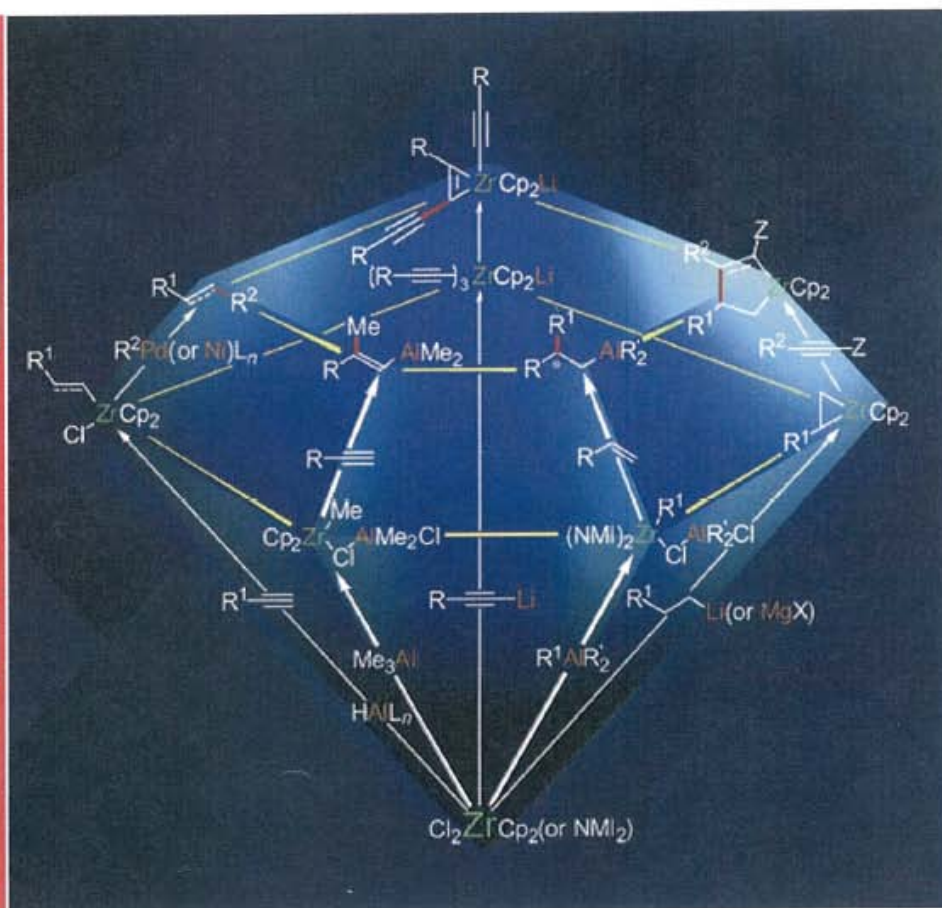
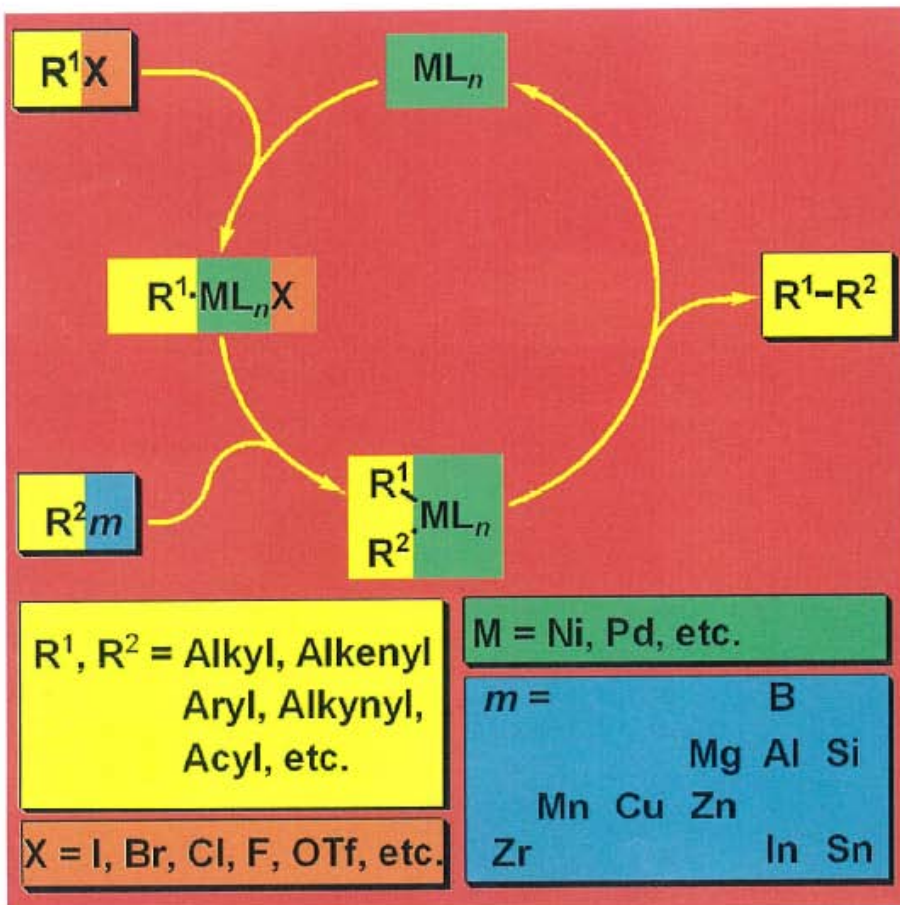


# Magical Power of Transition Metals: Past, Present, and Future

Ei-ichi Negishi, Purdue University



# How to Synthesize Any Organic Compounds in High Yields, Efficiently, Selectively, Economically, Safely



1. **Consider all usable elements (ca. 70).**

Avoid (i) radioactive, (ii) inert, and (iii) inherently toxic elements.

2. If desirable and necessary, **consider their binary combinations (ca. 5,000).**  
(Two is Better than One!)<sup>a</sup>

3. **Use metals for desirable reactivities.**


4. **Use transition metals mainly as catalysts.**


<sup>a</sup> E. Negishi, *CEJ* 1999, 5, 411-420.

# Anatomy of the Periodic Table

H																	He	
Li	Be											B	C	N	O	F	Ne	
Na	Mg											Al	Si	P	S	Cl	Ar	
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr	
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe	
Cs	Ba											Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra											Rf	Db	Sg	Bh	Hs	Mt	Unn
		La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu		
		Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr		

 = Radioactive elements (26)

 = Organic elements  
(12 - 1 = 11)

 = Main group metals (27 - 6 = 21)

 = Intrinsically toxic (?) (7)

 = d-Block transition metals (24 - 1 = 23)



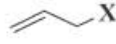






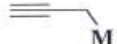
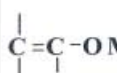
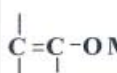
 = Inert gases (5)

**58 metals usable  
in Organic Synthesis**

 = f-Block transition metals (15 - 1 = 14)

# Scope and Limitations of Uncatalyzed Cross-Coupling with Grignard Reagents and Organoalkali Metals



$R^1M \backslash R^2X$	ArX						Alkyl X	RCOX
ArM	<ul style="list-style-type: none"> <li>These reactions do not proceed except in special cases.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	Limited scope Needs special procedures	Needs special procedures
								
								
								
								
								
Alkyl M								
$N \equiv C-M$								
								
$N \equiv C-M$	<ul style="list-style-type: none"> <li>Capricious and often nonselective</li> <li>Special procedures are better but need much improvement. <i>major</i></li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	Limited scope Needs special procedures	Needs special procedures	
$N \equiv C-M$								
	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	<ul style="list-style-type: none"> <li>Some work but they are of limited scope.</li> </ul>	Limited scope Needs special procedures	Needs special procedures	
$N \equiv C-M$								

Note: Cu-promoted and Cu-catalyzed reactions have provided some satisfactory procedures.








