2007.11.21 (Wed.)
Hiroyuki Morimoto (D2)

Synergy of Transition Metal Complexes with Acid/Base Catalysts

—An Approach to Truly Environmentally Benign Catalysis—

Contents

I. Introduction

1.1 Comparison of Transition Metal Catalysis with Acid/Base Catalysis

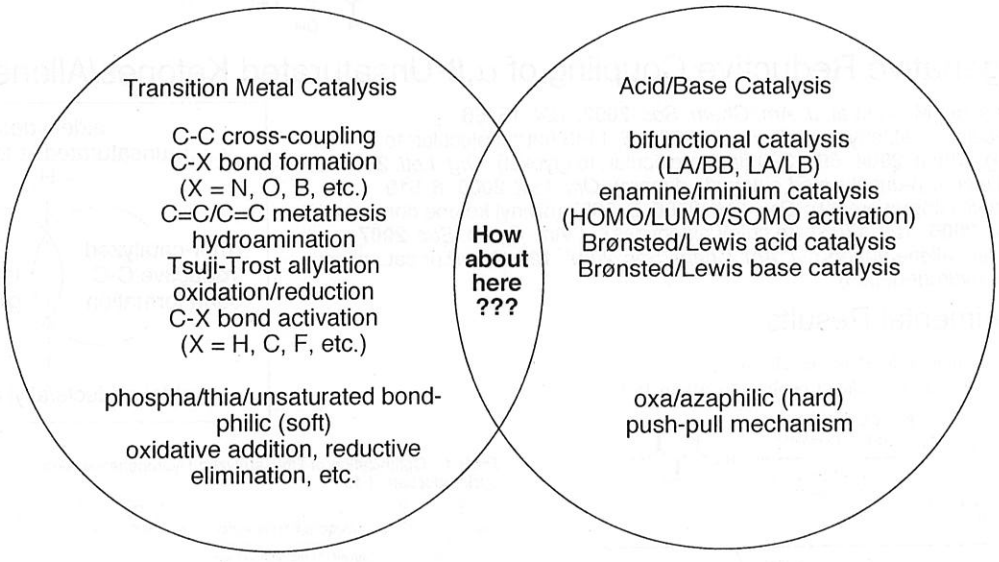


Figure 1. Classification of Catalysis.

1.2 Mr. Oisaki's Six Criteria for Development of Synthetically Useful Reactions

See Mr. Oisaki's Literature Seminar Handout 2007/10/13 for details.

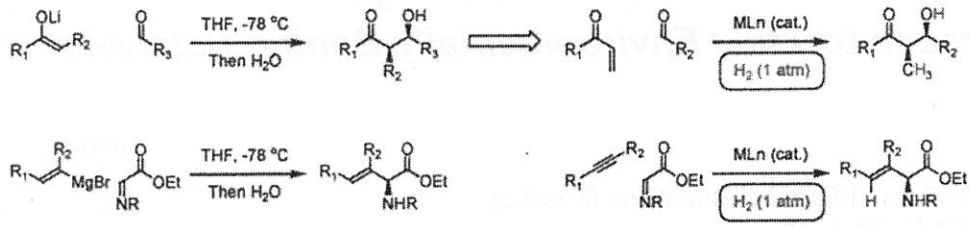
I) Develop Intermolecular C-C bond-forming reactions.
II) Develop cross reactions.
III) Use minimal co-redox agent as far as you can.
IV) Activator should be catalytic amount.
V) Use common FG.
VI) Create new stereogenic centers.

2. Hydrogenative C–C Bond-Forming Reactions

2.1 Backgroud and Mechanism

2.1.1 Background

Review: Krische, M. J.; et al. *J. Org. Chem.* **2007**, *72*, 1063; *Acc. Chem. Res.* **2004**, *37*, 653; *Acc. Chem. Res. ASAP*.
See also: Kanai, M.; Shibasaki, M.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 14440.

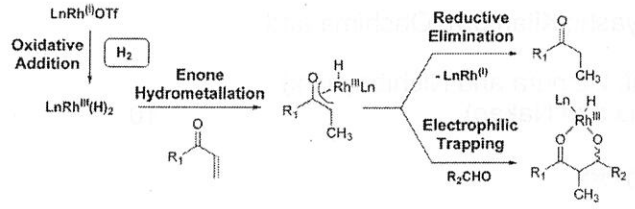


- Conventional acid/base chemistry usually requires a stoichiometric amount of metallic deprotonating agents to construct β-hydroxy ketone/allyl amine moieties.
- Reductive coupling reactions are usually performed using a stoichiometric amount of metallic reducing agents.

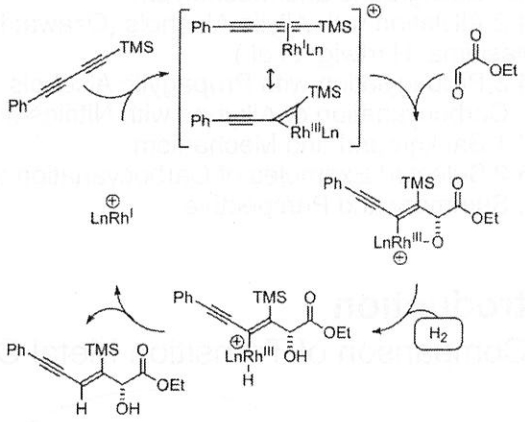
–> How about the use of **H_2 gas** itself as a reducing agent to construct C–C bond??

2.1.2 Mechanism

(1) Reductive Coupling of α,β-Unsaturated Ketones

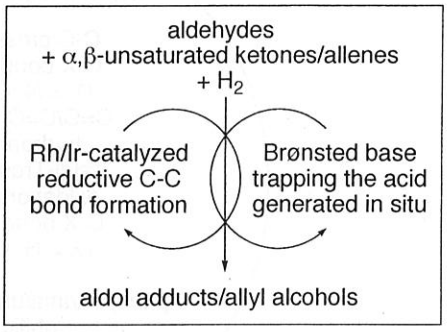


(2) Reductive Coupling of Alkynes



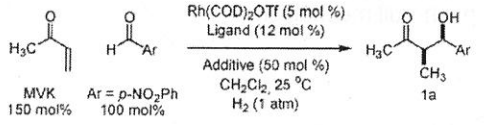
2.2 Hydrogenative Reductive Coupling of α,β-Unsaturated Ketones/Allenes

References: Krische, M. J.; et al. *J. Am. Chem. Soc.* **2002**, *124*, 15156 (intra/intermolecular; to aldehydes); *Org. Lett.* **2003**, *5*, 1143 (intramolecular; to ketones); *J. Org. Chem.* **2004**, *69*, 1380 (intermolecular; to glyoxal); *Org. Lett.* **2004**, *6*, 691 (intramolecular; α,β-unsaturated aldehyde donors); *Org. Lett.* **2004**, *8*, 519 (diastereoselectivity improvement); *Org. Lett.* **2006**, *8*, 5657 (divinyl ketone donors); *J. Am. Chem. Soc.* **2006**, *128*, 17051 (to chiral aldehydes); *J. Am. Chem. Soc.* **2007**, *129*, 12678 (Ir cat.; allene donors); *J. Am. Chem. Soc.* **2007**, *129*, *ASAP* (Ir cat.; allene donors; transfer hydrogenation).



2.2.1 Experimental Results

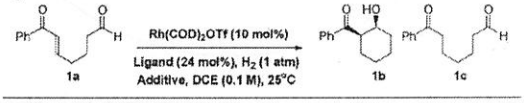
Table 1. Optimization of the Diastereoselective Hydrogen-Mediated Reductive Aldol Coupling To Afford **1a**[a,b]



entry	ligand	additive	[DCM], M	yield, %	dr
1	PPh_3	Li_2CO_3	0.1	31	3:1
2	$(2\text{-Fur})Ph_2P$	Li_2CO_3	0.1	24	6:1
3	$(2\text{-Fur})_2PhP$	Li_2CO_3	0.1	52	15:1
4	$(2\text{-Fur})_3P$	Li_2CO_3	0.1	74	19:1
5	$AsPh_3$	Li_2CO_3	0.1	17	7:1
6	$(2\text{-Fur})_3P$		0.1	63	19:1
7	$(2\text{-Fur})_3P$	Li_2CO_3	0.3	88	16:1
8	**$(2\text{-Fur})_3P$**	**Li_2CO_3 (10%)**	**0.3**	**91**	**16:1**

[a] **Optimized Procedure.** To a 13 mm × 100 mm test tube charged with Li_2CO_3 (5 mg, 0.066 mmol, 10 mol %), Fur_3P (18 mg, 0.079 mmol, 12 mol %), $Rh(COD)_2OTf$ (16 mg, 0.033 mmol, 5 mol %), and aldehyde (100 mg, 0.66 mmol, 100 mol %) was added dichloromethane (1.0 M). The test tube was sealed, and the reaction mixture was sparged with Ar(g) followed by H_2(g) for 20 s each. The reaction was placed under one atmosphere of hydrogen using a balloon, and MVK (81 μL, 0.99 mmol, 150 mol %) was added. The reaction mixture was allowed to stir until consumption of aldehyde was observed, as revealed by TLC analysis. The reaction mixture was evaporated onto silica, and the aldol product **1a** was isolated by flash chromatography (SiO_2: EtOAc/hexane). [b] The cited yields are of isolated material and represent the average of two runs.

Table 1. Optimization of Rh-Catalyzed Hydrogenative Aldol Cycloreduction of **1a**[a]



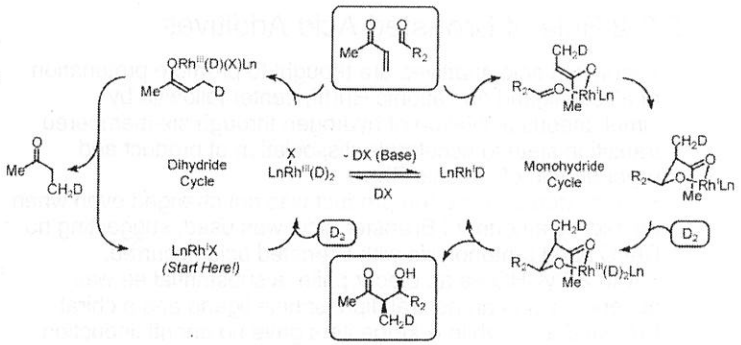
entry	ligand	additive (mol %)	yield[b] aldol (syn–anti)	yield[b] 1,4-reduction
1	PPh_3		21% (99:1)	25%
2	PPh_3	KOAc (30%)	59% (58:1)	21%
3	$(p\text{-}CF_3Ph)_3P$		57% (14:1)	22%
4	$(p\text{-}CF_3Ph)_3P$	KOAc (30%)	89% (10:1)	0.1%

[a] As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on a 1.48 mmol scale in 50 mL round-bottomed flasks. [b] Isolated yields after purification by silica gel chromatography.

- Addition of a catalytic amount of Brønsted base additives improved the yield of aldol adducts and the aldol/1,4-reduction ratio.
- Weak σ-donor/strong π-acceptor phosphine ligands gave better yield and dr.

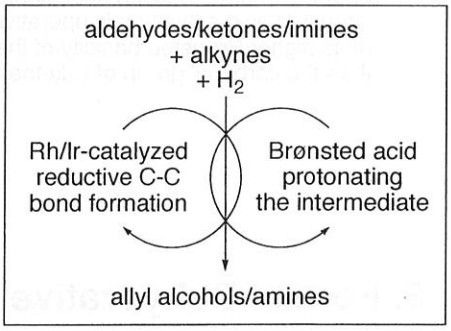
2.2.2 Role of Brønsted Base Additives

- Dihydride cycle (left) promotes 1,4-reduction of α,β-unsaturated ketones.
- Monohydride cycle (right) promotes reductive aldol reaction.
- Brønsted base additives remove DX from LnRh(III)X(D_2) catalyst to give LnRh(I)D, diminishing side products from the dihydride pathway.



