

# Organic Chemistry IV

## Organometallic Chemistry for Organic Synthesis

**Prof. Paul Knochel**

LMU

2018

# **OCIV**

**Prüfung:**

**13. Juli 2018**

**9-11 Uhr**

**Wieland HS**

**Nachholklausur:**

**17. September 2018**

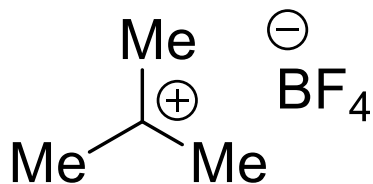
**10-12 Uhr**

**Baeyer HS**

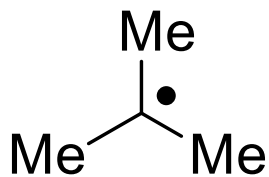
## Recommended Literature

1. **F. A. Carey, R. J. Sundberg, Advanced Organic Chemistry**, Fifth Edition Part A and Part B, Springer, 2008, ISBN-13: 978-0-387-68346-1
2. **R. Brückner, Organic Mechanisms**, Springer, 2010, ISBN: 978-3-642-03650-7
3. **L. Kürti, B. Czako, Strategic applications of named reactions in organic synthesis**, Elsevier, 2005, ISBN-13: 978-0-12-429785-2
4. **N. Krause, Metallorganische Chemie**, Spektrum der Wissenschaft, 1996, ISBN: 3-86025-146-5
5. **R. H. Crabtree, The organometallic chemistry of transition metals**, Wiley-Interscience, 2005, ISBN: 0-471-66256-9
6. **M. Schlosser, Organometallics in Synthesis – Third manual**, 3rd 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

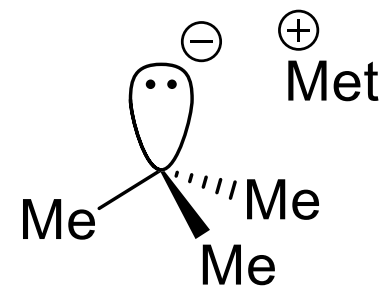
# Importance of organometallics



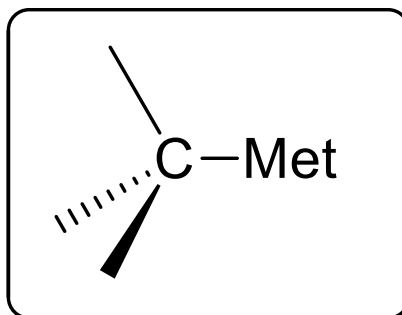
carbenium ion



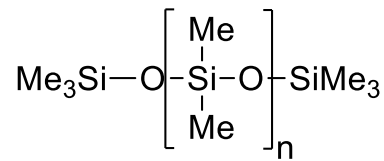
radical



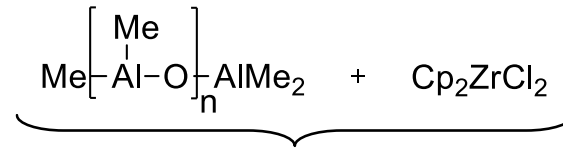
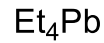
organometallic reagent



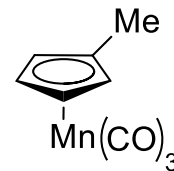
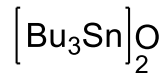
## Industrial production



Silicone



Kaminsky catalyst  
n=5-20 syndiotacticity of polypropylene

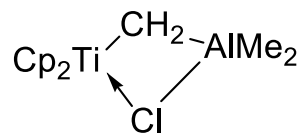
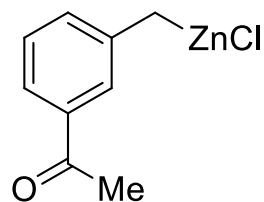
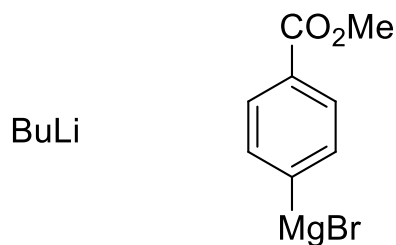


Industrial annual production of various organometallics

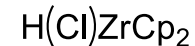
Organometallic	production [T / year]
Si	700 000
Pb	600 000
Al	50 000
Sn	35 000
Li	900

# Organometallic reagents and catalysts for the organic synthesis

organometallic reagents:

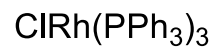
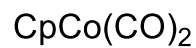


Tebbe reagent

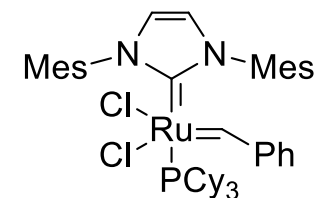


Schwarz reagent

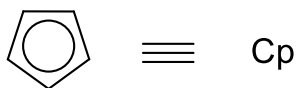
organometallic catalysts:



Wilkinson's catalyst

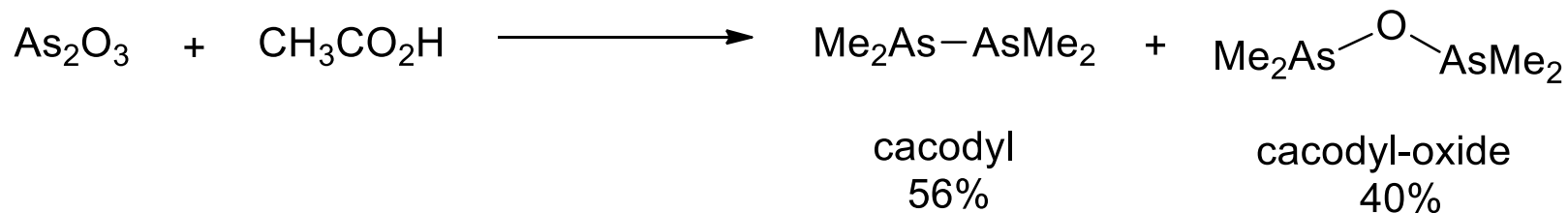


Grubbs II catalyst

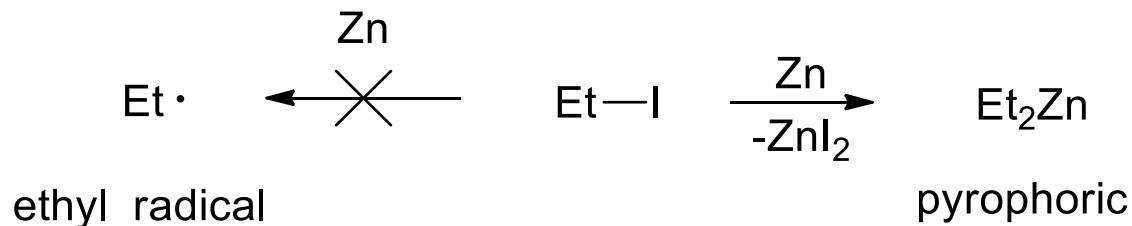


## Historic point of view

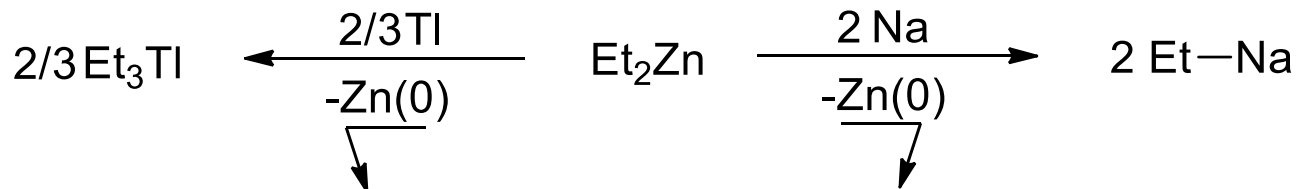
1757 - Louis Cadet de Gassicourt (parisian apothecary)



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

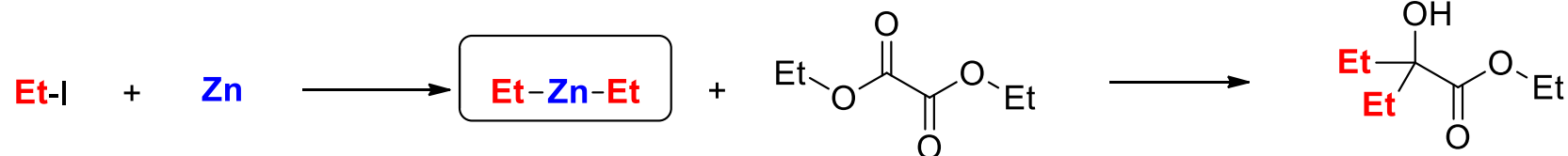


Universität Marburg (1848)

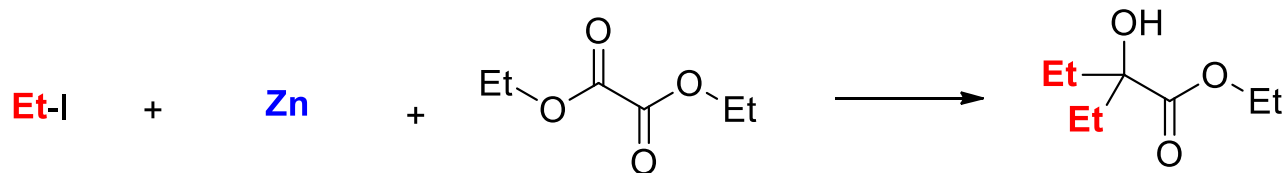


# Organometallic chemistry of the XIX century

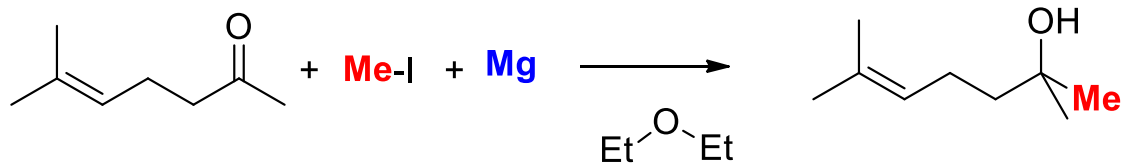
Frankland 1848, 1863



Beilstein 1862, Saytzeff 1870, Wagner 1875



Barbier 1899



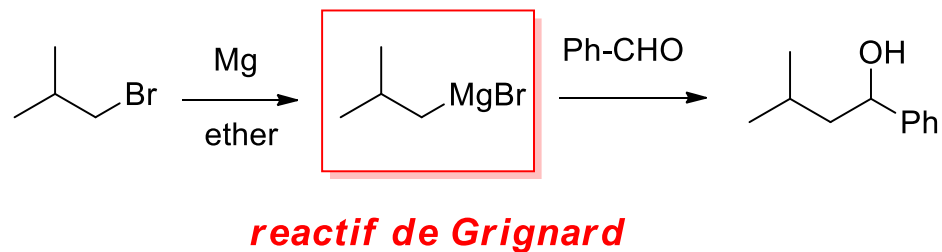
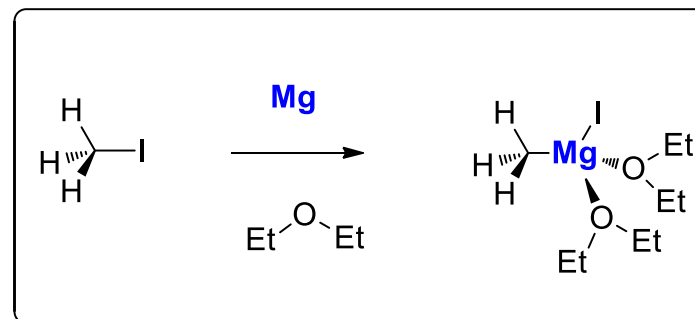
Ph. Barbier *Comptes Rendus de l'Académie des Sciences*, 1899, 128, 110



# Organometallic chemistry of the XIX century



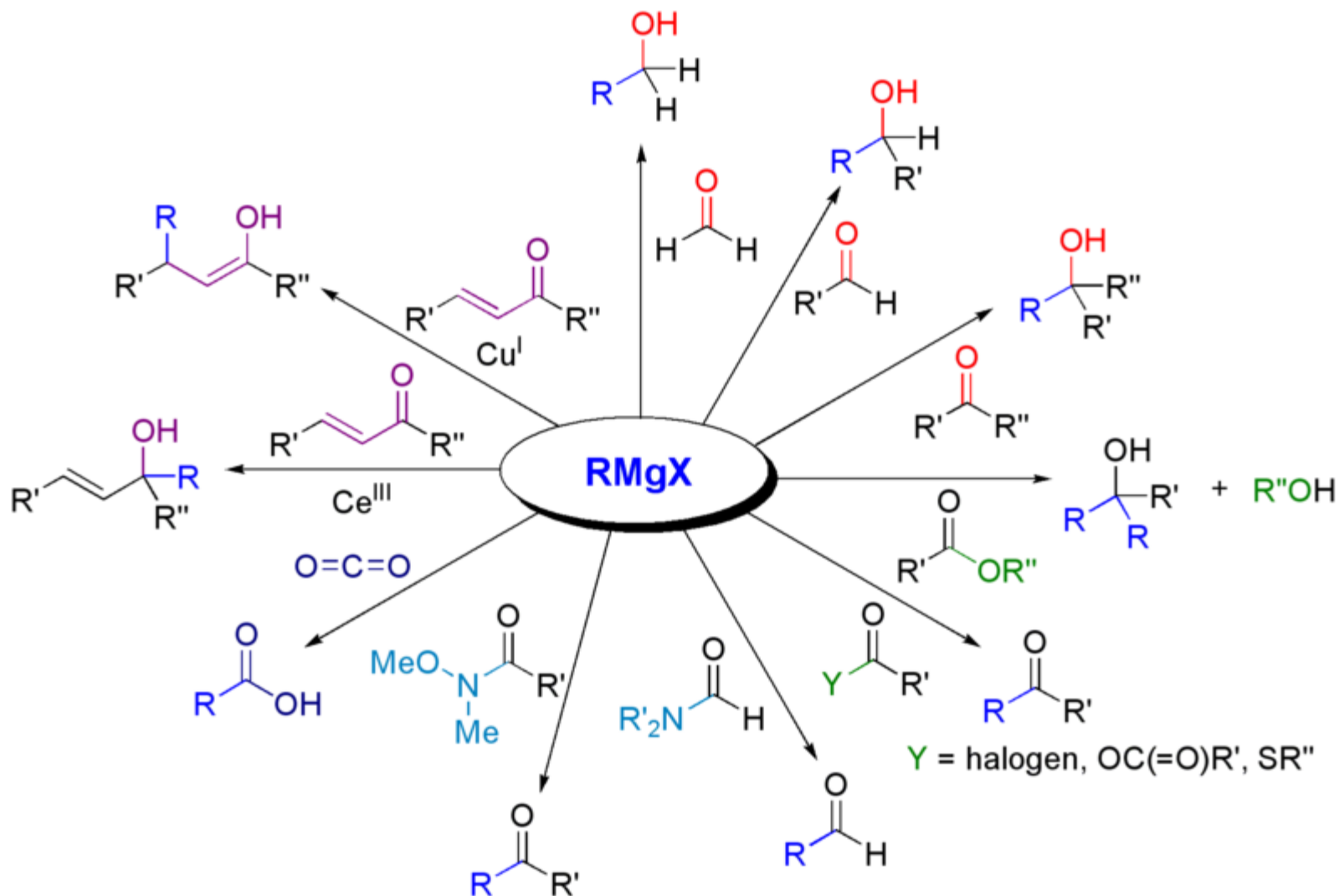
Pl. X. Victor Grignard dans son laboratoire de Nancy  
1912



V. Grignard

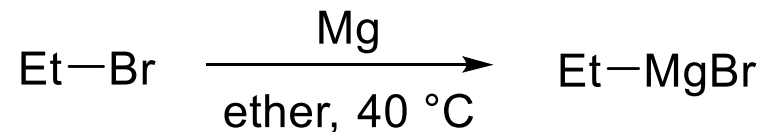
*Comptes Rendus de l'Académie des Sciences*, **1900**, 130, 1322

# Reactivity of the Grignard reagents

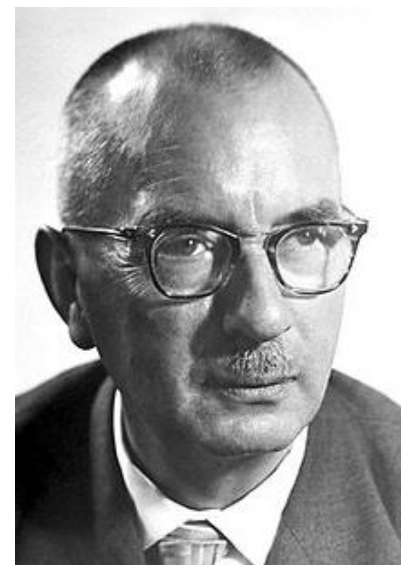
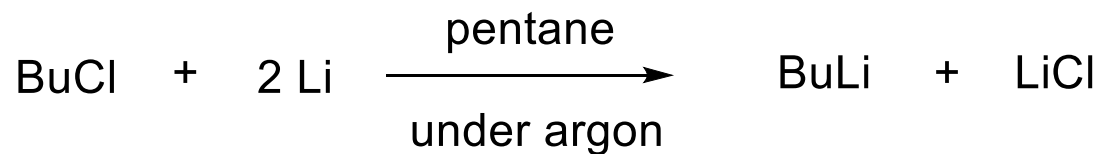


## Historic point of view

Victor Grignard (1900)



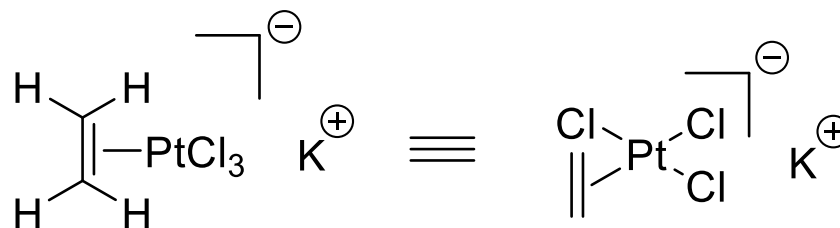
Karl Ziegler (1919)



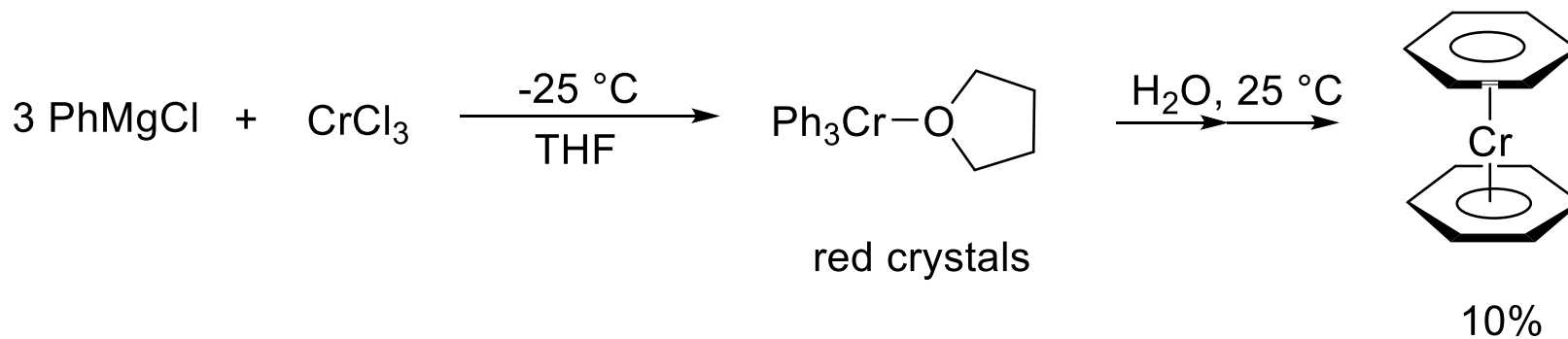
## Historic point of view

first transition metal organometallics:

Zeise's Salz (1827)



Hein (1919)

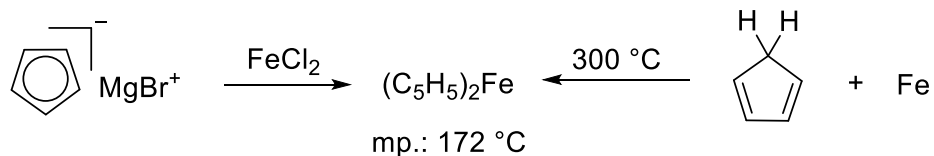


# Historic point of view

1951: synthesis of ferrocene

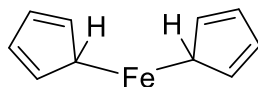
Pauson (Scotland) 7. August 1951

Miller 11. June 1951

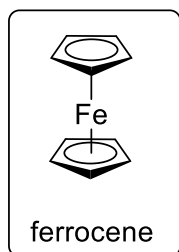


1952

structural proposal by Pauson:

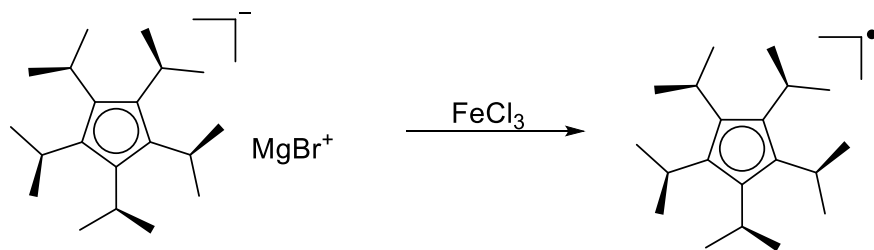


correct structure by G. Wilkinson and R. B. Woodward:

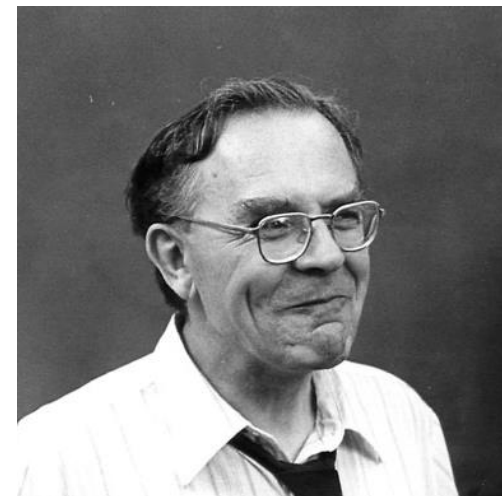


G. Wilkinson, R. B. Woodward *J. Am. Chem. Soc.* **1952**, 74, 2125

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



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



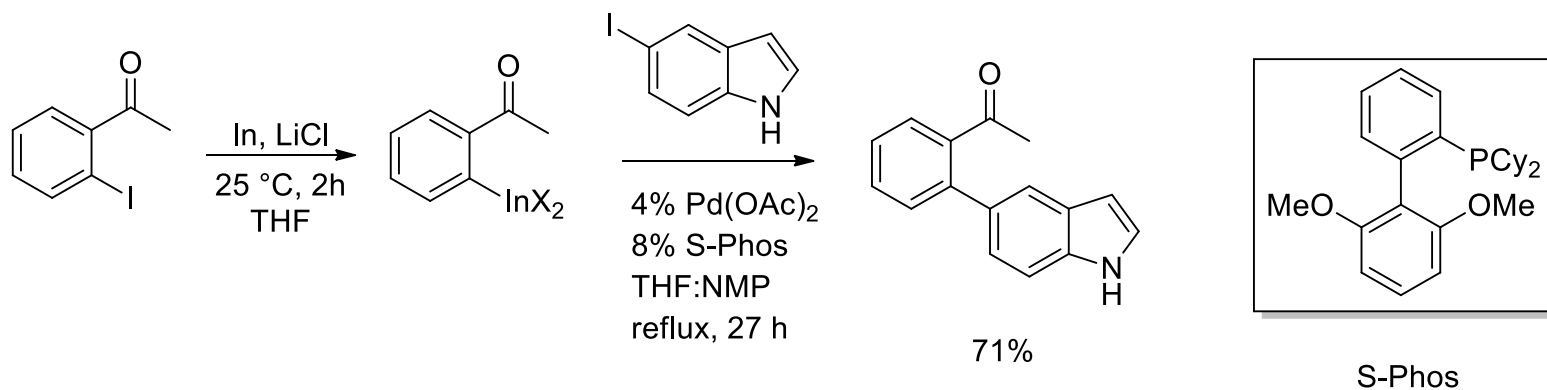
G. Wilkinson



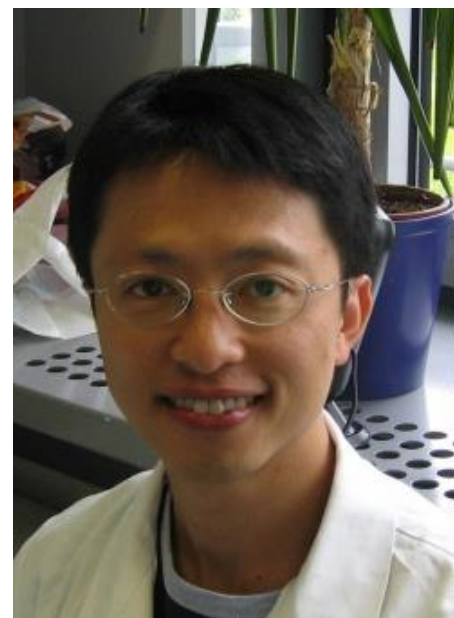
R. B. Woodward

## Goal of the lecture

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



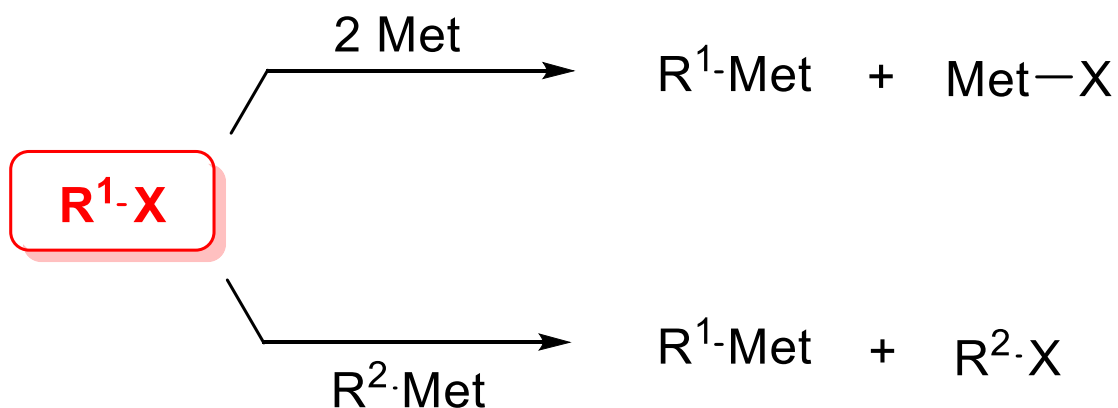
Y.-H. Chen, *Angew. Chem. Int. Ed.* **2008**, 47, 7648.



# General synthetic methods for preparing organometallic reagents

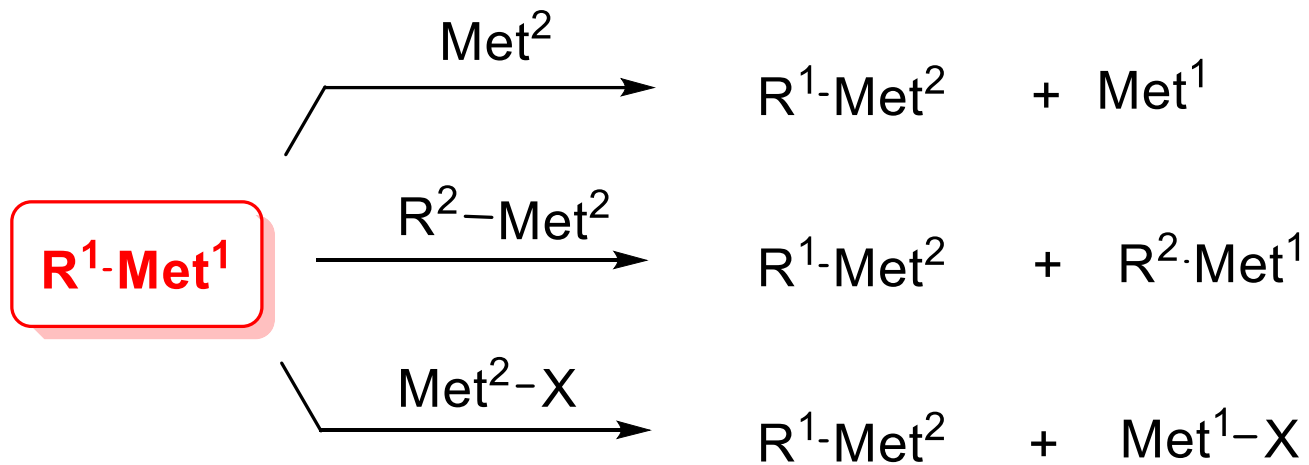
classification according to starting materials

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



## Classification according to starting materials

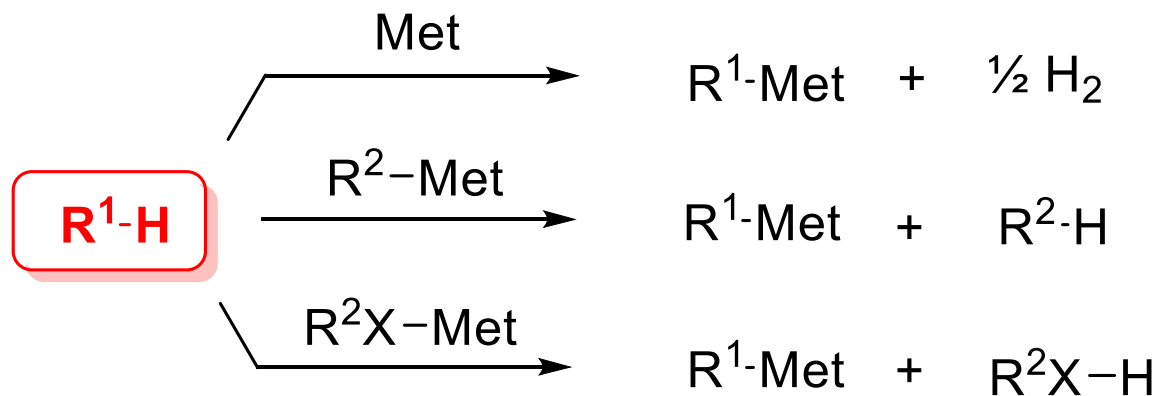
transmetalation





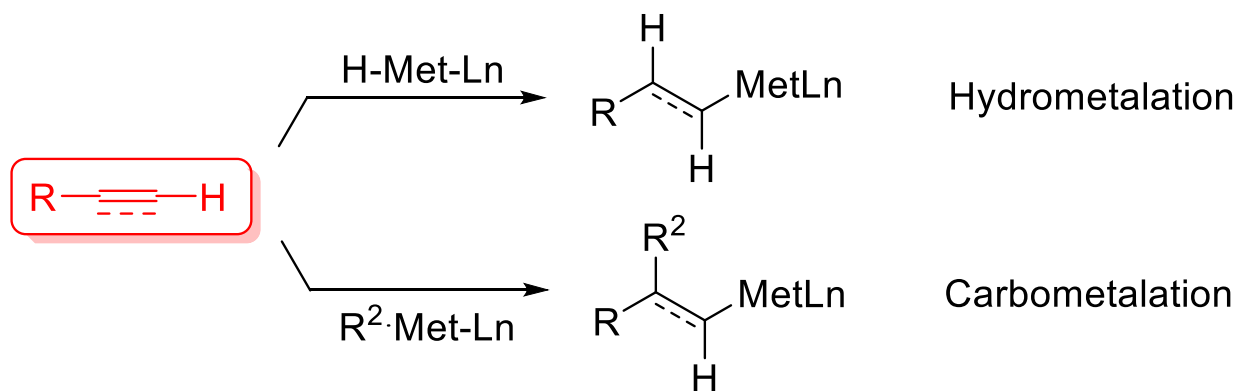
## Classification according to starting materials

metalation



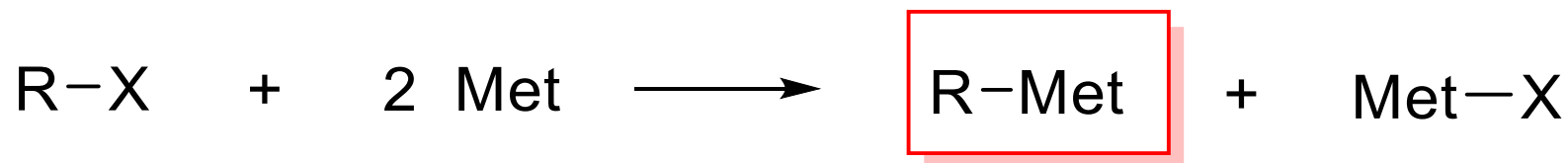
## Classification according to starting materials

carbometalation and hydrometalation



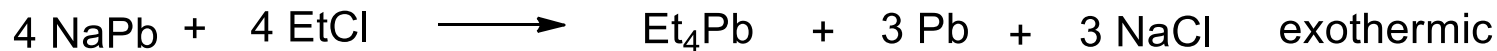
## Synthesis starting from organic halides

direct synthesis - oxidative addition



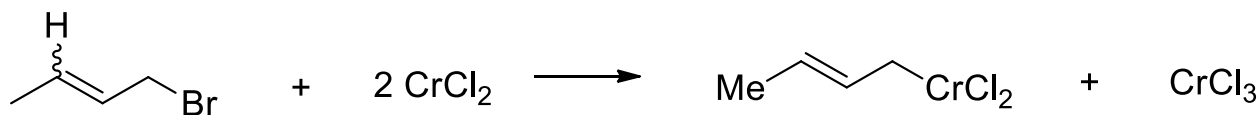
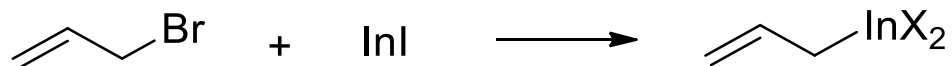
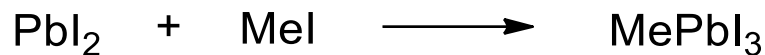
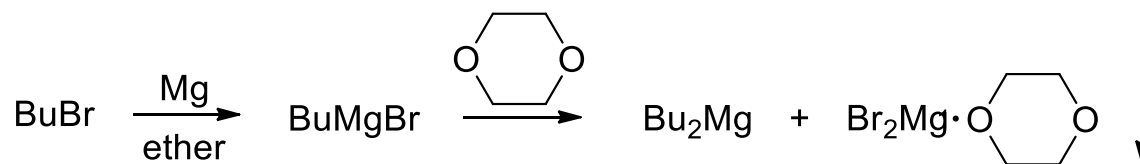
driving force of the reaction:

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



## Direct Synthesis - Oxidative Addition

examples:

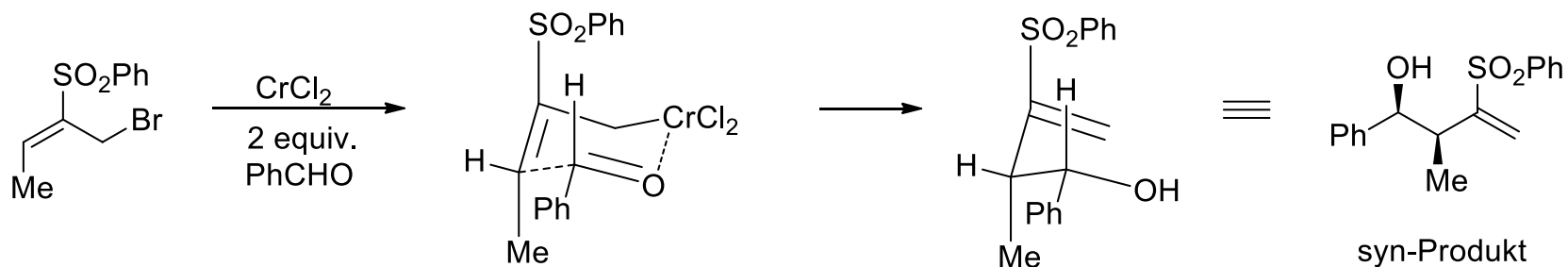
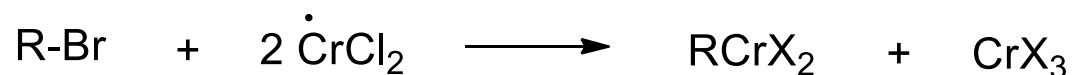
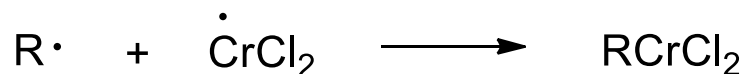
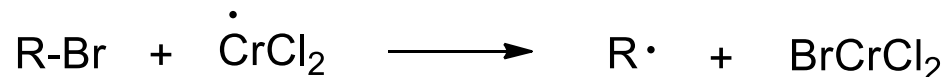


E/Z-mixture

pure E-isomer

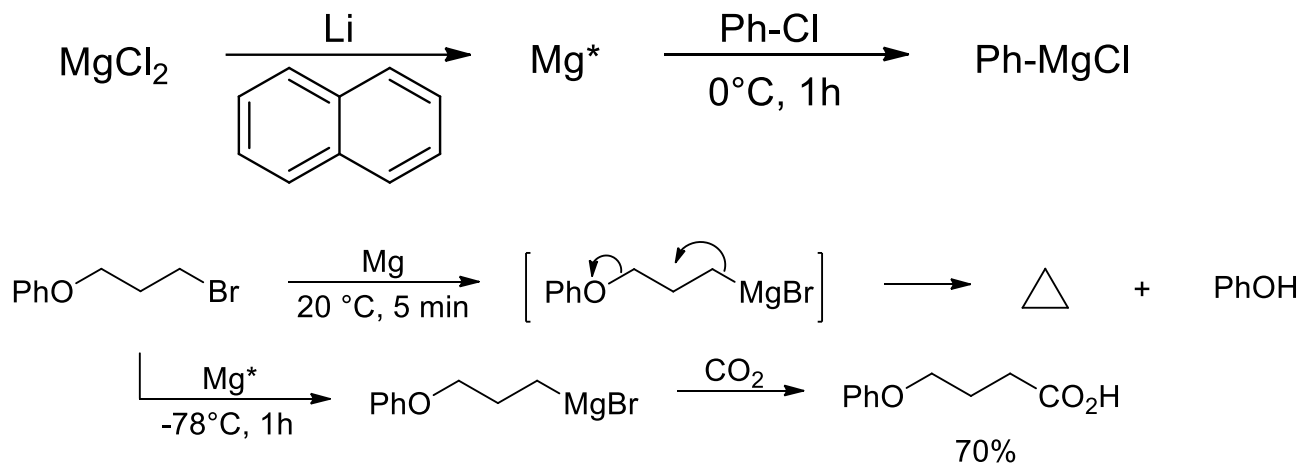
## Direct Synthesis - Oxidative Addition

mechanism:

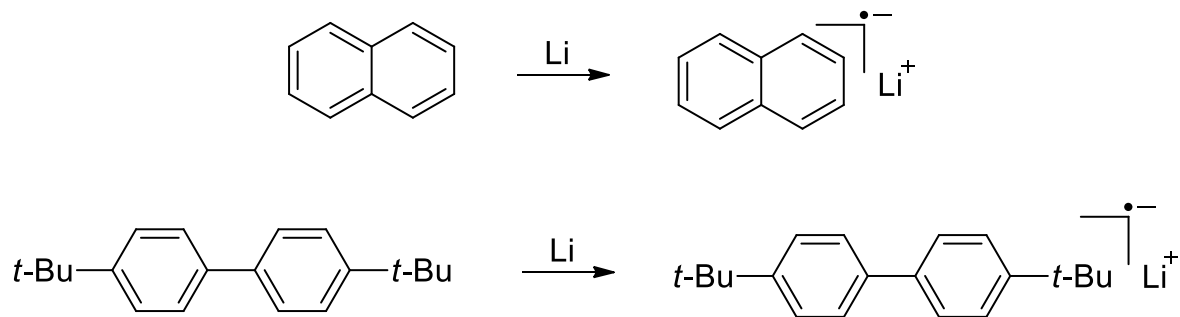


## Activation of the metal: the *Rieke*-approach

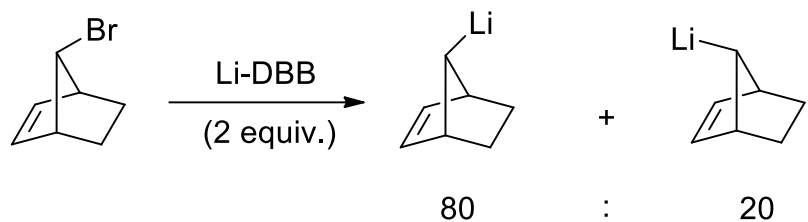
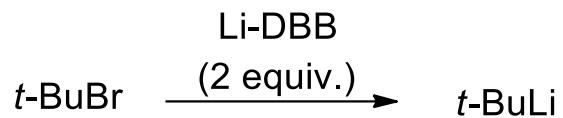
activation of the metal: R. D. Rieke, *Science* **1989**, 246, 1260



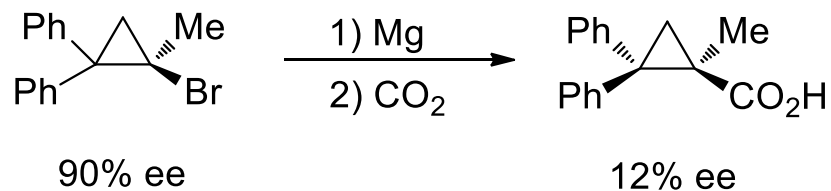
Activation of lithium: formation of soluble Li-sources:



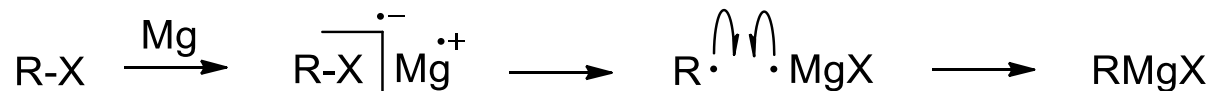
# Mechanism of the metal insertion



loss stereochemical information

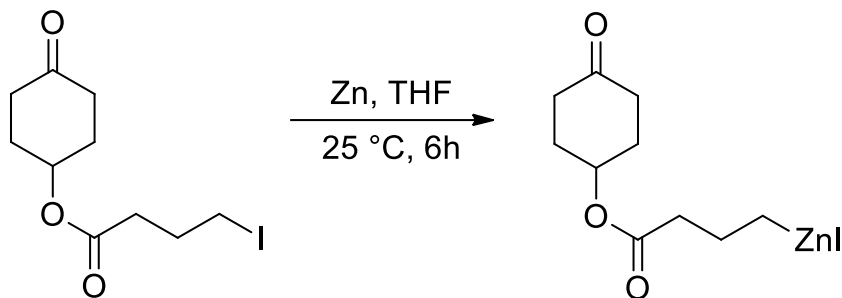
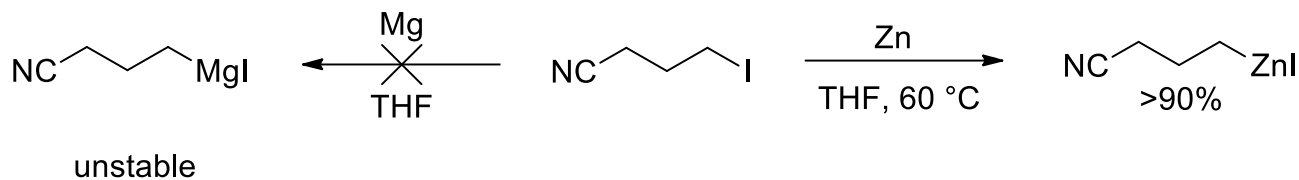


H.M. Walborsky: *J. Am. Chem. Soc.* **1989**, 11, 1896



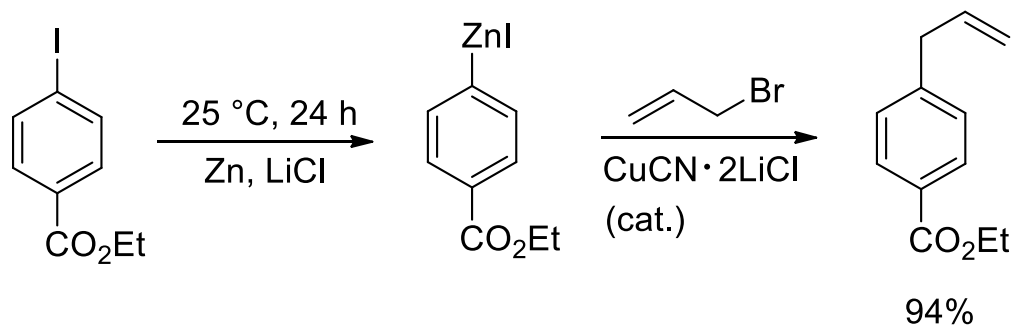
radical mechanism

## Preparation of functionalized organometallics



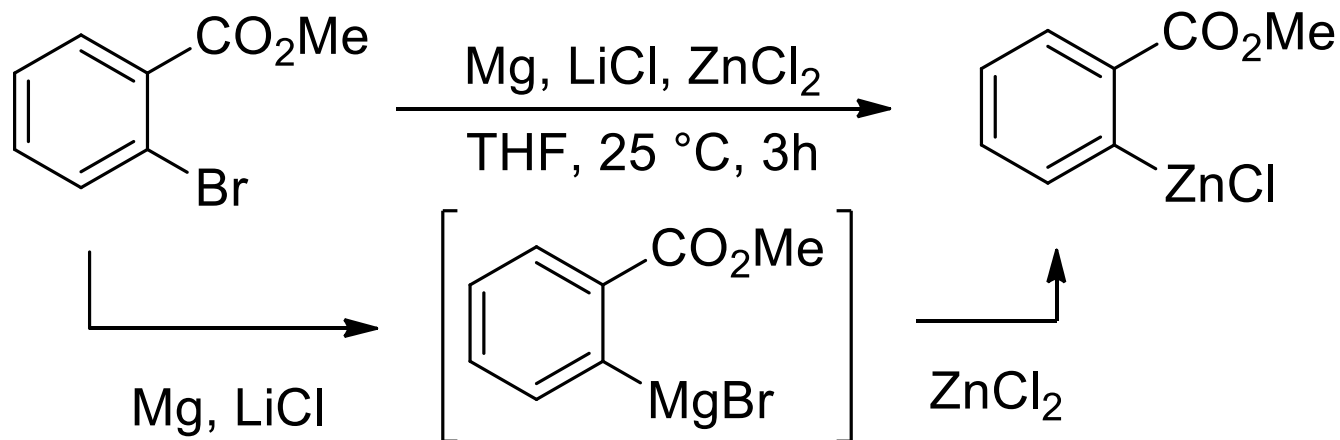
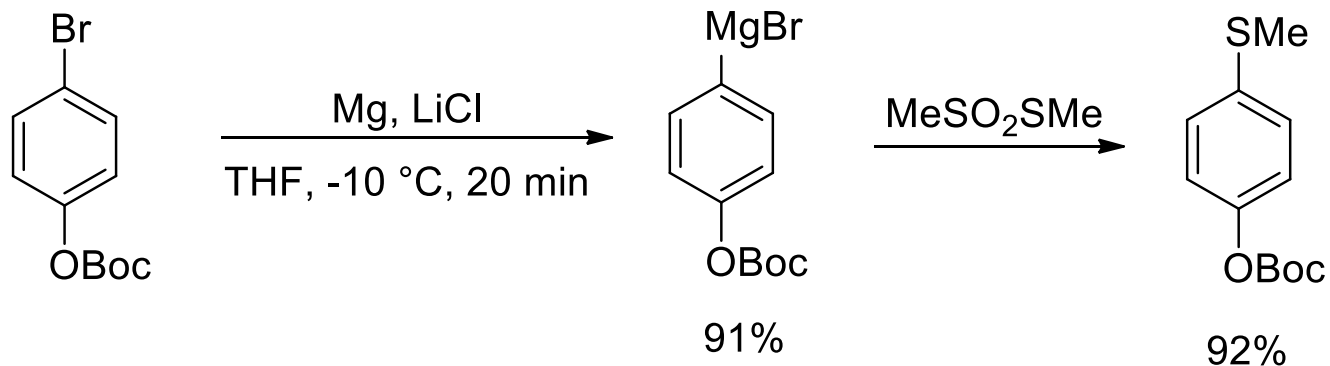
P. Knochel, *J. Org. Chem.* **1988**, 53, 2390

P. Knochel, *Org. React.* **2001**, 58, 417.



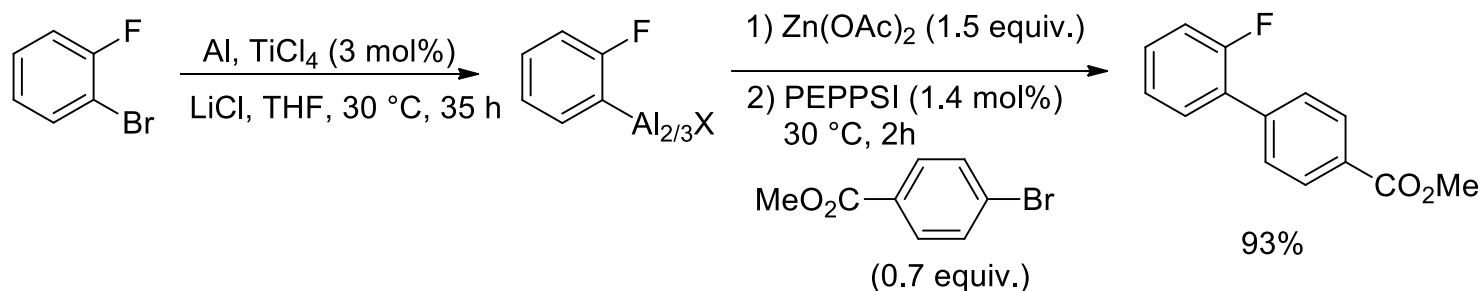


## Preparation of functionalized organometallics

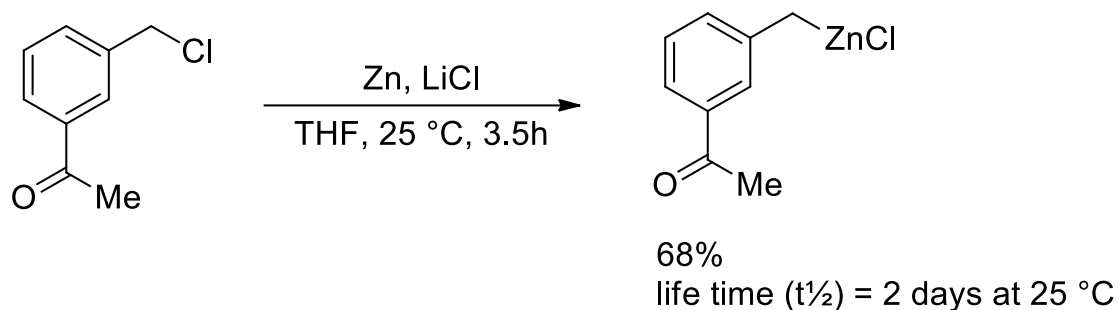


# Preparation of functionalized organometallics

activation of Al using LiCl and  $\text{TiCl}_4$ ,  $\text{BiCl}_3$ ,  $\text{PbCl}_2$  or  $\text{InCl}_3$

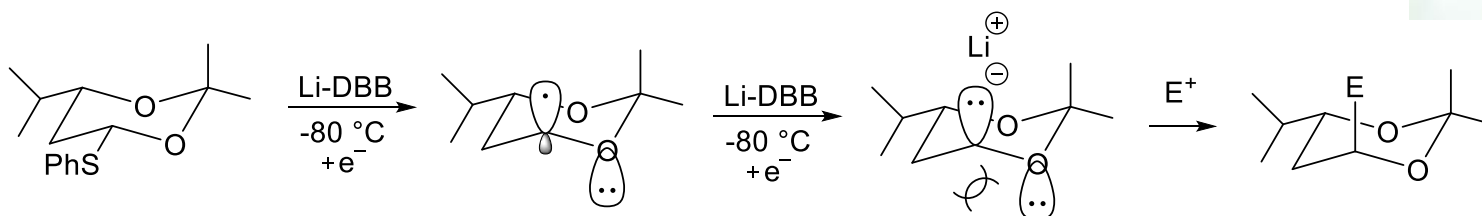
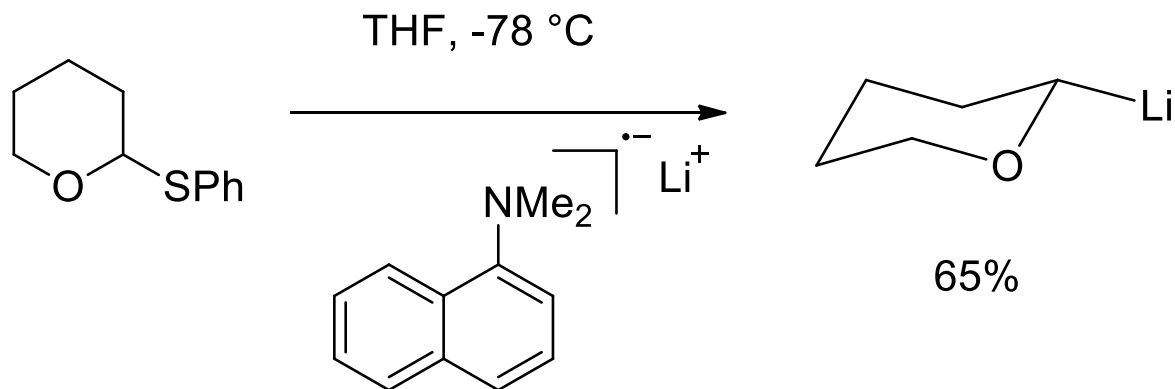


T. Blümke, Y.-H. Chen, P. Knochel *Nature Chemistry*, **2010**, 2, 313

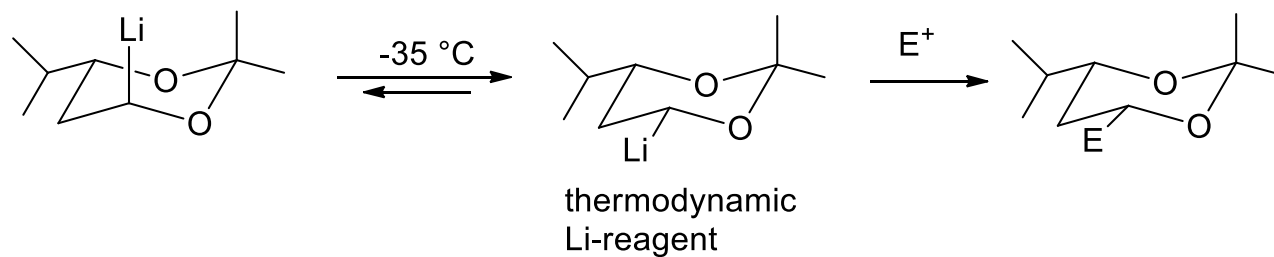


A. Metzger, P. Knochel *Org. Lett.* **2008**, 10, 1107

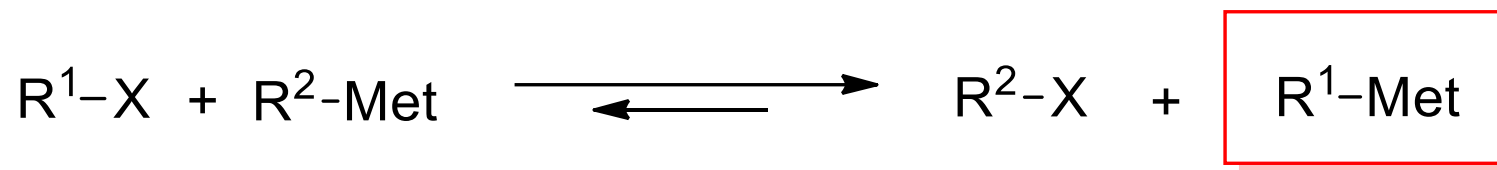
## Extension to insertion reactions to C-S bonds



