Organic Chemistry IV

Organometallic Chemistry for Organic Synthesis

Prof. Paul Knochel

LMU

2015

OCIV

Prüfung:

Freitag 17. Juli 2015

9-11 Uhr

Wieland HS

Wiederholungsklausur:

Donnerstag 17. September 2015

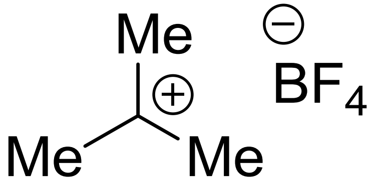
12-14 Uhr

Baeyer HS

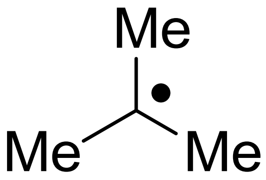
Recommended Literature

1. **F. A. Carey, R. J. Sundberg, Advanced Organic Chemistry**, Fifth Edition Part A and Part B, Springer, 2008, ISBN-13: 978-0-387-68346-1
2. **R. Brückner, Organic Mechanisms**, Springer, 2010, ISBN: 978-3-642-03650-7
3. **L. Kürti, B. Czako, Strategic applications of named reactions in organic synthesis**, Elsevier, 2005, ISBN-13: 978-0-12-429785-2
4. **N. Krause, Metallorganische Chemie**, Spektrum der Wissenschaft, 1996, ISBN: 3-86025-146-5
5. **R. H. Crabtree, The organometallic chemistry of transition metals**, Wiley-Interscience, 2005, ISBN: 0-471-66256-9
6. **M. Schlosser, Organometallics in Synthesis** – A manual, 2nd edition, Wiley, 2002, ISBN: 0-471-98416-7
7. **K. C. Nicolaou, T. Montagnon, Molecules that changed the world**, Wiley-VCH, 2008, ISBN: 978-527-30983-2
8. **J. Hartwig, Organotransition Metal Chemistry: From Bonding to Catalysis**, Palgrave Macmillan, 2009, ISBN-13: 978-1891389535
9. **P. Knochel, Handbook of Functionalized Organometallics**, Volume 1 und 2, Wiley-VCH, 2005, ISBN-13: 978-3-527-31131-6

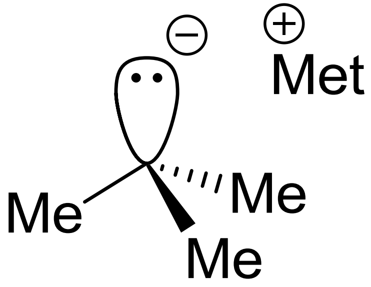
Importance of organometallics



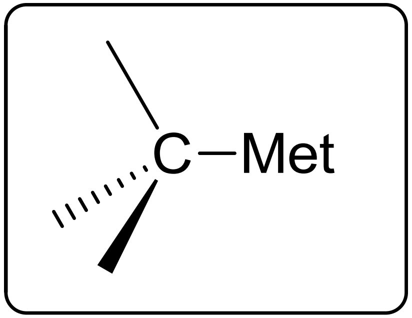
carbenium ion



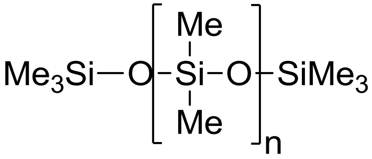
radical



organometallic
reagent



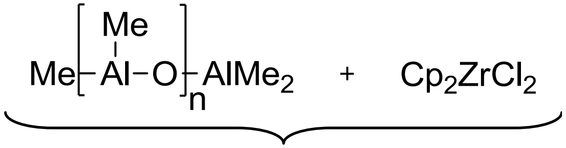
Industrial production



$Me_3Si-O-[Si(Me)_2-O]_n-SiMe_3$

Silicone

Et_4Pb

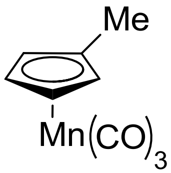


$Me-[Al(Me)-O]_n-AlMe_2 + Cp_2ZrCl_2$

Kaminsky catalyst
n=5-20   syndiotacticity of polypropylene

BuLi

$[Bu_3Sn]_2O$



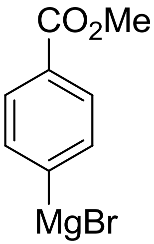
Industrial annual production of various organometallics

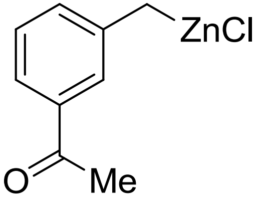
Organometallic	production [T / year]
Si	700 000
Pb	600 000
Al	50 000
Sn	35 000
Li	900

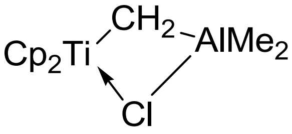
Organometallic reagents and catalysts for the organic synthesis

organometallic reagents:

BuLi







Tebbe reagent

H(Cl)ZrCp$_2$

Schwarz reagent

organometallic catalysts:

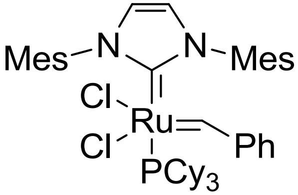
Pd(PPh$_3$)$_4$

CpCo(CO)$_2$

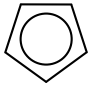
[RhCl(CO)$_2$]$_2$

ClRh(PPh$_3$)$_3$

Wilkinson's catalyst



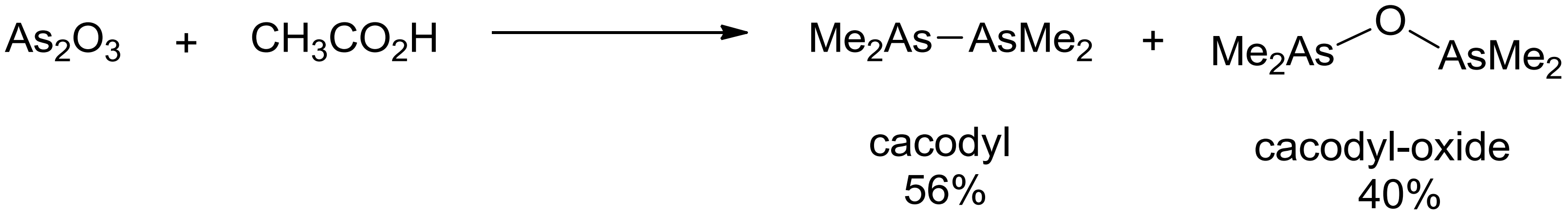
Grubbs II catalyst



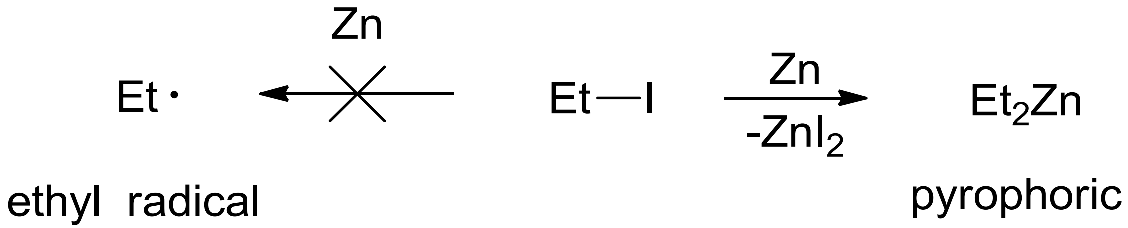
≡ Cp

Historic point of view

1757 - Louis Cadet de Gassicourt (parisian apothecary)



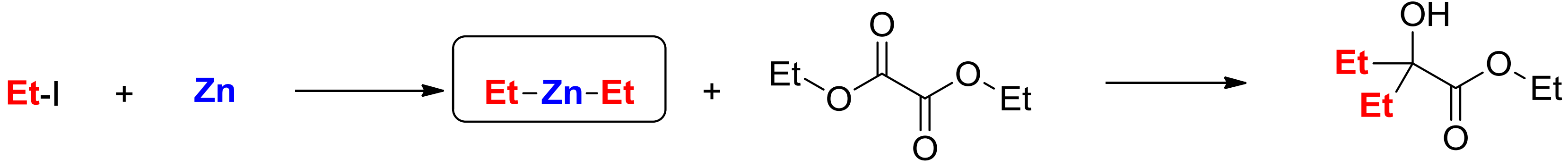
E. Frankland (1848), University of Marburg, initial goal: synthesis of an ethyl radical



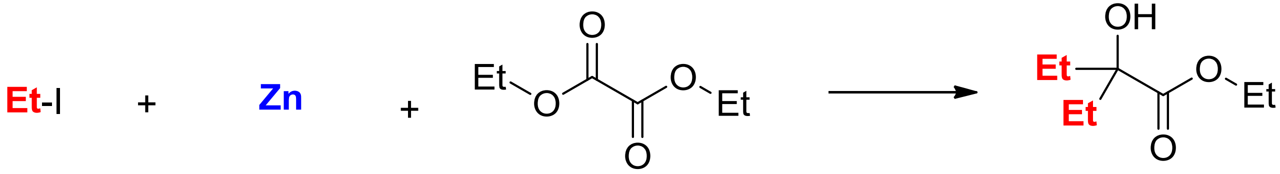
Universität Marburg (1848)

Organometallic chemistry of the XIX century

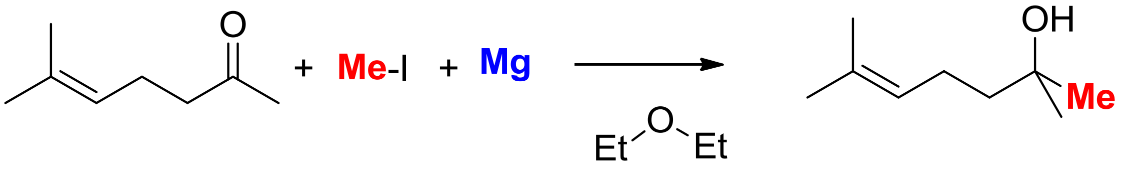
Frankland **1848**, **1863**



Beilstein **1862,** Saytzeff **1870,** Wagner **1875**



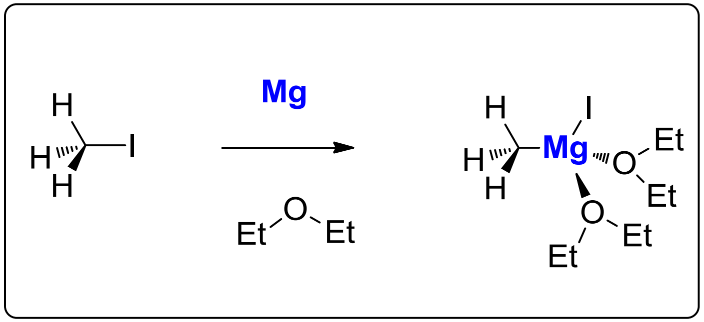
Barbier **1899**

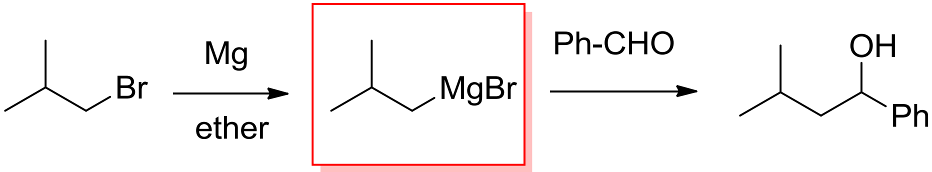


Ph. Barbier *Comptes Rendus de l'Académie des Sciences*, **1899**, *128*, 110

Organometallic chemistry of the XIX century

Pl. X. *Victor Grignard dans son laboratoire de Nancy*
1912



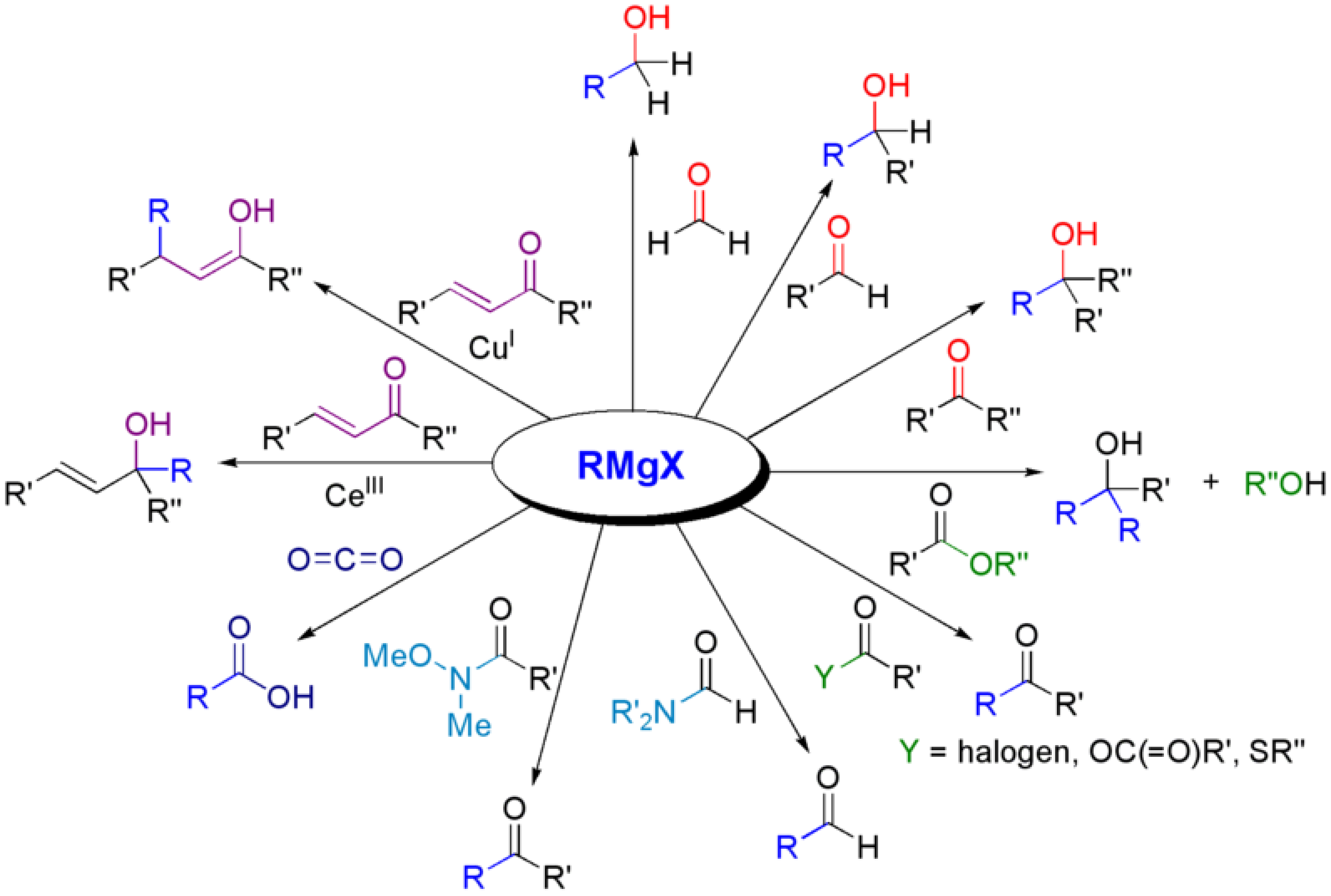


reactif de Grignard

V. Grignard

Comptes Rendus de l'Académie des Sciences, **1900**, *130*, 1322

Reactivity of the Grignard reagents



Y = halogen, OC(=O)R', SR''

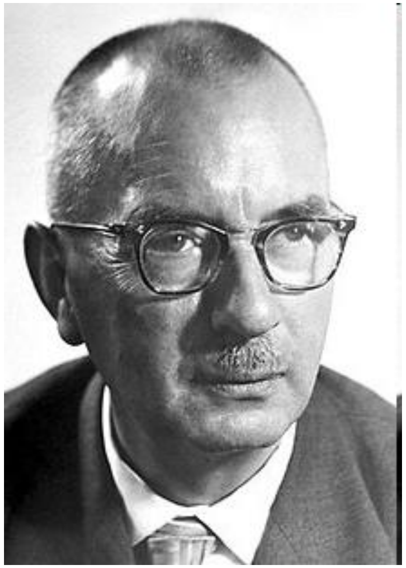
Historic point of view

Victor Grignard (1900)

$$\mathrm{Et{-}Br} \xrightarrow[\text{ether, 40 °C}]{\text{Mg}} \mathrm{Et{-}MgBr}$$

Karl Ziegler (1919)

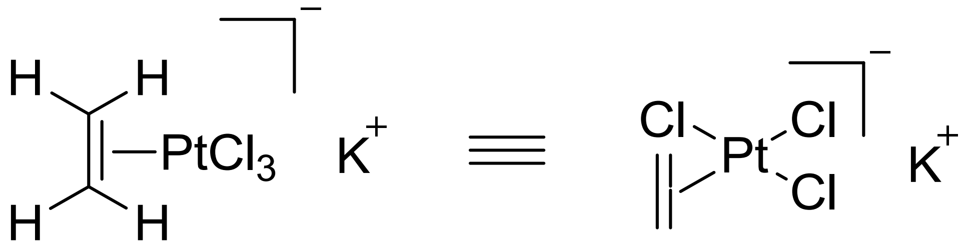
$$\mathrm{BuCl} + 2\mathrm{Li} \xrightarrow[\text{under Argon}]{\text{pentane}} \mathrm{BuLi} + \mathrm{LiCl}$$



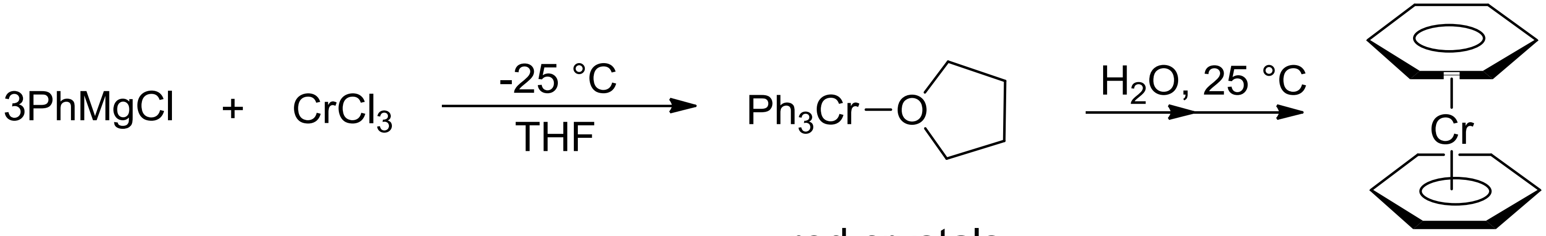
Historic point of view

first transition metal organometallics:

Zeise's Salz (1827)



Hein (1919)



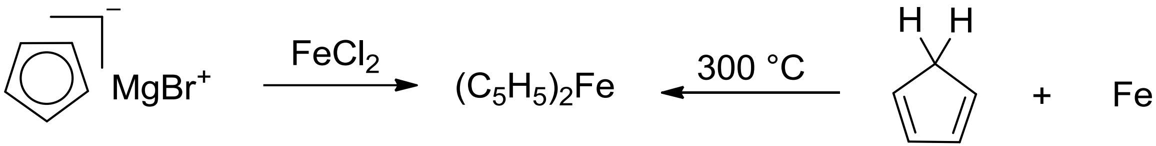
red crystals

10%

Historic point of view

1951 : synthesis of ferrocene

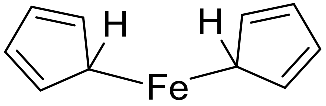
Pauson (Scotland)	7. August 1951
Miller	11. June 1951



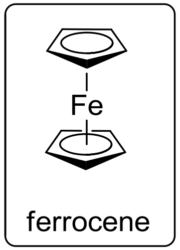
Smp.: 172 °C

G. Wilkinson

1952
structural proposal by Pauson



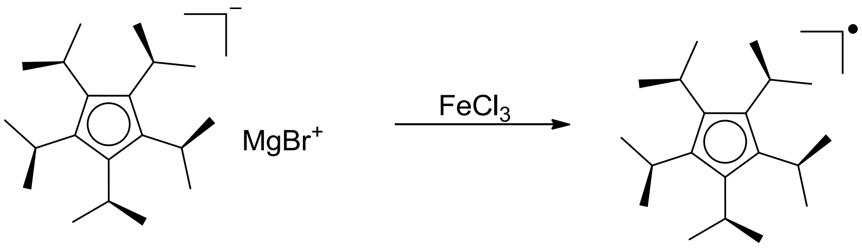
correct structure by G. Wilkinson and R. B. Woodward



ferrocene

G. Wilkinson, R. B. Woodward *J. Am. Chem. Soc*. **1952**, *74*, 2125
R.B. Woodward *J. Am. Chem. Soc*. **1952**, *74*, 3458

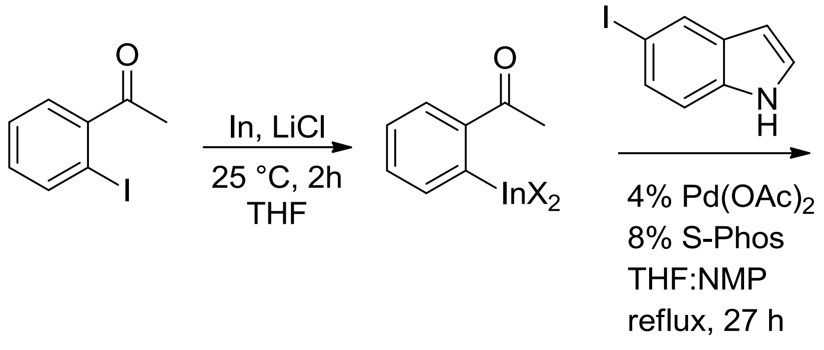
R. B. Woodward

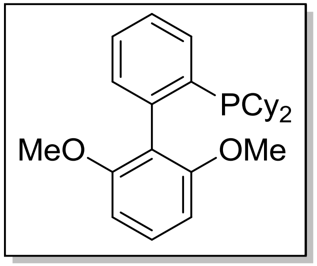


H. Sitzmann *J. Am. Chem. Soc*. **1993**, *115*, 12003 radical formation

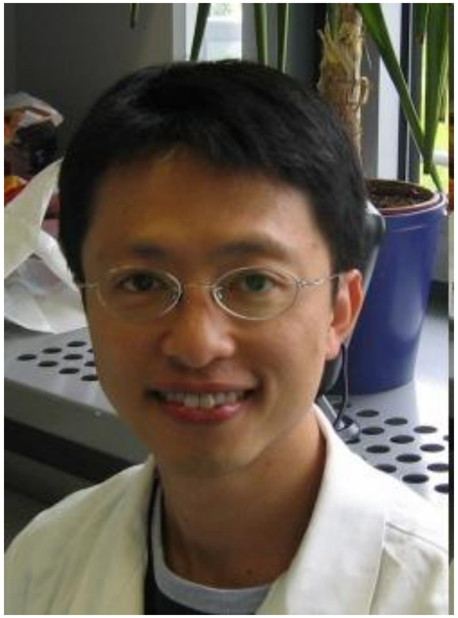
Goal of the lecture

main goal of this course: applications of organometallic compounds in modern organic synthesis





S-Phos

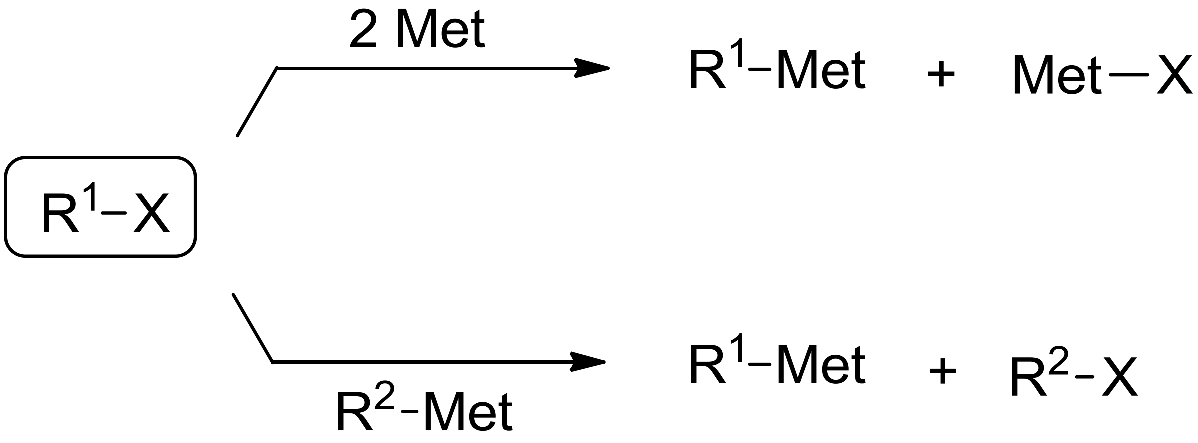


Y.-H. Chen, *Angew. Chem. Int. Ed*. **2008**, *47*, 7648.

General synthetic methods for preparing organometallic reagents

classification according to starting materials

direct synthesis *via* an oxidative addition and halogen-metal exchange

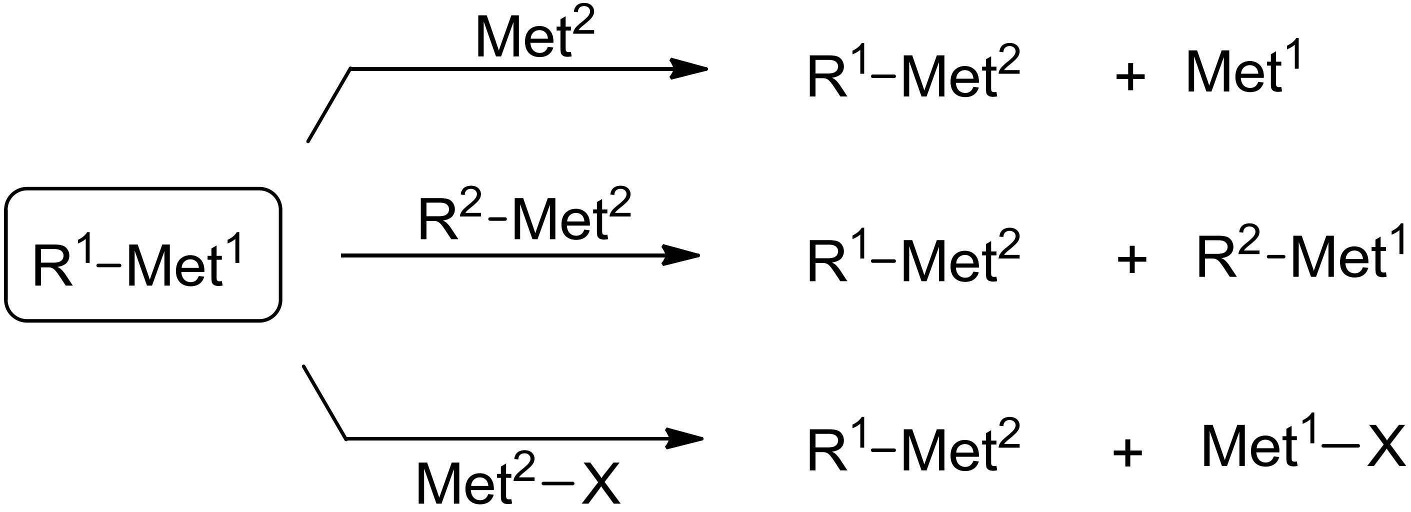


$$\boxed{R^1{-}X} \xrightarrow{2\ \text{Met}} R^1{-}\text{Met} + \text{Met}{-}X$$

$$\boxed{R^1{-}X} \xrightarrow[R^2\text{-Met}]{} R^1{-}\text{Met} + R^2{-}X$$

Classification according to starting materials

transmetalation



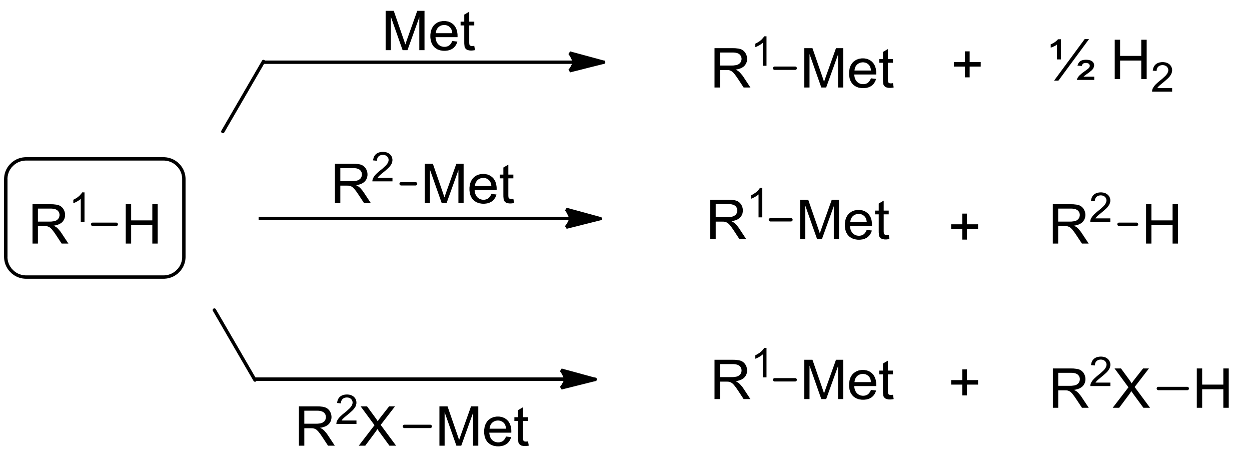
$$\boxed{R^1{-}Met^1} \xrightarrow{Met^2} R^1{-}Met^2 + Met^1$$

$$\boxed{R^1{-}Met^1} \xrightarrow{R^2\text{-}Met^2} R^1{-}Met^2 + R^2\text{-}Met^1$$

$$\boxed{R^1{-}Met^1} \xrightarrow[Met^2{-}X]{} R^1{-}Met^2 + Met^1{-}X$$

Classification according to starting materials

metalation



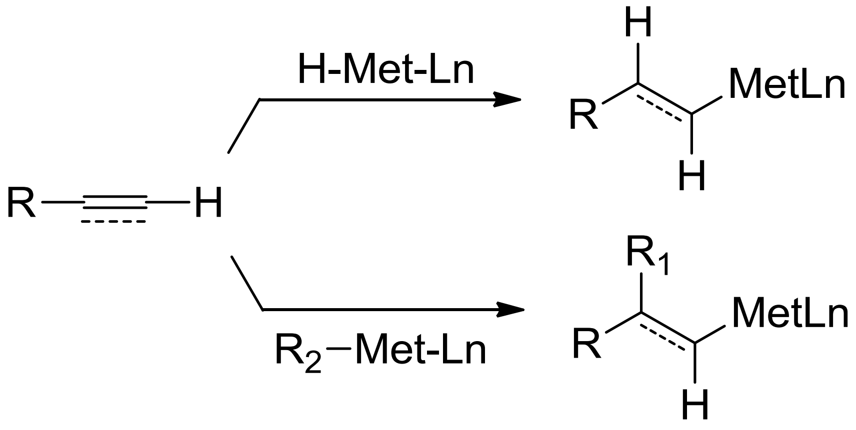
$$R^1{-}H \xrightarrow{Met} R^1{-}Met + \tfrac{1}{2}\,H_2$$

$$R^1{-}H \xrightarrow{R^2\text{-}Met} R^1{-}Met + R^2{-}H$$

$$R^1{-}H \xrightarrow[R^2X{-}Met]{} R^1{-}Met + R^2X{-}H$$

Classification according to starting materials

carbometalation and hydrometalation



Hydrometalation

Carbometalation

Synthesis starting from organic halides

direct synthesis - oxidative addition

$$\text{R}-\text{X} \quad + \quad 2\text{Met} \longrightarrow \boxed{\text{R}-\text{Met}} \quad + \quad \text{Met}-\text{X}$$

driving force of the reaction:

$$\Delta H = \Delta H\left[\text{Met}-\text{X}\right] + \Delta H\left[\text{C}-\text{Met}\right] - \Delta H\left[\text{C}-\text{X}\right] - \text{lattice energy}$$

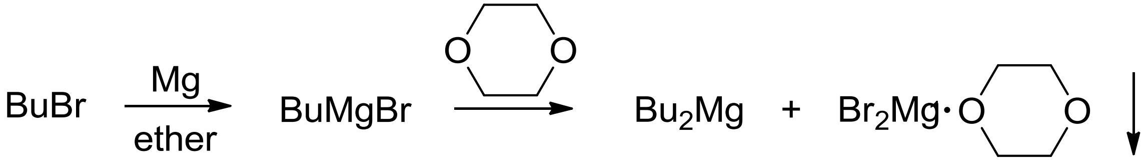
$4\,\text{EtCl} + 3\,\text{Pb} \longrightarrow \text{Et}_4\text{Pb} + 2\,\text{PbCl}_2$ endothermic

$4\,\text{NaPb} + 4\,\text{EtCl} \longrightarrow \text{Et}_4\text{Pb} + 3\,\text{Pb} + 3\,\text{NaCl}$ exothermic

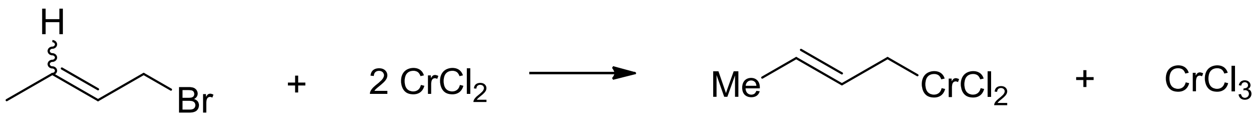
Direct Synthesis - Oxidative Addition

examples:

$$\mathrm{BuCl} \xrightarrow{2\ \mathrm{Li}} \mathrm{BuLi} + \mathrm{LiCl}$$



$$\mathrm{PbI_2} + \mathrm{MeI} \longrightarrow \mathrm{MePbI_3}$$



E/Z-mixture

pure E-isomer

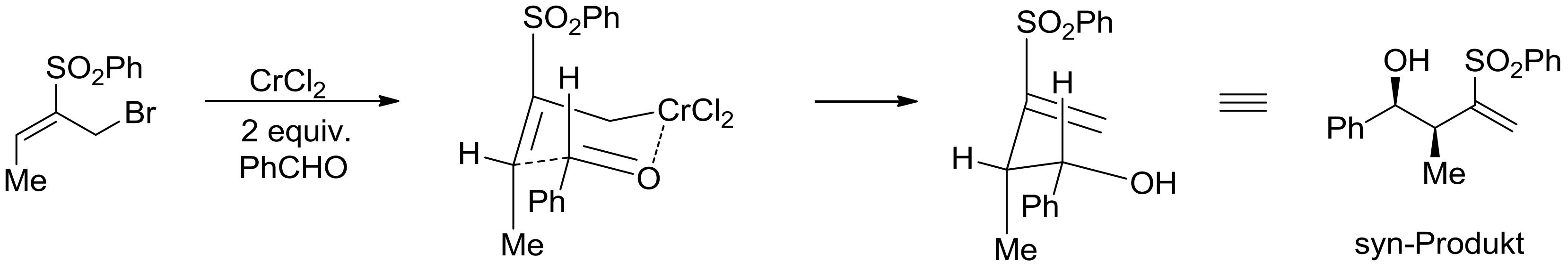
Direct Synthesis - Oxidative Addition

mechanism:

$$\text{R-Br} + \dot{\text{C}}\text{rCl}_2 \longrightarrow \text{R}\cdot + \text{BrCrCl}_2$$

$$\text{R}\cdot + \dot{\text{C}}\text{rCl}_2 \longrightarrow \text{RCrCl}_2$$

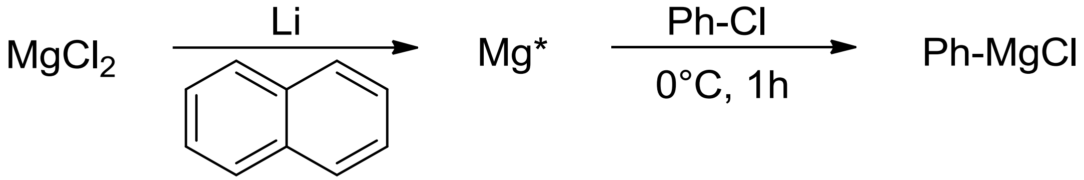
$$\text{R-Br} + 2\,\dot{\text{C}}\text{rCl}_2 \longrightarrow \text{RCrX}_2 + \text{CrX}_3$$

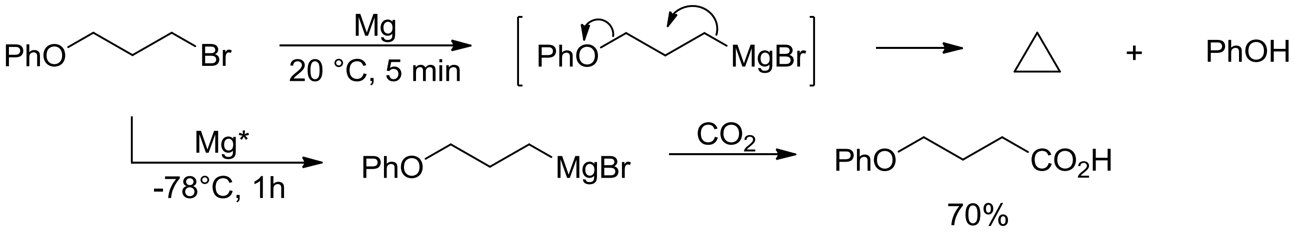


P. Knochel *Tetrahedron Lett*. **1986**, *27*, 5091

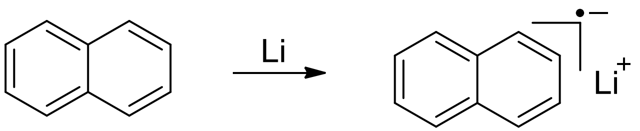
Activation of the metal: the *Rieke*-approach

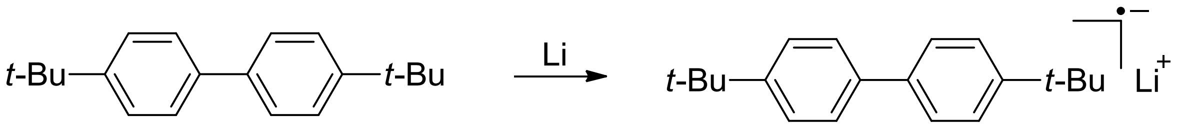
activation of the metal: R. D. Rieke, *Science* **1989**, *246*, 1260





Activation of lithium: formation of soluble Li-sources:

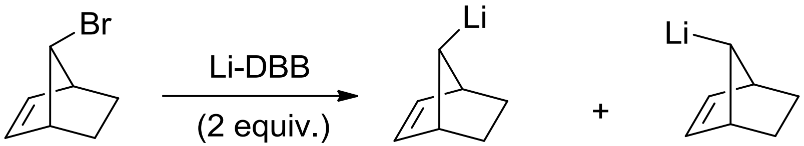




P.P. Freeman, L.L. Hutchinson *J. Org. Chem*. **1983**, *48*, 4705

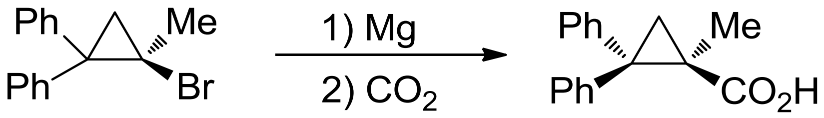
Mechanism of the metal insertion

$t\text{-BuBr} \xrightarrow{\text{Li-DBB (2 equiv.)}} t\text{-BuLi}$



80 : 20

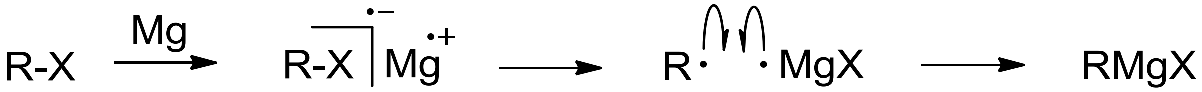
loss stereochemical information



90% ee

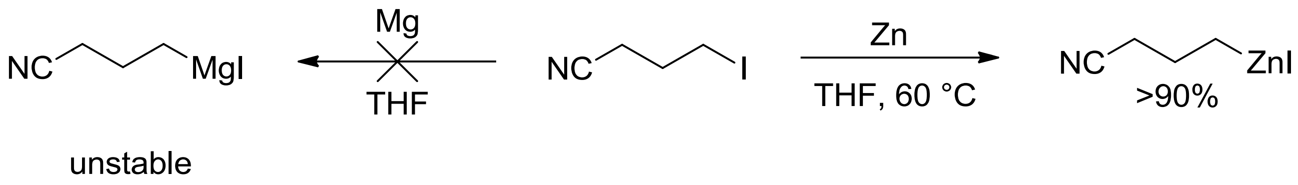
12% ee

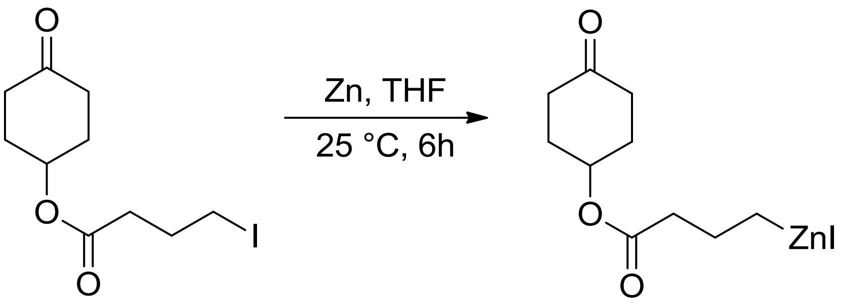
H.M. Walborsky: *J. Am. Chem. Soc*. **1989**, *11*, 1896



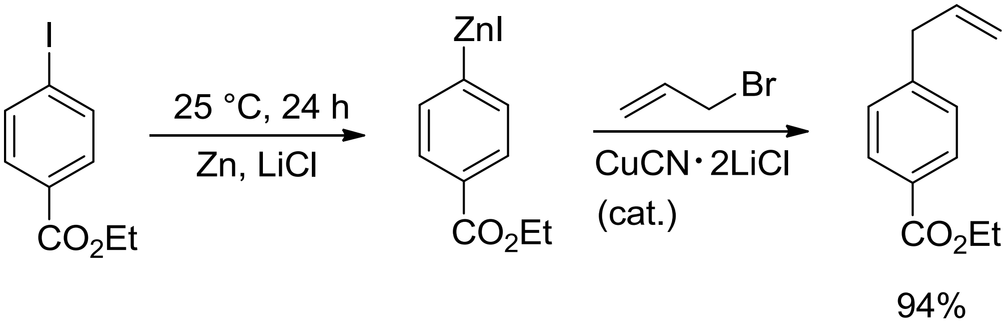
radical mechanism

Preparation of functionalized organometallics



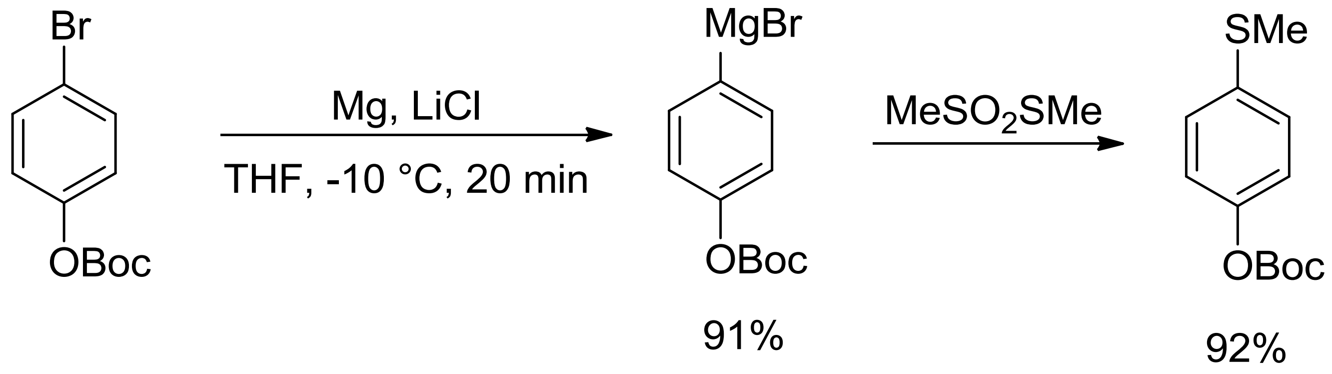


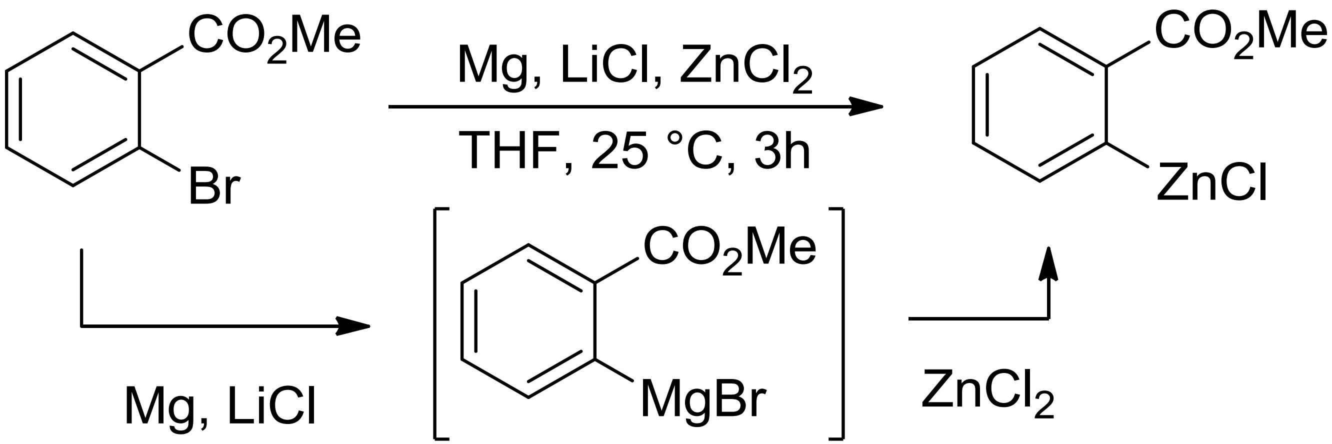
P. Knochel, *J. Org. Chem*. **1988**, *53*, 2390
P. Knochel, *Org. React*. **2001**, *58*, 417.



A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed*. **2006**, *45*, 6040.

