Organic Chemistry IV

Organometallic Chemistry for Organic Synthesis

Prof. Paul Knochel

LMU

2017

OCIV

Prüfung:

28. Juli 2017

9-11 Uhr

Wieland HS

Wiederholungsklausur:

5. September 2017

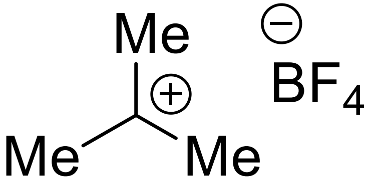
10-12 Uhr

Wieland HS

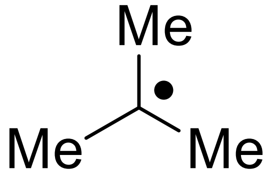
Recommended Literature

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** – Third manual, 3nd edition, Wiley, 2013, ISBN: 978-0-470-12217-4
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

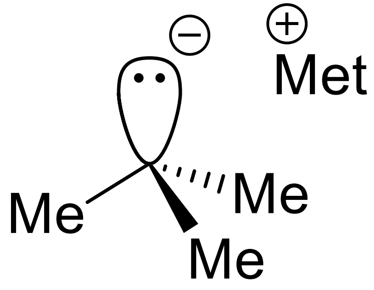
Importance of organometallics



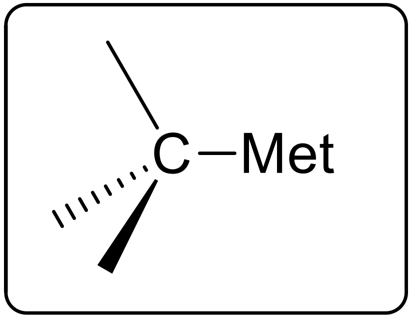
carbenium ion



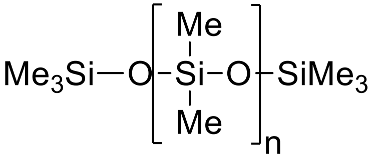
radical



organometallic
reagent



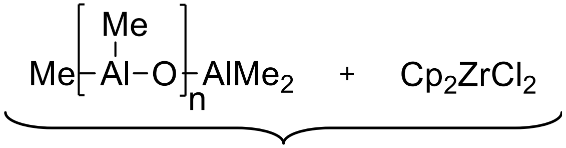
Industrial production



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

Silicone

Et_4Pb

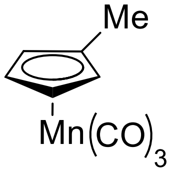


$\underbrace{Me{-}[Al(Me){-}O]_n{-}AlMe_2 \quad + \quad Cp_2ZrCl_2}$

Kaminsky catalyst
n=5-20   syndiotacticity of polypropylene

BuLi

$[Bu_3Sn]_2O$



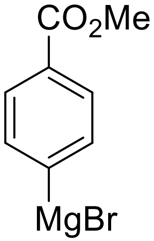
Industrial annual production of various organometallics

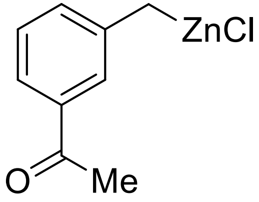
Organometallic	production [T / year]
Si	700 000
Pb	600 000
Al	50 000
Sn	35 000
Li	900

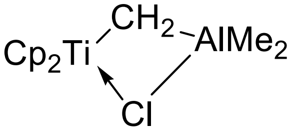
Organometallic reagents and catalysts for the organic synthesis

organometallic reagents:

BuLi







Tebbe reagent

$H(Cl)ZrCp_2$

Schwarz reagent

organometallic catalysts:

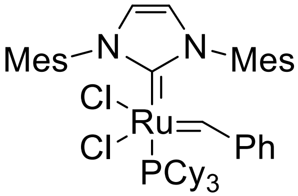
$Pd(PPh_3)_4$

$CpCo(CO)_2$

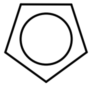
$[RhCl(CO)_2]_2$

$ClRh(PPh_3)_3$

Wilkinson's catalyst



Grubbs II catalyst



$\equiv$ Cp

Historic point of view

1757 - Louis Cadet de Gassicourt (parisian apothecary)

$$As_2O_3 + CH_3CO_2H \longrightarrow Me_2As{-}AsMe_2 + Me_2As{-}O{-}AsMe_2$$

cacodyl
56%

cacodyl-oxide
40%

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

$$Et^{\bullet} \;\cancel{\xleftarrow{\quad Zn \quad}}\; Et{-}I \xrightarrow[-ZnI_2]{Zn} Et_2Zn$$

ethyl radical

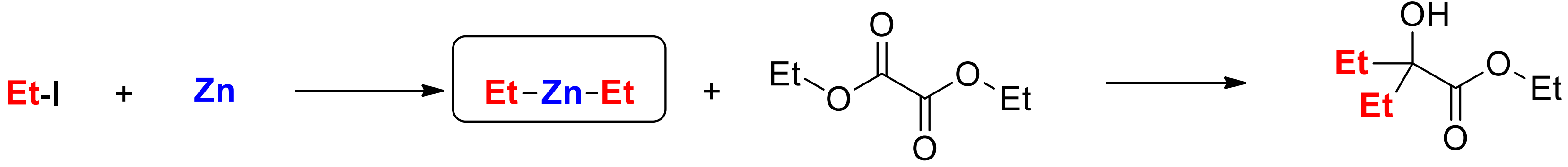
pyrophoric

Universität Marburg (1848)

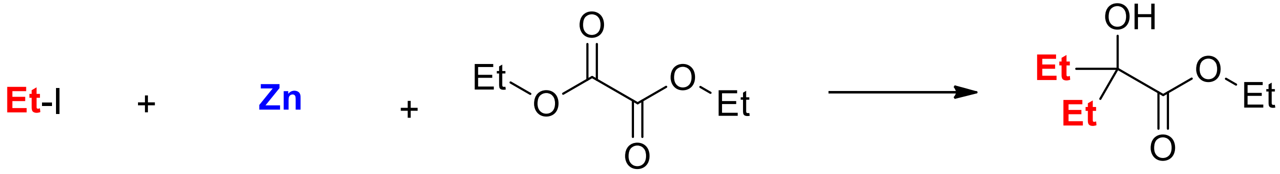
$$2/3\,Et_3Tl \xleftarrow[-Zn(0)\downarrow]{2/3\,Tl} Et_2Zn \xrightarrow[-Zn(0)\downarrow]{2\,Na} 2\,Et{-}Na$$

Organometallic chemistry of the XIX century

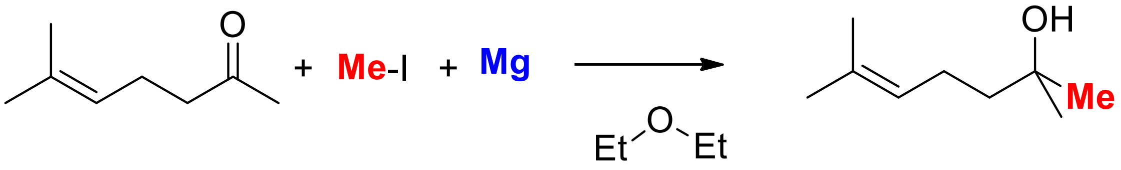
Frankland **1848**, **1863**



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



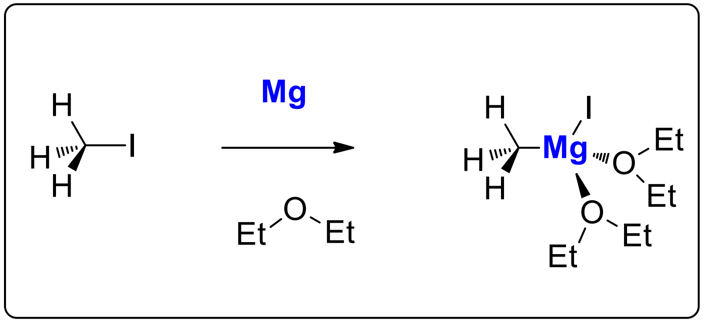
Barbier **1899**

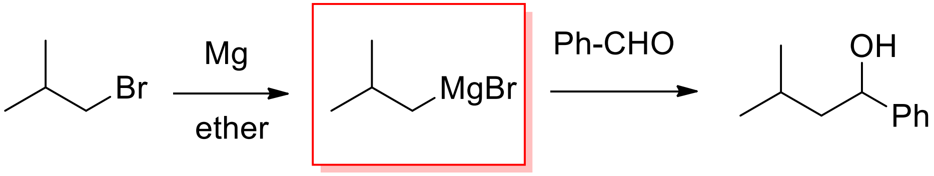


Ph. Barbier *Comptes Rendus de l'Académie des Sciences*, **1899**, *128*, 110

Organometallic chemistry of the XIX century

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



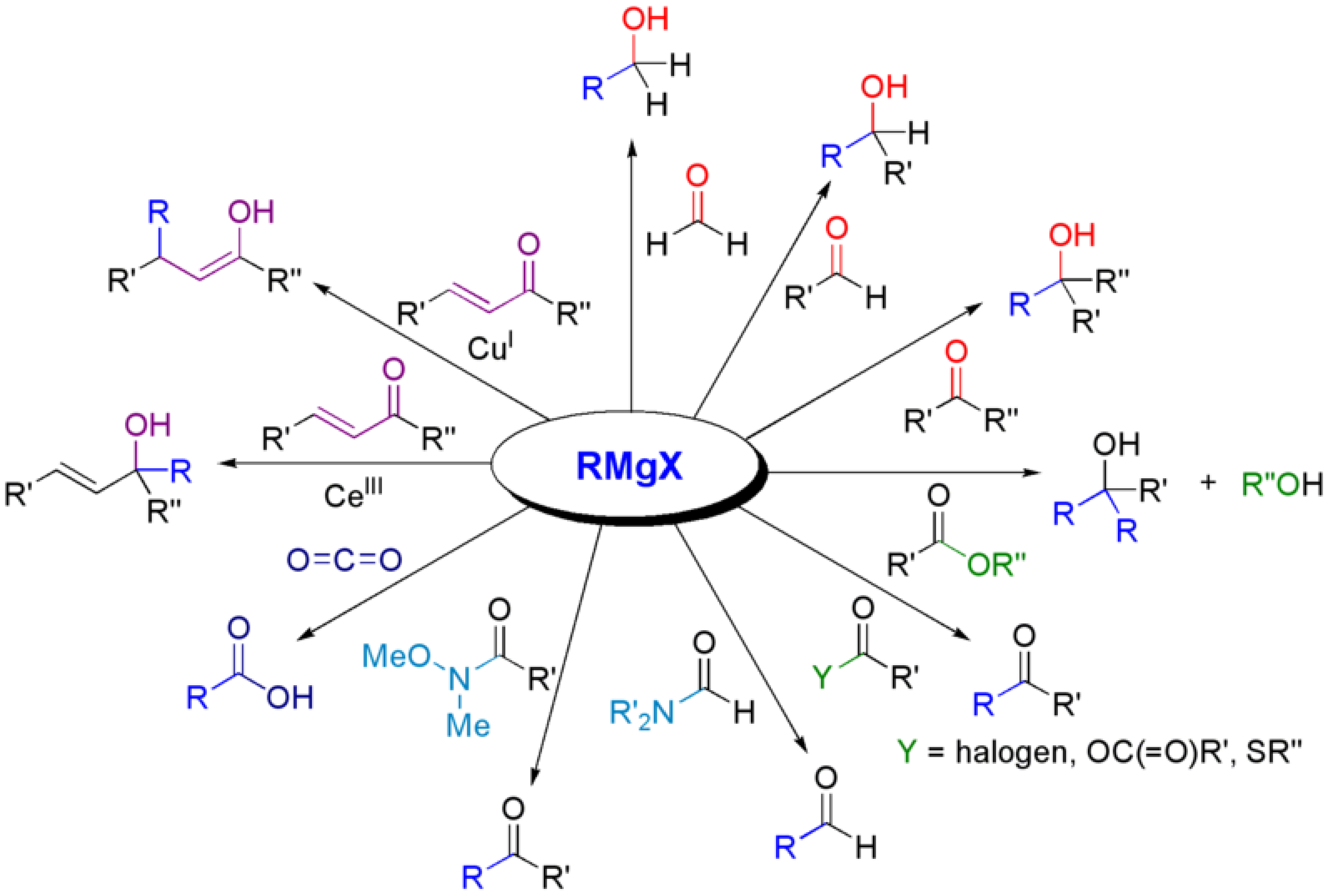


reactif de Grignard

V. Grignard

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

Reactivity of the Grignard reagents



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

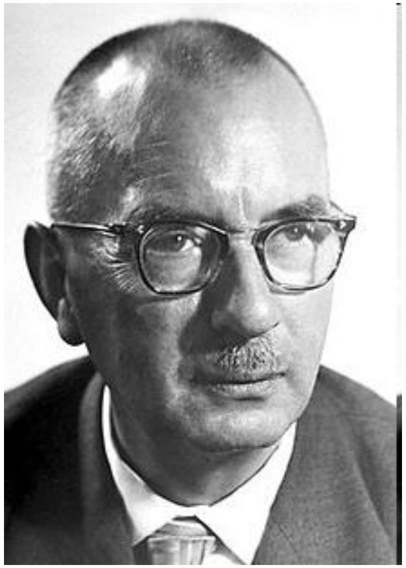
Historic point of view

Victor Grignard (1900)

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

Karl Ziegler (1919)

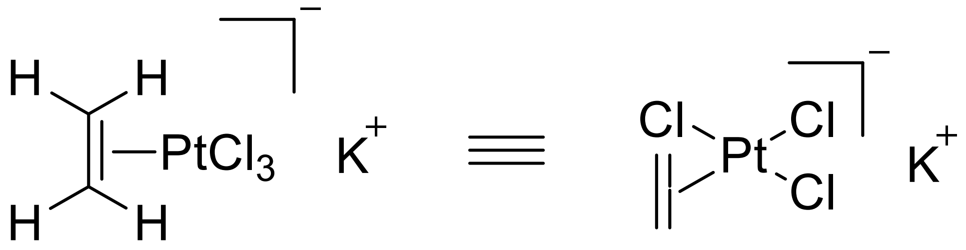
$$\mathrm{BuCl} + 2\mathrm{Li} \xrightarrow[\text{under Argon}]{\text{pentane}} \mathrm{BuLi} + \mathrm{LiCl}$$



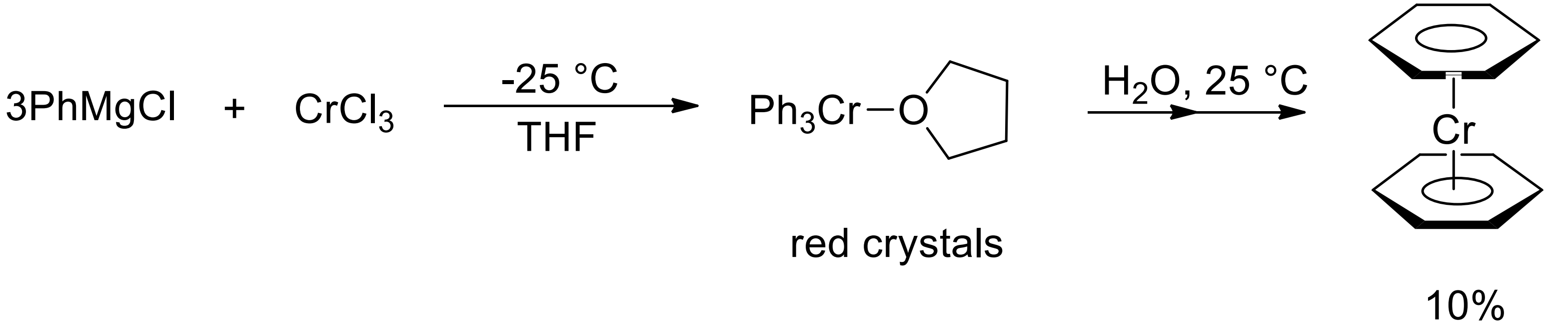
Historic point of view

first transition metal organometallics:

Zeise's Salz (1827)



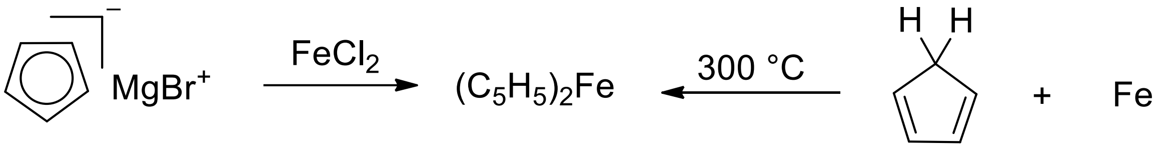
Hein (1919)



Historic point of view

1951 : synthesis of ferrocene

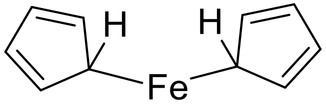
Pauson (Scotland)	7. August 1951
Miller	11. June 1951



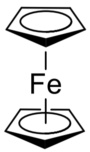
Smp.: 172 °C

G. Wilkinson

1952
structural proposal by Pauson



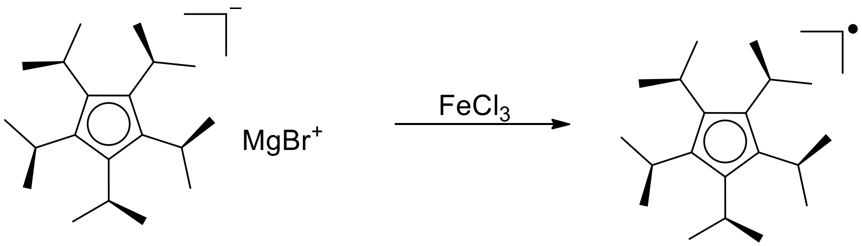
correct structure by G. Wilkinson and R. B. Woodward



ferrocene

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

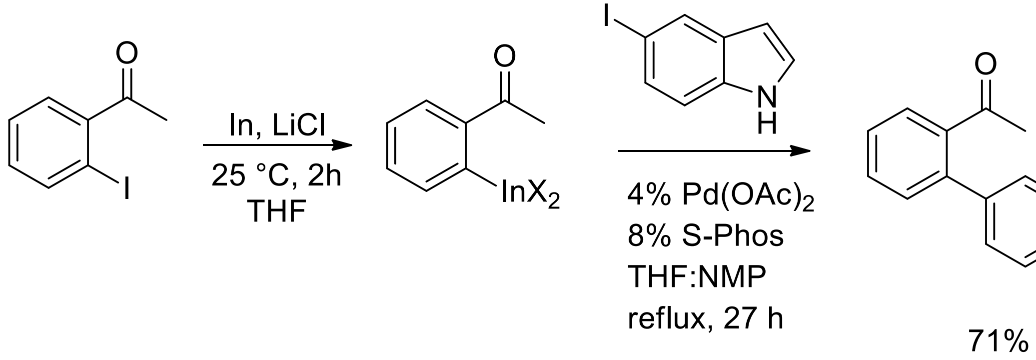
R. B. Woodward

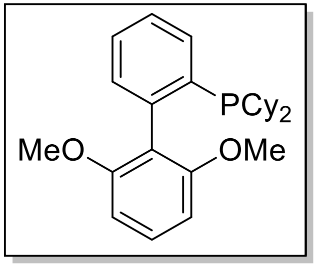


H. Sitzmann *J. Am. Chem. Soc.* **1993**, *115*, 12003 radical formation

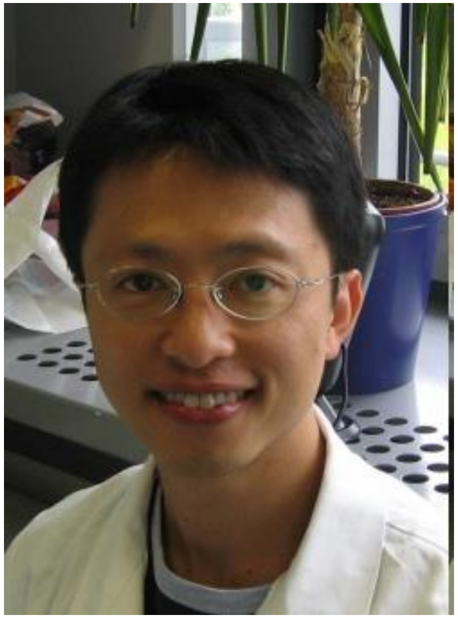
Goal of the lecture

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





S-Phos

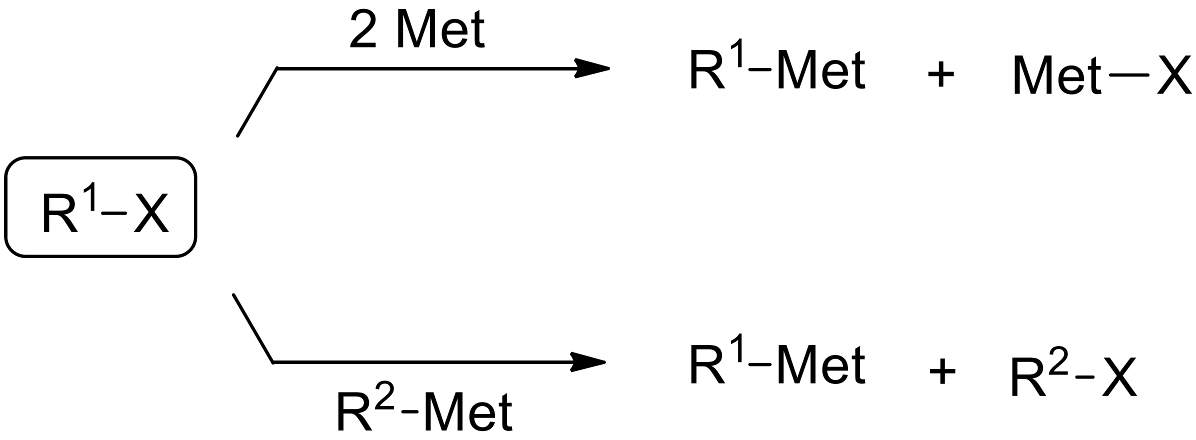


Y.-H. Chen, *Angew. Chem. Int. Ed*. **2008**, *47*, 7648.

General synthetic methods for preparing organometallic reagents

classification according to starting materials

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

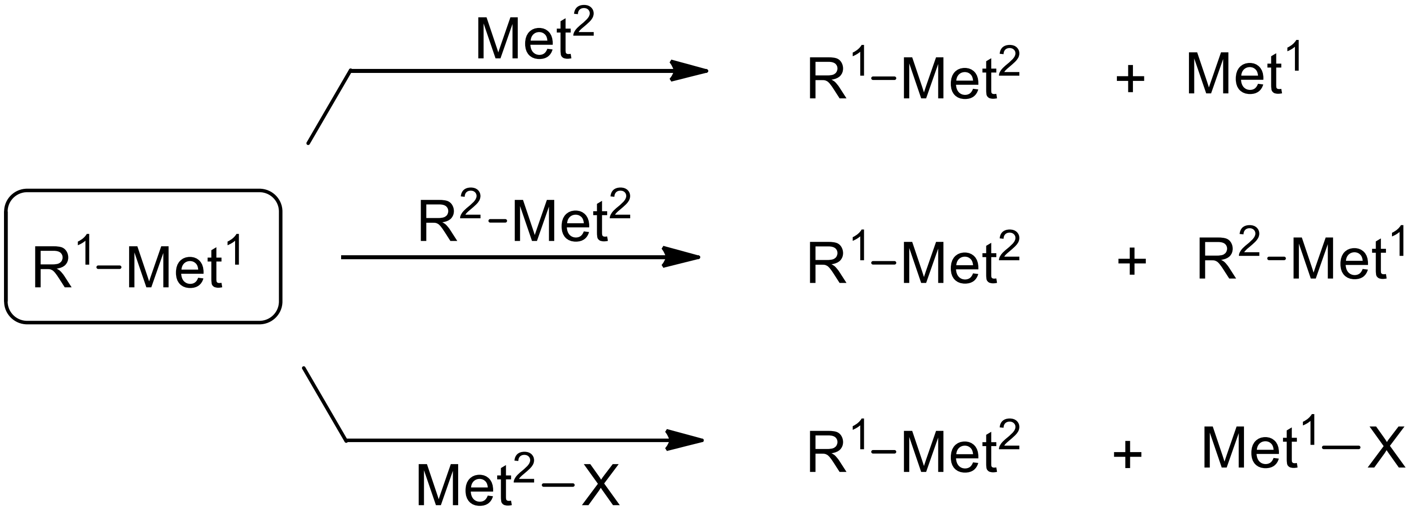


$$R^1\text{–}X \xrightarrow{2\ \mathrm{Met}} R^1\text{–}\mathrm{Met} + \mathrm{Met}\text{–}X$$

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

Classification according to starting materials

transmetalation



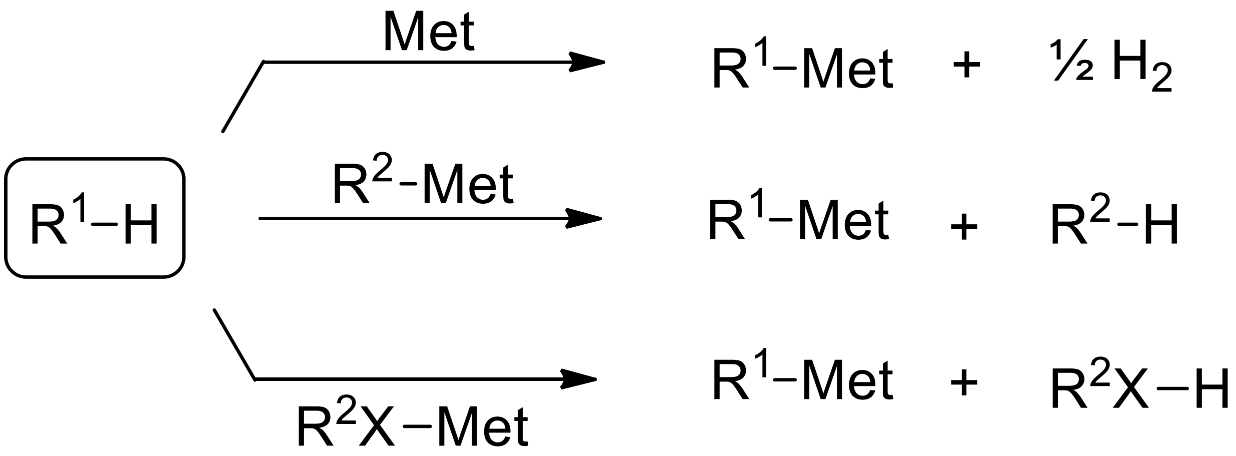
$$\boxed{R^1\text{–}Met^1} \xrightarrow{Met^2} R^1\text{–}Met^2 + Met^1$$

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

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

Classification according to starting materials

metalation



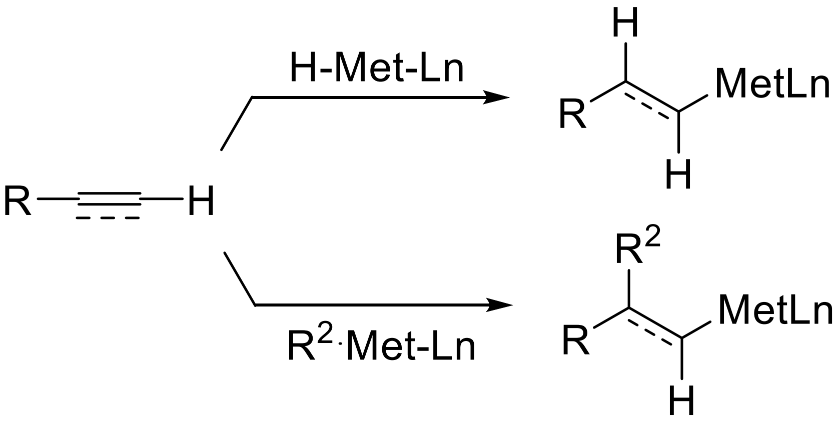
$$R^1\text{–H} \xrightarrow{\text{Met}} R^1\text{–Met} + \tfrac{1}{2}\,H_2$$

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

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

Classification according to starting materials

carbometalation and hydrometalation



Hydrometalation

Carbometalation

Synthesis starting from organic halides

direct synthesis - oxidative addition

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

driving force of the reaction:

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

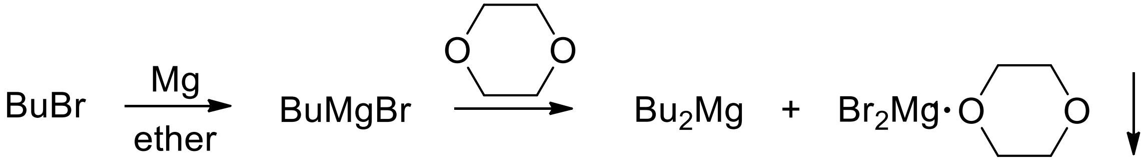
$$4\ \mathrm{EtCl} \quad + \quad 3\ \mathrm{Pb} \longrightarrow \mathrm{Et_4Pb} \quad + \quad 2\ \mathrm{PbCl_2} \qquad \text{endothermic}$$

$$4\ \mathrm{NaPb} \quad + \quad 4\ \mathrm{EtCl} \longrightarrow \mathrm{Et_4Pb} \quad + \quad 3\ \mathrm{Pb} \quad + \quad 3\ \mathrm{NaCl} \qquad \text{exothermic}$$

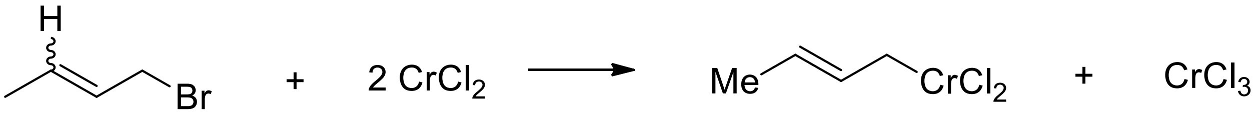
Direct Synthesis - Oxidative Addition

examples:

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



$$PbI_2 + MeI \longrightarrow MePbI_3$$



E/Z-mixture

pure E-isomer

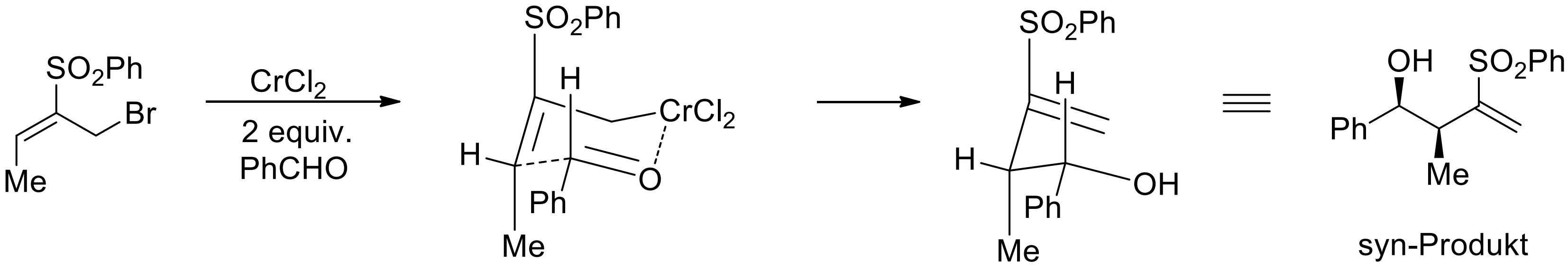
Direct Synthesis - Oxidative Addition

mechanism:

$$\mathrm{R\text{-}Br} + \dot{\mathrm{Cr}}\mathrm{Cl_2} \longrightarrow \mathrm{R}\cdot + \mathrm{BrCrCl_2}$$

$$\mathrm{R}\cdot + \dot{\mathrm{Cr}}\mathrm{Cl_2} \longrightarrow \mathrm{RCrCl_2}$$

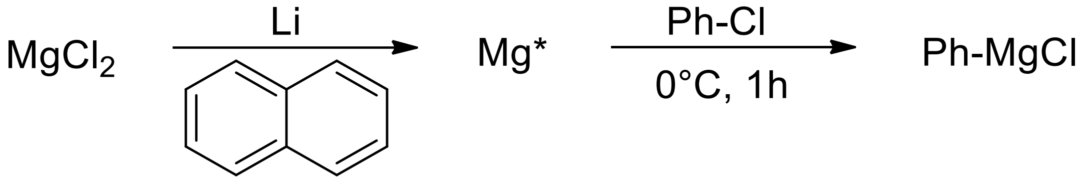
$$\mathrm{R\text{-}Br} + 2\,\dot{\mathrm{Cr}}\mathrm{Cl_2} \longrightarrow \mathrm{RCrX_2} + \mathrm{CrX_3}$$

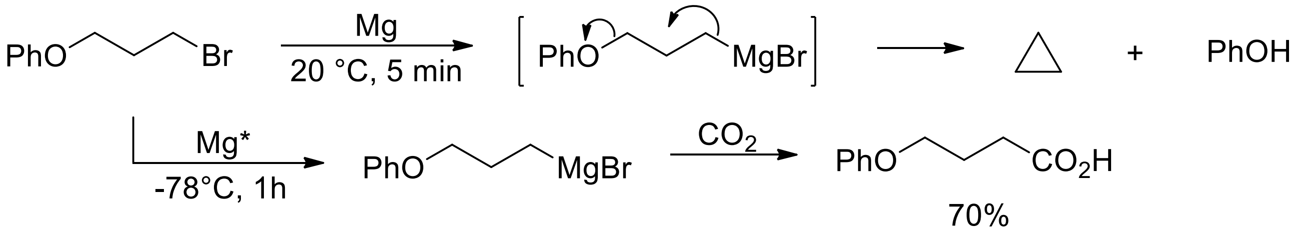


P. Knochel *Tetrahedron Lett*. **1986**, *27*, 5091

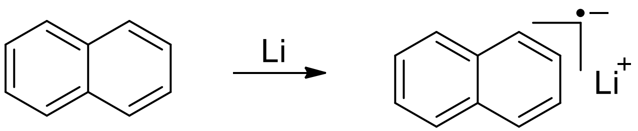
Activation of the metal: the *Rieke*-approach

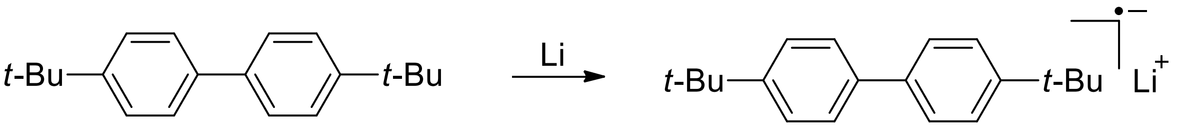
activation of the metal: R. D. Rieke, *Science* **1989**, *246*, 1260





Activation of lithium: formation of soluble Li-sources:

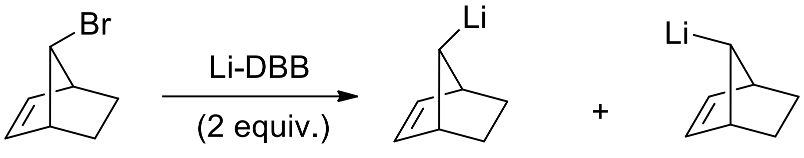




P.P. Freeman, L.L. Hutchinson *J. Org. Chem*. **1983**, *48*, 4705

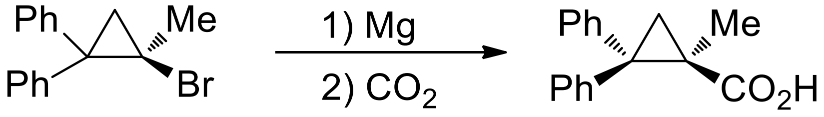
Mechanism of the metal insertion

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



80 : 20

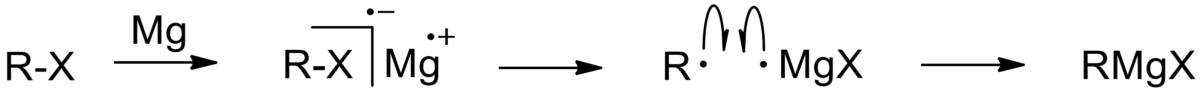
loss stereochemical information



90% ee

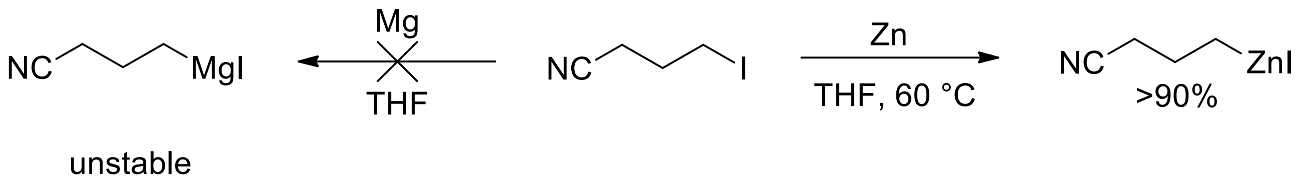
12% ee

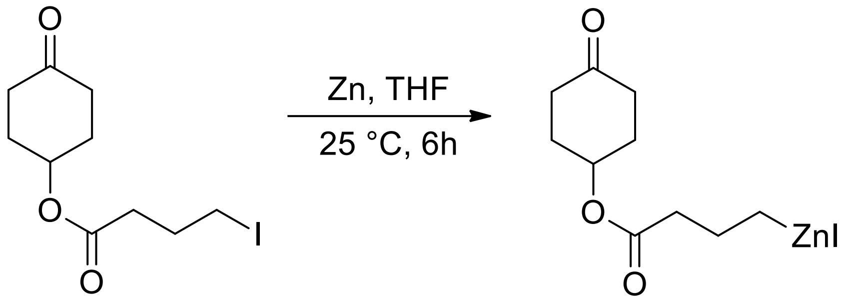
H.M. Walborsky: *J. Am. Chem. Soc*. **1989**, *11*, 1896



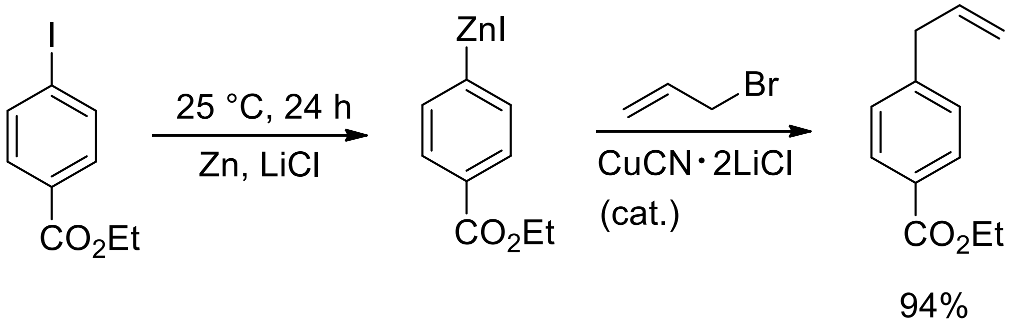
radical mechanism

Preparation of functionalized organometallics



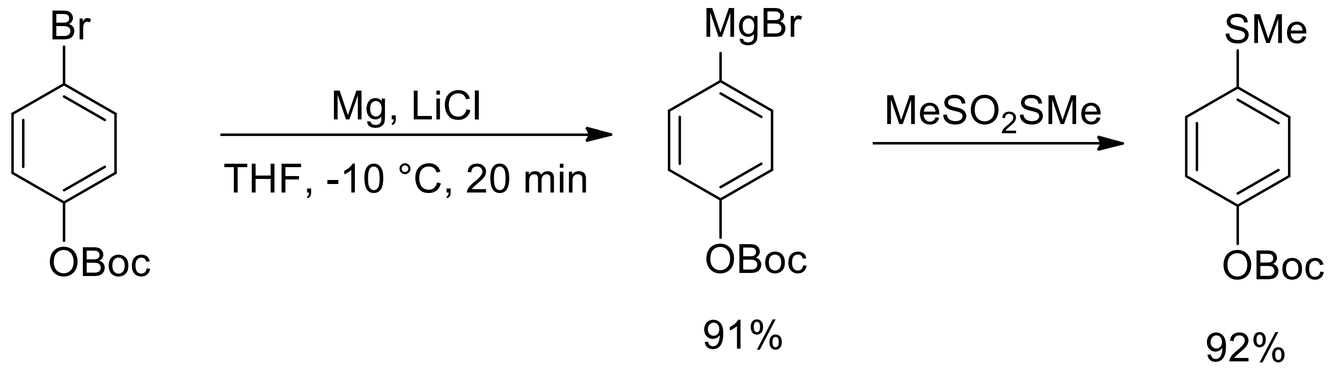


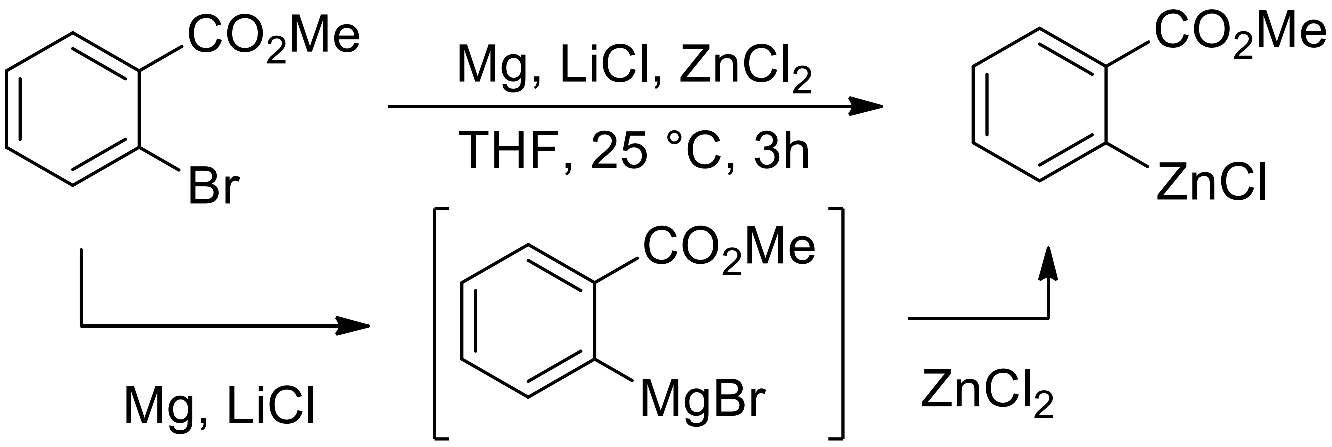
P. Knochel, *J. Org. Chem*. **1988**, *53*, 2390
P. Knochel, *Org. React*. **2001**, *58*, 417.



