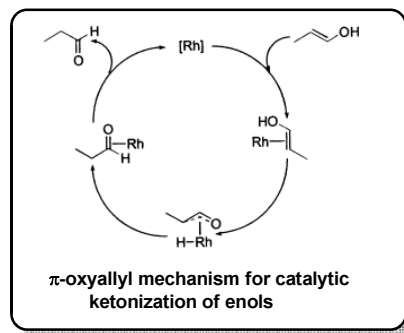
diphosphine	time ^a (min)	enol (%)	ketone (%)
Ph ₂ P(CH ₂) ₂ PPh ₂	14	89	11
Cy ₂ P(CH ₂) ₂ PCy ₂	<5	0	100
Ph ₂ P(CH ₂) ₃ PPh ₂	45	0	100
Ph ₂ P(CH ₂) ₄ PPh ₂	19	25	75
BINAP	21	80.4	19.6

^a Time required for ~98% conversion of allyl alcohol to propanal in (CD₃)₂CO at 25°C.

The nature of ligand has strong effect on kinetic of the reaction.
[Rh(Cyphos)]⁺ catalyzed reaction is quite rapid even at -80 °C



Postulated mechanism of formation of enol from allylic alcohol



Bergens, S.; Bosnich, B. *J. Am. Chem. Soc.* **1990**, 113, 958

Rh hydride catalysts (RhH(PPh₃)₃, RhH(PPh₃)₄)

RhH(PPh₃)₃ could be prepared easily and used in situ.
RhH(PPh₃)₃ also could be used for isomerization of highly sterically hindered derivatives
RhH(PPh₃)₄ could be used for primary and secondary alcohol, but is sensitive to oxygen and moisture

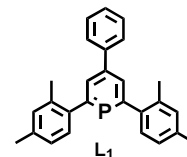
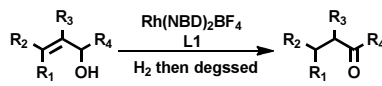


Table 4

Entry	R ₁	R ₂	R ₃	R ₄	solvent	temp.	time	Conv.	Selectivity(%)
1	H	H	H	Me	CH ₂ Cl ₂	23	0.5	100	100
2	H	H	H	Ph	Dioxane	60	1	100	93
3	H	H	Ph	Me	Dioxane	60	1	100	100
4	H	Ph	H	H	Dioxane	60	3.5	100	100
5	H	Me	H	Me	CH ₂ Cl ₂	23	0.5	100	100
6	H	Propyl	H	H	CH ₂ Cl ₂	23	0.5	100	98
7	H	Butyl	H	Me	dioxane	60	1	100	97
8	Propyl	H	H	H	CH ₂ Cl ₂	23	0.5	100	100
9	Me	Me	H	H	CH ₂ Cl ₂	23	16	100	90
10	H	Ph	Me	Me	dioxane	60	2	100	100

Rh(L₁)[H]nBF₄ could isomerize monosubstituted, disubstituted, trisubstituted allylic alcohol.

Manfred T. R.; Honhchao Guo *letter* **2006**, 2127

Metal hydride addition-elimination mechanism maybe be suitable for Rh-H catalytic reaction.

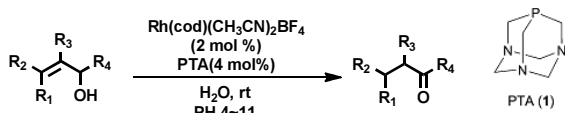
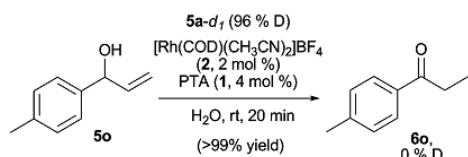


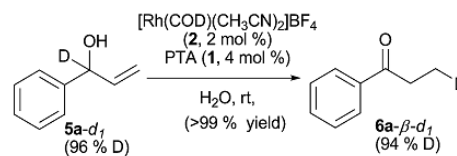
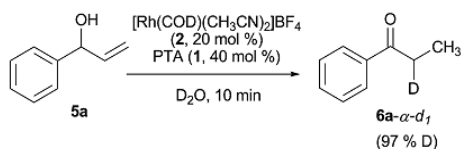
Table 5

Entry	R ₁	R ₂	R ₃	R ₄	time/min	yield
1	H	H	H	Ph	5	>99
2	H	H	H	p-F-Ph	15	99
3	H	H	H	p-MeO-Ph	15	>99
4	H	H	H	naph	60	>99
5	H	H	H	p-CF ₃ -Ph	15	>99
6	H	H	H	Et	80	>99
7	H	H	H	phenylethylene	180	92
8	H	Me	H	Me	80	>99
9	H	Me	H	Ph	5	>99
10	H	H	Me	Ph	5	>99
11	H	-(CH ₂) ₃ -	H	connecting to R ₂	720	>99
12	H	benzyl	H	H	45	>59

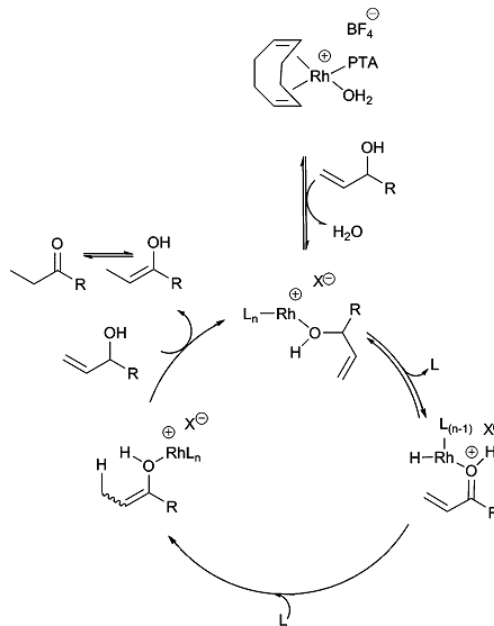
Entry 8, 9, 10 Temp. is, 50°C, 50°C, 80°C respectively.



intramolecular reaction



1, 3-hydride migration



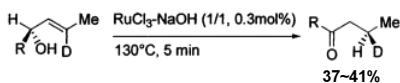
Proposed mechanism

Martin-Matute, et al. *Green Chemistry* 2010, 12, 1628-1633

2.2 Ruthenium complexes

RuCl₃, RuCl₃-NaOH

RuCl₃ can be employed for isomerization of various allylic alcohol and glycols. RuCl₃-NaOH can be used for chirality transfer.

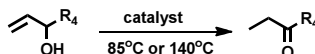


J. Organomet. Chem. 1975, 86, C17

J. Chem. Soc., Chem. Commun., 1980, 594-595

Pascal, J.-Y. et al *J. Mol. Catal.* 1980, 9, 59

Ru₃O(OCOCH₃)₇ & RuCl₂(PPh₃)₃



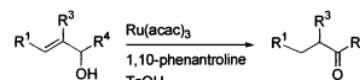
it is only operative for isomerization allyl alcohol without substituted group on double bond

Ru₃O(OCOCH₃)₇ can be recycled for several times

Blum, J. et al *J. Mol. Catal.* 1979, 6, 289

Blum, J. et al *J. Org. Chem* 1981, 46, 255

Ru(acac)₃



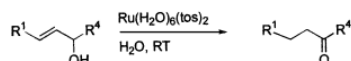
Scope is limited to less hindered allylic alcohol

Even in the presence of butadiene, the process could be performed (R₃=H).

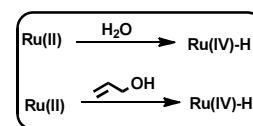
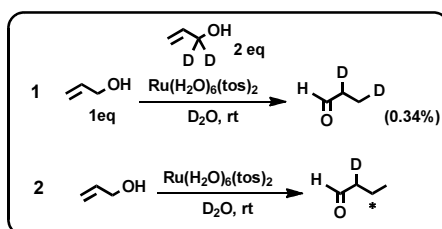
transformation of butadiene to ketone.

E. Drent, et al *Inorg. Chim. Acta* 1994, 222, 225-233

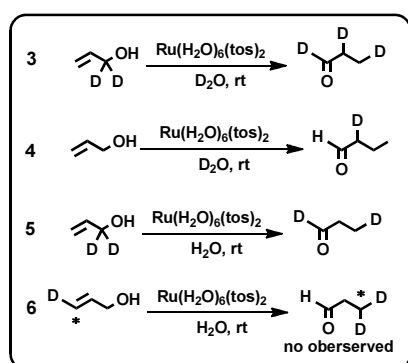
Ru(H₂O)₆(tos)₂ or Ru(H₂O)₆(tiff)₂



a: R¹ = R⁴ = H; b: R¹ = H, R⁴ = Me; c: R¹ = H, R⁴ = Et; d: R¹ = Me, R⁴ = H



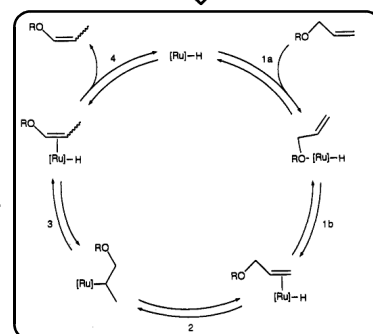
Possibility for generating Ru-H



intermolecular reaction

1, 2 step is irreversible

1, 3-hydride migration



Modified metal-hydride addition-elimination mechanism
Exclusive Markovnikov addition

