

# C-H ACTIVATION AND RELATED REACTIONS

## 0. Introduction

Today we often see the phrase "C-H activation."

But what does it stand for exactly?

*C-H activation means money.  
C-H activation begins just below one's own results.  
Pointed definitions of C-H activation  
(collected at a conference)*

*Angew. Chem. Int. Ed. 1999, 38, 1699*

cleave "unreactive bonds" with the aid of transition metal complexes in catalytic manners.

In this issue the term "bond activation" is used in two ways, one dealing with mechanistic aspects while other dealing with "overall transformation irrespective of the mechanism."

*Adv. Synth. Catal. 2003, 345, 1033*

Occasionally its a matter of debate<sup>[1]</sup> which research earns the ennobling title "C-H activation": should this term be restricted to unactivated  $sp^3$ -centered C-H bonds or should aromatic C-H bonds be included? What about the role of transition metals in catalysed processes: must the C-H activation take place via a preceding agostic interaction or is it sufficient when an electrophilic transition metal activates the C-H bond indirectly for the deprotonation by a base? If a base is involved: does it have to be a "superbase" or isn't every deprotonation a "C-H activation"? We plead for using this term in a very general sense, simply because of its fundamental character and because there is neither a convincing definition for a borderline nor the necessity for it.

*Adv. Synth. Catal. 2003, 345, 1127*

NO CONVINCING DEFINITION...

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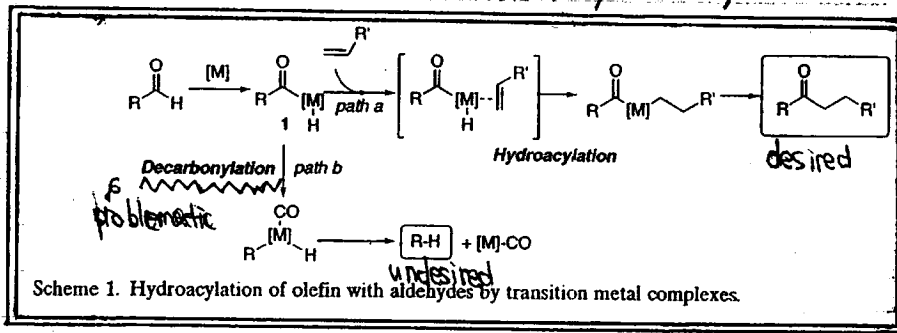
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For mechanistic aspects, see

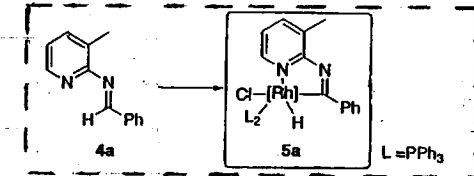
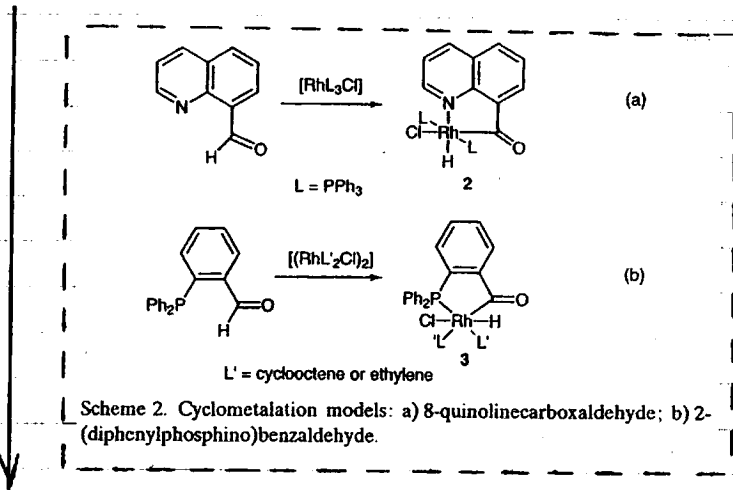
Okada san's literature seminar 020629  
Shigehisa's literature seminar 030507

# 1 Chelation-assisted hydroacylation

C-H. Jun et al.  
Chem. Eur. J. 2002, 8, 2423

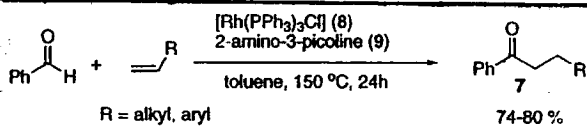


Decarbonylation is a serious problem.

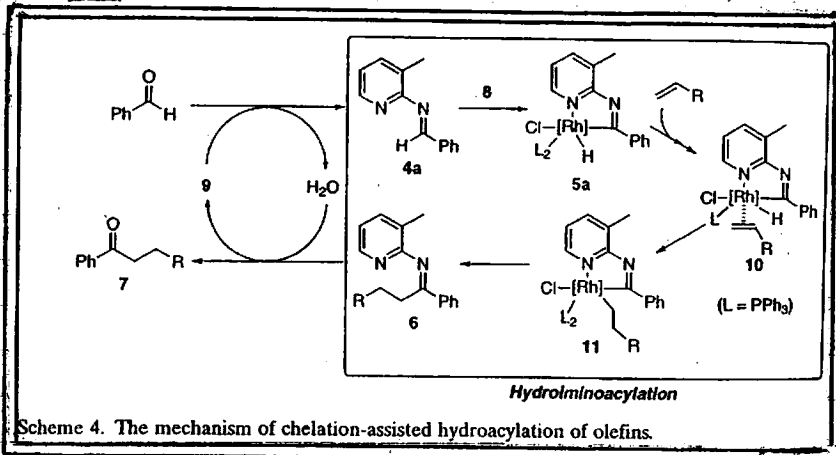


Another cyclometalation model  
decarbonylation is impossible  
J.W. Suggs, JACS, 1979, 101, 489

Five-membered metalacycles are so stable  
as to prevent decarbonylation.