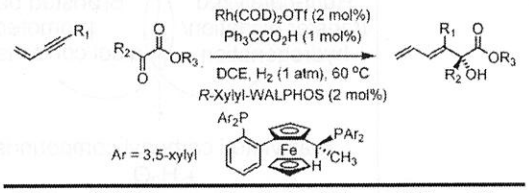
2.3 Hydrogenative Reductive Coupling of Alkynes

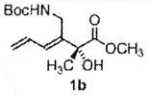
References: Krische, M. J.; et al. *JACS* **2003**, *125*, 11488 (enantioselective; 1,3-diyne donors; glyoxal acceptors); *JACS* **2004**, *126*, 4664 (1,3-enyne donors); *JACS* **2004**, *126*, 7875 (intramolecular; 1,6-diyne and 1,6-enynes); *JACS* **2005**, *127*, 6174 (intramolecular; enantioselective; 1,6-enynes); *JACS* **2005**, *127*, 11269 (chiral α-sulfinyliminoester acceptors); *JACS* **2006**, *128*, 718 (enantioselective; α-ketoester acceptors); OL **2006**, *8*, 891 (application to Bryostatin subunit); *OL* **2006**, *8*, 3873 (enantioselective; silyl-substituted 1,3-diyne donors); *JACS* **2006**, *128*, 10674 (enantioselective; intramolecular; Brønsted acid co-catalyst(BAC)); *JACS* **2006**, *128*, 16040 (enantioselective; an acetylene donor; dienylation; BAC); *JACS* **2006**, *128*, 16448 (enantioselective; heterocyclic aromatic aldehyde/ketone acceptors; BAC); *JACS* **2007**, *129*, 280 (Ir-cat.; simple alkyne donors; BAC); *JACS* **2007**, *129*, 7242 (enantioselective; dienylation; imine acceptors; BAC); *JACS* **2007**, *129*, 8432 (Ir-cat.; simple alkyne donors; imine acceptors; BAC); *OL* **2007**, *9*, 3745 (enantioselective; glyoxal acceptors; BAC); *JACS* **2007**, *129*, 12644 (enantioselective; Ir-cat.; simple alkyne donors; imine acceptors; BAC).



2.3.1 Experimental Results

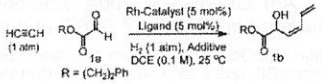
Table 1. Enantioselective Hydrogen-Mediated Reductive Coupling of Conjugated Enynes **1a**–**7a** to α-Ketoesters[a]



Entry	Substrate	Coupling Product	Yield	ee %
1				
	1a	**1b**	**88%**	**90%**
2	w/o Ph_3CCO_2H co-catalyst:		42%	87%

[a] Cited yields are of pure isolated material and represent the average of two runs. Reaction times are typically less than 3 h. See Supporting Information for detailed experimental procedures.

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	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 %.

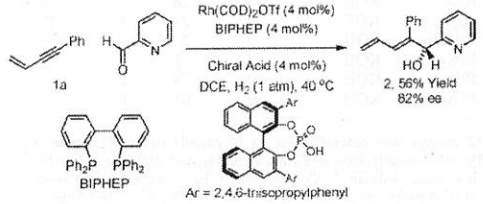
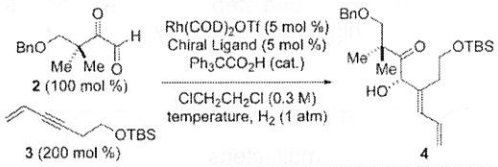
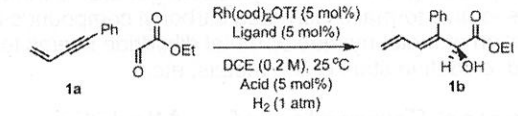


Table 1. Enantioselective Hydrogen-Mediated Reductive Coupling of Glyoxal **2** to 1,3-Enyne **3**[a]

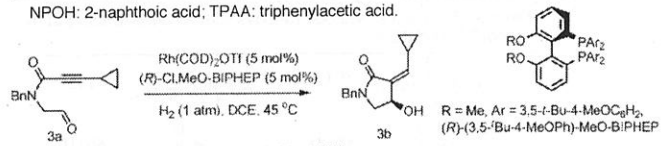


entry	chiral ligands	temp.	Ph_3CCO_2H	ee %	yield
4	(*R*)-Tol-BINAP	25 °C	5.0 mol %	48%	37%
5	(*R*)-Tol-BINAP	45 °C	5.0 mol %	67%	55%
6	(*R*)-Tol-BINAP	65 °C	5.0 mol %	78%	58%
7	(*R*)-Tol-BINAP	65 °C	2.5 mol %	86%	64%
8	**(*R*)-Tol-BINAP**	**65 °C**	**1.5 mol %**	**91%**	**70%**
9	(*R*)-Tol-BINAP	65 °C	---	90%	32%



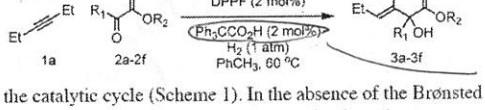
Entry	Rh-Catalyst	Chiral Ligand	Acid	Yield%	ee%
17	$Rh(cod)_2OTf$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	---	65	91
18	$Rh(cod)_2BF_4$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	---	65	90
19	$Rh(cod)_2BARF$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	---	66	93
20	$Rh(cod)_2OTf$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	NPOH	78	25
21	$Rh(cod)_2OTf$	(*R*)-(3,5-^{t}Bu-4-MeOPh)-MeO-BIPHEP	TPAA	82	95

NPOH: 2-naphthoic acid; TPAA: triphenylacetic acid.



In the Absence of Additive: 24% Yield, 95%ee
With 2-Naphthoic Acid (5 mol%): 67% Yield, 98%ee

Table 1. Hydrogen-Mediated Reductive Coupling of Alkyl-Substituted 3-Hexyne **1a** to α-Ketoesters **2a**–**2f**[a]



close the catalytic cycle (Scheme 1). In the absence of the Brønsted acid cocatalyst, the couplings proceed more slowly and are accompanied by over-reduction of the olefinic product. Excess Brønsted acid does not diminish the extent of deuterium incorporation. Recent

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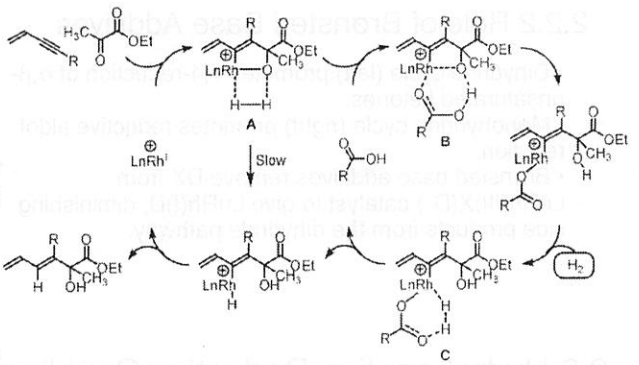
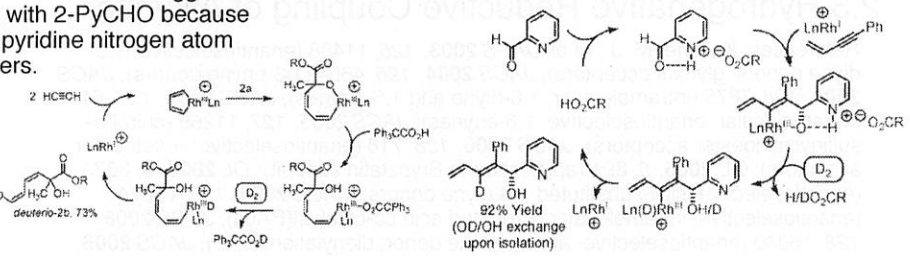
- Brønsted acid improved the yield and changed the ee.
- Chiral Brønsted acid could induce ee (but only for 2-PyCHO).

2.3.2 Role of Brønsted Acid Additives

- Brønsted acid additives are thought to promote protonation of alkoxo ligand on cationic Rh(III) center followed by simultaneous activation of hydrogen through six-membered transition state to accelerate dissociation of product and regeneration of cationic Rh(I).
- D incorporation into the product was not changed even when an excess amount of Brønsted acid was used, suggesting no Rh–C bond protonolysis with Brønsted acid occurred.
- With 2-PyCHO as an electrophile, a substantial ee was observed using an achiral diphosphine ligand and a chiral Brønsted acid, while α-ketoesters gave no enantioinduction under the same reaction conditions. These results suggest the Brønsted acid activation is operative with 2-PyCHO because of its higher Brønsted basicity of the pyridine nitrogen atom than the carbonyl group of α-ketoesters.



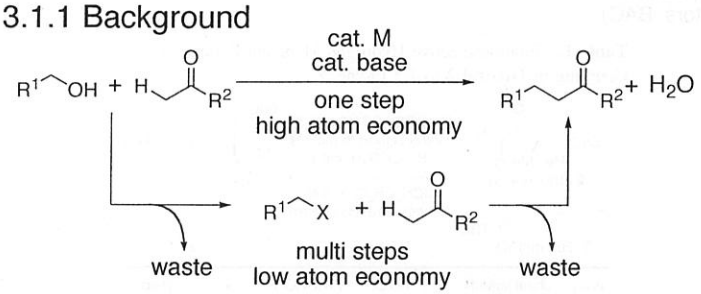


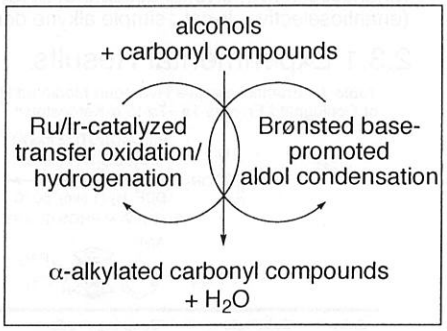
3. Formal Dehydrative α-Alkylation with Alcohols

3.1 Backgroud and Mechanism

Review: Ramón, D. J.; Yus, M.; et al. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358.

3.1.1 Background

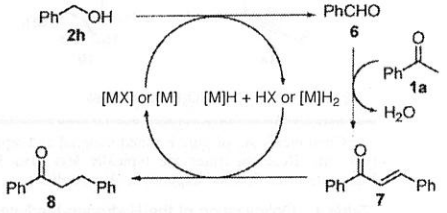




3.1.2 Mechanism

- Dehydrogenative oxidation of alcohols (transfer dehydrogenation) with transition metal complexes affords aldehydes, which in turn is condensed with carbonyl compounds catalyzed by Brønsted base additives (aldol reaction). The α,β-unsaturated carbonyl compounds formed are then hydrogenated with metal hydride species (transfer hydrogenation) generated from the above oxidation of alcohols to give formal α-alkylated carbonyl compounds as a product.
- Formation of metal hydride or metal dihydride seems to depend on the metals selected, oxidation state of the metals, etc.

Scheme 2

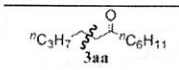
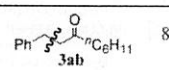
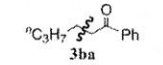
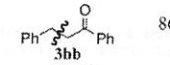
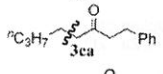
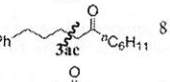
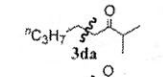
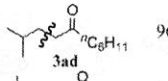
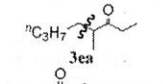
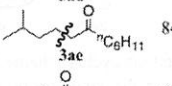
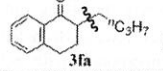
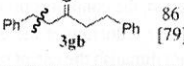


3.2 Selected Examples of α-Alkylation

3.2.1 α-Alkylation of Ketones (Ishii)[a]

- No TM w/o Brønsted Base (Table 1, entry 2)
- No solvent required
- Less hindered side of ketones alkylated
- Applicable for primary alcohols

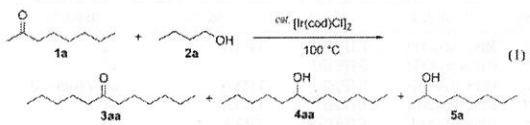
Table 3. Reaction of Various Ketones with Alcohols Catalyzed by $[Ir(cod)Cl]_2$ and KOH[a]

 3aa	80 (2)	 3ab	81 (3)
 3ba	88 (4)	 3bb	86 (10)
 3ca	71 (1)	 3ac	81 (2)
 3da	80 (<1)	 3ad	96 (1)
 3ea	47 (<1)	 3ae	84 (2)
 3fa	88 (<1) [80][g]	 3gb	86 (3) [79][g]

[a] Reaction conditions were the same as these of Table 1, run 1. [b] Numbers in parentheses show the corresponding alcohol. [c] **1b** (8 mmol) was used. [d] KOH (0.6 mmol) was used. [e] KOH (0.4 mmol) was used. [f] **2b** (8 mmol) was used. [g] Isolated yield.