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

Preparation of functionalized organometallics

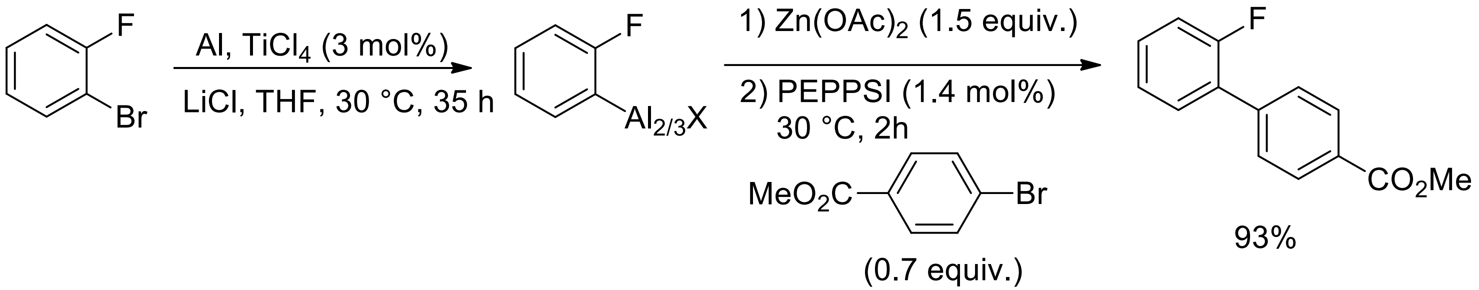




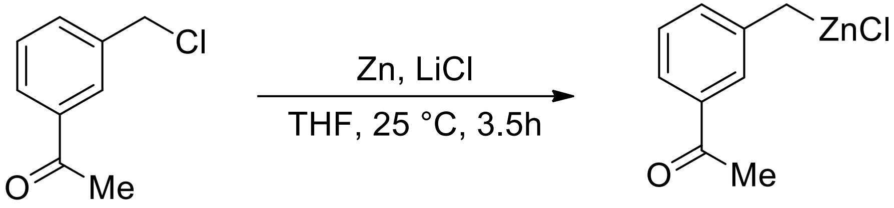
F. Piller, P. Knochel *Chem. Eur. J*. **2009**, *15*, 7192

Preparation of functionalized organometallics

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



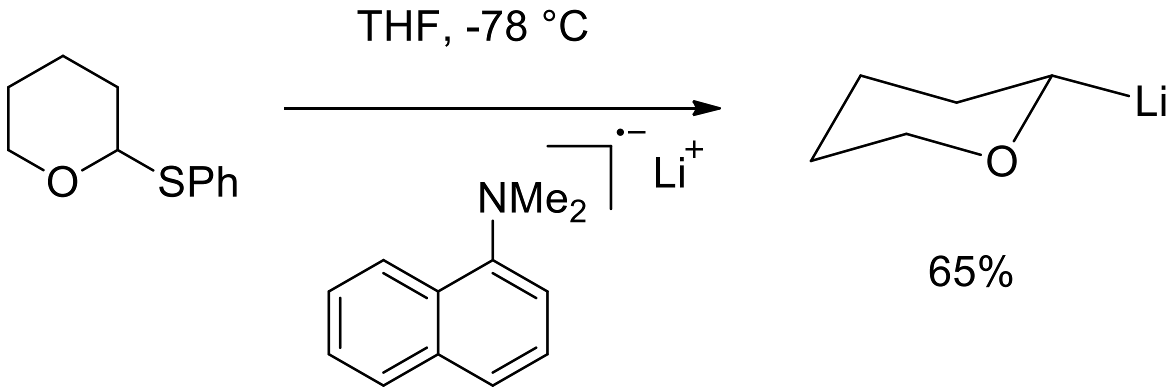
T. Blümke, Y.-H. Chen, P. Knochel *Nature Chemistry*, **2010**, *2*, 313

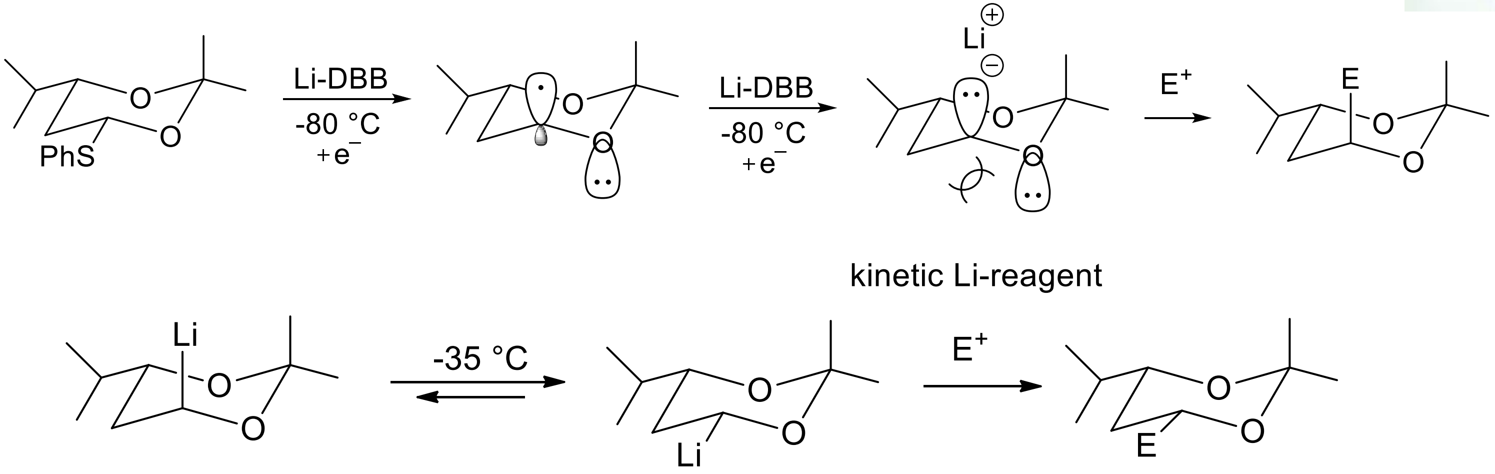


68%
life time (t½) = 2 days at 25 °C

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

Extension to insertion reactions to C-S bonds





kinetic Li-reagent

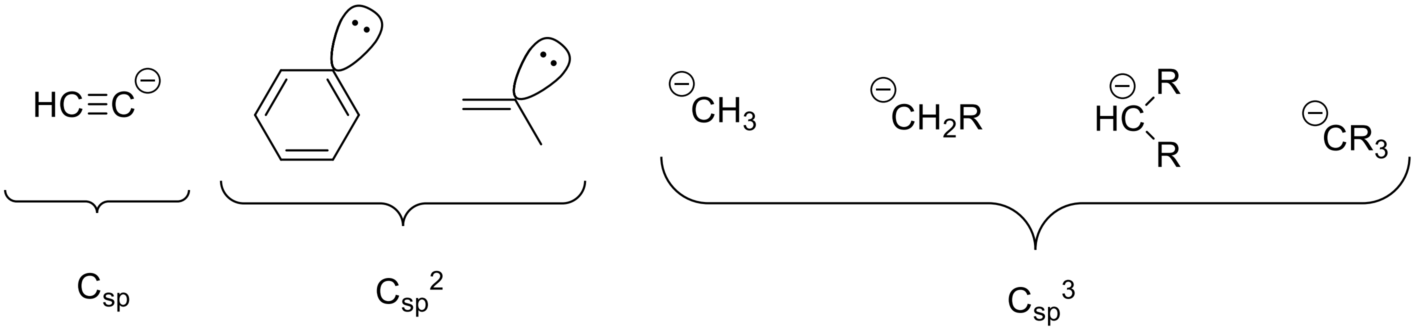
thermodynamic
Li-reagent

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

The Halogen-Metal-Exchange

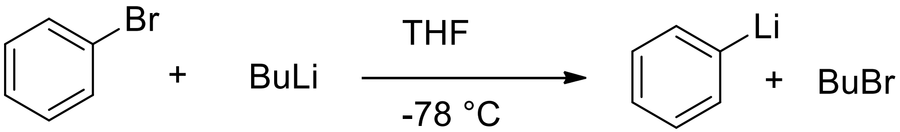
$$R^1{-}X \;+\; R^2{-}Met \;\rightleftharpoons\; R^2{-}X \;+\; \boxed{R^1{-}Met}$$

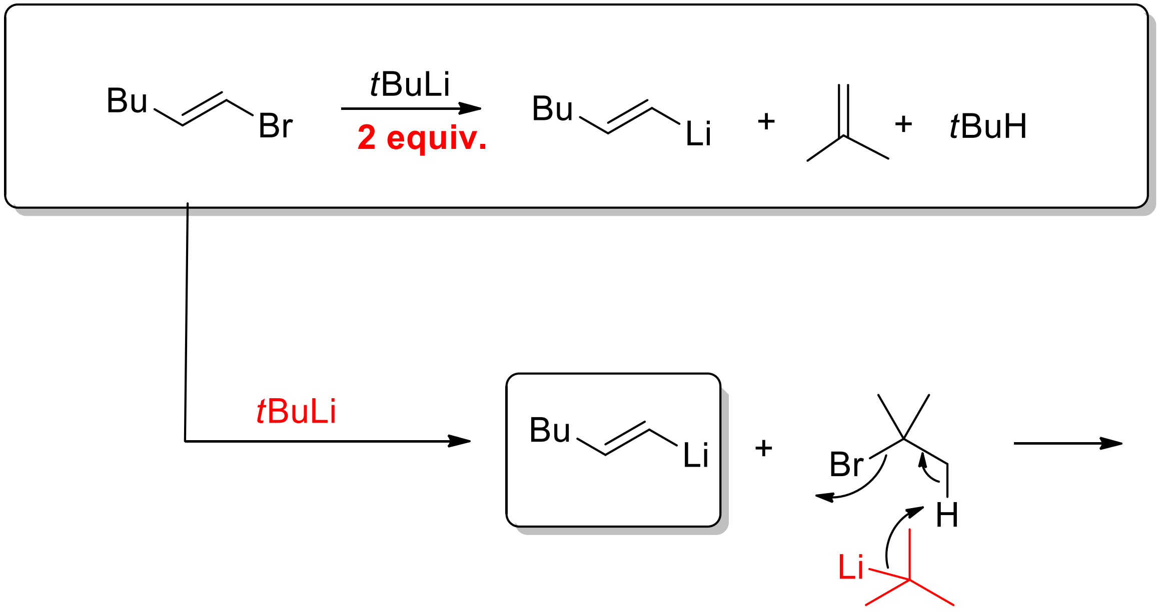
driving force: the most stable carbanion is always formed

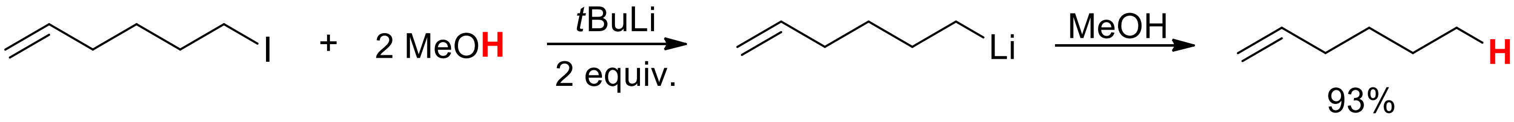


The Halogen-Metal-Exchange

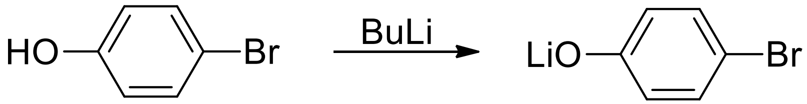
1939: the Wittig-Gilman reaction







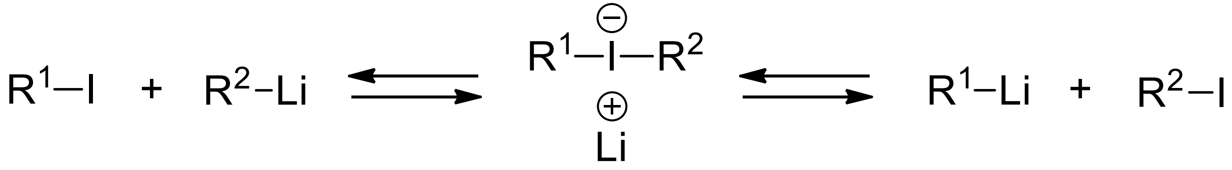
The Halogen-Metal-Exchange



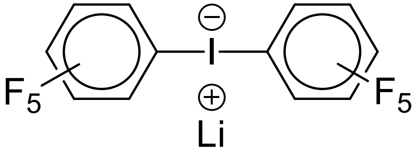
I >> Br >> Cl

rate of the halogen/metal exchange

mechanism:



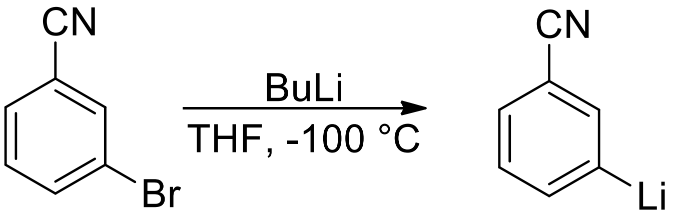
$$R^1-I + R^2-Li \rightleftharpoons R^1-\overset{\ominus}{\underset{\underset{Li}{\oplus}}{I}}-R^2 \rightleftharpoons R^1-Li + R^2-I$$



has been isolated

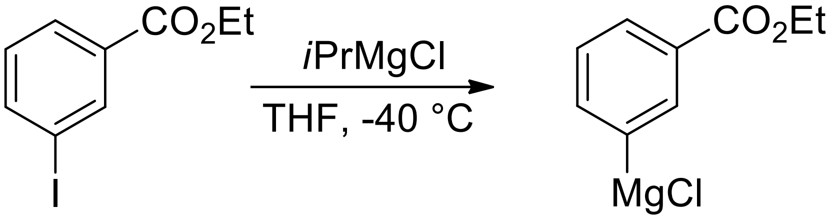
H. J. Reich, A. W. Sanders, A. T. Fiedler, M. J. Bevan *J. Am. Chem. Soc*. **2002**, *124*, 13386

The Halogen-Metal-Exchange : tolerance of functional groups



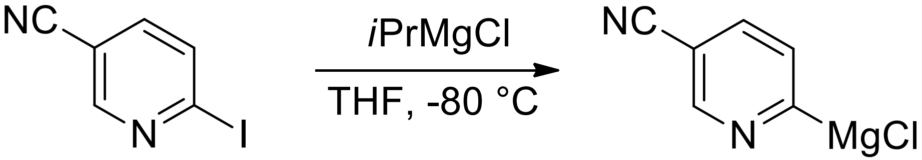
Stable only at -100 °C

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



> 90 %

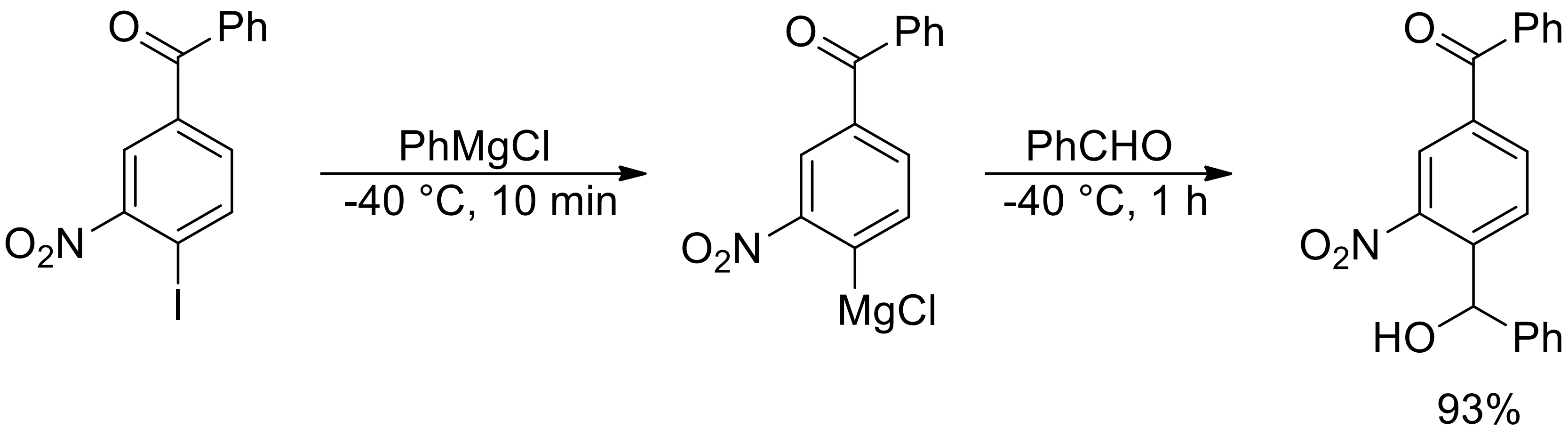
M. Rottländer, P. Knochel, Angew. Chem. Int. Ed. 1998, 40, 1801



> 90 %

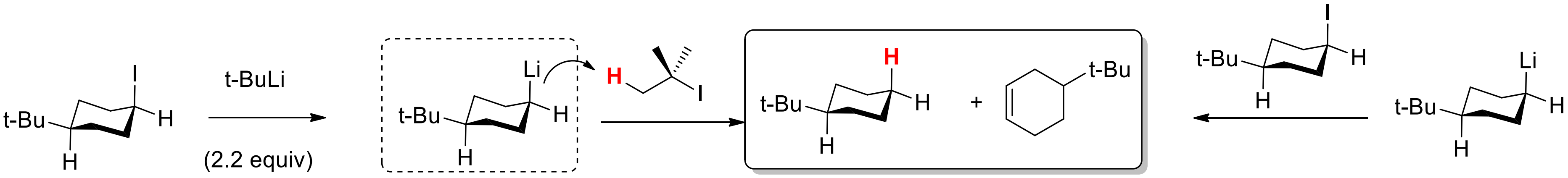
H. Ren, P. Knochel, Chem.Comm. **2006**, 726

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



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

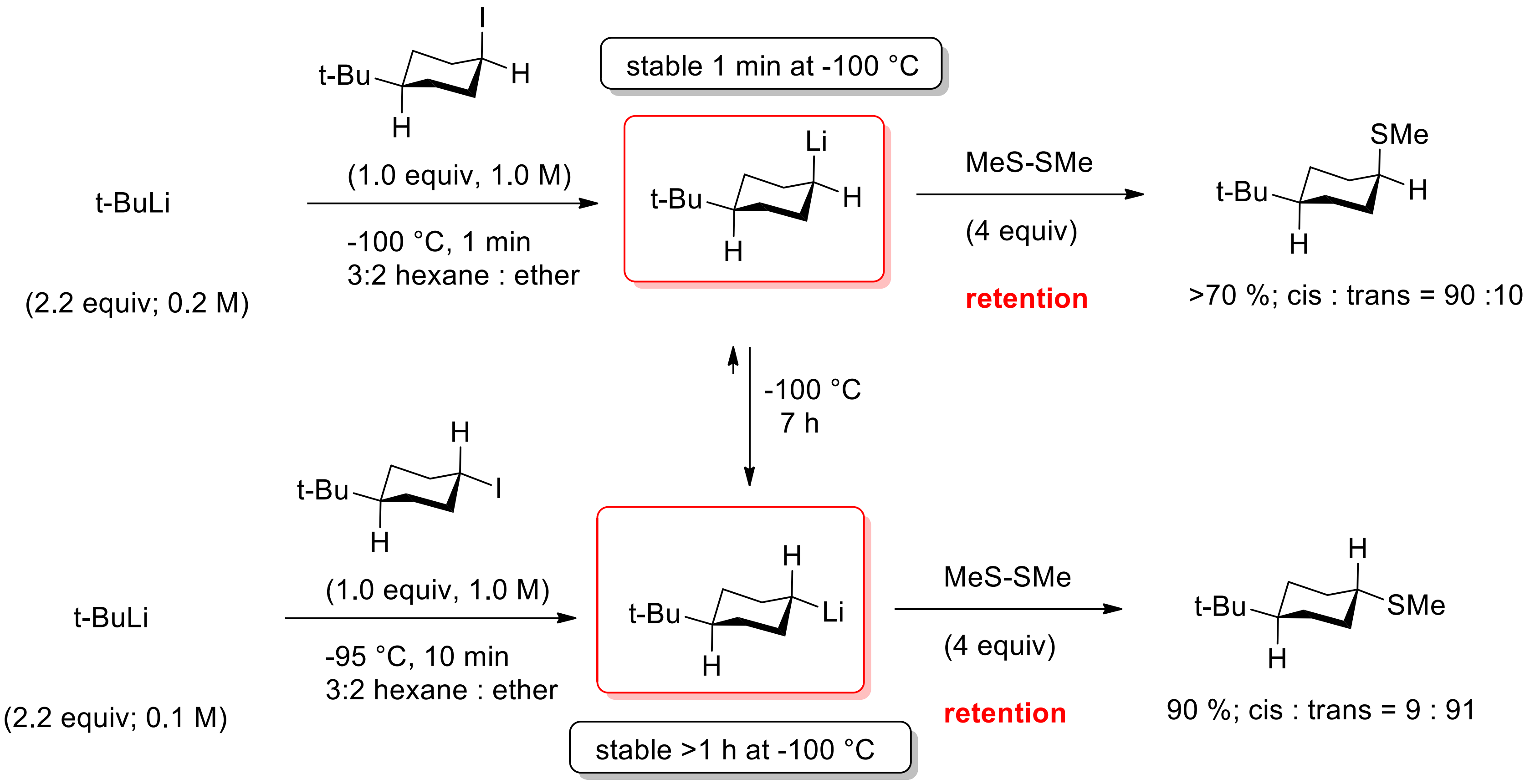
A secondary iodine/lithium exchange on cyclohexyl iodides



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

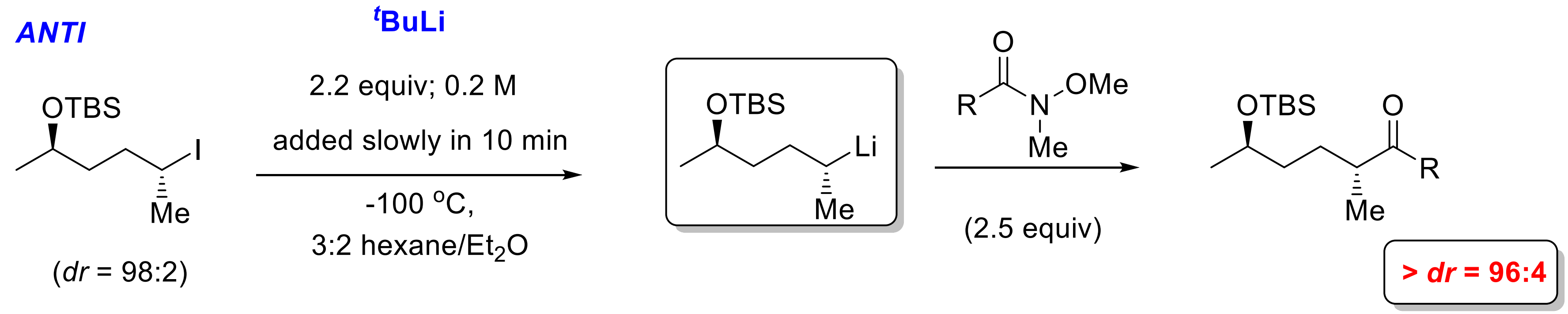
(4 equiv)

retention

90 %; cis : trans = 9 : 91

Stephanie SEEL

Stereoselective I/Li -exchange and acylations



ANTI

^{t}BuLi

2.2 equiv; 0.2 M

added slowly in 10 min

-100 °C,

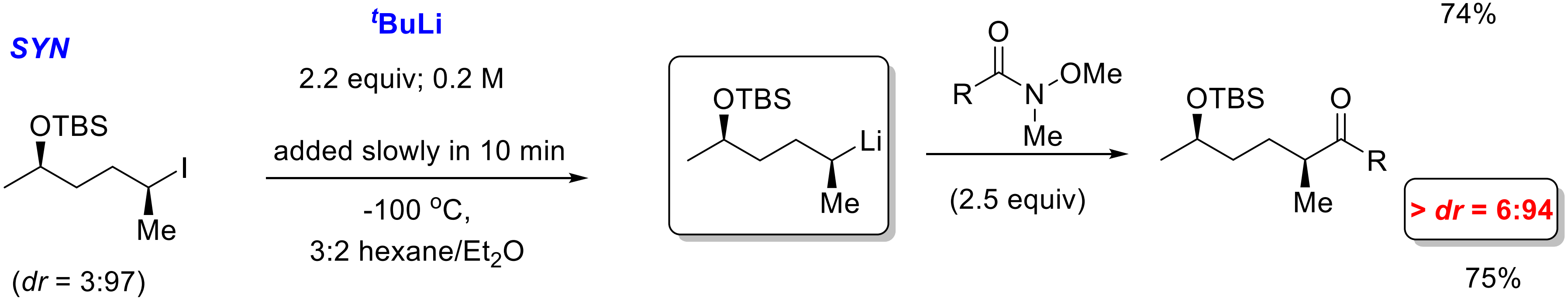
3:2 hexane/Et_2O

(*dr* = 98:2)

(2.5 equiv)

> *dr* = 96:4

74%



SYN

^{t}BuLi

2.2 equiv; 0.2 M

added slowly in 10 min

-100 °C,

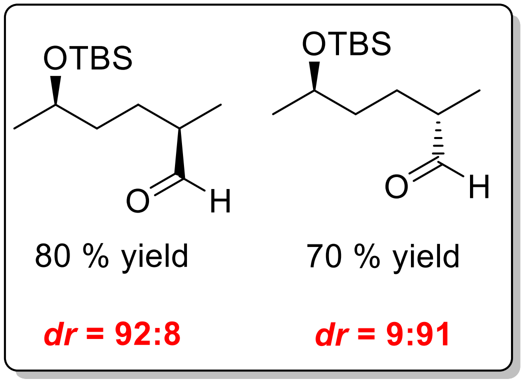
3:2 hexane/Et_2O

(*dr* = 3:97)

(2.5 equiv)

> *dr* = 6:94

75%

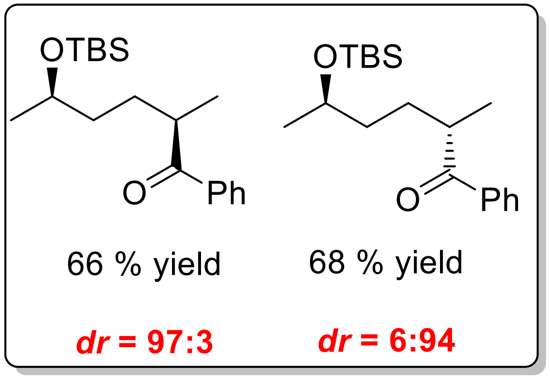


80 % yield

***dr* = 92:8**

70 % yield

***dr* = 9:91**

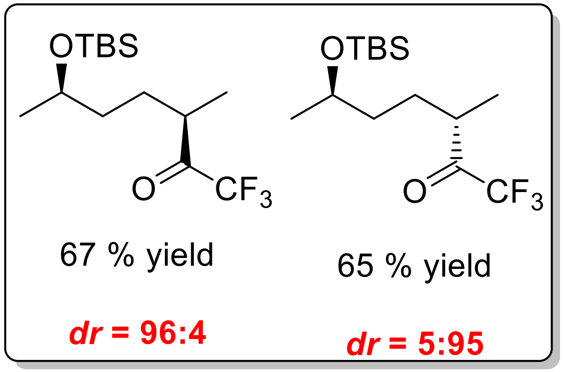


66 % yield

***dr* = 97:3**

68 % yield

***dr* = 6:94**



67 % yield

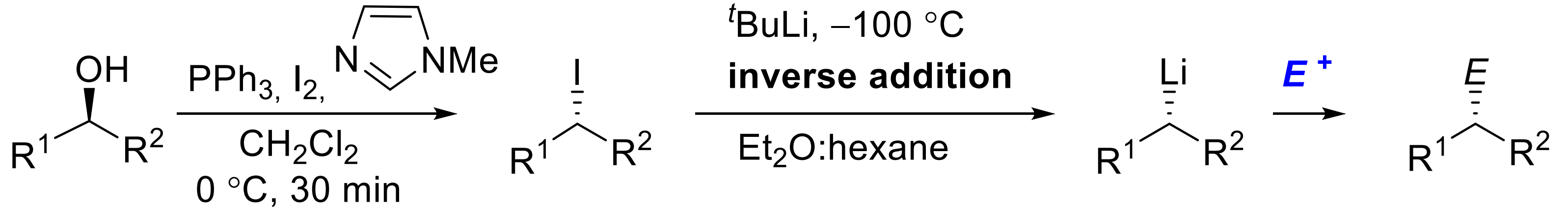
***dr* = 96:4**

65 % yield

***dr* = 5:95**

Dagousset, G.; Moriya, K.; Berionni, G.; Karaghiosoff, K.; Knochel, P. *Angew. Chem., Int. Ed*. **2014**, *53*, 1425.

Enantiomerically enriched secondary alkyllithium reagents



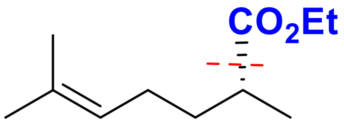
95-99% *ee*

(37-86% yield)

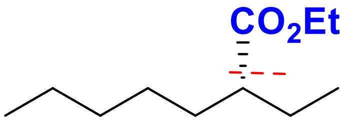
inversion

retention

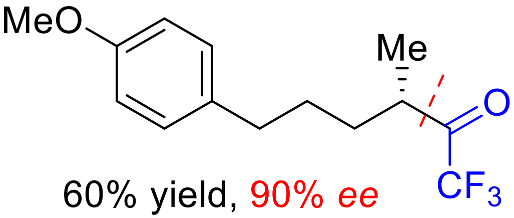
retention



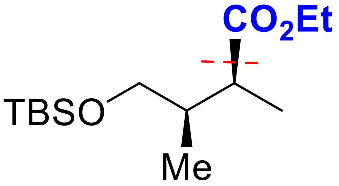
56% yield, 96% *ee*
(from 98% *ee*)



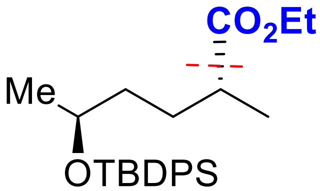
54% yield, 92% *ee*
(from 95% *ee*)



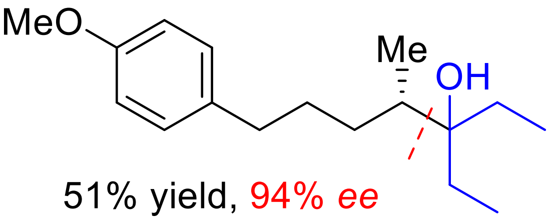
60% yield, 90% *ee*
(from 98% *ee*)



70% yield, 99% *ee*,
d.r.=95:5
(from 99% *ee* and d.r.=98:2)



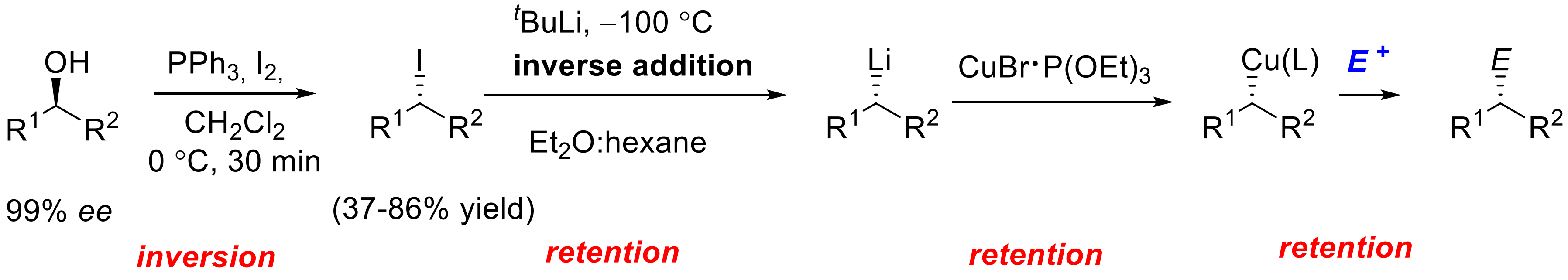
62% yield, 99% *ee*,
d.r.=99:1
(from 99% *ee* and d.r.=99:1)

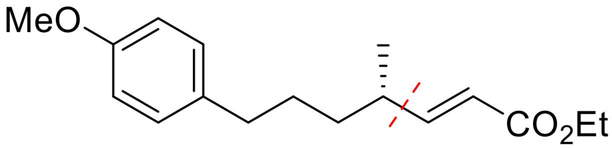


51% yield, 94% *ee*
(from 98% *ee*)

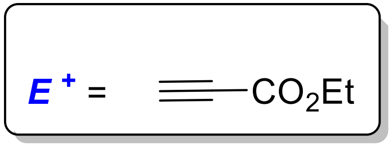
Varvara Morozova, Kohei Moriya, Paul Knochel, **2016**

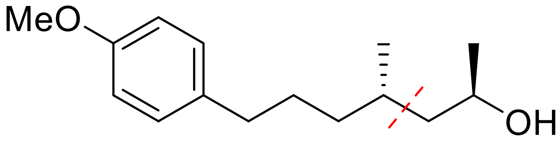
Enantiomerically enriched secondary alkylcopper reagents



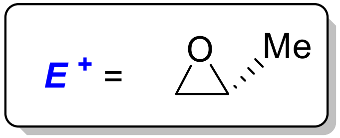


47% yield, **92% *ee***



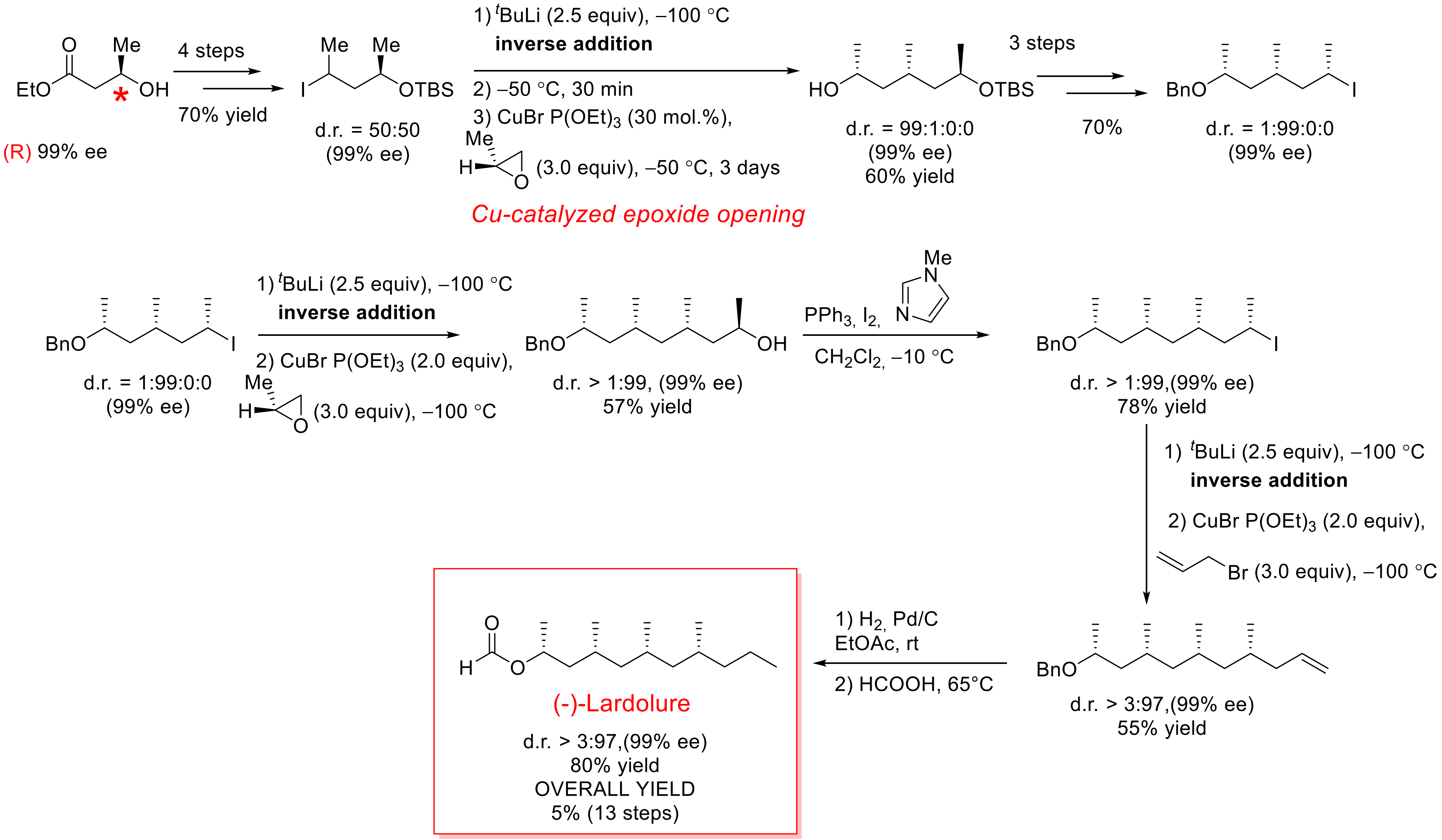


56% yield, **99% *ee***, d.r. = 90:10



Varvara Morozova, Kohei Moriya, Paul Knochel, **2016**

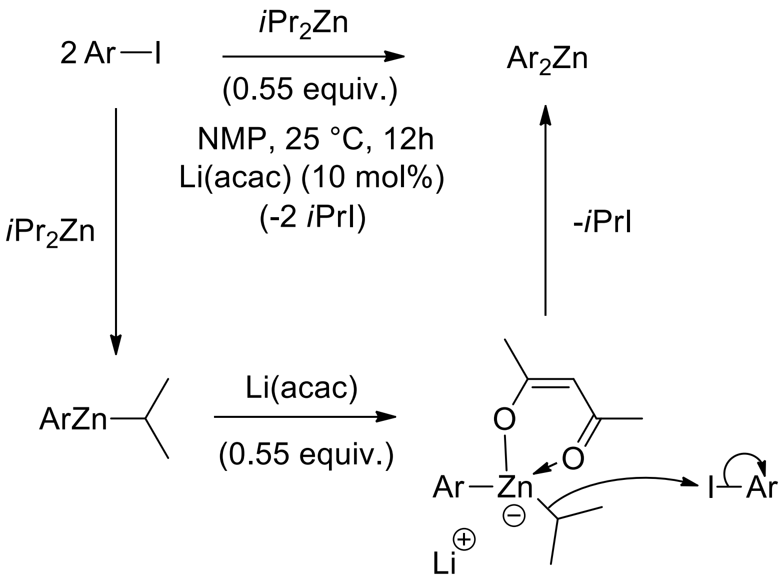
Synthesis of (-)-lardolure using enantiomerically enriched Li- and Cu-reagents

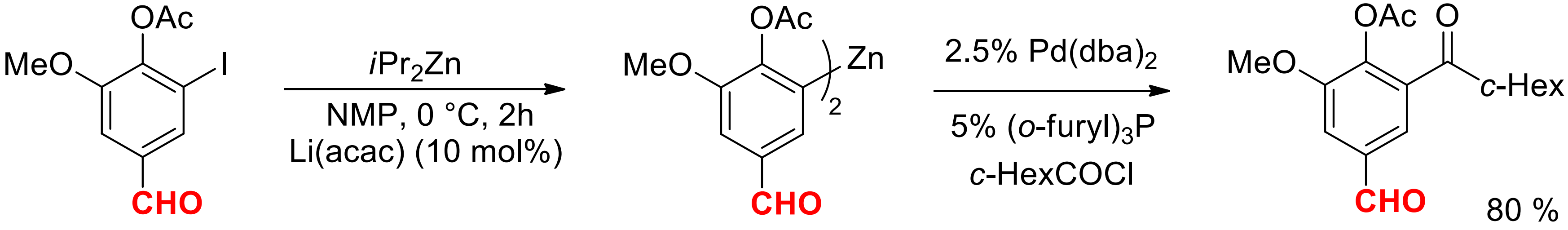


Varvara Morozova, Kohei Moriya, Paul Knochel, **2017**

The iodine/zinc-exchange

catalysis of the halogen-metal exchange

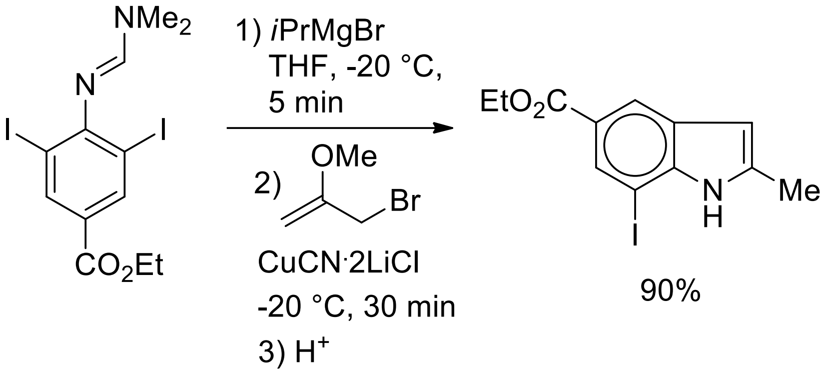




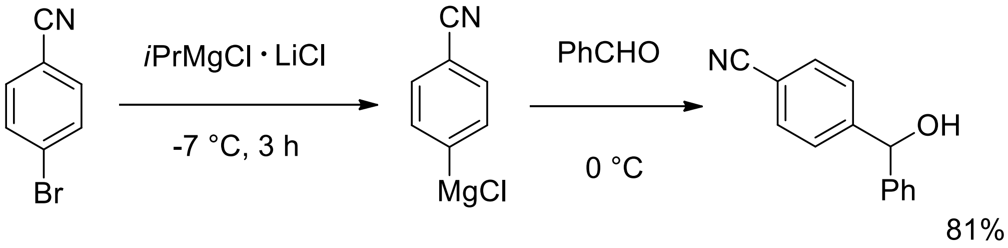
F. Kneisel, P. Knochel *Angew. Chem. Int. Ed*. **2004**, *43*, 1017

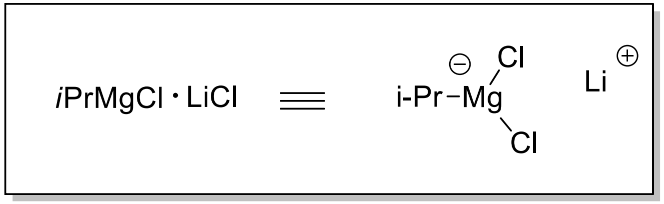
The Halogen-Metal-Exchange

indole-synthesis



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



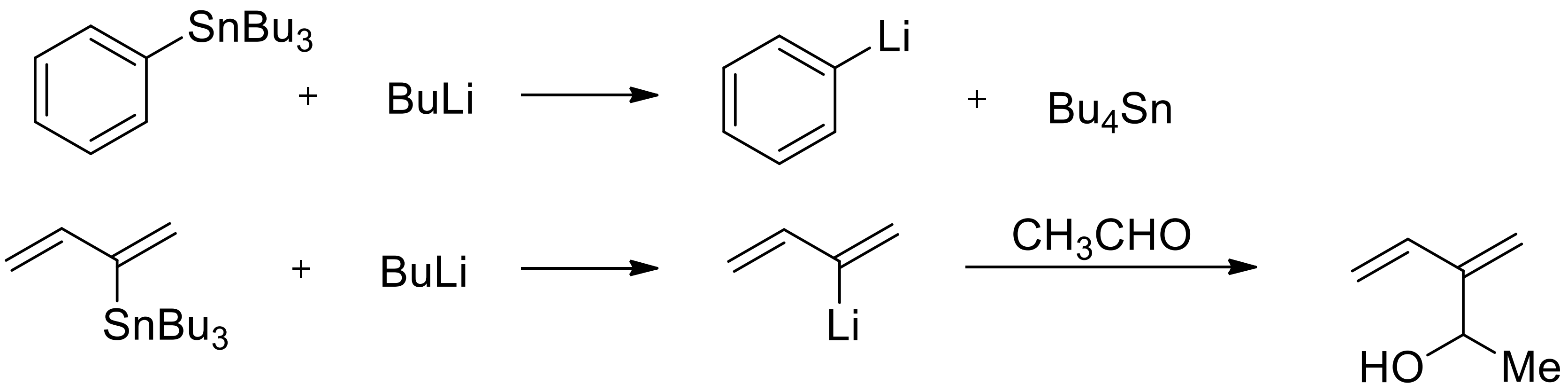


A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2004**, *43*, 3333

Transmetalation

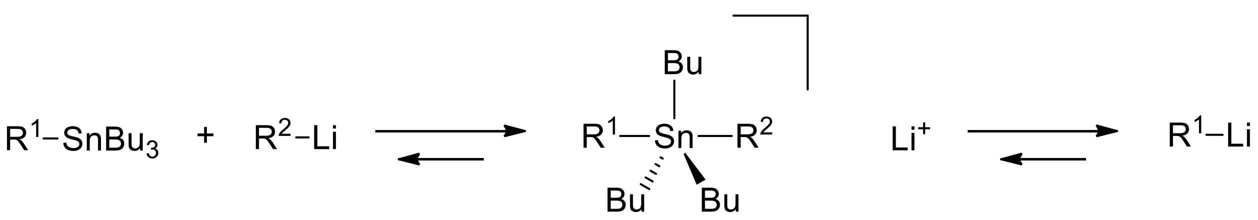
a) $$\boxed{R^1\text{–}Met^1} + R^2\text{-}Met^2 \rightleftharpoons \boxed{R^1\text{–}Met^2} + R^2\text{-}Met^1$$

the most stable carbanion is linked to the most electropositive metal

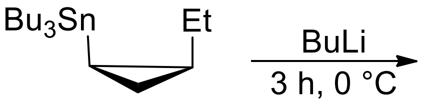


Transmetalation

mechanism:



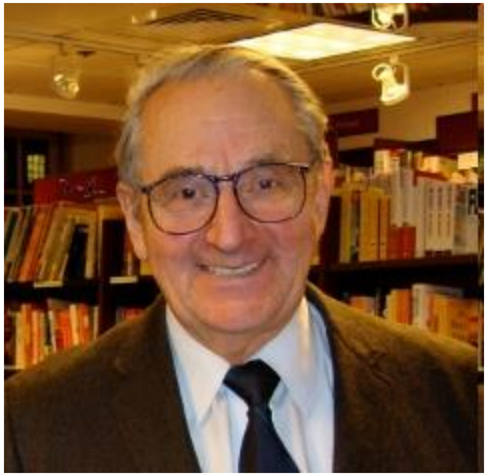
the most stable Li-organometallic is formed

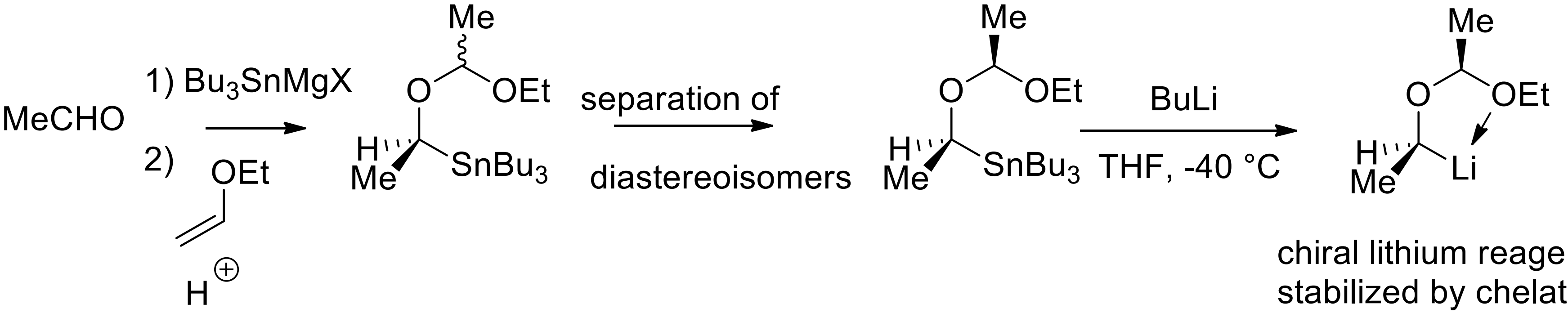


configurational stable

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)

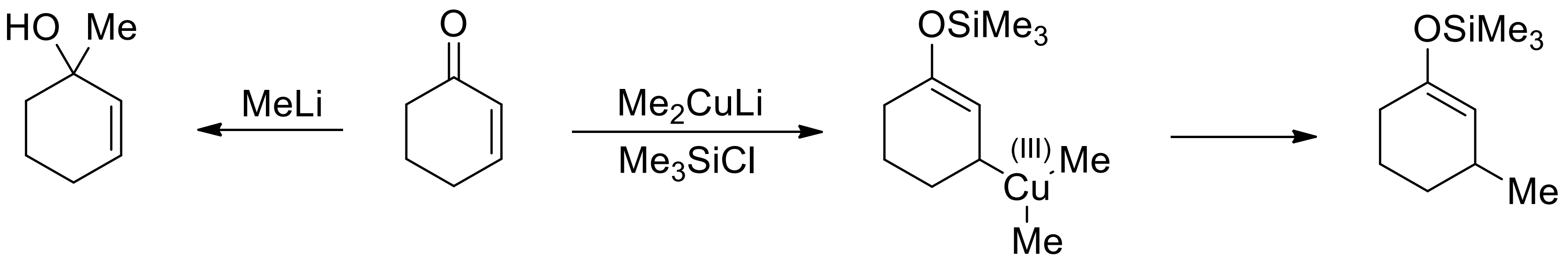
$$\boxed{R^1\text{–}Met^1 \xrightarrow{Met^2\text{–}X} R^1\text{–}Met^2}$$

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

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

Transmetalation

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

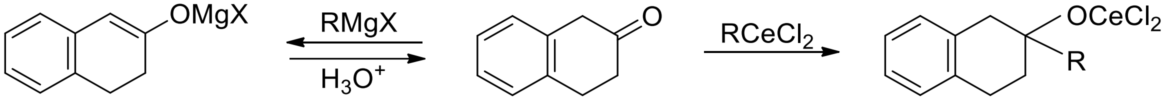


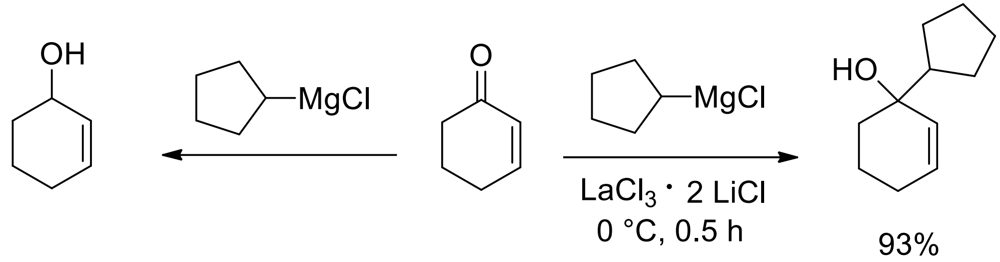
E. Nakamura, I. Kuwajima *J. Am. Chem. Soc*. **1984**, *106*, 3368

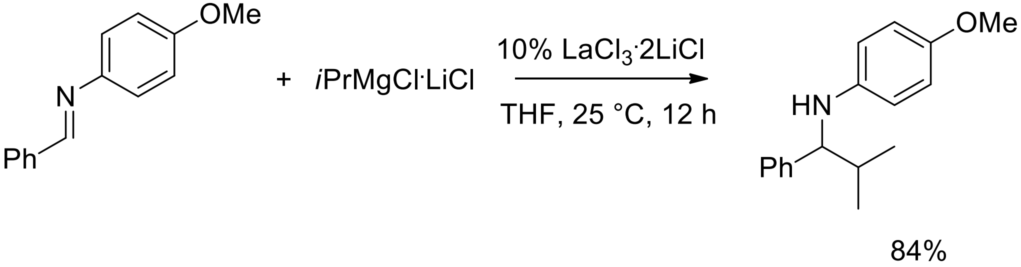
Transmetalation

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

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

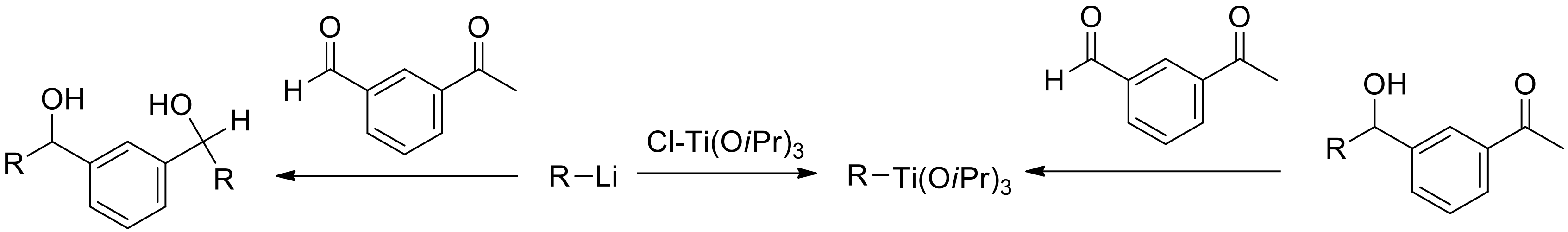






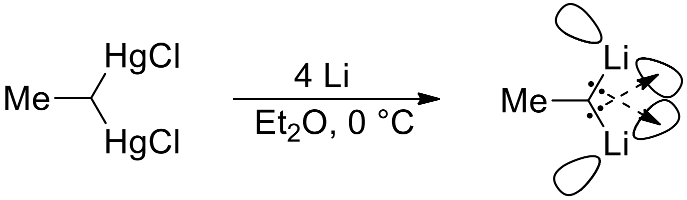
A. Krasovskiy, F. Kopp, P. Knochel *Angew. Chem. Int. Ed*. **2006**, *45*, 497

Transmetalation



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

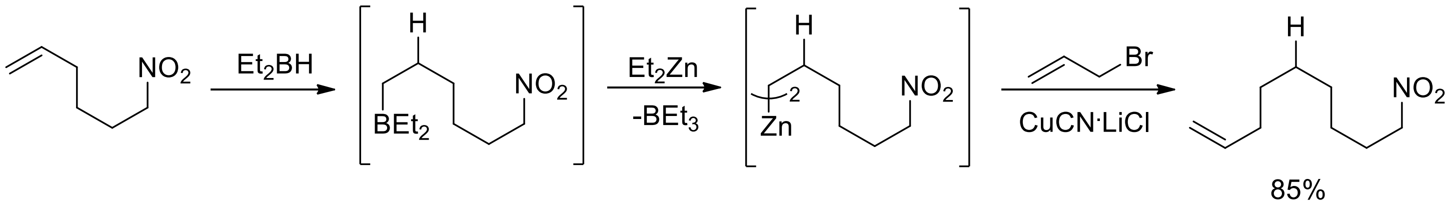
$$R^1\text{–}Met^1 \xrightarrow{Met^2} R^1\text{–}Met^2 \quad + \quad Met^1$$

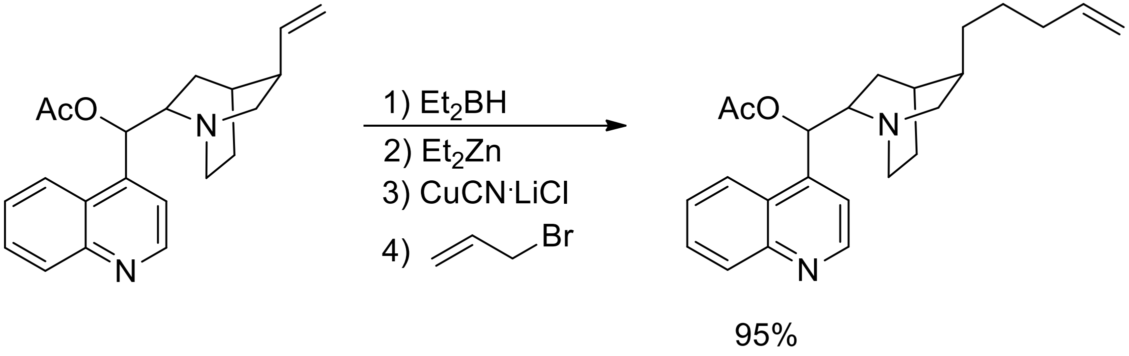


A. Maercker, M. Theis, A. Kos, P. Schleyer, *Angew. Chem*. **1983**, *95*, 755

Transmetalation

boron / zinc-exchange

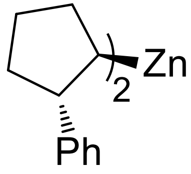




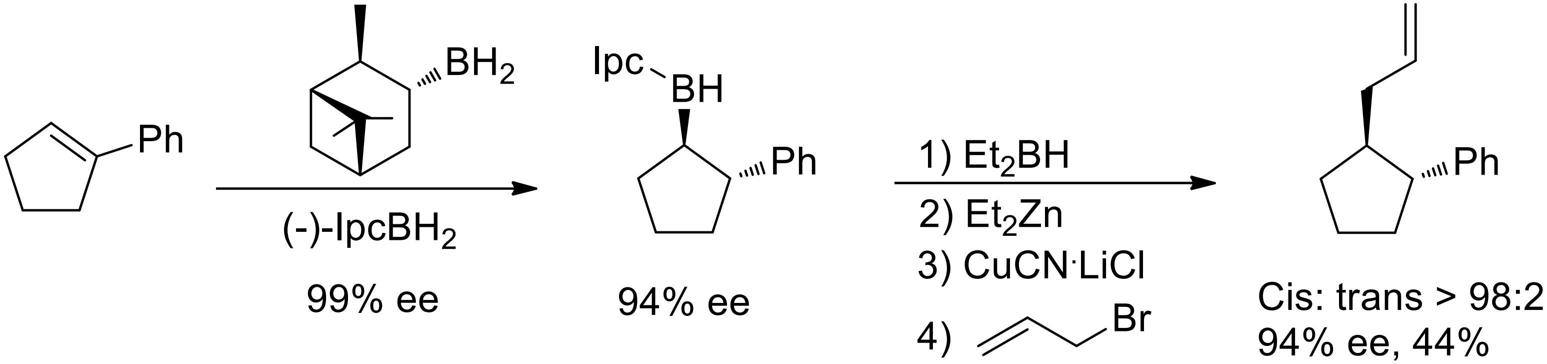
F. Langer, L. Schwink, P. Knochel *J. Org. Chem*. **1996**, *61*, 8229

Transmetalation

boron / zinc-exchange



94% ee



(-)-IpcBH_2

99% ee

94% ee

1) Et_2BH
2) Et_2Zn
3) $CuCN{\cdot}LiCl$
4) allyl bromide

Cis: trans > 98:2
94% ee, 44%

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

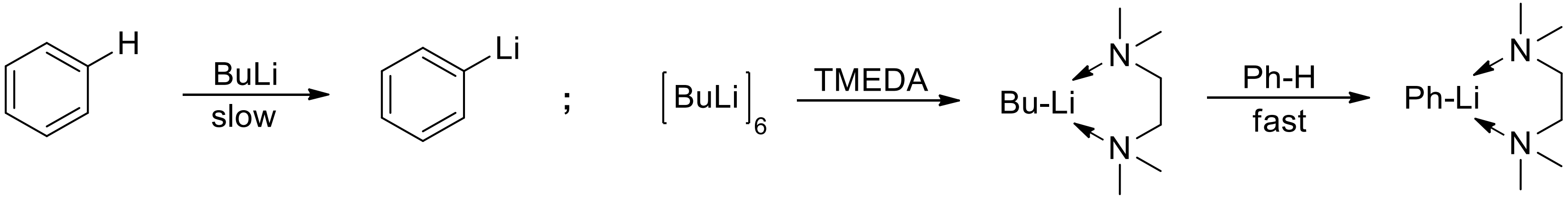
Metalation (starting from a compound with an acid proton)

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

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

R^1–Met : *t*-BuOK, LDA, BuLi, ...