J.W. Suggs, JACS, 1978, 100, 640  
JOC, 1997, 62, 1200



Other strategies to prevent  
decarbonylation

- high pressure of CO & olefins
- substrates bearing a coordination site

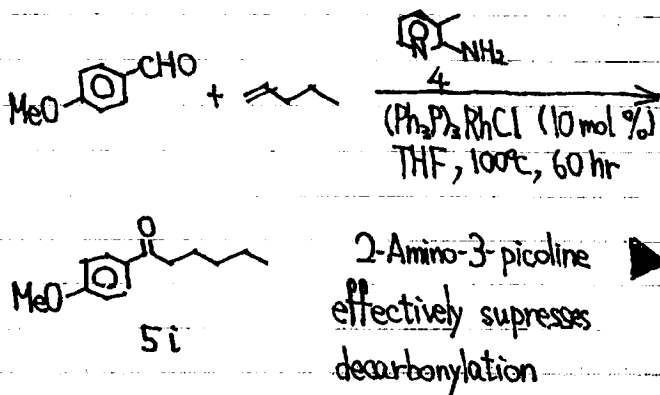
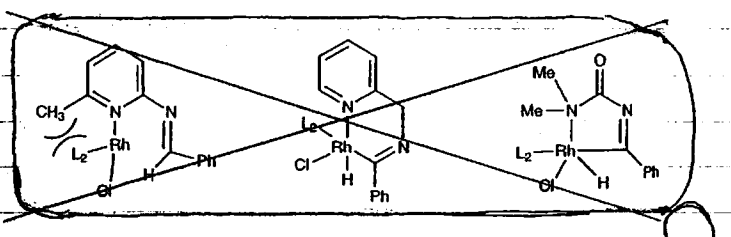
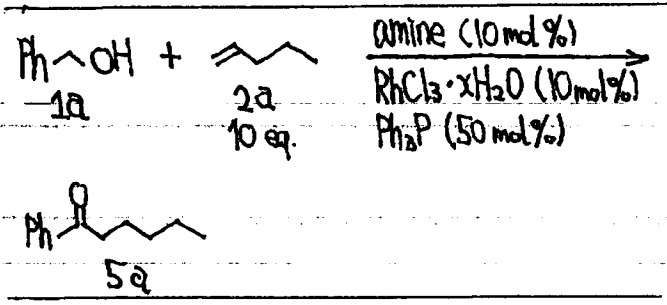


Table 2. Effect of 2-Amino-3-picoline (4) on Hydroacylation of 1b with 2b<sup>a</sup>

entry	mol % of 4	product ratio 5i:anisole	isolated yield (%) of 5i
1	0	0 <sup>b</sup> :100	0
2	10	58:42	14
3	20	85:15	57
4	50	85:15	70
5	70	90:10	80
6	100	93:7	83

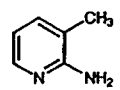
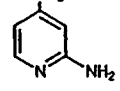
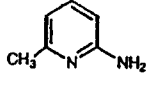
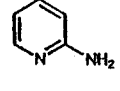
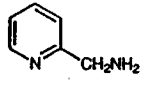
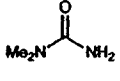
<sup>a</sup> Anisaldehyde (0.22 mmol), 1-pentene (1.08 mmol), (Ph<sub>3</sub>P)<sub>2</sub>RhCl (0.022 mmol) in THF (2 mL) at 100 °C for 60 h under different mol % of 2-amino-3-picoline based upon anisaldehyde. <sup>b</sup> 46% yield of anisole was obtained, determined by GC.



• 5-membered chelation  
 • sufficient reaction space ) are necessary

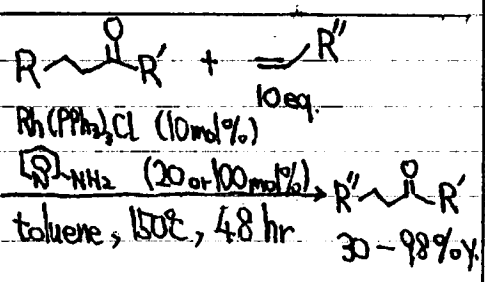
Angew. Chem. Int. Ed. 1998, 37, 145

Table 2. Results of the hydroacylation of 1-pentene (2a) with benzyl alcohol (1a) to give hexanophenone (5a) in the presence of RhCl<sub>3</sub> · xH<sub>2</sub>O and PPh<sub>3</sub> as catalyst system, as well as various amines (100 mol %).<sup>[a]</sup>

Entry	Amine	Yield [%] <sup>[b]</sup>
1	 4a	54
2	 4b	91
3	 4c	9
4	 4d	63
5	 4e	0
6	 4f	3
7	NEt <sub>3</sub> 4g	0

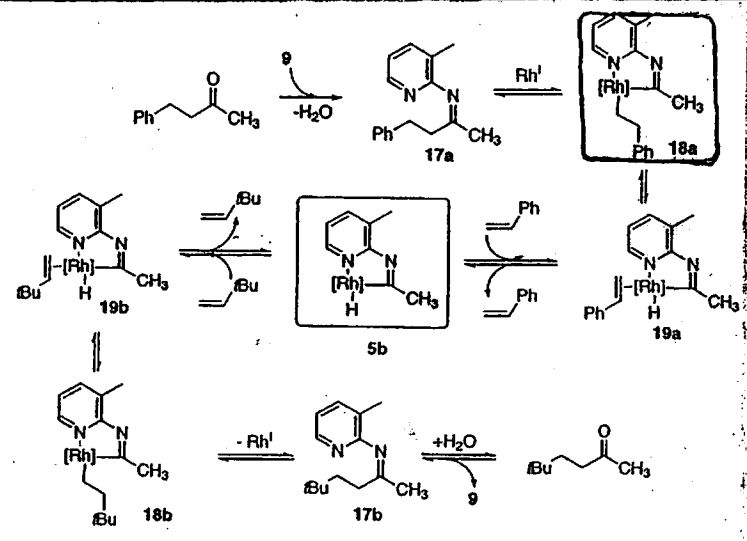
[a] A mixture of 1a (0.48 mmol), 2a (4.8 mmol), 3b (0.048 mmol), PPh<sub>3</sub> (0.24 mmol), and an amine (0.48 mmol) was heated for 40 h at 130°C. [b] Isolated 5a.

⊙ C-C bond activation



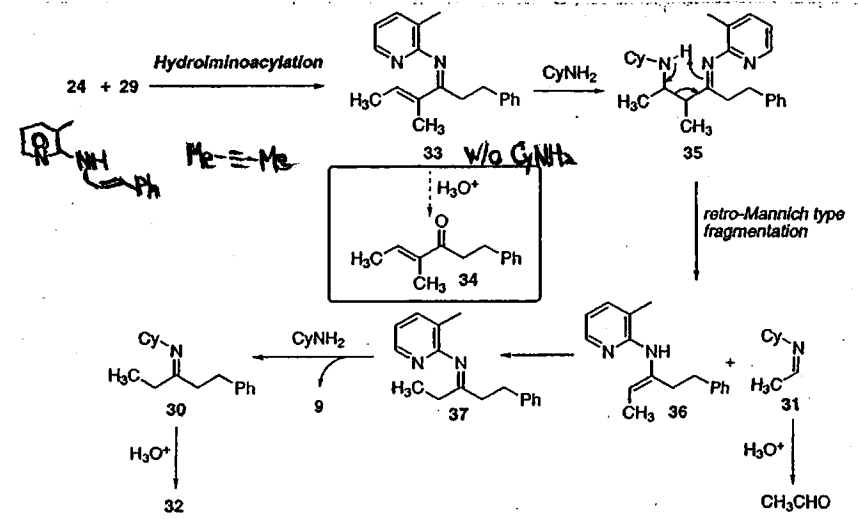
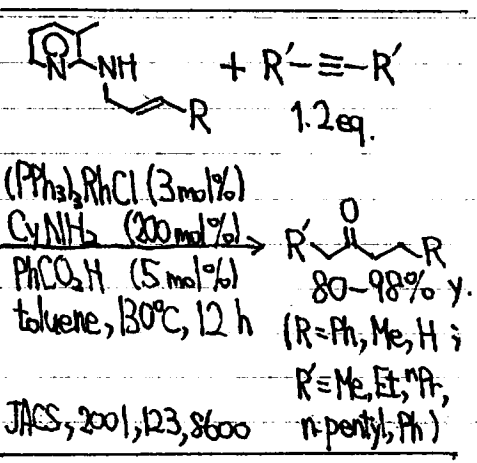
(R = Ph, <sup>n</sup>Bu, H; R' = Ph, Me)

JACS, 1999, 121, 880



Scheme 7. The proposed mechanism for the C-C bond activation of benzylacetone.