References: a) Ishii, Y.; et al. *J. Am. Chem. Soc.* **2004**, *126*, 72; b) Kaneda, K.; et al. *J. Am. Chem. Soc.* **2004**, *126*, 5662; c) Williams, J. M. J.; et al. *Tetrahedron Lett.* **2006**, *47*, 6787, and references therein.

Table 1. Reaction of 2-Octanone (**1a**) with 1-Butanol (**2a**) Catalyzed by $[Ir(cod)Cl]_2$ and Base under Various Conditions[a]



				product (%)[c]		
run	ligand	base	conv. (%)[b]	3aa	4aa	5a
1	PPh_3	KOH	96	80	2	7
2	PPh_3		3	n.d.	n.d.	1
3	PPh_3	CsOH	97	80	3	8
4	PPh_3	NaOH	98	79	trace	8
5	PPh_3	K_2CO_3	2	1	n.d.	2
6	PPh_3	NEt_3	2	n.d.	n.d.	2
7	PPh_3	$Ba(OH)_2$	44	27	1	15
8	PBu_3	KOH	84	63	2	16
9	PCy_3	KOH	82	48	2	15
10[d]	dppe	KOH	85	28	2	26
11[d]	dppp	KOH	92	23	3	27
12	$P(OPh)_3$	KOH	7	2		5
13[e]	PPh_3	KOH	94	81	3	6
14[f]	PPh_3	KOH	90	76	1	7
15[g]	PPh_3	KOH	80	68	1	5

[a] **1a** (2 mmol) was reacted with **2a** (4 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol), base (0.2 mmol), and ligand (0.08 mmol) at 100 °C for 4 h without solvent. [b] Conversion of **1a**. [c] Based on **1a** used. [d] Ligand (0.04 mmol) was used. [e] At 110 °C. [f] At 90 °C. [g] **2a** (2 mmol) was used.

3.2.2 α-Alkylation of Arylacetonitriles (Kaneda)[b]

- Heterogeneous Ru(IV)/HT (hydrotalcite, $Mg_6Al_2(OH)_{16}CO_3$) (Figure 1) was used as a bifunctional transfer oxidation/hydrogenation and Brønsted base catalyst (Scheme 1).
- A large excess amount of alcohols and high temp. (180 °C) required.
- Reaction under O_2 atmosphere didn't give TM (**3a**) but afforded only a trace amount of **4a** (Table 1, entry 2).
- Various arylacetonitriles and ketones were applicable (Table 2).
- Tandem α-alkylation-Michael addition proceeded with good yields (Scheme 2).

Treatment of the HT, $Mg_6Al_2(OH)_{16}CO_3$, with an aqueous solution of $RuCl_3{\cdot}nH_2O$ at room temperature afforded the Ru/HT as a gray powder. The absence of chlorine was confirmed by XPS

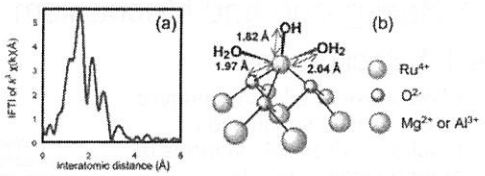
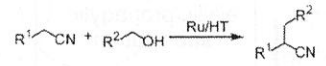


Figure 1. (a) Fourier transform (FT) of k^3-weighted Ru K-edge EXAFS of Ru/HT. (b) A proposed surface structure around Ru^{4+} of Ru/HT.

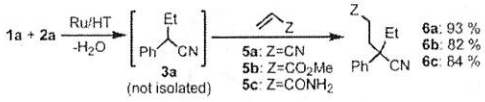
Table 2. α-Alkylation of Nitriles with Alcohols Using Ru/HT[a]



entry	donor		alcohol		product	yield (%)[b]
1	R^1 = Ph	1a	R^2 = Me	2a	3a	98 (94)
2	R^1 = 4-Cl–Ph	1b	2a		3b	83
3	R^1 = 4-Me–Ph	1c	2a		3c	99
4[c]	R^1 = 4-MeO–Ph	1d	2a		3d	92
5[c]	R^1 = 1-naphthyl	1e	2a		3e	89
6[c]	R^1 = 2-thiophenyl	1f	2a		3f	86
7	1a		R^2 = H	2b	3g	65
8	1a		R^2 = *n*-Pr	2c	3h	94 (86)
9[c]	1a		R^2 = *i*-Pr	2d	3i	85
10[d,e]	1a		R^2 = Ph	2e	3j	91 (77)
11[d,f]	$PhC(O)CH_3$	1g	2e		$PhC(O)CH_2Bn$	85
12[c,d,g]	*i*-PrC(O)CH_3	1h	2c		*i*-PrC(O)CH_2*n*-Bu	68

[a] Donor (1 mmol), alcohol (2 mL), Ru/HT (0.15 g, Ru: 0.0075 mmol), 180 °C, 20 h, Ar. [b] Based on donor. Values in parentheses are isolated yield. [c] Ru/HT (0.3 g, Ru: 0.015 mmol). [d] 2 mL of toluene was used. [e] **2e** (1.5 mmol). [f] **2e** (1.0 mmol). [g] **2e** (2.0 mmol).

Scheme 2



Scheme 1

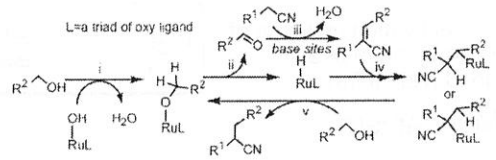
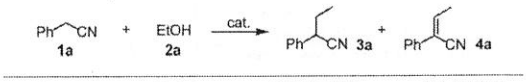


Table 1. Reaction of Phenylacetonitrile (**1a**) and Ethanol (**2a**) by Various Catalysts[a]

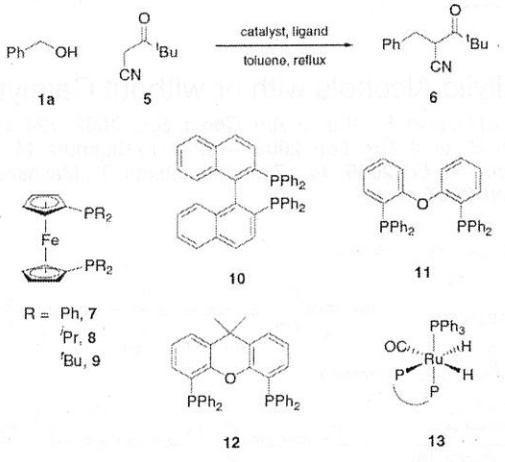


entry	catalyst	yield of 3a (%)[b]	yield of 4a (%)[b]
1	Ru/HT	98	trace
2[c]	Ru/HT	trace	10
3	Ru/Al_2O_3	14	trace
4	Ru/MgO	2	trace
5	$Ru/Al(OH)_3$	5	16
6	$Ru/Mg(OH)_2$	2	8
7[d]	HT	N.R.[e]	N.R.
8[f]	$RuCl_3{\cdot}nH_2O$	N.R.	N.R.

[a] **1a** (1 mmol), **2a** (2 mL), Ru catalyst (0.15 g, Ru: 0.0075 mmol), 20 h, 180 °C, Ar. [b] Based on **1a**. [c] Under O_2. [d] 0.15 g of HT was used. [e] No reaction. [f] 0.0075 mmol of Ru was used.

3.2.3 α-Alkylation of Active Methylene Compounds (Williams)[c]

- Combination of Ru(II) metal with bidentate phosphine ligands having large bite angles was the best.
- Piperidinium acetate was necessary to promote condensation.
- Applicable for both aromatic and aliphatic carbinols; 1:1 substrates ratio is enough.

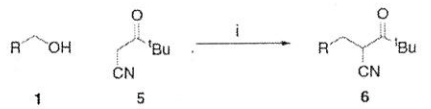


Scheme 2. Reaction of benzyl alcohol **1a** with ketonitrile **5**.

Table 1. Comparison of ligands for C–C bond formation[a]

Entry	Metal (loading, mol %)	Ligand	Time (h)	Conversion (%)
1[b]	Ir (5)	7	24	55
2	Ru (5)	—	18	56
3	Ru (0.5)	7	3	56
4	Ru (0.5)	8	3	91
5	Ru (0.5)	9	16	<1
6	Ru (0.5)	10	16	22
7	Ru (0.5)	11	3	8
8	Ru (0.5)	12	3	100

[a] Typical reaction conditions: Benzyl alcohol **1a** (1 equiv), ketonitrile **5** (1 equiv) were treated with $Ru(PPh_3)_3(CO)H_2$ (0.5 mol %), ligand (0.5 mol %), piperidinium acetate (5 mol %), PhMe, reflux.
[b] $[Ir(cod)Cl]_2$ (2.5 mol %), dppf **7** (5 mol %), K_2CO_3 (5 mol %), 3 Å molecular sieves, piperidinium acetate (25 mol %), PhMe, reflux.



Scheme 3. Alkylation of other alcohols with ketonitrile **5**. Reagents and conditions: (i) $Ru(PPh_3)_3(CO)H_2$ (0.5 mol %), Xantphos **12** (0.5 mol %), piperidinium acetate (5 mol %), PhMe, reflux, 4 h.

Table 2. C–C bond formation using the Ru/Xantphos catalyst[a]

Entry	Alcohol	Conversion (%)	Yield (%)
1	$PhCH_2OH$, **1a**	100	78
2	*p*-$MeOC_6H_4CH_2OH$, **1b**	100	83
3	*p*-$FC_6H_4CH_2OH$, **1c**	100	89
4	*p*-$F_3CC_6H_4CH_2OH$, **1d**	100	83
5	*p*-$O_2NC_6H_4CH_2OH$, **1e**	52	31
6	*p*-$BrC_6H_4CH_2OH$, **1f**	100	79
7	*o*-$MeOC_6H_4CH_2OH$, **1g**	100	82
8	Furfuryl alcohol, **1h**	11	Not isolated

[a] Typical reaction conditions: Alcohol (1 equiv), ketonitrile **5** (1 equiv) were treated with $Ru(PPh_3)_3(CO)H_2$ (0.5 mol %), ligand (0.5 mol %), piperidinium acetate (5 mol %), PhMe, reflux, 4 h.

Table 3. C–C bond formation using aliphatic alcohols[a]

Entry	Alcohol	Conversion (%)	Yield (%)
1	Furfuryl alcohol, **1h**	100	72
2	$PhCH_2CH_2OH$, **1i**	100	—
3[b]	$PhCH_2CH_2OH$, **1i**	100	87
4	Undecanol, **1j**	100	85
5	Cyclopropyl methanol, **1k**	100	69
6	Tryptophol, **1l**	100	76

[a] Typical reaction conditions: Alcohol (1 equiv) and ketonitrile **5** (1 equiv) were treated with $Ru(PPh_3)_3(CO)H_2$ (5 mol %), ligand (5 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 4 h.
[b] $Ru(PPh_3)_3(CO)H_2$ (2.5 mol %), ligand (2.5 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 4 h.

E = E' = CO_2Bn **14a** — **15a** = 8% — **16a** = 78%
E = CN, E' = CO_2Et **14b** — **15b** = 19% — **16b** = 73%
E = $PhSO_2$, E' = COPh **14c**[a] — **15c** = 46% — **16c** = 45%

Scheme 4. Use of other active methylene compounds in C–C bond formation. Reagents and conditions: (i) $Ru(PPh_3)_3(CO)H_2$ (5 mol %), Xantphos **12** (5 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 24 h. (ii) $Ru(PPh_3)_3(CO)H_2$ (2 mol %), Xantphos **12** (2 mol %), piperidinium acetate (25 mol %), PhMe, reflux, 4 h.

4. Dehydrative Allylation/Propagylation with Allylic/Propagylic Alcohols

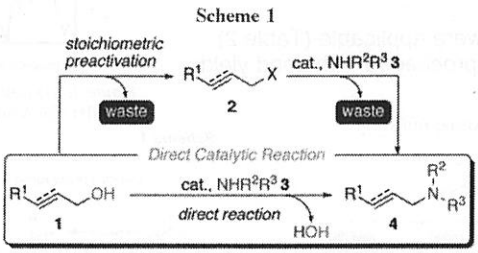
4.1 Backgroud and Mechanism

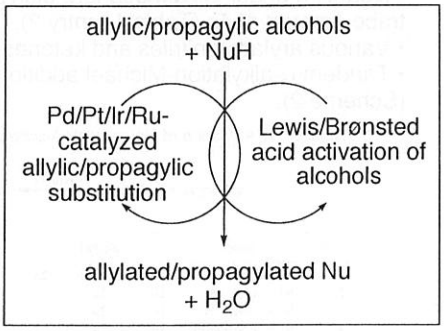
Reviews: For allylic substitution, see: Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077; *Tetrahedron* **2005**, *61*, 4179, and references cited therein. For propagylic substitution, see: Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. See also: Matsunaga, S.; Shibasaki, M.; et al. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

4.1.1 Background

- Direct use of allylic/propagylic alcohols in its substitution reaction is desirable in terms of atom economy, but this approach is usually difficult due to the poor leaving ability of OH group.
- Several activation methods of the OH group have been developed (vide infra).