Conventional Wisdom: **Avoid Cross-Coupling! But, should we?**

# LEGO Game Approach to C—C Bond Formation via Pd-Catalyzed Cross-Coupling Reactions

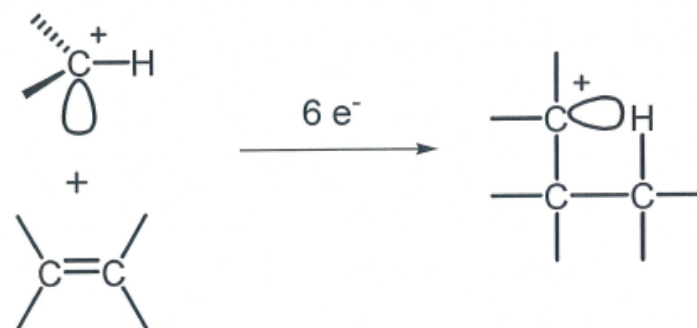
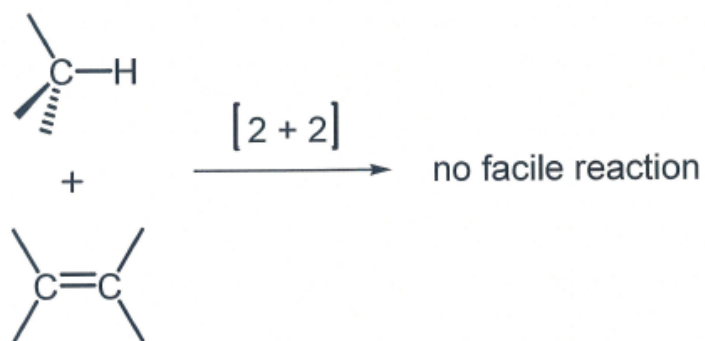


$R^1, R^2 = \text{C group}$ . See below.  $M = \text{Mg, Zn, B, Al, In, Si, Sn, Cu, Mn, Zr, etc.}$   $X = \text{I, Br, Cl, F, OTs, OTf, etc.}$

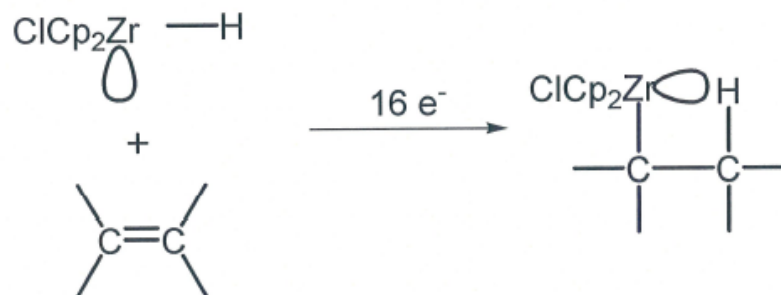
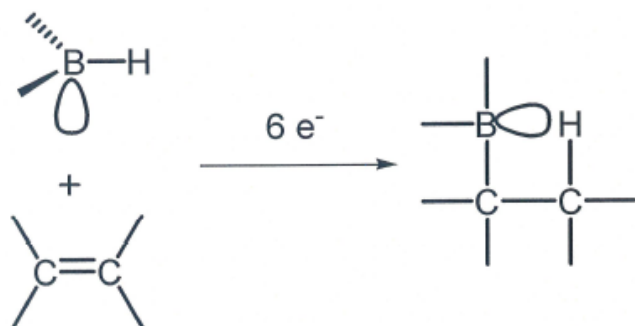
$M$  &  $X = \text{Regio- \& stereo-specifiers, which permit a genuine LEGO Game avoiding addition-ELIMINATION !!!}$

$R^1M \backslash R^2X$	$ArX$				$Ar-X$		Alkyl X	RCOX
$ArM$				$ArM + \text{alkenyl-X}$			Little known until recently	
		Alkenyl-alkenyl coupling	$\text{alkenyl-M} + \text{alkynyl-X}$	$\text{alkenyl-M} + \text{alkenyl-X}$				
$\equiv M$			Alkynyl-alkenyl coupling	Recently developed Satisfactory			Recent results promising	
	Use alternate routes. Follow the arrow						Consider also uncatalyzed and Cu-, Ni-, or Fe-catalyzed processes	
$Ar-M$								
								
Alkyl M							Consider Alkyl M as alternatives	
$N \equiv C-M$								
$\text{C}=\text{C}-OM$	Use of $\alpha$ -haloenones as enolate equivalents should be considered			Tsuji-Trost Reaction		Tsuji-Trost Reaction		

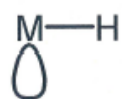
# Why Metals?



$\text{C}^+$  -- short-lived, uncontrolled



Bottom line:

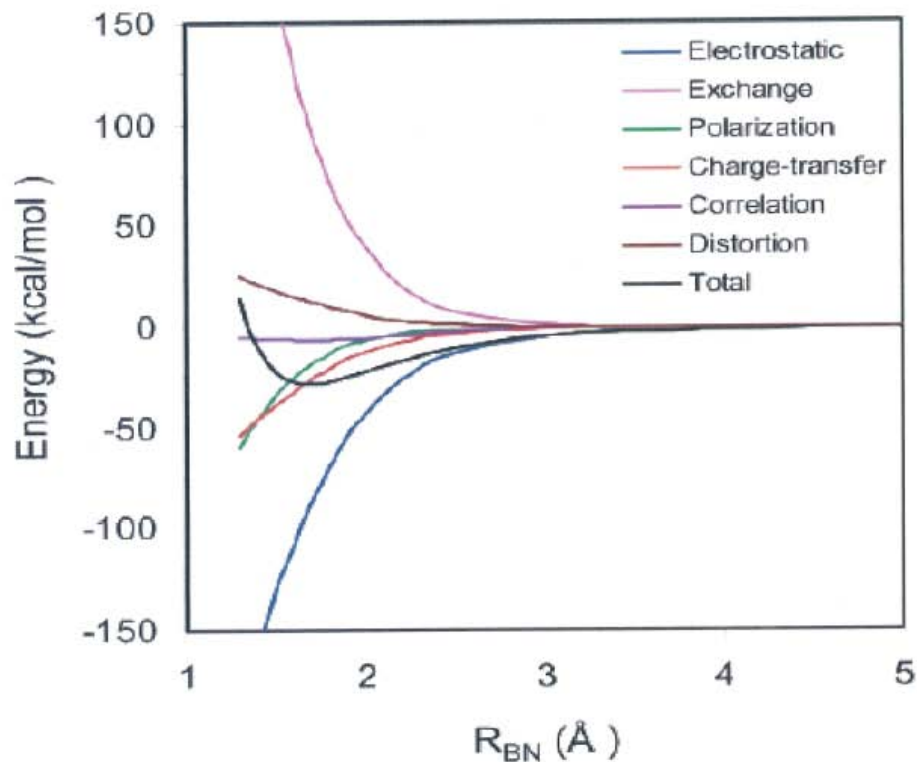


# Intermolecular Interaction in Donor-Acceptor Complexes



$$\Delta E_{\text{int}} = \Delta E_{\text{es}} + \Delta E_{\text{ex}} + \Delta E_{\text{pol}} + \Delta E_{\text{ct}} + \Delta E_{\text{c}} + \Delta E_{\text{dist}}$$

**Interaction** = Electrostatic + Exchange Repulsion + Polarization  
+ Charge Transfer + Correlation + Geometry Distortion



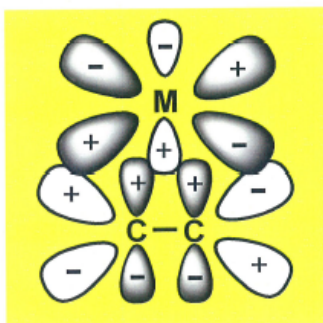
# 'Why d-Block Transition Metals ?