⊙ C≡C bond cleavage



Scheme 11. The plausible mechanism of the alkyne cleavage.

# 2. Catalysts for C-H activation

## Expanding the Scope of C-H Amination through Catalyst Design

Christine G. Espino, Kristin Williams Fiori, Mihyong Kim, and J. Du Bois\*  
 Department of Chemistry, Stanford University, Stanford, California 94305-5080

JACS, 2004, 126, 15378

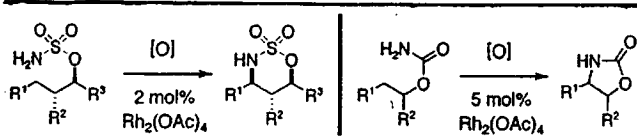


Figure 1. Rh-catalyzed oxidation of sulfamate and carbamate esters.

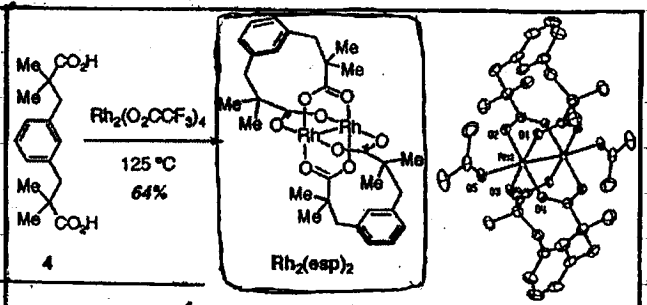
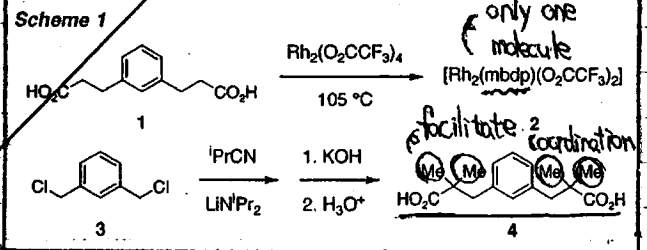
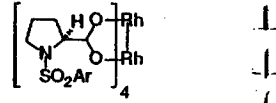


Figure 2. Preparation and X-ray analysis of [Rh2(esp)2]·(acetone)2.

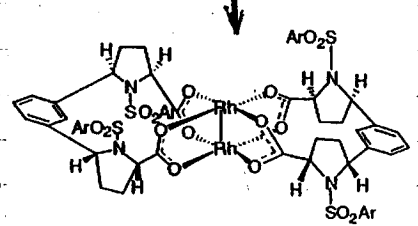
Carboxylate detachment from the dinuclear Rh core was responsible for catalyst decomposition?  
 ↓  
 "Joining of two carboxylate ligands"



cf. A precedent linked ligand for Rh dimer catalyst



1 Rh2(SDOSPr)4; Ar = p-C<sub>12</sub>H<sub>25</sub>C<sub>6</sub>H<sub>4</sub>



2 Rh2(SbTISP)2; Ar = 2,4,6-tri-PrC<sub>6</sub>H<sub>2</sub>

HML Doucet et al.,  
 OL, 2003,  
 5, 403

Substrate	Catalyst	Yield
5	0.15 mol% catalyst PhI(OAc) <sub>2</sub> , MgO, CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (O <sub>2</sub> C <sup>t</sup> Bu) <sub>4</sub> : 20% Rh <sub>2</sub> (esp) <sub>2</sub> : 92%
7	1 mol% catalyst PhI(OAc) <sub>2</sub> , MgO, CH <sub>2</sub> Cl <sub>2</sub>	Rh <sub>2</sub> (O <sub>2</sub> C <sup>t</sup> Bu) <sub>4</sub> : 15% Rh <sub>2</sub> (esp) <sub>2</sub> : 90%

Figure 3. Comparative data of Rh<sub>2</sub>(esp)<sub>2</sub> and Rh<sub>2</sub>(O<sub>2</sub>C<sup>t</sup>Bu)<sub>4</sub> as catalysts for intramolecular C-H amination with sulfamates.

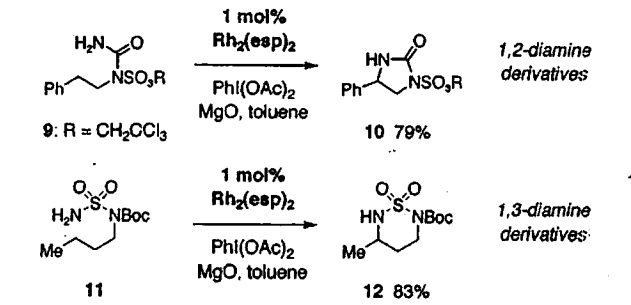


Figure 4. Oxidative cyclization of urea and sulfamide substrates.

Substrate	Catalyst	Yield
13 (1 equiv)	2 mol% catalyst PhI(OAc) <sub>2</sub> , H <sub>2</sub> NSO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	Rh <sub>2</sub> (O <sub>2</sub> C <sup>t</sup> Bu) <sub>4</sub> : 30% Rh <sub>2</sub> (esp) <sub>2</sub> : 71%
16	2 mol% Rh <sub>2</sub> (esp) <sub>2</sub> , PhI(OAc) <sub>2</sub> , H <sub>2</sub> NSO <sub>3</sub> CH <sub>2</sub> CCl <sub>3</sub>	equiv. 16: 1, yield: 31% equiv. 5: 5, yield: 84%

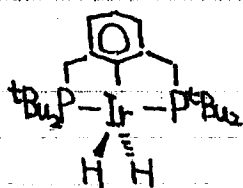
Figure 5. Intermolecular C-H insertion with catalytic Rh<sub>2</sub>(esp)<sub>2</sub>.

▲ Carried out @ 40°C

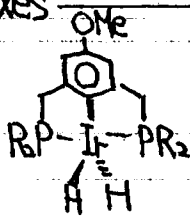
◀ Catalyst amount decreases & substrate generality is expanded.

Urea & sulfamide substrates — first examples

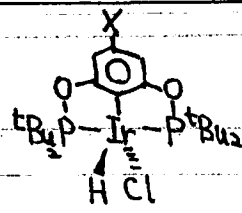
• Iridium PCP pincer complexes



C.M. Jensen et al.  
Chem. Commun., 1996, 2883



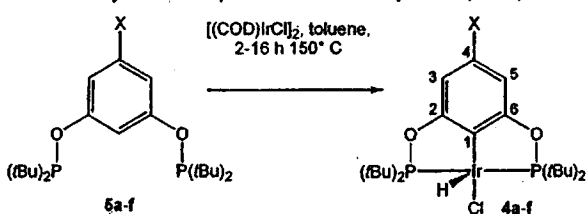
R = <sup>t</sup>Pr, <sup>t</sup>Bu  
A.S. Goldman et al.  
JACS, 2002, 124, 6797



X = MeO, Me, H, F, C<sub>6</sub>F<sub>5</sub>,   
M. Brookhart et al.  
JACS, 2004, 126, 1804

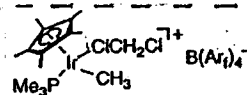
▲ These catalysts have long-term stability at 200°C & catalyze dehydrogenation of n-alkanes.

