UNIVERSITÉ DE STRASBOURG

Master de Chimie

FACULTÉ DE CHIMIE STRASBOURG

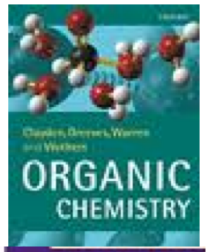
Chimie Organique

Tronc commun CMVS

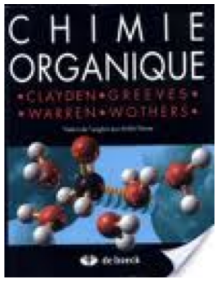
Synthèses stéréosélectives

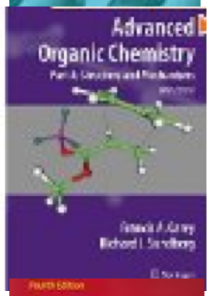
Cours: Pr Patrick Pale **TD:** Dr Stefan Chassaing

Bibliographie & Livres

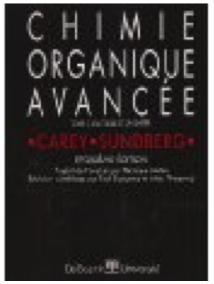


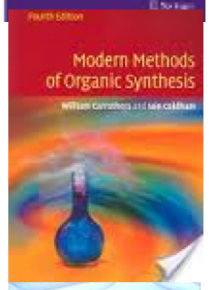
Chimie Organique
Clayden, Greeves, Warren, Wothers;
Ed Oxford (VO) Ed De Boeck (VF)



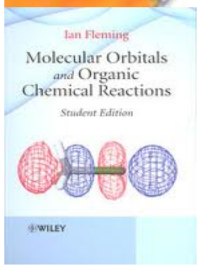


Chimie Organique Avancée
Carey, F. ; Sundberg, R.
5th Ed Springer Ed De Boeck (VF)

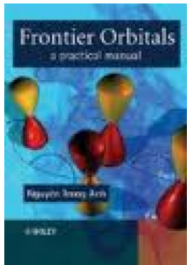




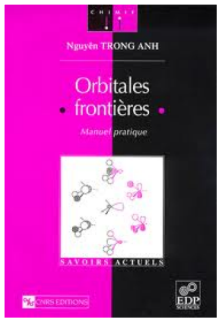
Modern Methods of Organic Synthesis
Carruthers, W.; Coldham I.
4th Ed Cambridge U. Pr



Frontier Orbitals & Organic Chemicals Reactions,
I. Fleming 1976 / 2009
Ed Wiley



Orbitals Frontières; Manuel pratique,
N. Trong Anh
Ed Wiley Ed EDP-CNRS



Plan

1- La chimie :

2- Carbanions et organométalliques

- 2-1 Qu'est ce qu'un carbanion ? Structures, stabilité conformationnelle
- 2-2 Formation
  - 2-2-1 déprotonation,
  - 2-2-2 déprotonation dirigée, orthométallation
  - 2-2-3 passage halogène-métal,
  - 2-2-4 addition sur une insaturation
- 2-3 Transmétallation

3- Additions Nucléophile & Electrophile

- 3-1 Orbitales frontières et réactivité
  - 3-1-1 HSAB,
  - 3-1-2 E/Nu réactivité,
  - 3-1-3 Règles de Baldwin,
  - 3-1-4 bases de synthèse asymétrique
- 3-2 Addition Nucléophile
  - 3-2-1-mécanisme,
  - 3-2-2 Modèles de Felkin & Anh
  - 3-2-3 Chelation
- 3-3 Addition Electrophile
  - 3-3-1 Mécanisme,
  - 3-3-2 Modèle de Houk

Plan, suite

4- Aldolisation

- 4-1 Enolates — structures, formation
- 4-2 Aldolisations simples (modèle Zimmermann-Traxler)
- 4-3 Aldolisation de Mukaiyama

5- Allylation

- 5-1 Allyl métaux — structures, stabilité conformationnelle
- 5-2 Allyl métaux — métal coordinant
  métal non coordinant
- 5-3 Allyl palladium

6 - Réactions de couplage (r. Heck, Stille, Suzuki, Sonogashira…)

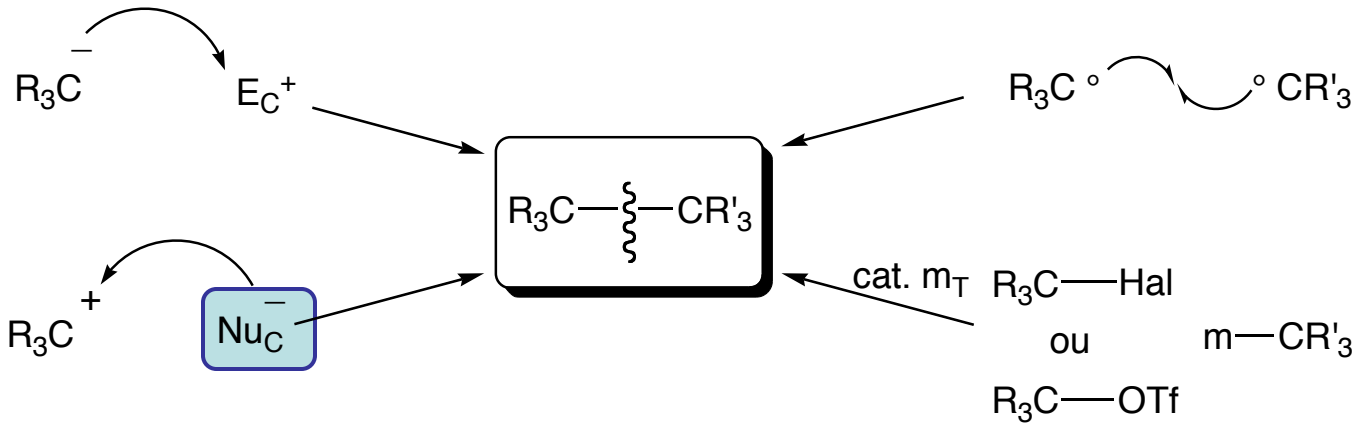
7- Formation de C=C

8- Réactions péricycliques

- 8-1 Historique & règles de Woodward-Hoffman
- 8-2 Cycloadditions
- 8-3 Sigmatropies

Chap. 2 Carbanions & Organométalliques

Carbanion : Outil principal de la chimie organique



2-1 Carbanion

- 2-1-1 Qu'est ce qu'un carbanion ?
- 2-1-2 Structures
- 2-1-3 stabilité conformationnelle

2-2 Formation

- 2-2-1 déprotonation
- 2-2-2 déprotonation dirigée, orthométallation
- 2-2-3 passage halogène-métal et rel.
- 2-2-4 addition sur énone, hydrométallation, carbométallation

2-3 Transmétallation

2.1. Carbanions

2-1-1 Qu'est ce qu'un carbanion ?

Carbanions: R_3C^- en fait, rarement « nu », tjs lié à un métal:

R_3C-m

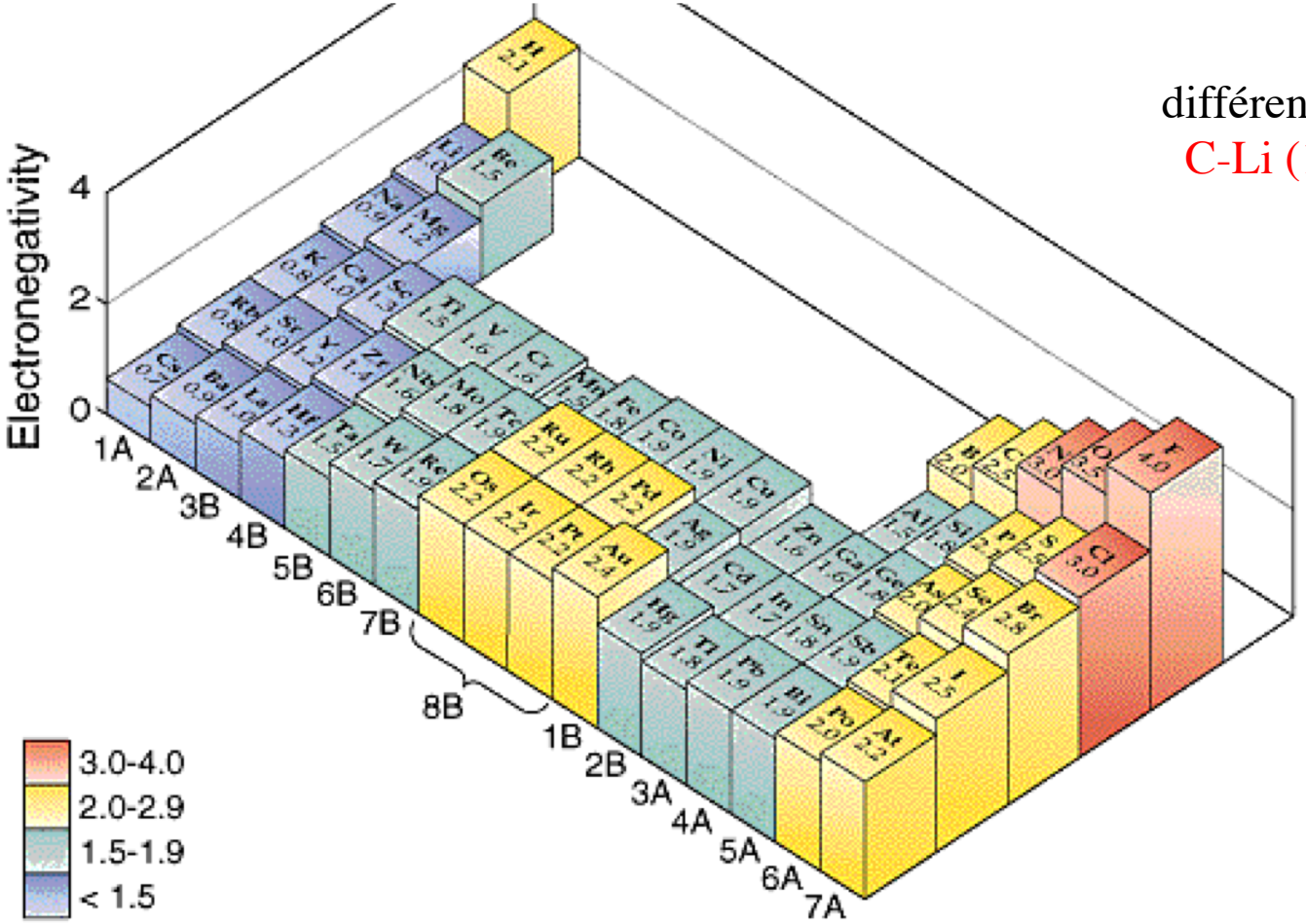
Le caractère carbanionique est dû à la liaison C-m:

- type de liaison ?

. Ionique ?

. Covalente ?

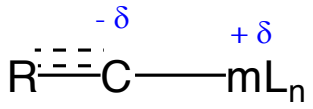
. Ionique ? Covalente ?



différence d'électronégativité

C-Li (1,5) même que C-F (1,5)

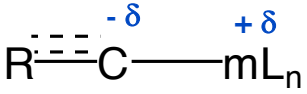
Liaison C-m : covalente ± polarisée



différence d'électronégativité pas très grande (≤ C-F)

ionique seul^{t} avec m = Na, K, Cs (NR_4^+)

- liaison C-m covalente:



. polarisation de la liaison

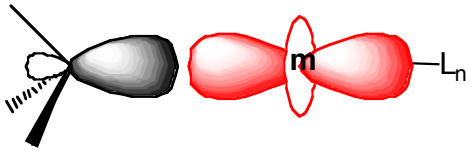
. coordinance du métal nombre et nature des ligands

- nature de la liaison covalente: fn des orbitales

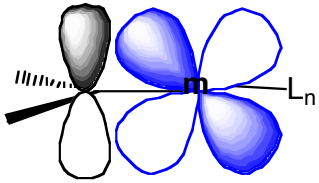
. hybridation du C et du m

. d ou non

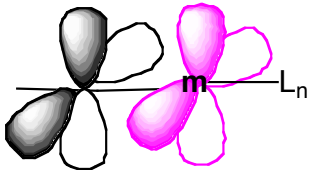
. « back-bonding » ou non,



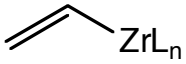
liaison σ

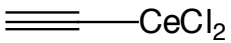


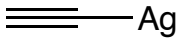
liaison π



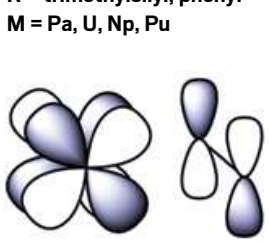
liaison δ

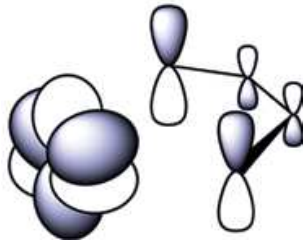




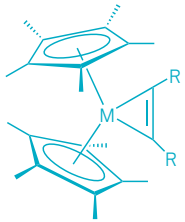


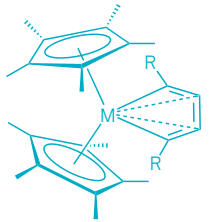
R = trimethylsilyl, phenyl
M = Pa, U, Np, Pu





liaison φ





could help separate actinide from lanthanide elements

⇒ process nuclear waste

Nat. Commun. 2020,
DOI: 10.1038/s41467-020-15197-w

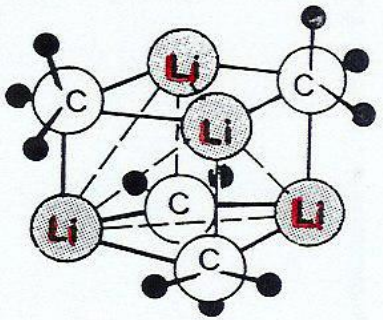
2-1-2 structures

Lithiens Rarement monomère C-Li

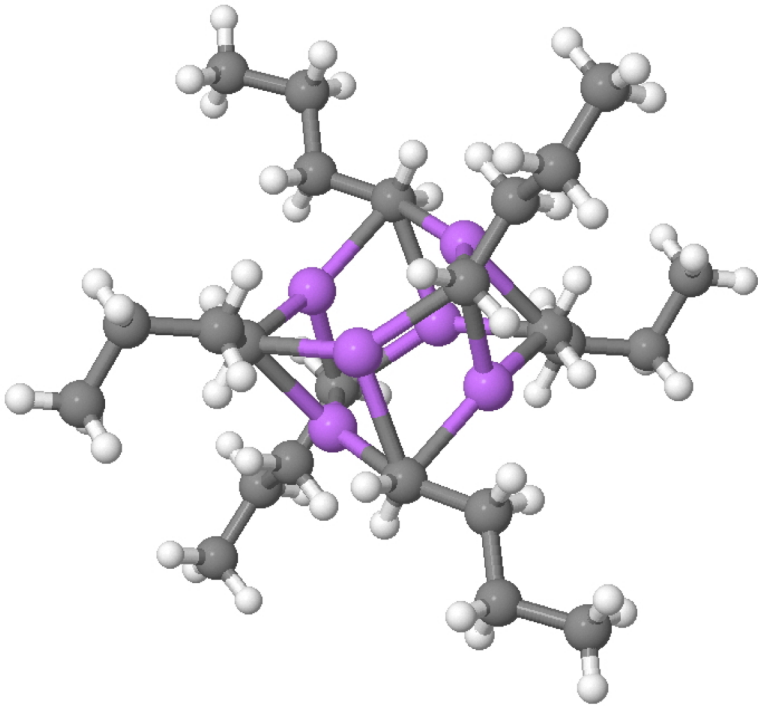
Cf Tab periodique: Li $2s^1$, 2p ⇨ tétravalent ⇨ tétrahèdrique

