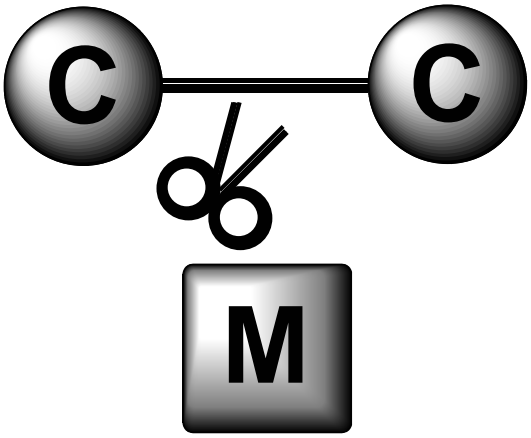
H. Mitsunuma (M1)
2010/09/08

Transition Metal Catalyzed Carbon-Carbon Bond Activation

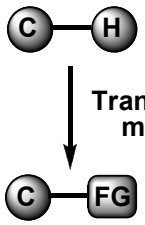


0. Introduction

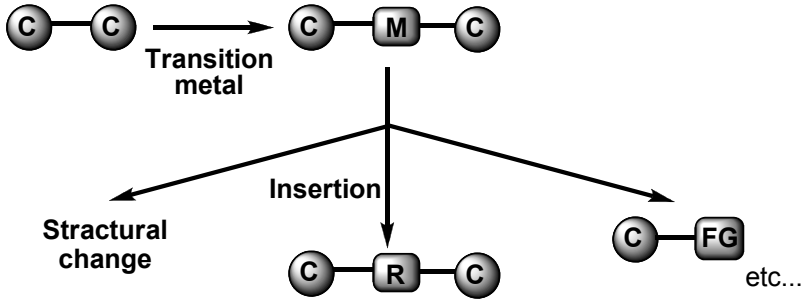
Currently, selective C-H and C-C bond activation by transition metal complexes has attracted much attentions.
Advantages: Ubiquitousness of C-H bond and C-C bond, atom economically good ...

This seminar's topic

C-H bond activation



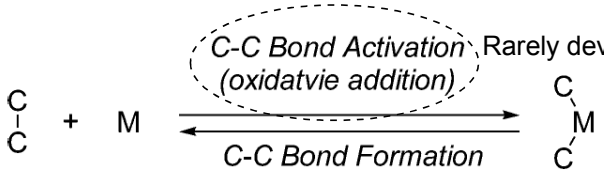
C-C bond activation



Compared to C-H activations, the development of related C-C activation reactions lags behind.

Difficult point in C-C bond activation

1. **High directionality of C-C bond**
2. **Steric effect (substituents)**
3. **Statistical abundance of C-H bond**

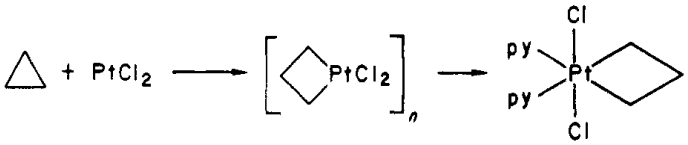


Contents

1. Basic strategy

In order to facilitate C-C bond activation, two basic strategies can be applied.
1. Increase the energy state of the starting materials
2. Lower the energy state of the C-C bond cleaved complexes

a. Strained starting materials



Tipper *et al. J. Chem. Soc.* **1955**, 2043.
Chatt *et al. J. Chem. Soc.* **1961**, 738.

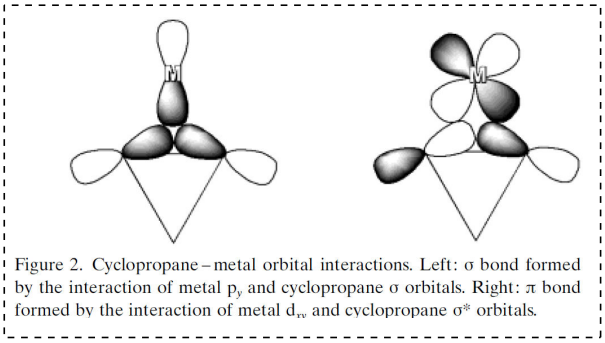
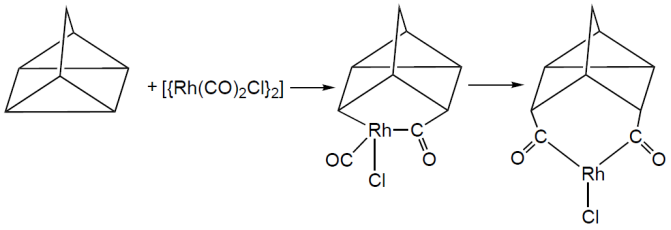
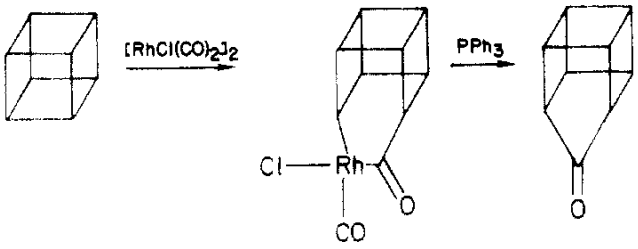


Figure 2. Cyclopropane–metal orbital interactions. Left: σ bond formed by the interaction of metal p_y and cyclopropane σ orbitals. Right: π bond formed by the interaction of metal d_{xy} and cyclopropane σ* orbitals.

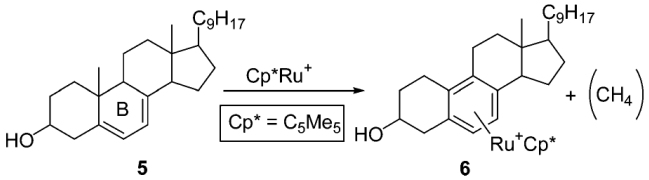


Halpern *et al. J. Chem. Soc. Chem. Commun.* **1970**, 1082.



Halpern *et al. J. Am. Chem. Soc.* **1970**, *92*, 3515.

b. Aromatization



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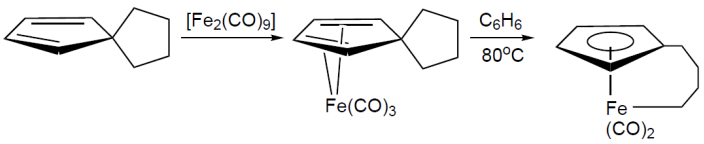
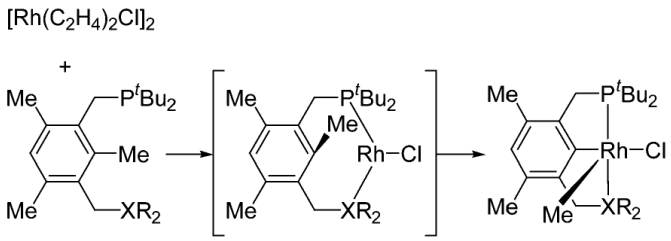
Chaudret *et al. Organometallics.* **1993**, *12*, 955.



Eilbracht *et al. J. Organomet. Chem.* **1977**, *135*, C2.

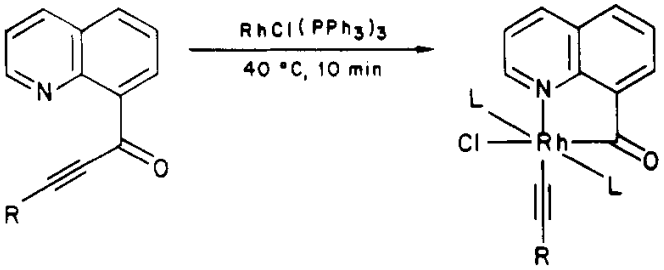
c. Chelation assistance



7 8

a: $XR_2 = P^tBu_2$ **b**: $XR_2 = NEt_2$

Milstein *et al. J. Am. Chem. Soc.* **2000**, *122*, 9848.



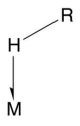
Suggs *et al. J. Organomet. Chem.* **1981**, *221*, 199.

Metal C-C bond interaction (agostic interaction)

What is agostic interaction?

Interaction of a coordinately-unsaturated transition metal with a C-H bond (sometimes C-C bond), when the two electrons involved in the C-H(C-C) bond enter the empty d orbital of a transition metal, resulting in a two electron three center bond

Structural and spectroscopic features (C-H bond)



Agostic

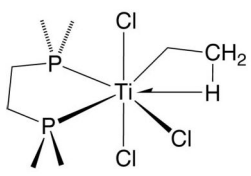
3–center–2–electron interaction

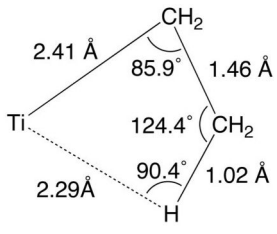
d(M–H) ≈ 1.8 – 2.3 Å

M–H–C ≈ 90 – 140°

δ_H upfield of uncoordinated CH

example

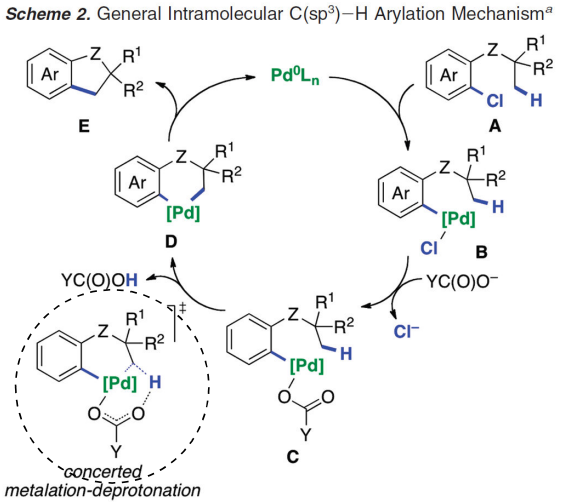




Brookhart *et al. PNAS.* **2007**, *104*, 6908.

electrophilic metal
steric influenece
etc

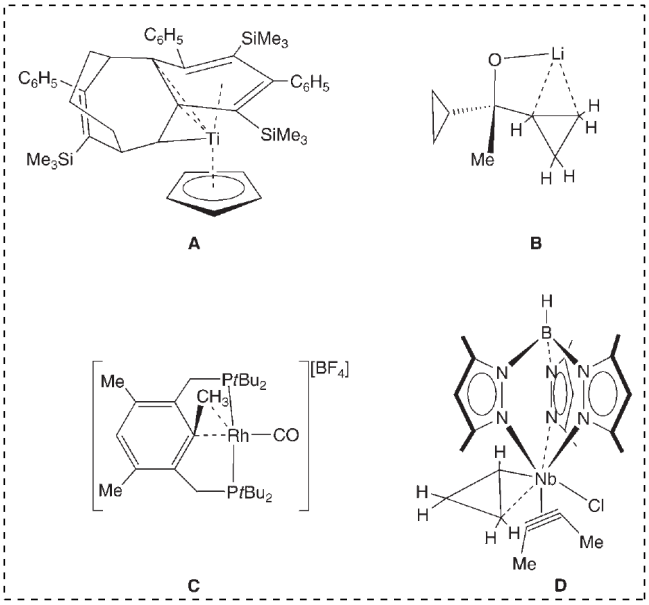
C-H activation (sp^3 C-H bond)



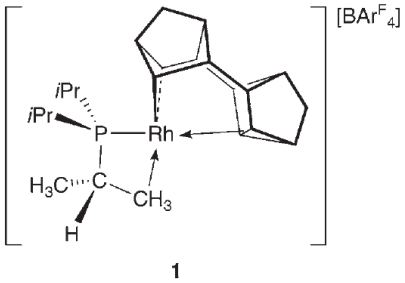
Agostic interaction assists non-acidic C-H bond deprotonation.