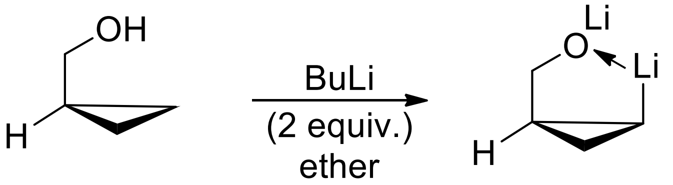
kinetic criteria (kinetic acidity)

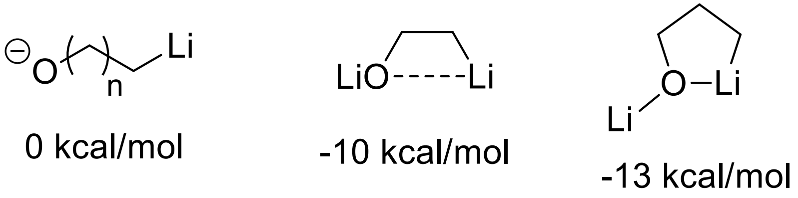


$PhCH_2Li$ reacts with benzene 10^4 times faster than with MeLi

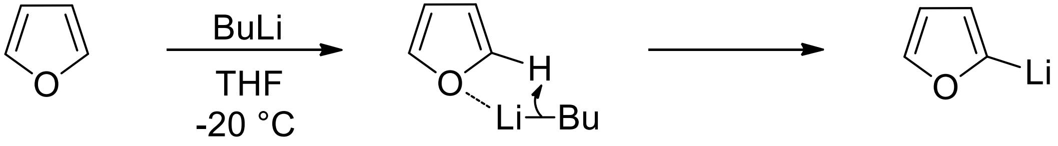
$PhCH_2Li$ is a monomer in THF, MeLi a tetramer

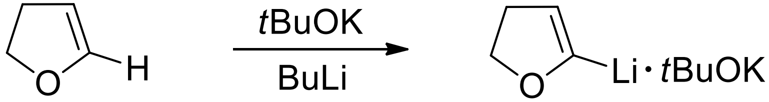
Directed metalation

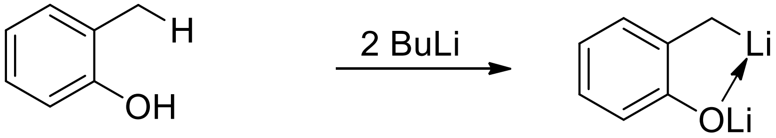




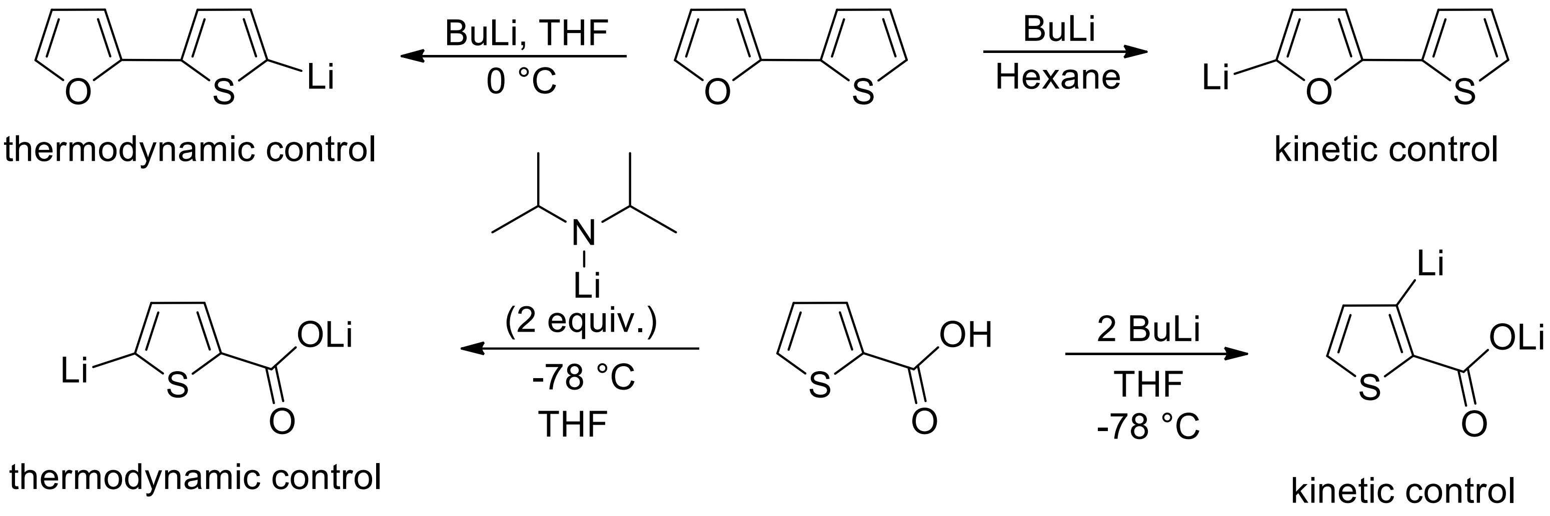
Directed metalation



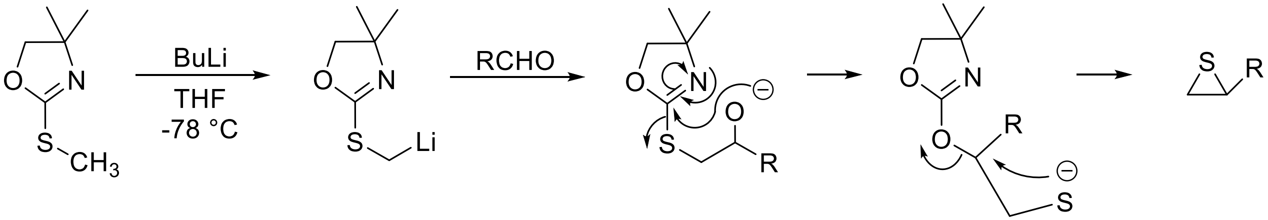




Metalation

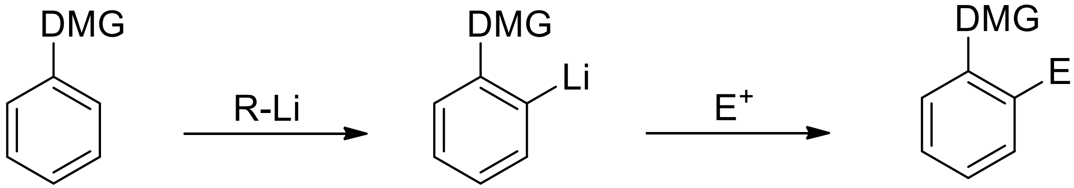


A rearrangement may occur :



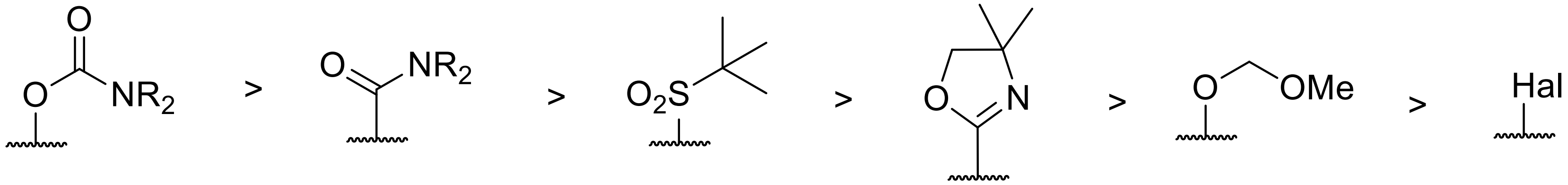
Metalation

directed lithiation



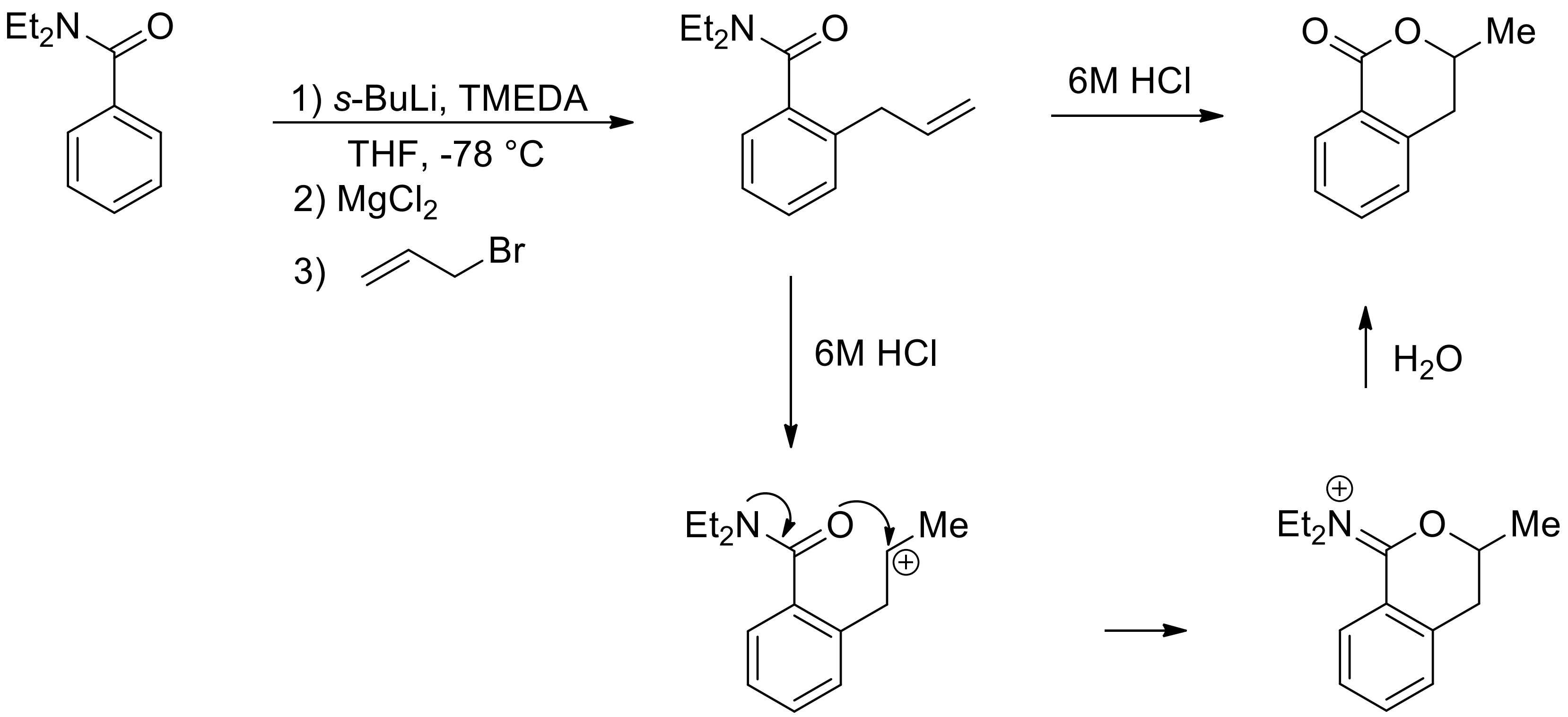
DMG = directing metalating group

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



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

Metalation



1) *s*-BuLi, TMEDA

THF, -78 °C

2) $MgCl_2$

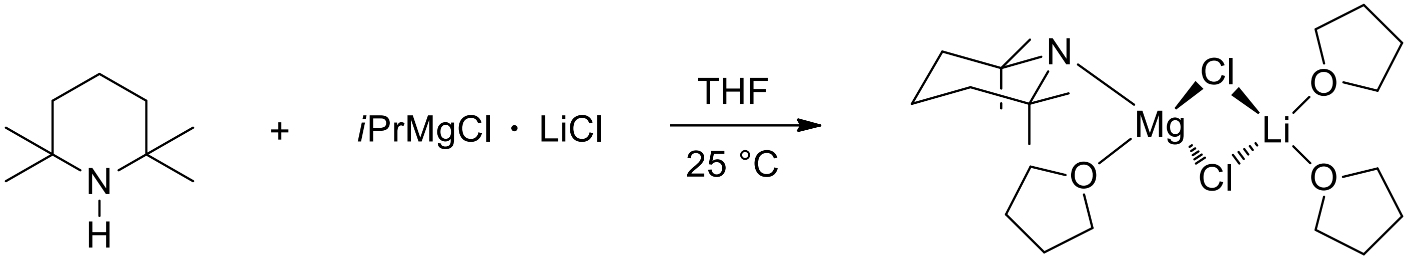
3)

6M HCl

6M HCl

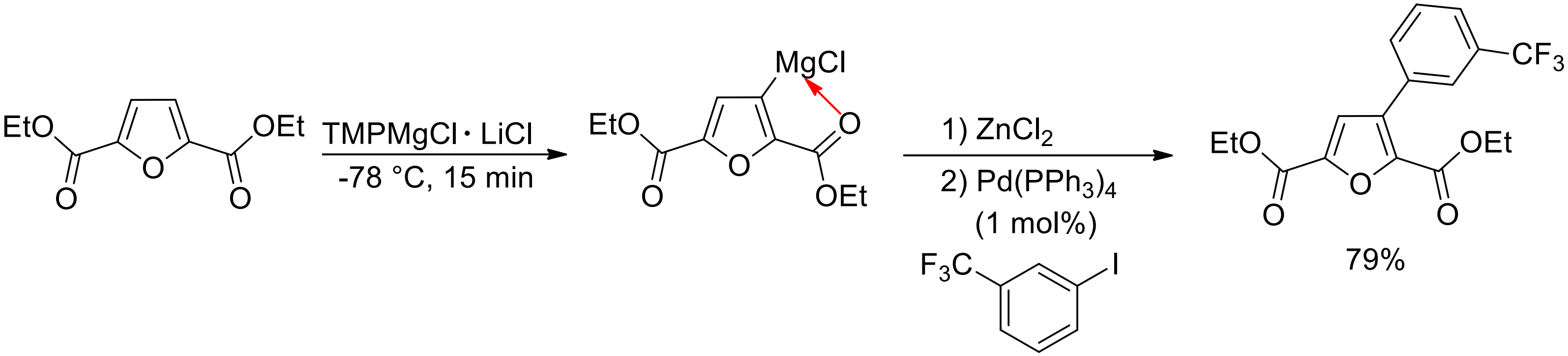
H_2O

Metalation



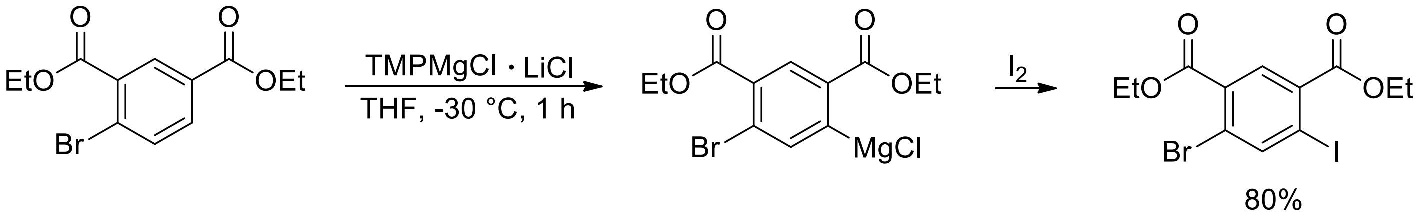
TMPMgCl·LiCl (1.2 M in THF)

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

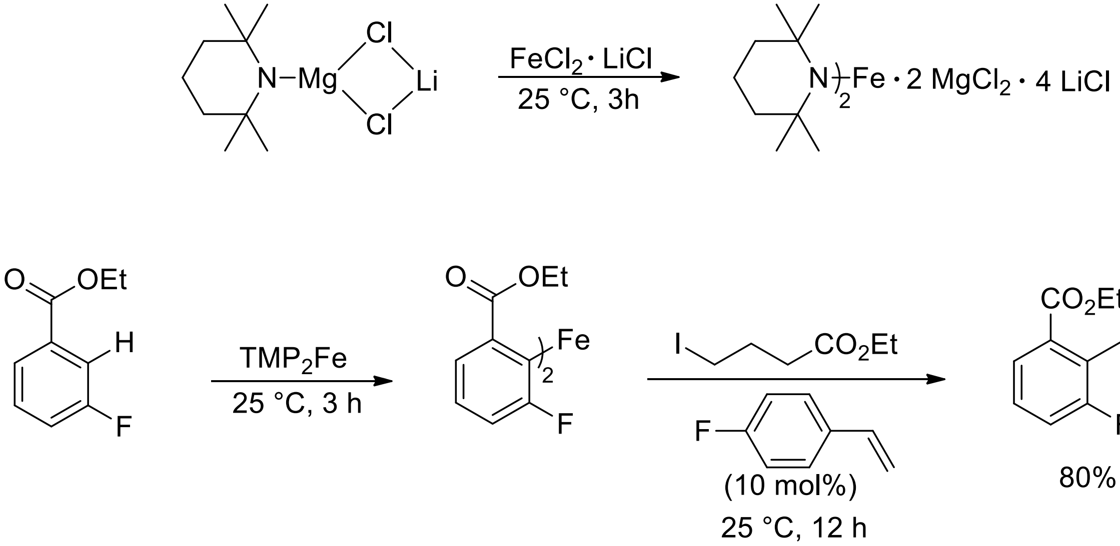


F. M. Piller, P. Knochel *Org. Lett*. **2009**, *11*, 445

Metalation

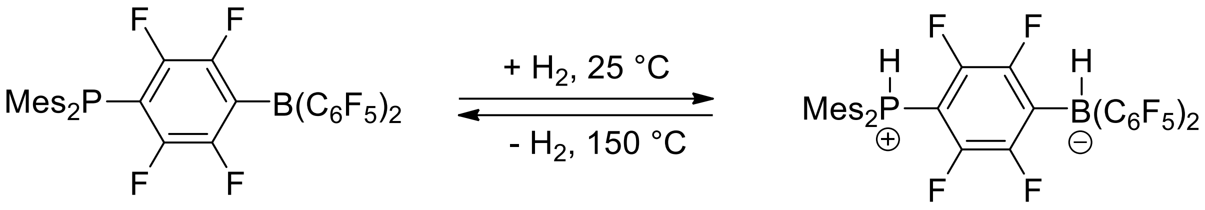


O. Baron, P. Knochel *Angew. Chem. Int. Ed*. **2006**, *45*, 2958

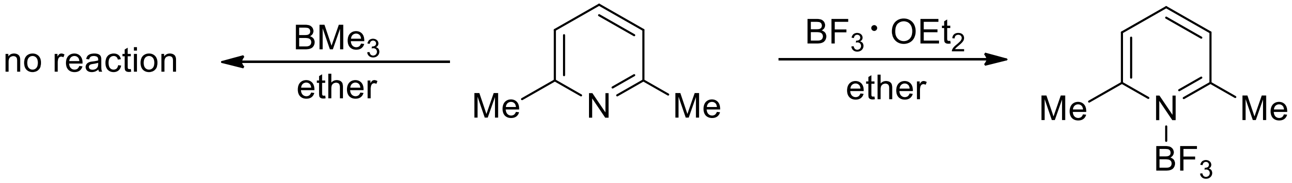


S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed*. **2009**, *48*, 9717

Frustrated Lewis Pairs



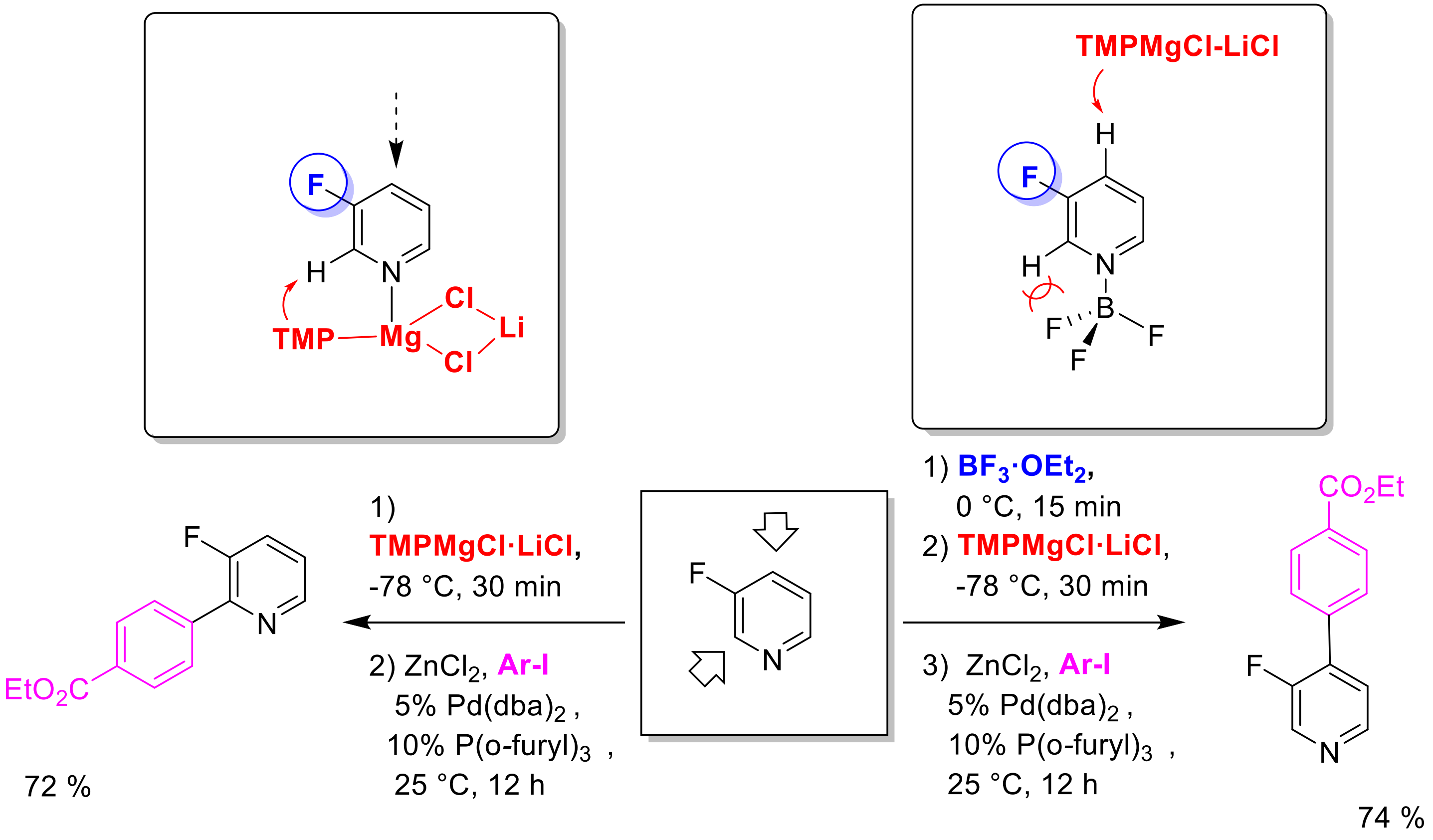
D. Stefan, G. Erker *Angew. Chem. Int. Ed*. **2010**, *49*, 46



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

BF_3-triggered selective metalations

$BF_3 \cdot OEt_2$ $\overset{\textit{compatible}}{\underset{\textit{up to - 30 °C}}{\Longleftrightarrow}}$ **TMPMgCl-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

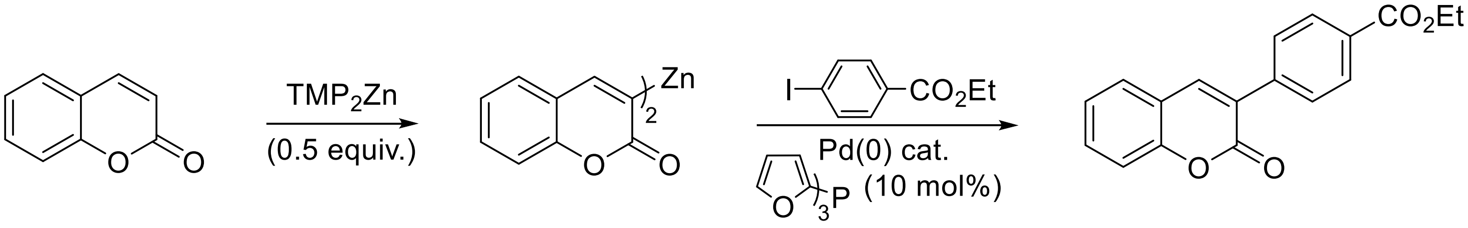
74 %

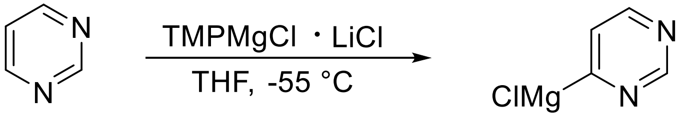
M. Jaric, B. Haag, A. Unsinn, K. Karaghiosoff, P. Knochel *Angew. Chem. Int. Ed.* **2010**, *49*, 5451-5455

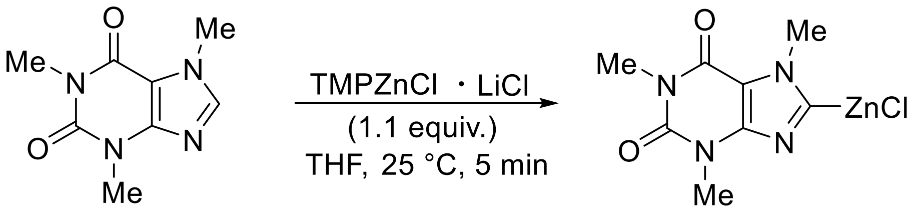
Metalation

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

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

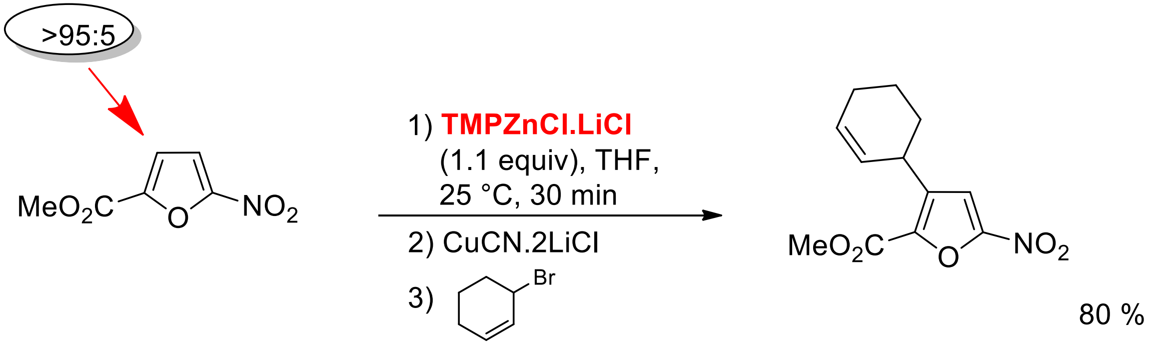






M. Mosrin, P. Knochel *Org. Lett*. **2008**, *10*, 2497
M. Mosrin, P. Knochel *Chem. Eur. J*. **2009**, *15*, 1468
M. Mosrin, P. Knochel *Org. Lett*. **2009**, *11*, 1837

Zincations in the presence of ester and nitro groups

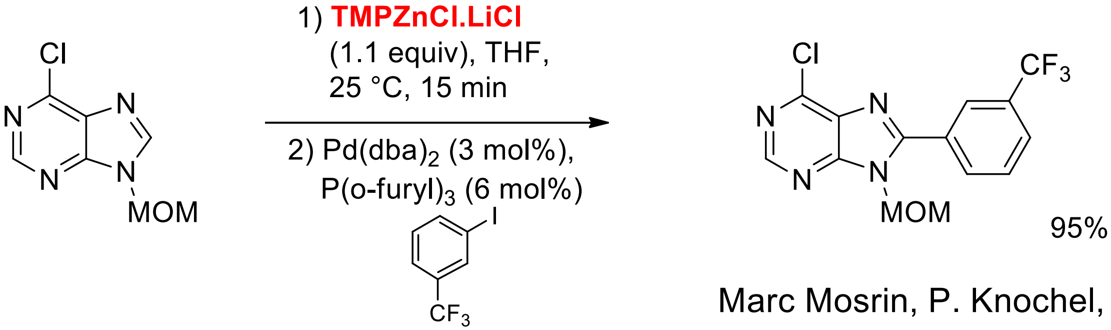


1) **TMPZnCl.LiCl** (1.1 equiv), THF, 25 °C, 30 min

2) CuCN.2LiCl

3)

80 %

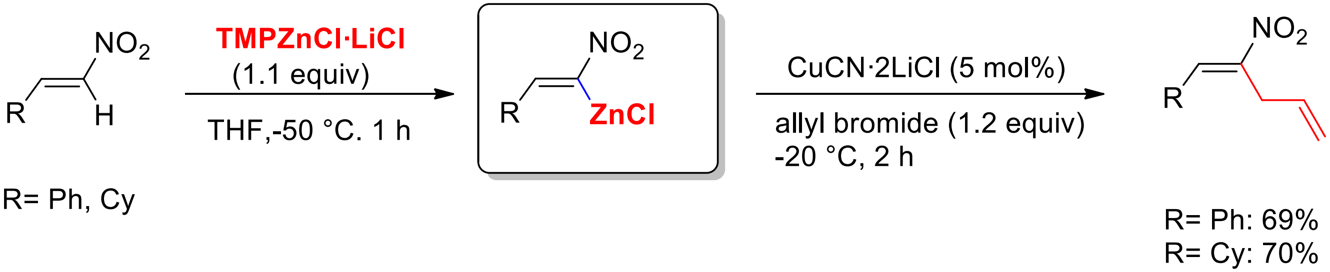


1) **TMPZnCl.LiCl** (1.1 equiv), THF, 25 °C, 15 min

2) $Pd(dba)_2$ (3 mol%), $P(o\text{-}furyl)_3$ (6 mol%)

95%

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



TMPZnCl·LiCl (1.1 equiv)

THF,-50 °C. 1 h

CuCN·2LiCl (5 mol%)

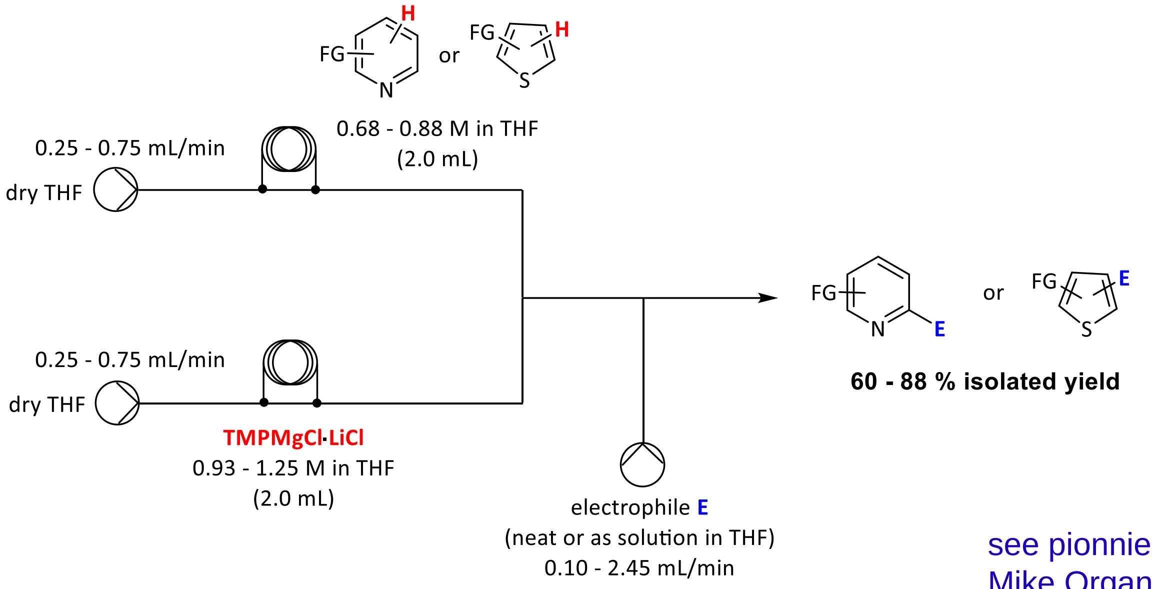
allyl bromide (1.2 equiv)
-20 °C, 2 h

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



0.68 - 0.88 M in THF
(2.0 mL)

0.25 - 0.75 mL/min
dry THF

0.25 - 0.75 mL/min
dry THF

TMPMgCl·LiCl
0.93 - 1.25 M in THF
(2.0 mL)

electrophile **E**
(neat or as solution in THF)
0.10 - 2.45 mL/min

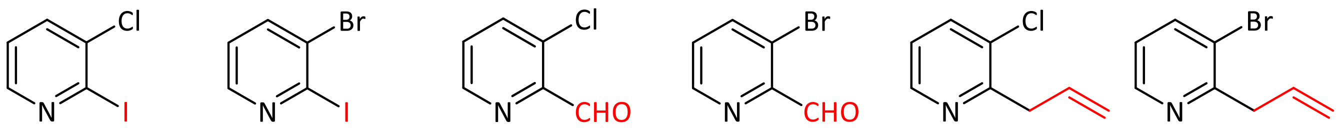
60 - 88 % isolated yield

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.

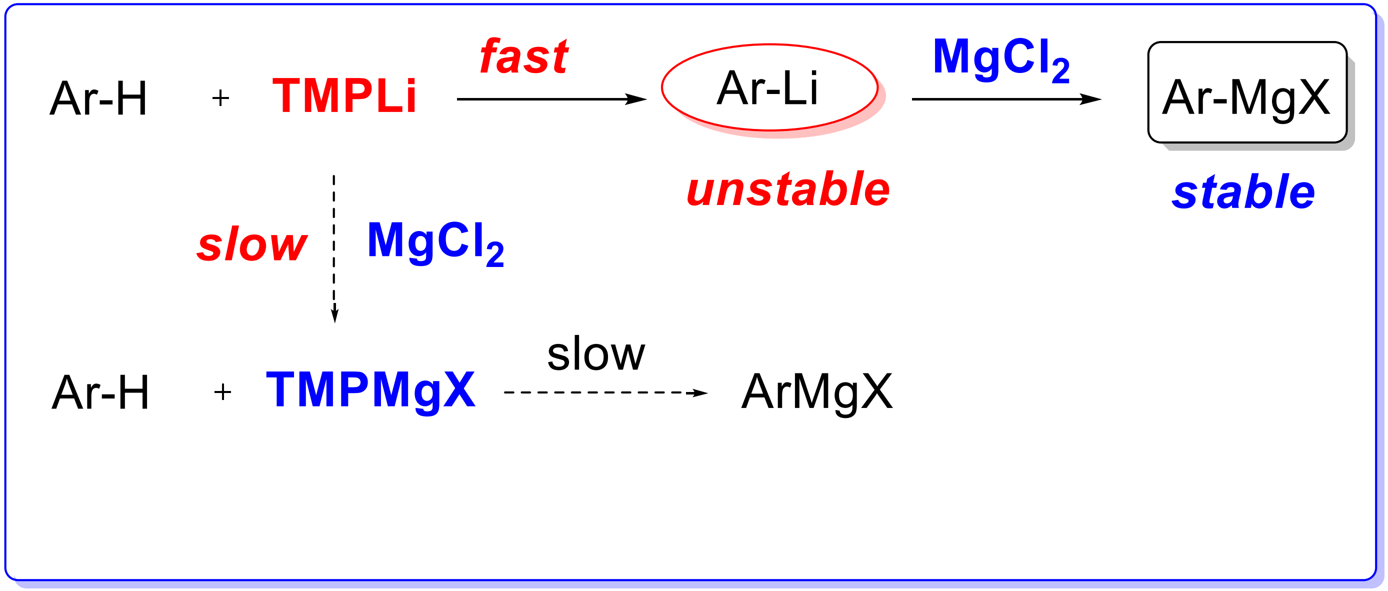
Batch conditions: Complete metalation of 3-chloropyridine after **45 min at -78 °C**

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 $MgCl_2$

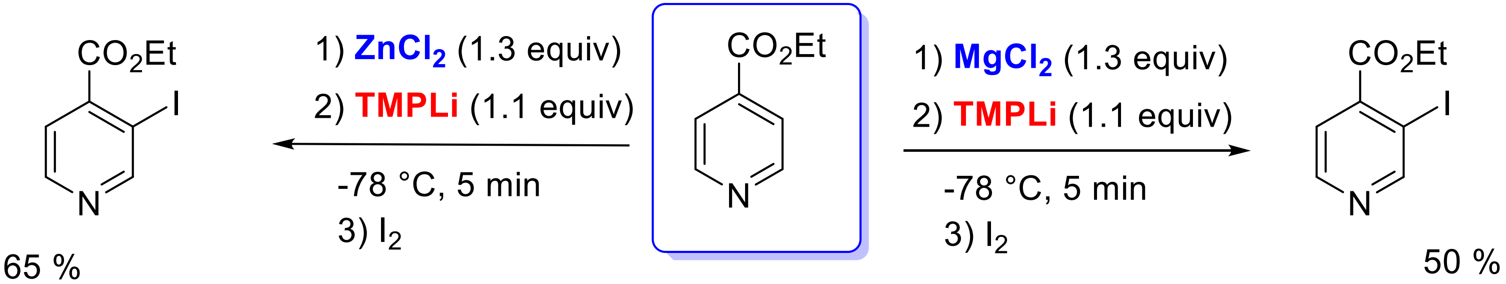


Ar-H + **TMPLi** $\xrightarrow{\textit{fast}}$ Ar-Li $\xrightarrow{MgCl_2}$ Ar-MgX

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

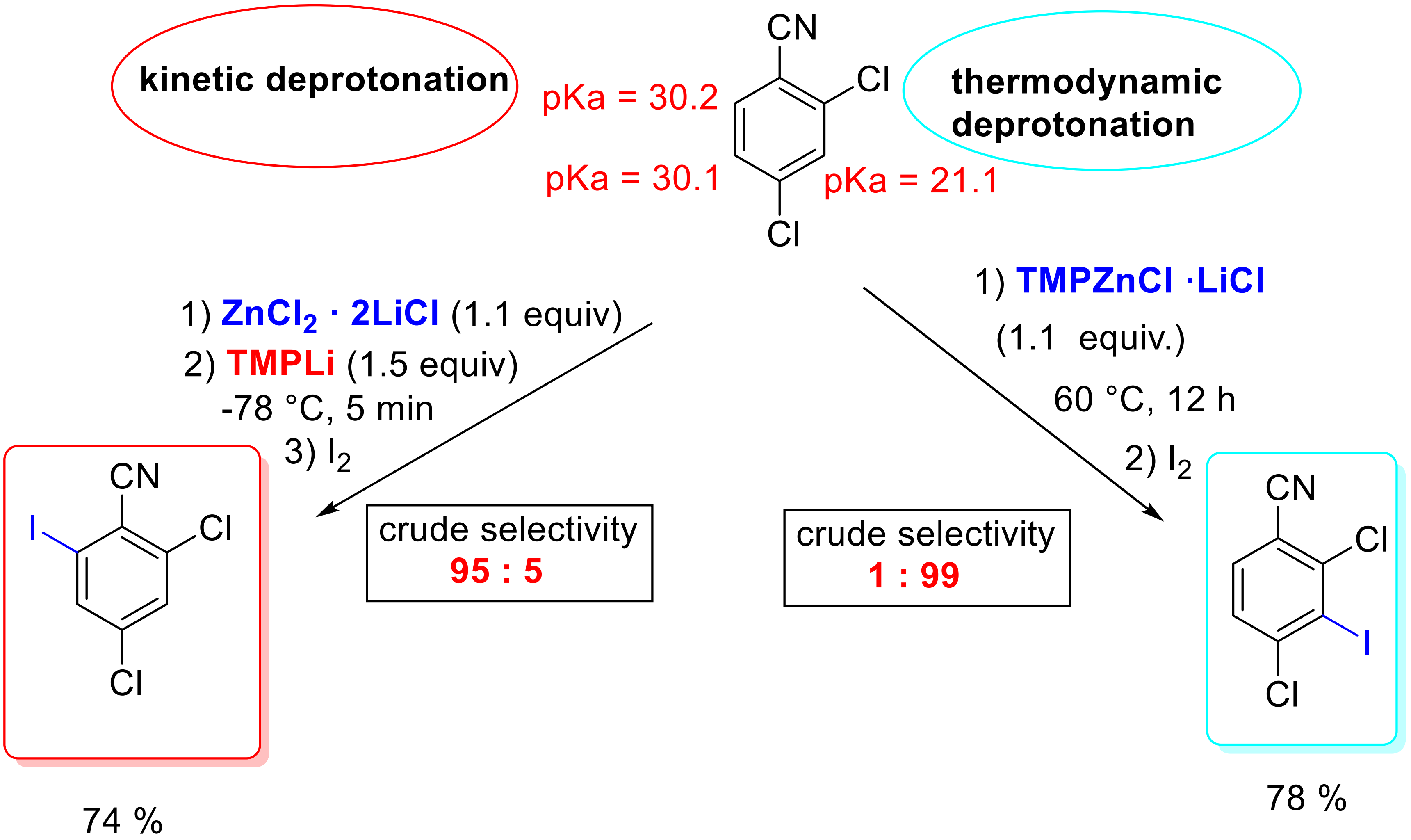
65 %

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

pKa = 30.2

pKa = 30.1

pKa = 21.1

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

crude selectivity
95 : 5

74 %

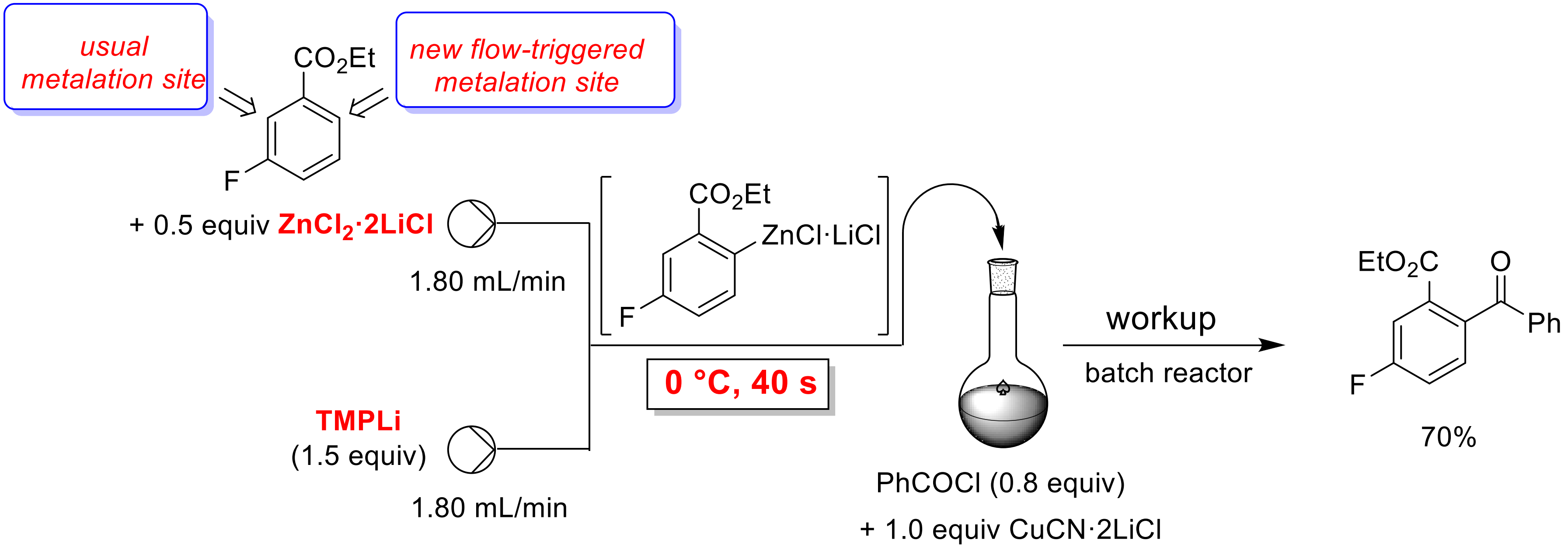
1) **TMPZnCl ·LiCl**
(1.1 equiv.)
60 °C, 12 h
2) I_2

crude selectivity
1 : 99

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



usual metalation site

new flow-triggered metalation site

+ 0.5 equiv **ZnCl$_2$·2LiCl**

1.80 mL/min

TMPLi
(1.5 equiv)