McGrath, D. V.; Grubbs, R. H. *Organometallics* 1994, 13, 224

CpRu(PPh₃)₂Cl

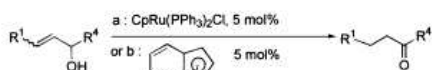
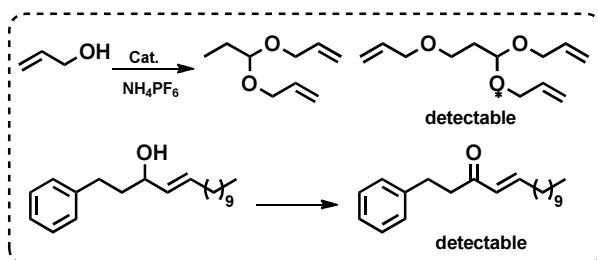
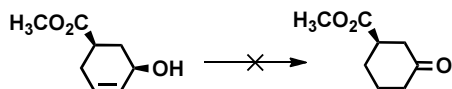
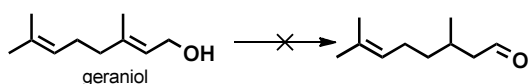


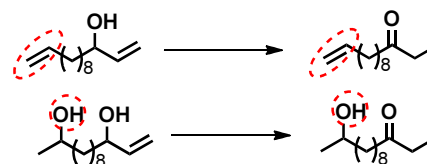
Table 1

R ¹	R ⁴	cat	time (h)	yield (%)
Ph	H	a	8	90
H	Cy	a	1.5	92
H	Ph(CH ₂) ₂	a	2	81
Ph	<i>n</i> -C ₄ H ₉	a	9	23
Ph	<i>n</i> -C ₄ H ₉	b	2	83
H	CH ₂ =CH-(CH ₂) ₈ -	a	1	87
H	HOCH ₂ -(CH ₂) ₉ -	a	1	52
H	HOCH(Me)-(CH ₂) ₈ -	a	1.5	90
H	Me-(CH ₂) ₁₀ -	a	2.5	91
<i>n</i> -C ₁₀ H ₂₁	Ph(CH ₂) ₂	a	24	53
<i>n</i> -C ₁₀ H ₂₁	Ph(CH ₂) ₂	b	3	81
H	CH ₂ =CHCH(OH)-(CH ₂) ₈ -	a	1.5	73
H	CH ₂ =CHCH(OMe)-(CH ₂) ₈ -	a	1	93
	-(CH ₂) ₅ -	a	24	31
	-(CH ₂) ₅ -	b	3	47
	-(CH ₂) ₉ -	a	9	84
	-(CH ₂) ₉ -	b	2.5	87
<i>n</i> -C ₅ H ₁₁	CH ₂ =C(Me)-(CH ₂) ₂ -	b	3	82
<i>n</i> -C ₄ H ₉	CH ₂ =CH-(CH ₂) ₂ -	b	8	77
				(2 isomers)
<i>n</i> -C ₄ H ₉	Me-CH(OH)-(CH ₂) ₈ -	b	10	69
	-CH(OH)-(CH ₂) ₈ -	b	4	35
	-CH(OAc)-(CH ₂) ₈ -	b	3	86
	-CH ₂ OCO-(CH ₂) ₈ -	b	6.5	28

- sterically hindered allylic alcohol and six membered allyl alcohol did not react

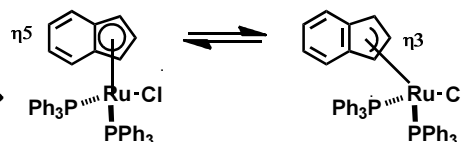


- Chemoselectivity



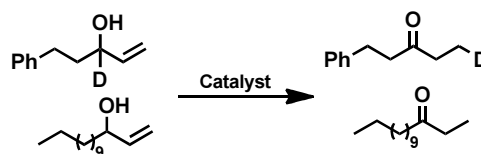
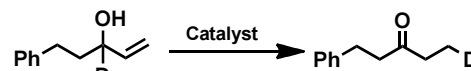
Remote double bond migrate slowly compared to that of allyl alcohol

- Indenyl-ruthenium complex is better than cyclopentadiene-ruthenium complex

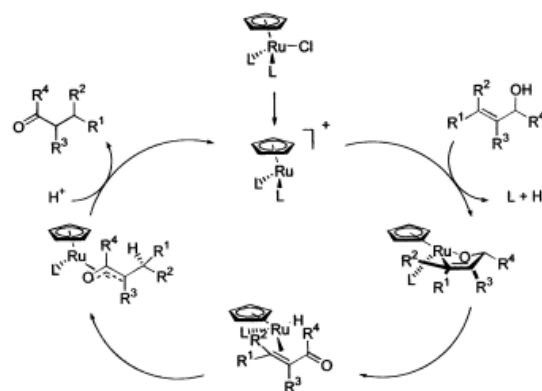


it is easier to open coordinated site of indenyl complex than Cp complex. So indenyl complex has higher reactivity.

- Increase the reactivity of catalyst complex by using AgOTf instead of Et₃NHPF₆ due to Ag⁺ is easy to sequestering chloride anion. But it has Lewis acid character often leading to nucleophilic addition by solvent.
- Deuterium labeling experiments



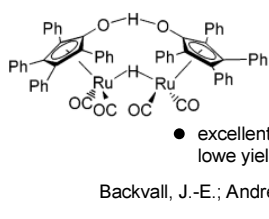
1,3 hydride migration and intramolecular reaction



Proposed mechanism

Trost, B. M.; Kuliawec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027

**RuCl₂(PPh₃)₃
[RuCl₂(p-cymene)]₂**



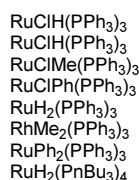
- Efficient catalysts for isomerization of allyl alcohol in presence of base such as K₂CO₃

- Bimetallic catalyst which itself can serve as a base led to a rapid reaction without adding base.

- excellent yield was in case of 7, 8 ring allyl alcohol. low yield was obtained in case of 6 ring allyl alcohol.

Backvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459

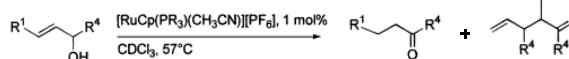
Ruthenium hydride complex



- Those Ruthenium complexes can be generated in situ. Only used for isomerization of less hindered secondary allyl alcohol.
- Primary allyl alcohol did not react in the presence of catalyst.

Sasson, Y.; Rempel, G. L. *Tetrahedron Lett.* **1974**, *47*, 4133
Uma, R.; Gre^{er}, R. *et al. Eur. J. Org. Chem.* **2001**, 3141

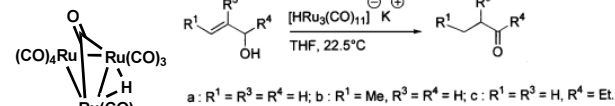
RuCp(PR₃)(CH₃CN)[PF₆]



- This catalyst was easy to form 16⁺ cationic ruthenium species compared to the CpRu(PPh₃)₂Cl.
- But it was operative for allyl alcohols of which less one substituted group on 1 and 3 position.

Slugovc, C.; Kirchner, K. *et al Organometallics* **1999**, *18*, 4230

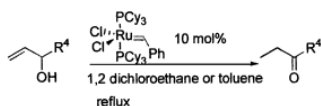
HRu₃(CO)₁₁K⁺



- limited in scope to simple, sterically less hindered allylic alcohols

Langenbahn, M.; Suss-Fink, G. *et al J. Organomet. Chem.* **1989**, *379*, 165

Grubb's catalyst



- Though only unsubstituted allylic alcohol have been tested, ester and ether functionalities are compatible in this condition.

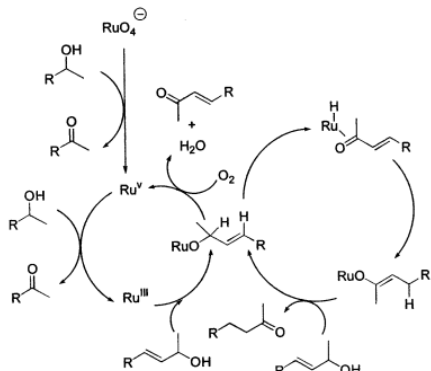
Gurjar, M. K.; Yakambam, P. *Tetrahedron Lett.* **2001**, 42, 3633
 Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, 1, 1123

Pr₄NRuO₄

Table 4

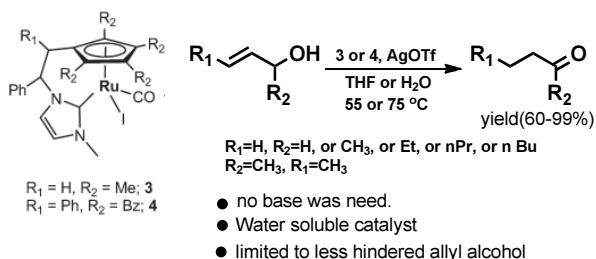
R ¹	R ²	R ⁴	yield (%)
H	H	Ph	90
H	H	PhCH ₂ CH ₂	92
H	H	<i>p</i> -Cl-Ph	87
<i>n</i> -C ₉ H ₁₉	H	H	41
Ph	H	Et	71
Ph	H	H	48
Me	Me ₂ C=CH-(CH ₂) ₂ -	H	52
H	-(CH ₂) ₃ -		89

- it is promising to isomerize the challenging allylic alcohol

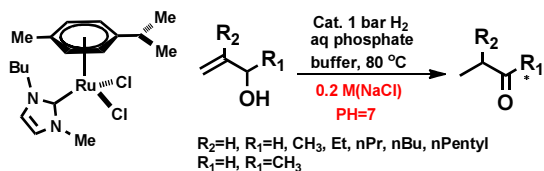


Proposed mechanism

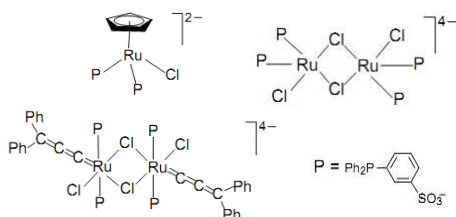
Marko, I. E. *et al Angew. Chem., Int. Ed.* **1999**, 38, 1960.