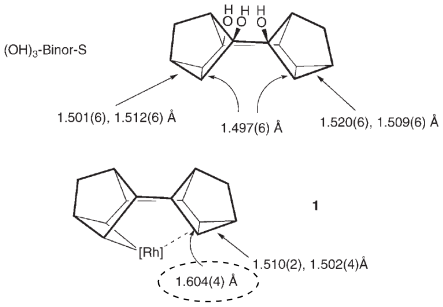
Fagnou *et al. J. Am. Chem. Soc.* **2010**, *132*, 10706.

Examples of metal C-C agostic interaction



C-C agostic interaction is very rare...





C-C bond is lengthened by ~0.1Å

Coordinated C-C single bond with atransition metal has been characterized structurally, spectroscopically, and by theoretical calculations.

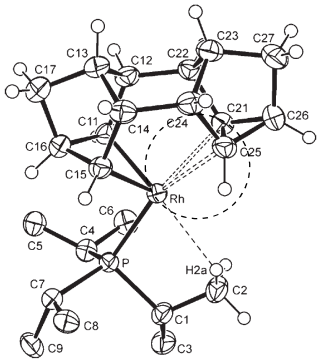
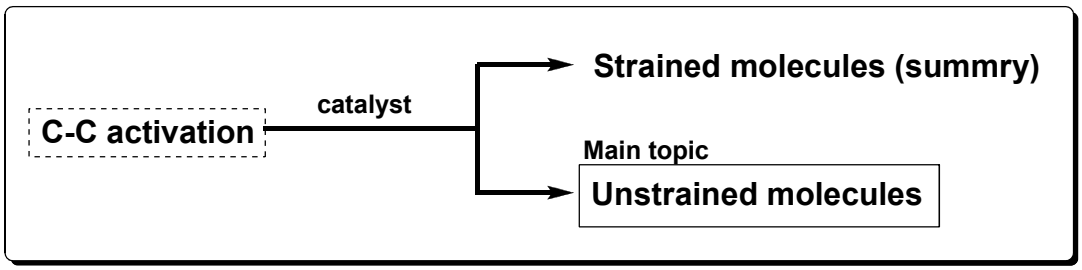


Figure 1. Solid-state structure of the cationic portion of **1**. Thermal ellipsoids are shown at the 50% probability level. Hydrogen atoms on the phosphine ligand, apart from those associated with C2, are omitted for clarity. Selected bond lengths [Å] and angles [°]: Rh−P 2.2693(7), Rh−C11 2.032(3), Rh−C15 2.042(3), Rh−C21 2.352(3), Rh−C25 2.369(3), Rh−C2 2.901(3), Rh−H2a 2.52(3), C21−C25 1.604(4), C21−C26 1.510(4), C25−C26 1.502(4), C11−C15 2.204(4), C21−H21 0.97(3), C25−H25 0.95(3); P-C1-C2 109.7(2), P-C1-C3 117.1(2).

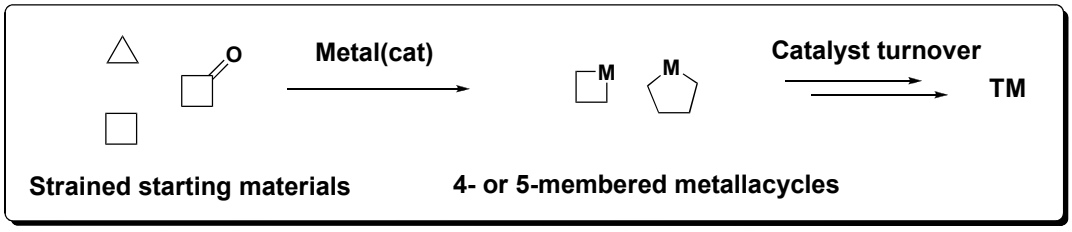
Weller *et al. Angew. Chem. Int. Ed.* **2006**, *45*, 452.

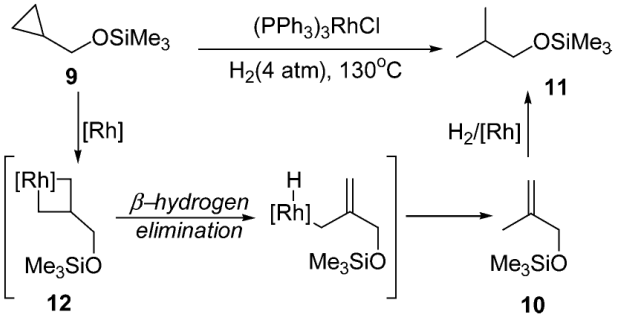
Classification of catalytic C-C activation



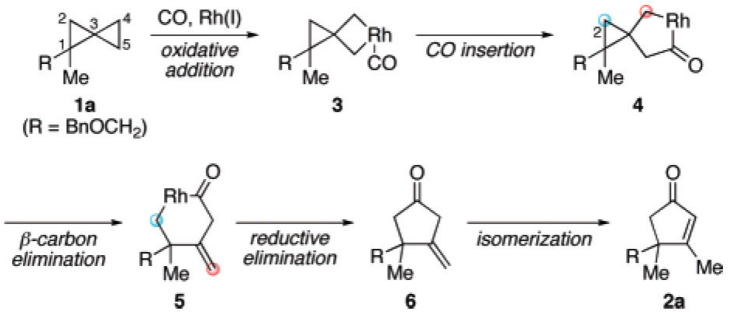
2. Activation of strained molecules

2.1 Direct cleavage of C-C bond by transition metal catalysis

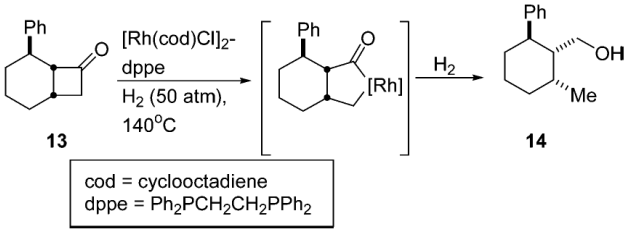




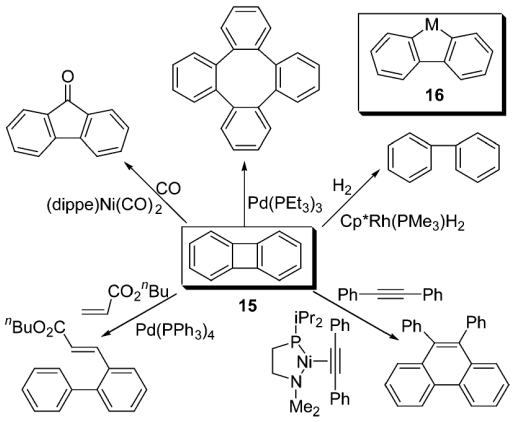
Chirik *et al. J. Am. Chem. Soc.* **2003**, *125*, 886.



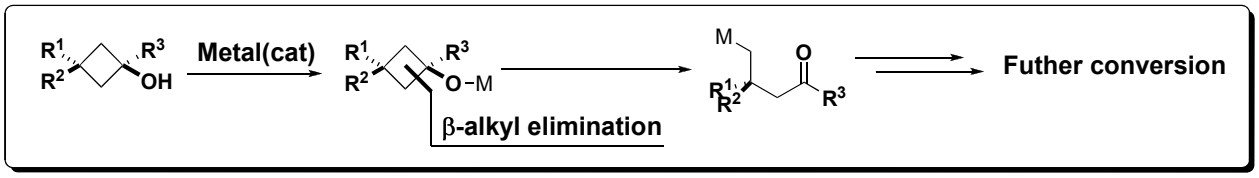
Murakami *et al. J. Am. Chem. Soc.* **2007**, *129*, 12596.



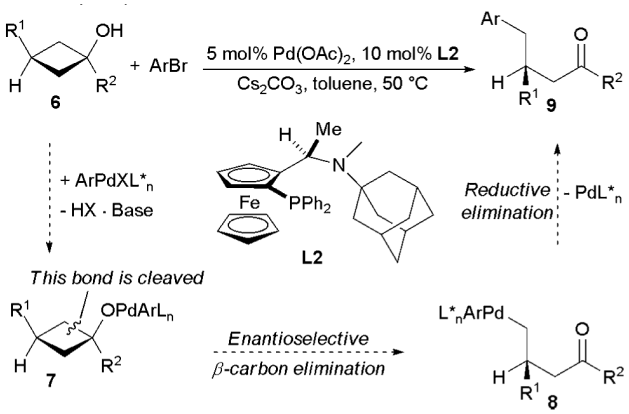
Murakami *et al. Nature.* **1994**, *370*, 18.