Le plus souvent, agrégats
Tétramère, héxamère

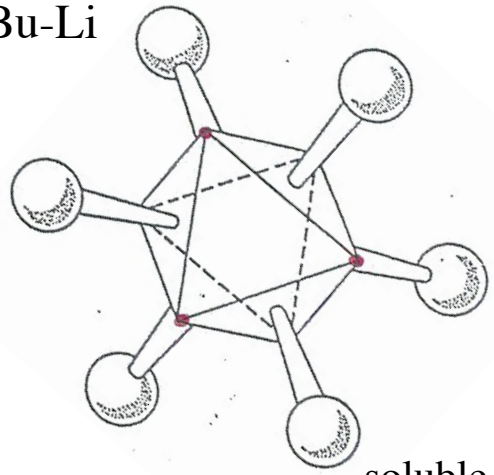
Me-Li



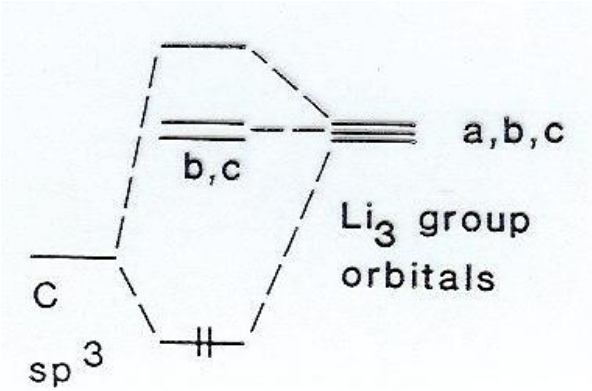
	d(Li—C)	= 231 pm	$(LiCH_3)_4$
	d(Li ·· C)	= 236 pm	$(LiCH_3)_4$
	d(Li—Li)	= 268 pm	$(LiCH_3)_4$
compare:	d(Li—Li)	= 267 pm	Li_2 (g)
	d(Li—Li)	= 304 pm	Li (m)

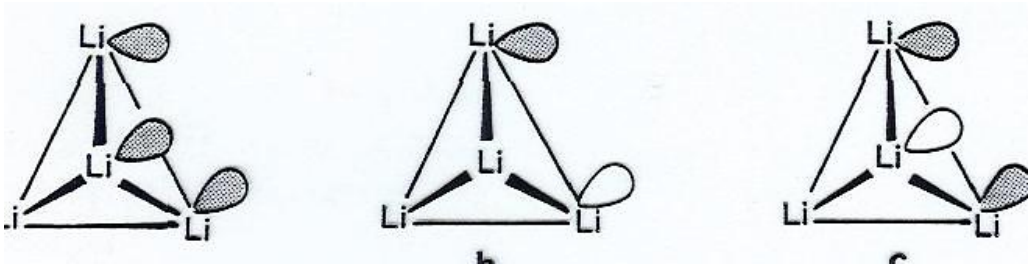


*n*Bu-Li



soluble dans hexane


a,b,c
b,c
Li_3 group orbitals
C
sp^3


Li
Li
Li
Li
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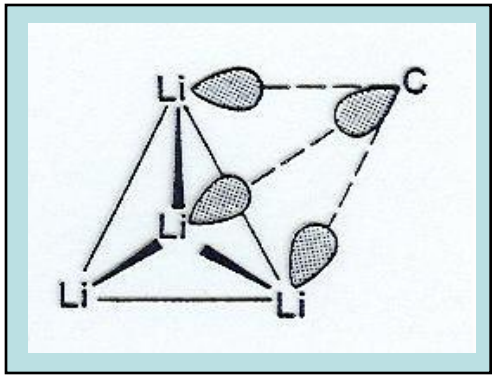
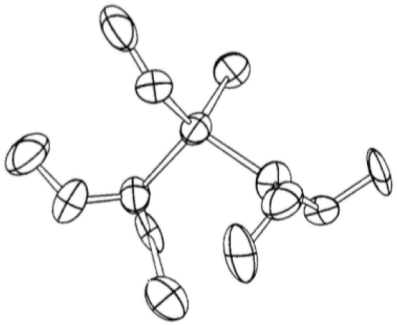
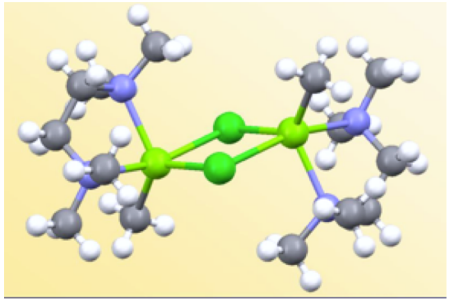
Li
Li


Li
C
Li
Li
Li

Magnésiens

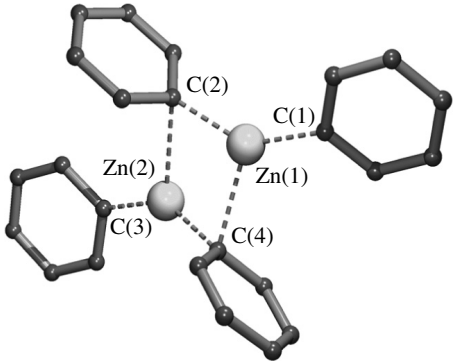


$EtMgBr(Et_2O)_2$
J. Am. Chem. Soc. **1968**, *90*,5375



$[MeMgCl(TMEDA)]_2$

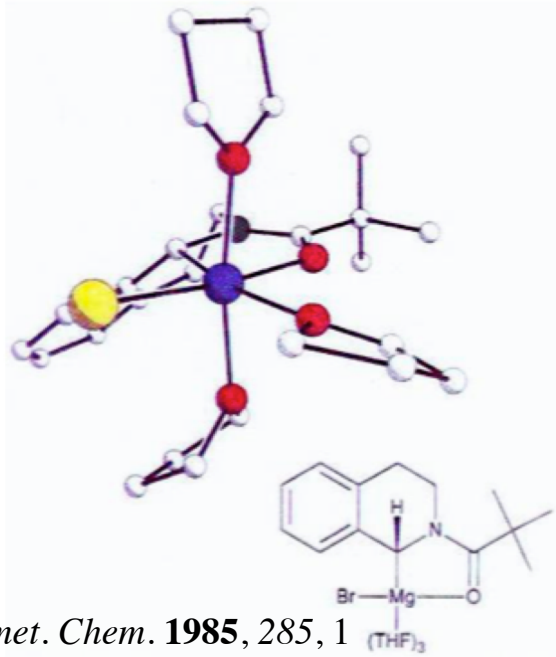
Zinciques



Ph_2Zn
Organomet. **1990**, *9*, 2243

Mg hexavalent, oct.

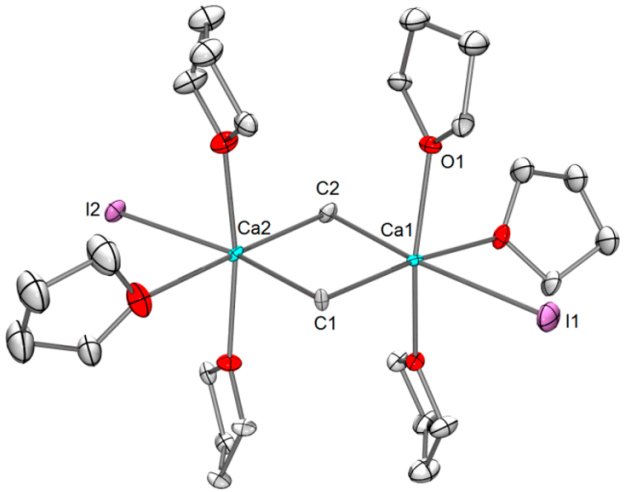
(NB: stéréogène)



Seebach et al. *J. Organomet. Chem.* **1985**, *285*, 1

Organomet. **1991**, *10*, 1531

etc

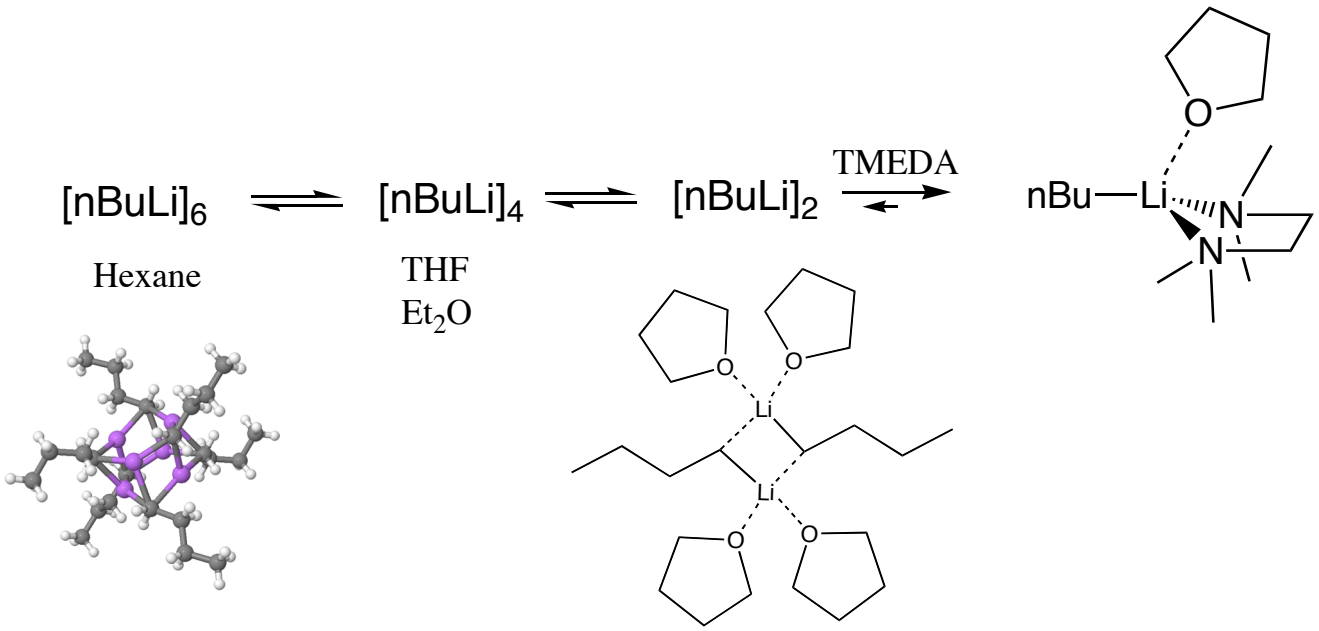


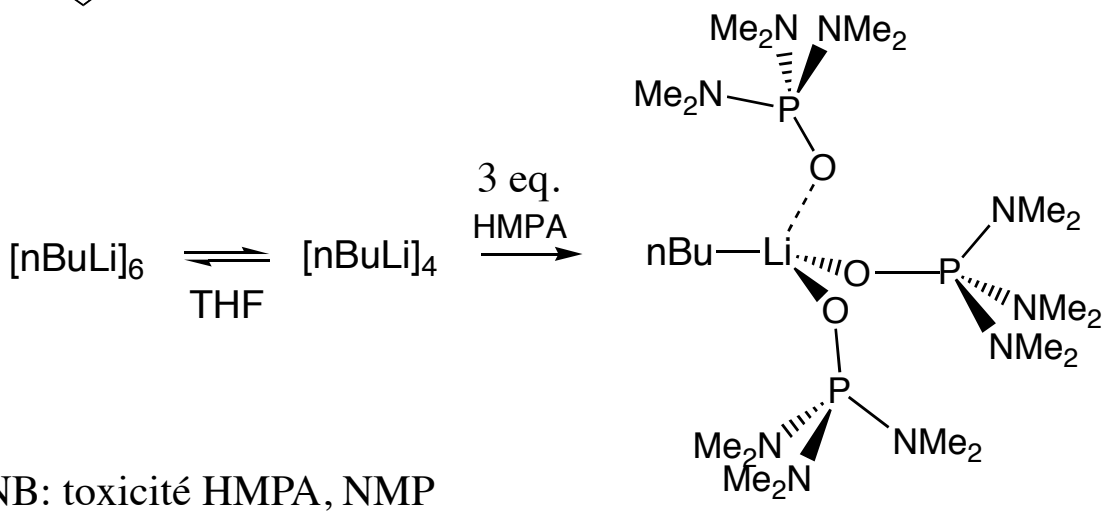
$[(thf)_3Ca(\mu_2\text{-}Me)(I)]_2$

J. Am. Chem. Soc. **2018**, *140*, 2373

Etat d'agrégation variable et modulable - selon solvant THF, Et_2O, DME, ….

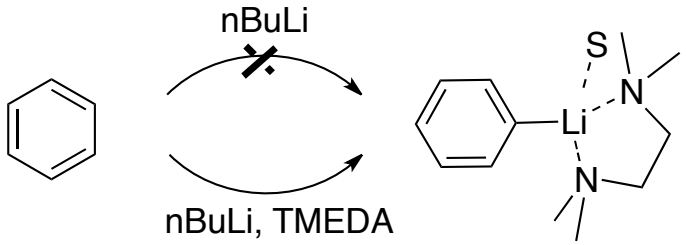
- selon additif TMEDA, HMPA, NMP, py, bipy, etc.



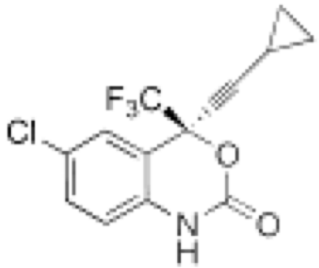


NB: toxicité HMPA, NMP

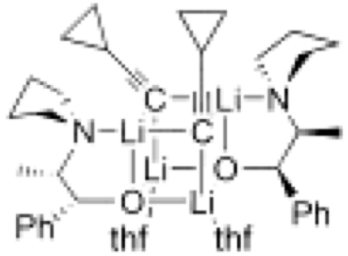
…influue sur la réactivité



Langer, A.W. *Adv. Chem. Ser.* **1974**, No.130.