Preparation of functionalized organometallics

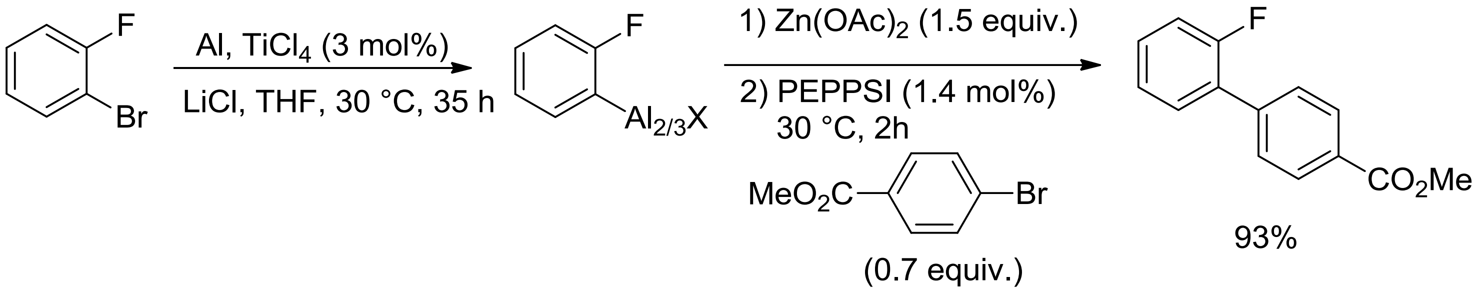




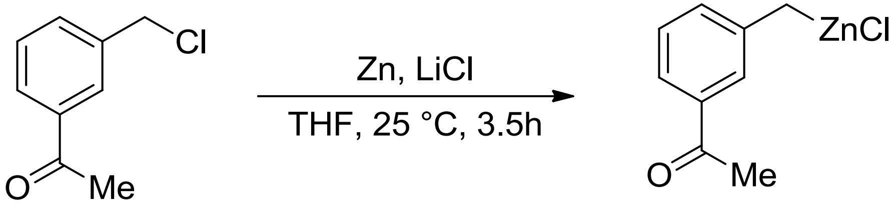
F. Piller, P. Knochel *Chem. Eur. J*. **2009**, *15*, 7192

Preparation of functionalized organometallics

activation of Al using LiCl and $TiCl_4$, $BiCl_3$, $PbCl_2$ or $InCl_3$



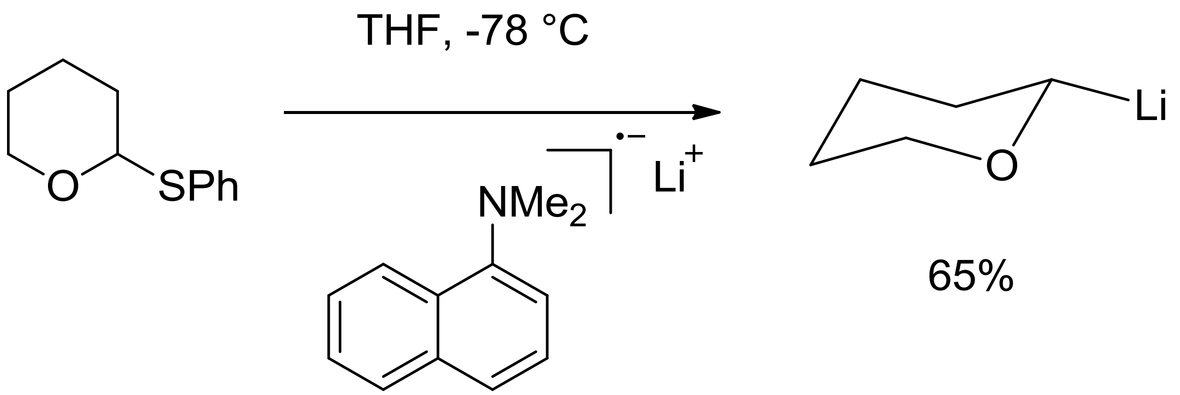
T. Blümke, Y.-H. Chen, P. Knochel *Nature Chemistry*, **2010**, *2*, 313

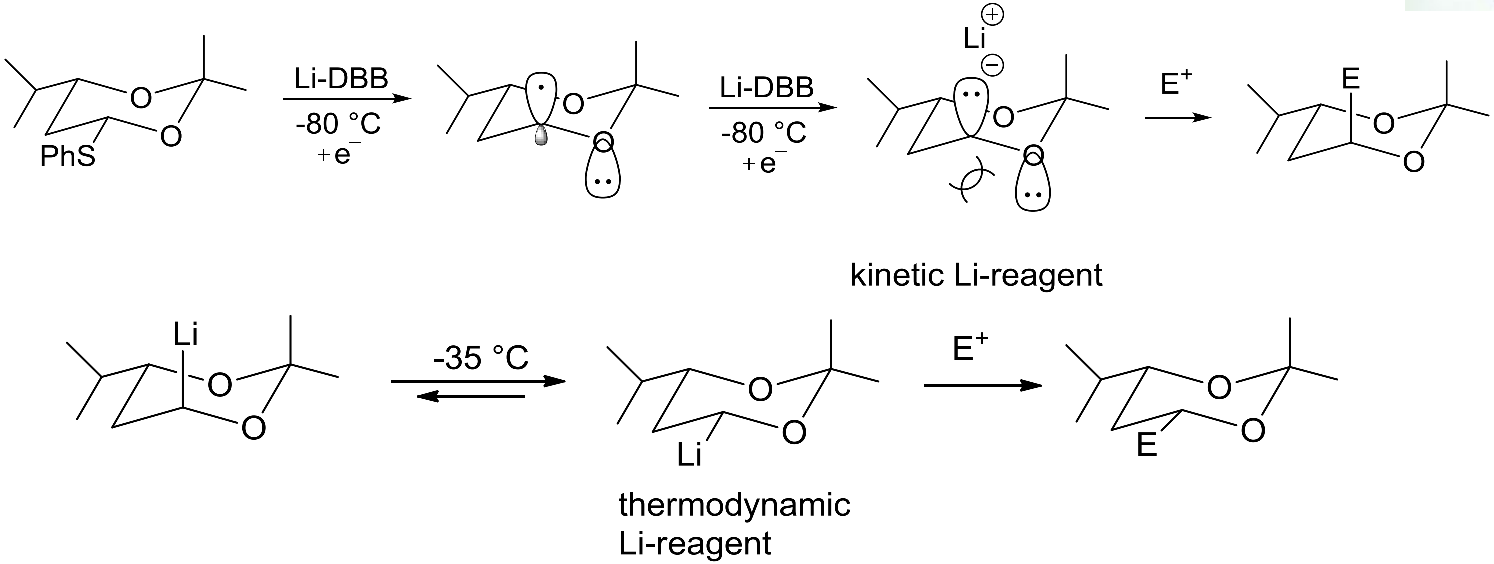


68%
life time (t½) = 2 days at 25 °C

A. Metzger, P. Knochel *Org. Lett*. **2008**, *10*, 1107

Extension to insertion reactions to C-S bonds



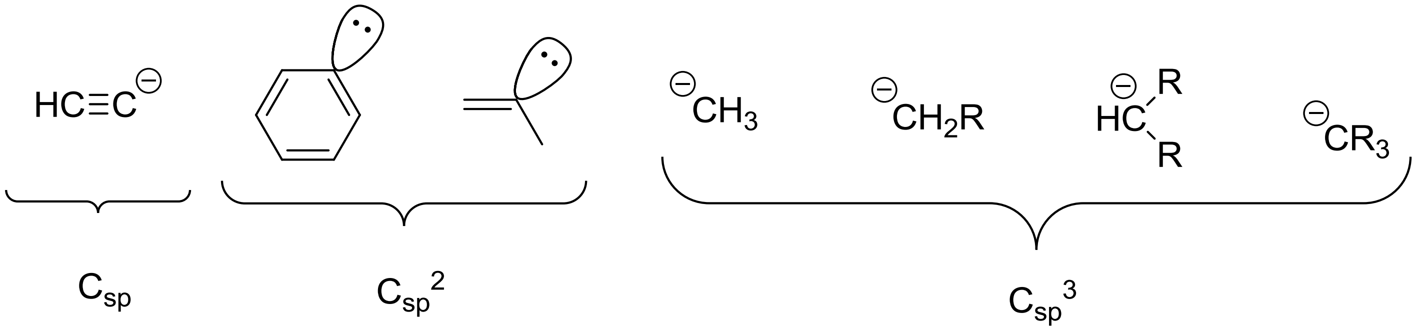


S. Rychnosvsky *J. Org. Chem*. **1989**, *54*, 4982; *J. Org. Chem*. **1990**, *95*, 5550

The Halogen-Metal-Exchange

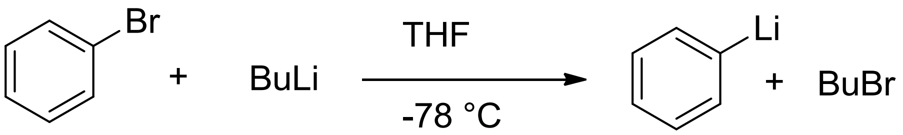
$$R^1{-}X \;+\; R^2\text{-}Met \;\rightleftharpoons\; R^2{-}X \;+\; \boxed{R^1{-}Met}$$

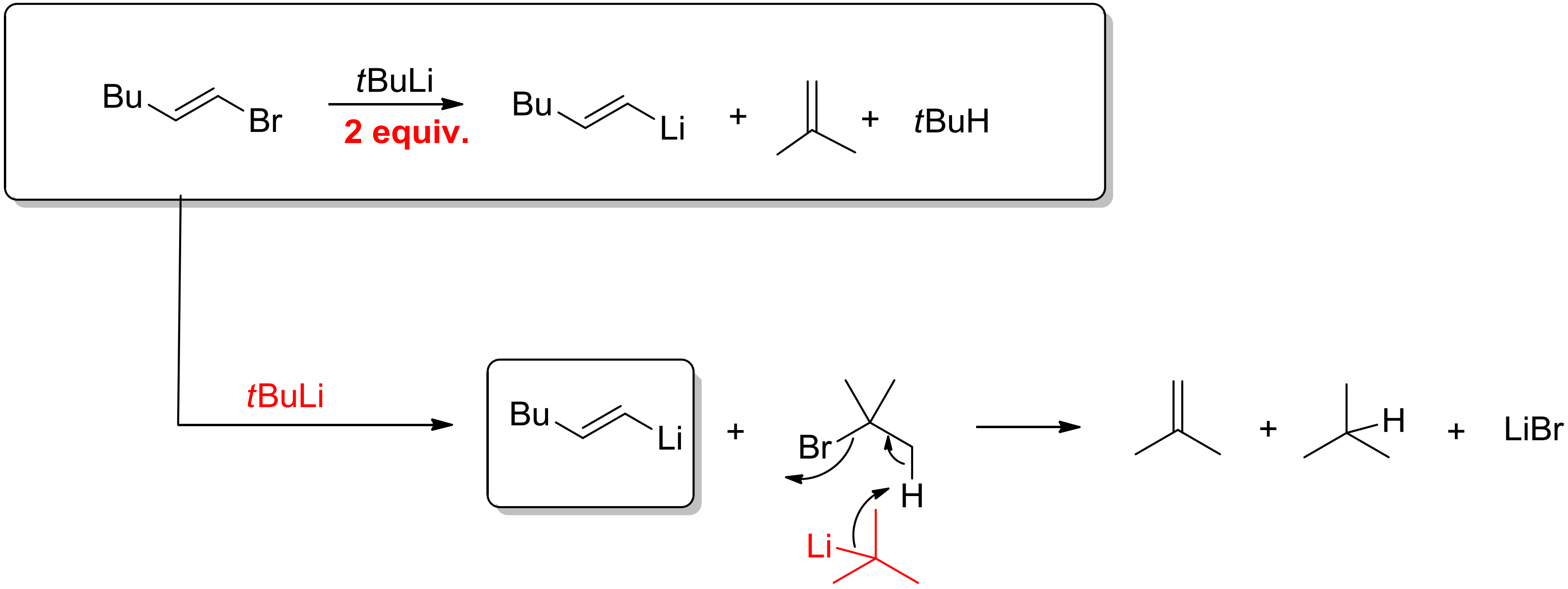
driving force: the most stable carbanion is always formed

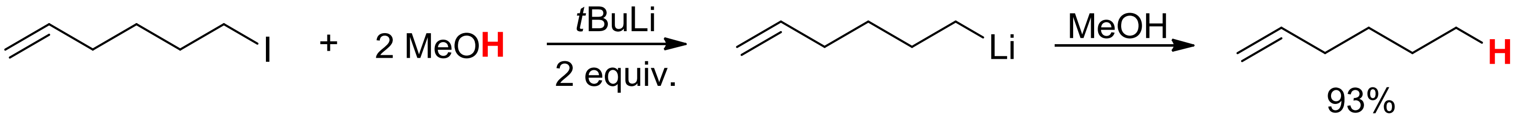


The Halogen-Metal-Exchange

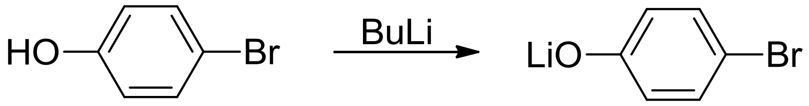
1939: the Wittig-Gilman reaction







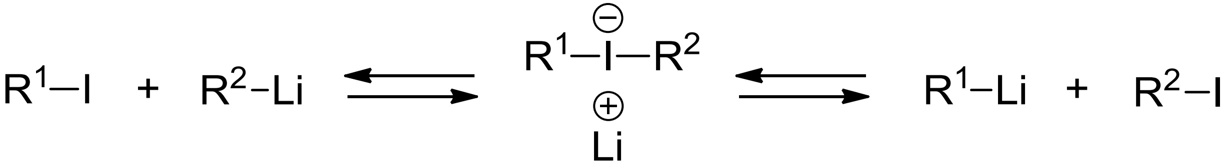
The Halogen-Metal-Exchange



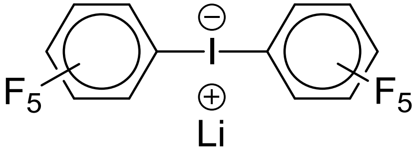
I >> Br >> Cl

rate of the halogen/metal exchange

mechanism:



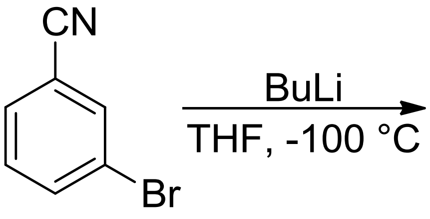
$$R^1{-}I + R^2{-}Li \rightleftharpoons \underset{\underset{Li}{\oplus}}{\overset{\ominus}{R^1{-}I{-}R^2}} \rightleftharpoons R^1{-}Li + R^2{-}I$$



has been isolated

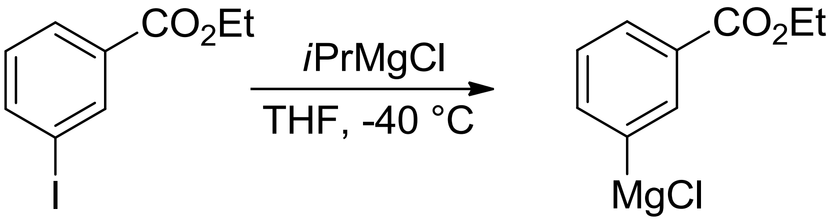
H. J. Reich, A. W. Sanders, A. T. Fiedler, M. J. Bevan *J. Am. Chem. Soc*. **2002**, *124*, 13386

The Halogen-Metal-Exchange : tolerance of functional groups



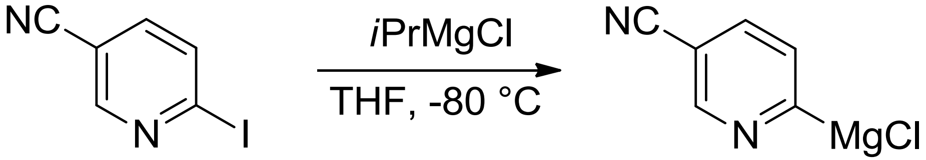
Stable only at -100 °C

W. E. Parham, L. D. Jones, Y. Sayed J. Org. Chem. 1975, 40, 2394



> 90 %

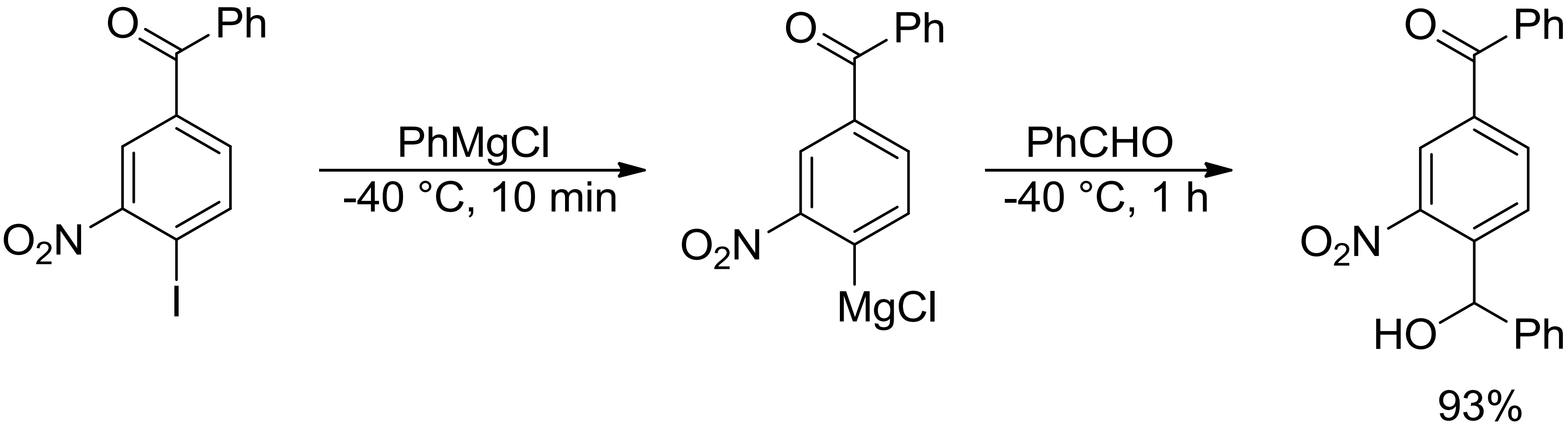
M. Rottländer, P. Knochel, Angew. Chem. Int. Ed. 1998, 40, 1801



> 90 %

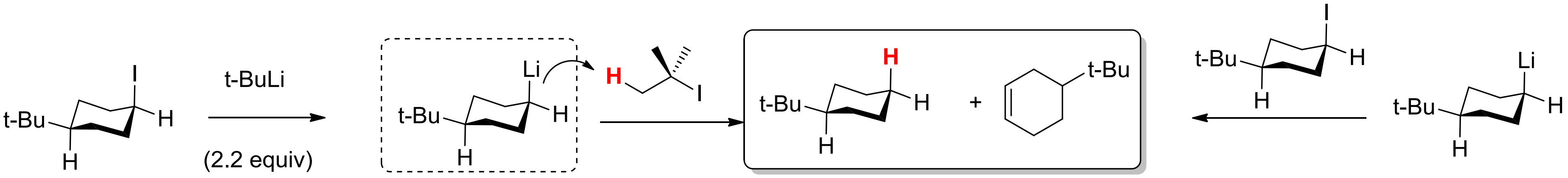
H. Ren, P. Knochel, Chem.Comm. **2006**, 726

The iodine- magnesium-exchange: compatibility with a nitro group



I. Sapountzis, P. Knochel *Angew. Chem. Int. Ed*. **2003**, *42*, 4438

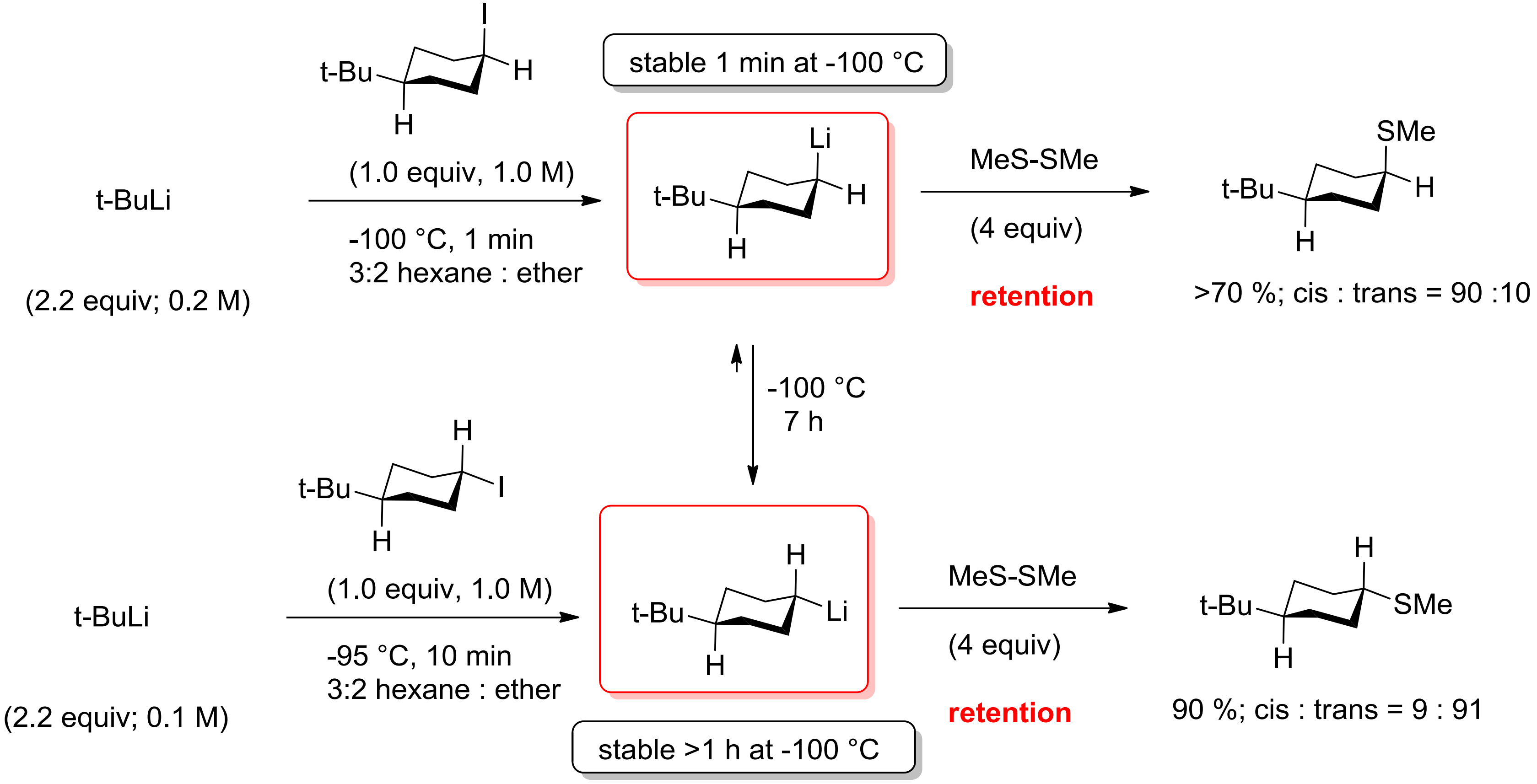
A secondary iodine/lithium exchange on cyclohexyl iodides



see W.F. Bailey, J.D. Brubaker, K.P. Jordan, *J. Organomet. Chem.* **2003**, *681*, 210

Stephanie SEEL

A secondary iodine/lithium exchange on cyclohexyl iodides



t-BuLi

(2.2 equiv; 0.2 M)

(1.0 equiv, 1.0 M)

-100 °C, 1 min
3:2 hexane : ether

stable 1 min at -100 °C

MeS-SMe

(4 equiv)

retention

>70 %; cis : trans = 90 :10

-100 °C
7 h

t-BuLi

(2.2 equiv; 0.1 M)

(1.0 equiv, 1.0 M)

-95 °C, 10 min
3:2 hexane : ether

stable >1 h at -100 °C

MeS-SMe

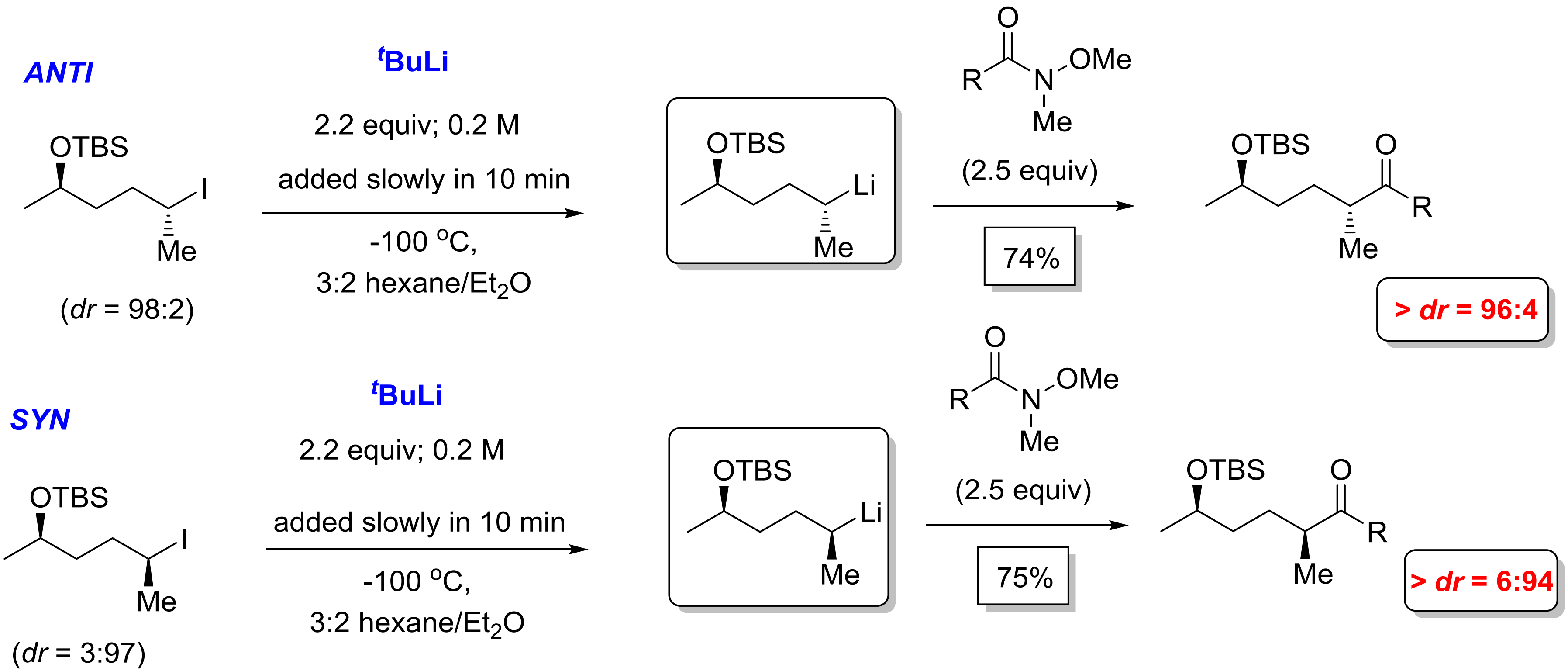
(4 equiv)

retention

90 %; cis : trans = 9 : 91

Stephanie SEEL

Acyclic systems: stereospecific I/Li exchange and reactions with C-electrophiles



ANTI

(*dr* = 98:2)

^{t}BuLi

2.2 equiv; 0.2 M

added slowly in 10 min

-100 °C,

3:2 hexane/Et_2O

(2.5 equiv)

74%

> *dr* = 96:4

SYN

(*dr* = 3:97)

^{t}BuLi

2.2 equiv; 0.2 M

added slowly in 10 min

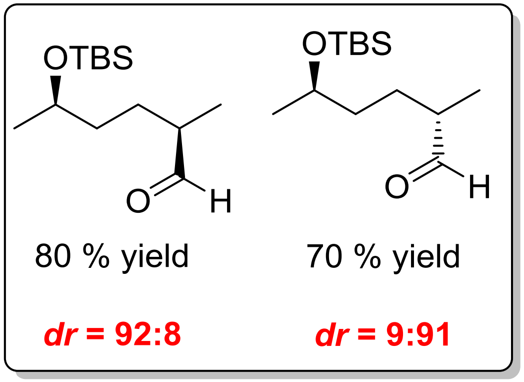
-100 °C,

3:2 hexane/Et_2O

(2.5 equiv)

75%

> *dr* = 6:94

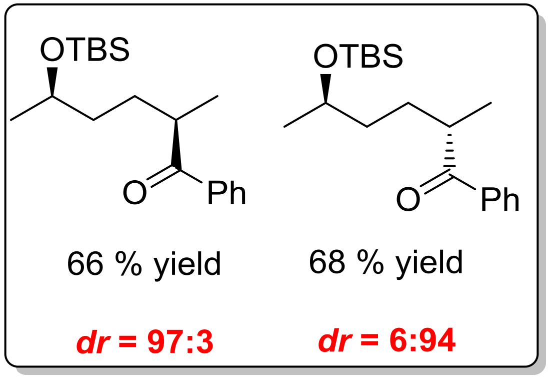


80 % yield

***dr* = 92:8**

70 % yield

***dr* = 9:91**

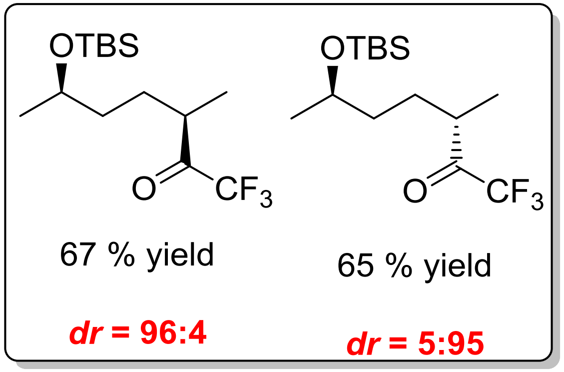


66 % yield

***dr* = 97:3**

68 % yield

***dr* = 6:94**



67 % yield

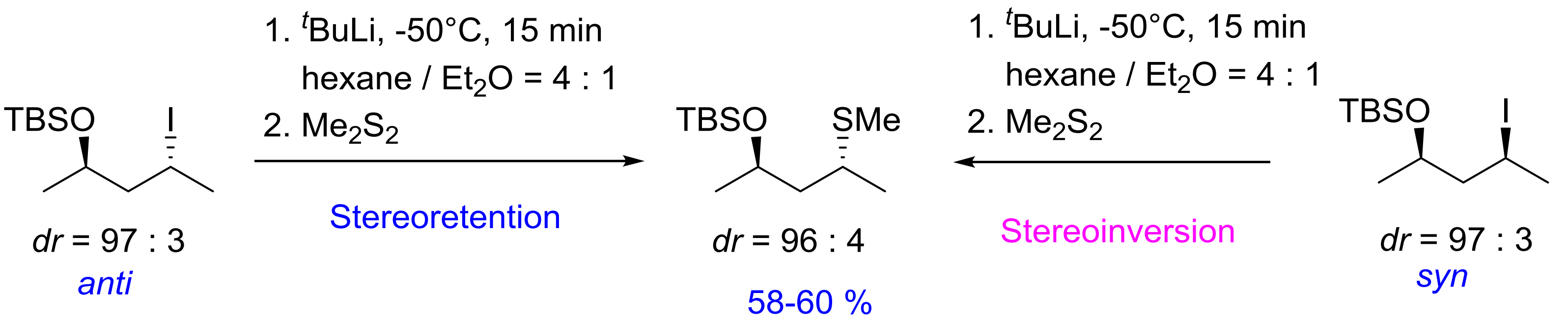
***dr* = 96:4**

65 % yield

***dr* = 5:95**

G. Dagousset, K. Moriya, R. Mose, G. Berionni, K. Karaghiosoff, P. Knochel in press, **2013**

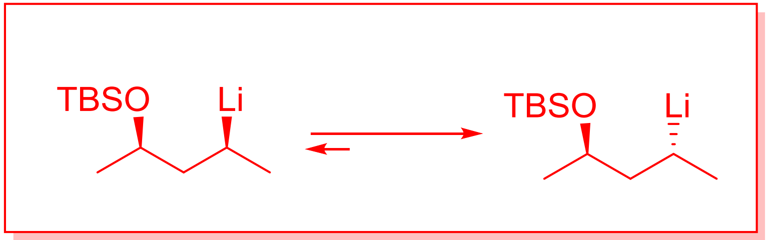
Stereoconvergent synthesis of Li-reagents

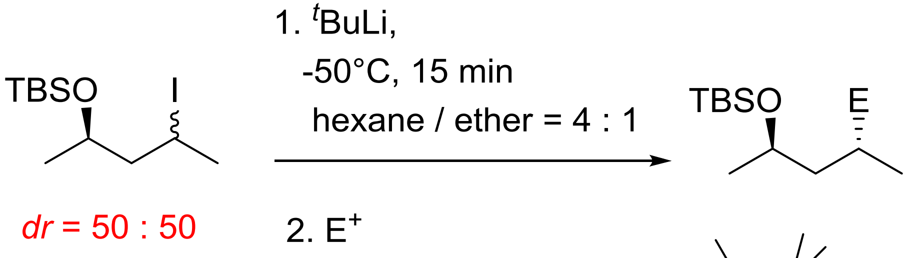


dr = 97 : 3
anti

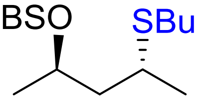
dr = 96 : 4
58-60 %

dr = 97 : 3
syn





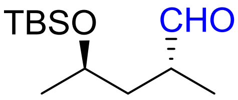
dr = 50 : 50



E^+ = Bu_2S_2

60 %

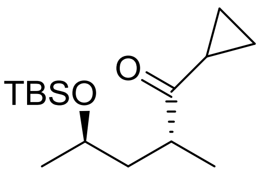
dr = 94 : 6



E^+ = DMF

74 %

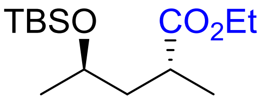
dr = 92 : 8



E^+ = DMF

67 %

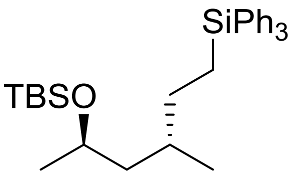
dr = 96 : 4

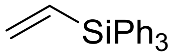


E^+ = Cl-CO_2Et

67 %

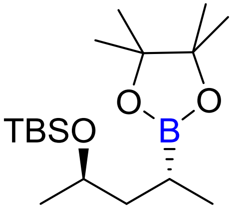
dr = 96 : 4



E^+ = 

63 %

dr = 99 : 1



E^+ = Pin-OMe

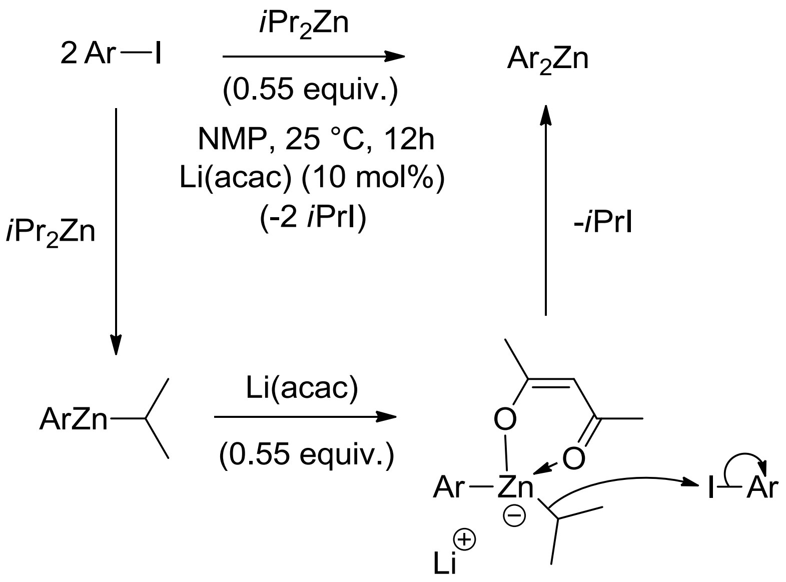
73 %

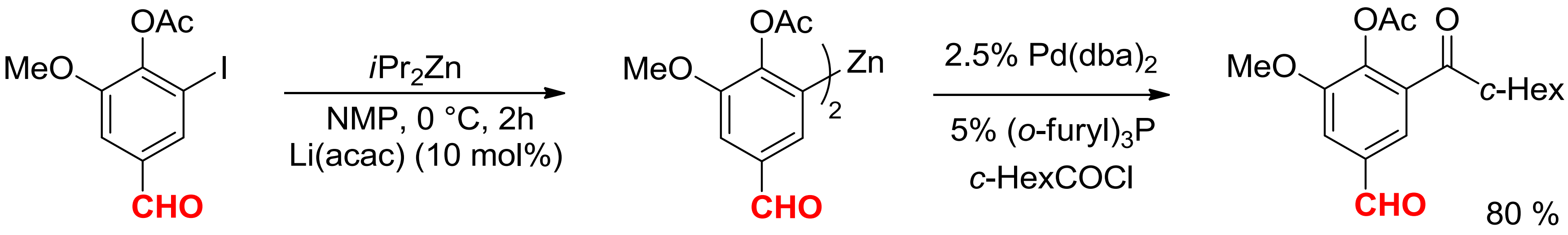
dr = 97 : 3

D. Didier, K. Moriya, **2014**

The iodine/zinc-exchange

catalysis of the halogen-metal exchange

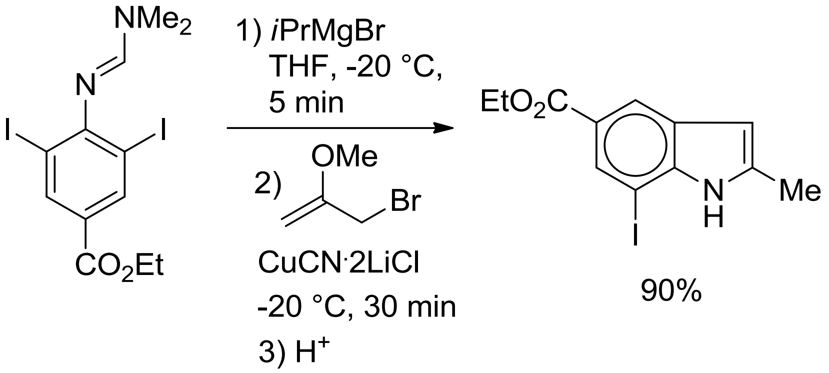




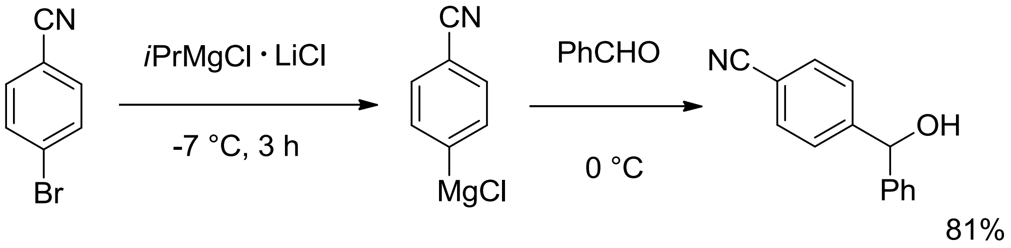
F. Kneisel, P. Knochel *Angew. Chem. Int. Ed*. **2004**, *43*, 1017

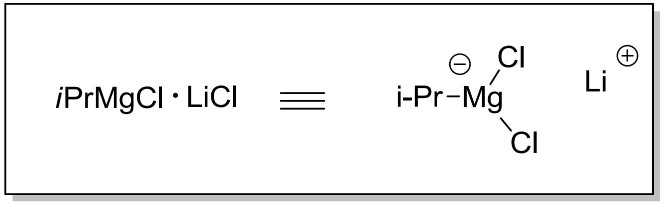
The Halogen-Metal-Exchange

indole-synthesis



D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp, P. Knochel *Org. Lett.*, **2002**, *4* , 1819



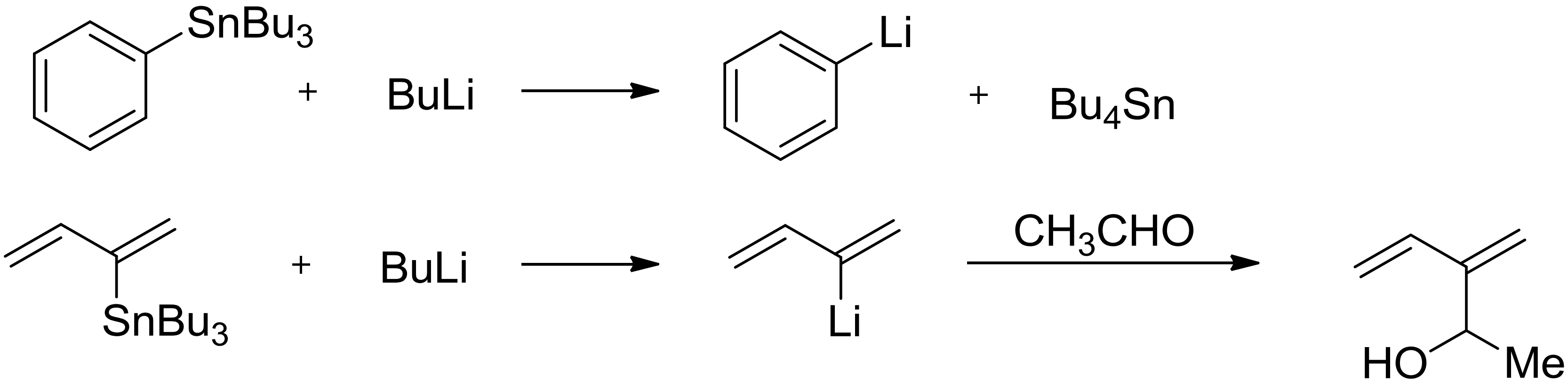


A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2004**, *43*, 3333

Transmetalation

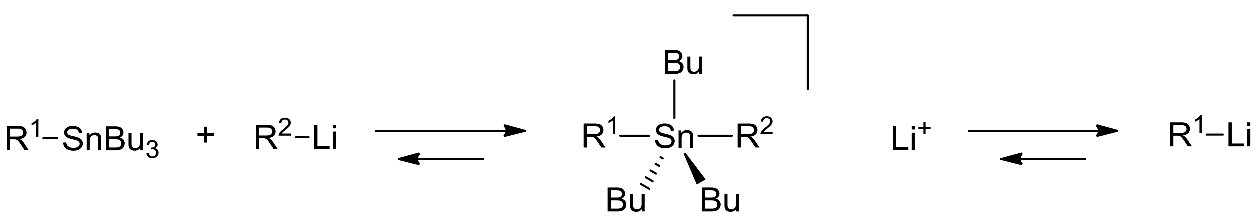
a) $$\boxed{R^1\text{–}Met^1} + R^2\text{-}Met^2 \rightleftharpoons \boxed{R^1\text{–}Met^2} + R^2\text{-}Met^1$$

the most stable carbanion is linked to the most electropositive metal

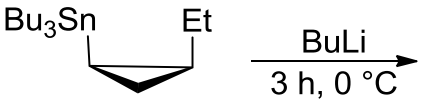


Transmetalation

mechanism:



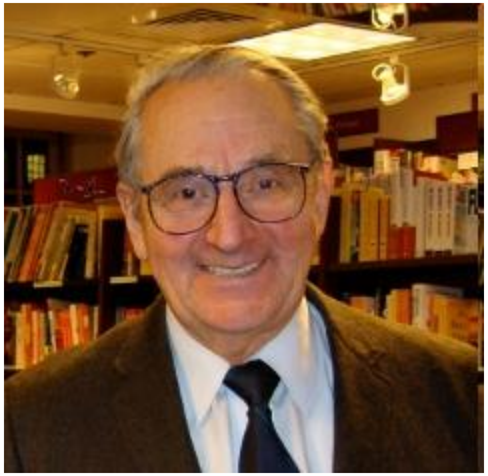
the most stable Li-organometallic is formed

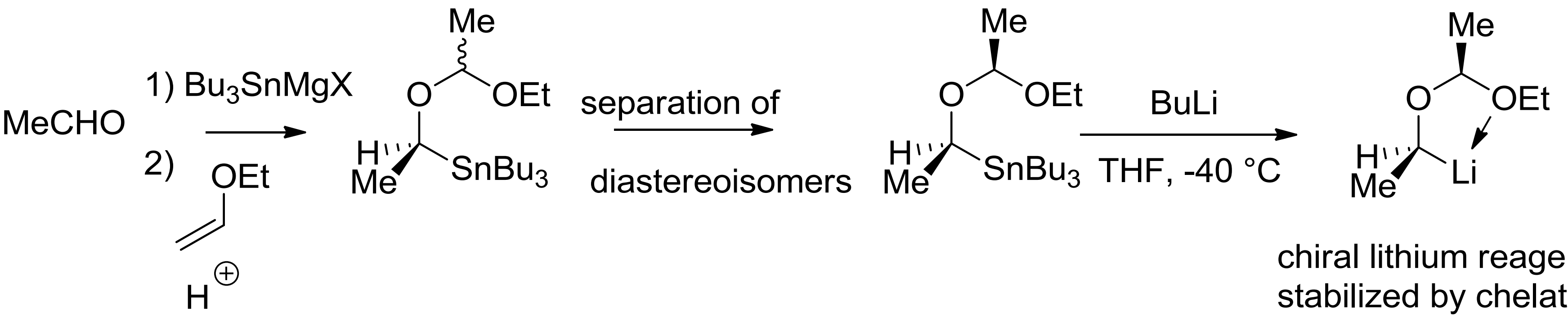


configurational stable

Li-reagent due to the ring strain

E. J. CoreyTetrahedron Lett. 1984, 25, 2415





chiral lithium reagent
stabilized by chelation

W. C. Still, *J. Am. Chem. Soc.* **1980**, *102*, 1201

Transmetalation

b)

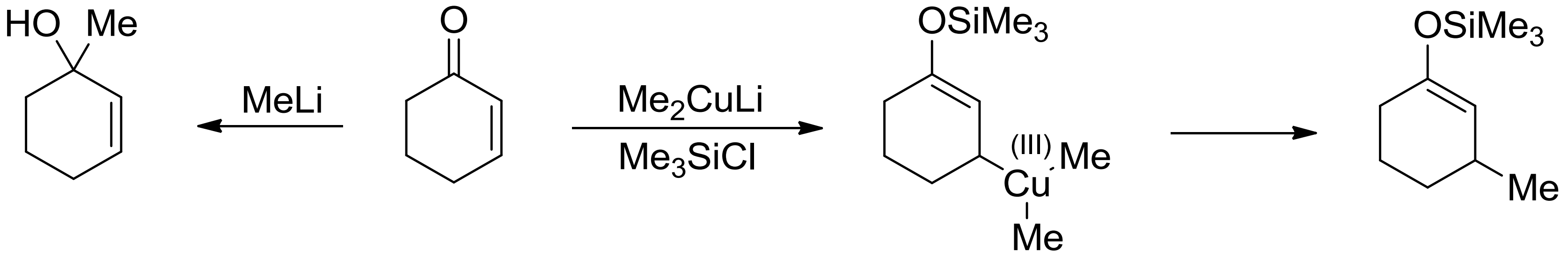
$$R^1\text{–}Met^1 \xrightarrow{Met^2\text{–}X} R^1\text{–}Met^2$$

$$RLi + MgBr_2 \longrightarrow RMgBr + LiBr \xrightarrow{ZnCl_2} RZnX + MgX_2$$

$$Me_3TaCl_2 \xleftarrow{{}^3/_2\ Me_2Zn} TaCl_5 \xrightarrow[-\ 5\ LiCl]{5\ MeLi} TaMe_5$$

Transmetalation

$$\text{Me-}\overset{\ominus}{\text{Cu}}\text{-Me}\ \overset{\oplus}{\text{Li}} \equiv \text{Me}_2\text{CuLi} \xleftarrow{\text{2MeLi}} \text{CuI} \xrightarrow{\text{2MeMgBr}} \text{MeCu}\cdot\text{MgBr}_2 + \text{MeMgI}$$

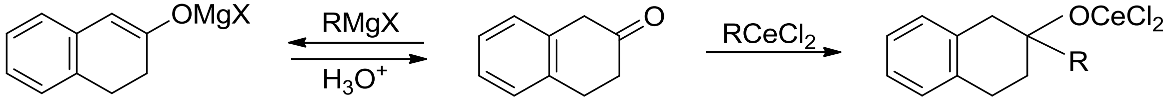


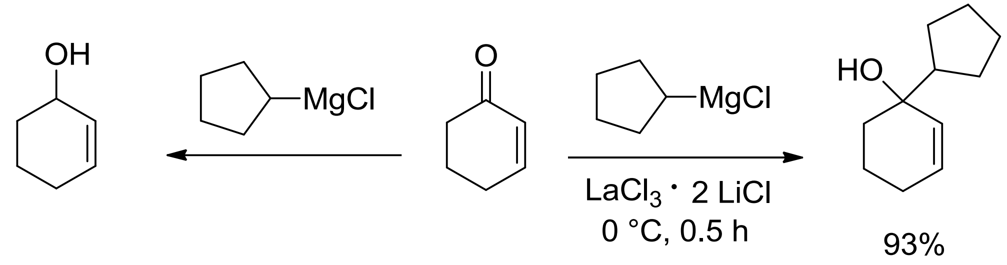
E. Nakamura, I. Kuwajima *J. Am. Chem. Soc*. **1984**, *106*, 3368

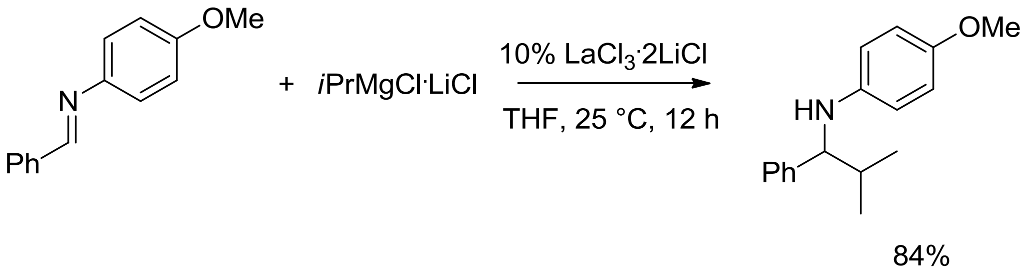
Transmetalation

$$RMgX + CeCl_3 \longrightarrow RCeCl_2 + ClMgX$$

T. Imamoto, Y. Sugiyura, N. Takiyama, *Tetrahedron Lett*. **1984**, *25*, 4233

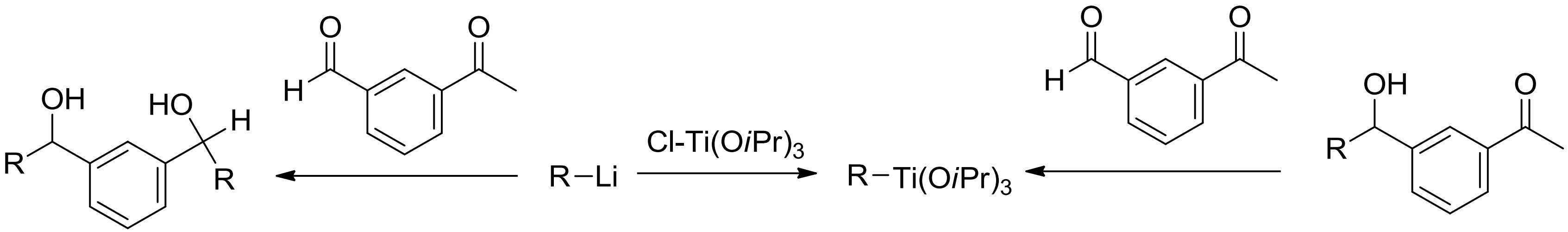






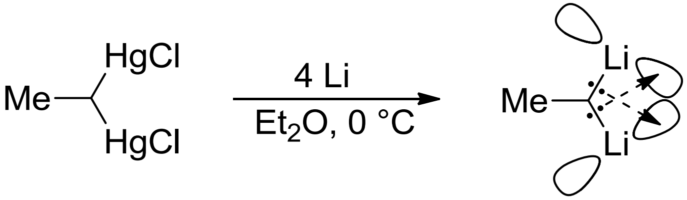
A. Krasovskiy, F. Kopp, P. Knochel *Angew. Chem. Int. Ed*. **2006**, *45*, 497

Transmetalation



M. Reetz, D. Seebach *Angew. Chem*. **1983**, *95*, 12

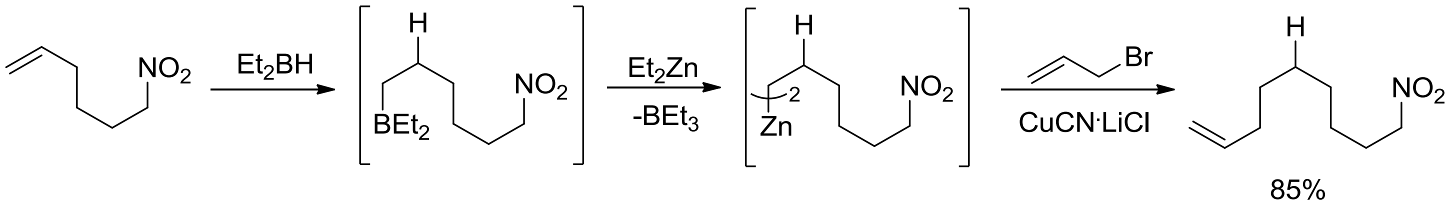
$$R^1\text{–}Met^1 \xrightarrow{Met^2} R^1\text{–}Met^2 \;+\; Met^1$$

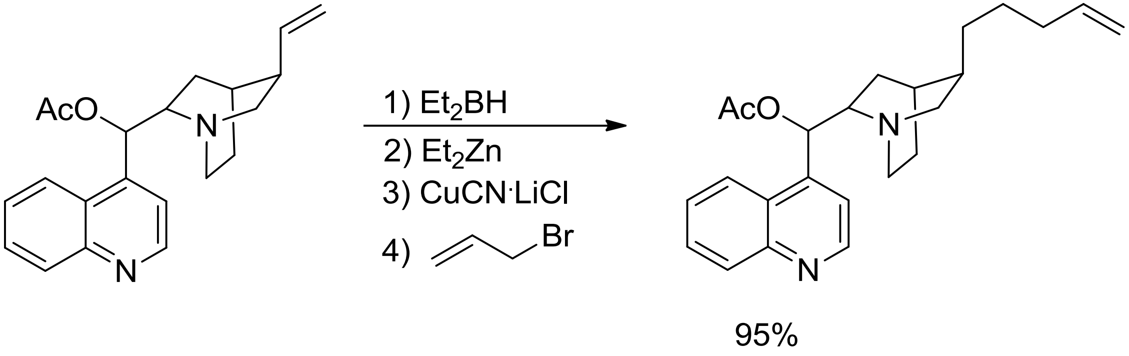


A. Maercker, M. Theis, A. Kos, P. Schleyer, *Angew. Chem*. **1983**, *95*, 755

Transmetalation

boron / zinc-exchange

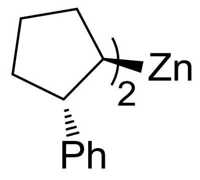




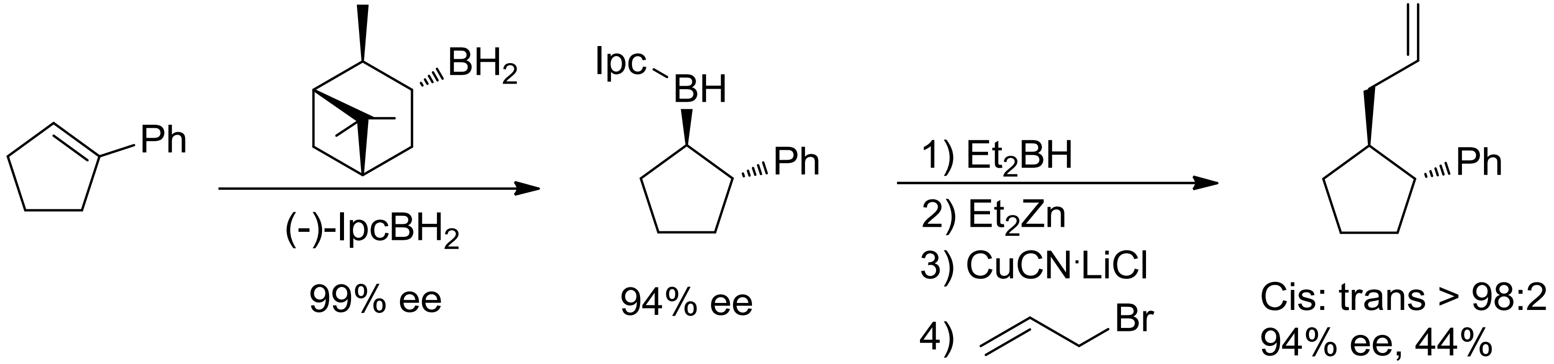
F. Langer, L. Schwink, P. Knochel *J. Org. Chem*. **1996**, *61*, 8229

Transmetalation

boron / zinc-exchange



94% ee



L. Micouin, M. Oestreich, P. Knochel *Angew. Chem. Int. Ed*. **1997**, *36*, 245

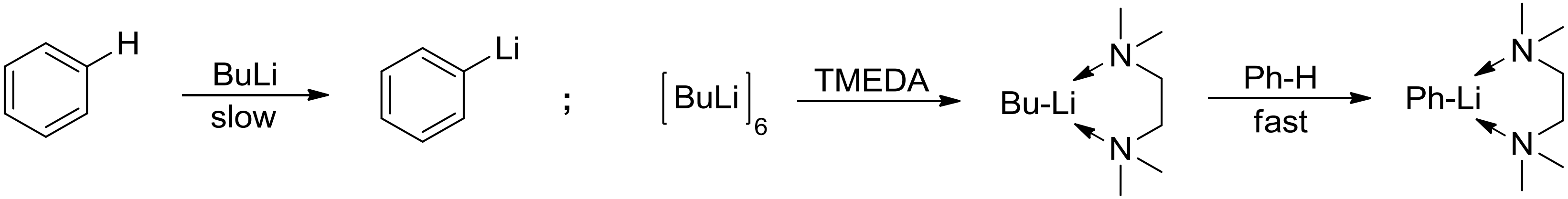
Metalation (starting from a compound with an acid proton)

$$R^2\text{–}H \xrightarrow{R^1\text{–Met}} R^2\text{-Met}$$

$\overset{\ominus}{R^2}$ must be more stable than $\overset{\ominus}{R^1}$ $\Longrightarrow$ $pKa(R^1\text{-H}) > pKa(R^2\text{-H})$ (thermodynamic criteria)

$R^1\text{–Met}$: *t*-BuOK, LDA, BuLi, ...

