UNIVERSITÉ DE STRASBOURG

Master de Chimie

FACULTÉ DE CHIMIE STRASBOURG

Chimie Organique
Tronc commun CMVS

Synthèses stéréosélectives

Cours: Pr Patrick Pale **TD:** Dr Stefan Chassaing

LASYROC Laboratoire de Synthèse et Réactivité Organiques et Catalyse

Pale Group
Department of Chemistry

Chap. 4 Enolates & Aldolisations

4-1 Enolates

- 4.1.1- Structures
- 4.1.2- Formations

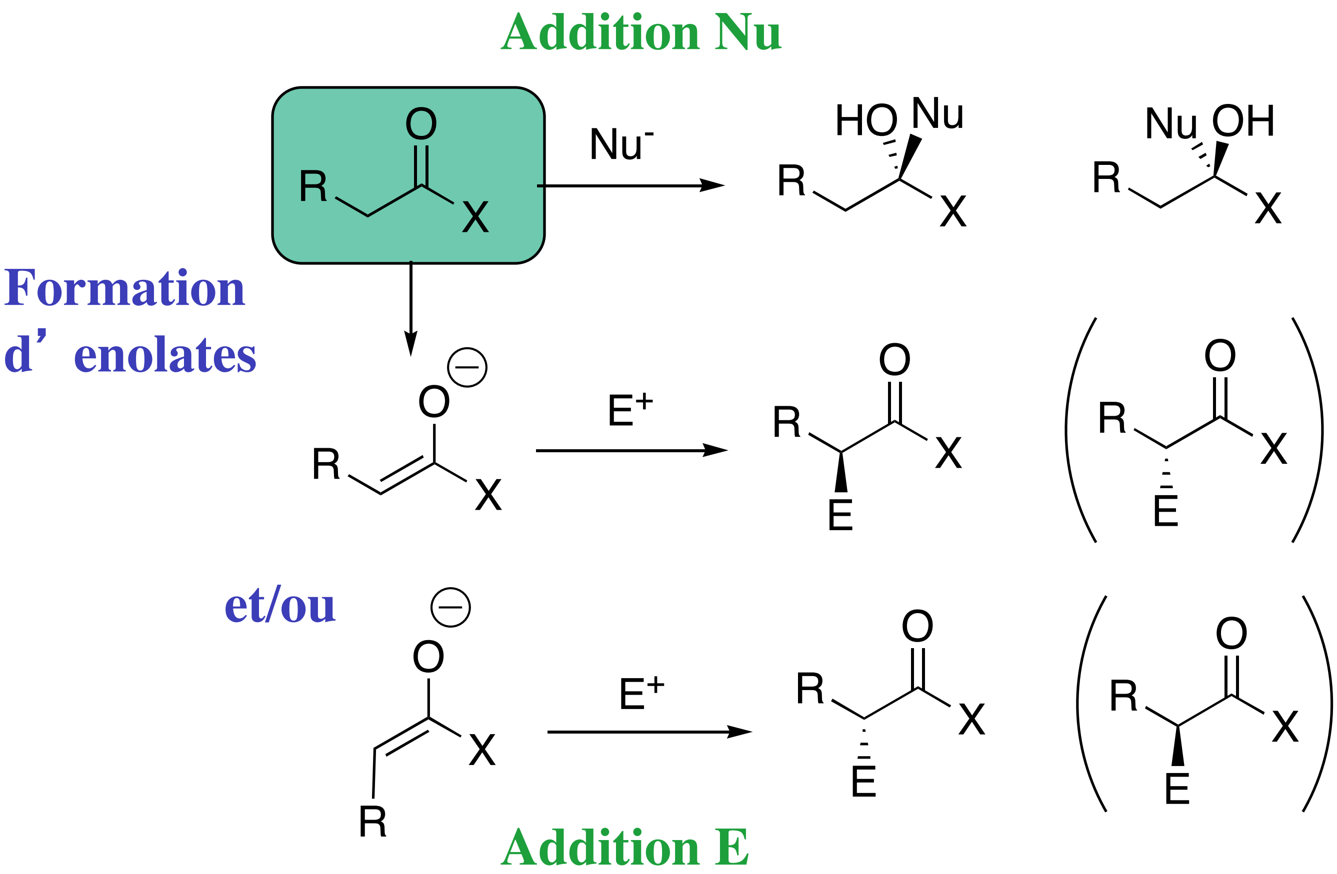
4-2 Aldolisation

- 4.2.1- mécanisme
- 4.2.2- modèle Zimmerman-Traxler

4-3 Aldolisation de Mukaiyama

- 4-3-1- mécanisme
- 4-3-2- modèle ouvert

4.1 Enolates



Addition Nu

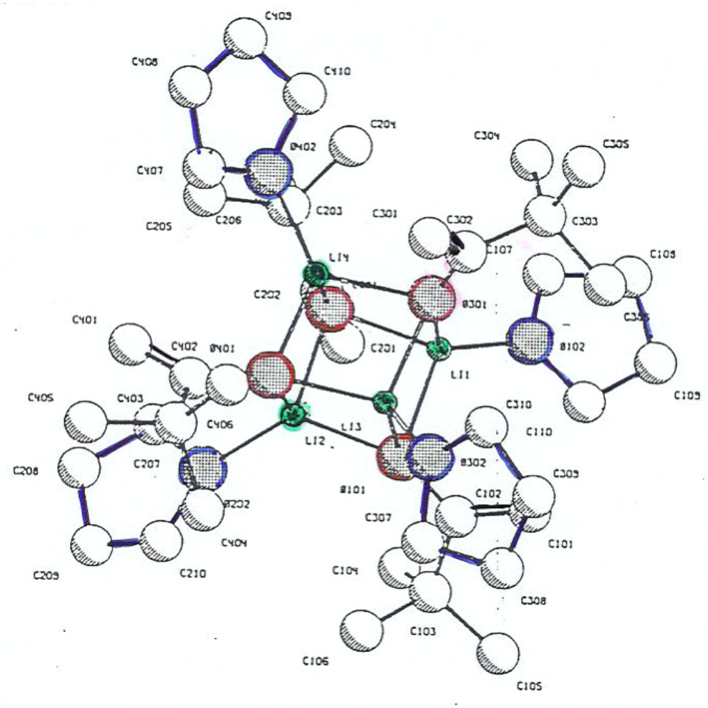
Formation d’ enolates

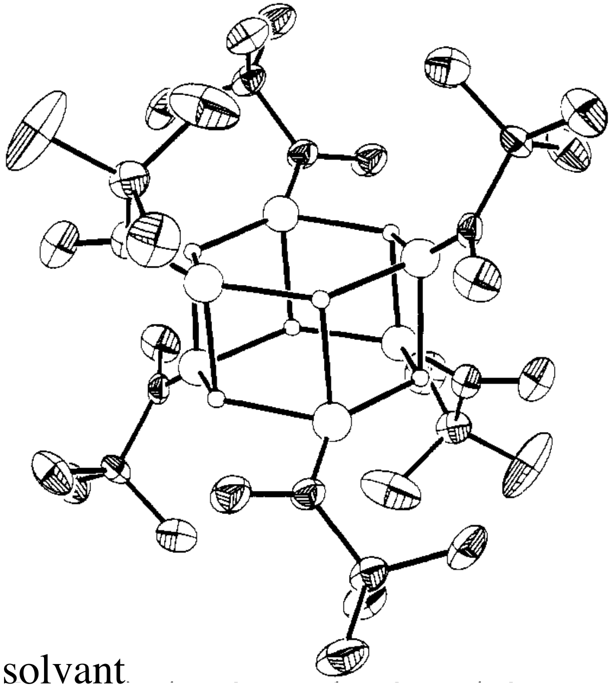
et/ou

Addition E

Stéréosélectivité dépend de la stéréochimie de l’ énolate

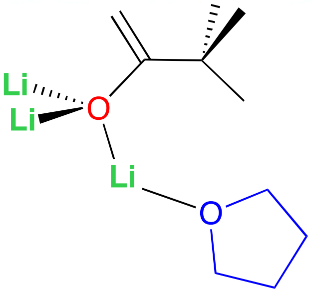
4.1.1- Structures des énolates

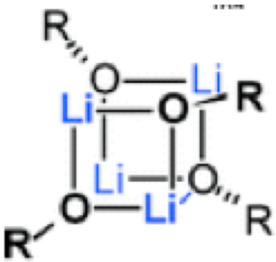


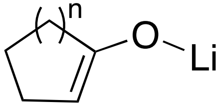


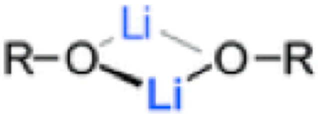
Idem sans solvant

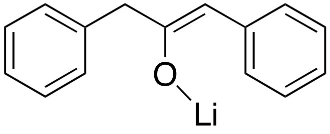
P. G. Williard*, G. B. Carpenter *J. Am. Chem. Soc.* **1985,** *107,* 3345







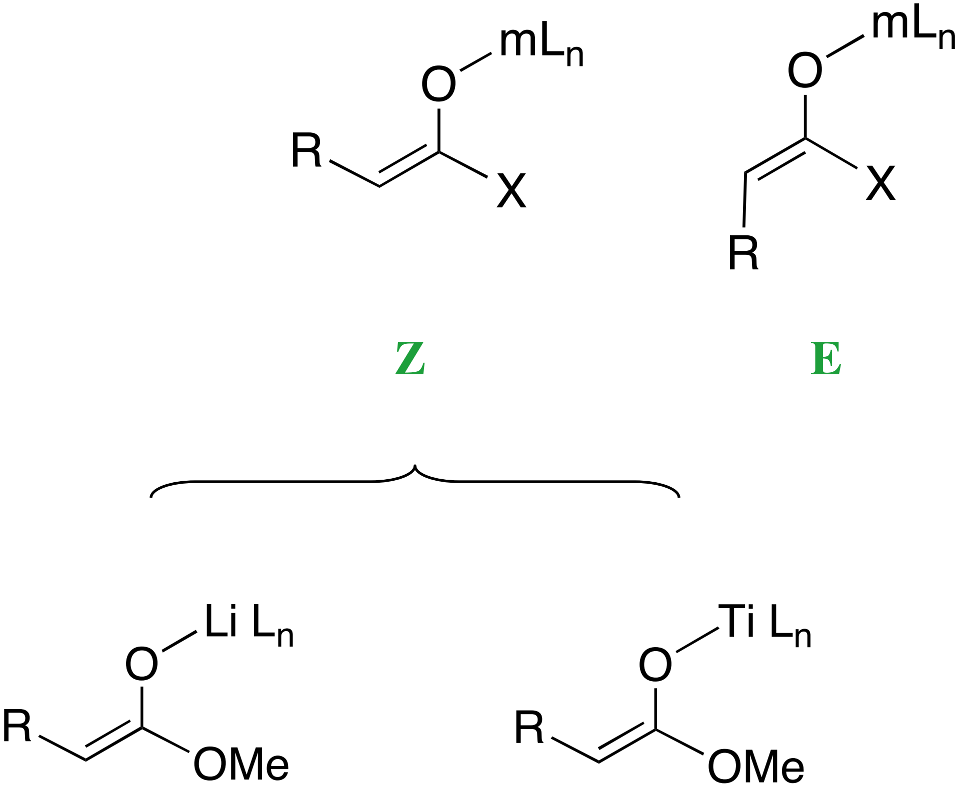




H. J. Reich et al. *J. Am. Chem. Soc.* **2009**, *131*, 11525

NB : Nomenclature spécifique énolates (D. Evans)

indépendante de la nature de m



4.1.2- Formations d' énolates

4.1.2.1- déprotonation classique

$$R{-}H + R'{-}mL_n \rightleftharpoons R{-}mL_n + R'{-}H$$

$$\equiv$$

$$A{-}H + B^- \rightleftharpoons A^- + B{-}H$$

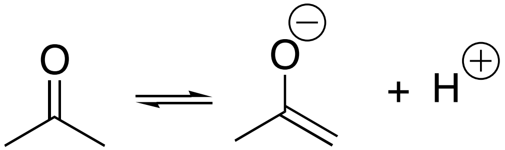
$$K_{eq} = K_{deprot}$$

$$K_{eq} = \frac{[A^-][B{-}H]}{[A{-}H][B^-]} = K_{a\,(AH/A-)} \cdot \frac{1}{K_{a\,(B-/BH)}}$$