1.80 mL/min

0 °C, 40 s

PhCOCl (0.8 equiv)
+ 1.0 equiv CuCN·2LiCl

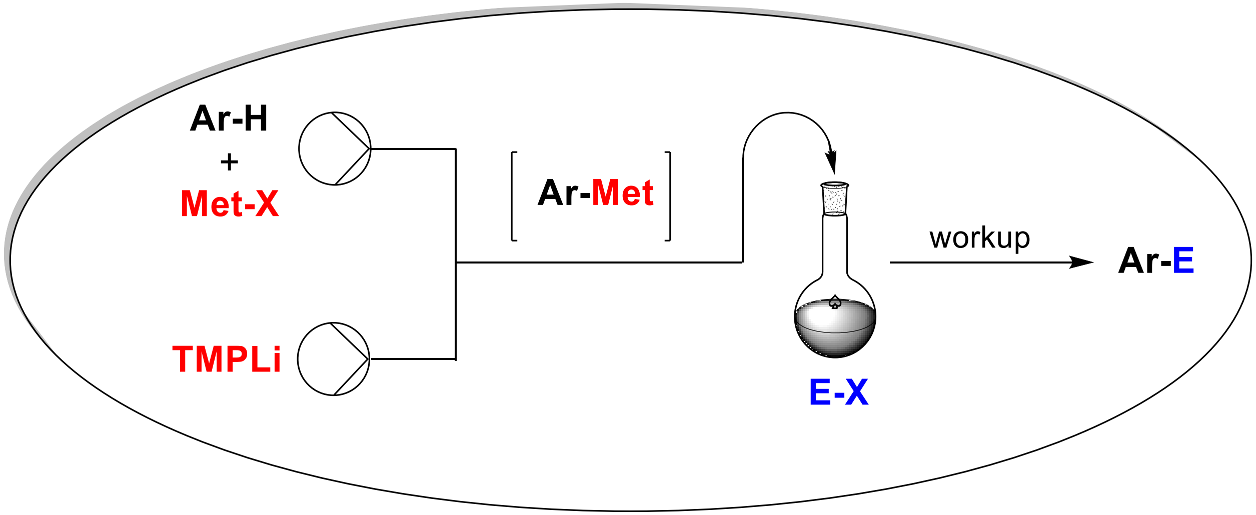
workup

batch reactor

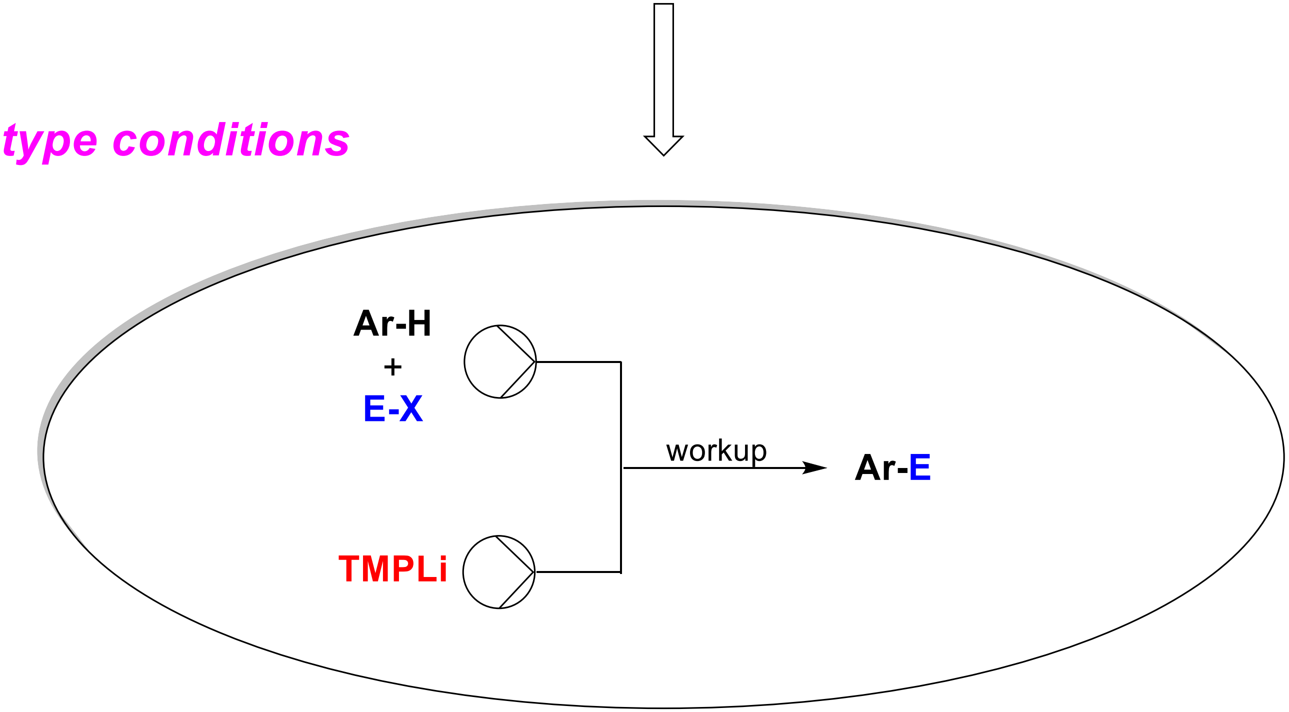
70%

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

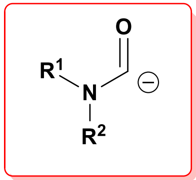
"*In situ*"- metalation procedures scope - further developments

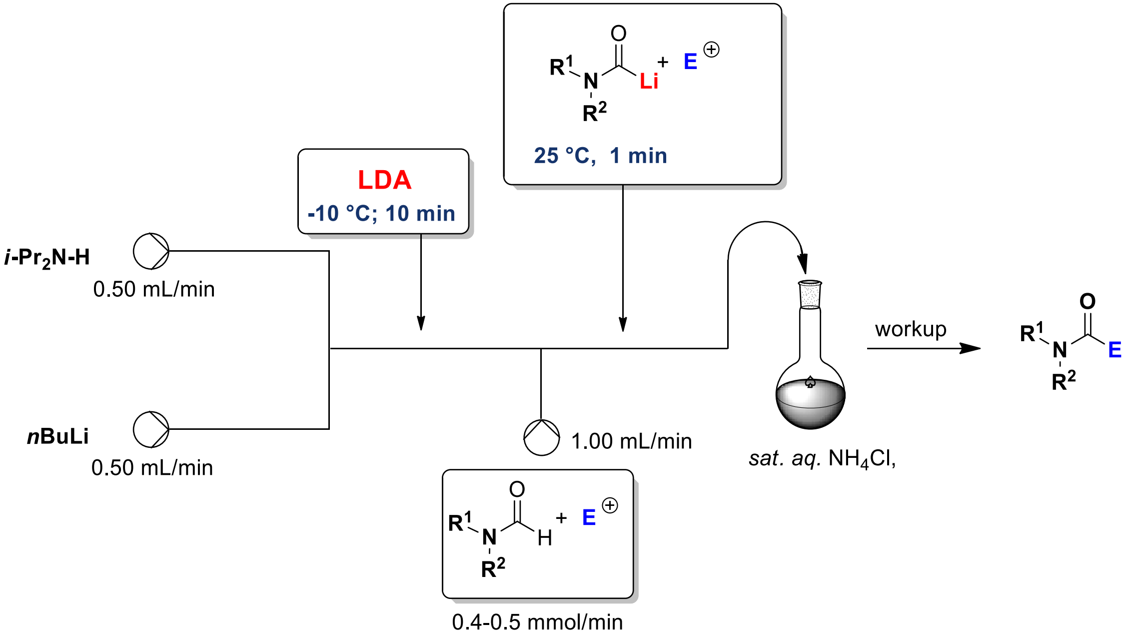


Barbier-type conditions

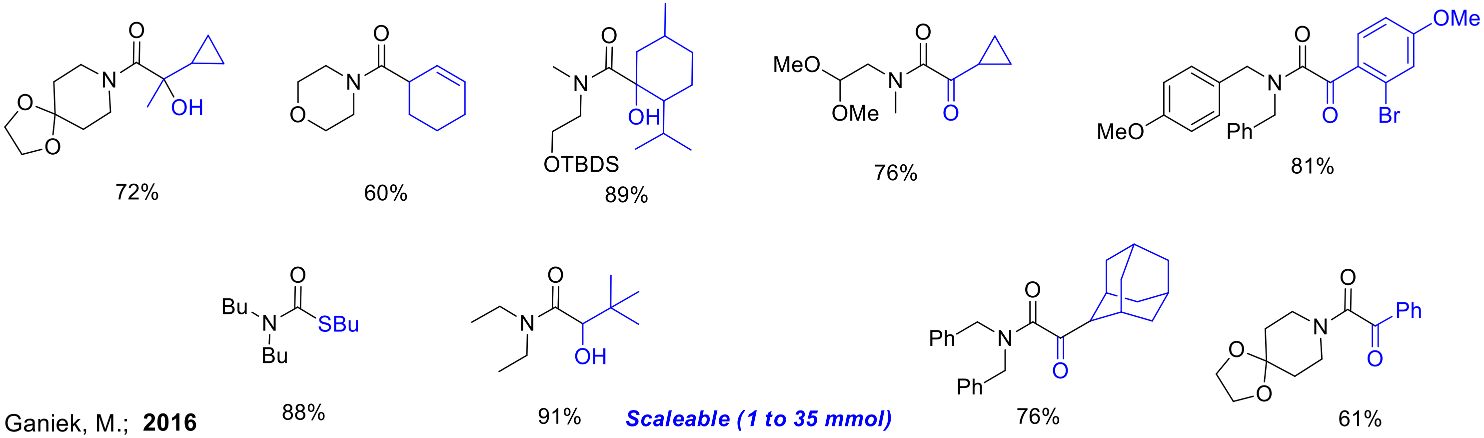


Flow generation of carbamoyllithiums using an extended *in situ* quench





E⊕ = ketones, aldehydes allylic bromides, disulfides, morpholino- and Weinreb-amides



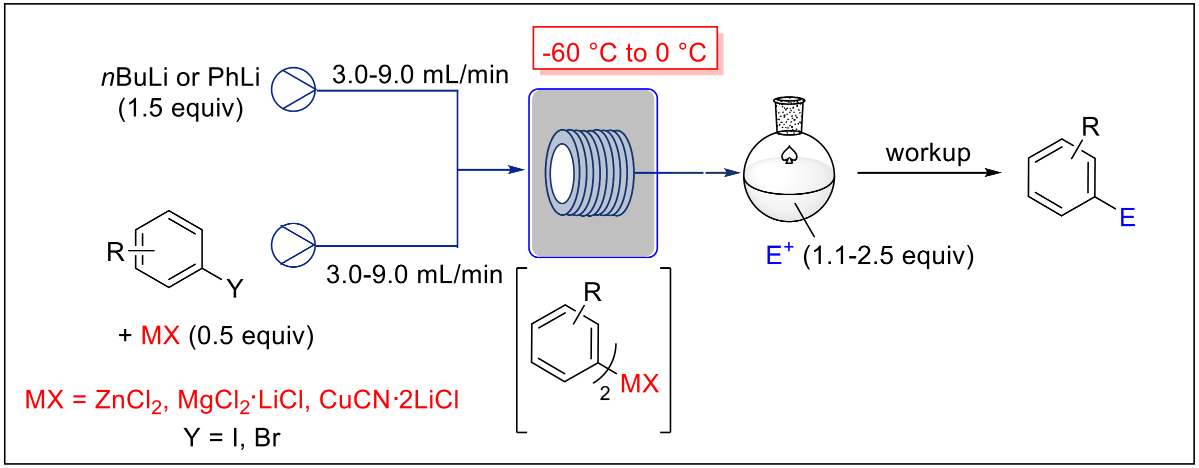
Ganiek, M.; **2016**

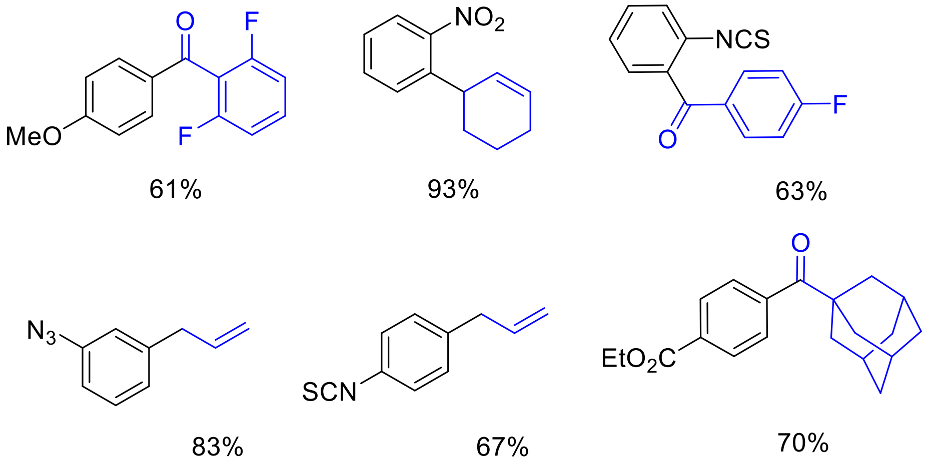
Scaleable (1 to 35 mmol)

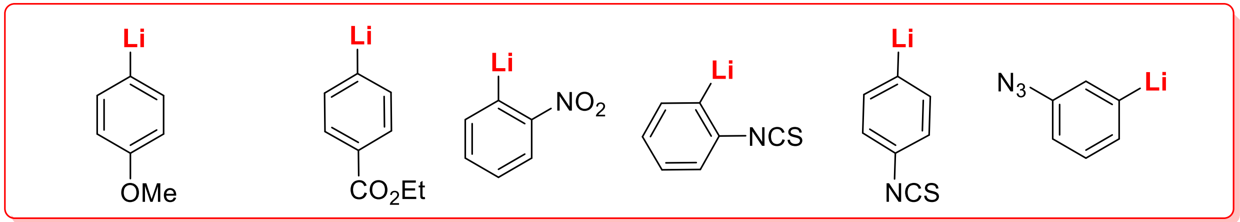
(a) B. Banhidai, U. Schöllkopf *Angew. Chem.* **1973**, *19*, 861. (b) D. Seebach, D. Enders *Angew. Chem.* **1973**, *24*, 1104. Recent flow protocol based on Li-insertion to carbamoyl chlorides: A.Nagaki, Y. Takahashi, J.-i.Yoshida *Angew. Chem. Int. Ed.* **2016**, *55*, 5327

Jonathan T. Reeves, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, *J.Am.Chem.Soc.* **2013**, *135*, 5565

Halogen/Lithium Exchange in Continuous Flow

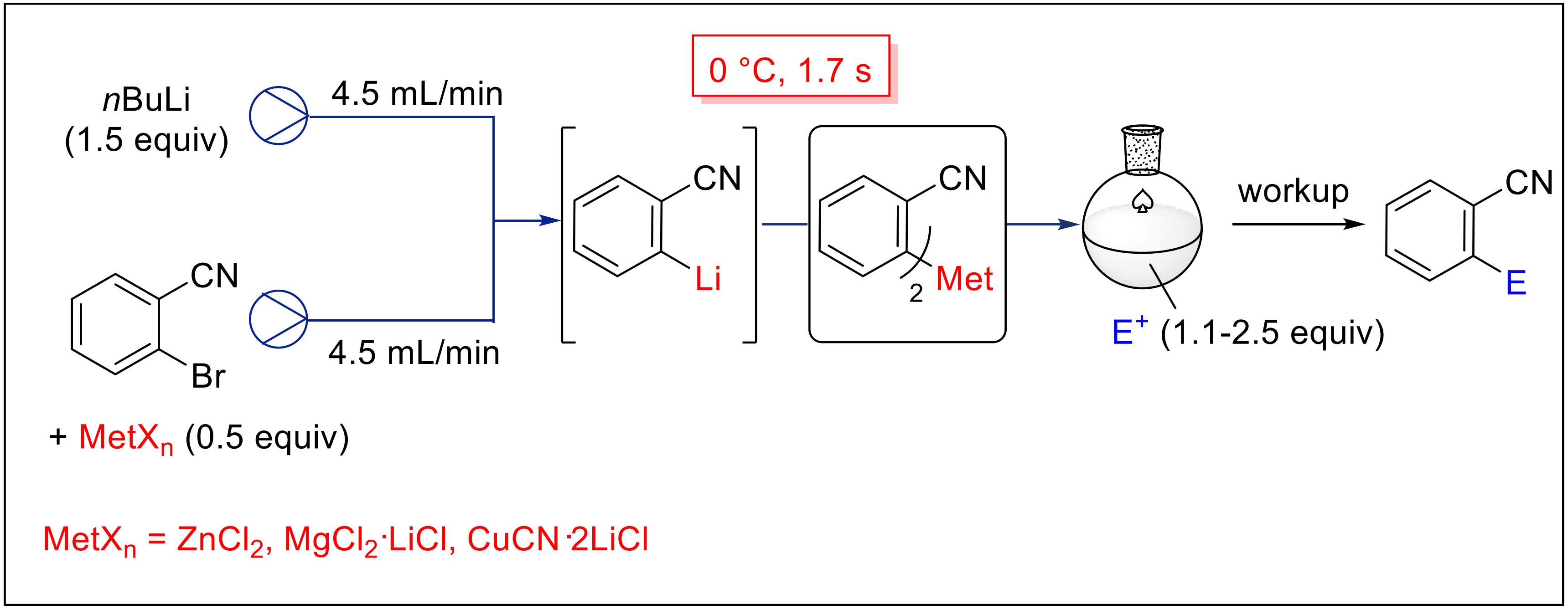




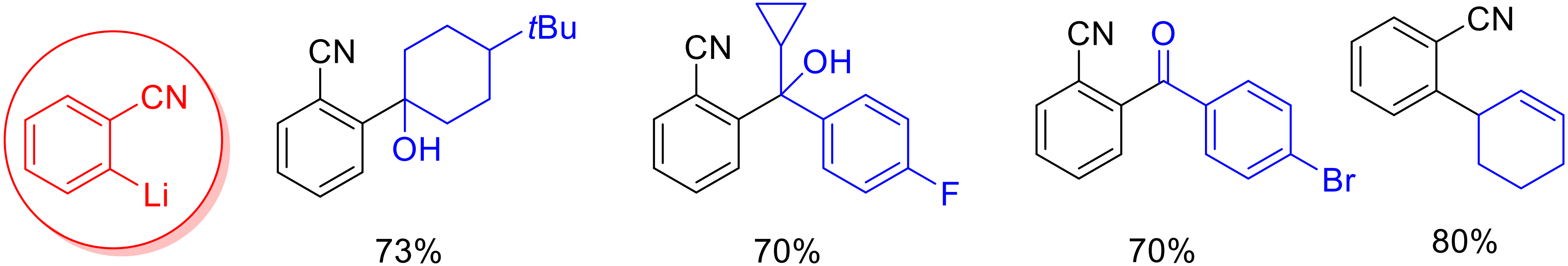


M. Ketels, M. Ganiek, N. Weidmann, P. Knochel 2017, manuscript in preparation

Halogen/lithium exchange and *In Situ* trapping with a metal salt in flow



$MetX_n$ = $ZnCl_2$, $MgCl_2 \cdot LiCl$, $CuCN \cdot 2LiCl$



73%
(d.r. = 84:16)

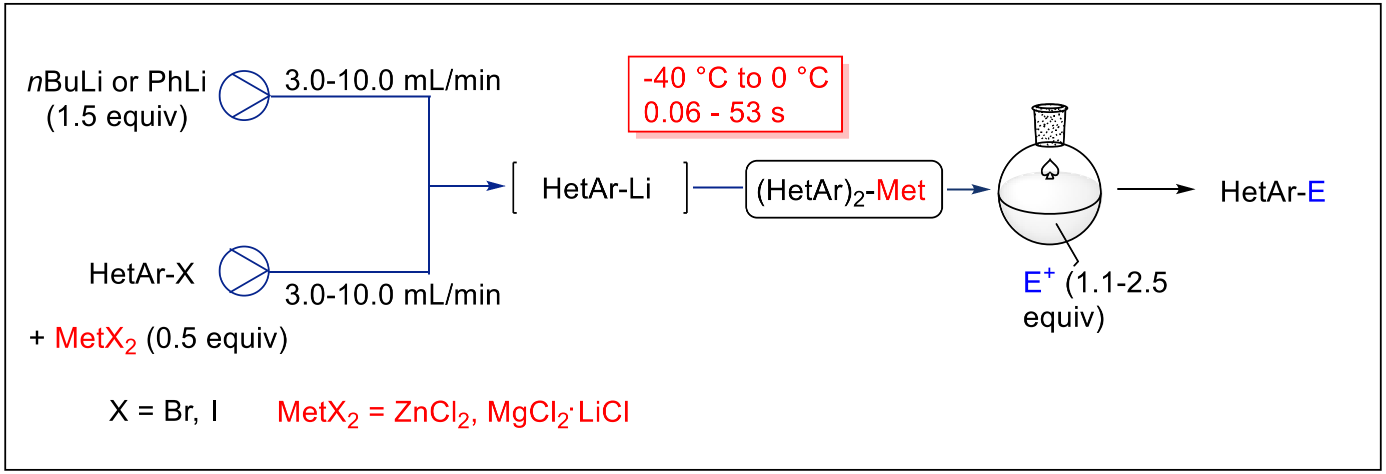
70%

70%

80%

M. Ketels, M. Ganiek, N. Weidmann, P. Knochel, 2017, manuscript in preparation.

Halogen/lithium exchange in continuous flow



*n*BuLi or PhLi (1.5 equiv)

3.0-10.0 mL/min

HetAr-X + $MetX_2$ (0.5 equiv)

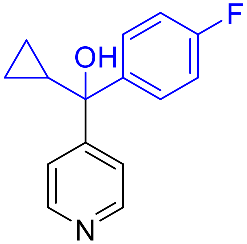
3.0-10.0 mL/min

-40 °C to 0 °C

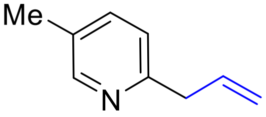
0.06 - 53 s

[HetAr-Li] — $(HetAr)_2$-Met → E^+ (1.1-2.5 equiv) → HetAr-E

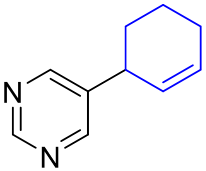
X = Br, I $MetX_2$ = $ZnCl_2$, $MgCl_2 \cdot LiCl$



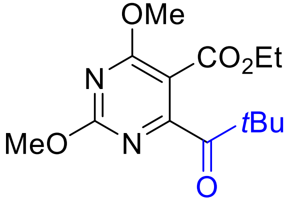
62% yield (X = I)



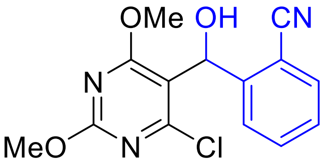
63% yield (X = Br)



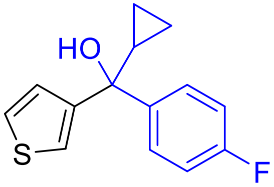
68% yield (X = Br)



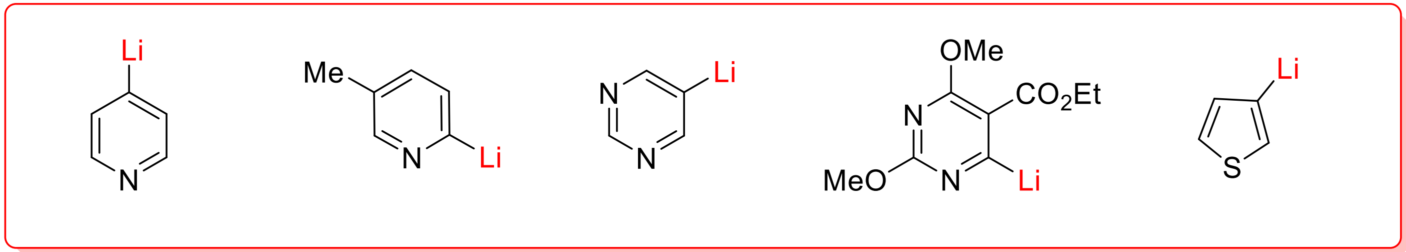
68% yield (X = I)



59% yield (X = I)

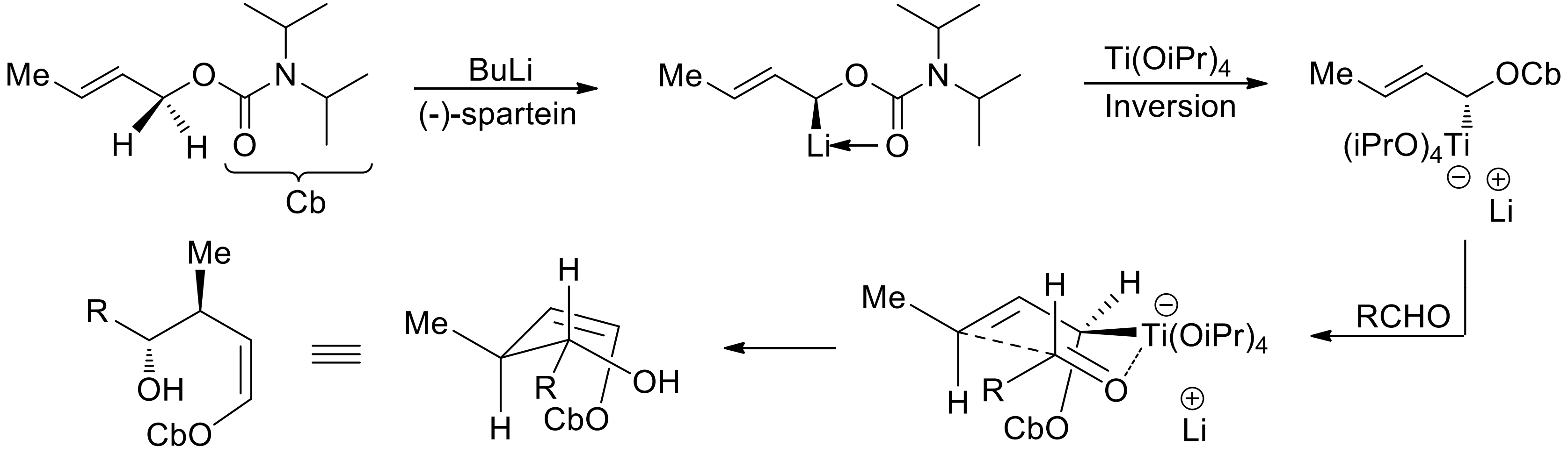


77%



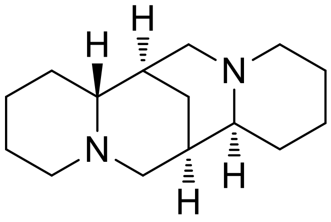
M. Ketels, M. Ganiek, N. Weidmann, P. Knochel, 2017, manuscript in preparation.

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

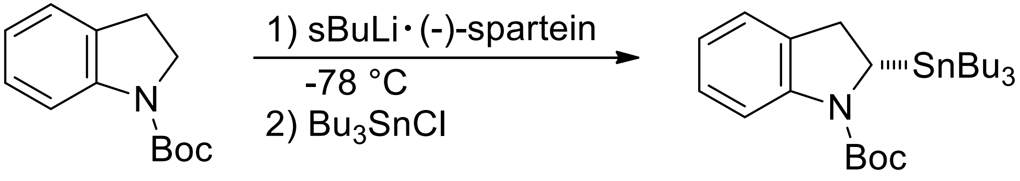


82-92% ee

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



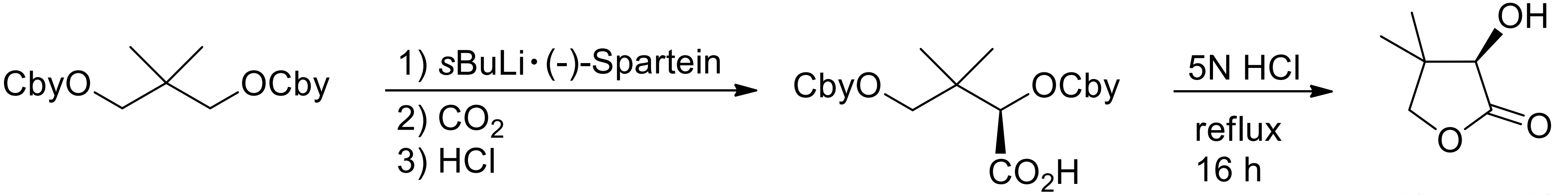
(S)-(-)-spartein



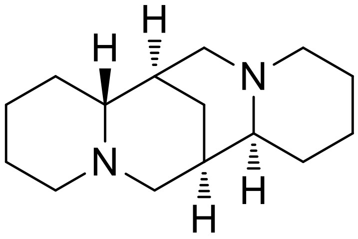
98% ee

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

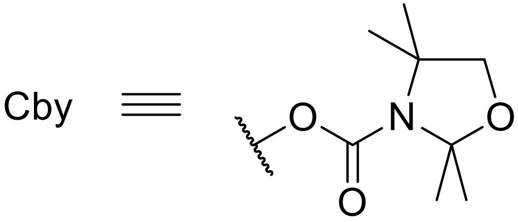
Asymmetric metalation using (*S*)-(-)-spartein



73%; > 95 %ee

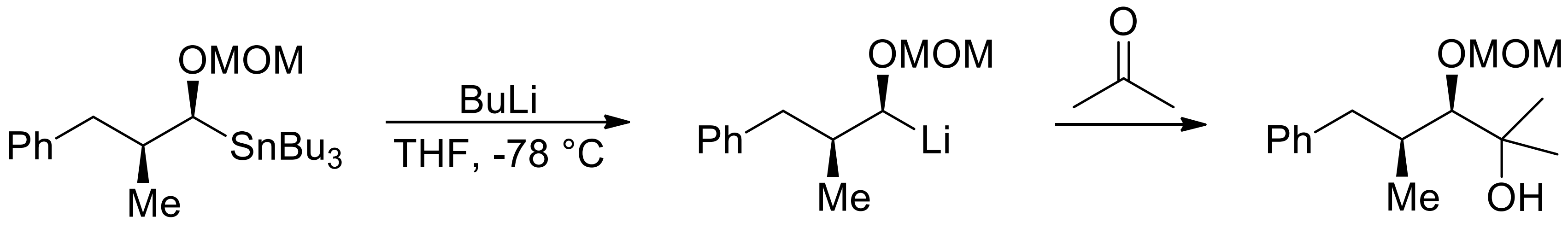


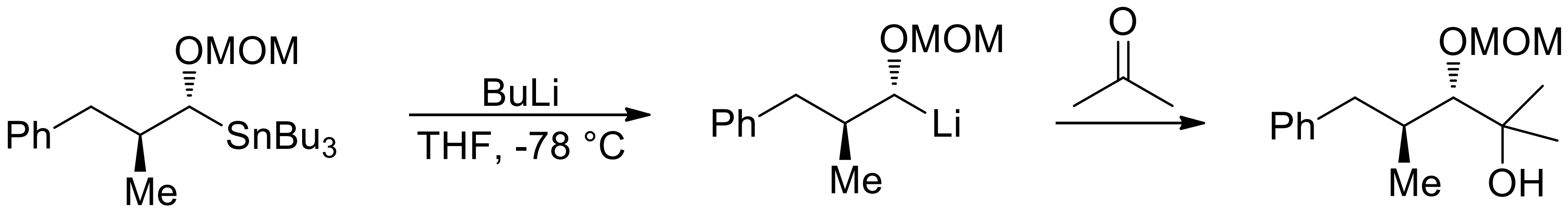
(S)-(-)-Spartein

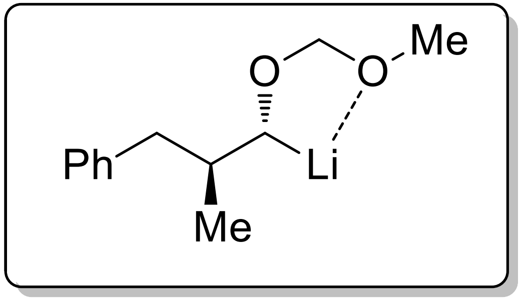


D. Hoppe *Tetrahedron Lett*. **1992**, *33*, 5327

Diastereoselective transmetalation

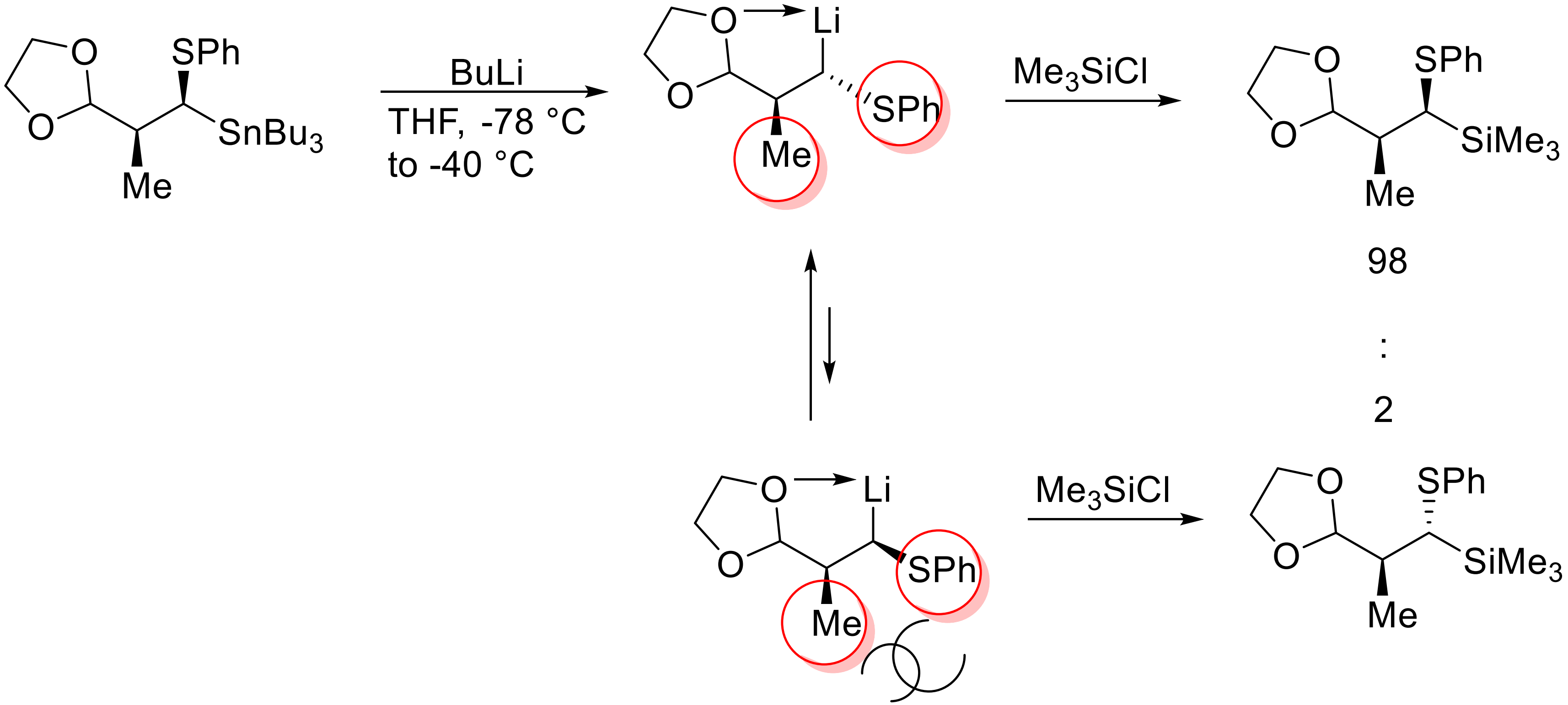






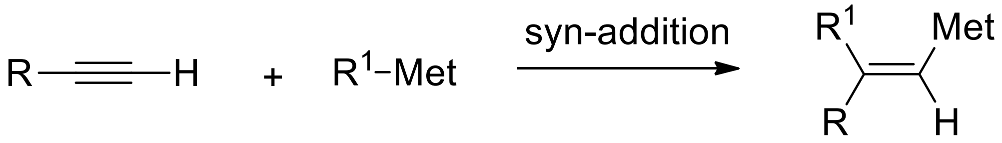
W. C. Still J. *Am. Chem. Soc*. **1980**, *102*, 1201

Diastereoselective transmetalation

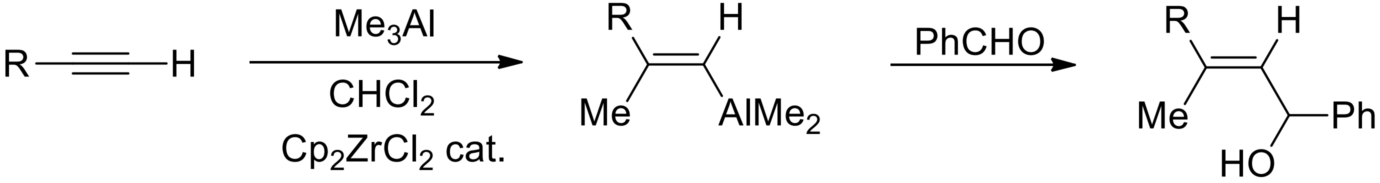


P. G. McDougal, *Tetrahedron Lett*. **1988**, *29*, 2547

Carbometalation

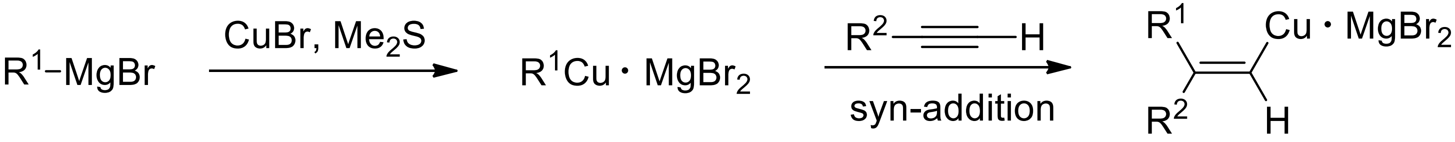


Negishi-reaction: carboalumination



79%

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

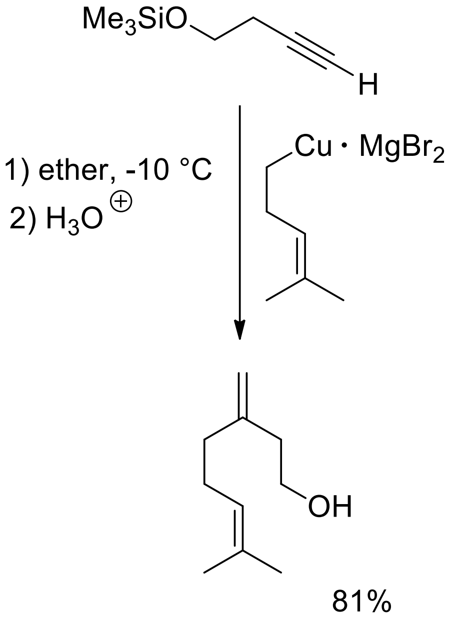


> 90%

Normant-reaction: carbocupration

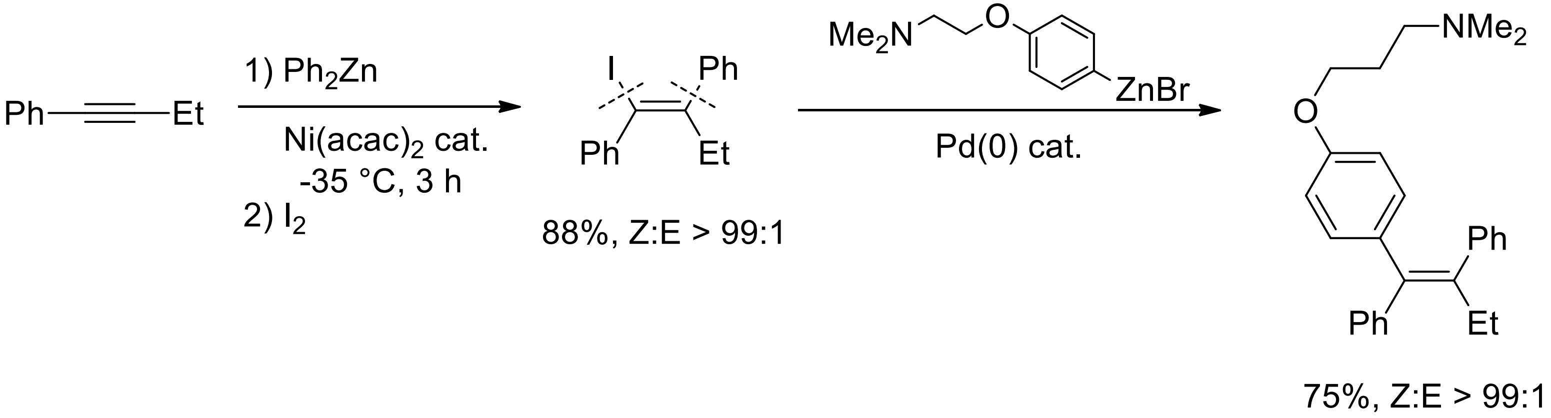
Review: A. Alexakis, J. F. Normant, *Synthesis* **1981**, 841.

Carbometalation



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

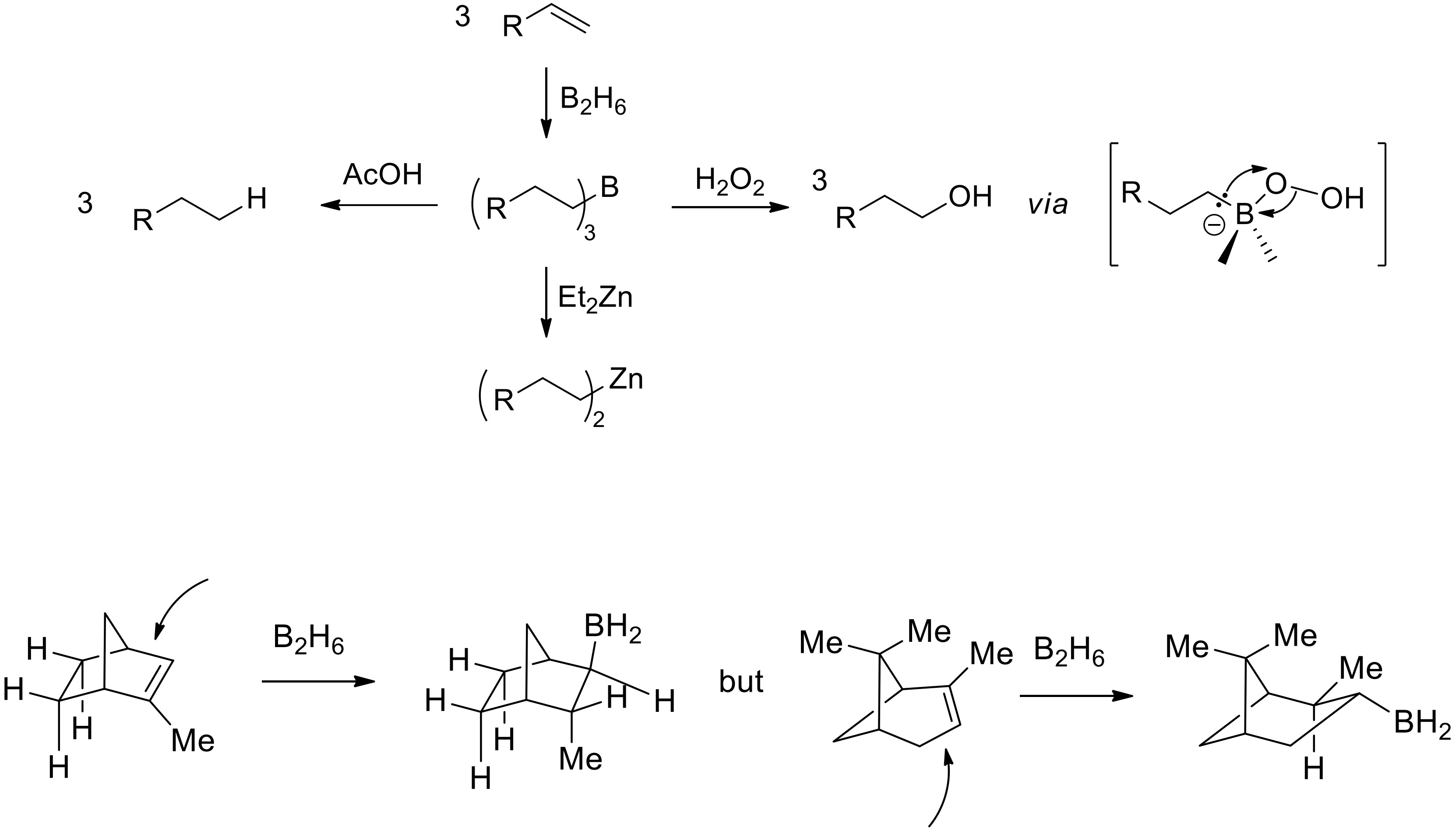
Tamoxifen-Synthesis: Carbozincation



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

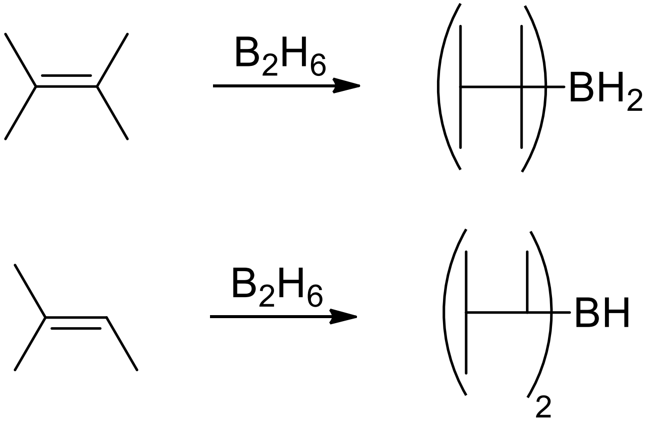
Hydrometalation and application of organoboranes in organic chemistry

hydroboration



Hydroboration

selective hydroborating reagents



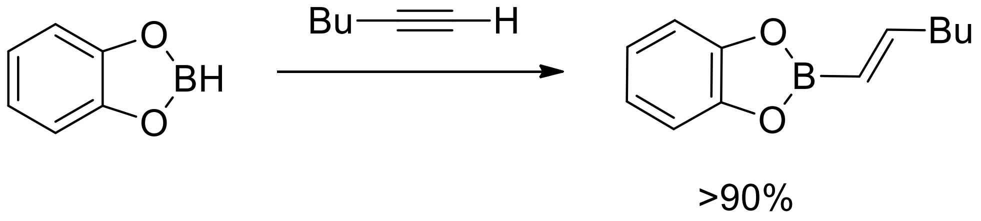
Thexylborane $\quad$ $ThexBH_2$

Disiamylborane $\quad$ Sia_2BH

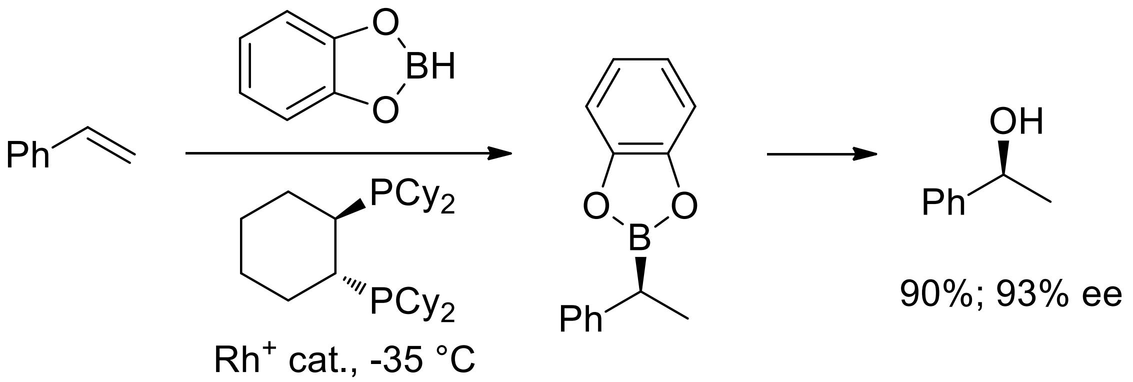
H. C. Brown, E. Negishi *J. Am. Chem. Soc*. **1975**, *97*, 2799

Hydroboration

catecholborane



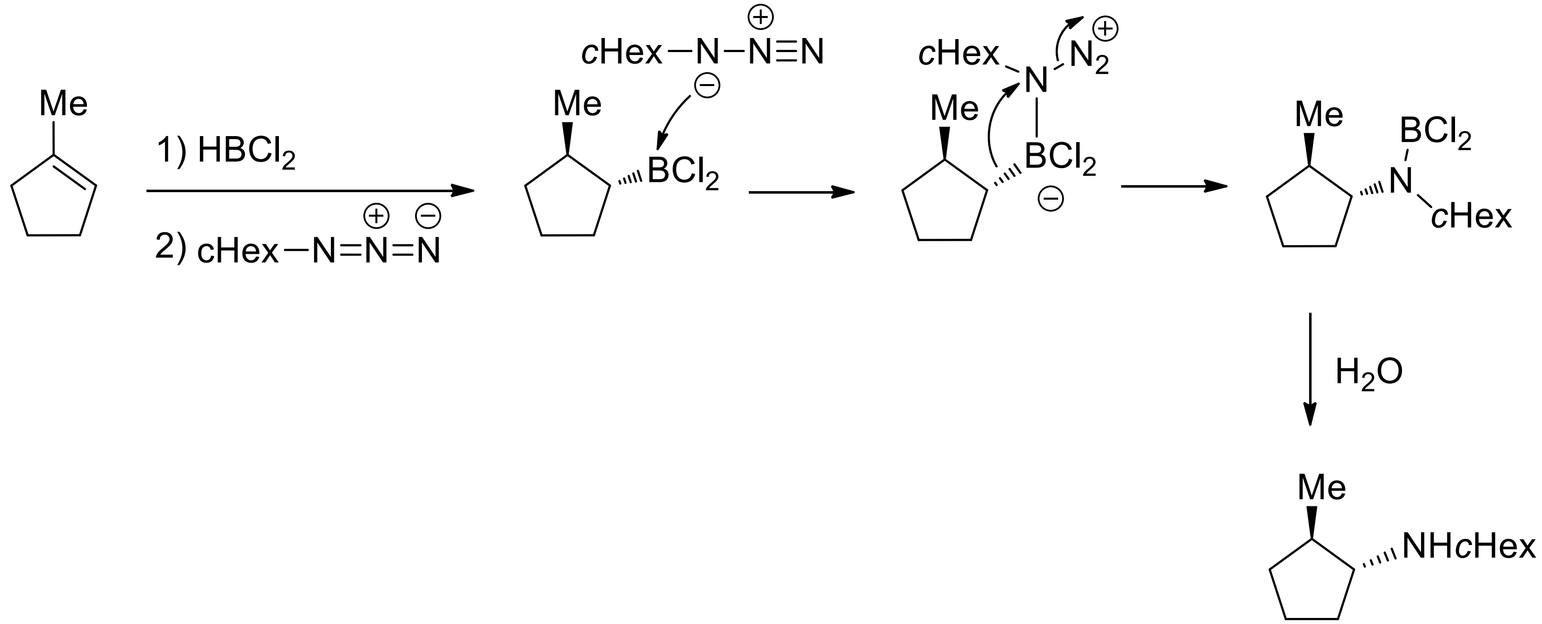
A. Arase, et al., *Synth. Comm*. **1995**, *25*, 1957.