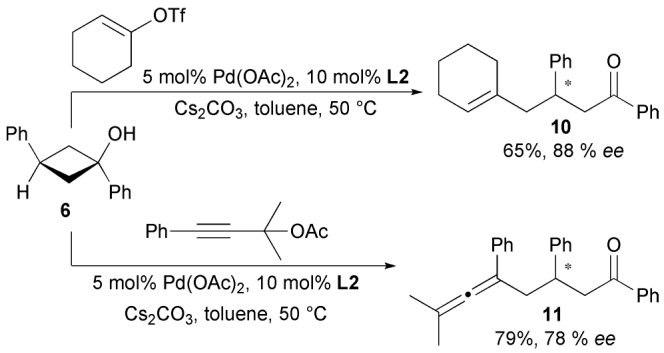


2.2 β-alkyl elimination of strained molecules

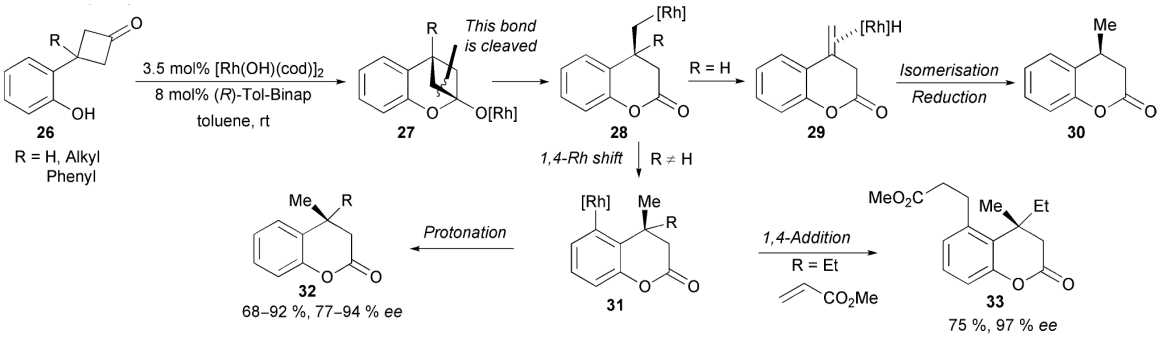


Currently,many enantioselective β-alkyl eliminations are reported.

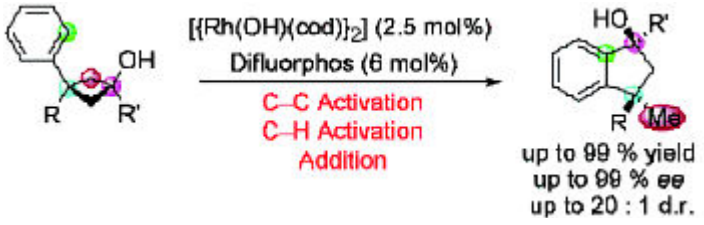




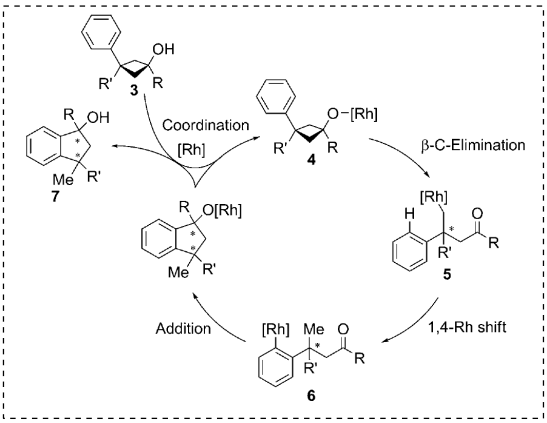
Uemura *et al. J. Am. Chem. Soc.* **2003**, *125*, 8862.

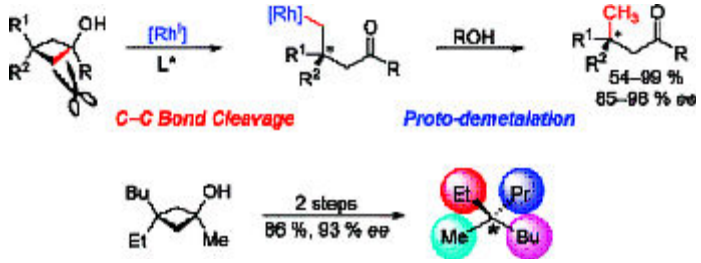


Murakami *et al. J. Am. Chem. Soc.* **2007**, *129*, 12086.



Cramer *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 6320.





Cramer *et al. J. Am. Chem. Soc.* **2010**, *132*, 5340.

3. Activation of unstrained molecules

3.1 β-alkyl elimination of unstrained molecules

Ruthenium-Catalyzed β-Allyl Elimination Leading to Selective Cleavage of a Carbon-Carbon Bond in Homoallyl Alcohols

Mitsudo *et al. J. Am. Chem. Soc.* **1998**, *120*, 5587.

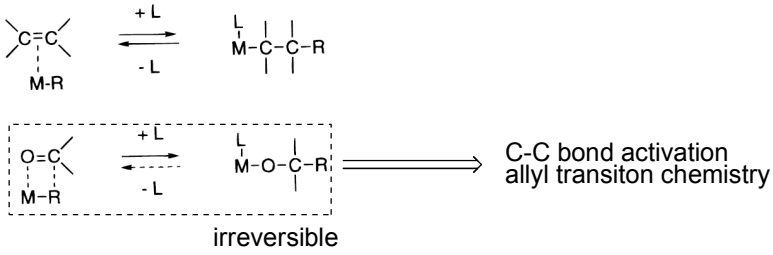
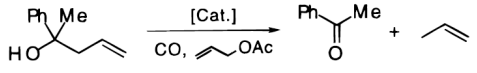


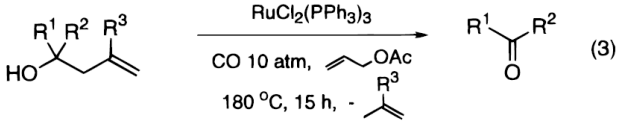
Table 1. Catalytic Activity of Several Transition-Metal Complexes in Deallylation of **1a** to **2a**[a]



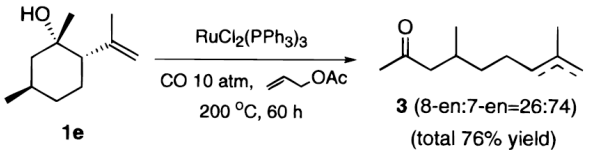
1a **2a**

catalyst	yield of **2a** (%)[b]
$RuCl_2(PPh_3)_3$	(91)
cis-$RuCl_2(CO)_2(PPh_3)_2$	65
Cp*RuCl(cod)	64
$Ru_3(CO)_{12}$[c]	45
$RhCl(PPh_3)_3$	53
$NiBr_2(PPh_3)_2$	0
$PdCl_2(PPh_3)_2$	0
cis-$PtCl_2(PPh_3)_2$	0

[a] Compound **1a** (4.0 mmol), catalyst (0.20 mmol), allyl acetate (30 mmol), THF (8.0 mL), CO (10 atm), 180 °C, 15 h. [b] GLC yield (isolated yield). [c] $Ru_3(CO)_{12}$ (0.067 mmol).

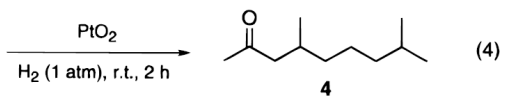


1a : R^1=Ph, R^2=Me, R^3=H — **2a** : 91%
1b : R^1=R^2=Ph, R^3=H — **2b** : 87%
1c : R^1=R^2=Bu, R^3=H — **2c** : 71%
1d : R^1=Ph, R^2=Me, R^3=Me — **2d** : 85%



1e

3 (8-en:7-en=26:74)
(total 76% yield)



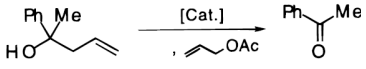
4
(overall 73% isolated yield)

Role of carbon monoxide and allyl acetate

The presence of both carbon monoxyde and allyl acetate was crucial.

Carbon monoxyde: **π-acid**

After the reaction, $RuCl_2(PPh_3)_3$ was quantitatively converted into cis-$RuCl_2(CO)_2(PPh_3)_2$.
In the case of maleic anhydride

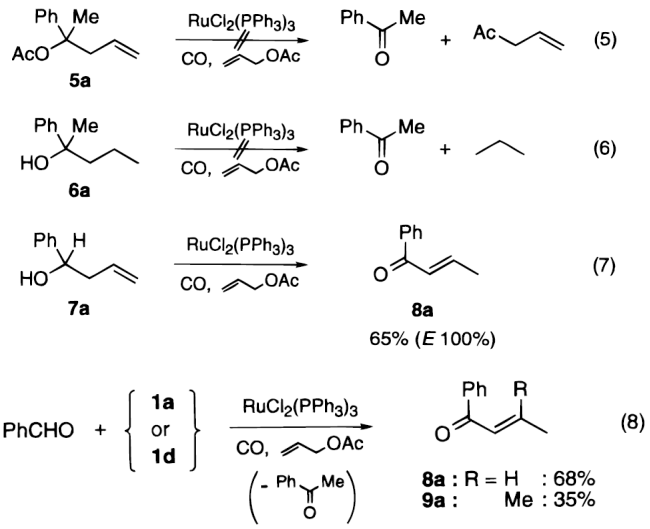


1a maleic anhydride 50eq **2a** 65% y.

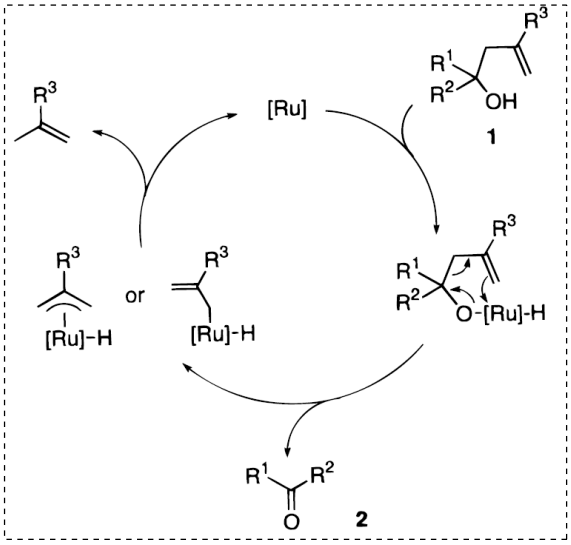
Carbon monoxyde and maleic anhydride may coordinate to an active ruthenium center and promote the reductive elimination of propene from a (hydro)(allyl)ruthenium intermediate, as well as control the electronic condition of an active ruthenium center.