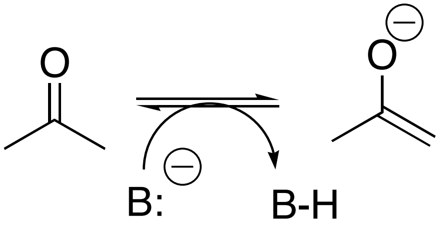
$$K_{eq} = 10^{-pK_{a\,(AH/A-)}} \cdot \frac{1}{10^{-pK_{a\,(B-/BH)}}}$$

$$K_{eq} = 10^{-pK_{a\,(AH/A-)}+pK_{a\,(B-/BH)}}$$

pour avoir $K_{eq} > 0$, $pK_{a\,(B-/BH)} >> pK_{a\,(AH/A-)}$



pKa 20-25



pKa B > $pKa_{cétone}$

mH **pKa 25-30** NaH, KH

mNR_2 **pKa 30-35** $LiNH_2$, $NaNH_2$

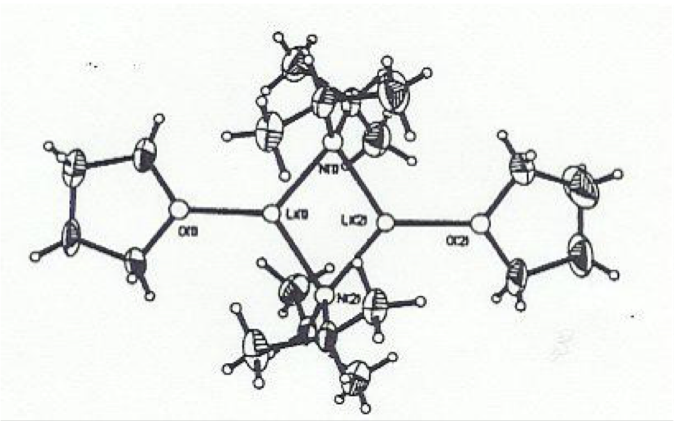
$LiNiPr_2$ (LDA),

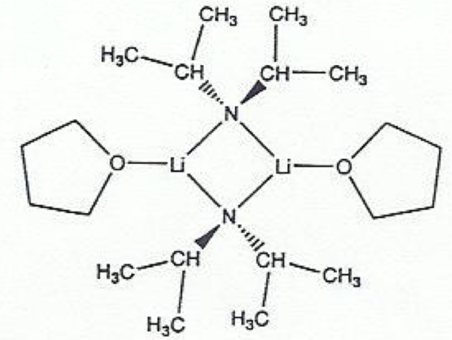
LiNiPrcHex (LICA)

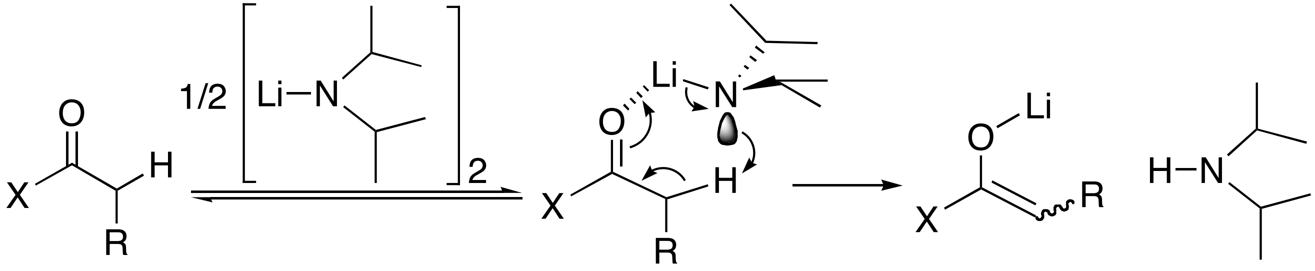
Na $N(SiMe_3)_2$ (NaHMDS)

Li Tétraméthylpipéridine (LiTMP)

P.G. Williard, J.M. Salvino
J. Org. Chem. **1993**, *58*, 1-3

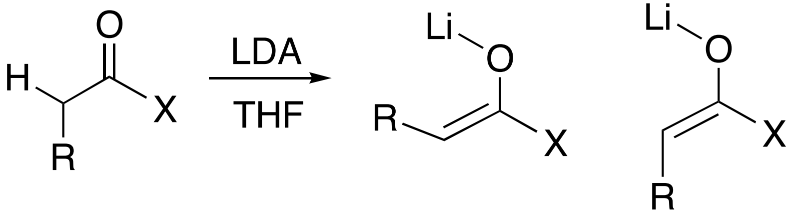






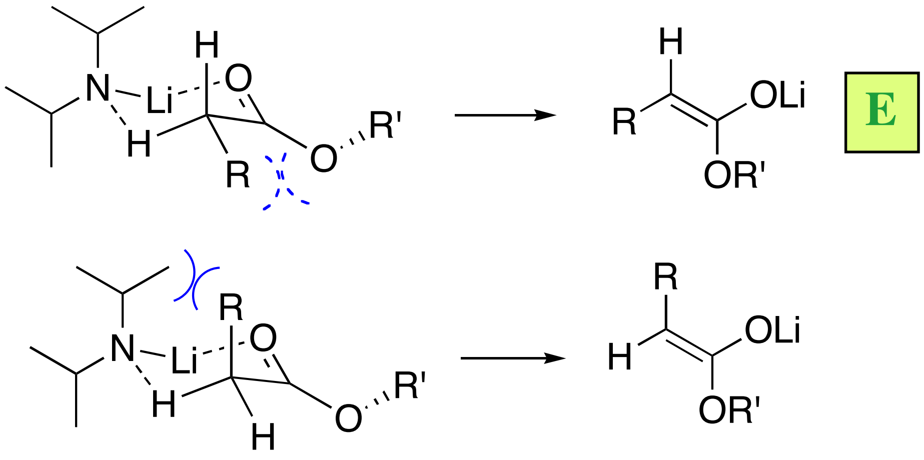
Stéréochimie ?

Modèle d’Ireland

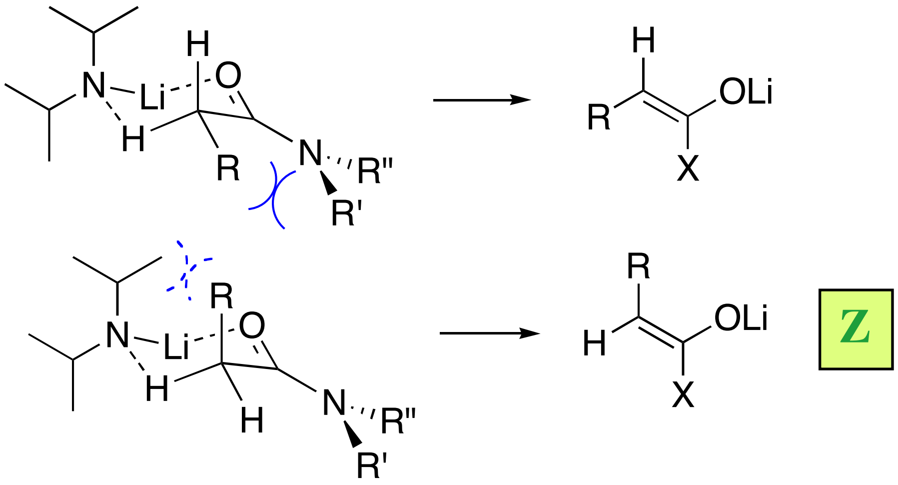


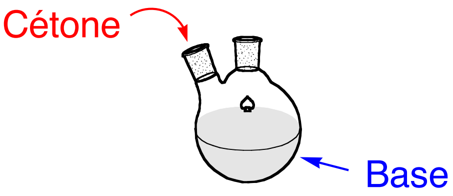
X = OMe	**5**	**95**
X = OtBu	**5**	**95**
X = NEt_2	**100**	**0**
X = Et	**23**	**77**
X = iPr	**60**	**40**
X = tBu	**100**	**0**

