

Chap. 6 Formation de liaisons C=C

liaisons C=C : rôle majeur en chimie

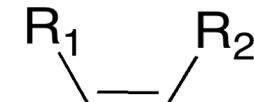
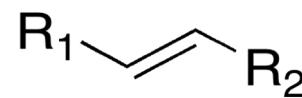
très fréquents dans produits naturels (bioactifs)

nombreuses réactions

complexification & fonctionnalisation mlc

stéréochimie & création de stéréocentres si addition

Formation de liaisons C=C : plusieurs méthodes
 pb de stéréosélectivité



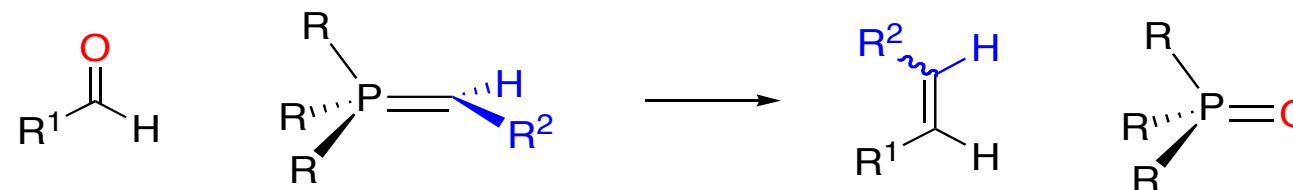
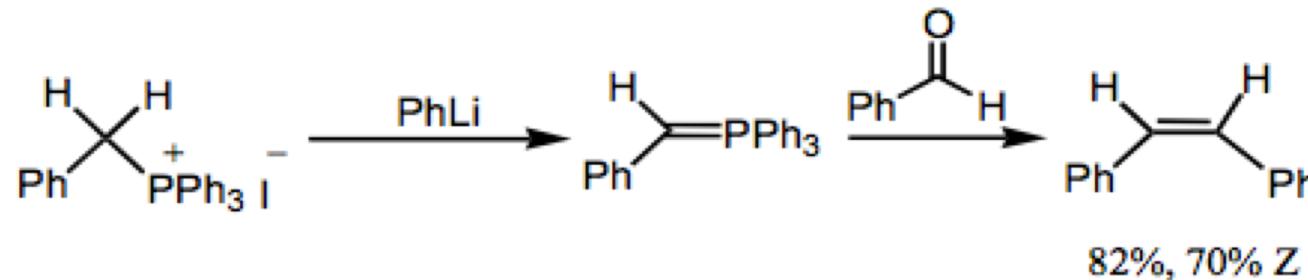
6.1 réaction de Wittig



G. Wittig
1897-1987
Nobel 1979 (avec H. Brown)



Wittig, G.; Geissler G. *Liebigs Ann.* **1953**, 580, 44-57.
Wittig, G. et. al. *Chem. Ber.* **1954**, 87, 1318



Industriel :

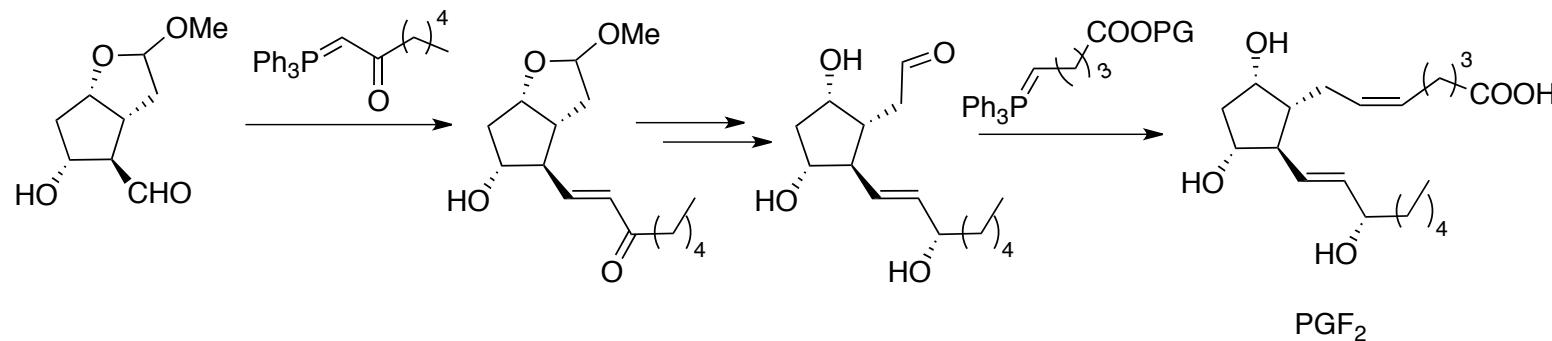


BASF 1956

Carotene

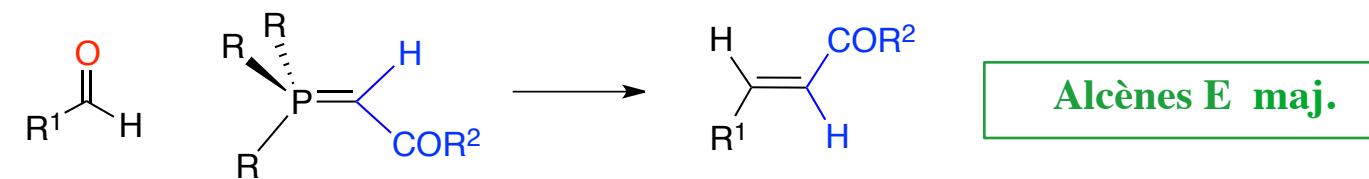
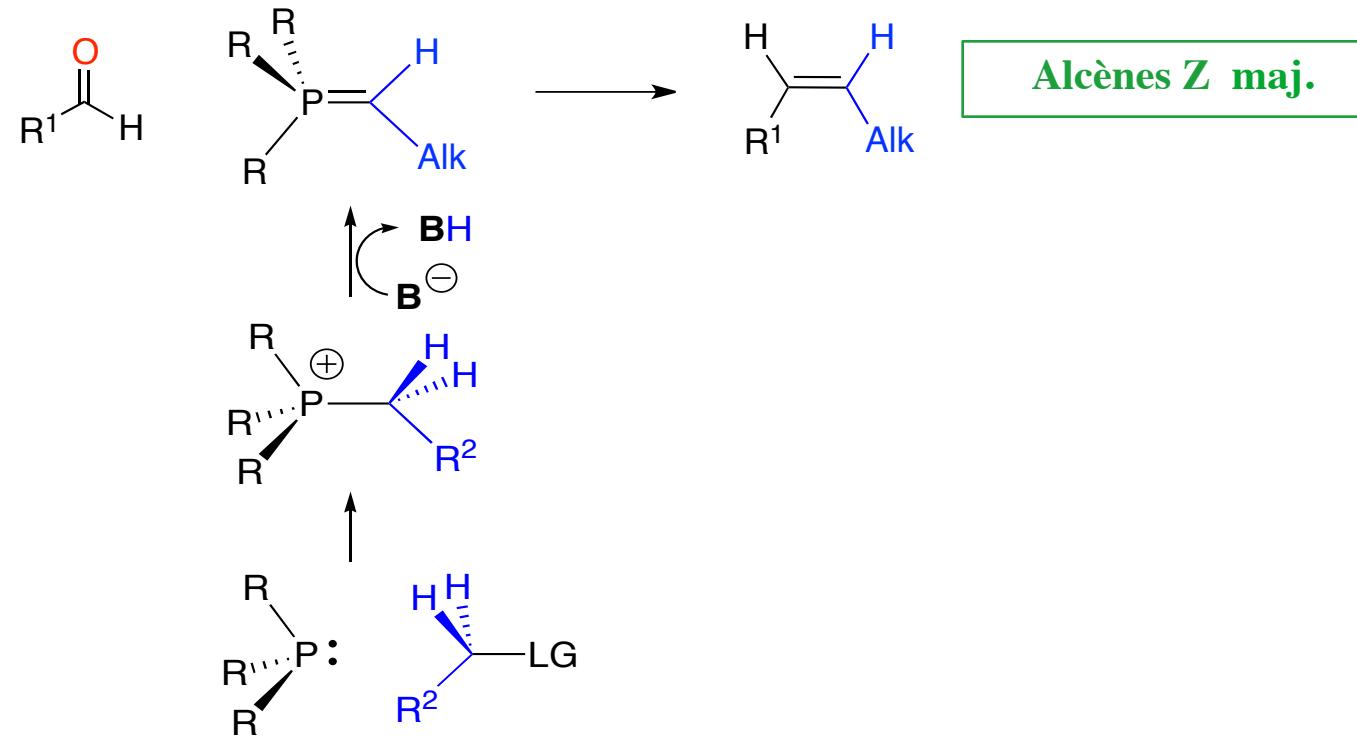
Citranaxanthine

etc



etc

Général :



Expériences :

- Bétaïnes indétectables
- Pas/peu d'effet de solvant
- Effet de sel

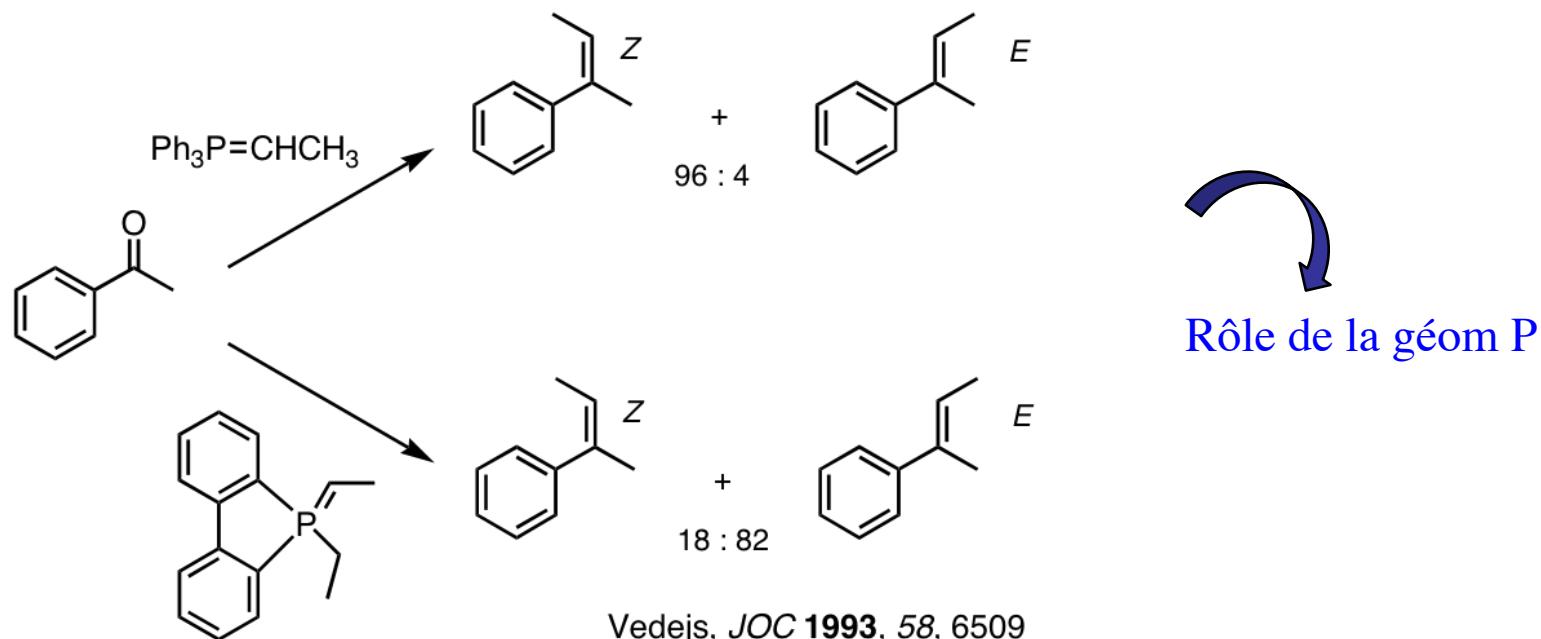


 salt free
LiI

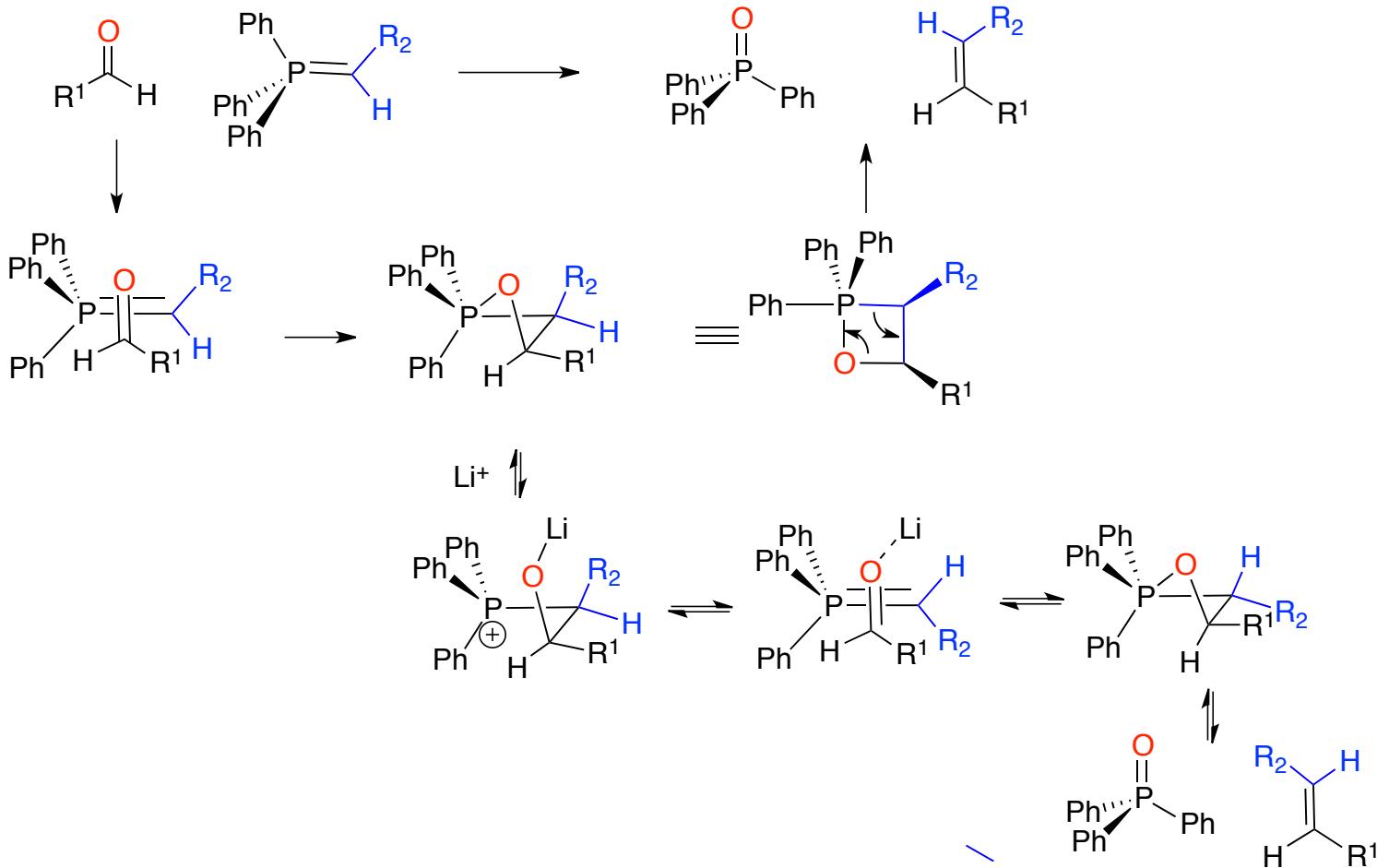
Rôle du Li^+

10 : 90
42 : 58

- Effet des L du P



Méca



Alcène Z

Alcène E

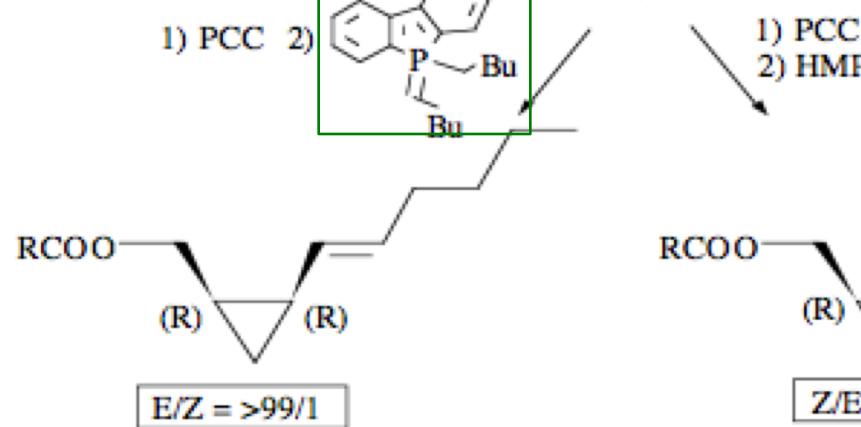
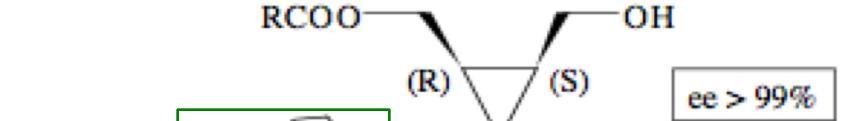
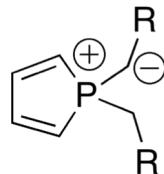
Revues :

Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863

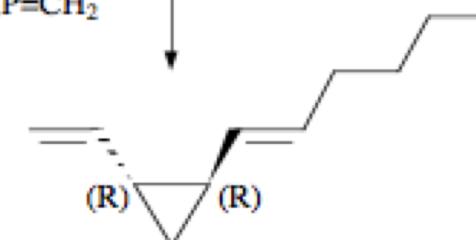
E. Vedejs, M. J. Peterson, *Top. Stereochem.* **1994**, 21, 1–157

Version *E* sélective :

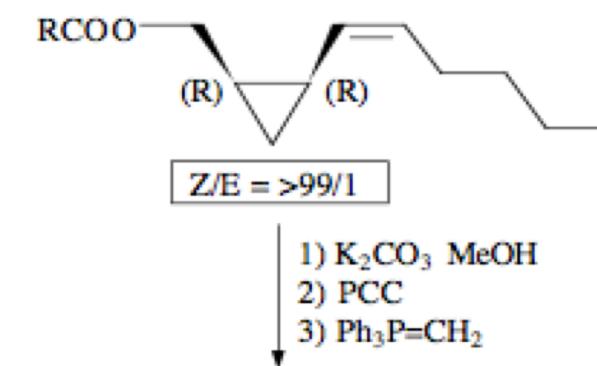
cf Vedejs



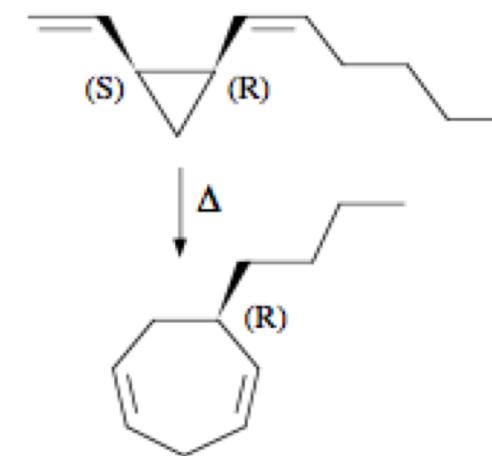
- 1) K_2CO_3 MeOH
- 2) PCC
- 3) NaOMe
- 4) $\text{Ph}_3\text{P}=\text{CH}_2$



(+)-Dictyopterene A
7 steps; 50% overall yield

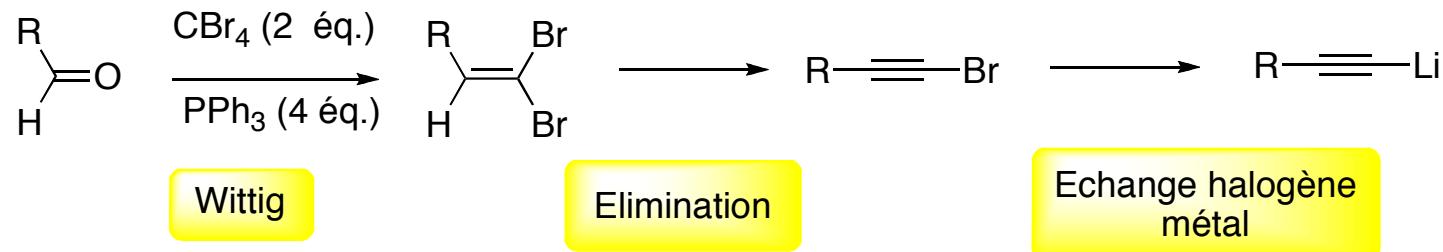


- 1) K_2CO_3 MeOH
- 2) PCC
- 3) $\text{Ph}_3\text{P}=\text{CH}_2$



(-)-Dictyopterene C'
7 steps; 70% overall yield

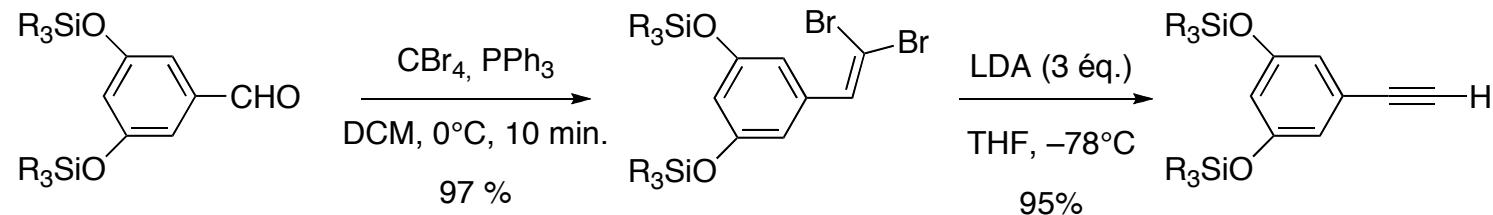
Version vinyldibromé & Formation d'alcynes :



F. Ramirez, N.B. Desai, N. McKelvie, *J Am Chem Soc* **1962**, 84, 1745

Corey, E. J. ; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 36, 3769-3772

D. Grandjean, P. Pale, J. Chuche *Tetrahedron Lett.* **1994**, 35, 3529



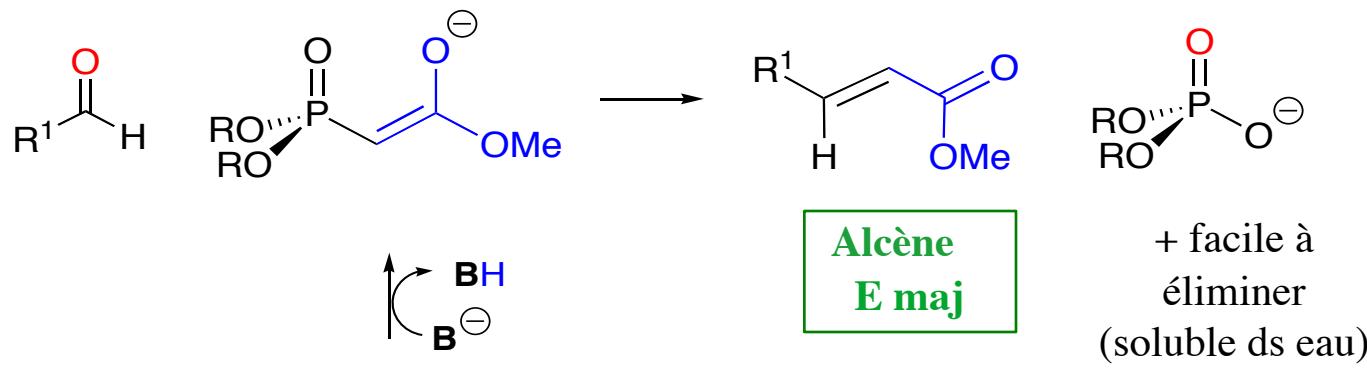
T. Gibtner, F. Hampel, J.-P. Gisselbrecht, A. Hirsch, *Chem. Eur. J.*, 2002, 68, 408-432.