Costa, A. P. Peris E. *et al Organometallics*, **2010**, 29, 1832-1838.

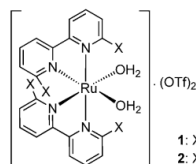


Joo, F. *et al Catalysis Communications* **2006**, 7, 783-786



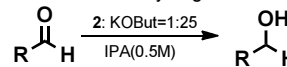
Those catalysts are efficient for isomerization simple, less hindered allyl alcohol in water

Joo, F. *et al J. Organometallic Chem.* **2008**, 693 468-474

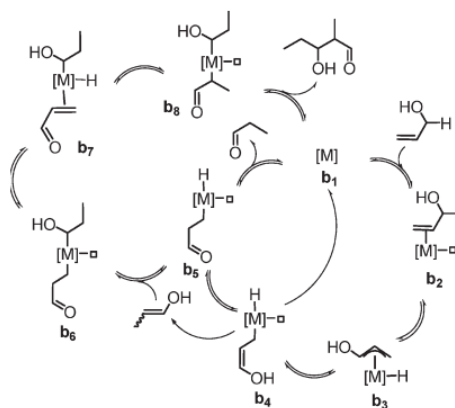
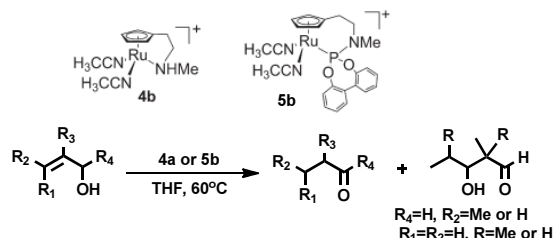


- Catalyst 1 can be using for isomerization of most of secondary alcohols except disubstituted group at the terminal carbon of double bond.
- it seems not to isomerize the primary alcohol.
- it is very interesting that catalyst 2 could hydrogenate aldehyde to aldohol.

IPA was added as hydrogen source and solvent.

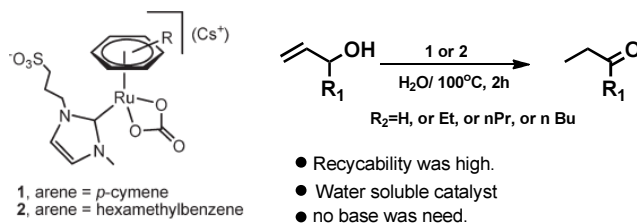


Lau C. P. *et al Adv. Synth. Catal.* **2011**, 353, 275-280

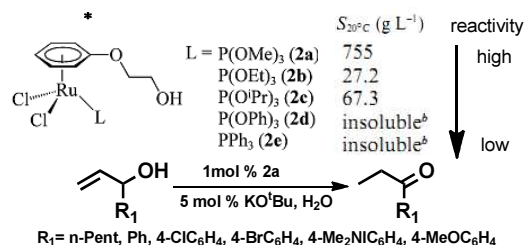


- No base was added.
- it is interesting that some aldol type product was observed.
- Substrate scope was wide.
- It was able to isomerize secondary alcohol and primary alcohol (including cyclohex-2-enol)

Cristina G., *et al Organometallics* **2010**, 29, 2166-2175

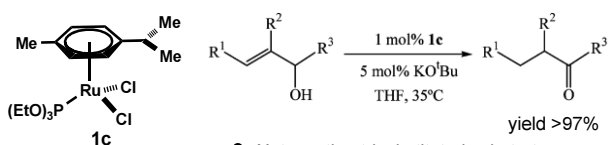


Peris E. *et al Organometallics*, **2010**, 29, 3661-3664.



- Scope of substrate is limited to monosubstituted on C1.

Crochet P. *et al Green Chem.*, **2009**, 11, 1681-1686



- Noteworthy, trisubstituted substrate are readily converted at 35 °C, for example R₁=Ph, R₂=Me, R₃=Ph

Crochet P. *et al Organometallics* **2006**, 25, 4846-4849

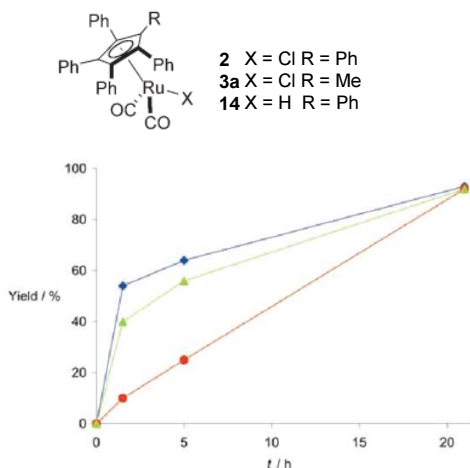


Figure 2. Isomerization of **4a** (0.5M in toluene) to ketone **6a** catalyzed by: ruthenium chloride **2** (5 mol%) after treatment with KOtBu (●), ruthenium hydride **14** (5 mol%) in the presence of benzylideneacetone **19** (5 mol%) (▲), and ruthenium hydride **14** (●).

1. Was η^5 ruthenium hydride intermediates active species?
2. Involve ruthenium alkoxide for the reaction or not?

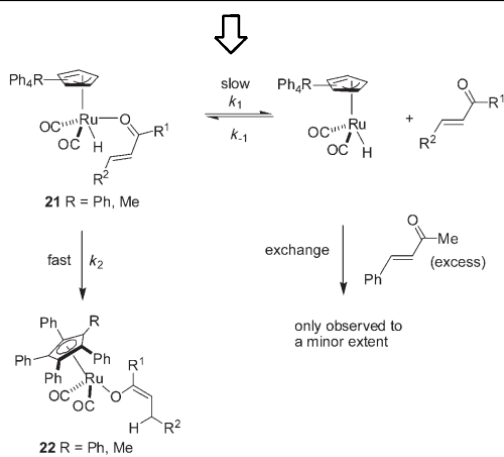


Table 2

	Substrate	t [h]	T [°C]	Product	Yield [%] ^[b,c]
1	4a	1.5	RT	6a	96 (96)
2	4b	2.5	RT	6b	99 (94)
3	4c	3	RT	6c	97 (92)
4	4d	2.5	RT	6d	95 (94)
5	4e	2	80	6e	95 ^[d] (94)
6	4f	23	80	6f	22

[a] Unless otherwise noted, KOtBu (7 mol%, 0.5M in THF) was added to a solution of the Ru catalyst **3a** (5 mol%) in toluene (substrate concentration: 0.5M) under an argon atmosphere. The mixture was stirred for 4 min before adding the alcohol. [b] Determined by GC or ¹H NMR spectroscopy. [c] Isolated yield in parentheses. [d] After 1 h the yield determined by NMR spectroscopy is 87%.

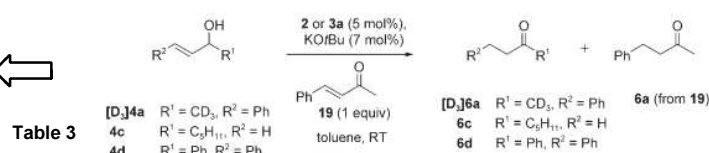
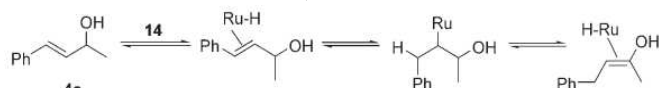
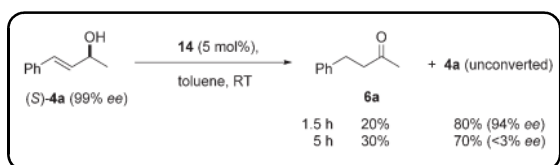


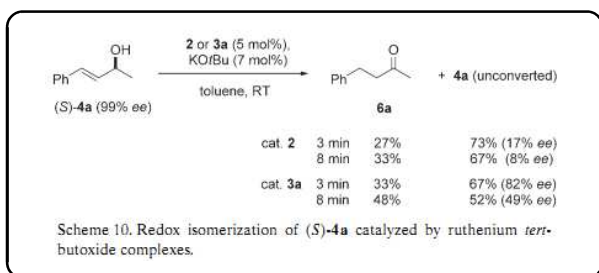
Table 3

	Substrate	Catalyst	t [h]	Product	Yield [%] ^[b]	6a [%] ^[b]
1	4c	3a	3	6c	94	6
2	4d	3a	2.5	6d	86	6
3	4d	2	14	6d	100	0
4	[D]4a	2	14	[D]6a	78 (84% D ₃)	10 ^[c]

[a] Unless otherwise noted, KOtBu (70 μ L, 0.5M in THF) was added to a solution of the Ru catalyst **3a** or **2** (5 mol%) in toluene (0.5 mL) under an argon atmosphere. The mixture was stirred for 4–6 min before adding a solution of the allylic alcohol and **19** in toluene (0.5 mL). [b] Determined by GC or ¹H NMR spectroscopy. [c] Calculated by ¹H NMR spectroscopy considering the degree of deuteration of **[D]6a**: 94% D₃.