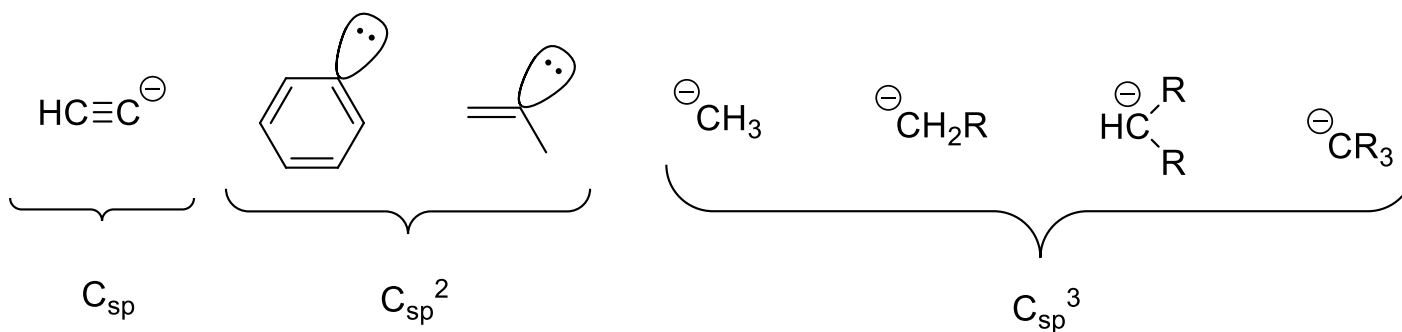
kinetic Li-reagent



## The Halogen-Metal-Exchange

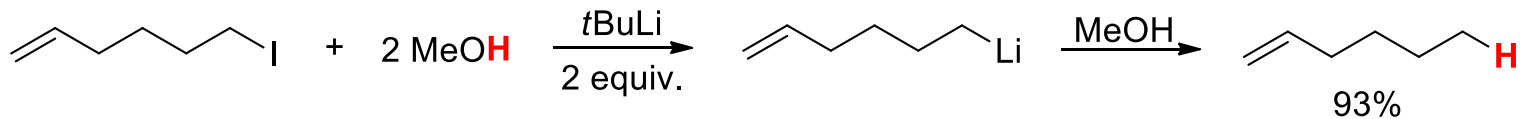
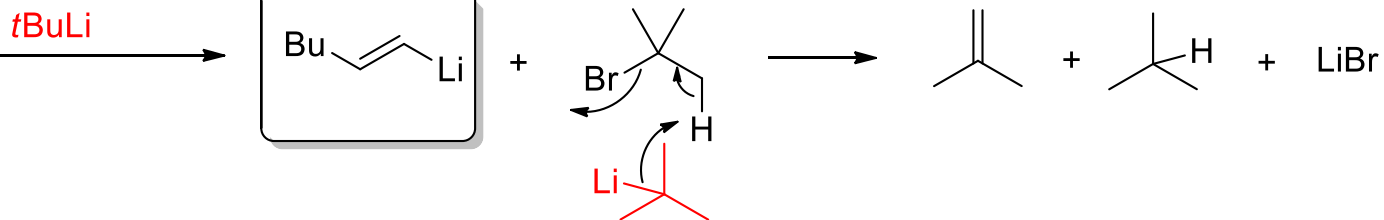
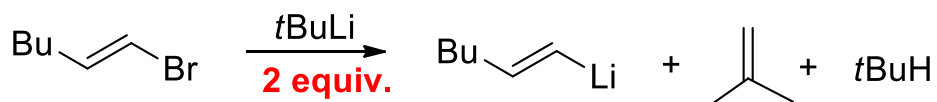
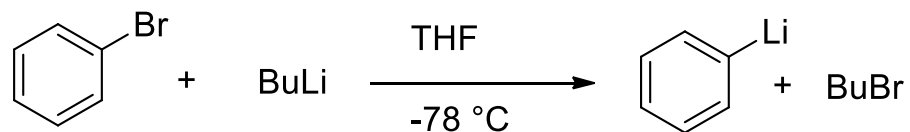


driving force: the most stable carbanion is always formed

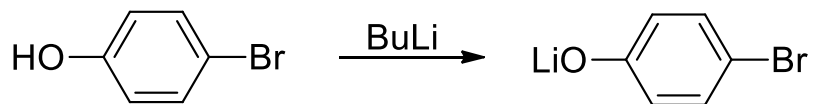


# The Halogen-Metal-Exchange

1939: the Wittig-Gilman reaction



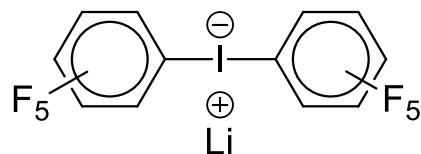
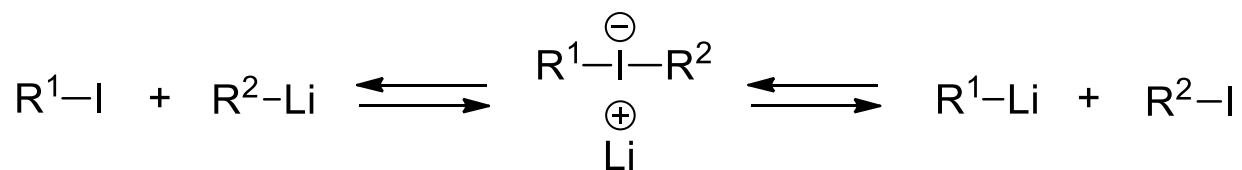
# The Halogen-Metal-Exchange



I >> Br >> Cl

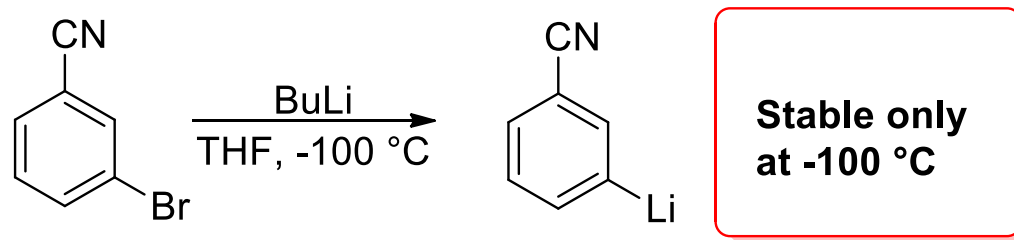
rate of the halogen/metal exchange

mechanism:

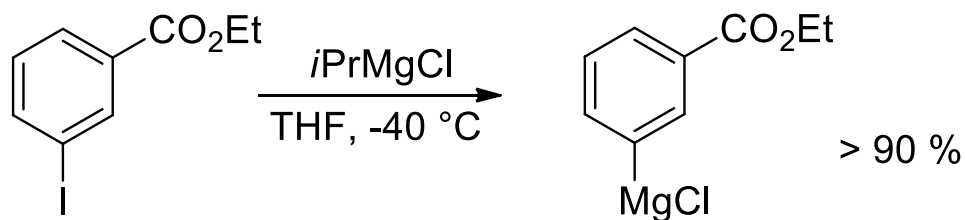


has been isolated

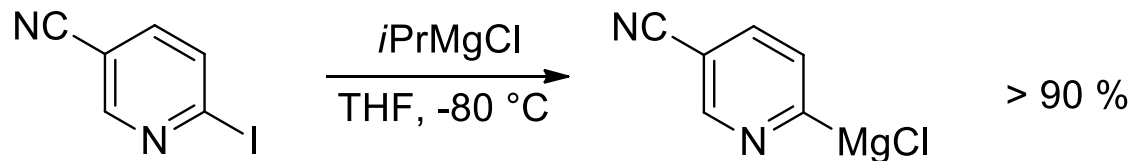
## The Halogen-Metal-Exchange : tolerance of functional groups



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

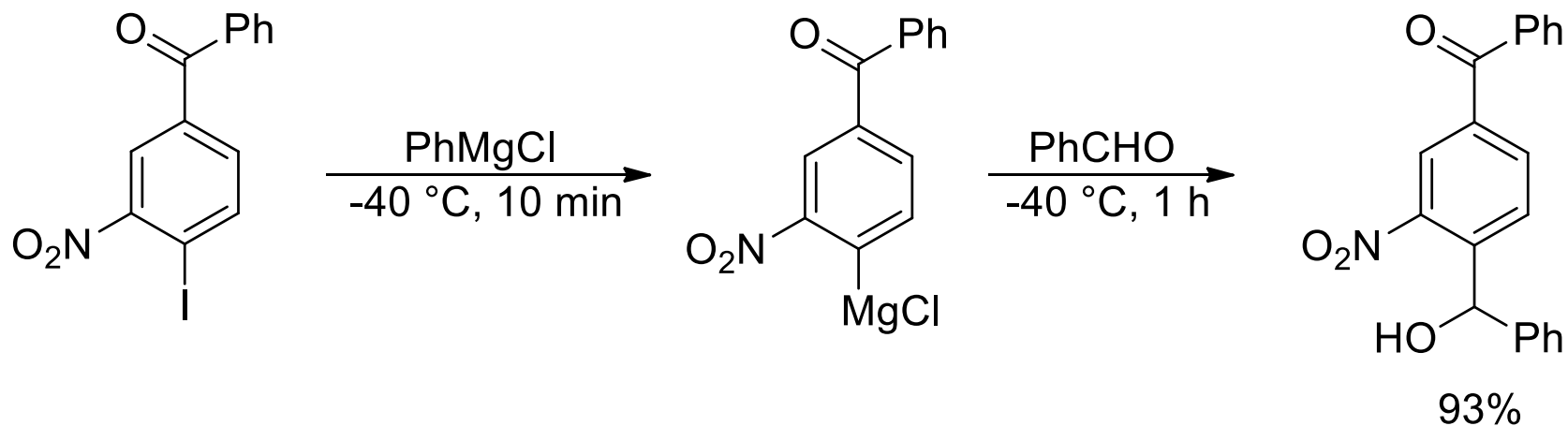


M. Rottländer, P. Knochel, Angew. Chem. Int. Ed. 1998, 40, 1801



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

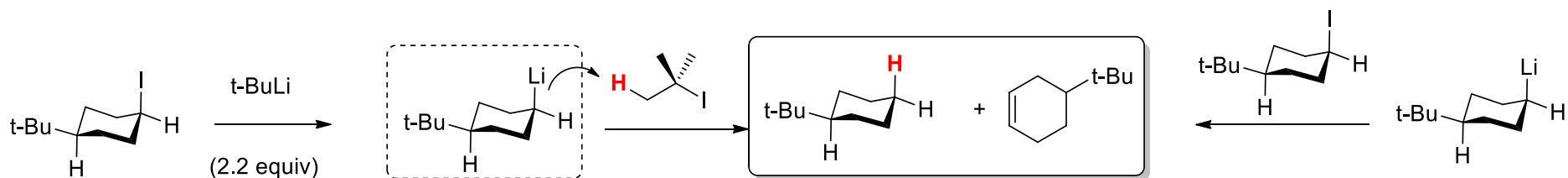
# The iodine- magnesium-exchange: compatibility with a nitro group



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



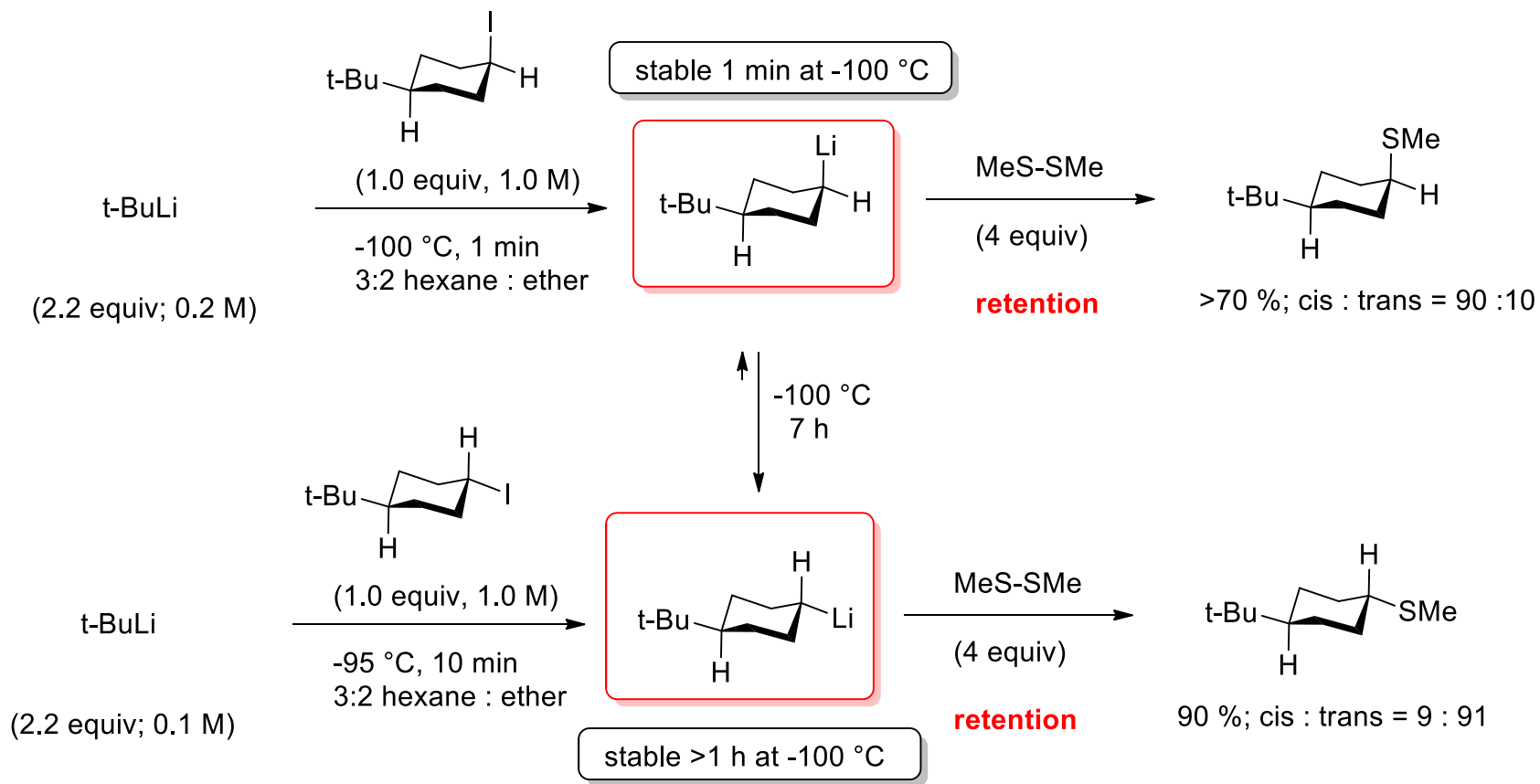
## A secondary iodine/lithium exchange on cyclohexyl iodides



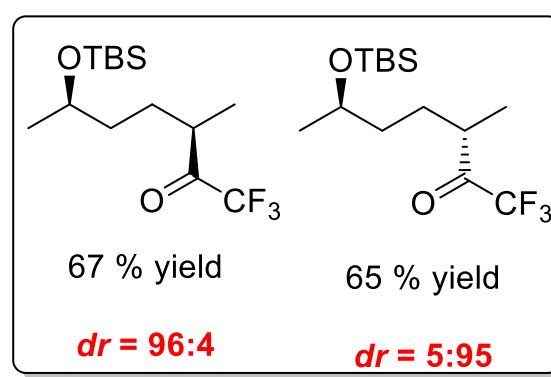
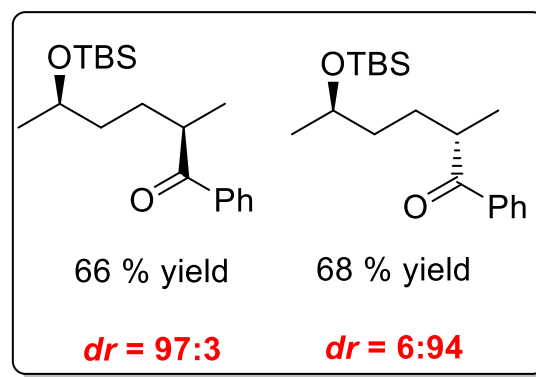
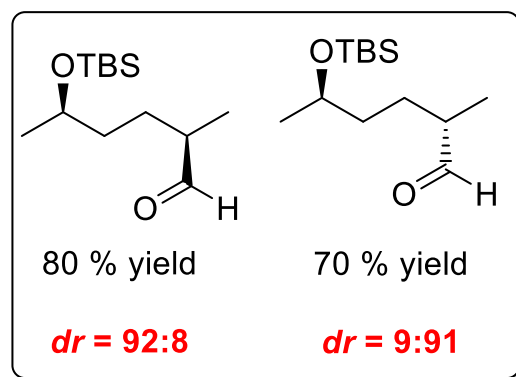
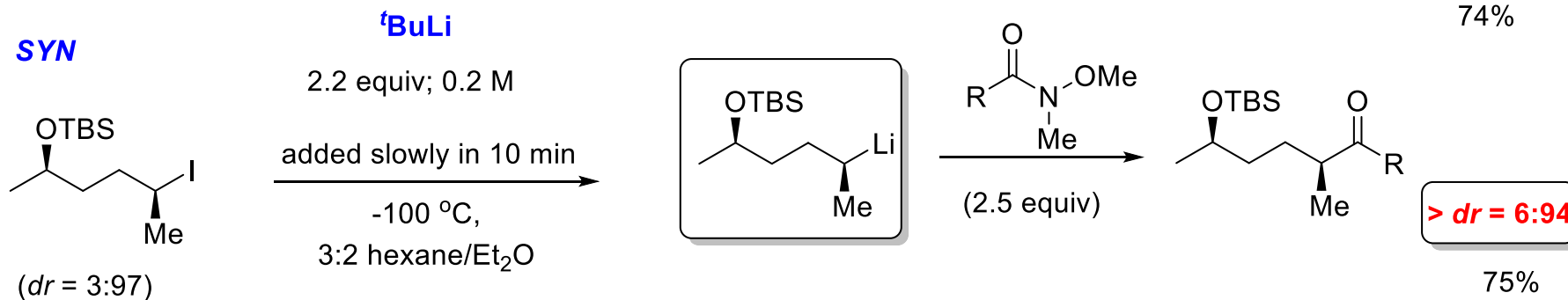
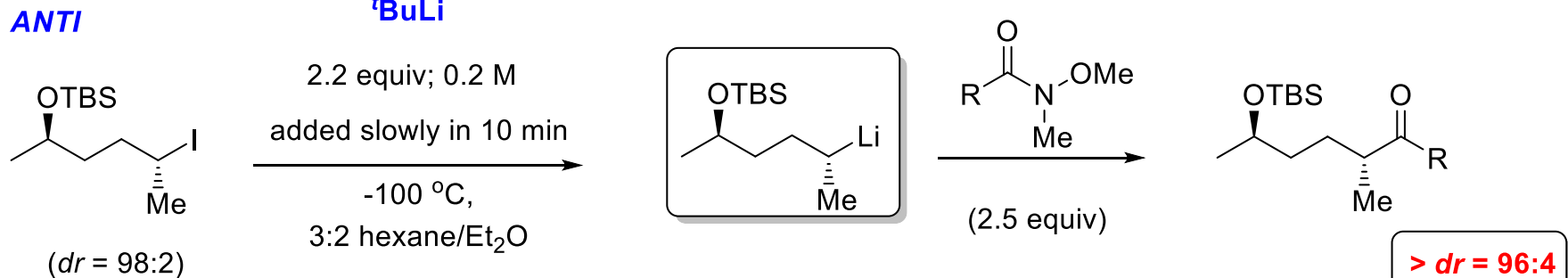
see W.F. Bailey, J.D. Brubaker, K.P. Jordan, *J. Organomet. Chem.* **2003**, 681, 210