enolates d' esters

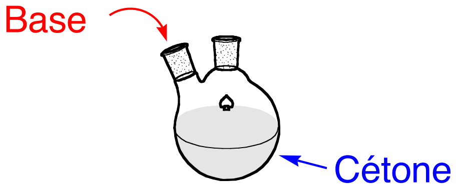


enolates d' amides

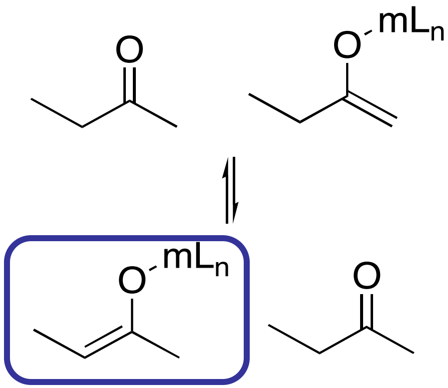




xs base ⇒ déprotonation ⇒ **Conditions cinétiques**

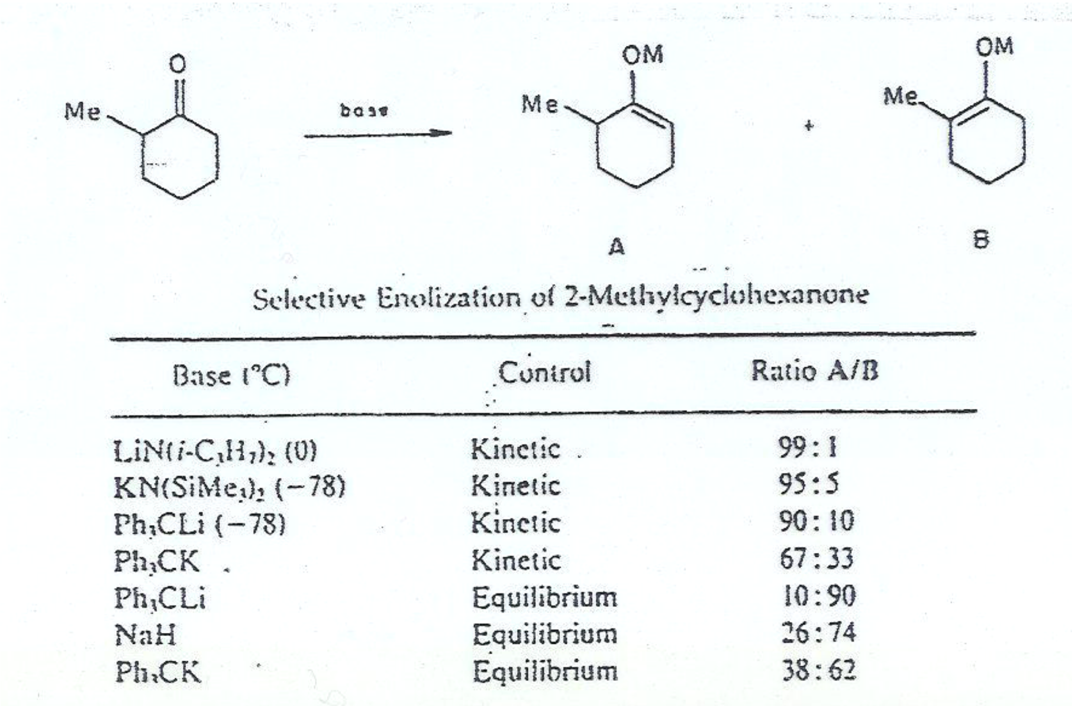


xs cétone



⇒ Équilibration possible

⇒ **Conditions thermodynamiques**

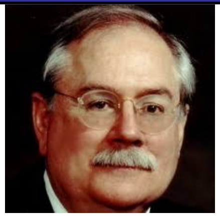


Selective Enolization of 2-Methylcyclohexanone

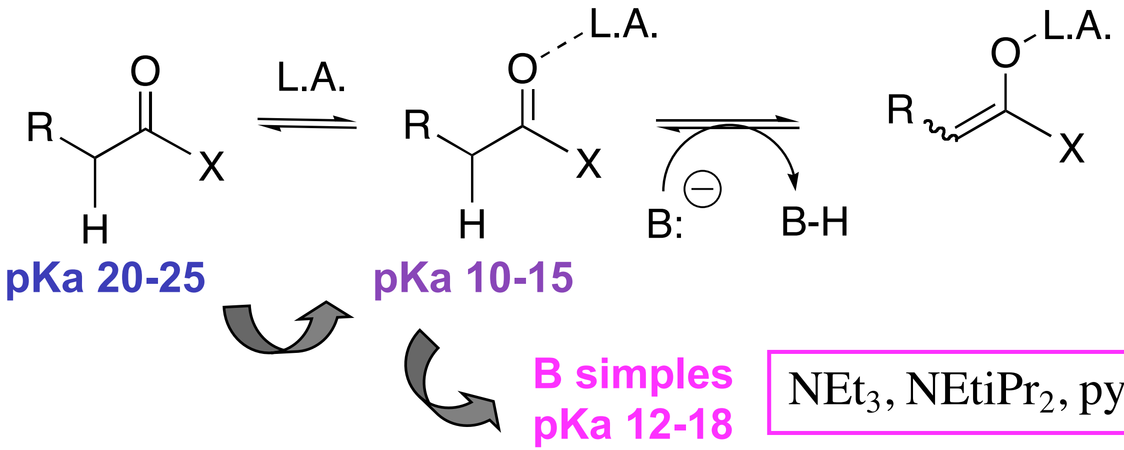
Base (°C)	Control	Ratio A/B
$LiN(i\text{-}C_3H_7)_2$ (0)	Kinetic	99 : 1
$KN(SiMe_3)_2$ (−78)	Kinetic	95 : 5
Ph_3CLi (−78)	Kinetic	90 : 10
Ph_3CK	Kinetic	67 : 33
Ph_3CLi	Equilibrium	10 : 90
NaH	Equilibrium	26 : 74
Ph_3CK	Equilibrium	38 : 62

4.1.2.2- déprotonation assistée par Ac Lewis

HARVARD UNIVERSITY



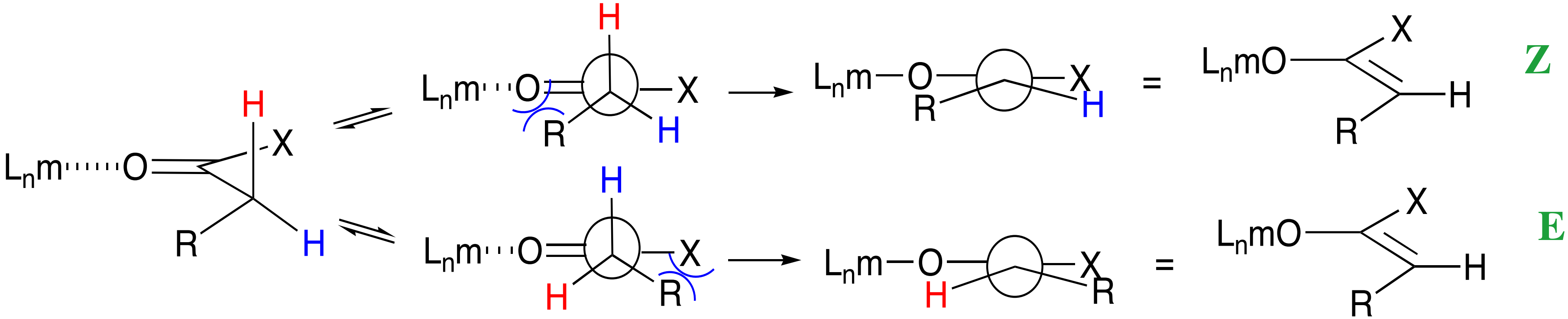
D. Evans



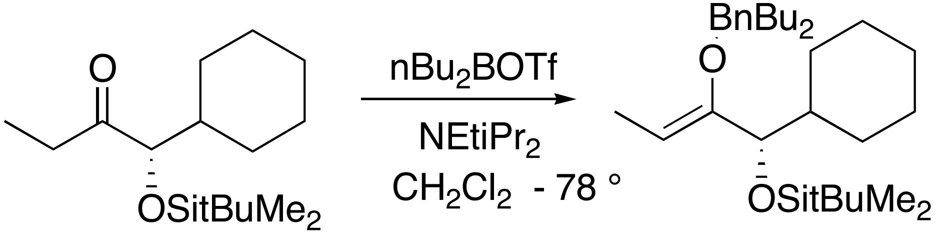
Stéréochimie ?

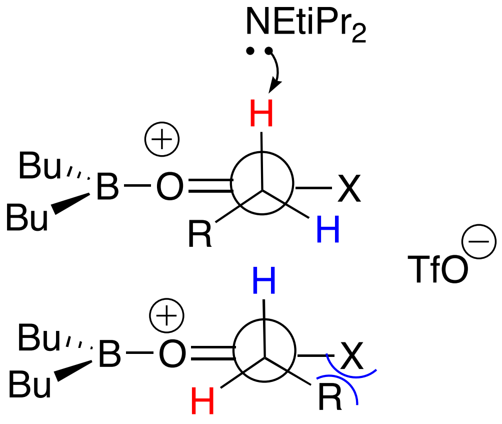
B simples
pKa 12-18

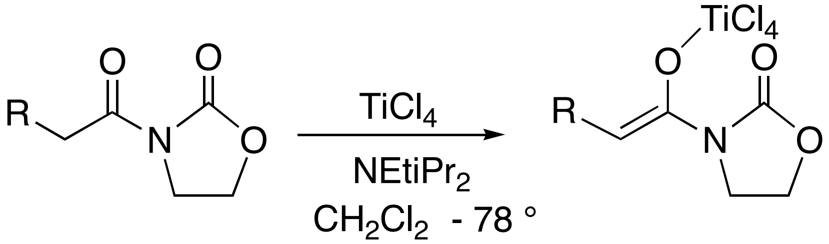
NEt$_3$, NEtiPr$_2$, py



D. Evans
1983


O
OSitBuMe$_2$
nBu$_2$BOTf
NEtiPr$_2$
CH$_2$Cl$_2$ - 78 °
BnBu$_2$
O
OSitBuMe$_2$


NEtiPr$_2$
H
⊕
Bu
B
O
X
Bu
R
H
TfO⊖
H
⊕
Bu
B
O
X
Bu
H
R

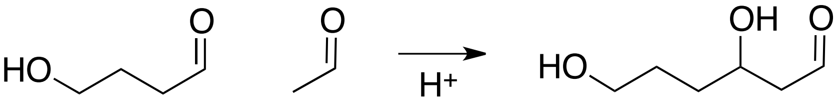

R
O
O
N
O
TiCl$_4$
NEtiPr$_2$
CH$_2$Cl$_2$ - 78 °
TiCl$_4$
O
O
R
N
O

4.2 Aldolisations

Charles Wurtz
1817-1884
Strasbourg
1839 « chef de travaux »
faculté de Strasbourg
1843 docteur

Alexandre Borodine
1833-1887
St-Petersbourg
1846 concerto
1856 Prof chimie
1858 Dr médecine

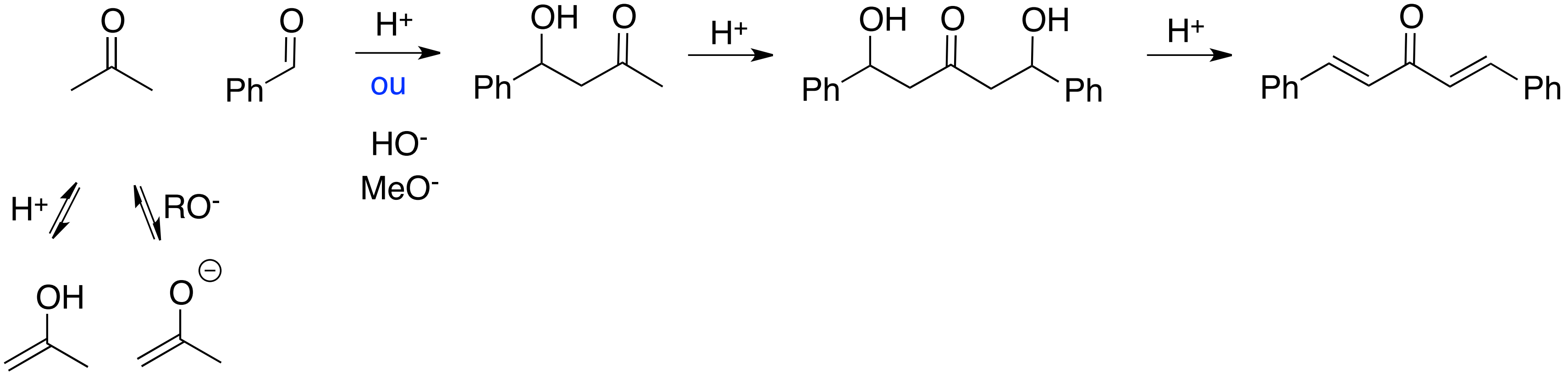
C. A. Wurtz
Bull. Soc. Chim. Fr. **1872**, *17*, 436-442



Aldol et condensation 1861-72

NB: Réaction ne porte pas leurs noms

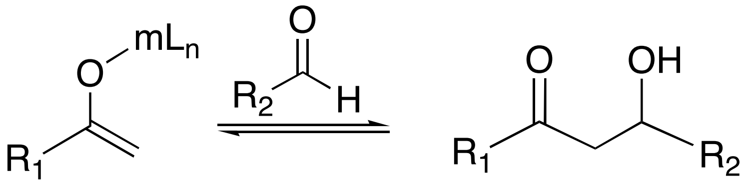
Aldolisations classiques :



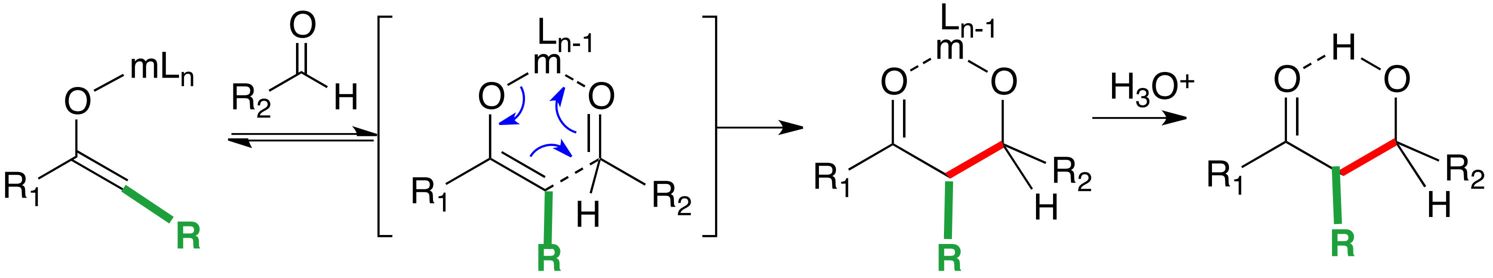
Intérêt :
- formation liaison C-C
- système fonctionnalisé

Pb :
- conditions pas compatibles avec bcp fn
- pas contrôle stéréochimie

Aldolisations modernes



Mécanisme :

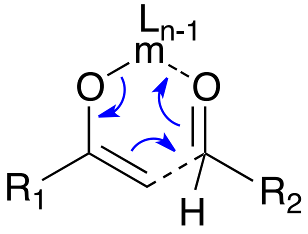


Intérêt : - formation liaison C-C

- création de 1 ou 2 stéréocentres ⇒ **Contôle de la stéréochimie ?**
- système fonctionnalisé

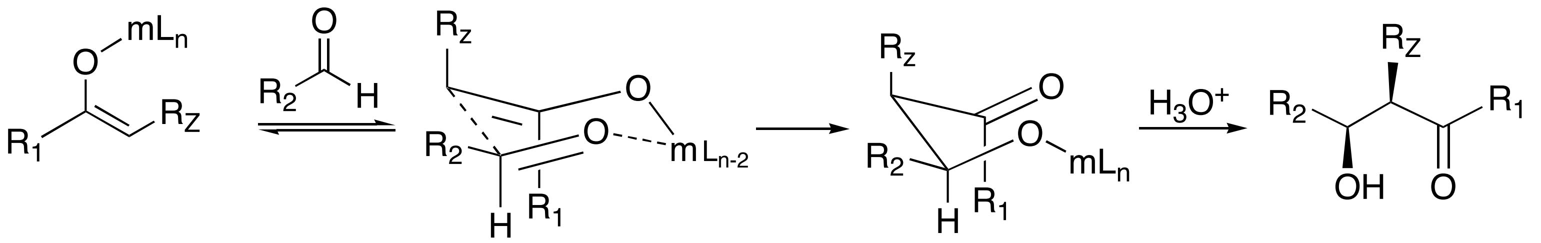
⇒ synthèse mlc + complexes

Stéréochimie ?