Scheme 3. Synthesis of p-XPCPIrHCl Complexes (4a-f)



X	4 [%] <sup>a</sup>
4a MeO	89
4b Me	87
4c H	93
4d F	93
4e C <sub>6</sub> F <sub>5</sub>	88
4f Ar <sup>F</sup>	93

<sup>a</sup> isolated yield



C-H activation @ 100°C (stoichiometric)!

See Yamatsugu's literature seminar 050119

◀ Prepared via C-H activation

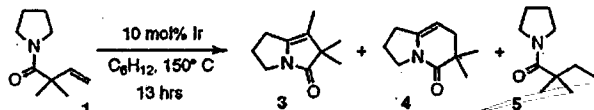
Cross-Coupling of sp<sup>3</sup> C-H Bonds and Alkenes: Catalytic Cyclization of Alkene-Amide Substrates

Brenton DeBoef, Stefan J. Pastine, and Dalibor Sames\*

Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027

JACS, 2004, 126, 6556

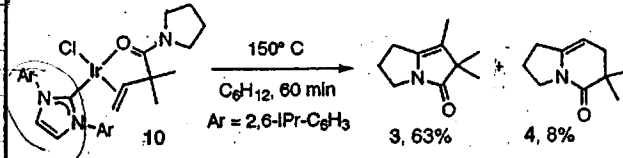
Table 1. Catalytic Oxidative Cyclization, Lead Discovery



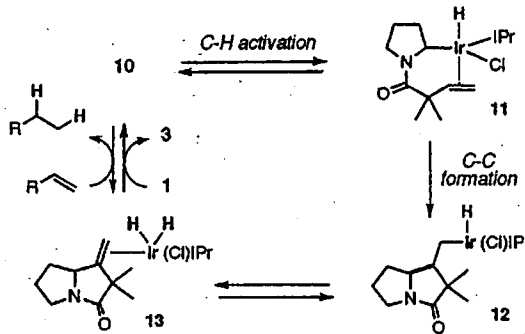
entry	complex	NMR yields <sup>a</sup>		
1	[Ir(COE) <sub>2</sub> Cl] <sub>2</sub> / PCy <sub>3</sub> (2 eq)	26	11	25
2	[Ir(COE) <sub>2</sub> Cl] <sub>2</sub> / IPr (2 eq)	41	4	41
3	[Ir(COE) <sub>2</sub> Cl] <sub>2</sub> / IPr (2 eq) + 4 eq NBE	66	17	10
4	(Cy <sub>3</sub> P) <sub>2</sub> Ir(Cl)H <sub>2</sub> , 6	9	0	20
5	(Cy <sub>3</sub> P) <sub>2</sub> Ir(CF <sub>3</sub> CO <sub>2</sub> )H <sub>2</sub> , 7	0	0	24
6		trace	0	trace
7		0	0	0

<sup>a</sup> Reported yields were determined by NMR using an internal standard (average of three runs). NBE, norbornene. Total loading of Ir catalyst was 10 mol %.

Scheme 1. Stoichiometric Reaction



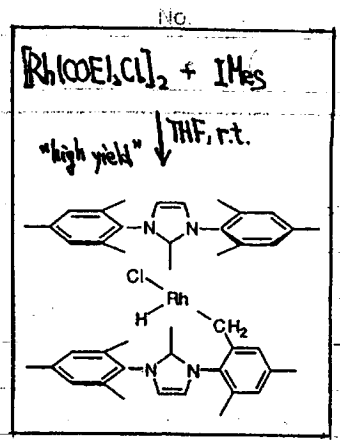
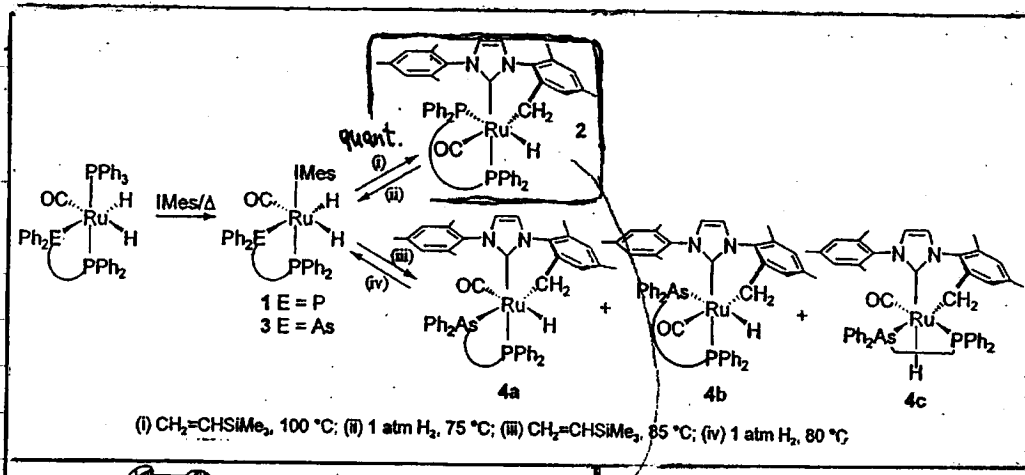
Scheme 2. Proposed Catalytic Cycle



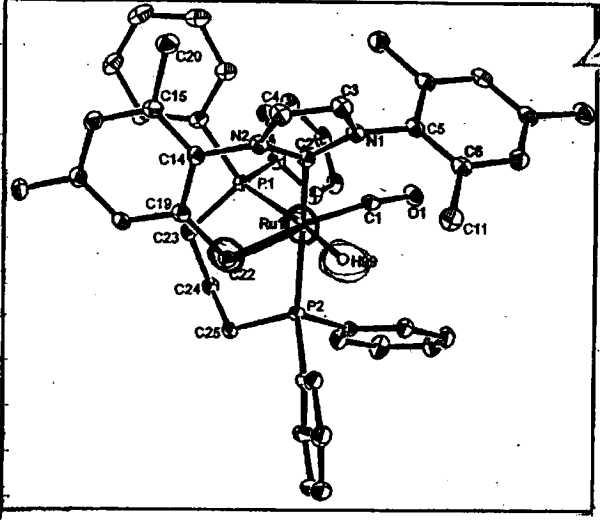
▲ N-Heterocyclic carbene - Ir complex in entry 3 improved the results.

— Why this complex worked well?