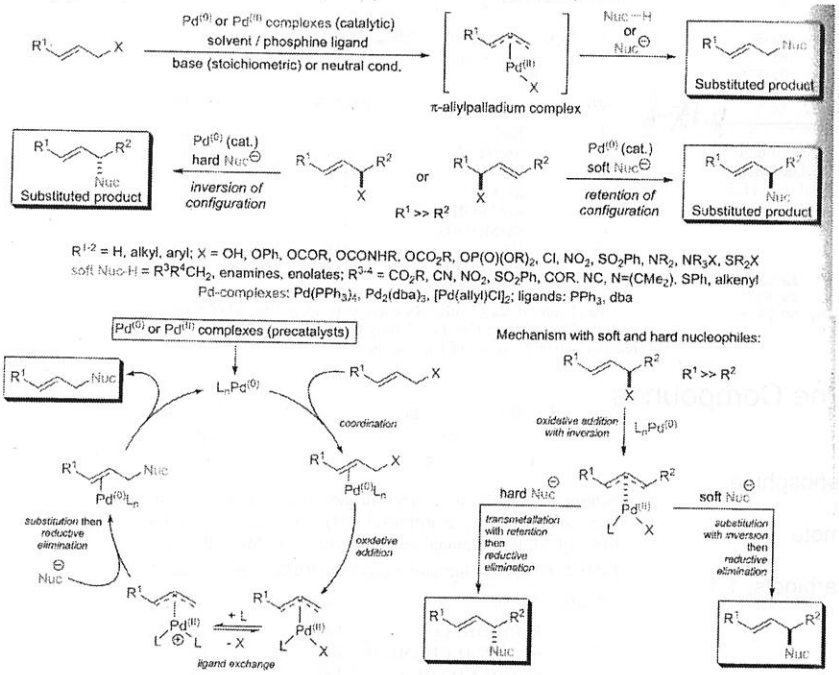
Scheme 1



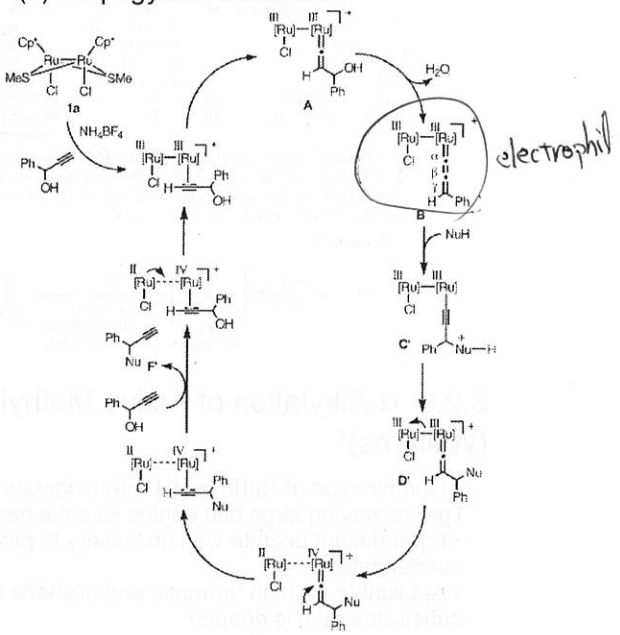


4.1.2 Mechanism

(1) Allylic Substitution (Tsuji-Trost Reaction)



(2) Propagylic Substitution



Scheme 13. A full reaction pathway of the catalytic propargylic substitution reaction.

4.2 Allylation with Allylic Alcohols

4.2.1 Selected Examples of Racemic Allylation with Allylic Alcohols with or without Catalytic Amounts of Brønsted Acid Activators

References: a) Ozawa, F.; et al. *J. Am. Chem. Soc.* **2002**, *124*, 10968; b) Kobayashi, S.; et al. *Org. Lett.* **2003**, *5*, 3241; c) Kitamura, M.; et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 1730; d) Ohshima, T., Mashima, K.; et al. *Org. Lett.* **2007**, *9*, 3371.

(1) Allylic Amination with Aniline (Ozawa)[a]

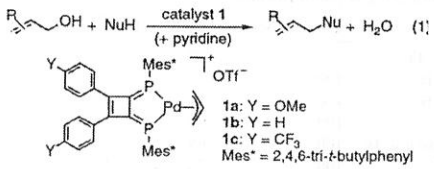


Table 1. Catalytic Allylation of Aniline with Allylic Alcohols[a]

run	(allyl)OH	time (h)	(allyl)NHPh (%)[b]			(allyl)$_2$NPh (%)
1	2a	2		96		3
2[c]	2a	2	NHPh	91		8
3[d]	2a	2		82		16
4	2b	6	NHPh (E/Z = 7/1)	85	NHPh 10	4
5	2c	6	NHPh (E/Z = 6/1)	84	NHPh 11	4
6	2d	7	C_3H_7 NHPh (E/Z = 9/1)	97		3
7	2e	7	C_3H_7 NHPh (E/Z = 9/1)	96		3
8	2f	10	Ph NHPh	90		8
9[e]	2g	3	Ph NHPh	92 (98.5% ee)		<1

[a] Reaction conditions: 1.0 mmol (allyl)OH, 2.0 mmol $PhNH_2$, 0.1 mol % **1a**, 1 mL of toluene, 0.25 g of $MgSO_4$, room temperature. [b] Monoallylation products in runs 4–7 were obtained as a mixture of stereo- and/or regioisomers, whose ratio was determined by GLC. [c] **1b** was used in place of **1a**. [d] **1c** was used in place of **1a**. [e] **1a** was used in 2 mol %.

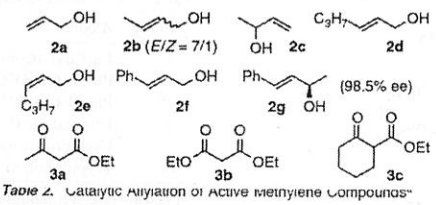
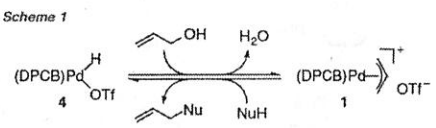


Table 2. Catalytic Allylation of Active Methylene Compounds[a]

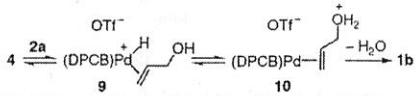
run	(allyl)OH	CH_2Z_2	time (h)	(allyl)CHZ_2 (%)		(allyl)$_2CZ_2$ (%)
1	2a	3a	3	COMe CO_2Et	92	7
2	2d	3a	10	C_3H_7 COMe CO_2Et	93	<1
3	2f	3a	7	Ph COMe CO_2Et	85	12
4	2a	3b	12	CO_2Et CO_2Et	92	<1
5	2a	3c	12	OEt	95	

[a] Reaction conditions: 2.0 mmol (allyl)OH, 4.0 mmol CH_2Z_2, 2 mol % **1a**, 10 mol % pyridine, 0.25 g of $MgSO_4$, 50 °C.

Scheme 1



Scheme 3

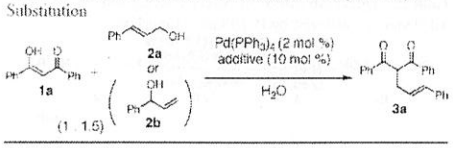


- Reaction proceeded at rt.
- No additional activator required
- Allylation mainly proceeded from less-hindered side.
- Reactions proceeded without the loss of enantiopurity of starting alcohol.
- Hydrido ligand on Pd(II) works as H^+ due to strong π-acceptor property of the sp^2-hybridized phosphine ligand.
- Active methylene compounds also can be utilized.

sp^2型のPは強いπ-acceptor.
Pdよりの電子を引き抜いている。

(2) Pd(0)-Catalyzed Allylation of Active Methylene Compounds in Water (Kobayashi)[b]

Table 1. Effect of Additives on Palladium-Catalyzed Allylic Substitution



entry	additive	conditions	yield (%)[a]
1	—	70 °C, 30 min	1
2	$CH_3(CH_2)_{10}CO_2H$	70 °C, 30 min	28
3[b]	$CH_3(CH_2)_{10}CO_2H$	70 °C, 30 min	0
4	$PhCO_2H$	70 °C, 30 min	13
5	CH_3CO_2H	70 °C, 30 min	12
6	4-Oct$C_6H_4CO_2H$	70 °C, 30 min	10
7	Ph_2CHCO_2H	70 °C, 30 min	4
8	$PhOCH_2CO_2H$	70 °C, 30 min	2
9	1-AdCO_2H	70 °C, 30 min	30
10	C_6F_5OH	70 °C, 30 min	6
11	HCl	reflux, 30 min	13
12	DBSA	reflux, 30 min	7
13	—	reflux, 30 min	39
14	$CH_3(CH_2)_{10}CO_2H$	reflux, 15 min	93 (86)[c]
15	1-AdCO_2H	reflux, 15 min	98 (87)[c]
16[d]	1-AdCO_2H	reflux, 15 min	81
17[e]	1-AdCO_2H	reflux, 15 min	92
18[f]	1-AdCO_2H	reflux, 15 min	89
19[g]	—	reflux, 30 min	6
20[g]	$CH_3(CH_2)_{10}CO_2H$	reflux, 30 min	1
21[h]	—	reflux, 30 min	2
22[h]	$CH_3(CH_2)_{10}CO_2H$	reflux, 30 min	3

[a] NMR yield. [b] Without $Pd(PPh_3)_4$. [c] Isolated yield. [d] $Pd(OAc)_2$ (2 mol %) and PPh_3 (10 mol %) were used instead of $Pd(PPh_3)_4$. [e] **1a**:**2a** = 1:1 [f] **2b** was used instead of **2a**. [g] In toluene. [h] In 1,4-dioxane.

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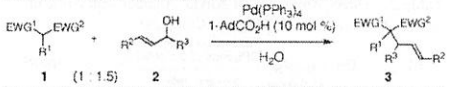
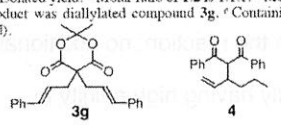
Table 2. Allylic Substitution of Various Substrates

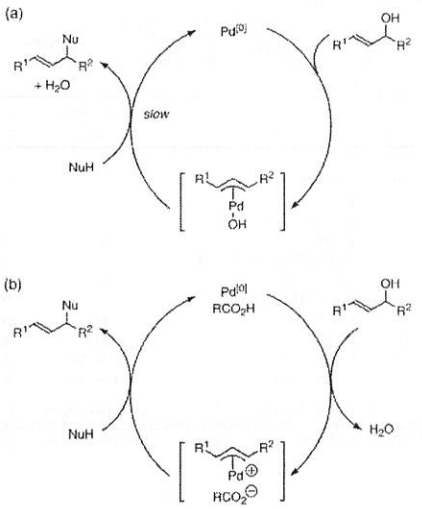


entry	1	2	$Pd(PPh_3)_4$ (mol %)	conditions	product	yield[a] (%)
1	 **1b**	**2a**	5	reflux, 5 h	**3b**	90
2	 **1c**	**2a**	2	reflux, 10 min	**3c**	92
3	 **1d**	**2a**	2	reflux, 10 min	**3d**	76
4	**1e**	**2a**	5	reflux, 1 h	**3e**	78
5[b]	 **1f**	**2a**	2	80 °C, 1.5 h	**3f**	>99
5[c]	 **1g**	**2a**	0.5	80 °C, 30 min	**3g**	74[d]
7	**1a**		**2c** 5	80 °C, 30 min	**3h**	73
8	 **1h**	**2c**	5	80 °C, 20 min	**3i**	93
9	**1a**		**2d** 5	80 °C, 2 h	**3j**	80[e]
10[b]	**1a**		**2e** 5	reflux, 30 min	**3k**	88

[a] Isolated yield. [b] Molar ratio of **1**:**2** is 1:1.1. [c] Molar ratio of **1**:**2** is 1:2.2. [d] Product was diallylated compound **3g**. [e] Containing regioisomer **4** (4% yield).