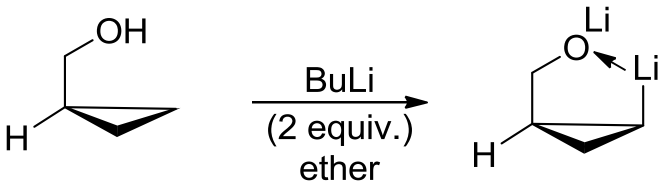
kinetic criteria (kinetic acidity)

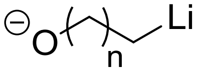


$PhCH_2Li$ reacts with benzene 10^4 times faster than with MeLi

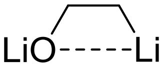
$PhCH_2Li$ is a monomer in THF, MeLi a tetramer

Directed metalation

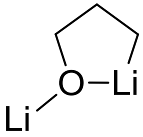




0 kcal/mol

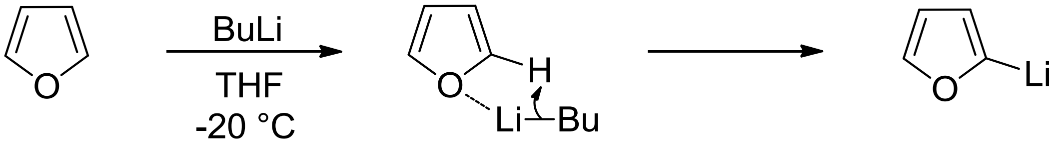


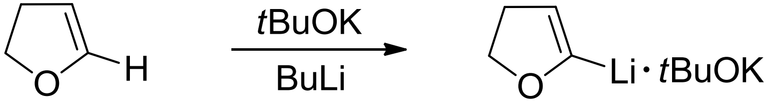
-10 kcal/mol

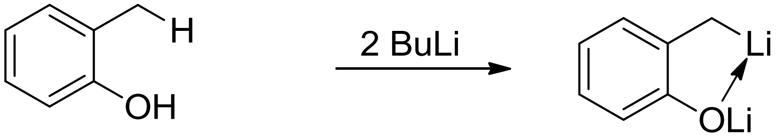


-13 kcal/mol

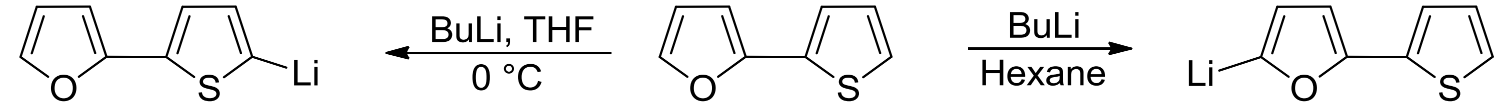
Directed metalation





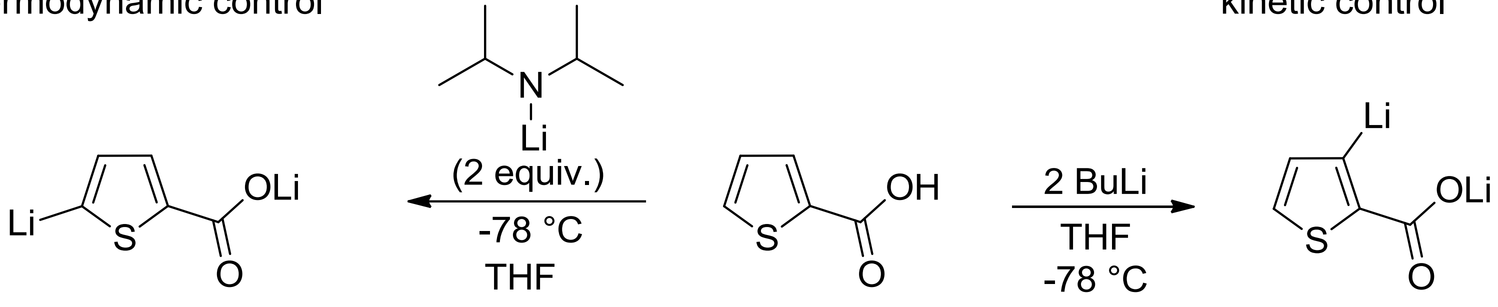


Metalation



thermodynamic control

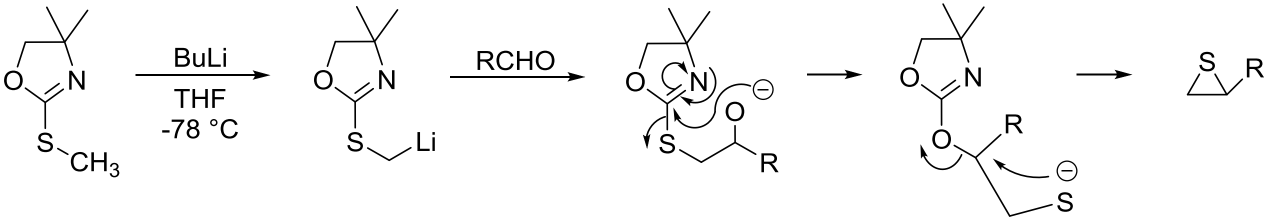
kinetic control



thermodynamic control

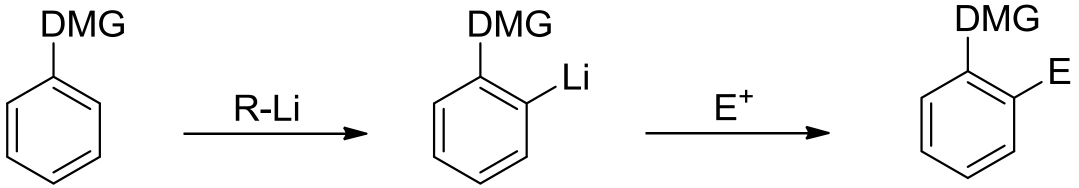
kinetic control

A rearrangement may occur :



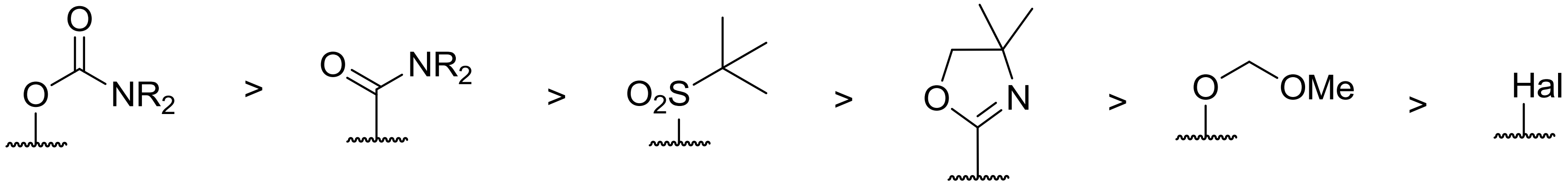
Metalation

directed lithiation



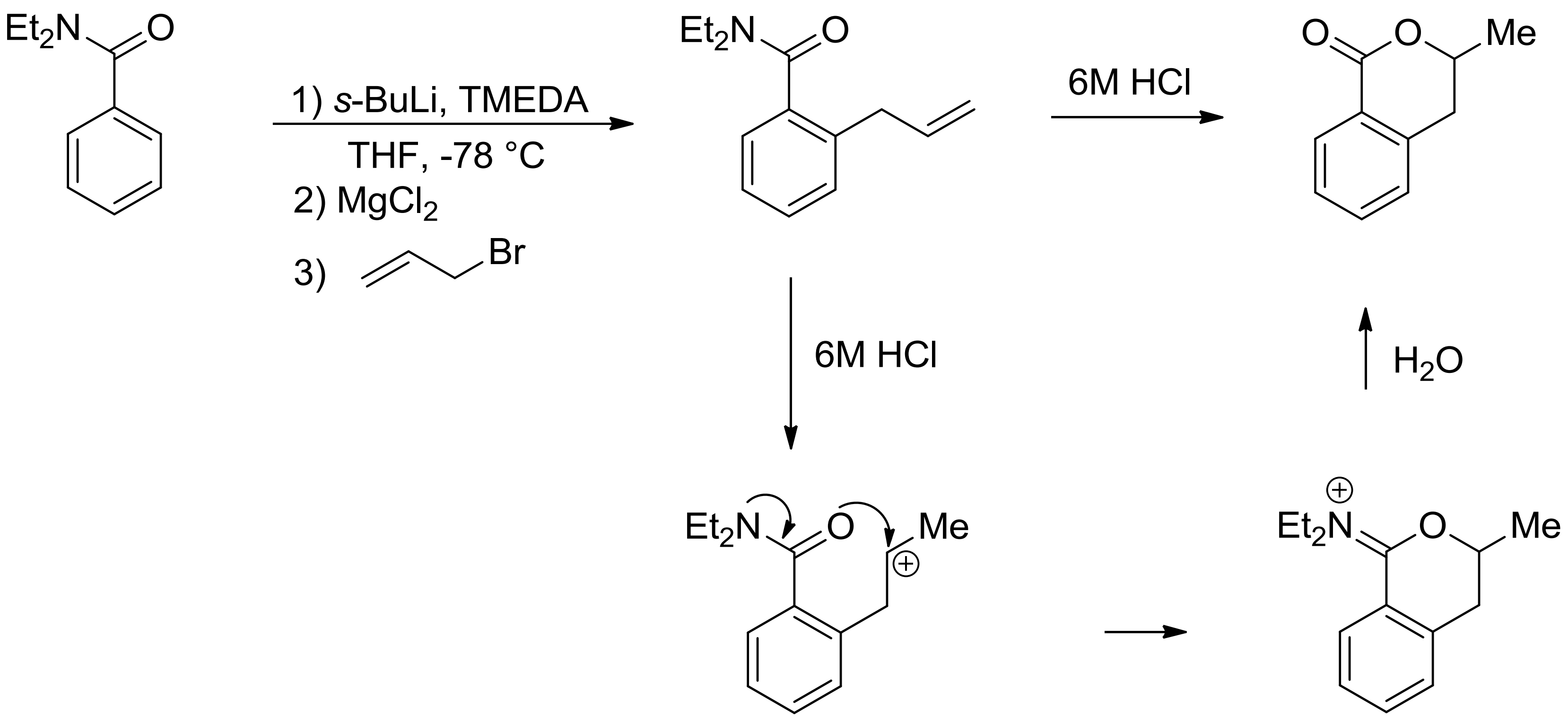
DMG = directing metalating group

V. Snieckus, *Chem Rev*. **1990**, *90*, 879

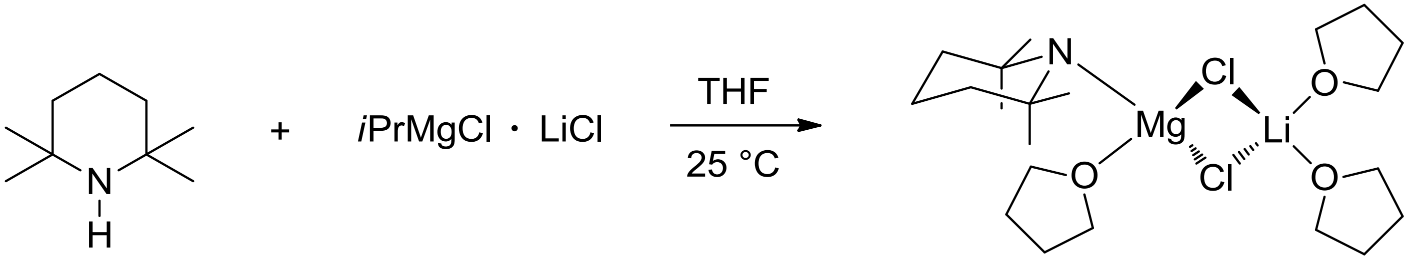


P. Beak, V. Snieckus, *Angew. Chem. Int. Ed*. **2004**, *43*, 2206

Metalation

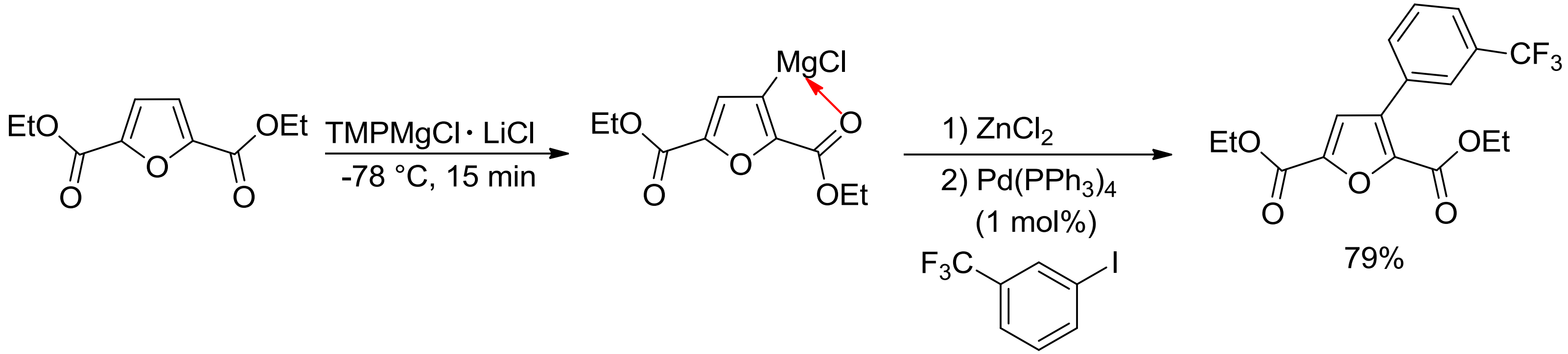

Et$_2$N
O
1) s-BuLi, TMEDA
THF, -78 °C
2) MgCl$_2$
3)
Br
Et$_2$N
O
6M HCl
O
O
Me
6M HCl
H$_2$O
Et$_2$N
O
Me
+
+
Et$_2$N
O
Me

Metalation



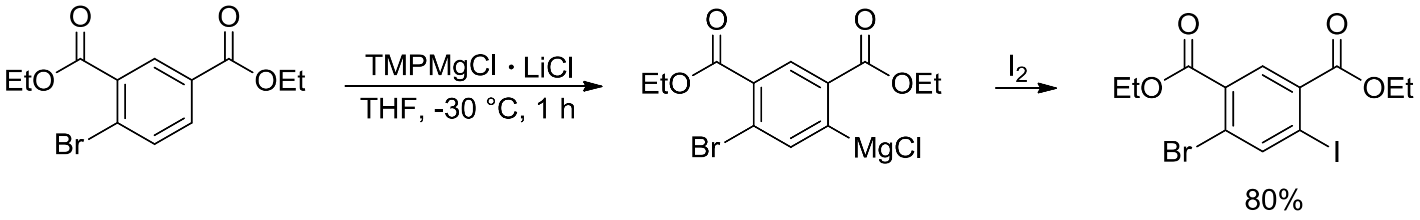
TMPMgCl·LiCl (1.2 M in THF)

A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed*. **2006**, *45*, 2958
R. E. Mulvey, *Angew. Chem. Int. Ed*. **2008**, *47*, 8079

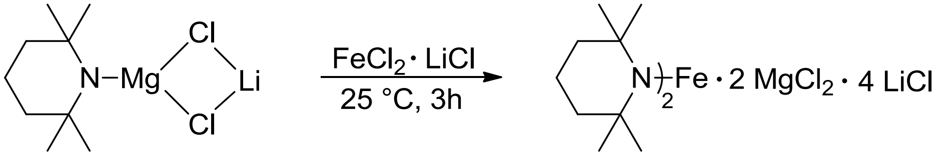


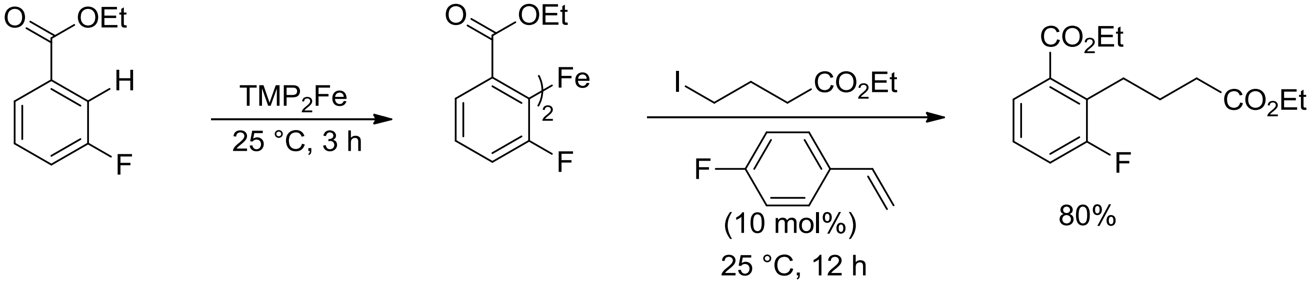
F. M. Piller, P. Knochel *Org. Lett*. **2009**, *11*, 445

Metalation



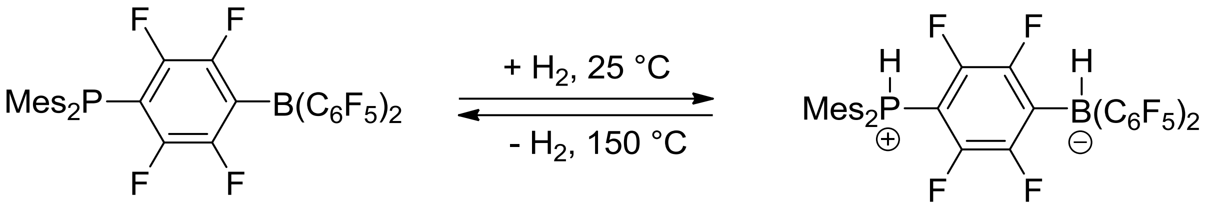
O. Baron, P. Knochel *Angew. Chem. Int. Ed*. **2006**, *45*, 2958



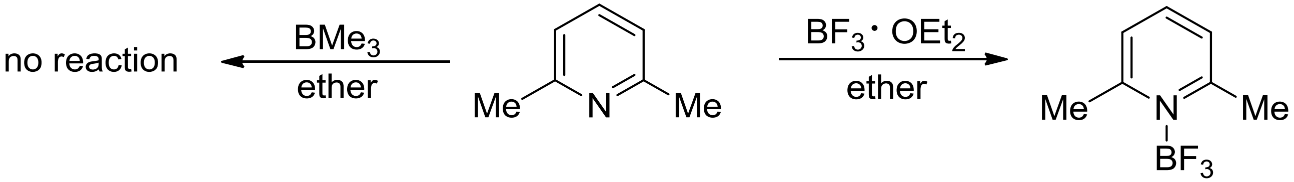


S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed*. **2009**, *48*, 9717

Frustrated Lewis Pairs



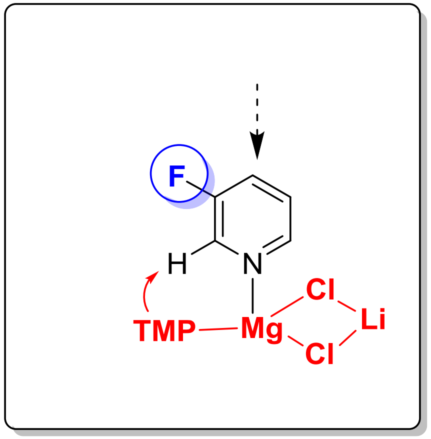
D. Stefan, G. Erker *Angew. Chem. Int. Ed*. **2010**, *49*, 46

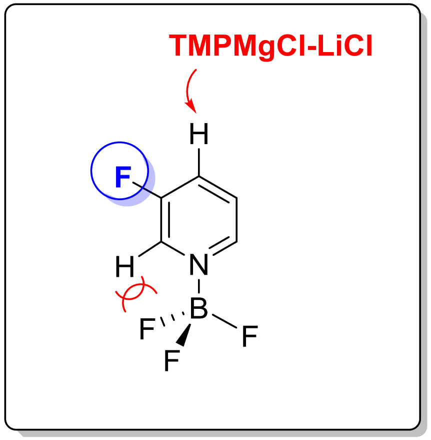


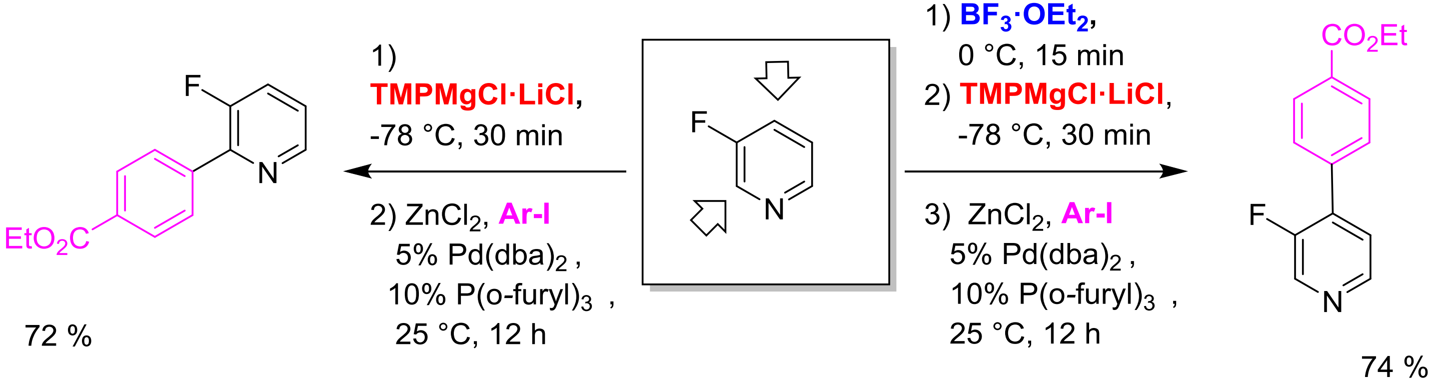
H. C. Brown *J. Am. Chem. Soc*. **1942**, *64*, 325

BF_3-triggered selective metalations

$$\mathbf{BF_3\cdot OEt_2} \xLeftrightarrow[\textit{up to - 30 °C}]{\textit{compatible}} \mathbf{TMPMgCl\text{-}LiCl}$$







1) **TMPMgCl·LiCl,**
-78 °C, 30 min

2) $ZnCl_2$, **Ar-I**
5% $Pd(dba)_2$,
10% $P(o\text{-}furyl)_3$,
25 °C, 12 h

72 %

1) **$BF_3\cdot OEt_2$,**
0 °C, 15 min
2) **TMPMgCl·LiCl**,
-78 °C, 30 min

3) $ZnCl_2$, **Ar-I**
5% $Pd(dba)_2$,
10% $P(o\text{-}furyl)_3$,
25 °C, 12 h

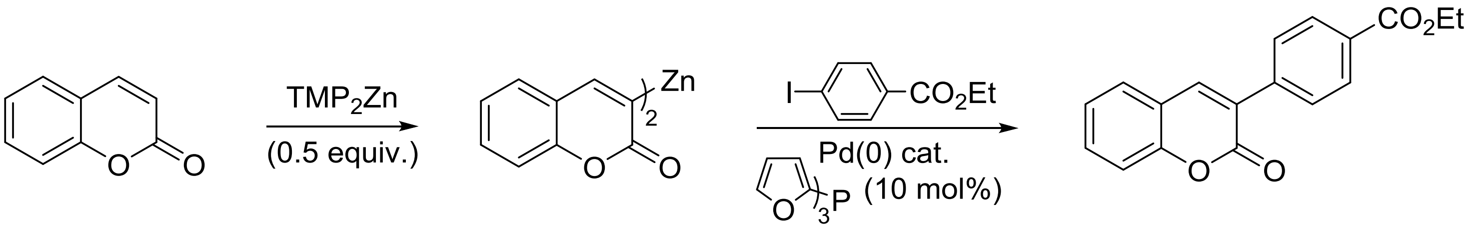
74 %

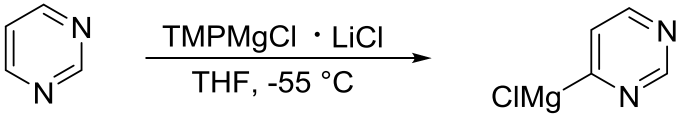
M. Jaric, B. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel *Angew. Chem. Int. Ed.* **2010**, *49*, 5451-5455

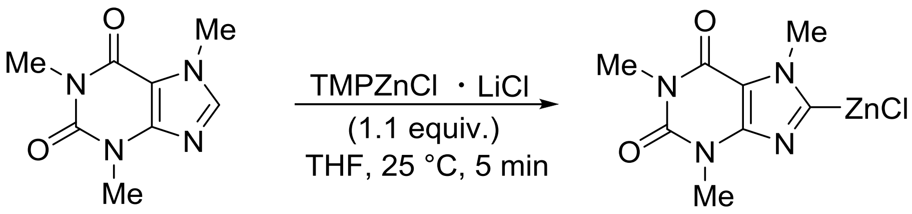
Metalation

$$\text{TMP-MgCl}\cdot\text{LiCl}\xrightarrow[\text{THF, 25 °C, 15 h}]{\text{ZnCl}_2}\text{TMP}_2\text{Zn}\cdot 2\text{LiCl}\cdot 2\text{MgCl}_2$$

S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed*. **2007**, *46*, 7685

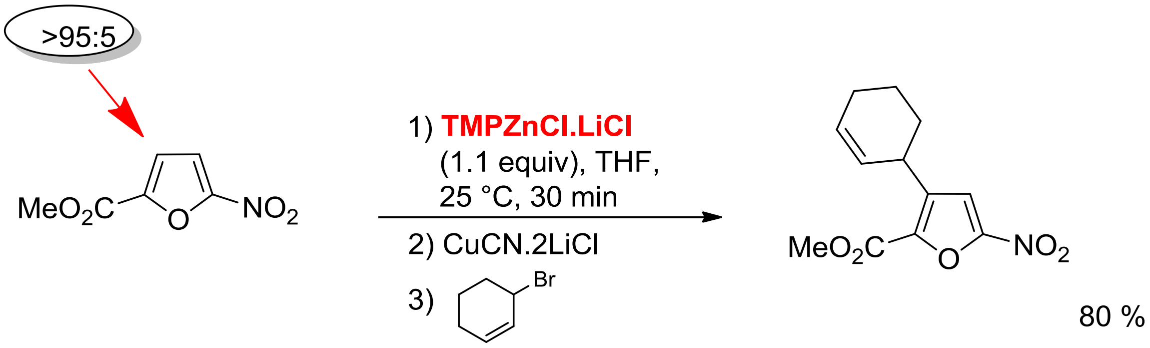


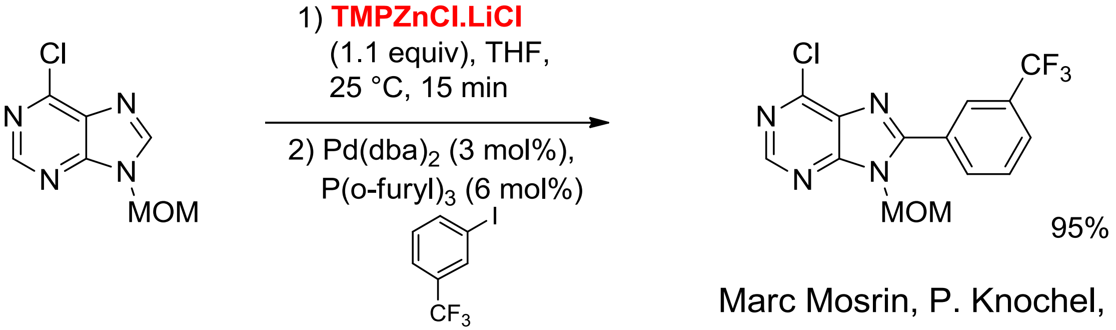




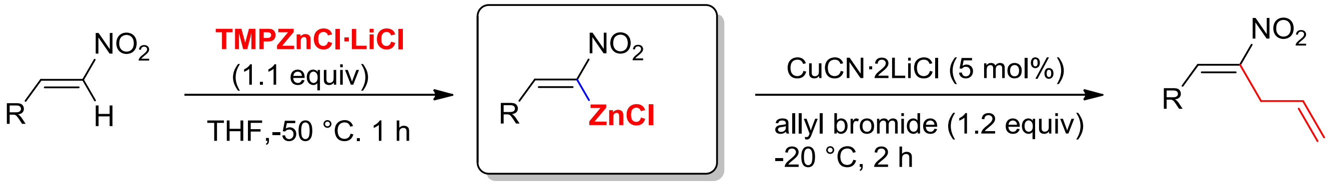
M. Mosrin, P. Knochel *Org. Lett*. **2008**, *10*, 2497
M. Mosrin, P. Knochel *Chem. Eur. J*. **2009**, *15*, 1468
M. Mosrin, P. Knochel *Org. Lett*. **2009**, *11*, 1837

Zincations in the presence of ester and nitro groups





Marc Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837-1840.

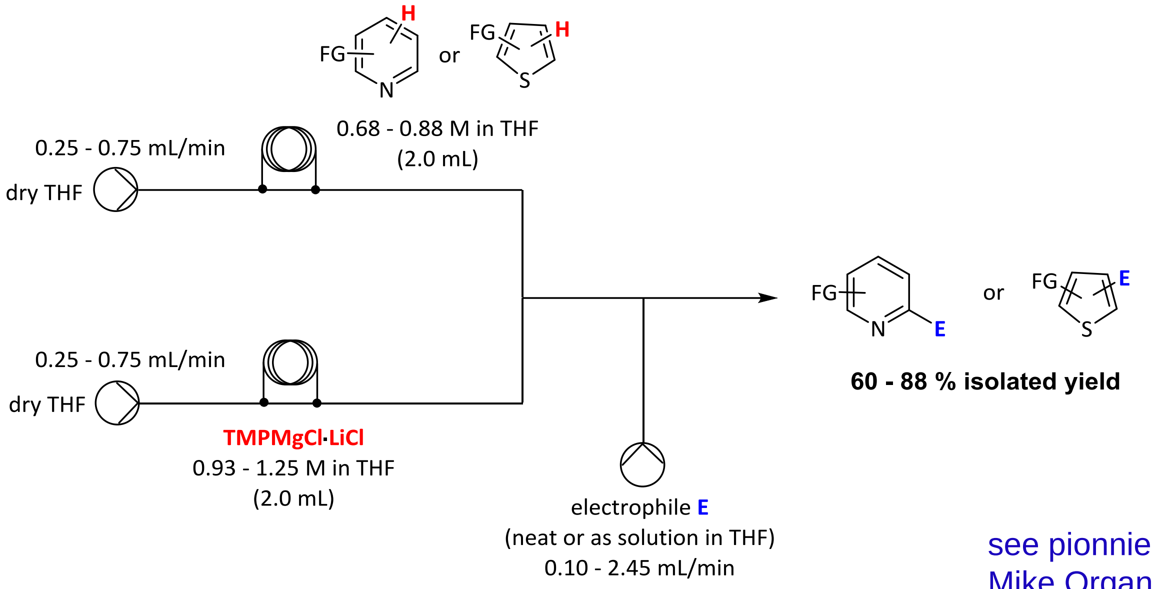


R= Ph, Cy

R= Ph: 69%
R= Cy: 70%

Tomke Bresser, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50,* 1914

Metalations under batch and flow conditions using TMPMgCl·LiCl



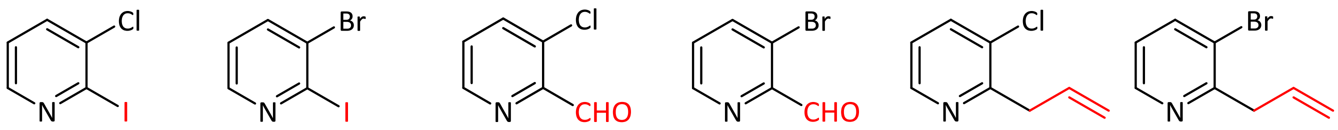
60 - 88 % isolated yield

see pionnier contributions of
Mike Organ, Jun-ichi Yoshida, Steven V. Ley

T.P. Peterson, M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2014**, *53*, 7933.

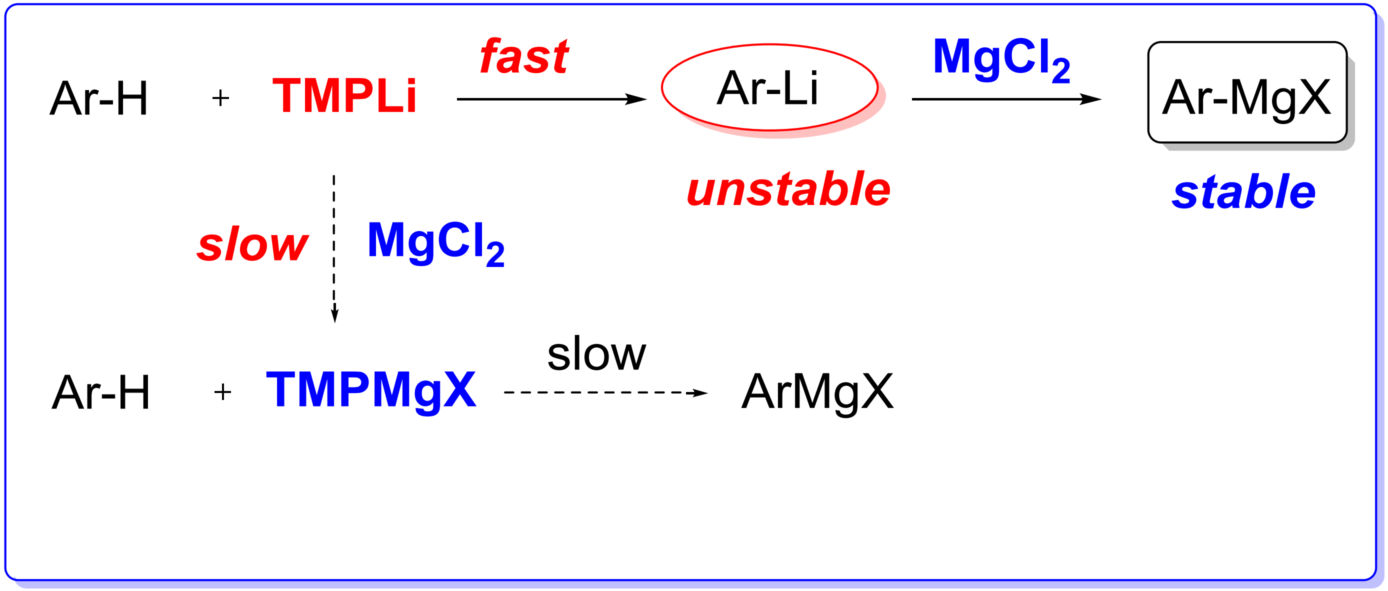
Batch conditions: Complete metalation of 3-chloropyridine after **45 min at -78 °C**

Flow conditions: Complete metalation of 3-halogeno-bromopyridine after **60 s at 25 °C**



Electrophile	I_2 (1.1 equiv.)		DMF (6.0 equiv.)		Allyl bromide (1.2 equiv.) with 3 mol% CuCN·2LiCl	
Metalation time	60 s	60 s	60 s	60 s	60 s	60 s
Isolated yield	**66%**	**71%**	**78%**	**84%**	**74%**	**78%**

Compatibility of the TMPLi with $ZnCl_2$ or $MgCl_2$

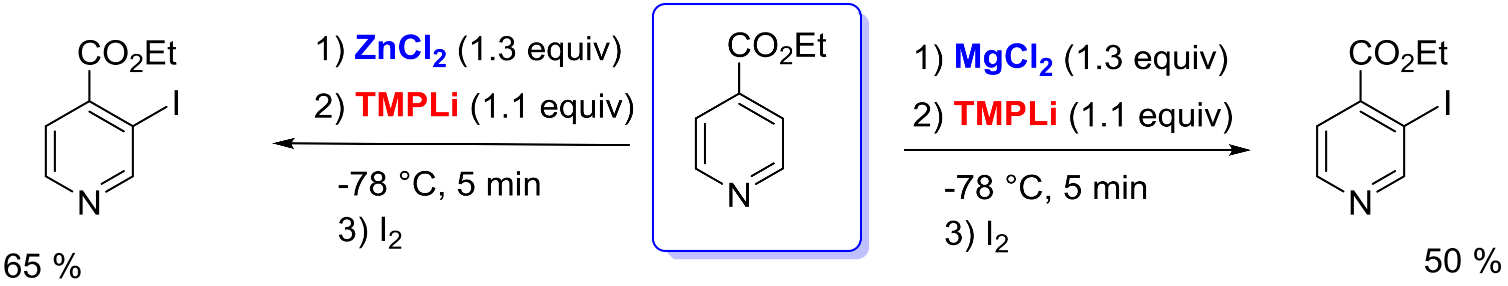


Ar-H + **TMPLi** $\xrightarrow{\text{fast}}$ Ar-Li $\xrightarrow{MgCl_2}$ Ar-MgX

unstable *stable*

slow $MgCl_2$

Ar-H + **TMPMgX** $\xrightarrow{\text{slow}}$ ArMgX



1) **$ZnCl_2$** (1.3 equiv)
2) **TMPLi** (1.1 equiv)
-78 °C, 5 min
3) I_2

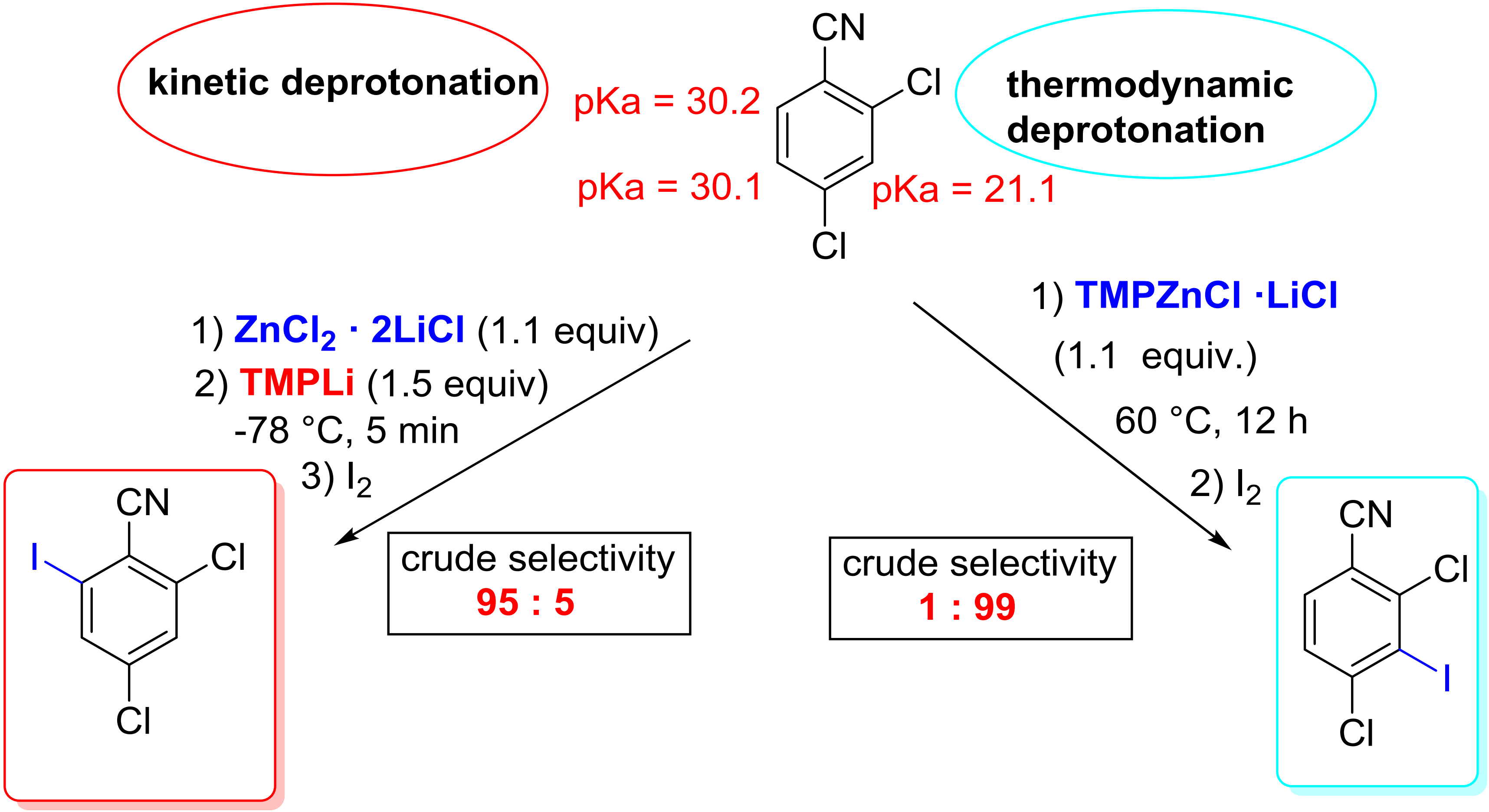
65 %

1) **$MgCl_2$** (1.3 equiv)
2) **TMPLi** (1.1 equiv)
-78 °C, 5 min
3) I_2

50 %

A. Frischmuth, H. Zipse, N. Barl, H. Mayr, P. Knochel *Angew.Chem.Int. Ed.* **2014**, *53*, 7928

Selectivity switch with (TMPLi and $ZnCl_2$) or TMPZnCl-LiCl



kinetic deprotonation

thermodynamic deprotonation

1) **$ZnCl_2$ · 2LiCl** (1.1 equiv)
2) **TMPLi** (1.5 equiv)
-78 °C, 5 min
3) I_2

crude selectivity
95 : 5

1) **TMPZnCl ·LiCl**
(1.1 equiv.)
60 °C, 12 h
2) I_2

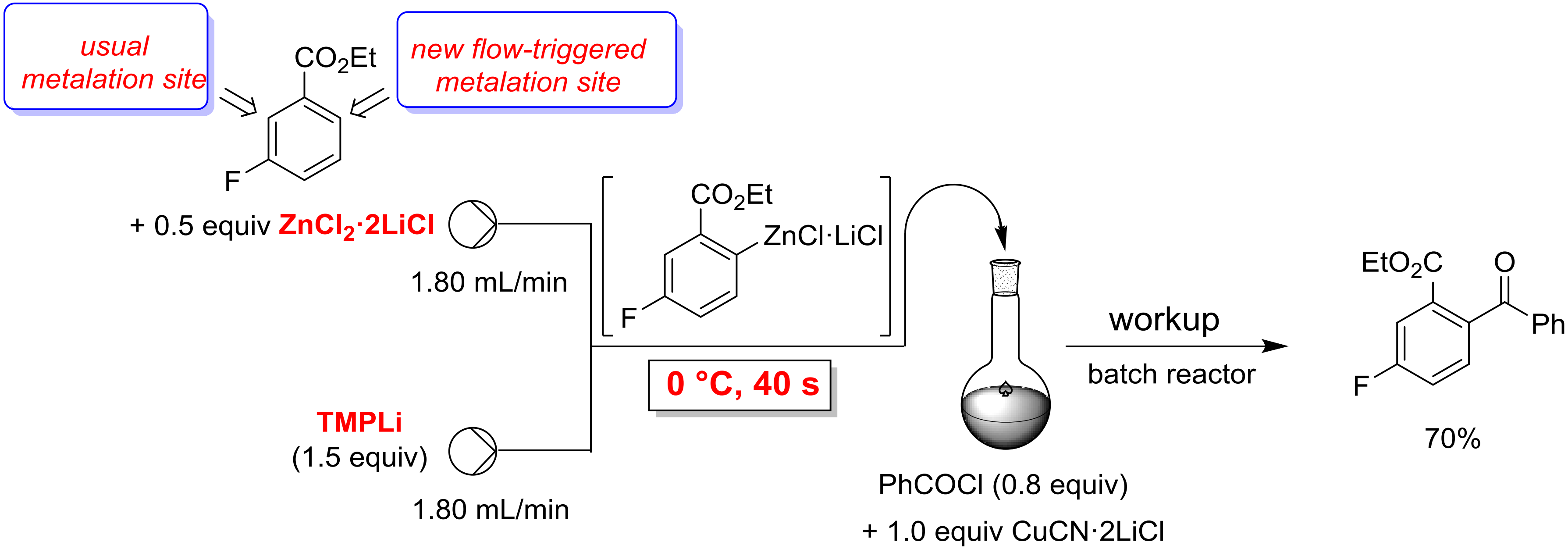
crude selectivity
1 : 99

74 %

78 %

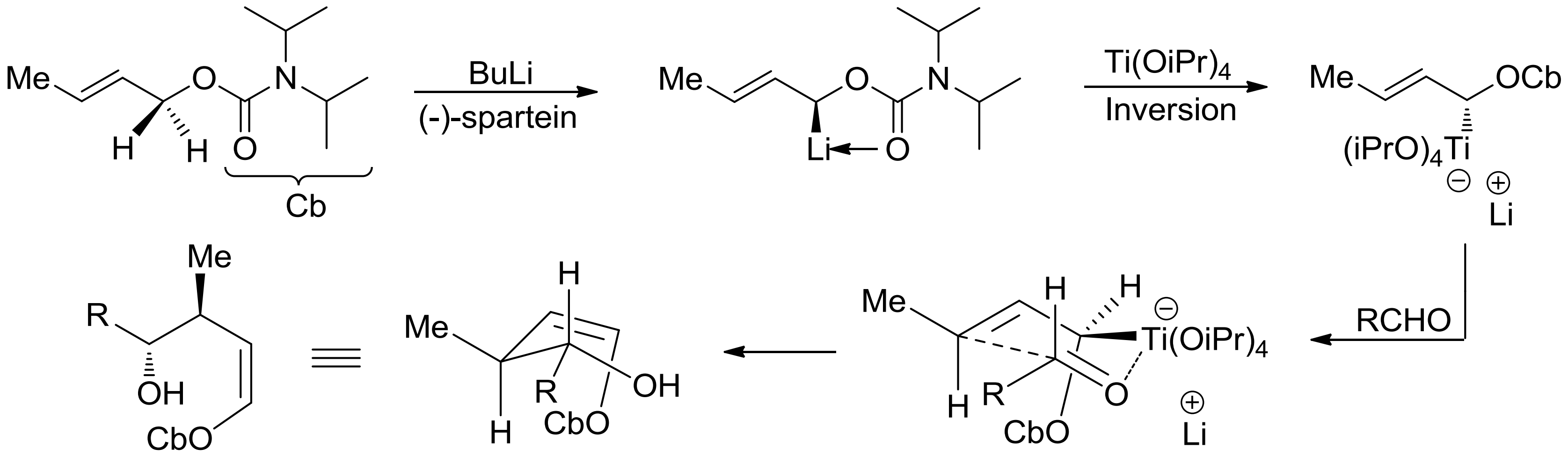
A. Frischmuth, H. Zipse, N. Barl, H. Mayr, P. Knochel *Angew.Chem.Int. Ed.* **2014**, *53*, 7928

"*in situ*"-Trapping Metalations with Metal Salts in Flow Mode



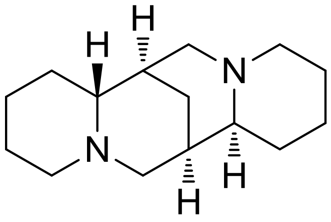
M. R. Becker, P. Knochel, *Angew.Chem.Int. Ed.* **2015**, *54, in press*

Asymmetric metalation using (*S*)-(-)-spartein

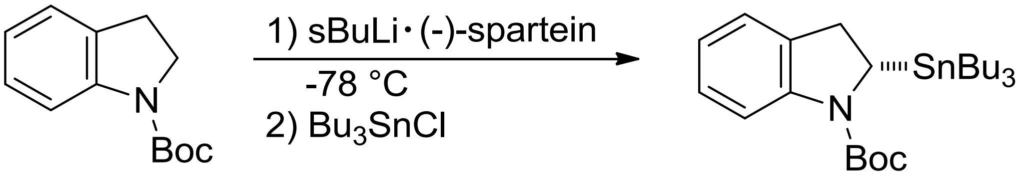


82-92% ee

D. Hoppe, et al. *Pure Appl. Chem*. **1994**, *66*, 1479.



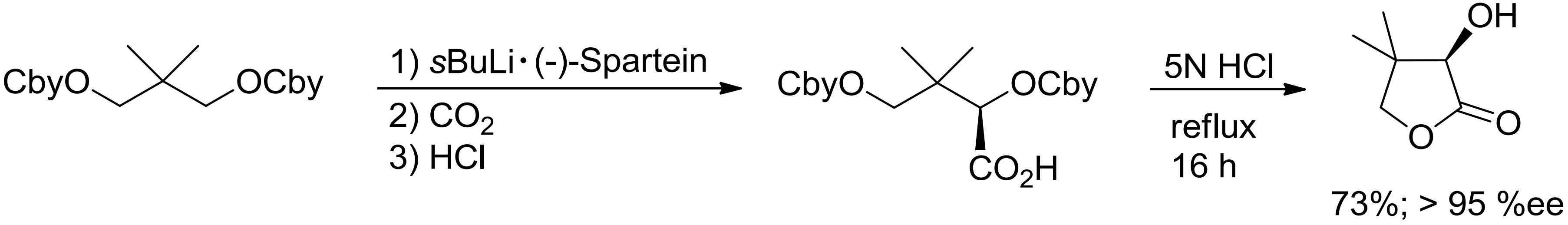
(S)-(-)-spartein

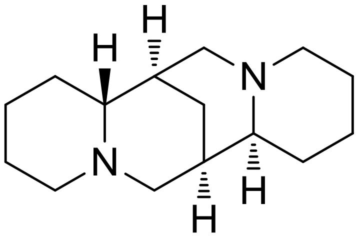


98% ee

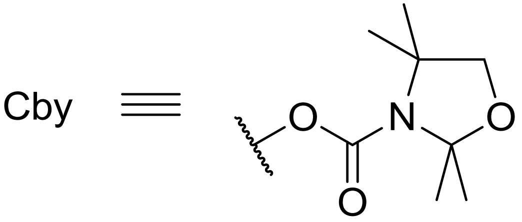
P. Beak *J. Org. Chem*. **1997**, *62*, 7679