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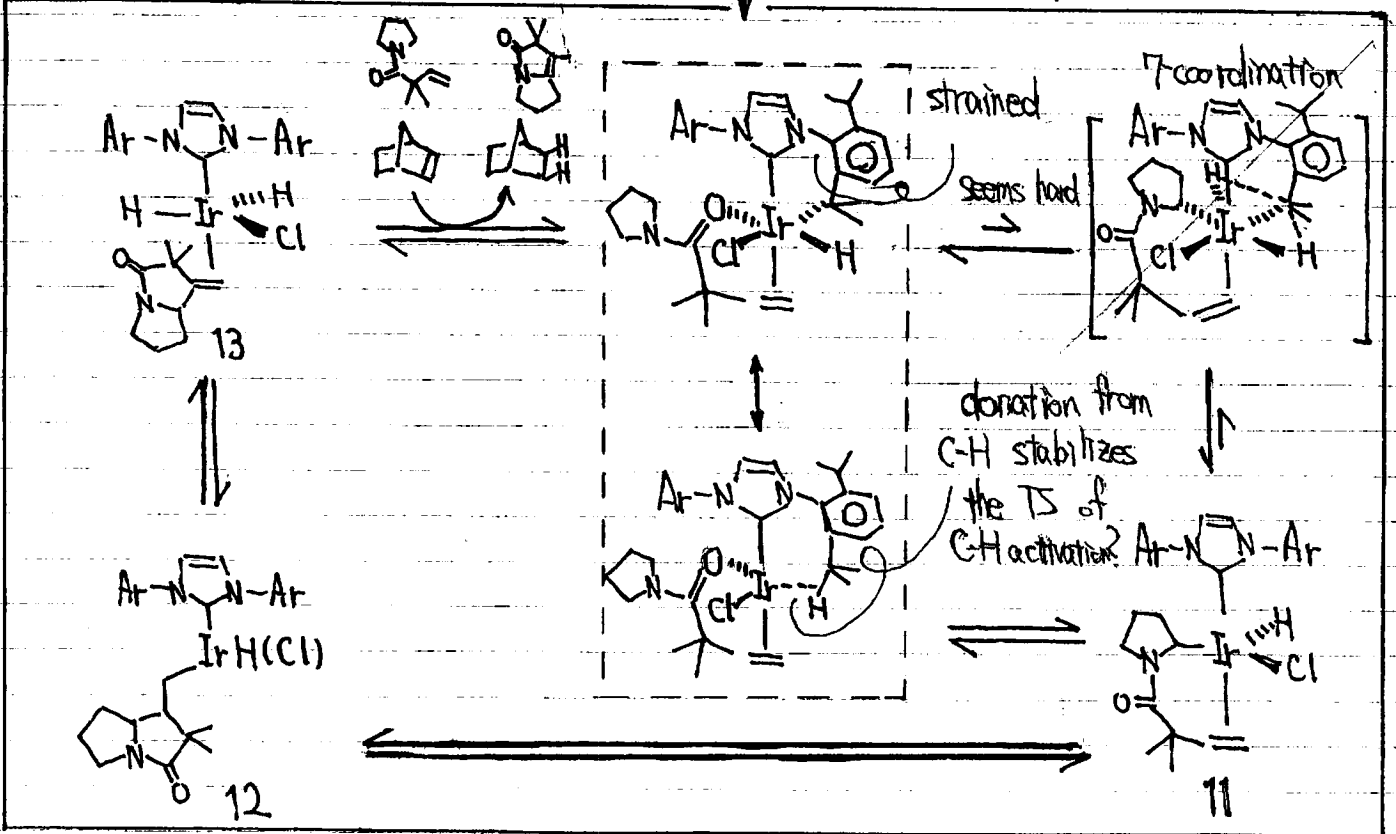
SP Nolan et al. Organometallics, 2000, 19, 1194



Several examples of intramolecular C-H activation of N-heterocyclic carbene complexes are known.

M.K. Whittney et al. Adv. Synth. Catal., 2003, 345, 1111

This intramolecular C-H activation facilitates the intermolecular one, too?



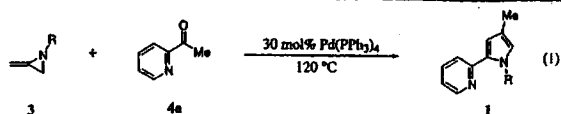
Pendant C-H ligands for C-H & other unactivated bonds activation?

**Synthesis of Pyridinylpyrrole Derivatives via the Palladium-Catalyzed Reaction of Acetylpyridines with Methyleneaziridines**

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Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

3. Activation of  $\alpha$ -C-H of carbonyl group  
JACS, 2004, 126, 13898



3a: R = CH<sub>2</sub>Ph  
3b: R = CH(Me)Ph  
3c: R = Hex  
3d: R = CH(Me)Cyclohexyl  
3e: R = CH<sub>2</sub>Ph(p-Cl)  
3f: R = CH<sub>2</sub>CH(OMe)<sub>2</sub>  
3g: R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OMe

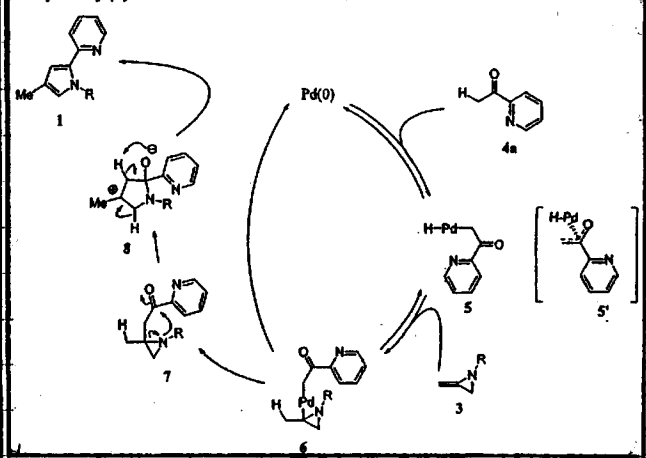
1a: R = CH<sub>2</sub>Ph  
1b: R = CH(Me)Ph  
1c: R = Hex  
1d: R = CH(Me)Cyclohexyl  
1e: R = CH<sub>2</sub>Ph(p-Cl)  
1f: R = CH<sub>2</sub>CH(OMe)<sub>2</sub>  
1g: R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OMe

**Table 1. Palladium-Catalyzed Reactions of o-Acetylpyridine 4a with the Methyleneaziridines 3<sup>a</sup>**

entry	3	product 1	yield of 1/% <sup>b</sup>
1	3a	1a	69
2	3b	1b	75
3	3c	1c	74
4	3d	1d	87
5	3e	1e	43
6	3f	1f	78
7	3g	1g	74

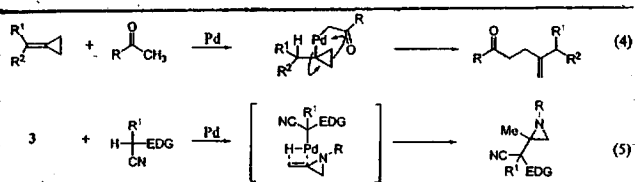
<sup>a</sup> The reaction of 3 (0.3 mmol) with 4a (0.6 mmol) was carried out in the presence of 30 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> without solvent at 120 °C for 3 days in a pressure vial under Ar atmosphere. <sup>b</sup> Isolated yield based on 3.