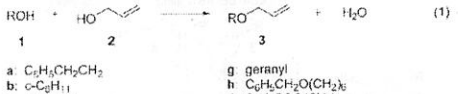
Scheme 1. Possible Catalytic Cycle of the Allylic Substitution of Allyl Alcohols



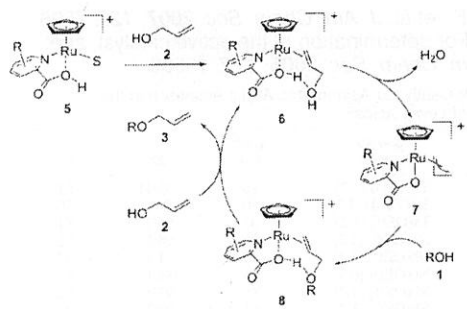
(9) This behavior was also observed at 100 °C. See Supporting Information. The reaction of **1a** with **2b** in the presence of 10 mol % 1-AdCO_2H in water at 70 °C for 10 min without the palladium catalyst gave only a trace amount of **3a**. This result indicates that the existence of another, acid-catalyzed pathway in the case of **2b** is not likely.

- Carboxylic acids accelerated the allylation.
- No organic solvent required
- Less-hindered side reacts.
- High reaction temp. necessary

(3) Cationic Ru(II)-Catalyzed Allylation of Alcohols (Kitamura)[c]



a: $C_6H_5CH_2CH_2$
b: c-C_6H_{11}
c: 2-indanyl
d: $C_6H_5CH_2C(CH_3)_2$
e: CH_2=$CHCH_2CH_2CH_2CH_2$
f: C_6H_5
g: geranyl
h: $C_6H_5CH_2O(CH_2)_6$
i: $C_6H_5COO(CH_2)_6$
j: $CH_3OCH_2O(CH_2)_6$
k: $\{t\text{-}C_4H_9)(C_6H_5)_2SiO(CH_2)_6$



Scheme 1. Supposed catalytic cycle for allyl ether formation.

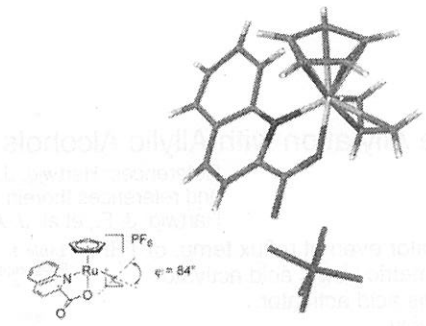
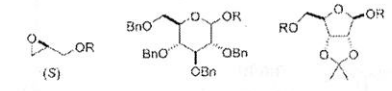
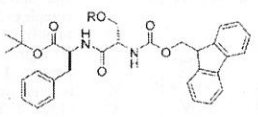


Figure 1. Molecular structure of $[CpRu(\pi\text{-}C_3H_5)(2\text{-quinolinecarboxylato})]PF_6$ [7; R = 5,6-$(CH)_4$] determined by X-ray crystallographic analysis.[15]





a: H
b: CH_2=$CHCH_2$

Table 1: Direct allylation of various monoalcohols with 2-propen-1-ol (**2**) catalyzed by $[CpRuPF_6]$–2-pyridinecarboxylic acid derivative combined systems [cf. Eq. (1)].[a]

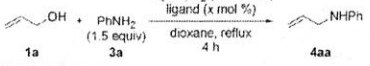
Entry	Alcohol	Ligand	t [h][b]	Yield [%][b]
1	**1a**	 **10**	6 (3)	90 (93)
2	**1a**	**10**	0.5 (0.5)	66 (58[c])
3	**1a**		0.5 (0.5)	16 (11[d])
4	**1a**		0.5 (0.5)	20 (1.3[e])
5	**1a**		0.5 (0.5)	21 (5.7[e])
6	**1a**		0.5 (0.5)	2 (0[c])
7	**1b**	**10**	24 (24)	76 (90)
8	**1c**	**10**	12 (5)	84 (92)
9	**1d**	**10**	3 (24)	29 (30)
10	**1e**	**10**	12 (5)	90 [d] (97)
11	**1f**	**10**	12 (5)	24 (62)
12	**1g**	**10**	12 (3)	92 (91)
13	**1h**	**10**	10 (6)	90 (94)
14	**1i**	**10**	3 (6)	92 (94)
15	**1j**	**10**	12 (6)	93 (92)
16	**1k**	**10**	12 (6)	91 (97)

[a] Reactions were performed at 70 °C without solvent in a 2000:2000:1:1 ratio of **1**/**2**/$[CpRu(CH_3CN)_3]PF_6$(**9**)/ligand. The yields were determined by GC analysis, see the Supporting Information for details. [b] The values in parentheses are those obtained at reflux temperature in CH_2Cl_2 ([**1**] = [**2**] = 500 mM; [**9**] = [ligand] = 1 mM). [c] S/C = 100. [d] S/C = 1000.

- Quinolinecarboxylic acid ligand dramatically accelarate the reaction rate.
- Reaction proceeded under neat conditions; 1/1 substrate ratio enough.
- Mild reaction conditions: epoxide, acetal, Boc, Fmoc intact.
- Only allylic alcohol.
- Less nucleophilic alcohols are bad substrates.

(4) Pt(0)-Catalyzed Monoallylation of Anilines and Amines (Ohshima, Mashima)[d]

Table 1. Ligand Effects on Pt-Catalyzed Direct Amination of Allyl Alcohol (**1a**)[a]



1a 3a 4aa

entry	ligand (*x*)	bite-angle (deg)[b]	yield (%)[d]
1	–		0
2	PPh_3 (4.0)		11
3	$P(OPh)_3$ (4.0)		7
4	P(2-furyl)$_3$ (4.0)		36
5	DPPE (2.0)	85	0
6	$(C_6F_5)_2PCH_2CH_2P(C_6H_5)_2$ (2.0)		1
7	DPPP (2.0)	90	0
8	$Ph_2P(CH_2)_5PPh_2$ (2.0)		9
9	DPPF (2.0)	90	29
10	BINAP (2.0)	93	4
11	DPEphos (2.0)	104 (106)[e]	91
12	Xantphos (2.0)	108 (108)[e]	86

[a] 1.0 mmol scale, dioxane (0.5 mL). [b] Bite-angle of Pd complex.[24] [c] Bite-angle of (ligand)Pt(π-allyl)Cl complex optimized with the B3LYP function (LANL2DZ for Pt and 6-31G** for others).[25] [d] Determined by GC analysis.

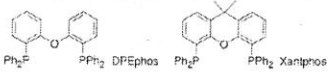
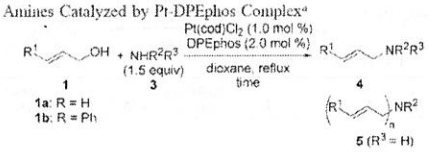


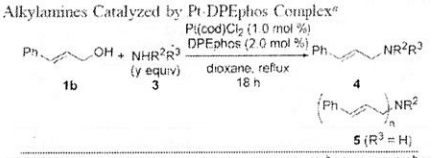
Table 2. Direct Amination of Allylic Alcohol with Aromatic Amines Catalyzed by Pt-DPEphos Complex[a]

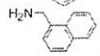


entry	1	3	time (h)	yield of 4 (%)[b]	yield of 5 (%)[b]
1	1a	 3a	6	86	6
2	1a	3b	6	89	5
3	1a	3c	6	86	6
4	1a	3d	6	82	8
5	1a	 3e	8	79	6
6	1a	 3f	6	86	nd[c]
7	1a	3g	6	88	nd[c]
8	1a	3h	18	80	–
9	1b	3a	18	79	7
10	1b	3f	18	92	1
11	1b	3h	18	82	–

[a] 4.0 mmol scale, dioxane (2.0 mL for **1a** and 0.8 mL for **1b**). [b] Isolated yield. [c] Not detected in the reaction mixture.

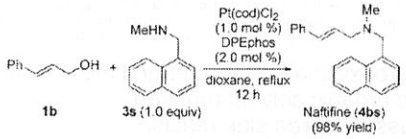
Table 3. Direct Amination of Allylic Alcohol with Alkylamines Catalyzed by Pt-DPEphos Complex[a]



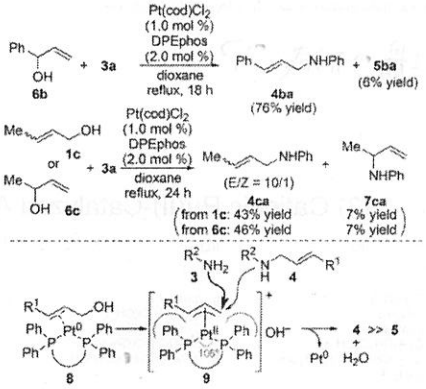
entry	3 (y)		yield of 4 (%)[b]	yield of 5 (%)[b]
1		3i (1.5)	59	20
2		3l (3.0)	79	10
3		3j (3.0)	78	9
4		3k (3.0)	78	10
5		3l (3.0)	86	6
6		3m (1.5)	82	9
7		3n (1.5)	86	7
8		3o (1.5)	90	3
9		3p (1.5)	89	–
10		3q (1.5)	96	–
11		3r (1.5)	94	–

[a] 4.0 mmol scale, dioxane (0.8 mL). [b] Isolated yield.

Scheme 2



Scheme 3

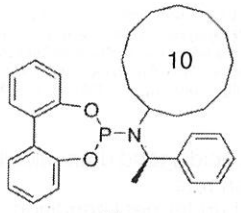


- Pt and large bite angle diphosphine ligand promote the reaction; no additional activator required.
- Not only anilines but also aliphatic amines, generally having high affinity to transition metal complexes, can be used.
- Monoallylated, terminal allylamines were selectively obtained.

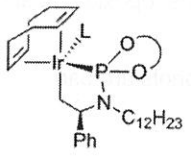
4.2.2 Catalytic Enantioselective Allylation with Allylic Alcohols

References: Hartwig, J. F.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 7508, and references therein. For determination of the active catalyst, see: Hartwig, J. F.; et al. *J. Am. Chem. Soc.* **2005**, *127*, 15506.

- No reaction proceeded w/o Lewis acid activator even at reflux temp. of THF.
- $Nb(O^iPr)_5$ was found to be the best stoichiometric Lewis acid activator.
- BPh_3 was found to be the best catalytic Lewis acid activator.
- Branched allylamines were obtained selectively.
- MS 4Å was necessary to maintain the catalyst activity.
- Not only anilines but also aliphatic amines can be used as a nucleophile.



L*



active form of the catalyst

Scheme 1

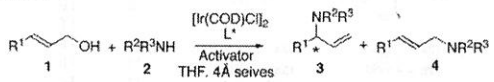


Table 2. Ir-Catalyzed Asymmetric Allylic Amination of Allylic Alcohols in the Presence of $Nb(OEt)_5$[a]

entry	1, R^1 =	2, R^2 =	yield[e] (%)	3/4[d]	ee[e] (%)
1	Ph	*p*-MeC_6H_4	85	>96/<4[f]	92
2	Ph	*p*-$MeOC_6H_4$	84	96/4[f]	89
3	Ph	*o*-$MeOC_6H_4$	66	>96/<4[f]	92
4	Ph	*m*-$MeOC_6H_4$	83	96/4[f]	81
5[g,h]	Ph	*p*-IC_6H_4	79	95/5	86
6[g,h]	Ph	*p*-ClC_6H_4	82	96/4	87
7[g]	Ph	Bn	72	96/4	93
8[g]	Ph	*p*-$MeOC_6H_4CH_2$	66	93/7	90
9	Ph	**2**=morpholine	90	98/2	94
10	*p*-$MeOC_6H_4$	Ph	85	98/2	89
11	*o*-$MeOC_6H_4$	Ph	78	99/1	70
12[i]	2-furyl	Ph	70	81/19	92
13	propyl	Ph	70	92/8	90
14[j]	isopropyl	Ph	45	88/12[f]	82
15	1-propenyl	Ph	67	79/14/7[k]	89

[a] The reaction was performed with **1** (1.0 mmol) and **2** (1.5 mmol) in THF (0.5 mL) at 50 °C for 24 h in the presence of 2 mol % of catalyst prepared from $[Ir(COD)Cl]_2$ (0.010 mmol), and **5a** (0.020 mmol), $Nb(OEt)_5$ (1.2 mmol), and 4 Å MS (50 mg) were used unless otherwise noted. [b] Except entry 10, R^3 = H. [c] Isolated yield of branched product **3**. [d] Ratio of **3** and **4** was determined by ^1H NMR analysis of the crude reaction mixture. [e] Enantiomeric excess of **3**. [f] Determined after isolation. [g] The Ir catalyst (3 mol %) was used. [h] **2** (2.0 mmol) was used. [i] The reaction was carried out at 40 °C. [j] The Ir catalyst (5 mol %) and aniline (2.0 mmol) were used. [k] Branched/5-phenylamino-1,3-hexadiene/linear.