Stephanie SEEL

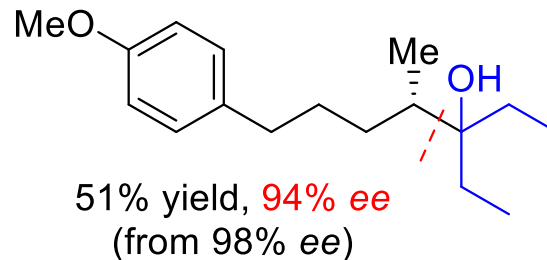
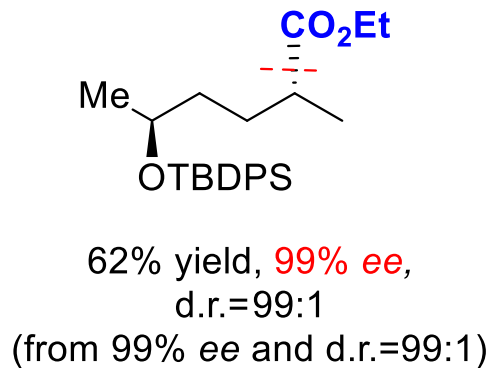
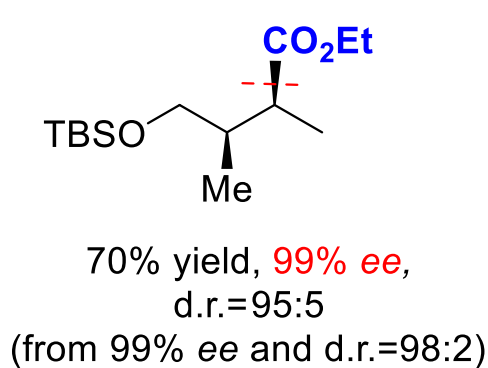
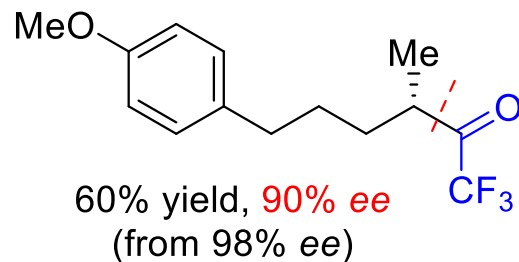
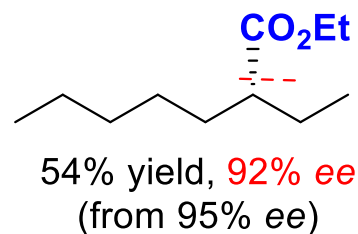
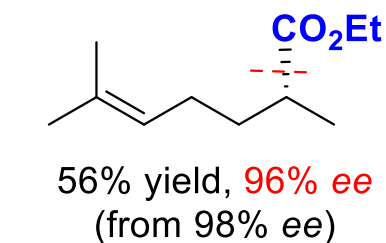
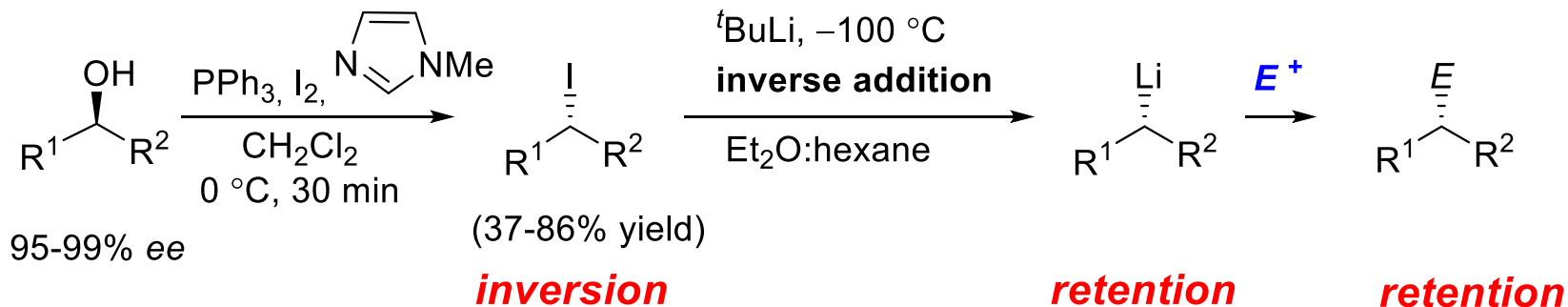
## A secondary iodine/lithium exchange on cyclohexyl iodides



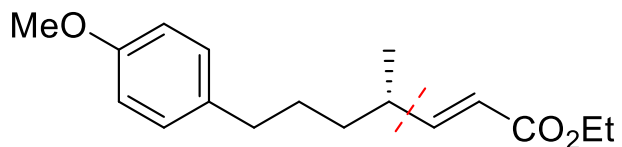
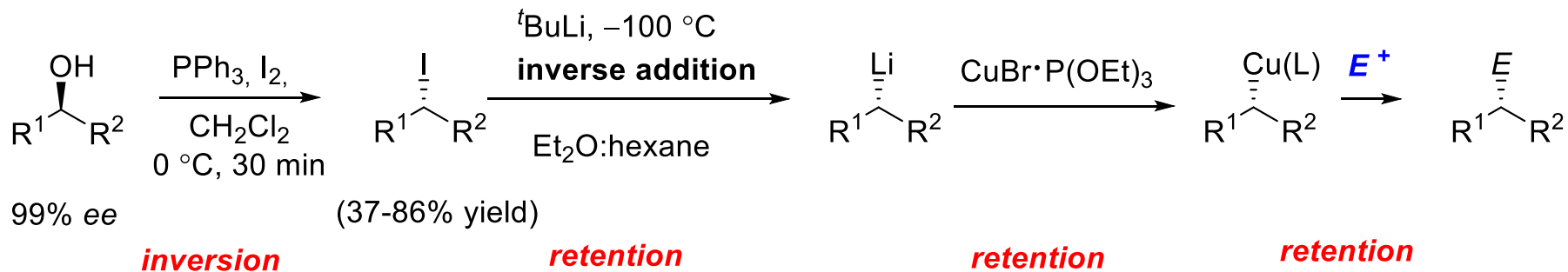
# Stereoselective I/Li -exchange and acylations



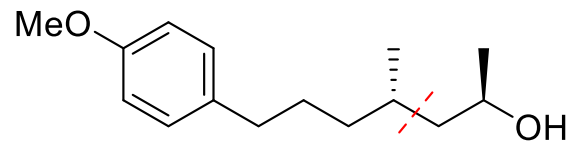
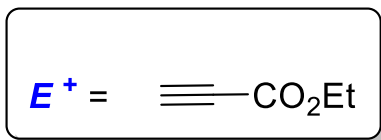
# Enantiomerically enriched secondary alkyllithium reagents



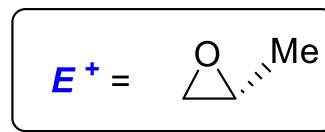
# Enantiomerically enriched secondary alkylcopper reagents



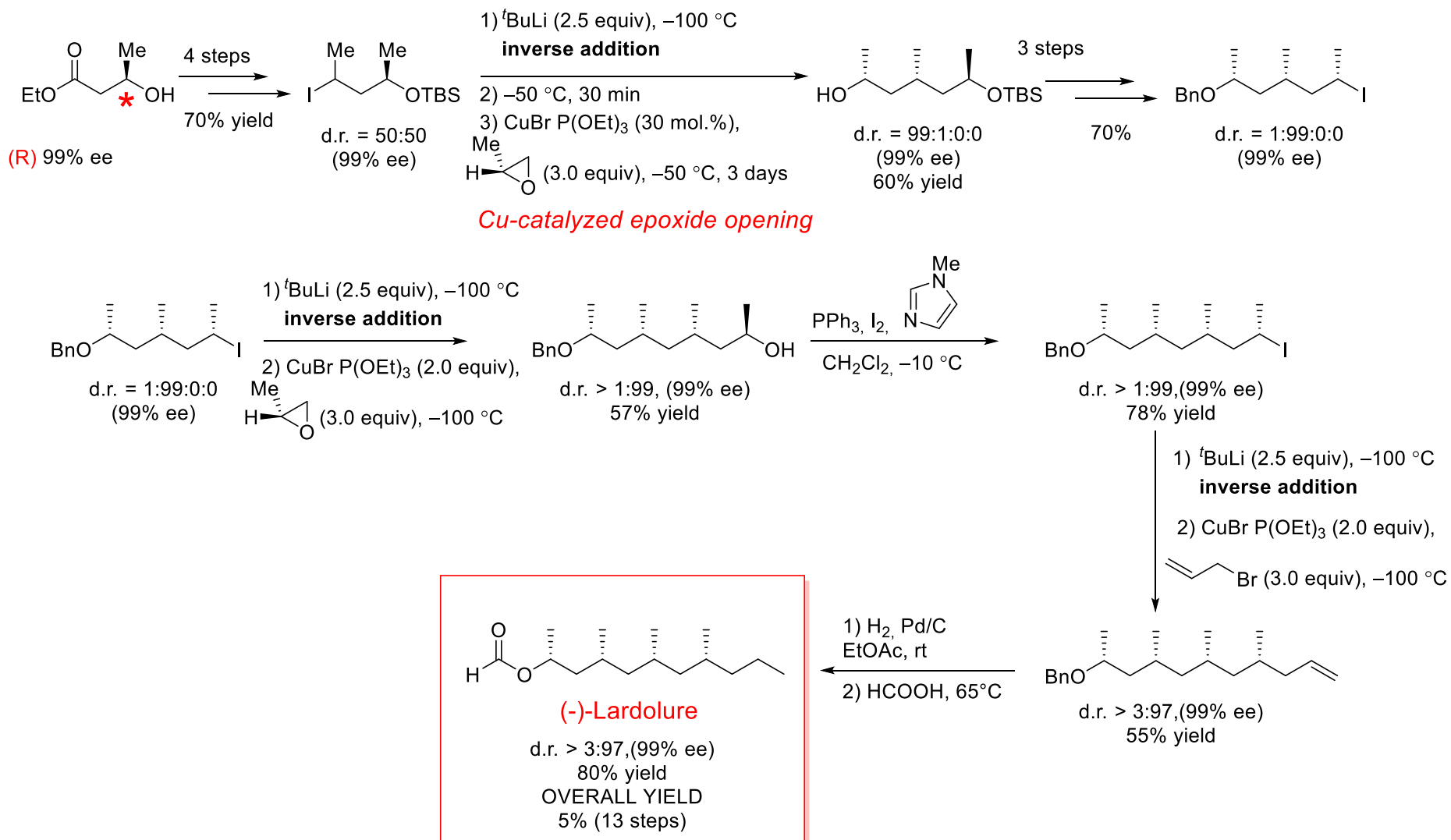
47% yield, **92% ee**



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

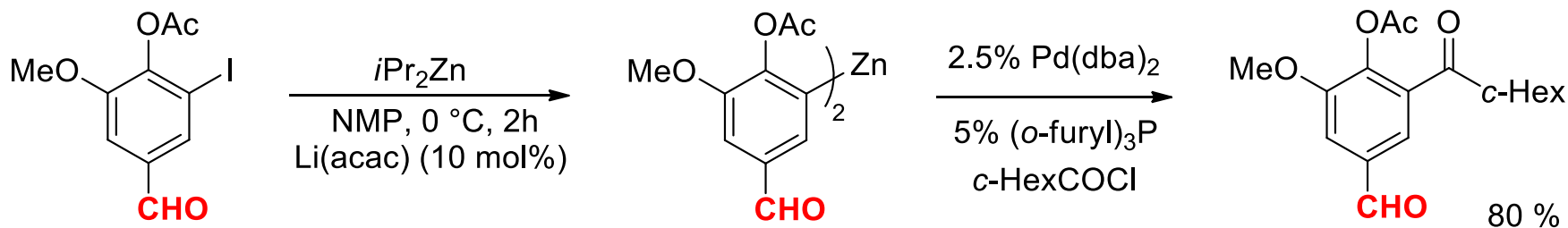
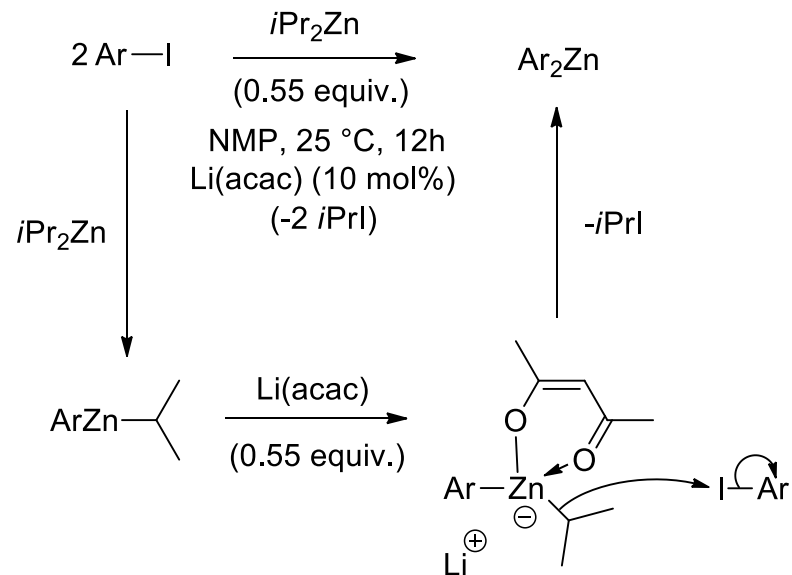


# Synthesis of (-)-lardolure using enantiomerically enriched Li- and Cu-reagents



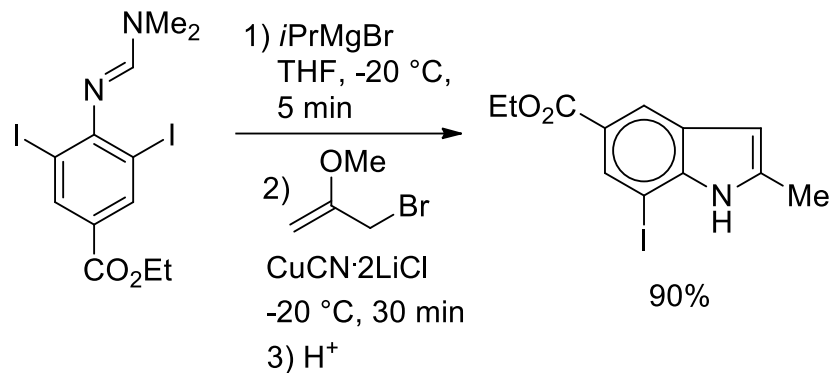
# The iodine/zinc-exchange

catalysis of the halogen-metal exchange

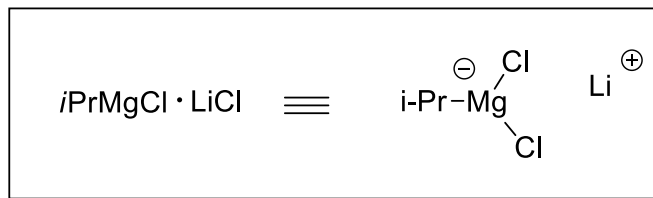
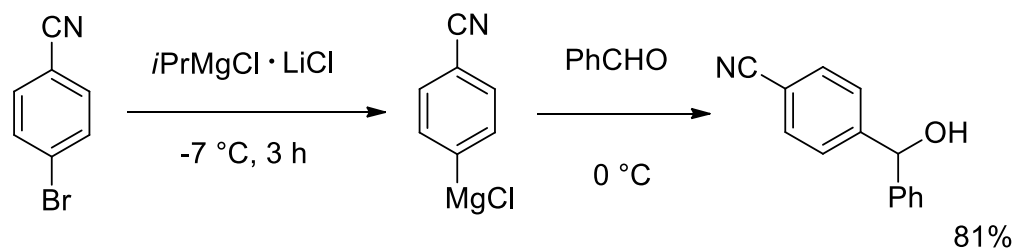


# The Halogen-Metal-Exchange

indole-synthesis



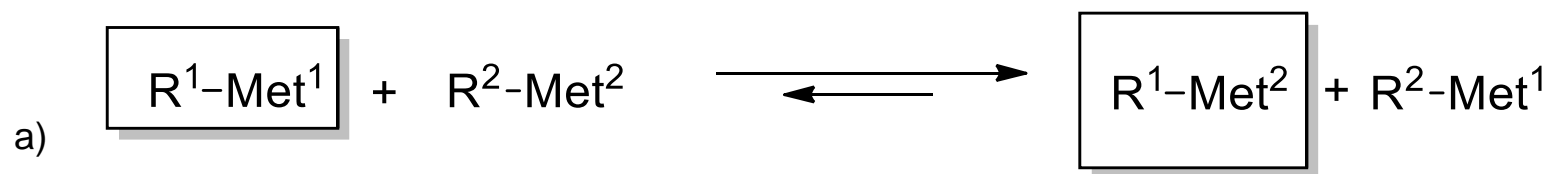
D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp, P. Knochel *Org. Lett.*, **2002**, 4, 1819



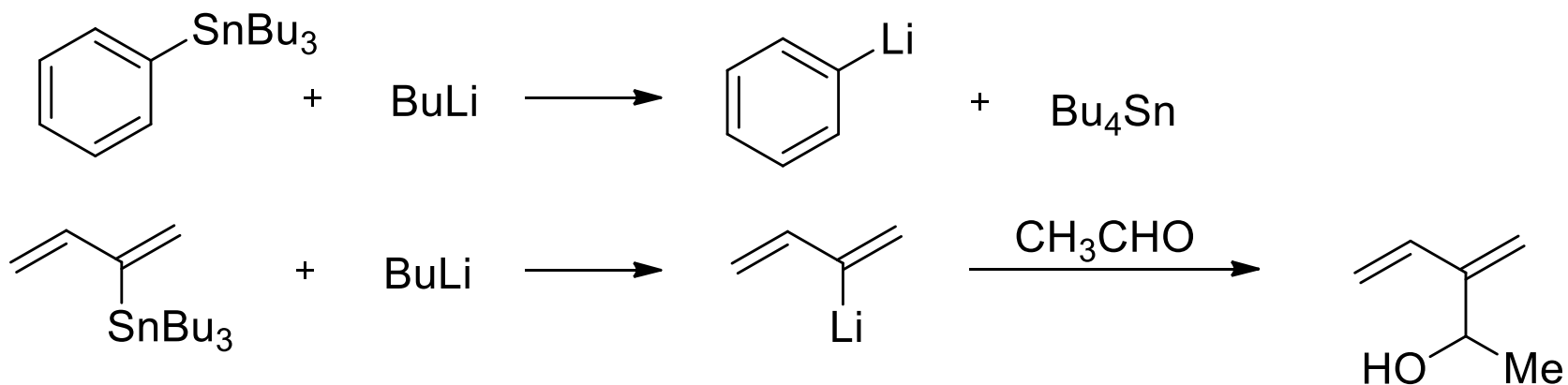
A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2004**, 43, 3333



# Transmetalation



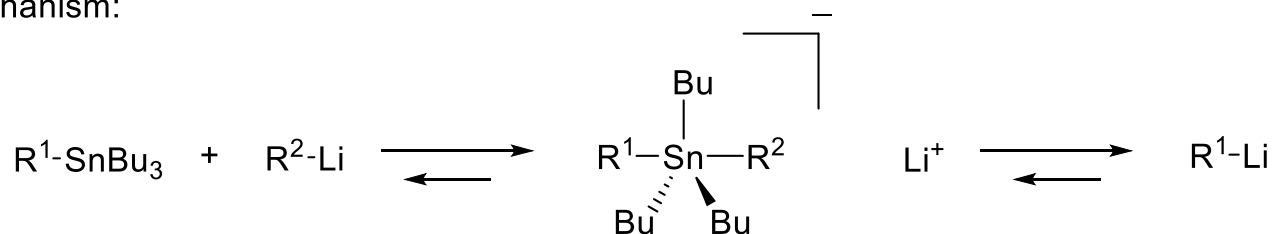
the most stable carbanion is linked to the most electropositive metal



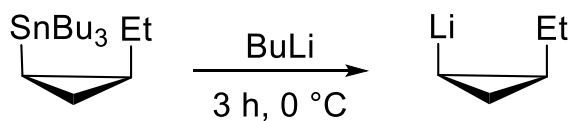
# Transmetalation



mechanism:



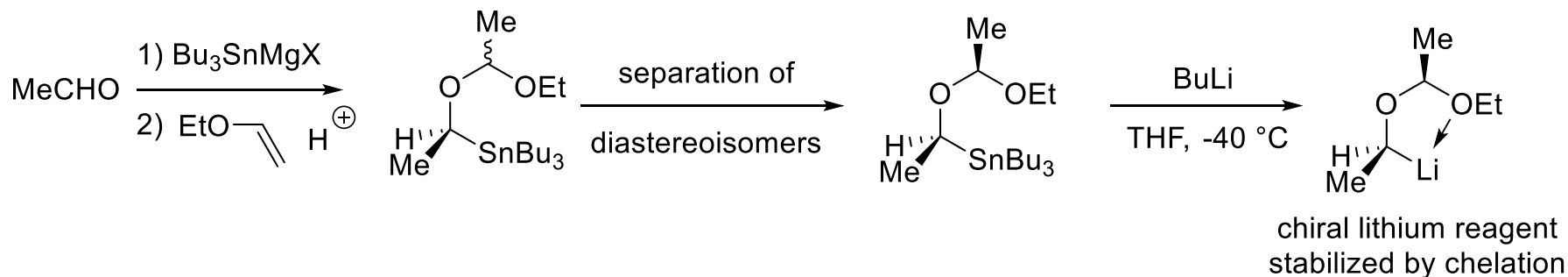
*the most stable Li-organometallic is formed*



*configurational stable*

*Li-reagent due to the ring strain*

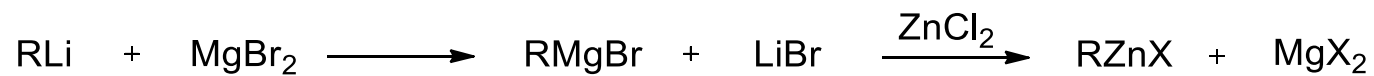
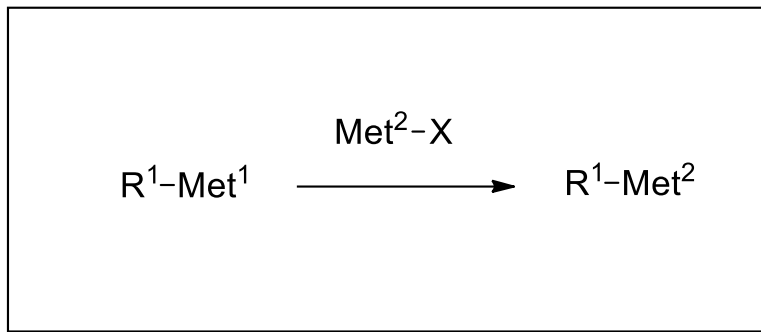
E. J. Corey *Tetrahedron Lett.* **1984**, 25, 2415.