**Scheme 2. Plausible Mechanism for the Formation of o-Pyridinylpyrrole 1.**



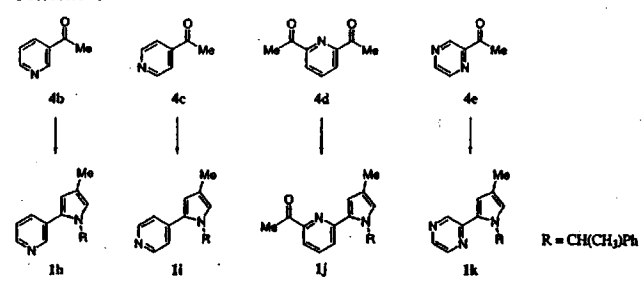
Chelation effect is not essential but the acidity of  $\alpha$ -C-H group is a key.

"O-H activation"



TL, 2002, 43, 2903  
TL, 2002, 43, 9625

**Scheme 1**

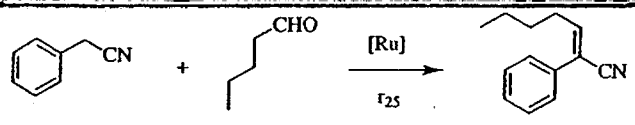


**Table 2. Palladium-Catalyzed Reactions of Various Acetylpyridines 4b-d and Acetylpyrazine 4e with 3b<sup>a</sup>**

entry	4	product 1	yield of 1/% <sup>b</sup>
1	4b	1h	72
2	4c	1i	88
3	4d	1j	72
4	4e	1k	96

<sup>a</sup> The reaction of 3b (0.3 mmol) with 4 (0.6 mmol) was carried out in the presence of 30 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> without solvent at 120 °C for 3 days. <sup>b</sup> Isolated yield based on 3b.

C-H activation could make it possible to selectively activate  $\alpha$ -C-H of CN in the presence of enolizable aldehyde.



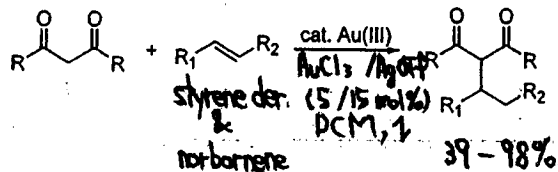
107                      108                      109 (98%)  
Scheme 25. Reaction conditions  $\tau_{25}$ : 3 mol % [RuH<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub>], THF, room temperature, 24 h.

S. I. Murahashi et al.  
Bull. Chem. Soc. Jpn., 1996, 69, 1805

8/11

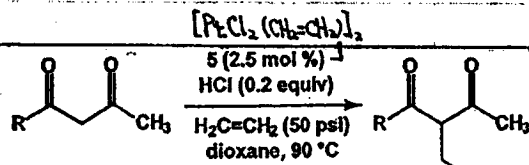
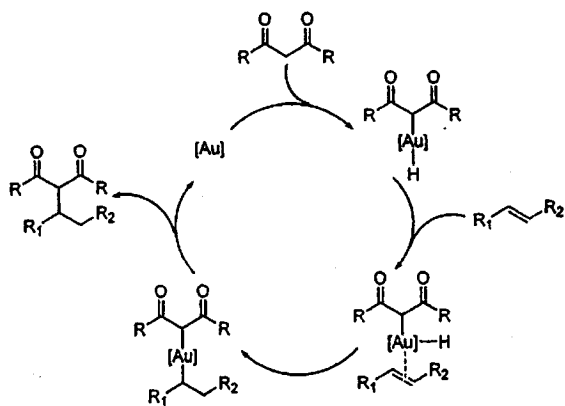
# cf. Catalytic alkylation reactions of 1,3-dicarbonyl compounds with unactivated olefins

Scheme 1. Addition of Activated Methylene to Alkenes



C.-J. Li et al. JACS, 2004, 126, 884

Scheme 2. Tentative Mechanism for the Gold-Catalyzed Addition Reaction



2 (R = n-C<sub>5</sub>H<sub>11</sub>)  
 R = Ph  
 R = 2-furyl

R.A. Wiedenhofer et al. Chem. Commun. 2004, 66

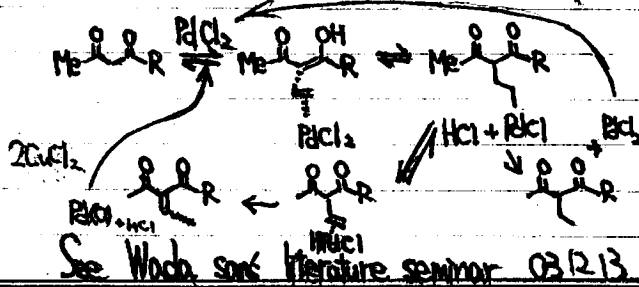
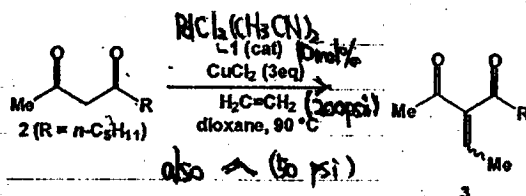
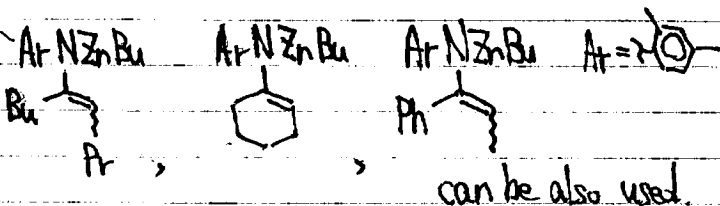


Table 1.  $\alpha$ -Alkylation of 3-Pentanone with Various Alkenes

entry	olefin	conditions	product <sup>a</sup>	% yield
1	1	1 atm, hexane 60 °C, 12 h	10	94 <sup>b</sup>
2	2	1 atm, hexane 65 °C, 60 h	11 12	88 <sup>b</sup>
3	3 n-Hex	1.2 eq, hexane 65 °C, 12 h	13 14 <sub>syn</sub>	92 <sup>d</sup>
4	4 Ph	1.2 eq, hexane 30 °C, 12 h	15 16 <sub>syn</sub>	90 <sup>d</sup>
5	5	3.0 eq, neat 65 °C, 72 h	17	77 <sup>c</sup>
6	6	4 atm, neat 65 °C, 60 h	18	85 <sup>b</sup>
7	7	5 atm, neat 80 °C, 36 h	19	84 <sup>b</sup>

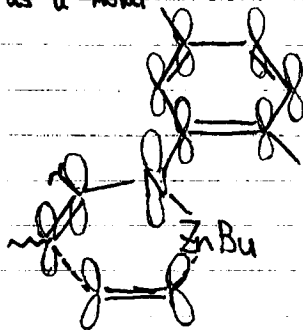
<sup>a</sup> Regioselectivity of the carbocation was >99:1 unless otherwise noted. <sup>b</sup> Determined by GC analysis with decane or tridecane as internal standard. <sup>c</sup> Isolated yield. <sup>d</sup> Syn:anti = 67:33. \* Linear (13):branched (14) = 46:54, syn:anti = 66:34.



Stoichiometric amount of base, but very reactive.

- "Bu" ligand on Zn
- "Ar" with electron donating group
- "Zn" as a metal

seem important.



"Bu", instead of Cl, & electron donating groups on "Ar" both enhance the affinity for olefin substrates?