Table 1. Ir-Catalyzed Asymmetric Allylic Amination in the Presence of Lewis Acids[a]

entry	activator (equiv)	yield[b] (%)	3/4[c]	ee (%)
1	$Ti(O^iPr)_4$ (1.2)	16	89/11	81
2	$Ti(O^tBu)_4$ (1.2)	30	94/6	89
3	$Ta(OEt)_5$ (1.2)	62	96/4	81
4	$Nb(OEt)_5$ (1.2)	82	98/2	92
5[d]	$Nb(OEt)_5$ (1.2)	47	91/9	92
6	$Nb(OEt)_5$ (0.5)	64	84/16	63
7[e]	$Nb(OEt)_5$ (1.2)	85	97/3	92
8[f]	$Nb(OEt)_5$ (1.2)	64	98/2	94
9[e,g]	$Nb(OEt)_5$ (1.2)	42	98/2	95

[a] The reaction was performed with methyl cinnamyl carbonate (1.0 mmol) and aniline (1.2 mmol) in THF (0.5 mL) at 50 °C for 24 h, and the Ir complex (2 mol %) prepared from $[Ir(COD)Cl]_2$ (0.010 mmol) and **5a** (0.020 mmol), Lewis acid activator, and powdered 4 Å molecular sieves (4 Å MS, 50 mg) were used unless otherwise noted. [b] Isolated yield of branched product **3**. [c] Ratio of **3**:**4** determined by ^1H NMR analysis of the crude reaction mixture. [d] Without 4 Å MS. [e] 1.5 mmol of aniline was used. [f] Ligand **5b** was used. [g] Conducted at room temperature.

Table 3. Ir-Catalyzed Asymmetric Allylic Substitutions of **1** with **2** in the Presence Catalytic BPh_3[a]

entry	1, R^1 =	2, R^2 =	yield[b] (%)	3/4[c]	ee (%)
1	Ph	*p*-MeC_6H_4	74	97/3	88
2	Ph	*p*-$MeOC_6H_4$	72	94/6	93
3	Ph	*o*-$MeOC_6H_4$	52[d]	95/5	94
4	Ph	*p*-ClC_6H_4	53	>94/<6	92
5	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	72	96/4	92
6	*p*-$MeOC_6H_4$	*m*-$MeOC_6H_4$	61	>97/<3	83
7	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	66	95/5	93
8	*p*-MeC_6H_4	*p*-MeC_6H_4	66[d]	>95/<5	94
9	*p*-BrC_6H_4	*p*-MeC_6H_4	61	>92/<8	87

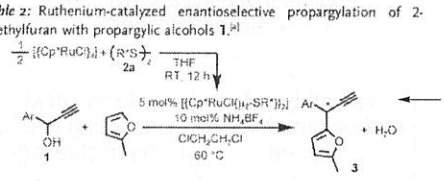
[a] The reaction was performed by using **1** (1.5 mmol) and **2** (1.0 mmol) in dioxane (2.0 mL) at 50 °C for 24 h in the presence of a chiral Ir complex (5 mol %) prepared from $[Ir(COD)Cl]_2$ (0.025 mmol) and **5a** (0.050 mmol), BPh_3 (0.08 mmol), and 4 Å MS (300 mg) unless otherwise noted. [b] Isolated yield of branched product **3**. [c] Ratio of **3** and **4** was determined by GC analysis of the crude reaction mixture. [d] The reaction was conducted for 40 h.

4.2 Propagylation with Propagylic Alcohols

4.2.1 Catalytic Enantioselective Propagylation of Electron-Rich Arenes[a]

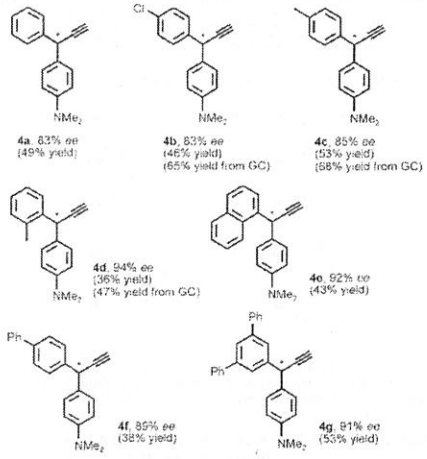
References: a) Nishibayashi, Y.; et al. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488, b) Nishibayashi, Y.; et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715; c) Nishibayashi, Y.; Nakamura, E.; et al. *J. Am. Chem. Soc.* **2005**, *127*, 9428; d) Nishibayashi, Y.; Hidai, M.; Uemura, S.; et al. *Chem. Eur. J.* **2005**, *11*, 1433, and references therein. See also: Dr. Suto's Lit. Seminar Handout 2004/10/27 for earlier studies.

Table 2: Ruthenium-catalyzed enantioselective propargylation of 2-methylfuran with propargylic alcohols 1.[a]

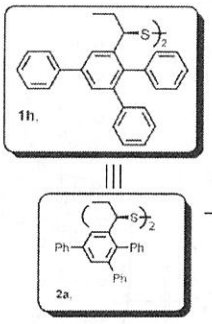


Entry	Ar	t [h]	Yield of 3 [%][b]	ee of 3 [%][c]
1	**1a**, Ph	3	**3a**, 75	77
2	**1b**, *p*-MeC_6H_4	3	**3b**, 67	82
3	**1c**, *o*-MeC_6H_4	3	**3c**, 44	86
4	**1d**, *p*-$MeOC_6H_4$	6	**3d**, 40	81
5	**1e**, *p*-ClC_6H_4	3	**3e**, 63	68
6	**1f**, *o*-PhC_6H_4	6	**3f**, 52	94
7	**1g**, *p*-PhC_6H_4	3	**3g**, 77	89
8	**1h**, 3,5-$Ph_2C_6H_3$	3	**3h**, 83	76
9	**1i**, 1-napthyl	6	**3i**, 59	86
10	**1j**, 2-naphthyl	3	**3j**, 67	83
11[d]	**1a**, Ph	2	**3k**, 59	79

[a] All reactions of **1** (0.20 mmol) with 2-methylfuran (2.00 mmol) were carried out in the presence of a Ru complex (0.010 mmol, generated in situ from $[\{Cp^*RuCl\}_4]$ and **2a**) and NH_4BF_4 (0.020 mmol) in $ClCH_2CH_2Cl$ (5 mL) at 60 °C. [b] Yield of isolated product. [c] Determined by HPLC (see the Supporting Information for details). [d] 2-Ethylfuran (2.00 mmol; 10 equiv) was used in place of 2-methylfuran at 80 °C.

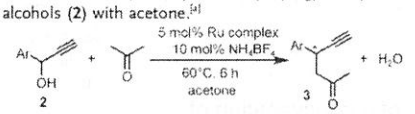


Scheme 2. Reactions of 1-aryl-2-propyn-1-ols **1** with *N,N*-dimethylaniline in the presence of chiral thiolate-bridged diruthenium complex, generated in situ from $[\{Cp^*RuCl\}_4]$ and chiral disulfide **2a**. All yields are of the isolated product.



4.2.2 Catalytic Enantioselective Propagylation of Acetone[b]

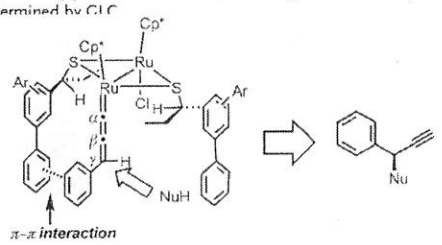
Table 1: Ruthenium-catalyzed asymmetric propargylic alkylation of propargylic alcohols (**2**) with acetone.[a]



Without NH_4BF_4: No reaction.

Entry	2, Ar	3, yield [%][b]	ee of 3 [%][c]
1	**2a**, Ph	**3a**, 56	74
2	**2b**, *o*-MeC_6H_4	**3b**, 61	72
3	**2c**, *p*-$MeOC_6H_4$	**3c**, 14	68[d]
4	**2d**, *p*-ClC_6H_4	**3d**, 57	68[d]
5	**2e**, 1-naphthyl	**3e**, 42	70
6	**2f**, 2-napthyl	**3f**, 50	70
7	**2g**, *p*-PhC_6H_4	**3g**, 50	70
8	**2h**, 3,5-$Ph_2C_6H_3$	**3h**, 58	82

[a] All reactions of **2** (0.300 mmol) with acetone were carried out in the presence of ruthenium complex (0.015 mmol, generated in situ from $[\{Cp^*RuCl\}_4]$ and **1h**) and NH_4BF_4 (0.030 mmol) in acetone (4.5 mL) at 60 °C for 6 h. [b] Yield of isolated product. [c] Determined by HPLC. [d] Determined by GLC.



Scheme 1. Nucleophilic attack of acetone on the C_γ atom of the allenylidene complex.

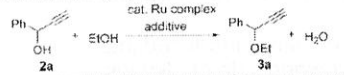
- Reaction proceeded with terminal propagylic alcohols.
- Addition of catalytic amount of NH_4BF_4 improve the reactivity of the neutral di-Ru catalyst. The role was thought to be anion exchange to generate catalytically active cationic Ru intermediate.
- All reactions are supposed to proceed via Ru-allenylidene intermediate.
- Electron-rich, soft nucleophiles are generally used; high loading of nucleophiles are generally recommended.
- The best ligand was the same for both reacitons.

cl ↔ I exchange

4.2.3 Expeimental Supports of Brønsted Acid Cooperation[c,d]

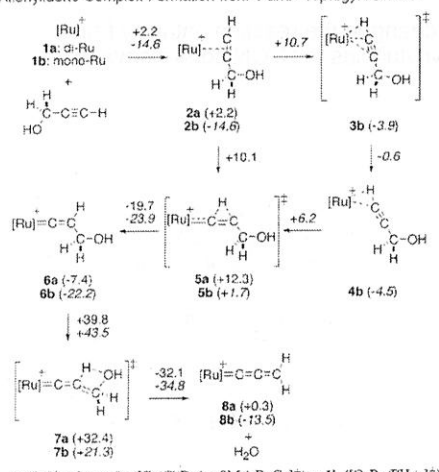
- Based on DFT calculation, 1) spontaneous dehydration from the vinylidene intermediate was very difficult, and 2) alcohols accelerated the dehydration step significantly.
- Without alcohols as solvent, catalytic NH_4BF_4 added might work as an activating agent to facilitate dehydration step through Brønsted acid cooperation.

Table 1. Propargylic substitution reaction of propargylic alcohol 2a with EtOH.[a]



	Ruthenium catalyst (mol%)[b]	Additive (mol%)[b]	Conditions T [°C]/t [min]	GLC yield [%]
1	$[(Cp^*)RuCl(SMe)]_2$ (**1a**) (5)	–	60/15	85
2	$[(Cp^*)RuCl(SMe)]_2$ (**1a**) (5)	NH_4BF_4 (10)	60/15	95 (88)[c]
5	...[d]	NH_4BF_4 (10)	60/15	0

Scheme 2. Reaction Pathway for Mono- and Di-Ruthenium Allenylidene Complex Formation from **1** and Propargyl Alcohol[a]



[a] [Ru]+ refers to **1a** ($[\{Cp(Cl)Ru(\mu_2\text{-}SMe)_2RuCp\}^+$) or **1b** ($[CpRu(PH_3)_2]^+$). Free energies (kcal/mol) are relative to [**1** + $HCCCH_2OH$] (diruthenium in roman and monoruthenium in italic). Energy changes are shown above arrows.