Allyl acetate: unclear(it is required for generation and stabilization of a catalytically active ruthenium species?)

Mechanistic study



Proposed catalytic cycle

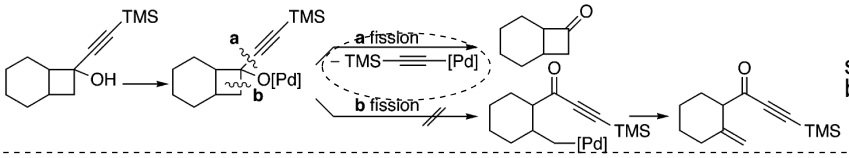


(5): First step of the reaction is oxidative addition of a hydroxy group to ruthenium.
(6): Driving force of this reaction is the formation of an allylruthenium species.
(7): In the presence of β-hydrogen, unsaturated ketone is formed predominantly.
(8): Formation of an allylruthenium intermediate

Palladium-Catalyzed Oxidative Alkynylation of Alkenes via C-C Bond Cleavage under Oxygen Atmosphere

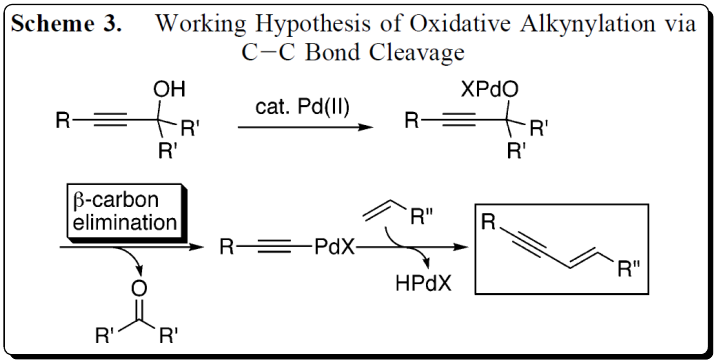
Uemura *et al. Org. Lett.* **2003**, *5*, 2997.

In precedent work...



sp^3-sp bond cleavage occured in preference to sp^3-sp^3 bond cleavageof the cyclobutane ring.

Uemura *et al. J. Am. Chem. Soc.* **1999**, *121*, 2645.



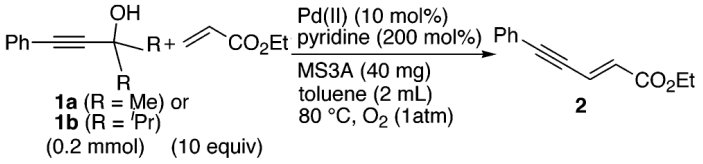


Table 1. Effect of Pd(II) Salts

entry	substrate	Pd(II) salt	time (h)	GLC yield (%)
1	**1a**	$Pd(OAc)_2$	24	30[a]
2	**1a**	$PdCl_2$	24	tr
3	**1a**	$Pd(acac)_2$	25	49[a]
4	**1b**	$Pd(OAc)_2$	48	41
5	**1b**	$Pd(acac)_2$	48	57
6	**1a**	$Pd(acac)_2$	48	57
7[b]	**1a**	$Pd(acac)_2$	24	0
8[c]	**1a**	$Pd(acac)_2$	24	4
9[d]	**1a**	$Pd(acac)_2$	48	61

[a] Isolated yield. [b] In the absence of pyridine. [c] Under N_2. [d] DMF was used as a solvent.

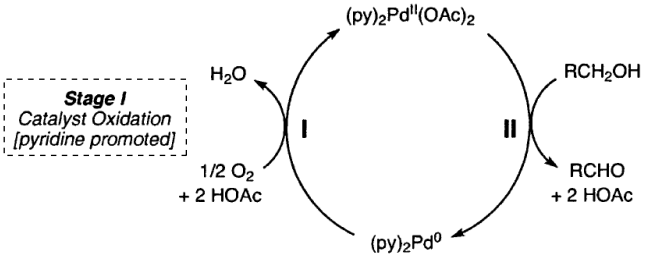
$Pd(acac)_2$ was found to be the most effective palladium source.

DMF was the best solvent.

What is the role of pyridine?

The effect of pyridine

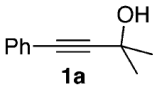
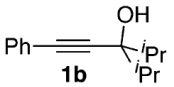
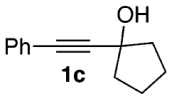
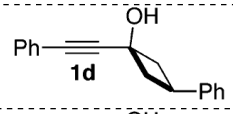
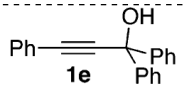
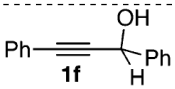
Uemura oxidation



Without pyridine, only stoichiometric alcohol oxidation is observed with concomitant formation of palladium black.

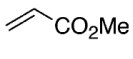
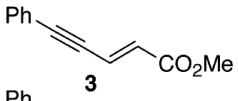
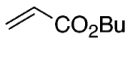
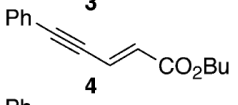
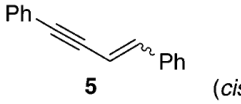
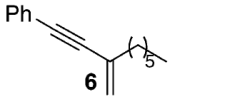
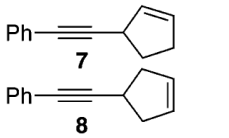
Stahl *et al. Org. Lett.* **2002**, *4*, 4179.

Result

entry	alcohol	GLC yield (%) of **2**
1	 **1a**	57
2		61[a]
3	 **1b**	57
4	 **1c**	45
5	 **1d**	60[b,c]
6	 **1e**	52[c]
7	 **1f**	26
8		32[a]

β-hydrogen elimination

[a] DMF was used as a solvent. [b] Isolated yield. [c] The formation of the corresponding eliminated ketone was also confirmed.

entry	alkene	product	isolated yield (%)
1		 **3**	49
2		 **4**	57
4		 **5**	54[b] (*cis*/*trans* = 1/4)
5		 **6**	33[b]
6		 **7** **8**	40 (**7**/**8** = 2/1)

[a] Reaction conditions: $Pd(acac)_2$ (10 mol %), pyridine (0.8 mmol), **1a** (0.4 mmol), alkene (4 mmol), and MS3Å (80 mg) in toluene (4 mL) at 80 °C for 48 h under O_2 (1 atm). [b] In DMF (4 mL).

Cleavage rate

sp^3-sp > sp^3-sp^3(cyclobutanol) > sp^3-sp^2, sp^3-sp^3

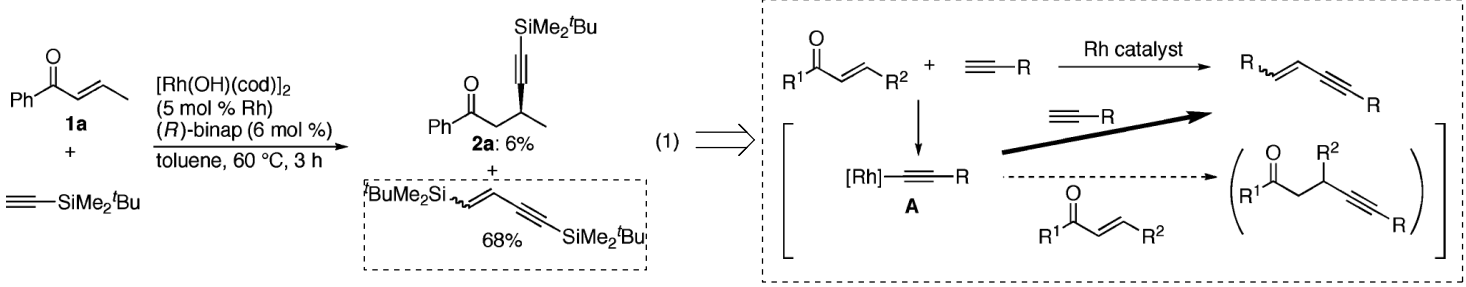
Rhodium-Catalyzed Asymmetric Rearrangement of Alkynyl Alkenyl Carbinols: Synthetic Equivalent to Asymmetric Conjugate Alkynylation of Enones

Hayashi *et al. J. Am. Chem. Soc.* **2007**, *129*, 14158.

Steric Tuning of Silylacetylenes and Chiral Phosphine Ligands for Rhodium-Catalyzed Asymmetric Conjugated Alkynylation of Enones

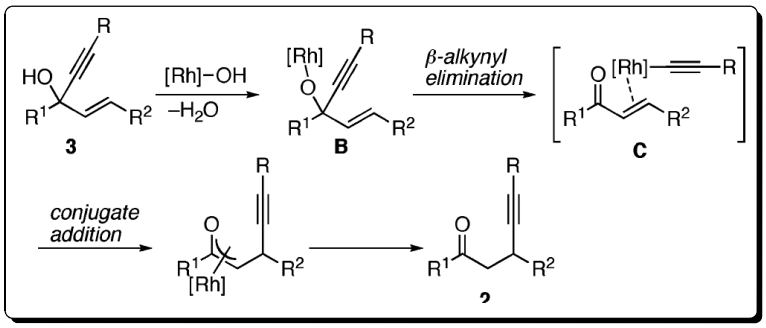
Hayashi *et al. J. Am. Chem. Soc.* **2008**, *130*, 1576.

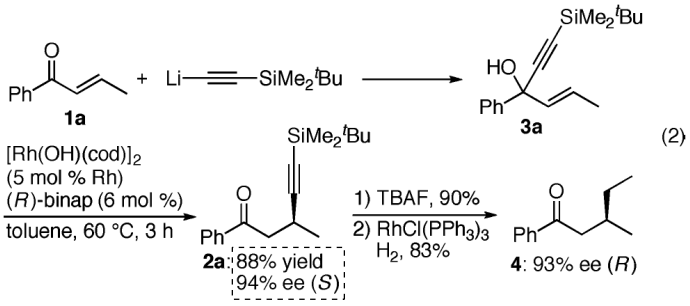
Under one of the standard reaction conditions for the rhodium-catalyzed asymmetric addition...



Wrong reaction pathway is caused by the presence of a terminal alkyne as a stoichiometric reagent, which is more reactive than β-substituted enone toward the insertion.