Asymmetric metalation using (*S*)-(-)-spartein



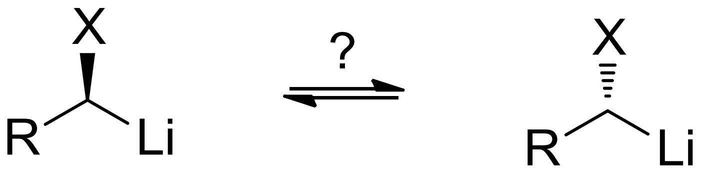


(S)-(-)-Spartein

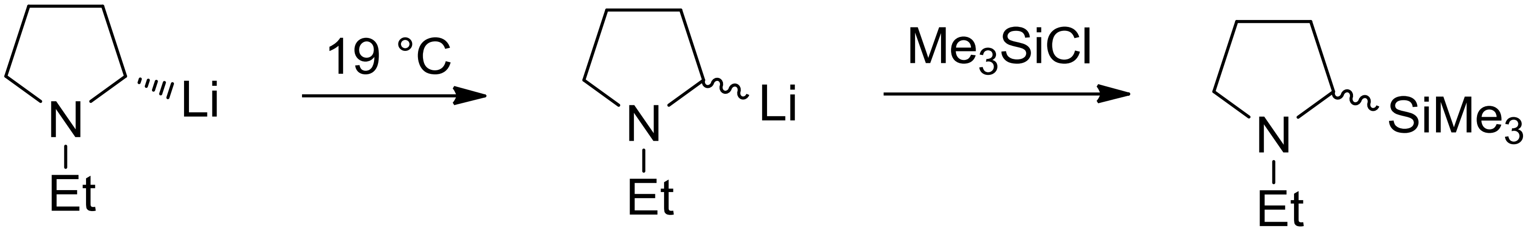


D. Hoppe *Tetrahedron Lett*. **1992**, *33*, 5327

Configurational stability

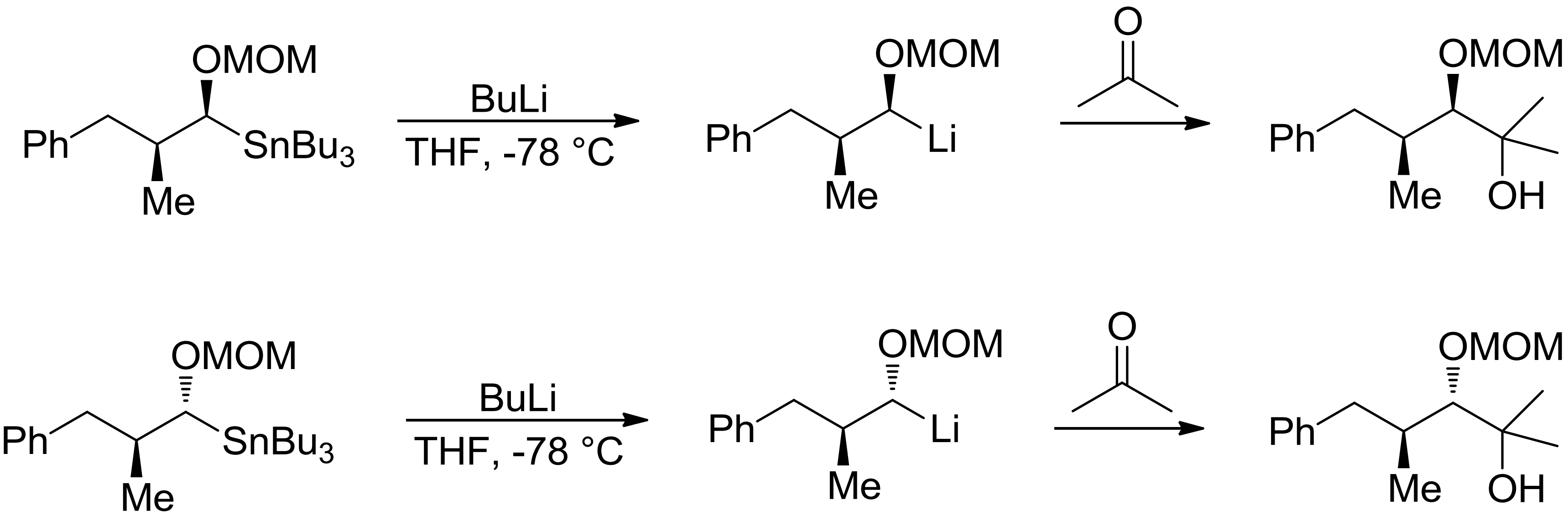


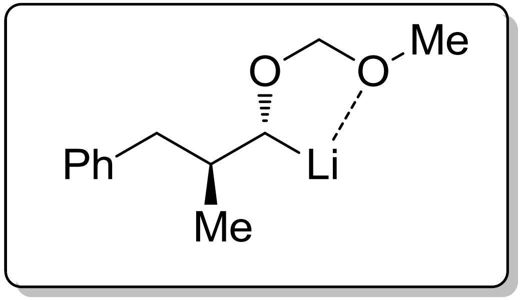
X=Br, SePh, SPh, OCH_2OMe, $OCONiPr_2$



R. E. Gawley, *J. Am. Chem. Soc*. **2005**, *127*, 449

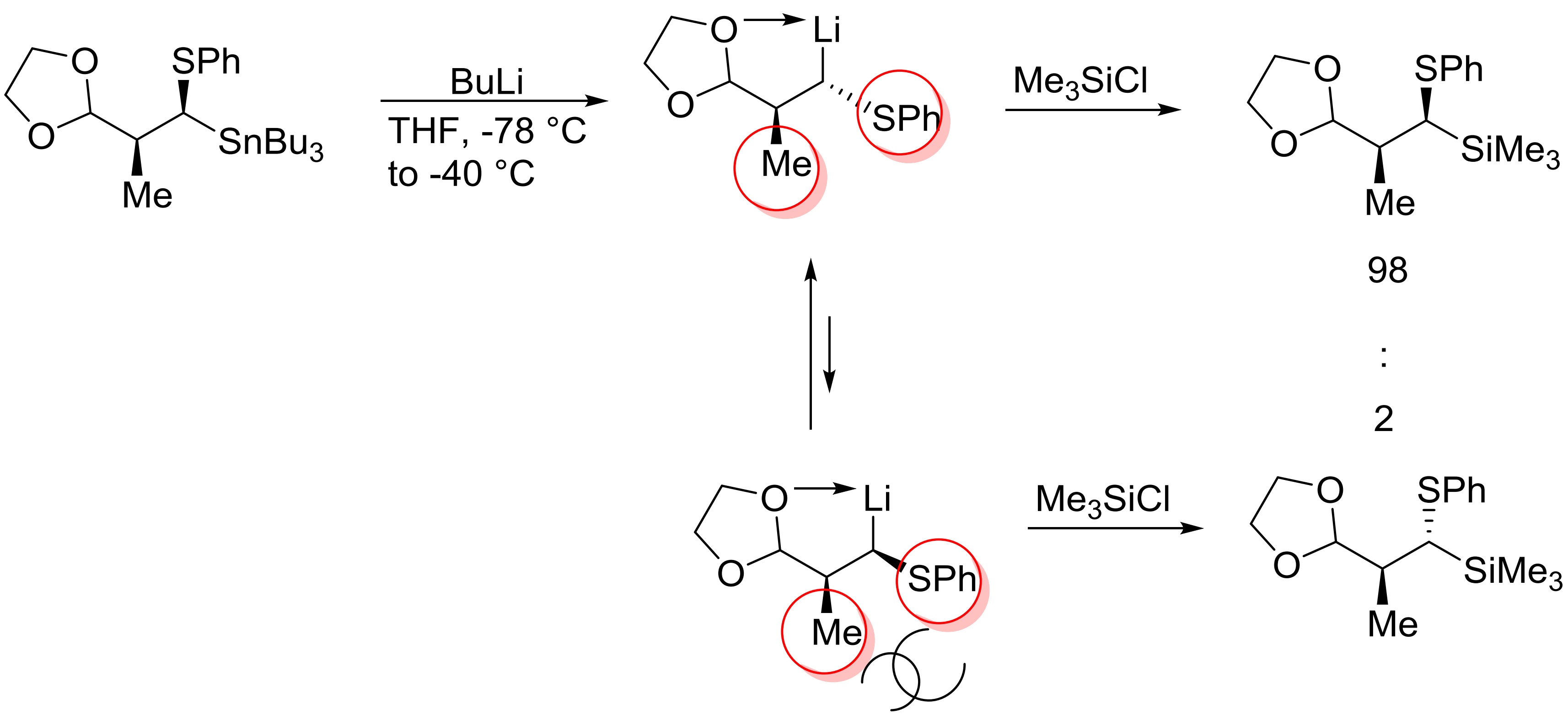
Diastereoselective transmetalation





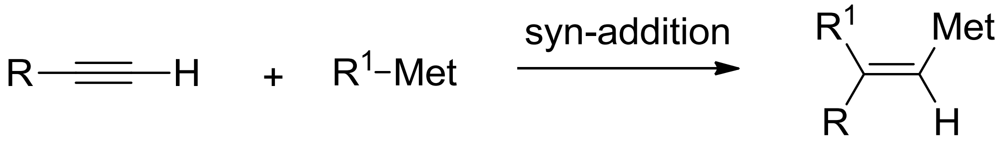
W. C. Still J. *Am. Chem. Soc*. **1980**, *102*, 1201

Diastereoselective transmetalation

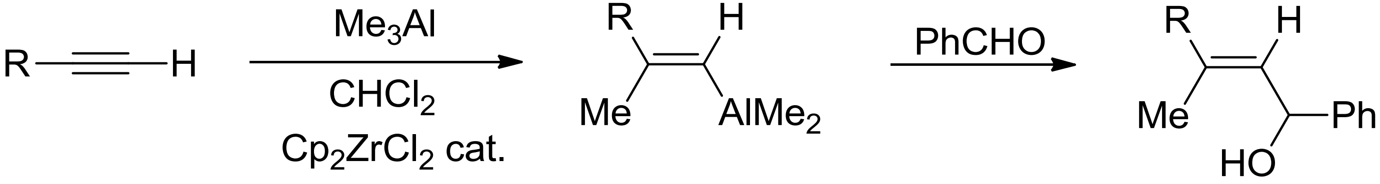


P. G. McDougal, *Tetrahedron Lett*. **1988**, *29*, 2547

Carbometalation

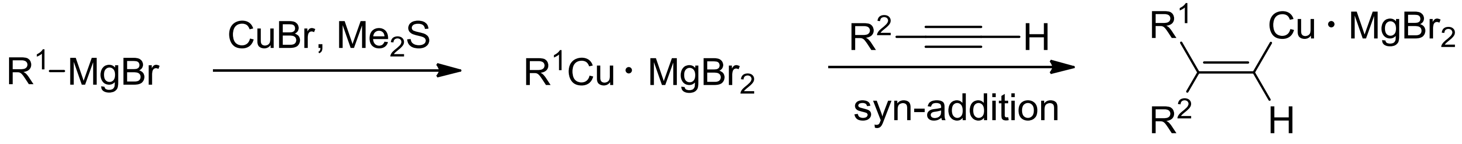


Negishi-reaction: carboalumination



79%

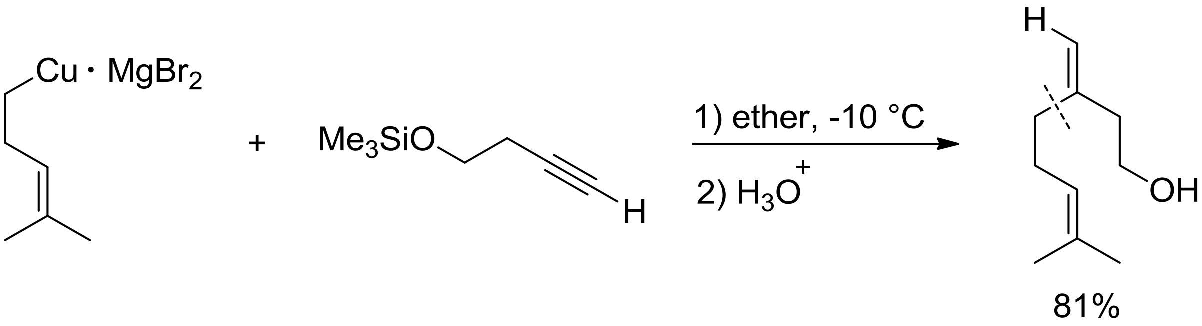
E. Negishi *J. Am. Chem. Soc*. **1976**, *98*, 6729



> 90%

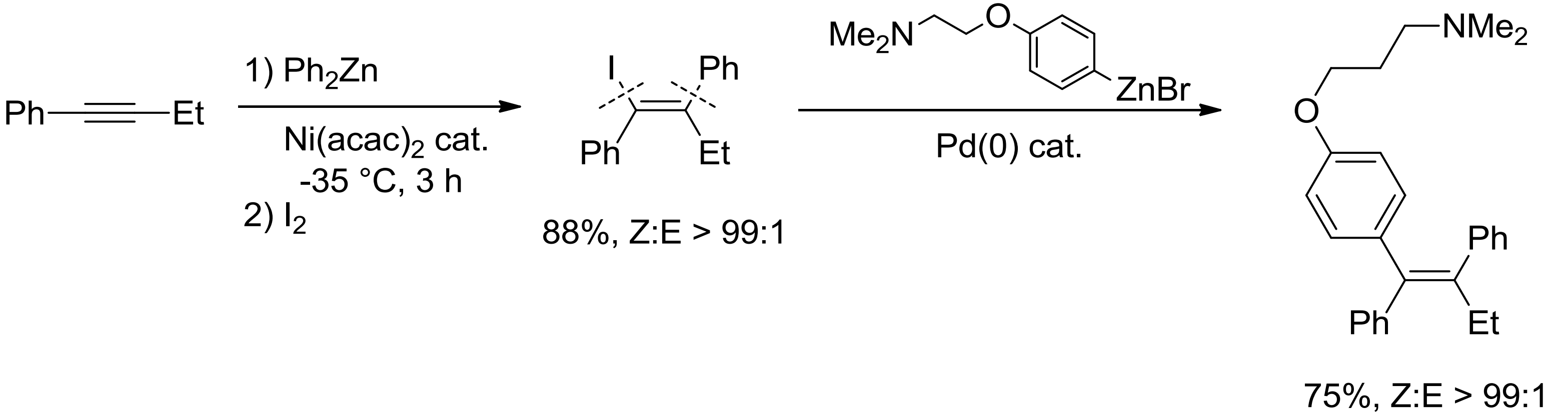
Normant-reaction: carbocupration
Review: A. Alexakis, J. F. Normant, *Synthesis* **1981**, 841.

Carbometalation



A. Alexakis, J. F. Normant, *J. Organomet. Chem*. **1975**, *96*, 471

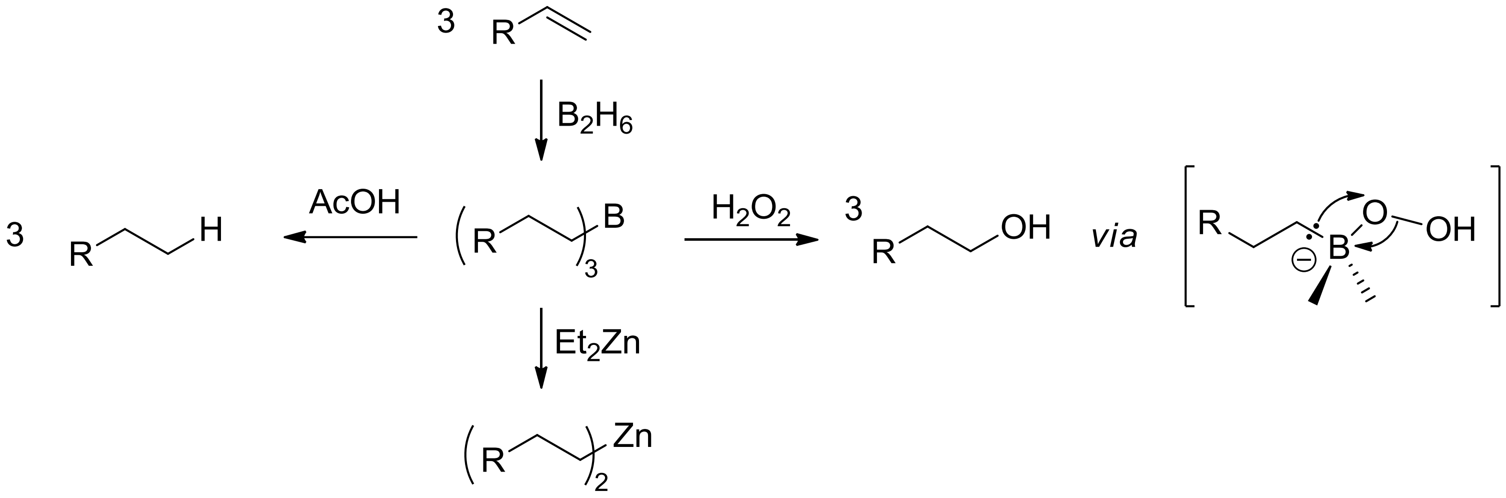
Tamoxifen-Synthesis: Carbozincation

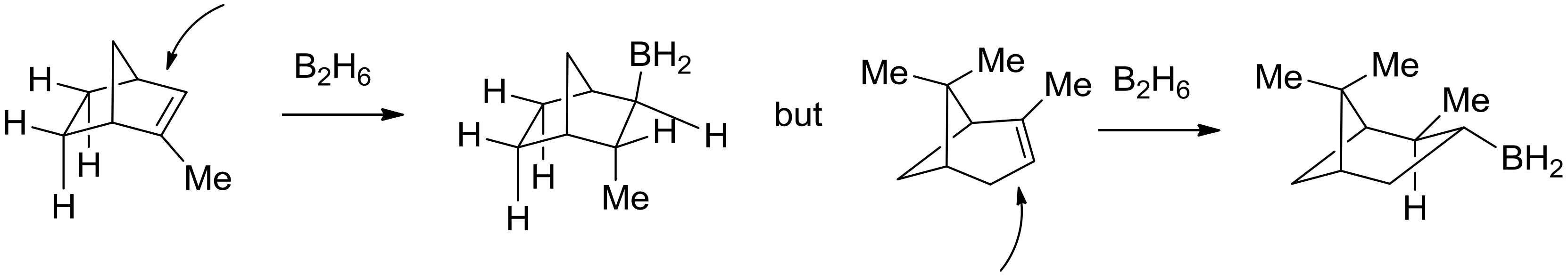


T. Stüdemann, P. Knochel *Angew. Chem*. **1997**, *109*, 132

Hydrometalation and application of organoboranes in organic chemistry

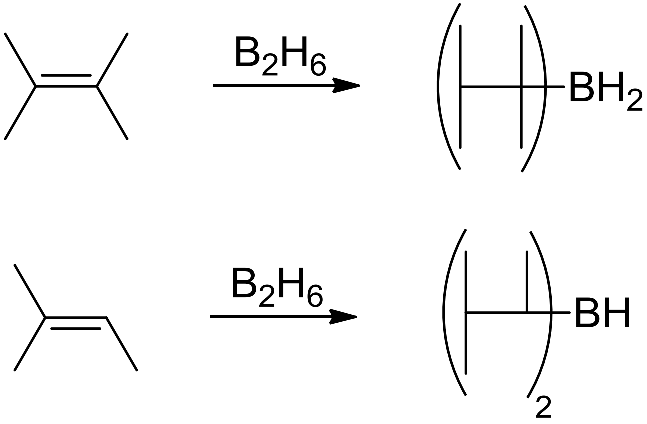
hydroboration





Hydroboration

selective hydroborating reagents



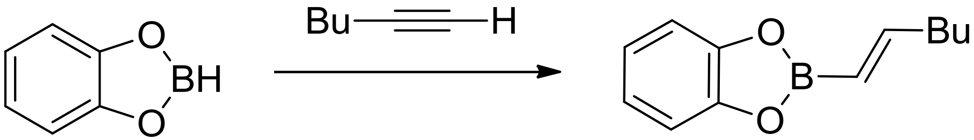
Thexylborane ThexBH$_2$

Disiamylborane Sia$_2$BH

H. C. Brown, E. Negishi *J. Am. Chem. Soc*. **1975**, *97*, 2799

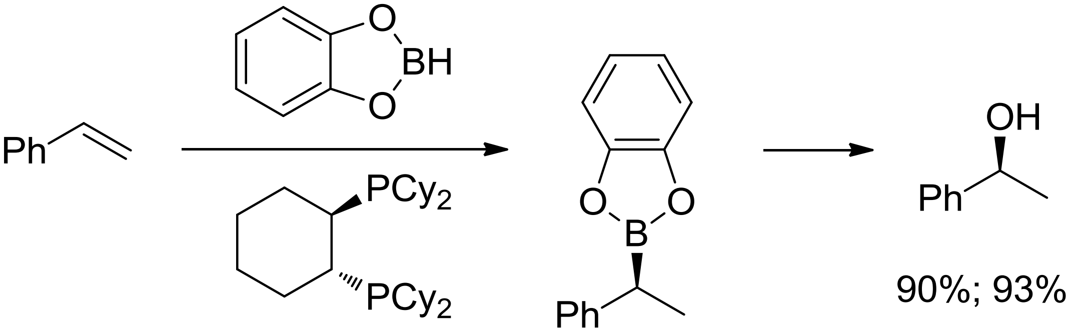
Hydroboration

catecholborane



>90%

A. Arase, et al., *Synth. Comm*. **1995**, *25*, 1957.



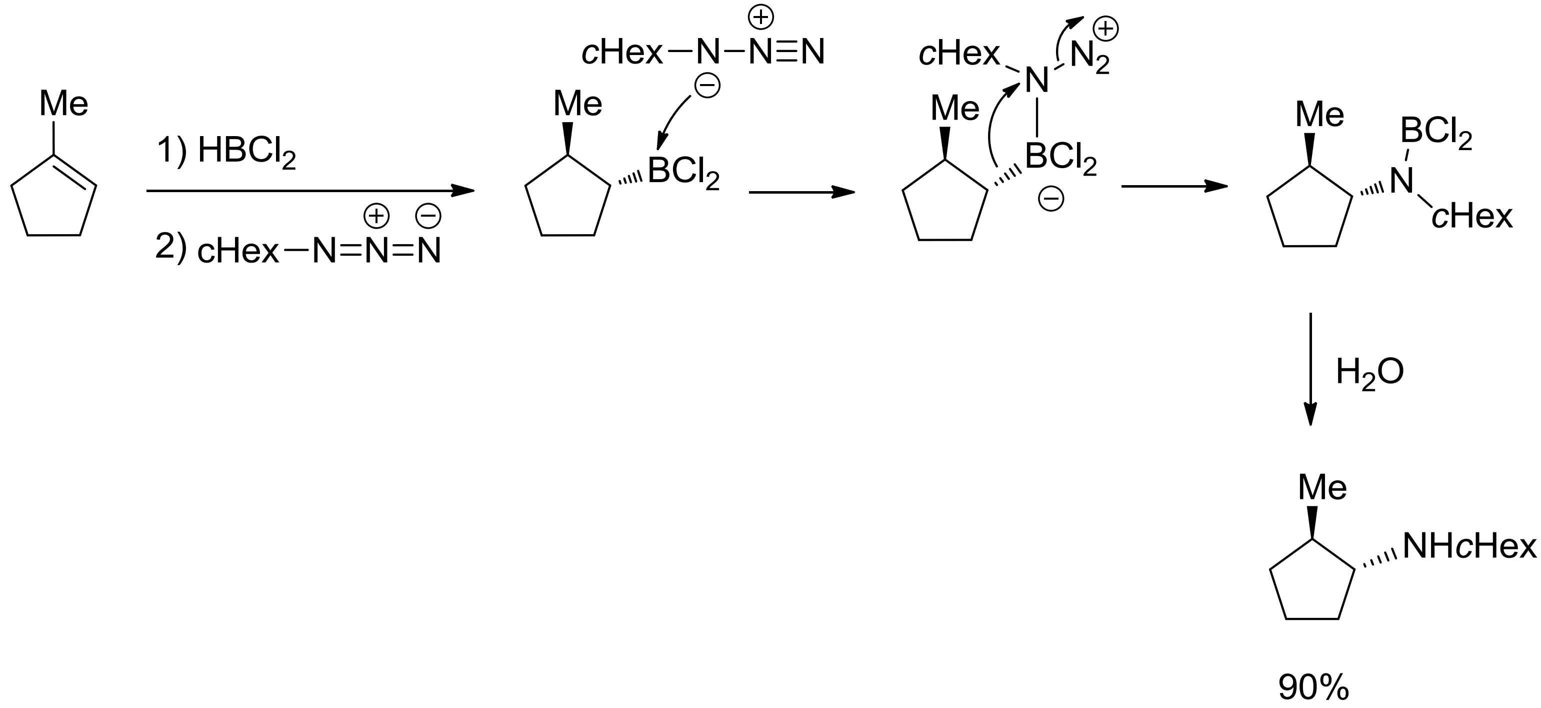
Rh$^+$ cat., -35 °C

90%; 93% ee

S. Demay, M. Lotz, P. Knochel *Tetrahedron: Asymmetry* **2001**, *12*, 909

Hydroboration

amination

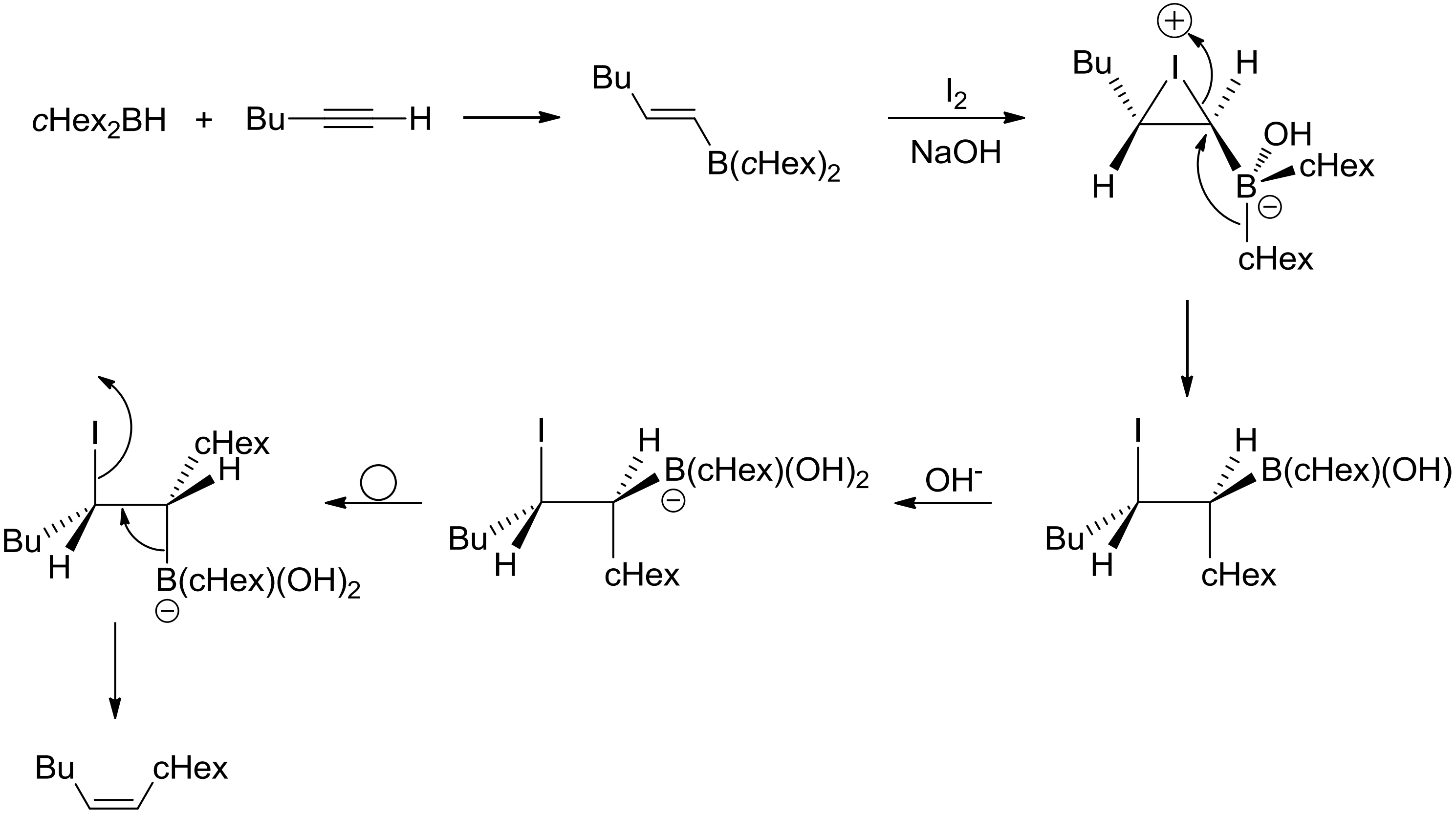


H. C. Brown, et al. *Tetrahedron* **1987**, *43*, 4079

Hydroboration

stereoselective synthesis of olefins

Z-olefins

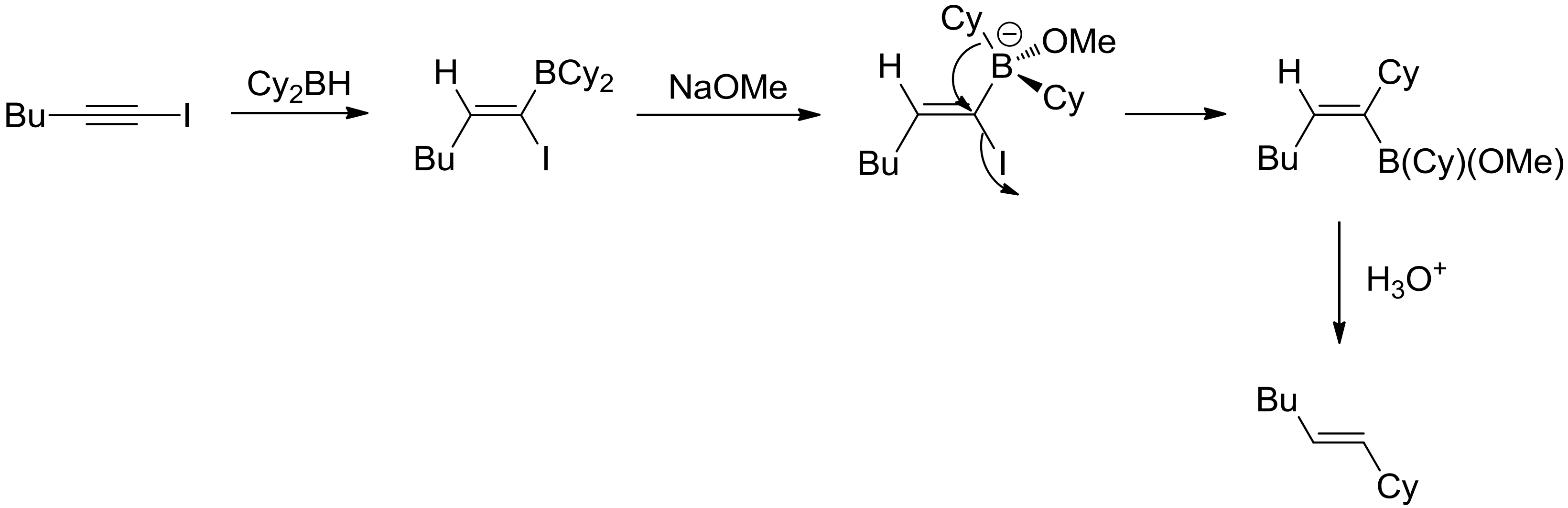


G. Zweifel, et al. *J. Am. Chem. Soc*. **1972**, *94*, 6560.

Hydroboration

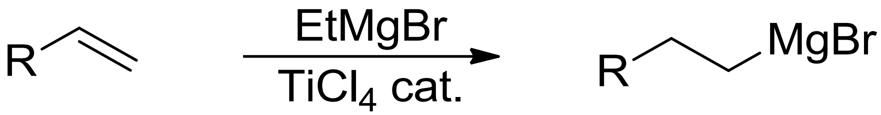
stereoselective synthesis of olefins

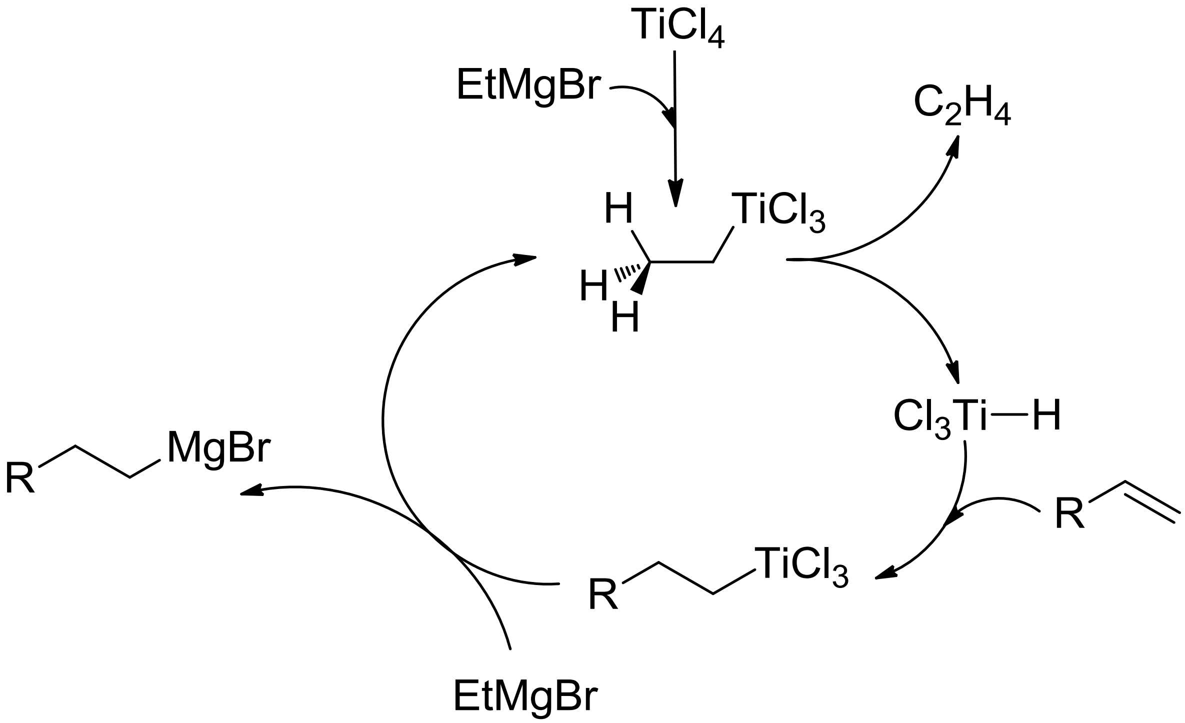
E-olefins



H. C. Brown, et al *J. Org. Chem*. **1989**, *54*, 6064.

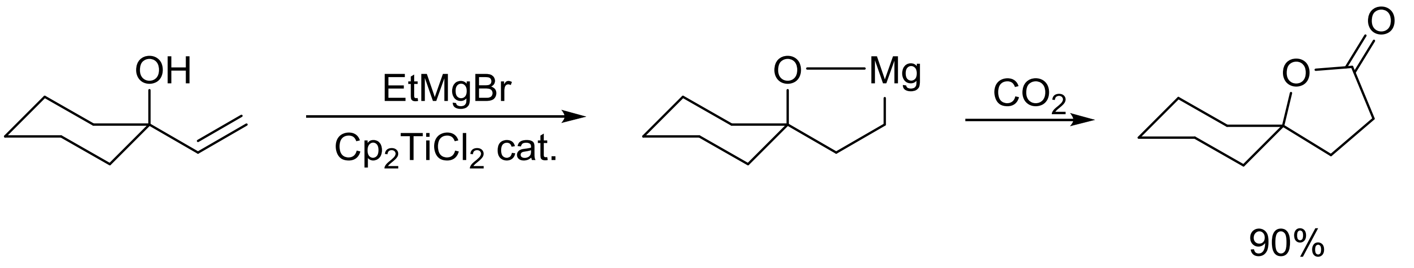
Hydromagnesiation

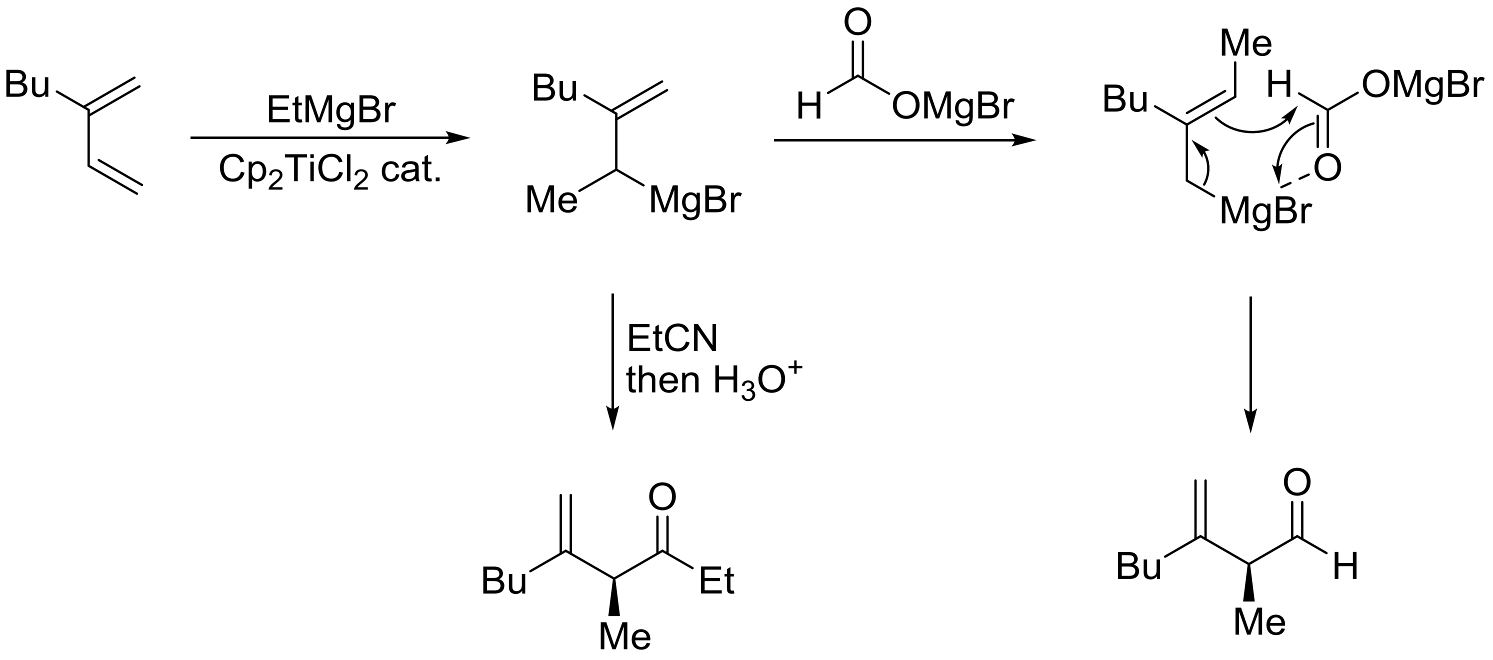




F. Sato, *Chem. Rev*. **2000**, *100*, 2835; *Synlett* **2000**, 753

Hydromagnesiation

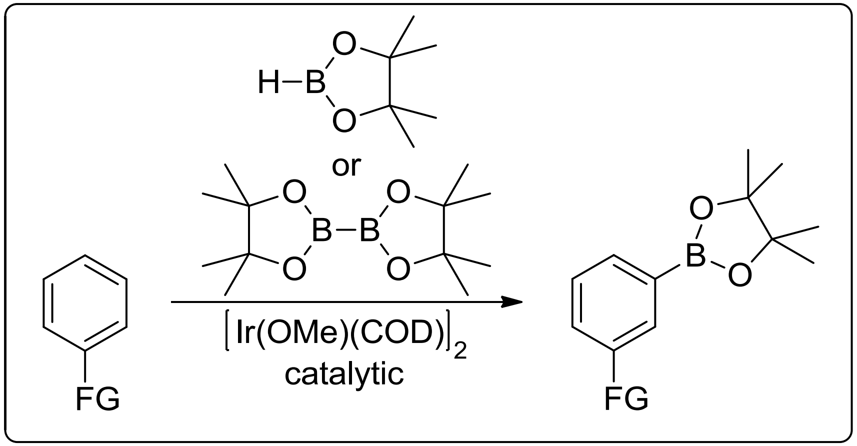


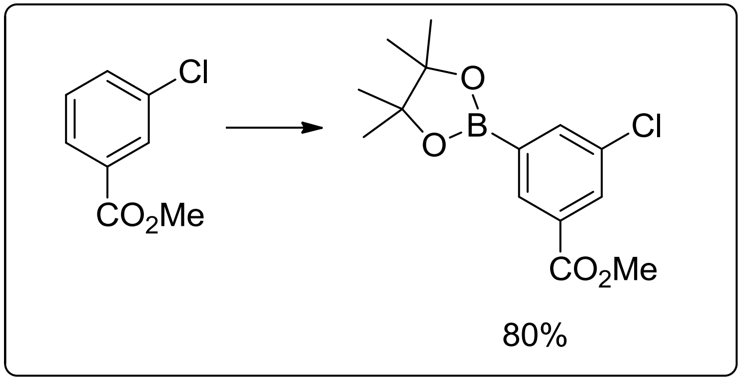


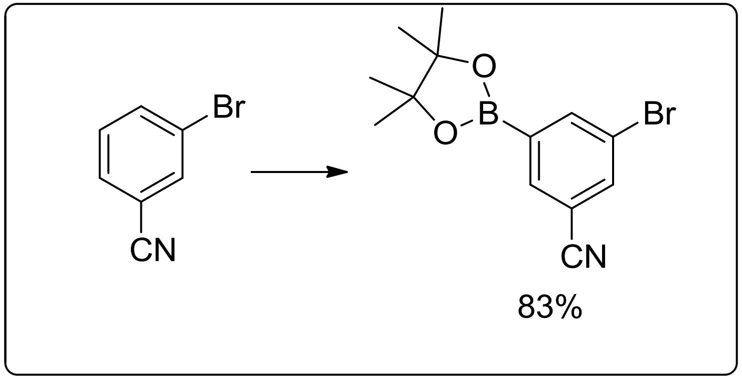
F. Sato, *Chem. Rev*. **2000**, *100*, 2835

Synthesis of aryl boronic acids

transition-metal catalyzed synthesis of aryl boronic acids

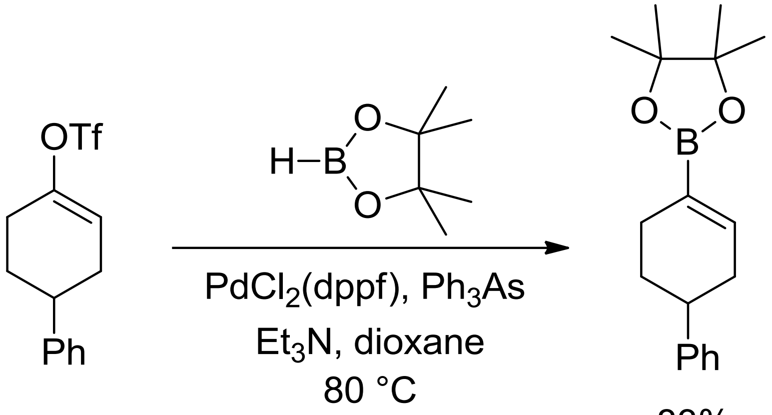






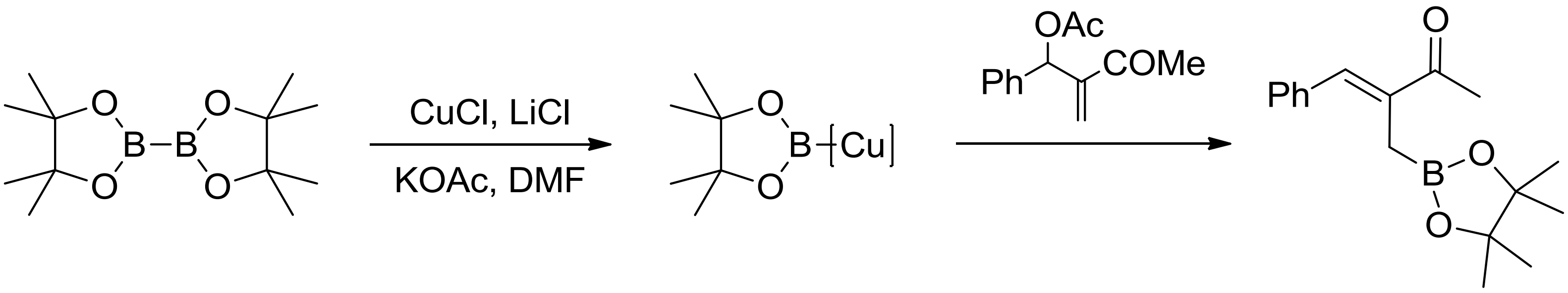
J. F. Hartwig, N. Miyaura, *Chem. Comm*. **2003**, 2924;
J. Am. Chem. Soc. **2002**, *124*, 390; *Angew. Chem. Int. Ed*. **2002**, *45*, 3056

Synthesis of aryl boronic acids



83%

M. Murata *Tetrahedron Lett*. **2000**, *41*, 5877
M. Murata *Synth. Comm*. **2002**, *32*, 2513

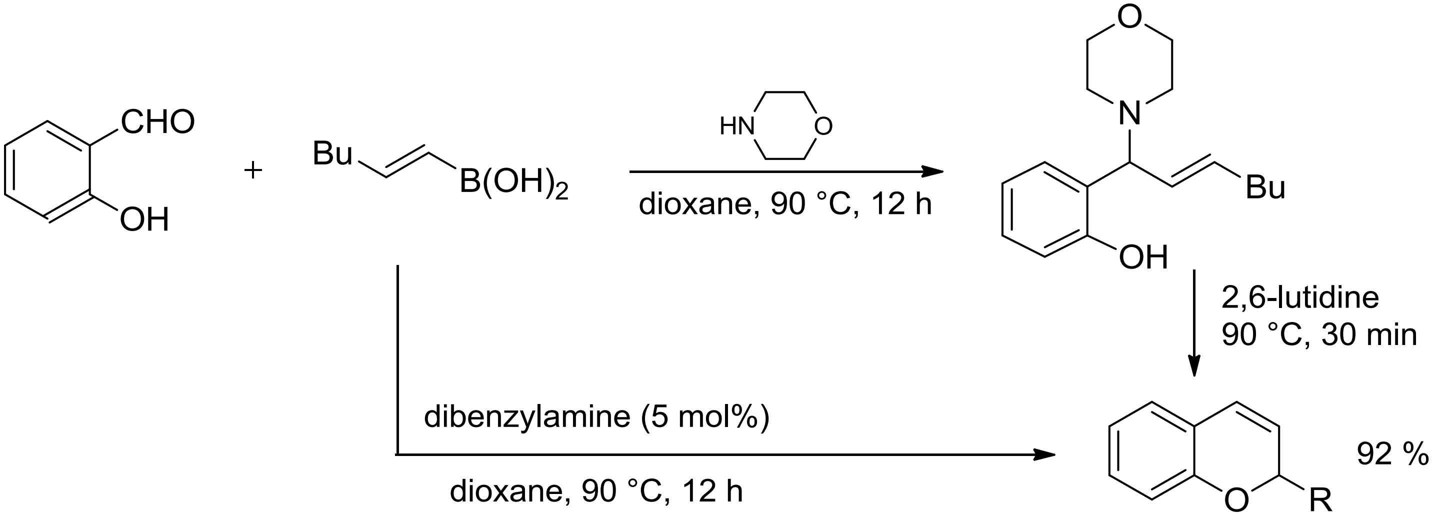


92%

P. V. Ramachandran *Org. Lett*. **2004**, *6*, 481

Reactivity of unsaturated boronic derivatives

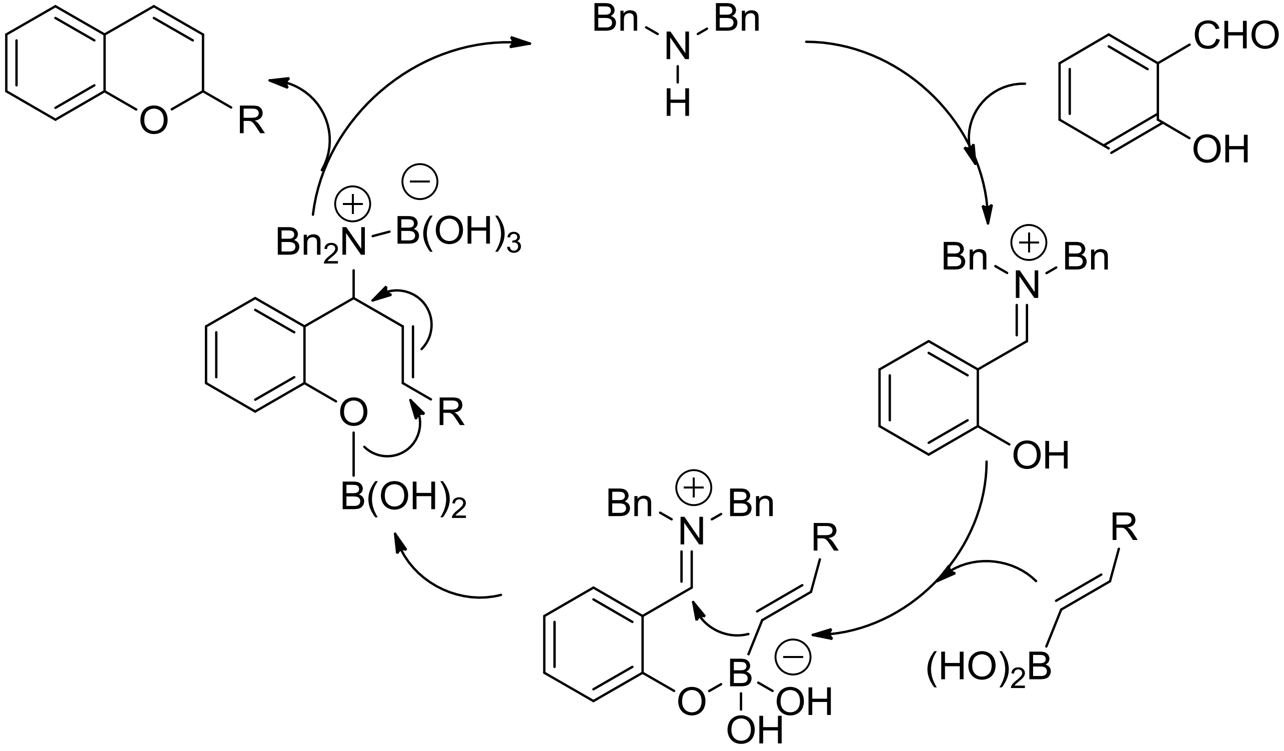
the Petasis-reaction - a short synthesis to 2H-chromenes