## Two Major Reasons (#1)

### I. Simultaneous Availability of Empty and Filled Non-bonding Orbitals (LUMOs and HOMOs)

**Note 1:** Strong Affinity toward  $\pi$ -Bonds Explained and Expected.

**Note 2:** Highly Reactive and yet **Stable, and Reversible.** ("**Super-Carbenoidal**")



- M. J. S. Dewar
- K. Fukui
- R. Hoffmann
- R. B. Woodward

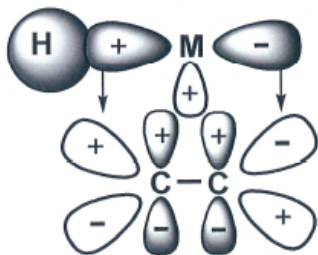


**Note:** This has been applied to 1,5-diene synthesis as detailed later.

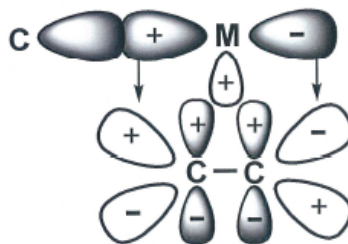
**Note 3:** Non-bonding Orbitals can be substituted with  $\sigma$ -Orbitals ("**Elemento-metalation**")

(These are available to main group metals as well. The only key requirement --- an empty orbital.)

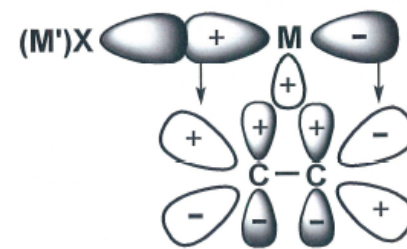
Hydrometalation



Carbometalation



Hetero(Metallo)metalation



The significance of **concerted synergistic** (HOMO-LUMO & HOMO-LUMO) bonding cannot be overemphasized.

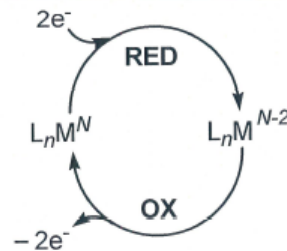


# Why d-Block Transition Metals ?

## Two Major Reasons (#2)

### II. Ready and Reversible Reduction and Oxidation under One Set of Reaction Conditions !

- Essential to REDOX Catalysis
- Very difficult to devise REDOX Catalysis without using transition metals.

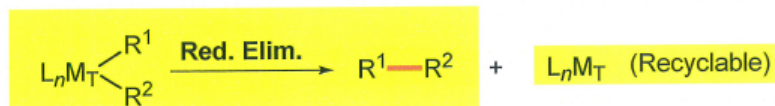


## Four Basic Processes of C-C (and C-X) Bond Formation with Transition Metals

### (1) Reductive Elimination

Ex. Pd- or Ni-cat. cross-coupling

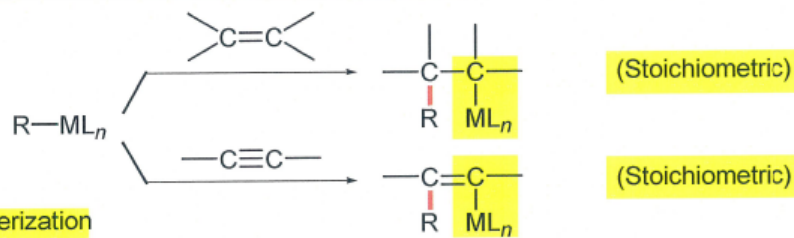
(LEGO Game Approach)



### (2) Carbometalation<sup>a,b</sup>

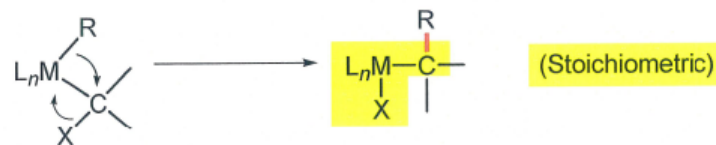
Ex. Ziegler-Natta polymerization

- Reppe and Wilke alkyne- and diene cyclooligomerization
- Olefin metathesis



### (3) Migratory Insertion<sup>a,b</sup>

Ex. Oxo and other carbonylation reactions



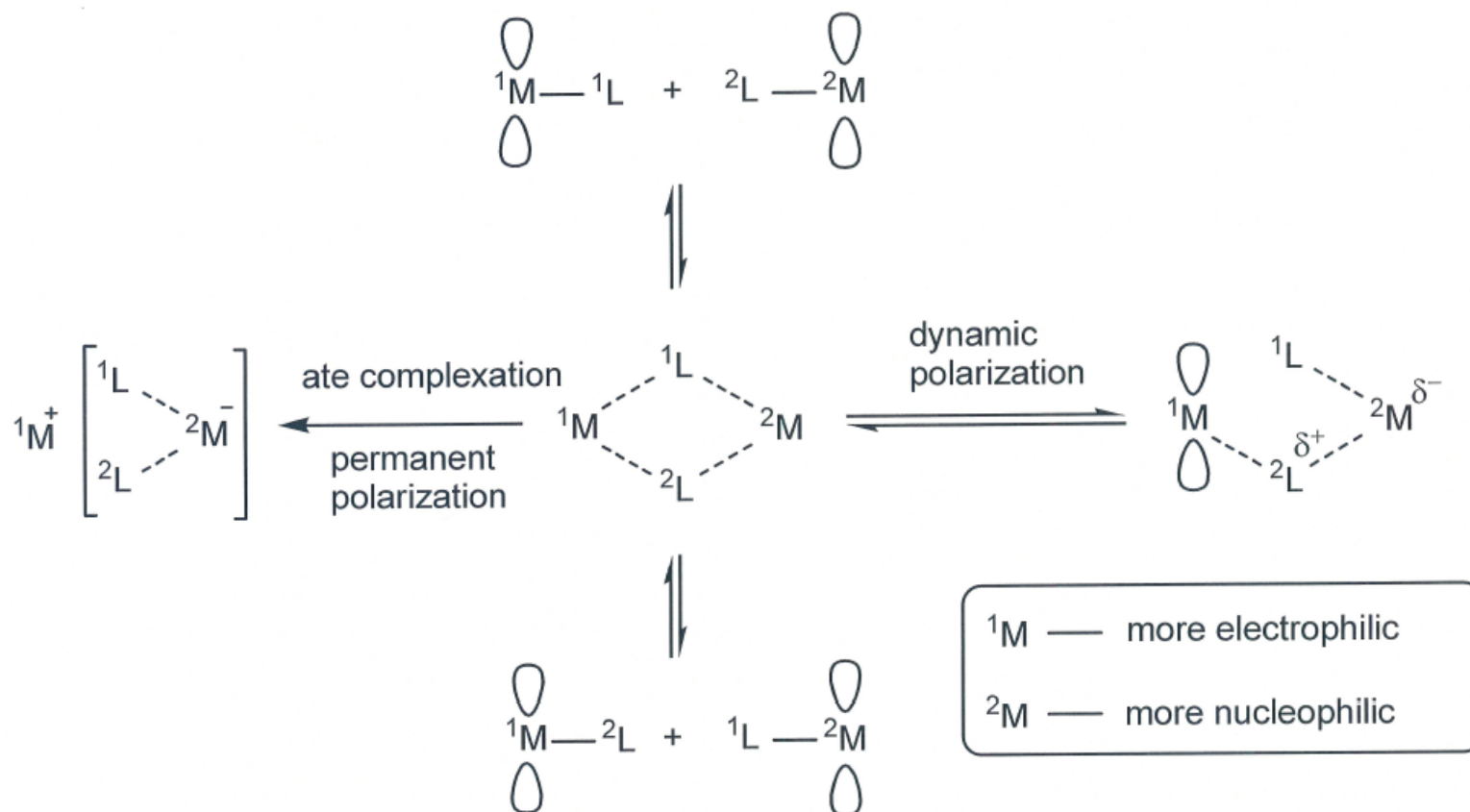
### (4) Nucleophilic and Electrophilic Attack on Ligands<sup>a</sup>

Ex. Wacker oxidation

- Tsuji-Trost reaction

**Note:** (a) Missing links must be provided for catalysis.  
 (b) Main group metals also work but not catalytically.

# Interactions between Two Coordinatively Unsaturated Metal Species



**Bottom line:** Two is better than one

# Genealogy of Pd-Catalyzed Cross-Coupling

## Several Independent Discoveries(1975-1979)

**Mg:** S. I. Murahashi, N. Ishikawa,  
J. F. Fauvarque (1975 & 1976)  
(Following **Mg-Ni** version of  
Tamao, Kumada and Corriu, 1972)