Efavirenz (**1**)



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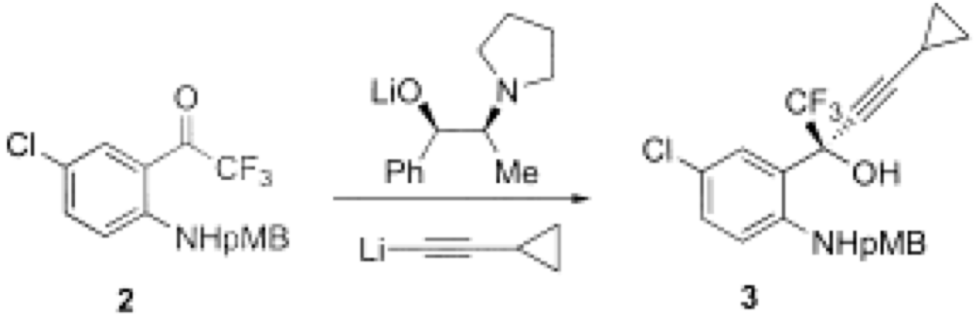


2 **3**

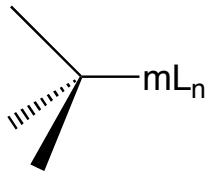
Key enantioselective step in the synthesis of Efavirenz (anti-HIV)

Ang. Chem. Int. Ed. **2005**, *44*, 1448

2-1-3 stabilité conformationnelle

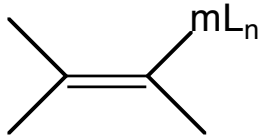
-fn structure

C sp^3



± stables

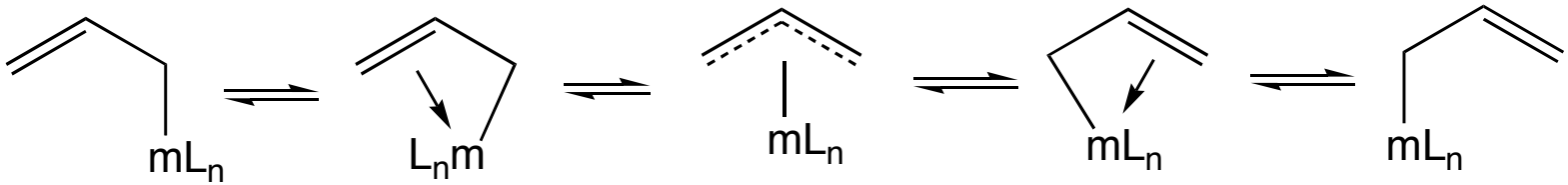
C sp^2

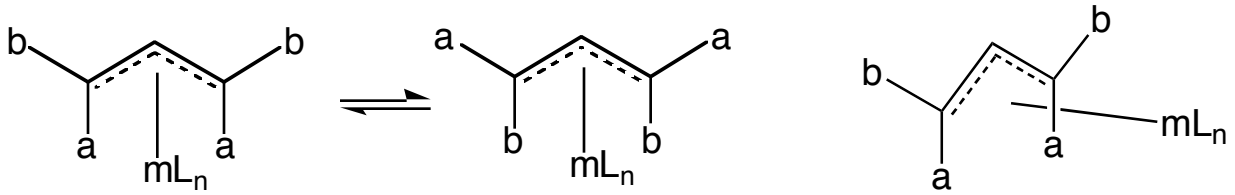


stables

Allyl

± stables





⇒ **Réactions stéréosélectives & asymétrique**

2.2 Formation de carbanions

2-2-1 déprotonation

2-2-2 déprotonation dirigée, orthométallation

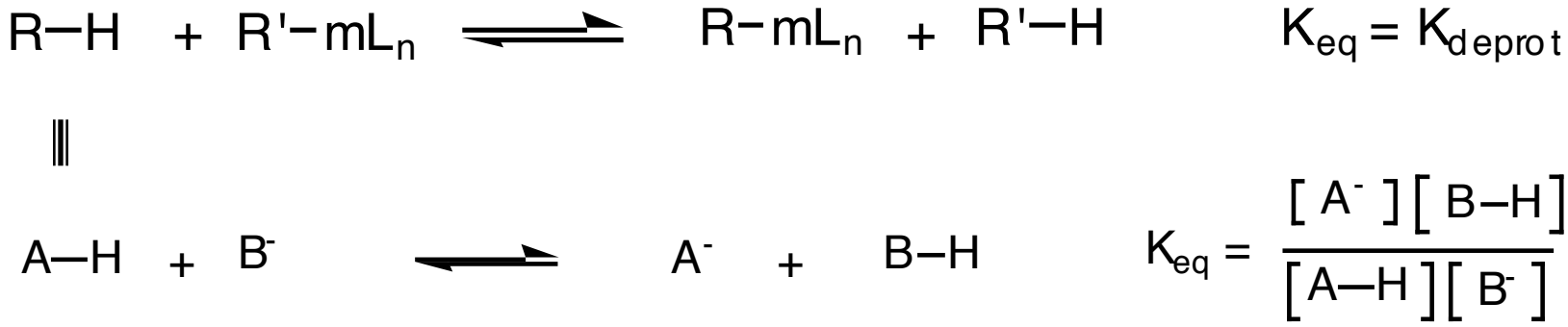
2-2-3 passage halogène-métal et rel.

2-2-4 addition sur une insaturation

2-2-1 déprotonation

une des méthodes les plus utilisées

Équation:



Mais quelle base choisir ?

$$K_{deprot} = K_{eq} \nearrow \quad [A^-] \nearrow$$

L'efficacité de la déprotonation dépend de l'acidité de l'espèce carbonée (R-H = A-H) et de la force de la base ($R'\text{-}mL_n = B^-$):

$$R\text{–}H + R'\text{–}mL_n \rightleftharpoons R\text{-}mL_n + R'\text{–}H \qquad K_{eq} = K_{deprot}$$

$$A\text{–}H + B^- \rightleftharpoons A^- + B\text{–}H \qquad K_{eq} = \frac{[A^-][B\text{–}H]}{[A\text{–}H][B^-]}$$

$$A\text{–}H + B^- + H^+ \rightleftharpoons A^- + B\text{–}H + H^+ = \begin{cases} A\text{–}H \rightleftharpoons A^- + H^+ & K_{a\,(AH/A-)} \\ B^- + H^+ \rightleftharpoons B\text{–}H & 1/K_{a(B-/BH)} \end{cases}$$

$$K_{eq} = \frac{[A^-][B\text{–}H][H^+]}{[A\text{–}H][B^-][H^+]} = \frac{[A^-][H^+]}{[A\text{–}H]} \cdot \frac{[B\text{–}H]}{[B^-][H^+]}$$

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

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

$pK_a = -\log K_a$ ⇓ $K_a = 10^{-pKa}$

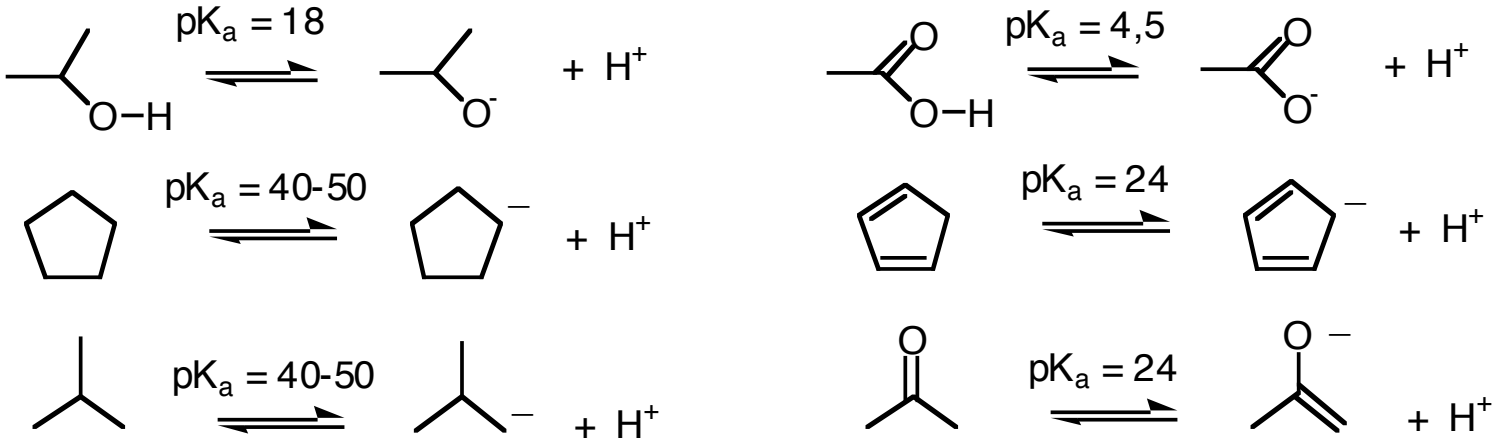
$$K_{eq} = 10^{-pK_{a\,(AH/A-)} + pK_{a\,(B-/BH)}}$$

pour avoir $K_{eq} > 0$, $pK_{a\,(B-/BH)} >> pK_{a\,(AH/A-)}$ ➡ $\Delta pKa > 3$

Types bases	Gamme de pKa	Exemples	Conditions	courantes
NR_3	8-12 10	NEt_3, $NEtiPr_2$, DBU, DBN (Pyridine,Collidine)	CH_2Cl_2	0-20°
mOR	16-20 20	NaOH, KOH MeONa tBuOK	MeOH, EtOH MeOH,THF tBuOH, THF	0-20° " "
mH	25-30 25	NaH, KH	THF, DMF	≤0°
mNR_2	30-35	$LiNH_2$, $NaNH_2$ K 3-Aminopropylamidure (KAPA) Li*N*iPr_2 (LDA), Li*N*iPrcHex (LICA) Li ou Na $N(SiMe_3)_2$ (Li-NaHMDS) Li Tétraméthylpipéridine (LiTMP)	NH_3, THF DMSO THF " " "	≤-30° 0-20° -78° " "
mCR_3	35-45	MeLi, *n*BuLi, *s*BuLi, tBuLi *n*BuLi-tBuOK	THF	-78° "

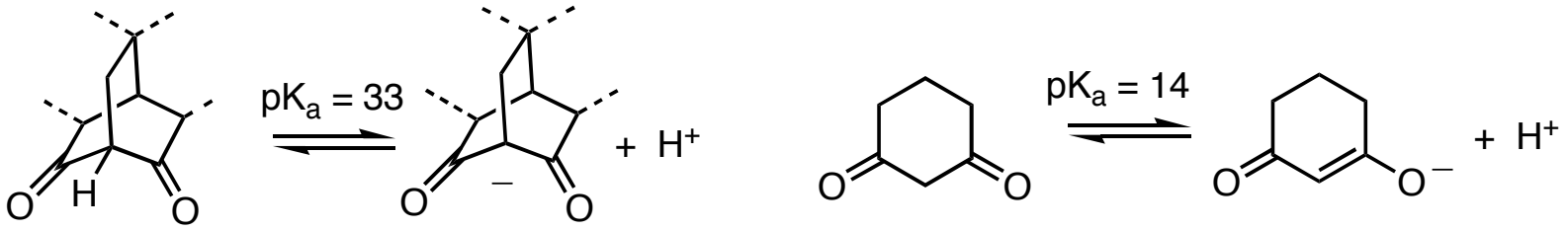
Facteurs régissant les pKa :

-délocalisation

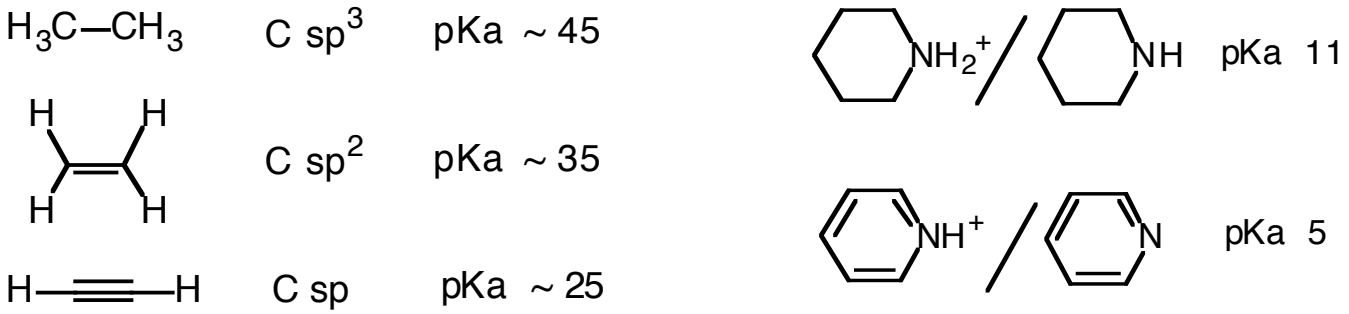


NB effet important de la conjugaison (Δ 15-25)

mais stéréoélectronique : (NB importance hyperconjugaison)

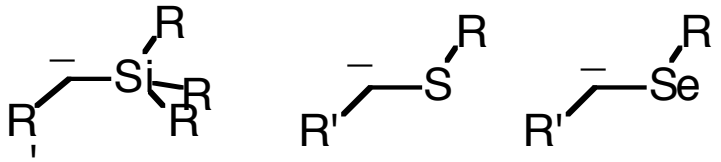


-hybridation

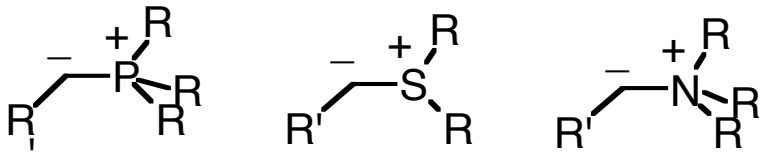


Facteurs régissant les pKa :

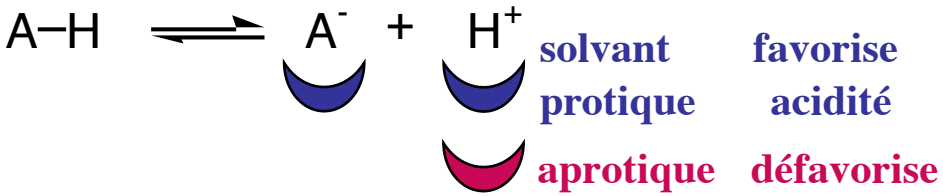
-stabilisation par orbitales d (hyperconjugaison)