Reactivity of unsaturated boronic derivatives

The Petasis-reaction

mechanism



M. G. Finn, *Org. Lett*. **2000**, *2*, 4063

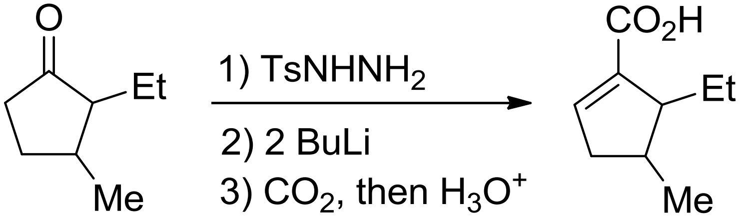
ÜBUNG

1. Problem set

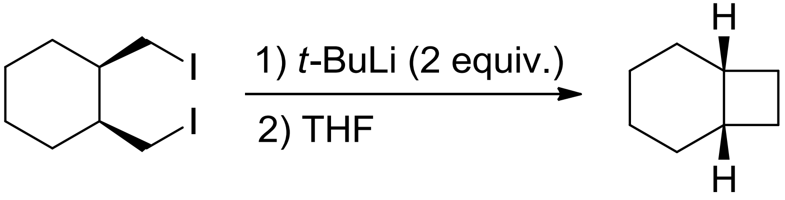
First Problem Set for OC IV

1) Give a mechanism for the following reactions:

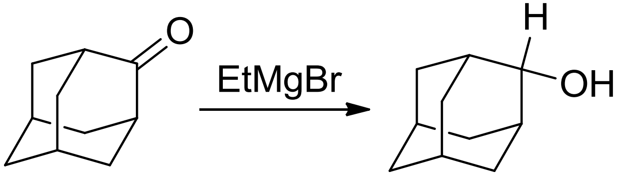
a)



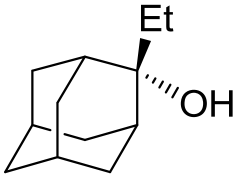
b)



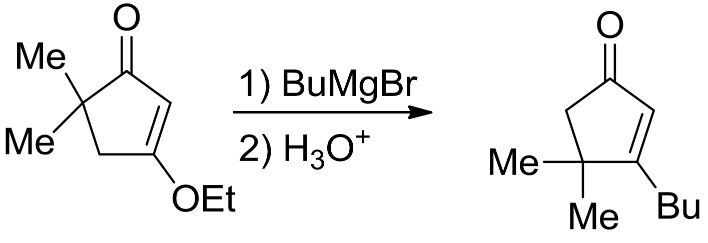
c)



How would you prepare



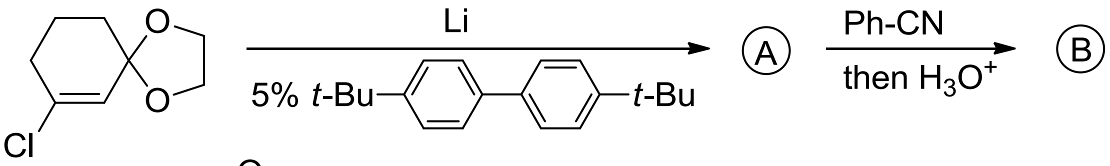
d)



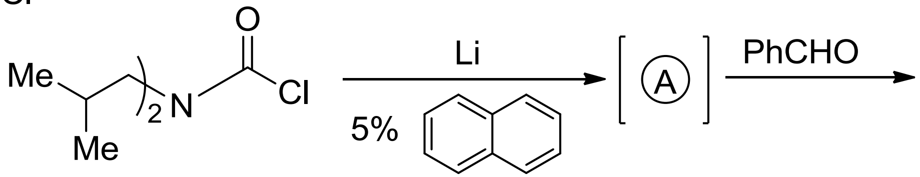
First Problem Set for OC IV

2) Give the following reaction products:

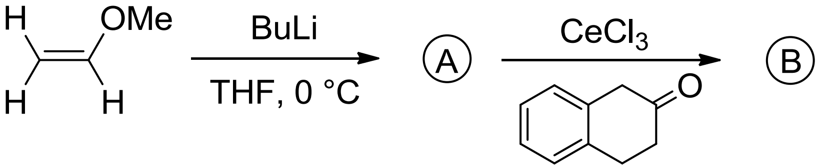
a)



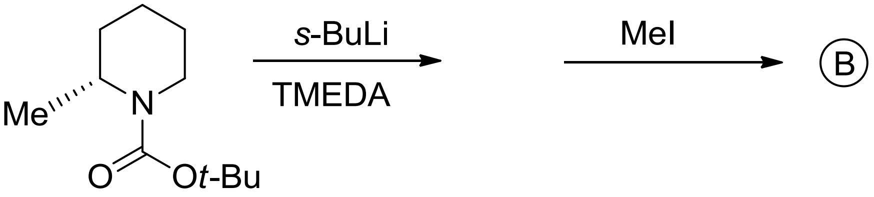
b)



c)

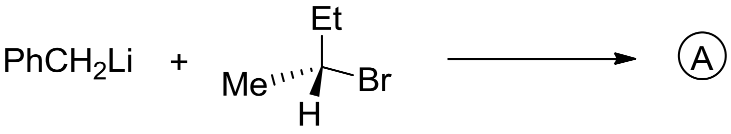


d)

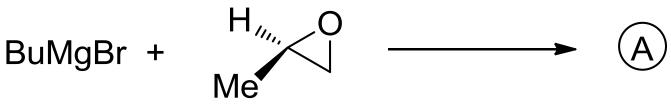


stereochemie?

e)

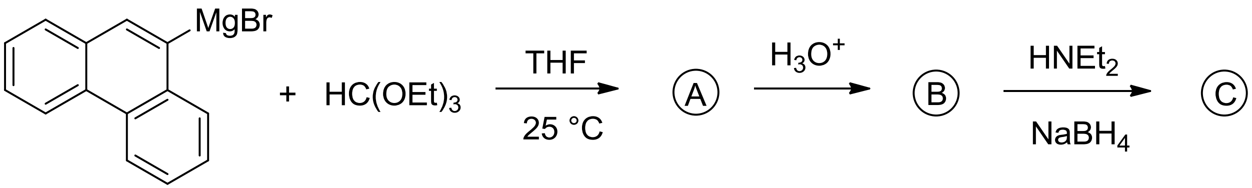


f)

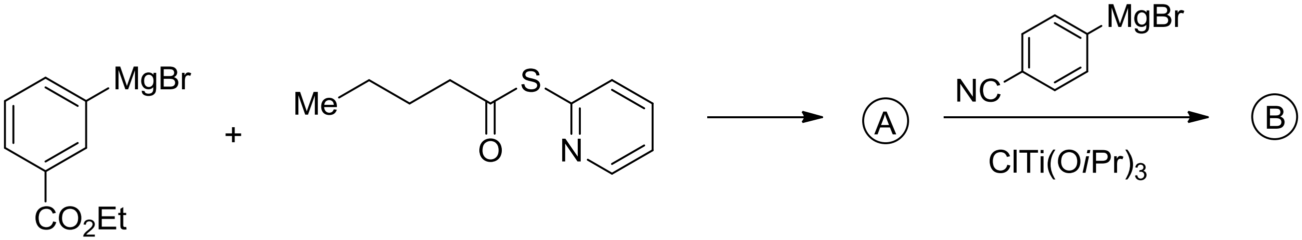


First Problem Set for OC IV

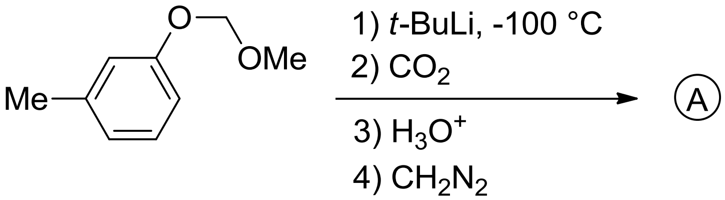
g)



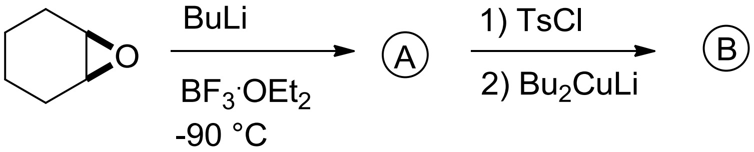
h)



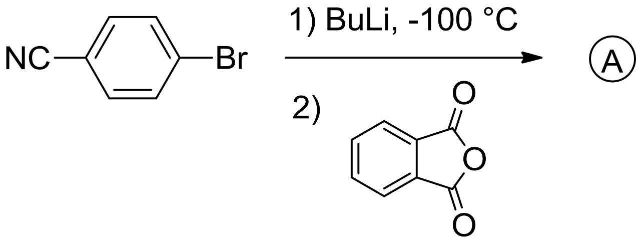
i)



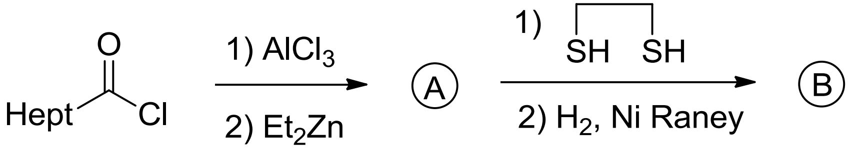
j)



k)

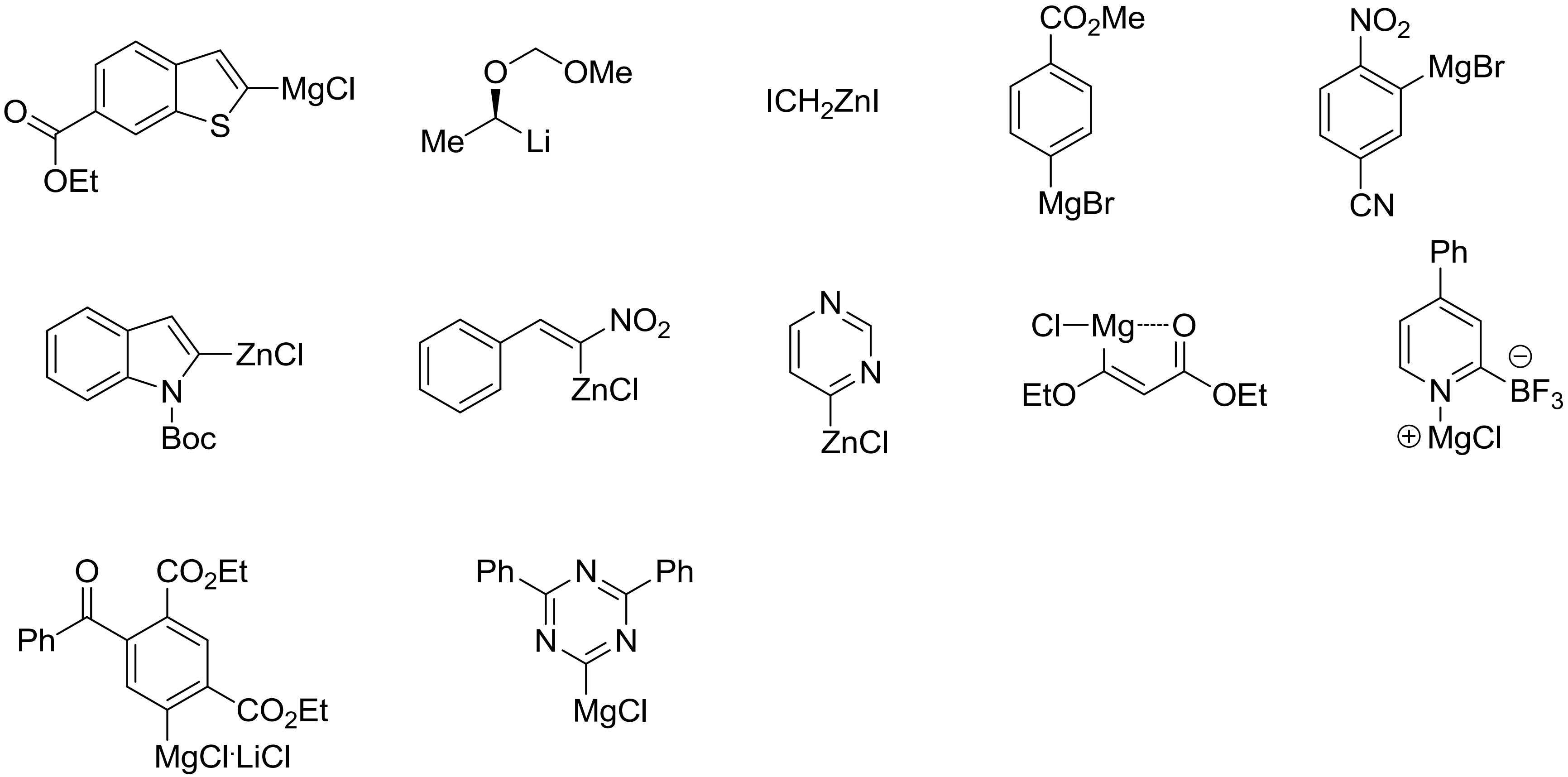


l)



First Problem Set for OC IV

3. How you would prepare following organometallics:

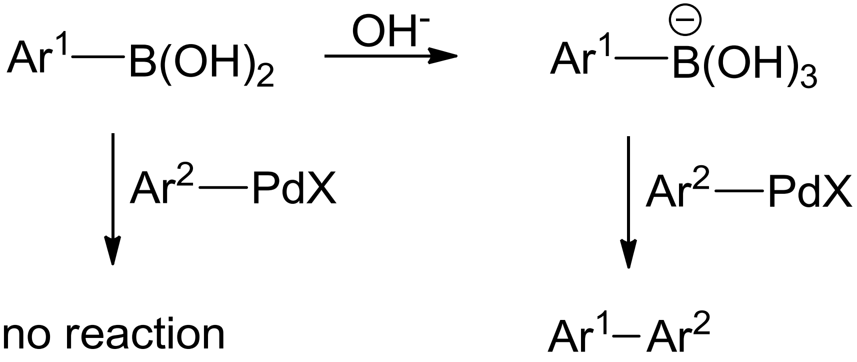


The Suzuki cross-coupling reaction

$$Ar^1{-}B(OH)_2 + Ar^2{-}X \xrightarrow[\text{base}]{\text{Pd(0) cat.}} Ar^1{-}Ar^2$$

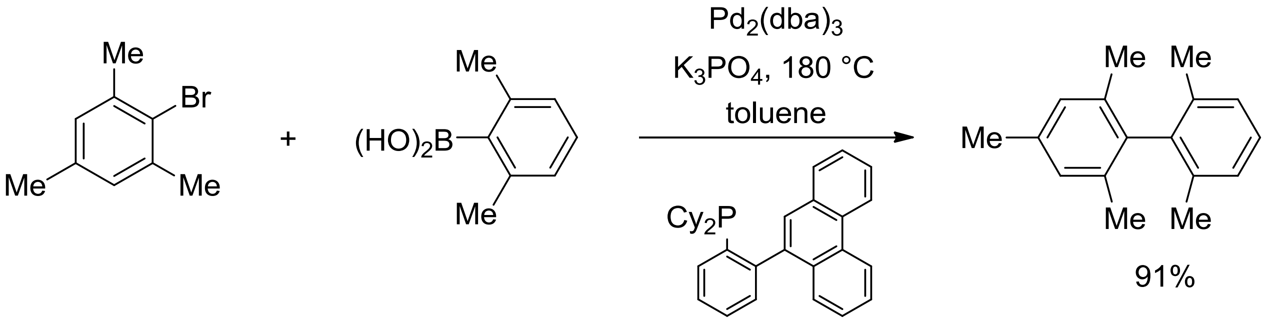
N. Miyaura, A. Suzuki *Chem. Rev*. **1995**, *95*, 2457
Cross-Coupling Reactions. A practical guide. N. Miyaura (Ed.), Springer, **2002**

Key step

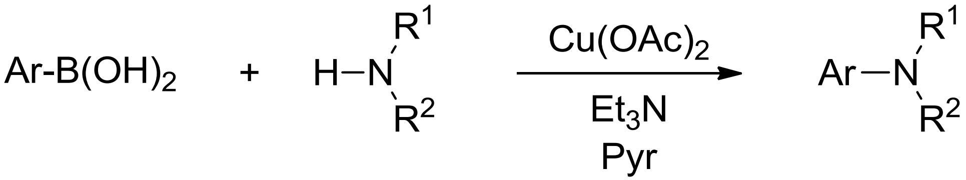


S. Buchwald, *J. Am. Chem. Soc*. **2002**, *124*, 1162
C. Amatore, A. Jutand, G. Le Duc *Chem. Eur. J*. **2011**, *17*, 2492
B. P. Carrow, J. F. Hartwig *J. Am. Chem. Soc*. **2011**, *133*, 2116

The Suzuki cross-coupling reaction

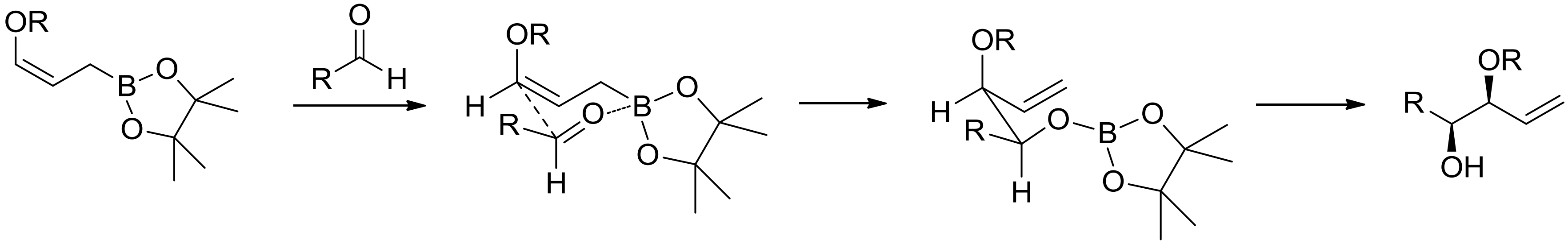


R. E. Sammelson, M. J. Kurth, *Chem. Rev*. **2001**, *101*, 137



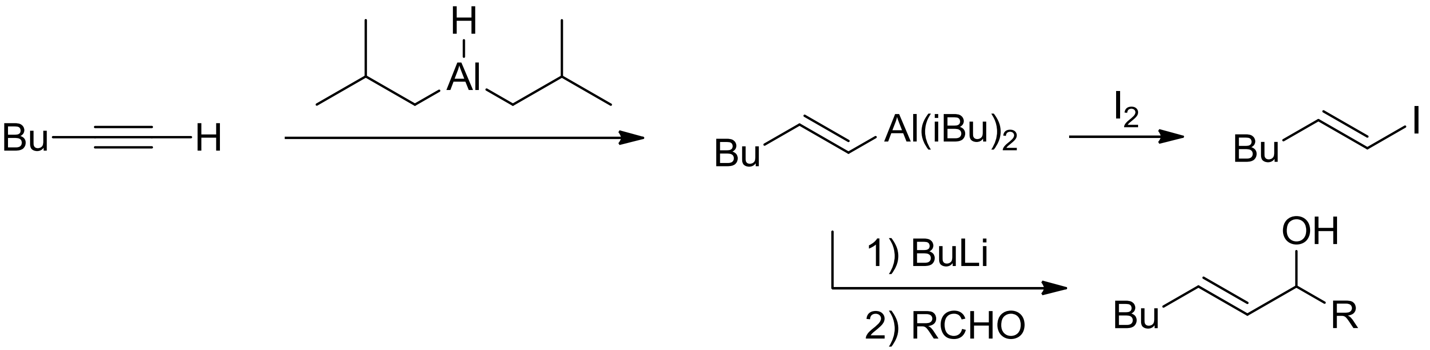
D. A. Evans, *Tetrahedron Lett*. **1998**, *39*, 2937
S. Ley, *Angew. Chem. Int. Ed*. **2003**, *42*, 5400

Chemistry of allyl boranes



R. W. Hoffmann, *Tetrahedron* **1984**, *40*, 2219

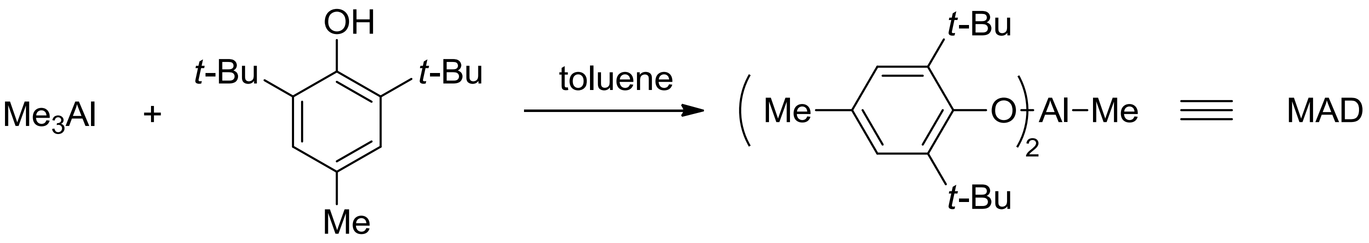
Hydroalumination

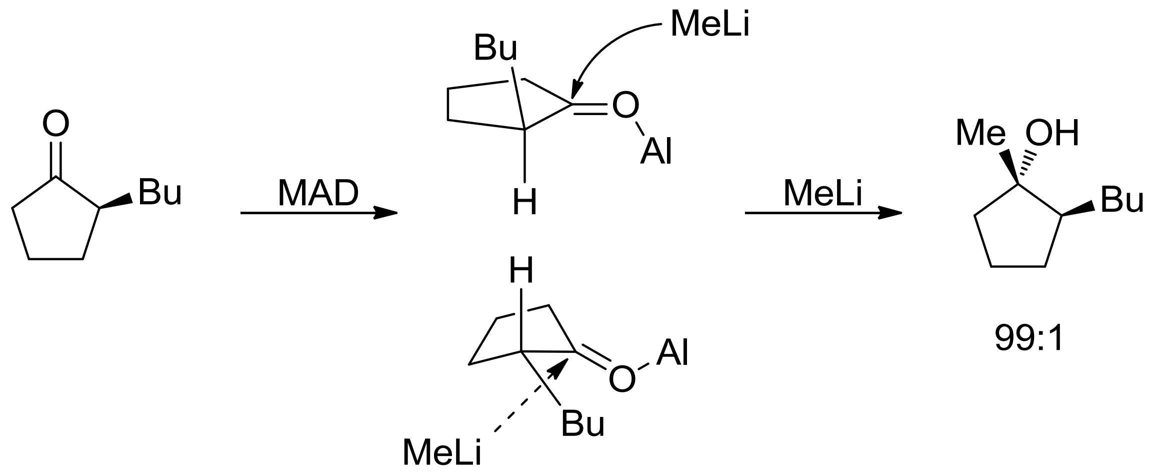


G. Zweifel, *Org. React*. **1984**, *32*, 375

Hydroalumination

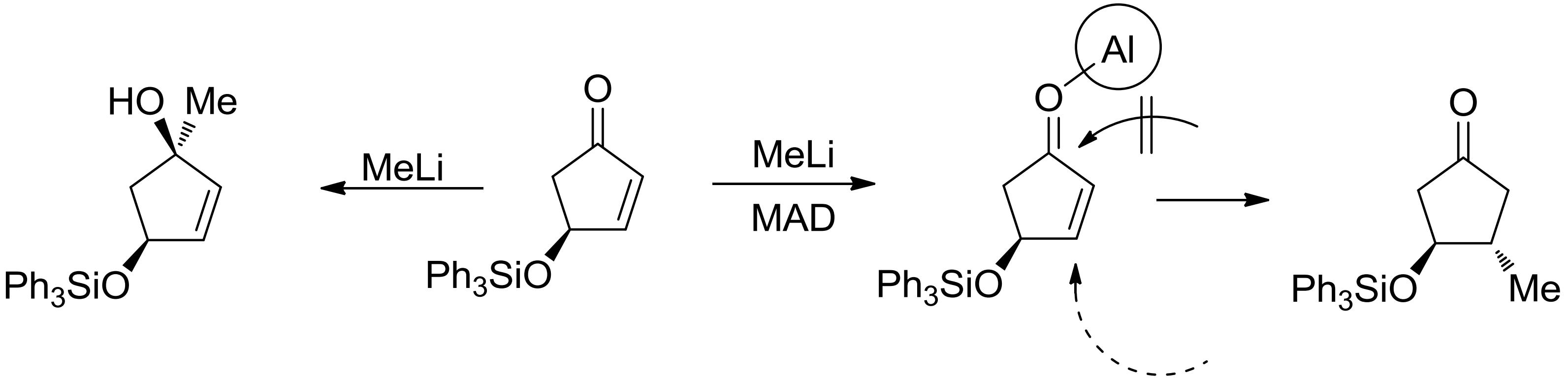
Special Al-reagents

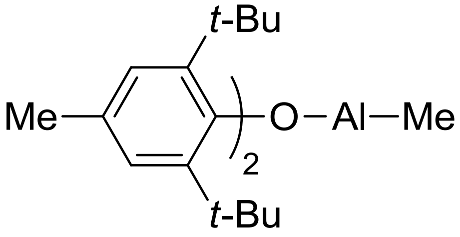




H. Yamamoto *J. Am. Chem. Soc*. **1988**, *110*, 3588
H. Yamamoto *Chem. Comm*. **1997**, 1585

Hydroalumination





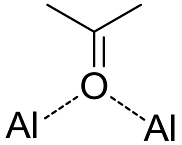
MAD

K. Maruoka, H. Yamamoto, Kagaku, Zokan (Kyoto, Japan) **1988**, *115*, 127
S. Nagahara, K. Maruoka, H. Yamamoto, *Bull Chem Soc*. **1993**, *66*, 3783

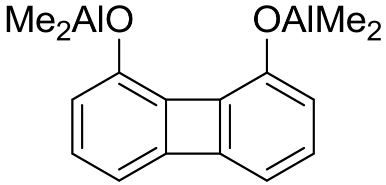
Hydroalumination

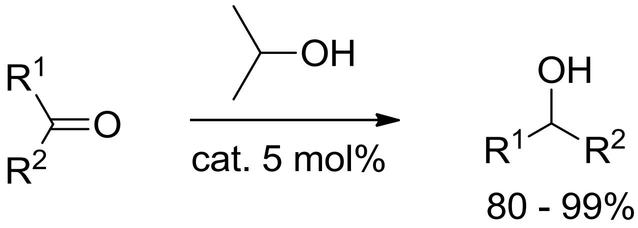
Verley-Meerwein-Ponndorf reduction

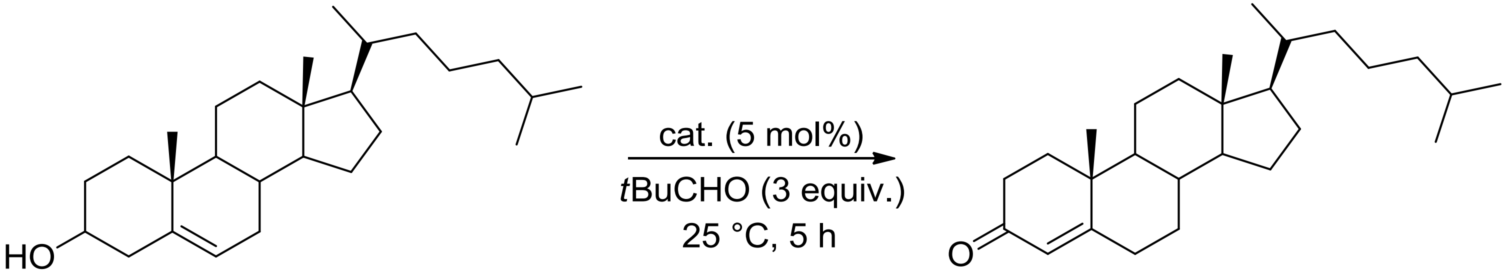
activating a carbonyl group twice



is possible using

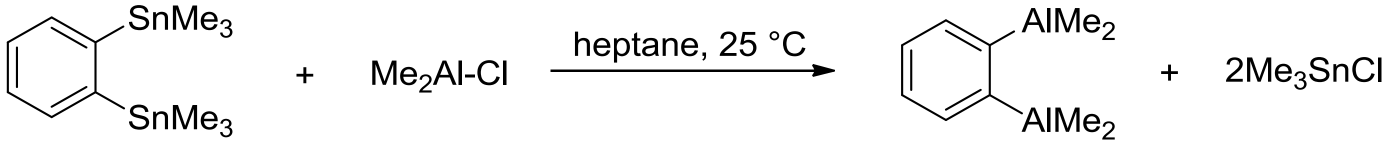






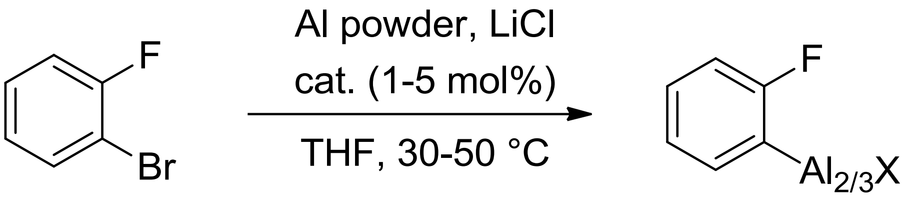
K. Maruoka *Angew. Chem*. **1998**, *110*, 2524

Other preparation of aluminium compounds



K. Dimroth, *Angew. Chem. Int. Ed*. **1964**, *3*, 385

Direct synthesis of organoaluminium reagents



cat. = $InCl_3$, $BiCl_3$, $PbCl_2$, $TiCl_4$

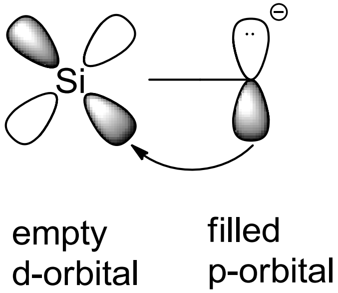
T. Blümke, Y.-H. Chen, Z. Peng, *Nature Chem*. **2010**, *2*, 313

The organic chemistry of main-group organometallics

Silicium

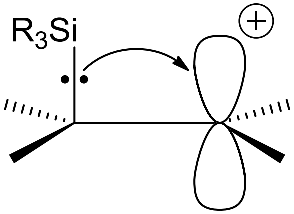
The effect of a Me_3Si-substituent:

1) inductive effect: weak donor-effect
2) retrodonation of π-electrons (d-p bond)



stabilization of carbanions in α-position

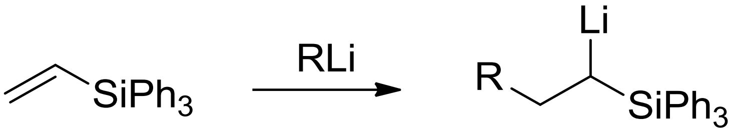
3) hyperconjugation: interaction of σ-framework with the π-system



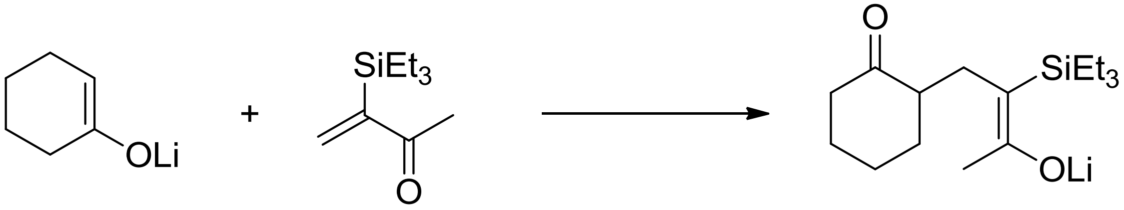
stabilization of a cation in β-position

Silicium

Applications:



low yields

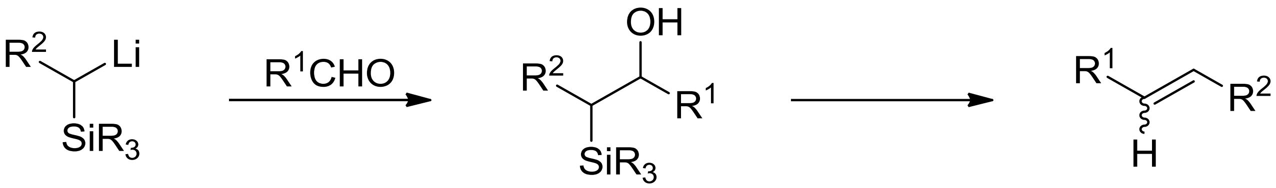


high yield: stabilized lithium enolate
(no polymerization)

G. Stork *J. Am. Chem. Soc*. **1973**, *95*, 6152; **1974**, *96*, 6181

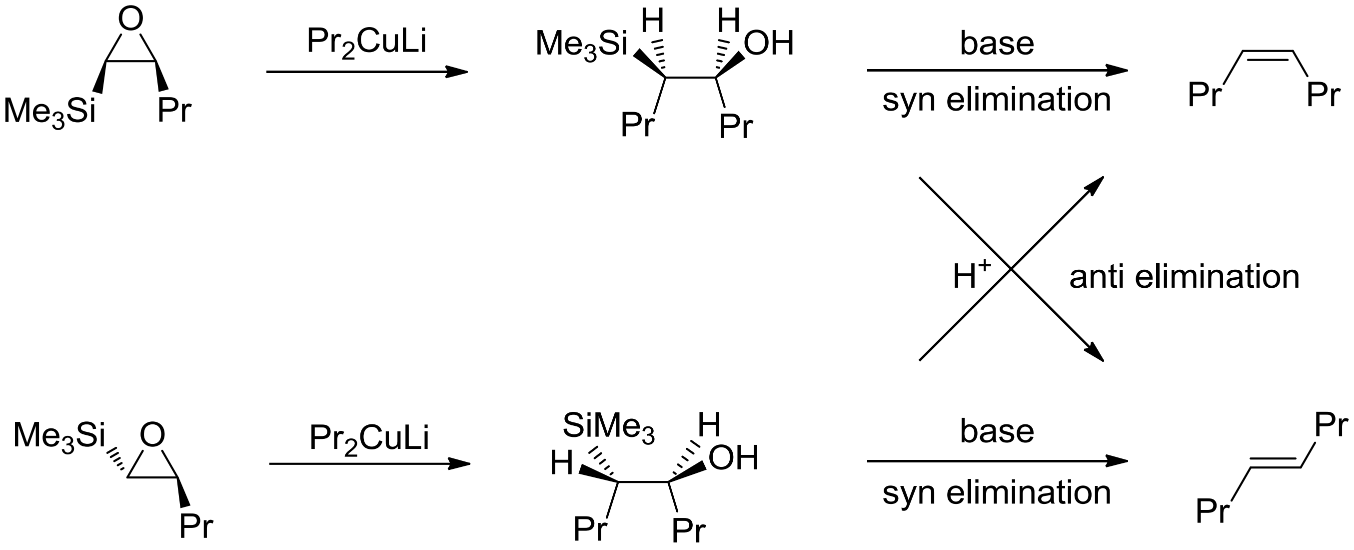
Silicium

Peterson olefination



D. J. Ager *Synthesis* **1984**, 384

Stereochemistry of the *Peterson*-elimination

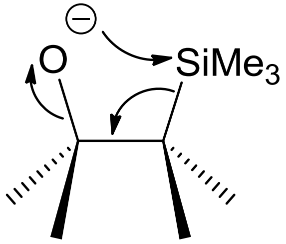


P. F. Hudrlik, D. Peterson, R. J. Rona *J. Org. Chem*. **1975**, *40*, 2263

Silicium

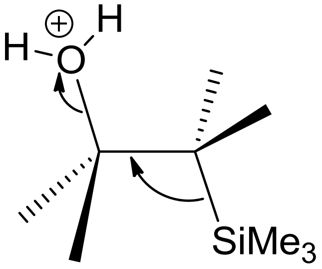
key steps:

basic media



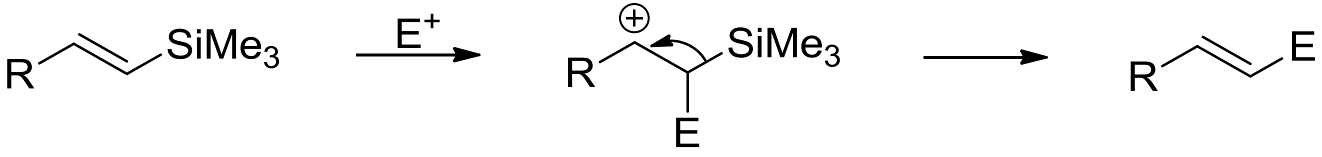
syn elimination

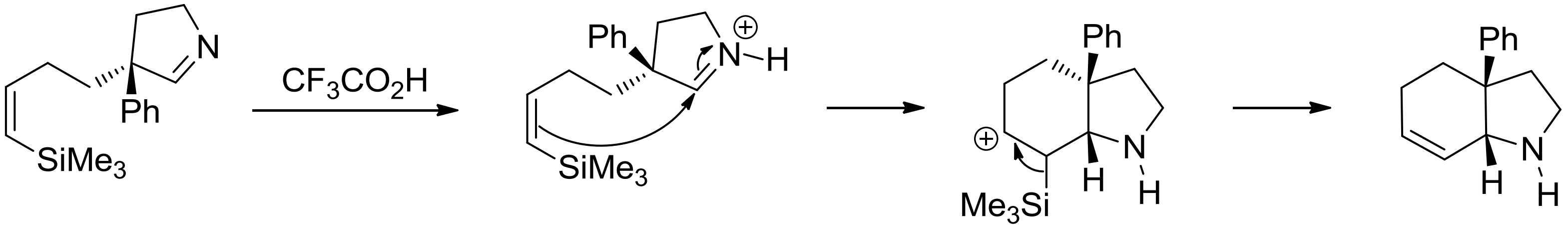
acidic media



anti elimination

Reactivity of alkenylsilanes

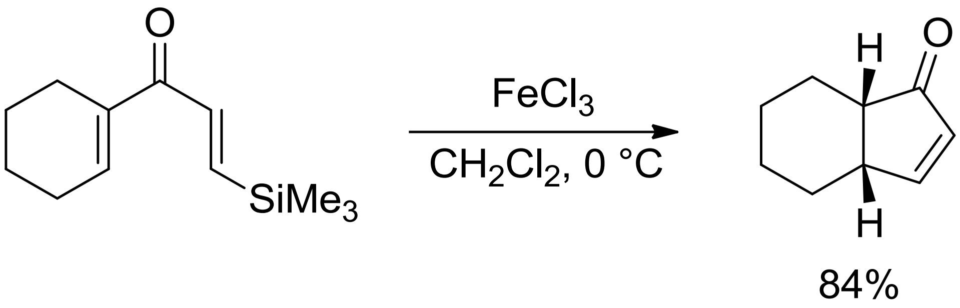




L. E. Overman, *Tetrahedron Lett*. **1984**, *25*, 5739

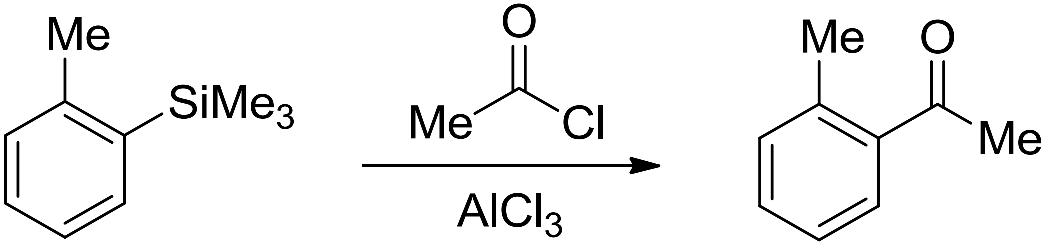
Reactivity of alkenylsilanes

Sila-Nazarov-reaction



S. E. Denmark *J. Am. Chem. Soc*. **1982**, *104*, 2642

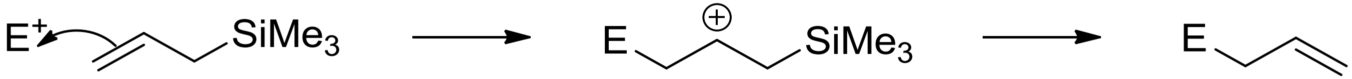
Aromatic ipso-substitution



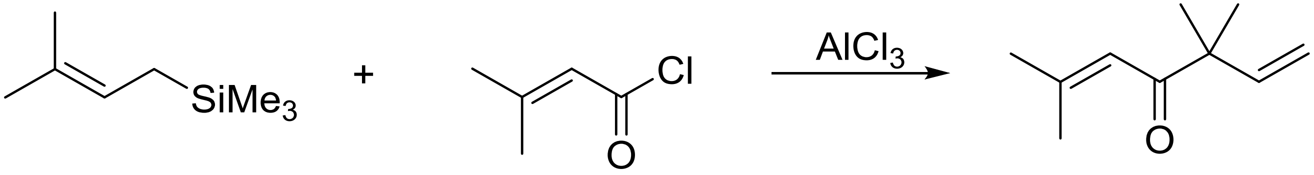
The reaction with $ArSnMe_3$ is 10^4 time faster

Allylic silanes in organic synthesis

General reactivity

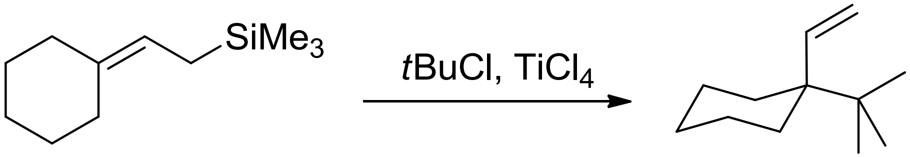


Acylation

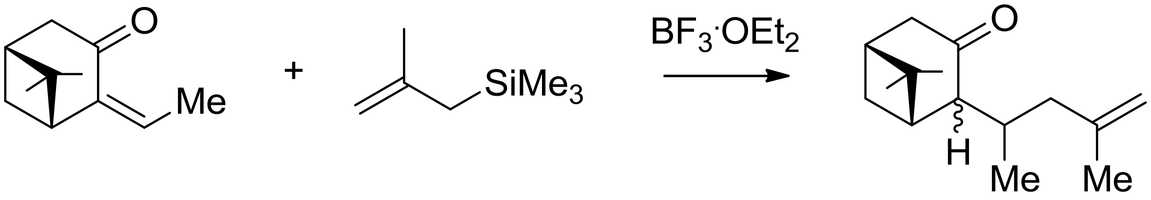


Allylic silanes in organic synthesis

Allylation



1,4-addition



T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Chem. Soc. Chem. Commun*. **1979**, 525.
T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Org. Chem*. **1980**, *45*, 607.

Indium

Element	**Cost in Euro/Mol**
In	167 Euro/Mol
Mg	1,5 Euro/Mol
Zn	3 Euro/Mol
Li	10 Euro/Mol

$$\mathrm{In} \xrightarrow[\text{SET}]{-\,e^{\ominus}} \mathrm{In}^{\oplus}$$

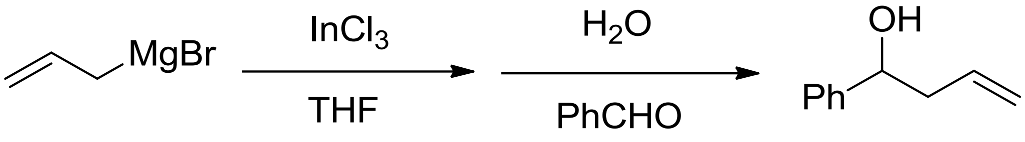
strong oxophilicity

The first ionization potential of indium (5,8 eV)
is close to lithium and sodium

Key contributions:

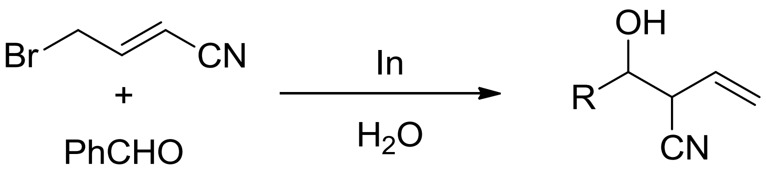
S. Araki *Main Group Metals in Organic Synthesis* **2004**, *1*, 323
T.-P. Loh *Acid Catalysis in Modern Organic Synthesis* **2008**, *1*, 377

Indium. Allylation reactions



with H_2O: 73%
without H_2O: 98%

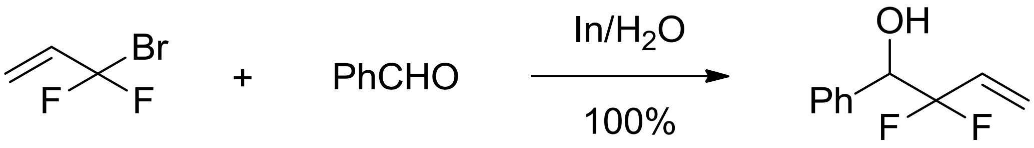
S. Akira, *J. Chem. Soc. Perkin Trans. I*, **1991**, 2395

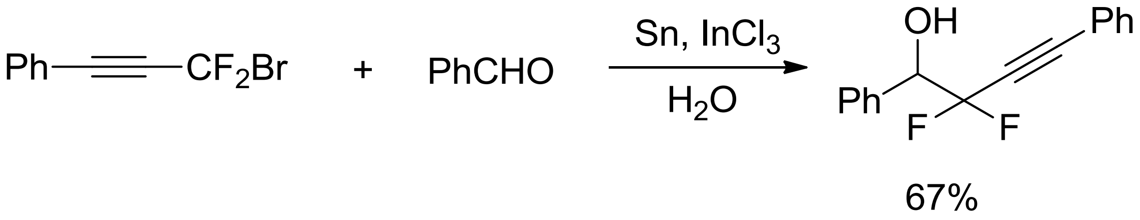


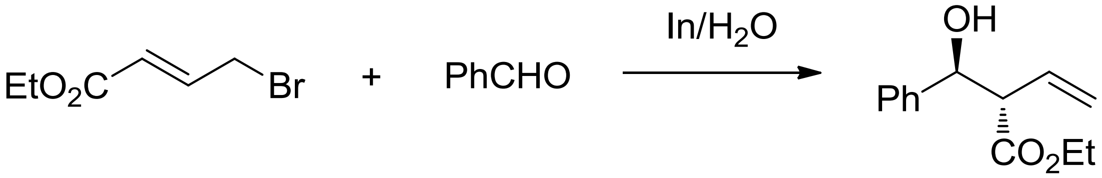
E:Z mixture

B. Manze, *Synth. Commun*. **1996**, *26*, 3179

Indium





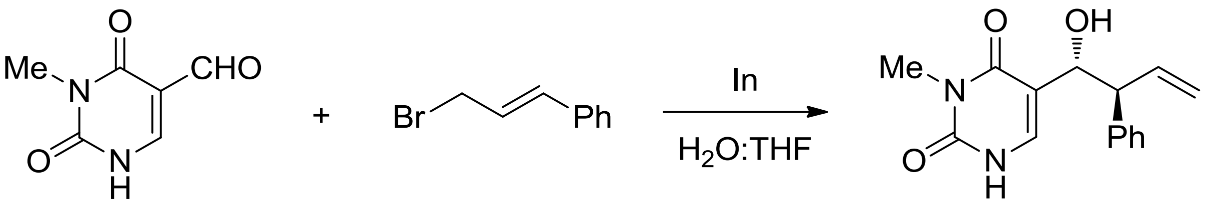


without $La(OTf)_3$: 59% anti:syn = 86 : 14
with $La(OTf)_3$: 99% anti:syn = 90 : 10

L. A. Paquette, *Tetrahedron Lett*. **1999**, *40*, 4129

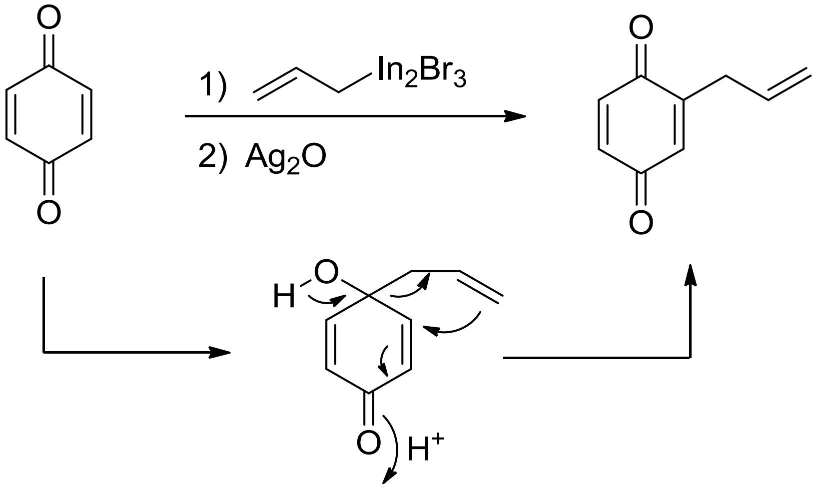
Indium

Applications in nucleoside chemistry:



62%
> 99:1 ee

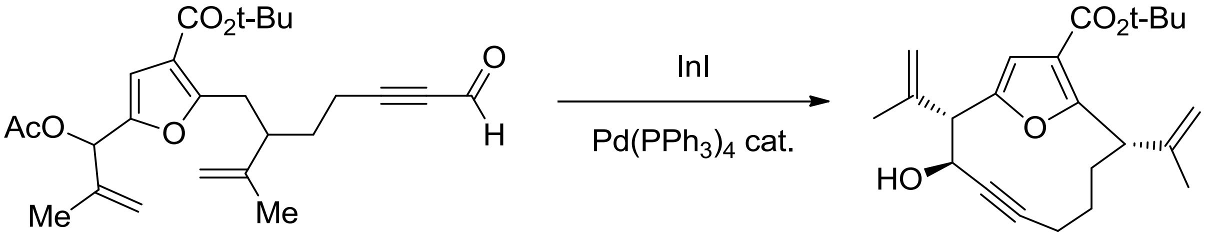
S. Kumar, *Tetrahedron Lett*. **2001**, *42*, 7039



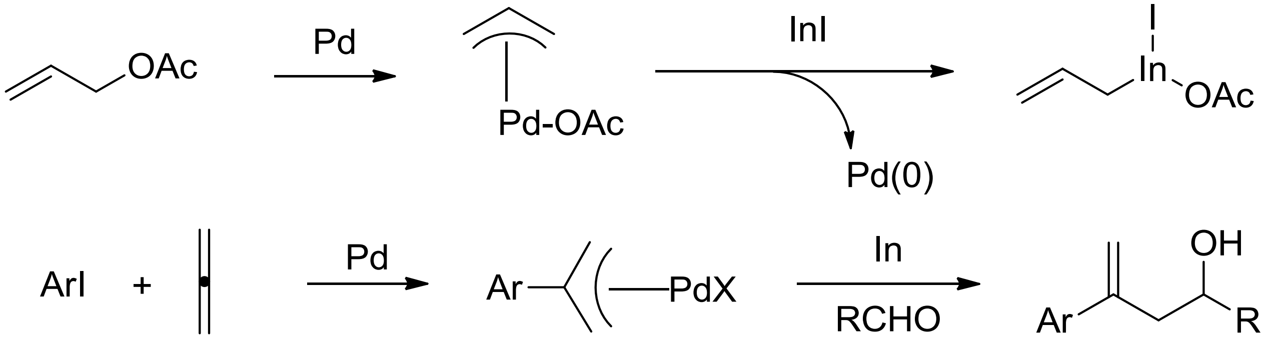
S. Akiva, *J. Organomet. Chem*. **1991**, *415*, 7