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

Hydroboration

amination



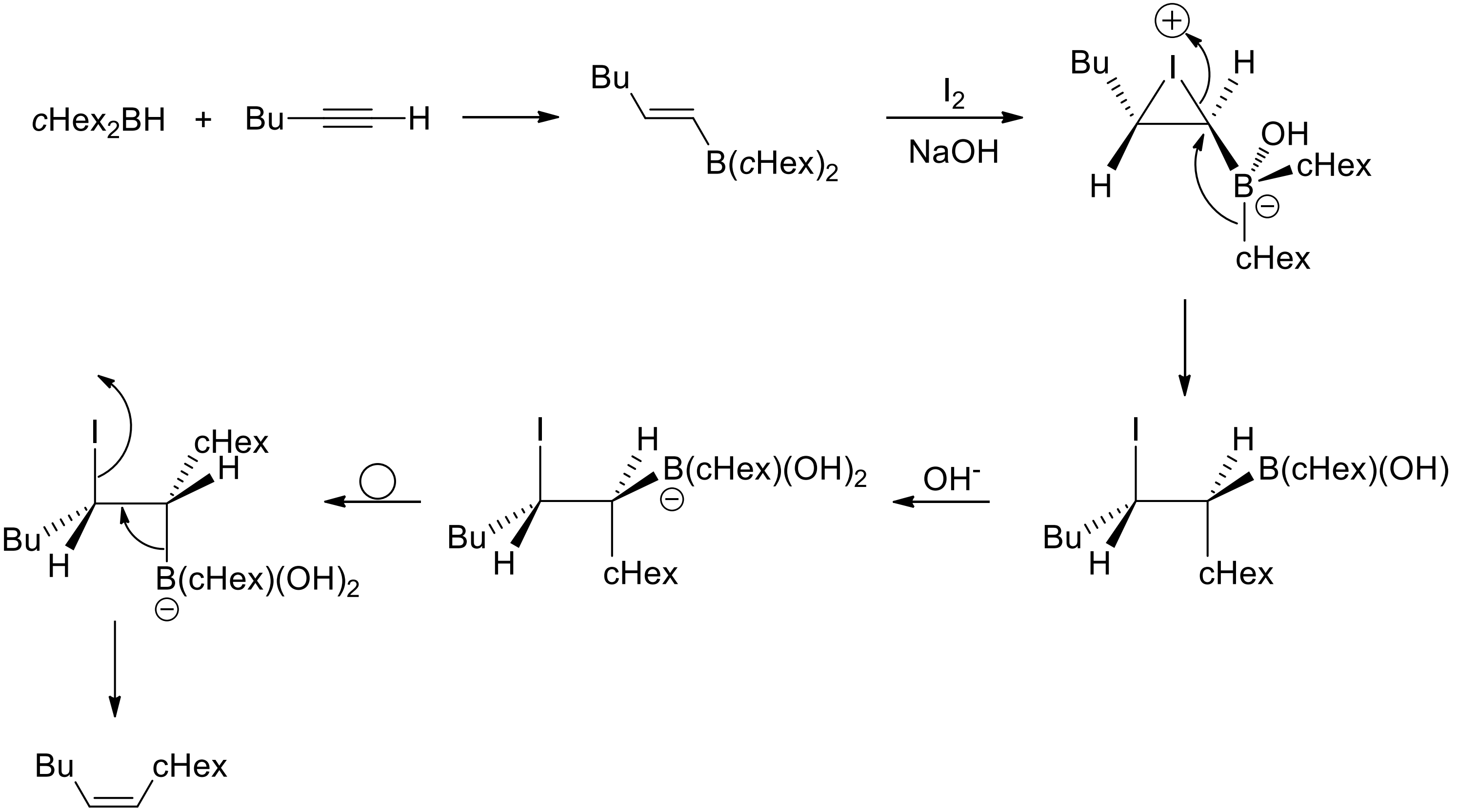
90%

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

Hydroboration

stereoselective synthesis of olefins

Z-olefins

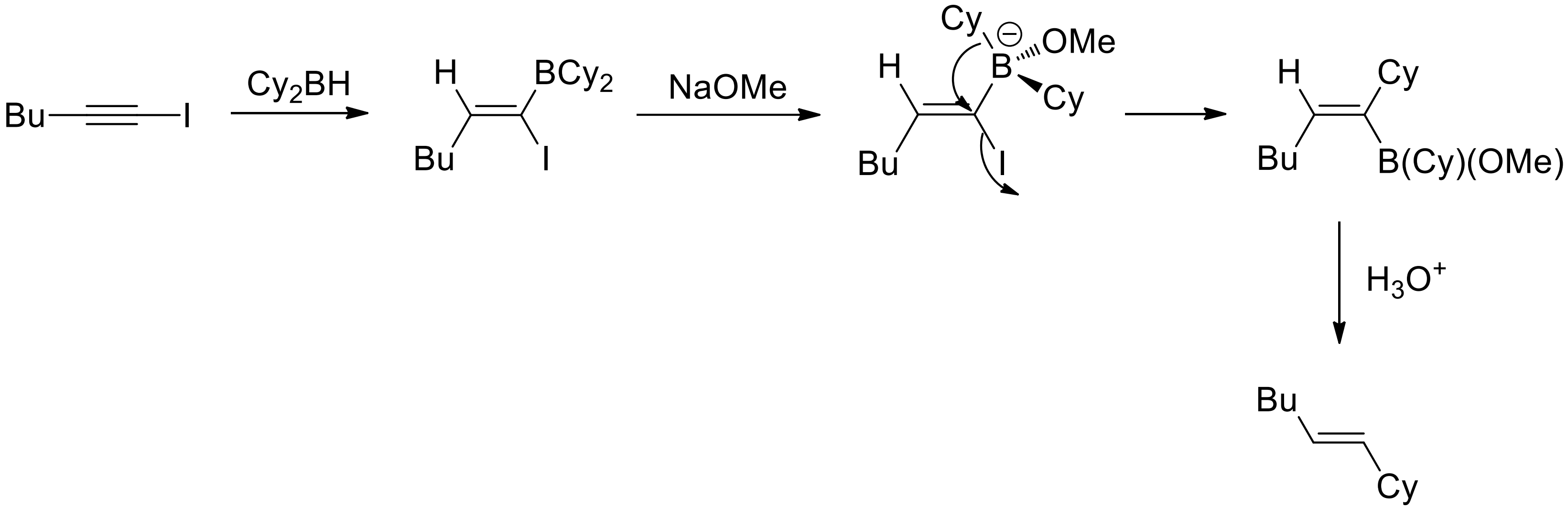


G. Zweifel, et al. *J. Am. Chem. Soc*. **1972**, *94*, 6560.

Hydroboration

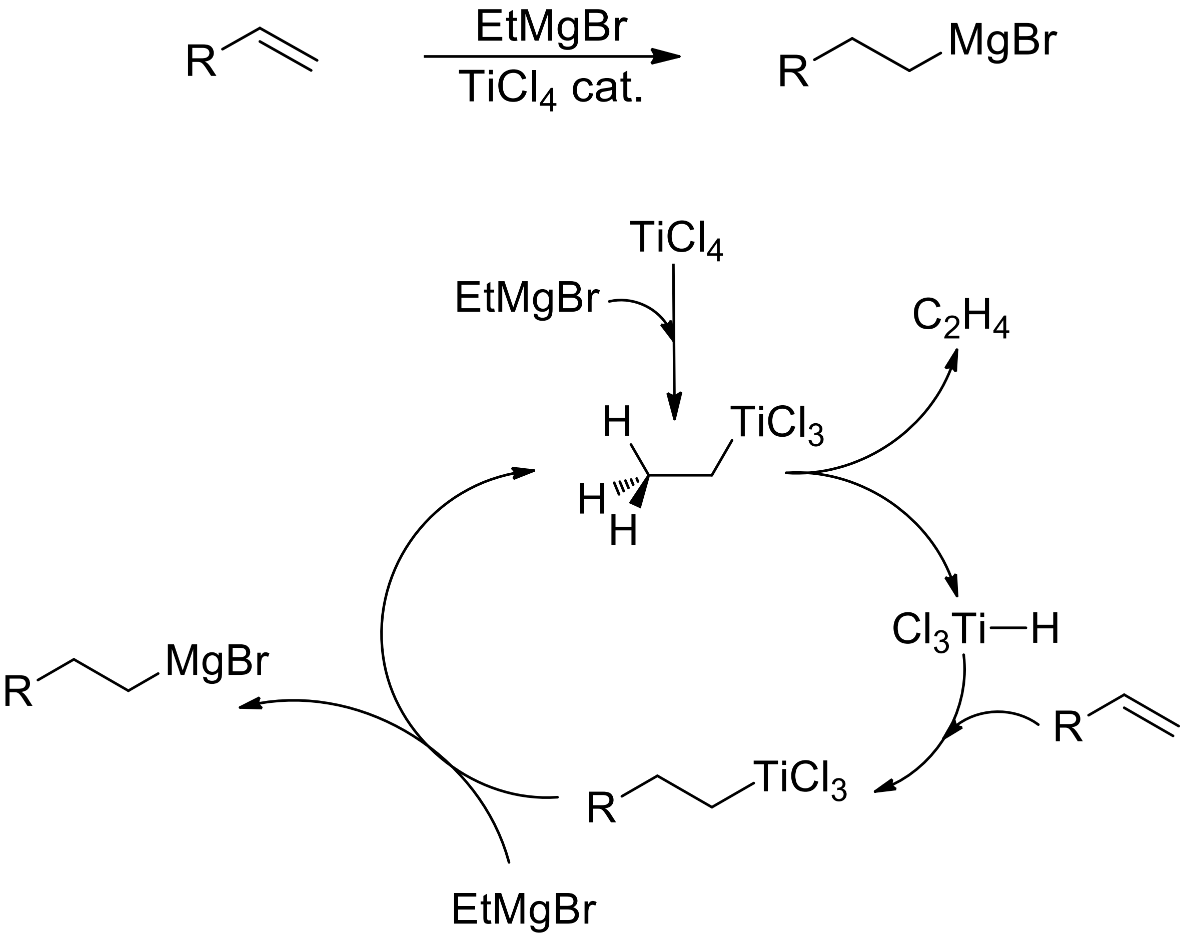
stereoselective synthesis of olefins

E-olefins



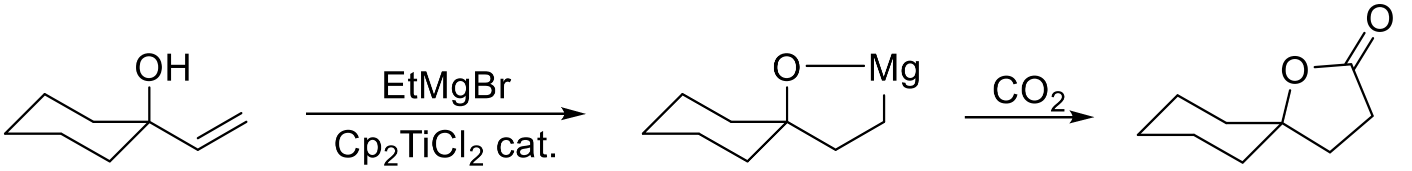
H. C. Brown, et al *J. Org. Chem*. **1989**, *54*, 6064.

Hydromagnesiation



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

Hydromagnesiation



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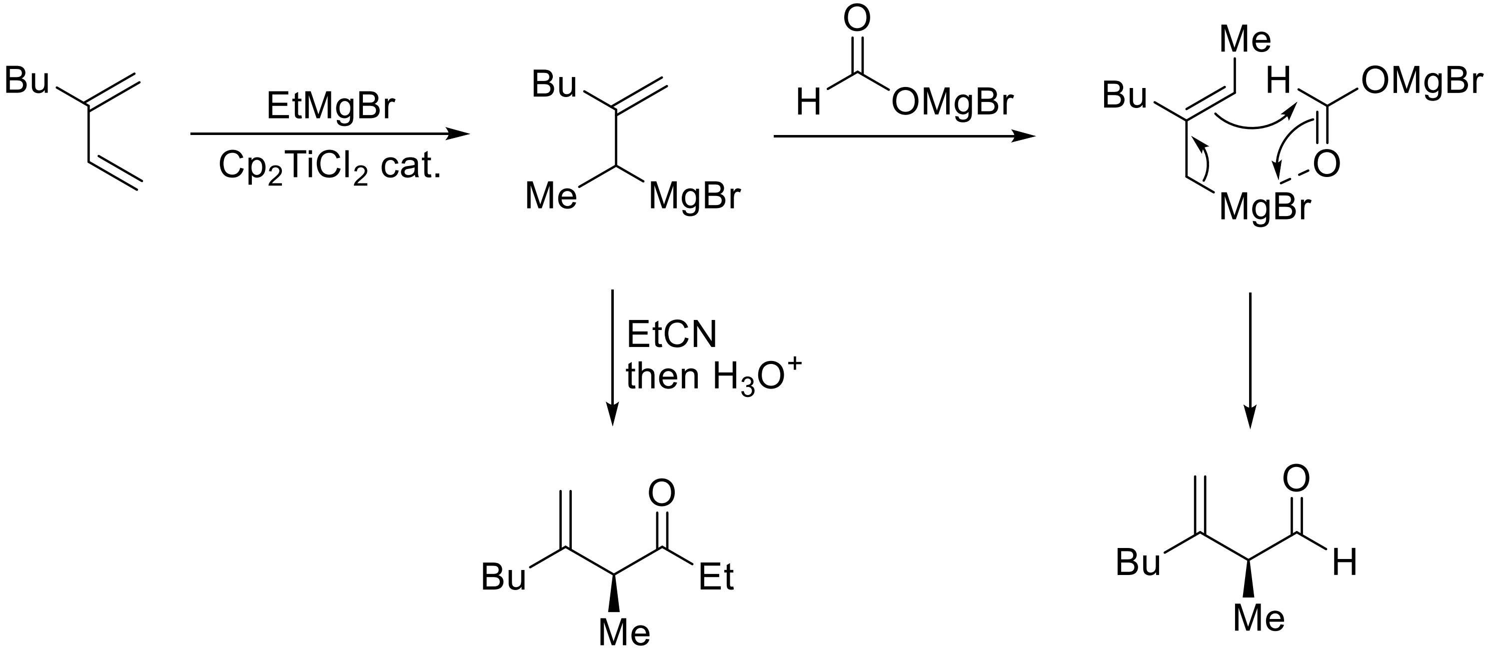
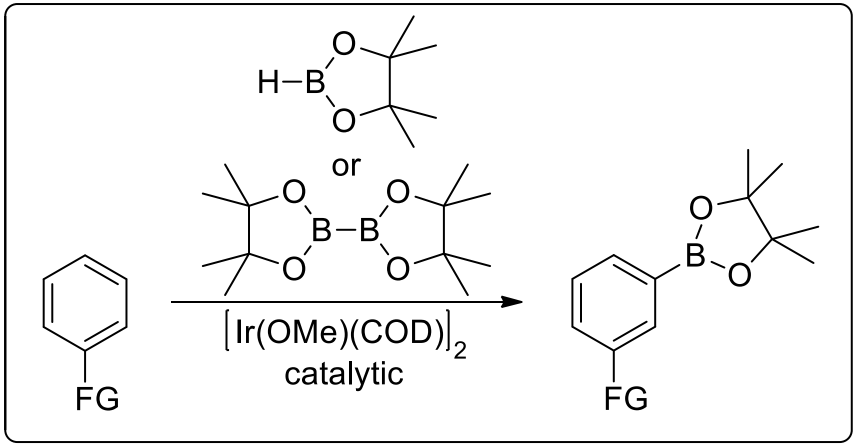
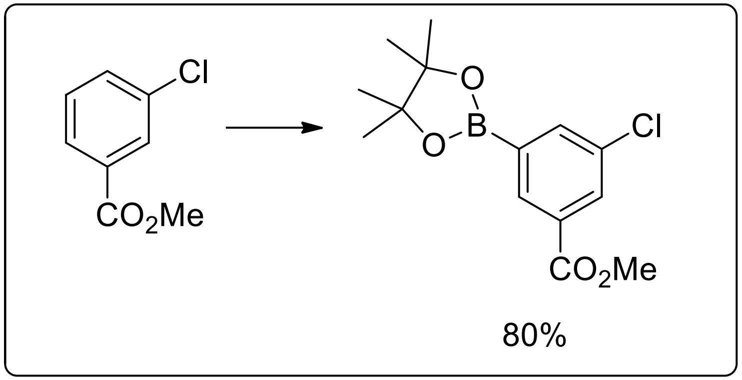


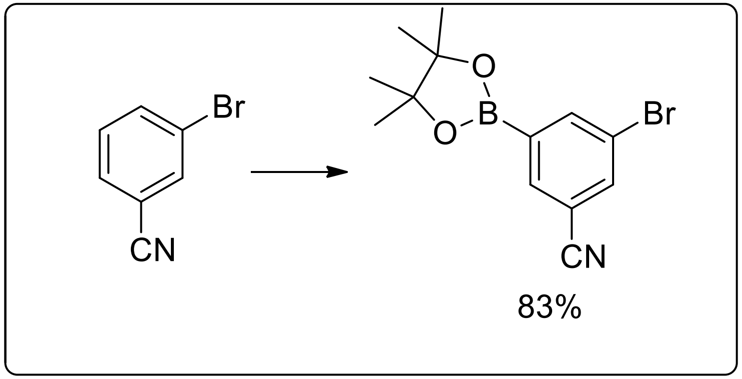
F. Sato, *Chem. Rev*. **2000**, *100*, 2835

Synthesis of aryl boronic acids

transition-metal catalyzed synthesis of aryl boronic acids

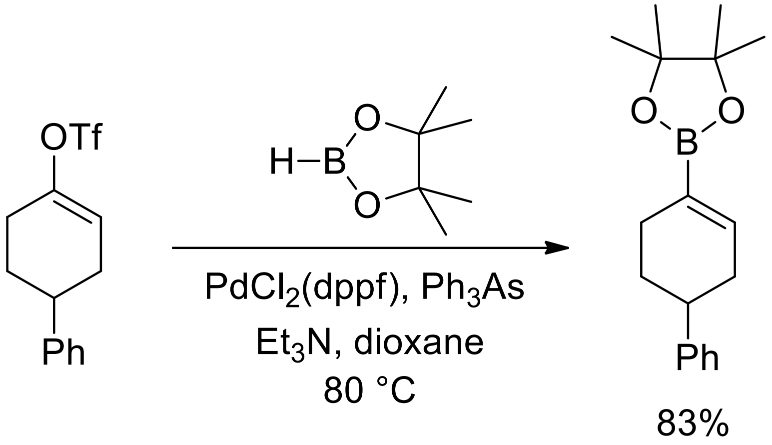




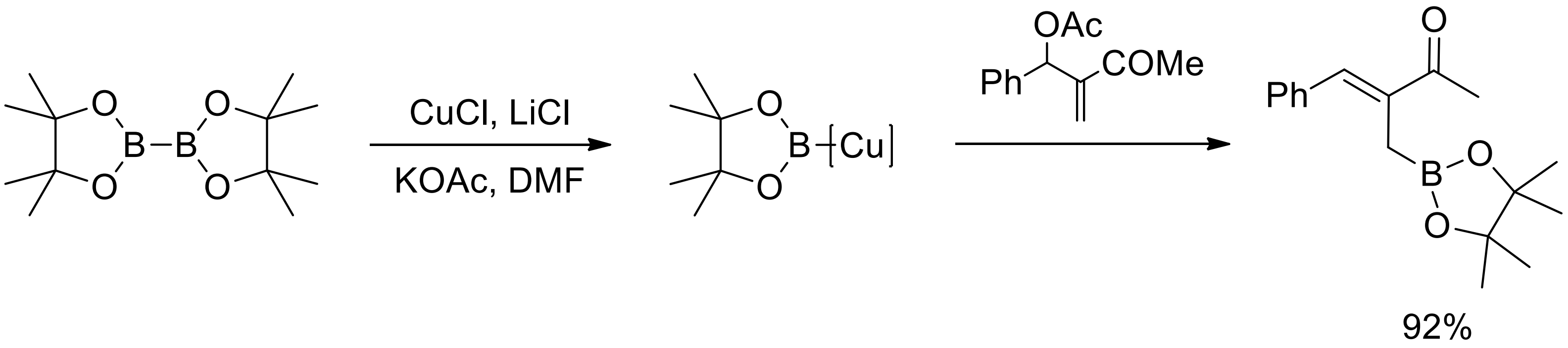


J. F. Hartwig, N. Miyaura, *Chem. Comm*. **2003**, 2924;
J. Am. Chem. Soc. **2002**, *124*, 390; *Angew. Chem. Int. Ed*. **2002**, *45*, 3056

Synthesis of aryl boronic acids



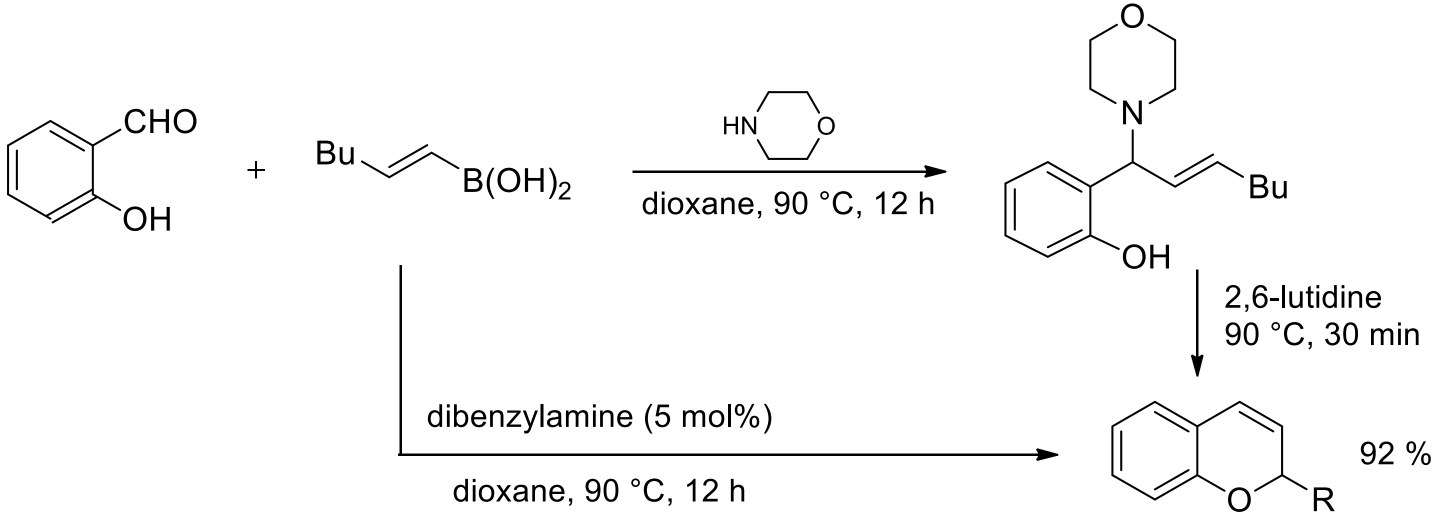
M. Murata *Tetrahedron Lett*. **2000**, *41*, 5877
M. Murata *Synth. Comm*. **2002**, *32*, 2513



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

Reactivity of unsaturated boronic derivatives

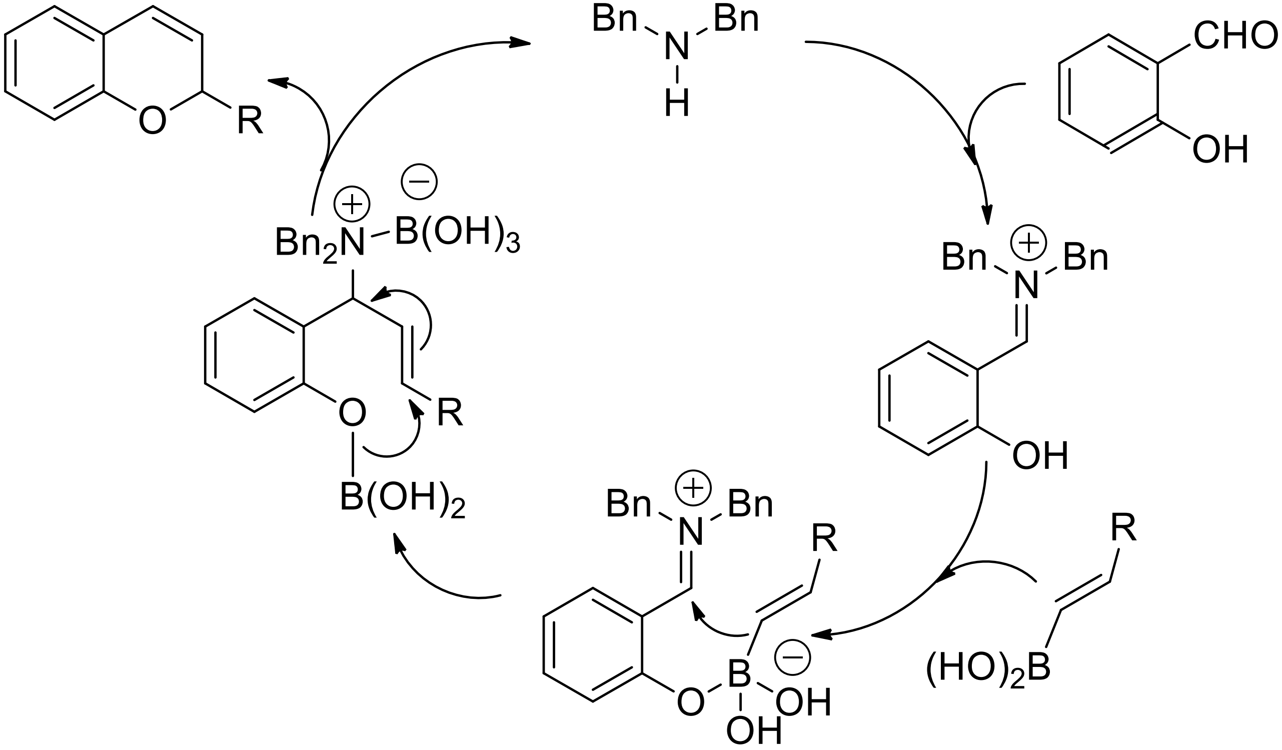
the Petasis-reaction - a short synthesis to 2H-chromenes



Reactivity of unsaturated boronic derivatives

The Petasis-reaction

mechanism



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

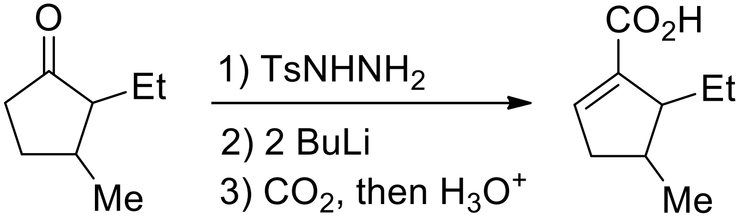
ÜBUNG

1. Problem set

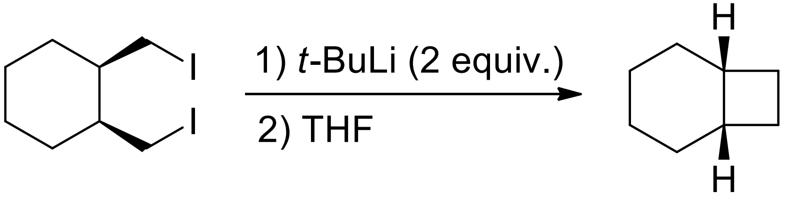
First Problem Set for OC IV

1) Give a mechanism for the following reactions:

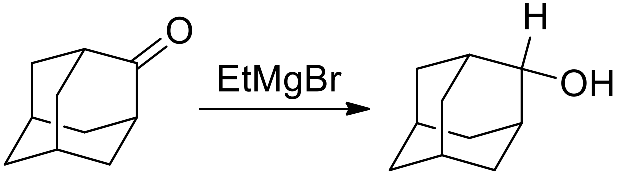
a)



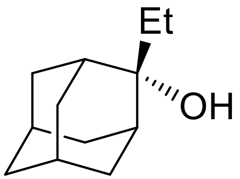
b)



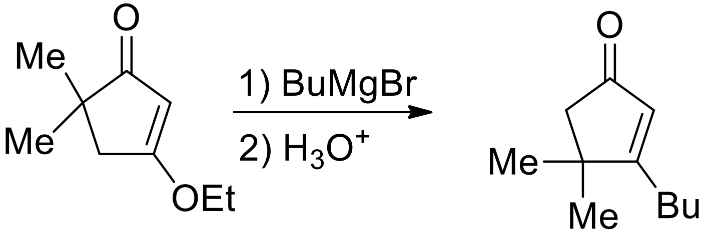
c)



How would you prepare



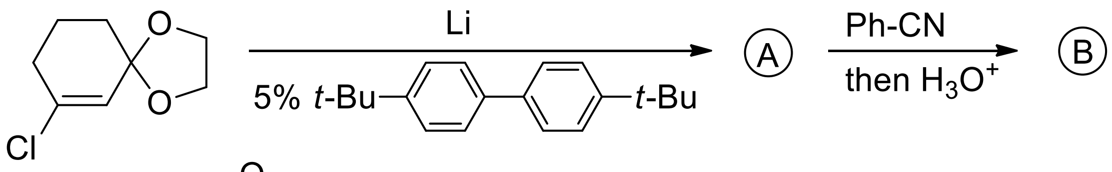
d)



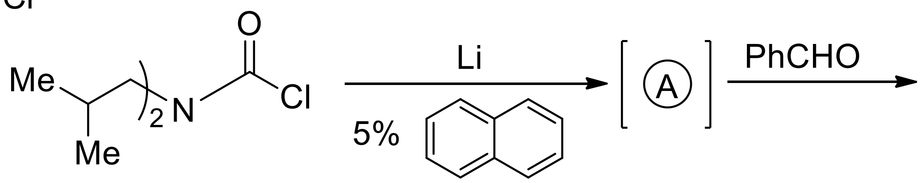
First Problem Set for OC IV

2) Give the following reaction products:

a)



b)



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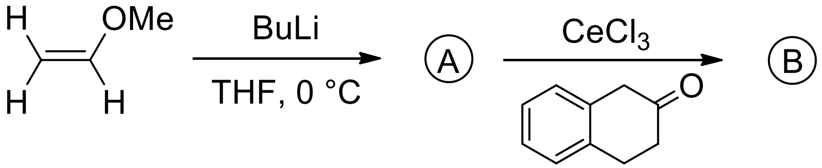

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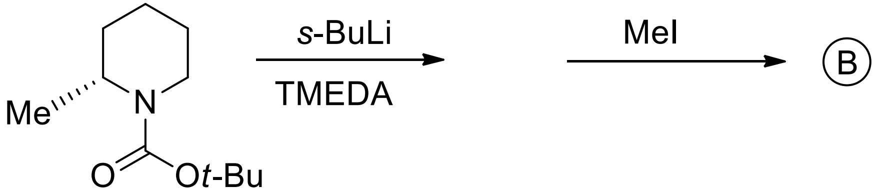
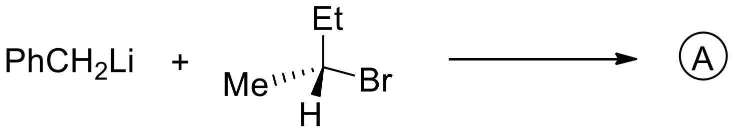
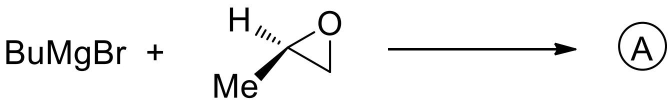


stereochemie?

e)

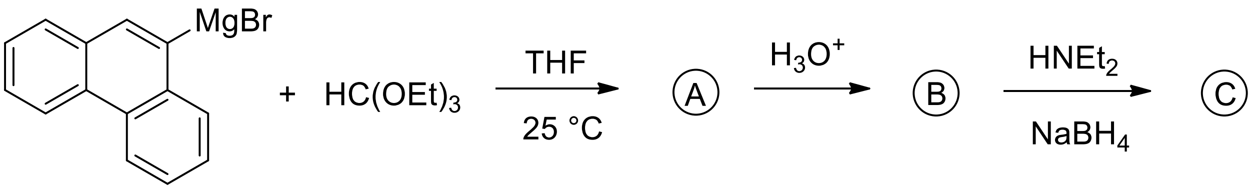


f)



First Problem Set for OC IV

g)



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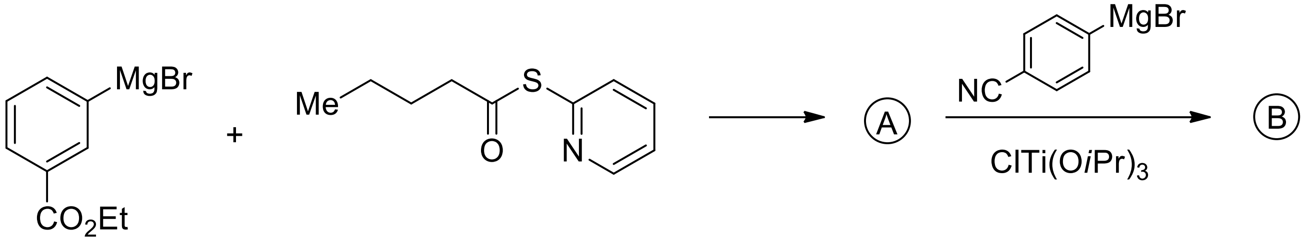
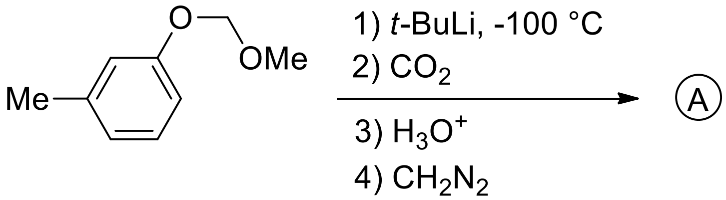


i)



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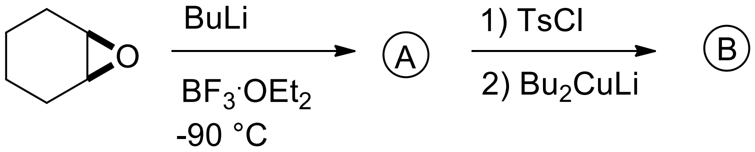
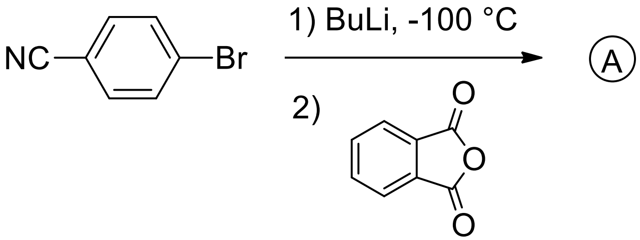
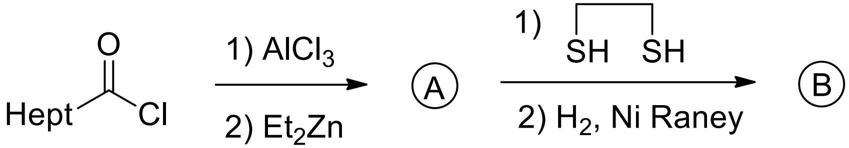


k)

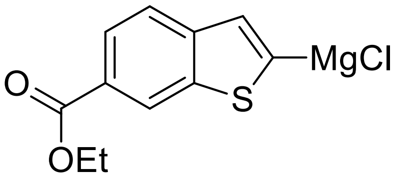


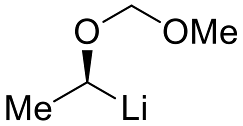
l)



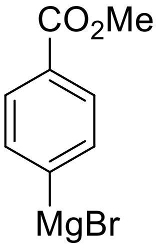
First Problem Set for OC IV

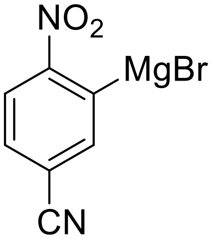
3. How you would prepare following organometallics:

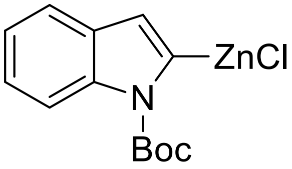


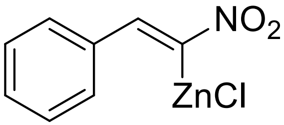


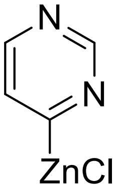
ICH_2ZnI

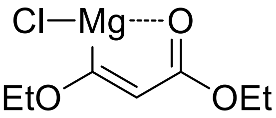


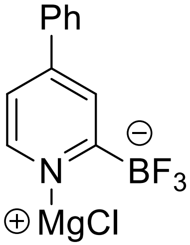


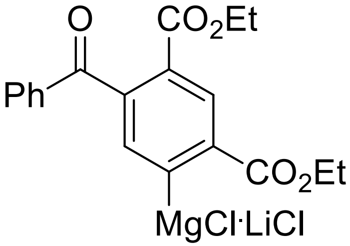


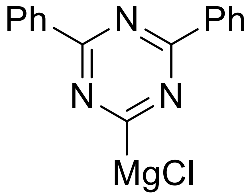




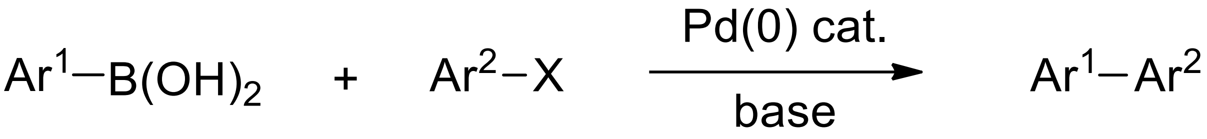








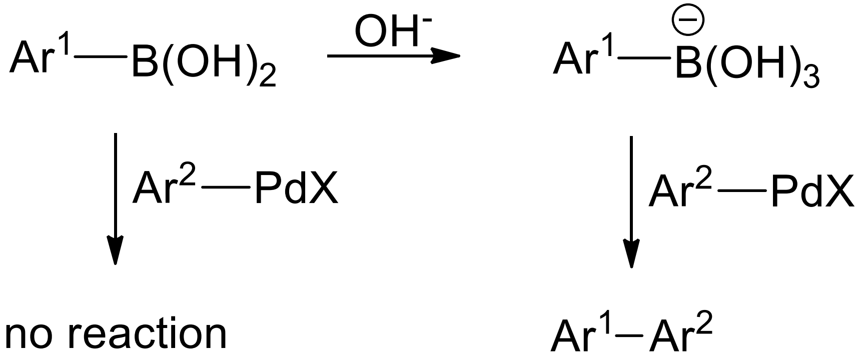
The Suzuki cross-coupling reaction



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

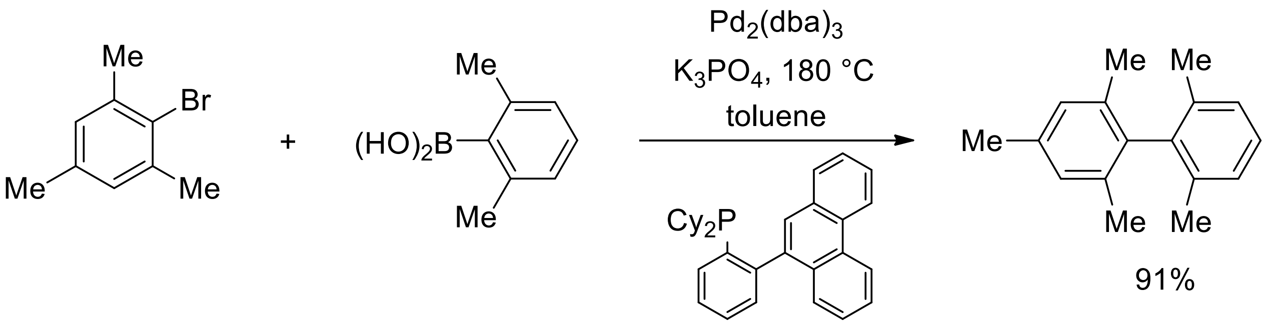
N. Miyaura, A. Suzuki *Chem. Rev*. **1995**, *95*, 2457
Cross-Coupling Reactions. A practical guide. N. Miyaura (Ed.), Springer, **2002**

Key step

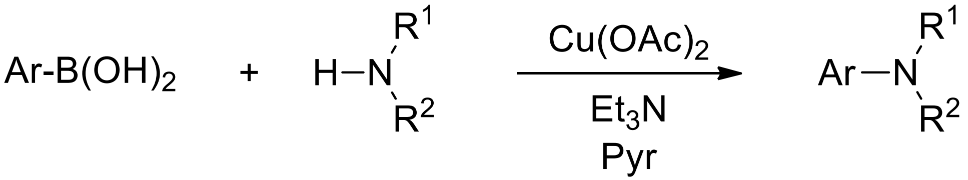


S. Buchwald, *J. Am. Chem. Soc*. **2002**, *124*, 1162
C. Amatore, A. Jutand, G. Le Duc *Chem. Eur. J*. **2011**, *17*, 2492
B. P. Carrow, J. F. Hartwig *J. Am. Chem. Soc*. **2011**, *133*, 2116

The Suzuki cross-coupling reaction

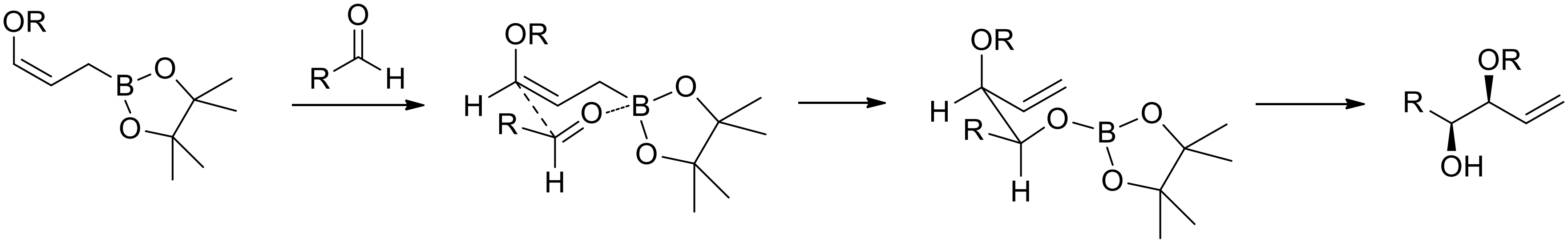


R. E. Sammelson, M. J. Kurth, *Chem. Rev*. **2001**, *101*, 137



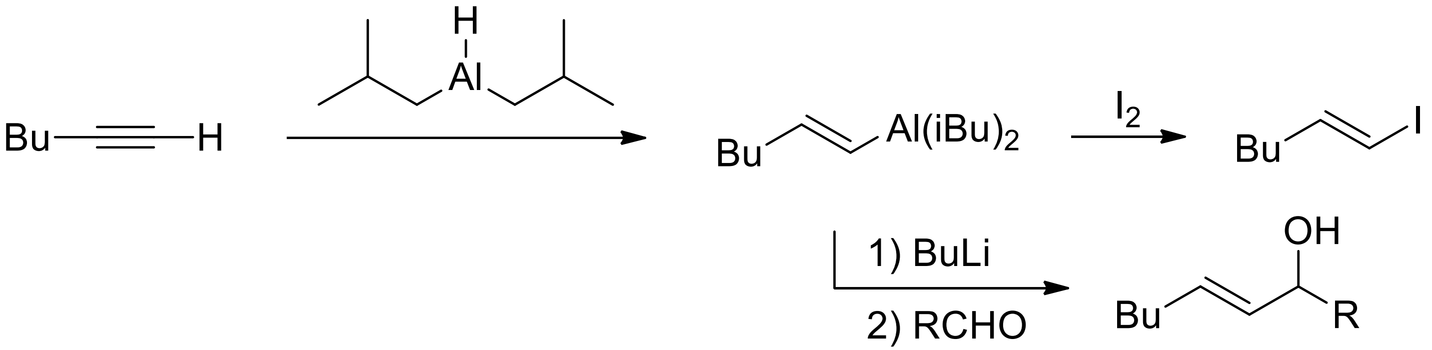
D. A. Evans, *Tetrahedron Lett*. **1998**, *39*, 2937
S. Ley, *Angew. Chem. Int. Ed*. **2003**, *42*, 5400

Chemistry of allyl boranes



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

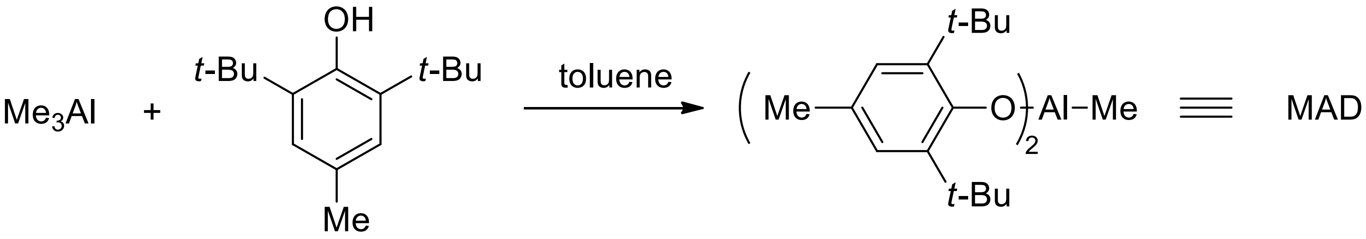
Hydroalumination

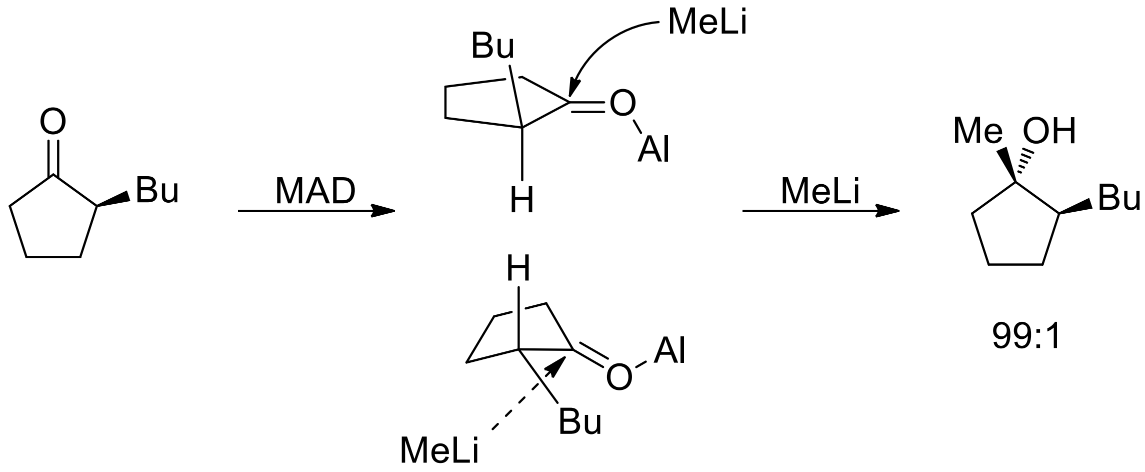


G. Zweifel, *Org. React*. **1984**, *32*, 375

Hydroalumination

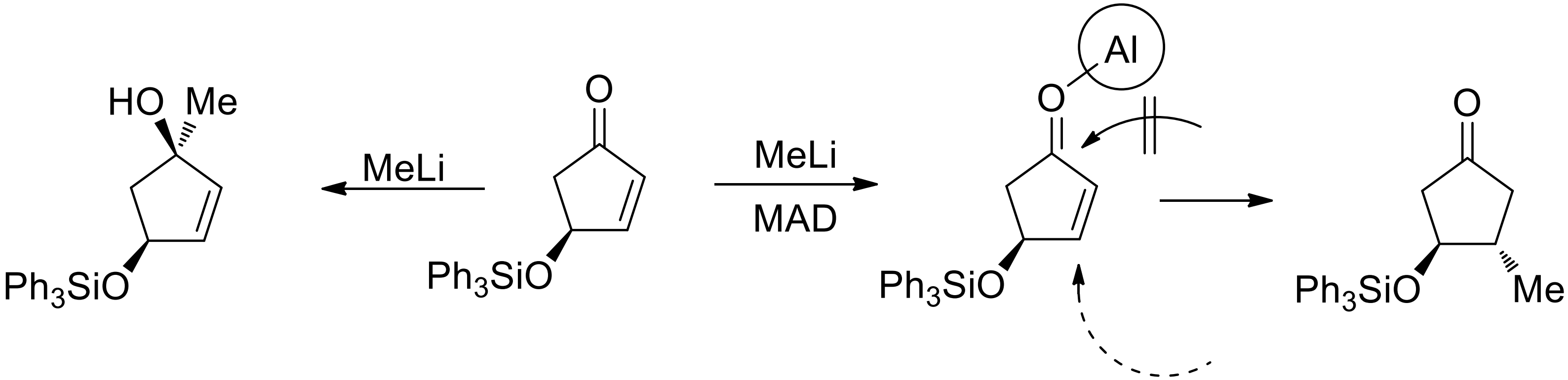
Special Al-reagents

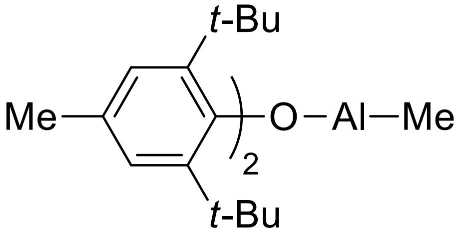




H. Yamamoto *J. Am. Chem. Soc*. **1988**, *110*, 3588
H. Yamamoto *Chem. Comm*. **1997**, 1585

Hydroalumination





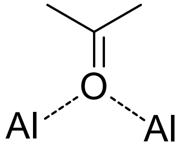
MAD

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

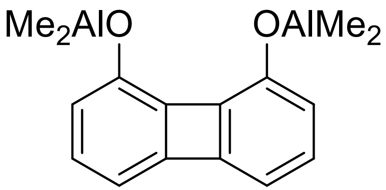
Hydroalumination

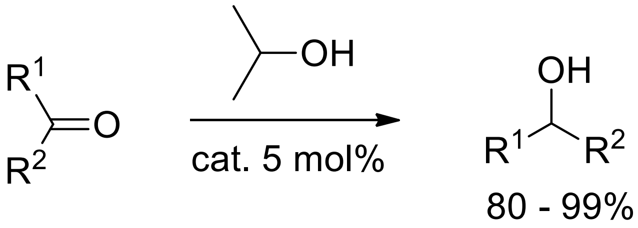
Verley-Meerwein-Ponndorf reduction

activating a carbonyl group twice



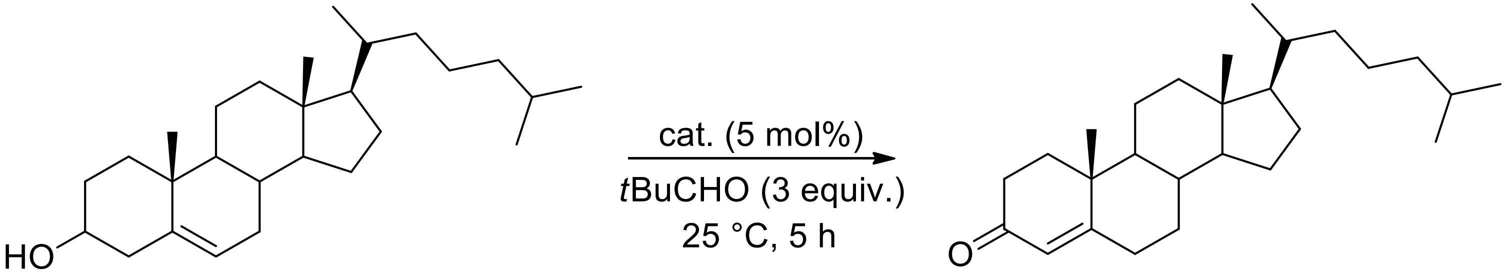
is possible using





cat. 5 mol%

80 - 99%



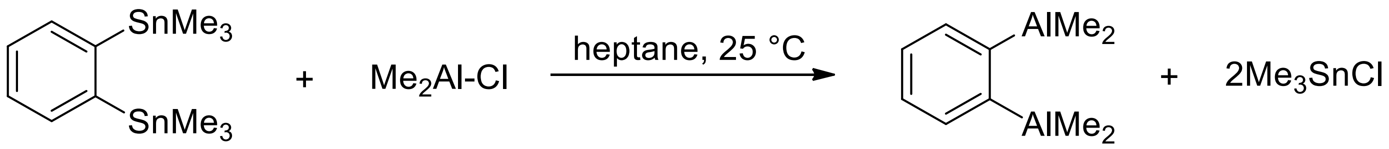
cat. (5 mol%)

*t*BuCHO (3 equiv.)