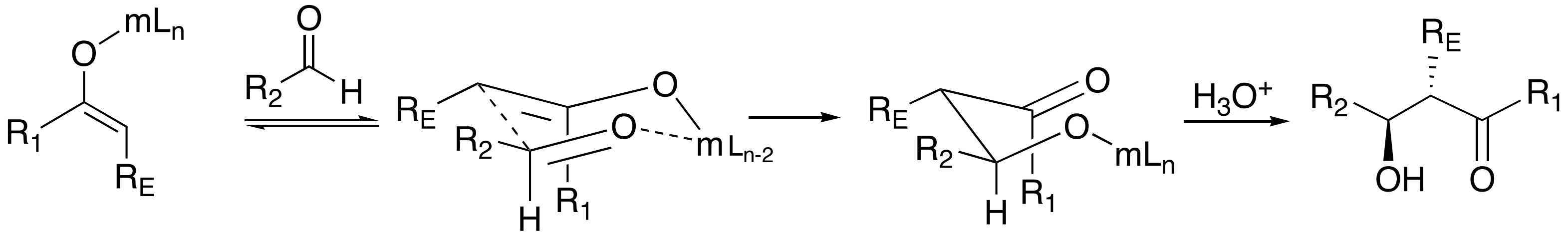


État de transition
à 6 centres 6 électrons ⇒ Conformation
(pseudo)chaise

⇓



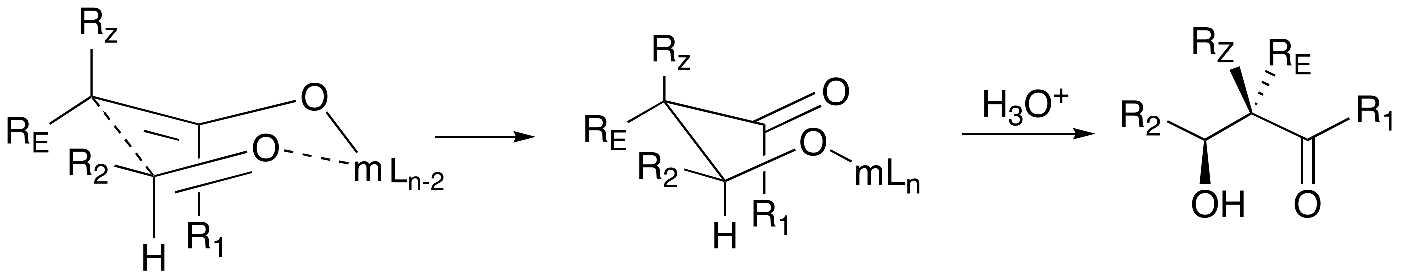
syn



anti

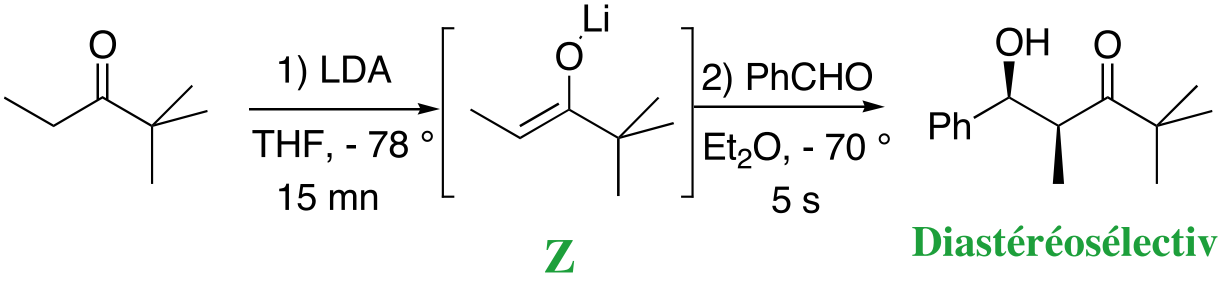
NB:
stéréochimies
relatives

⇓



Modèle de Zimmerman-Traxler

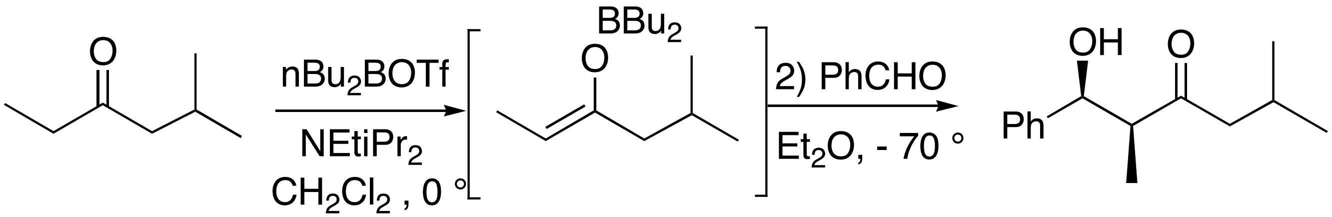
C. Heathcock



78%

Diastéréosélectivité 100%

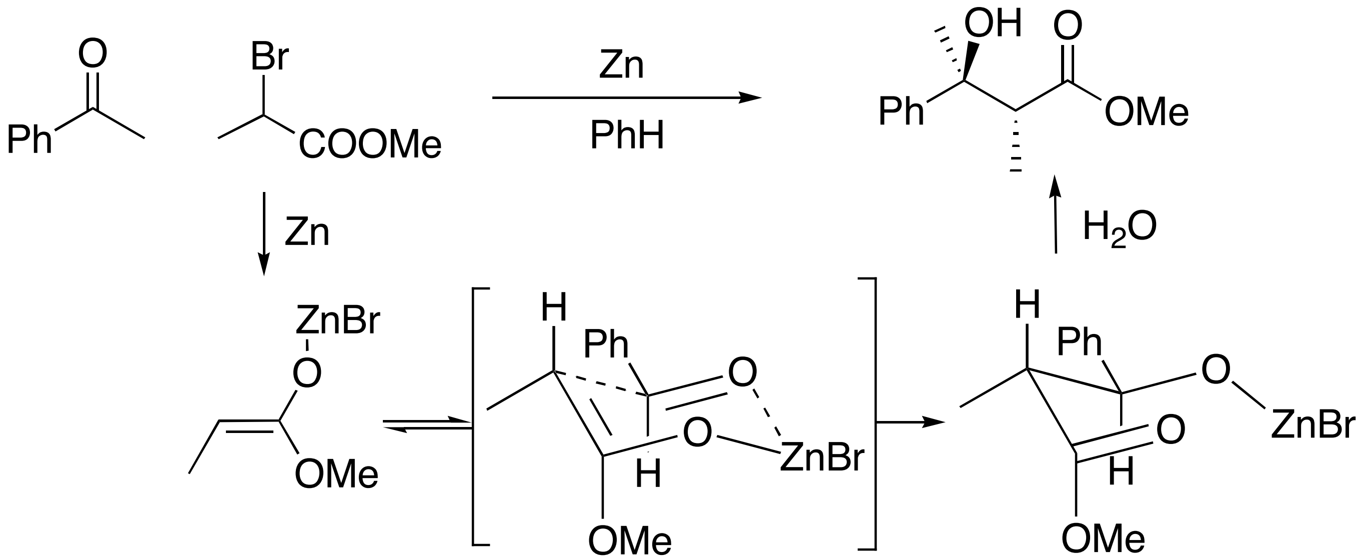
D. Evans
1983



82%

Diastéréosélectivité 99%

S. N. Reformatsky
1887



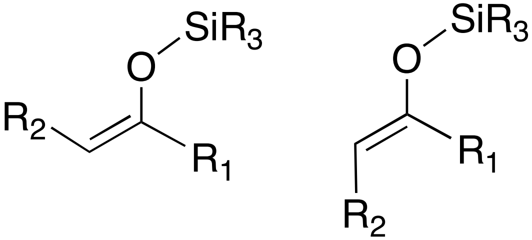
4.2 Aldolisation de Mukaiyama

T. Mukaiyama
1927-
PhD 1957
Tokyo University of Science

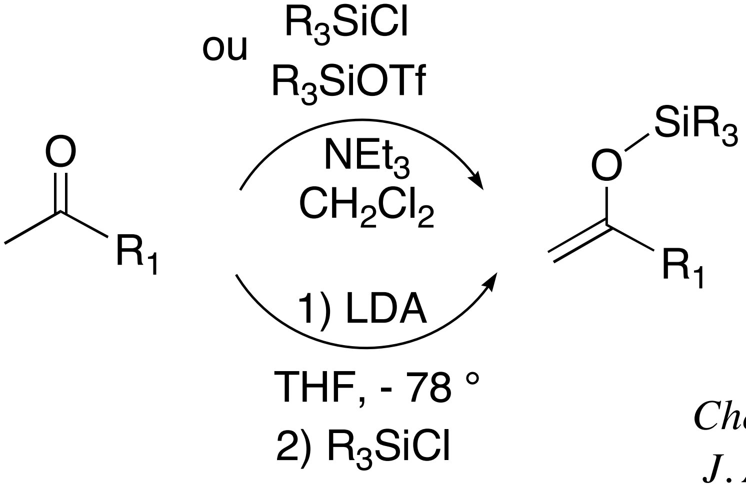
Éthers d’enol silylés

= enolates silylés

= enolates stables



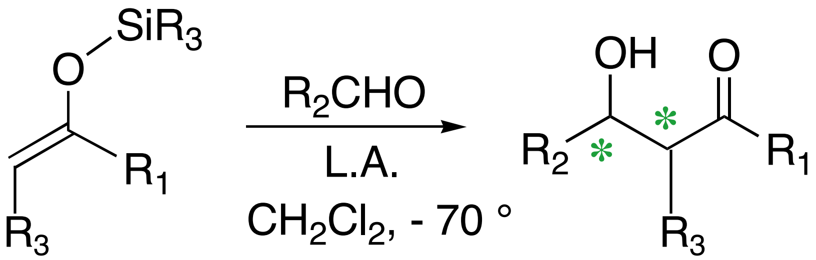
- relativement stables
- isolables
- régio- et stéréoisomères séparables