-stabilisation par charges



-solvant & conditions : solvatation différente selon que solvant protique ou aprotique

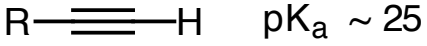


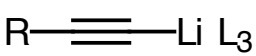
solvant protique — **favorise acidité**

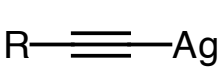
solvant aprotique — **défavorise**

	H_2O	DMSO	THF
HO–H / OH^-	pK_a 15,7	31	
EtO–H / EtO^-	pK_a 18	30	
	pK_a 20	26	
Ph_3CH / Ph_3C^-		31	35

-nature de mL_n

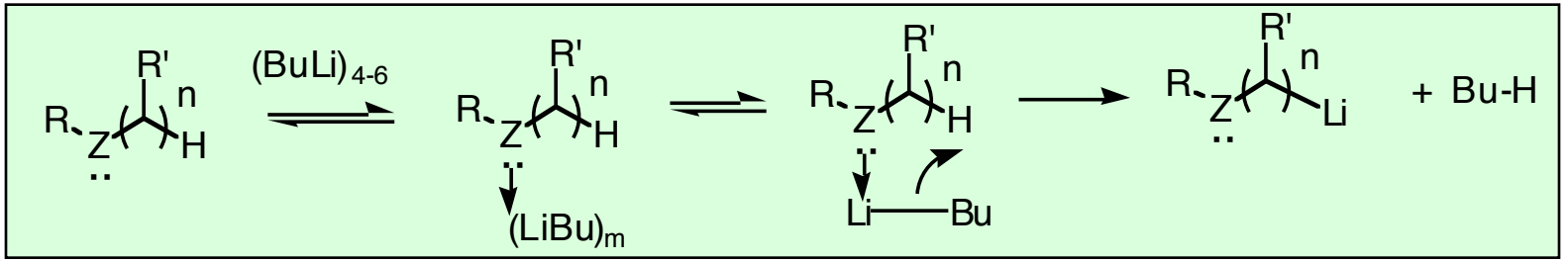
 pK_a ~ 25

 **instable & réagit dans ROH**

 **stable & formé dans $MeOH/H_2O$**

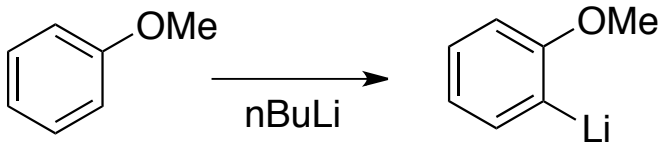
2-2-2 déprotonation dirigée, orthométallation

Principe:



Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, 61, 109.
Wittig, G.; Fuhrman, G. *Chem. Ber.* **1940**, 73, 1197.

anisole

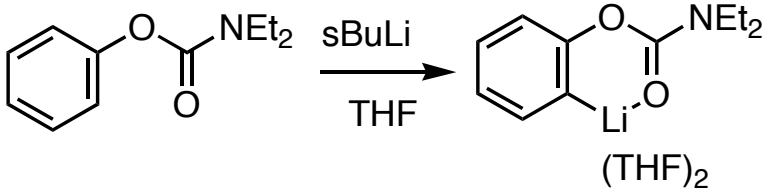


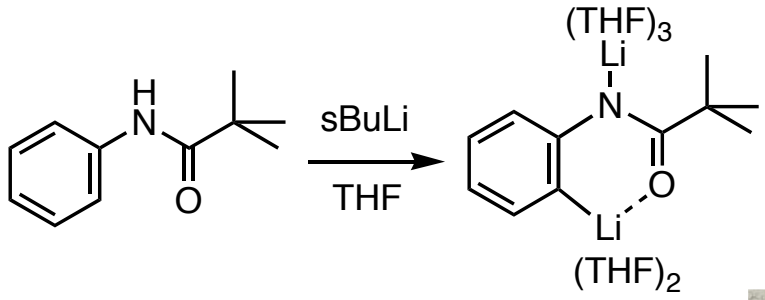
NB : cinétique; pas diff pKa *o*, *m*, *p*

Mécanisme:

←

Exemples: V. Snieckus *Chem. Rev.* **1990**, 90, 879 Heterocycles *Chem. Soc. Rev.* **2007**, 36, 1069 & 1161





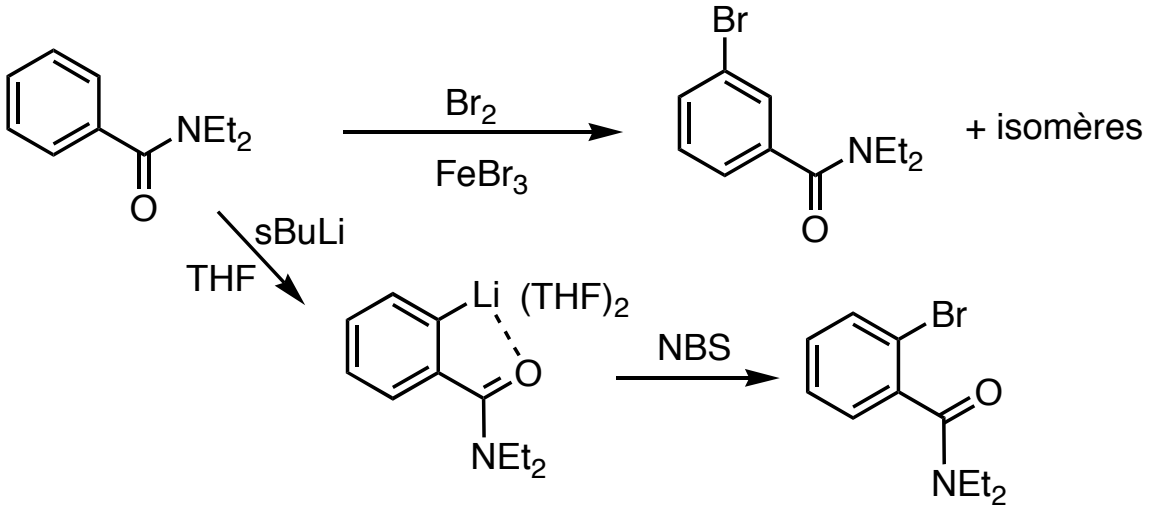
etc....

V. Snieckus

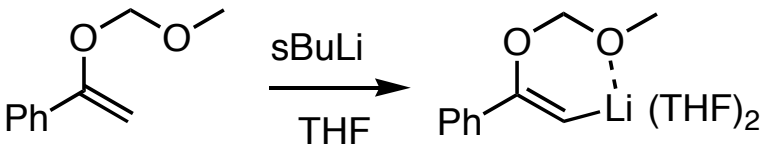
Directed Metalation Groups (DMGs)

Intérêt : Inversion de polarité

Umpolung



Pas limité aux Aryls :

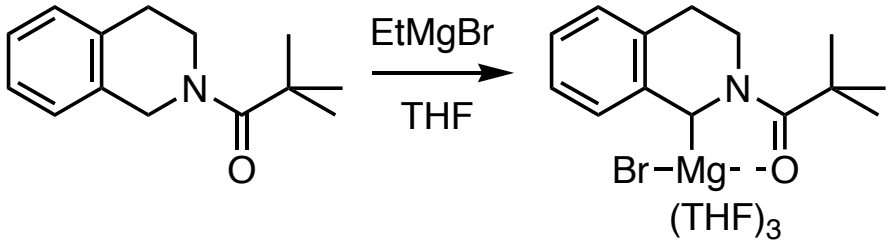


régiosélectif

stéréosélectivité alcène

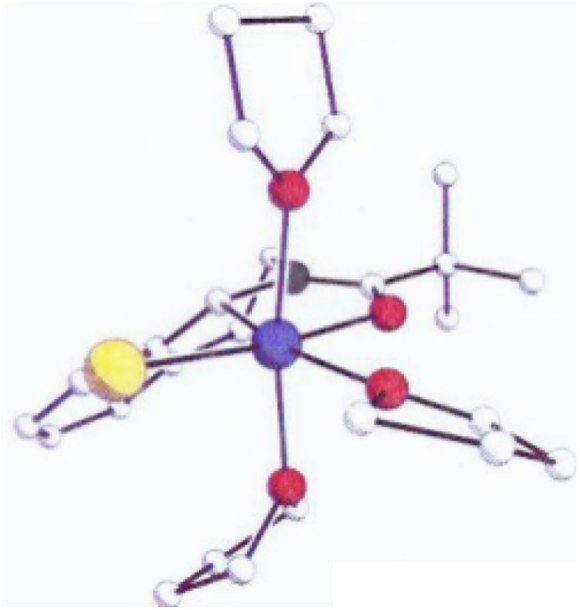
Tet. Lett **84**, 5977

Pas limité aux lithiens :



A. Meyers

stéréosélectif



2-2-3 passage halogène-métal

2.2.3.1- addition oxydante (magnésiens, lithiens, zinciques)

Réactifs de Grignard

V. Grignard (1871-1935; Nobel 1912)

$$R{-}Hal + Mg^{\circ} \longrightarrow R{-}Mg^{II}{-}Hal$$

Grignard, V. *Compt. Rend. Acad. Sci.* **1900**, *130*,1322

NB: umpolung

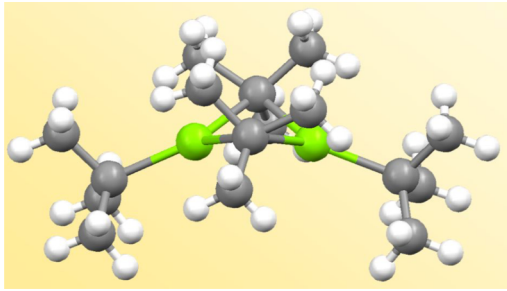
R-MgX = Nu, Ba, ET

$$2\ R{-}Mg^{II}{-}Hal \rightleftharpoons R{-}Mg^{II}{-}R + MgHal_2$$

Eq de Schlenk

Eq. ± déplacé vers R_2Mg selon cond
e.g. + dioxane, MgX_2 précipite

Schlenk, W.; Schlenk, W., Jr. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 920



$[t\mathrm{Bu}_2\mathrm{Mg}]_2$

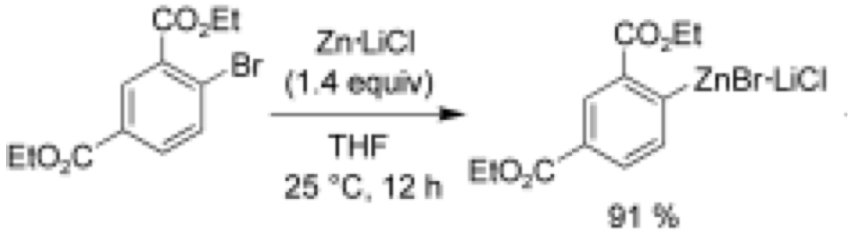
Seyfert, D. Organometallics **2009**, *28*, 1598

lithiens $2\ R{-}Hal + 2\ Li^{\circ} \longrightarrow R{-}Li^{I} + LiHal$

zinciques $R{-}Hal + Zn^{\circ} \longrightarrow R{-}Zn^{II}{-}Hal \rightleftharpoons 1/2(\ R{-}Zn^{II}{-}R + ZnHal_2\ )$

Frankland **1849** Et-I + Zn ⟶ « $Et^{\bullet}$ » EtZnI

(Hist) Seyfert, D.
Organometallics **2001**, *20*, 2941

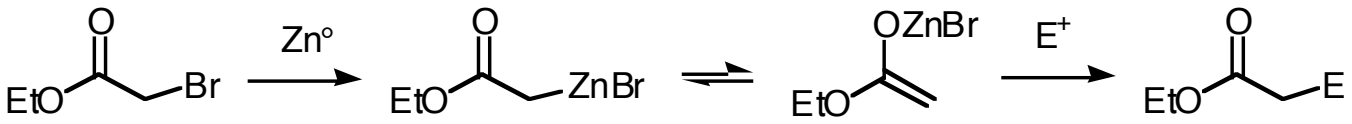


Knochel, P. et al.
Angew. Chem., Int. Ed. **2006**, *45*, 6040

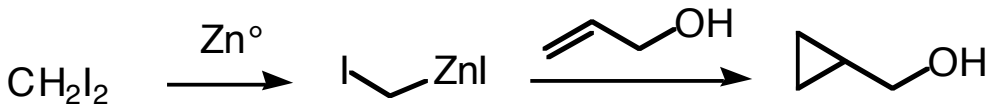
via mécanisme SET

J. Garst *Acc. Chem. Res.* **1991**, *24*, 95;
H. M. Walborski, *Tetrahedron Lett.* **1989**, *30*, 7345

Réact. Reformatsky



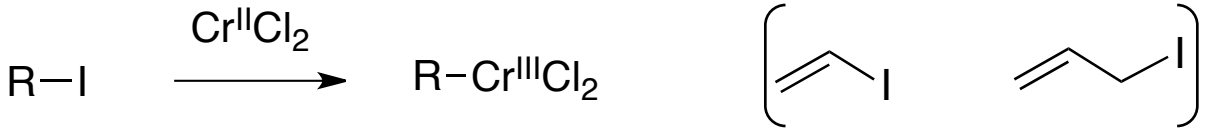
Réact. Simmons-Smith



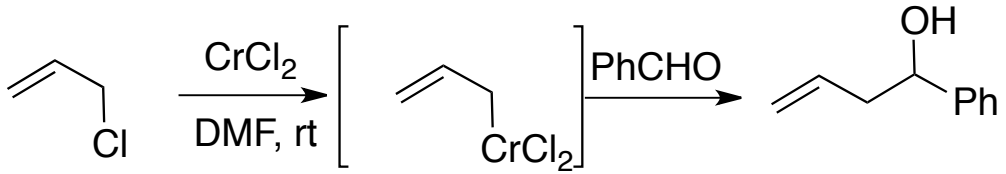
carbenoïdes

Autres métaux :

Réact. Nozaki-Hiyama-Kishi



Y. Okude, S. Hirano, T. Hiyama, H. Nozaki
JACS **1977**, *99*, 3179



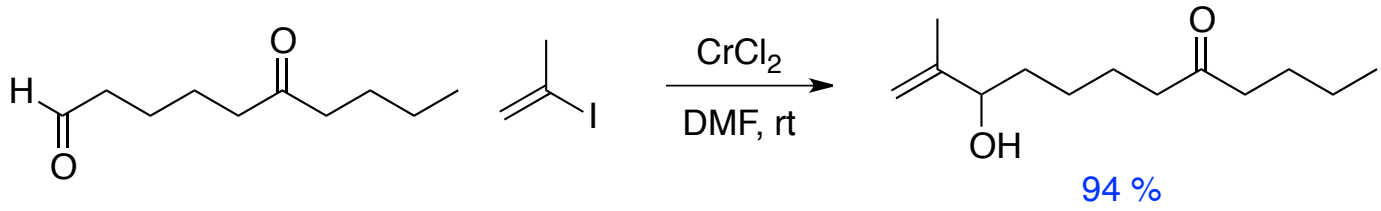
R-CrX_2 = bon Nu, peu Ba

Jin, H.; Uenishi, J.; Christ, W.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644
Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048