25 °C, 5 h

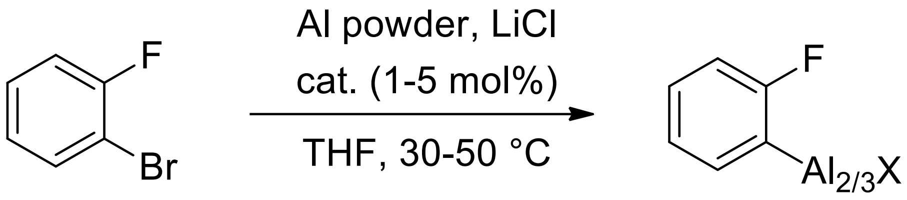
K. Maruoka *Angew. Chem*. **1998**, *110*, 2524

Other preparation of aluminium compounds



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

Direct synthesis of organoaluminium reagents



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

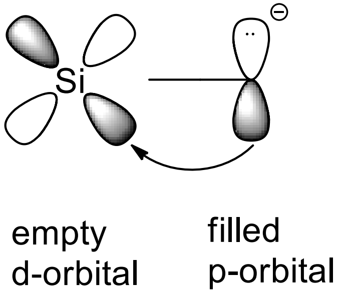
T. Blümke, Y.-H. Chen, Z. Peng, *Nature Chem*. **2010**, *2*, 313

The organic chemistry of main-group organometallics

Silicium

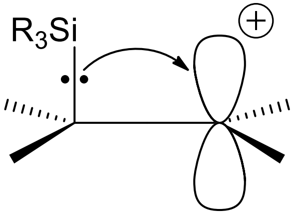
The effect of a Me_3Si-substituent:

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



stabilization of carbanions in α-position

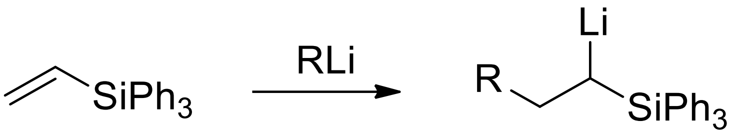
3) hyperconjugation: interaction of σ-framework with the π-system



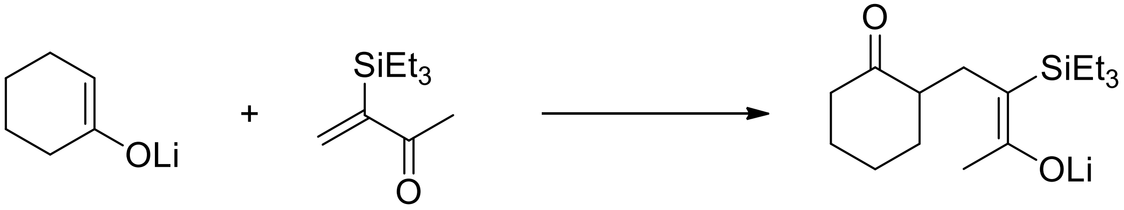
stabilization of a cation in β-position

Silicium

Applications:



low yields

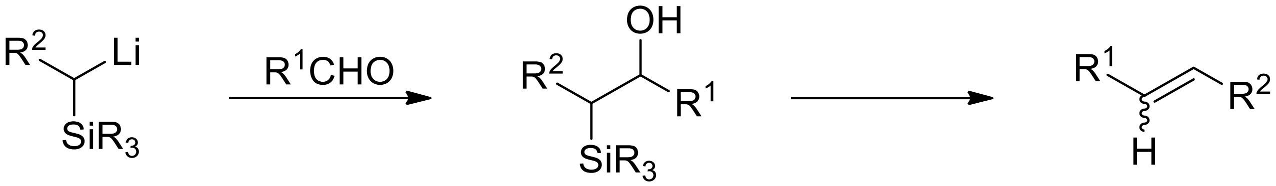


high yield: stabilized lithium enolate
(no polymerization)

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

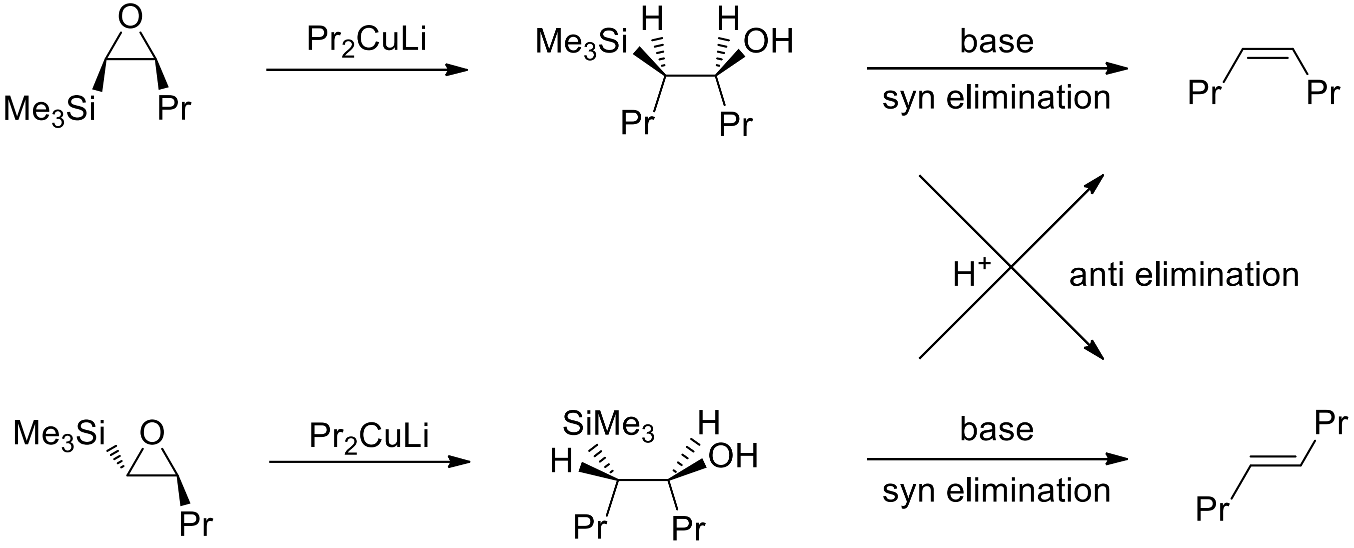
Silicium

Peterson olefination



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

Stereochemistry of the *Peterson*-elimination

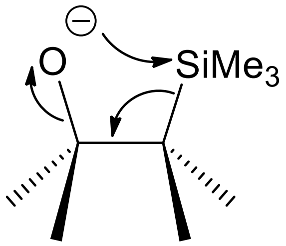


P. F. Hudrlik, D. Peterson, R. J. Rona *J. Org. Chem*. **1975**, *40*, 2263

Silicium

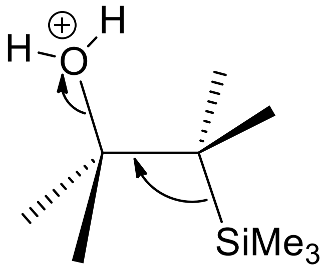
key steps:

basic media



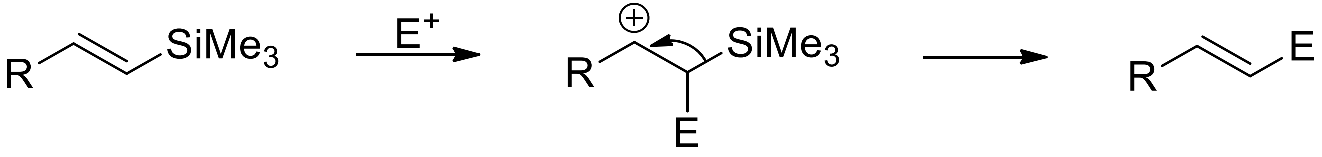
syn elimination

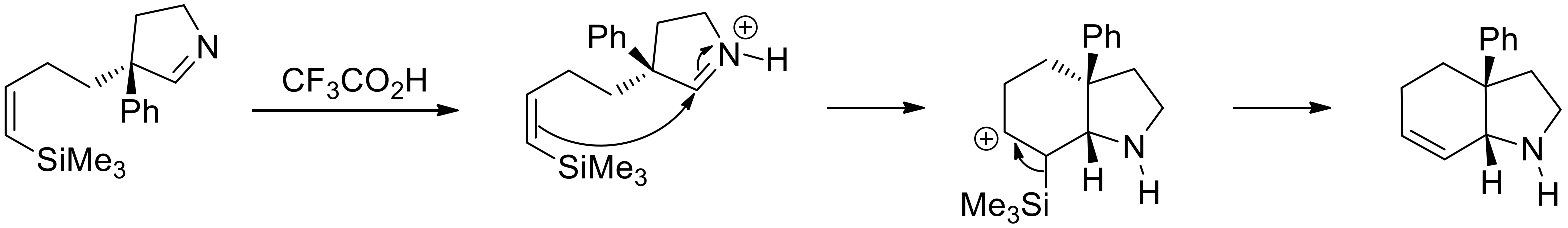
acidic media



anti elimination

Reactivity of alkenylsilanes

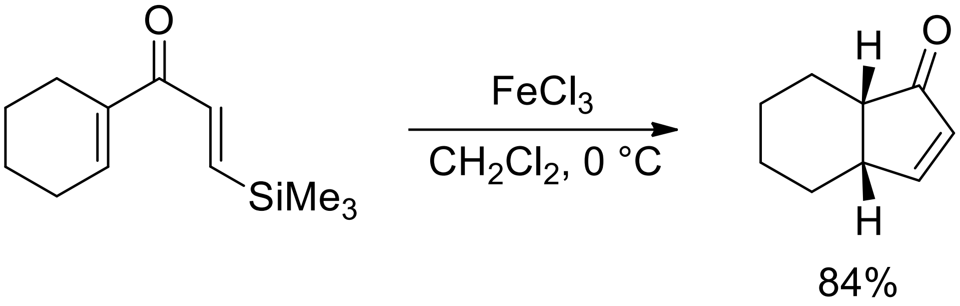




L. E. Overman, *Tetrahedron Lett*. **1984**, *25*, 5739

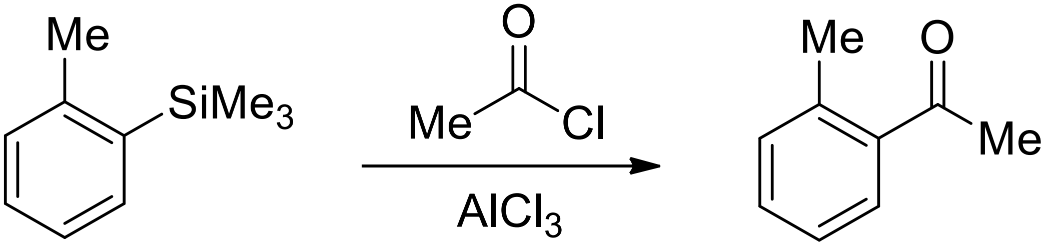
Reactivity of alkenylsilanes

Sila-Nazarov-reaction



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

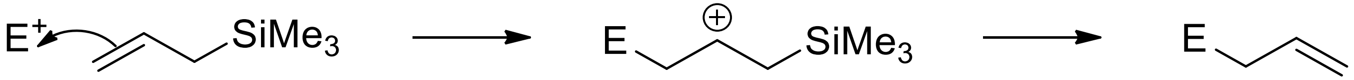
Aromatic ipso-substitution



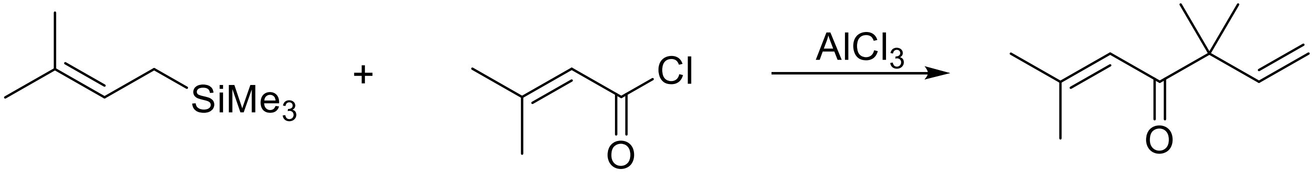
The reaction with $ArSnMe_3$ is 10^4 time faster

Allylic silanes in organic synthesis

General reactivity

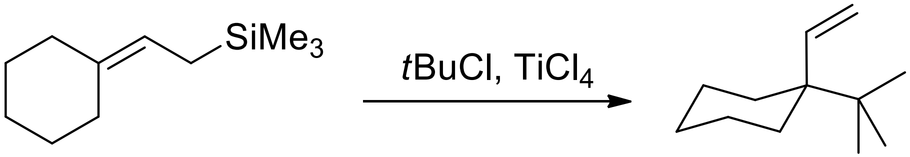


Acylation

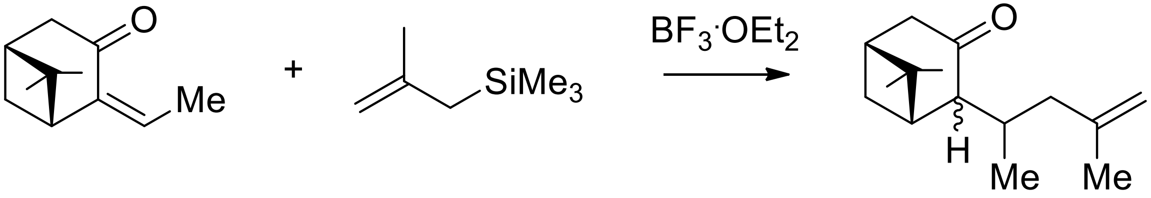


Allylic silanes in organic synthesis

Allylation

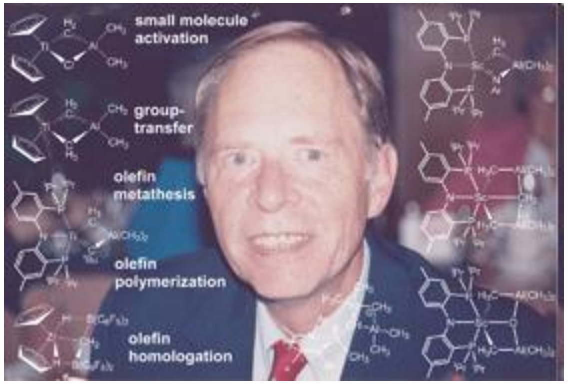


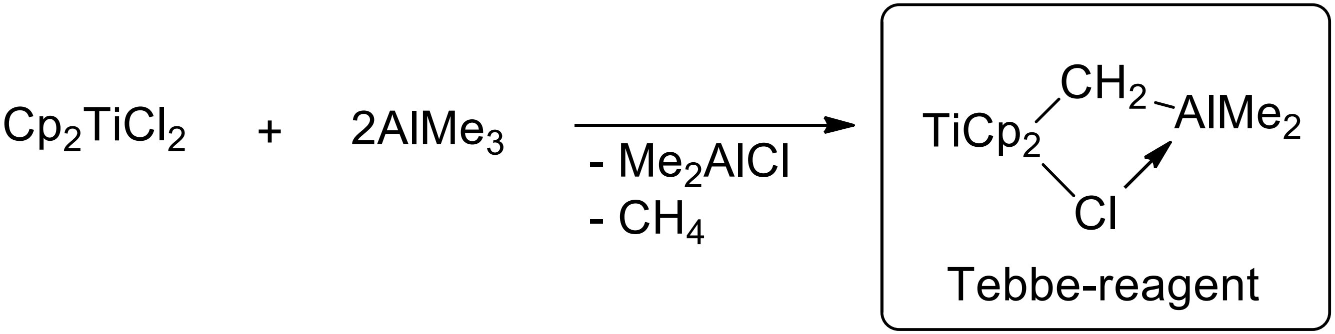
1,4-addition



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.

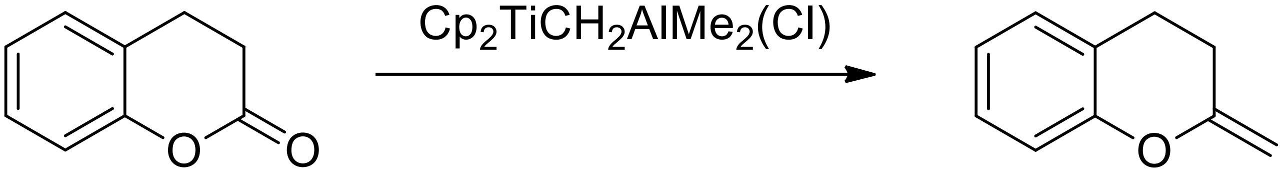
Early transition metal organometallics:
Titanium





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

Tebbe-reagent

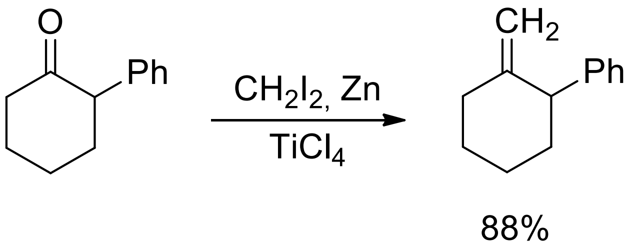


84%

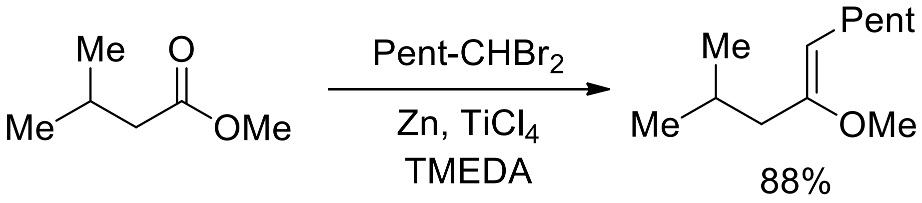
S. H. Pine *Org. React*. **1993**, *43*, 1

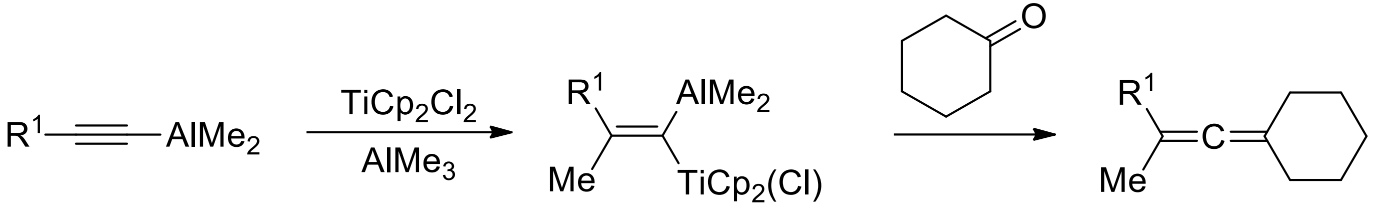
Titanium

Lombardo-reagent



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

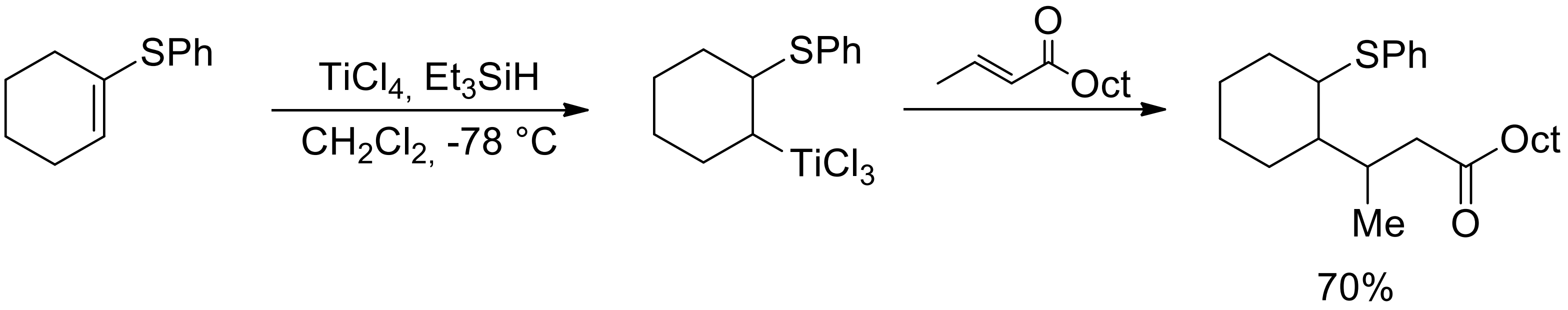




S. Buchwald, R. H. Grubbs *J. Am. Chem. Soc*. **1983**, *105*, 5490

Titanium

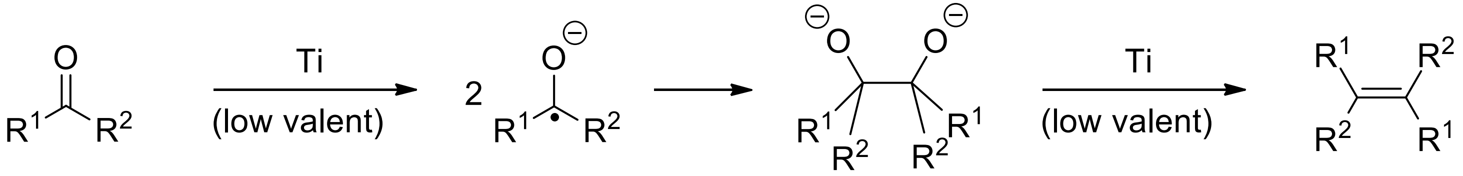
Hydrotitanation

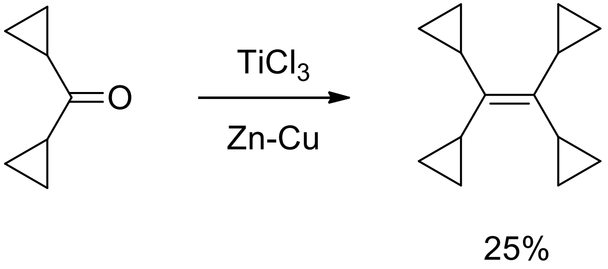


T. Takeda, *Tetrahedron Lett*. **1985**, *26*, 5313

Titanium

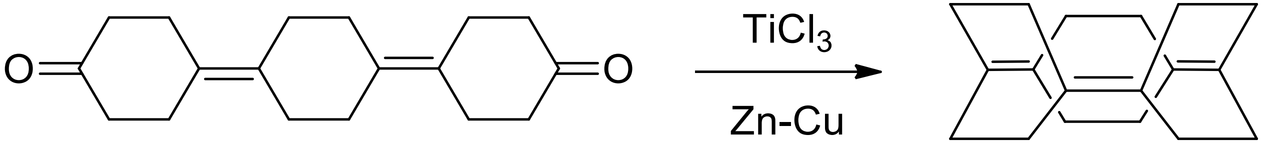
Reductive coupling: The McMurry Reaction

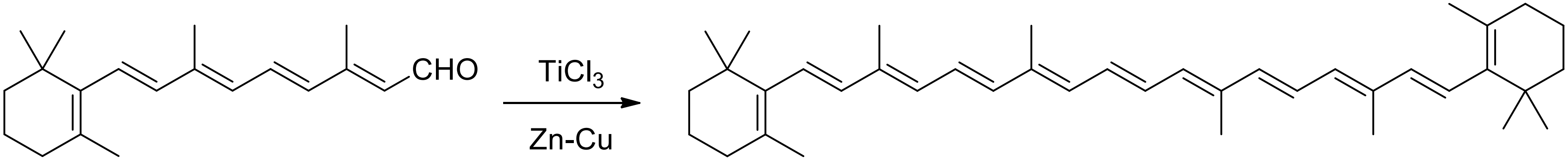




Review:
A. Fürstner, Ed. M. Beller, C. Bolm, Transition Metals for Organic Synthesis (2nd Edition) **2004**, *1*, 449.

Titanium

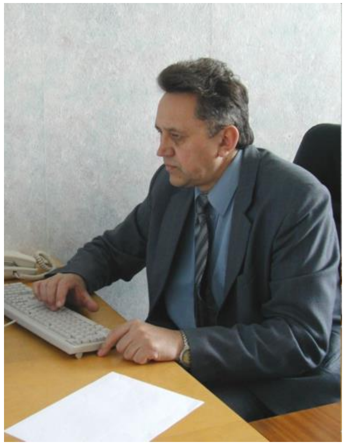




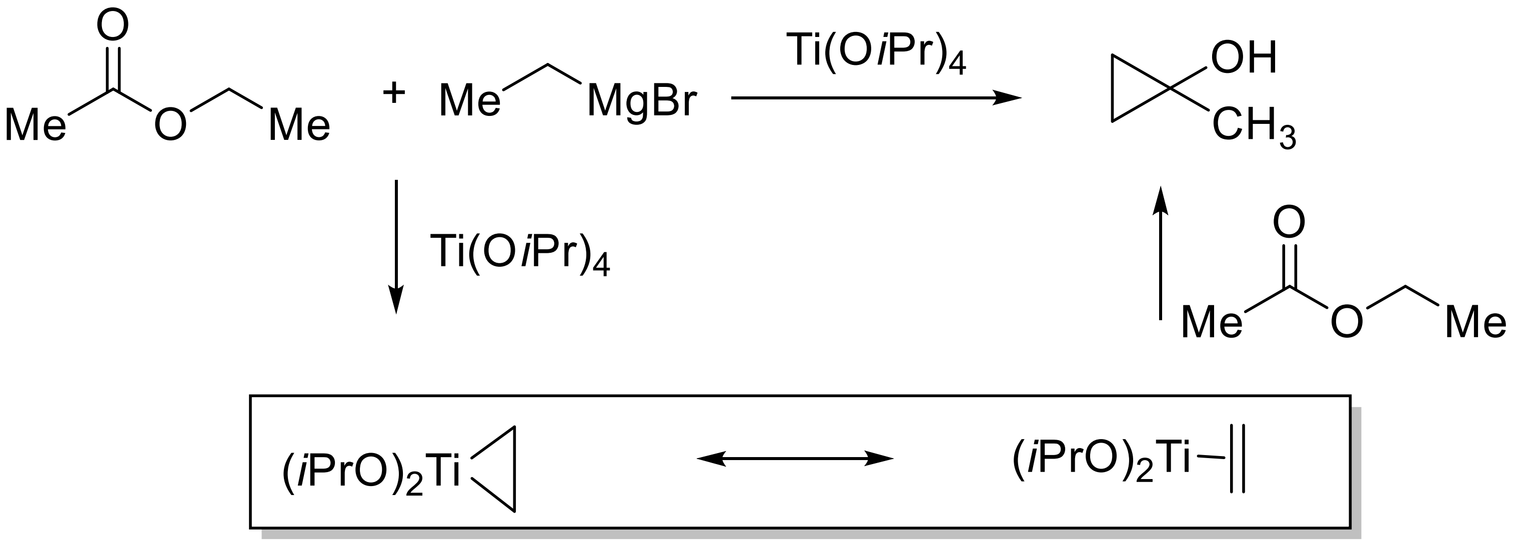
β -Caroten: 94%

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

Titanium

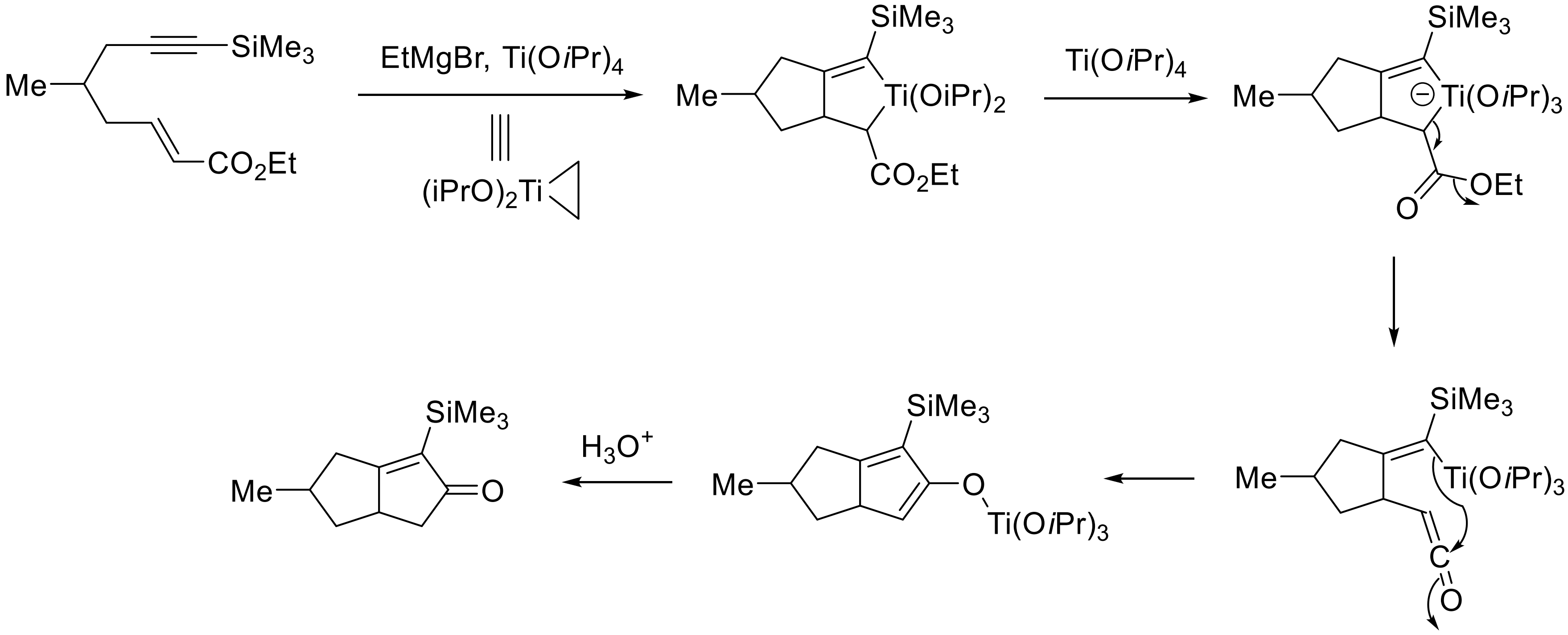


Kulinkovich-reaction



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

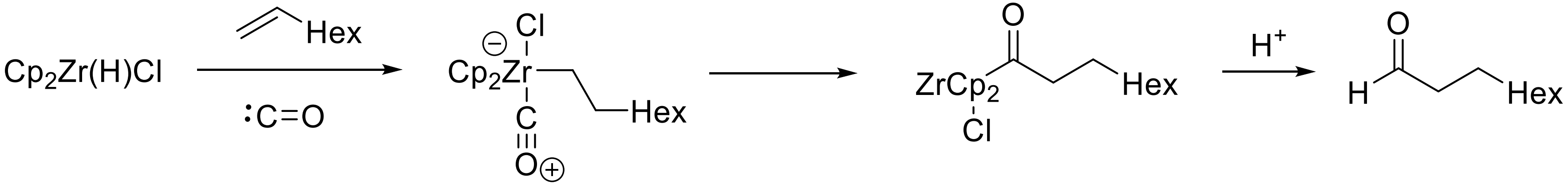
Schwartz’s reagent:

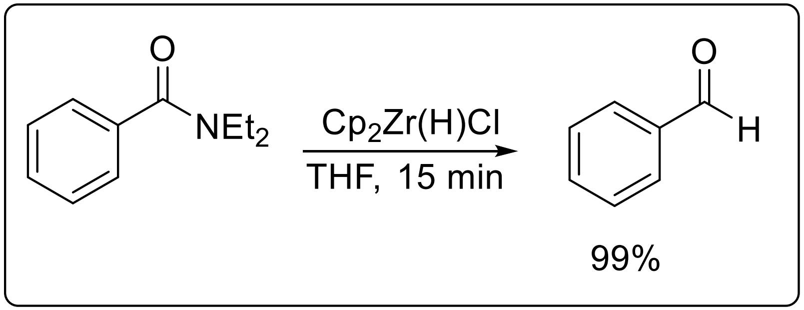
$$\mathrm{ZrCp_2Cl_2} \xrightarrow[\mathrm{THF}]{\mathrm{LiAl(H)(O}t\mathrm{Bu)_3}} \mathrm{Cp_2Zr(H)Cl}$$

90%

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

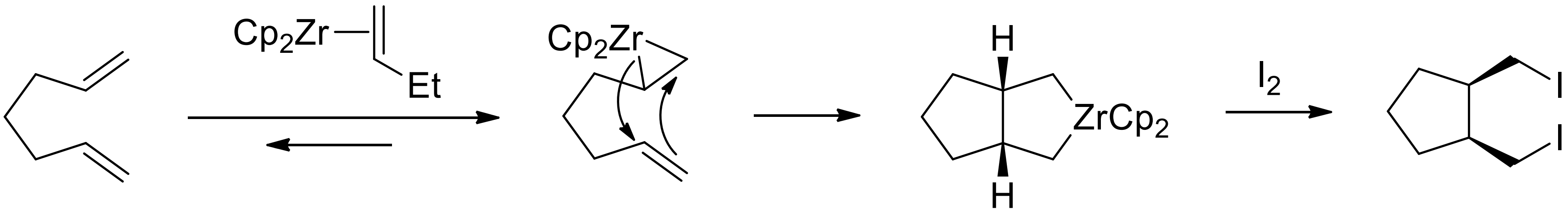
Zirconium

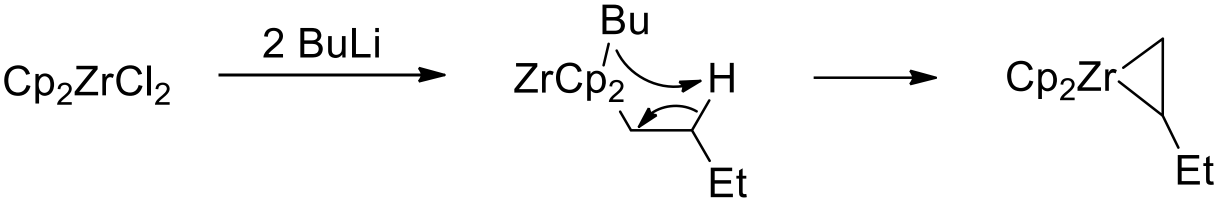




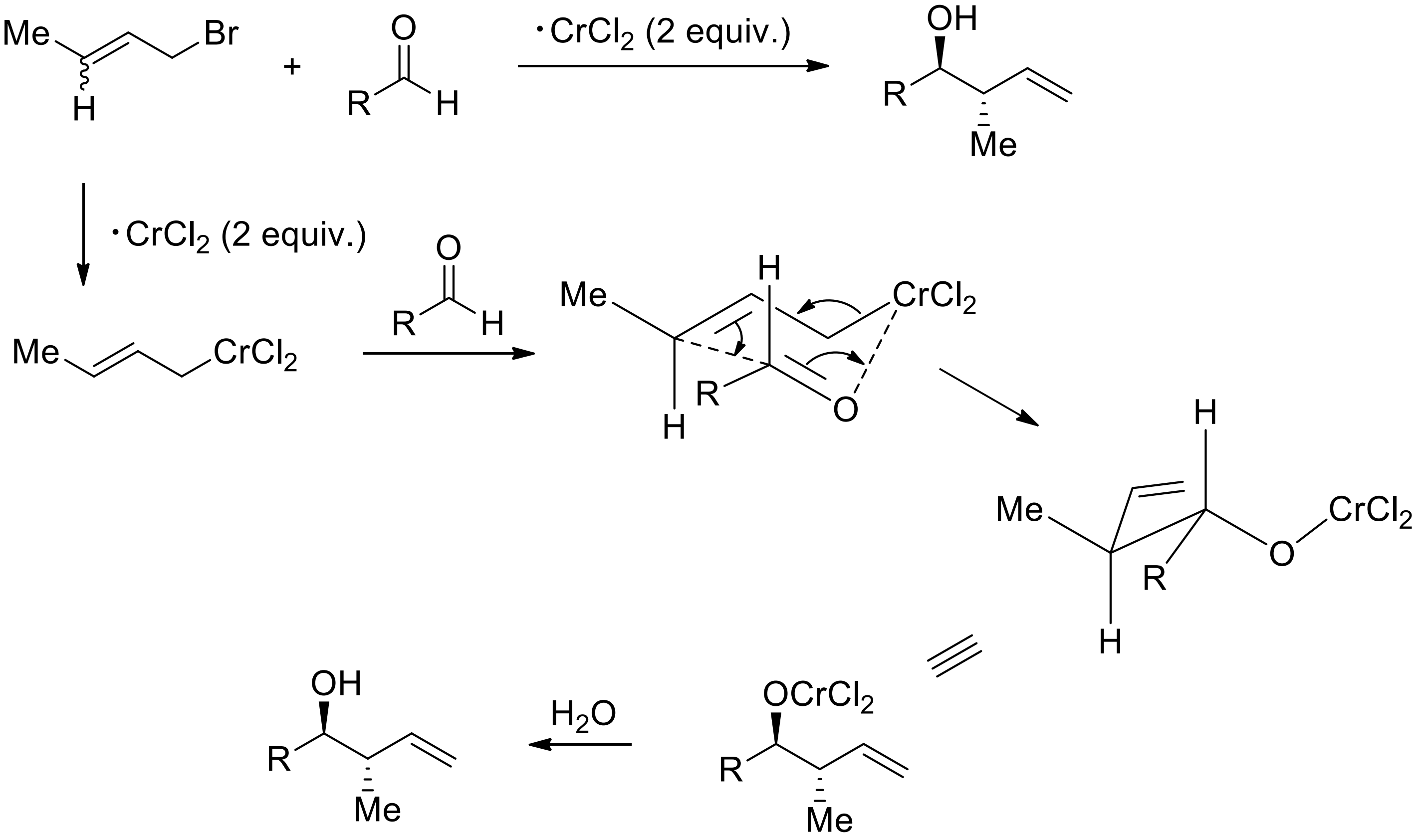
G. I. Georg *J. Am. Chem. Soc*. **2007**, *129*, 3408

Zirconium


Cp2Zr
Et
Cp2Zr
H
ZrCp2
H
I2
I
I

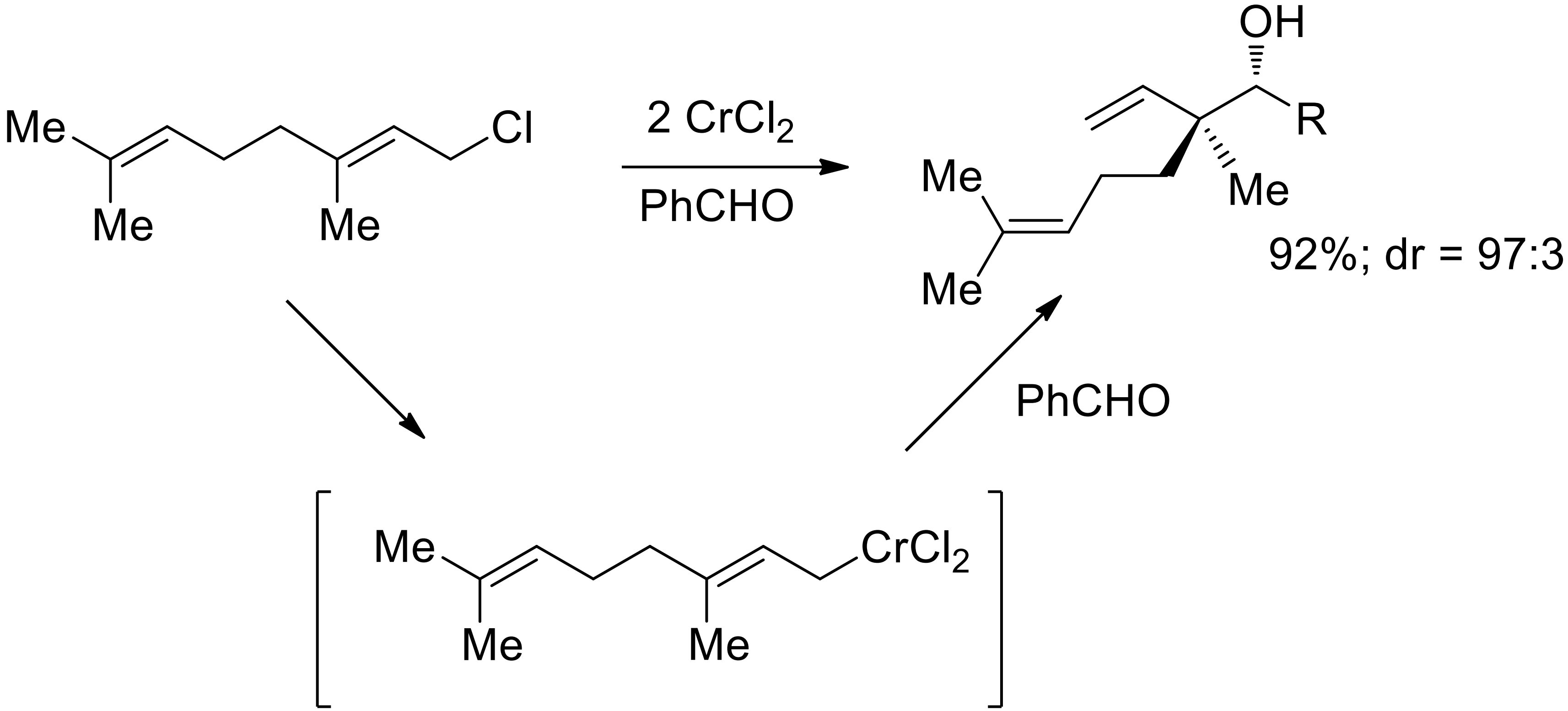

Cp2ZrCl2
2 BuLi
Bu
ZrCp2
H
Et
Cp2Zr
Et

Early transition metal organometallics: Chromium



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

Chromium

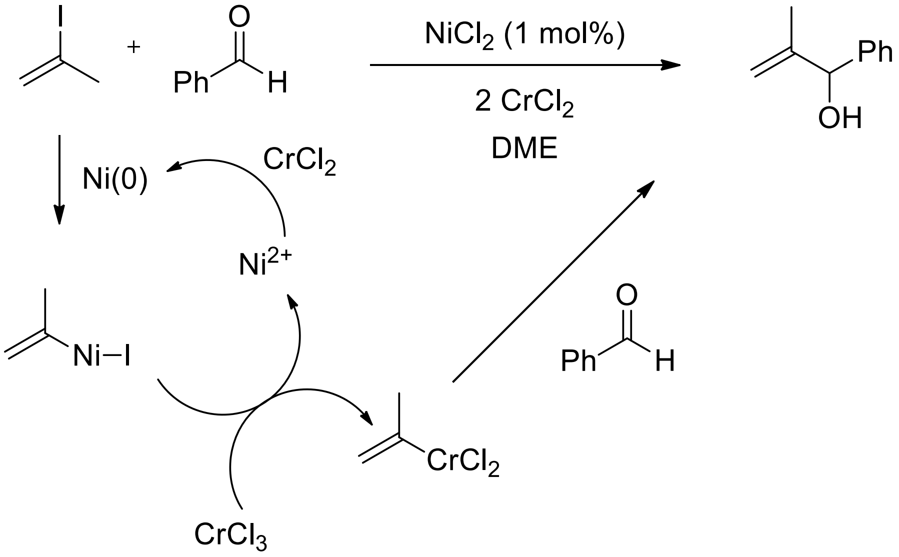


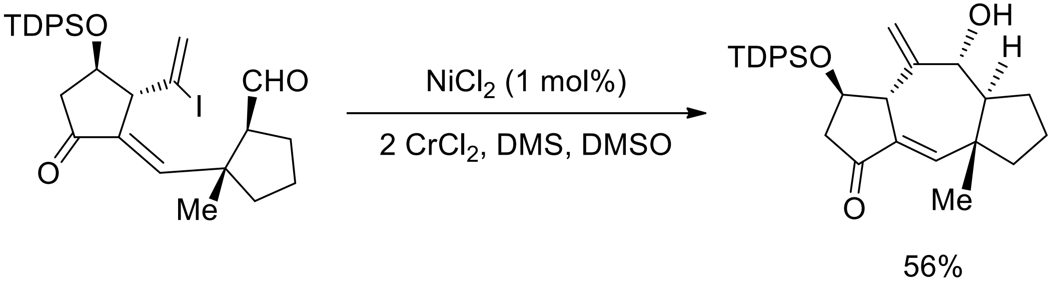
92%; dr = 97:3

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

Chromium

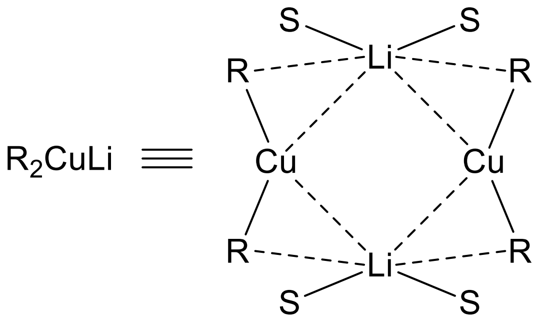
Hiyama-Kishi-reaction

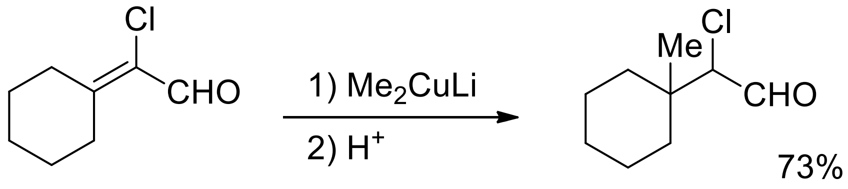


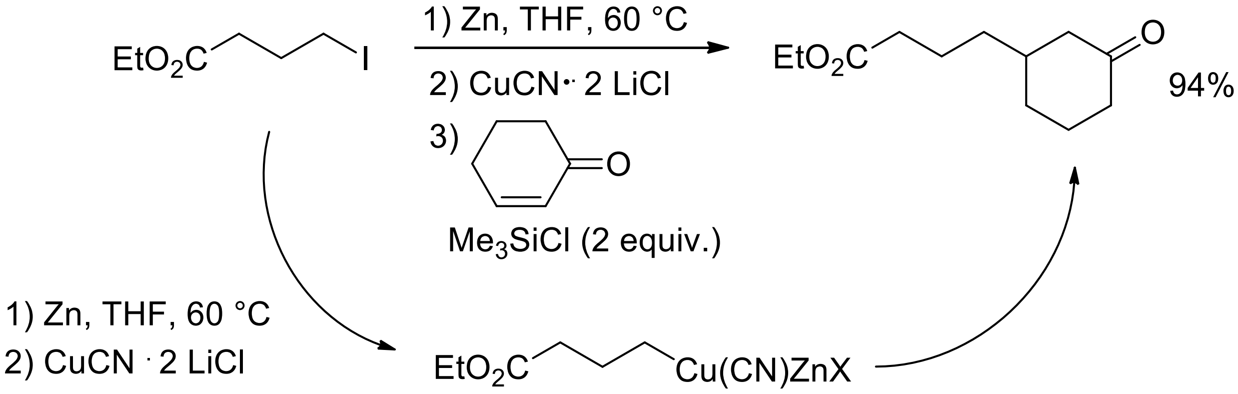


Y. Kishi *J. Am. Chem. Soc*. **1989**, *111*, 2735.

Early transition metal organometallics:
Copper

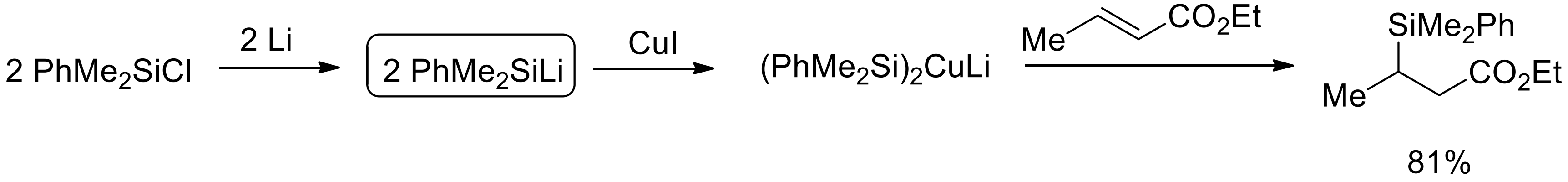




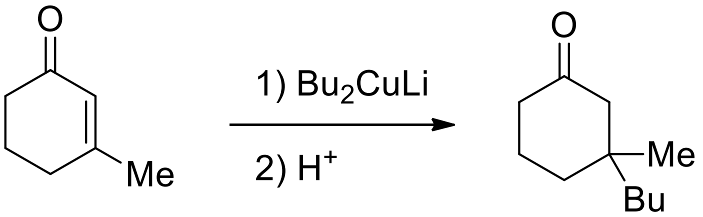


P. Knochel, et al. *J. Org. Chem*. **1988**, *53*, 2390.

Copper



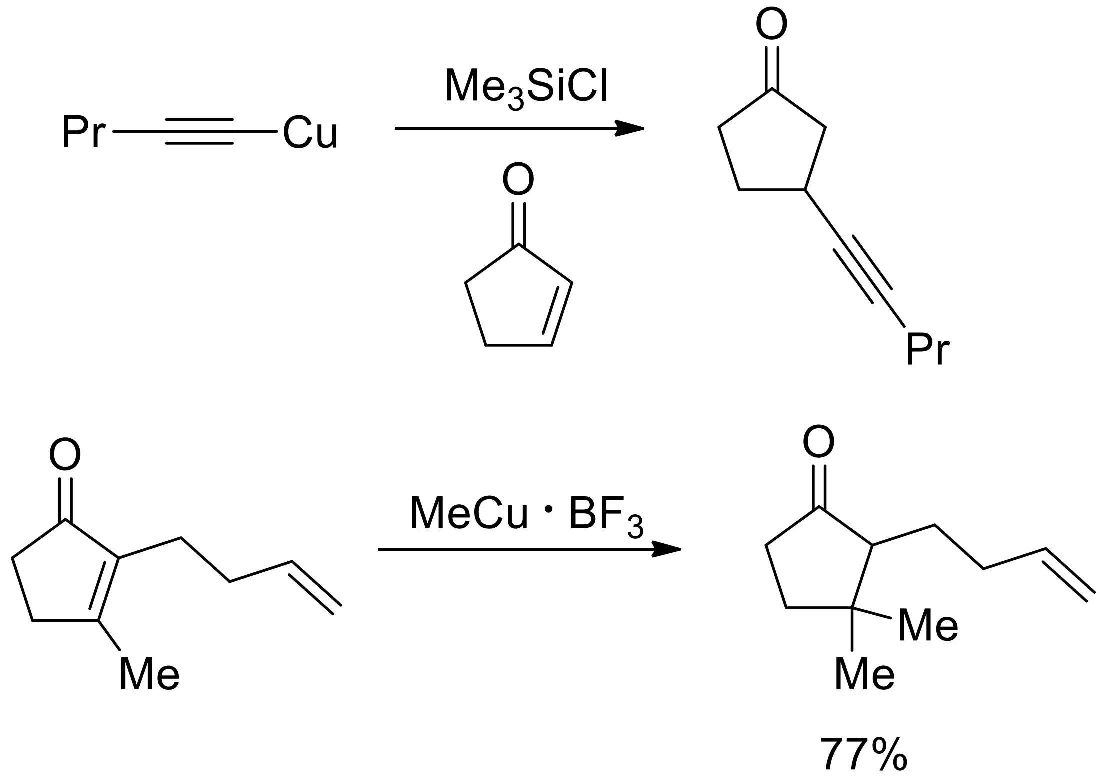
I. Fleming et al. *J. Chem. Soc., Perkin Trans*. **1998**, *1*, 1209.