6.2 réaction de Horner-Wadsworth-Emmons

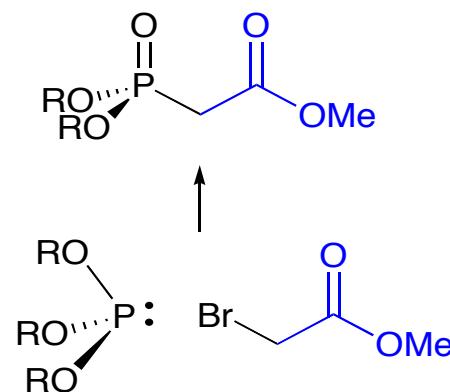
Réaction de Wittig-Horner

Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61

Wadsworth, W. S.; Emmons, W. D. *J. Org. Chem.* **1961**, *83*, 1733



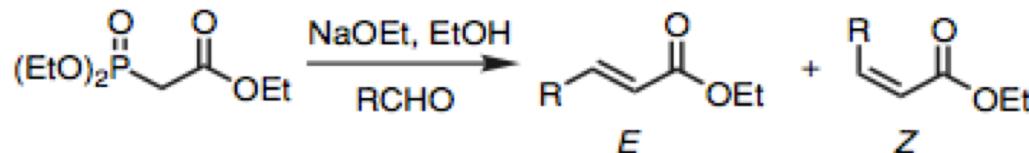
Réaction d'Arbusov



Arbusov, A. E.; Durin, A. A.
J. Russ. Phys. Chem. Soc. **1914**, *46*, 295

Chem. Rev. **1981**, *81*, 415

Un ex :

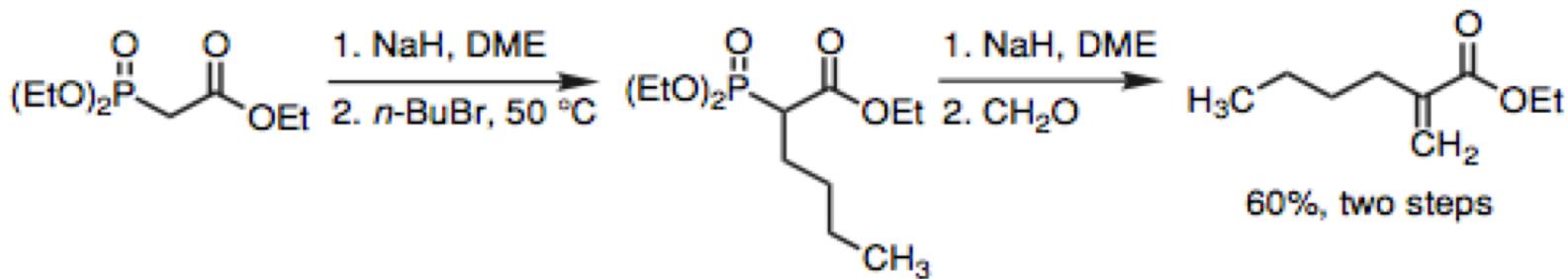


Aldehyde	Ratio of products (E : Z)
PhCHO	98 : 2
<i>n</i> -PrCHO	95 : 5

Alcène E
T. maj

Alkylation de l'anion stabilisé par le phosphonate possible

NB: difficile avec ylures de phosphonium

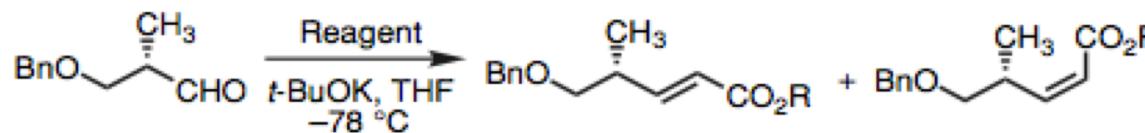


Ratio $E : Z$ augmente :

- dans le DME vs THF,
- à + hautes températures,

- avec $M^+ = Li > Na > K$,
- avec la substitution en α du carbonyle (aldehyde),
- avec la substitution du phosphonate et du carboxylate

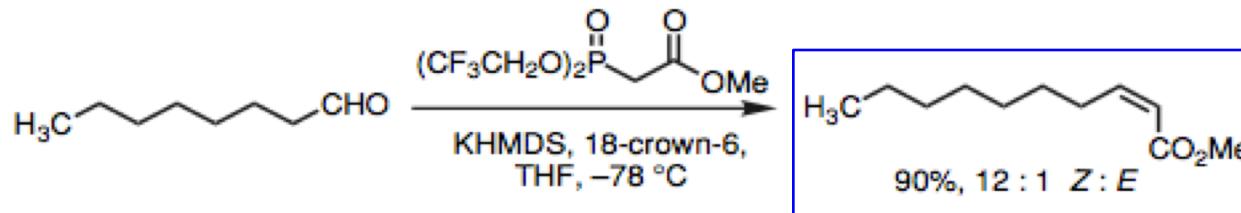
Nagaoka, H.; Kishi, Y.
Tetrahedron **1981**, 37, 3873



Reagent	Ratio of products ($E : Z$)
$(i\text{-PrO})_2\text{P}(\text{CH}_2)\text{CO}_2\text{Et}$	95 : 5
$(\text{MeO})_2\text{P}(\text{CH}_2)\text{CO}_2\text{OMe}$	1 : 3

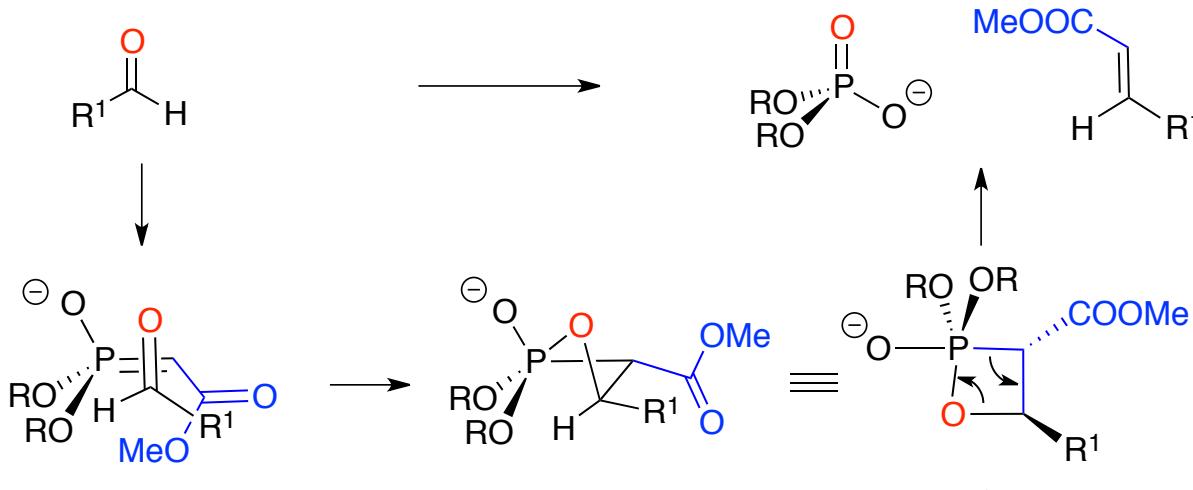
Version Z sélective :

Still, W.C.; Gennari, C.
Tetrahedron Lett. **1983**, 24, 4405



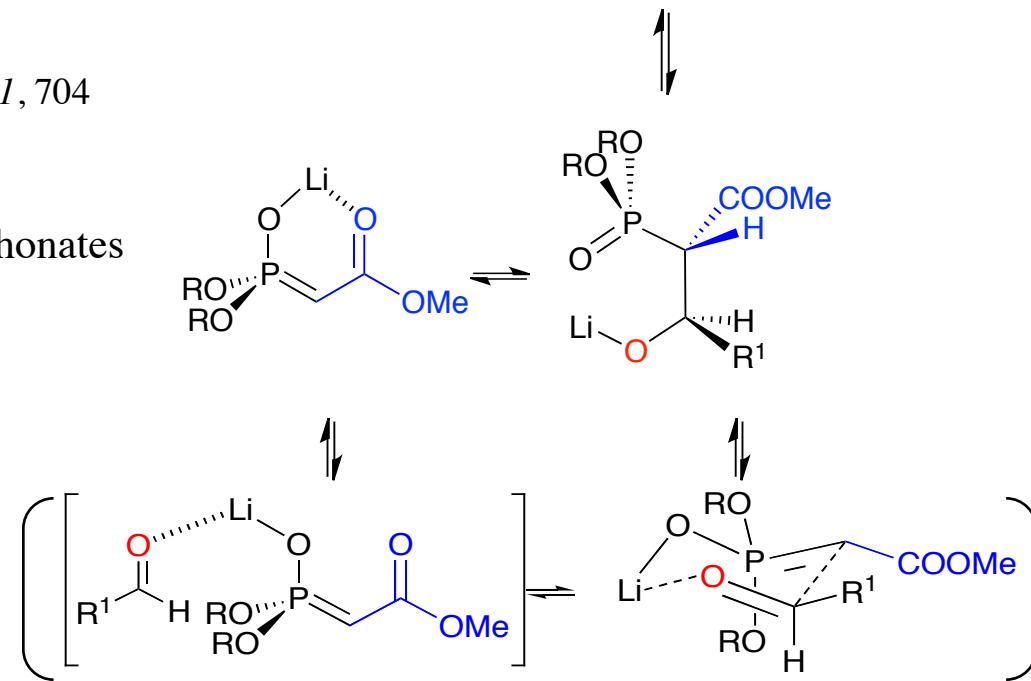
aldehyde	product	$Z : E$	yield, %
$\text{H}_3\text{C}\text{---CH}_2\text{---CH}=\text{CH}_2\text{---CHO}$	$\text{H}_3\text{C}\text{---CH}_2\text{---CH}=\text{CH---CH}=\text{CH---CO}_2\text{Me}$	$>50 : 1$	87
cyclohexanecarbaldehyde	cyclohexene-1,2-dicarboxylate	4 : 1	74
benzaldehyde	styrene-1,2-dicarboxylate	$>50 : 1$	>95

Mécanisme :



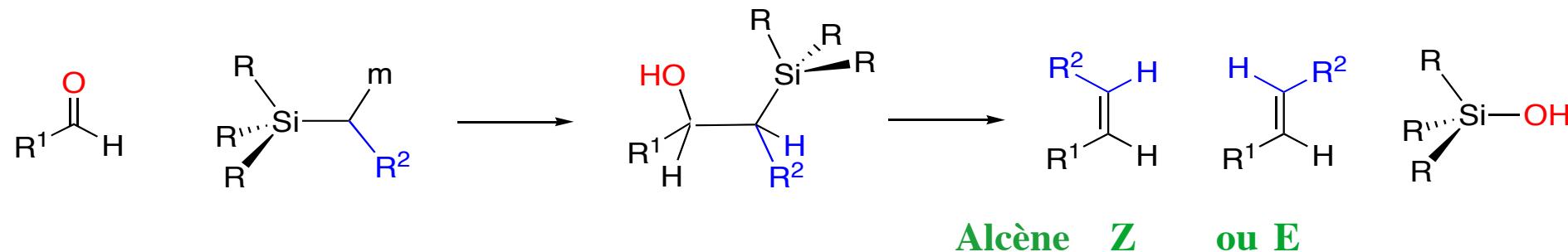
H. Mayr & coll. *J. Am. Chem. Soc.* **2009**, *131*, 704

Li^+ réduit x 100 la réactivité des phosphonates

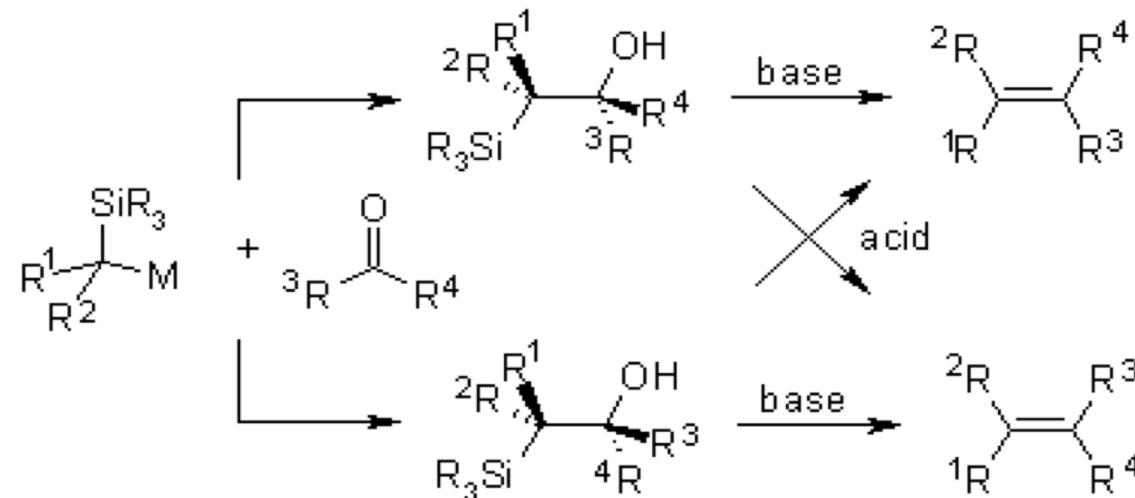


6.3 réaction de Peterson

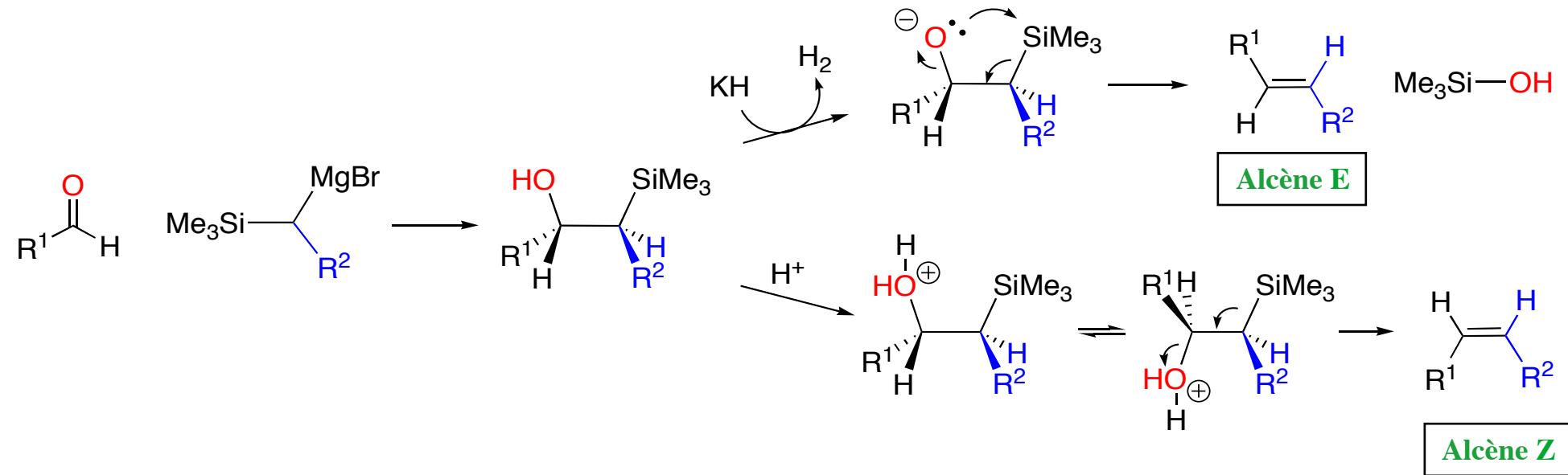
Peterson et al. *J. Org. Chem.* **1968**, 33, 780–784



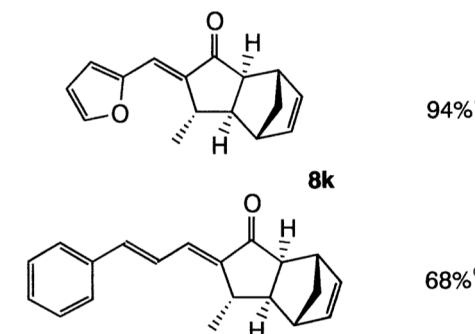
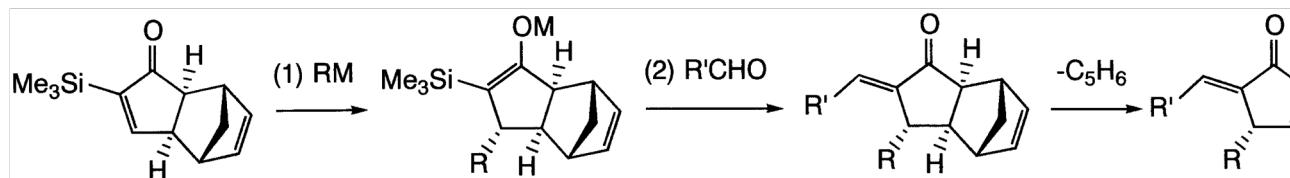
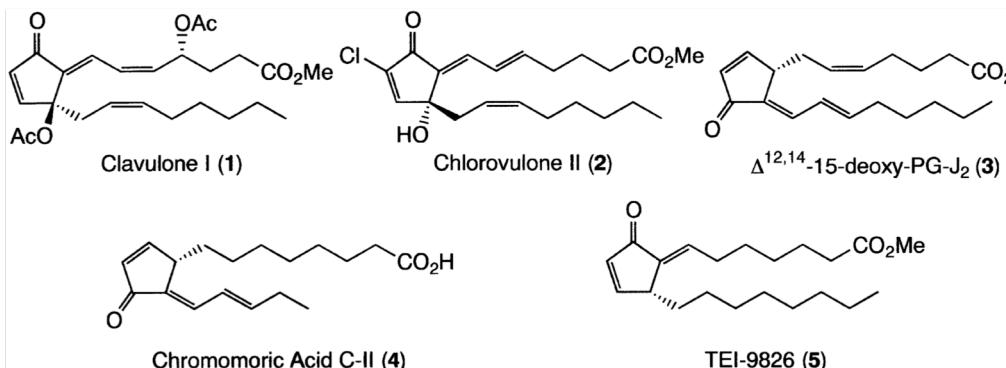
Stéréosélectivité fn des conditions :



Mécanismes :



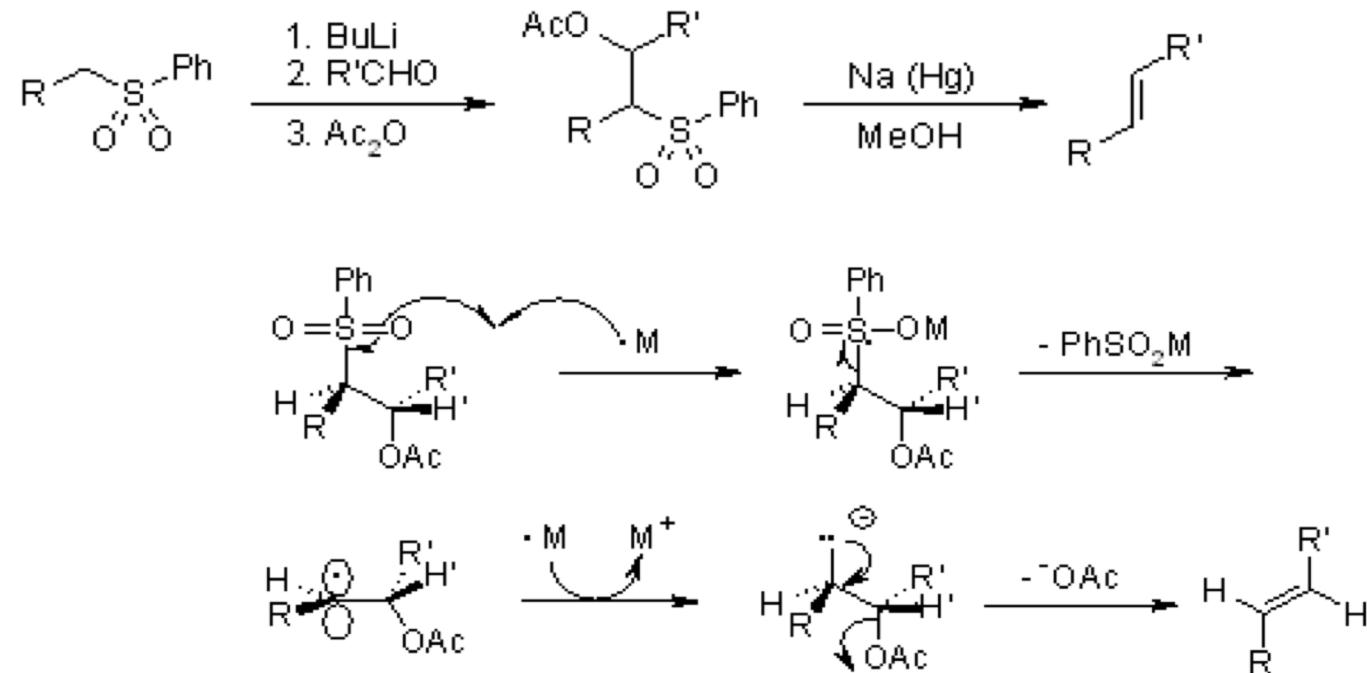
Applications :



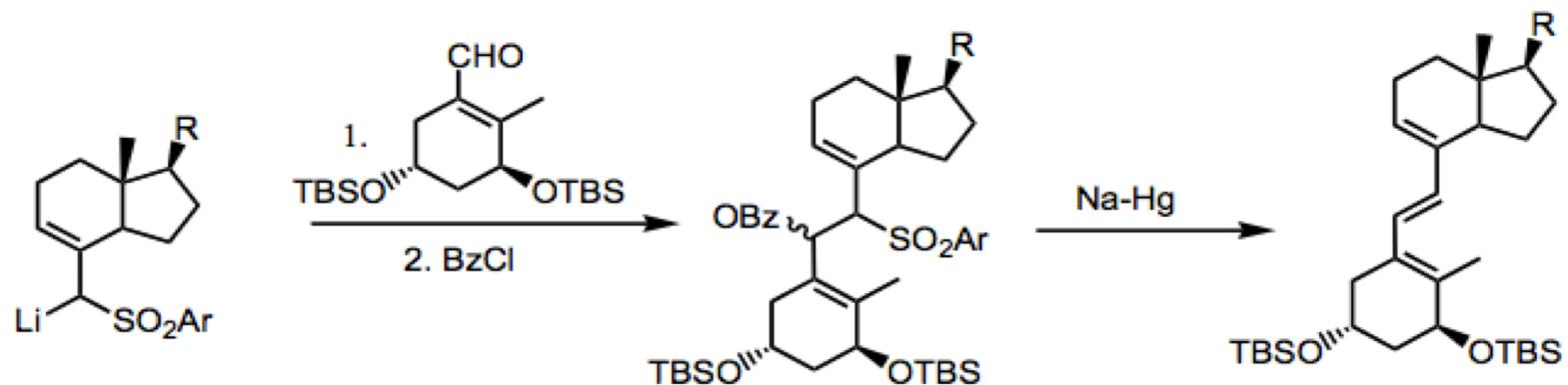
6.4 Autres réactions

6.4.1 Réaction de Julia

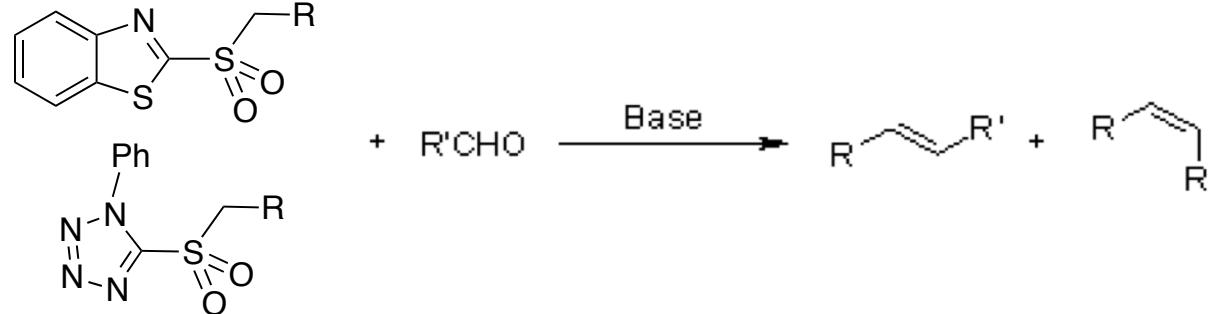
M. Julia J-M. Paris
Tetrahedron Lett. **1973**, 14, 4833



Alcène E
 T. maj

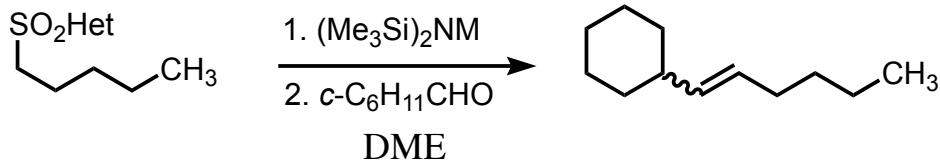


Réaction de Julia-Kociensky

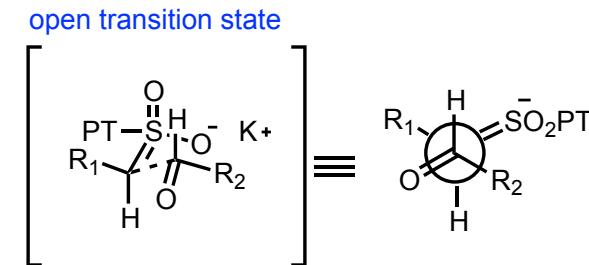


P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley
Synlett **1998**, 26-28

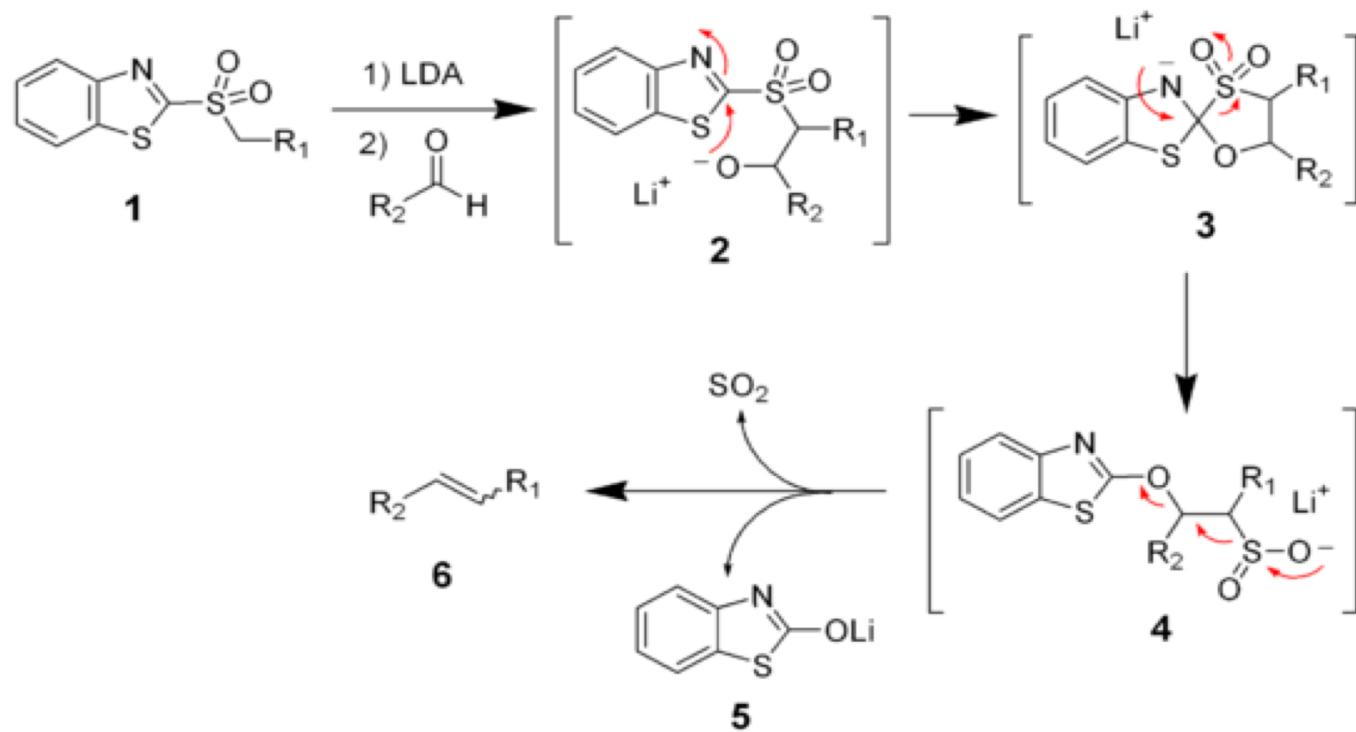
Stéréosélectivité :



M	BT-sulfone		PT-sulfone		<i>E/Z</i>
		Yield (%)		Yield (%)	
Li	2	70 : 30	94	72 : 28	
Na	32	75 : 25	95	89 : 11	
K	4	76 : 24	81	99 : 1	



Mécanisme :



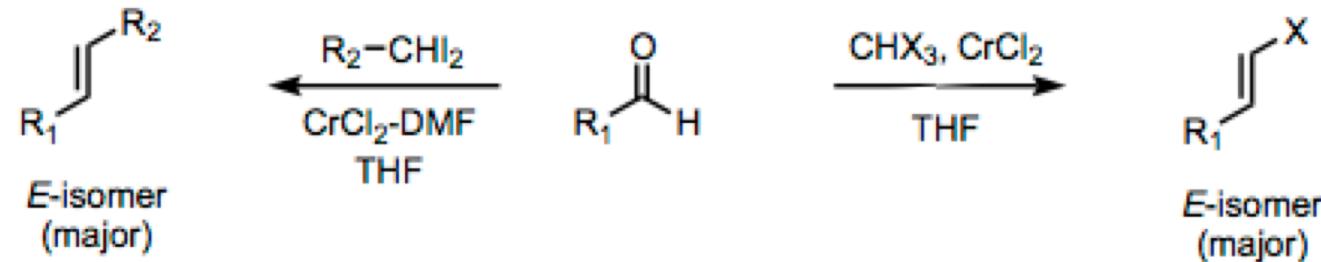
6.4.2 Réaction de Takai

Takai, K.; Utimoto, K. et. al. *JACS*. **1987**, *109*, 951

Revues:

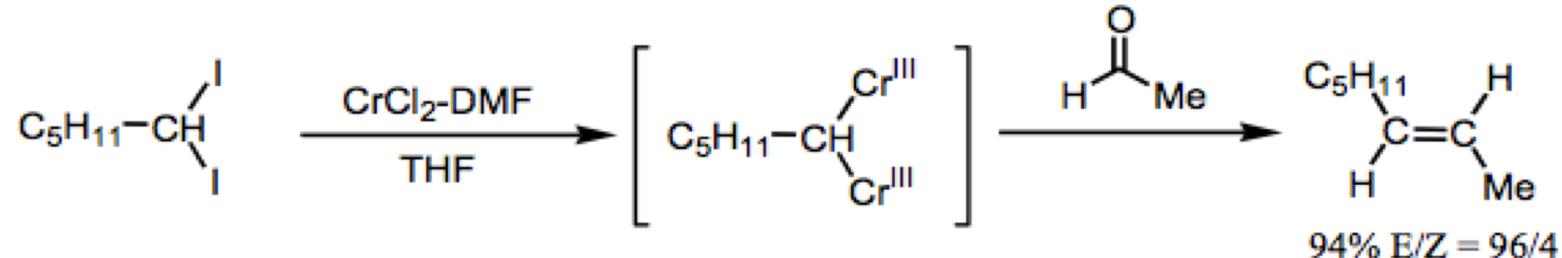
Furstner, A. *Chem. Rev.* **1999**, *99*, 991–1045.

Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36

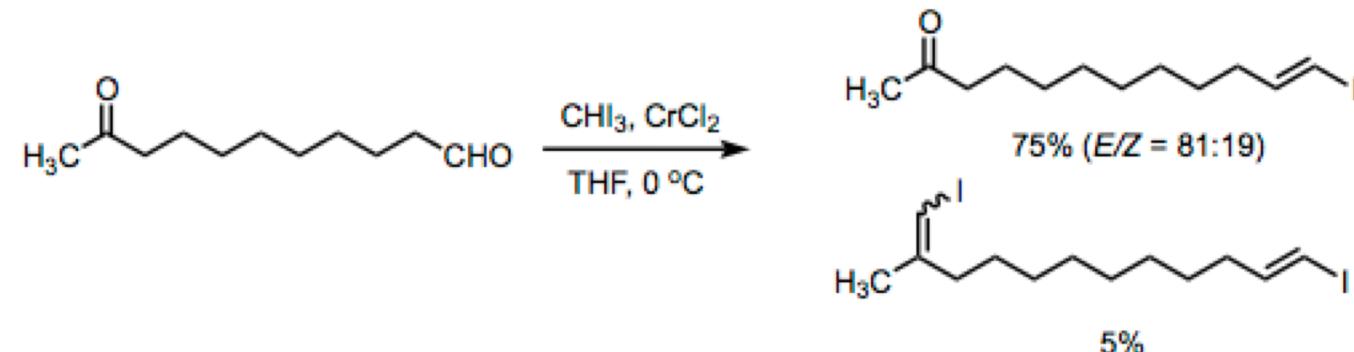


Alcène E
T. maj

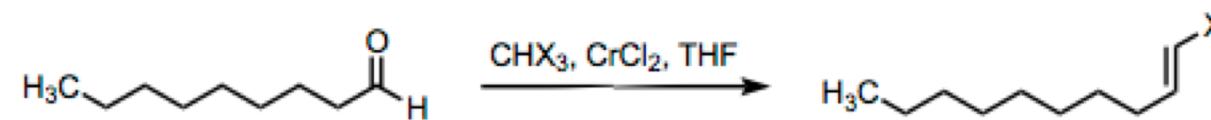
Mécanisme :



T. stéréosélective



T. chimiosélective

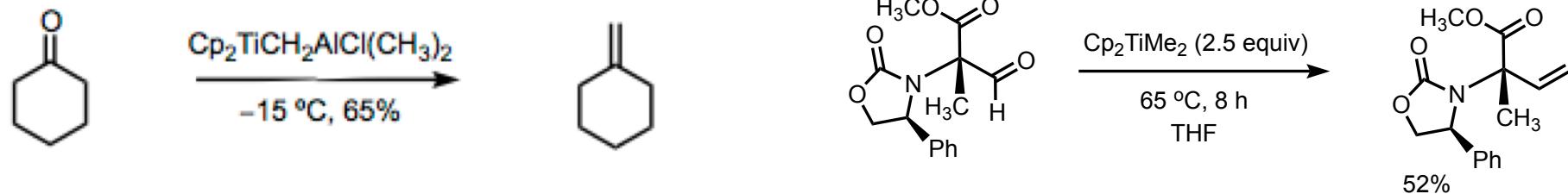
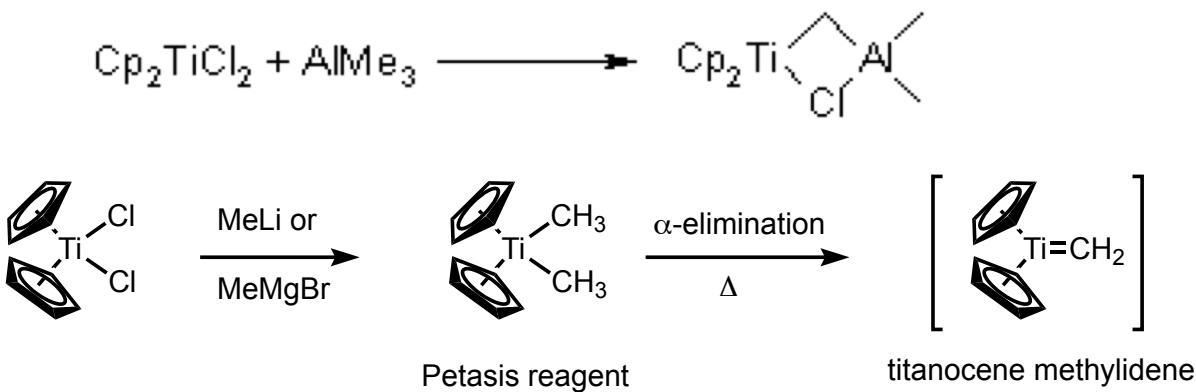


X ^a	Temp (°C)	time (h)	yield (%)	E/Z
Cl	65	2	76	95/5
I	0	2	82	83/17
Br ^b	50	1	76	95/5

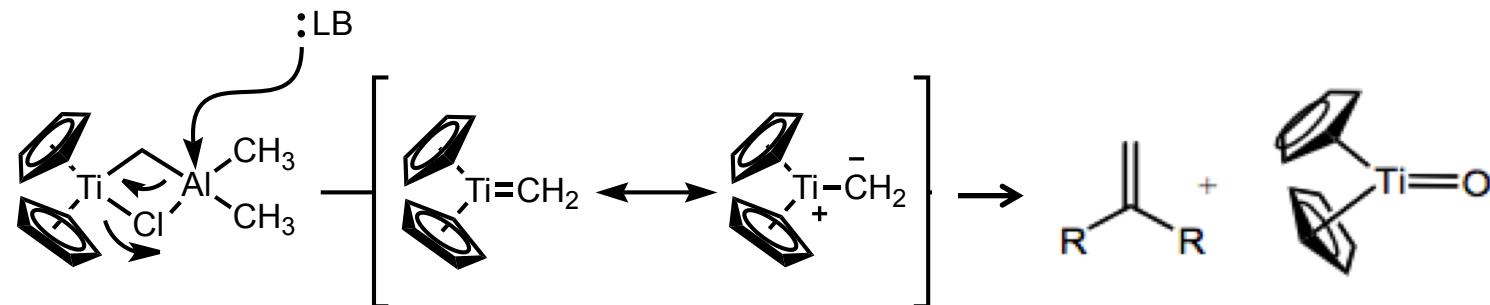
6.4.3 Réaction de Tebbe

Tebbe et. al. *JACS*. **1978**, *100*, 3611-3613
Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.*
1990, *112*, 6392

Revue :
Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.*
2000, *100*, 2789–2834.

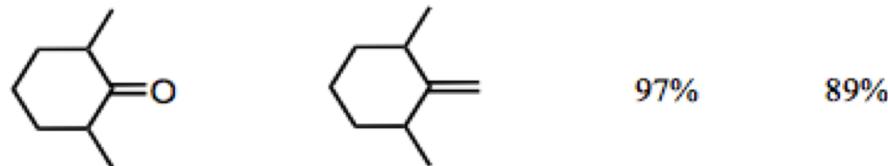


Mécanisme :

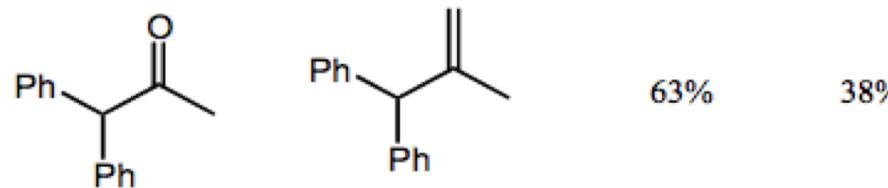
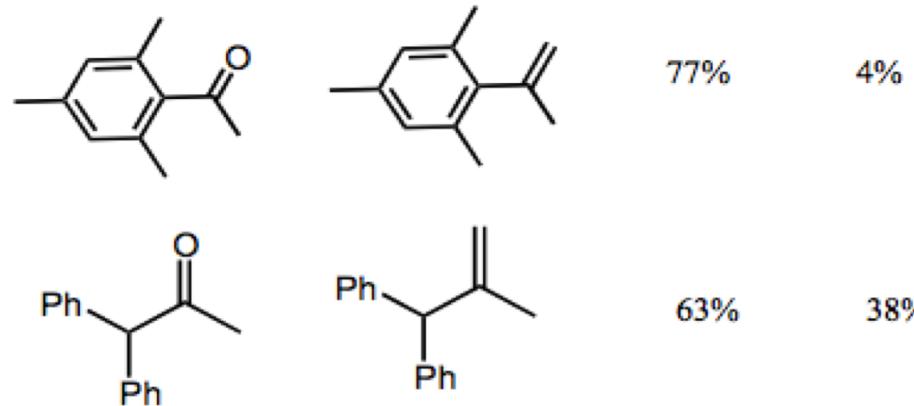


+ réactif, - basique que r. Wittig :

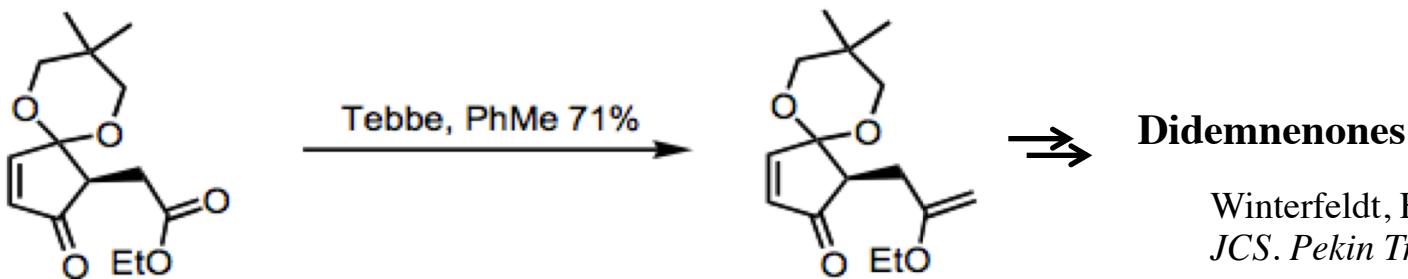
Tebbe Wittig



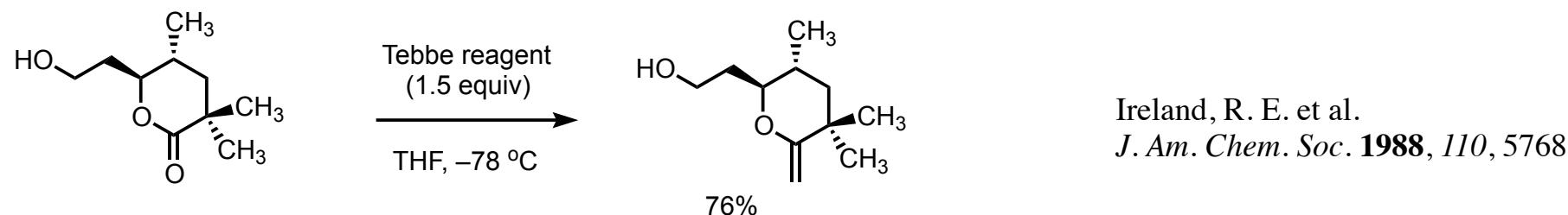
Pine, S. H.; Shen, G. S., Hoang, H.
Synthesis, **1991**, 165



Réaction de Tebbe efficace sur esters, amides, chlorures ou anhydride d'acide :



Didemnenones
Winterfeldt, E. et. al.
JCS. Pekin Trans I **1994**, 3525



Ireland, R. E. et al.
J. Am. Chem. Soc. **1988**, *110*, 5768

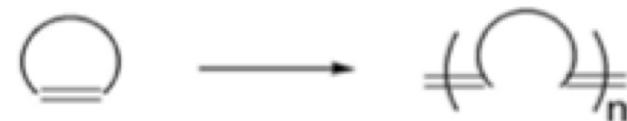
6.5 synthèse d'alcènes par métathèse

6.5.1 Historique

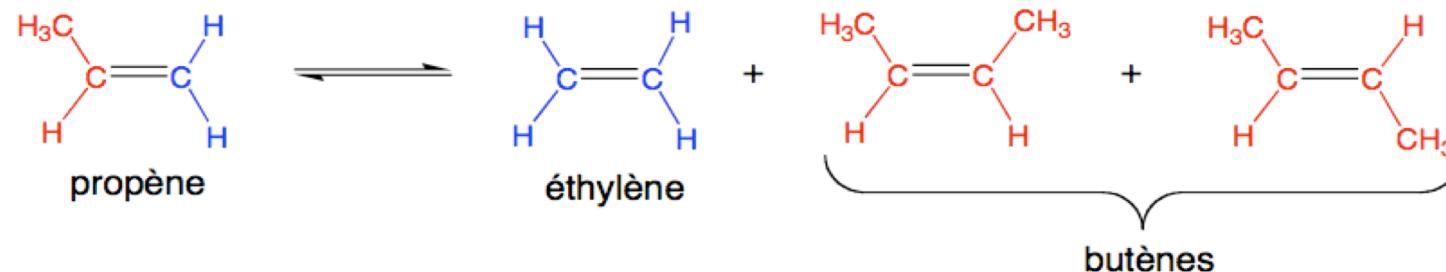
Pétrochimie & Polymérisation des alcènes & alcynes

Mo, W, Ru, Re...

1956, Herbert S. Eleuterio, Du Pont's petrochemicals, polymérisation du norbornène



1966 G. Natta (Nobel 1963) polym & disproportionation des alcènes



Études mécanistiques

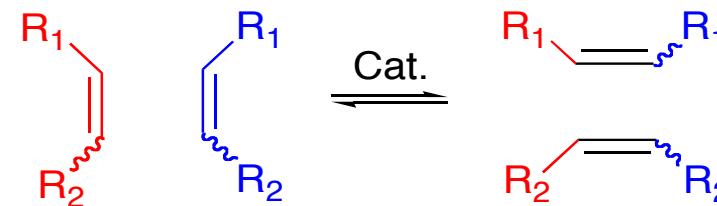
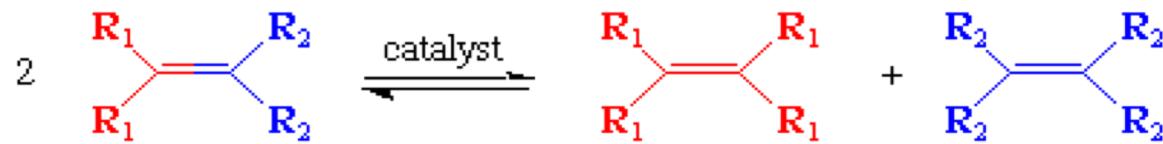
1971 Y. Chauvin, IFP Lyon

Études & extension

R. Schrock, MIT

R. Grubbs, CalTech

Principe : recombinaison d'alcènes



NB : idem pour alcynes



A. Mortreux *Chem. Comm.* **1974**, 19, 786

The metathesis reactions: from a historical perspective to recent developments

D. Astruc *New J. Chem.* **2005**, 29, 42 - 56



Nobel 2005

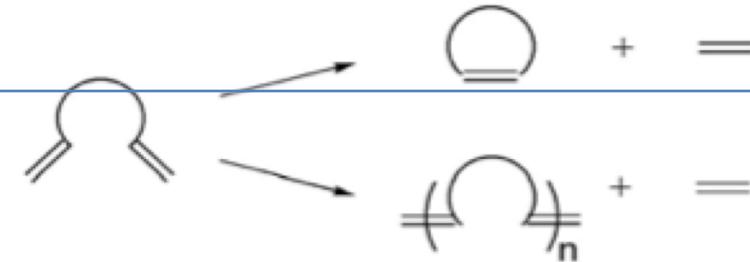
Y. Chauvin, R. Schrock, R. Grubbs

6.5.2 plusieurs versions

Cross metathesis (CM)



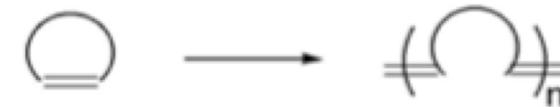
Ring-closing metathesis (RCM)



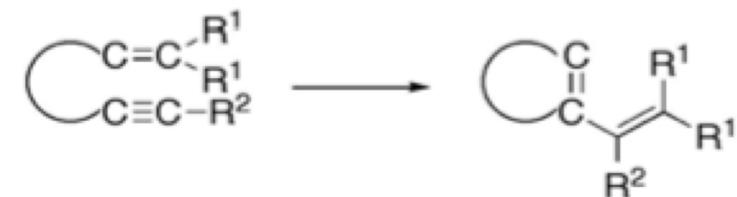
Acyclic diene metathesis polymerization (ADMEP)



Ring-opening metathesis polymerization (ROMP)



Enyne metathesis (EYM)



Ring-opening cross metathesis (ROCM)



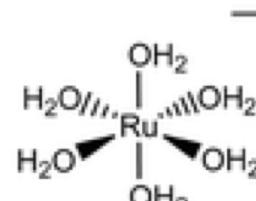
6.5.3 Mécanisme de la métathèse d'alcène

Y. Chauvin, IFP Lyon 1970

1980, R. R. Schrock, M.I.T $M=CH_2$ ou $M=CHR$

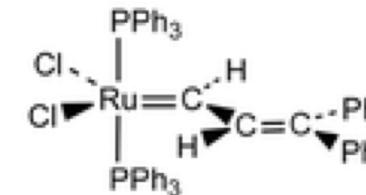


Natta, 1965
Grubbs, 1988

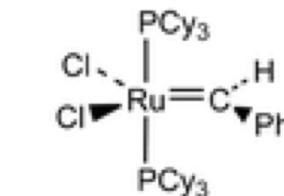


Grubbs, 1988

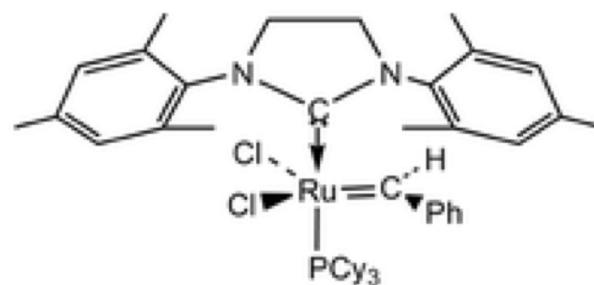
$2+$
2 OTs⁻



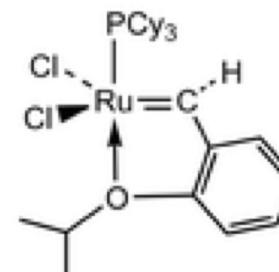
Grubbs, 1992



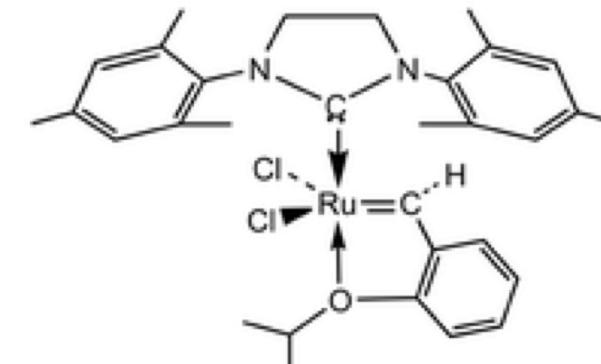
Grubbs, 1995
commercial, 1st generation
most used catalyst



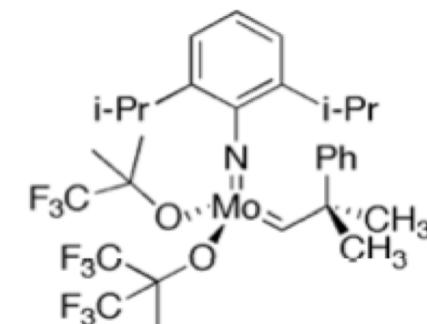
Nolan, Grubbs, Herrmann, Fürstner, 1999
2nd generation, commercial, second most used catalyst



Hoveyda, 1999
commercial

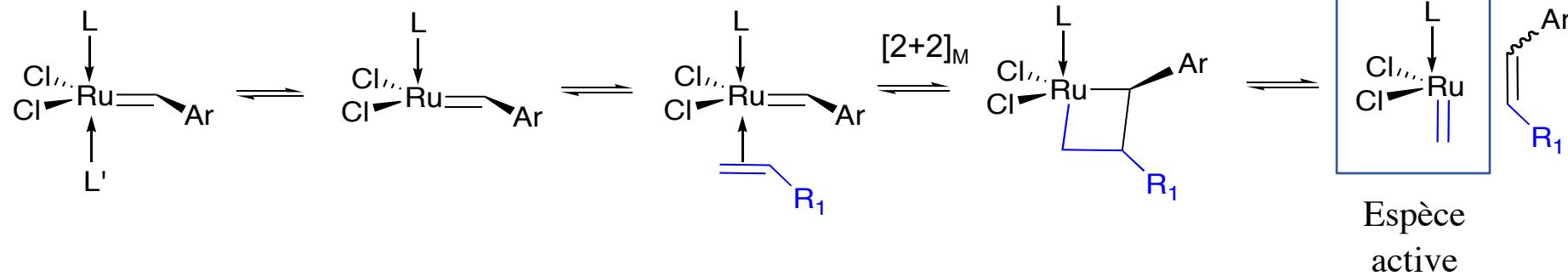


Hoveyda, 1999
commercial

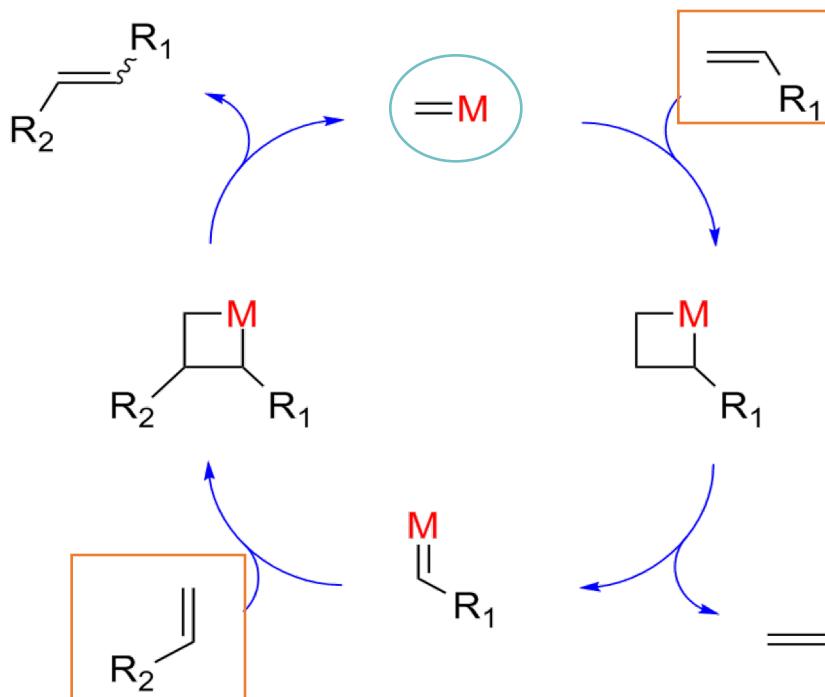


A. Fürstner

Initiation:

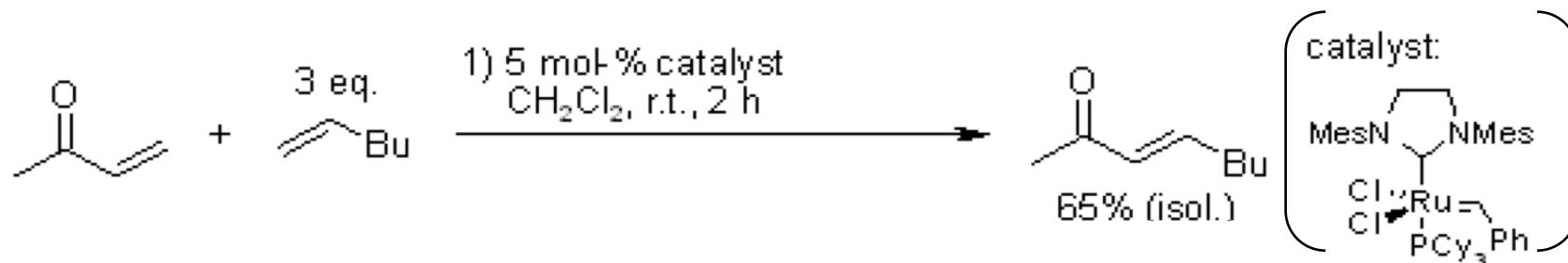


Catalytic Cycle:

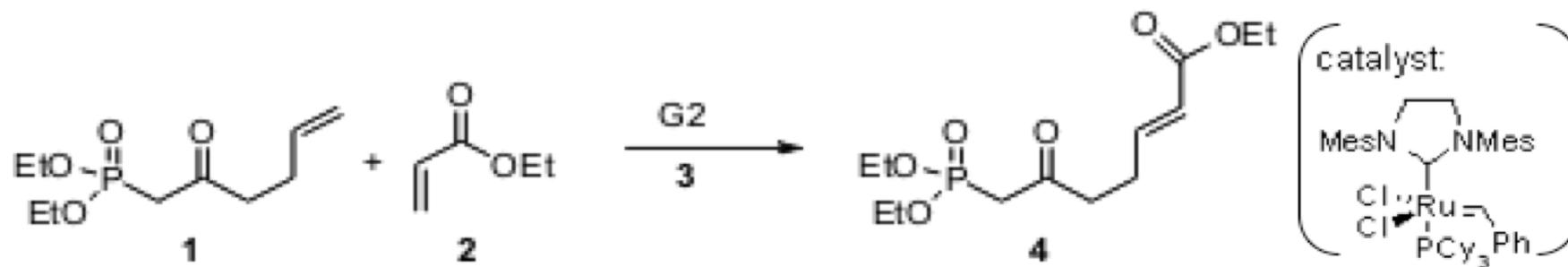


6.5.4 Synthèse d'alcène par Métathèse croisée

(cross-metathesis)