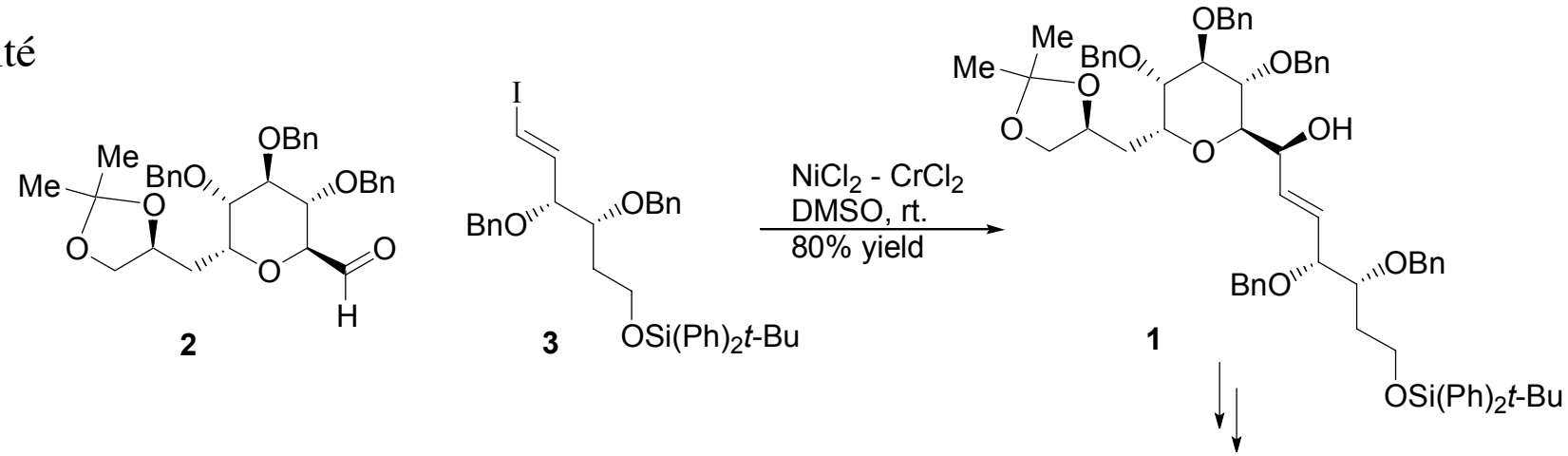
Réact. Nozaki-Hiyama-Kishi

A. Gil, F. Albericio, M. Alvarez, *Chem. Rev.* **2017**, *117*, 8420

chimiosélectif



compatibilité



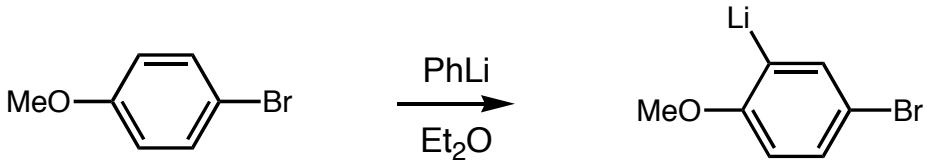
Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343

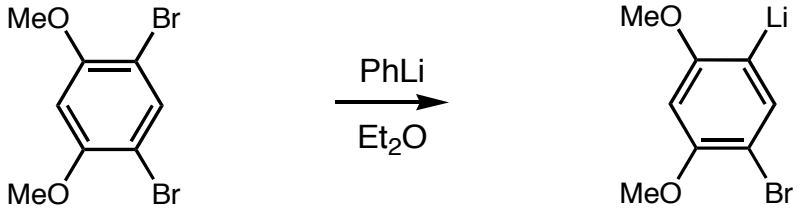
Palytoxin

2.2.3.2- échange halogène-métal

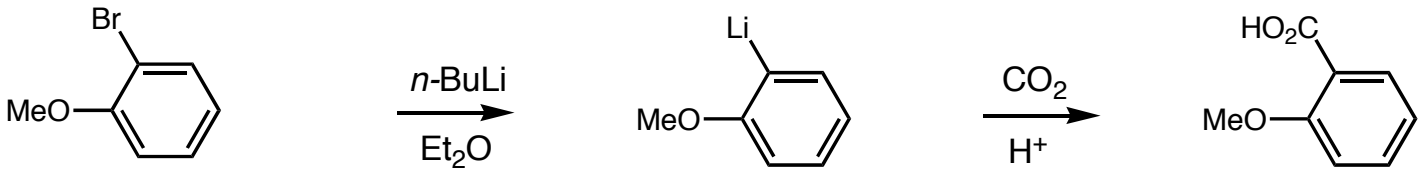
lithiens

G. Wittig, G. Fuhrmann
Ber. Dtsch. Chem. Ges.
1938, *71*,1903

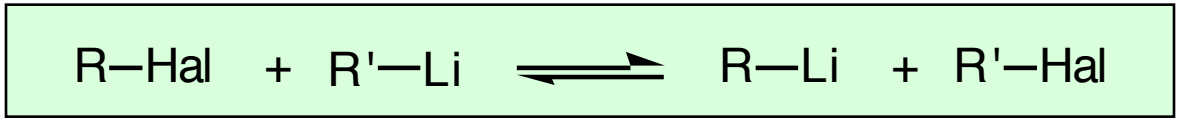




H. Gilman et al. *JACS* **1939**, *61*, 106



Principe :



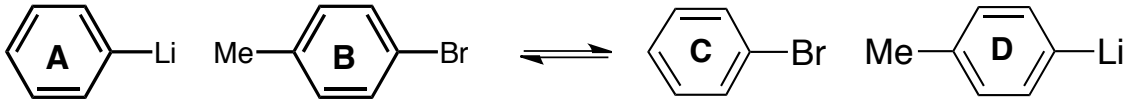
Conditions: -100° (< -80°)
THF ou Et_2O

I > Br >> Cl

C_{sp}-Hal = C_{sp2}-Hal > C_{sp3}-Hal

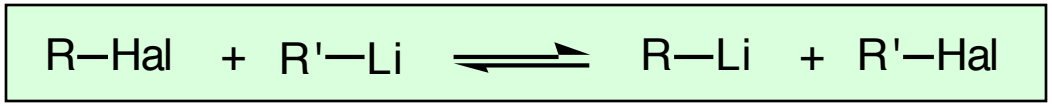
chimio- stéréo sélectivité

Winkler, H. J. S.; Winkler, H.
JACS **1965**, *88*, 964 & 969



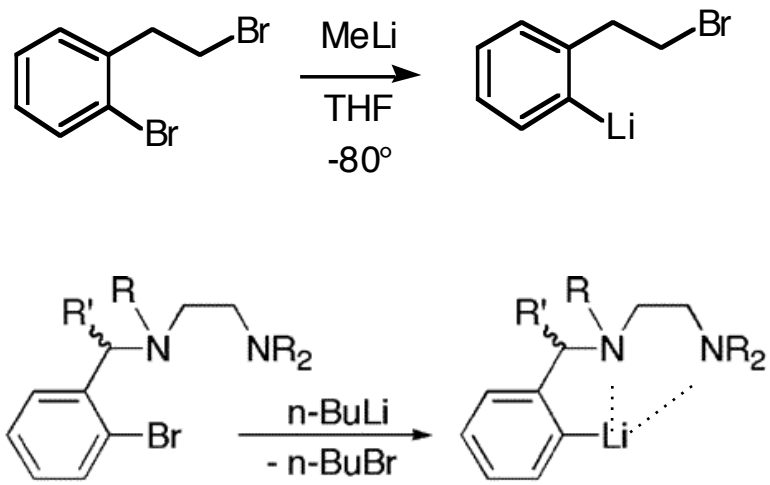
0.6 0.6 0.3 0.3 → Equilibre

0.3 0.6 0.6

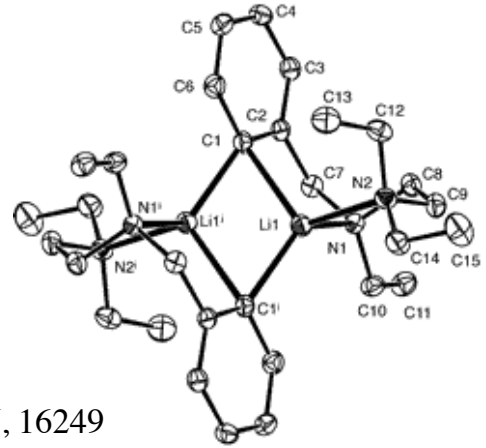


Equilibre: régit par

- stabilité de l'organolithien

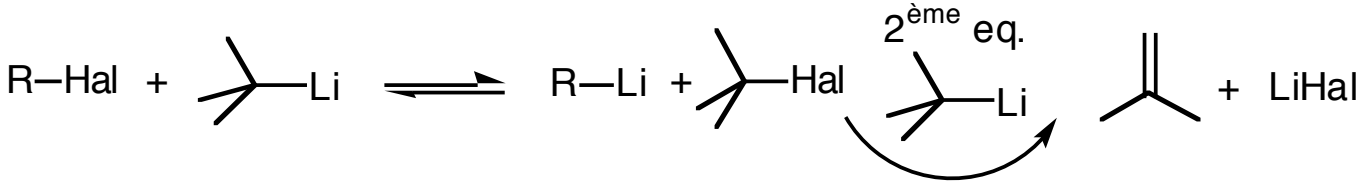


sélectif



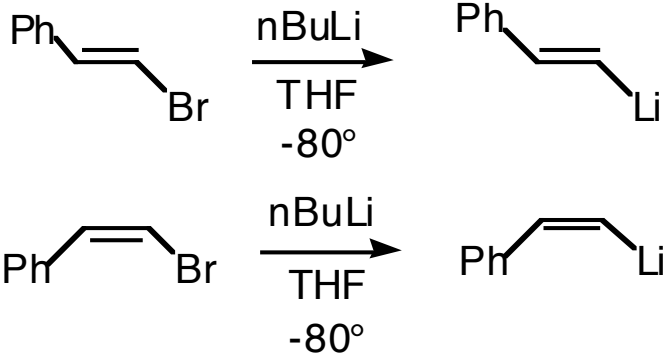
G. Van Koten et al. *J. Am. Chem. Soc.* **2004**, *126*, 16249

- astuce: déplacement de l'équilibre par élimination

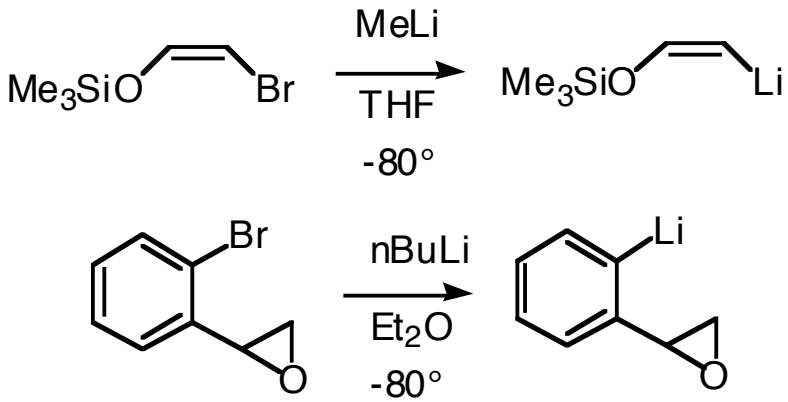


Intérêt: **Chimiosélectif, stéréospécifique** cf exemples

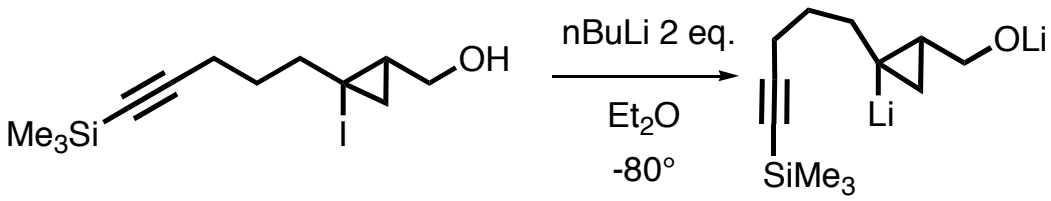
Exemples :



stéréospécifique

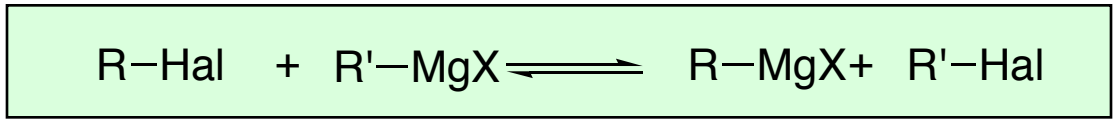


chimiosélectif



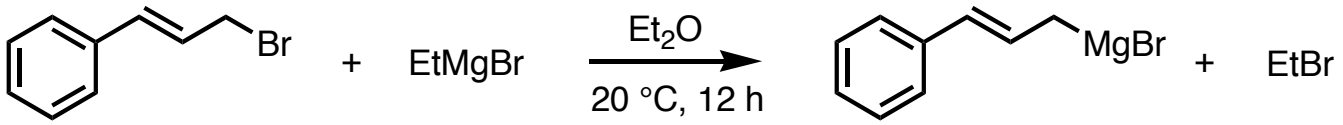
Piers *Synthesis* **96**, 502

Magnésiens Grignard

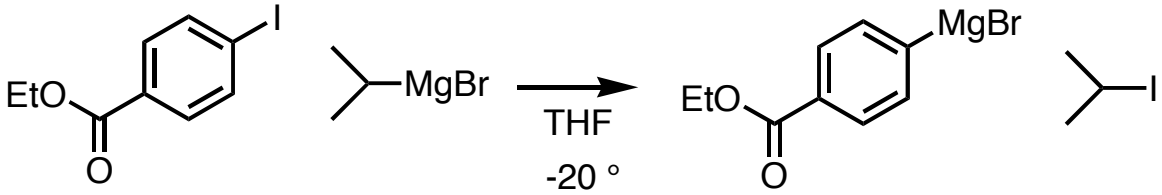


C. Prévost

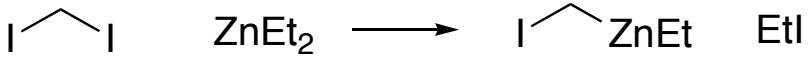
Bull. Soc. Chim. Fr. **1931**, *49*, 1372