Indium

Applications in natural product syntheses:

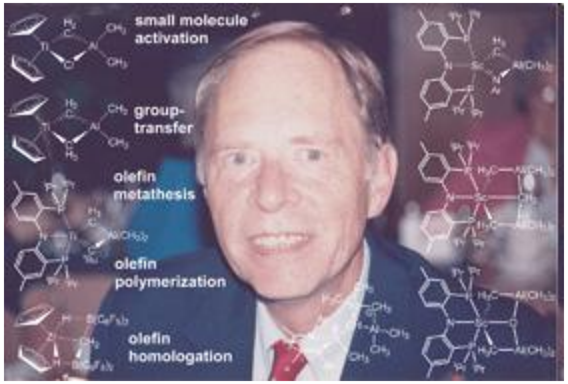


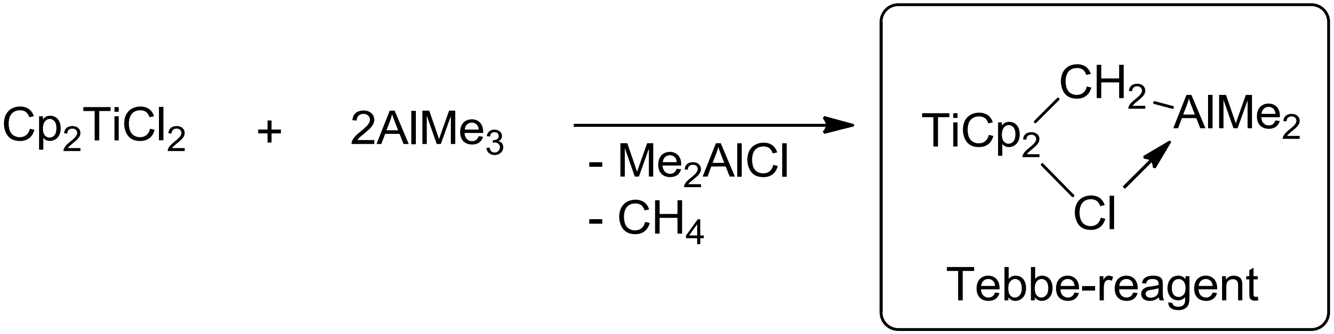
J. A. Marshall, *J. Org. Chem*. **1999**, *64*, 5193



S-K. Kang S-W. Lee J. Jung Y. Lim *J. Org. Chem*. **2002**, *67*, 4376

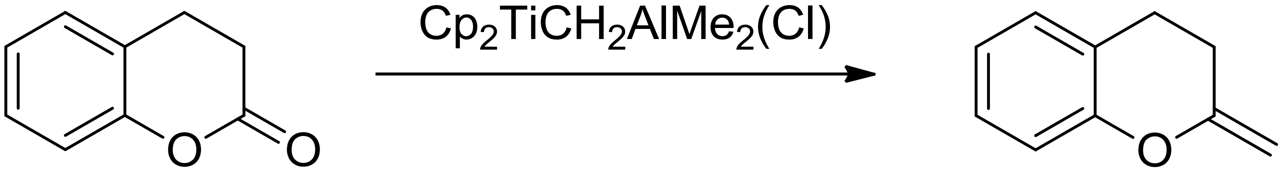
Early transition metal organometallics: Titanium





$Cp_2TiCl_2 + 2AlMe_3 \xrightarrow[- CH_4]{- Me_2AlCl}$

Tebbe-reagent



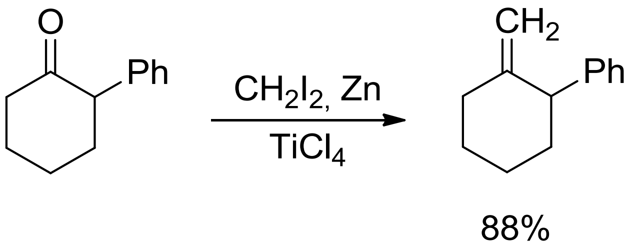
$\xrightarrow{Cp_2TiCH_2AlMe_2(Cl)}$

84%

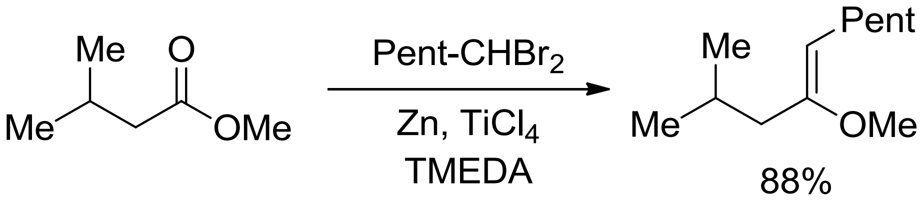
S. H. Pine *Org. React*. **1993**, *43*, 1

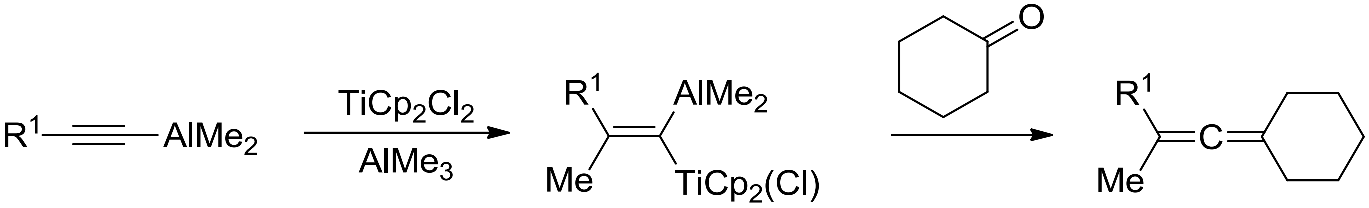
Titanium

Lombardo-reagent



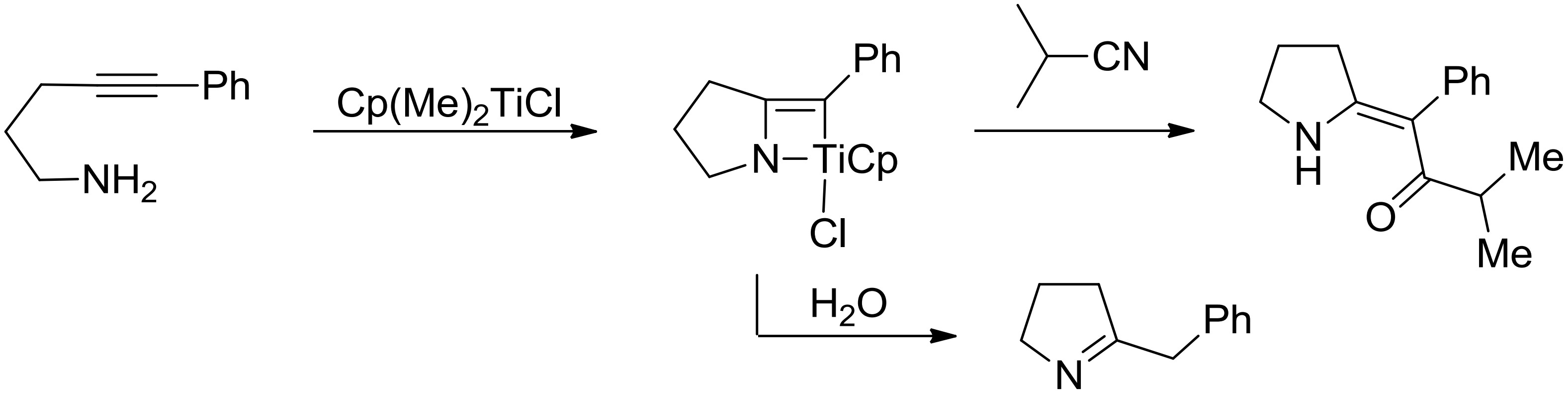
K. Takai, *J. Org. Chem*. **1994**, *59*, 2668





S. Buchwald, R. H. Grubbs *J. Am. Chem. Soc*. **1983**, *105*, 5490

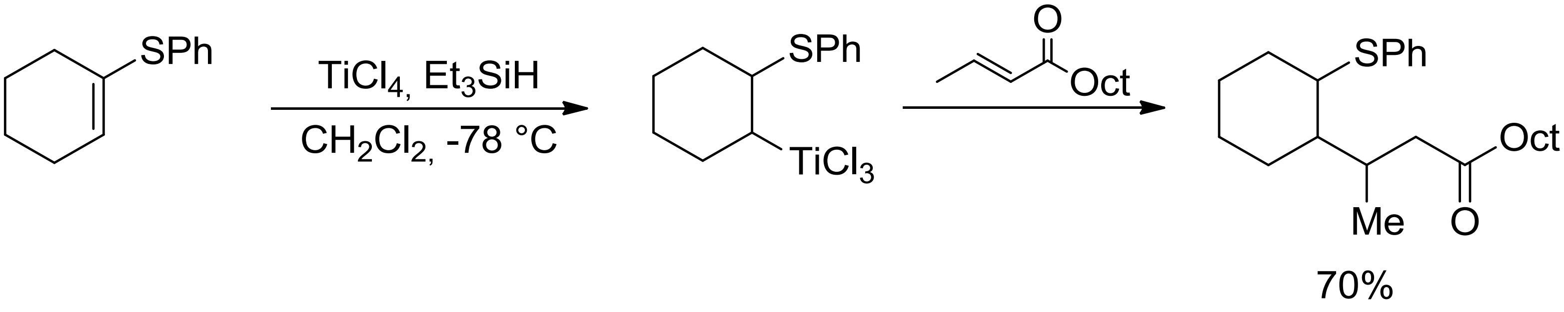
Titanium



T. Livinghouse, *J. Am. Chem. Soc*. **1992**, *114*, 5459

Titanium

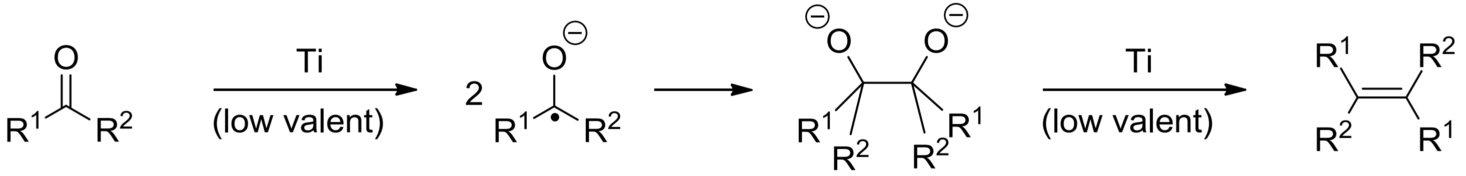
Hydrotitanation

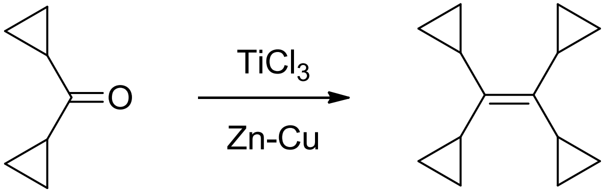


T. Takeda, *Tetrahedron Lett*. **1985**, *26*, 5313

Titanium

Reductive coupling: The McMurry Reaction

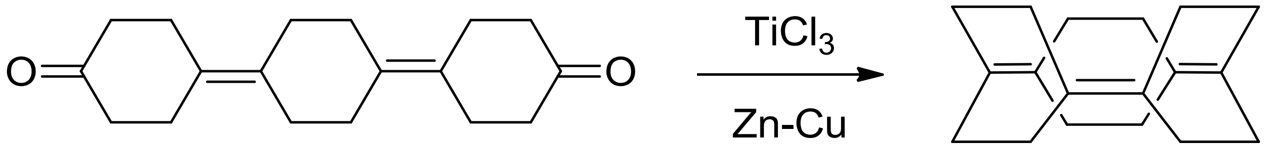


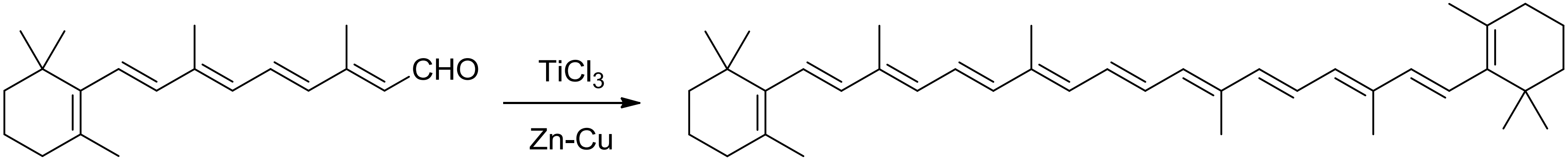


25%

Review:
A. Fürstner, Ed. M. Beller, C. Bolm, Transition Metals for Organic Synthesis (2nd Edition) **2004**, *1*, 449.

Titanium

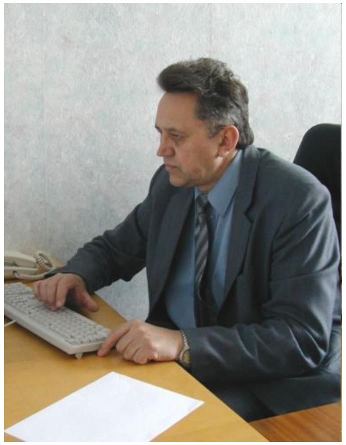




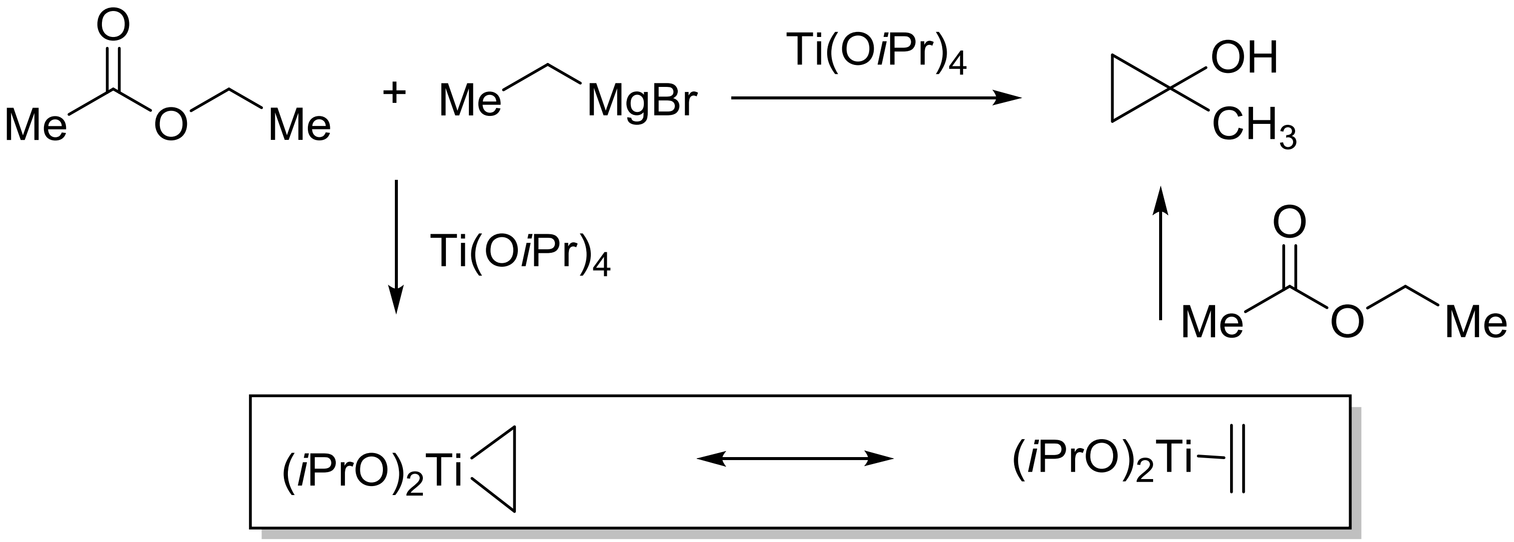
β -Caroten: 94%

J. E. McMurry et al. *J. Am. Chem. Soc*. **1984**, *106*, 5018.

Titanium

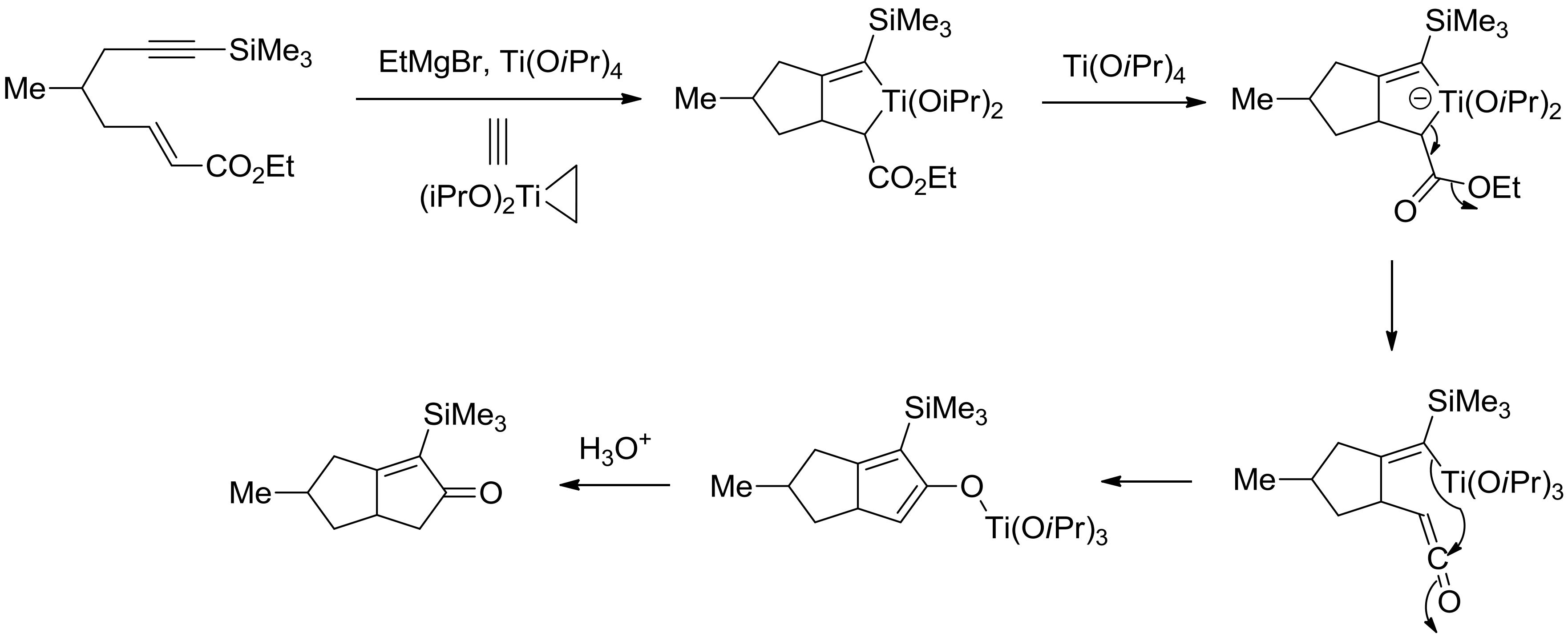


Kulinkovich-reaction



O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, T. S. Pritytskaya, *Zh. Org. Khim.* **1989**, 25, 2244.
O. Kulinkovich, S.V. Sviridov, D.A. Vasilevski, *Synthesis,* ***1991***, 234.

Titanium



F. Sato *J. Org. Chem*. **1988**, *53*, 5590.

Early transition metal organometallics: Zirconium

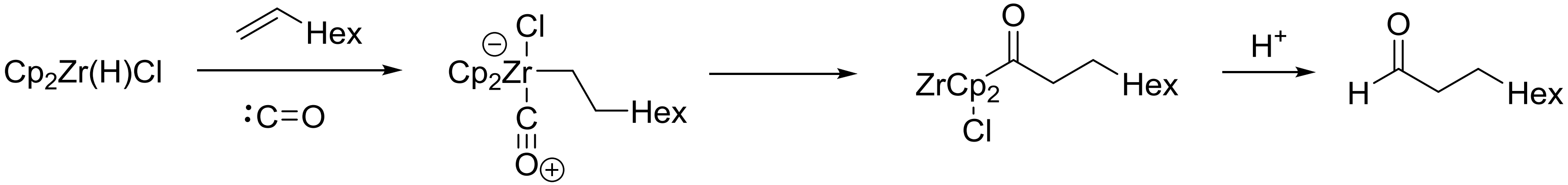
Schwartz's reagent:

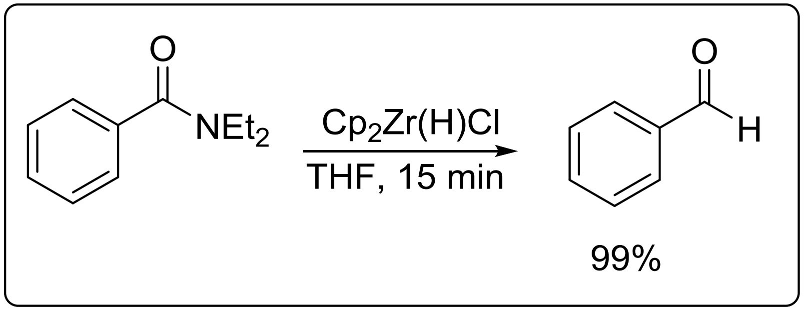
$$\mathrm{ZrCp_2Cl_2} \xrightarrow[\mathrm{THF}]{\mathrm{LiAl(H)(O}t\mathrm{Bu)_3}} \mathrm{Cp_2Zr(H)Cl}$$

90%

Inorg. Synth. **1979**, *19*, 223

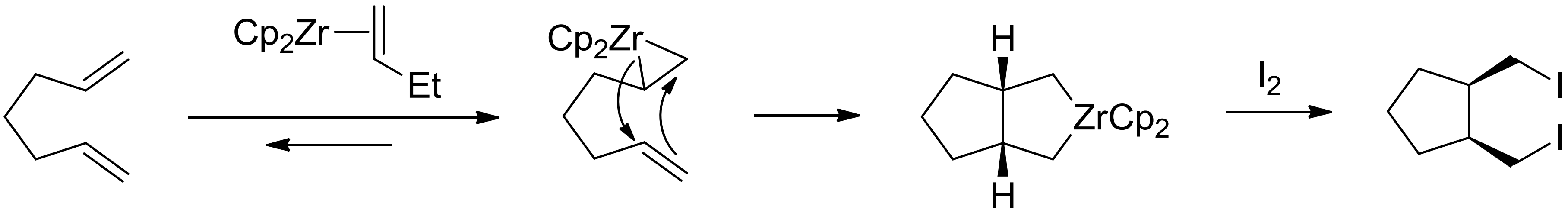
Zirconium

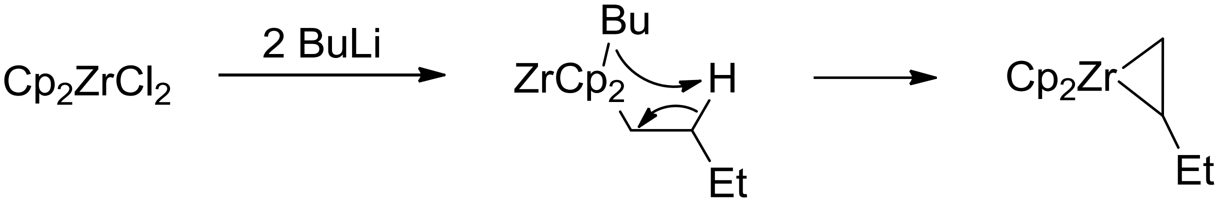




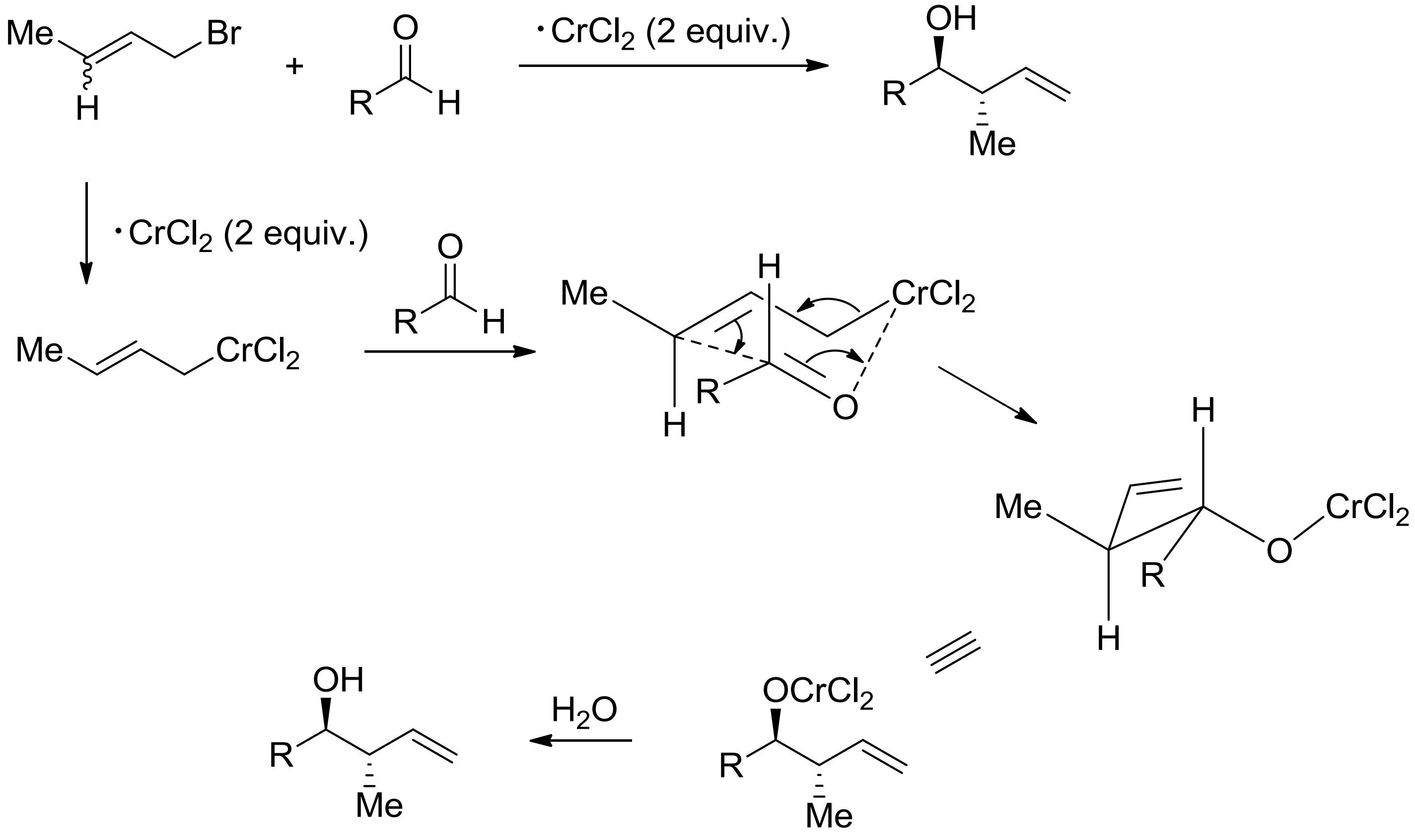
G. I. Georg *J. Am. Chem. Soc*. **2007**, *129*, 3408

Zirconium


Cp$_2$Zr
Et
Cp$_2$Zr
H
H
ZrCp$_2$
I$_2$
I
I

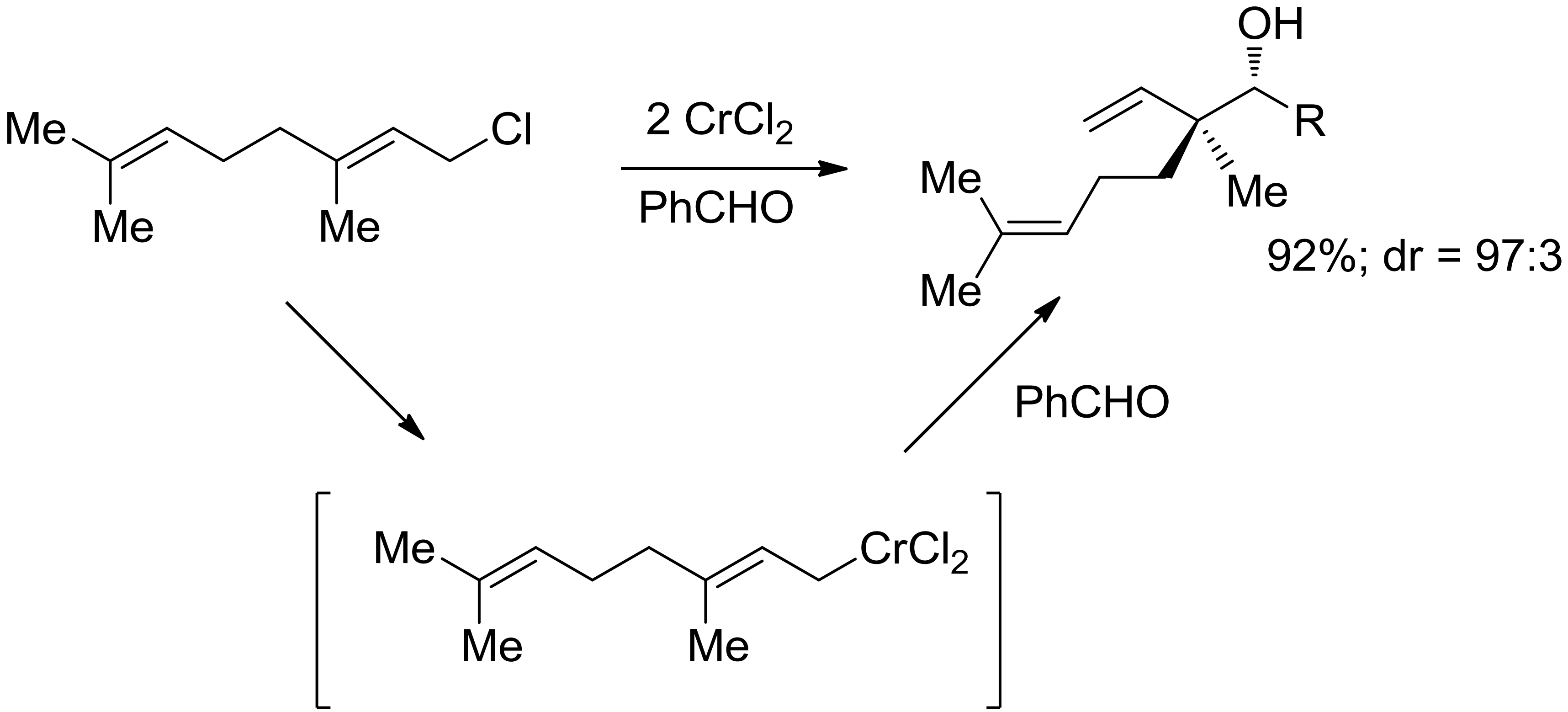

Cp$_2$ZrCl$_2$
2 BuLi
Bu
ZrCp$_2$
H
Et
Cp$_2$Zr
Et

Early transition metal organometallics: Chromium



Hiyama reaction *Bull. Soc. Chem. Jpn* **1982**, *55*, 567; *J. Am. Chem. Soc*. **1977**, *99*, 3175

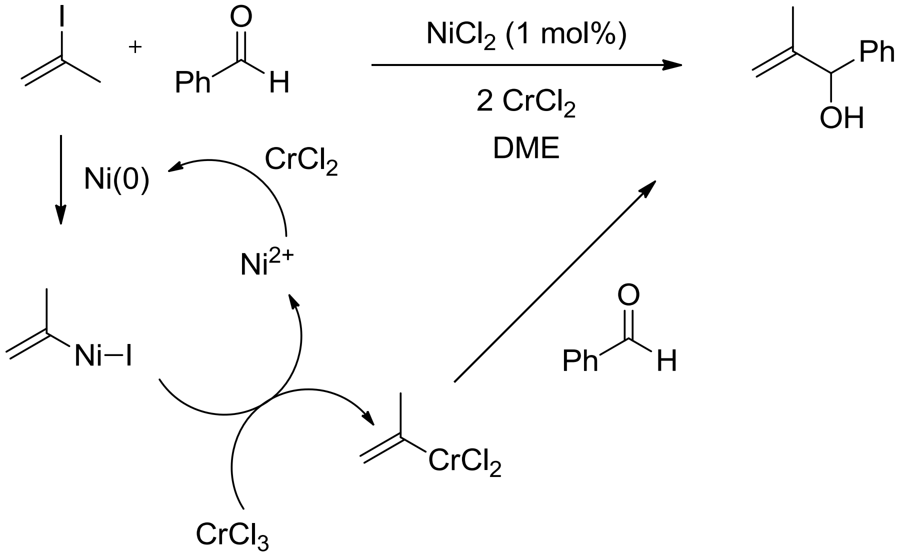
Chromium

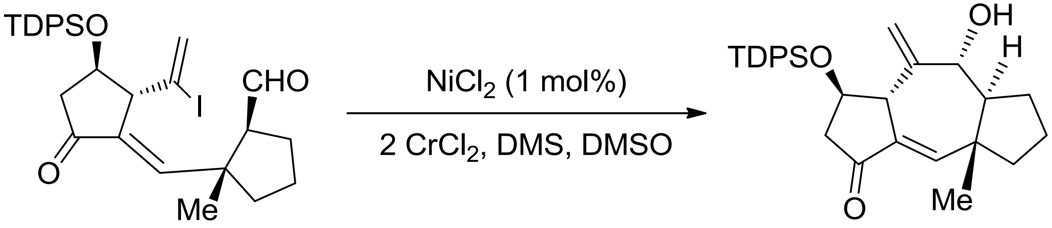


K. Belyk, M. J. Rozema, P. Knochel *J. Org. Chem*. **1992**, *57*, 4070.

Chromium

Hiyama-Kishi-reaction

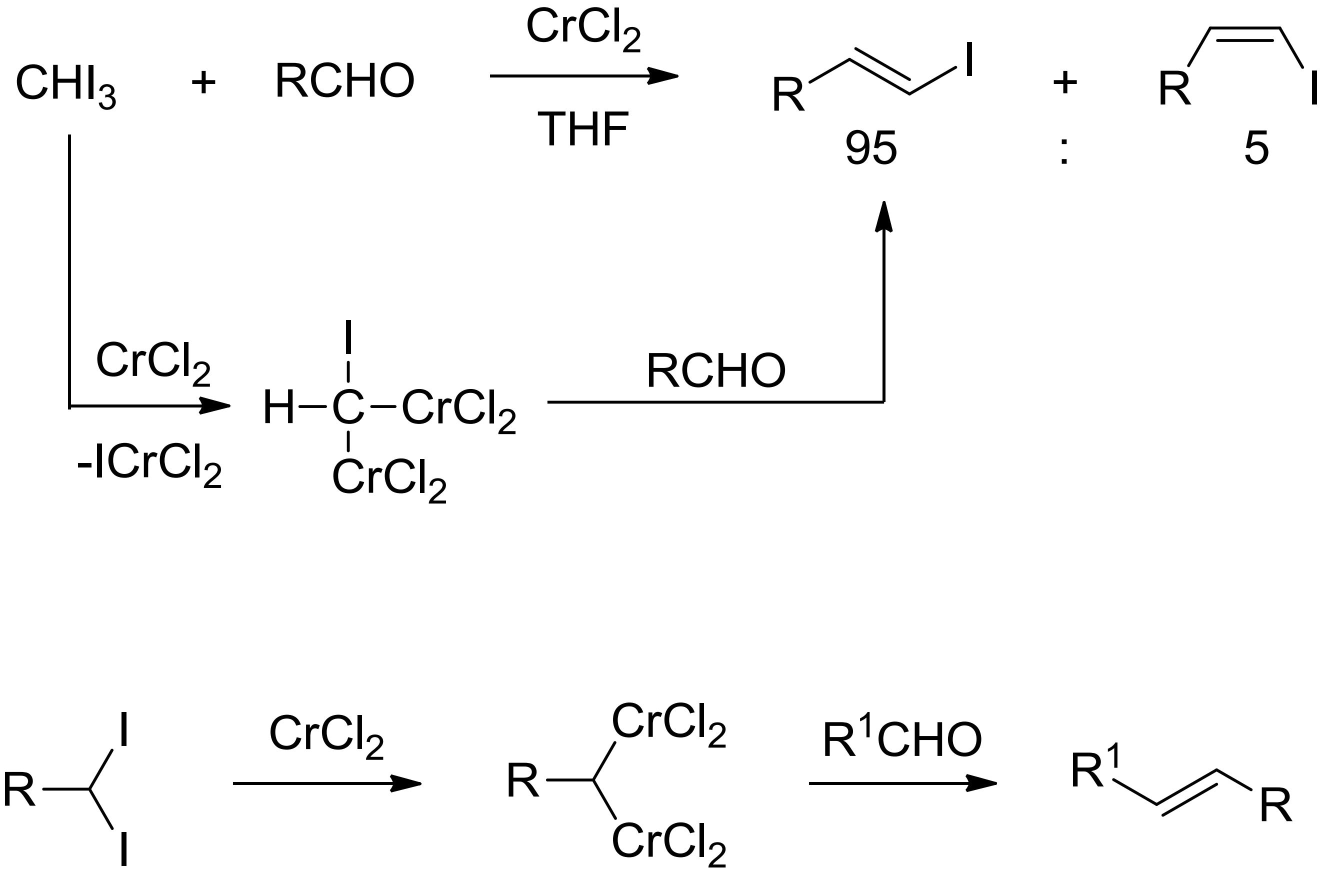




56%

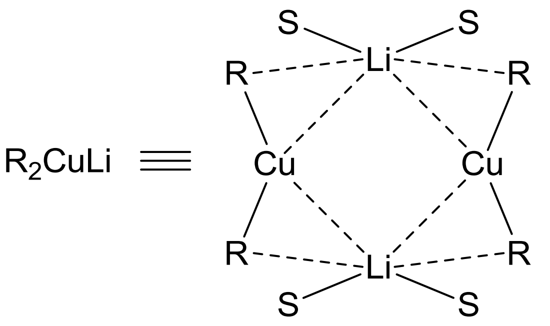
Y. Kishi *J. Am. Chem. Soc*. **1989**, *111*, 2735.

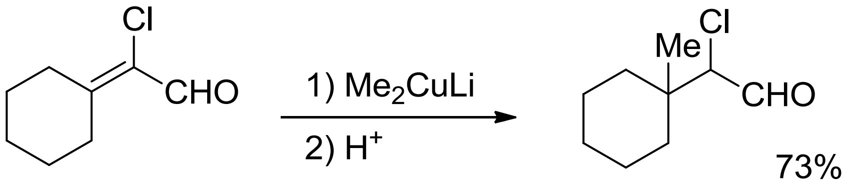
Chromium

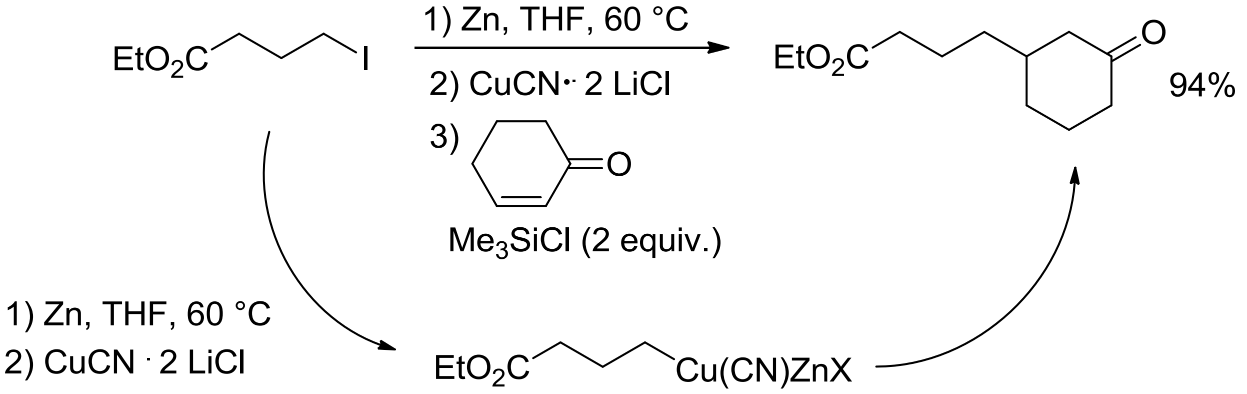


K. Takai *J. Am. Chem. Soc*. **1986**, *108*, 7408

Early transition metal organometallics: Copper

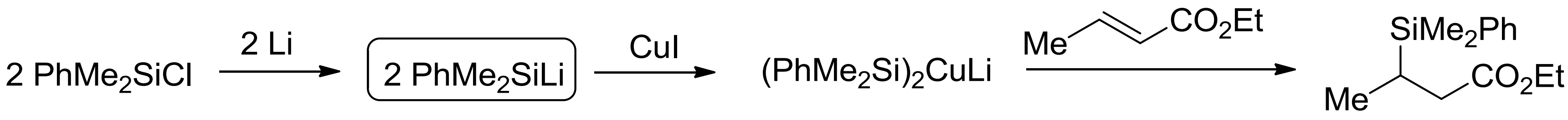






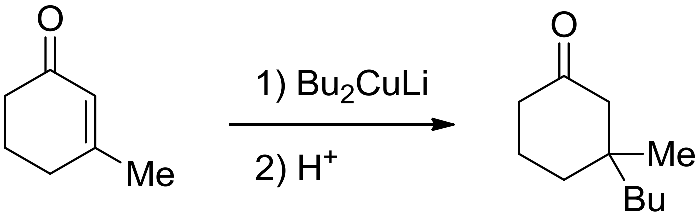
P. Knochel, et al. *J. Org. Chem*. **1988**, *53*, 2390.

Copper



81%

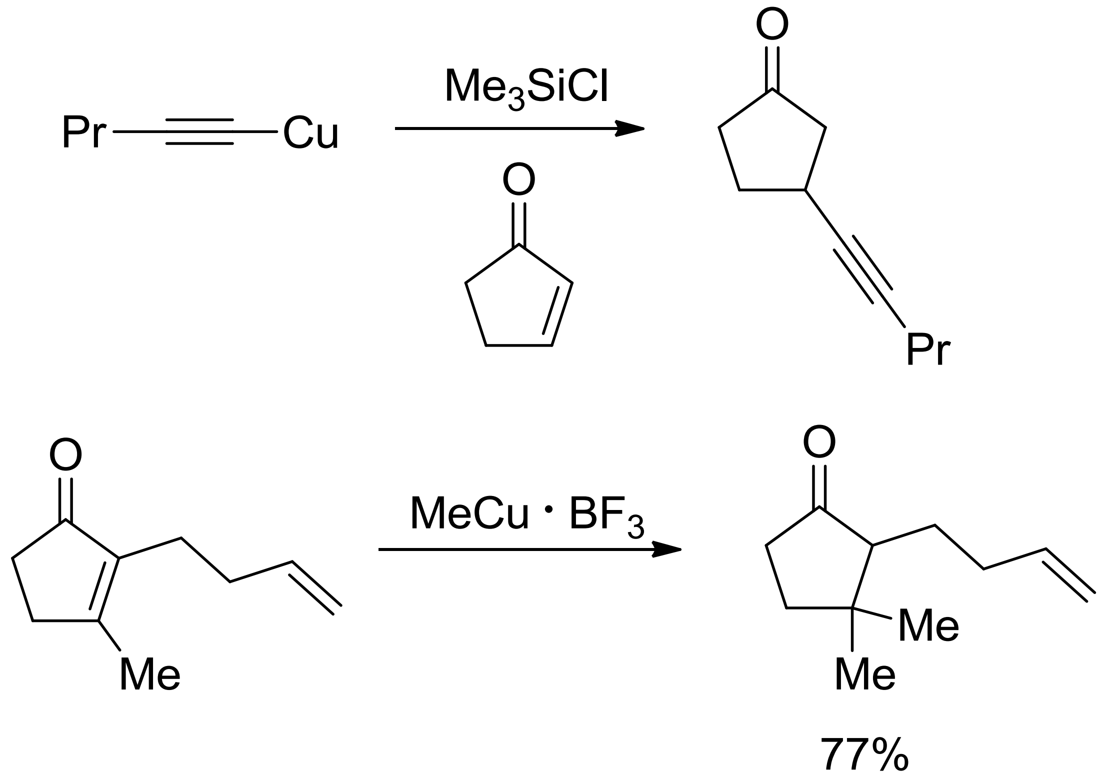
I. Fleming et al. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 1209.



without additives: 28%
Me_3SiCl (2 equiv.): 99%

E. Nakamura et al. *Tetrahedron Lett*. **1986**, *27*, 4029.

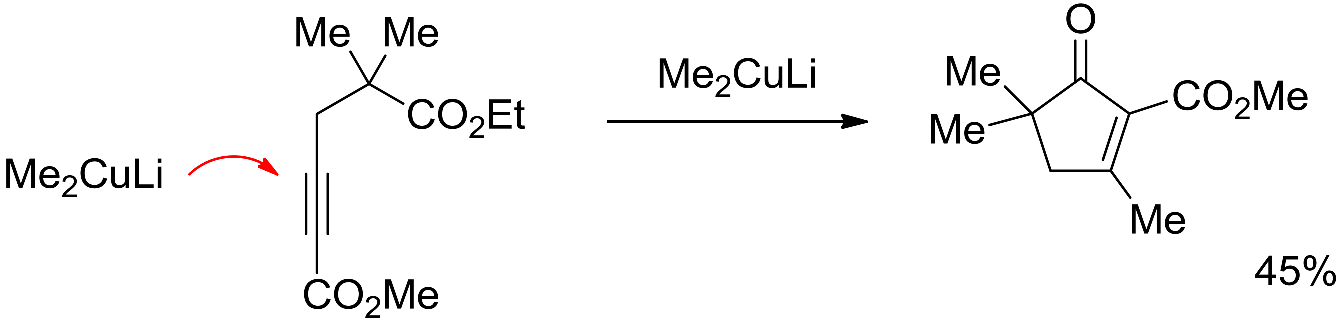
Copper-mediated 1,4-addition



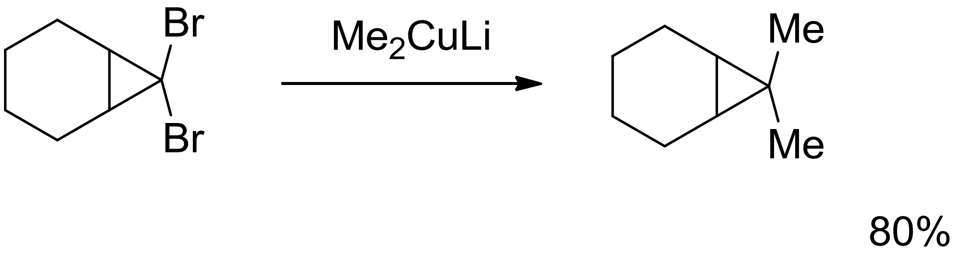
Y. Yamamoto, *Angew. Chem*. **1986**, *98*, 945.