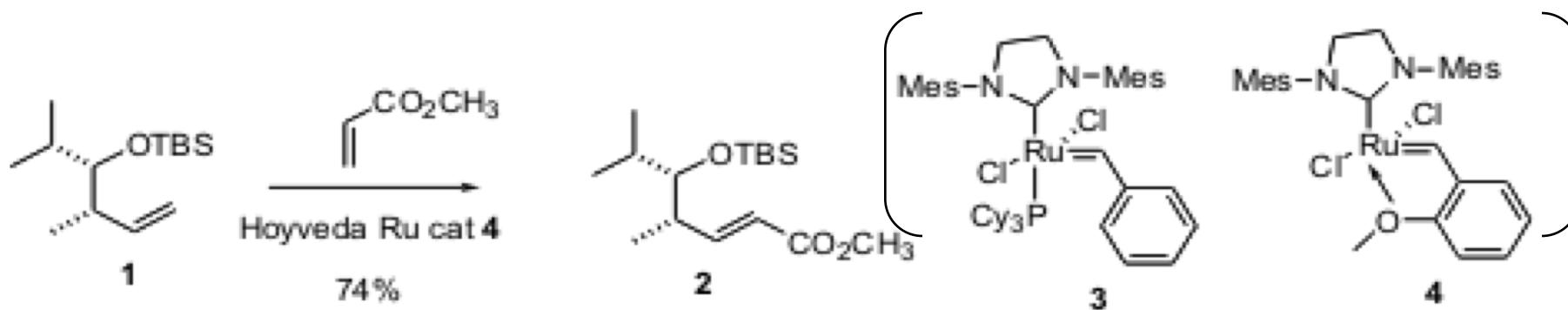
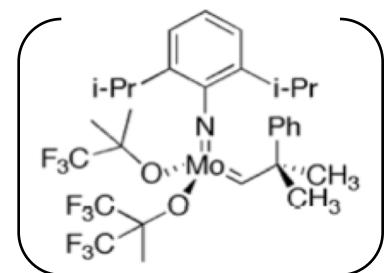
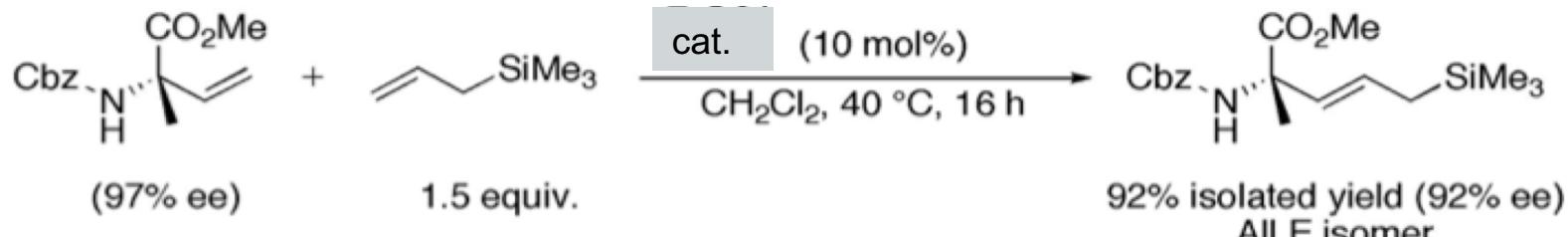


B. R. Galan, K. P. Kalbarczyk, S. Szczepankiewicz, J. B. Keister, S. T. Diver, *Org. Lett.*, **2007**, 9, 1203



W. V. Murray Johnson & Johnson, NJ
J. Org. Chem. **2005**, 70, 9636

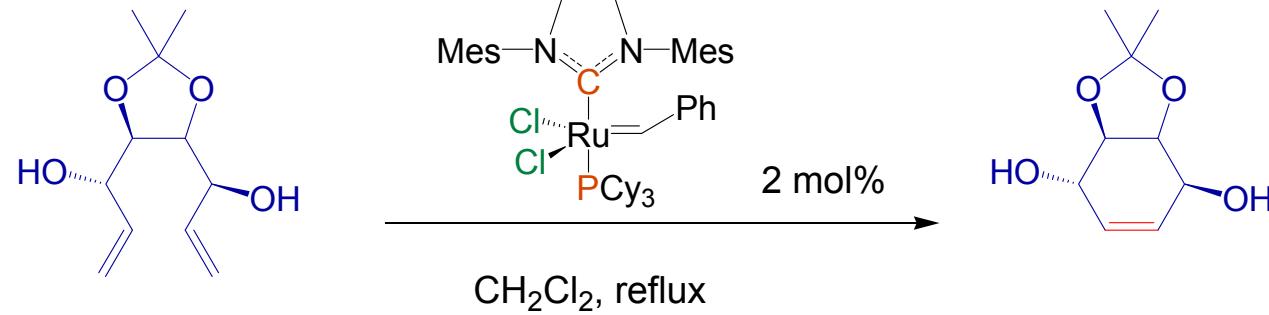
24 hours at rt, CH₂Cl₂
2 hours in refluxing CH₂Cl₂.
15 minutes, microwave irradiation



macrolide RK-397, Frank McDonald et al. *J. Am. Chem. Soc.* **2004**, 126, 2495

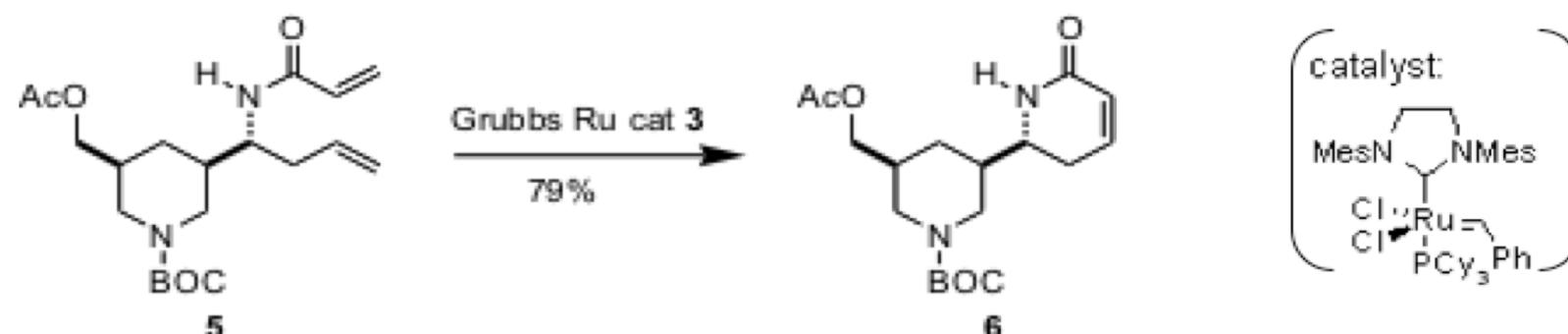
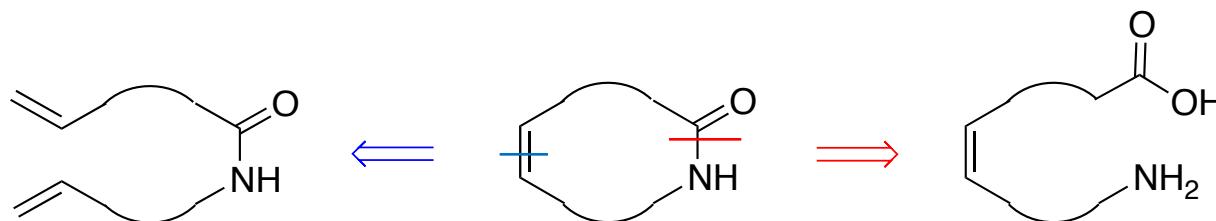
6.5.4 Synthèse d'alcène par Métathèse cyclisante

(ring closing metathesis -RCM)



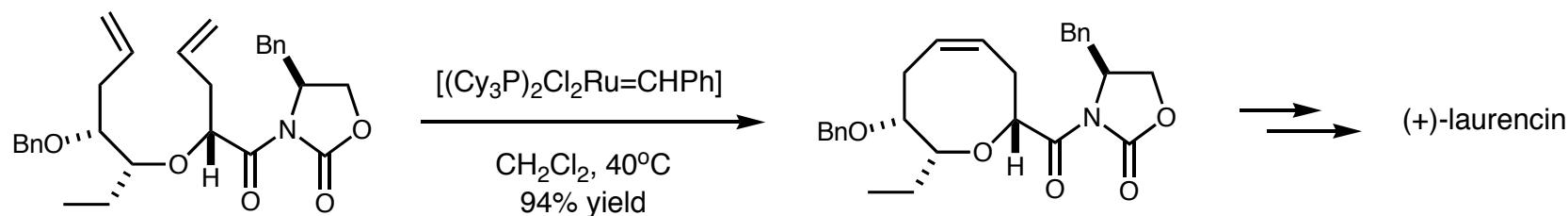
Org. Lett. 2002, 4, 1359

NB: stratégie complètement différente vers les hétérocycles

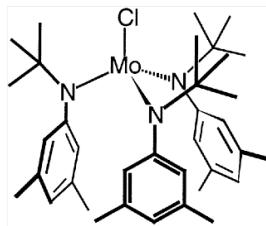
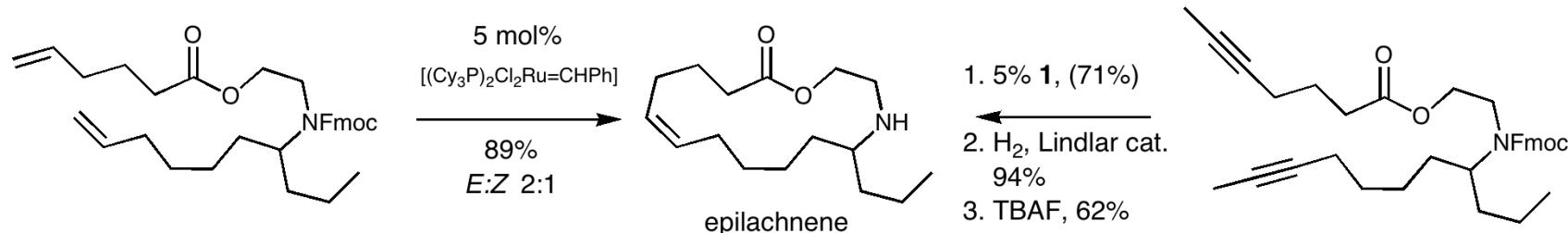
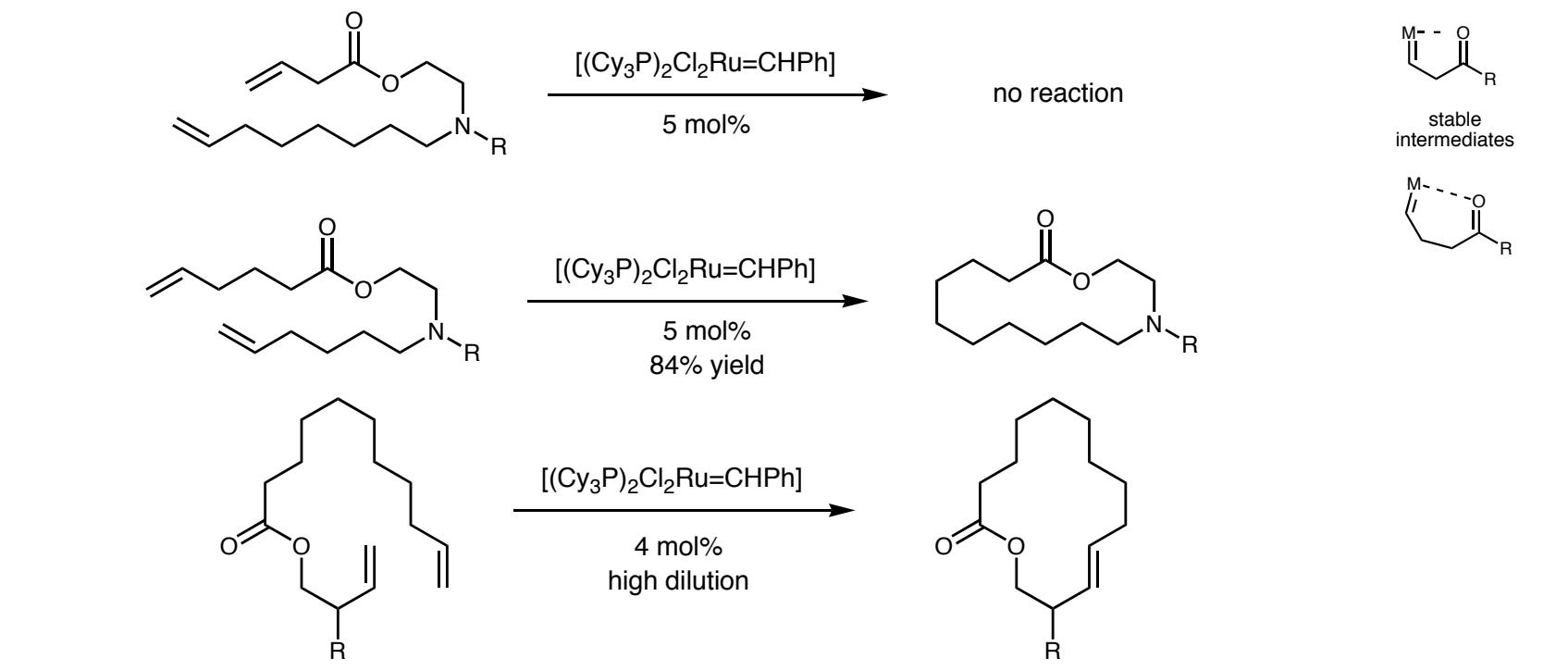


synthesis of (-)-cytisine

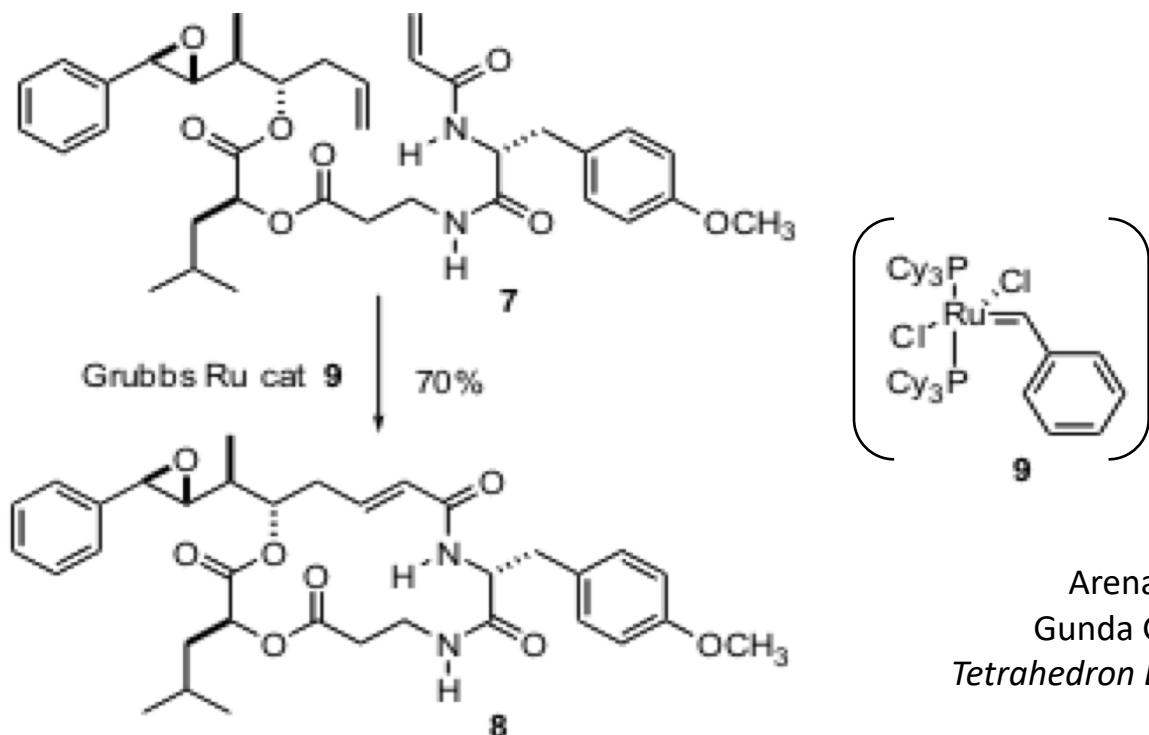
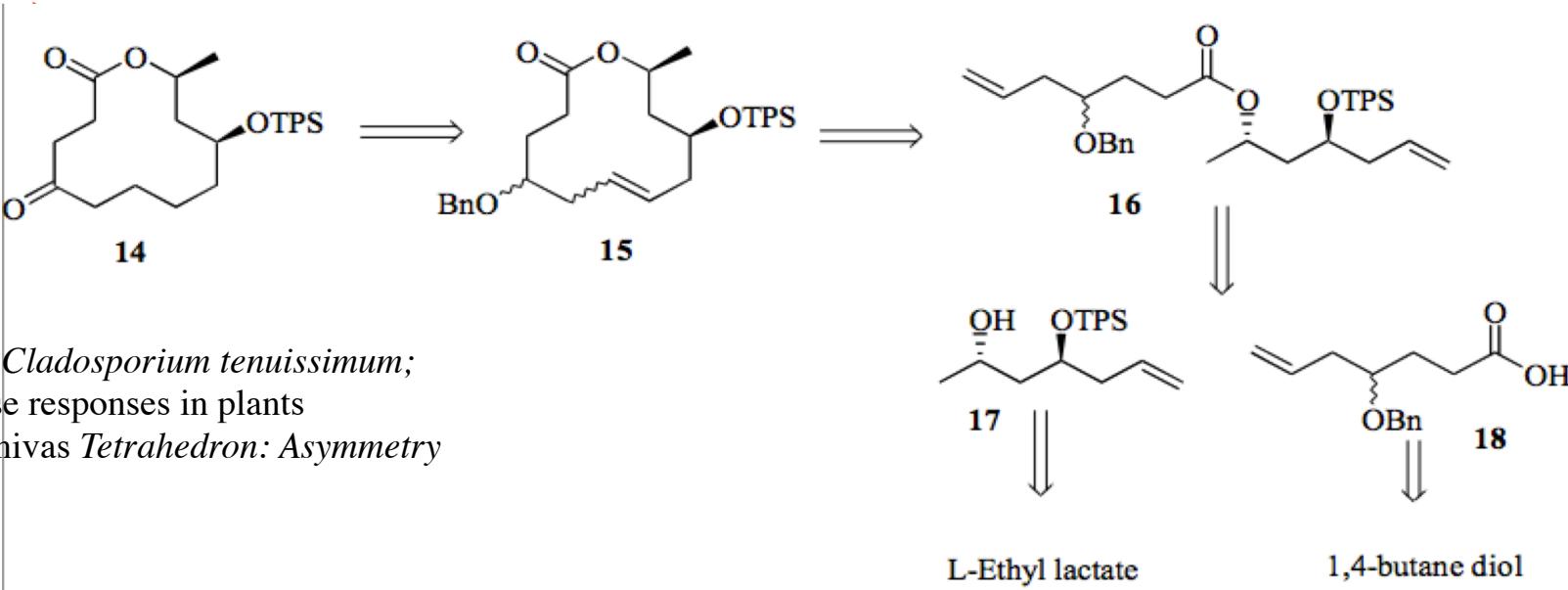
G. Lesma, A. Silvani, U. Milan *Org. Lett.* **2004**, 6, 493



Crimmins, M.T.; Emmitte, K.A. *Org. Lett.* **1999**, 1, 2029



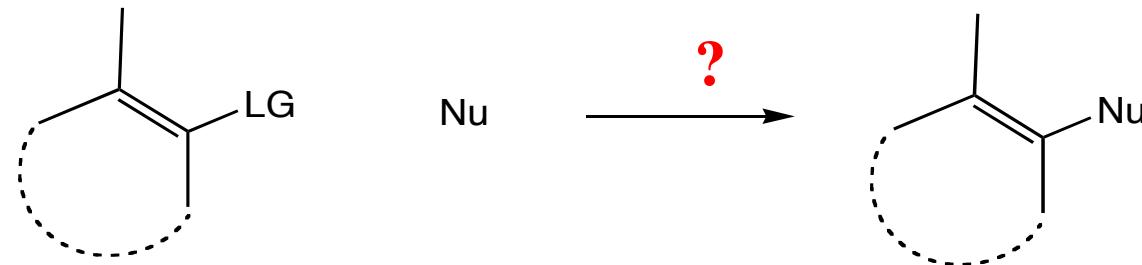
endophytic fungal strain *Cladosporium tenuissimum*;
induce systematic defense responses in plants
P. Radha Krishna, R. Srinivas *Tetrahedron: Asymmetry*
2008, 19, 1153



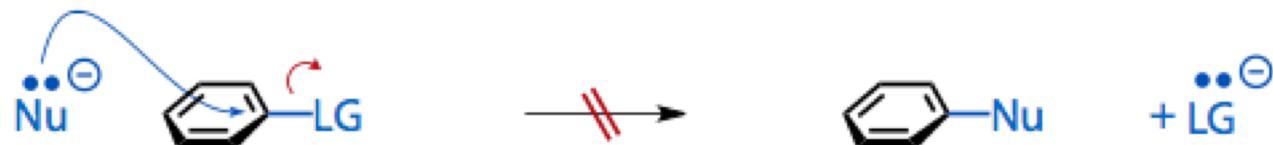
Arenastatin A **8**,
Gunda G. U. Kansas
Tetrahedron Lett. **2004, 45, 5309**

Chap. 7 Réactions de couplage

Formation de liaisons C-C, C-O, C-N sur Csp^2 , Csp :



SN_2 pas possible

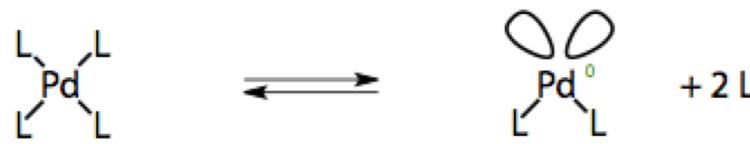


SN_1 ne marche pas

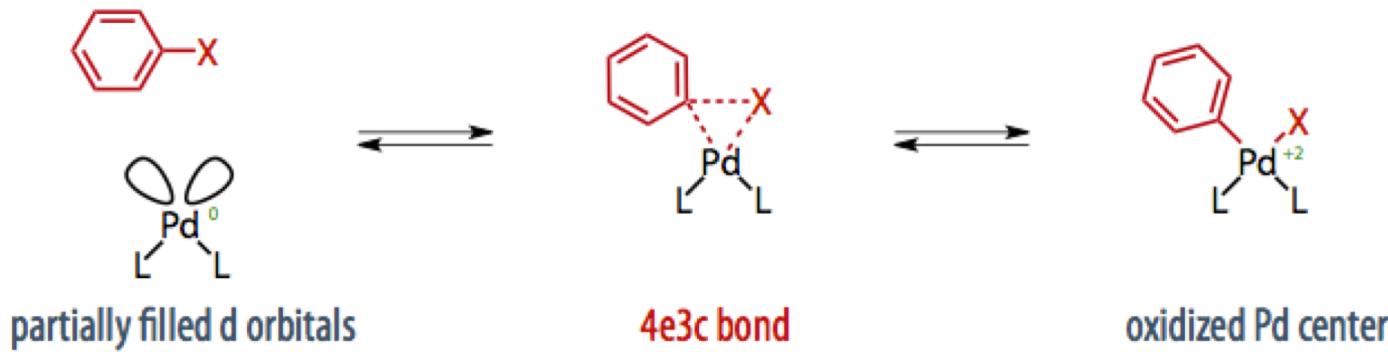


Basé sur les propriétés des m_T :

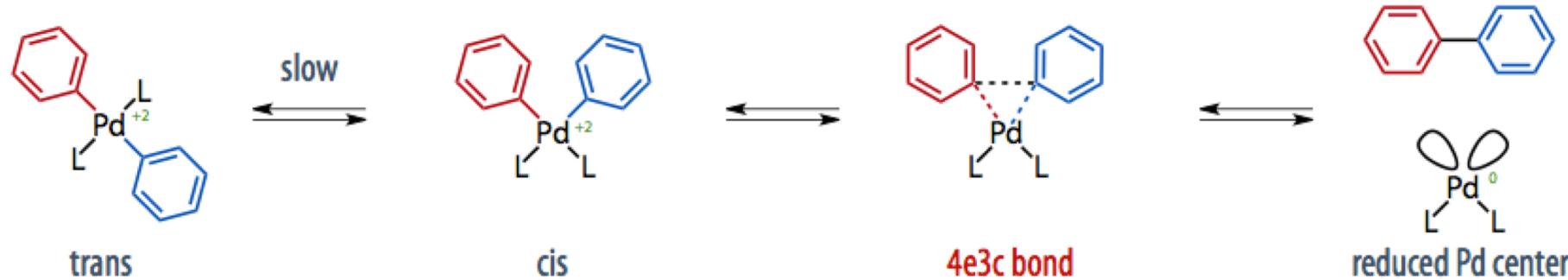
- Dissociation de ligand



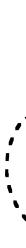
- Addition oxydante



- Elimination réductrice

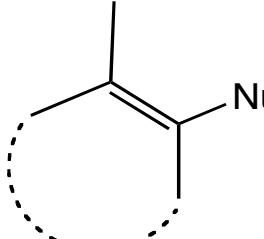


couplages catalysés par m_T :



Nu

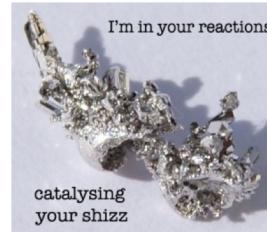
cat. m_T



LG = Hal
OSO₂CF₃
OPO(OR)₂

Nu =

- $m\text{---}\begin{array}{c} \text{C}=\text{C} \\ | \\ \text{C}=\text{C} \end{array}$
- $m\text{---}\equiv\text{C}$
- $m\text{---CN}$
- $m\text{---OR}$
- $m\text{---NR}_2$



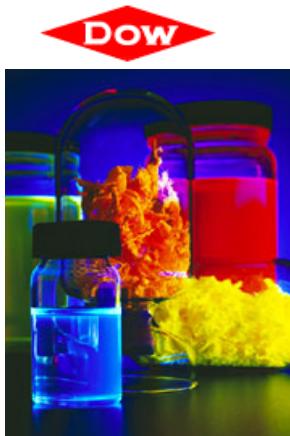
- Très nombreuses applications en synthèse, en industrie

Nicolaou et al.

Pd in Total Synthesis *Angew. Chem. Int. Ed.* **2005**, *44*, 4442



Nobel Prize in Chemistry 2010
"for palladium-catalyzed cross couplings in organic synthesis".