Chem. Lett. **1973**, 1011
J. Am. Chem. Soc. **1974**, *96*, 7503

Aldolisation de Mukaiyama

T. Mukaiyama, K. Narasaka, K. Banno
Chem. Lett. **1973**, *2*, 1011.

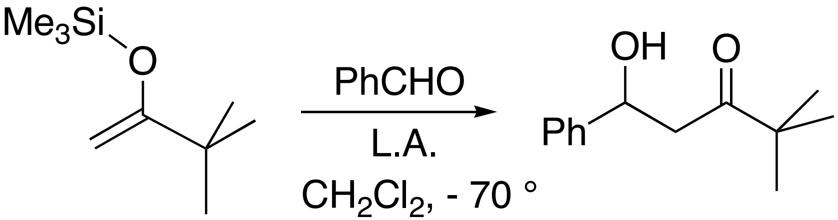


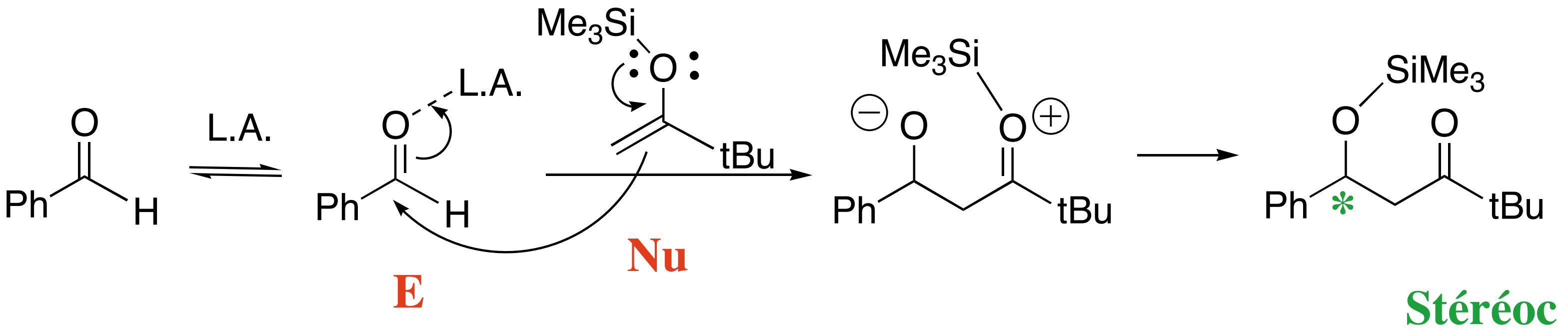
Formation d' aldols

Aldolisation :

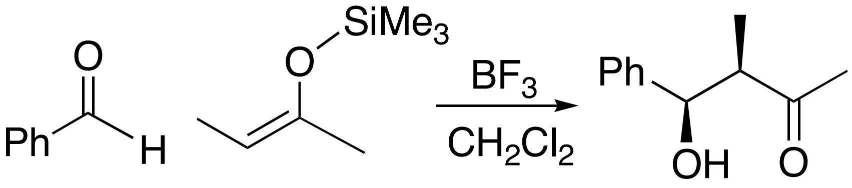
- formation liaison C-C
- création de 1 ou 2 stéréocentres
- système fonctionnalisé

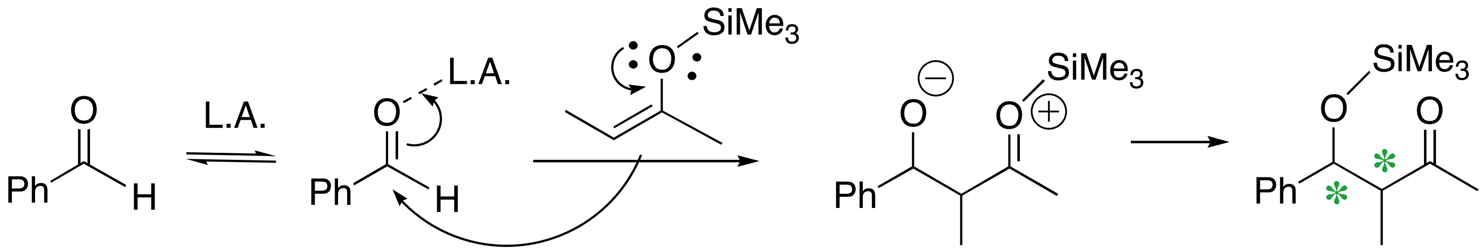
Mécanisme :





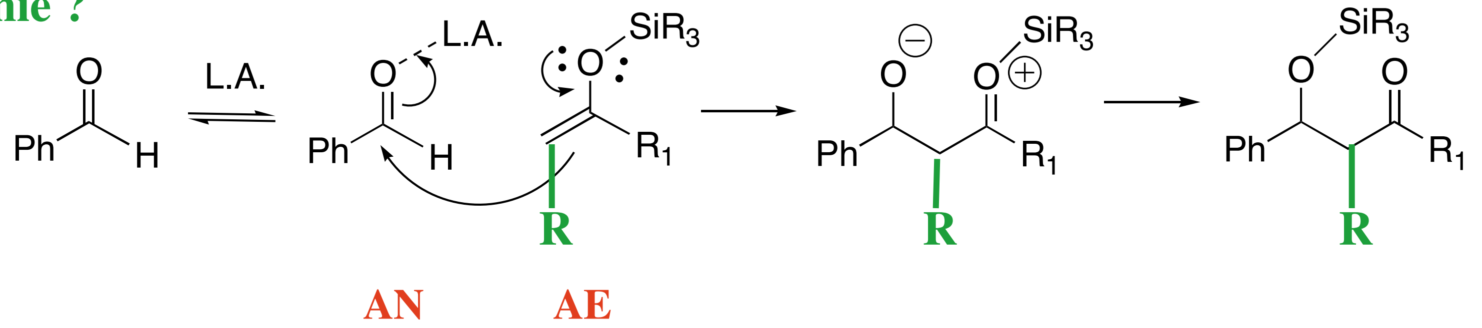
Stéréochimie ?

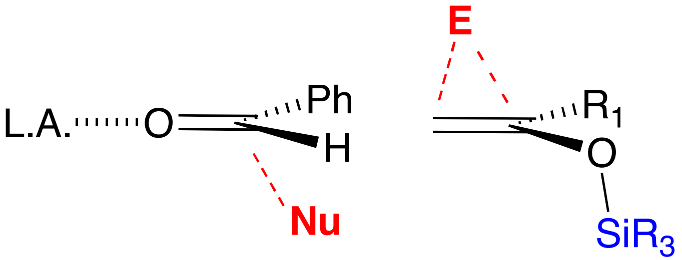




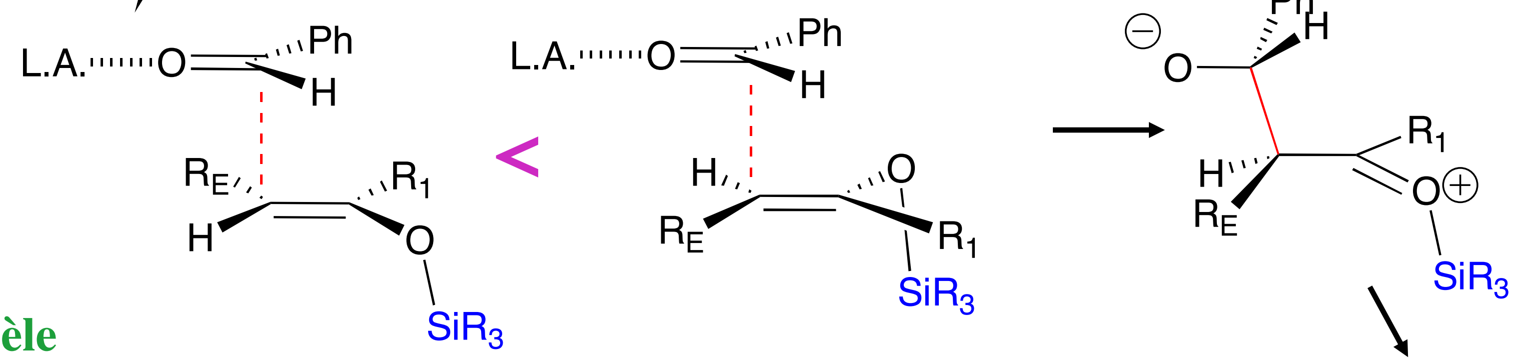
Stéréochimie ?

Stéréochimie ?

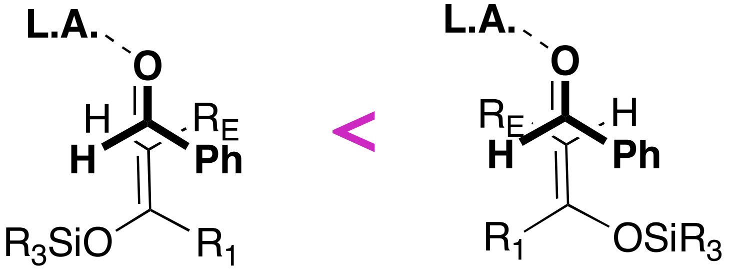


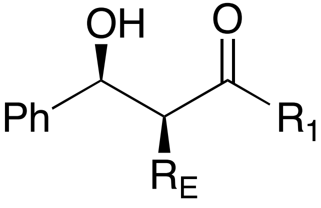


combinaison



Modèle ouvert
(Noyori)



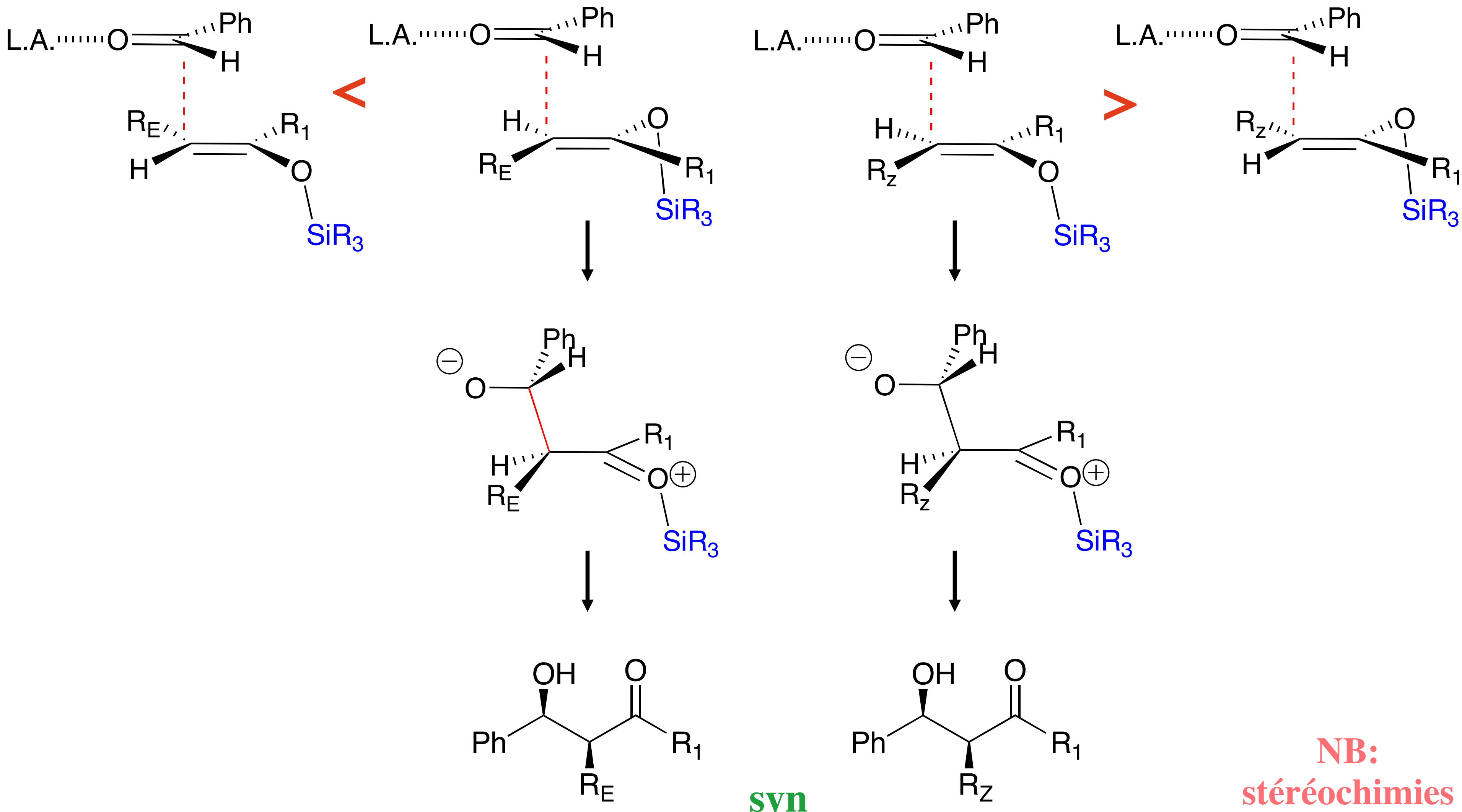


syn

Stéréochimie fn de celle du silyl énol éther ?