Copper-mediated reactions

Michael-addition



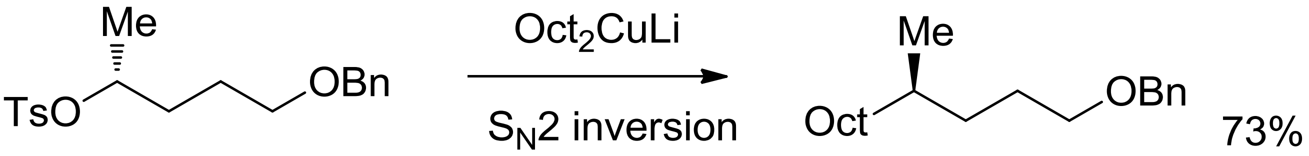
Substitution reactions

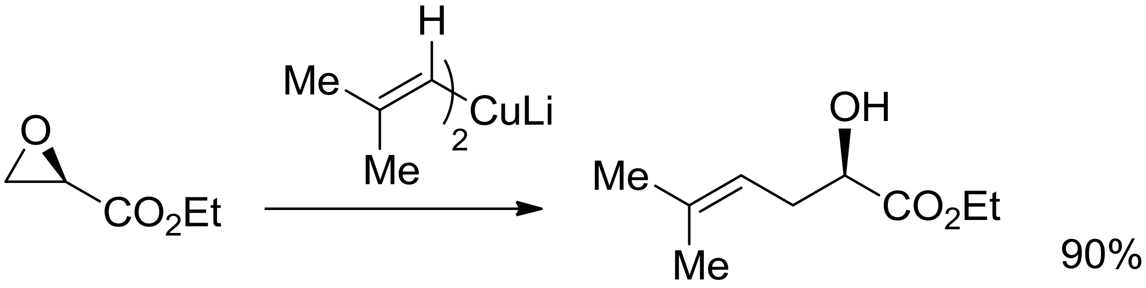


G. Posner, *Org. React*. **1975**, *22*, 253.

R. J. K. Taylor (Ed.), *Organocopper reagents*, Oxford University Press, Oxford, **1994**.

Copper; substitution reactions

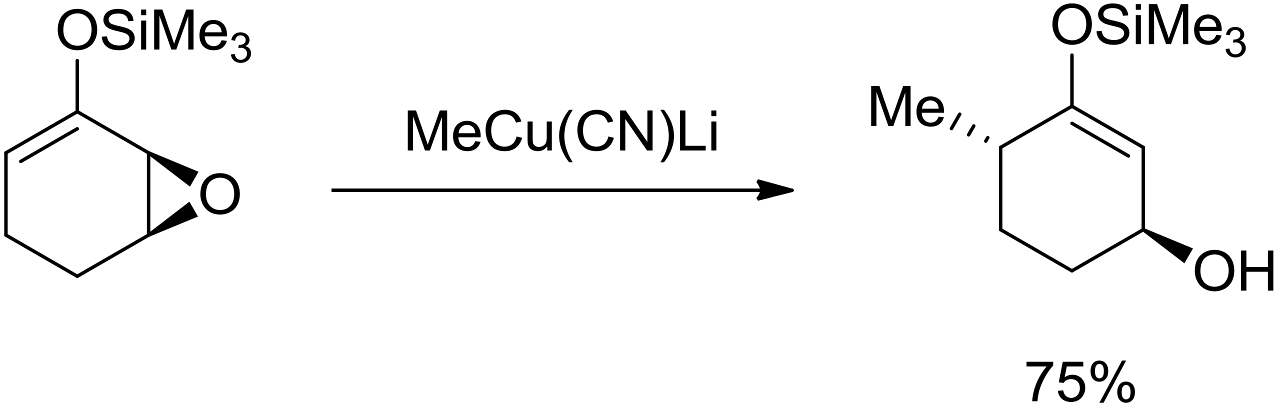


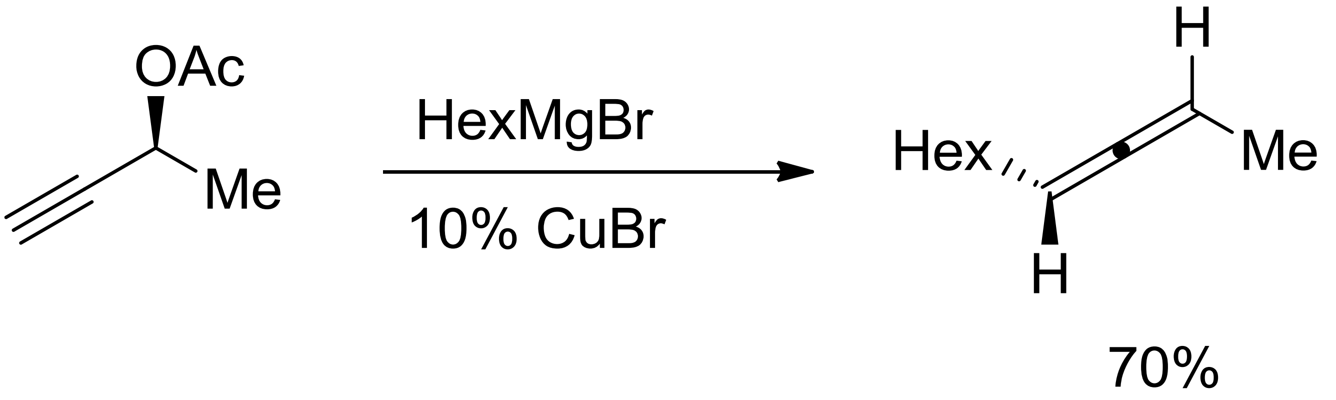


$$t\text{BuMgCl} + \text{PhCH}_2\text{Cl} \xrightarrow[\text{0.25 mol\%}]{\text{Li}_2\text{CuCl}_4} \text{PhCH}_2t\text{Bu}$$

M. Larcheveque, Y. Petit, *Bull. Soc. Chim. Fr*. **1989**, *1*, 130.

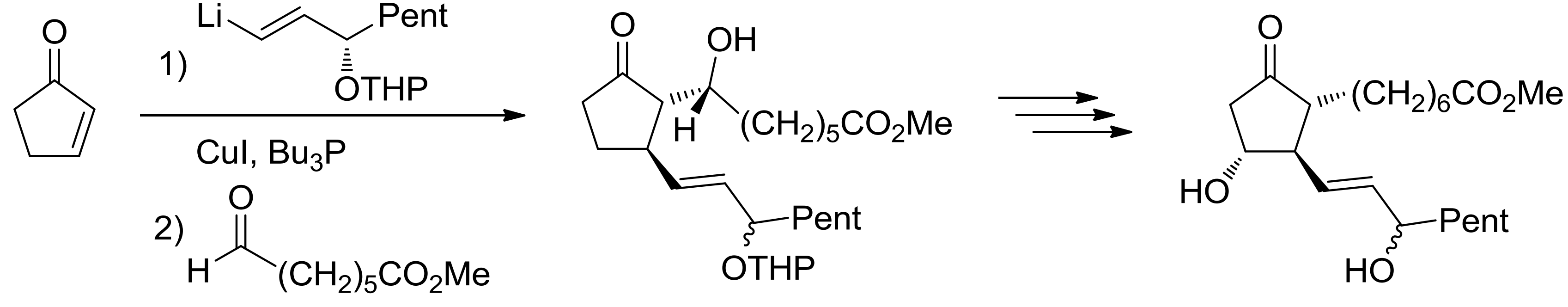
Copper: allylic and propargylic substitution





A. Alexakis, *Pure Appl. Chem*. **1992**, *64*, 387.

Copper: Prostaglandin synthesis



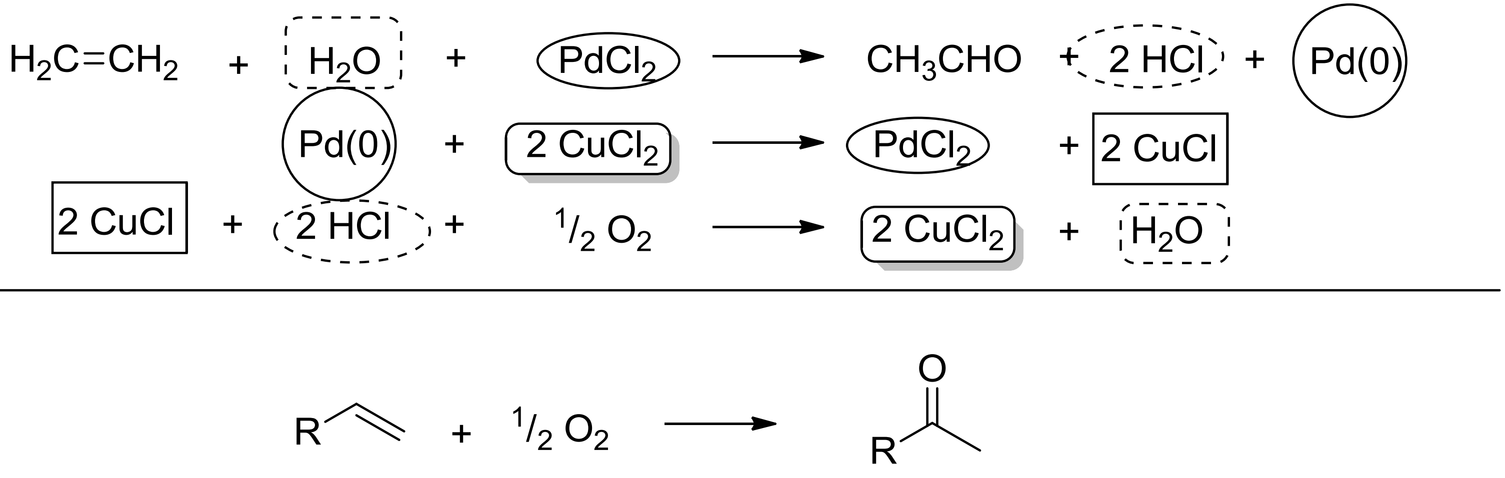
Prostaglandin E1

F. Sato *J. Org. Chem*. **1988**, *53*, 5590

Palladium

Price of Pd: **1.0**
Pt: 3.3
Au: 1.9
Ru: 0.2
Rh: 2.8

Wacker-Reaction:



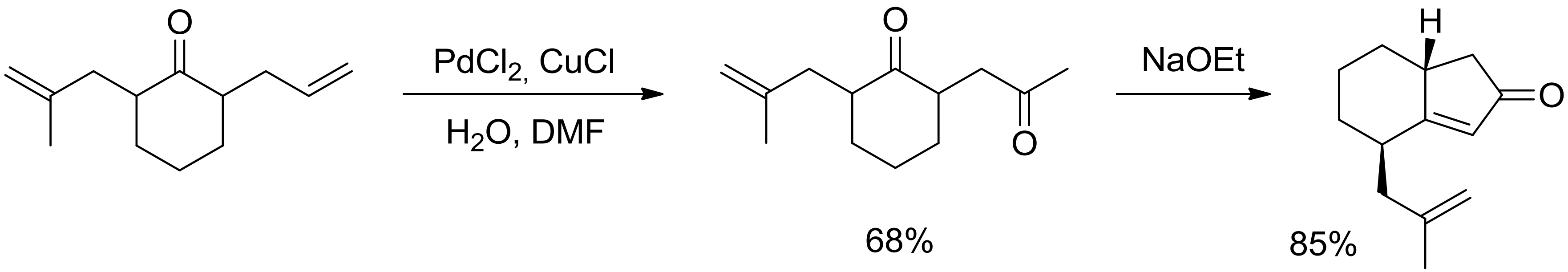
$$H_2C{=}CH_2 + H_2O + PdCl_2 \longrightarrow CH_3CHO + 2\,HCl + Pd(0)$$

$$Pd(0) + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl$$

$$2\,CuCl + 2\,HCl + {}^{1}/_{2}\,O_2 \longrightarrow 2\,CuCl_2 + H_2O$$

J. Schmidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, J. Sabel, *Angew. Chem. Int. Ed*. **1962**, *1*, 80.

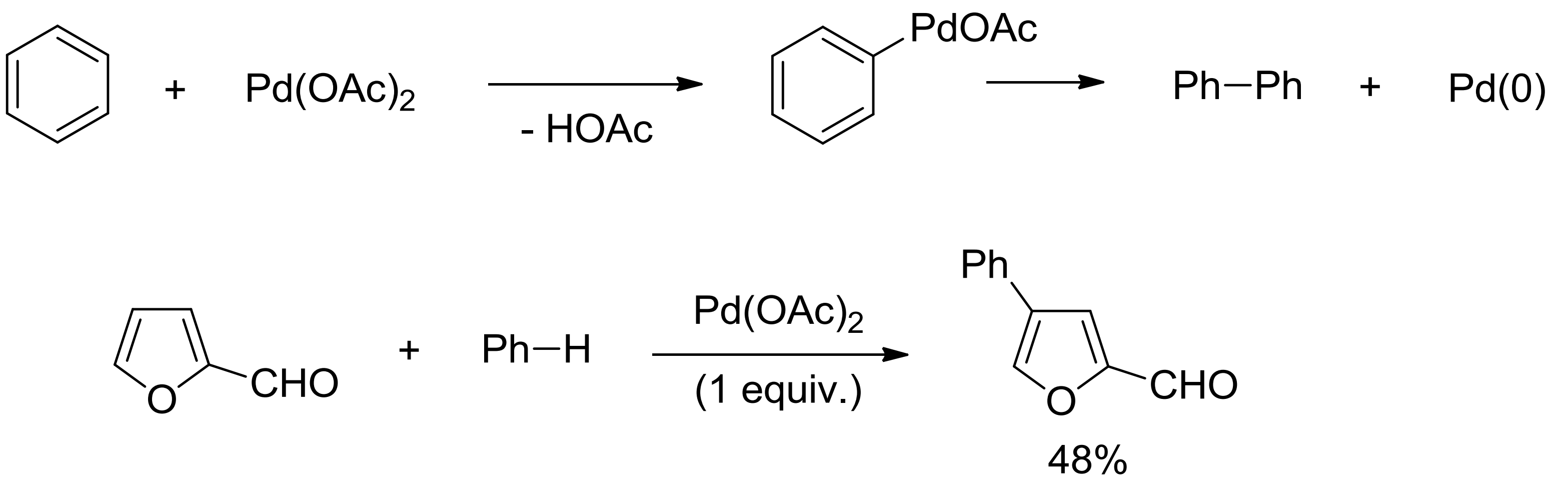
Palladium



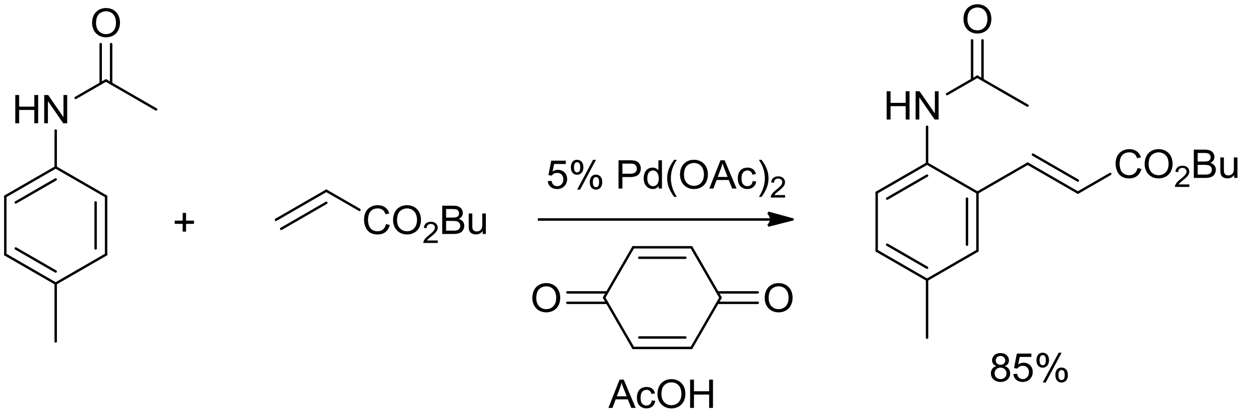
J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett*. **1976**, *34*, 2975.

Palladium

C-H activation



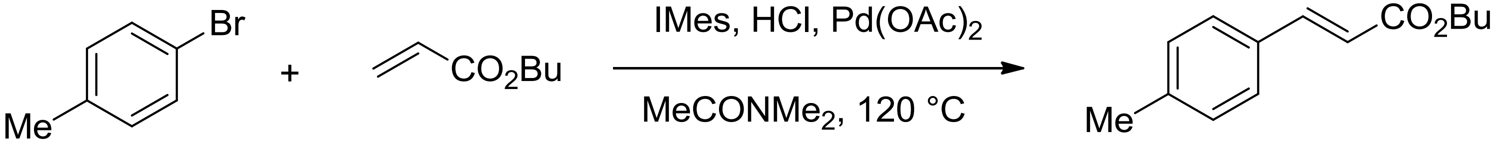
T. Itahara, *J. Org. Chem*. **1985**, *50*, 5272.

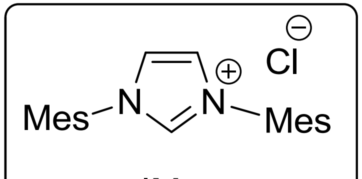


J. G. de Vries *J. Am. Chem. Soc*. **2002**, *124*, 1586.

Palladium

Heck Reaction





IMes

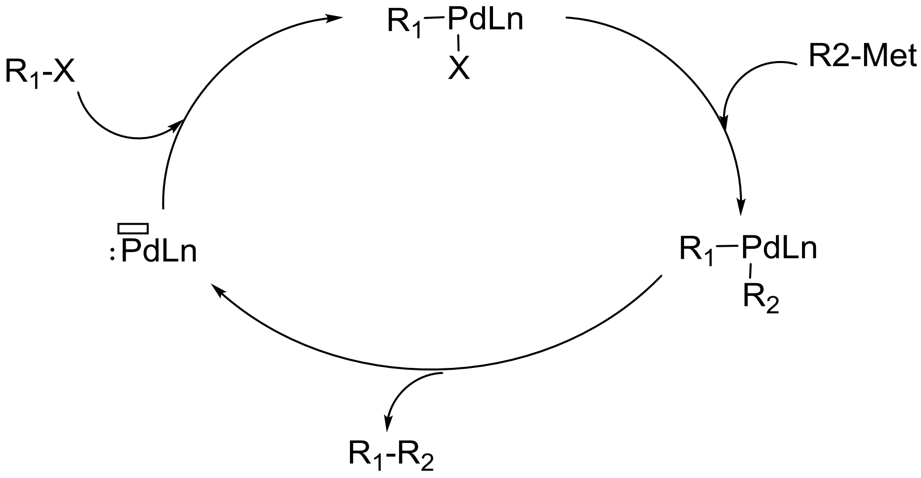
The method of T. Jeffery uses Bu_4NBr at 25 °C.

T. Jeffery *Chem. Comm*. **1984**, 1287

Palladium-catalyzed cross-coupling

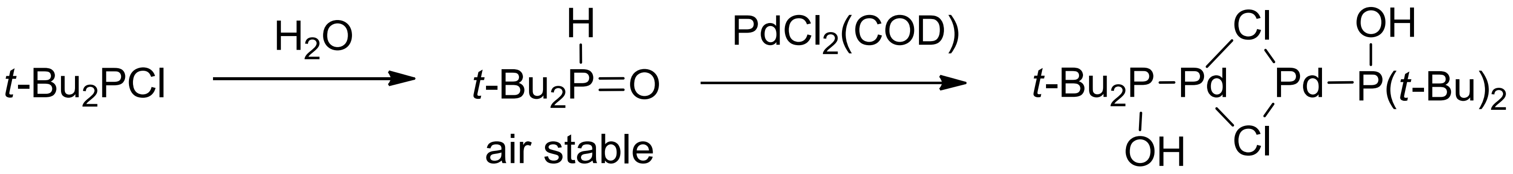
Cross-coupling using Pd(0)-catalysts

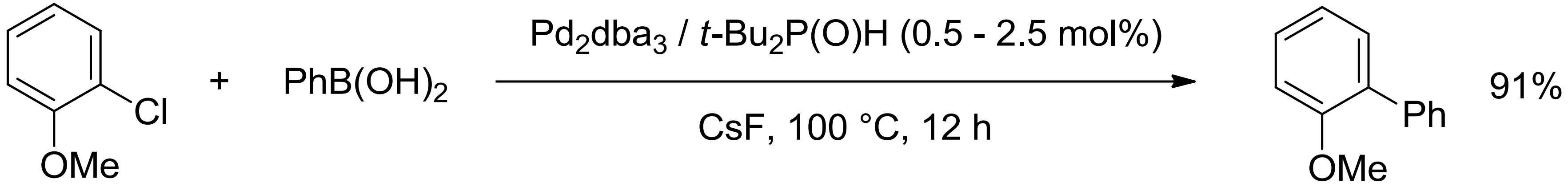
$$\boxed{R_1\text{-}X \quad + \quad R_2\text{-Met} \xrightarrow[\text{Pd(0) or Ni(0)}]{} R_1\text{-}R_2}$$



Suzuki-coupling	Met = $B(OH)_2$
Stille-coupling	Met = SnR_3
Negishi-coupling	Met = ZnX
Kumada-coupling	cat = Ni; Met = MgX
Sonogashira-coupling	$Csp\text{-}Csp^2$

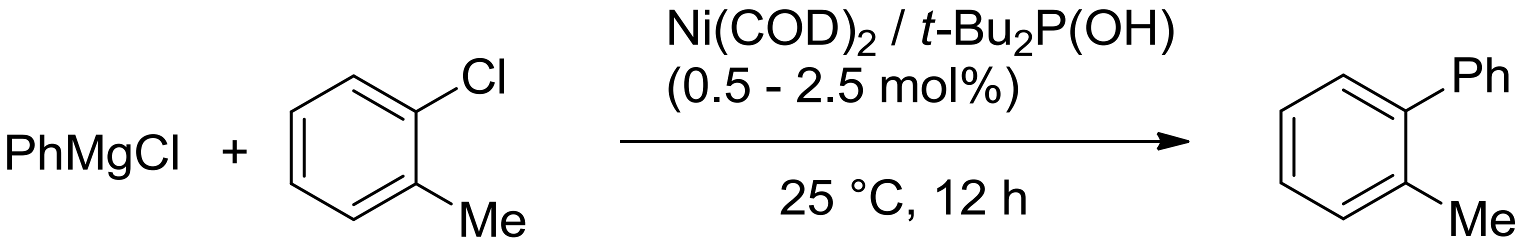
Palladium





G. Y. Li, *Angew. Chem. Int. Ed*. **2001**, *40*, 1513.

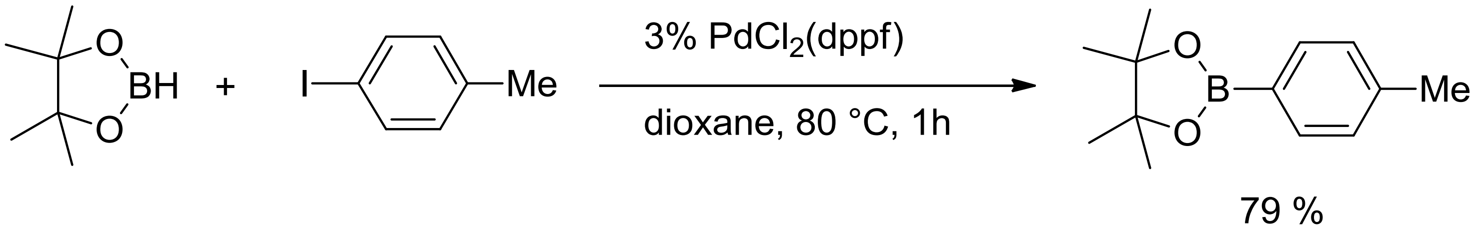
Palladium



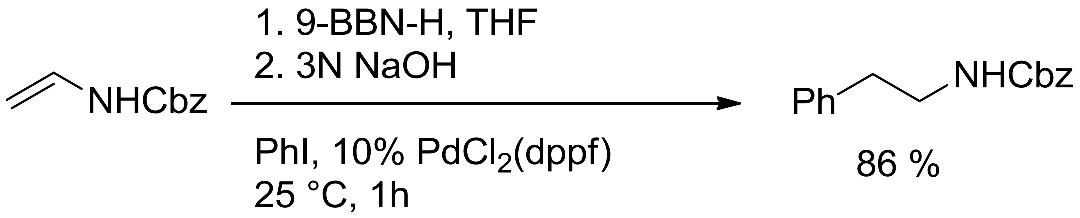
$$\text{PhBr} + \text{HS-}t\text{-Bu} \xrightarrow[\text{Pd}_2\text{dba}_3\text{, } t\text{-Bu}_2\text{PCl, H}_2\text{O (0.5 - 2.5 mol\%)}]{\text{NaO}t\text{-Bu, 25 °C, 24 h}} \text{Ph}-\text{S}-t\text{-Bu}$$

G. Y. Li, *Angew. Chem. Int. Ed*. **2001**, *40*, 1513.

Palladium



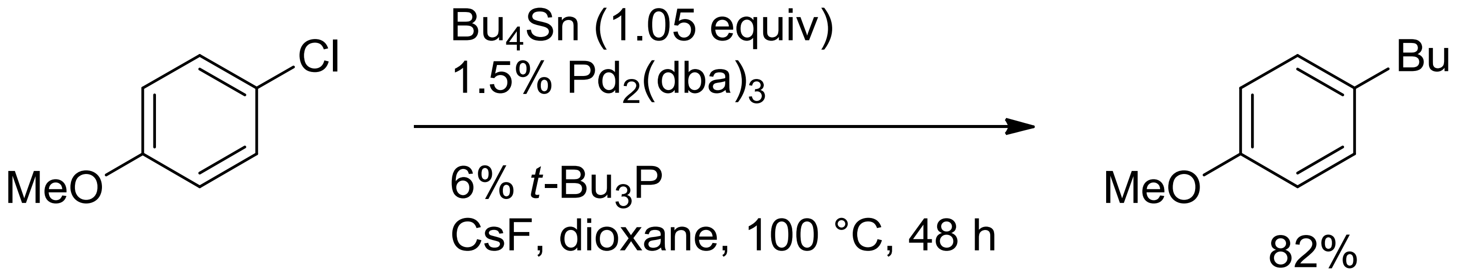
M. Murata, *J. Org. Chem*. **2000**, *65*, 164.



L. E. Overman, *J. Org. Chem*. **1999**, *64*, 8743.

Palladium

Stille cross-coupling



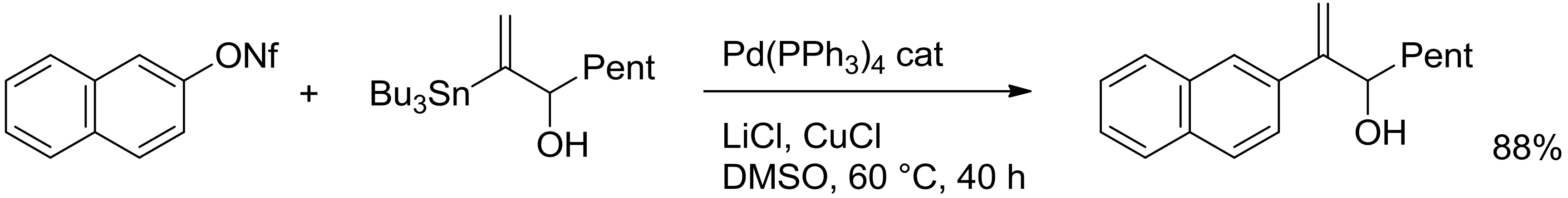
G. C. Fu, *Angew. Chem. Int. Ed*. **1999**, *38*, 2411.

On the mechanism of the Stille cross-coupling:

P. Espinet *J. Am. Chem. Soc*. **1998**, *120*, 8978.
J. Am. Chem. Soc. **2000**, *122*, 1771.

Palladium

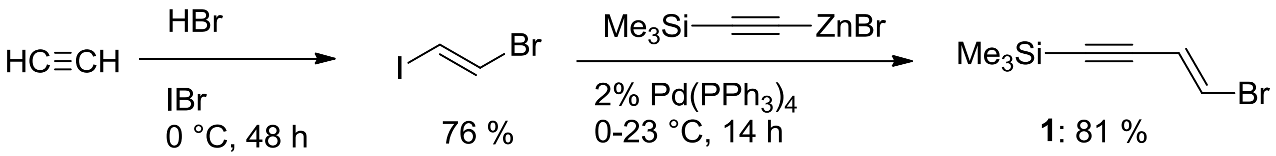
Cu-accelerated Stille-reaction

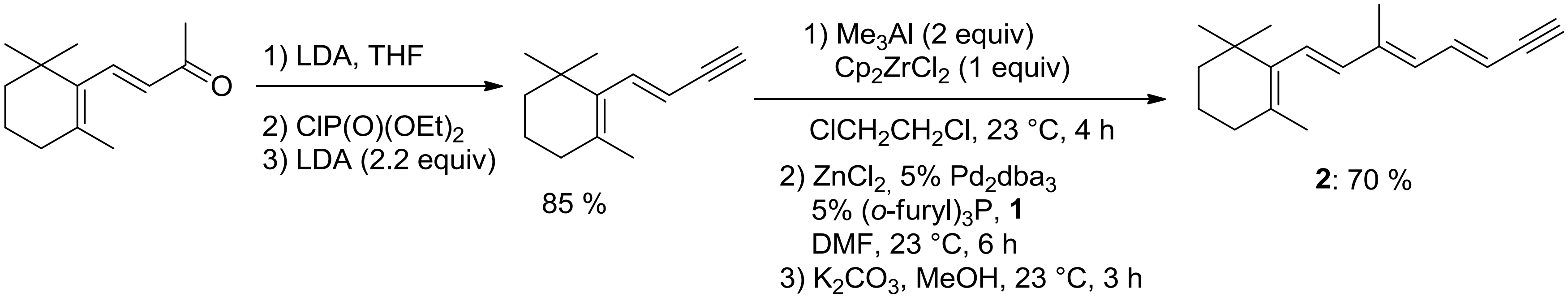


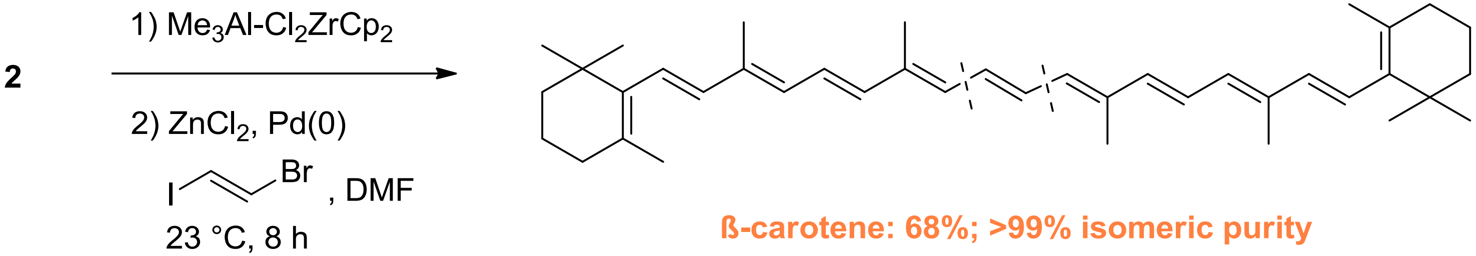
E. J. Corey, *J. Am Chem. Soc*. **1999**, *121*, 7600.

Negishi reactions

Synthesis of carotenoids *via* Zr-catalyzed carboalumination and Pd /Zn-catalyzed cross-couplings:





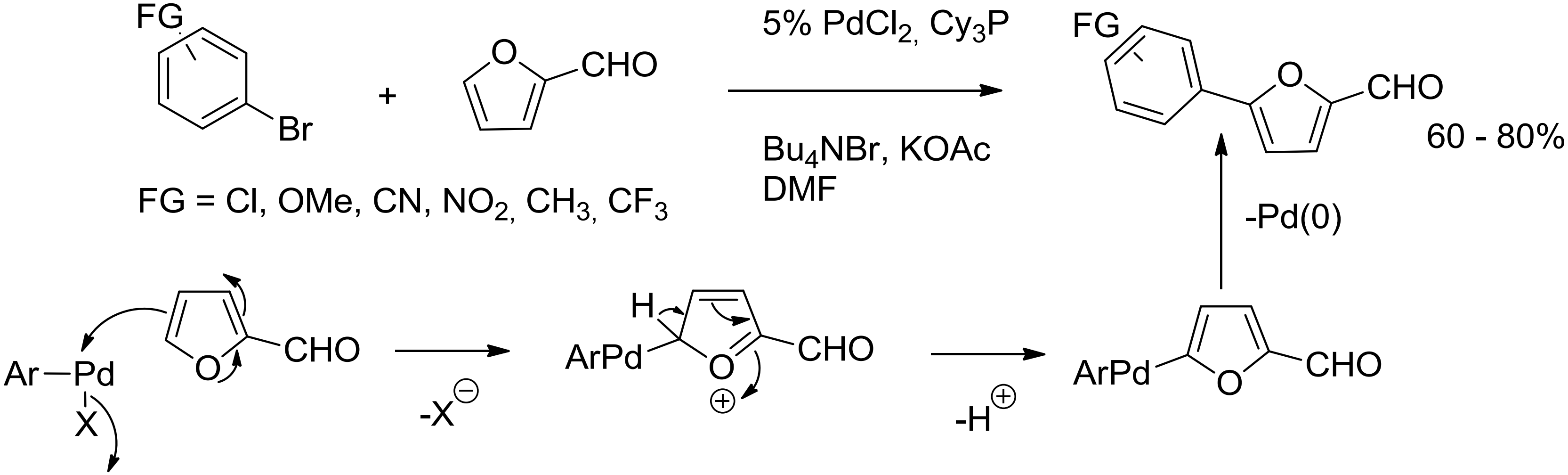


ß-carotene: 68%; >99% isomeric purity

E. Negishi, *Org. Lett*. **2001**, *3*, 719.

Palladium

Regioselective Pd-catalyzed arylation of 2-furaldehyde using a C-H activation

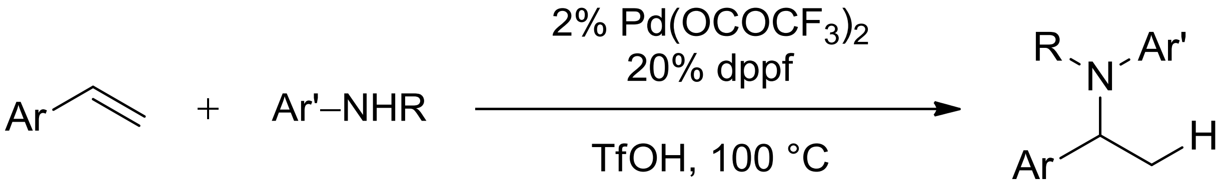


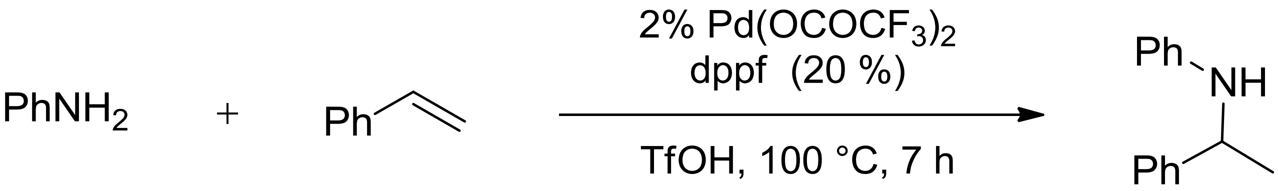
FG = Cl, OMe, CN, NO_2, CH_3, CF_3

M. S. McClure, *Org. Lett*. **2001**, *3*, 1677

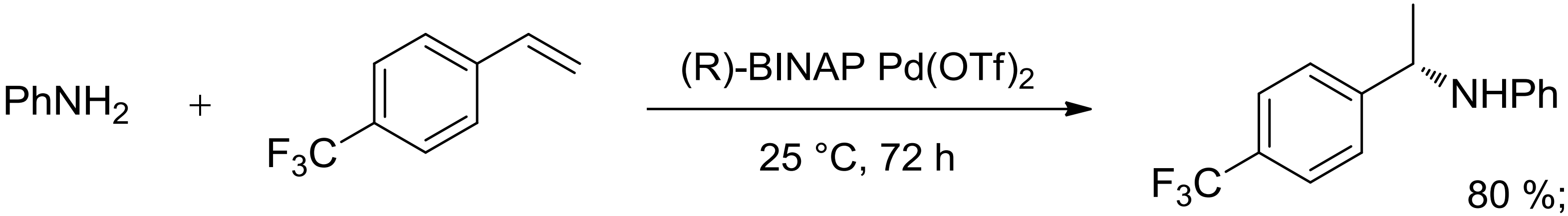
Palladium

Pd - catalyzed hydroamination of vinylarenes





99 %

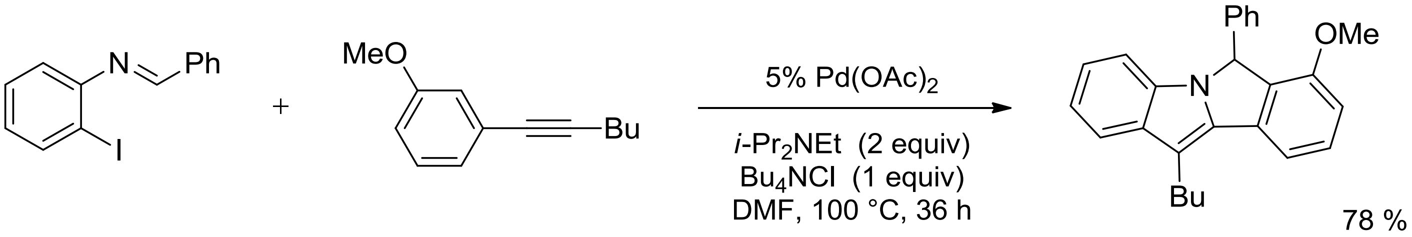


80 %; 81 %*ee*

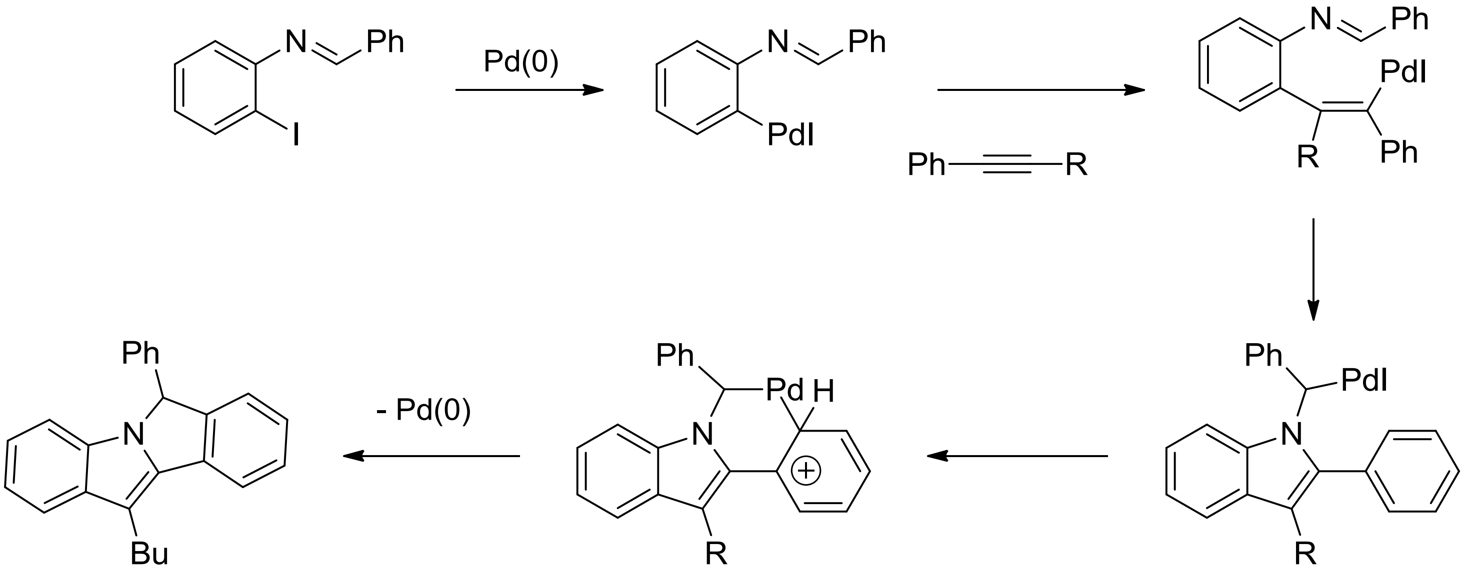
H. Hartwig *J. Am. Chem. Soc*. **2000**, *122*, 9546

Palladium

Pd -catalyzed heterocycle synthesis

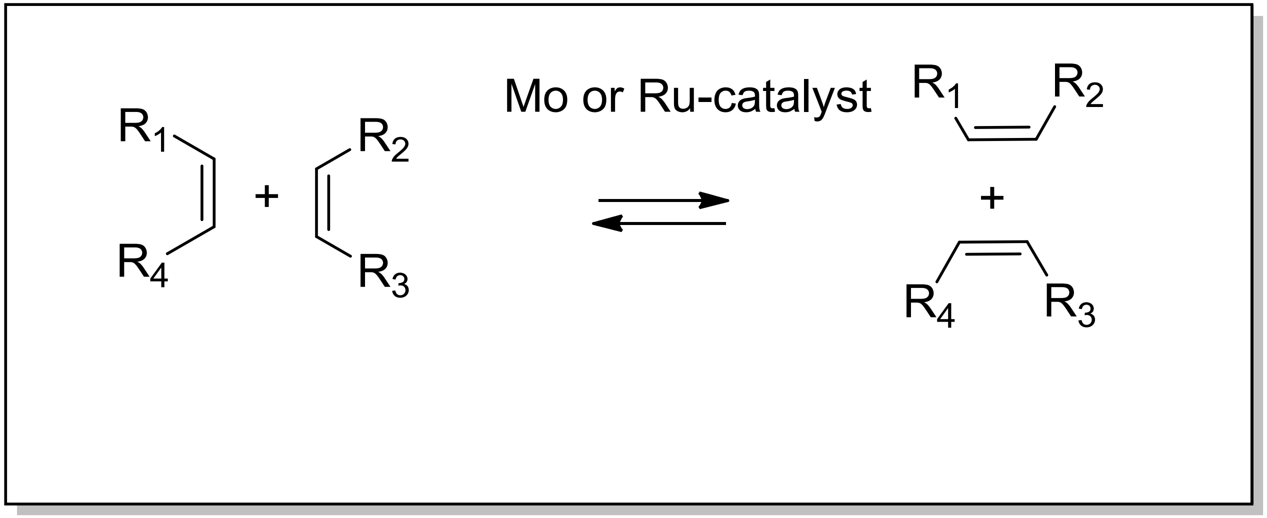


Mechanism



R.C. Larock, *J. Org. Chem*. **2001**, *66*, 412

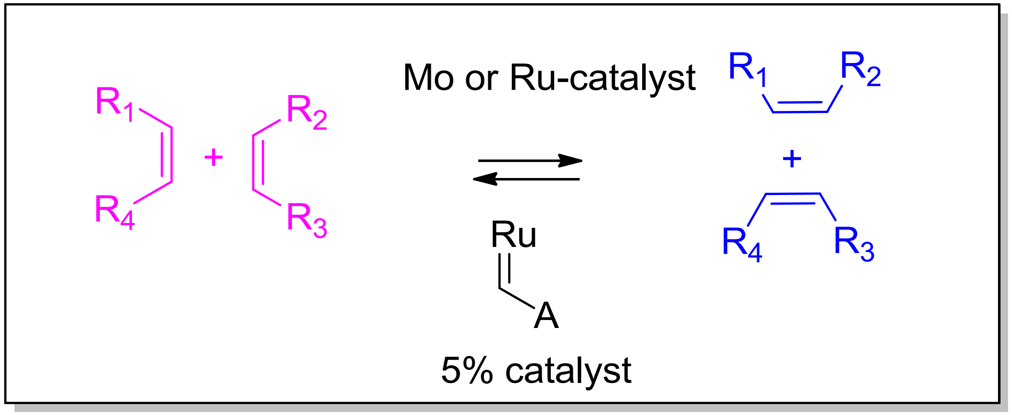
Olefin metathesis

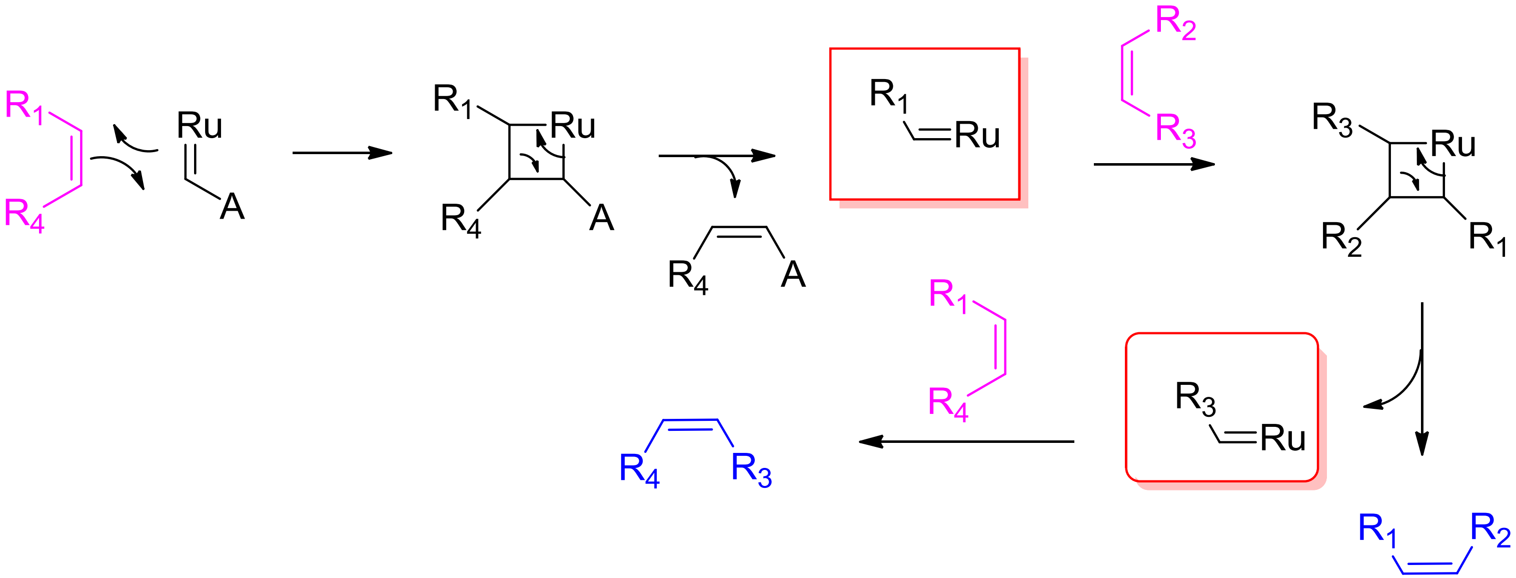


Reviews:

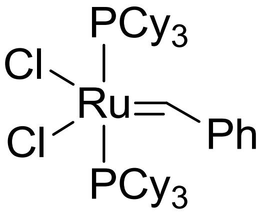
R.H. Grubbs, *Tetrahedron* **1998**, *54*, 4413.
A.S.K. Hashmi, *J. Prakt. Chemie* **1997**, *339*, 1954.
M.E. Maier, *Angew. Chem. Int. Ed*. **2000**, *39*, 2073.
S.Blechert, *Angew. Chem*. **1997**, *109*, 2124.
A.Fürstner, (Ed.) Alkene Metathesis in Organic Synthesis
in Top. Curr. Chem., Springer Verlag, Berlin, **1998**.
E.M. Carreira, *Synthesis* **2000**, 857.
Mechanistic study: R.H. Grubbs, *J. Am. Chem. Soc*. **2001**, *123*, 749.

Olefin metathesis mechanism

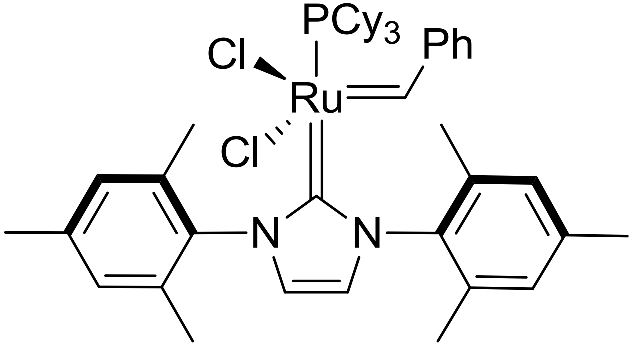




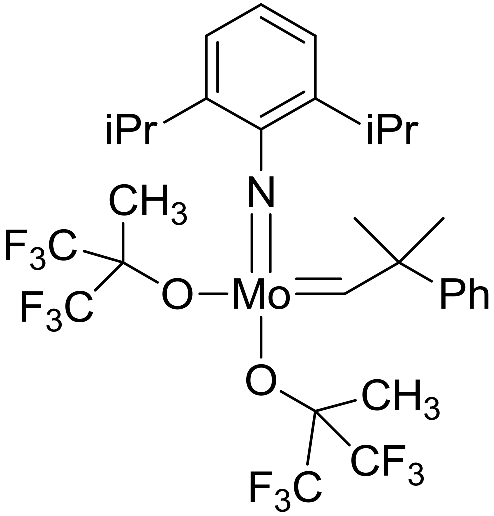
Olefin metathesis



1: Grubbs-catalyst
first generation
J. Am. Chem. Soc.
1995, *117*, 2108.

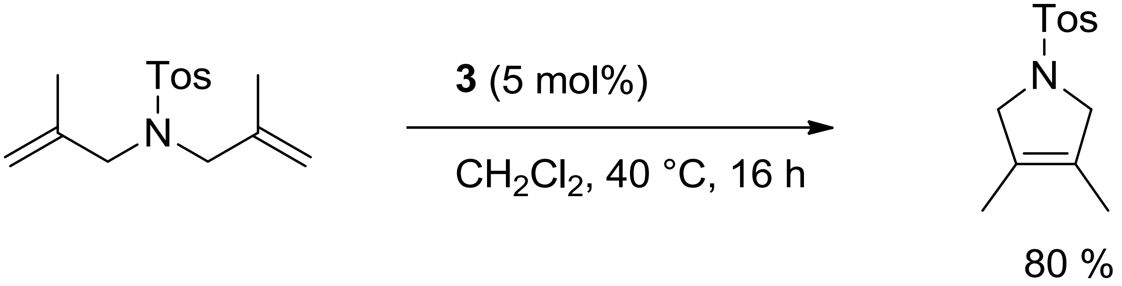


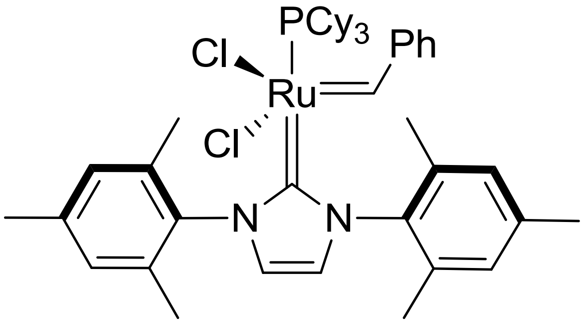
2: Grubbs-catalyst
second generation
US Patent No. 6,111,121
and 7,329,758



3: Schrock-catalyst
J. Am. Chem. Soc.
1998, *120*, 4041.

Olefin metathesis



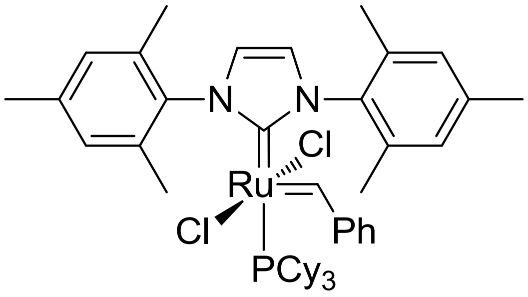


3

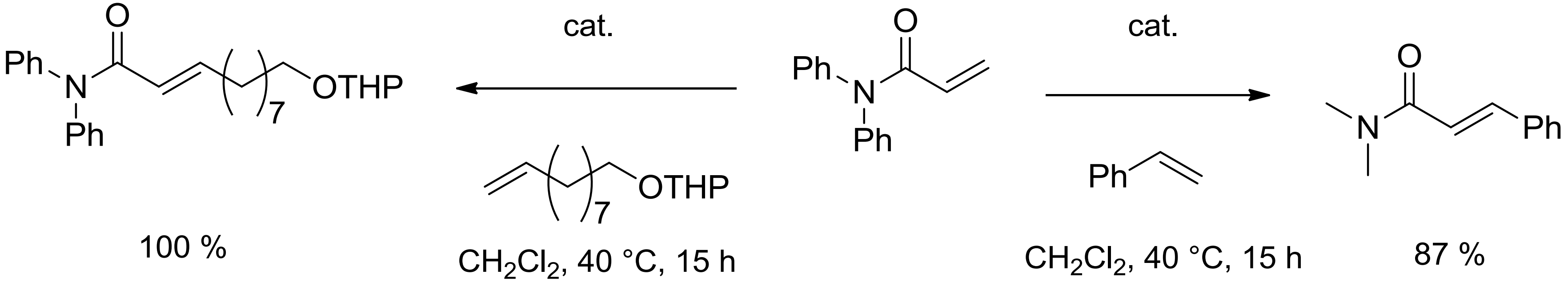
A. Fürstner, W.A. Herrmann, *Tetrahedron Lett*. **1999**, *40*, 4787

Olefin metathesis

Synthesis of α,β -unsaturated amides by olefin cross-metathesis



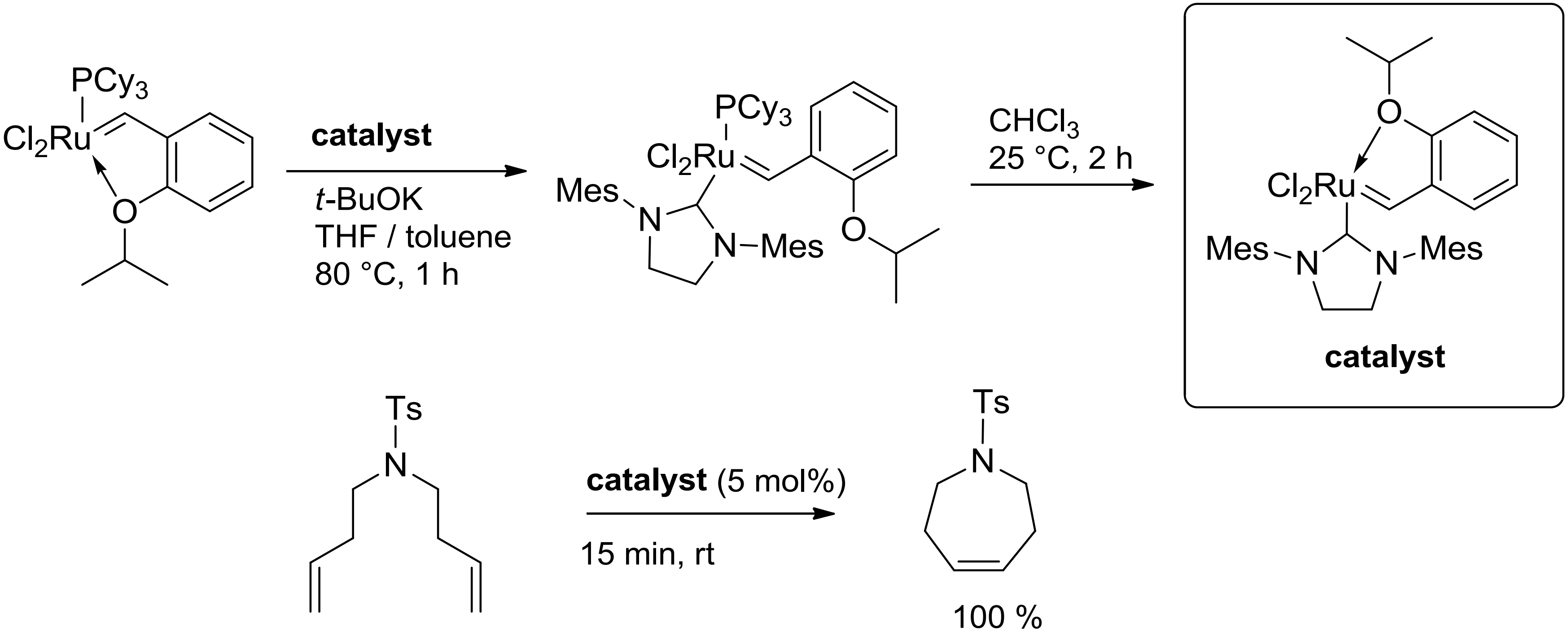
Cat.