**Al, Zn, Zr:** E. Negishi (1976-1977)

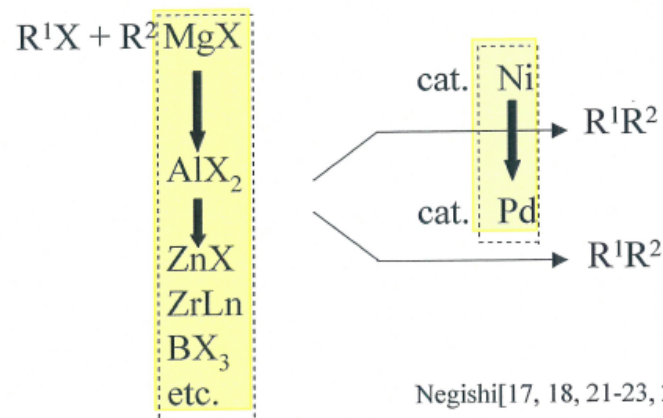
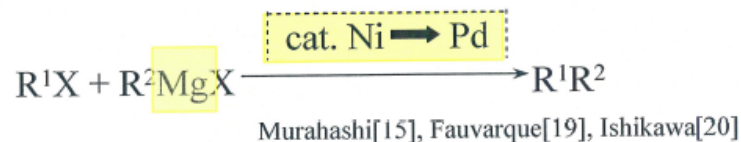
**B:** E. Negishi (1978) → A. Suzuki (1979)

**Sn:** M. Kosugi (1977) → J. K. Stille (1978)

Other metals: **Li, Na, K, Cu, In, Si, Mn**

### Negishi group contributions:

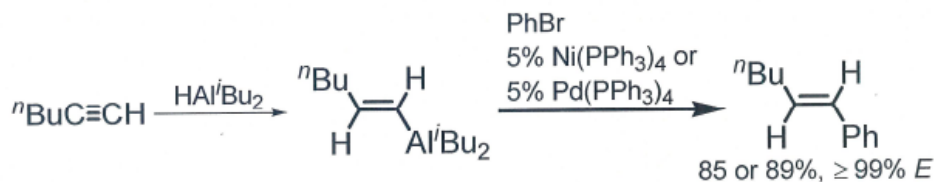
1. Co-discovery of Pd-Catalyzed Cross-Coupling
2. Discovery of Al, B, Zn, Zr, etc. as Effective Metal Counteranions
3. Discovery of Hydrometallation—Cross-Coupling & Carbometallation—Cross-Coupling Tandem Reactions
4. Discovery of Double Metal Catalysis, especially with  $ZnX_2$



• Negishi, E., *J. Organomet. Chem.* **2002**, 653, 34.

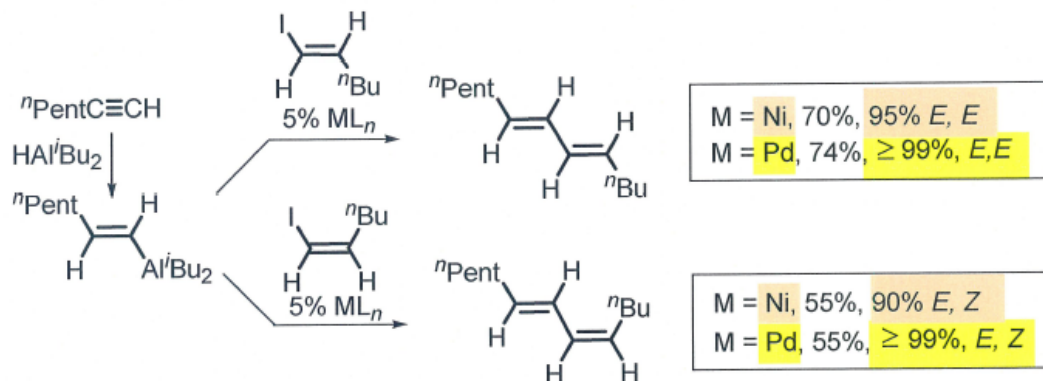
• Negishi, E., Ed., *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002**, Wiley, Part III, pp 285-1119.

# First Highly Selective and General Pd-catalyzed Cross-Coupling Route to Conjugated Dienes (1976-1979)



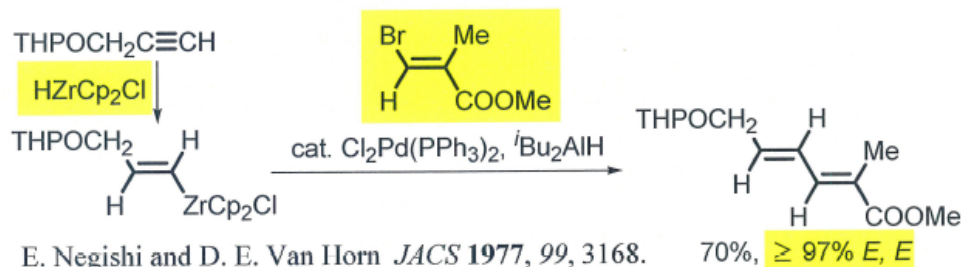
E. Negishi and S. Baba *CC* **1976**, 596.

- Pd was used, but no advantage over Ni revealed.
- First Al – Ni or Al – Pd reaction.
- First hydrometallation – cross-coupling tandem process.



S. Baba and E. Negishi *JACS* **1976**, 98, 6729.

- First highly (>98%) selective and general synthesis of conjugated 1,3-dienes.
- Some distinct advantages of Pd over Ni in cross-coupling shown for the first time.
- First Zr – Ni or Zr – Pd reaction

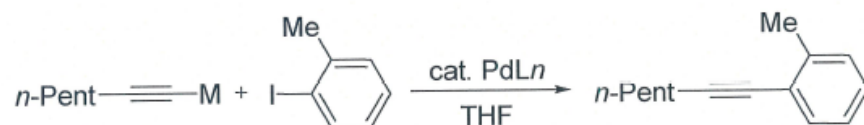


E. Negishi and D. E. Van Horn *JACS* **1977**, 99, 3168.

E. Negishi et al. *TL* **1978**, 19, 1027.

**Bottom Line:** (a) Superior selectivity associated with Pd over Ni reported for the first time.  
 (b) Discovery of the hydrometallation–cross-coupling tandem process.

# First Systematic Screening of Metal Counteranions



Entry	M of $n\text{-PentC}\equiv\text{CM}$	Reaction Cond. <sup>a</sup>		Product Yield (%)	Residual Ar-I (%)
		Temp (°C)	Time (h)		
1	Li	22	1	trace	88
2	Li	22	24	30	80
3	Na	reflux	24	58	41
4	MgBr	22	1	29	55
5	MgBr	22	24	49	33
6	ZnCl	22	1	91	8
7	ZnCl	22	3	88	2
8	HgCl	22	1	trace	92
9	HgCl	reflux	6	trace	88
10	BBu <sub>3</sub> Li	22	3	10	76
11	BBu <sub>3</sub> Li	reflux	1	92	5
12	AlBu <sub>3</sub> Li	22	3	4	80
13	AlBu <sub>3</sub> Li	reflux	1	38	10
14	AlBu <sub>2</sub>	22	3	49	46
15	SiMe <sub>3</sub>	reflux	1	trace	94
16	SnBu <sub>3</sub>	22	1	75	14
17	SnBu <sub>3</sub>	22	6	83	6
18	ZrCp <sub>2</sub> Cl	reflux	3	0	80

→ Negishi Coupling

→ Suzuki Coupling

→ Stille Coupling

"Aspects of Mechanism and Organometallic Chemistry", J. H. Brewster, Ed.,  
Plenum Press, New York, 1978.

SELECTIVE CARBON-CARBON BOND FORMATION *via* TRANSITION METAL

CATALYSIS: IS NICKEL OR PALLADIUM BETTER THAN COPPER?

Ei-ichi Negishi

Department of Chemistry, Syracuse University

Syracuse, New York 13210

[I wish to dedicate this paper to my former mentor, Professor H. C. Brown of Purdue University, on the occasion of his 66th birthday.]