LUMATION*
Light-Emitting Polymers



fungicide boscalid plant (São Paulo, Brazil)



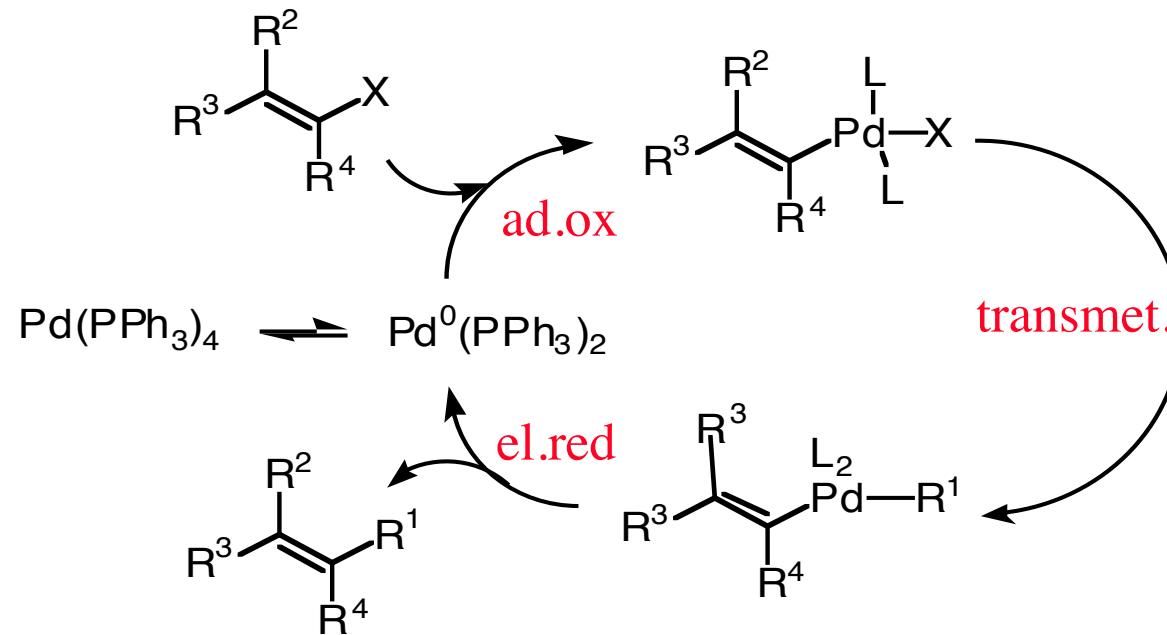
J-L Parrain, P. Pale
Pour la Science **2011** Dossier 73, 58-63

7.1 Les réactions de couplage catalysées par Pd°

Plusieurs mécanismes selon type de couplages

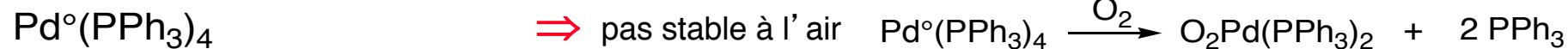
3 types de couplage

- début, fin ~ toujours identique (addition oxydante, élimination réductrice)
- varie selon l' étape intermédiaire (transmétallation ou autres)

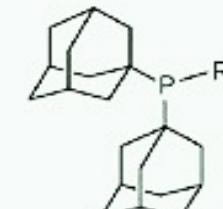
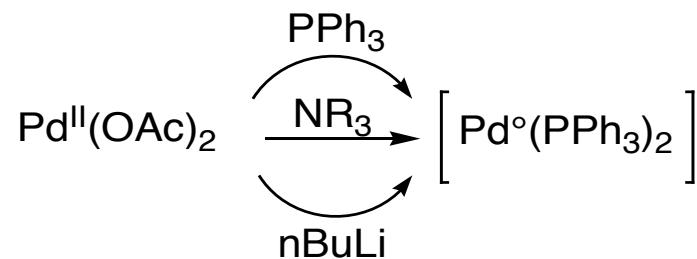
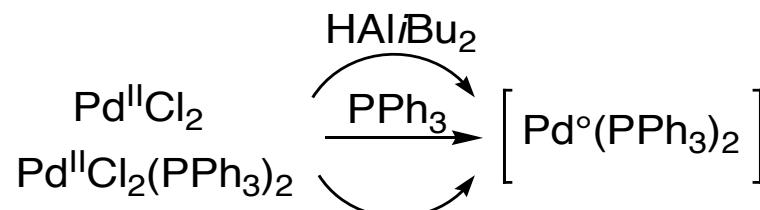


NB : espèce active toujours $\text{Pd}^\circ \text{ L}_2$ (mieux pour addition oxydante)

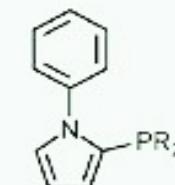
commerciaux



...mais souvent formé *in situ* par transmétallation et élimination réductrice

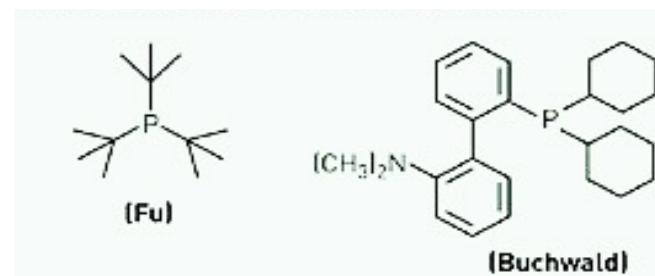
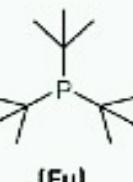


cataCXium A (Degussa)

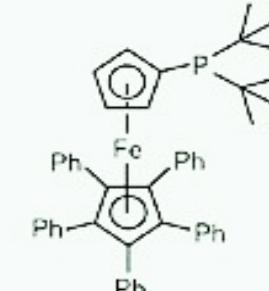


cataCXium P (Degussa)

...et large gamme de phosphines



(Buchwald)



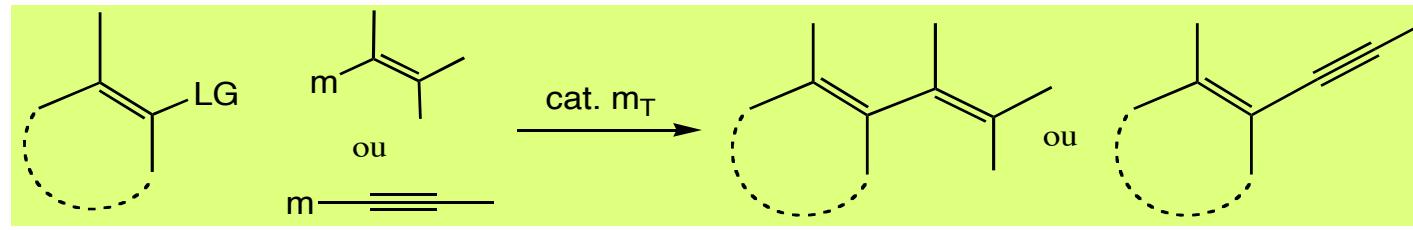
Q-Phos (Johnson Matthey)



SK-CC01-A (Solvias)

$\text{Ph} = \text{C}_6\text{H}_5$

7.2.1 couplage avec organométalliques préformés



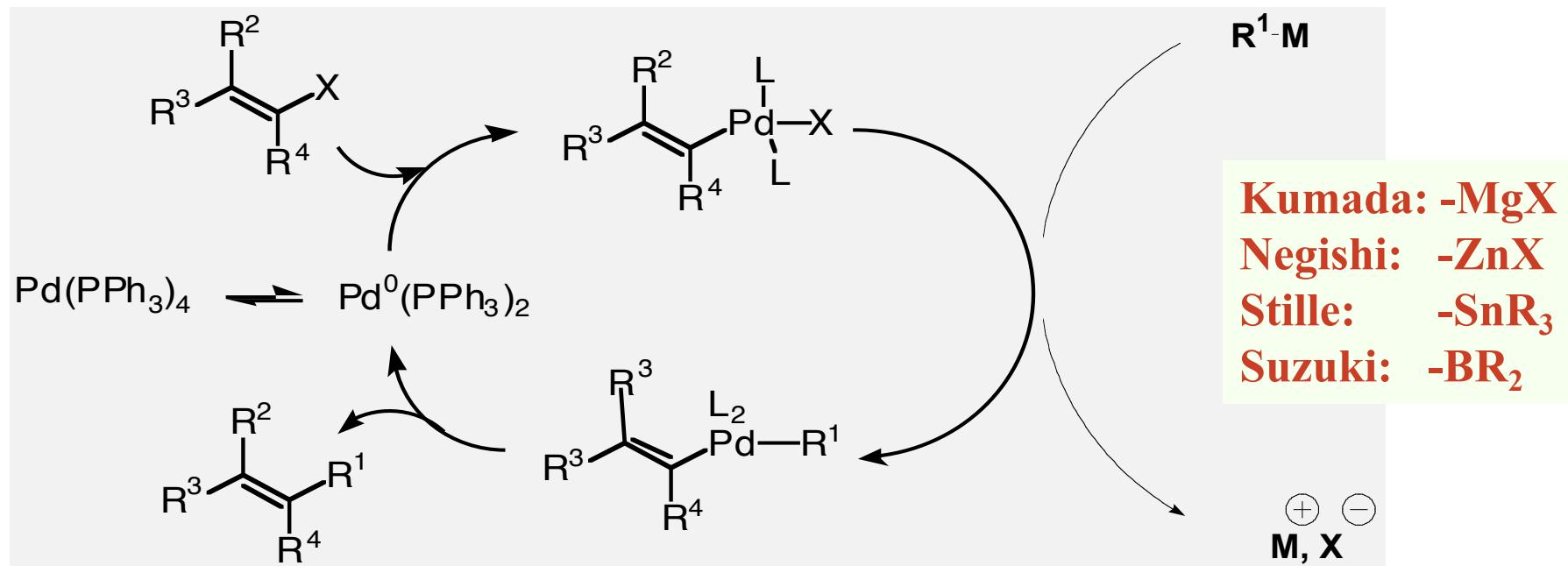
LG = Hal

OSO_2CF_3

$\text{OPO}(\text{OR})_2$

NB: addition oxydante suit force liaison $\Rightarrow \text{OTf} \approx \text{I} > \text{Br} \gg \text{Cl}$

Couplage : transmétallation avec organométalliques déjà formés



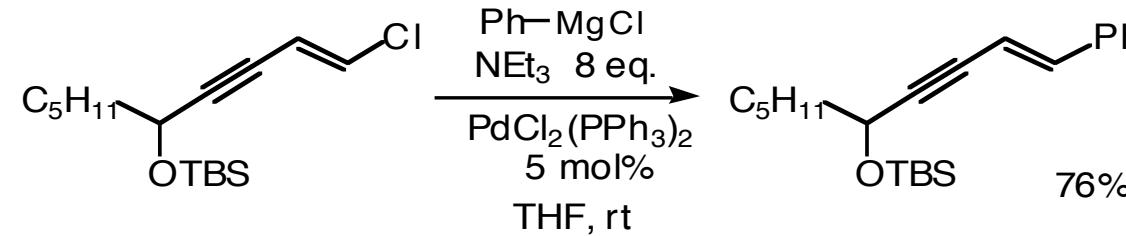
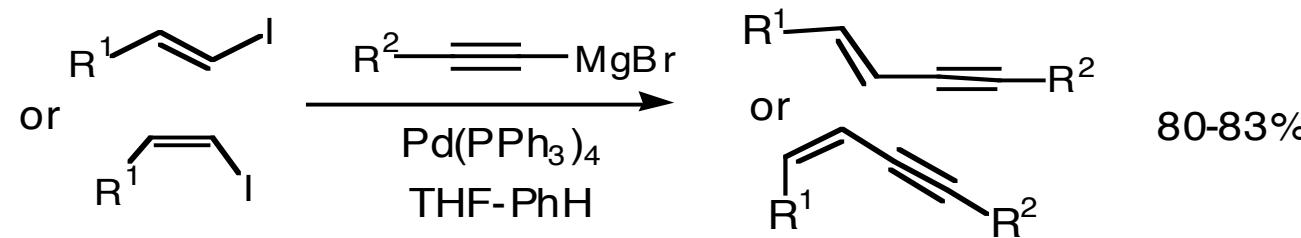
- couplage de Corriu-Kumada **R-MgX**

Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, 94, 4374;

Corriu, R. J. P.; Masse, J. P.; *J. Chem. Soc. Chem. Commun.* **1972**, 144

Yamamura, M.; Moritani, I.; Murahashi, S-i *J. Organomet. Chem.* **1975**, 91, C39;

Fauvarque, J. F.; Jutand, A. *Bull. Soc. Chim. Fr.* **1976**, 765



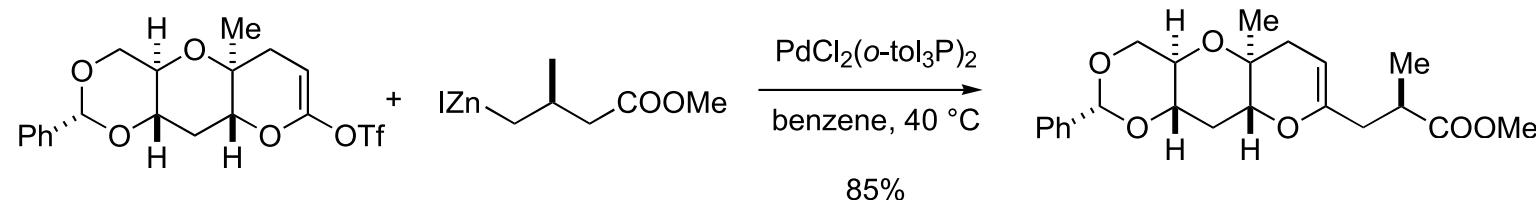
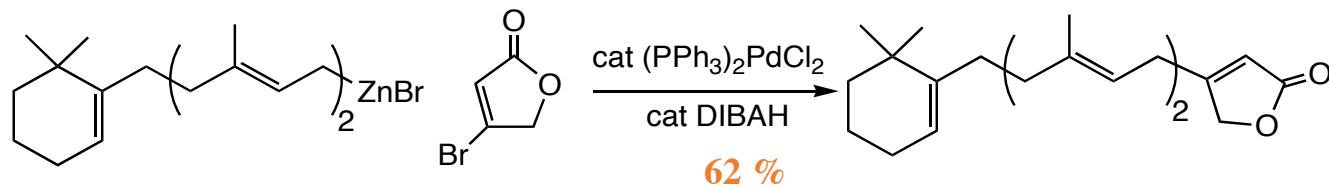
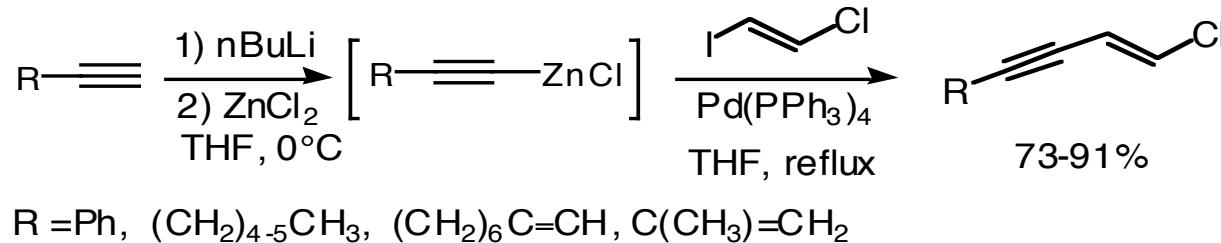
Ramasiandra, P.; Bréhon, B.; Thivet, A.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* **1997**, 38, 2447

- couplage de Negishi R-ZnX

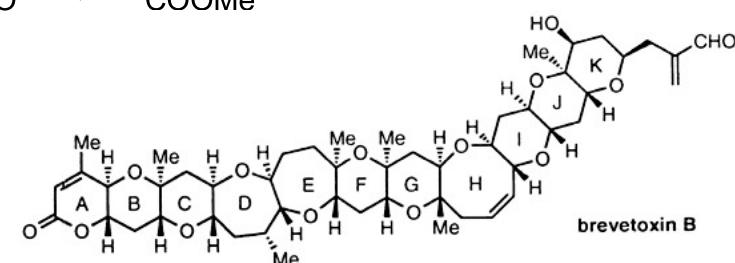
King, A.O.; Okukado, N.; Negishi, E.-i. *J. Chem. Soc. Chem. Commun.* **1977**, 683-684;
Fauvarque, J. F.; Jutand, A. *Bull. Soc. Chim. Fr.* **1976**, 765



The Nobel Prize in Chemistry 2010
Richard F. Heck, Ei-ichi Negishi, Akira Suzuki



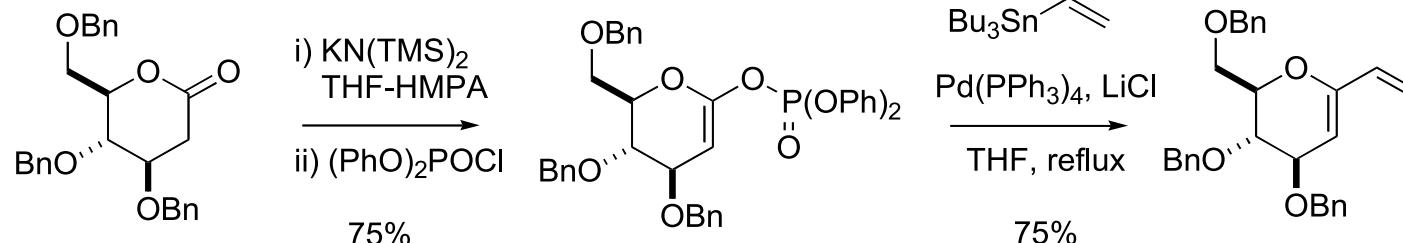
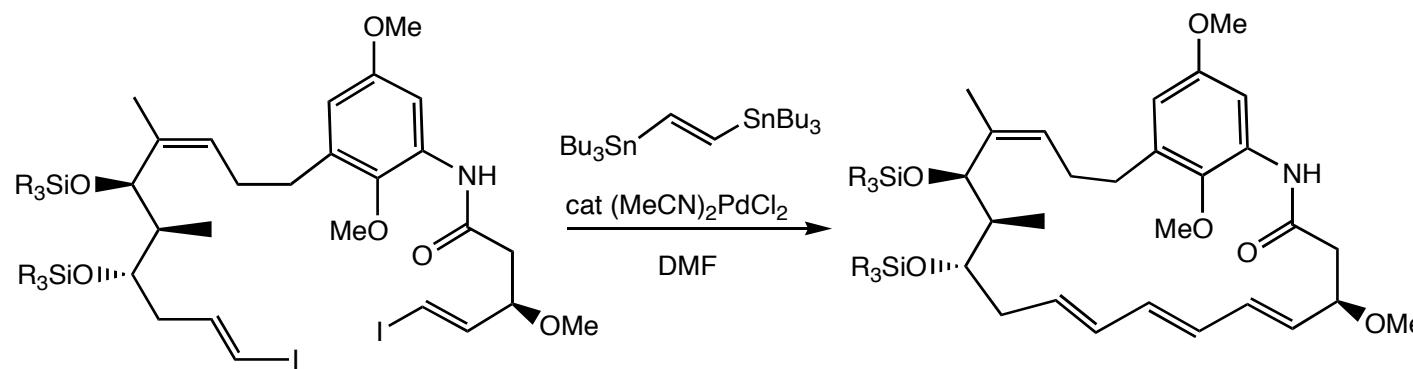
Kadota I, Takamura H, Nishii H, Yamamoto Y *J Am Chem Soc* **2005** 127, 9246



- couplage de Migita-Stille **R-SnR'**₃

Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301
Milstein, D.; Stille, J.K. *J. Am. Chem. Soc.* **1978**, 100, 3636

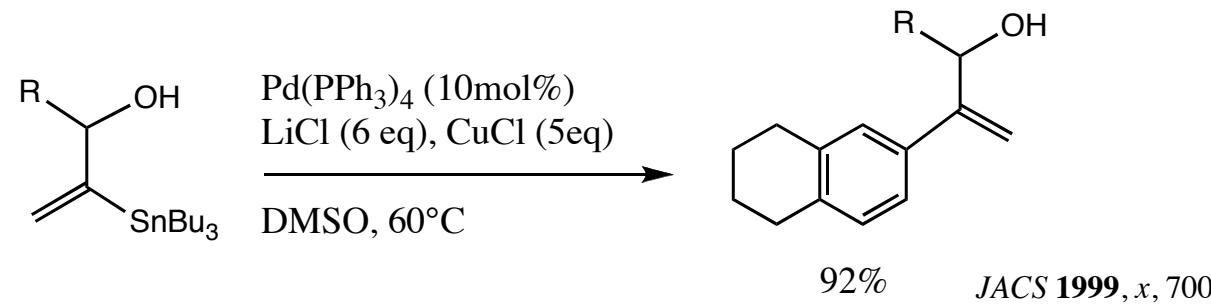
Avantages: facile d' accès, stable
Désavantage = toxicité, svt chauffage



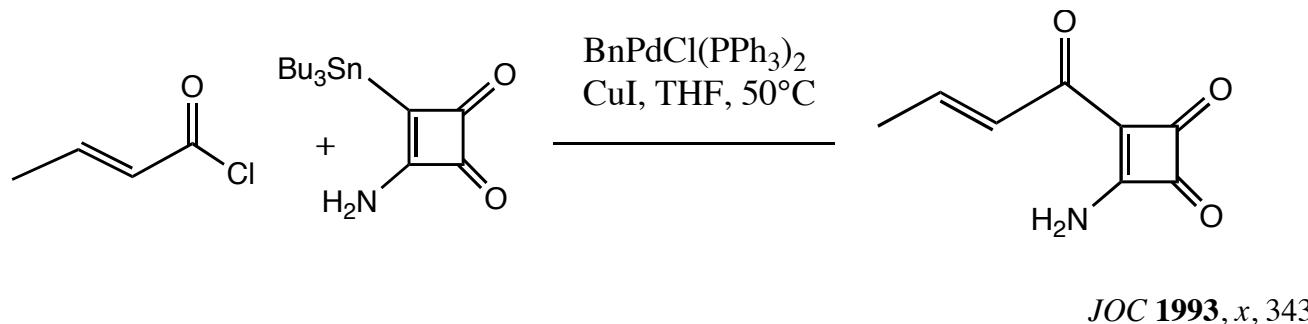
Avantages:
Désavantage

facile d'accès, stable
toxicité, svt chauffage

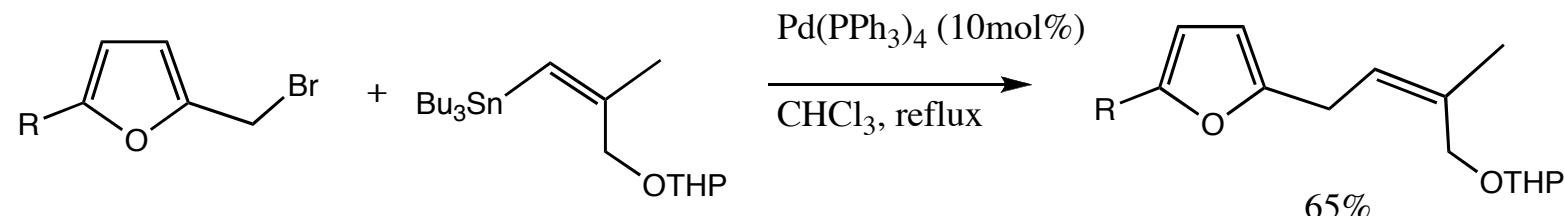
+ rapide si LiCl xs
si transmet CuX



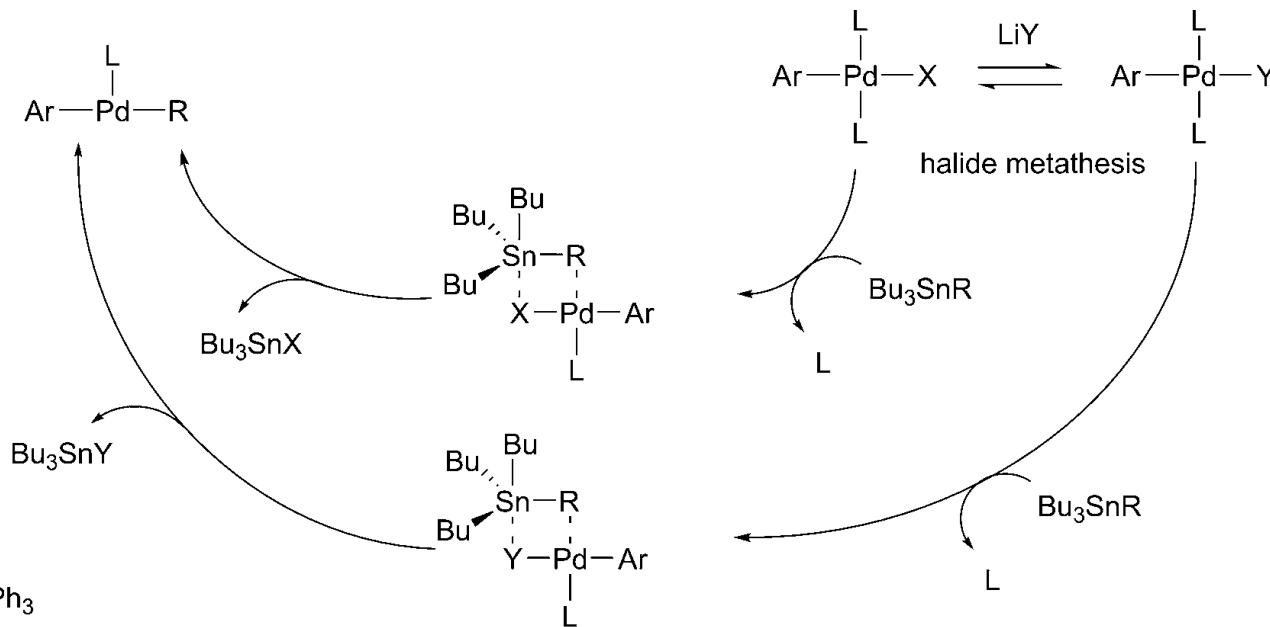
- Cl d'acide



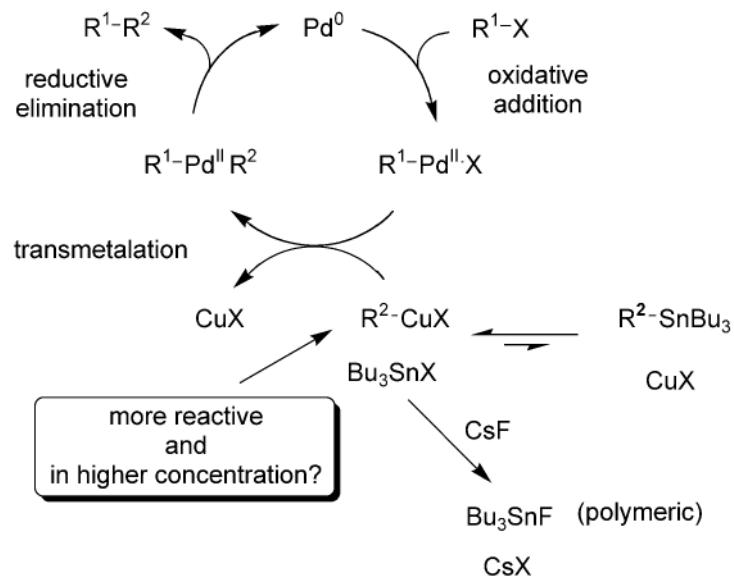
- Couplages benzyliques possibles



mécanisme



A. Jutand and coll. *Chem. Eur. J.* **2010**, *16*, 12831



- couplage de Suzuki **R-BR'**₂

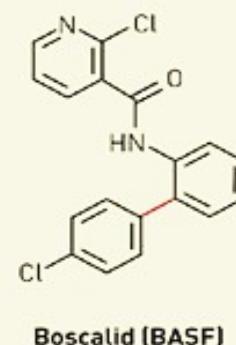
Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457



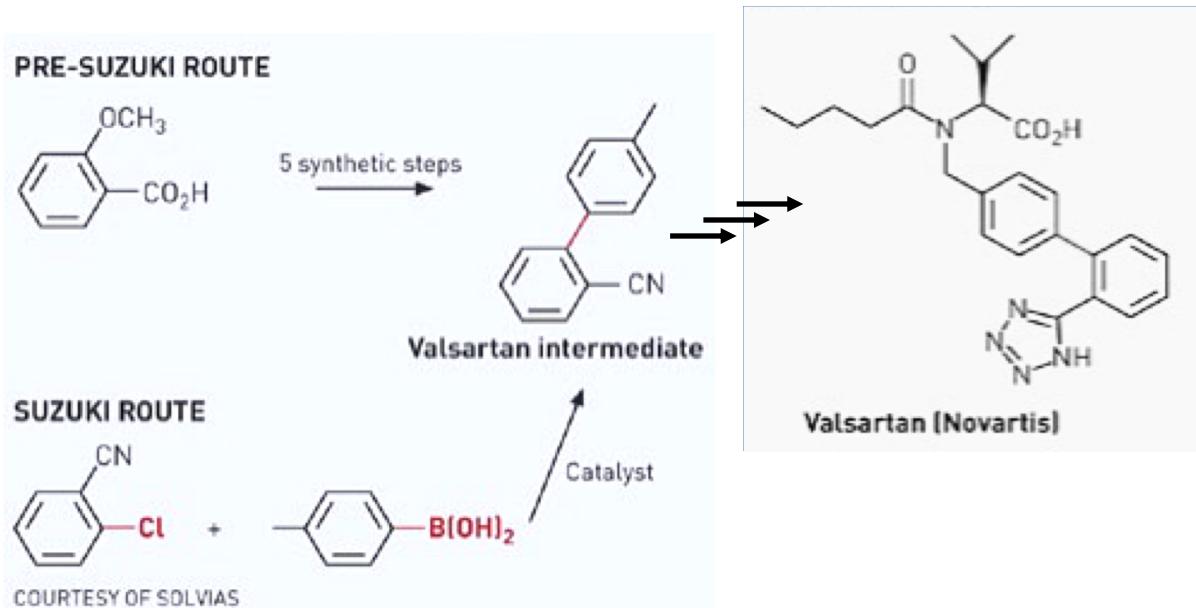
Le + utilisé,
industrialisé :



BASF plant in
Guaratingueta,
São Paulo.