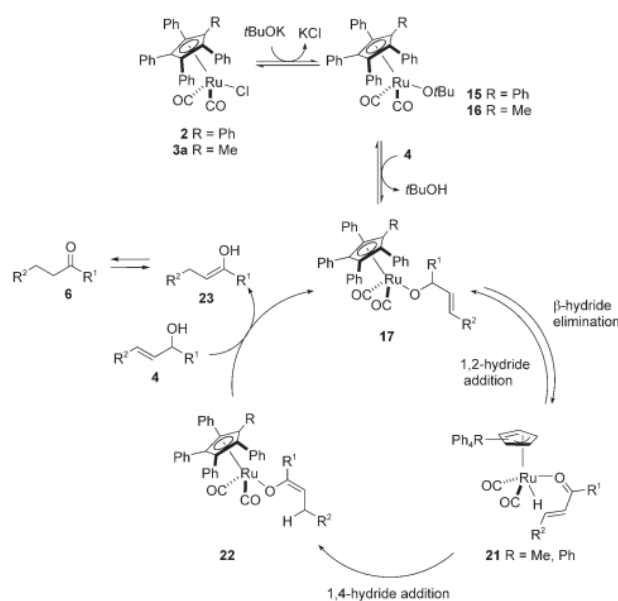
Scheme 7. Isomerization mechanism catalyzed by ruthenium hydride complexes.



Scheme 10. Redox isomerization of (S)-**4a** catalyzed by ruthenium *tert*-butoxide complexes.

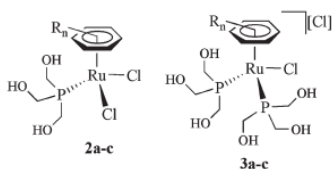
ee% of **4a** decreased as reaction time increased.

Reversible 1,2 addition takes place, which was reason of slow isomerization of primary alcohol (aldehyde was more electrophilic species).

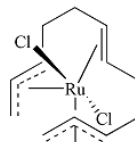


Mechanism of isomerization of allyl alcohol by ruthenium cyclopentadienyl complexes,

Martin-Matute, B. *et al Chem. Eur. J.* 2005, 11, 5832 – 5842



- water-soluble catalyst
- recycling at 8 times at least

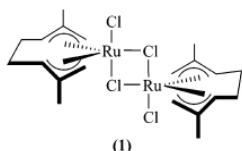


- Catalyst could isomerizes monosubstituted on double bond of allyl alcohol to aldehyde, but fails to isomerization in the presence of conjugated diene.
- An efficient catalyst in organic or aqueous media was able to recycle for three times at least.

Cadierno V. et al *Chem. Commun.*, **2004**, 232–233

Arene = C₆H₆ (a), *p*-cymene (b), C₆Me₆ (c)

Cadierno V. et al *Dalton Trans.*, **2004**, 3635–3641

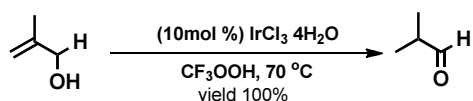


- Extend the substrate scope to disubstituted at the terminal of double bond and cycloallyl alcohol. Entry 13, at 90°C 3-methyl-butylaldehyde could be obtained at 89% yield.

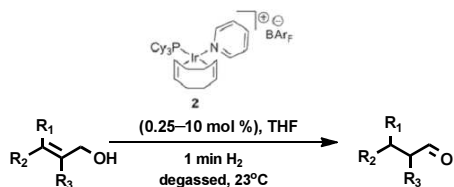
- Catalyst remained active in presence of diene for example isoprene.
- η³-oxo-allyl mechanism was proposed.

Cadierno V. et al *JACS.*, **2006**, 1360–1370

2.3 Iridium complexes



J. Organomet. Chem. **1975**, 86, C17



- An efficient catalyst for isomerization of primary allyl alcohol in mild condition with almost quantitative yield

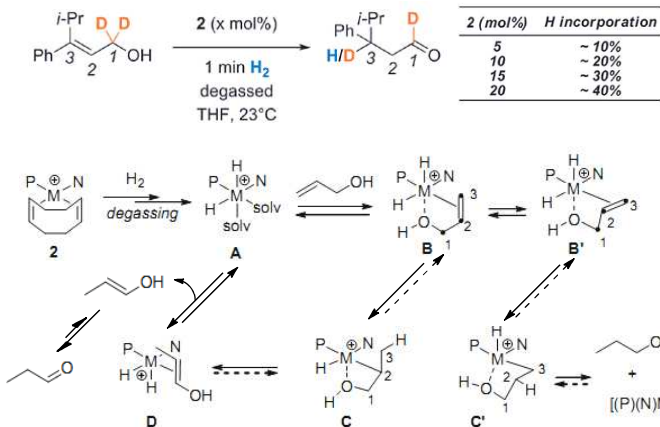
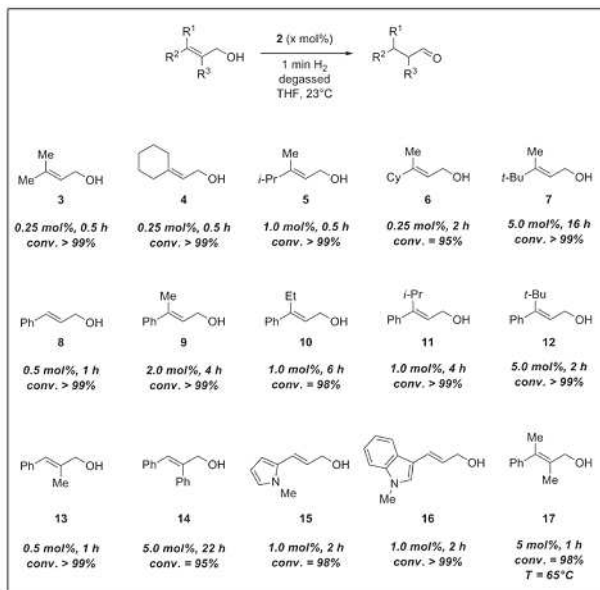
[(cod)Ir(PMePh₂)₂][PF₆]

Table 1

entries	R ¹	R ²	R ³	R ⁴	time (h)	temp (°C)	yield (%)
a	H	H	H	H	0.5	20	100
b	H	H	H	Me	1	20	100
c	H	H	Me	H	0.5	20	100
d	Me	H	H	H	24	20	88
e	Me	H	H	Me	15	20	15
	Me	H	H	Me	18	65	80
f	H	H	Me	Me	2	20	4
g	H	-(CH ₂) ₅ -	H	-(CH ₂)-	2	65	6
h	Me	Me ₂ C=CH-(CH ₂) ₂	H	H	15	65	12
i	Me	Me	H	H	15	65	12
j	Me	Me	H	Me	15	65	0

- High yield was obtained for less hindered allyl alcohol compared to disubstituted on the olefin and trisubstituted derivatives.
- Similar catalysts: [(cod)Ir(PPh₂)₂][ClO₄] and [(cod)Ir(PhCN)(PPh₃)] [ClO₄]

Felkin, H et al. *Nouv. J. Chim.* **1978**, 2, 355

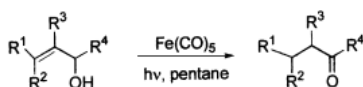


Mazet C. et al *Chimia* **2009**, 63,35–37

2.4 Other metal complexes

Iron complexes

Fe(CO)₅, Fe₂(CO)₉ & Fe₃(CO)₁₂



- Disubstituted and trisubstituted on olefine of allyl alcohol can be isomerized to ketone or aldehyde.
- primary allylic alcohol without α-substituent give low yield. It appears to be due to aldolization

Gree, R. et al *Tetrahedron* **2001**, 57,2379.

Cobalt complexes: HCo(CO)₄

palladium complexes

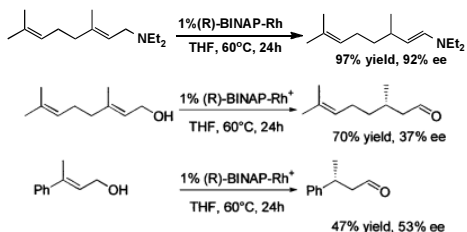
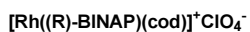
Pd(OH)₂/C, H₂ pre-activated

Gowravaram Sabitha* et al *Org. Lett.*, **2011**, 13 (3), pp 382–385

n-Bu₄NBr + PdCl₂ or Pd(OAc)₂

Ganchegui B. et al. *J. Mol. Cat. A: Chem.* **2004**, 214, 65–69

3 Asymmetric isomerization of allylic alcohol



- Compared to asymmetric isomerization of allyl amine, asymmetric isomerization of allylic alcohol was far away from success.

Tani, K. *Pure & Appl. Chem.* **1985**, 57, 1845

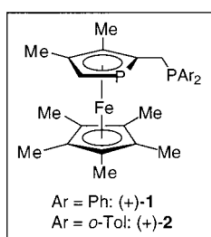
G. Fu's catalyst.