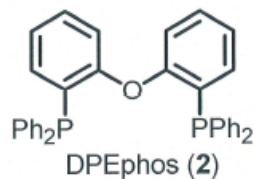
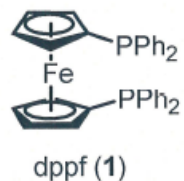
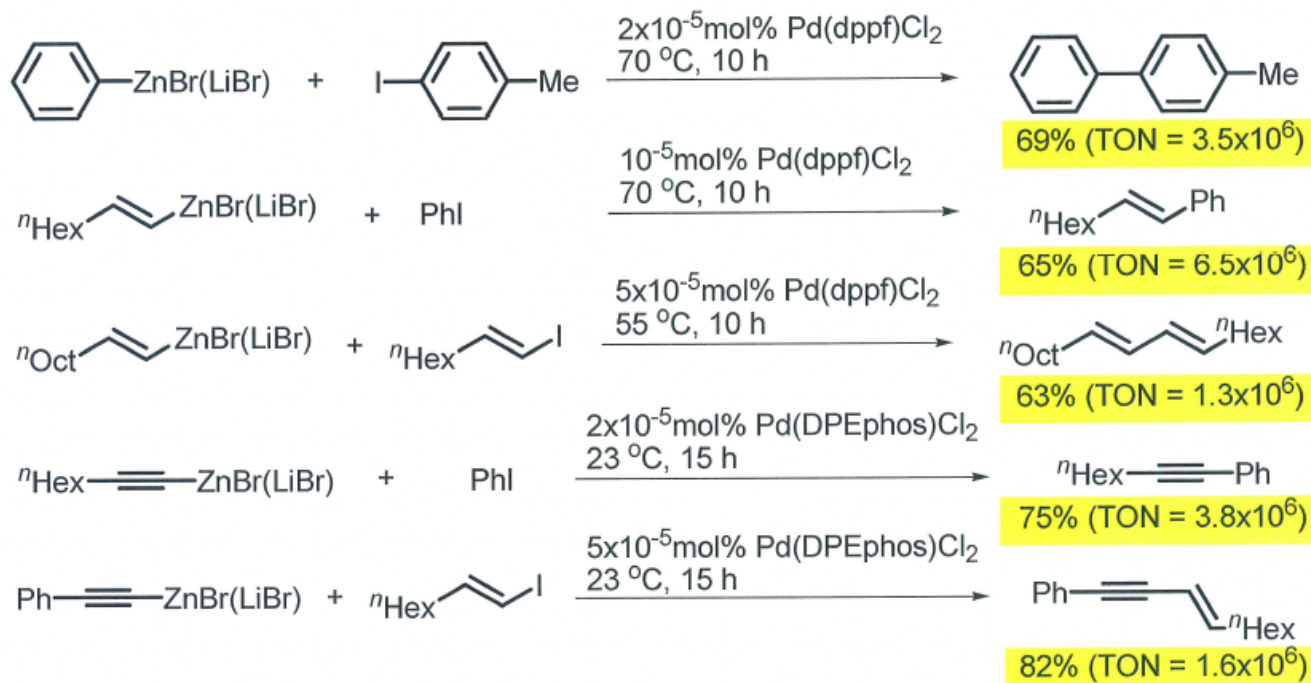
#### INTRODUCTION

The cross-coupling reaction involving the interaction of organometallic species, such as those containing lithium and magnesium, with organic halides and related electrophilic derivatives represents one of the most straightforward methods of carbon-carbon bond formation (eq 1).



Despite its inherent simplicity, however, its synthetic utility had been rather limited until the mid-1960s, due to various complications, such as competitive elimination and halogen-metal exchange reactions and the general lack of chemoselectivity.

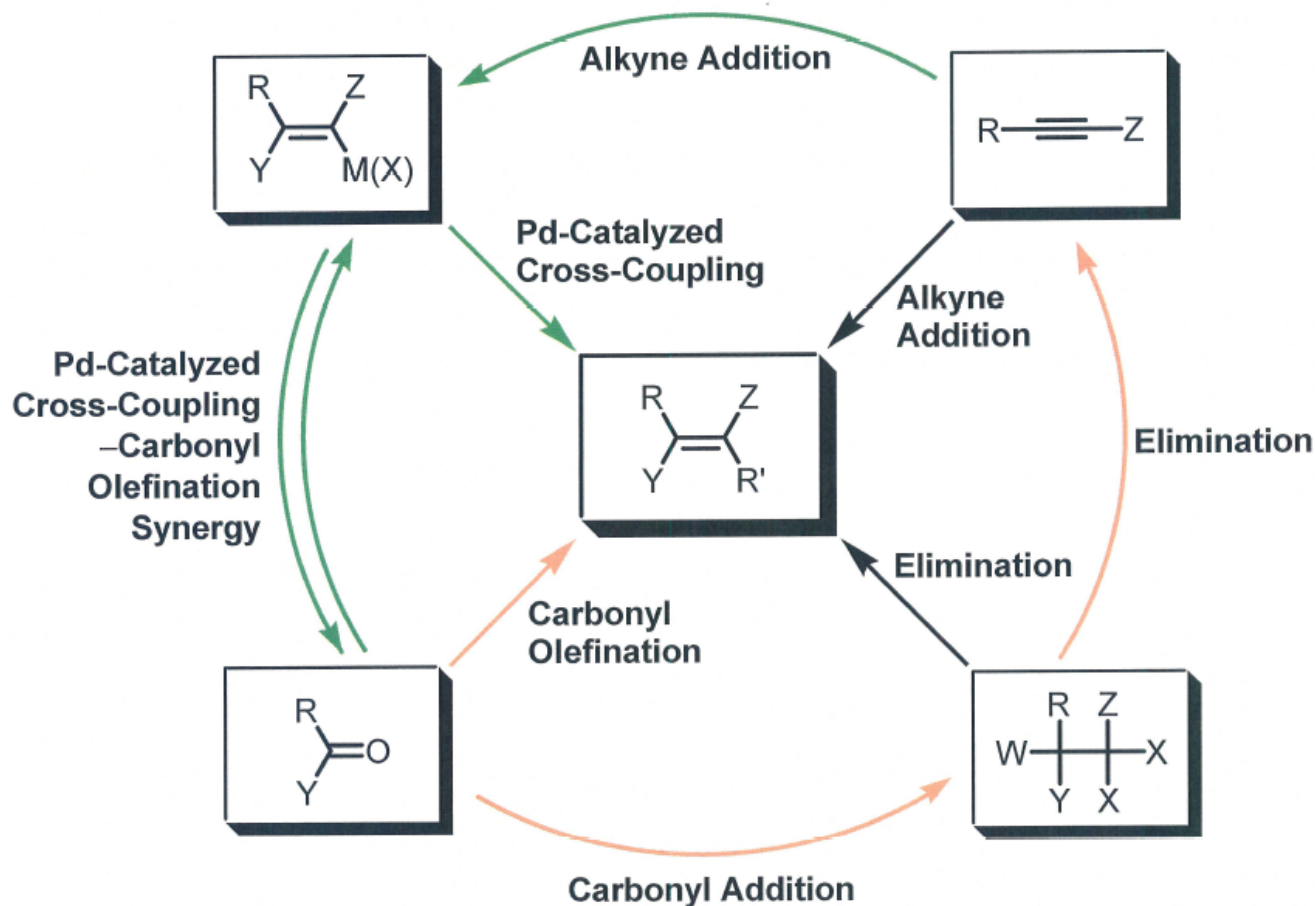
# High Turnover Numbers Observed in the Pd-Catalyzed Cross-Coupling with Pd(dppf)Cl<sub>2</sub> or Pd(DPEphos)Cl<sub>2</sub> as a Catalyst



**Bottom Line:** Use of **Zn** and **chelating ligands** can lead to **very high TONs**.

# How to Synthesize any Alkenes\* Efficiently and Selectively

\*Mostly acyclic alkenes considered.