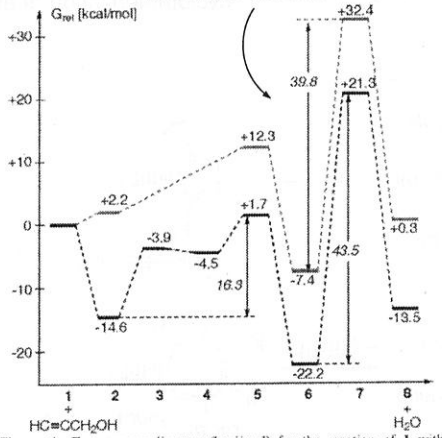
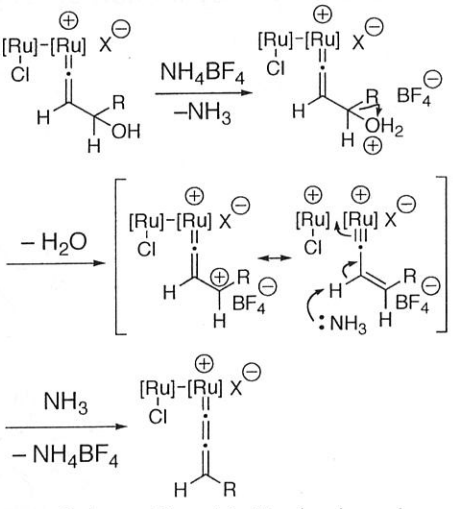


Figure 1. Free energy diagram (kcal/mol) for the reaction of **1** with propargyl alcohol. Di-Ru (red) and mono-Ru reactions (black) are color-coded throughout this article.

ΔG = ~15 kcal/mol when one MeOH involved; ~7 kcal/mol when two MeOHs involved.



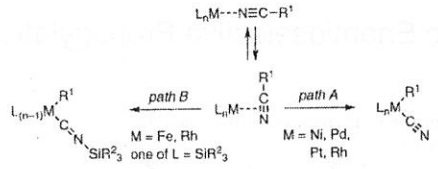
Schene. Plausible Mechanism of Brønsted Acid Cooperation

5. Carbocyanation of Alkynes with Nitriles

5.1 Backgroud and Mechanism

Review: Nakao, Y.; Hiyama, T. *J. Synth. Org. Chem., Jpn.* **2007**, *65*, 999.

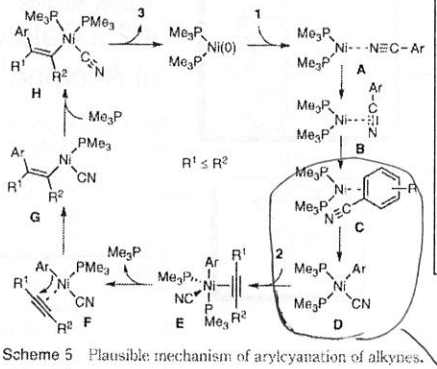
5.1.1 Background



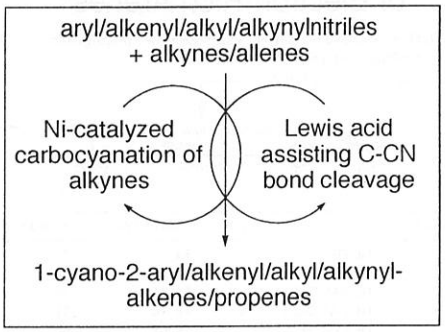
Scheme 2 Possible modes of activation of C–CN bonds by transition metal complexes.

- Low efficiency of carbocyanation of alkynes without Lewis acid co-catalysts was sometimes problematic.
(ex. R^1 = electron-rich aryl –> very slow)

5.1.2 Mechanism



Scheme 5 Plausible mechanism of arylcyanation of alkynes.



- Initial migratory insertion of CN to alkyne followed by reductive elimination of Ni(II) is also possible.

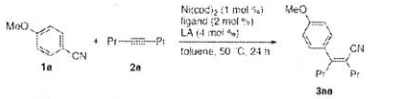
Lewis acid が促進する？

5.2 Selected Examples of Carbocyanation of Alkynes

5.2.1 Aryl/alkenyl/alkylcyanation of Alkynes[a]

References: a) Nakao, Y.; Hiyama, T.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 2428; b) Nakao, Y.; Hiyama, T.; et al. *Angew. Chem., Int. Ed.* **2007**, *46*, *Early View*, and references therein.

Table S1. Optimization of a combination of a ligand and Lewis acid for the nickel-catalyzed addition of **1a** across **2a**.

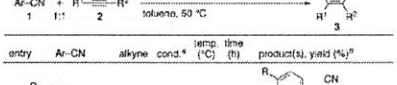


	Lewis acid/%GC yield of **3aa** (%)[a]			
ligand	BPh_3	$AlMe_3$	$AlMe_2Cl$	none
PMe$_3$	31	60	88	1
P(*n*-Bu)$_3$	39	63	41	<1
$PPhMe_2$	78	95	>99	<1
PPh_2Me	92	92	98	<1
PPh_2Cy	79	95	50	<1
P(4-MeO–C$_6$H$_4$)$_3$	53	29	6	<1
$Ph_2P(CH_2)_2PPh_2$	60	72	66	<1

[a] Other Lewis acids including $AlMeCl_2$, $AlCl_3$, $Al(OR)_3$ (R = Et, *i*-Pr, and Ph), $AlPh_3$, $B(C_6F_5)_3$, BEt_3, and BF_3OEt_2 were ineffective. [b] GC yields estimated using dodecane as an internal standard.

- Lewis acid co-catalysts significantly enchanced the reaction rate.
- The most suitable combination of phosphine ligand and Lewis acid is likely determined by experiment.
- Sterically congested tetrasubstituted alkenes were obtained in good yields.
- Aryl, alkenyl, and alkyl C–CN bond could be activated in the presence of Lewis acid.
- CN was preferencially introduced into less-sterically crowded side of alkynes.
- Aryl-Cl and Br bonds were intact.

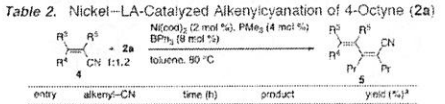
Table 1. Nickel–LA-Catalyzed Arylcyanation of Alkynes



entry	Ar–CN	alkyne	cond.[a]	temp (°C)	time (h)	product(s), yield (%)[b]
1	R = MeO: **1a**	**2a**	A	50	16	**3aa**, 95
2	MeO_2C: **1b**	**2a**	A	80	25	**3ba**, 93
3	AMe_2SiO: **1c**	**2a**	B	50	42	**3ca**, 90
4	Me_2N: **1d**	**2a**	A	60	21	**3da**, 87
5	Ph_2N: **1e**	**2a**	B	50	47	**3ea**, 91
6[d]	Br: **1f**	**2a**	A	50	27	**3fa**, 72
7	Cl: **1g**	**2a**	B	50	18	**3ga**, 94
8[d]		**1h**	**2a**	A	100	134	**3ha**, 78%
9		**1i**	**2a**	A	50	115	**3ia**, 58%
			R^1—≡—R^2				4-Cl-C$_6$H$_4$—CN + NC—C$_6$H$_4$-4-Cl
			R^1, R^2 =				R^1 R^2 R^1 R^2
10[e]	**1g**		Et, *p*-Anis: **2b**	A[f]	60	32	**3gb**, 53%[g] **3'gb**, 27%
11[d]	**1g**		Me, $SiMe_3$: **2c**	A[h]	80	13	**3gc**, 70%[i] **3'gc**, 9%
12[d]	**1g**		*p*-Anis, $SiMe_3$: **2d**	A[h]	60	37	**3gd**, 73%[i] **3'gd**, <5%

[a] Condition A, $PPhMe_2$ and $AlMe_2Cl$; condition B, PPh_2Cy and $AlMe_3$. [b] Isolated yields of isomerically pure products, unless otherwise noted. [c] Ar = 2-(THPOCH$_2$)C$_6$H$_4$. [d] The reaction was carried out using Ni(cod)$_2$ (5 mol %), ligand (10 mol %), and $AlMe_2Cl$ (20 mol %). [e] The reaction was carried out using 1.2 equiv of the alkyne. [f] PPh_2Me was used as a ligand. [g] (*E*)-**3gb** was also obtained in 5% yield. [h] PPh_2(*i*-Pr) (10 mol %) was used as a ligand. [i] (*E*)/(*Z*) = 59:41 (78:22 at 5 h). [j] (*E*)/(*Z*) = 47:53 (57:43 at 12 h).

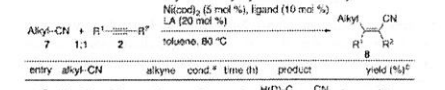
Table 2. Nickel–LA-Catalyzed Alkenylcyanation of 4-Octyne (**2a**)



entry	alkenyl–CN	time (h)	product	yield (%)[a]
1	Ph, CN **4a**	20	**5aa**	94
2	Et, CN **4b**	15	**5ba**	78[b]
3	CN **4c**	21	**5ca**	91
4	Ph, Ph, CN **4d**	46	**5da**	94
5[c]	Ph, CN, CN **4e**	13	**5ea**	81[d]

[a] Isolated yields of isomerically pure products, unless otherwise noted. [b] 4*Z*/4*E* = 84:16. [c] The reaction was carried out using Ni(cod)$_2$ (4 mol %), dppb (4 mol %), and BPh_3 (16 mol %). [d] An isomer was also obtained in ~2% yield.

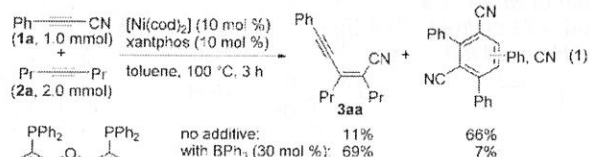
Table 3. Nickel–LA-Catalyzed Alkylcyanation of Alkynes

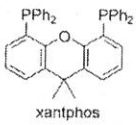


entry	alkyl–CN		alkyne	cond.[a]	time (h)	product	yield (%)[b]
1[c]	Me–CN	**7a**	**2a**	C	4	**8aa**	71
2	CD_3–CN	**7a**-d_3	**2a**	C	5	**8aa**-d_3	66[d]
3	Me_3Si—CN	**7b**	**2a**	D	17	**8ba**	29
4[e]	Et–CN	**7c**	**2a**	D	20	**8ca**	24
5[e]	**7a**		Hex—≡—$SiMe_3$ **2e**	D[f]	12	**8ae**	74[g]

[a] Condition C, PPh_2(*t*-Bu) and $AlMe_3$; condition D, 2-Mes-C$_6$H$_4$-PCy_2 and $AlMe_2Cl$. [b] Isolated yields of isomerically pure products, unless otherwise noted. [c] The reaction was carried with a 10 mmol scale. [d] 99% deuteration. [e] The reaction was carried out using 2.0 equiv of **7a** and Ni(cod)$_2$ (10 mol %). [f] $PPhCy_2$ (20 mol %) and $AlMe_2Cl$ (40 mol %) were used. [g] (*Z*)/(*E*) = 91:9 (93:7 at 3 h).

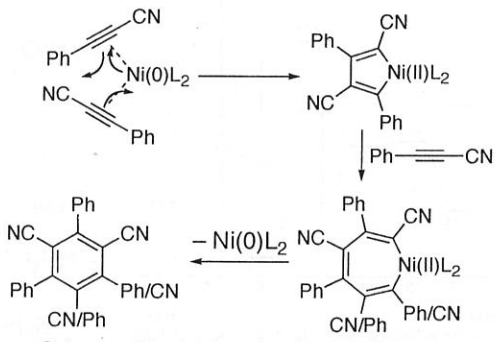
5.2.2 Alkynylcyanation of Alkynes/Allenes[b]



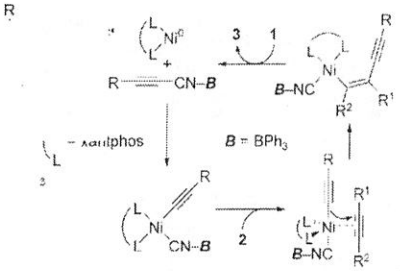


no additive:	11%	66%
with BPh_3 (30 mol %):	69%	7%

- Lewis acid co-catalyst changed the reaction pathway from cyclotrimerization of alkynylnitriles to C–CN bond cleavage.