New approach ~asymmetric 1,3-rearrangement~

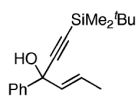
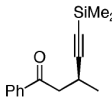
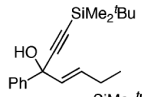
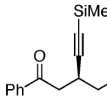
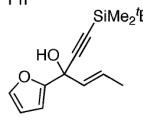
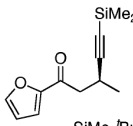
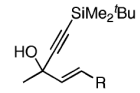
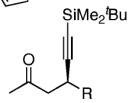
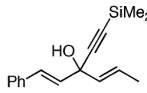
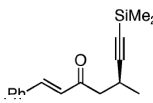
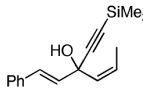
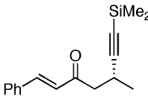
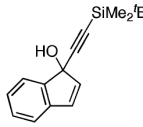
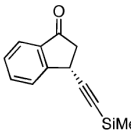




Free terminal alkynes are minimized in the reaction media.

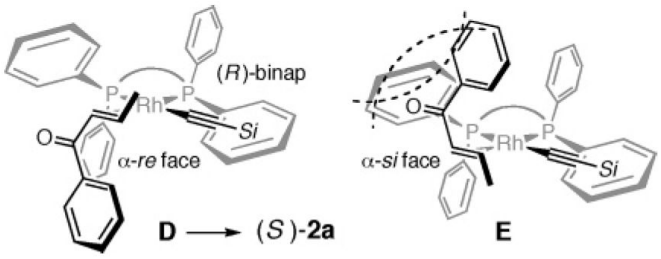
Result

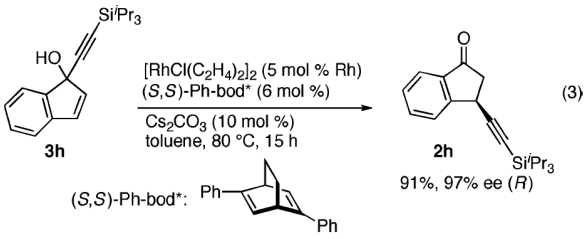
Table 1. Asymmetric Rearrangement of Alkynyl Alkenyl Carbinols[a]

entry	alcohol		product	
1		**3a**		**2a**: 88%, 94% ee (*S*)
2		**3b**		**2b**: 91%, 98% ee (*S*)
3		**3c**		**2c**: 89%, 91% ee (*S*)
4[b]		**3d**: R = CH_3		**2d**: 78%, 98% ee (*S*)
5		**3e**: R = C_5H_{11}		**2e**: 78%, 81% ee (*S*)
6[c]		(*E*,*E*)-**3f**		**2f**: 78%, 96% ee (*S*)
7[c]		(*E*,*Z*)-**3f**		**2f**: 88%, 81% ee (*R*)
8[d]		**3g**		**2g**: 86%, 71% ee (*S*)

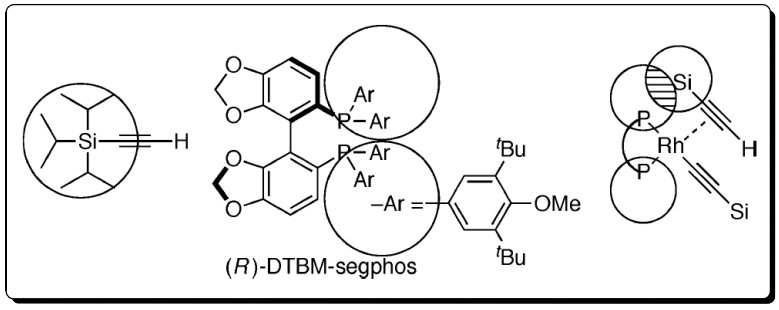
[a] Reaction conditions: alcohol **3** (0.20 mmol), $[Rh(OH)(cod)]_2$ (5 mol % of Rh), (*R*)-binap (6 mol %), toluene (1.0 mL) at 60 °C for 3 h. Enantiomeric excess values were determined by HPLC analysis. The absolute configuration of **2b**–**g** were assigned by consideration of the stereochemical pathway. [b] At 50 °C for 12 h. [c] For 6 h. [d] For 24 h.

Proposed stereochemical pathway





Toward asymmetric conjugate alkynylation of enones...



Sterically bulky substituents on the silicon and phosphorus atoms should hinder the acetylene from approaching the alkynyl-rhodium intermediate?

(R)-DMM-binap

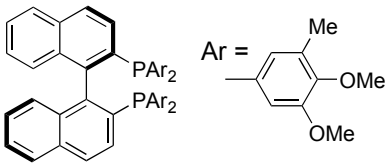
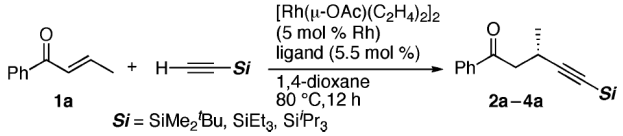


Table 1. Rhodium-Catalyzed Asymmetric Conjugate Addition of Silylacetylenes to Enone **1a**[a]

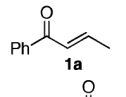
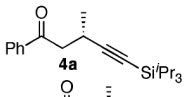
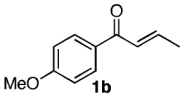
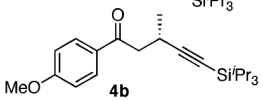
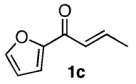
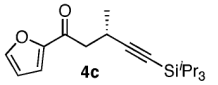
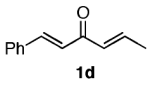
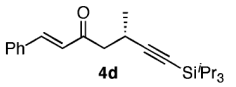
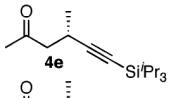
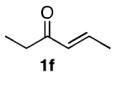
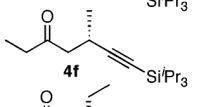
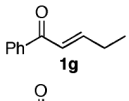
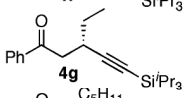
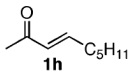
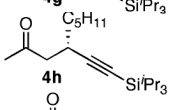
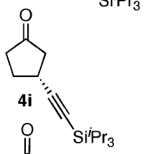
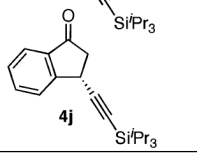


entry	ligand	***Si***	product	yield (%)[b]
1	(*R*)-binap	$SiMe_2{}^tBu$	**2a**	9
2	(*R*)-binap	$SiEt_3$	**3a**	10
3	(*R*)-binap	Si^iPr_3	**4a**	35
4	(*R*)-segphos	Si^iPr_3	**4a**	36
5	(*R*)-DMM-binap	Si^iPr_3	**4a**	49
6	(*R*)-DTBM-segphos	Si^iPr_3	**4a**	87
7[c]	(*R*)-DTBM-segphos	Si^iPr_3	**4a**	99 (91)[d]

[a] Reaction conditions: enone **1a** (0.20 mmol), silylacetylene (0.40 mmol), $[Rh(\mu\text{-}OAc)(C_2H_4)_2]_2$ (5 mol % of Rh), ligand (5.5 mol %), 1,4-dioxane (0.4 mL) at 80 °C for 12 h. [b] NMR yield. [c] For 24 h. [d] Enantiomeric excess (%) determined by HPLC analysis with a chiral stationary phase column: Chiralcel OJ-H.

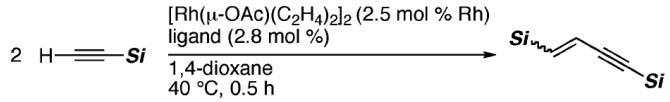
Result

Table 3. Asymmetric Conjugate Addition of (Triisopropylsilyl)acetylene to Enones[a]

entry	enone	product	isolated yield and ee[b]
1	 **1a**	 **4a**	99%, 91% ee (*S*)
2	 **1b**	 **4b**	88%, 91% ee (*S*)
3	 **1c**	 **4c**	99%, 93% ee (*S*)
4	 **1d**	 **4d**	78%, 95% ee (*S*)
5	 **1e**	 **4e**	90%, 95% ee (*S*)
6	 **1f**	 **4f**	92%, 92% ee (*S*)
7	 **1g**	 **4g**	80%, 89% ee (*S*)
8	 **1h**	 **4h**	90%, 97% ee (*S*)
9[c]	 **1i**	 **4i**	67%, 88% ee (*R*)
10	 **1j**	 **4j**	54%, 95% ee (*S*)

[a] Reaction conditions: enone **1** (0.20 mmol), (triisopropylsilyl)acetylene (0.40 mmol), [Rh(μ-OAc)(C_2H_4)$_2$]$_2$ (5 mol % of Rh), (*R*)-DTBM-segphos (5.5 mol %), 1,4-dioxane (0.4 mL) at 80 °C for 24 h. [b] Enantiomeric excess values were determined by HPLC. The absolute configurations of **4b**−**4j** were assigned by consideration of the stereochemical pathway. [c] For 42 h.

Table 2. Rhodium-Catalyzed Dimerization of Silylacetylenes[a]



entry	ligand	*Si*	conversion (%)[b]
1	(*R*)-binap	$SiEt_3$	95
2	(*R*)-binap	Si^iPr_3	86
3	(*R*)-DTBM-segphos	$SiEt_3$	25
4	(*R*)-DTBM-segphos	Si^iPr_3	4

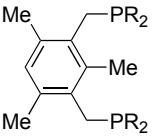
[a] Reaction conditions: silylacetylene (0.40 mmol), [Rh(μ-OAc)(C_2H_4)$_2$]$_2$ (2.5 mol % of Rh), ligand (2.8 mol %), 1,4-dioxane (0.8 mL) at 40 °C for 0.5 h. [b] Determined by GC.

Streric bulkness of silicon and phosphorus part reduces dimerization.

3.2 C-C bond activation by chelation assistance

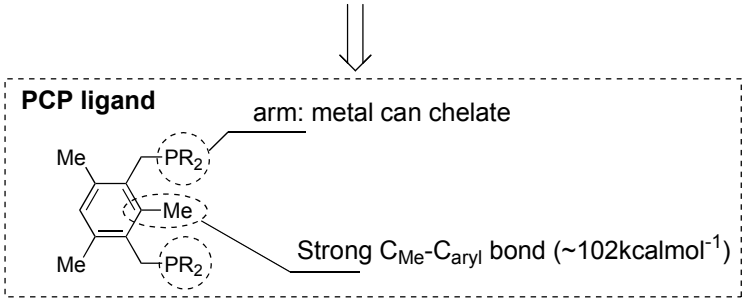
3.2.1 Milstein's chemistry (PCP system)

For an unclear demonstration and mechanistic evaluation of metal insertion into a C-C bond, it is desirable that this process would be irreversible and that the C-C activation product would be stable and readily characterized.