E. Nakamura et al. JACS, 2004, 126, 11817



**CuBr-Catalyzed Efficient Alkynylation of sp<sup>3</sup> C-H Bonds Adjacent to a Nitrogen Atom**

Zhiping Li and Chao-Jun Li\*

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, Quebec H3A 2K6, Canada

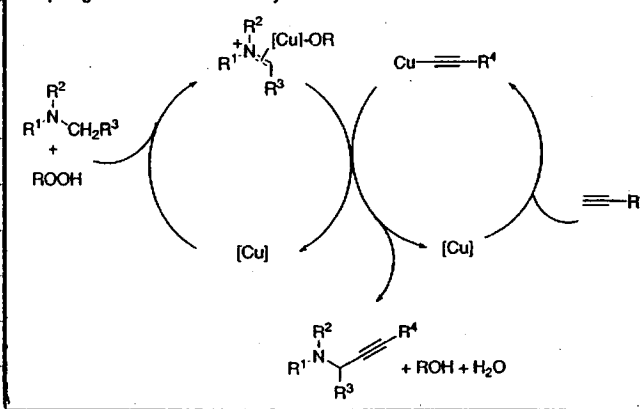
4. Activation of  
N-Csp<sup>3</sup>-H  
JACS, 2004, 126, 11810

Table 2. Copper-Catalyzed Alkynylation of Amines<sup>a</sup>

entry	Ar	R	product	yield <sup>b</sup>
1	Ph	Ph	3a	74
2	Ph	4-MeOPh	3b	82
3	Ph	4-McPh	3c	74
4	Ph	4-BrPh	3d	74
5	Ph	4-PhPh	3e	60
6	Ph	2-Py	3f	36
7	Ph	HOCH <sub>2</sub>	3g	40
8	Ph	EtCOOCH <sub>2</sub>	3h	58
9	Ph	CH <sub>3</sub> OCO	3i	25
10	Ph	Bu	3j	12
11	4-McPh	Ph	3k	73
12	2-McPh	Ph	3l	53
13	4-BrPh	Ph	3m	69

<sup>a</sup> 4.0 mmol amine, 2.0 mmol alkyne, 0.1 mmol copper bromide, and 0.4 mL BuOOH (5–6 M in decane). <sup>b</sup> Isolated yields were based on alkynes.

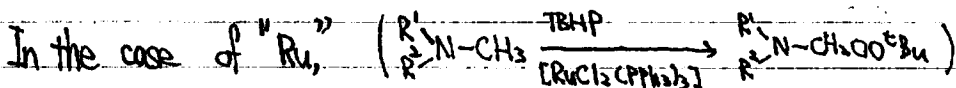
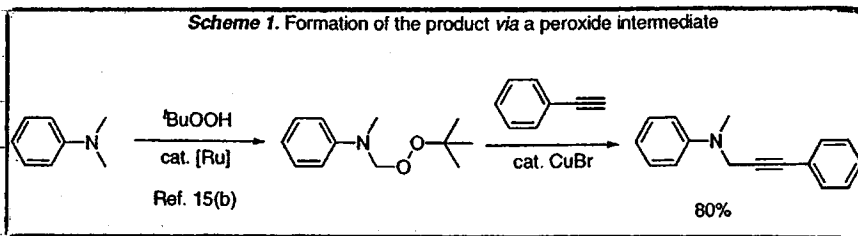
Scheme 5. Tentative Mechanism for the Direct Oxidative Coupling of Amine with Alkyne



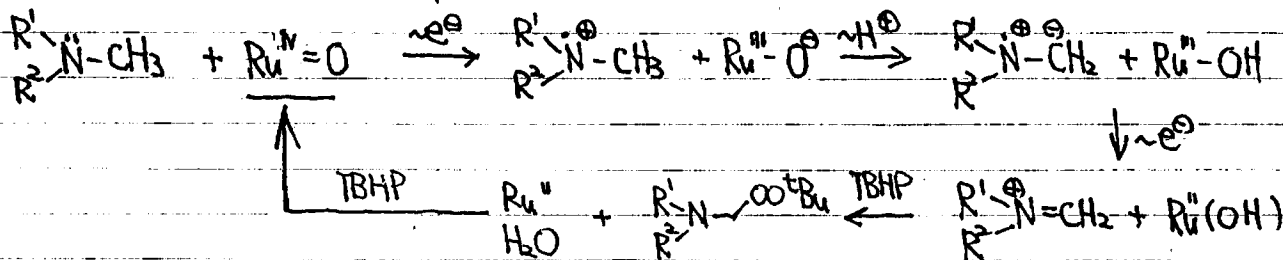
or they also propose

▲ Up to 82% y.

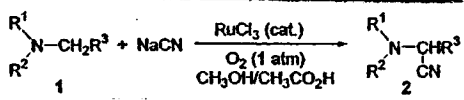
Hydrolysis of iminium cation intermediate takes place?



Electron transfer x 2 & deprotonation (In this case, too?)



S.-I. Murahashi et al., JACS, 1988, 110, 8256



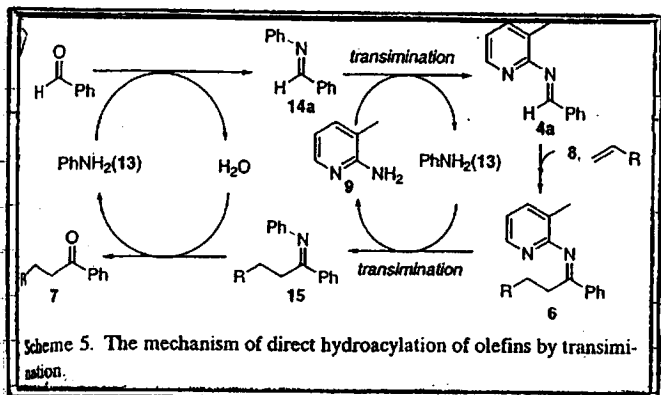
◀ <sup>-</sup>CN as nucleophile  
S.-I. Murahashi et al., JACS, 2003, 125, 15312

10/11

No.

# APPENDIX

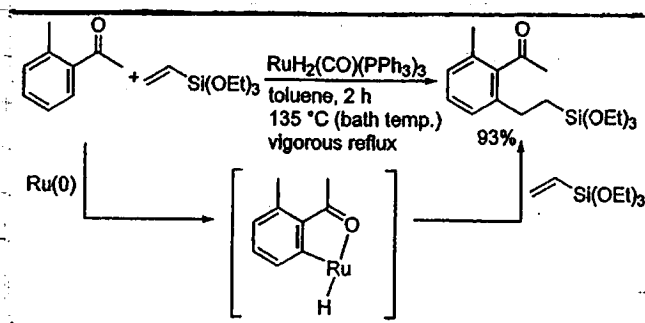
## 1. HYDROACYLATION



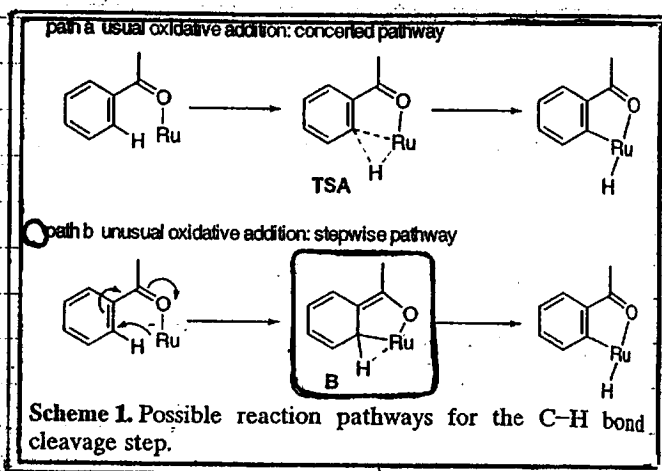
◀ The most advanced system for C-H Jun's hydroacylation

(Transimination is effective to facilitate the formation of 4a, which is otherwise the rate-determining step.)