P. Knochel

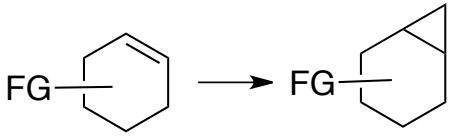


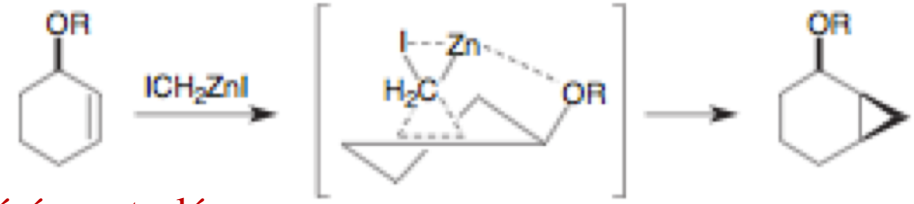
zinciques



Furukawa

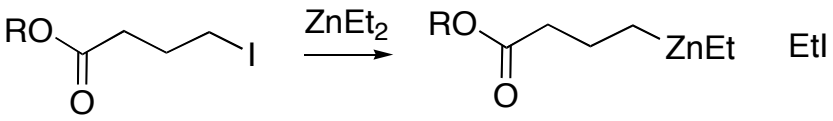
cf Simmons-Smith

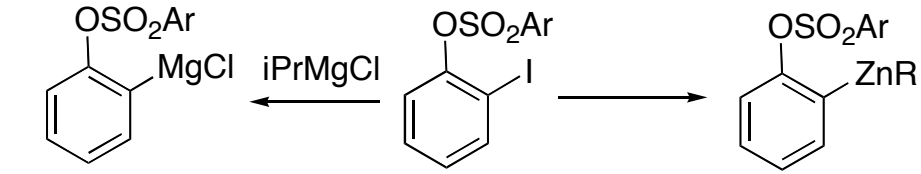




stéréocontrolé

I. Marek, P. Knochel





instable > - 20°
réagit à - 78°

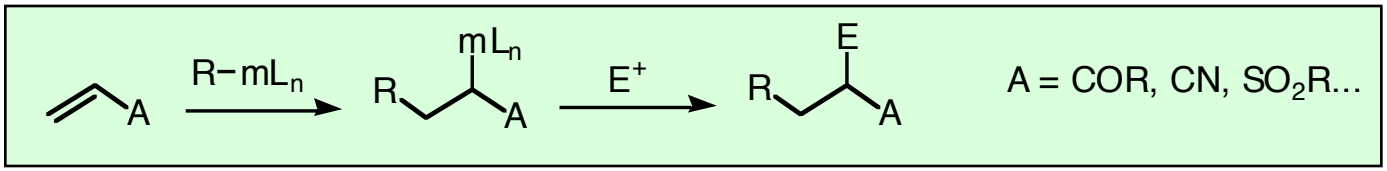
stable rt

2-2-4 Addition sur une insaturation

2.2.4.1- addition sur une énone ou équiv.

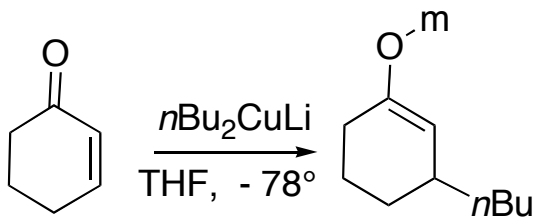
Principe :

= Add Michael



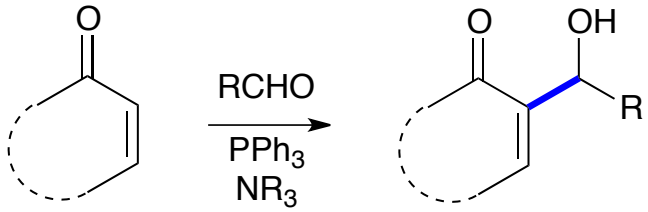
Exemples :

AN-1,4

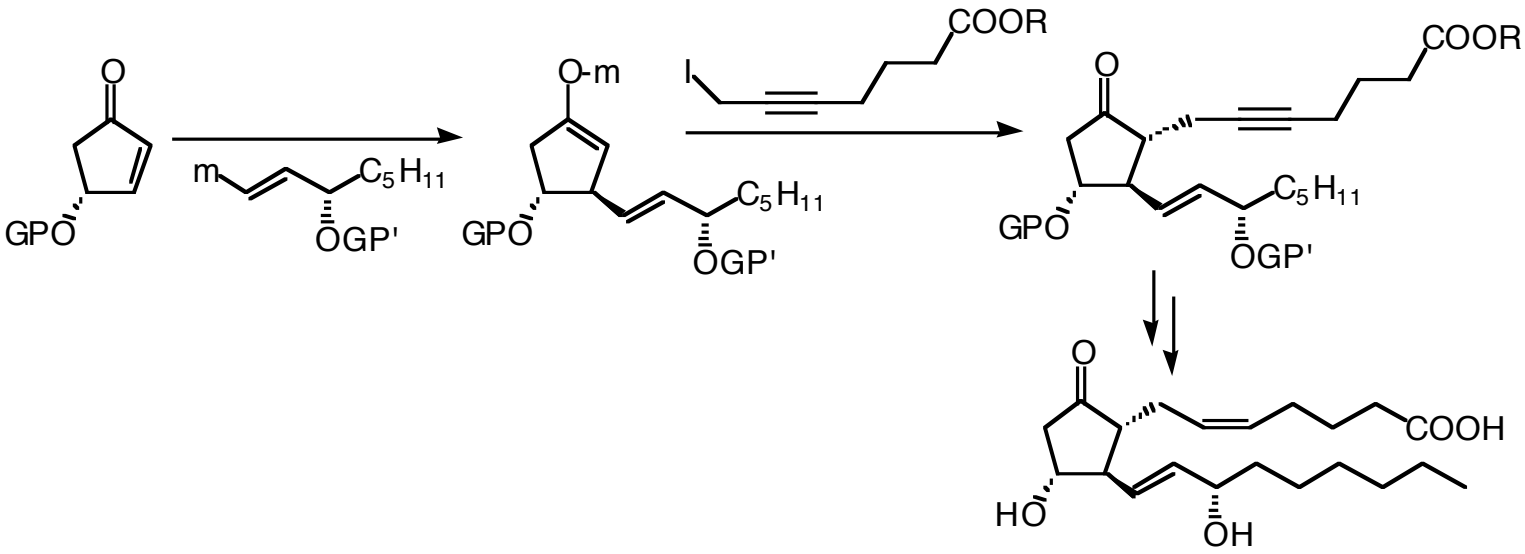


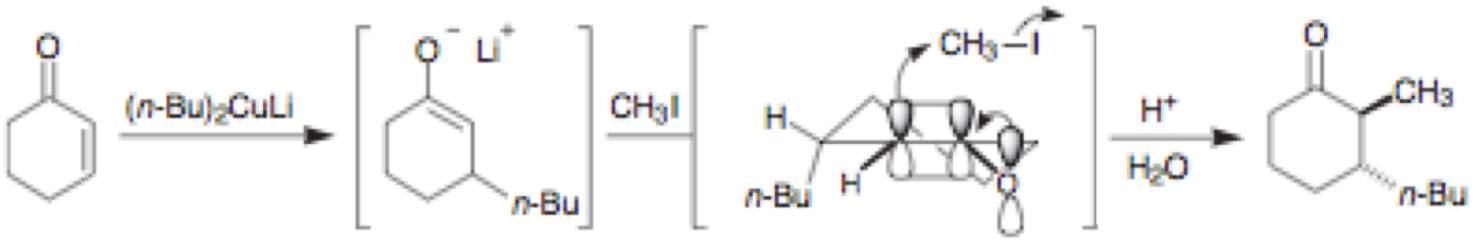
régio- & stéréo sélectif

Réaction Baylis-Hillman

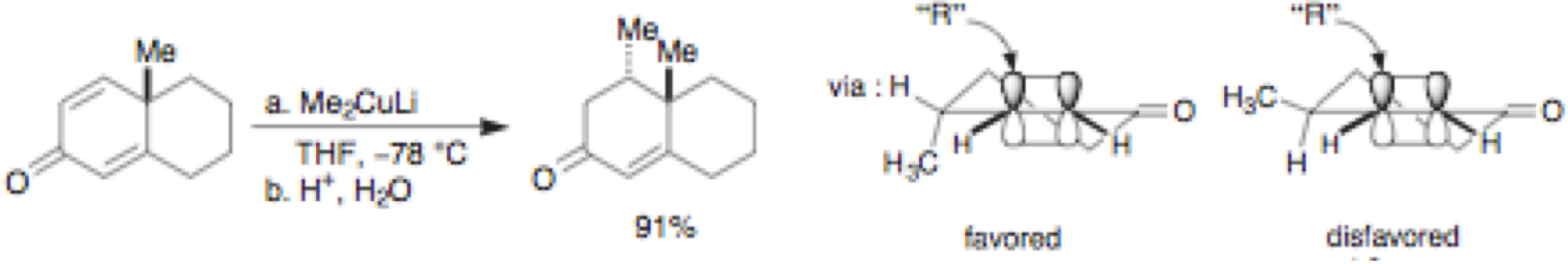


R. Noyori
Nobel 2001

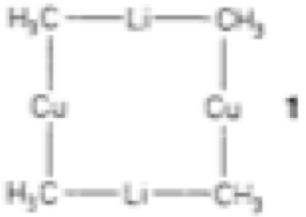




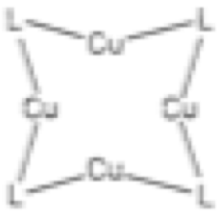
E.J. Corey
Nobel 2009



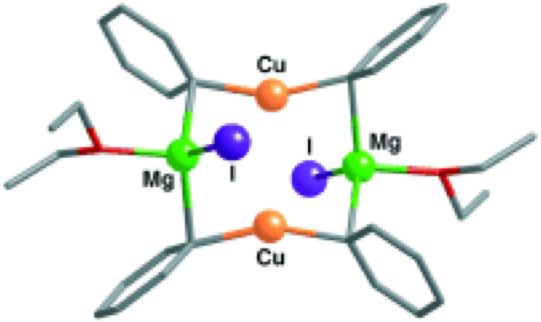
Mécanisme :

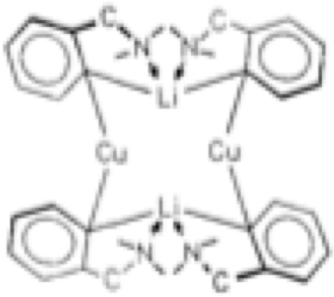


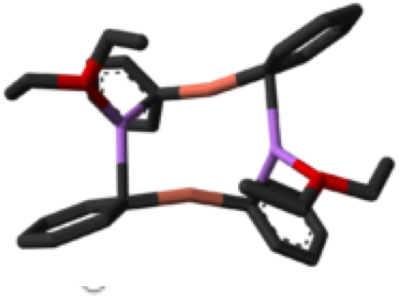
1

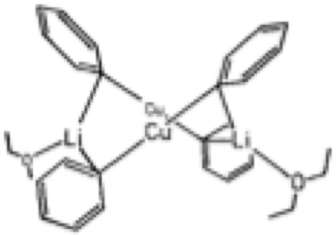


$CuCH_2SiMe_3$ 1972 Lappert



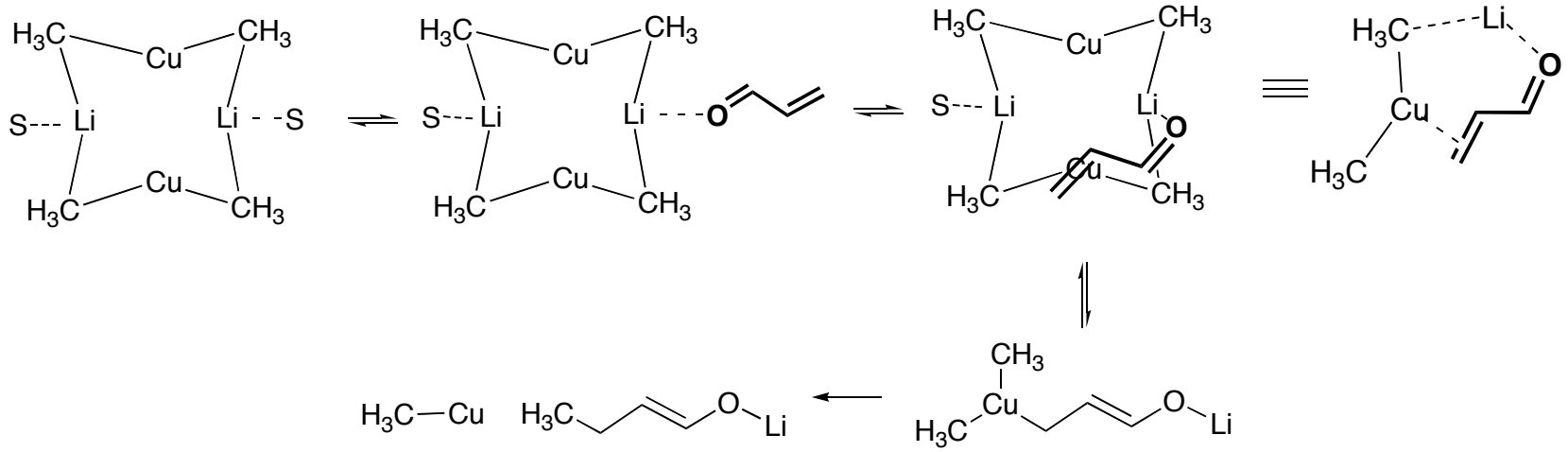






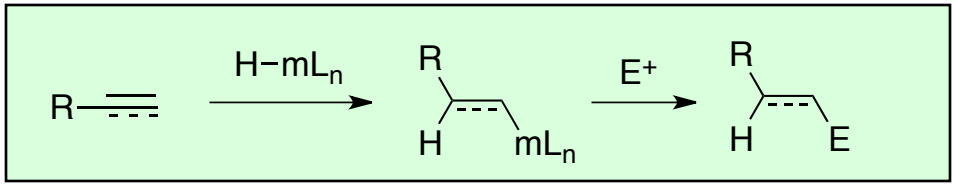
E. Weiss et al. *Angew. Chem. Int. Ed.* **1990**, *29*, 300

E. I Nakamura et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 3750

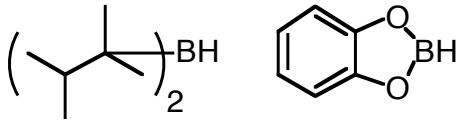


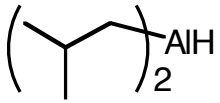
2.2.4.2- addition sur un alcène ou alcyne: **hydrométallation**