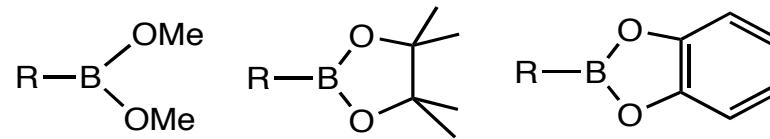


The Nobel Prize in Chemistry 2010
Richard F. Heck, Ei-ichi Negishi, Akira Suzuki

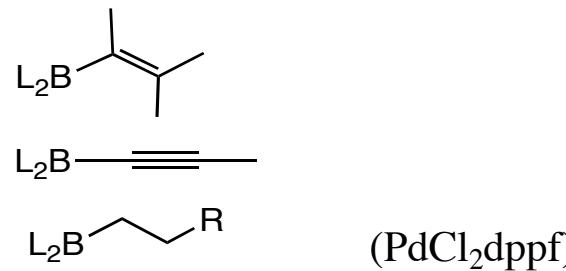


- couplage de Suzuki **R-BR'**₂

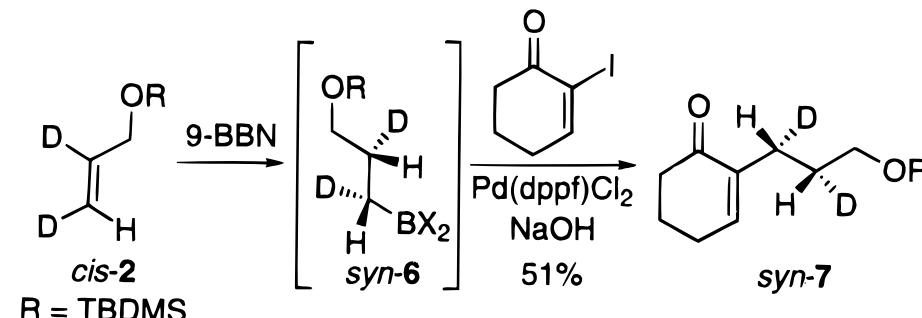
Avantages: facile d' accès, stable, non-toxique



alkylboranes utilisables (pas β -elim)



Rétention de configuration alkylboranes

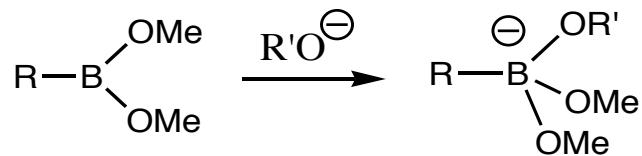


Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461-470;
Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458

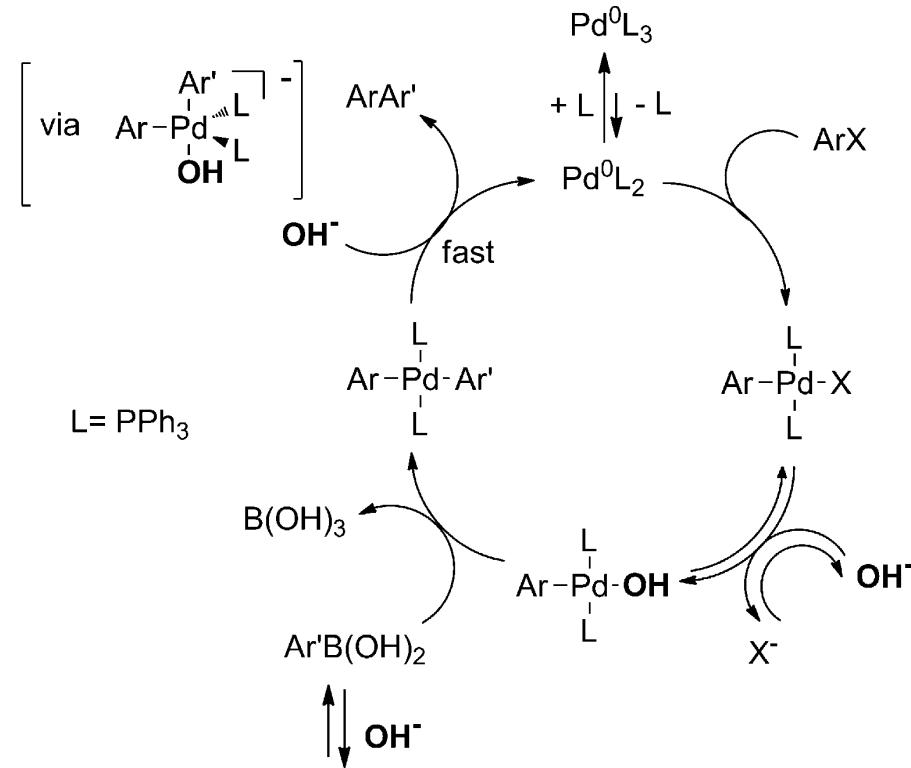
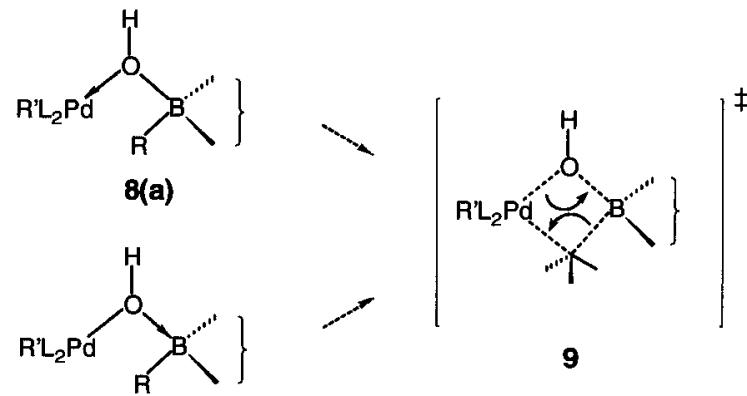
- couplage de Suzuki **R-BR'**₂

Avantages: cf avant

Désavantage = activation basique



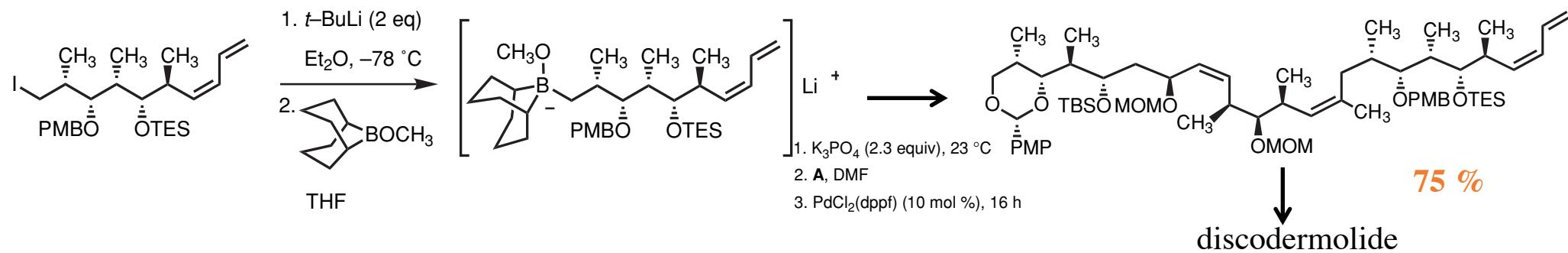
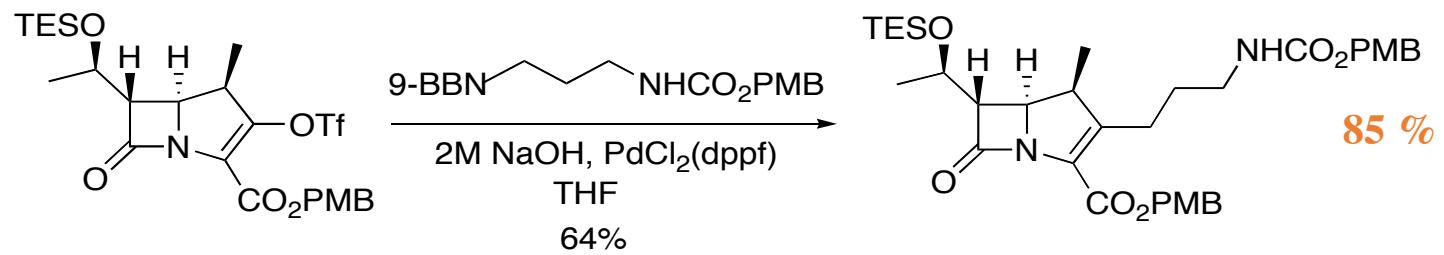
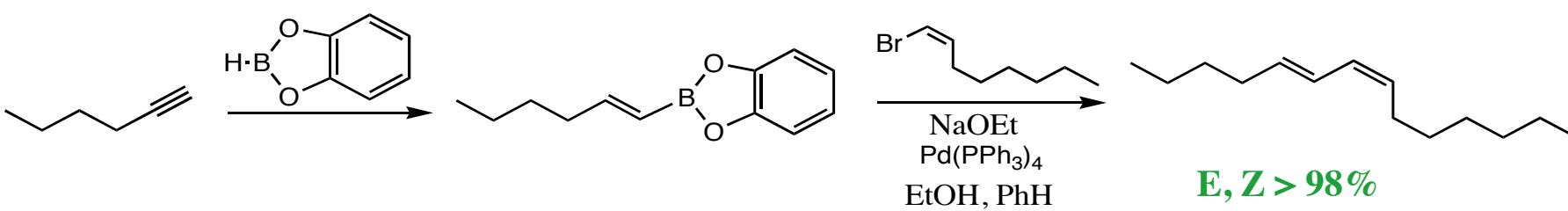
nécessaire pour transmétallation ?



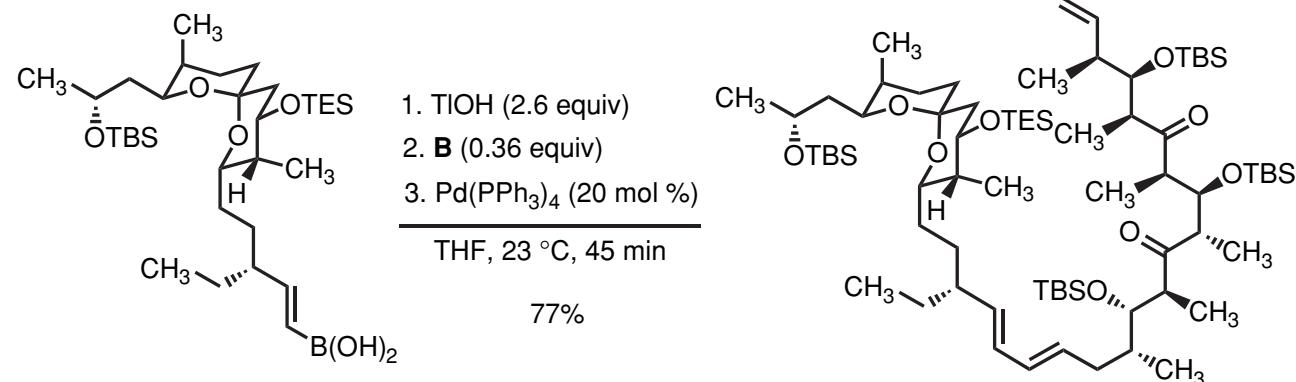
Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461-470;
Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458

unreactive $\text{Ar}'\text{B}(\text{OH})_3^-$

A. Jutand and coll. *Chem. Eur. J.* **2013**, *19*, 10082

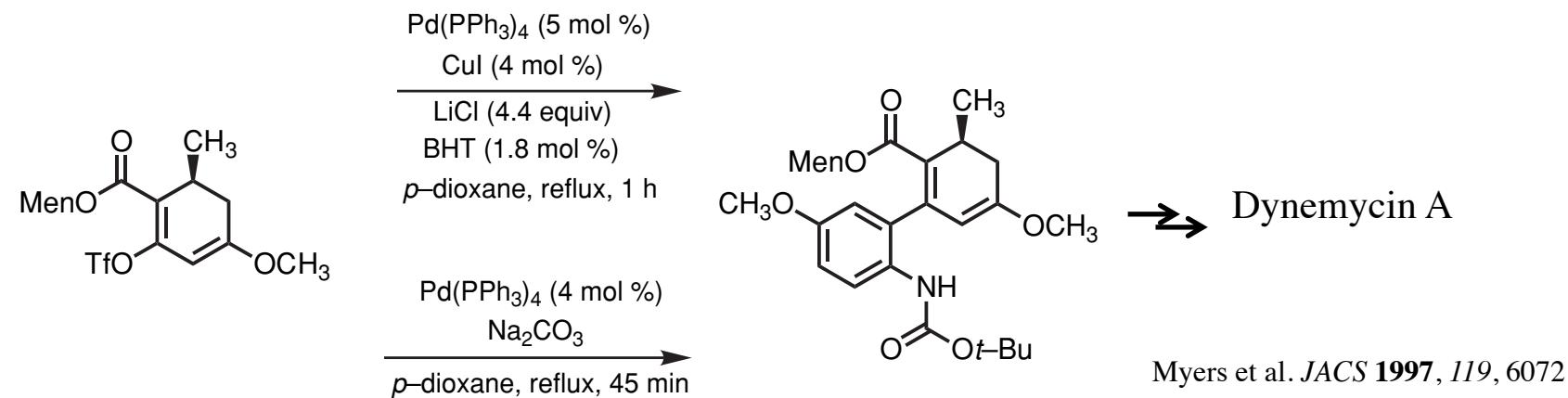
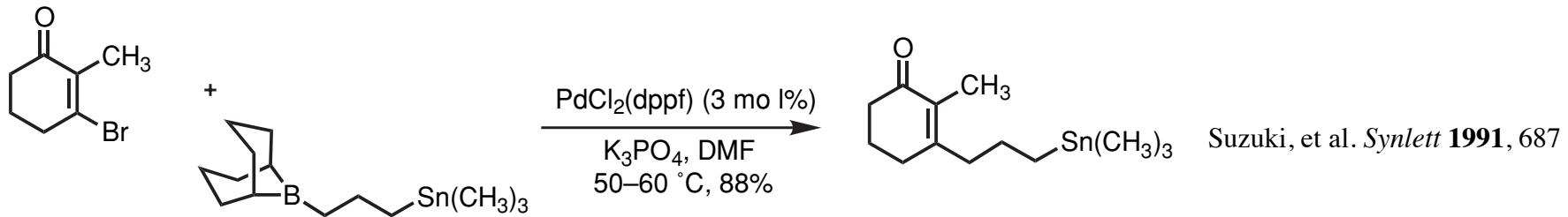


Marshall, J. A.; Johns, B. A
J. Org. Chem. **1998**, *63*, 7885

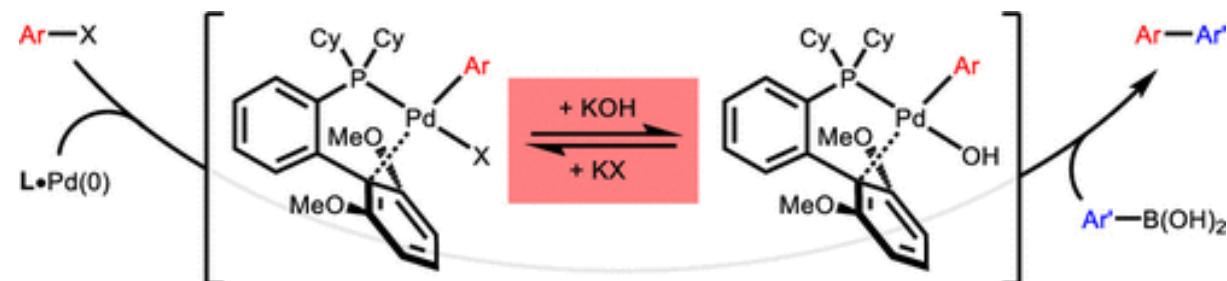


Evans, D. A.; Ng, H. P.; Rieger, D. L
J. Am. Chem. Soc. **1993**, *115*, 11446

+ efficace que réact. Stille

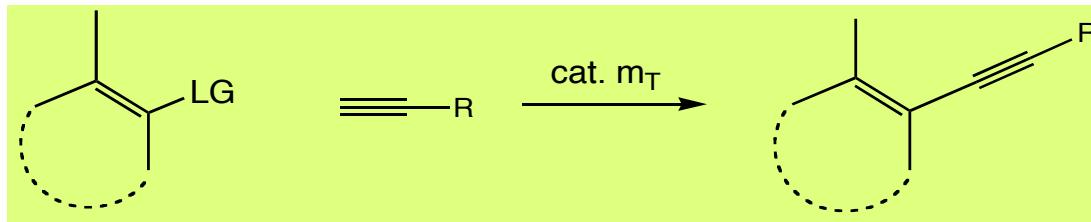


+ efficace avec L Buchwald-Hartwig



J. J. Fuentes-Rivera, M. E. Zick, M. A. Dufert, P. J. Milne,
Org. Proc. Res. Dev. 2019, 23, 1631

7.2.2 couplage avec organométalliques formés *in situ*

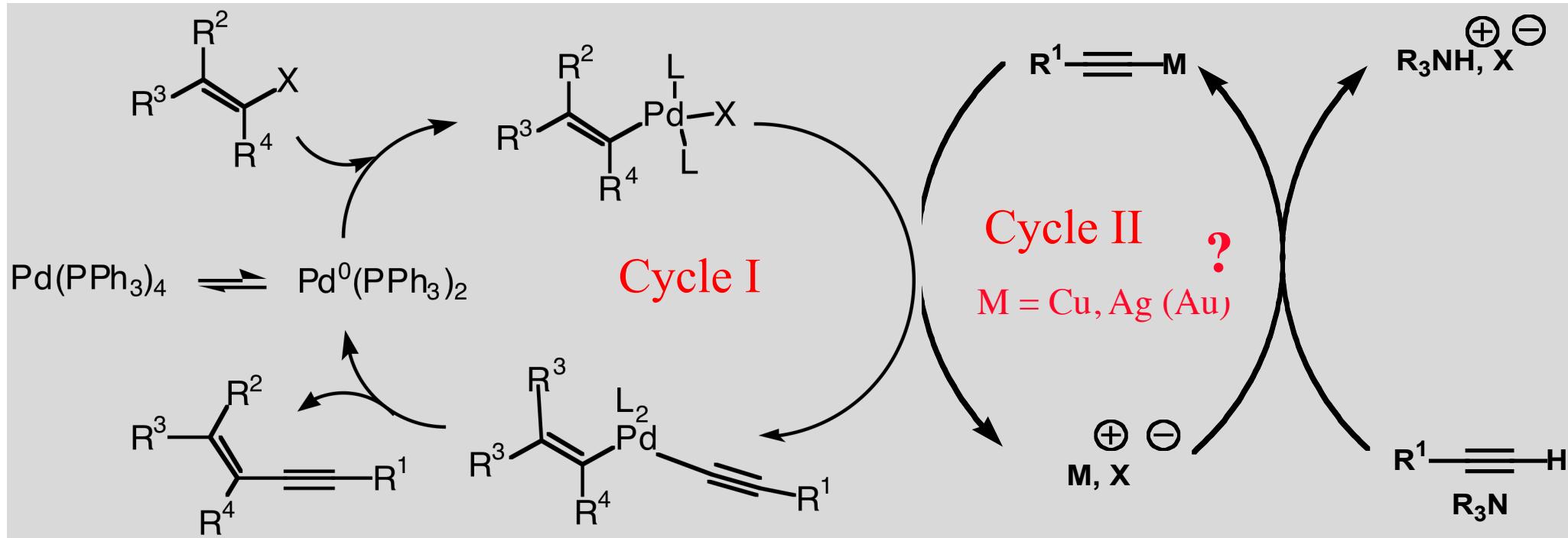


Sonogashira,
Tetrahedron Lett.
1975, 16, 4467

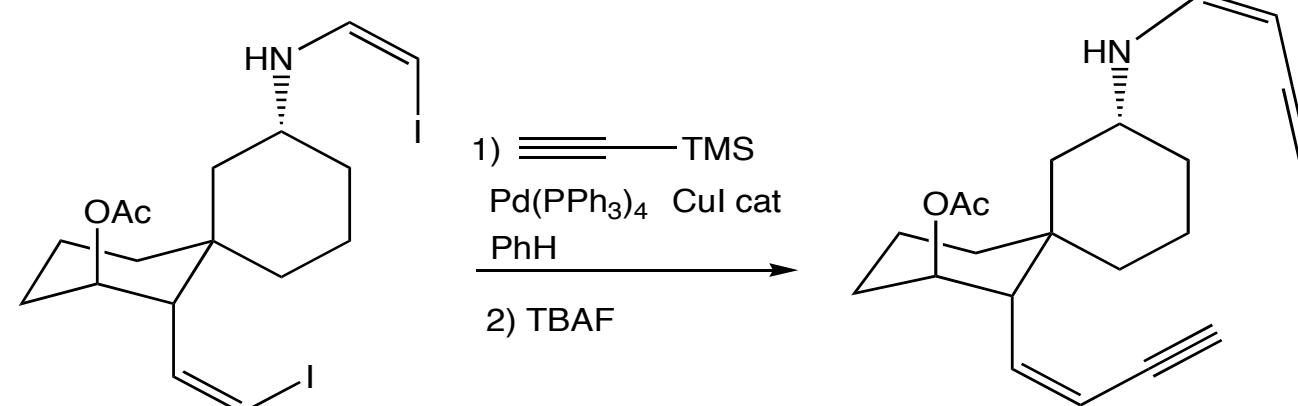
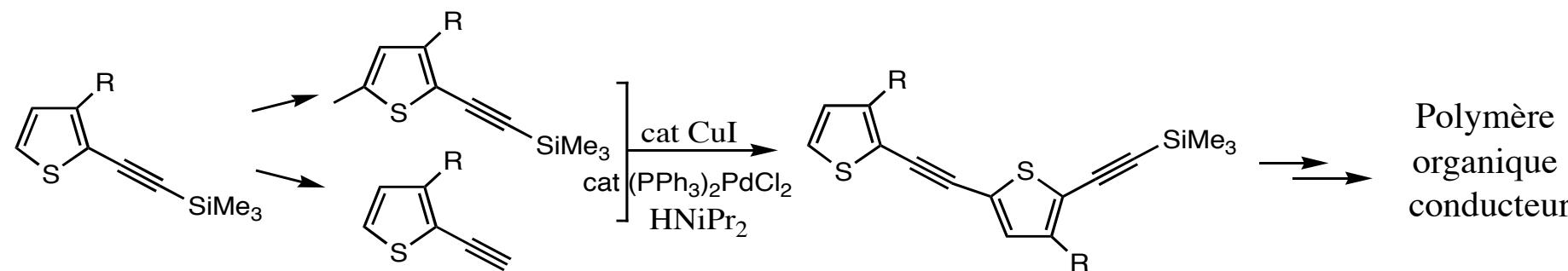
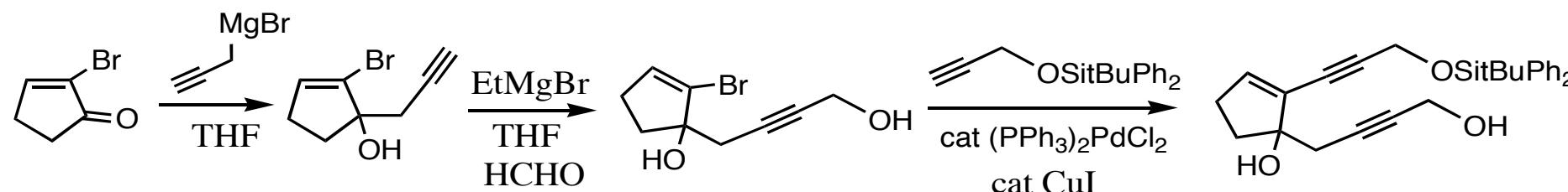
Cacchi
Synthesis **1986**, 320