## 2. MECHANISM (S. Murai's aromatic C-H/olefin coupling reaction)



Nature, 1993, 366, 529



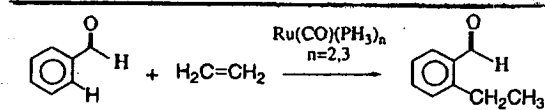
On the basis of *ab initio* theoretical calculations, path b is reasonable.

Metalacycle B is the key.

Activation energy for path a — 20.1 kcal/mol

path b — 1.8–3.0 kcal/mol

The model reaction is



As is often the case in theoretical calculations, this reaction would proceed hardly.

Decarbonylation should occur.

K. Morokuma et al., JACS, 1998, 120, 2692

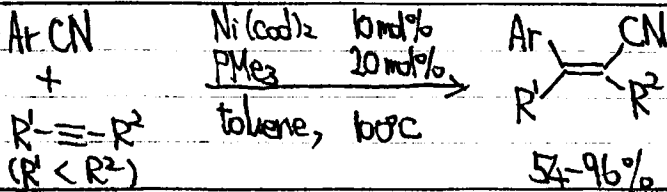
# 3. C-C ACTIVATION

JACS, 2004, 126, 13904

## Nickel-Catalyzed Arylcyanation of Alkynes

Yoshiaki Nakao,\* Shinichi Oda, and Tamejiro Hiyama\*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan



Alkynyl cyanide — N.R.

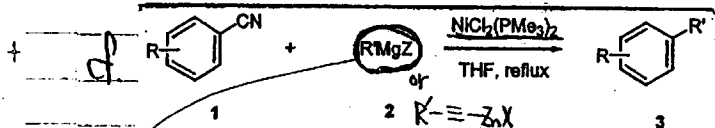
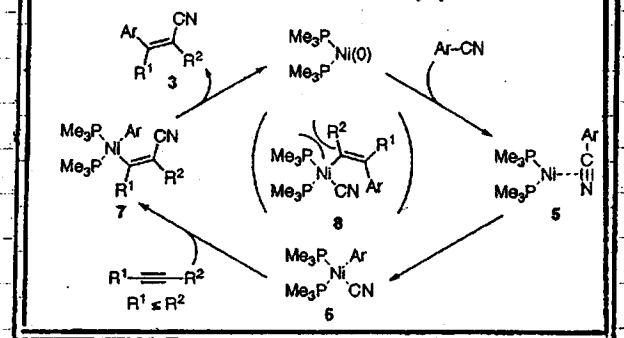
Terminal alkynes — oligomerization

Table 1. Arylcyanation of 4-Octyne

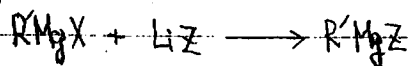
entry	catalyst	solvent	yield of 3a (%) <sup>a</sup>
1	Ni(cod) <sub>2</sub> /2 PMe <sub>3</sub>	toluene	84 (80) <sup>b</sup>
2	(Me <sub>3</sub> P) <sub>2</sub> NiCl <sub>2</sub> /2 DIBAL-H	toluene	80
3	Ni(cod) <sub>2</sub> /2 PMe <sub>2</sub> Ph	toluene	76
4	Ni(cod) <sub>2</sub> /2 PMePh <sub>2</sub>	toluene	44
5	Ni(cod) <sub>2</sub> /2 PPh <sub>3</sub>	toluene	31
6	Ni(cod) <sub>2</sub> /2 PBu <sub>3</sub>	toluene	30
7	Ni(cod) <sub>2</sub> /2 PCy <sub>3</sub>	toluene	35
8	Ni(cod) <sub>2</sub> /2 P( <i>t</i> -Bu) <sub>3</sub>	toluene	13
9	Ni(cod) <sub>2</sub> /2 PMe <sub>3</sub>	1,4-dioxane	60
10	Ni(cod) <sub>2</sub> /2 PMe <sub>3</sub>	DMF	47

<sup>a</sup> Determined by <sup>19</sup>F NMR using 4-F<sub>3</sub>C-C<sub>6</sub>H<sub>4</sub>-I as an internal standard.  
<sup>b</sup> Isolated yield.

Scheme 1. Plausible Mechanism of the Arylcyanation



Scheme 1. Nickel(0) promoted cross-coupling of alkyl- and alkenylmagnesium reagents and benzonitriles (see Table 1).



(R' = Ar, alkenyl; Z = *t*Bu, SPh)

See Akiba's literature seminar 030521

J.A. Miller et al., *JL*, 2001, 42, 6991 /  
*JL*, 2003, 44, 1907 / *JL*, 2004, 45, 4989

\* The same catalyst as Hiyama's case is used, but in this case -CN is only a leaving group, which can be substituted by halogens.

C-C activation is generally more difficult than C-H activation.

BDE (M-H) > BDE (M-C)

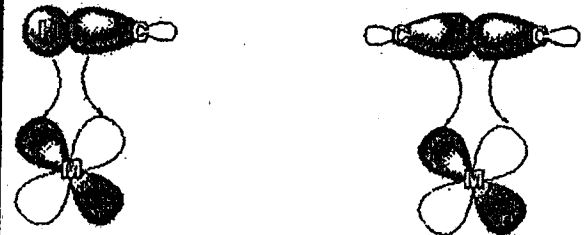
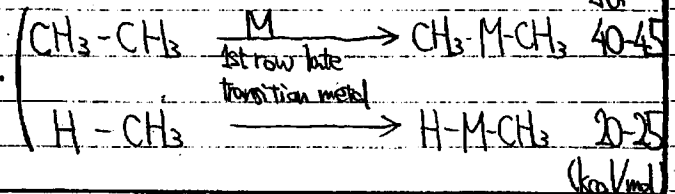
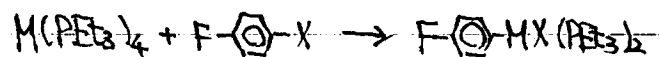


Figure 1. Schematic representation of R-H (left) and R-R bond cleavage (right) showing the influence of C-C and C-H orbital directionality on the oxidative addition process.

But from the reactions



(M = Ni, Pd, Pt; X = Cl, Br, I, CN)

the reaction rates I > Br > Cl > CN >> F

Angew. Chem. Int. Ed., 1999, 38, 870 / JACS, 1974, 96, 2360