Table 1

$\text{R}^1 \text{R}^2 \text{CH}=\text{CHCH}_2\text{OH} \xrightarrow[\text{THF, 100}^\circ\text{C}]{5\% [\text{Rh}(\text{cod})((+)\text{-}2)]\text{BF}_4} \text{R}^1 \text{R}^2 \text{CH}_2\text{CH}(\text{R}^1)\text{CHO}$

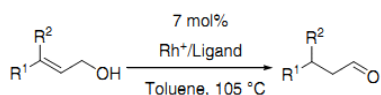
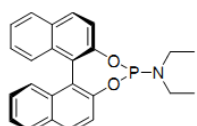
Entry	Allylic Alcohol	Yield (%) ^{a,b}	ee (%) ^a
1	Me Ph $\text{CH}=\text{CHCH}_2\text{OH}$	91 (82)	75 (56)
2	Et Ph $\text{CH}=\text{CHCH}_2\text{OH}$	96	76
3	$i\text{-Pr}$ Ph $\text{CH}=\text{CHCH}_2\text{OH}$	98 (81)	92 (78)
4 ^c	$i\text{-Pr}$ $o\text{-Tol}$ $\text{CH}=\text{CHCH}_2\text{OH}$	86 (8)	92 (87)
5	$i\text{-Pr}$ $p\text{-Tol}$ $\text{CH}=\text{CHCH}_2\text{OH}$	90 (85)	91 (64)
6	$i\text{-Pr}$ $p\text{-ClC}_6\text{H}_4$ $\text{CH}=\text{CHCH}_2\text{OH}$	86 (79)	92 (73)

^a Average of two runs (first run, new catalyst; second run, catalyst recovered from the previous reaction); the values in parentheses are for Rh/1. ^b Isolated yields. ^c Reaction was carried out at 150 °C.



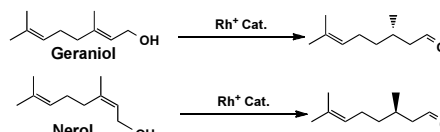
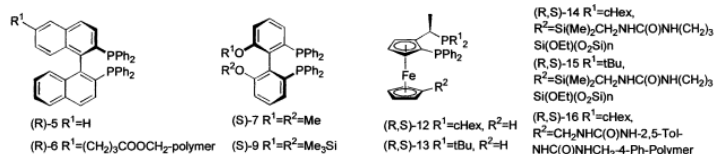
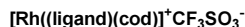
cationic planar chiral phosphaferrrocene-rhodium complexes

- Catalyst 1 performed well only for Z-configuration. Catalyst 2 is more general and displayed activities for E and Z isomers.
- Satisfactory isomerization yield and enantioselectivity was obtained for most substrated surveyed.
- Labeling and crossover experiment was investigated, verifying 1,3 migration of hydrogen and intramolecular reaction mechanism
- Aromatic ring group seems to be required for the allyl alcohol. Only one with aliphatic disubstituted groups on the terminal of the double was investigated.



Crevisy C. et al *Tetrahedron letters* 2006, 47, 5021-5024

- Compared to Fu's catalyst, no improvement in activity, selectivity, scope was achieved.



5 give best result: 88% yield, 60%ee for Geraniol
90% yield, 51%ee for Nerol

- Changing perchlorate to triflate, ee increased, but not satisfied.

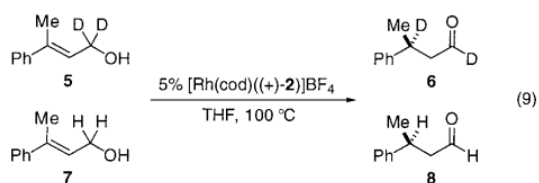
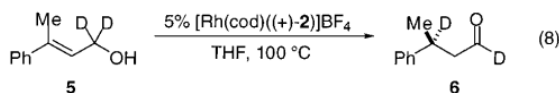
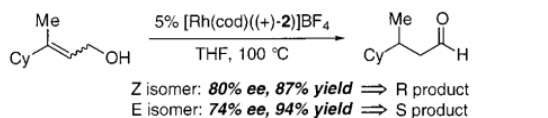
C. Chapuis, M. Barthe, J.-Y. de Saint Laumer, *Helv. Chim. Acta* **2001**, 84, 230

Table 2

$\text{R}^1 \text{R}^2 \text{CH}=\text{CHCH}_2\text{OH} \xrightarrow[\text{THF, 100}^\circ\text{C}]{5\% [\text{Rh}(\text{cod})((+)\text{-}2)]\text{BF}_4} \text{R}^1 \text{R}^2 \text{CH}_2\text{CH}(\text{R}^1)\text{CHO}$

Entry	Allylic Alcohol	Yield (%) ^{a,b}	ee (%) ^a
1	Ph Me $\text{CH}=\text{CHCH}_2\text{OH}$	80	59
2	Ph Et $\text{CH}=\text{CHCH}_2\text{OH}$	78	57
3	Ph $i\text{-Pr}$ $\text{CH}=\text{CHCH}_2\text{OH}$	82	82
4	Ph $t\text{-Bu}$ $\text{CH}=\text{CHCH}_2\text{OH}$	90	90
5 ^c	$o\text{-Tol}$ $i\text{-Pr}$ $\text{CH}=\text{CHCH}_2\text{OH}$	60	81
6	$p\text{-Tol}$ $i\text{-Pr}$ $\text{CH}=\text{CHCH}_2\text{OH}$	83	77
7	$p\text{-ClC}_6\text{H}_4$ $i\text{-Pr}$ $\text{CH}=\text{CHCH}_2\text{OH}$	83	85

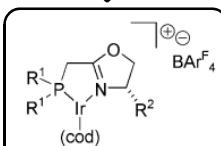
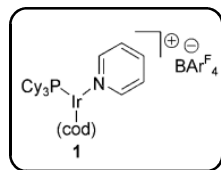
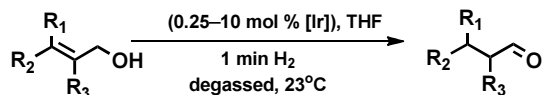
^a Average of two runs (first run, new catalyst; second run, catalyst recovered from the previous reaction, except for entry 6). ^b Isolated yields. ^c Reaction was carried out at 150 °C.



- Reaction needs to perform in high temperature more than boiling point of solvent (typically at 100-150°C)
- Reactivity is not high enough, even in such forcing conditions, the reaction time ranged from 24-28 hs, with yield varying from 60-90%

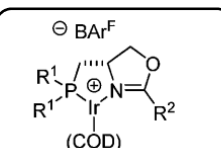
G. Fu et al *JACS* **2000**, 122, 9870-9871
G. Fu et al *JOC* **2001**, 66, 8177-8186

C. Mazet's work



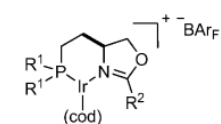
First generation ligand

- 6a: R¹ = Cy ; R² = *i*Pr
- 6b: R¹ = *t*Bu ; R² = *i*Pr
- 6c: R¹ = Cy ; R² = CH₂Ph
- 6d: R¹ = *t*Bu ; R² = CH₂Ph
- 6e: R¹ = Cy ; R² = Ph
- 6f: R¹ = *t*Bu ; R² = Ph
- 6g: R¹ = 1-Ad ; R² = Ph
- 6h: R¹ = Cy ; R² = *t*Bu
- 6i: R¹ = *t*Bu ; R² = *t*Bu
- 6j: R¹ = 1-Ad ; R² = *t*Bu



Second generation ligand

- 2a: R¹ = Cy; R² = Ph
- 2b: R¹ = *t*-Bu; R² = Ph
- 2c: R¹ = 1-Ad; R² = Ph
- 2d: R¹ = Cy; R² = *t*-Bu
- 2e: R¹ = *t*-Bu; R² = *t*-Bu
- 2f: R¹ = 1-Ad; R² = *t*-Bu



Third generation ligand

- 3a: R¹ = Cy ; R² = 1-Ad
- 3b: R¹ = *t*Bu ; R² = 1-Ad
- 3c: R¹ = 1-Ad; R² = 1-Ad
- 3d: R¹ = Cy ; R² = Ph
- 3e: R¹ = *t*Bu ; R² = Ph
- 3f: R¹ = 1-Ad; R² = Ph
- 3g: R¹ = *t*Bu ; R² = 3,5-(Me)₂-C₆H₃
- 3h: R¹ = *t*Bu ; R² = Mesityl
- 3i: R¹ = *t*Bu ; R² = 4-OMe-C₆H₄

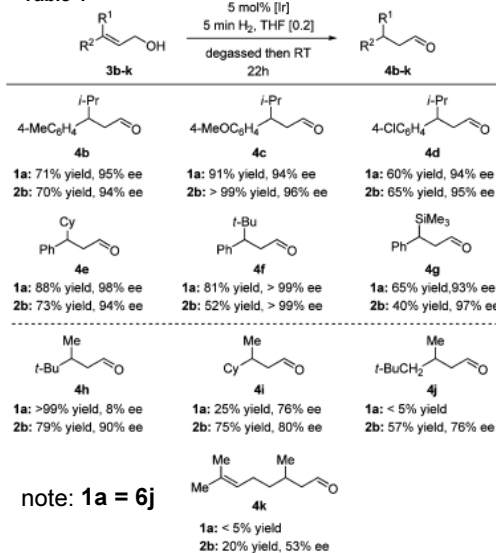
An efficient catalyst for isomerization of allylic alcohol
Performing reaction at room temperature
Accessible to get high yield for Z/E isomers of substrates
Wide range from monosubstituted to Tetrasubstituted olefin

Mazet C. et al *Tetrahedron Letters* 2009, 50, 4141–4144

- Highly active and selective iridium catalysts for the asymmetric isomerization of primary alcohol were developed.
- As R¹ alkyl substituent become small, a decrease was observed in conv. yield and enantioselectivity (entry 8-17)
- Z-configuration primary allylic alcohol did not provide satisfactory results.(entry 21-22)
- Accompanied isomerization of the allylic alcohol double was observed for Z-configuration (entry 10, 21)

Mazet C. et al *Angew. Chem. Int. Ed.* 2009, 48, 5143–5147

Table 4



- Aromatic primary allylic alcohol with small alkyl groups(entry 5, 6) were isomerized in modest yields but with a significant improvement of the enantioselectivity value.
- Electron-rich aromatic ring of substrate had a beneficial impact both on the activity and the enantioselectivity.
- *ortho* position was barely tolerated in term of catalyst activity.(entry 10)
- Some challenging substrate for example Geraniol also give modest yield and satisfactory result.
- Z-configuration primary alcohols are remain challenging problem.