Principe :



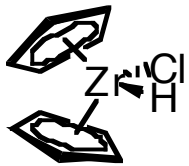
Chimiosélectif **Très régiosélectif** (coté plus dégagé) **Très stéréosélectif** (*syn* addition)

hydroboration 

hydroalumination 

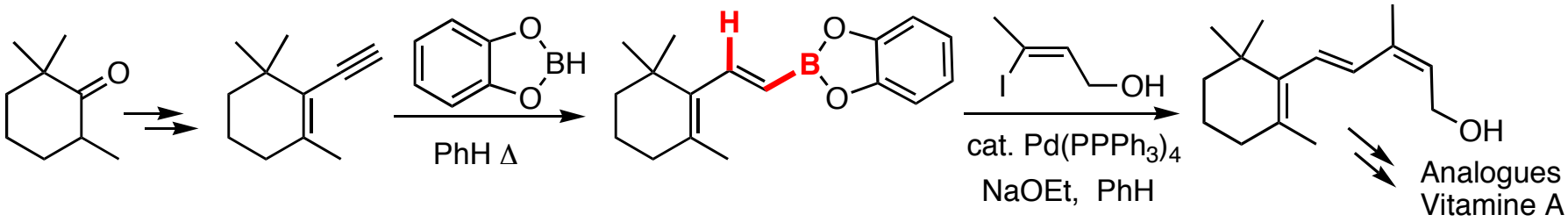
hydrostannation nBu_3SnH (+ cat Pd°)

hydrosilylation Me_3SiH (+ cat Pt^{II})

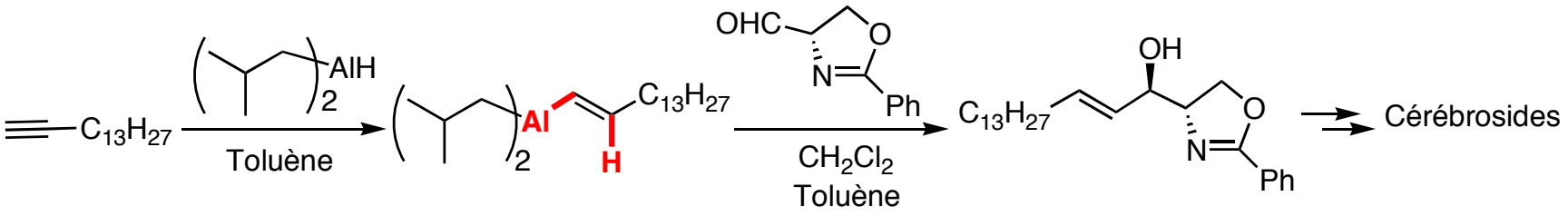
hydrozirconation 

Exemples :

hydroboration



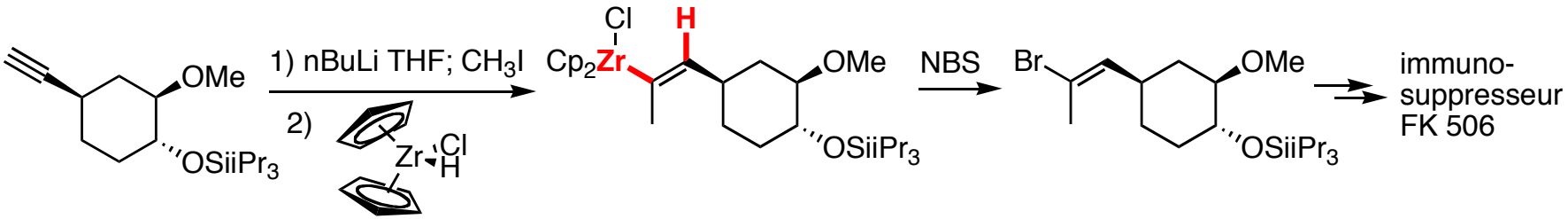
hydroalumination

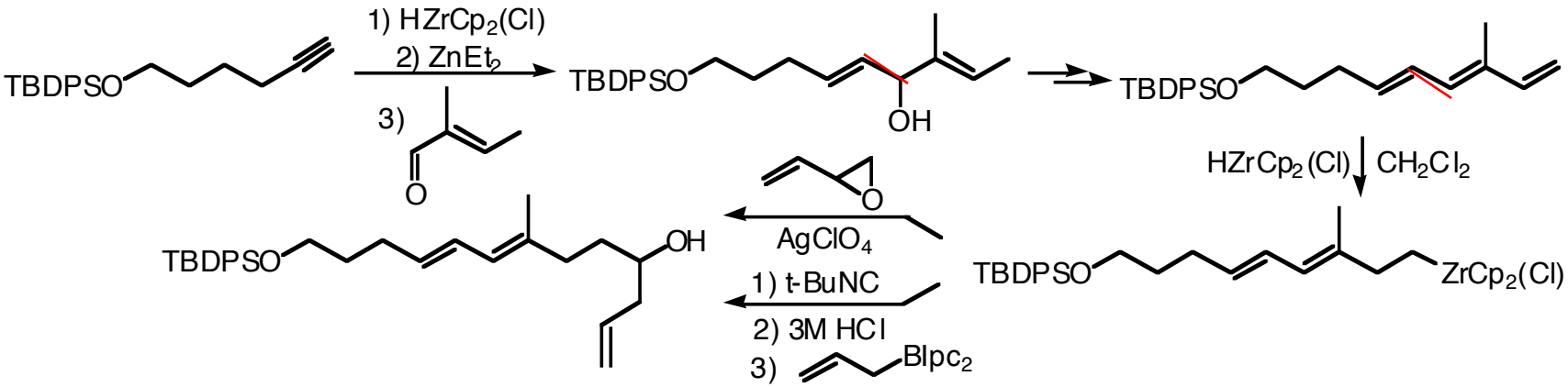


Tet. Lett **90**, 4309

Exemples :

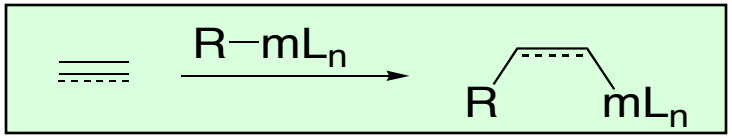
hydrozirconation





2.2.4.3- addition sur un alcène ou alcyne: **carbométallation**

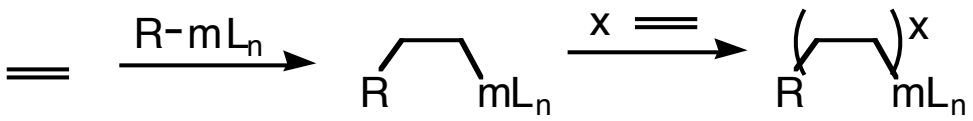
Principe :



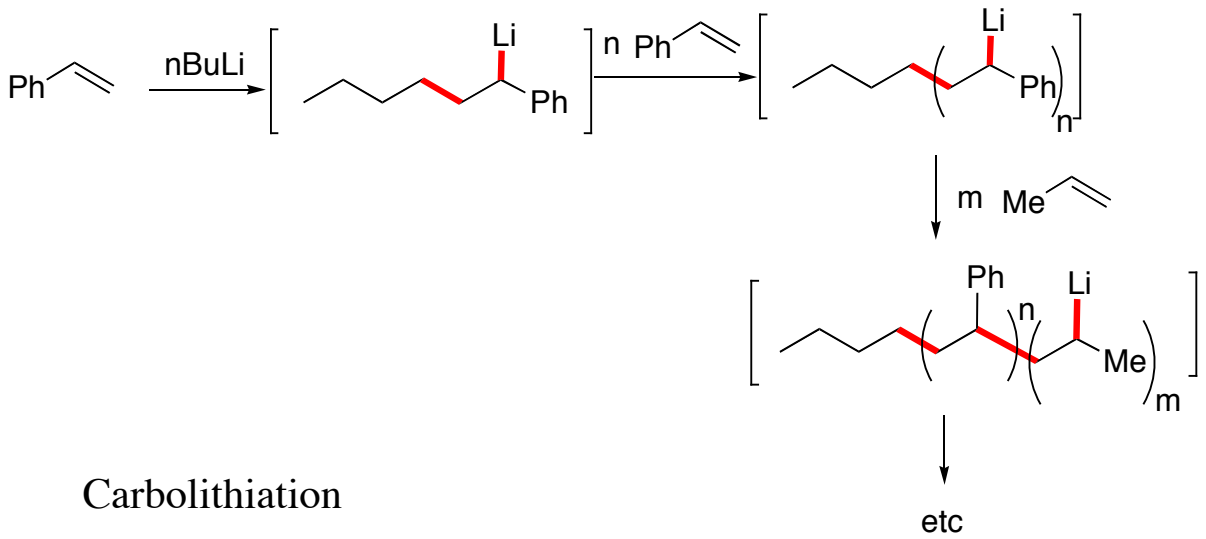
Chimiosélectif
Très régiosélectif (coté + dégagé)
Très stéréosélectif (syn addition)

Exemples : Polymèrisation anionique

K. Ziegler, K. Bähr
Ber. Dtsch. Chem. Ges. **1928**, *61*, 253



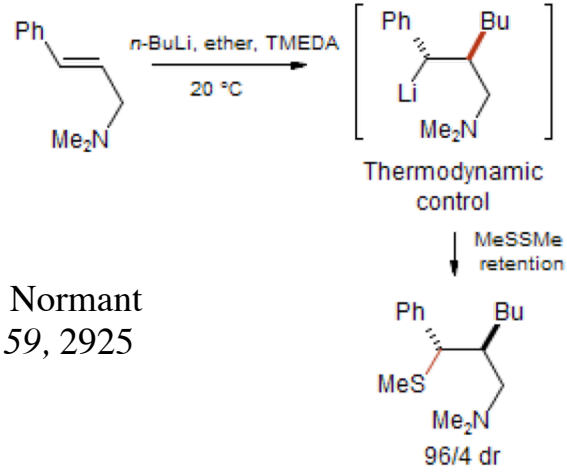
Polymère « vivant »



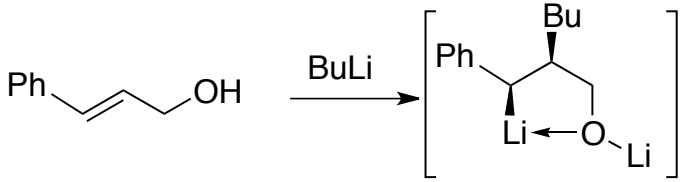
Carbolithiation

Carbolithiation :

intermoléculaire



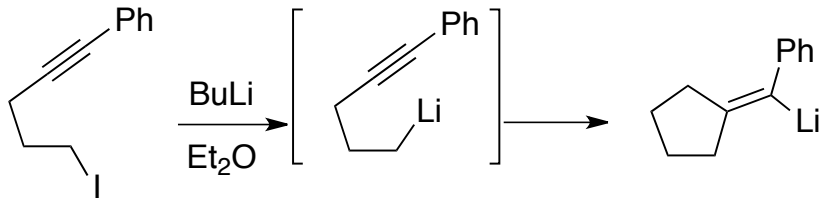
Klein, I. Marek, J. F. Normant
J. Org. Chem. **1994,** *59,* 2925

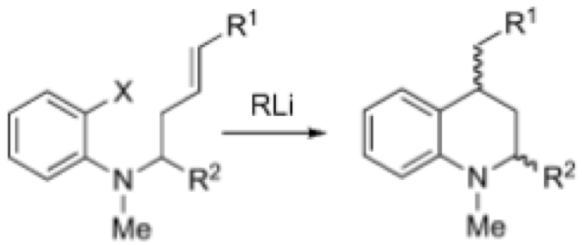


Beilstein J. Org. Chem. **2013,** *9,* 313

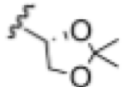
Régio- & stéréosélectif
(syn addition)

intramoléculaire



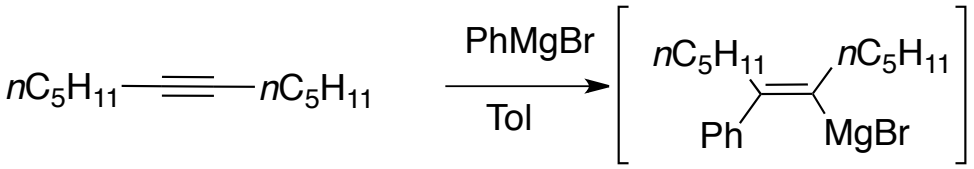


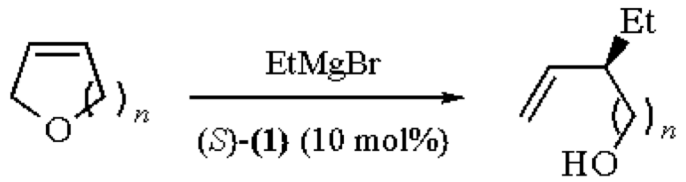
R^1 = H, $CONEt_2$, CONMeOMe
R^2 = H, CO_2Et, CH_2OBn



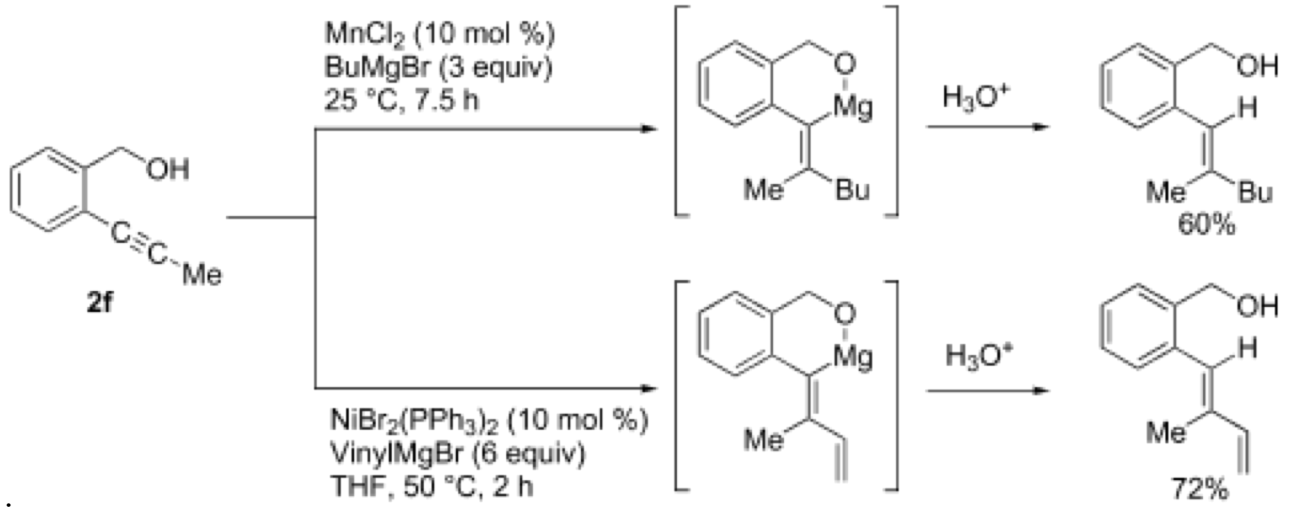
Okujima et al.
Heterocycles **2014,** 88, 417