silyl énol éther E

silyl énol éther Z



NB: stéréochimies relatives

Chap. 5 Allylations

5-1 Principe

5-2 Allyl métaux η^1

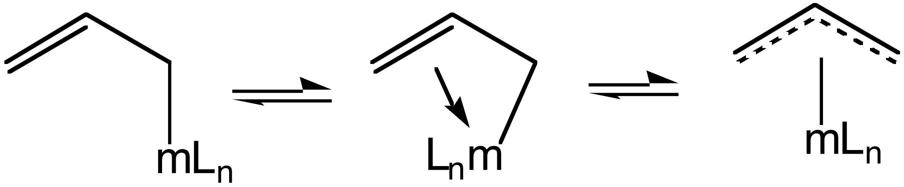
- 5.2.1- métaux coordinants
- 5.2.2- métaux non-coordinants

5-3 Allylation assistée par le palladium

- 5-3-1
- 5-3-2 d
- 5-3-3 p

5-1 Principe

Allyl métaux



η^1

⦀

Carbanions Allyliques

⦀

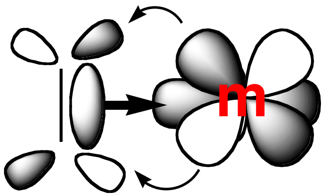
Nu

⇓

Fait des A.Nu

η^3

⦀



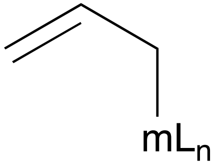
⦀

E

⇓

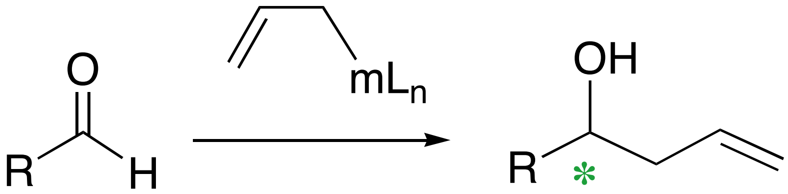
Subit des A.Nu

5-2 Allyl métaux η^1



Nu ⇒ - Alkylations

- AN sur carbonyle



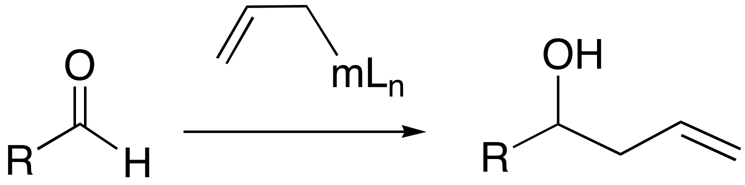
Intérêt :

- formation liaison C-C
- création de 1 ou 2 stéréocentres
- système fonctionnalisé

⇒ **Contôle de la stéréochimie ?**

⇒ Autres réactions,
synthèse mlc + complexes

Mécanismes : fonction de la nature du métal



Métal : Li, Mg, B, Al, m_T

⇓

Coordinant

chelation

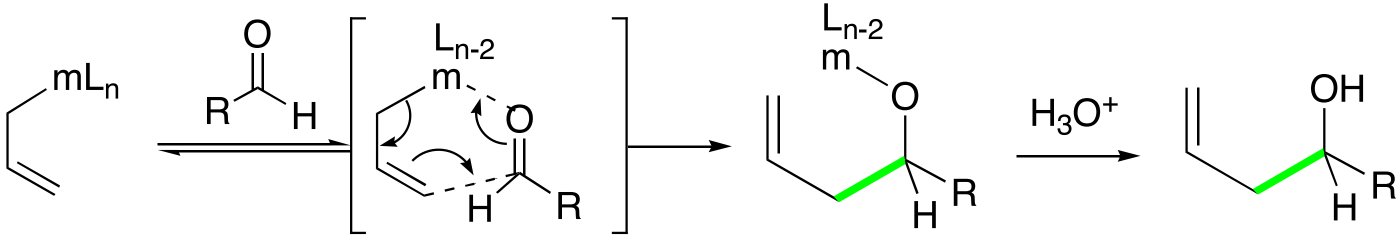
Métal : Si, Sn

⇓

Non-coordinant

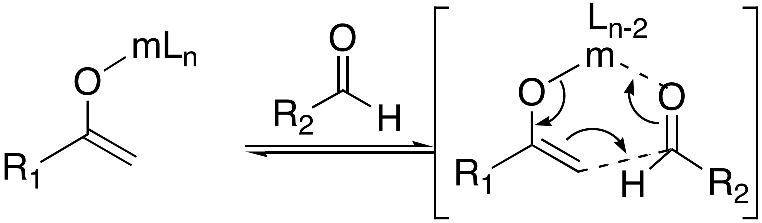
5.2.1- allyl métaux η^1 coordinants

Mécanisme

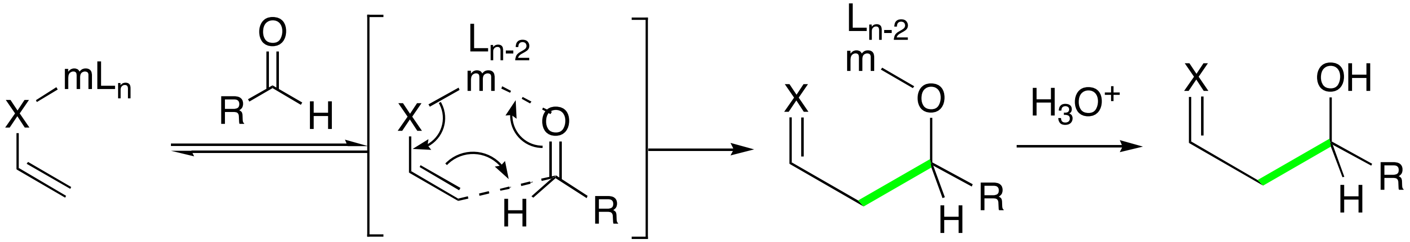


État de transition
à 6 centres 6 électrons

NB : **similaire aux aldolisations**



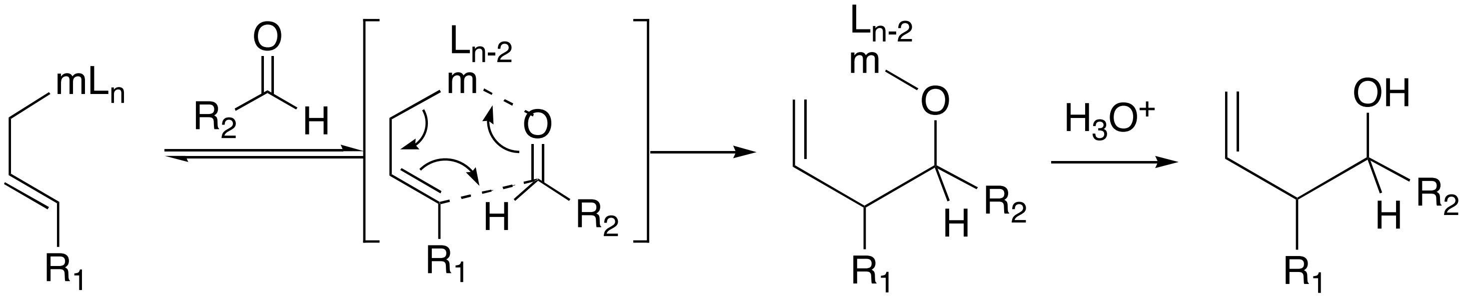
**Mécanisme
général**



X = CHR, O, NR, etc

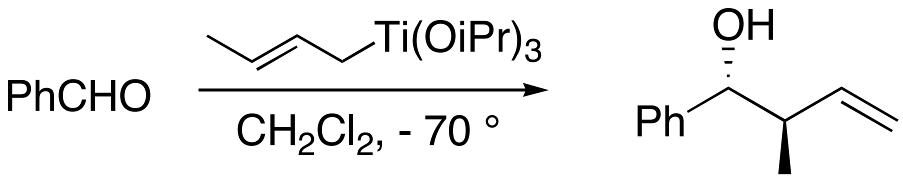
Régio- & Stéréochimie : idem aldolisations

Régio



Tjs γ Li, Mg, B, m$_T$, Ln

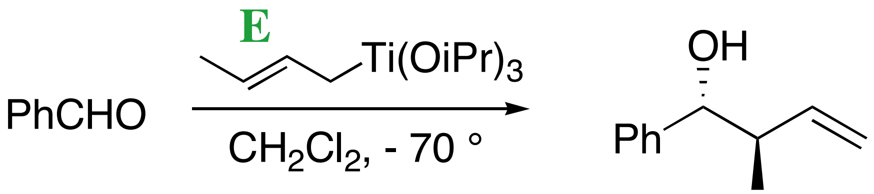
Qq exceptions : α Ba, Sm



Stéréochimie ?

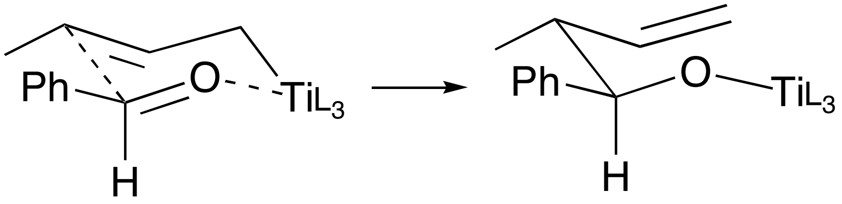
Régio- & Stéréochimie : idem aldolisations

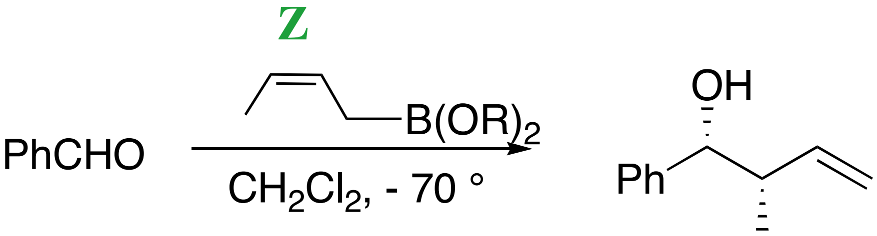
Stéréo

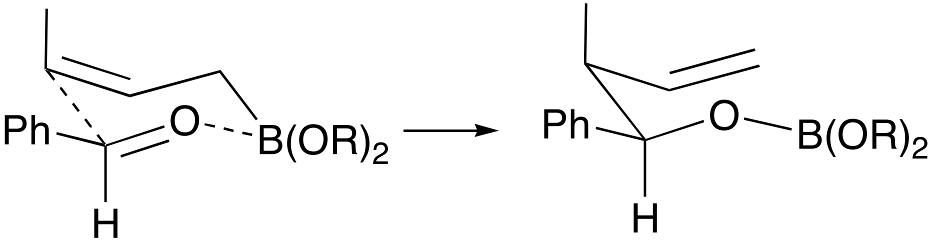


État de transition
à 6 centres 6 électrons

⇒ Conformation
pseudo-chaise





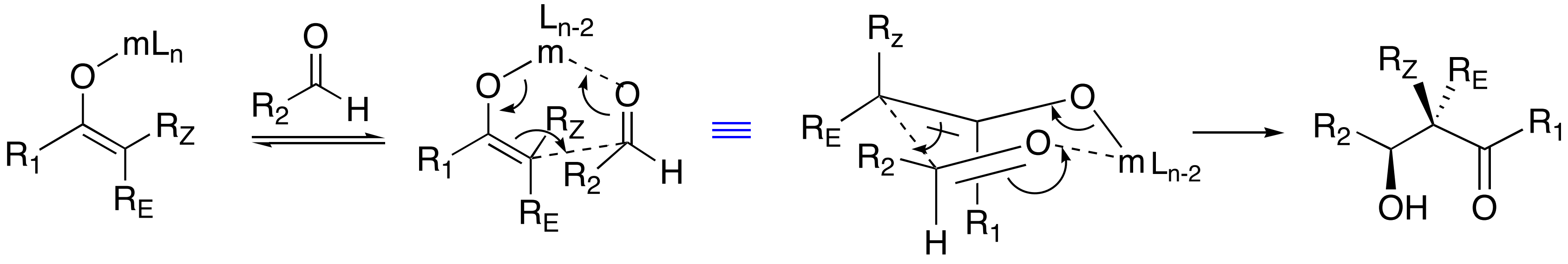


**NB:
stéréochimies
relatives**

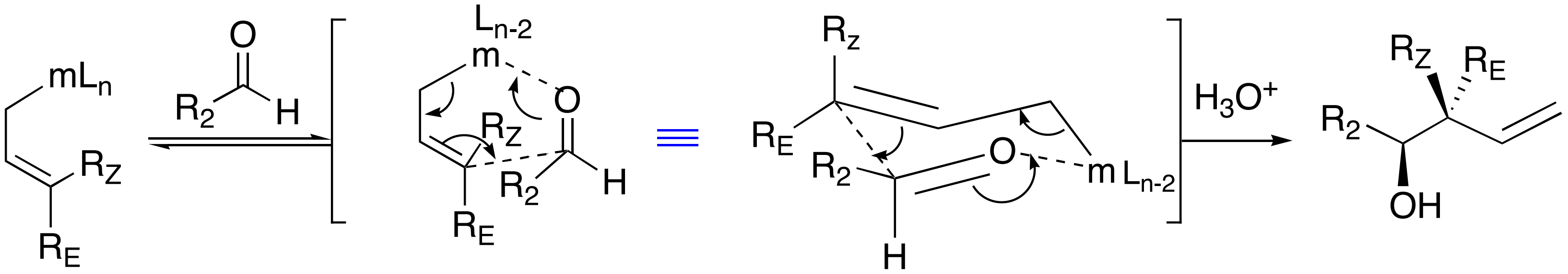
Régio- & Stéréochimie : idem aldolisations