Linstrumelle
Tetrahedron Lett.
1993, 34, 6403

Pale
J. Organomet. Chem.
1998, 567, 173

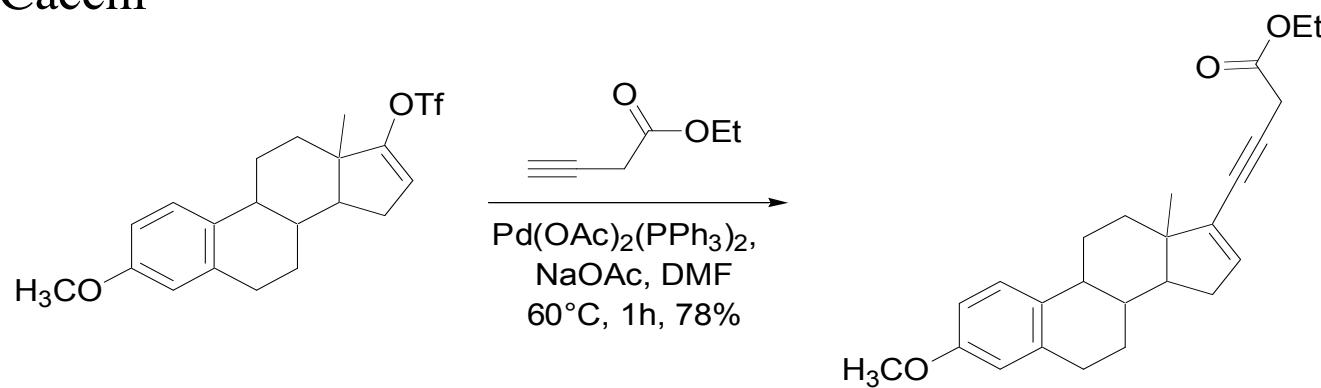


- couplage de Sonogashira

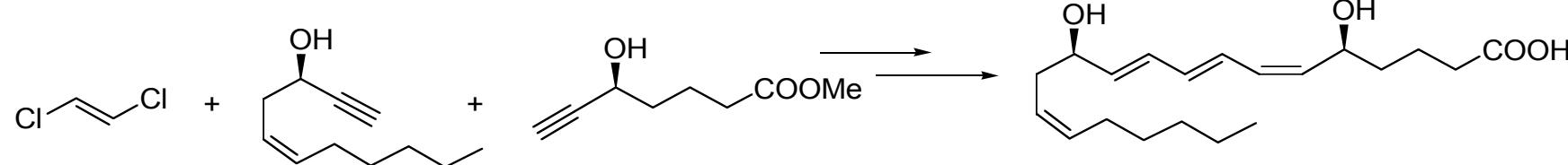
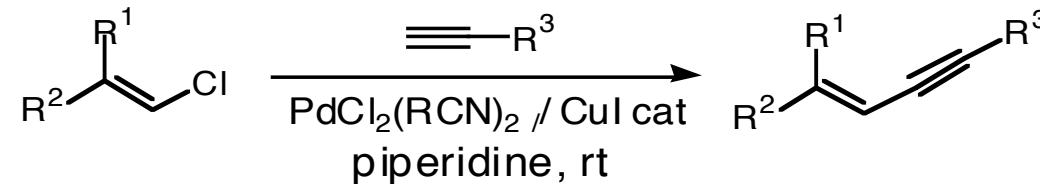
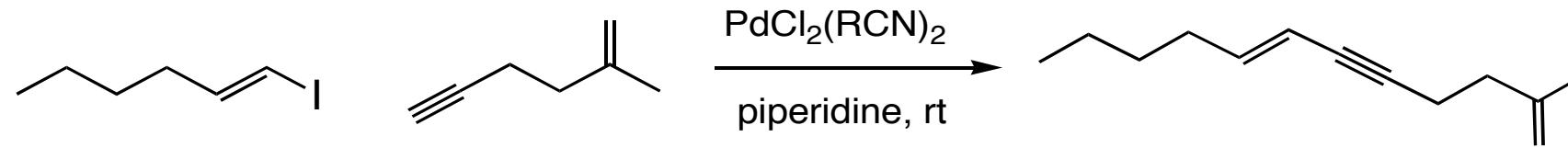


$(-)$ -Histrionicotoxin

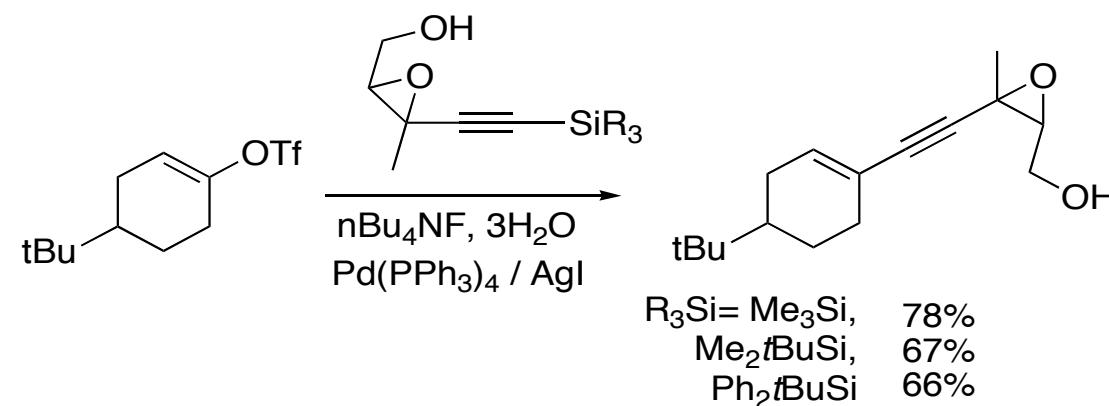
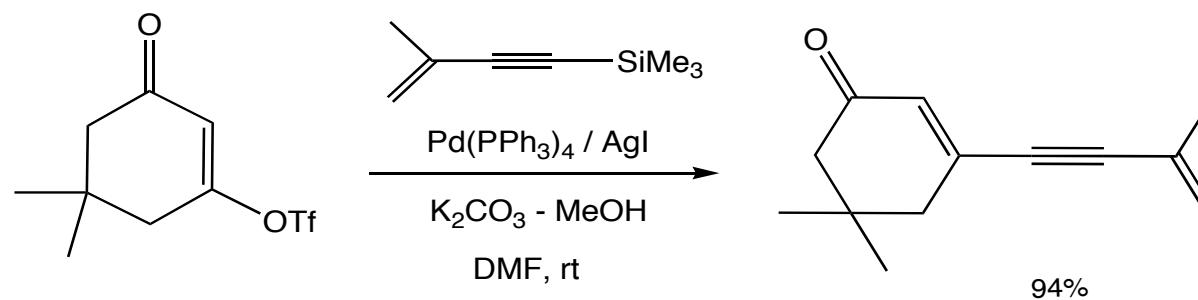
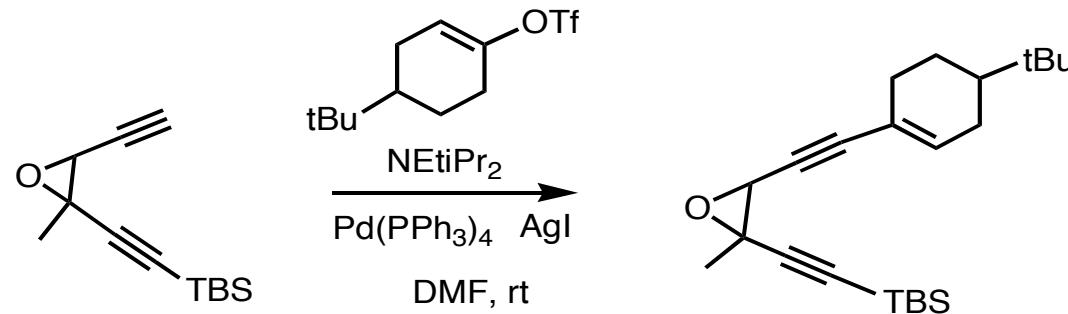
- couplage de Cacchi

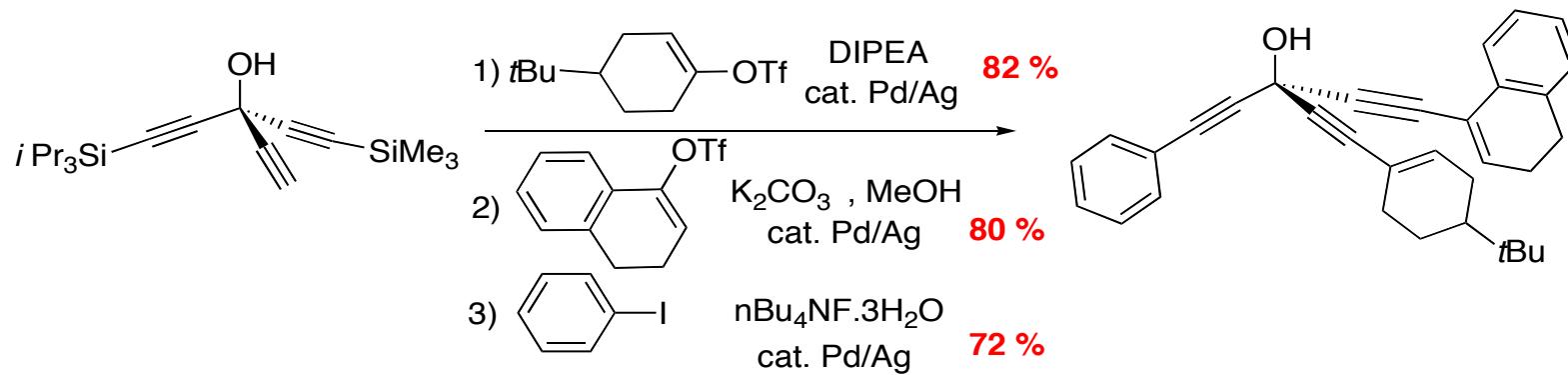
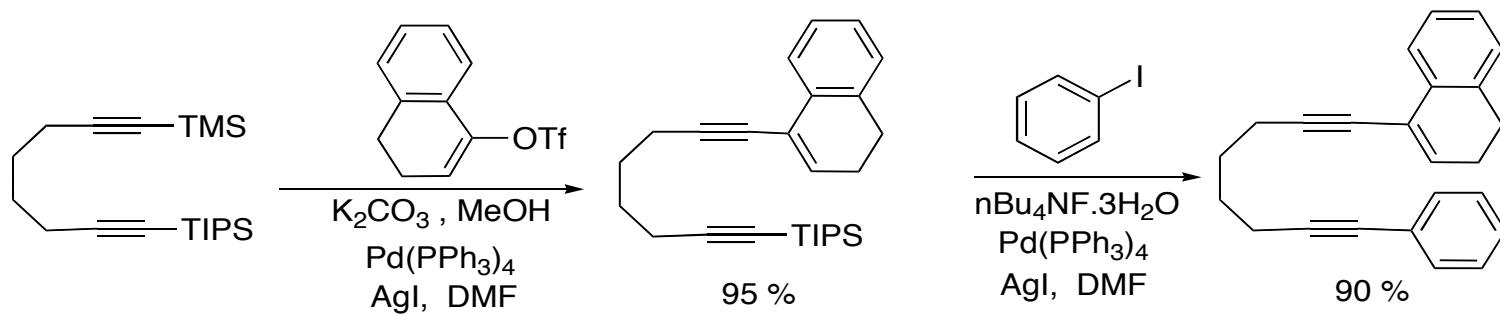


- couplage de Linstrumelle



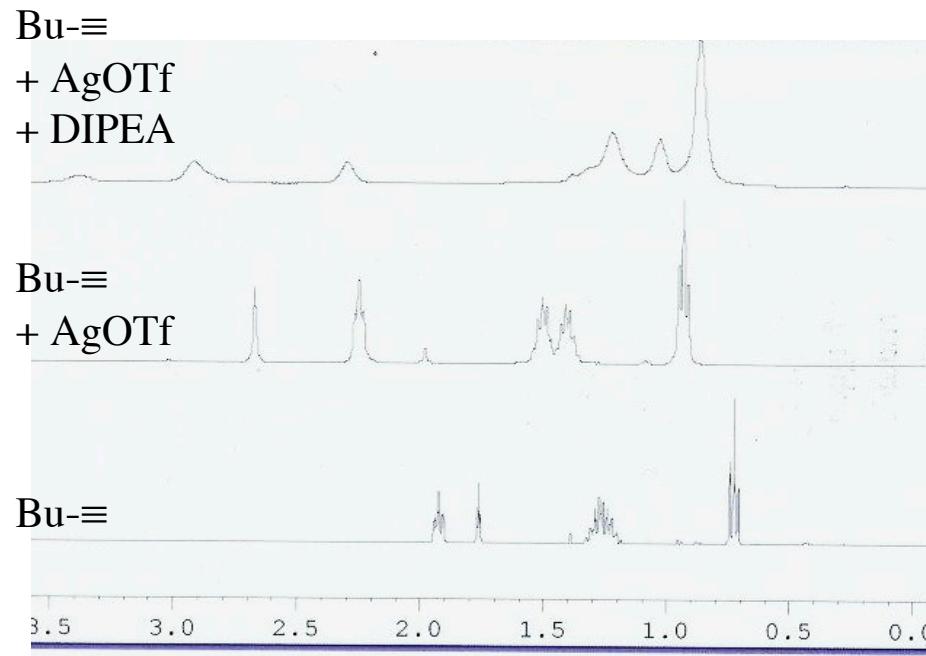
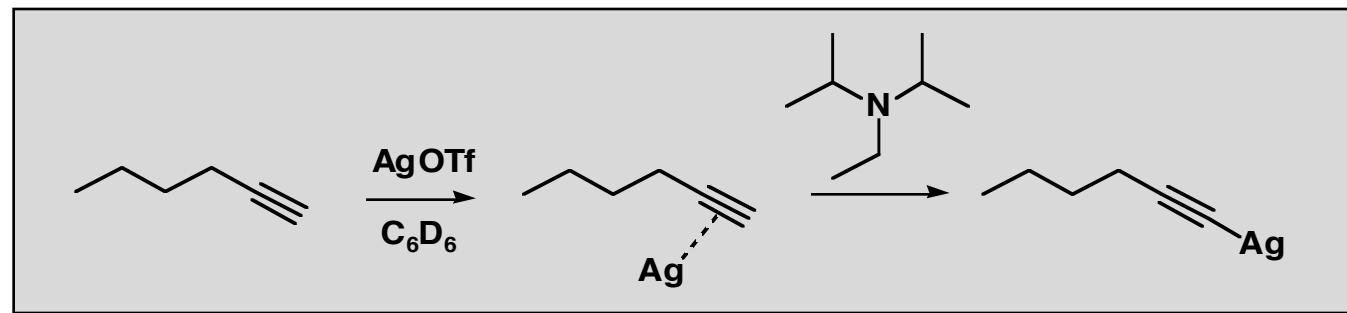
- couplages



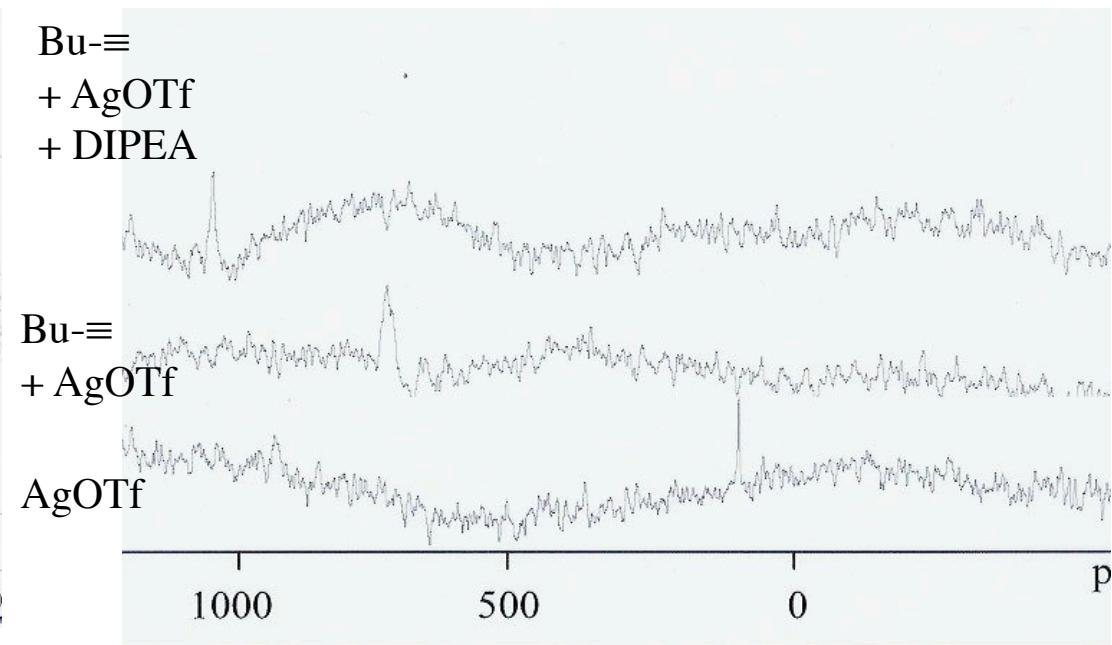


- couplage type Sonogashira: mécanisme

Pale et al. *J. Org. Chem.* **2005**, 70, 9185



RMN ^1H



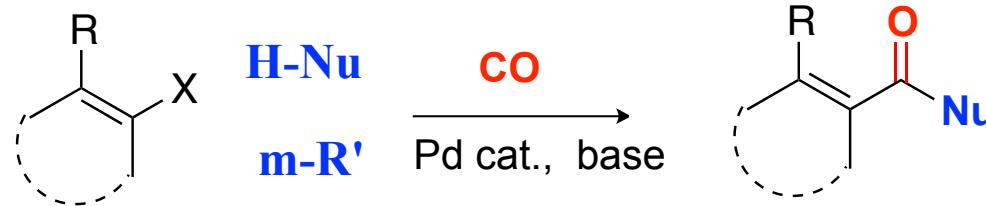
RMN ^{109}Ag

7.2.3 couplages avec insertion

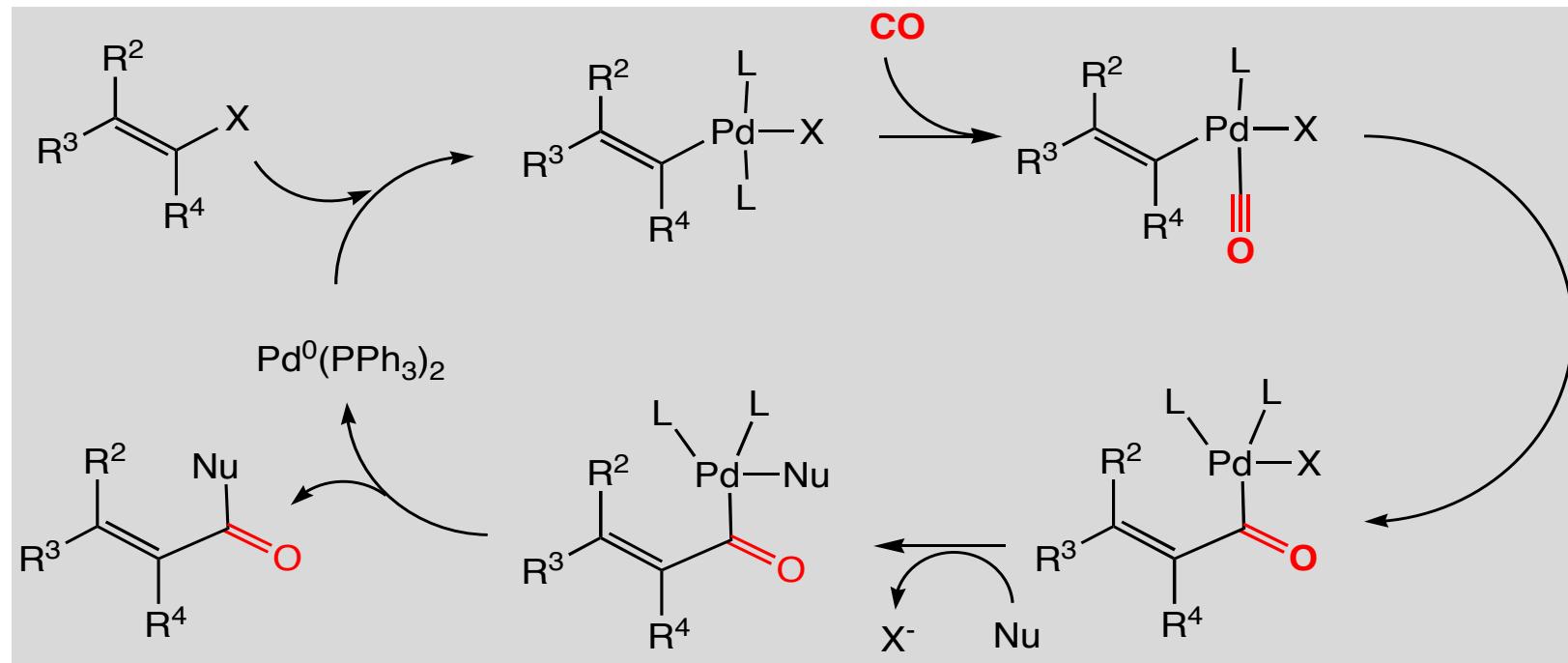
couplages où étape supplémentaire d' insertion

- CO
- alcènes

- couplages avec insertion de CO (carbonylation)

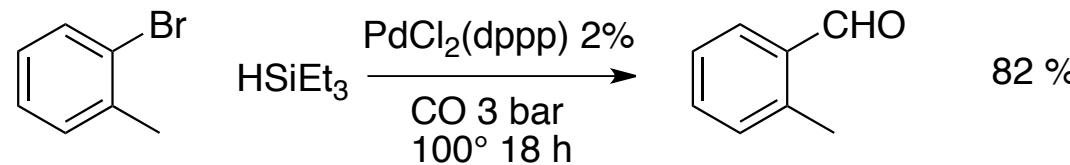
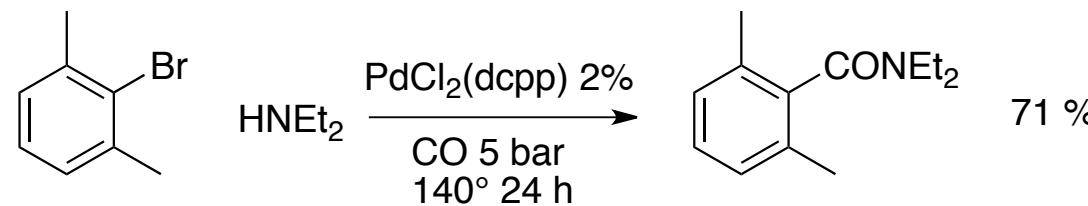
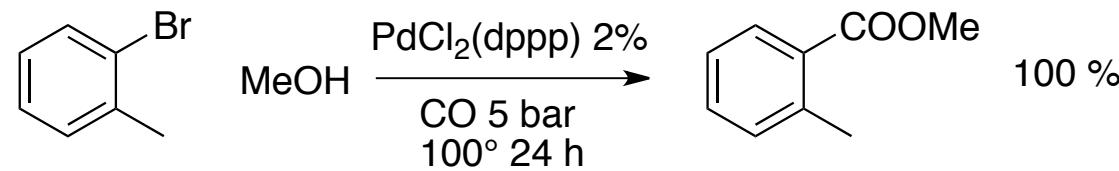


- Mécanisme:

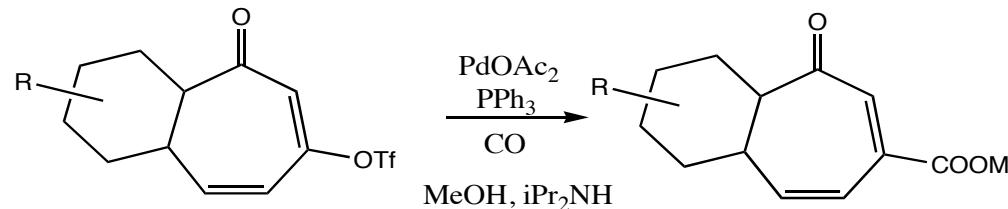


- couplages avec insertion de CO (carbonylation)

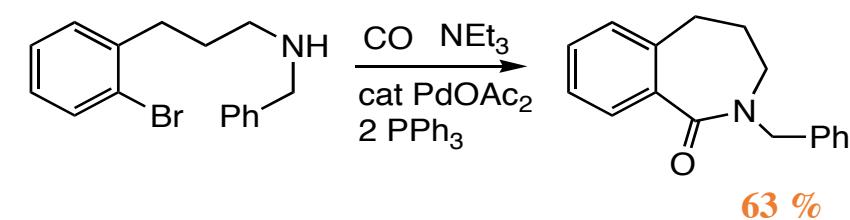
Rev.: C. Barnard (Johnson Matthey) *Organomet.* **2008**, *27*, 5402; S.T. Gadge, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 10367