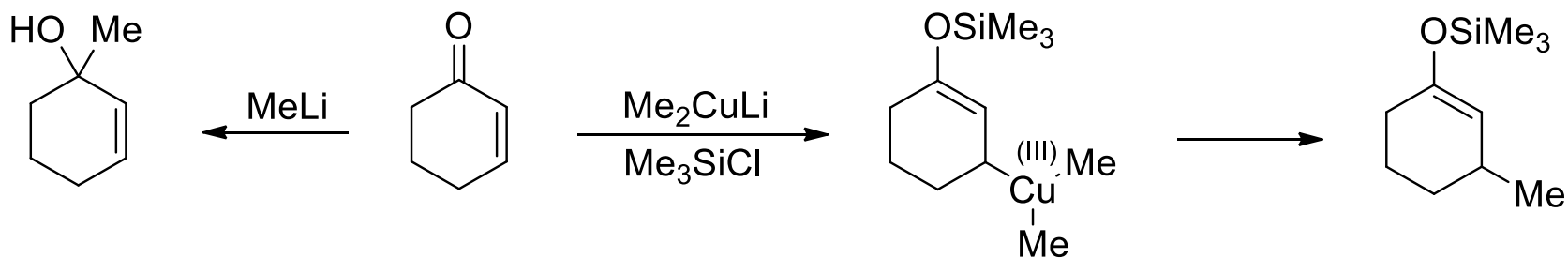
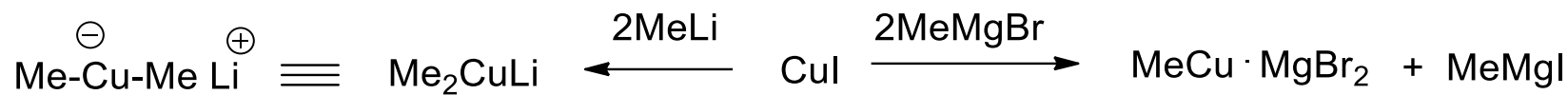
W. C. Still, *J. Am. Chem. Soc.* **1980**, 102, 1201.

# Transmetalation

b)

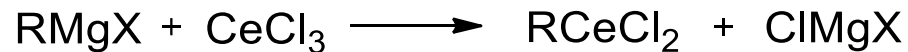


# Transmetalation

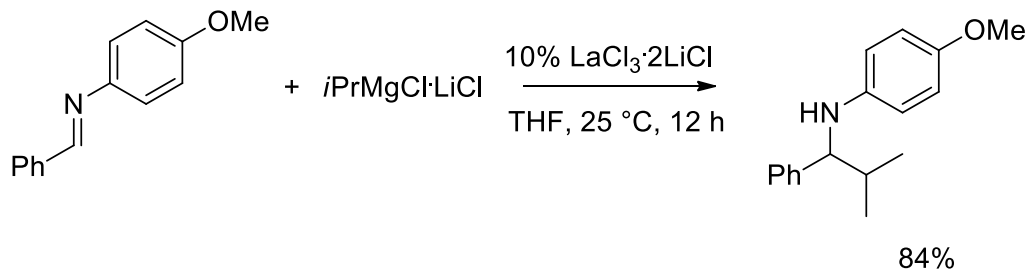
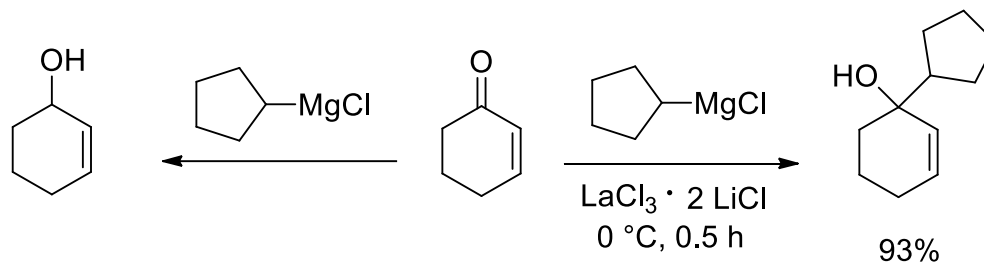
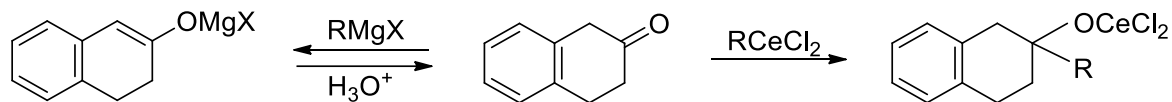


E. Nakamura, I. Kuwajima *J. Am. Chem. Soc.* **1984**, *106*, 3368

# Transmetalation

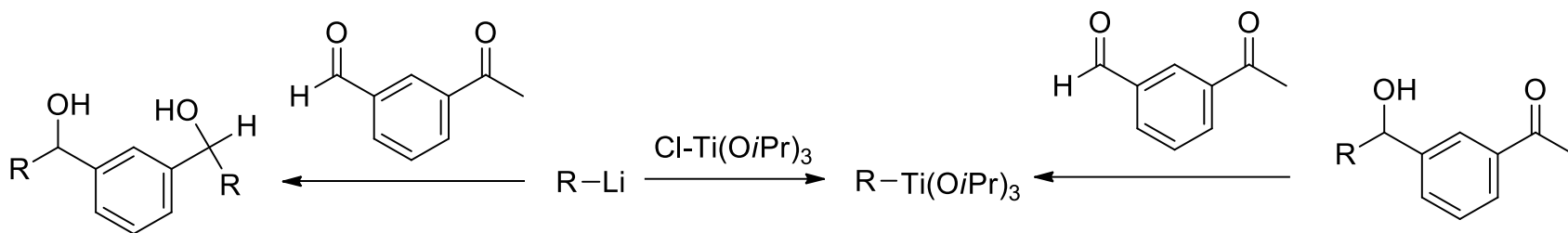


T. Imamoto, Y. Sugiyura, N. Takiyama, *Tetrahedron Lett.* **1984**, 25, 4233

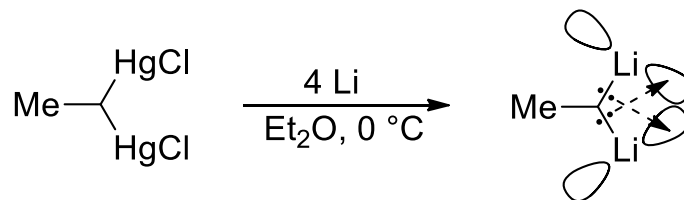


A. Krasovskiy, F. Kopp, P. Knochel *Angew. Chem. Int. Ed.* **2006**, 45, 497

# Transmetalation



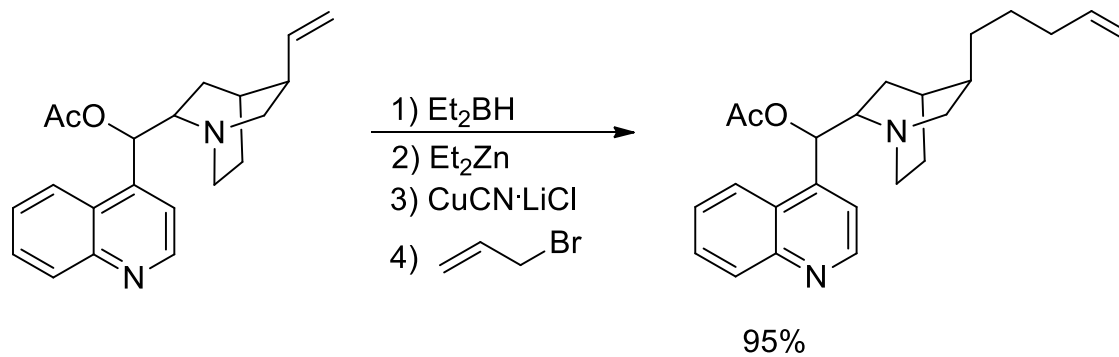
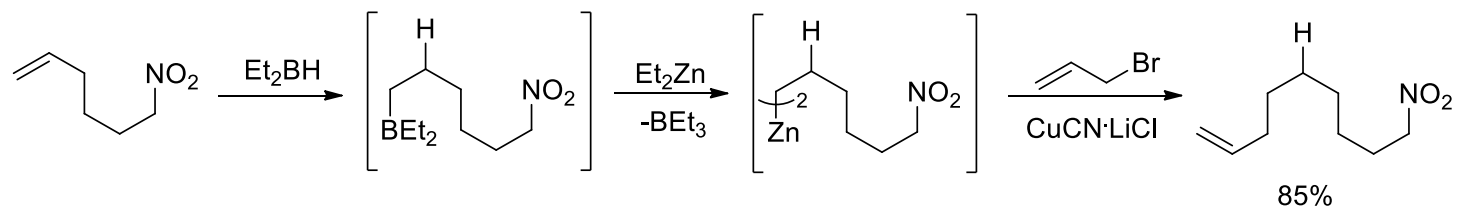
M. Reetz, D. Seebach *Angew. Chem.* **1983**, 95, 12



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

# Transmetalation

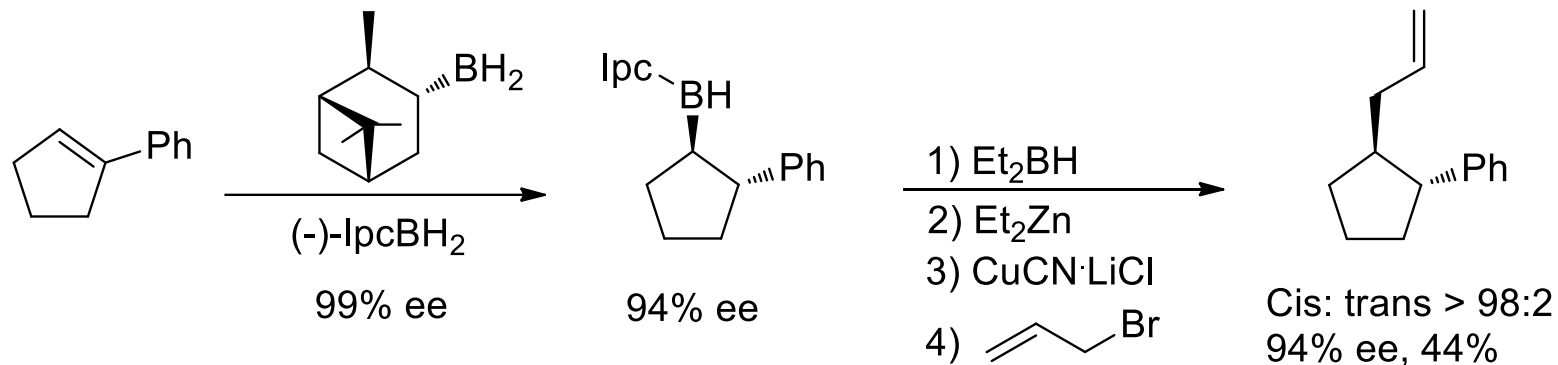
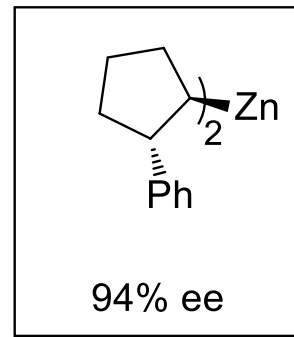
boron / zinc-exchange



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

# Transmetalation

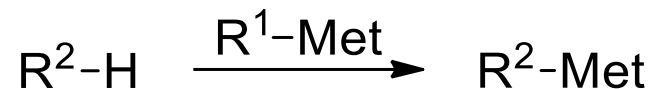
boron / zinc-exchange



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



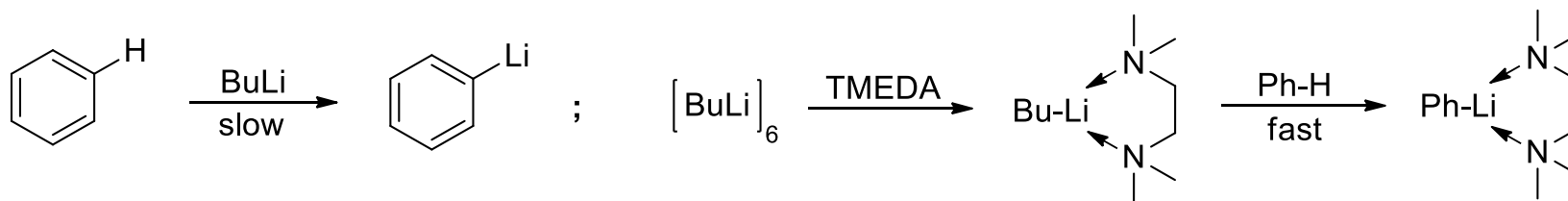
## Metalation (starting from a compound with an acid proton)



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

$R^1-Met$  : *t*-BuOK, LDA, BuLi, ...

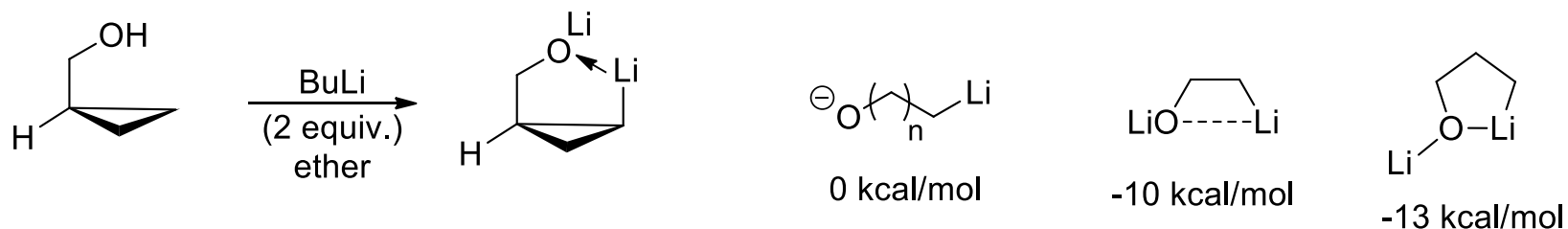
kinetic criteria (kinetic acidity)



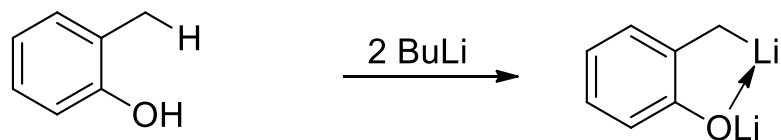
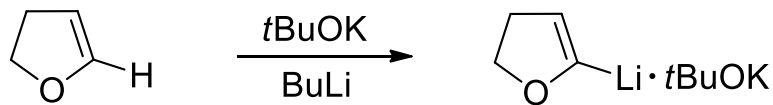
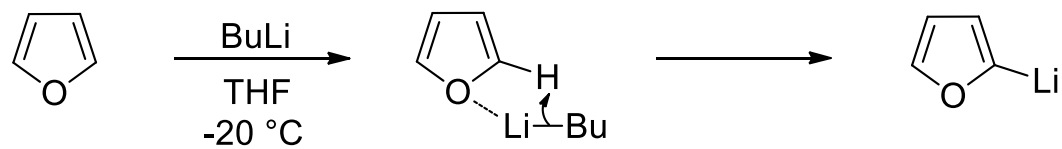
PhCH<sub>2</sub>Li reacts with benzene 10<sup>4</sup> times faster than with MeLi

PhCH<sub>2</sub>Li is a monomer in THF, MeLi a tetramer

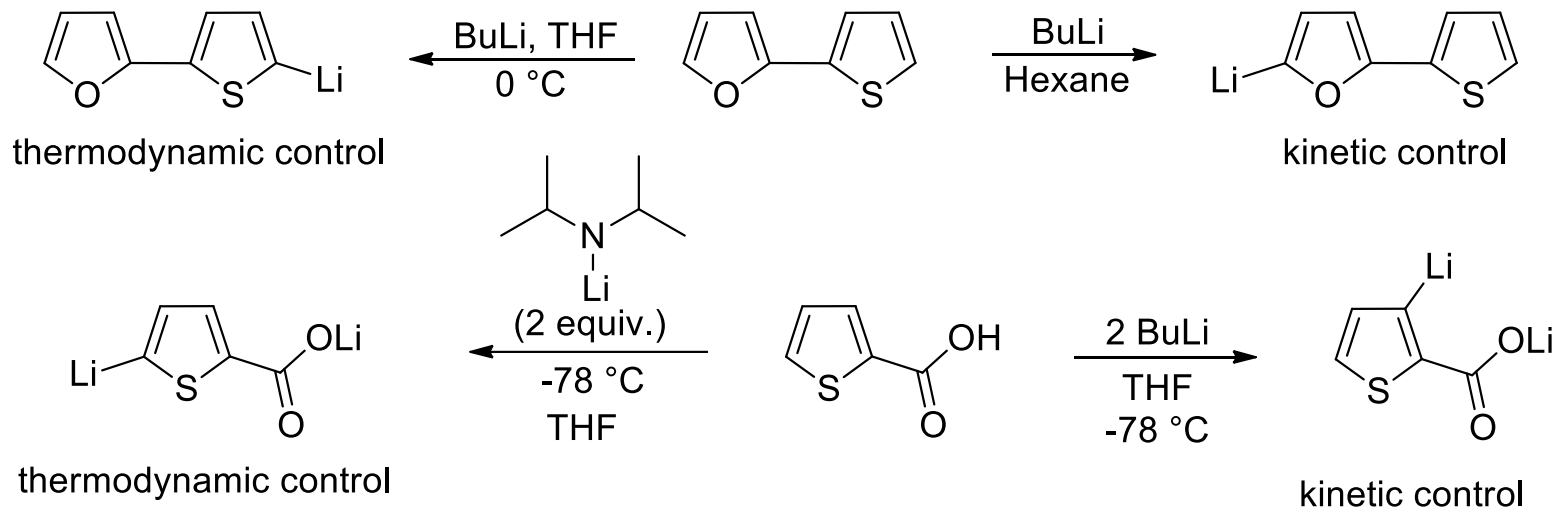
## Directed metalation



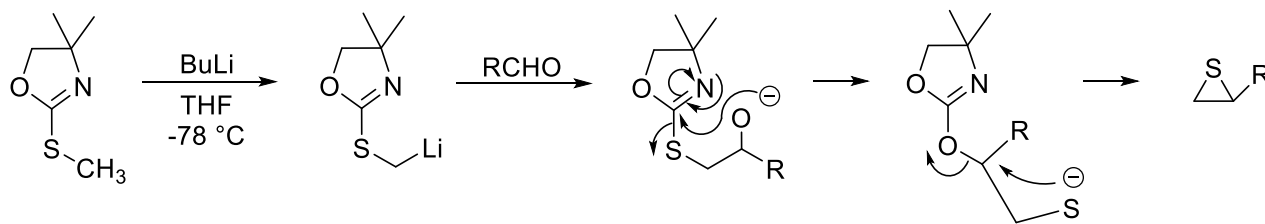
## Directed metalation



# Metalation

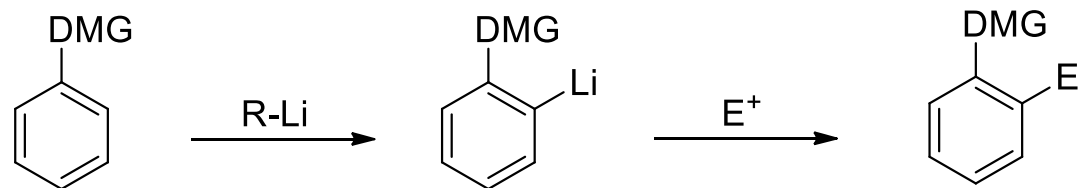


A rearrangement may occur :