Carbomagnesiation





Hoveyda, A. H.; Morken, J. P.
JOC **1993**, *58*, 4237

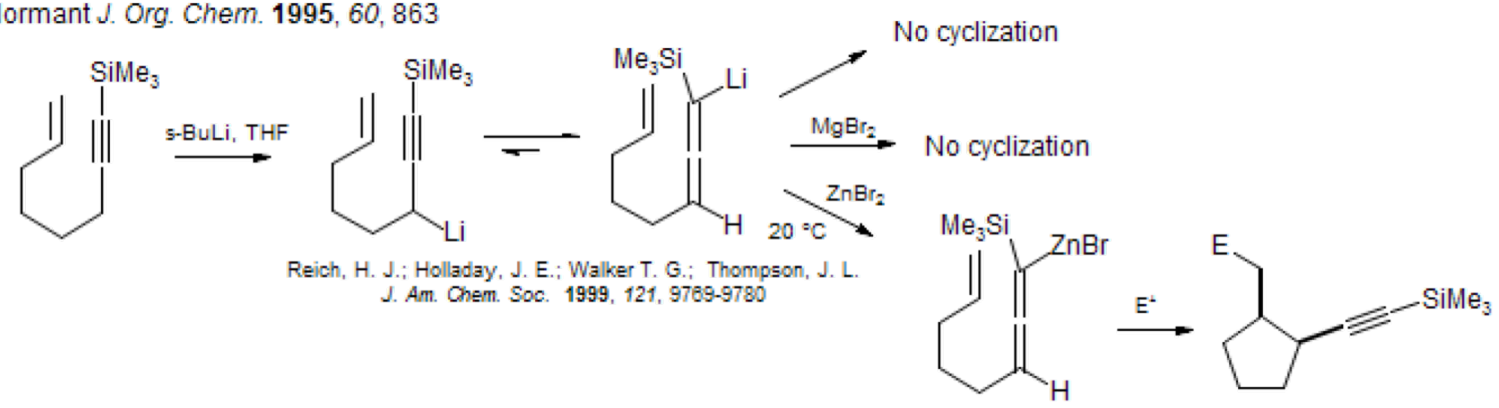


Régiosel. chelation

Murakami, Yorimitsu
Beilstein J. Org. Chem. **2013,** *9*, 278

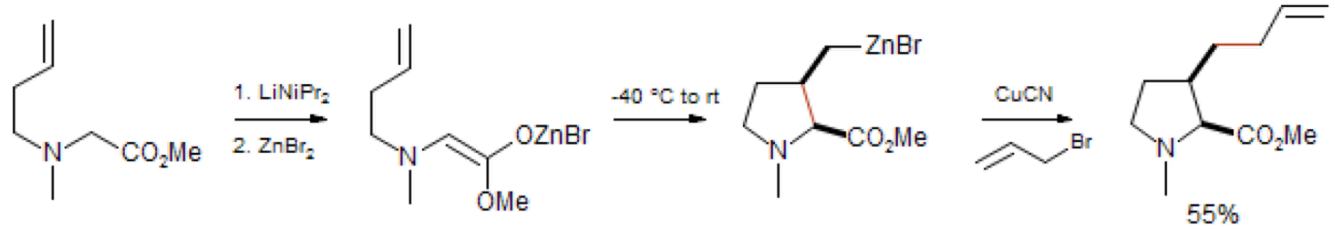
Carbozincation

Normant *J. Org. Chem.* **1995**, *60*, 863



Reich, H. J.; Holladay, J. E.; Walker T. G.; Thompson, J. L.
J. Am. Chem. Soc. **1999**, *121*, 9769-9780

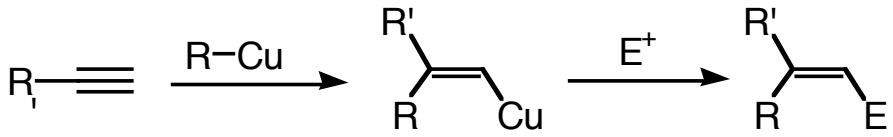
Régiosel.
Stéréosel.



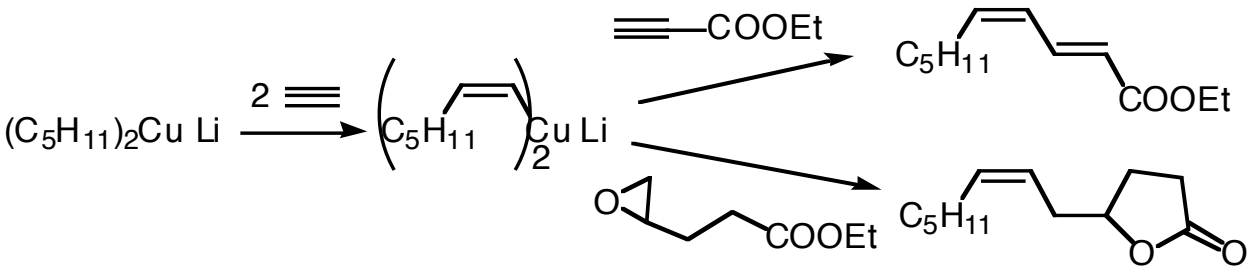
Lorthiois, I. Marek, J. F. Normant
J. Org. Chem. **1998,** *63*, 2442

Carbocupration

Réact. **Normant-Alexakis** J. F. Normant, A. Alexakis, *Synthesis* **1981**, 841



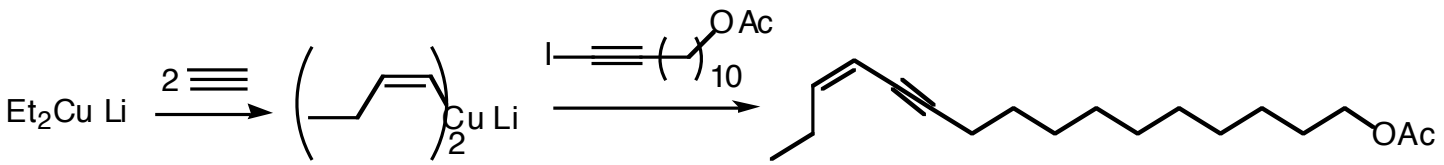
Régio- & stéréosélectif
(syn addition)



Arome Poire Williams
4 t/an
NB si 0,5 % (E,E)
odeur différente

Arome Peche

A. Alexakis

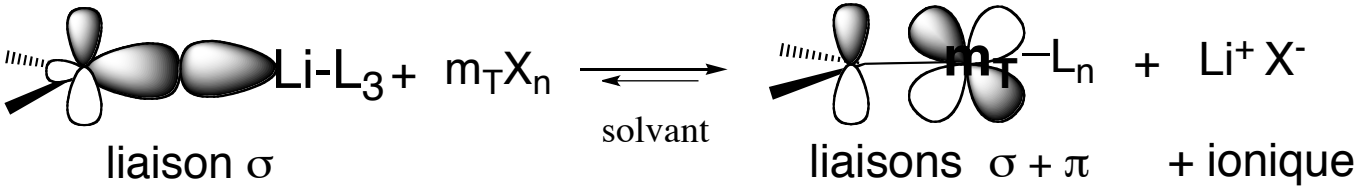


Carbo M etc …

2.3 Transmétallation

Principe : $R\text{-}m_1L_n + m_2X_m \rightleftharpoons R\text{-}m_2L_{n'} + m_1X_{m'}$

Equilibre: régit par -stabilité de l'organométallique et du sel formés



Intérêt: - polarisation de la liaison C-m,

- ± basique
- agrégats différents (coordinance du métal)
- orbitales d

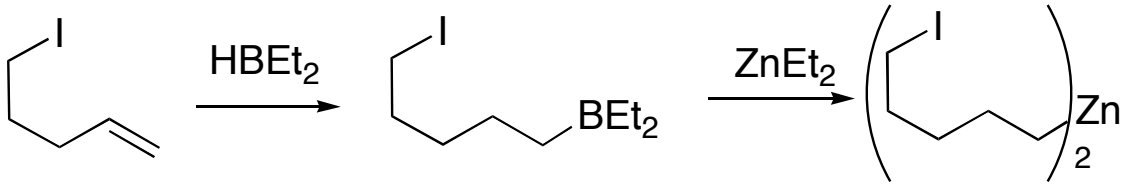
modulation de la réactivité

Echanges métal-métal

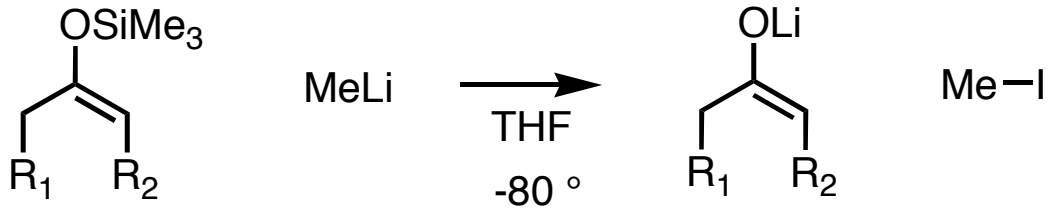
Intérêt: **chimiosélectif, stéréospécifique**

Processus analogue aux échanges Hal-m

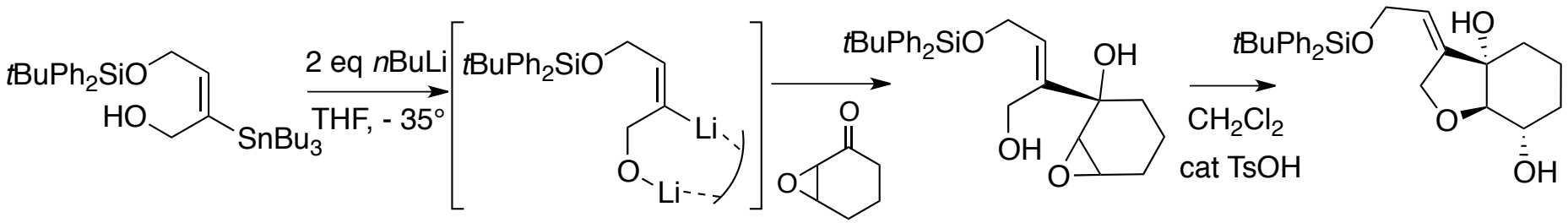
Echange bore-zinc



Échange silyl-lithium



Echange étain-lithium

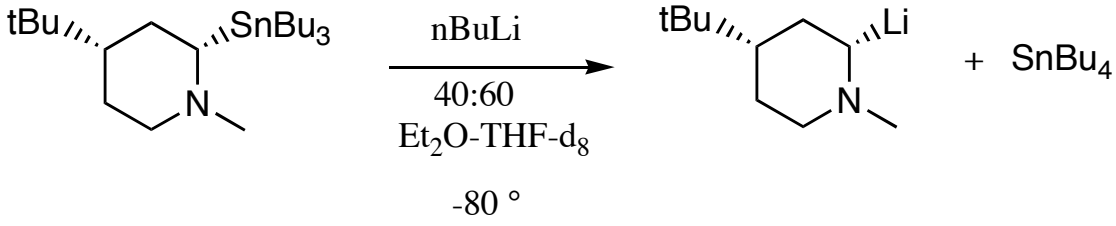


A. Barrett et al.
J. Org. Chem. **1989**, *54*, 4247

stéréospécifique

J. Clayden

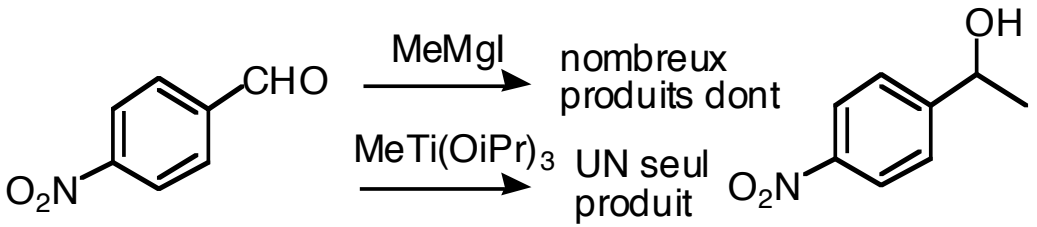
énantiospécifique



Chambournier, G.; Gawley, R. E.
Org. Lett. **2000**, *2*, 1561

Intérêts :

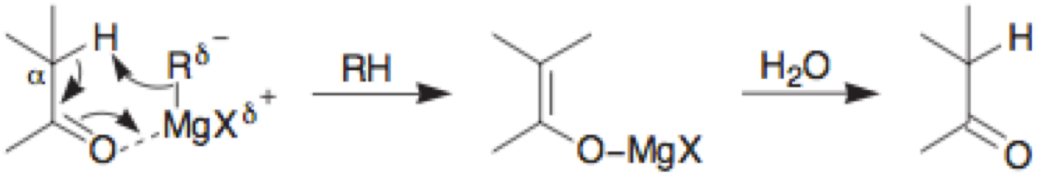
- pour améliorer la réactivité:



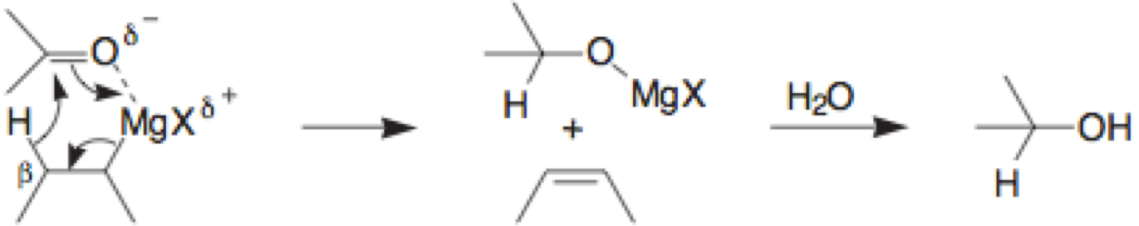
NB: Pb réactivité des lithiens, magnésiens:

- nucléophiles

- bases



- réducteurs



- radicaux

- pour améliorer la stéréosélectivité:

Organozinc Reagents are Configurationally Stable

Klein, Marek, Normant *J. Org. Chem.* **1994**, *59*, 2925