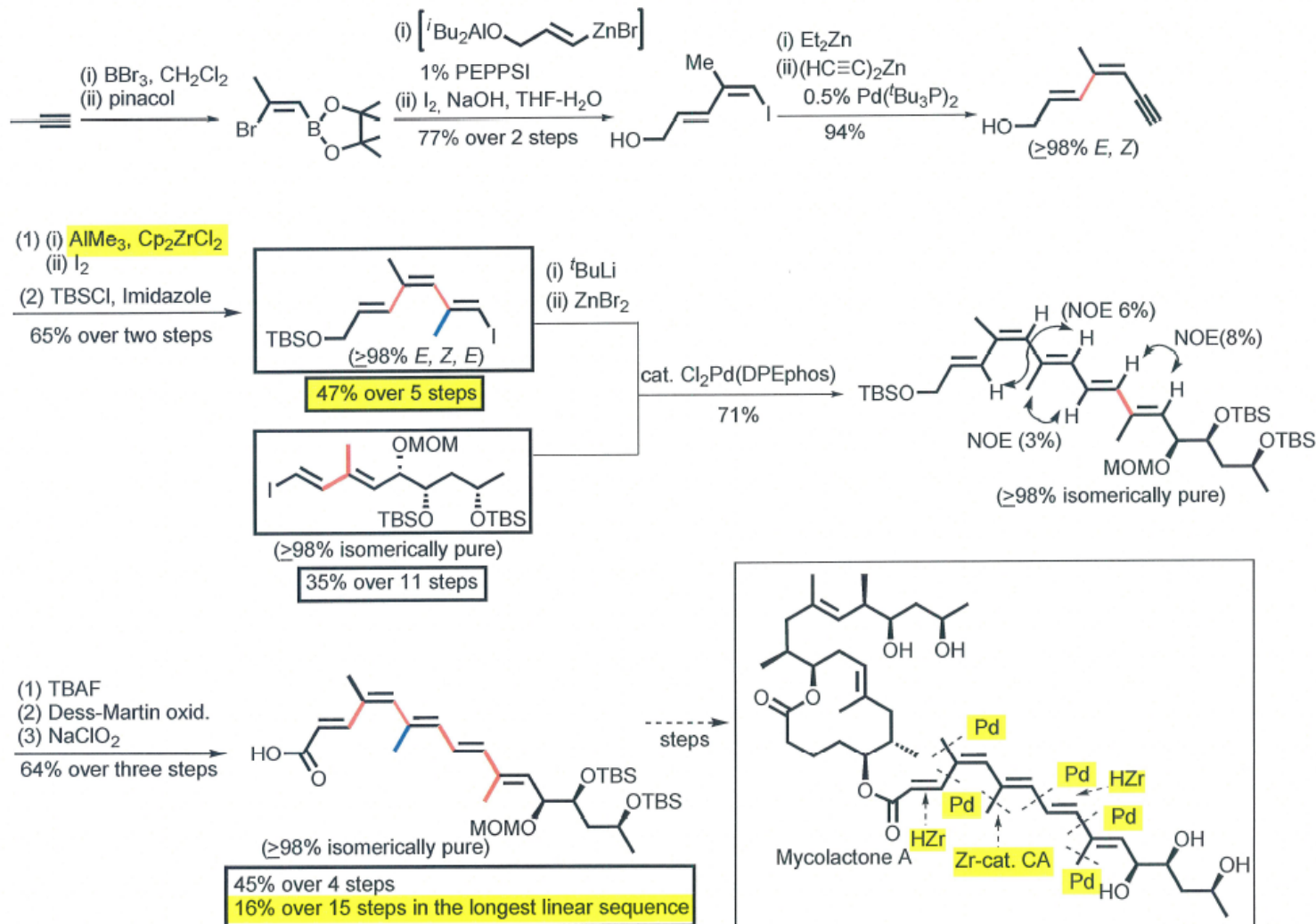
R, R' = C or H. M = Metal. W, X, Y, Z = H, C, Halogen, Metal, and other Heteroatoms.

**It takes Alkynes to make a world.**



# Efficient and Selective Synthesis of Mycolactone A Side Chain

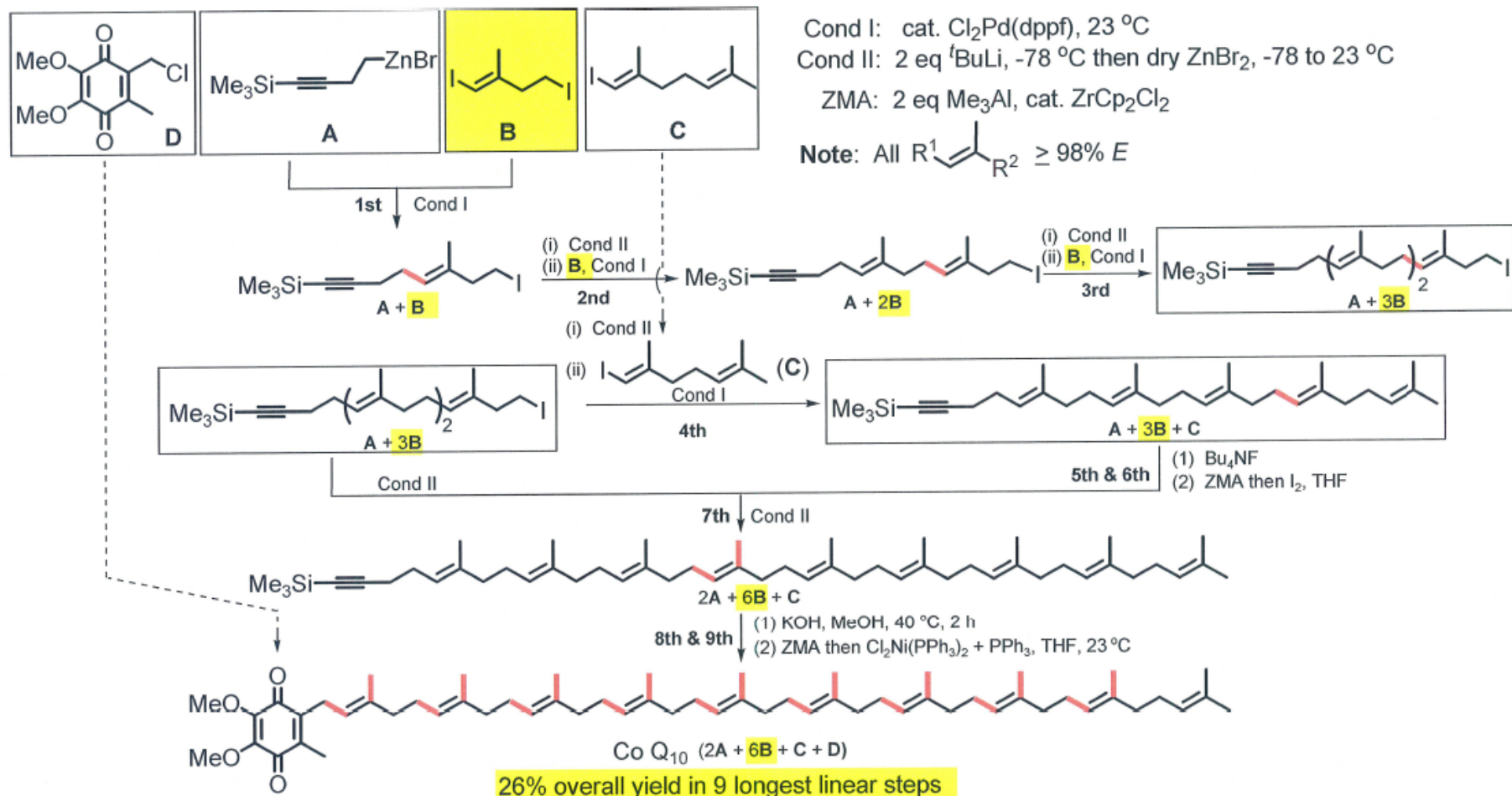
## LEGO Game Approach. Carbonyl Olefination–Pd-Catalyzed Alkenylation Synergy



(a) N. Yin, G. Wang, E. Negishi, *Angew. Chem. Int. Ed.* **2006**, 45, 2916-2920.

(b) G. Wang, N. Yin, E. Negishi, submitted.