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

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

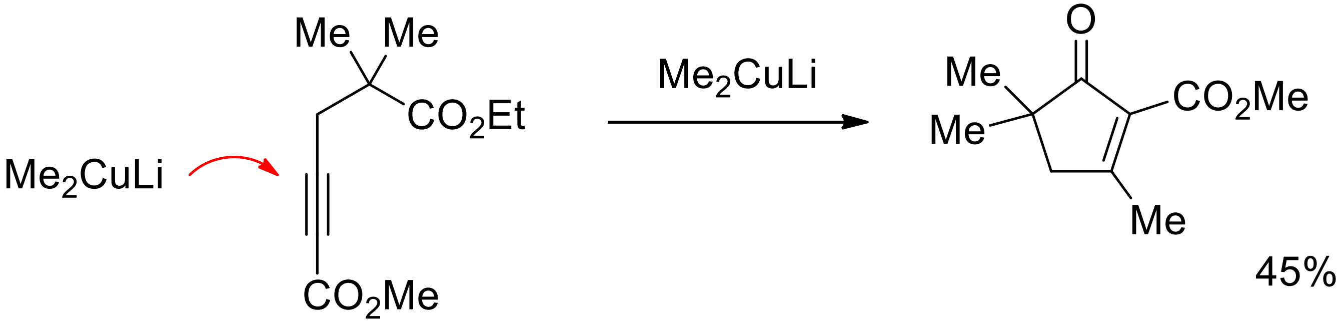
Copper-mediated 1,4-addition



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

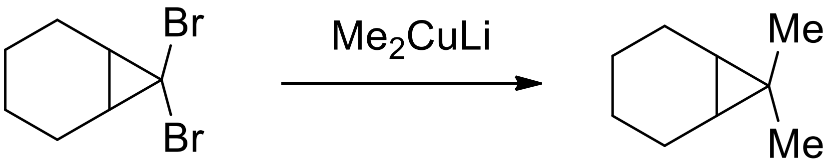
Copper-mediated reactions

Michael-addition



45%

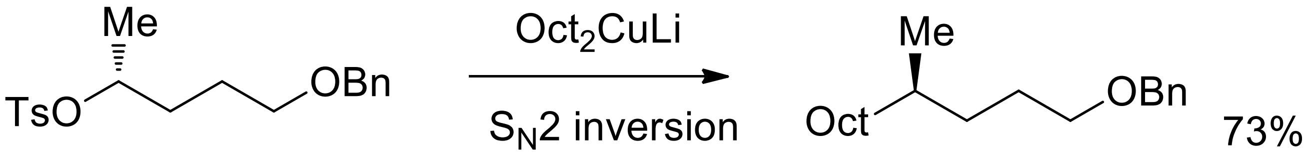
Substitution reactions

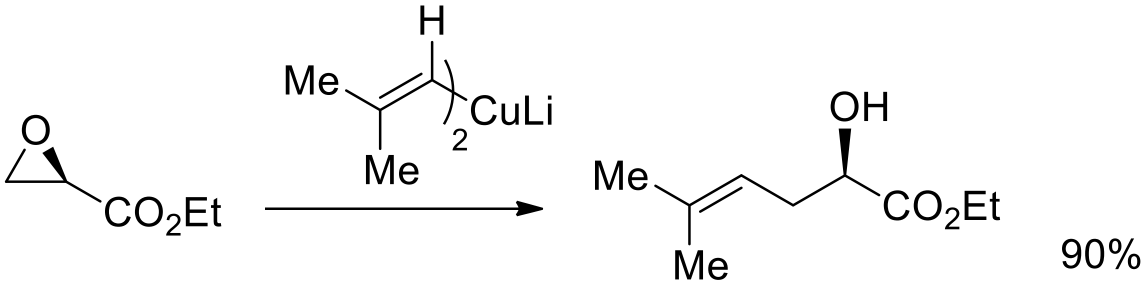


80%

G. Posner, *Org. React*. **1975**, *22*, 253.
R. J. K. Taylor (Ed.), *Organocopper reagents*, Oxford University Press, Oxford, **1994**.

Copper; substitution reactions

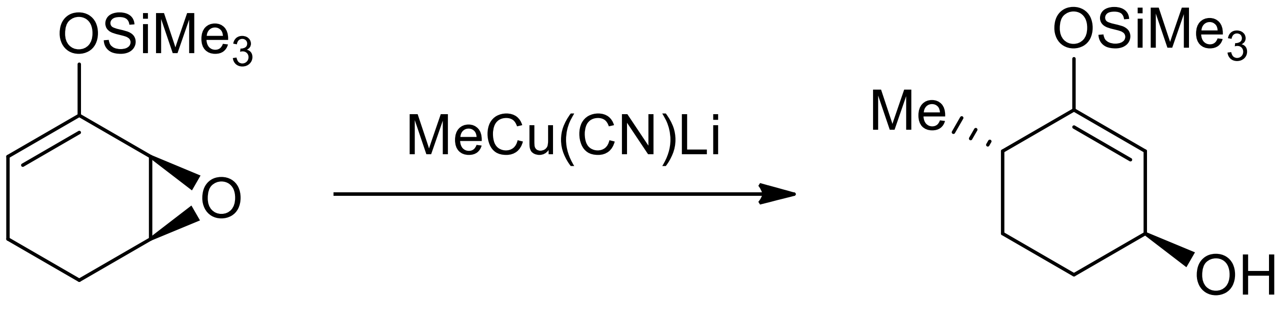




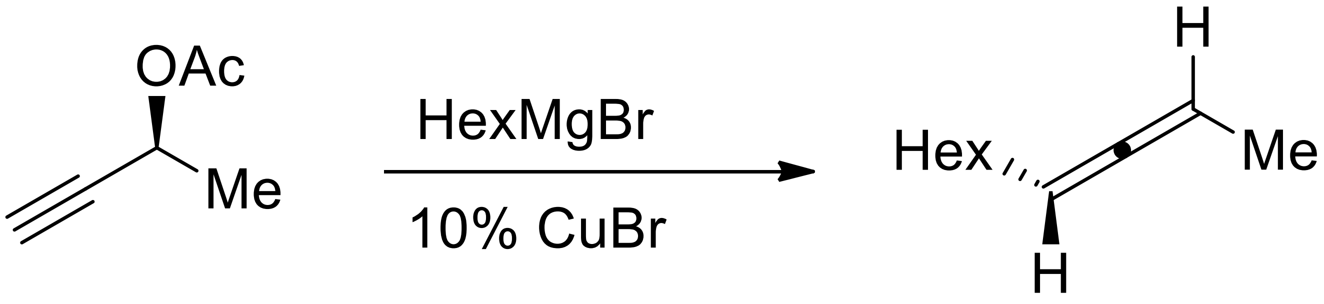
$$t\text{BuMgCl} \quad + \quad \text{PhCH}_2\text{Cl} \xrightarrow[\text{0.25 mol\%}]{\text{Li}_2\text{CuCl}_4} \text{PhCH}_2t\text{Bu}$$

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

Copper: allylic and propargylic substitution



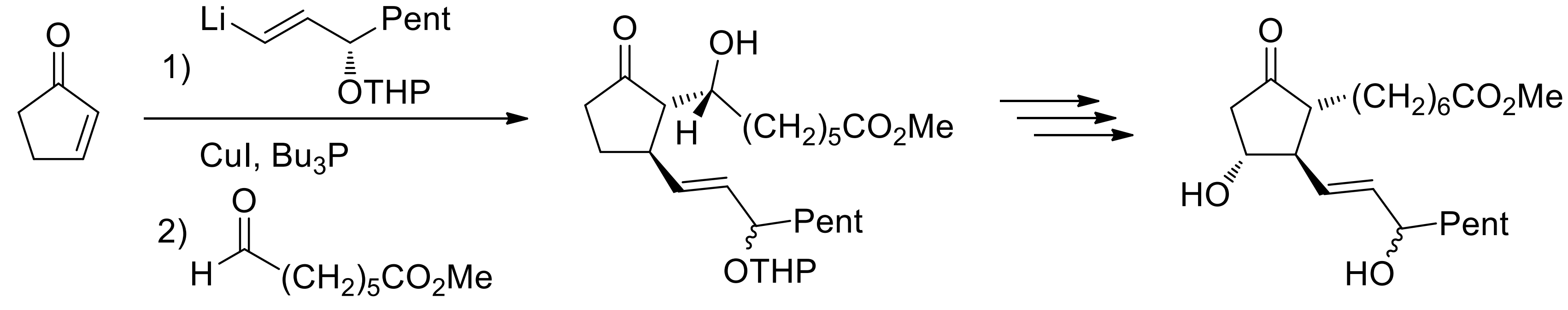
75%



70%

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

Copper: Prostaglandin synthesis



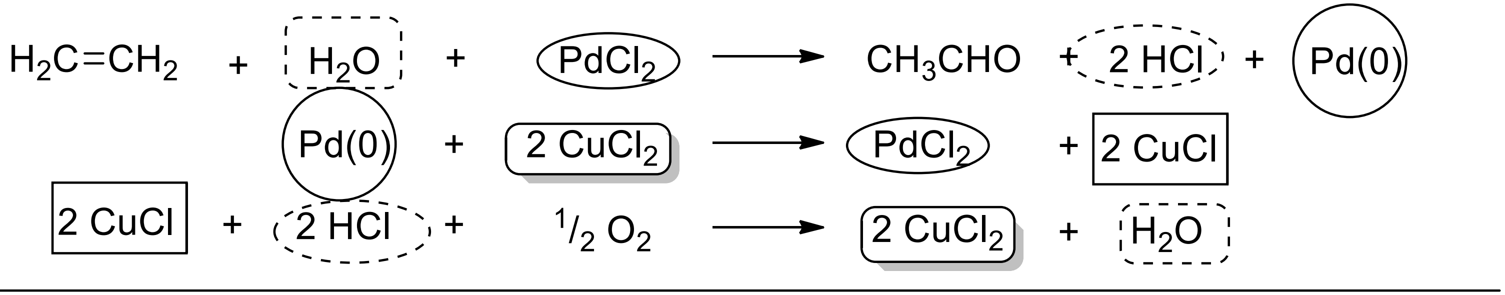
Prostaglandin E1

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

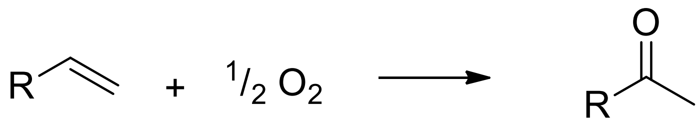
Wacker-Reaction:



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

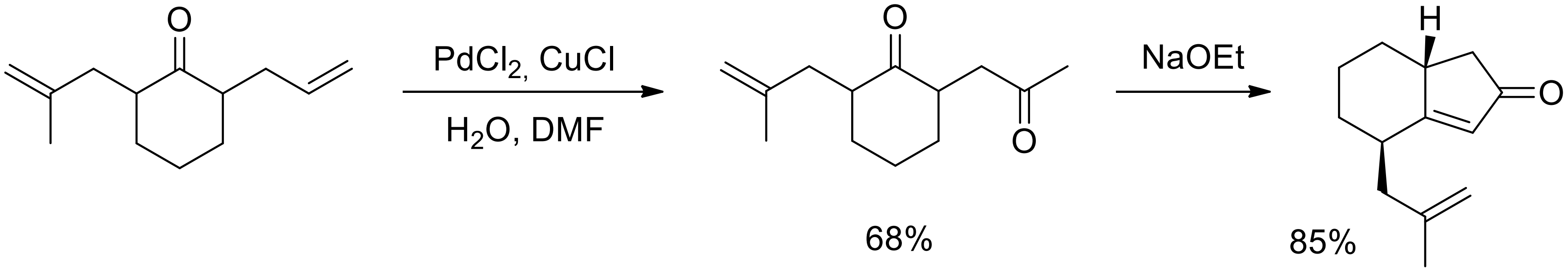
$$Pd(0) + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl$$

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



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

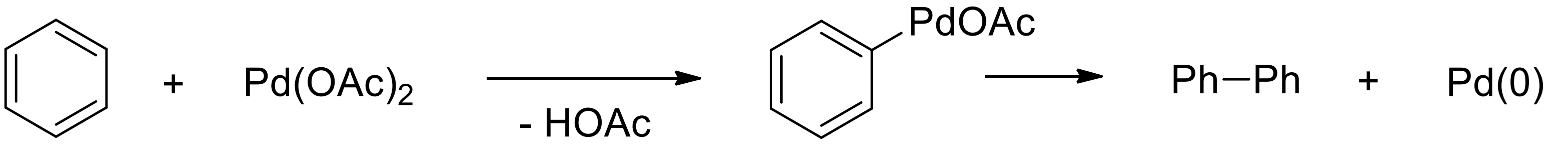
Palladium

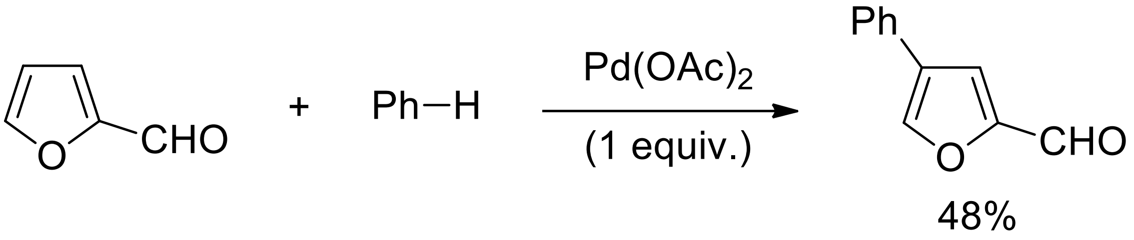


J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett*. **1976**, *34*, 2975.

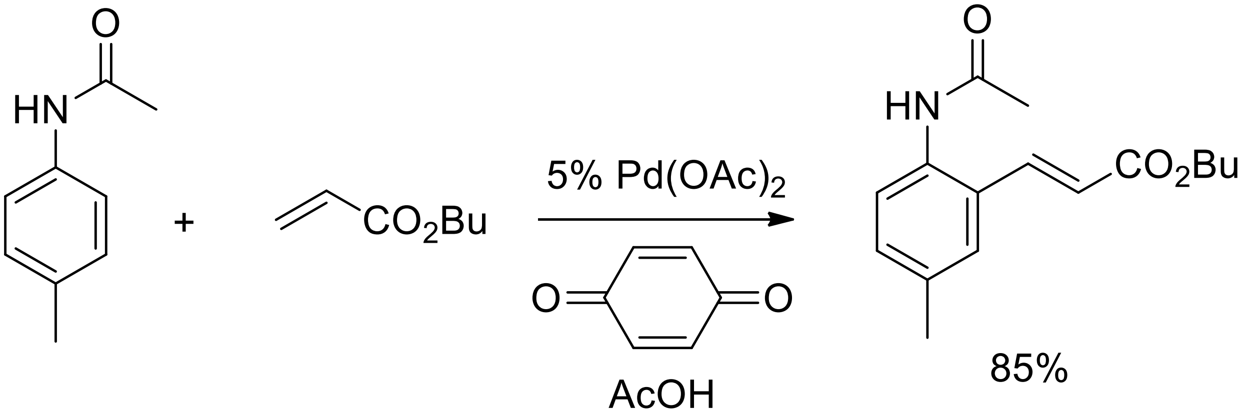
Palladium

C-H activation





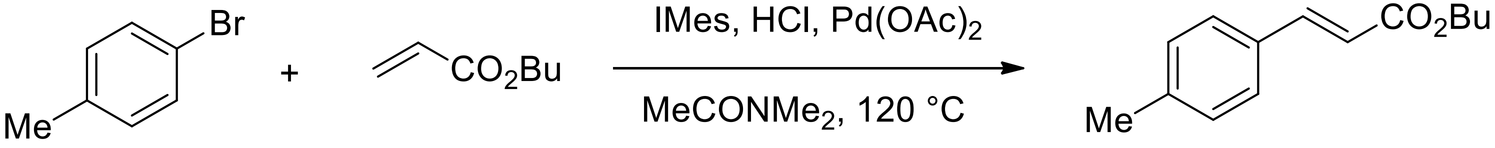
T. Itahara, *J. Org. Chem*. **1985**, *50*, 5272.

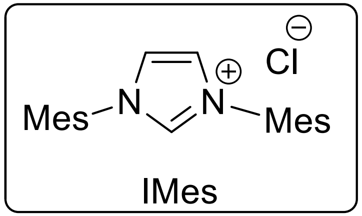


J. G. de Vries *J. Am. Chem. Soc*. **2002**, *124*, 1586.

Palladium

Heck Reaction





IMes

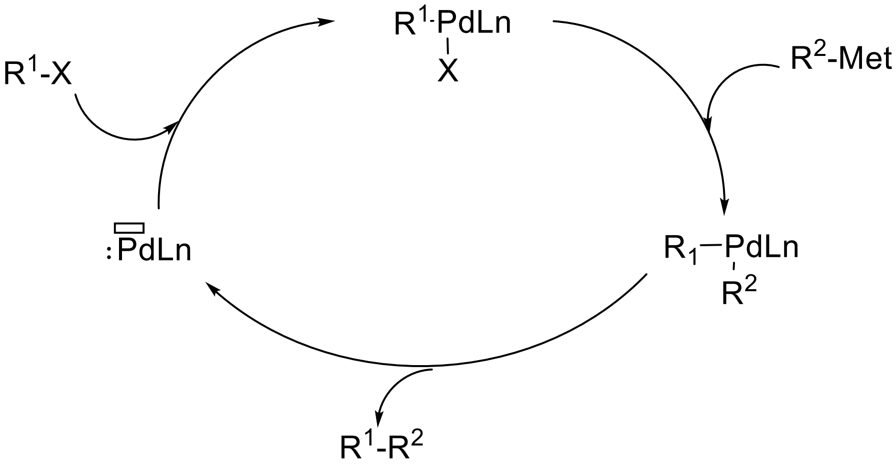
The method of T. Jeffery uses Bu_4NBr at 25 °C.

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

Palladium-catalyzed cross-coupling

Cross-coupling using Pd(0)-catalysts

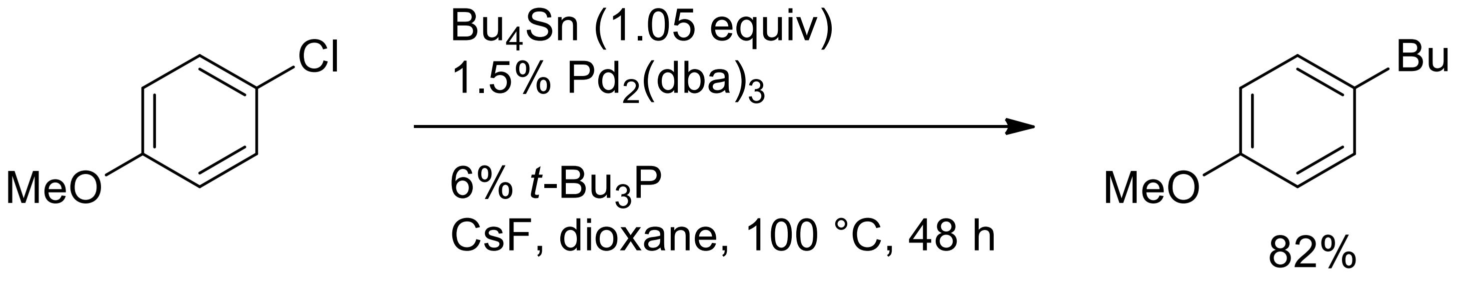
$$\boxed{R^1\text{-}X \quad + \quad R^2\text{-Met} \xrightarrow[\text{Pd(0) or Ni(0)}]{} R^1\text{-}R^2}$$



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

Palladium

Stille cross-coupling



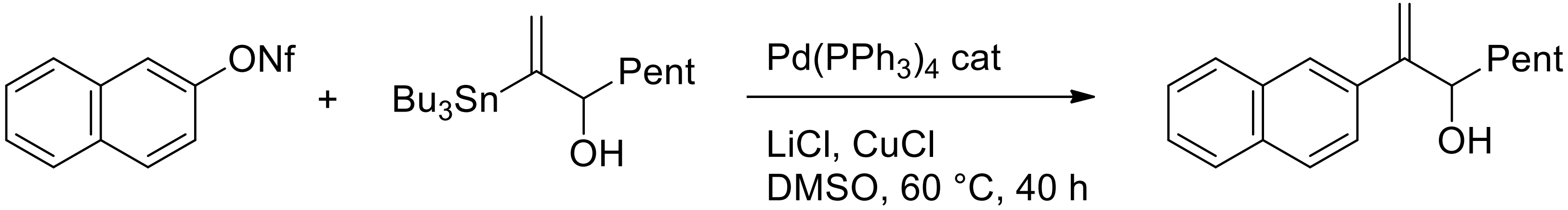
G. C. Fu, *Angew. Chem. Int. Ed*. **1999**, *38*, 2411.

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



$Pd(PPh_3)_4$ cat

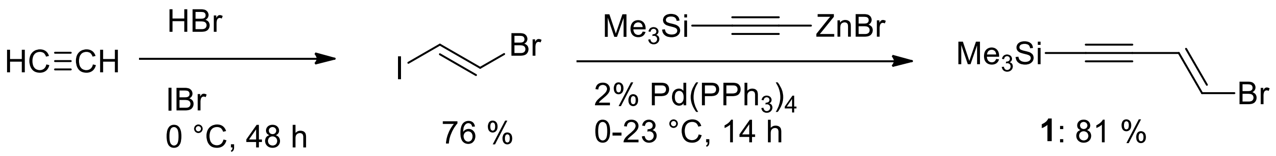
LiCl, CuCl
DMSO, 60 °C, 40 h

88%

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

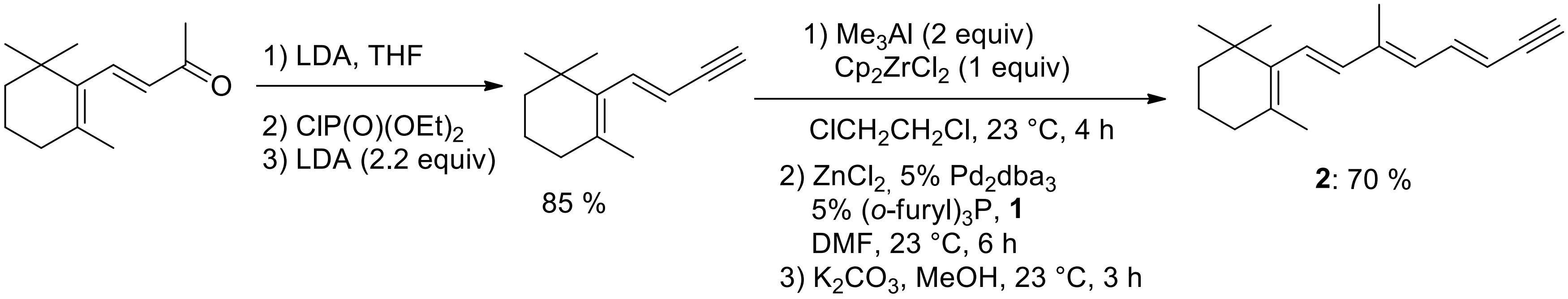
Negishi reactions

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



HC≡CH, HBr, IBr, 0 °C, 48 h → 76 %

Me_3Si—≡—ZnBr, 2% $Pd(PPh_3)_4$, 0-23 °C, 14 h → **1**: 81 %



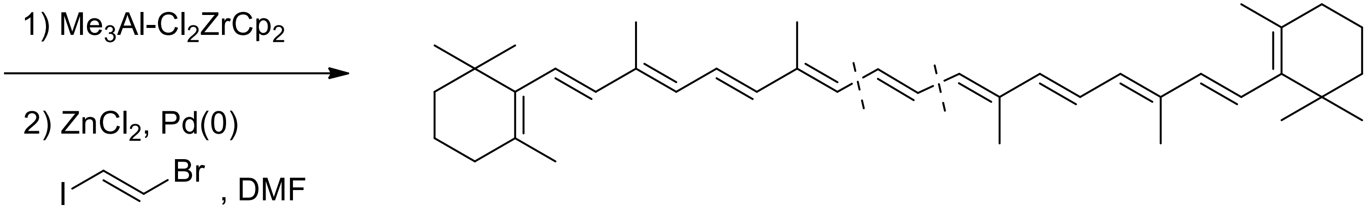
1) LDA, THF
2) $ClP(O)(OEt)_2$
3) LDA (2.2 equiv)

85 %

1) Me_3Al (2 equiv)
Cp_2ZrCl_2 (1 equiv)
$ClCH_2CH_2Cl$, 23 °C, 4 h
2) $ZnCl_2$, 5% Pd_2dba_3
5% (*o*-furyl)$_3$P, **1**
DMF, 23 °C, 6 h
3) K_2CO_3, MeOH, 23 °C, 3 h

2: 70 %

2



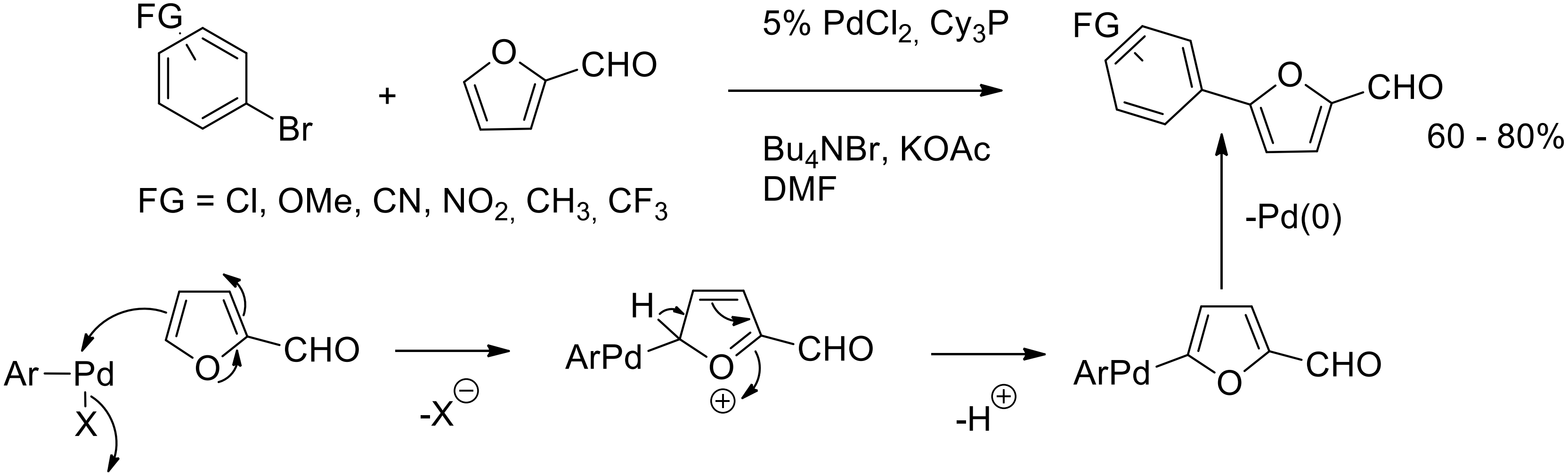
1) $Me_3Al\text{-}Cl_2ZrCp_2$
2) $ZnCl_2$, Pd(0)
I⁄⁄Br, DMF
23 °C, 8 h

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

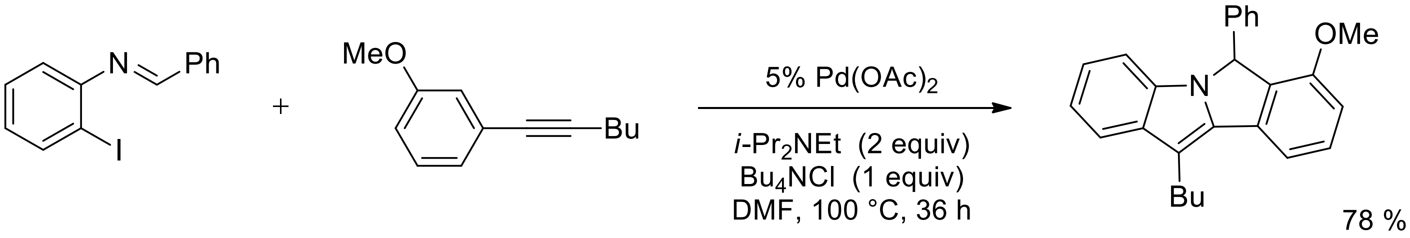


FG = Cl, OMe, CN, NO_2, CH_3, CF_3

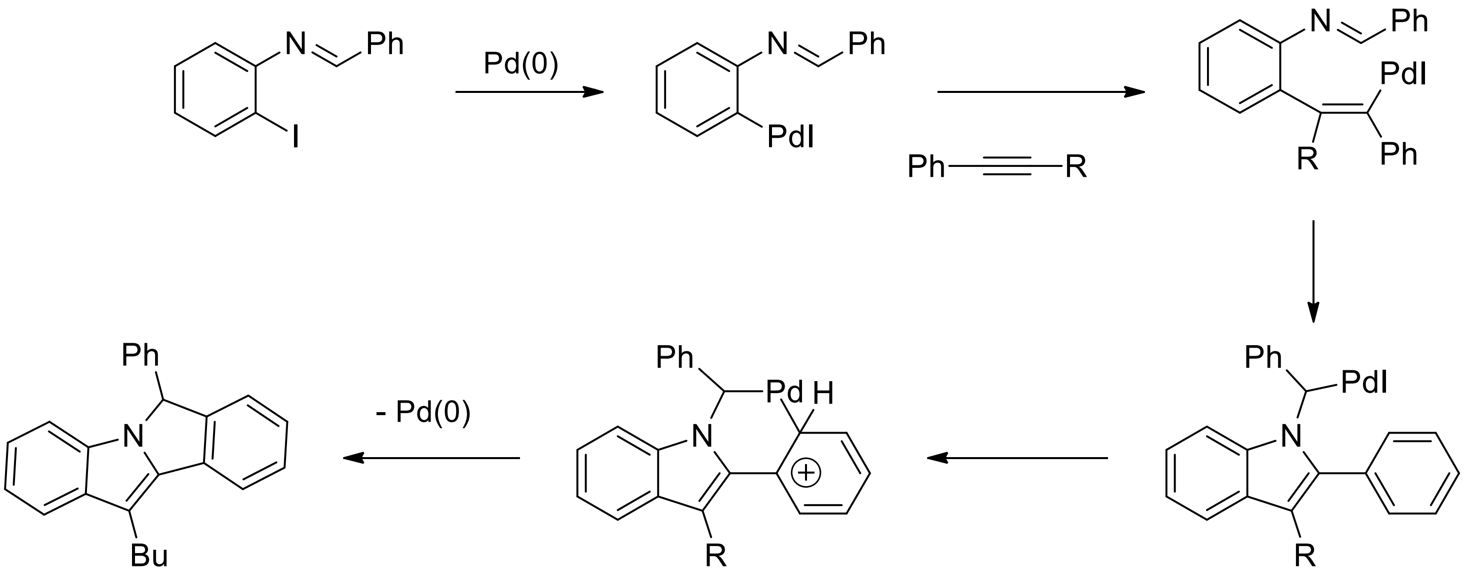
M. S. McClure, *Org. Lett*. **2001**, *3*, 1677

Palladium

Pd -catalyzed heterocycle synthesis

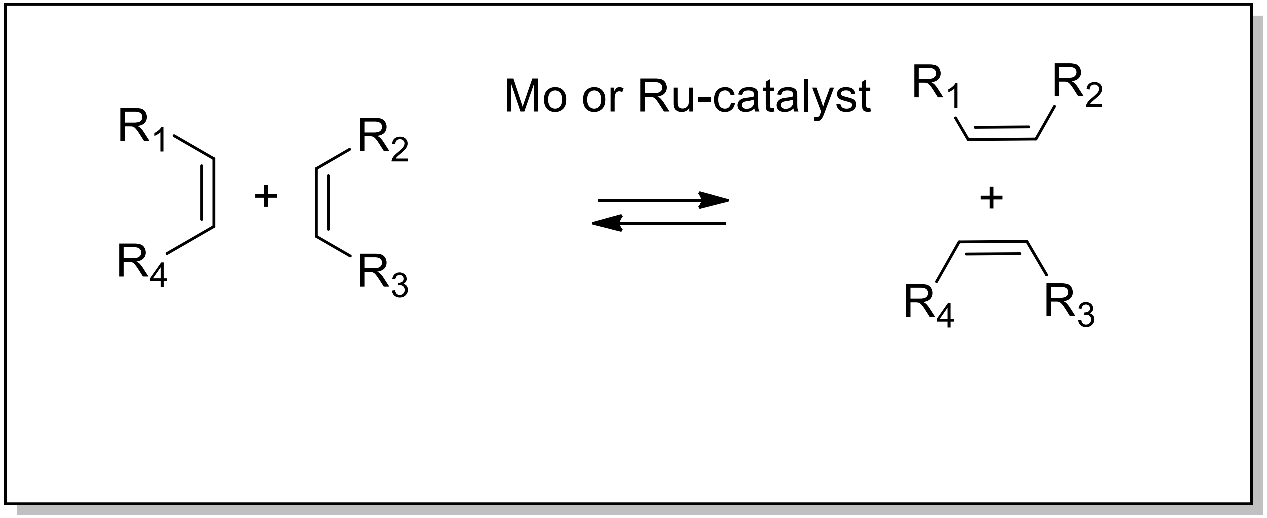


Mechanism



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

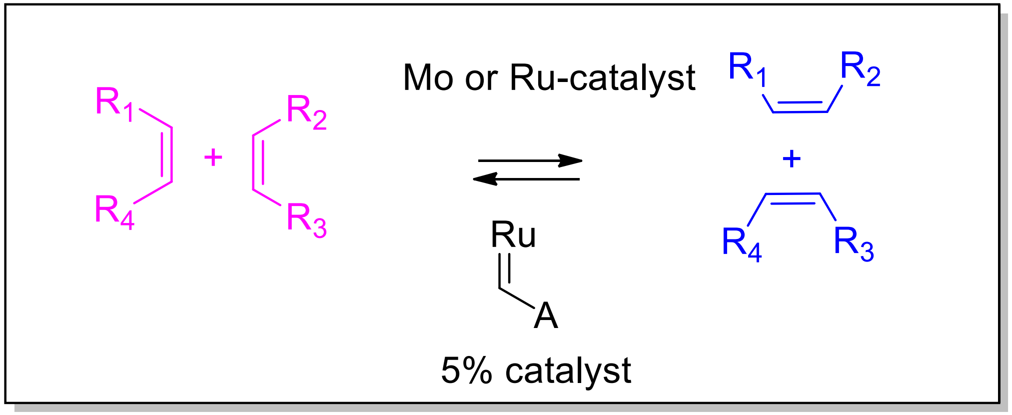
Olefin metathesis



Reviews:

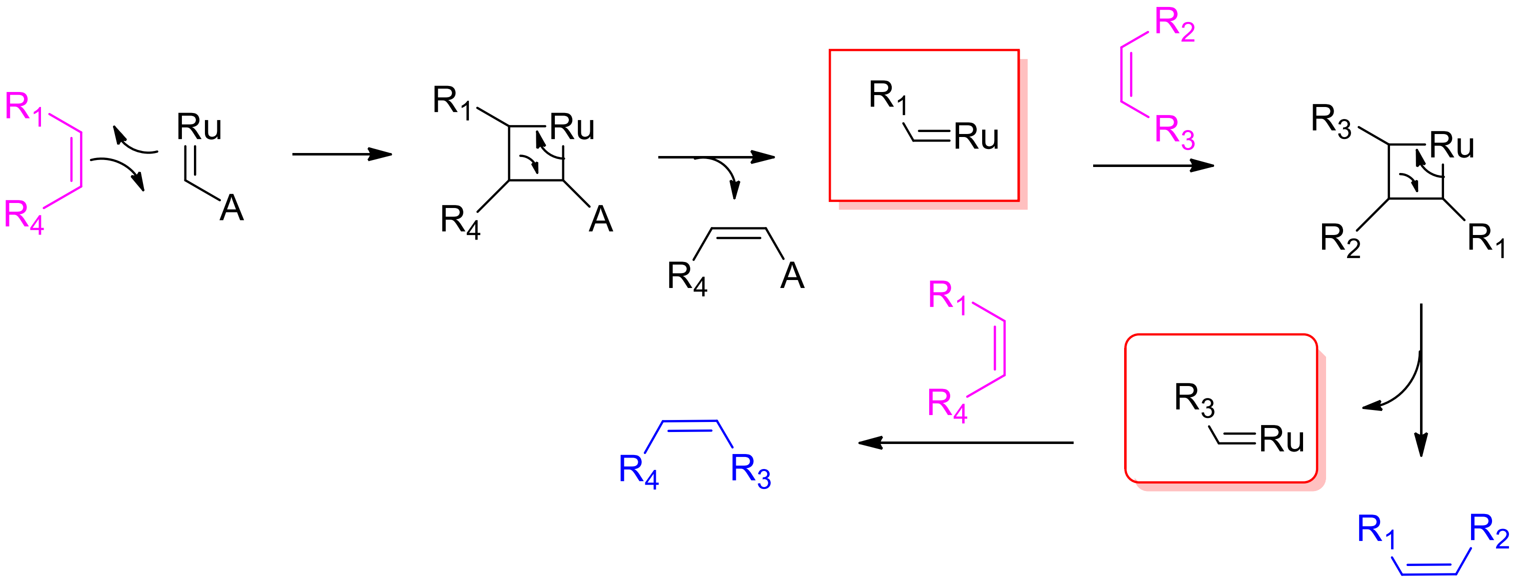
R.H. Grubbs, *Tetrahedron* **1998**, *54*, 4413.
A.S.K. Hashmi, *J. Prakt. Chemie* **1997**, *339*, 1954.
M.E. Maier, *Angew. Chem. Int. Ed*. **2000**, *39*, 2073.
S.Blechert, *Angew. Chem*. **1997**, *109*, 2124.
A.Fürstner, (Ed.) Alkene Metathesis in Organic Synthesis
in Top. Curr. Chem., Springer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

Olefin metathesis mechanism

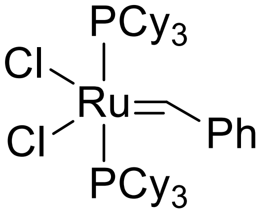


Mo or Ru-catalyst

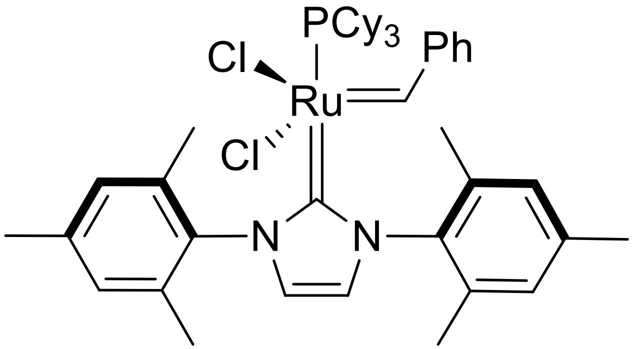
5% catalyst



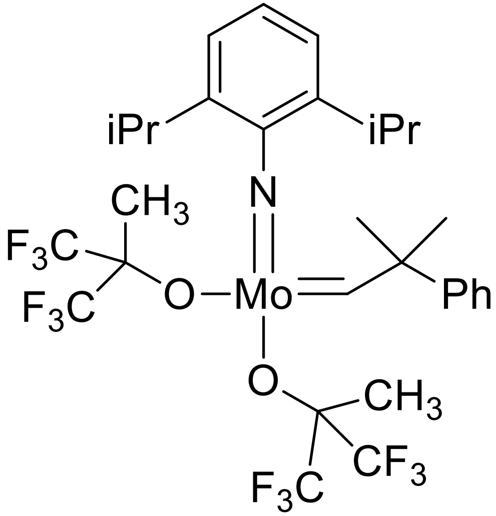
Olefin metathesis



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

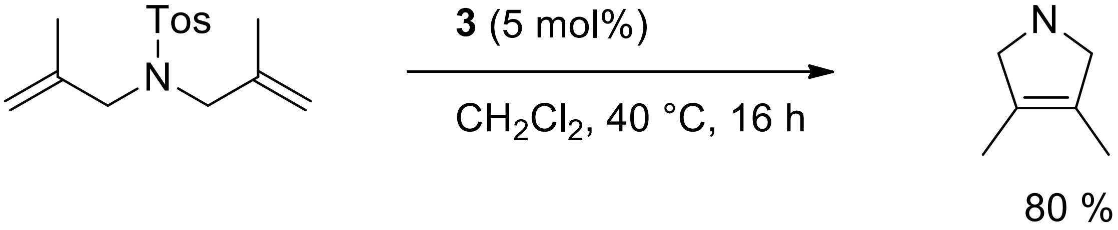


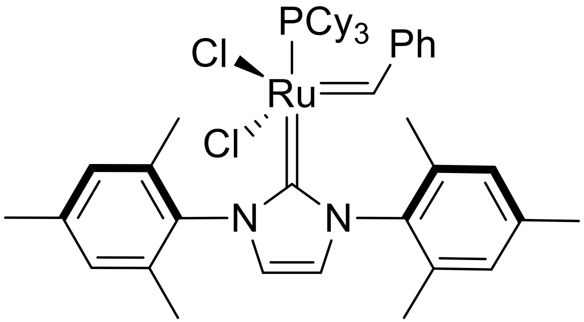
2: Grubbs-catalyst
second generation
US Patent No. 6,111,121
and 7,329,758



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

Olefin metathesis



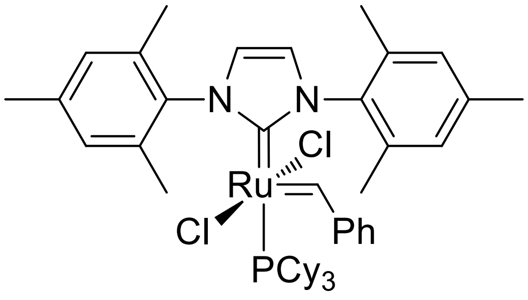


3

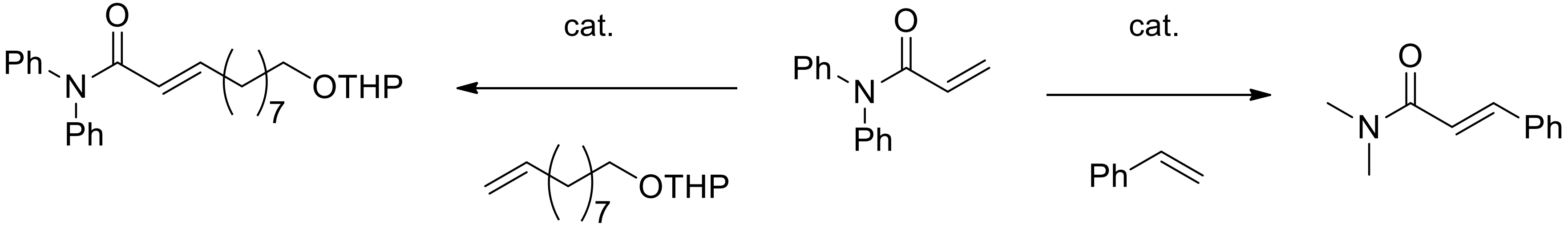
A. Fürstner, W.A. Herrmann, *Tetrahedron Lett*. **1999**, *40*, 4787

Olefin metathesis

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



Cat.



cat.