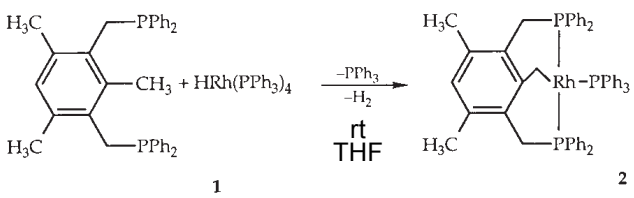
Scematic representation of the PCP ligands

PCP ligand

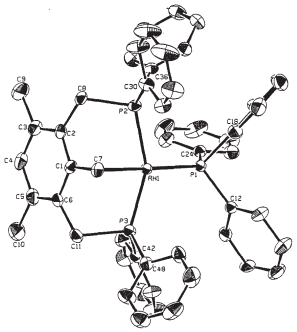


⟹ **Disire structure for C-C bond activation**

Demonstration of the process Milstein *et al*. *Nature*. **1993**, *364*, 699.



1 2

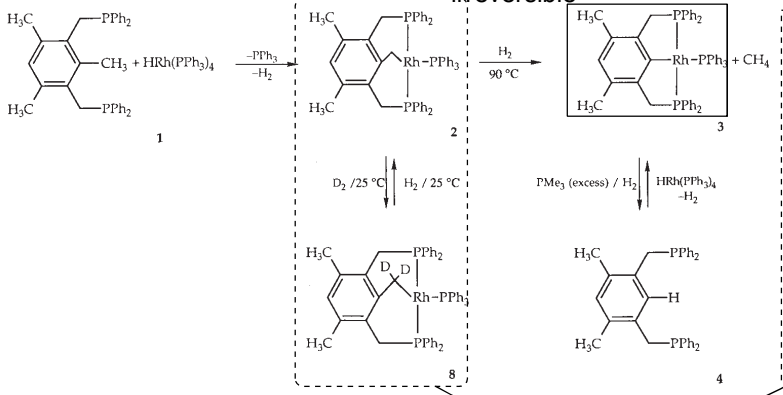


1. C_{Me}-C_{aryl} bond is not weakened relative to **1**.

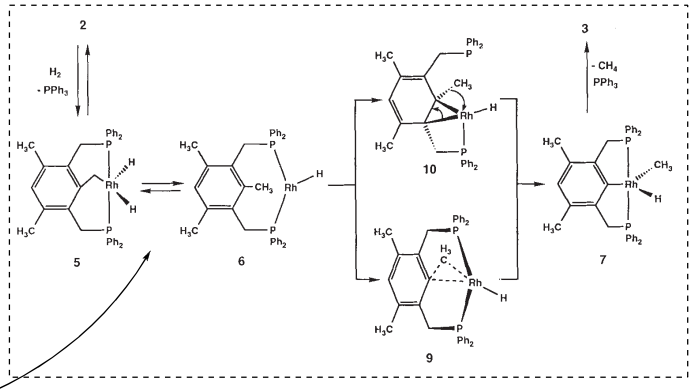
2. There is no distortion from aromaticity.

3. To maintain a fovorable square-planer arrangement around the rhodium atom, a relatively weak Rh-C bond is formed.

C-C activation pathway



Proposed mechanism



In this reaction, C-C activation process is thermodynamically more favorable than the overall C-H activation sequence.

C-C versus C-H activation ~thermodynamics~

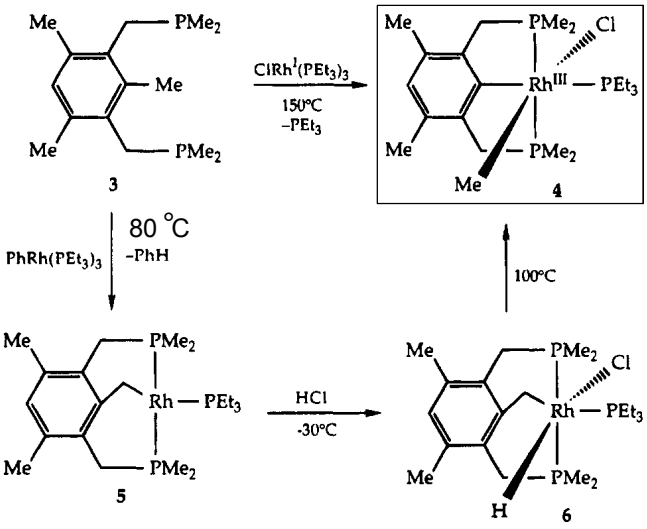
Milstein *et al. J. Am. Chem. Soc.* **1995**, *117*, 9774.

Employment of hydrogen in the above mentioned process masks the relative thermodynamic stability of the C-H and C-C activation product...

⇓

Direct observation of oxidative addition of a strong unactivated C-C bond to a metal is needed.

Scheme 1. Direct Insertion of a Rhodium Complex into a C−C Bond and a Reaction Sequence Proving That This Process Is Thermodynamically More Favorable Than Insertion into a C−H Bond



X-ray structure of **4**

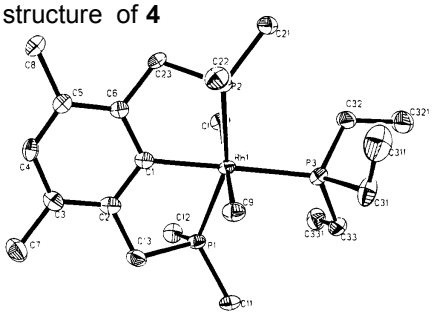


Figure 2. Perspective view (ORTEP) of complex **4**, clearly showing that the rhodium atom has selectively inserted into one of the aryl−carbon bonds. Bond distances (Å) and angles (deg, errors in last digits in parentheses) are Rh(1)−C(1) = 2.094(3); Rh(1)−C(9) = 2.114(3); Rh(1)−P(1) = 2.287(1); Rh(1)−P(3) = 2.372(1); C(1)−C(2) = 1.409-(5); C(3)−C(7) = 1.511(5); C(1)−Rh(1)−C(9) = 88.4 (1); C(1)−Rh-(1)−P(3) = 178.2(1); P(1)−Rh(1)−P(2) = 157.64(3).

Rh insertion into the C-C bond in this system is **thermodynamically** more favorable than insertion into the C-H bond.

Reaction **3** to **5** indicates that C-H activation is **kinetically** favorable in this system.

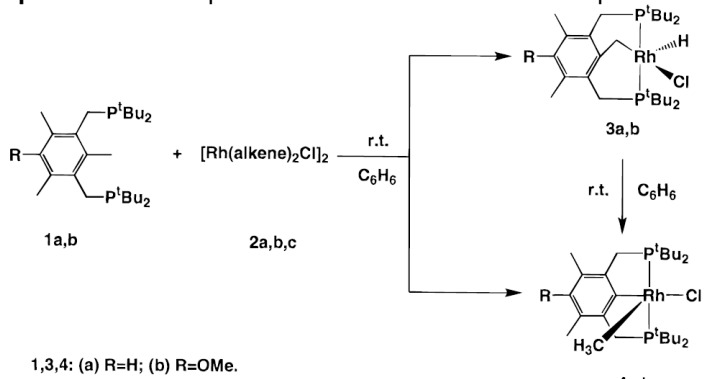
Total stability(caluculated from bond strength) and strong Rh-aryl bond is a driving force.

C-C versus C-H activation ~mechanism~

Milstein *et al. J. Am. Chem. Soc.* **1996**, *118*, 12406.

How about reaction mechanism?
Is the mechanism polar or nonpolar?
What is the role of the aromatic ring in this process?
Is it a direct process or does it require prior C-H activation followed by some rearrangement to the C-C activation product?

Experiment1: Comparison of different rhodium olefin precursors



1,3,4: (a) R=H; (b) R=OMe.
2: alkene = (a) cyclooctene; (b) ethylene; (c) tert-butyl ethylene.

Result

1. Initially, parallel formation of the two complexes occured (**3a**:**4a** = ~1.25:1).
2. **3a** was converted into **4a** within several hours.

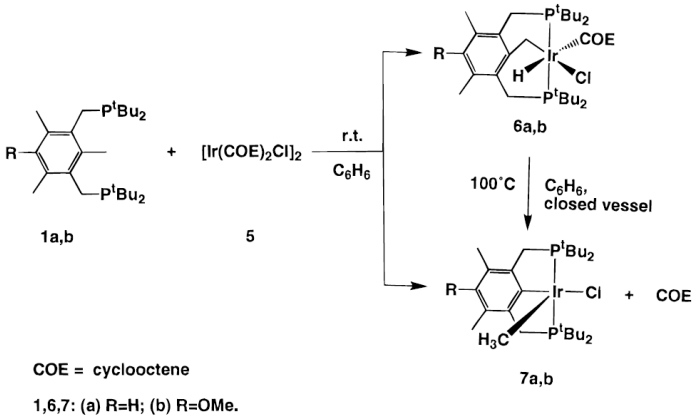
See Figure 2(next page)

3. In NMR analysis of crude mixture, only **1a**, **3a** and **4a** was obserbed.
4. Ligand reactivity order: **2b**>**2a**>>**2c**

⇓

Initial coordination of the diphosphine ligand to the rhodium olefin complexes is the rate-determining step .

Experiment2: C-C and C-H bond activation by iridium



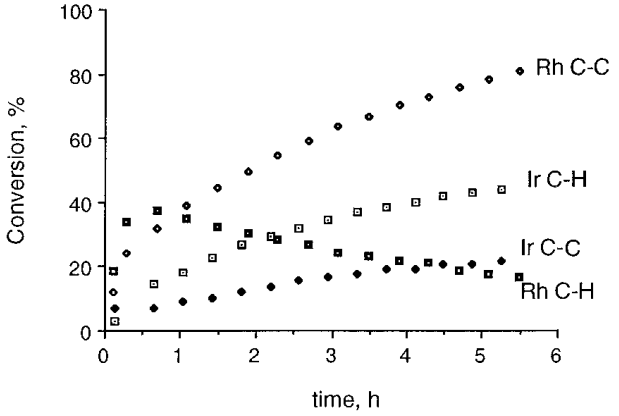


Figure 2. Followup of the C−C and C−H activation reactions of [Ir(COE)$_2$Cl]$_2$ (**5**) and [Rh(COE)$_2$Cl]$_2$ (**2a**) with the DTBPM ligand (**1a**) in C_6D_6 at 30 °C.