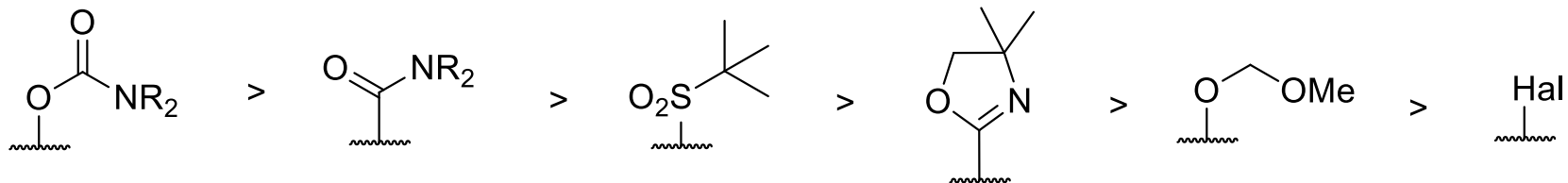
# Metalation

directed lithiation



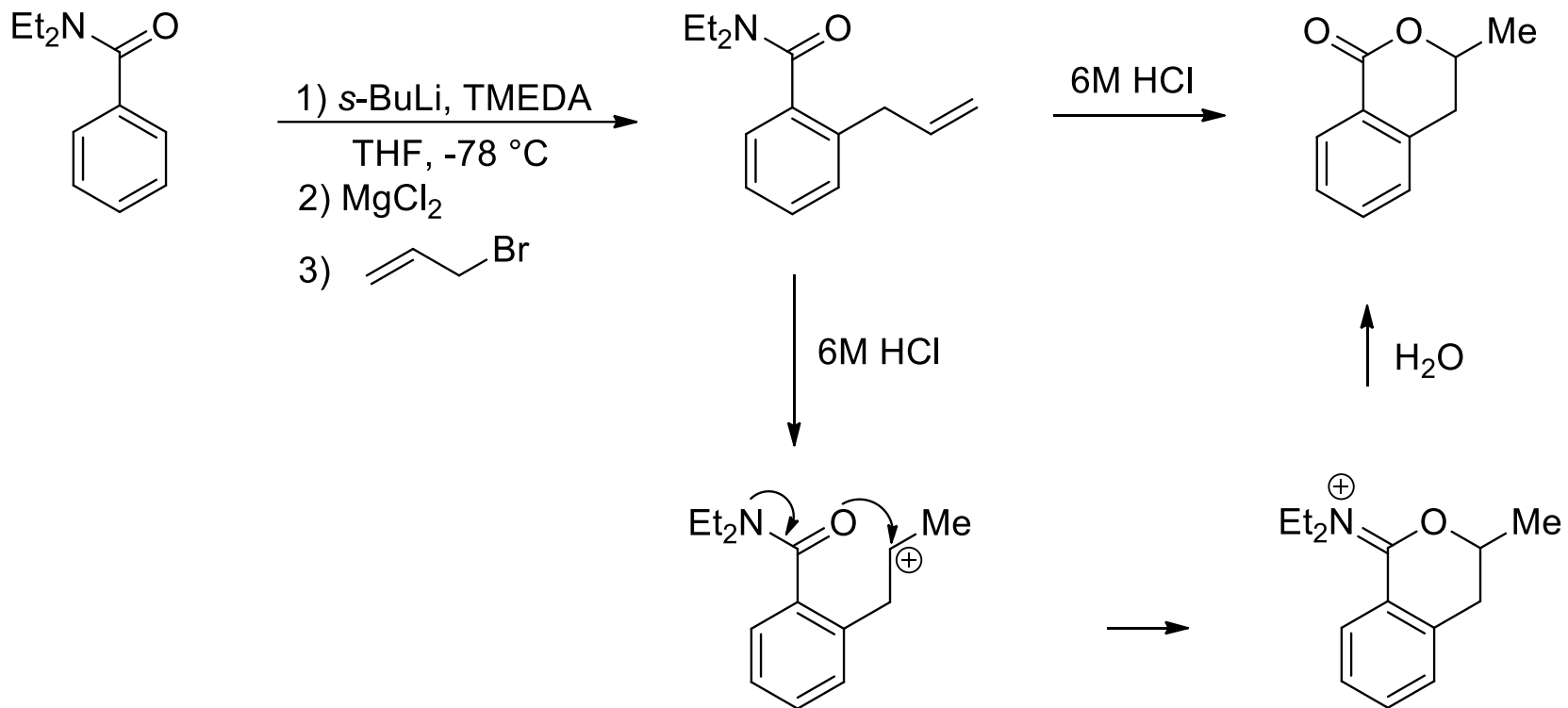
DMG = directing metalating group

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

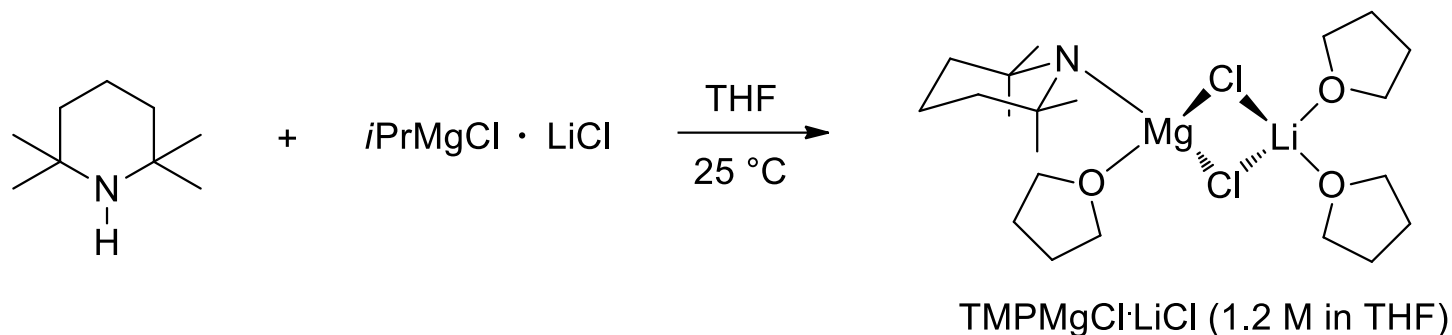


P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206

## Metalation

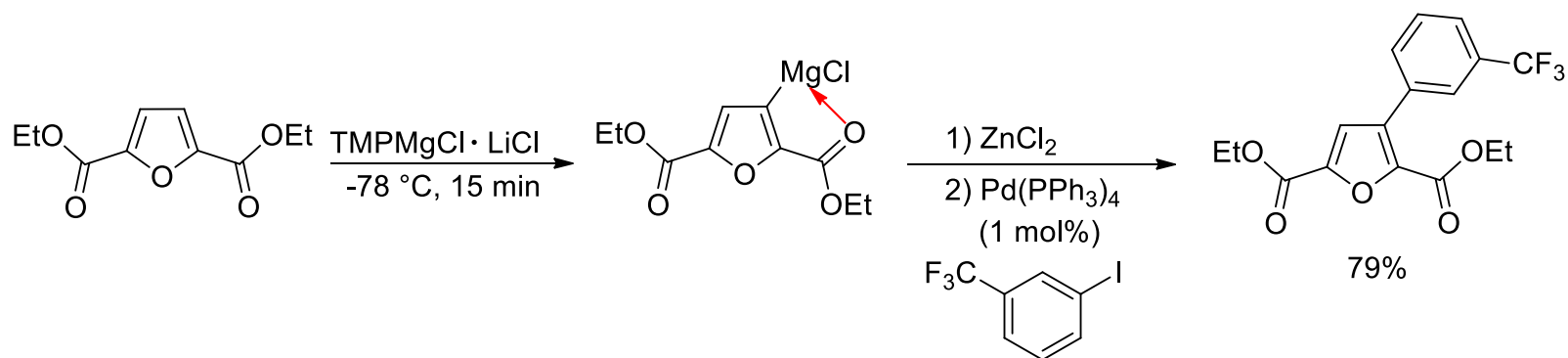


## Metalation

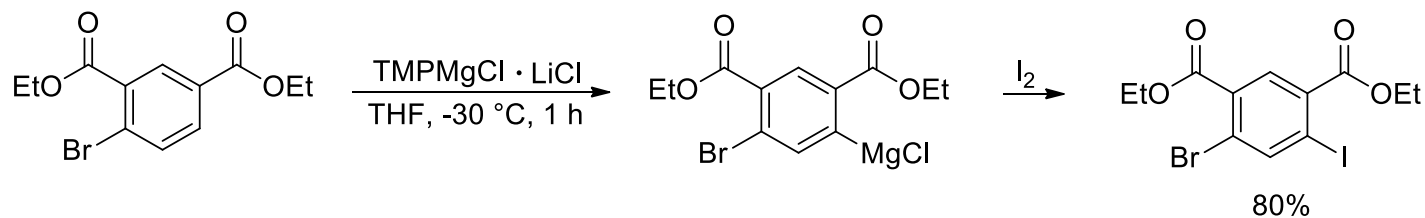


A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 2958

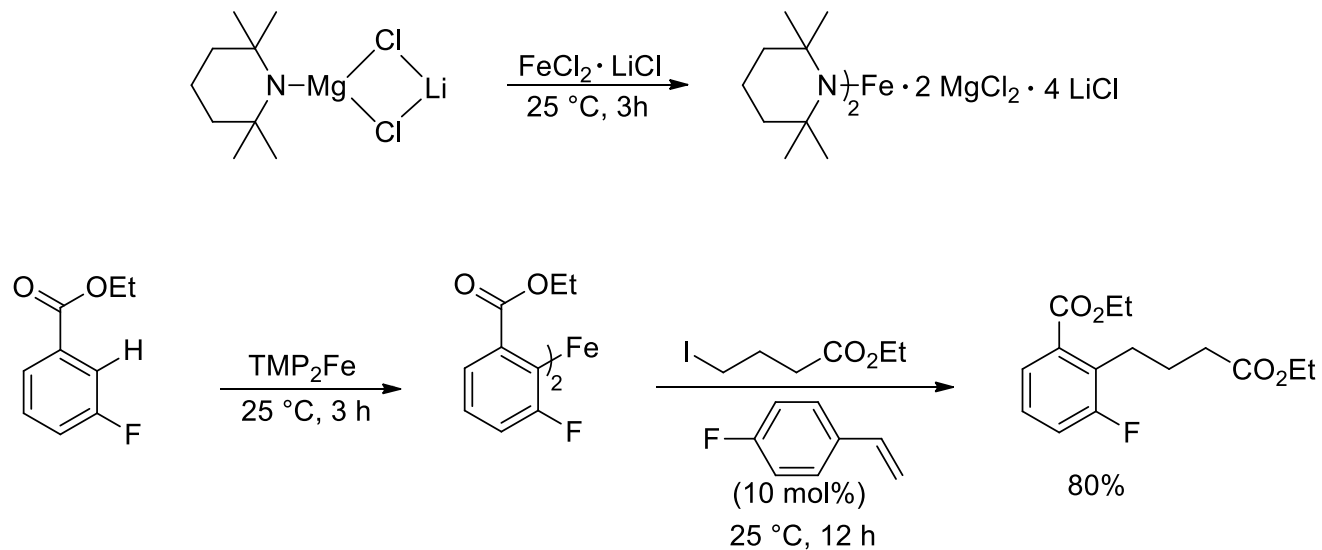
R. E. Mulvey, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079



## Metalation

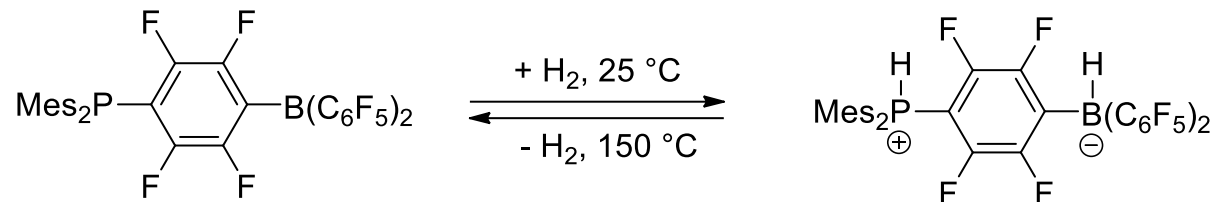


O. Baron, P. Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 2958

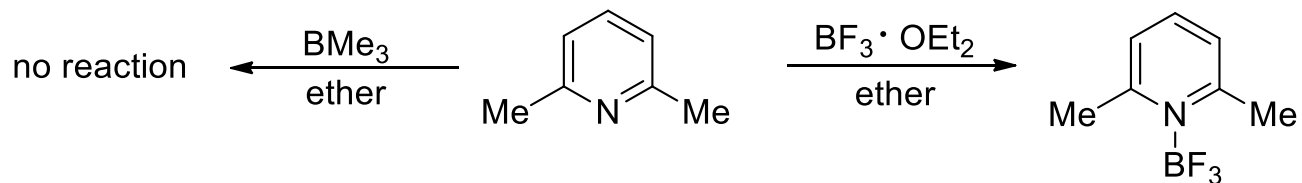


S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed.* **2009**, *48*, 9717

# Frustrated Lewis Pairs



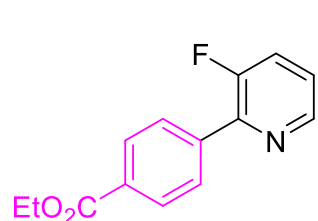
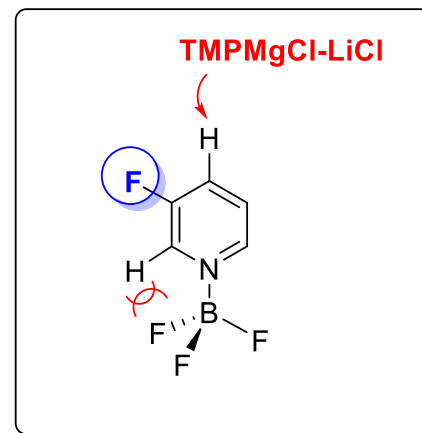
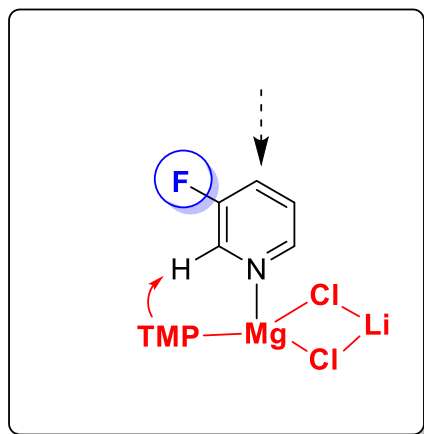
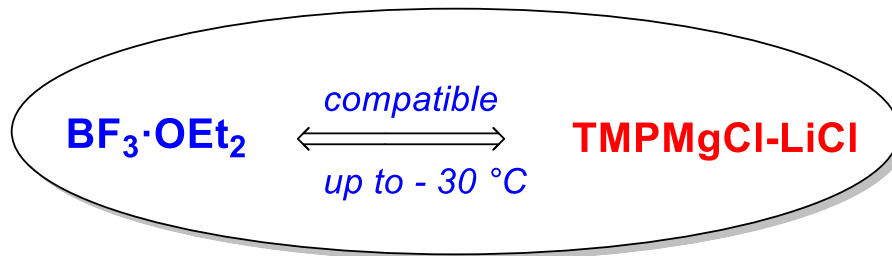
D. Stefan, G. Erker *Angew. Chem. Int. Ed.* **2010**, 49, 46



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

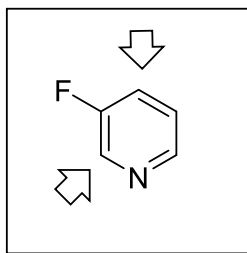


# BF<sub>3</sub>-triggered selective metalations

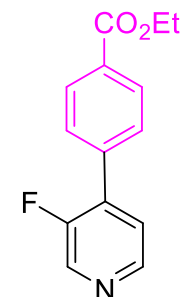


72 %

- 1) **TMPMgCl·LiCl**,  
-78 °C, 30 min
- 2) ZnCl<sub>2</sub>, **Ar-I**,  
5% Pd(dba)<sub>2</sub>,  
10% P(o-furyl)<sub>3</sub>,  
25 °C, 12 h

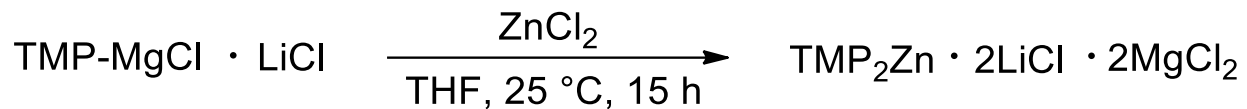


- 1) **BF<sub>3</sub>·OEt<sub>2</sub>**,  
0 °C, 15 min
- 2) **TMPMgCl·LiCl**,  
-78 °C, 30 min
- 3) ZnCl<sub>2</sub>, **Ar-I**,  
5% Pd(dba)<sub>2</sub>,  
10% P(o-furyl)<sub>3</sub>,  
25 °C, 12 h