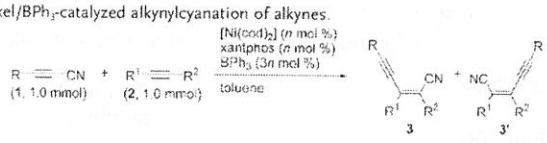


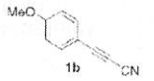
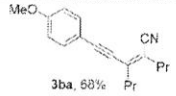
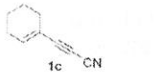
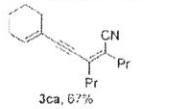
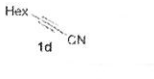
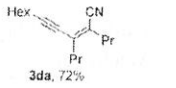
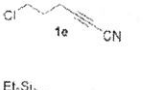
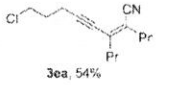
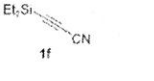
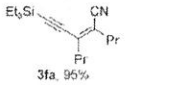
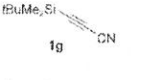
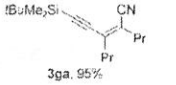
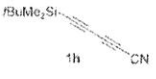
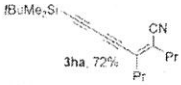
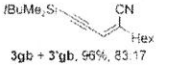
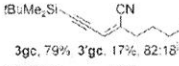
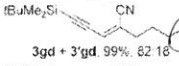
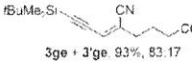
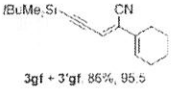
Scheme. Cyclotrimerization of alkynes.



Scheme. Possible mechanism for the nickel/BPh_3-catalyzed alkynylcyanation.

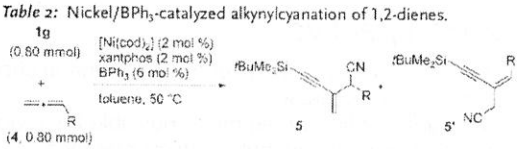
Table 1: Nickel/BPh_3-catalyzed alkynylcyanation of alkynes.

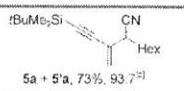
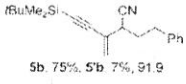
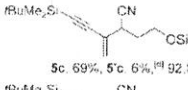
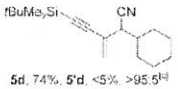


Entry	1	2	n	T [°C]	t [h]	Major product yield,[a] 3/3'[b]
1[c]		2a	10	100	2	 3ba, 68%
2[c]		2a	10	80	2	 3ca, 67%
3[c]		2a	10	100	3	 3da, 72%
4[c]		2a	10	100	3	 3ea, 54%
5		2a	1	80	24	 3fa, 95%
6		2a	1	80	21	 3ga, 95%
7		2a	3	80	21	 3ha, 72%
8	1g	 2b	1	40	15	 3gb + 3'gb, 96%, 83:17
9	1g	 2c	1	40	15	 3gc, 79%, 3'gc, 17%, 82:18[d]
10	1g	 2d	1	40	15	 3gd + 3'gd, 99%, 82:18
11[e]	1g	 2e	1	40	17	 3ge + 3'ge, 93%, 83:17
12	1g	 2f	1	40	15	 3gf + 3'gf, 86%, 95:5

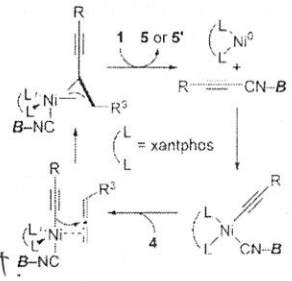
[a] Yield of isolated product based on 1. [b] Estimated by ^{1}H NMR analysis of the crude product or an isolated mixture of 3 and 3'. [c] 2.0 mmol of 2a was used. [d] Calculated based on yield of isolated product. [e] 1.1 mmol of 2e was used.

Table 2: Nickel/BPh_3-catalyzed alkynylcyanation of 1,2-dienes.



Entry	1,2-Diene	t [h]	Major product, yield,[a] 5/5'[b]
1	 4a	19	 5a + 5'a, 73%, 93:7[c]
2	 4b	24	 5b, 75%, 5'b, 7%, 91:9
3	 4c	17	 5c, 69%, 5'c, 6%,[d] 92:8
4	 4d	59	 5d, 74%, 5'd, <5%, >95:5[d]
5	 4e	66	 5e, <5%, 5'e, 55%, 5:>95

[a] Yield of isolated product. [b] Calculated based on yields of isolated products. [c] Estimated by ^{1}H NMR analysis of the isolated mixture of 5a and 5'a. [d] $E/Z = 11{:}89$.

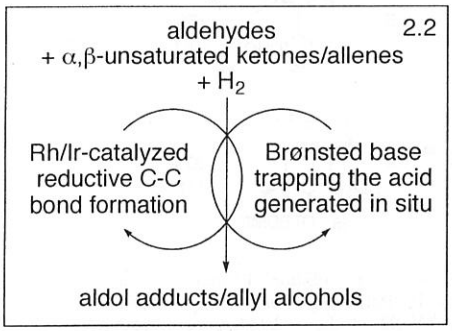


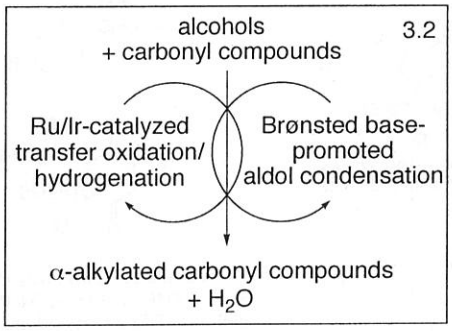
Scheme 1. A plausible mechanism for the nickel/BPh_3-catalyzed alkynylcyanation.

- The present reaction system were also applicable for terminal alkynes and allenes.
- Alkylnitrile moiety intact.

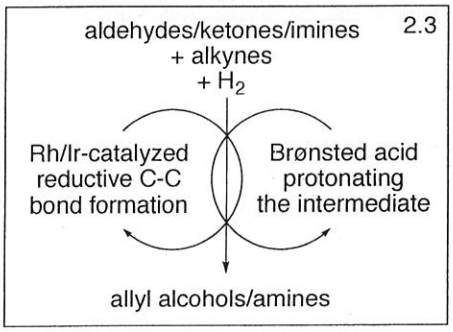
6. Summary and Perspective

6.1 Summary of the Reactions Outlined Today





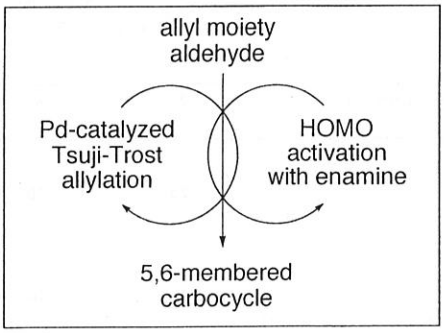
- Substrates containing both soft and hard moieties are generally used (2.2, 2.3, 4.2, 4.3, 5.1).
- Simultaneous activation (4.2, 4.3, 5.1) vs. sequential reaction (2.2, 2.3, 3.2)
- Brønsted/Lewis acid (2.3, 4.2, 4.3, 5.1) vs. Brønsted base (2.2, 3.2)
- Bond reorganization (2.2, 2.3, 5.1)
- Bond formation with a minimum amount of side product (3.2, 4.2, 4.3)



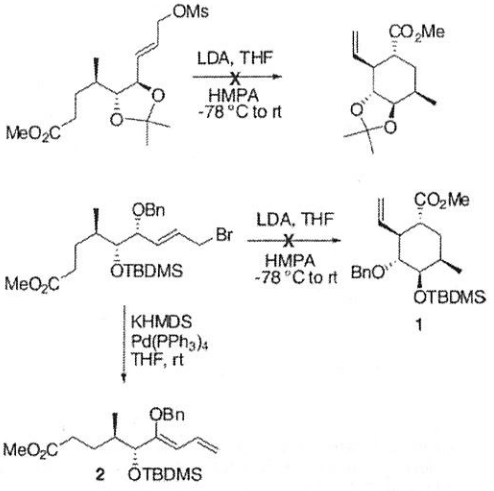
6.2 Perspective

Reference: Saicic, R. N.; et al. *Org. Lett.* **2007**, *9*, *ASAP*.

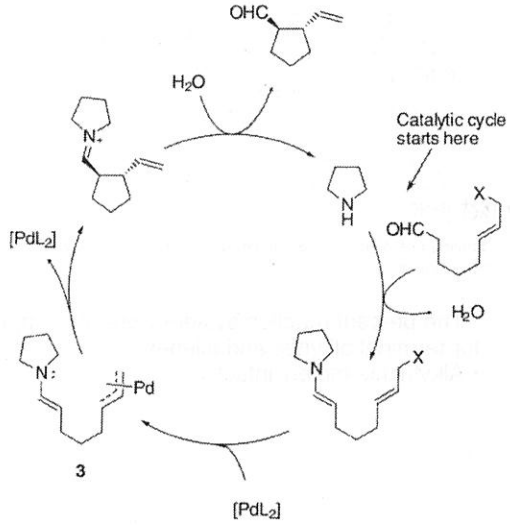
- Enormous combinations of transition metal chemistry and acid/base catalysis are available.
- The combination would make possible the reactions that cannot be achieved by conventional catalysis methods.



Scheme 1. Attempted Intramolecular Allylation of Esters



Scheme 2. Mechanism of the [Pd]/Amine Cocatalyzed Cyclization



Scheme 3. Catalytic Asymmetric Cyclizations

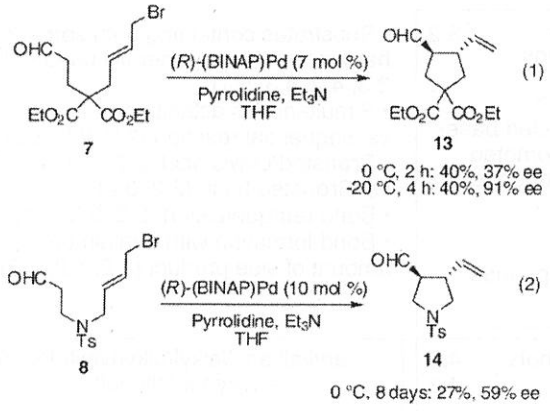
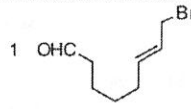
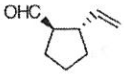
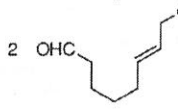
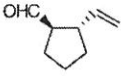
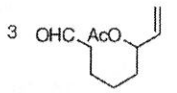
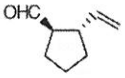
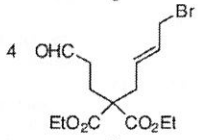
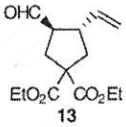
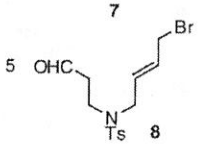
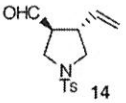
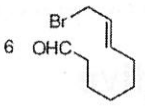
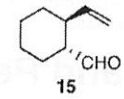
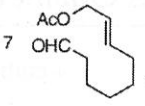
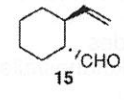
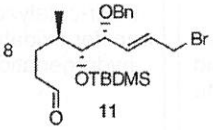
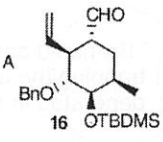


Table 1. [Pd]/pyrrolidine-Cocatalyzed Cyclizations of Aldehydes

entry	reactant	method[a]	product	yield[b] *trans/cis*
1	 **4**	A	 **12**	72%[c] *11/1*
2	 **5**	B	 **12**	63%[c] *10/1*
3	 **6**	B	 **12**	53% *2/1*
4	 **7**	A	 **13**	75% *13/1*
5	 **8**	A	 **14**	80% *10/1*
6	 **9**	A	 **15**	60% *7/1*
7	 **10**	B	 **15**	65% *10/1*
8	 **11**	A	 **16**	95%[d] *7/1*

[a] Method A: $Pd(PPh_3)_4$ (5 mol %), pyrrolidine (40 mol %), Et_3N (1 equiv), THF, rt, 30 min. Method B: $Pd(PPh_3)_4$ (5 mol %), pyrrolidine (40 mol %), DMSO, rt, 30 min. [b] Yield of the isolated, pure compound. [c] Isolated as the corresponding alcohol, after the reduction with $NaBH_4$. [d] 10 mol % of $Pd(PPh_3)_4$.