État de transition
à 6 centres 6 électrons

Aldolisation

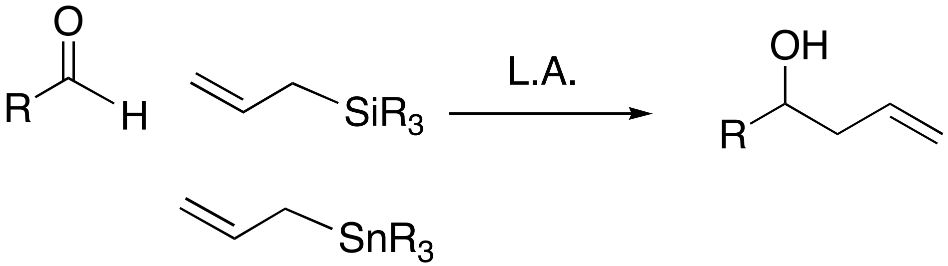


Allylation

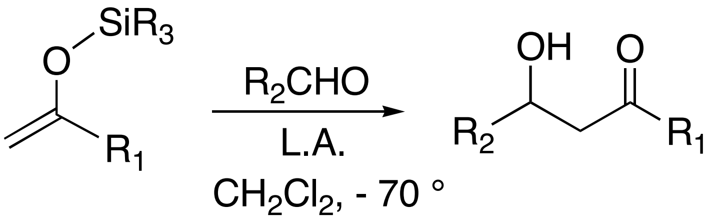


**NB:
stéréochimies
relatives**

5.2.1- allyl métaux η^1 non-coordinants

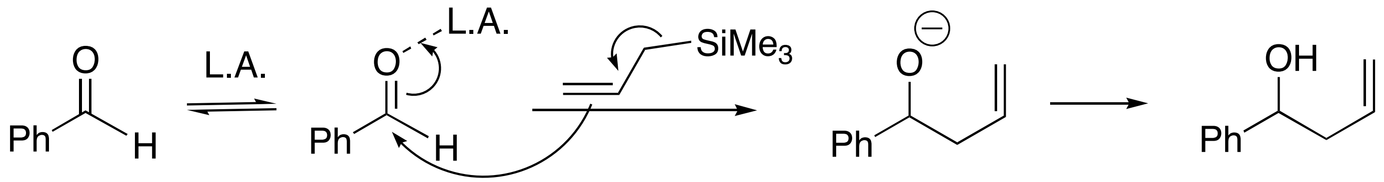


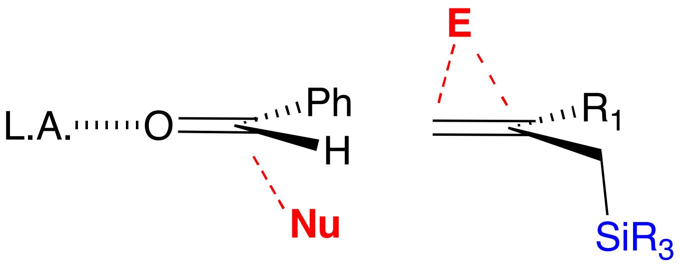
NB : similaire aux aldolisations de Mukaiyama



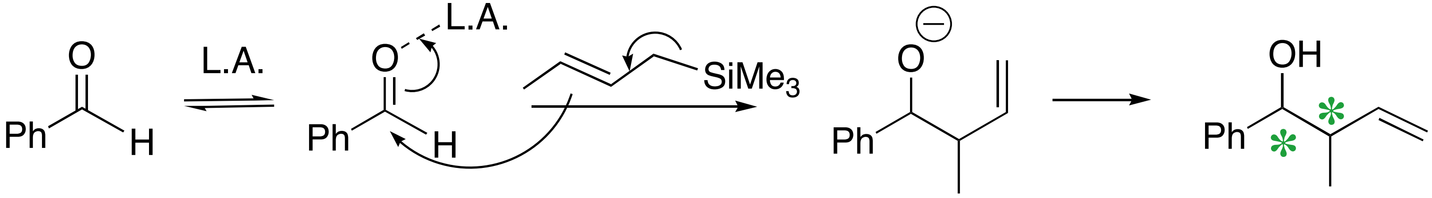
⇒ Même mécanisme

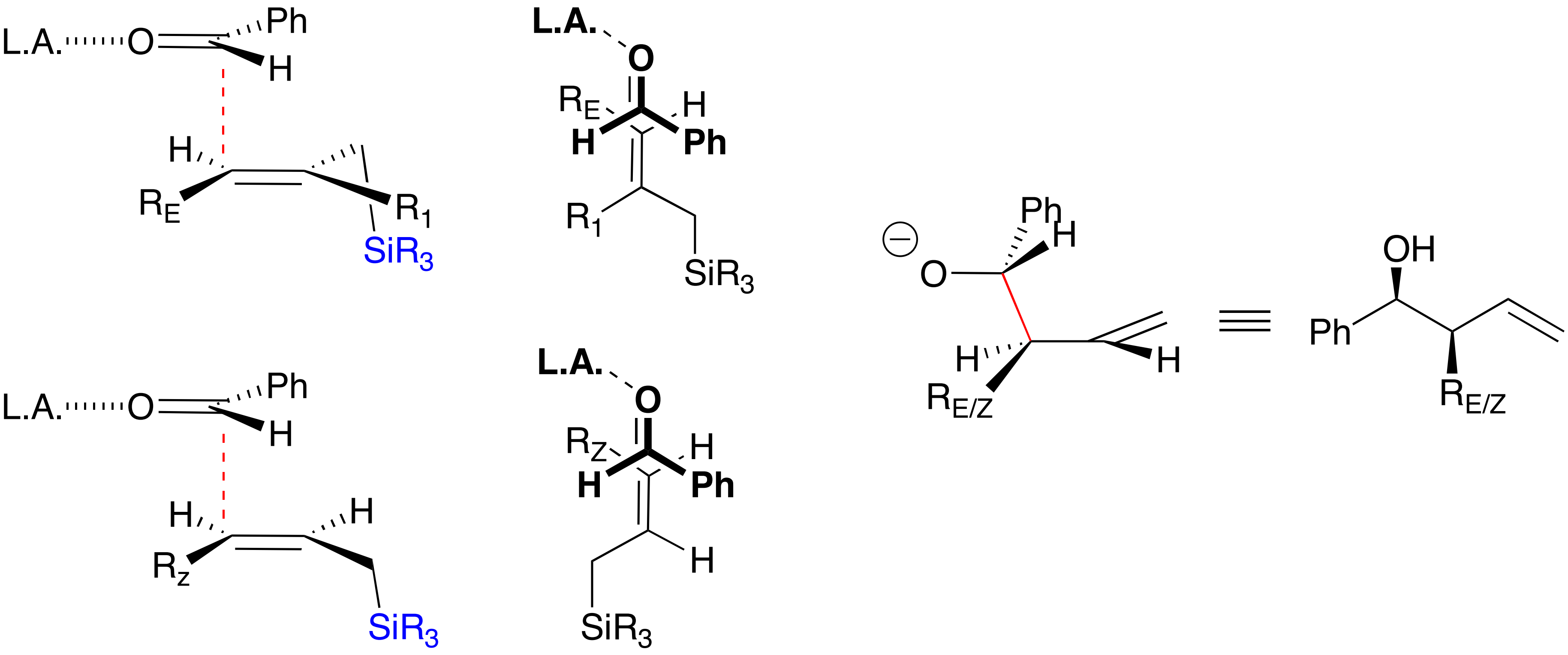
mécanisme





Stéréochimie ?