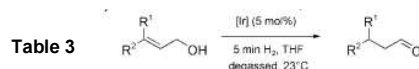
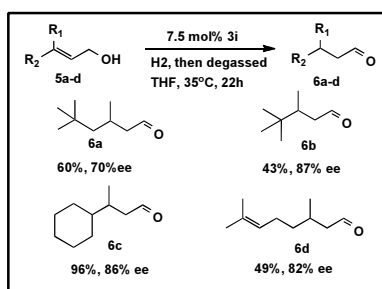


Table 3

Entry ^[a]	Catalyst	R ¹	R ²	t [h]	Conv. [%] ^[b]	ee [%] ^[c]
1	(R)-6f	<i>i</i> Pr	4-Me-C ₆ H ₄	22	50	56 (R)
2	(R)-6g	<i>i</i> Pr	4-Me-C ₆ H ₄	22	84	86 (R)
3	(S)-6j	<i>i</i> Pr	4-Me-C ₆ H ₄	22	71	95 (S)
4	(R)-6g	<i>i</i> Pr	4-MeO-C ₆ H ₄	22	>99	90 (R)
5	(S)-6j	<i>i</i> Pr	4-MeO-C ₆ H ₄	22	91	94 (S)
6	(R)-6g	<i>i</i> Pr	4-Cl-C ₆ H ₄	22	88	82 (R)
7	(S)-6j	<i>i</i> Pr	4-Cl-C ₆ H ₄	22	60	94 (S)
8	(R)-6f	Me	C ₆ H ₅	22	30	34 (S)
9	(R)-6g	Me	C ₆ H ₅	22	10	57 (S)
10	(S)-6h	Me	C ₆ H ₅	22	< 5 ^[d]	n.d.
11	(R)-6f	Et	C ₆ H ₅	8	35	60 (S)
12	(R)-6g	Et	C ₆ H ₅	22	30	73 (S)
13	(R)-6f	Cy	C ₆ H ₅	6	78	87 (R)
14	(R)-6g	Cy	C ₆ H ₅	6	85	94 (R)
15	(S)-6j	Cy	C ₆ H ₅	22	88	98 (S)
16	(R)-6g	<i>t</i> Bu	C ₆ H ₅	22	80	99 (R)
17	(S)-6j	<i>t</i> Bu	C ₆ H ₅	22	81	> 99 (S)
18	(R)-6f	Me	Cy	22	70	60 (S)
19	(R)-6g	Me	Cy	22	90	68 (S)
20	(S)-6j	Me	Cy	18	25	76 (R)
21	(R)-6g	Ph	<i>i</i> Pr	22	26 ^[e]	46 (S)
22	(R)-6g	Ph	Me	22	18	25 (R)

[a] Reported results are the average of at least two runs. [b] Determined by GC or ¹H NMR methods. [c] Determined by GC or SFC methods using a chiral stationary phase. Absolute configuration (shown in parentheses) based on the sign of the optical rotation and by comparison with literature data. See Ref. [3b]. [d] A 3:1 mixture of E/Z isomers was recovered. [e] The remaining 74% is a 3.5:1 mixture of E/Z isomers.

- They display similar reactivity and selectivity with first generation catalysts.
- This second generation of catalysts is available from dialkylphosphine precursors and inexpensive L- or D- Serine.
- This second generation outperformed first generation catalyst in isomerization of 3,3-dialkyl primary allylic alcohol.
- Low conversions and enantioselectivities along with substantial competing(E/Z) isomerization for Z-primary allylic alcohol still existed.

Mazet C. et al *Chem. Commun.*, 2010, 46, 445–447

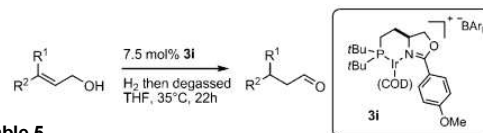
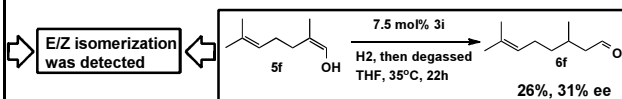


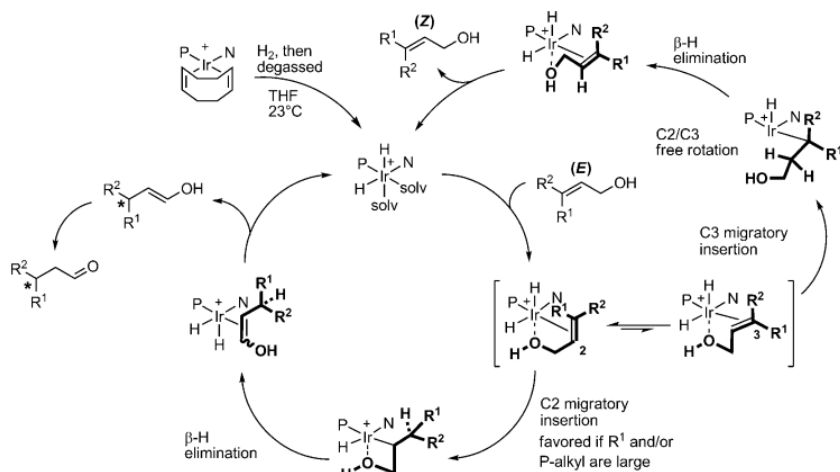
Table 5

R ¹	R ²	Olefin config	Yield [%] ^[c]	ee [%] ^[d]	
1	<i>t</i> Bu	Ph	E	55	99 (R)
2	<i>i</i> Bu	Ph	E	50	96 (R)
3	Cy	Ph	E	85	98 (R)
4	<i>i</i> Pr	Ph	E	64	98 (R)
5	Et	Ph	E	24	90 (S)
6	Me	Ph	E	26	80 (S)
7	<i>i</i> Pr	4-OMe-C ₆ H ₄	E	87	99 (R)
8	<i>i</i> Pr	4-Me-C ₆ H ₄	E	77	98 (R)
9	<i>i</i> Pr	4-Cl-C ₆ H ₄	E	50	97 (R)
10	Me	2-Me-C ₆ H ₄	E	12	92 (S) ^[e]
11	SiMe ₃	Ph	Z	60	97 (S)
12	Ph	Me	Z	< 5	nd ^[d]
13	Ph	<i>i</i> Pr	Z	19	61 (S)

[a] Average of at least two runs. [b] Reaction on a 0.1 mmol scale using 7.5 mol % of catalyst. [c] Determined by ¹H NMR spectroscopy using an internal standard and/or GC analysis. [d] Determined by chiral GC or SFC. [e] Catalyst 3f was used. [f] Not determined.



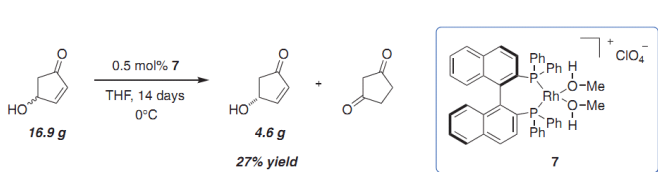
Mazet C. et al *Chem. Eur. J.* 2010, 16, 12736 – 12745



Mechanism for the isomerization of primary allylic alcohols using iridium catalysts

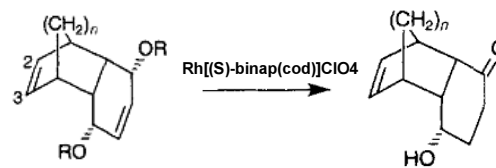
- Though those catalysts were efficient for isomerization of disubstituted at terminal double bond of primary allylic alcohol, not operative for tetrasubstituted or 2,3-disubstituted primary allylic alcohol.
- Homoallylic alcohol and secondary allylic alcohols were not isomerized
- Scope of substrate was limited to the *E*-configuration. For *Z*-configuration of primary allylic alcohols were not obtained satisfactory result.