R. H. Grubbs, *Angew. Chem. Int. Ed*. **2001**, *40*, 1277

Olefin metathesis

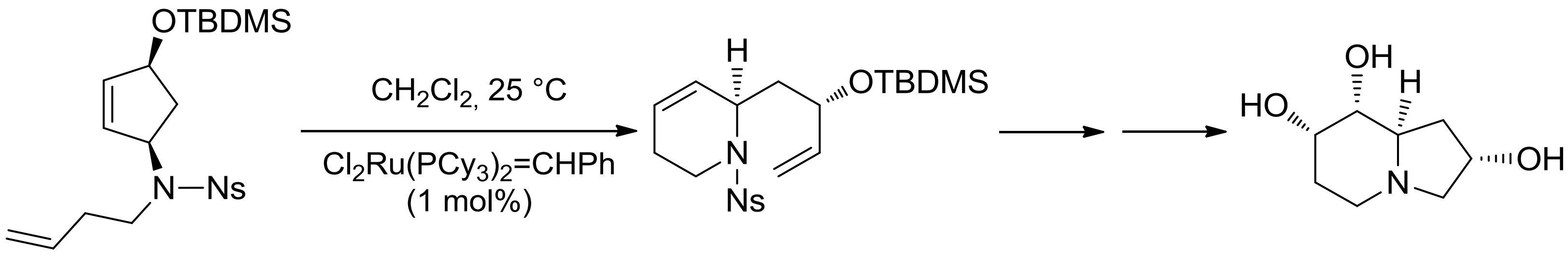
New phosphine-free metathesis catalyst



S. Blechert, *Tetrahedron Lett*. **2000**, *41*, 9973

Application to the synthesis of natural products

Synthesis of aza sugars

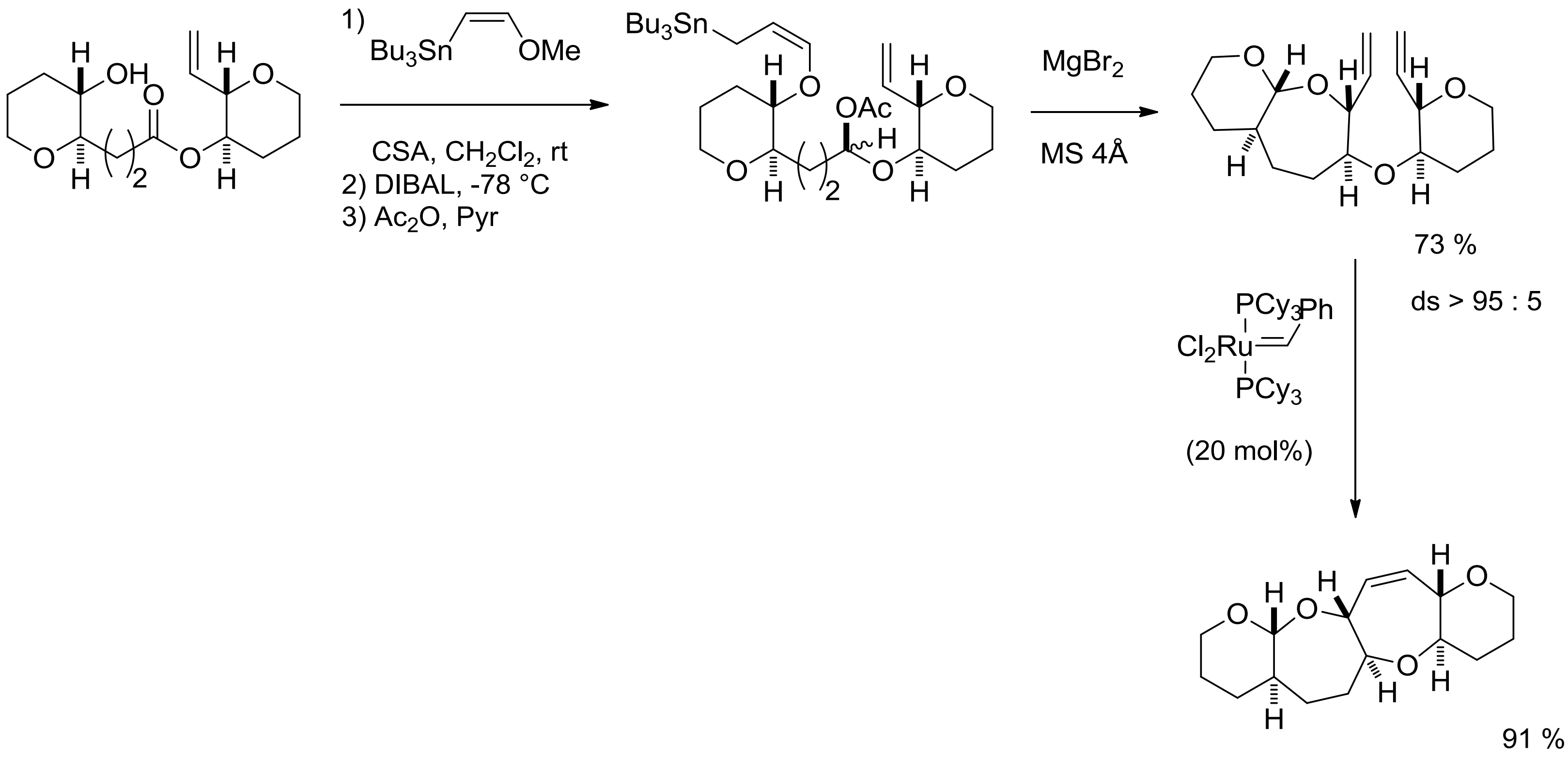


Ns = (*o*-NO_2)$C_6H_4SO_2$-

S. Blechert, *Org. Lett*. **2000**, *2*, 3971

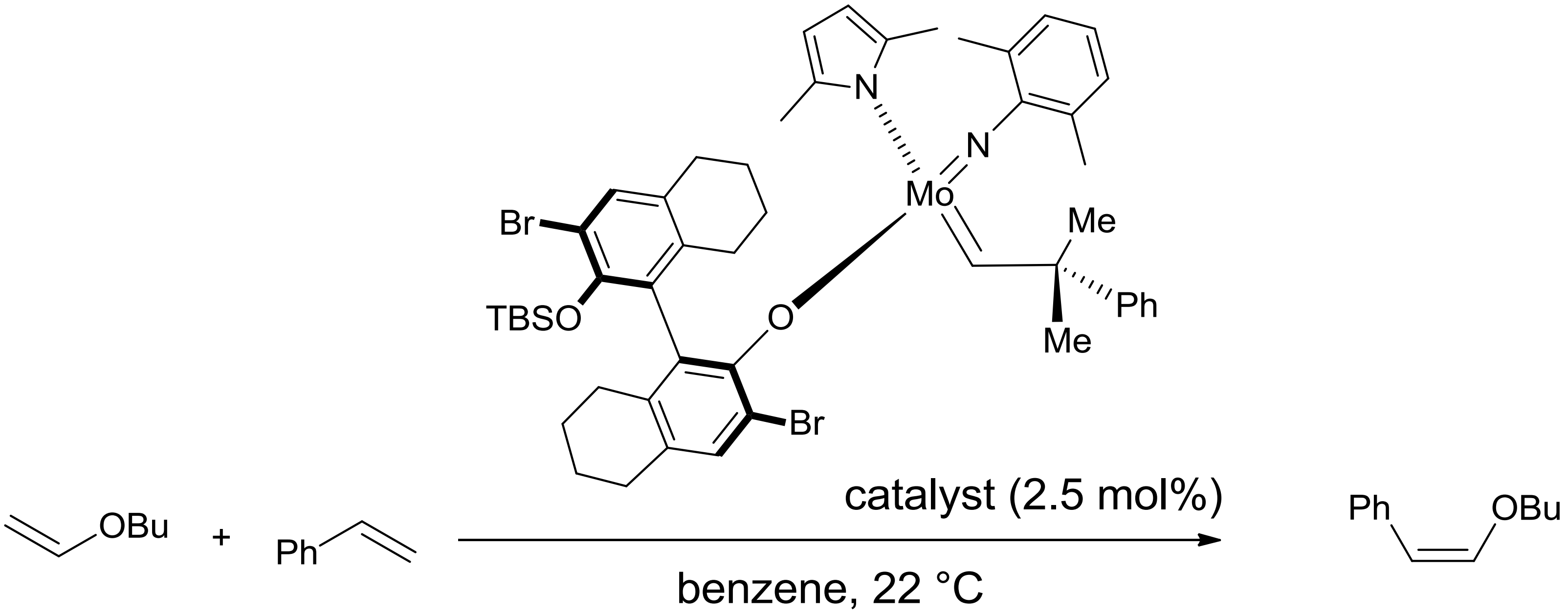
Olefin metathesis

Synthesis of complex ring-systems *via* metathesis



Y. Yamamoto, *J. Am. Chem. Soc*. **2001**, *123*, 6702

State of the art

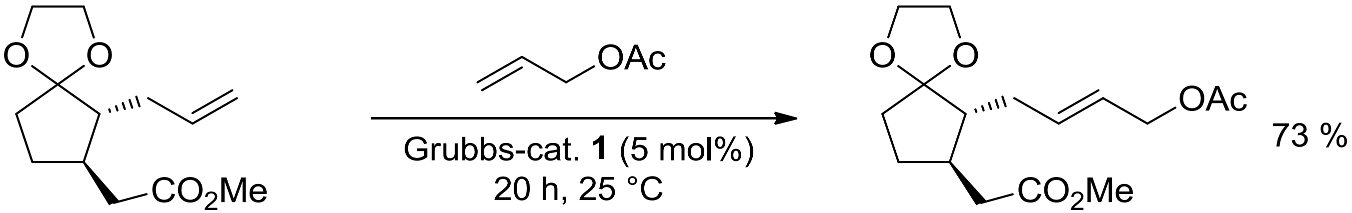


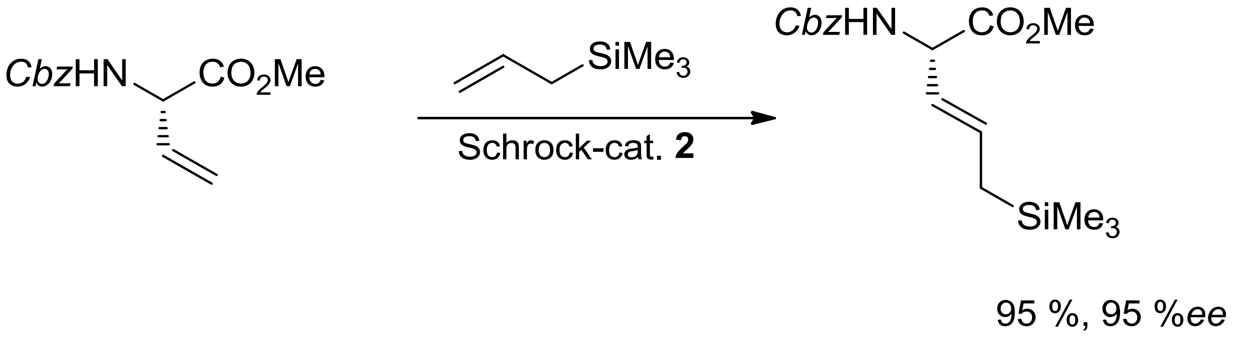
73%; Z:E > 98:2

A. H. Hoveyda, *Nature* **2011**, *471*, 461
A. H. Hoveyda, *Nature* **2008**, *456*, 933

Olefin metathesis

Synthesis of jasmonic acid derivatives

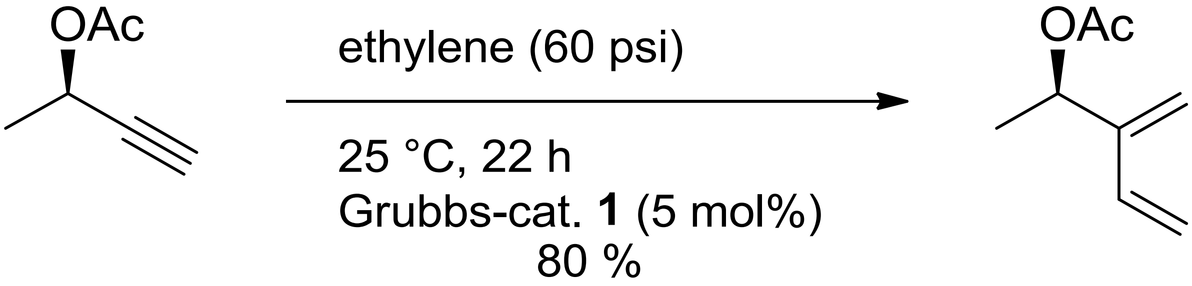




S. Blechert, *Chem. Eur. J*. **1997**, *3*, 441
S.E. Gibson, *Chem. Commun*. **1997**, 1107
S. Blechert, *Chem. Commun*. **1997**, 1949

Olefin metathesis

Cross-metathesis of alkynes with ethylene



ethylene (60 psi)

25 °C, 22 h

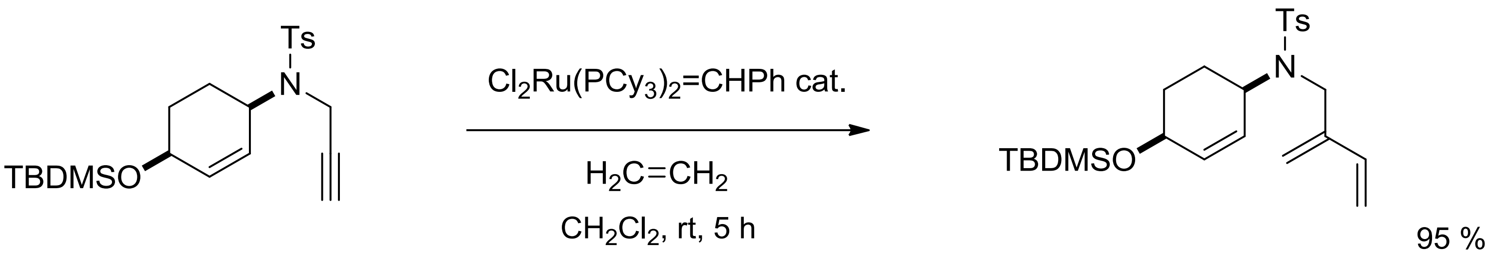
Grubbs-cat. **1** (5 mol%)

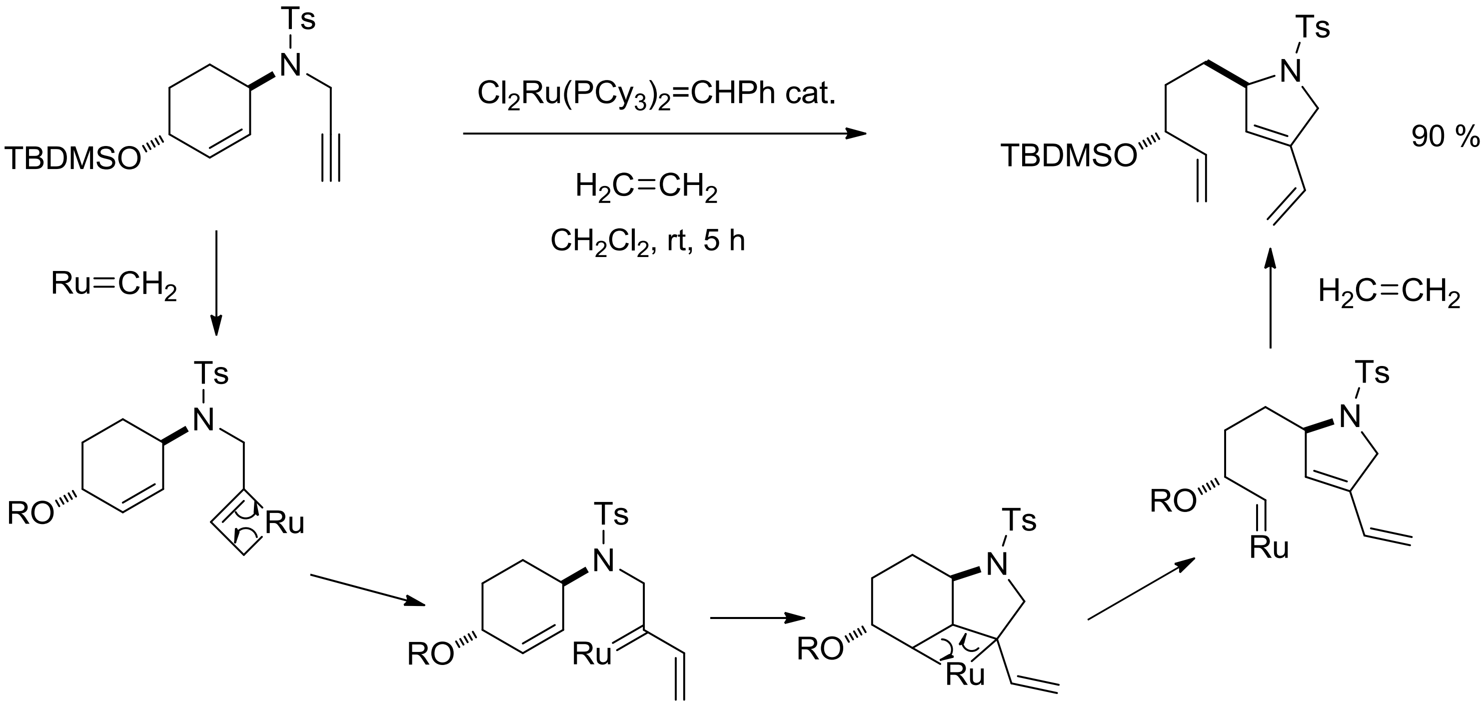
80 %

S.T. Diver, *J. Org. Chem*. **2000**, *2*, 1788

Olefin metathesis

Ru-catalyzed Ring-Opening and –Closing Enyne Metathesis

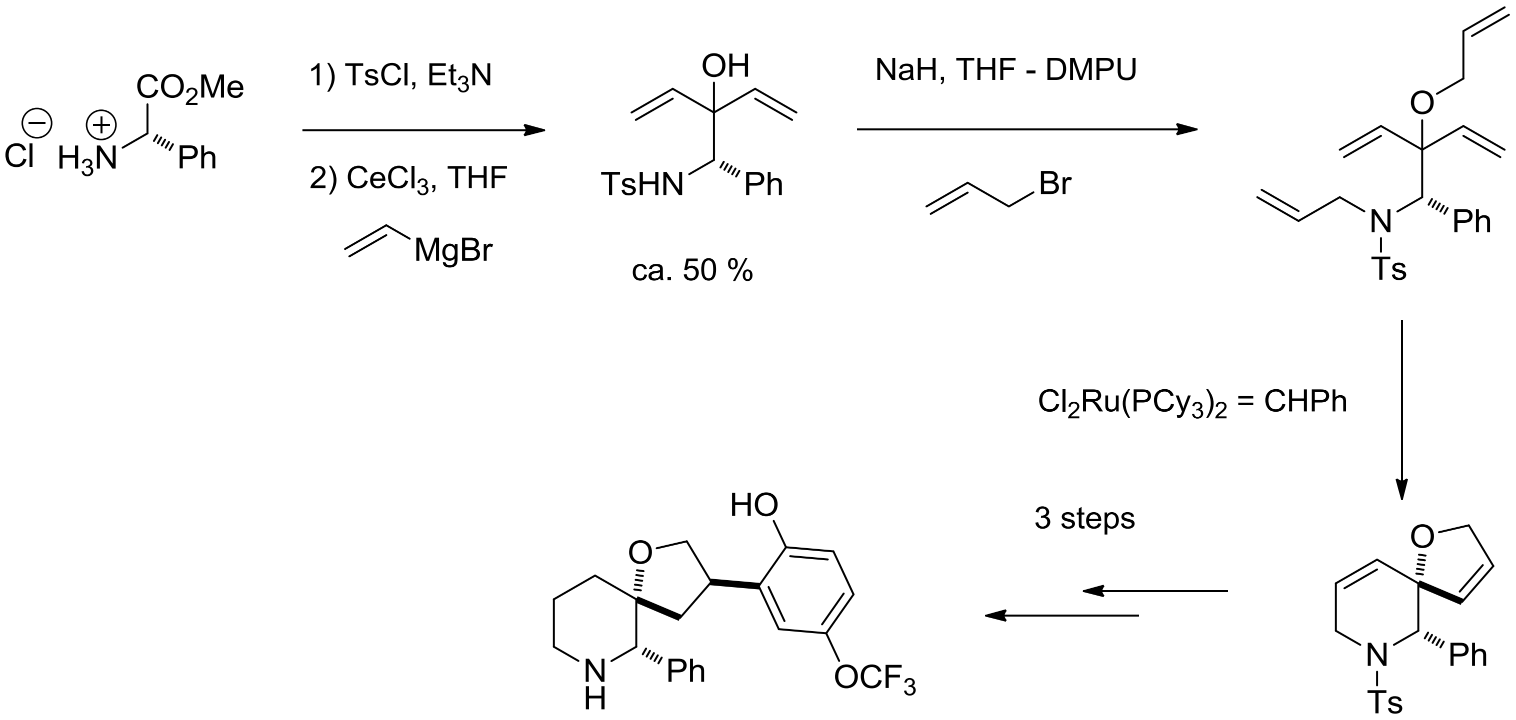




M. Mori, *Org. Lett*. **2001**, *3*, 1161

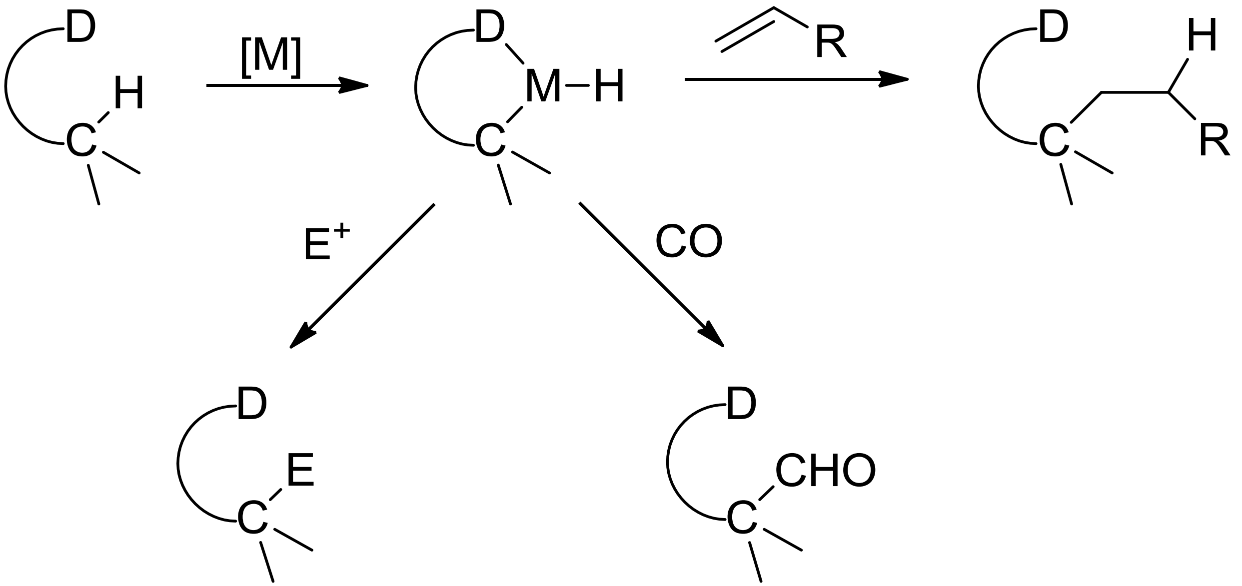
Olefin metathesis

A double ring closing metathesis for the synthesis of NK-1 receptor antagonists



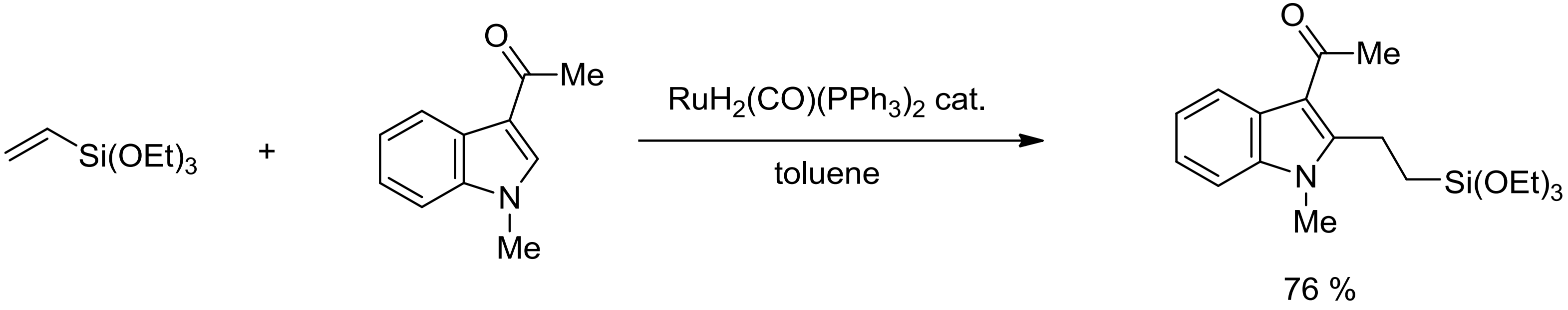
Merck-team *Org. Lett*. **2001**, *3*, 671

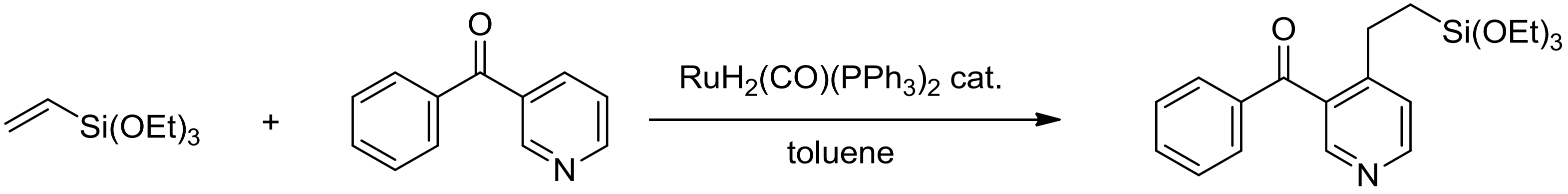
New C-H activation reactions



Book: S. Murai, (Ed.) Activation of Unreactive C-H Bonds in Organic Synthesis, Topics in Organometallic Chemistry, Springer, **1999**.

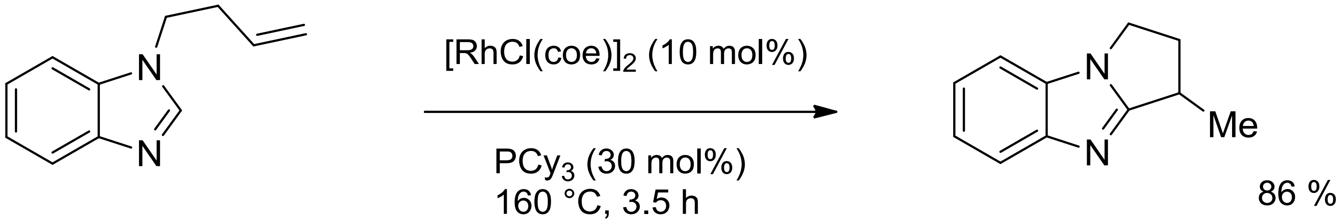
The Murai-reaction





R. Grigg, *Tetrahedron Lett*. **1997**, *38*, 5737
S. Murai, *Nature*, **1993**, *366*, 529
S. Murai, *J. Organomet. Chem*. **1995**, *504*, 151

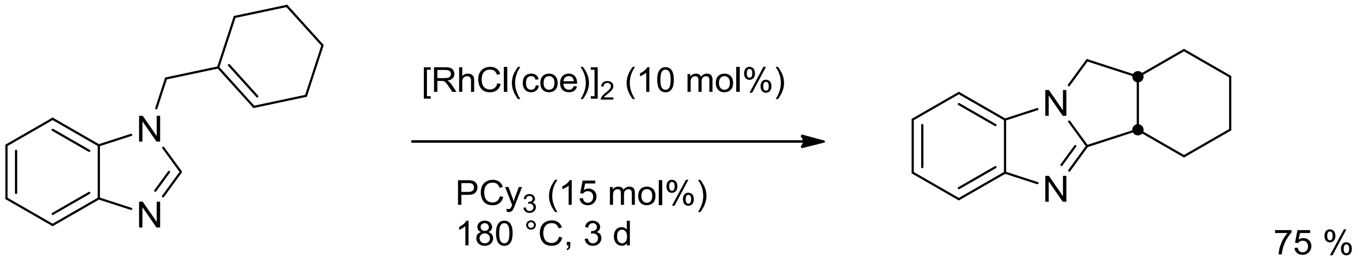
Annulation of heterocycles *via* a Rh-catalyzed C-H-activation



$[RhCl(coe)]_2$ (10 mol%)

PCy_3 (30 mol%)
160 °C, 3.5 h

86 %



$[RhCl(coe)]_2$ (10 mol%)

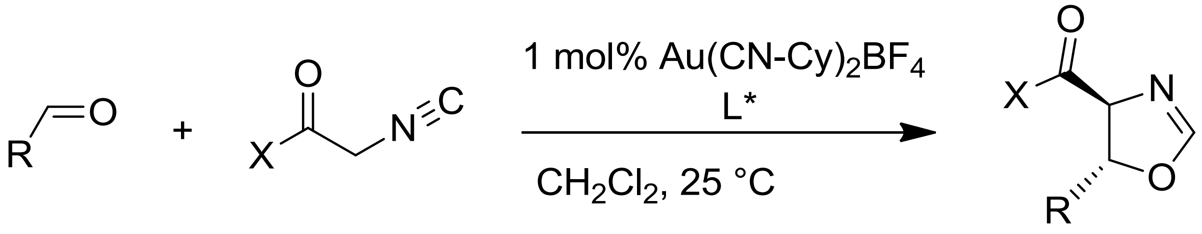
PCy_3 (15 mol%)
180 °C, 3 d

75 %

R. G. Bergman, J. Ellman, A. *J. Am. Chem. Soc*. **2001**, *123*, 2685

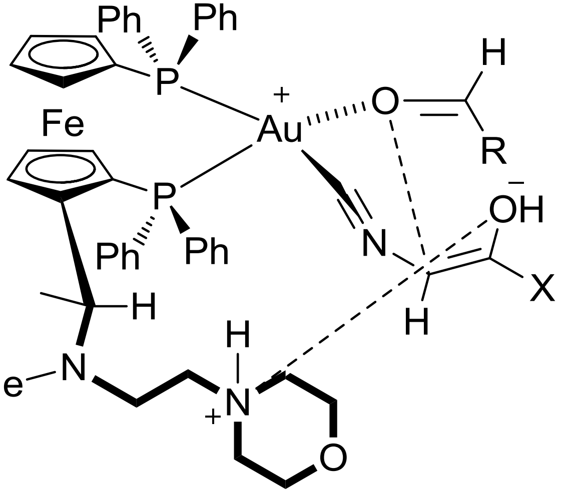
Gold-catalyzed organic reactions

Asymmetric aldol reaction



86-97%

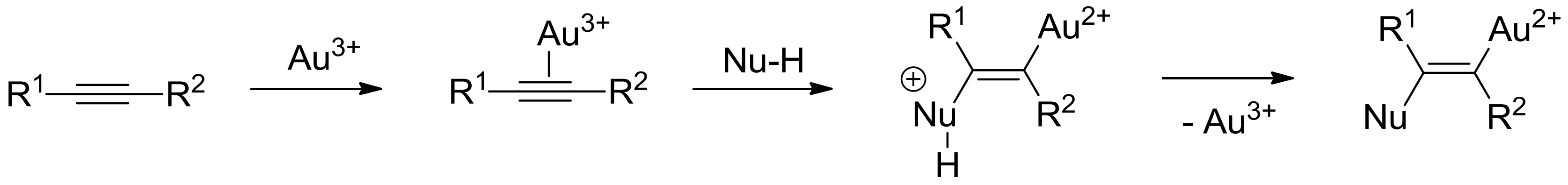
trans : *cis* up to 93 : 7
up to 94% ee

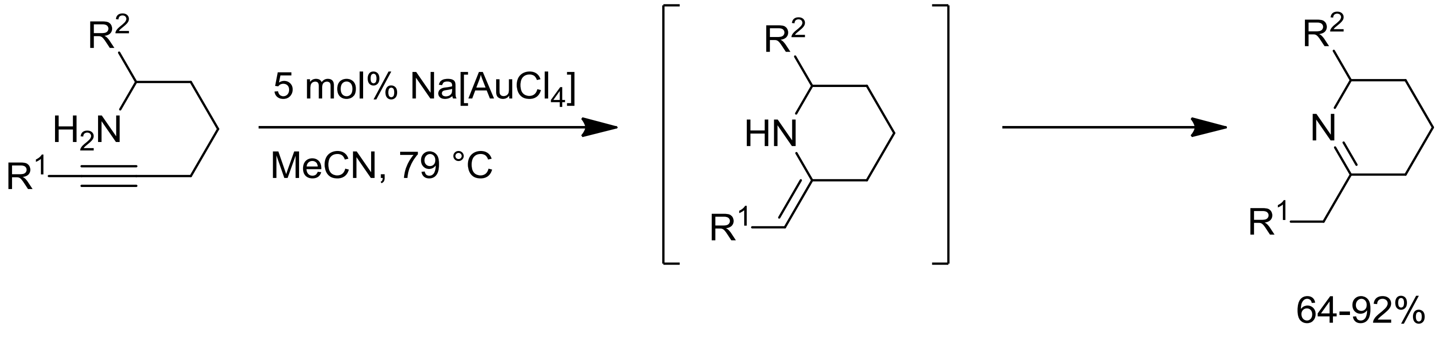


T. Hayashi *J. Am. Chem. Soc*. **1986**, *108*, 6405

Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds



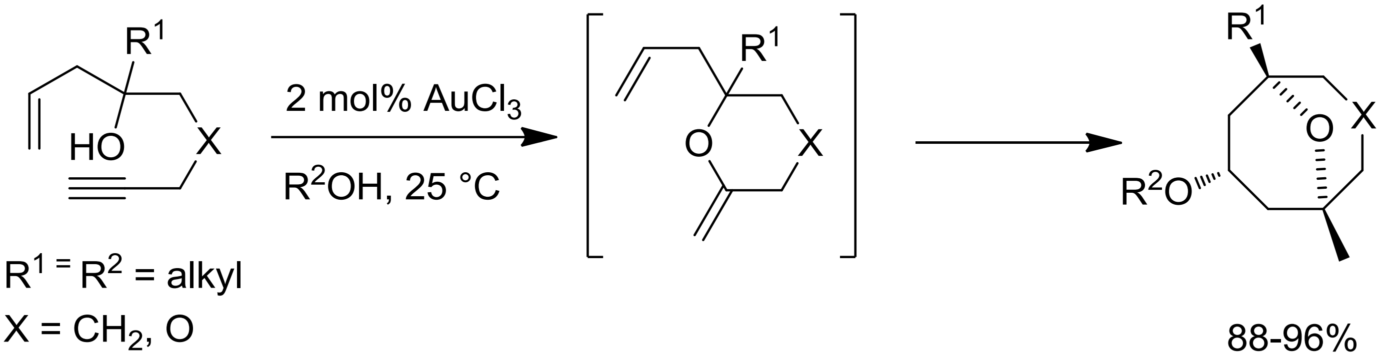


For a review see: A. S. Hashmi, *Chem. Rev*. **2007**, *107*, 3180

Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds:

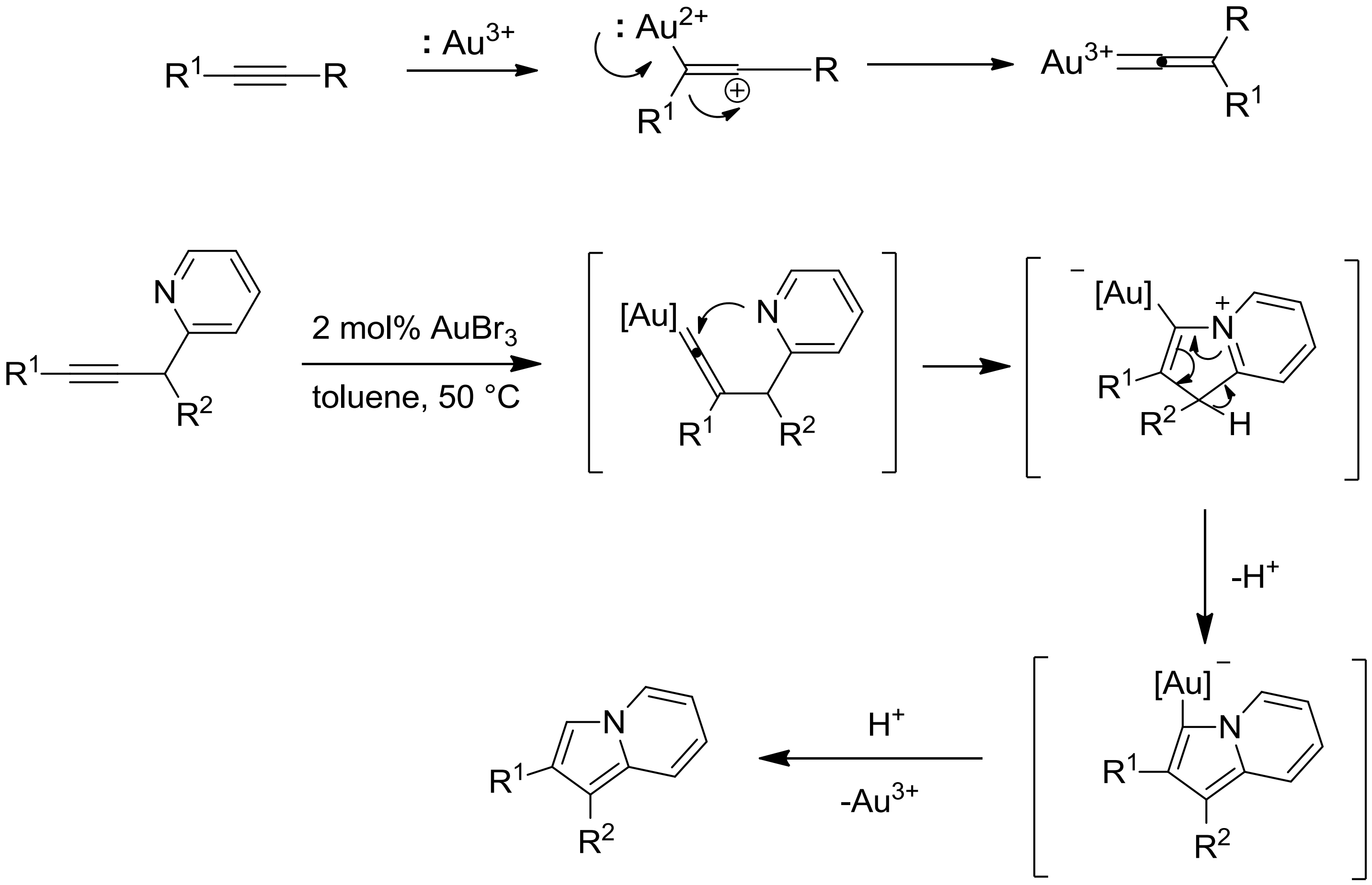
Au^{3+}-catalyzed cyclization followed by a Prins type cyclization



For a review see: A. S. Hashmi, *Chem. Rev*. **2007**, *107*, 3180

Gold-catalyzed organic reactions

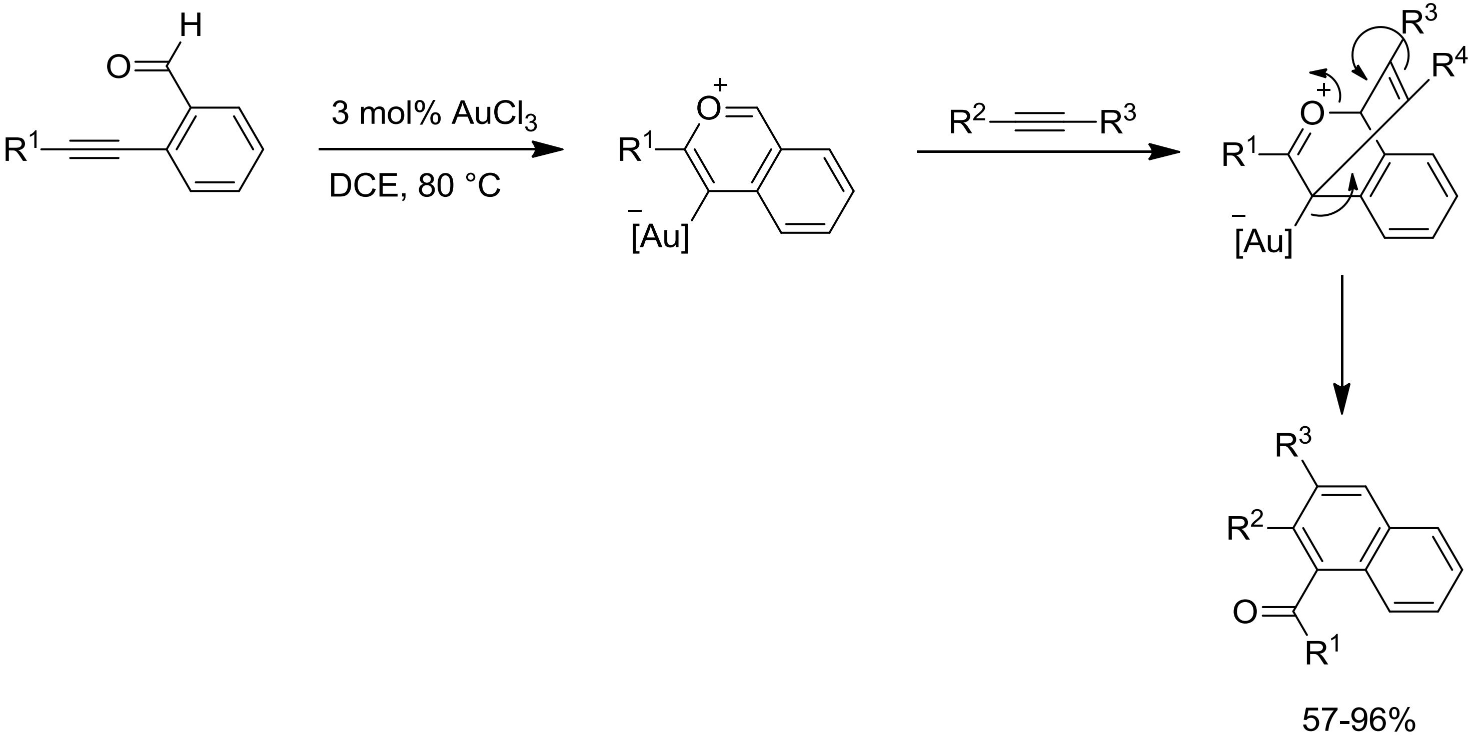
Gold(III)-triggered rearrangements



35-96%

Gold-catalyzed organic reactions

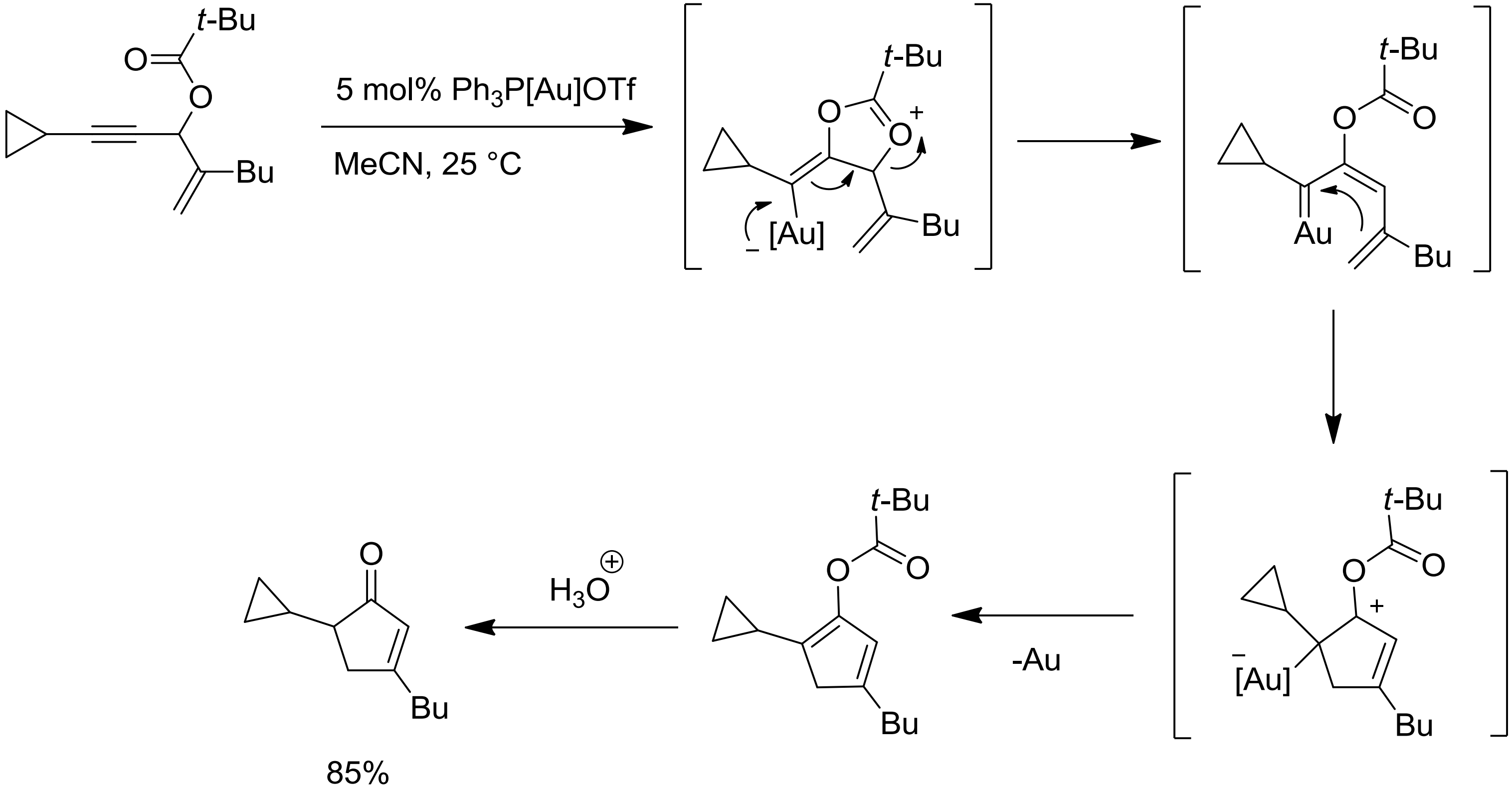
Au^{3+}-initiated cycloadditions



Y. Yamamoto, *J. Am. Chem. Soc*. **2003**, *125*, 10921

Gold-catalyzed organic reactions

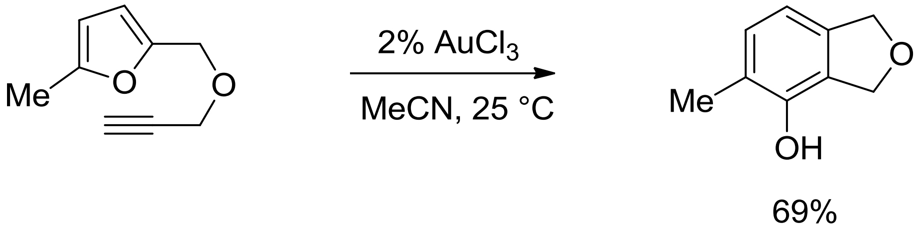
Use of electrophilic Gold(I)-complexes: Ph_3P-Au-OTf

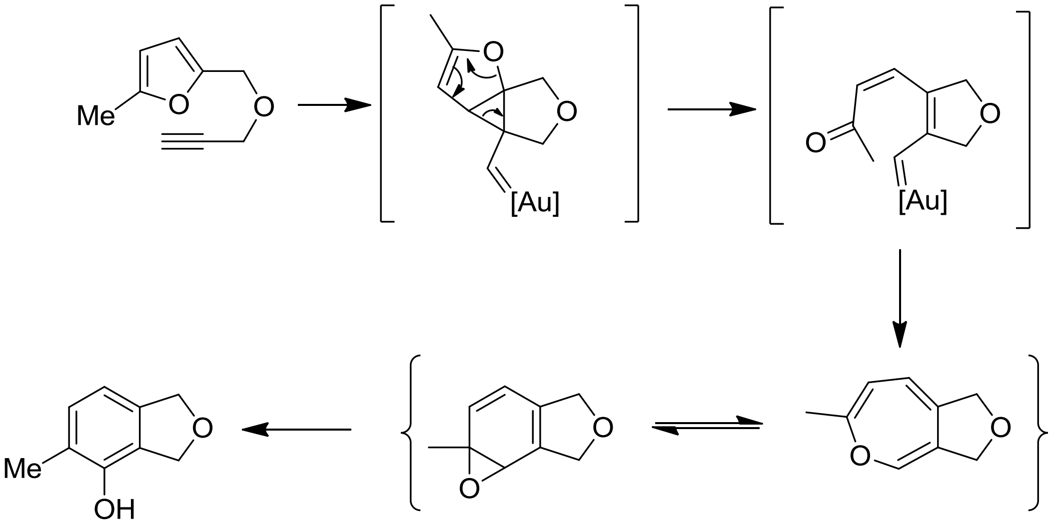


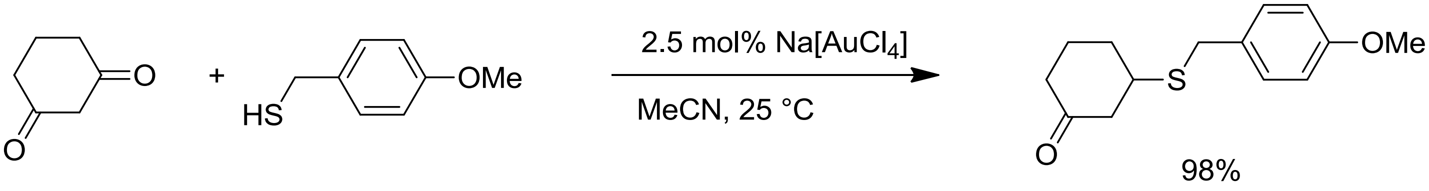
F. D. Toste *J. Am. Chem. Soc*. **2005**, *127*, 5802

Gold-catalyzed organic reactions

Intramolecular phenol synthesis







A. S. Hashmi, *J. Am. Chem. Soc*. **2000**, *122*, 11553