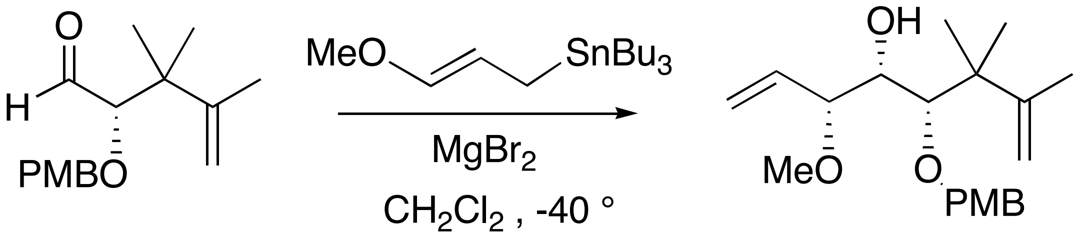


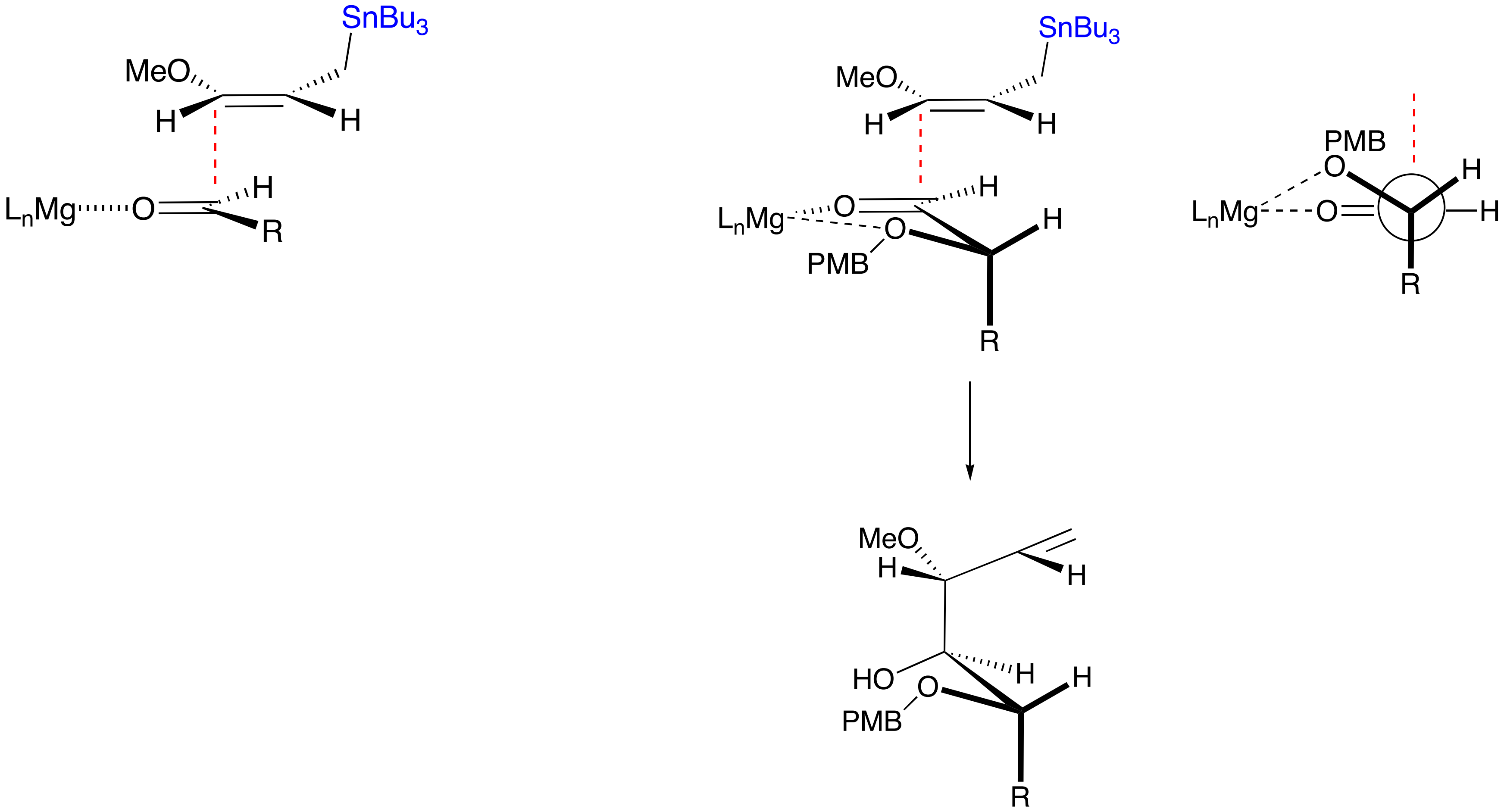


Allyl Si chiraux : démonstration de stéréoch anti add

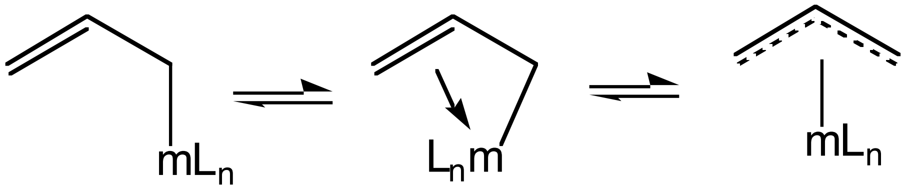
Kumada et al. *JACS* **1982**, *104*, 4962

D. Evans, Synth Calyculine, **1995**



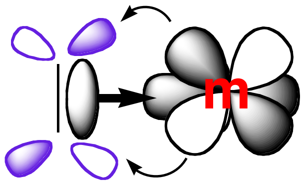


5-3 Allylation assistée par le palladium



η^3

cf



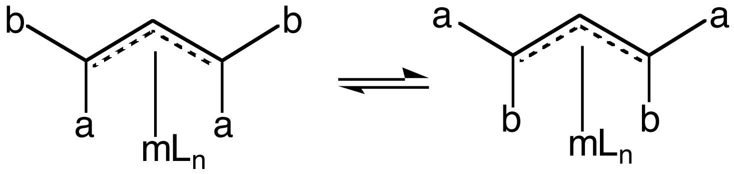
⦀

E

⇓

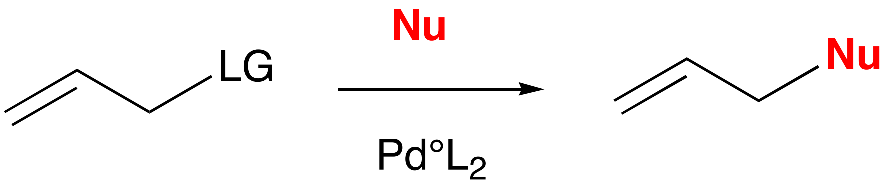
Subit des A.Nu

Métal : Pd, Ni, etc



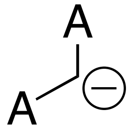
J. Tsuji et al
B. Trost et al.
1980-85

Réaction de Tsuji - Trost



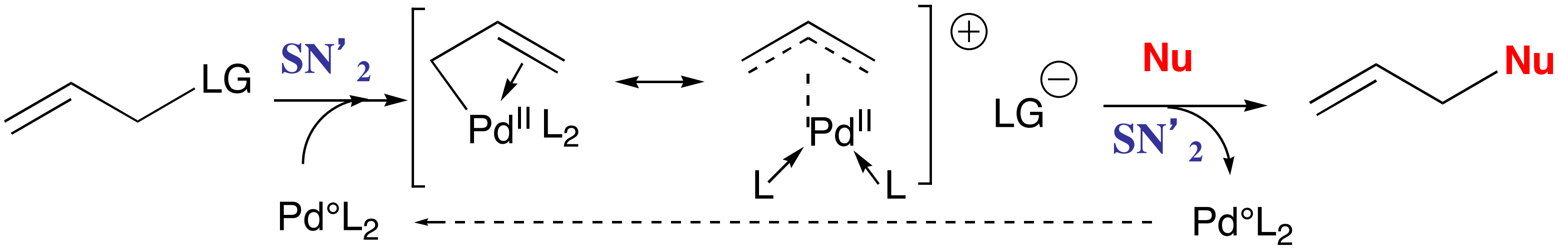
LG = Br
OOCR
OCOOR
$OPO(OR)_2$

Nu =

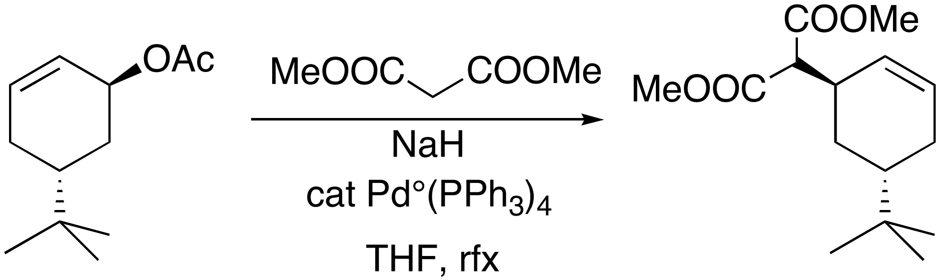


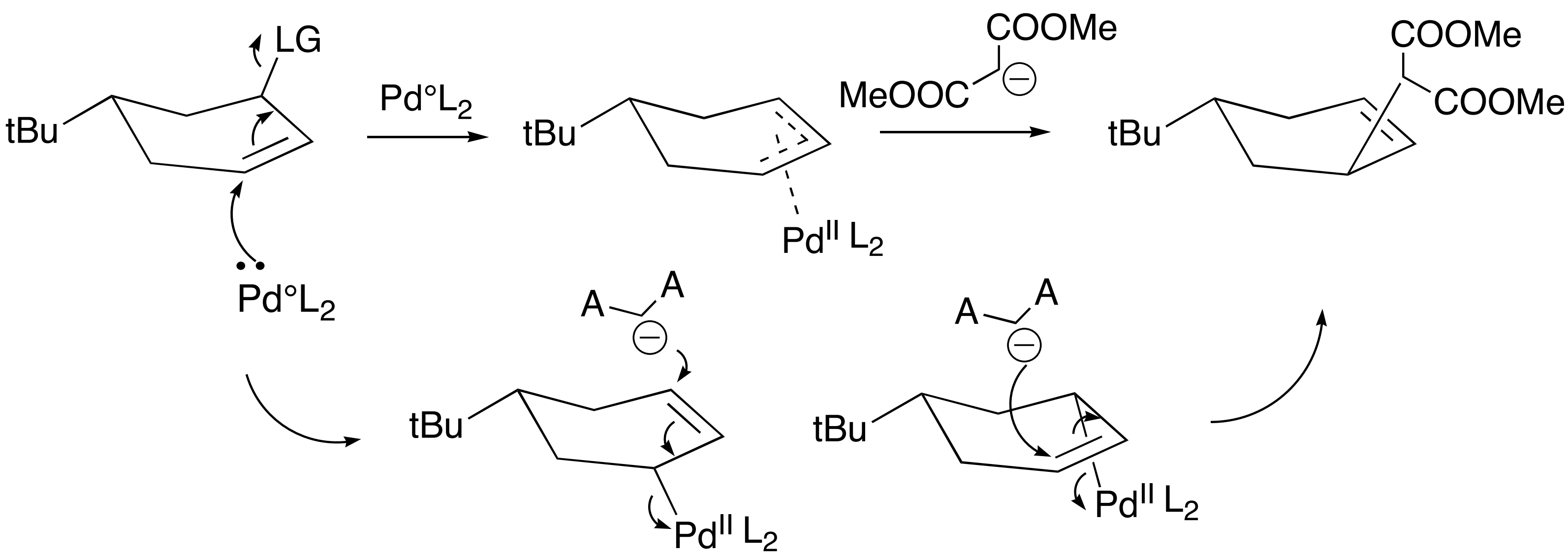
A = COOR
COR
SO_2R

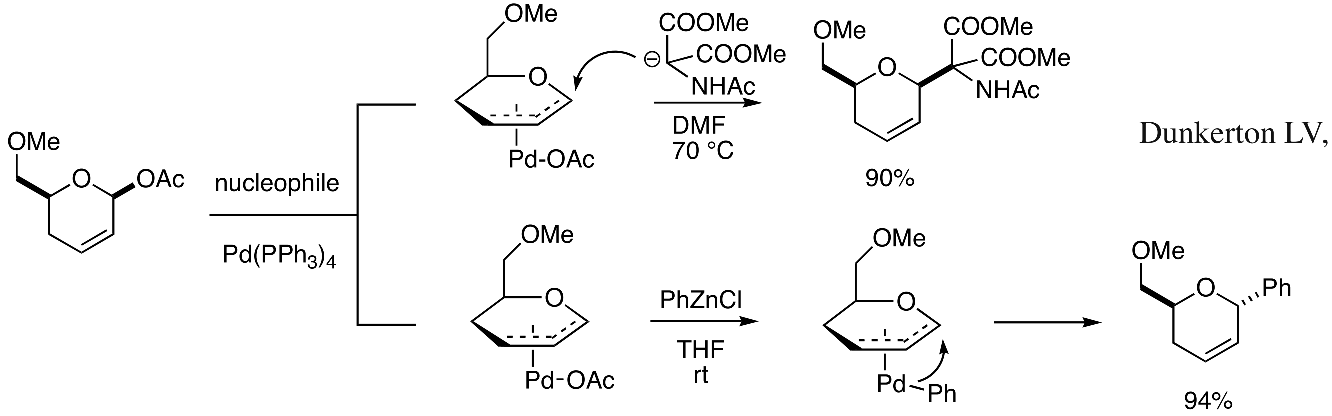
mécanisme **Via 2 SN'$_2$ et allyl-palladium** :



Stéréochimie

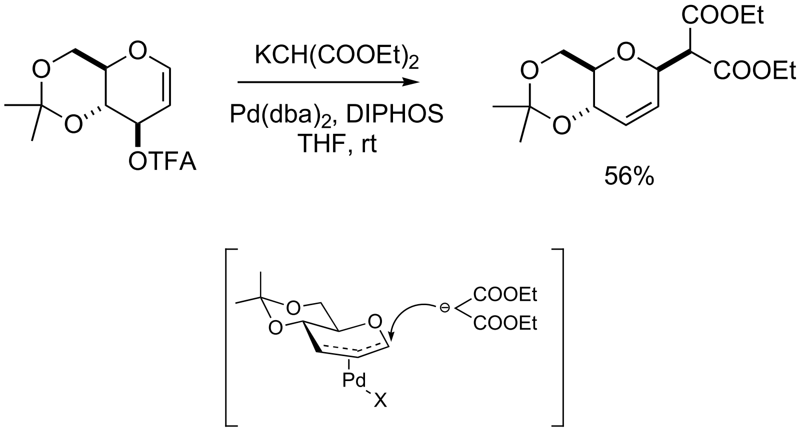






Dunkerton LV, Serino AJ *J Org Chem* **1982** *47*, 2814

Moineau C, Bolitt V, Sinou D *J Org Chem* **1998** *63,* 582



RajanBabu TV, *J Org Chem* **1985** *50*, 3642