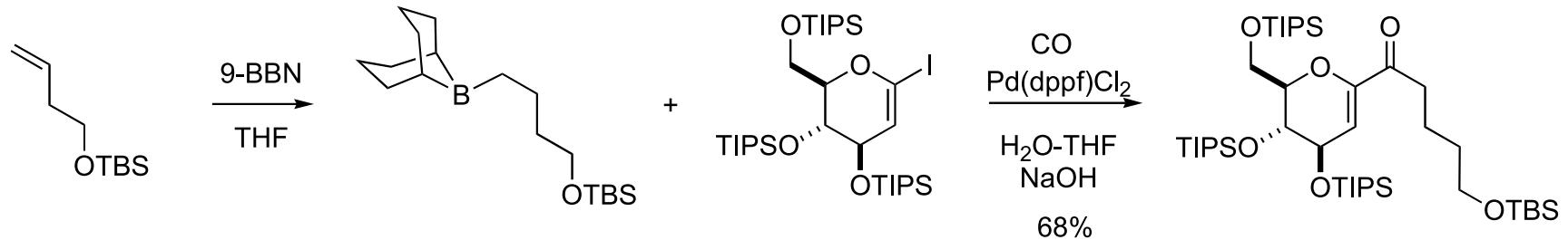


pas limité au Br

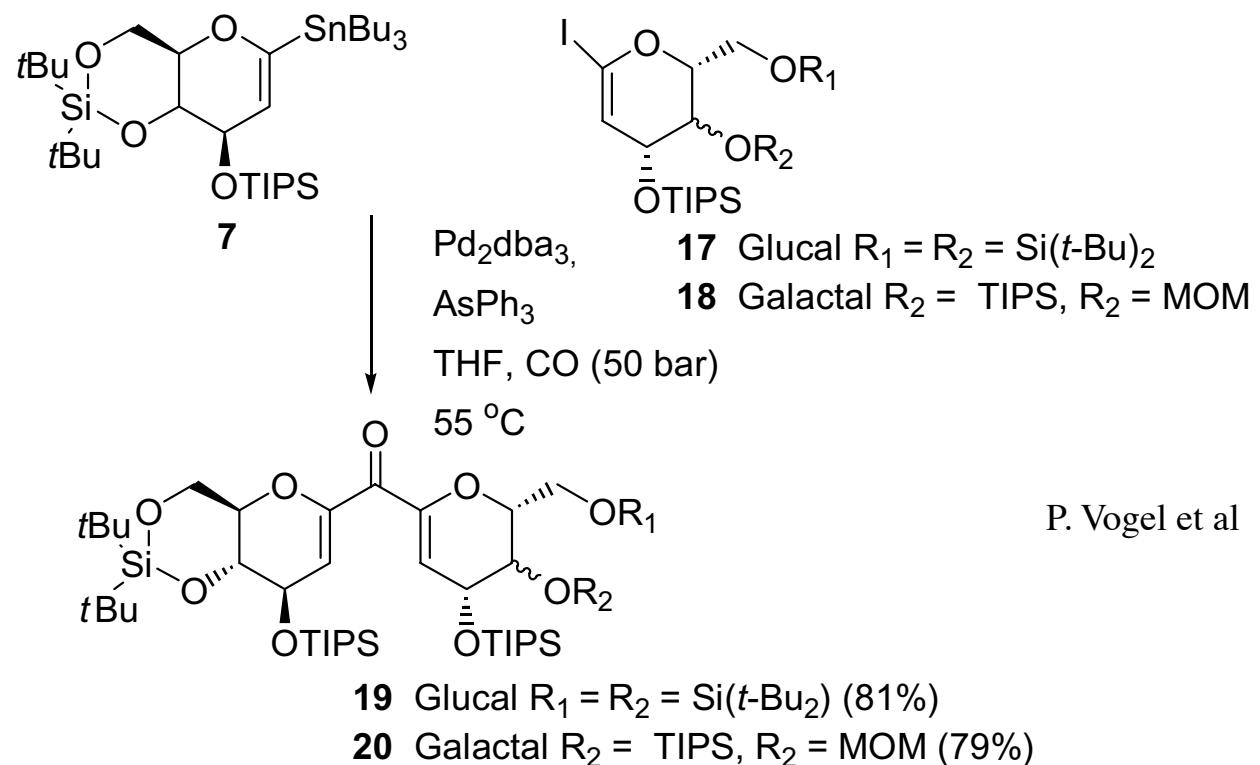


version intramoléculaire



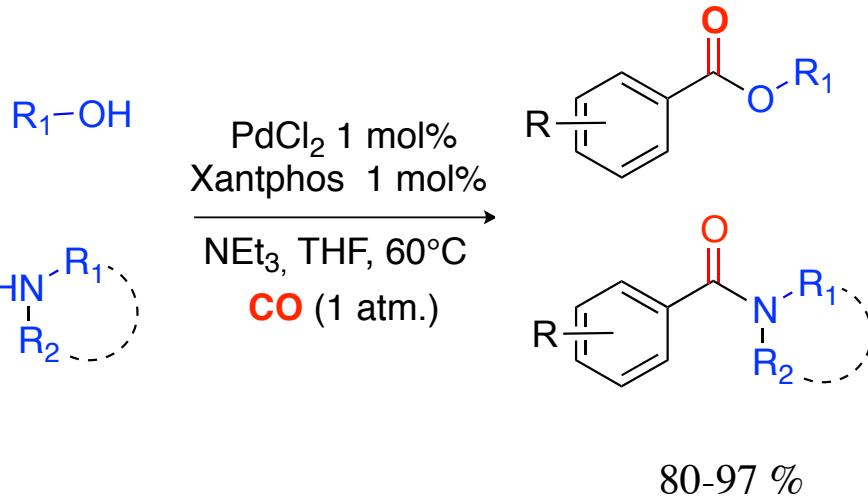
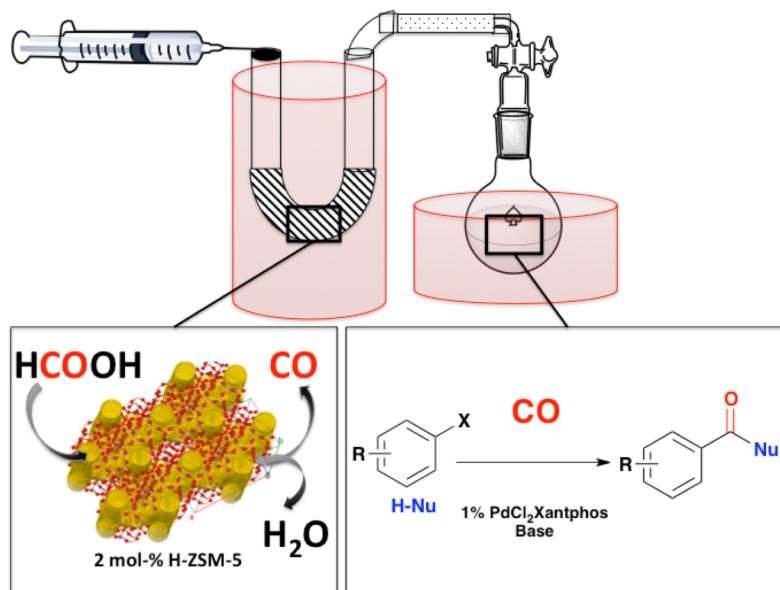


Potuzak JS, Tan DS
Tetrahedron Lett **2004** 45, 1797



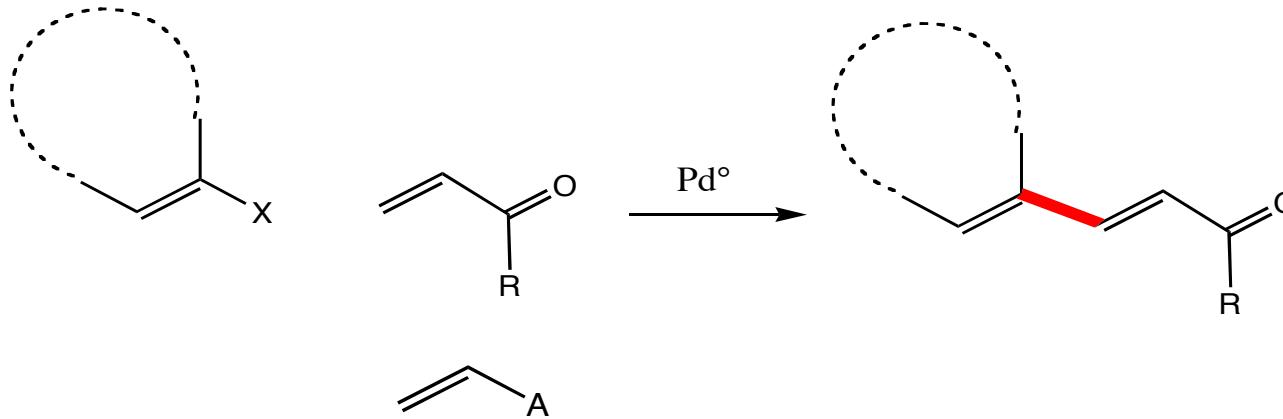
P. Vogel et al *Tet Asym* **2005**, 16, 337

- Pb toxicité/sécurité CO & pression



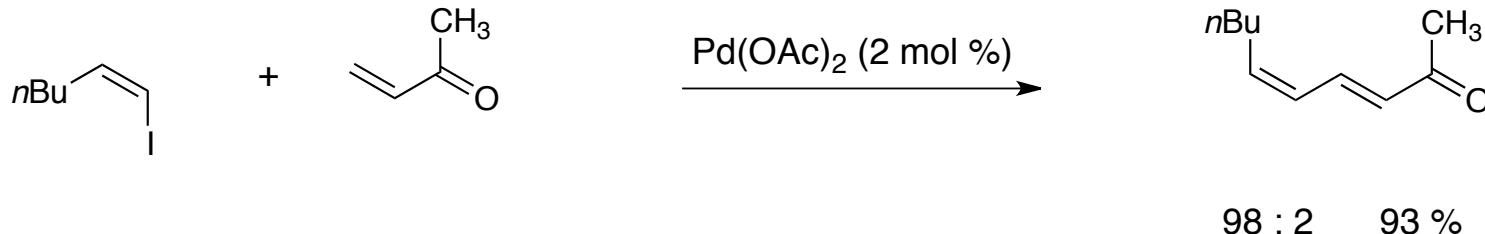
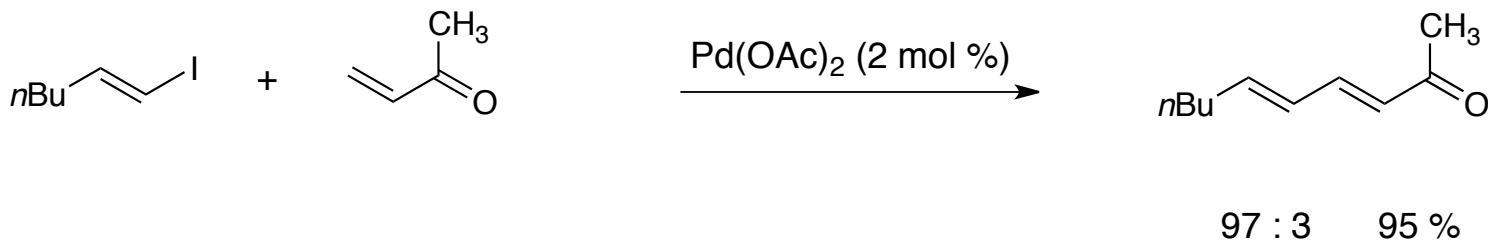
Green production of CO from HCOOH
Pale & coll. *Adv. Synth. Catal.* **2015**, 357, 2931

- couplages avec insertion d' alcène (Réaction de Heck)

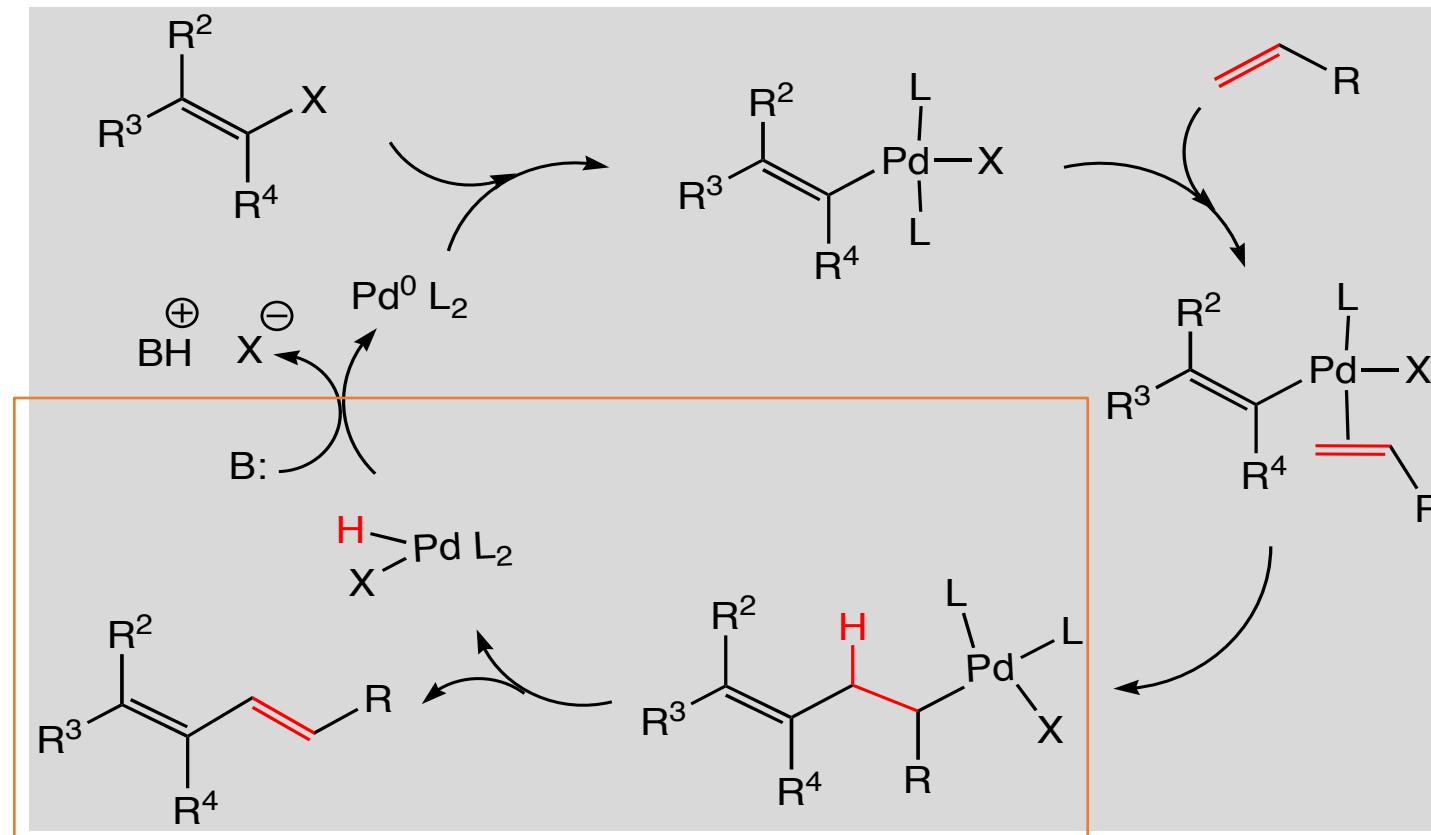


The Nobel Prize in Chemistry 2010
Richard F. Heck, Ei-ichi Negishi, Akira Suzuki

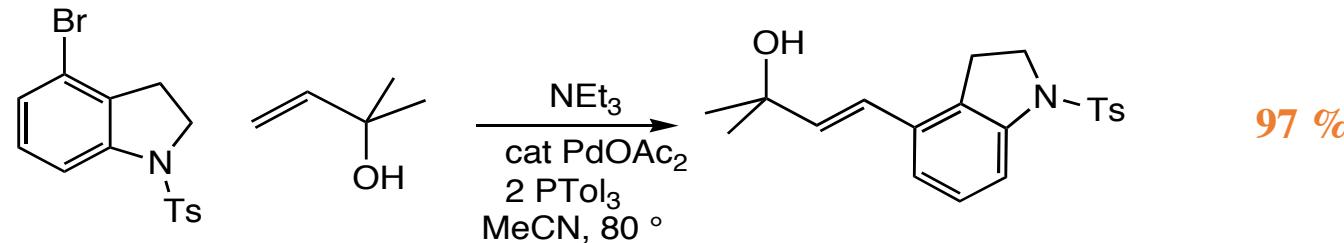
Amatore, C. *JACS* **1991**, 8375



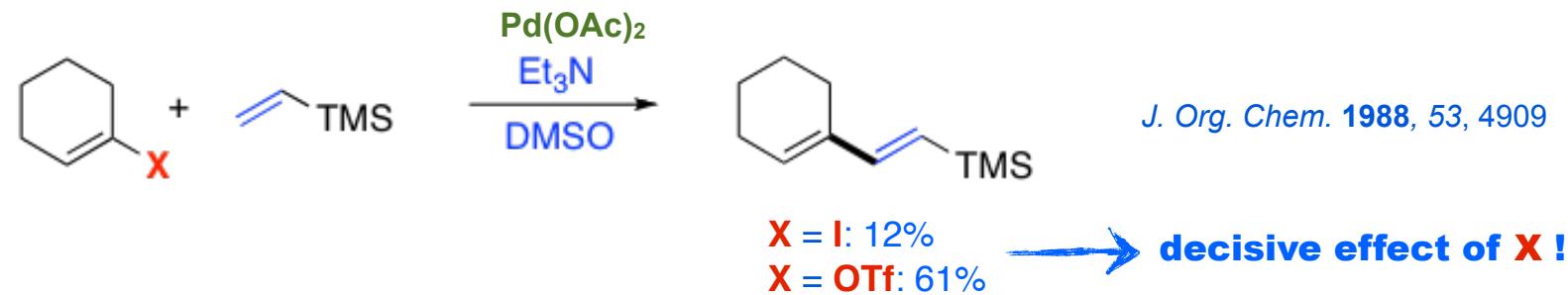
- couplages avec insertion d' alcène (Réaction de Heck)



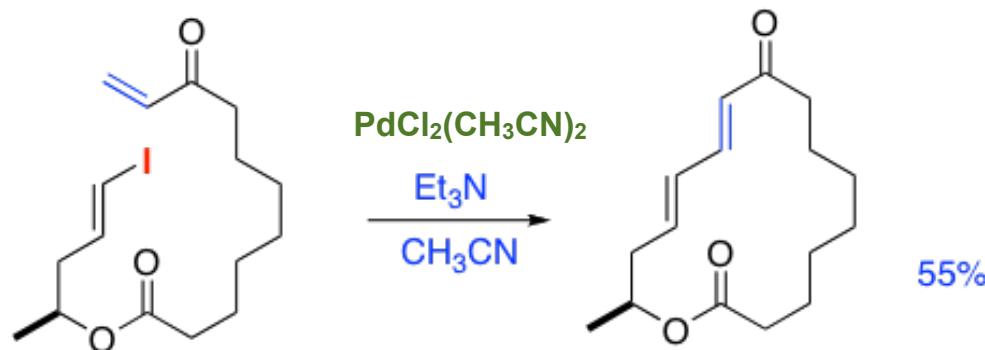
- Intermoléculaire



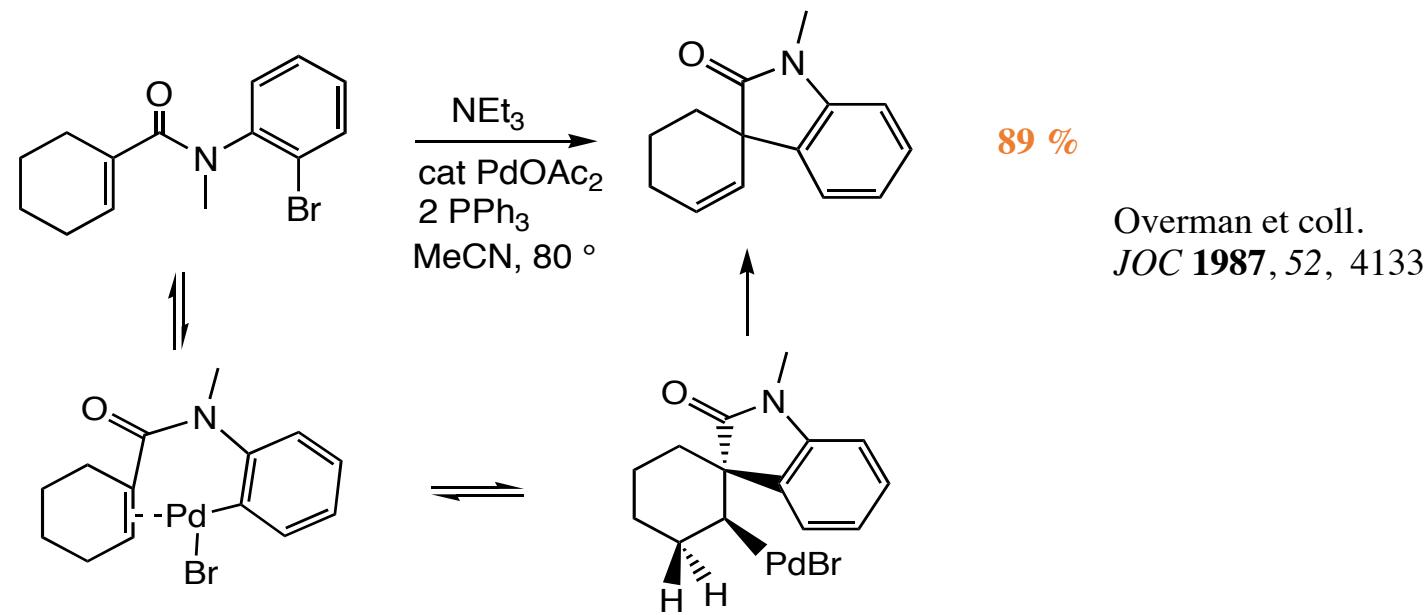
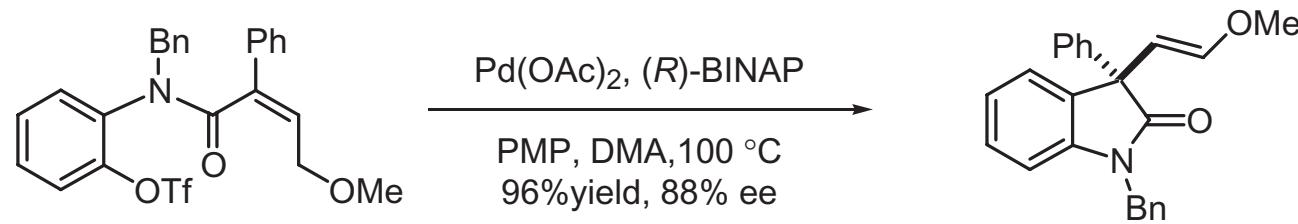
accès à des 1,3-diènes



- Intramoléculaire: accès à des macrocycles



- Formation de cycle fn de l'étape de β -élimination



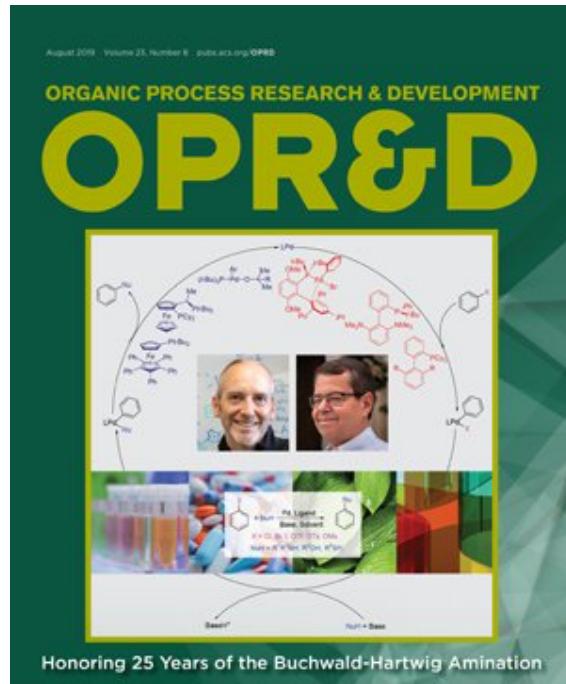
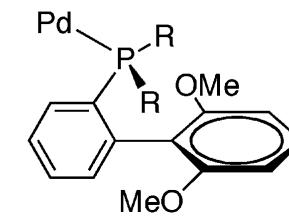
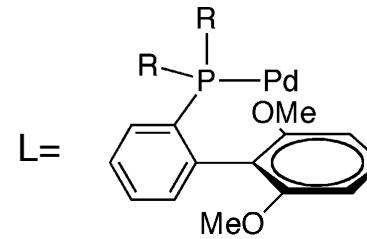
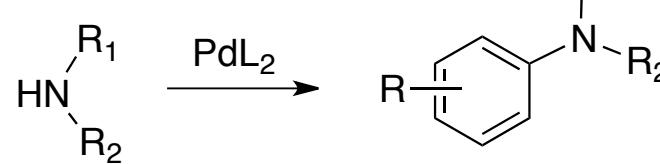
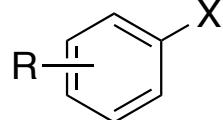
7.2.4 autres couplages

couplages où formation de liaisons C-N, C-O, etc...

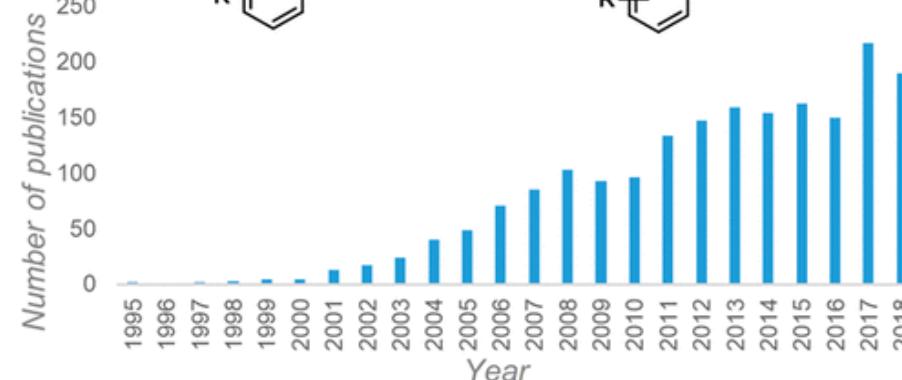
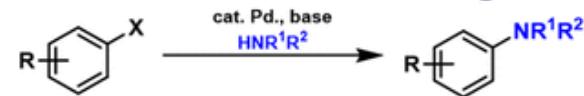
Buchwald-Hartwig

Hartwig, J. F. *Synlett* **1997**, 329

Rev: Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, 116, 12564-

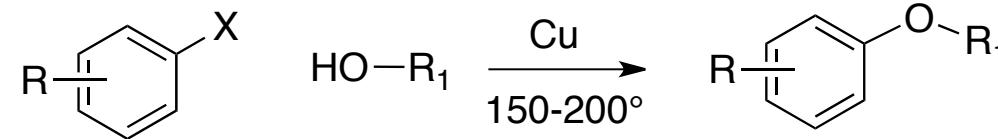


25 years of the Buchwald-Hartwig Amination



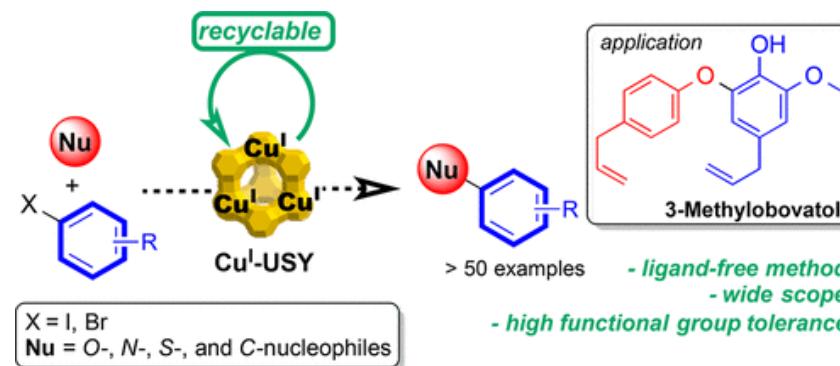
Ullmann

Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, 36, 2382



Taillefer

Cu-L, < 100°



Chassaing, Pale & coll.
Org. Lett. **2015**, 17, 4494
J. Org. Chem. **2018**, 83, 6408

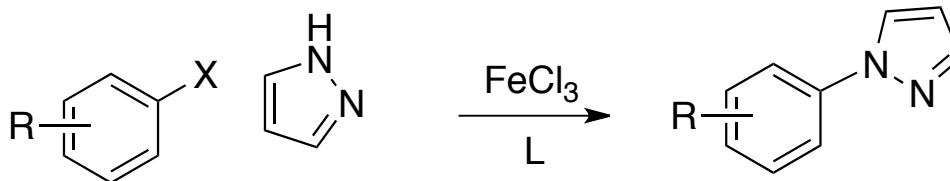
Buchwald-Hartwig

Pd-L

7.2.4 couplages avec autres métaux

couplages où Ni

couplages où Fe



Metal salt	Yield, %
> 98% FeCl_3 (Merck)	87
> 99.99% FeCl_3 (Aldrich)	9
> 99.99% $\text{FeCl}_3 + 5 \text{ ppm Cu}_2\text{O}$	78
No Fe + 5 ppm Cu_2O	77