CH_2Cl_2, 40 °C, 15 h

100 %

cat.

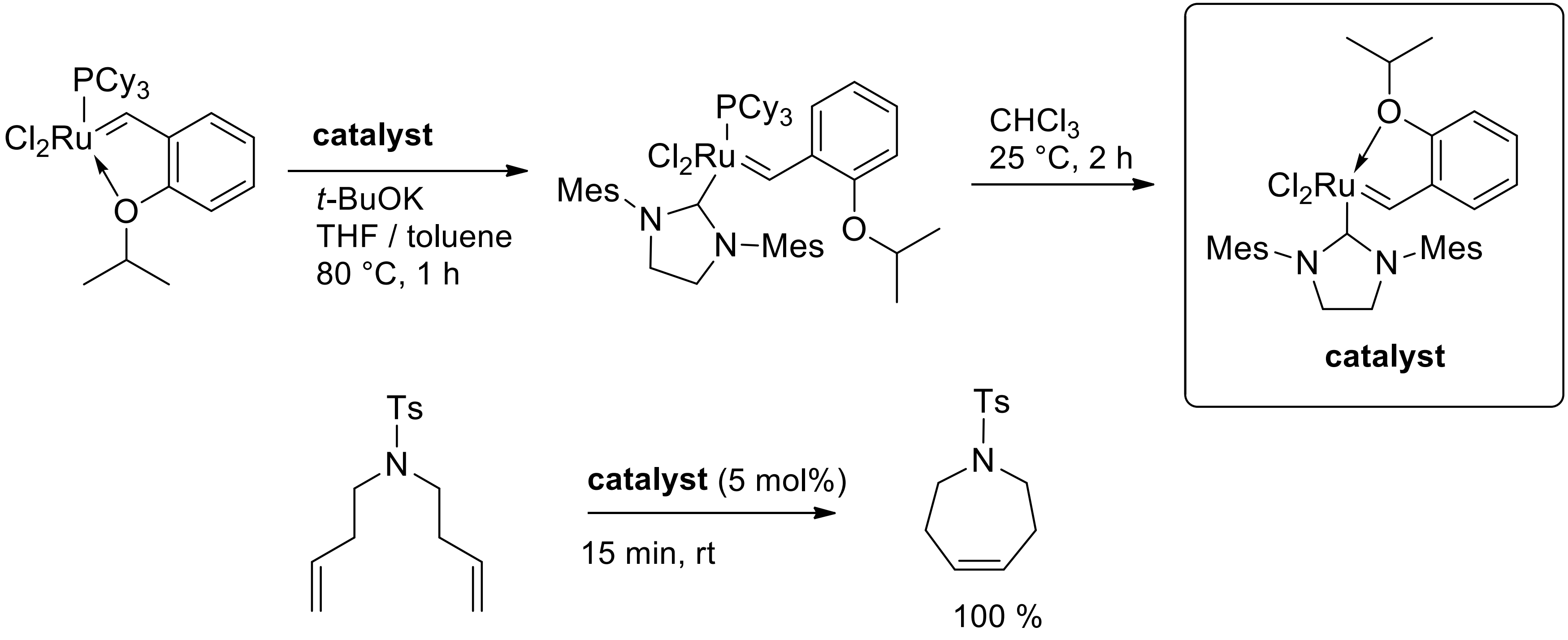
CH_2Cl_2, 40 °C, 15 h

87 %

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

Olefin metathesis

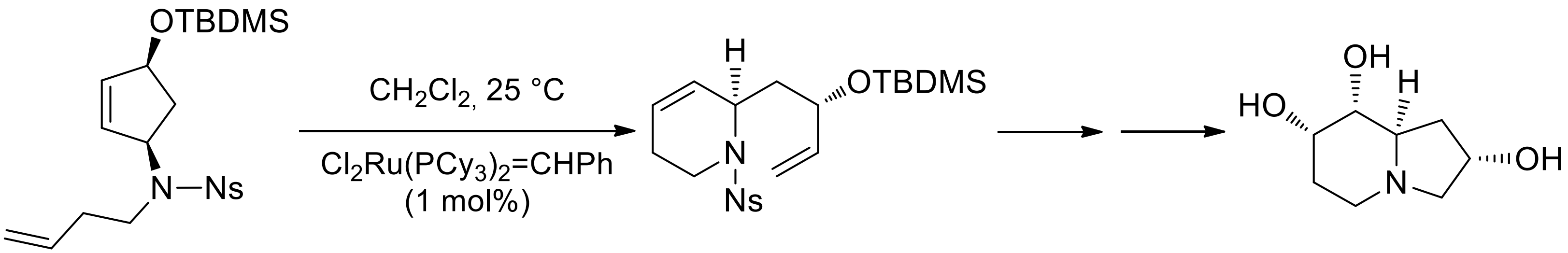
New phosphine-free metathesis catalyst



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

Application to the synthesis of natural products

Synthesis of aza sugars

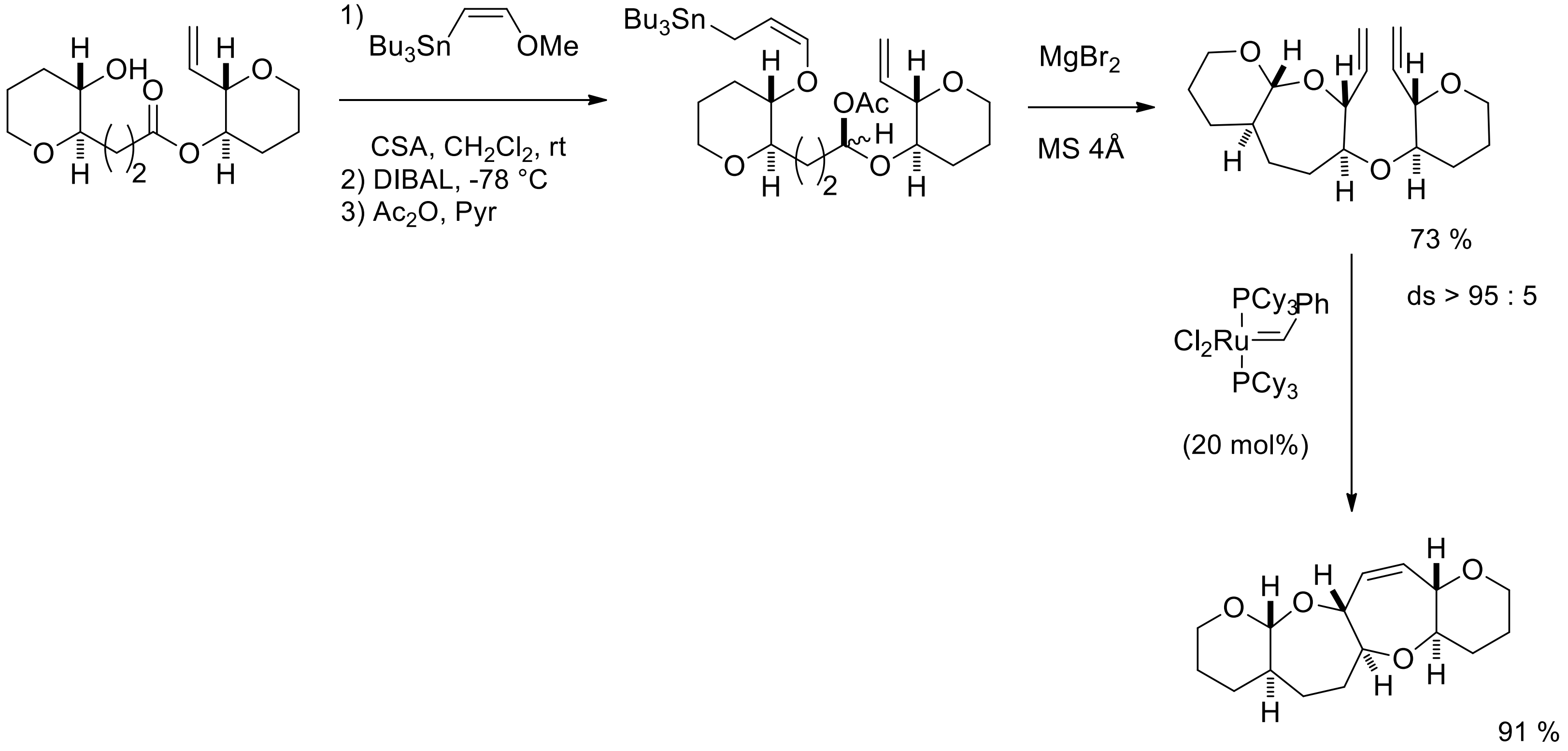


Ns = (*o*-NO_2)$C_6H_4SO_2$-

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

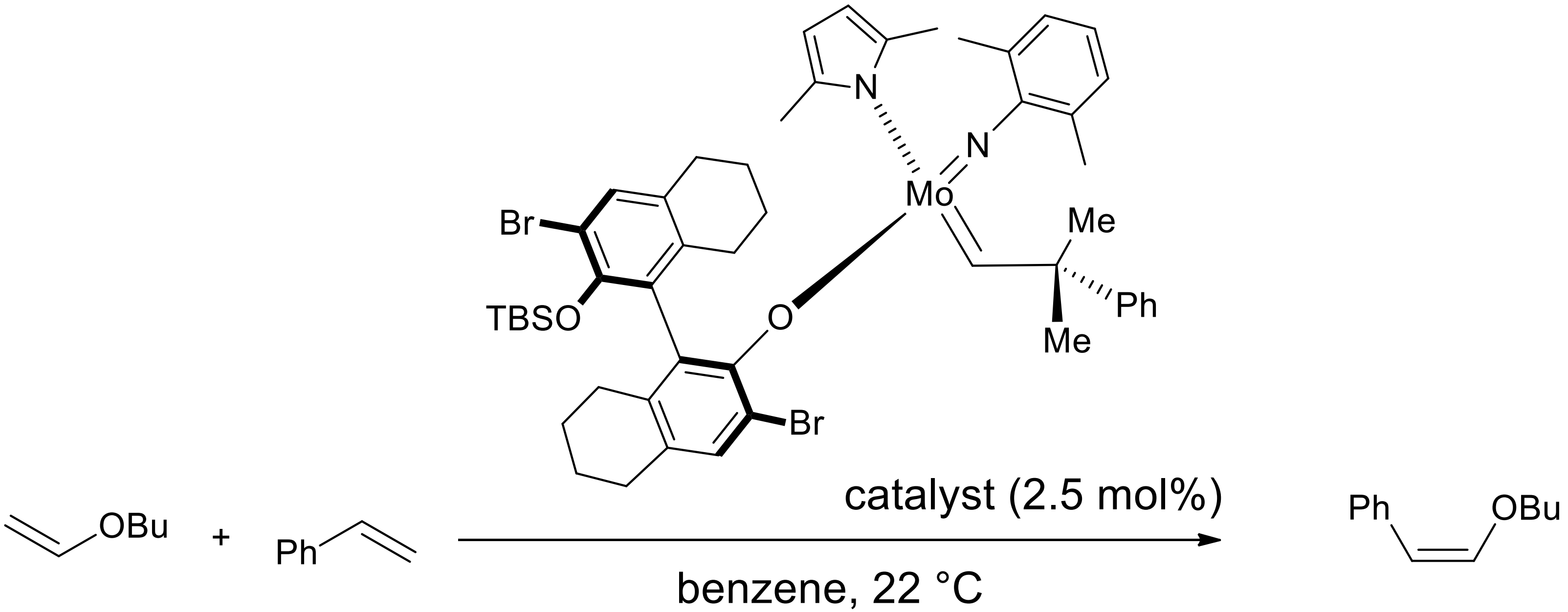
Olefin metathesis

Synthesis of complex ring-systems *via* metathesis



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

State of the art

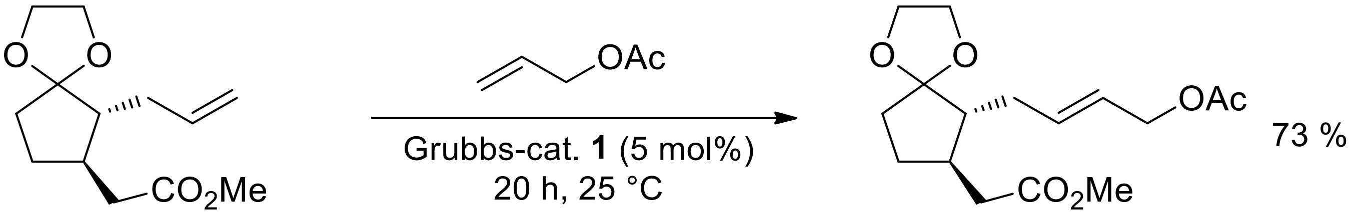


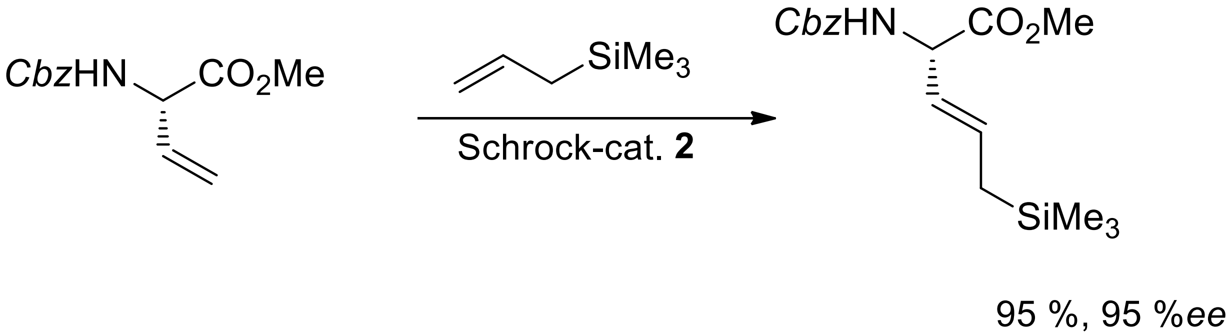
73%; Z:E > 98:2

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

Olefin metathesis

Synthesis of jasmonic acid derivatives

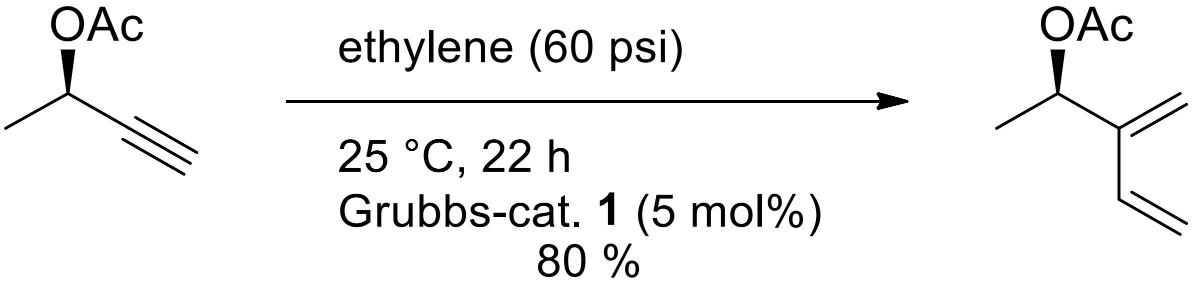




S. Blechert, *Chem. Eur. J*. **1997**, *3*, 441
S.E. Gibson, *Chem. Commun*. **1997**, 1107
S. Blechert, *Chem. Commun*. **1997**, 1949

Olefin metathesis

Cross-metathesis of alkynes with ethylene



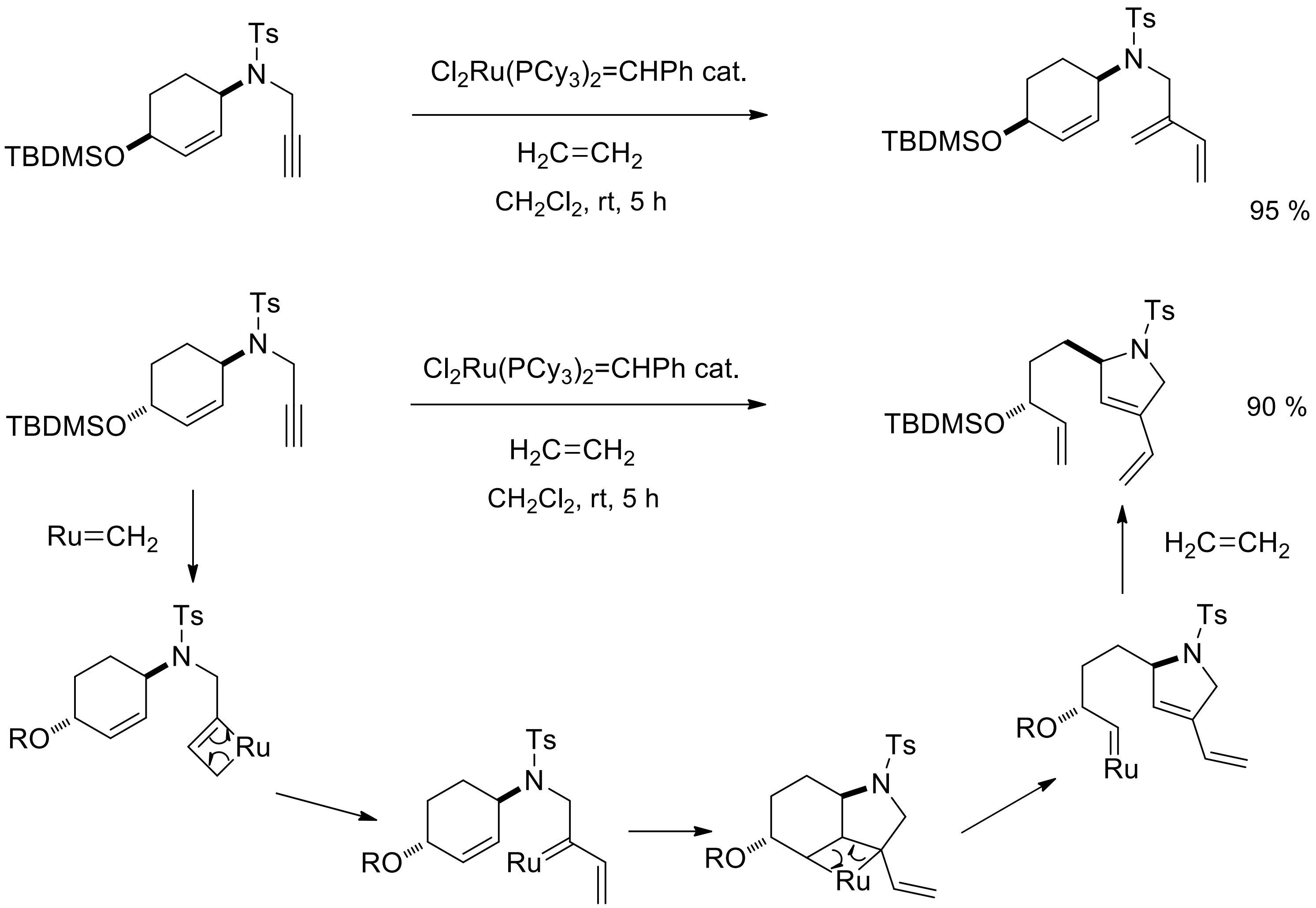
ethylene (60 psi)

25 °C, 22 h
Grubbs-cat. **1** (5 mol%)
80 %

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

Olefin metathesis

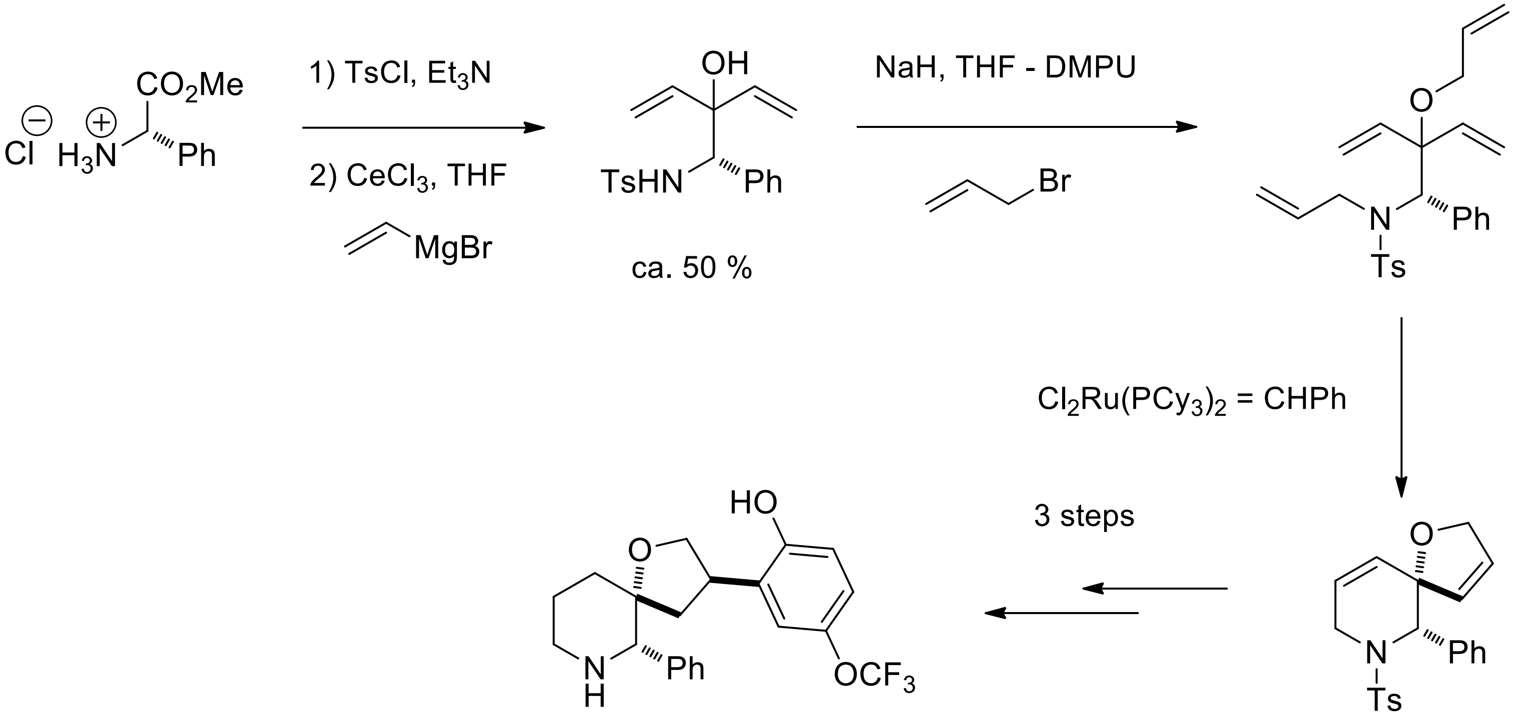
Ru-catalyzed Ring-Opening and –Closing Enyne Metathesis



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

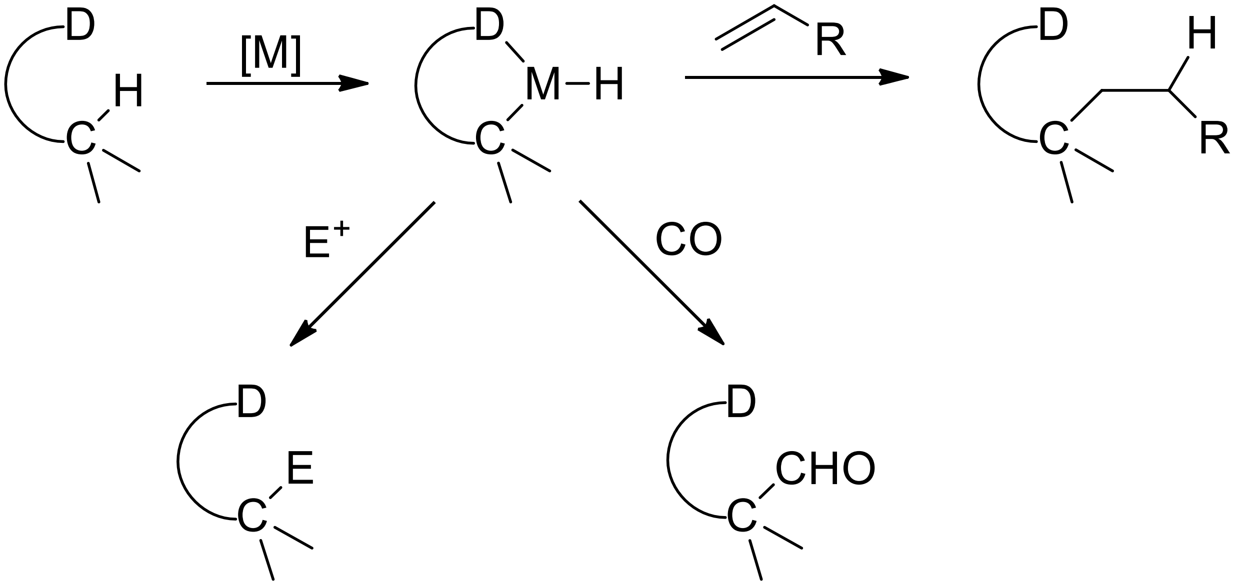
Olefin metathesis

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



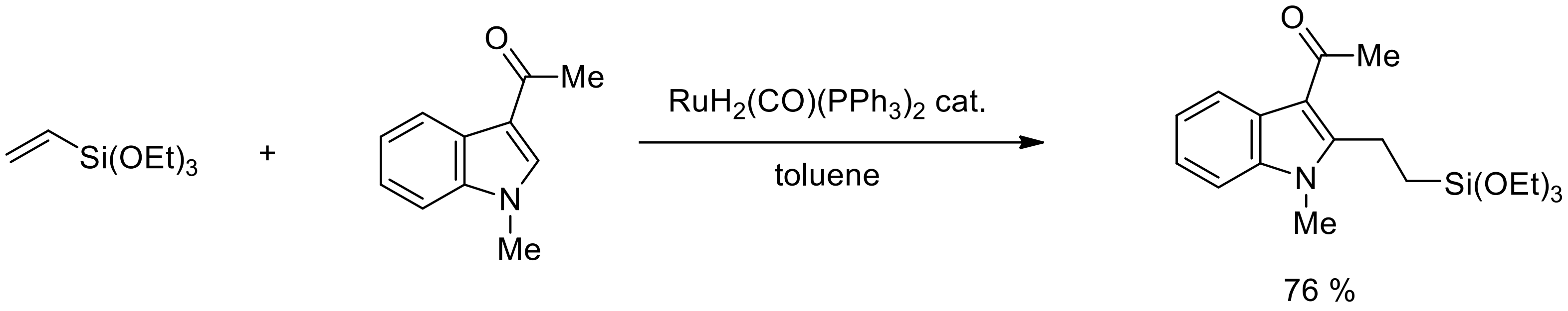
Merck-team *Org. Lett*. **2001**, *3*, 671

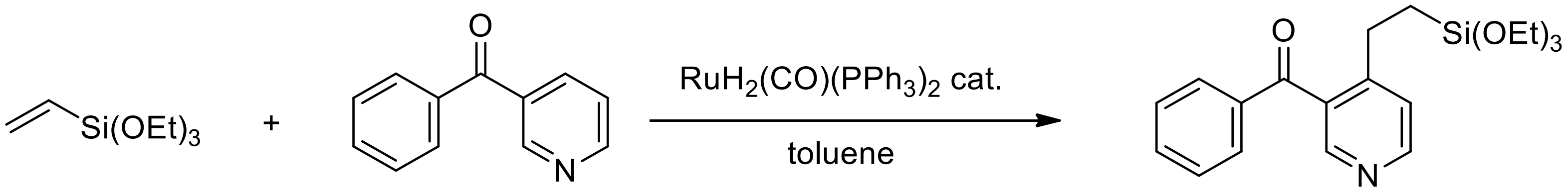
New C-H activation reactions



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

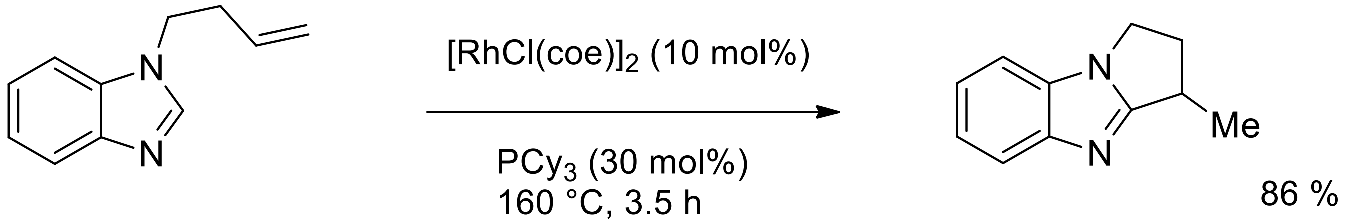
The Murai-reaction

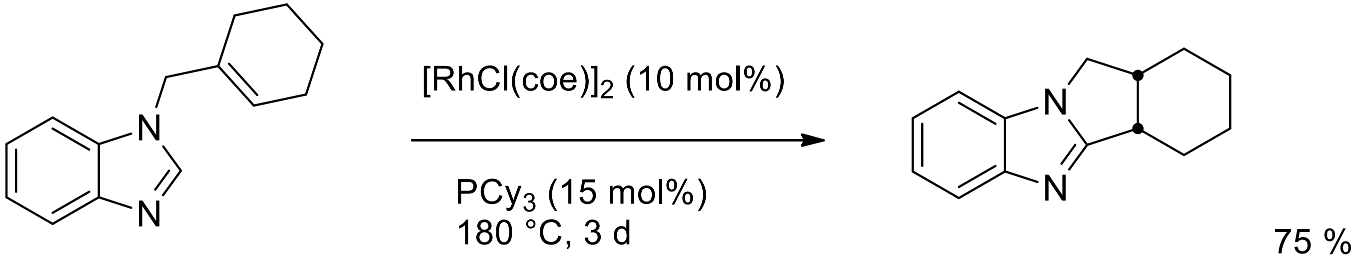




R. Grigg, *Tetrahedron Lett*. **1997**, *38*, 5737
S. Murai, *Nature*, **1993**, *366*, 529
S. Murai, *J. Organomet. Chem*. **1995**, *504*, 151

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

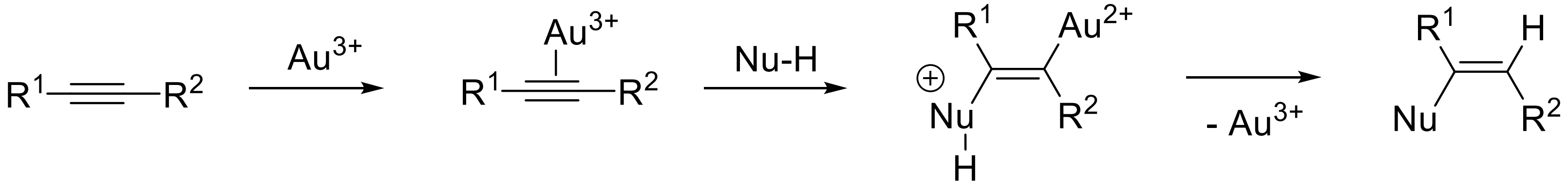


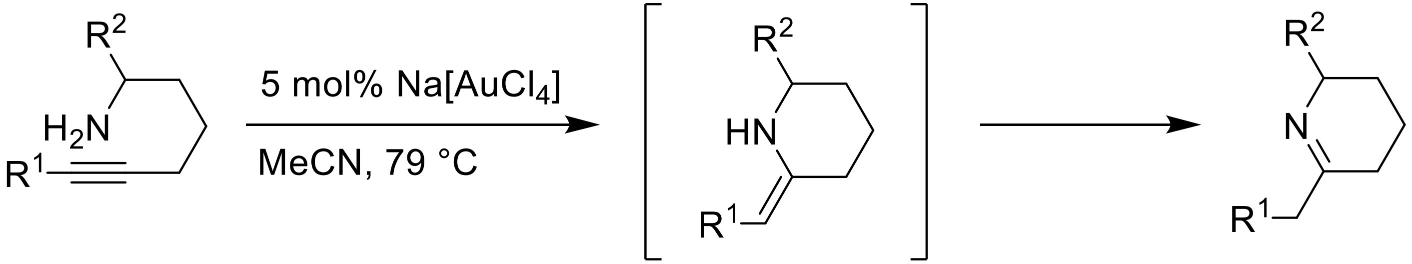


R. G. Bergman, J. Ellman, A. *J. Am. Chem. Soc*. **2001**, *123*, 2685

Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds





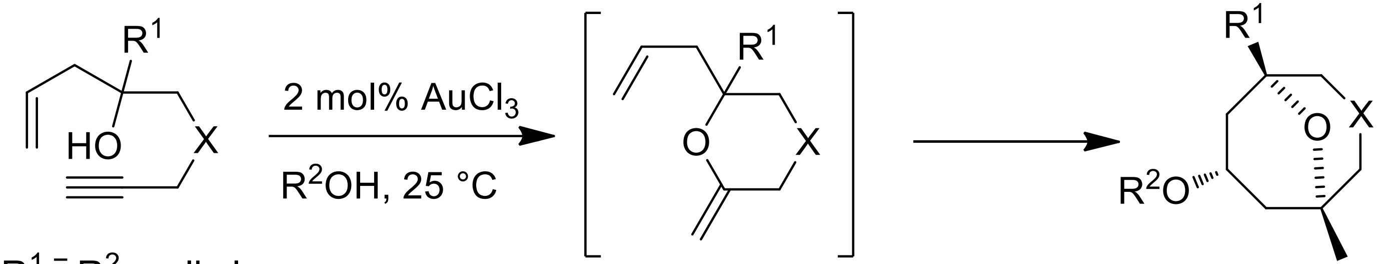
64-92%

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



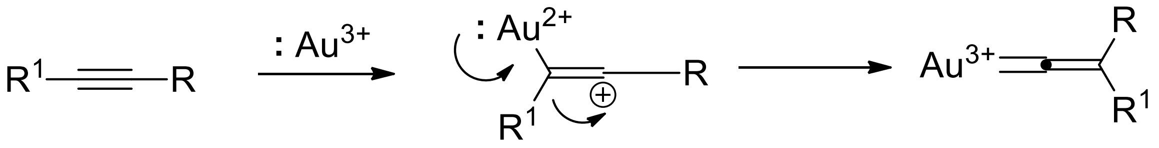
$R^1 = R^2$ = alkyl
X = CH_2, O

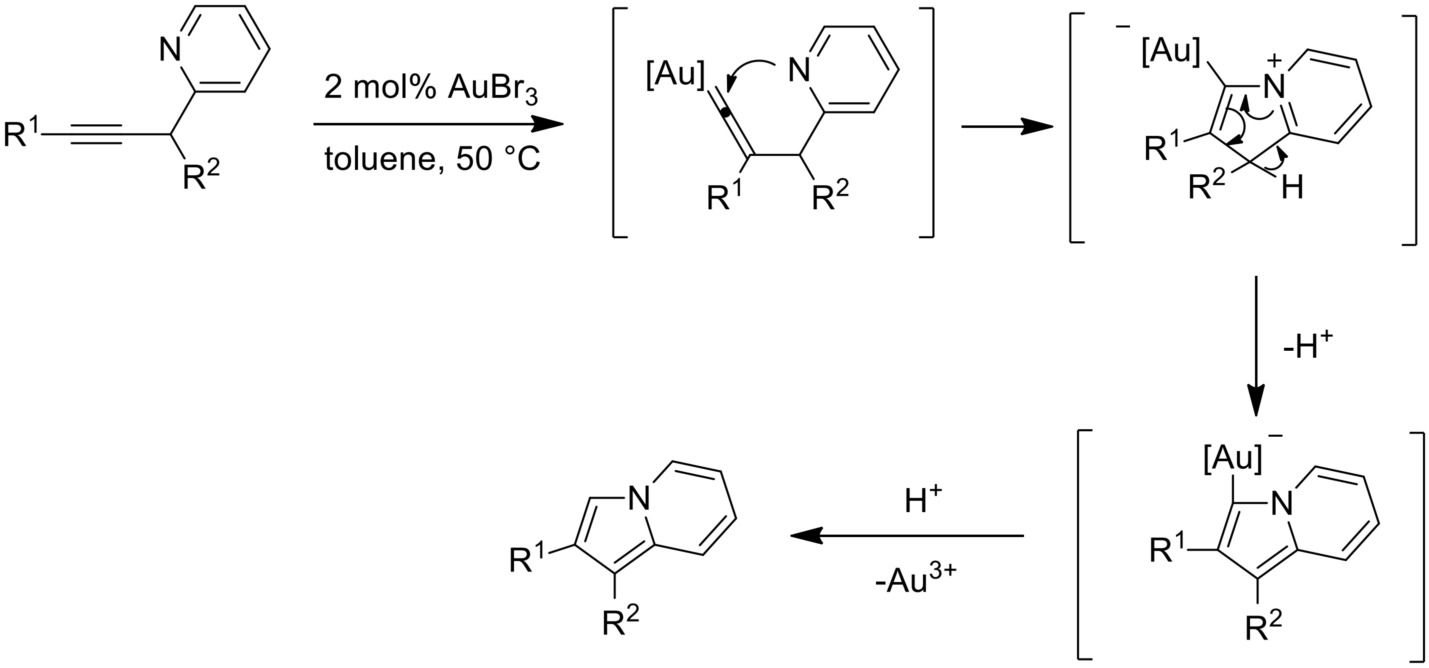
88-96%

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

Gold-catalyzed organic reactions

Gold(III)-triggered rearrangements

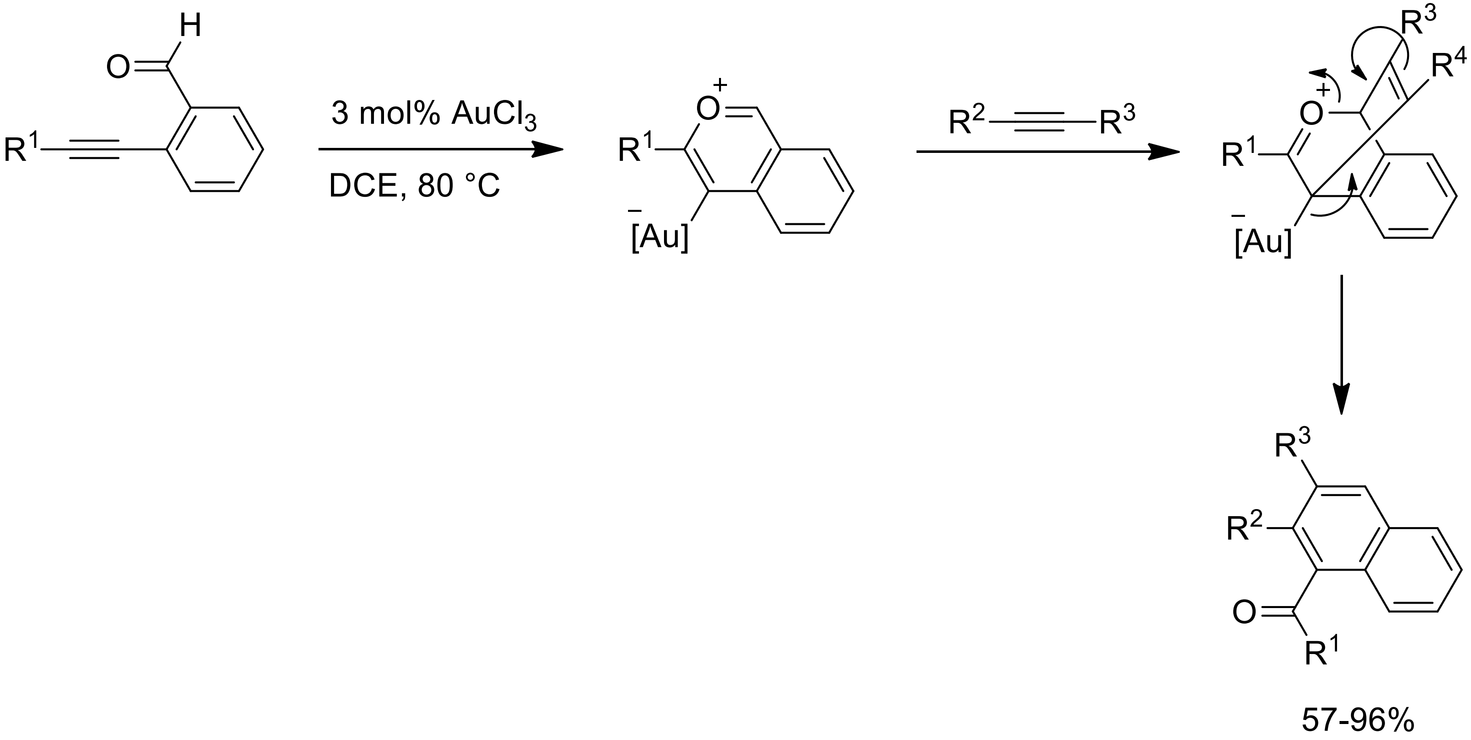




35-96%

Gold-catalyzed organic reactions

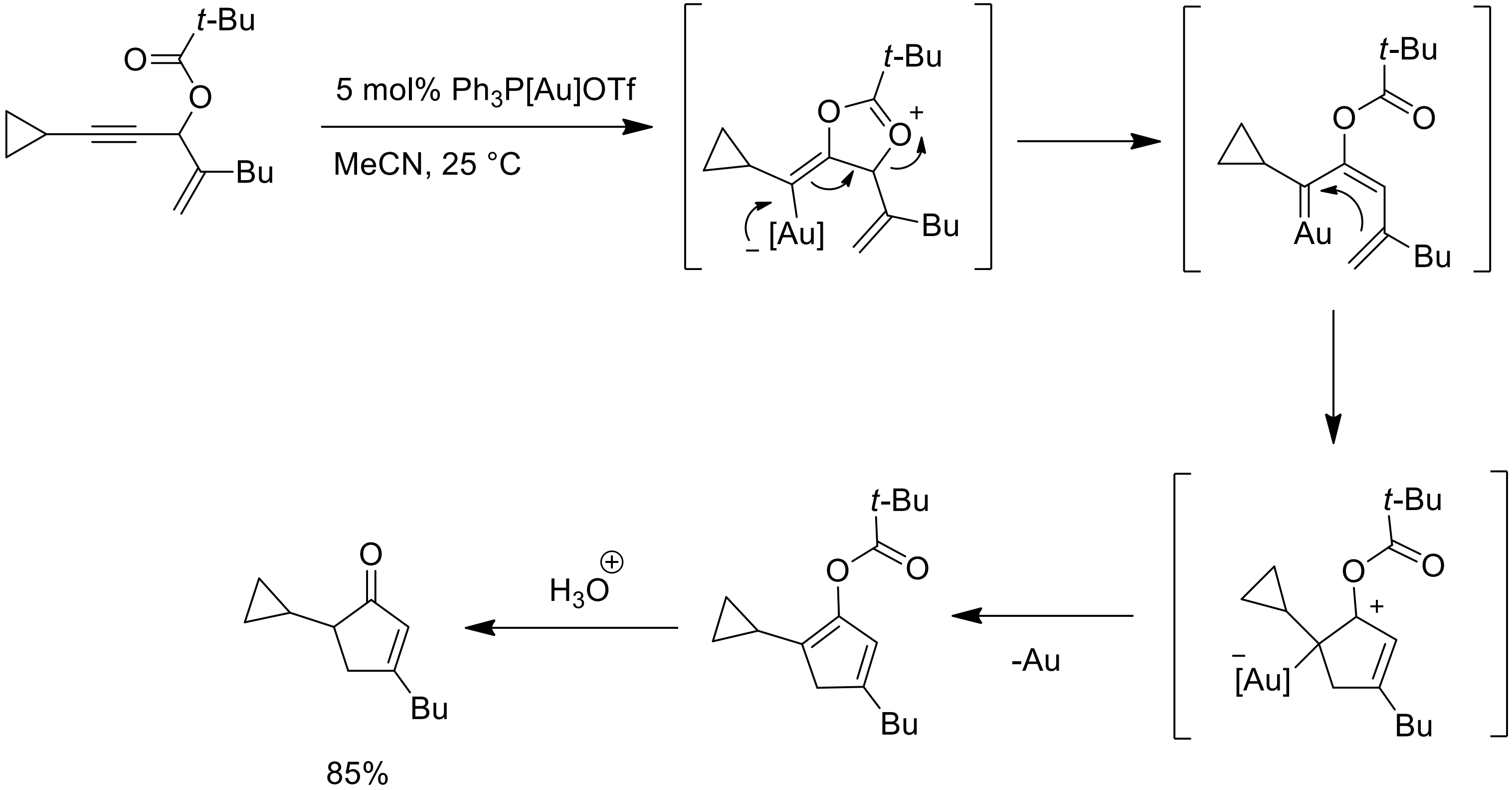
Au^{3+}-initiated cycloadditions



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

Gold-catalyzed organic reactions

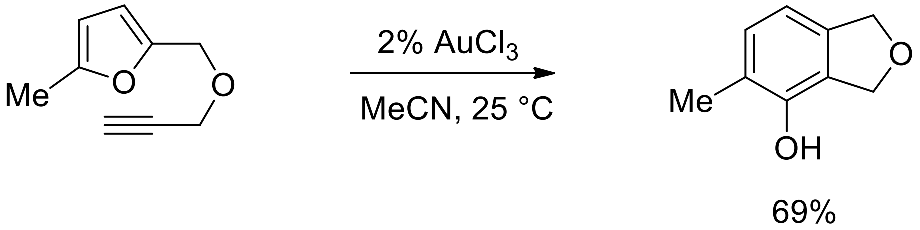
Use of electrophilic Gold(I)-complexes: $Ph_3P\text{-}Au\text{-}OTf$

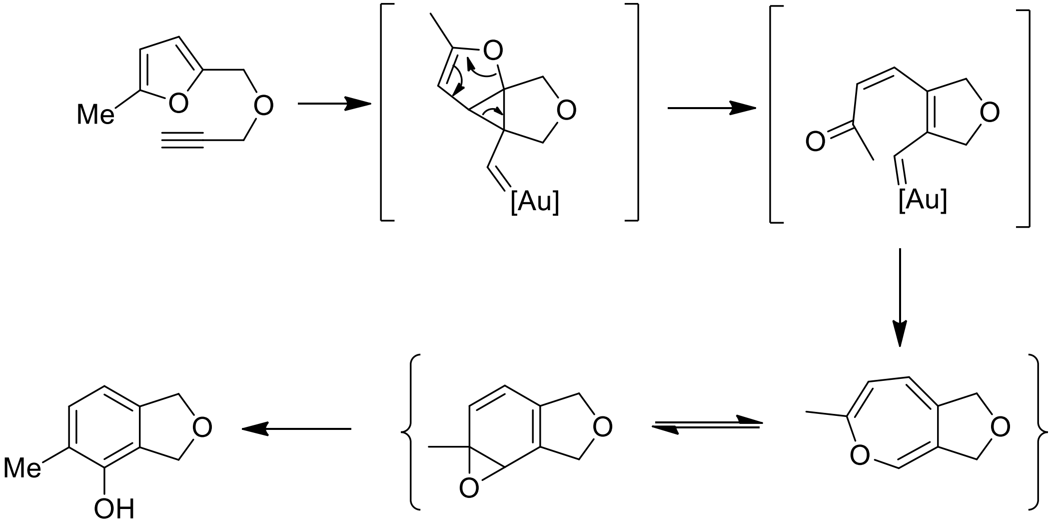


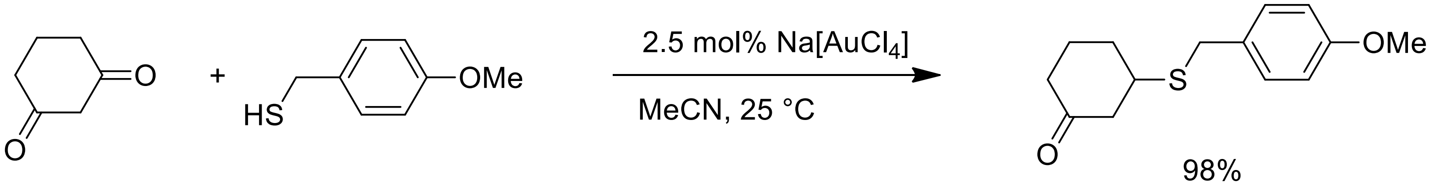
F. D. Toste *J. Am. Chem. Soc*. **2005**, *127*, 5802

Gold-catalyzed organic reactions

Intramolecular phenol synthesis







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