Result

1. Parallel formation of **6a** and **7a**, in approximate 2:1 ratio was observed.
2. In **6a**, COE is coordinated to the metal(stable in benzene or THF).
3. **6a** is converted into **7a** and free COE at 100° C.

From experiments above...

3a and **6a** are irreversibly converted into **4a** and **7a**. ⟹ **Iridium and rhodium insertion into the C-C bond is thermodynamically more favorable than their insertion into the C-H bond.**

Experiment3: Solvent and temperature effects

Table 2. Ratio between the C−H Activated (**6a**) and C−C Activated (**7a**) Complexes at Different Temperatures in Benzene and THF (by $^{31}P\{^1H\}$ NMR)

temp, K	C−H:C−C in benzene	C−H:C−C in THF	temp, K	C−H:C−C in benzene	C−H:C−C in THF
293	100:60		313	100:56	100:43
303	100:56		323	100:56	100:46
305		100:42	333	100:57	

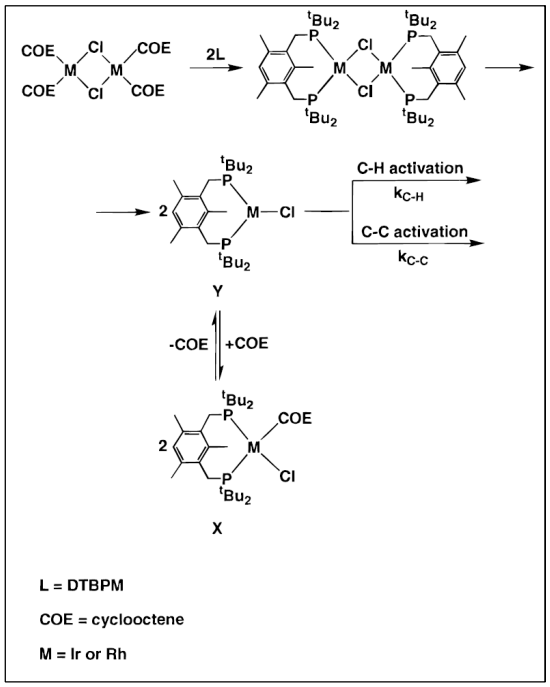
Result

The ratio between the products is constant at different temperatures during the reaction course and remain the same after the reaction is complete.

⇓

C-C and C-H activation processes are kinetically controlled, while the constant ratio demonstrates that the complexes are formed in two independent concurrent processes.

Postulated route



The temperature independence of the ratio between the C-C and C-H activation products (iridium) and value of the ratio (~1:2)

⇓

Overall processes leadind to C-C and C-H activation proceed by very similar pathway (via a common intermediate).

In the case of **rhodium**, the reaction proceedas via the intermediate **Y**.

Rhodium complexes bearing two bulky phosphine ligands in trans configuration are unlikely to coordinated bulky olefin. (as some precedents show)

Both COE and ethylene rhodium dimers give the same ratio of C-C and C-H activated products at the beginning of the reaction.

In the case of **iridium**, the reaction proceedas via the intermediate **Y**.

An excess of free COE did not affect the ratio between **6a** and **7a**.

Sterics in **X** is unfavorable for approaching the hidden C-C bond.

Unsaturated three-coordinated Ir has high reactivity in oxidative addition.

C-C and C-H activation proceeds via **Y**, the ratio between **6a** and **7a** is equal to the ratio between the rate constants.

Thermodynamics caluculation

Surprisingly, the C-C bond activation process is slightly kinetically more favorable than C-H bond activation.

1. Specific directionality of C-C and C-H bond in the **Y**
2. Interaction of the metal with the π-system of the aryl ring
3. Ring strain difference in the transition state (different chelating size)

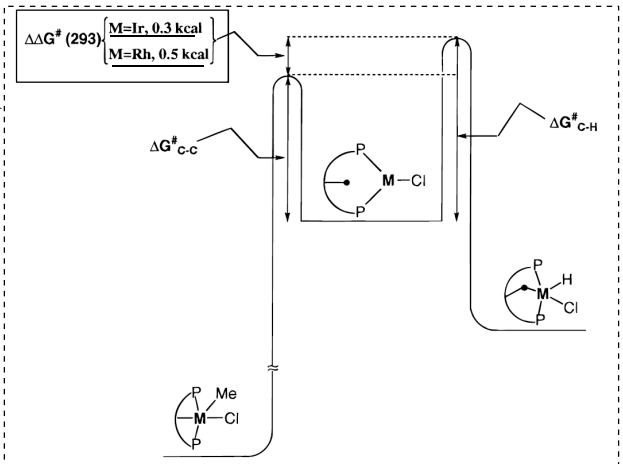
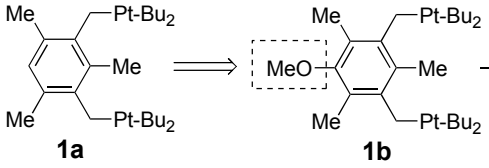


Figure 3. Reaction coordinate for C−C and C−H bond activation.

Experiment4: Toward insights into transition state ~effect of ligand~

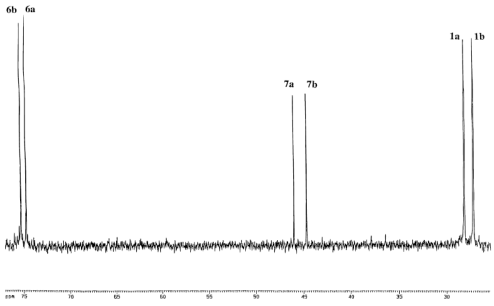


1a **1b**

Same reaction condition → No change in the reaction rateor in the products ratio was observed.

Small substituent effect
+
Independence of solvent polarity

1a(1eq), **1b**(1eq), **5**(1eq)



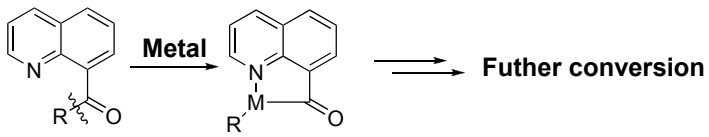
→ almost 1:1

C-C bond cleavage most probably proceeds through a three-center nonpolar transition state.

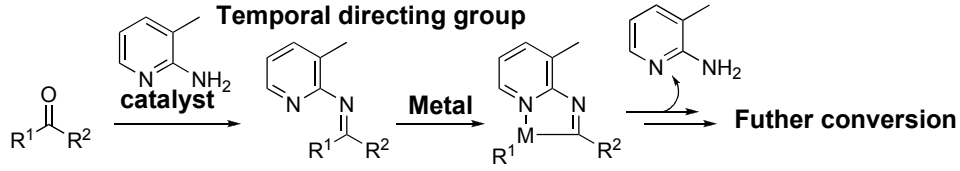
3.2.2 Pyridine directed type activation

There are mainly two types.

1.

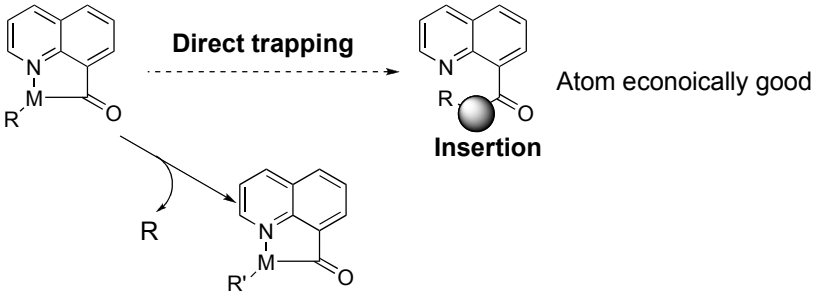


2.



See Shimizu-san's lit sem (D3)

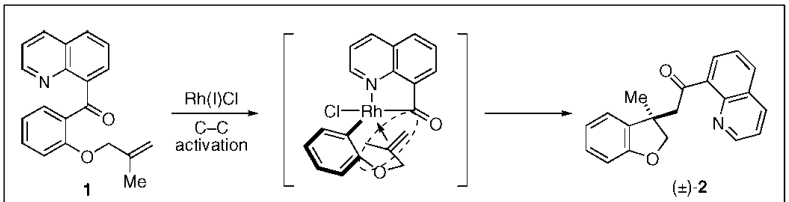
Most of the reaction above are just fragmentation reactions...



Catalytic Carbon-Carbon s Bond Activation: An Intramolecular Carbon-Acylation Reaction with Acylquinolines

Douglas *et al. J. Am. Chem. Soc.* **2009**, *131*, 412.

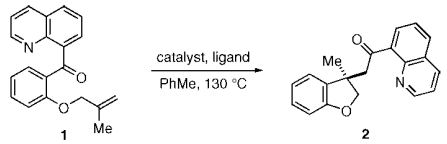
Working hypothesis



Intramolecular trapping by alkene group

Result

Table 1. Optimization of Catalytic Conditions



entry	catalyst	mol %	L_n	yield **2** (%)
1	$\{RhCl(C_2H_4)_2\}_2$	5	none	*95*
2	$Rh(OTf)(COD)_2$	5	none	62
3	$RhCl(PPh_3)_3$	10	none	*96*
4	$RhCl(PPh_3)_3$	2	none	90[a]
5	$\{RhCl(C_2H_4)_2\}_2$	5	PCy_3	62
6	$\{RhCl(C_2H_4)_2\}_2$	5	PMe_3	53
7	$Rh(OTf)(COD)_2$	5	PMe_3	72
8	$Rh(OTf)(COD)_2$	5	BINAP	<5[b]
9	Pd_2dba_3	5	none	0
10	$Ni(COD)_2$	5	none	0
11	Pd_2dba_3	5	PPh_3	0[a,c]
12	$Ni(COD)_2$	5	PPh_3	0

[a] As determined using ^1H NMR spectroscopy after 48 h. [b] The major product resulted from alkene isomerization to an enol ether. [c] Cleavage of the allyl ether to the corresponding phenol was the major product.