Secondary allylic alcohols



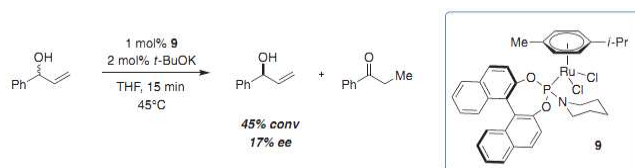
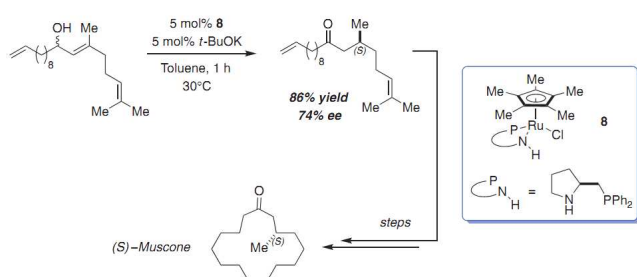
Catalyst 7 was used for kinetic resolution. R enantiomer was obtained in 91% ee and 27% yield.

Noyori R. *et al Tetrahedron Letters*, 1987, 28, 4 4719-4720,



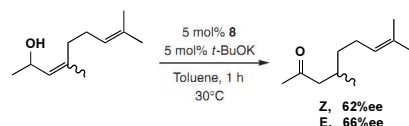
$n=1, R=H$, yield =100% 43.3% ee
 $n=1, R=TES$, yield= 86% 98% ee

Ogasawara K. *Angew. Chem. Int. Ed.* 1995, 34, 2287–2288



Though the ee% was low, phosphoramidite ligand was developed. It will be beneficial to generate new catalyst analogues to 9

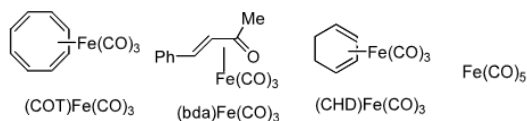
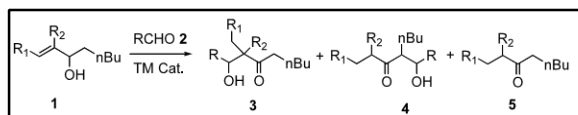
Pascale Crochet *et al Dalton Trans.*, 2010, 39, 7780–7785



Ikariya T. *et al J. Am. Chem. Soc.* 2005, 127, 6172

4 Relevant reaction after isomerization

isomerization-aldolization reaction



- 1. (bda)Fe(CO)₃ show higher activity than Fe(CO)₅ (table 1)
- 2. (COT)Fe(CO)₃ gives better result than Fe(CO)₅ for the bulky aldehyde but is inefficient in the case of allylic alcohols (table 3 entry i and j)
- 3. (CHD)Fe(CO)₃ is less reactive than Fe(CO)₅

Table 1. Tandem isomerization-aldolization condensation of alcohol 1 using bdaFe(CO)₃ as the catalyst

Entry	R	R ₁	R ₂	Time (min)	3+4 (yield %)	3+4 Fe(CO) ₅ as cat. ²	3 _{syn} /3 _{anti} /4/4'
a	Ph	H	H	40	91	74	49/46/3/2
b	Ph	Me	H	75	70	46	57/32/7/4
c	Ph	H	Me	120	85	73	90/-/6/4
d	(Me) ₂ CH	H	H	120	62	<20	61/32/4/3
e	<i>p</i> -AcNHPh	H	H	90	58	^a	37/60/3<1 ^b

^a Unknown.

^b Ratio calculated on the mixture after chromatography.

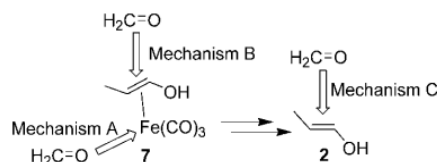
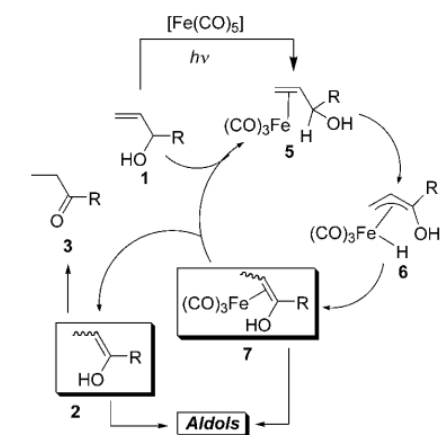
Table 3. Tandem isomerization-aldolization condensation of alcohol 1 using (COT)Fe(CO)₃ as the catalyst

Entry	R	R ₁	R ₂	Cat. (%)	Time (min)	3+4 (yield %)	3+4 Fe(CO) ₅ as cat. ²	3 _{syn} /3 _{anti} /4/4'
a	Ph	H	H	2	20	84	74	64/28/5/3
b	H	H	H	4	45–60	84	64	94/-/6
c	Me ₂ CHCH ₂	H	H	3	35	72	54	63/27/5/5
d	Me ₂ CH	H	H	3	35	63	<20	53/34/7/6
e	Cy	H	H	3	35	64	<20	59/33/4/2
f	Et ₂ CH	H	H	3	35	36	^a	65/32/-
g	EtCH=CH(CH ₂) ₂	H	H	4	180	78	^a	55/36/5/4
h	<i>p</i> -AcNHPh	H	H	5	180	54	^a	57/36/4/3
i	Ph	Me	H	5	4 h	<20% conv.	46	
j	Ph	H	Me	5	4 h	<20% conv.	73	

^a Unknown.

Gree R. *et al Tetrahedron Letters* 2003, 44, 6187–6190 10

Three mechanisms were proposed by Gree R.



Mechanism A: First, formaldehyde coordinate to the iron atom of [(enol)Fe(CO)₃] complex **7**, second, formation of key C-C bond for the aldolization process occurs at a later stage.

Mechanism B: Formaldehyde was attacked directly by the enol of [(enol)Fe(CO)₃] complex **7**.

Mechanism C: Formaldehyde reacts with free enol **2** after enol decoordination from complex **7**

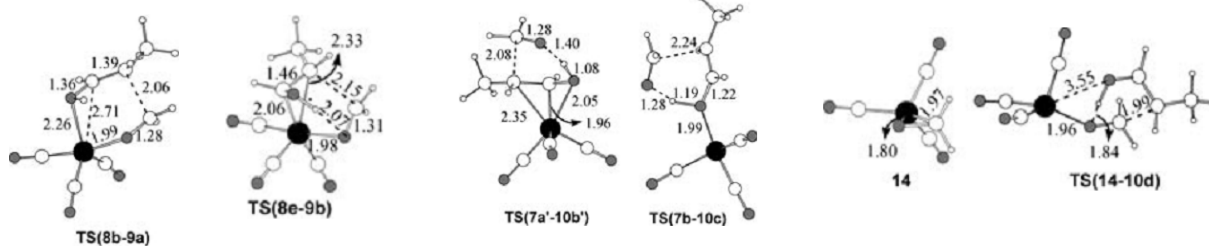


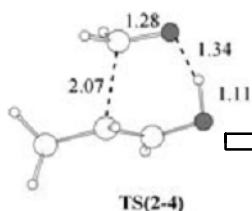
Table 3. Gibbs activation energies^[a] for the rate-determining transition states^[b] corresponding to different mechanisms of aldol formation for reactions with formaldehyde and acetaldehyde.

Mechanism	Transition state	Formaldehyde gas phase	Formaldehyde cyclohexane	Acetaldehyde gas phase
A	TS(8b-9a)	26.4 (26.3)	26.0	31.0
A	TS(8e-9b)	26.2 (26.3)	26.6	33.3
B	TS(7a'-10b')	25.1 (25.1)	27.0	28.5
B	TS(7b-10c)	27.6 (27.6)	28.3	30.4
C	TS(2-4) ^[c]	13.5 (13.6)	12.7	19.4
C	TS(14-10d)	25.7 (26.1)	25.3	33.1

Key step: an efficient transfer from enol proton transfer from enol to aldehyde

Mechanism C is highly favored.