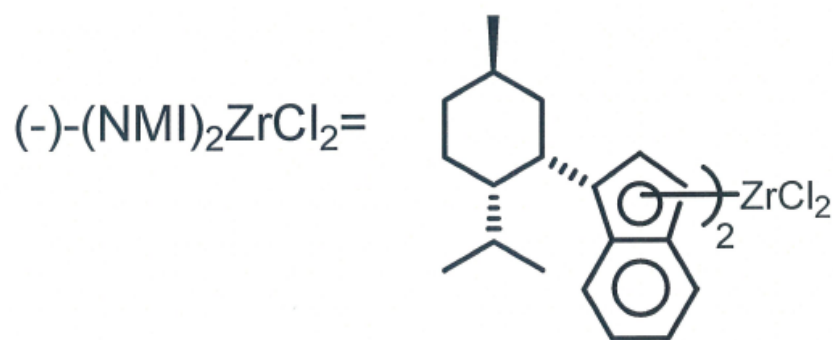
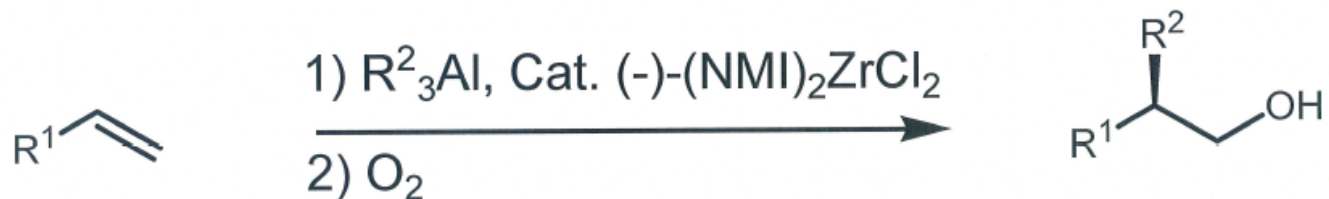
# Alkyne ZMA–Pd-Catalyzed Alkyl–Alkenyl Coupling: LEGO Game Route to CoQ10



S.-Y. Liou, C. Xu, S. Huo & EN. *OL*, **2002**, 261

B. Lipshutz, G. Bulow, F. Fernandez-Lazaro, S.-K. Kim, R. Lowe, P. Mollard, K. Stevens. *J. Am. Chem. Soc.* **1999**, 11664

# Zr-catalyzed Asymmetric Carboalumination of Alkenes (ZACA reactions)



$R^2 = \text{Me}$ , 68-92% yield, 70-90% ee

$R^2 = \text{Et}$ , 56-90% yield, 85-95% ee

$R^2 =$  Higher primary alkyl groups,  
74-85% yield, 90-95% ee

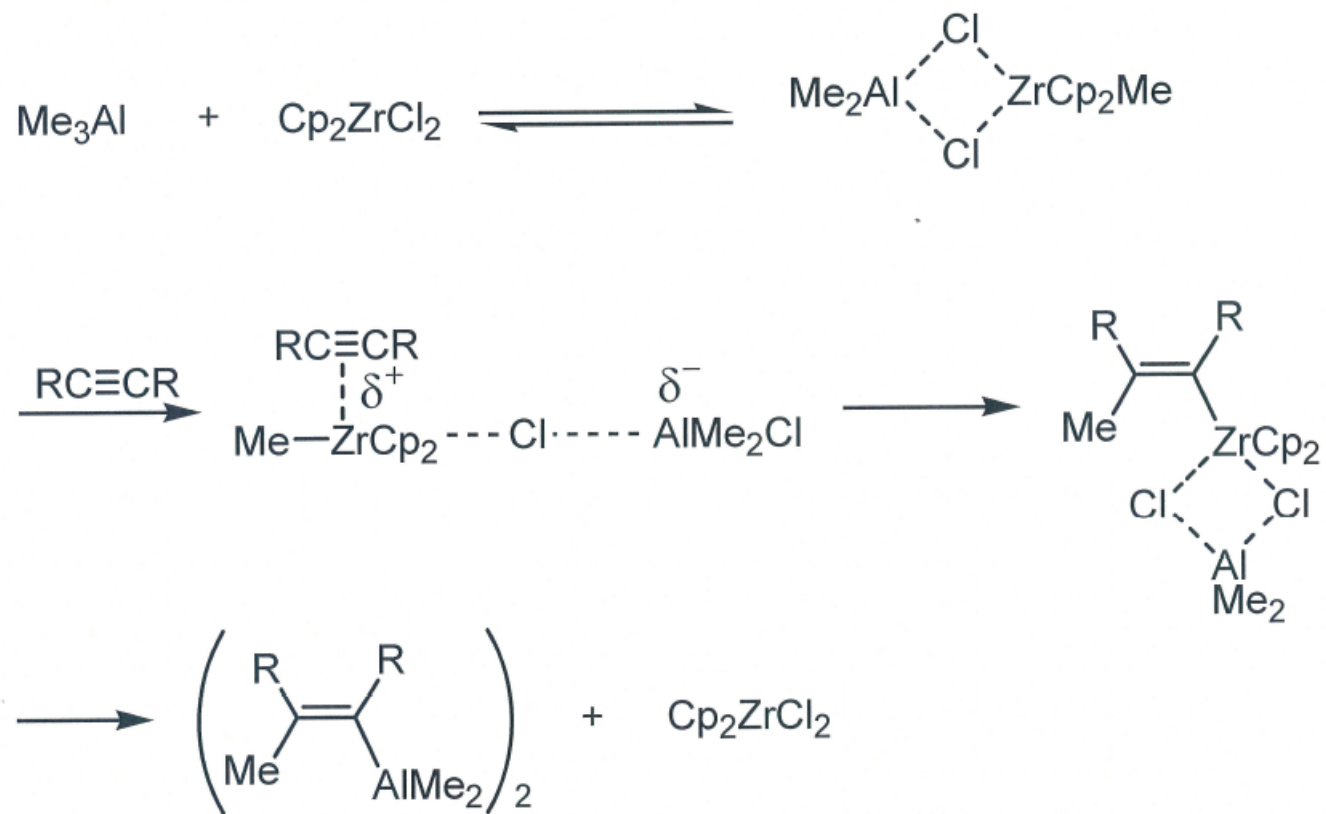
## Early Contributions

- Kondakov, D. Y.; Negishi, E., 1995 *JACS* 10771, 1996 *JACS* 1577.
- Huo, S.; Negishi, E., 2001 *OL* 3253.
- Huo, S.; Shi, J.; Negishi, E., 2002 *ACIE* 2141.