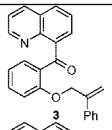
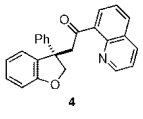
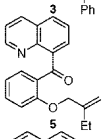
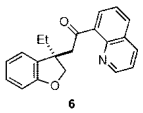
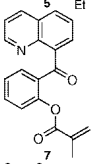
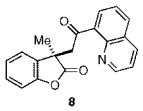
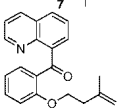
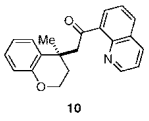
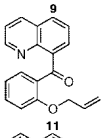
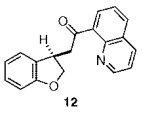
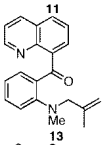
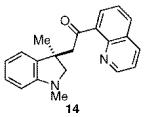
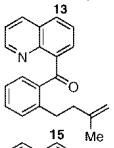
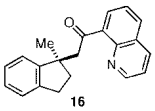
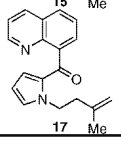
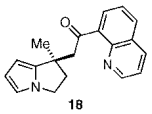
Phosphine did not gave positive ffect.

In the case of BINAP, alkene isomerization took place rather than C-C activation.

⇓

Steric bulkness around metal center?

Other late-transition metals did not gave TM.

entry	substrate	cond.	product	% yield[a]
1		A		94
2		A		82
3		A		80[b]
4		A		81
5		B		25
6		C		75
7		A		93
8		A		63

[a] Isolated yield after chromatography with SiO_2. [b] Reaction stopped after 24 h. [c] Condition A: 5 mol% $\{RhCl(C_2H_4)_2\}_2$, PhMe, 130 °C, 48 h. Condition B: 5 mol% $Rh(OTf)(COD)_2$, PhMe, 130 °C, 24 h. Condition C: 10 mol% $RhCl(PPh_3)_3$, PhMe, 130 °C, 24 h.

The cyclization of **7** required the addition of 10mol% of hydroquinone to inhibit thermal polymerization of methacrylate ester.

In the case of **11**, β-hydride elimination did not appear to be the main problem. Rather, cleavage of the allyl ester to phenol proved to be the dominant decomposition pathway.

In the case of **13**, diminished reactivity of the phosphine free catalysts was obtained.

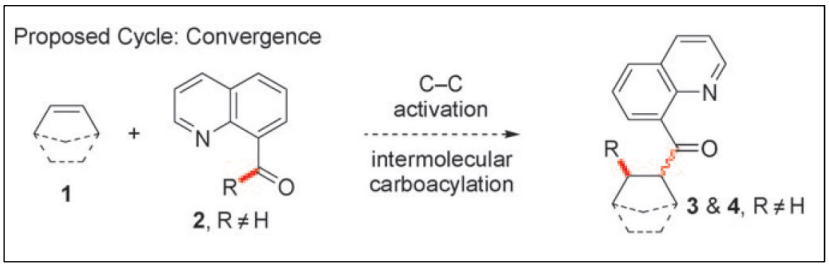
1. C-C bond activation is slower because ketone is less electrophilic, owing to electron donation.
2. Anthranilic ketone coordinates to the catalyst, inhibiting C-C activation.

Total comsumption of **1** and the formation of **2** was obtained even in the presence of **13**.

Chemoselectivity in Catalytic C-C and C-H Bond Activation: Controlling Intermolecular Carboacylation and Hydroarylation of Alkenes

Douglas *et al. J. Am. Chem. Soc.* **2009**, *131*, 412.

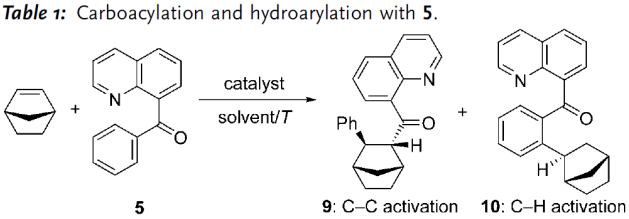
How about intermolecular reaction?



No syn β-hydrides

Screening

Table 1: Carboacylation and hydroarylation with **5**.



Entry	Catalyst[b]	Solvent	T	Yield, 9/10[a]
1	$[Rh(PPh_3)_3]Cl$	$PhCH_3$	130 °C	>10%, –
2	$[\{RhCl(C_2H_4)_2\}_2]$[c]	$PhCH_3$	130 °C	**79%, 0:1**
3	$[\{RhCl(C_2H_4)_2\}_2]$[c]	CH_3CN	100 °C	35%, ≈1:20
4	$[Rh(cod)_2]BF_4$	$PhCH_3$	130 °C	38%, 1:6
5	$[Rh(cod)_2]OTf$	$PhCH_3$	130 °C	56%, 4:5
6	$[Rh(cod)_2]OTf$	$PhCF_3$	130 °C	44%, 1:5
7	$[Rh(cod)_2]OTf$	$(CH_2Cl)_2$	130 °C	62%, 1:7
8	$[Rh(cod)_2]OTf$	CH_3CN	100 °C	41%, 5:3
9	$[Rh(cod)_2]OTf$	THF	100 °C	**50%, 1:0**
10	$[Rh(cod)_2]OTf$	THF[d]	100 °C	20%, 1:0
11	$[Rh(cod)_2]OTf$	THF[e]	100 °C	12%, 1:0

[a] Yields and ratios by ^1H NMR spectroscopy with an internal standard. [b] Catalyst loading 10 mol% unless otherwise noted. [c] 5 mol% catalyst used. [d] With 20 mol% PPh_3. [e] With 20 mol% $P(tBu)_3$. The values in bold show the most selective reactions. cod = 1,5-cyclooctadiene, THF = tetrahydrofuran, OTf = trifluoromethane sulfonate.

In the screening, addition of phosphine gave lower reactivity.

Alkene **13** and **15** did not undergo carboacylation.
(diol **15** cyclized)

Selectivity was compete under condition **A** and **B** (**18**,**19**).

More electron rich aryl ketones undergo C-H activation more rapidly under condition **B**.

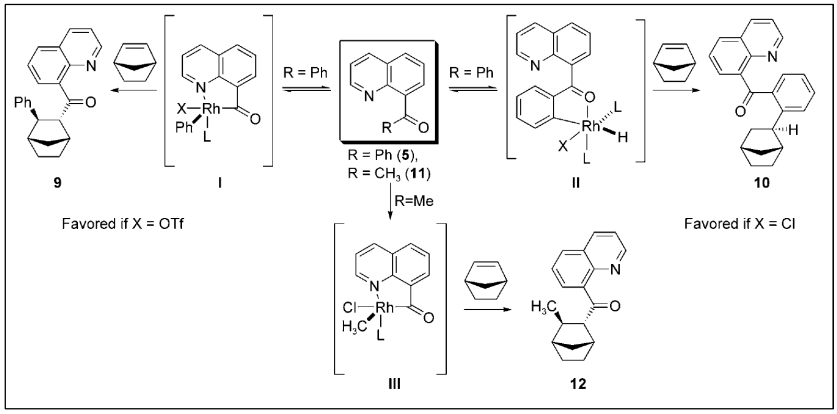
Result

Table 2: Variation of the quinoline and alkene substrates.

Quinoline	Alkene	Cond.[a]	Products	Yield[b]
11		A	**12**	39% (60%)
5	**13**	A	**14**	44% (65%)
5	**15**	A	**16**	41% (60%)
17		A	**18**	44% (64%)
17		B	**19**	30%, (66%), **18**/**19**; 1:1
20		B	**21**	24%
20	**22**	B	**23**	24%

[a] Conditions A: $[\{RhCl(C_2H_4)_2\}_2]$ (5 mol%), $PhCH_3$, 130 °C, 24 h. Conditions B: $[Rh(cod)_2]OTf$ (10 mol%), THF, 100 °C, 24 h. [b] Yields after chromatography, (%) yields based on recovered starting material.

Mechanistic consideration

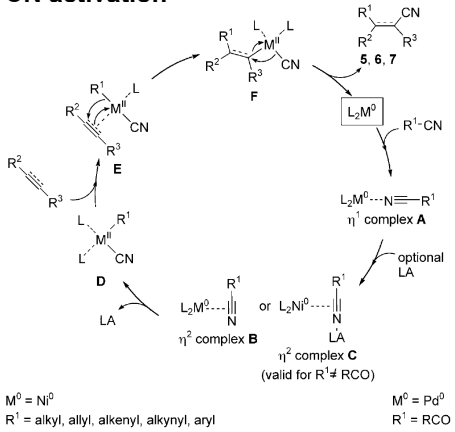


II is simply more apt toward migratory insertion than **I** when chloride is present in a nonpolar solvent.

By switching to a more polar solvent with OTf as the counteranion, the C-C activation pathway is selcted exclusively.

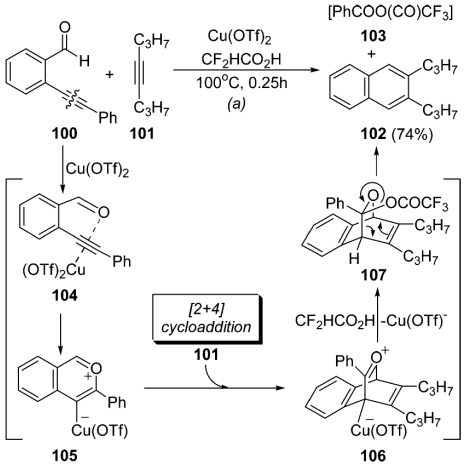
3.3 Other methods

C-CN activation



Scheme 3. General mechanism for the carbocyanation of alkenes and alkynes.

[4+2] Benzannulation



Alkene, alkyne metacesis

etc...

4. Summary

Current situation of C-C bond activation

Various types of C-C bond activation have emerged.

Recently, enantioselective reactions or tandem type reactions appear especially in the C-C bond activation of strained molecules.

Still, there are many hardships in this field.

1. **In many cases harsh condition is needed.**
2. **C-H activation, β-hydride elimination**
3. **Substrate scopes are limited in many cases.**
4. **Mechanism is usually unclear.**
5. **In some cases stoichiometric waste is produced.**