Carbonyl-ene-type reaction was suggested



Gree R. *et al Chem. Eur. J.* **2004**, *10*, 5795 – 5803

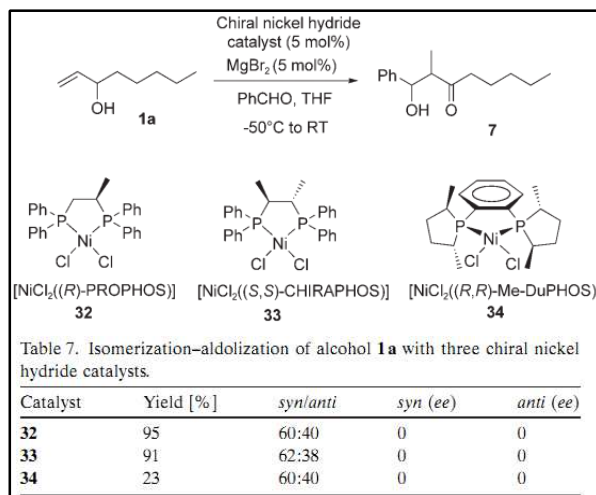
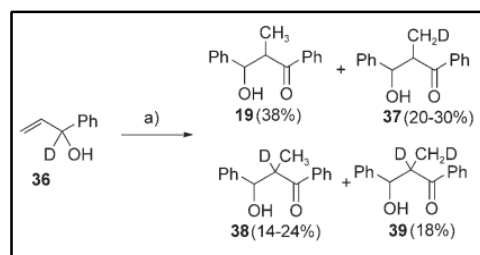
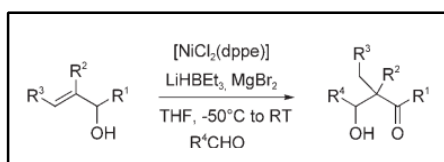
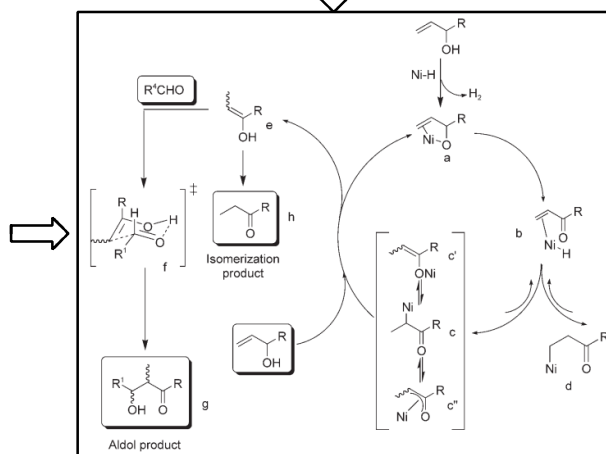
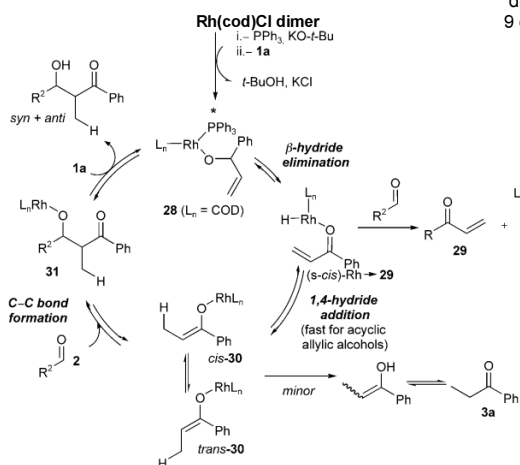
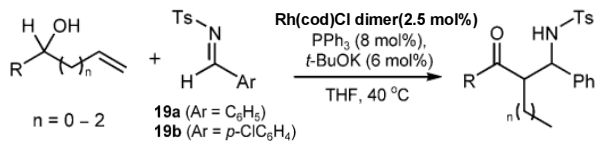
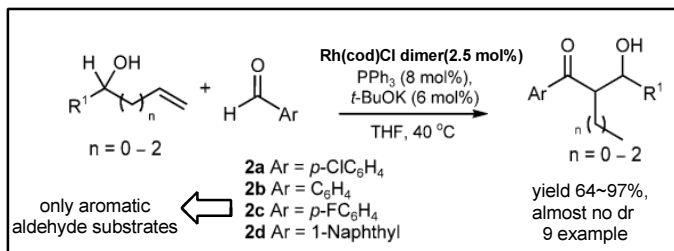


Table 7. Isomerization-aldolization of alcohol **1a** with three chiral nickel hydride catalysts.

Catalyst	Yield [%]	syn/anti	syn (ee)	anti (ee)
32	95	60:40	0	0
33	91	62:38	0	0
34	23	60:40	0	0

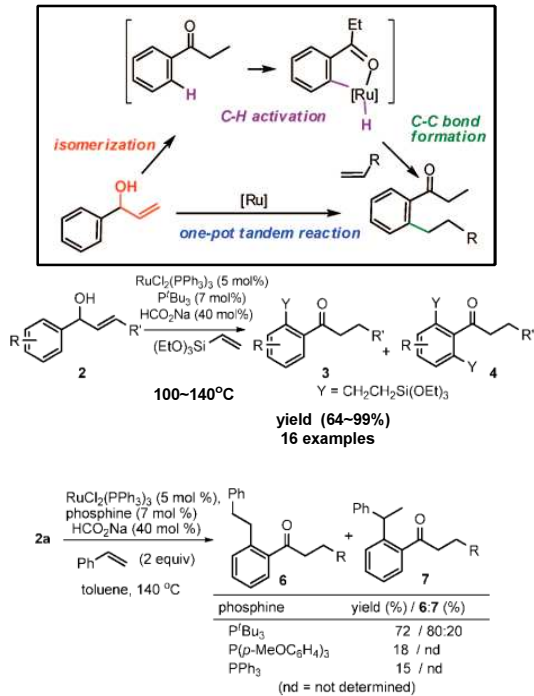


Gree R. *et al Chem. Eur. J.* **2006**, *12*, 3261–3274

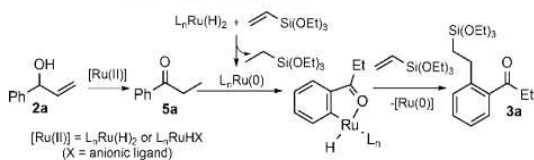


Martin-Matute B. et al. *Adv. Synth. Catal.* **2009**, 351, 2657 – 2666

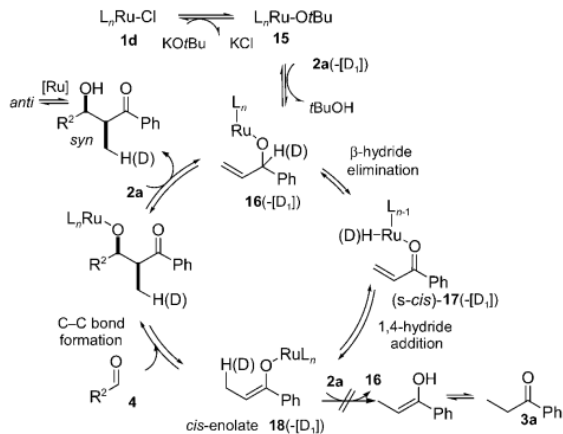
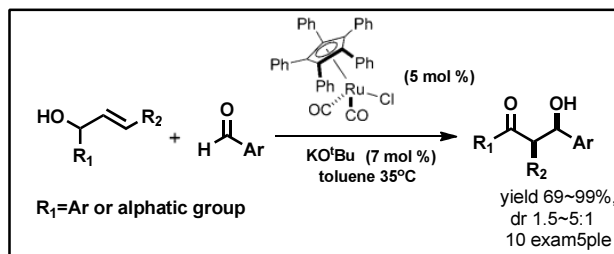
Tandem Isomerization/ C-H activation



Scheme 4. Proposed Mechanism

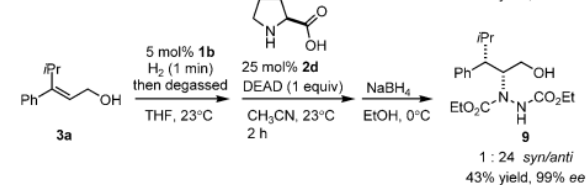
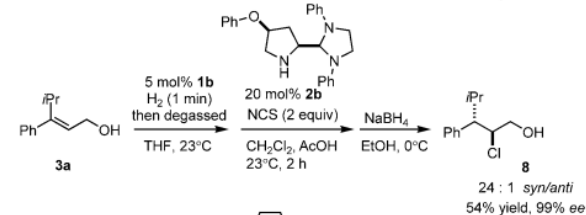
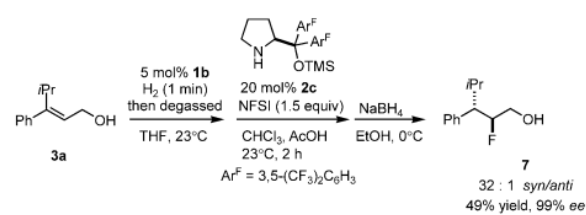
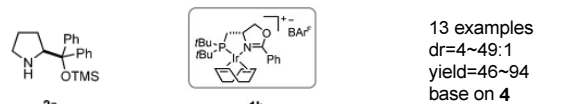
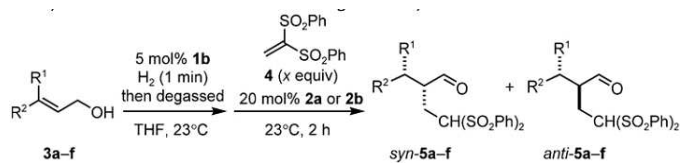
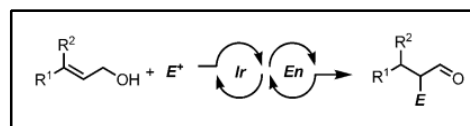


Martin-Matute B. et al. *Org. Lett.*, **2009**, 11, 1749–1752



Martin-Matute B. et al. *Chem. Eur. J.* **2008**, 14, 10547 – 10550

Sequential Ir Isomerization/ enamine catalysis



Mazet C. et al. *Angew. Chem. Int. Ed.* **2011**, 50, 2354 – 2358

Summary:

1. Many different catalysts were developed for isomerization of allyl alcohol, but corresponding Metals (for instance Rh, Ru, Ir) are very expensive. So issues concerning recycling need to be addressed or develop some efficient first-row transition Metal catalysts.
 2. As the substituents increase, the reaction becomes more difficult. So far, only one catalyst can isomerize the tetrasubstituted primary allylic alcohol. No catalyst is operative for the tetrasubstituted olefin of secondary alcohol. Lots of efficient catalysts need harsh conditions which limit the application of them.
 3. Asymmetric isomerization is still a challenging issue, albeit efficient catalysts for asymmetric isomerization of primary allylic alcohol developed by G. Fu and C. Mazet. More efficient asymmetric catalysts for isomerization of allylic alcohol at broad scope were highly required.
 4. Many new tandem reactions were developed from allylic alcohol. Especially, Tandem isomerization/aldolization was conducted in different metals and different conditions, giving different mechanisms. So such kind of reaction and mechanism need to be studied extensively.
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