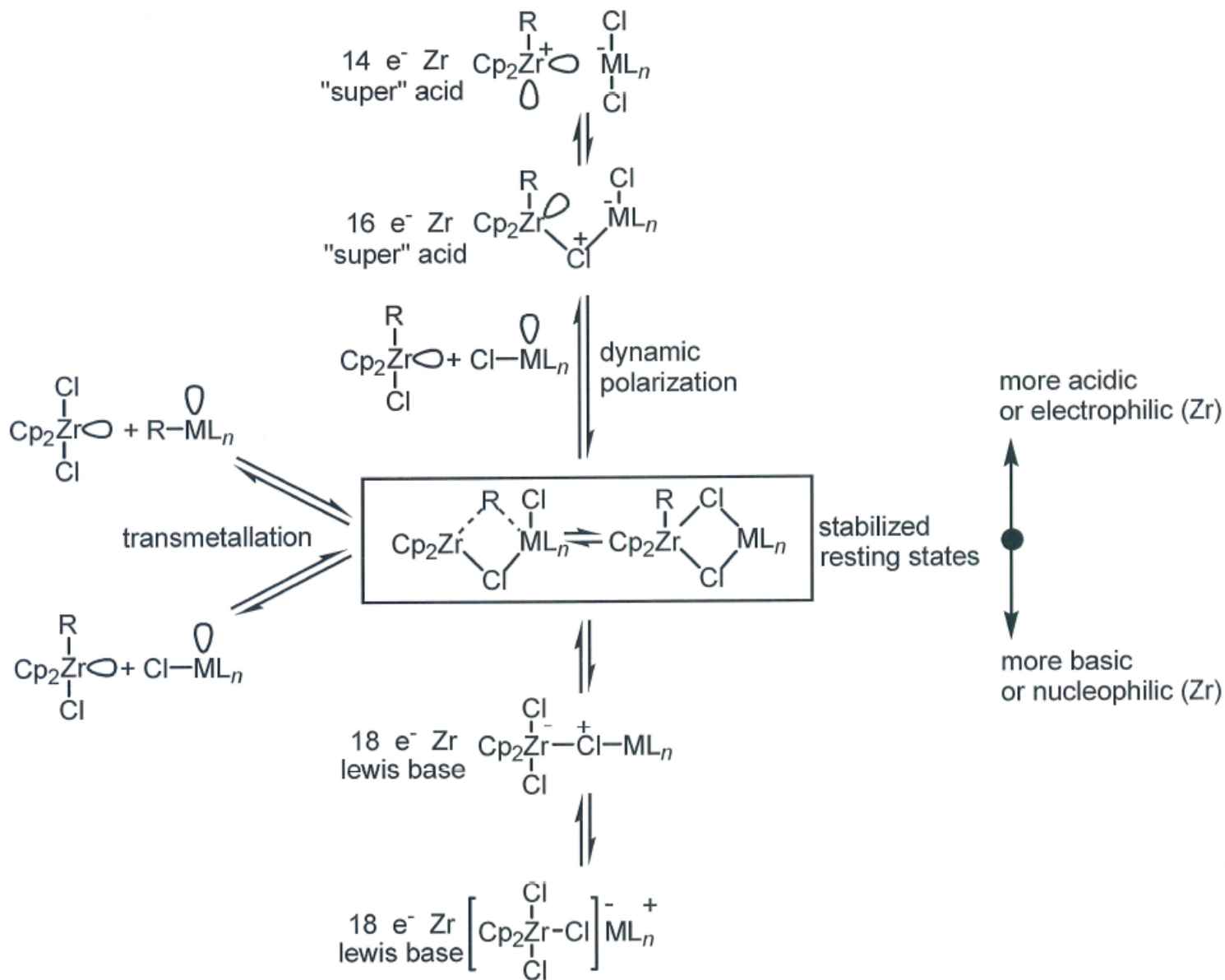
## Contributions by Others

- Erker, G. et al. 1993 *JACS* 4590
- Wipf, P.; Ribe, S. 2000 *OL* 1713

# Zirconium-catalyzed Carboalumination of Alkynes

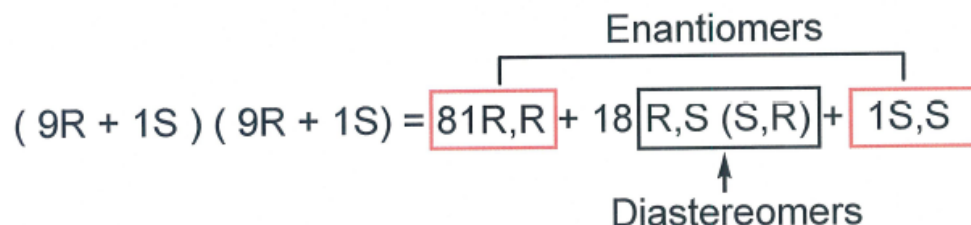


# Various Modes of Interaction between Two Lewis-Acidic Metal Compounds



## It's mathematical (or statistical)

If each step is 80%ee (90/10),



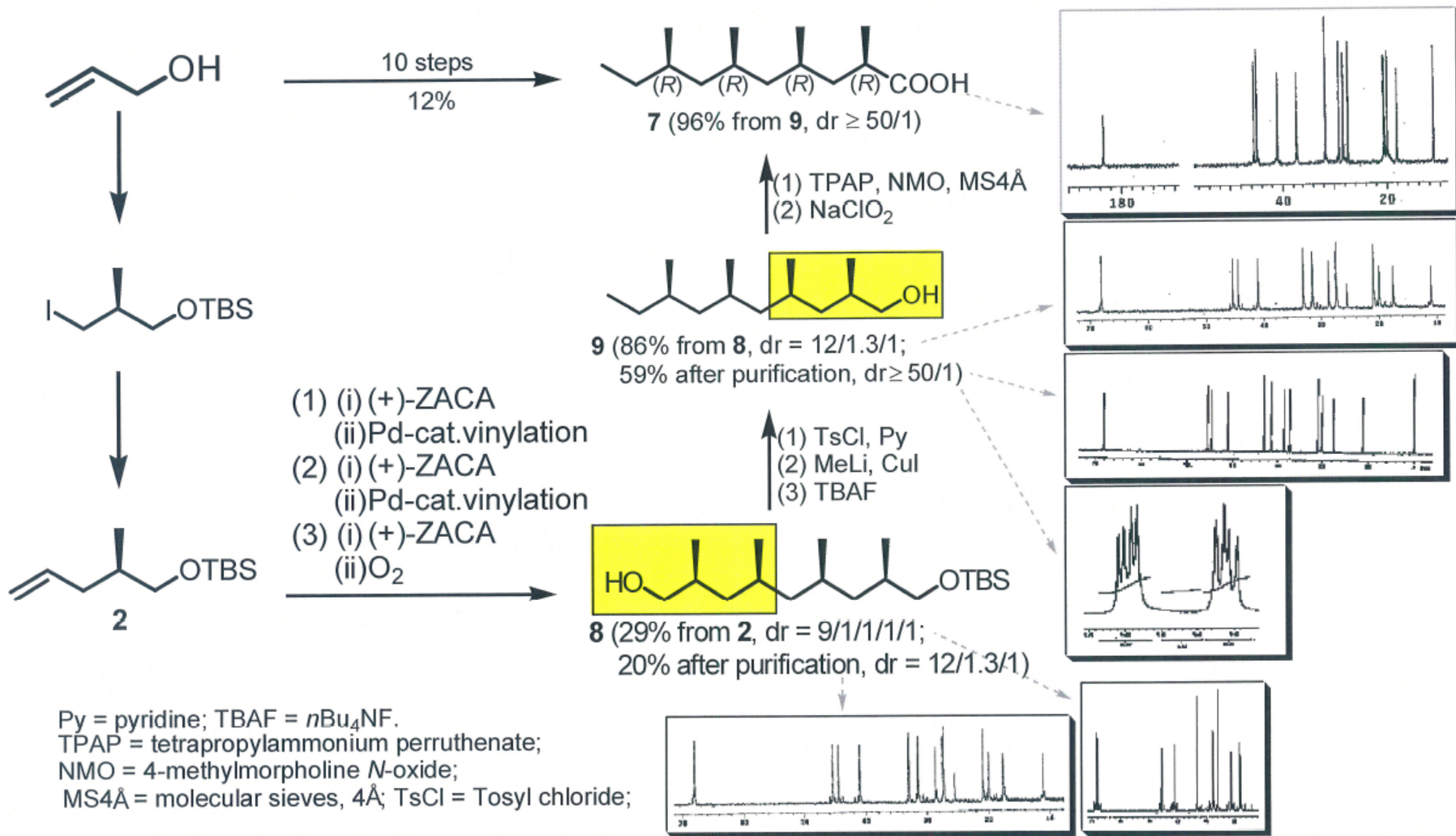
$$\frac{R,R}{S,S} = \frac{81}{1} \quad \therefore \text{Enantiomeric Excess} = \frac{81-1}{81+1} = \frac{80}{82} = 0.976 \approx \boxed{98\%ee}$$

$$(9R + 1S)^n = \boxed{9^n \times R^n} + \sum(\text{All Cross Terms}) + \boxed{1^n \times S^n}$$

↑  
Diastereomers

$n$	ee (%)
1	80
2	98 (= 97.6)
3	99.7
4	99.97
5	99.997

# Synthesis of (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethyldecanoic Acid, The Acid Component of Preen-Gland Wax of Graylag Goose, *Anser Anser*



# Acknowledgements

## Pd- or Ni-Catalyzed C–C Bond Formation

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<b>1976-1980</b>	Baba, S. King, A. O. Okukado, N. Kobayashi, M. Van Horn, D. E.	Valente, L. F. Silveira, A. Jr. Villani, F. J. Klima, W. L. Spiegel, B. I.	
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# Acknowledgements

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