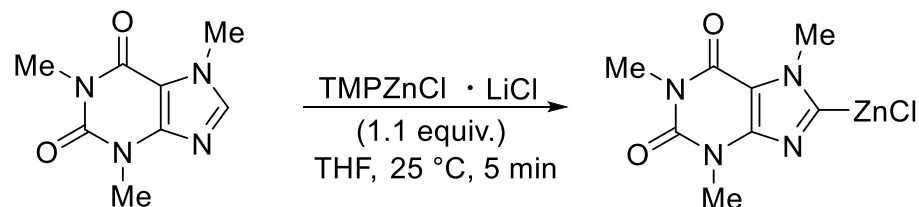
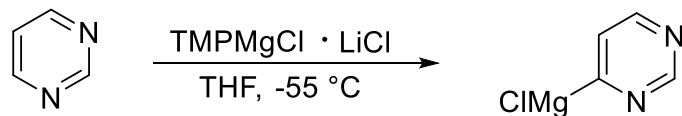
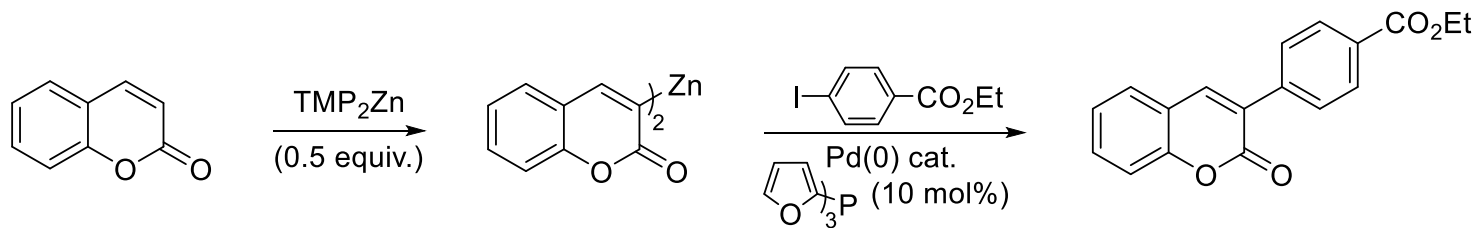


74 %

# Metalation



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

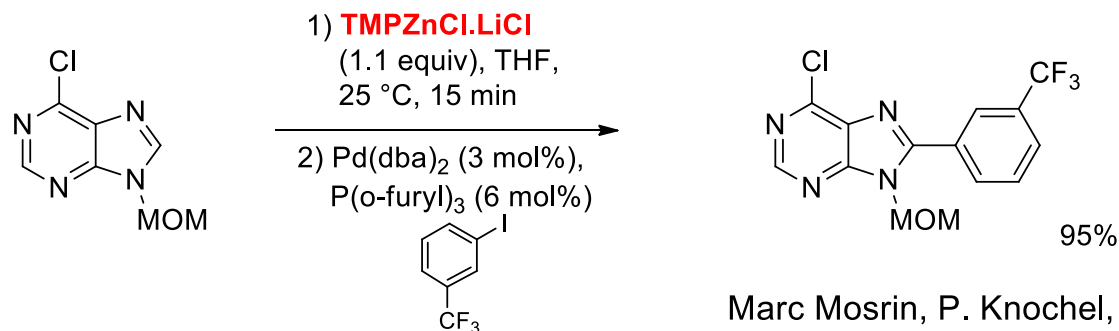
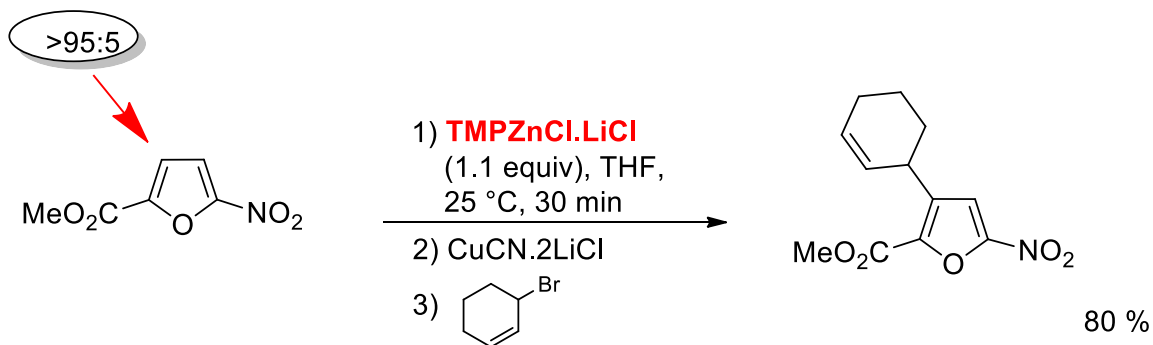


M. Mosrin, P. Knochel *Org. Lett.* **2008**, 10, 2497

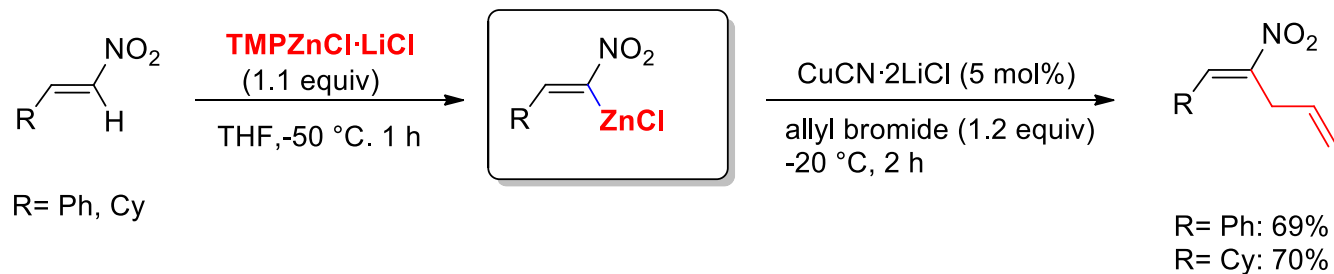
M. Mosrin, P. Knochel *Chem. Eur. J.* **2009**, 15, 1468

M. Mosrin, P. Knochel *Org. Lett.* **2009**, 11, 1837

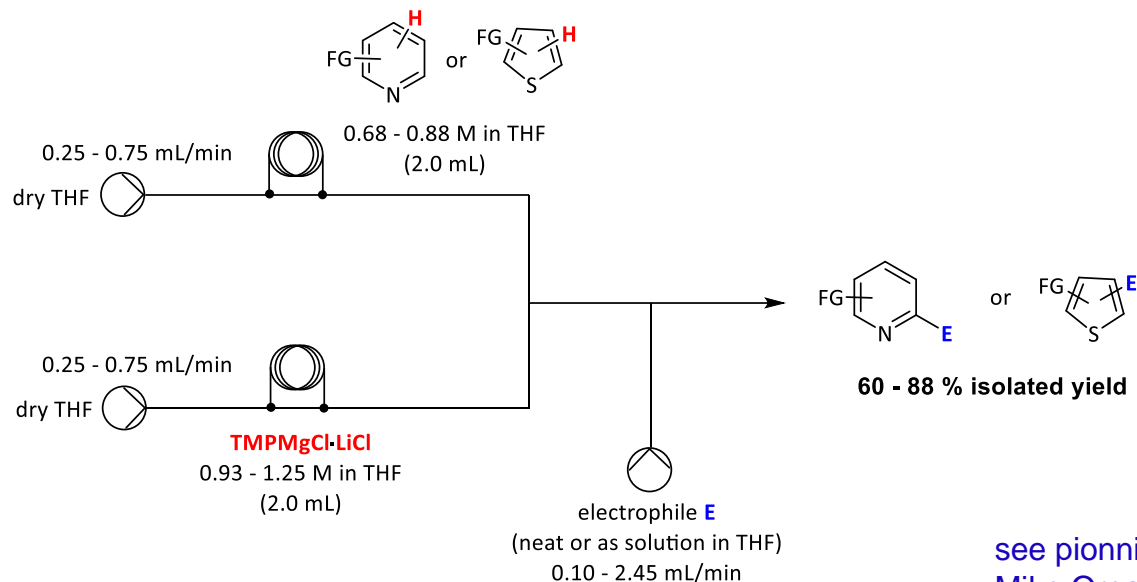
# Zincations in the presence of ester and nitro groups



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



# Metalations under batch and flow conditions using TMPMgCl-LiCl

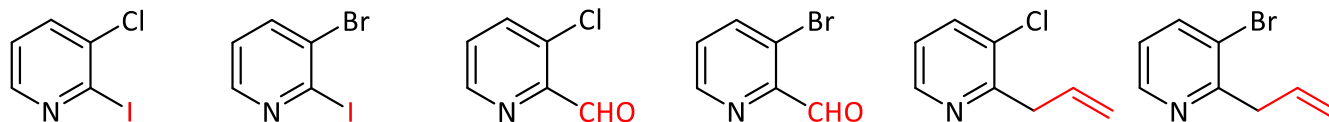


see pionnier contributions of  
Mike Organ, Jun-ichi Yoshida, Steven V. Ley

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

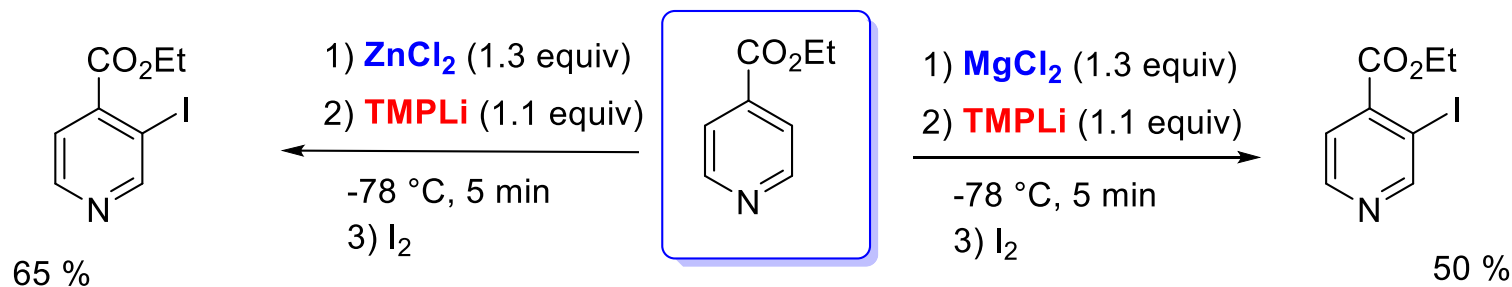
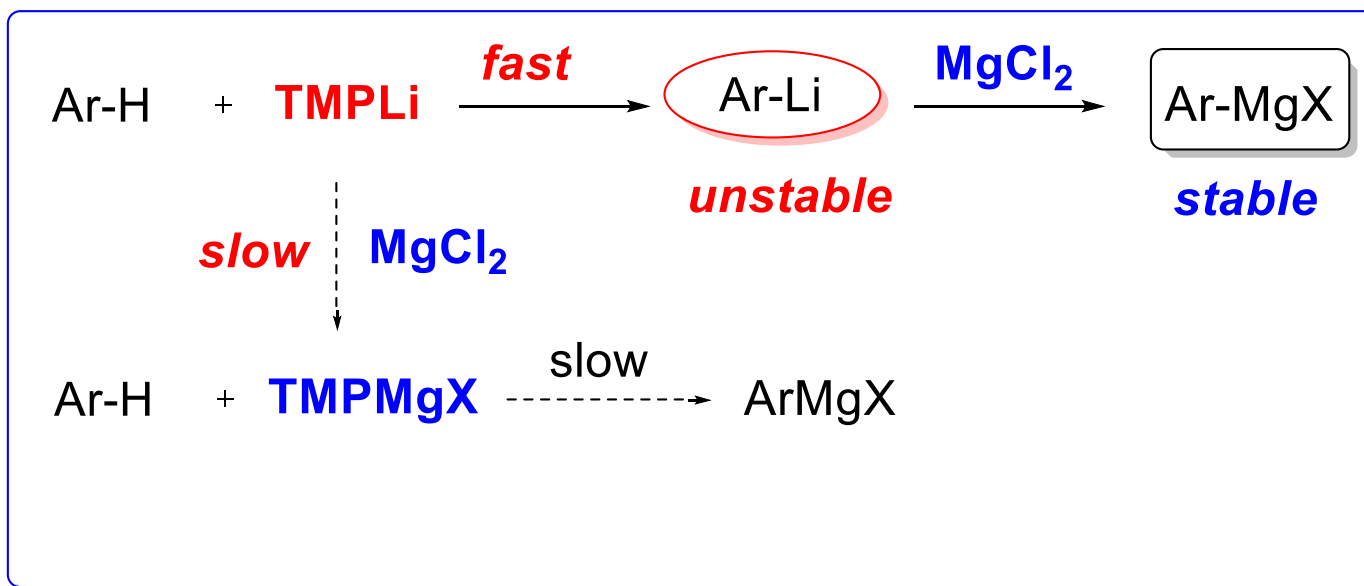
**Batch conditions:** Complete metalation of 3-chloropyridine after **45 min at -78 °C**

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

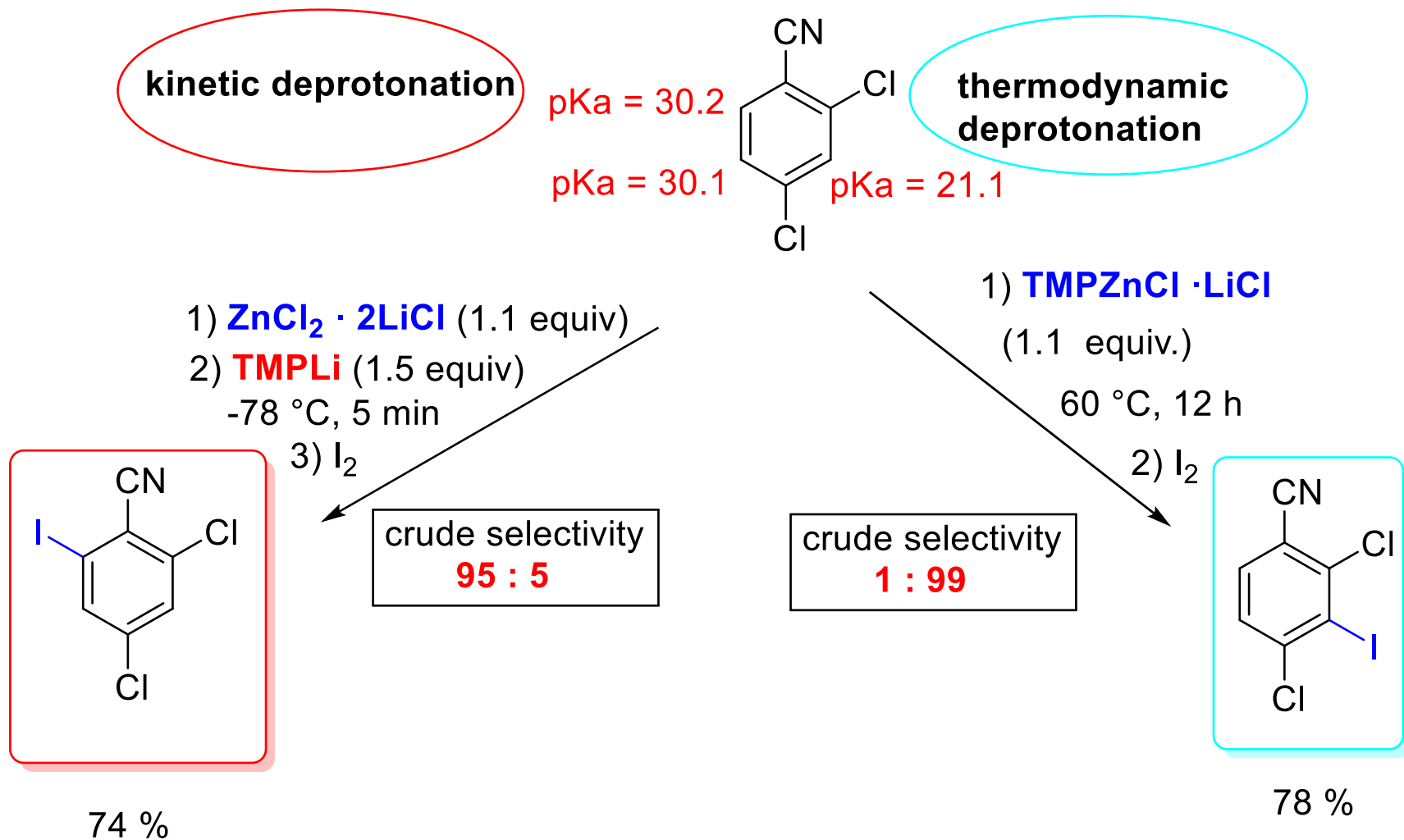


Electrophile	$I_2$ (1.1 equiv.)	DMF (6.0 equiv.)	Allyl bromide (1.2 equiv.) with 3 mol% $CuCN \cdot 2LiCl$
Metalation time	60 s	60 s	60 s
Isolated yield	<b>66%</b>	<b>71%</b>	<b>78%</b>

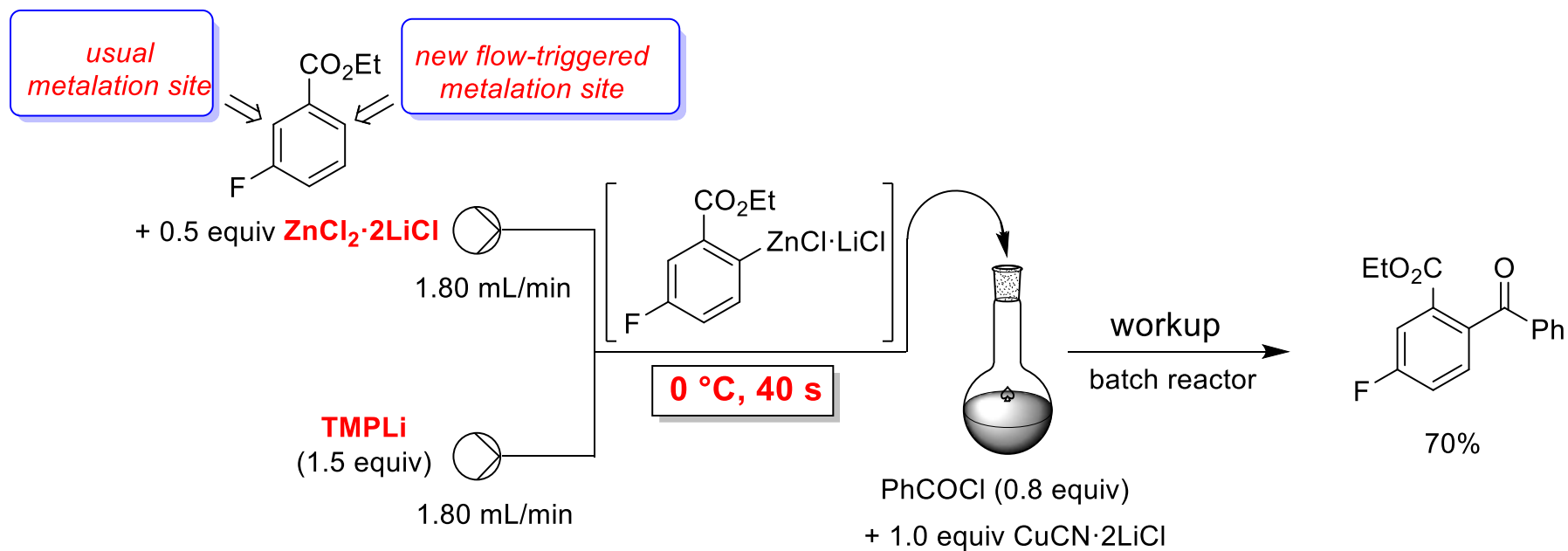
## Compatibility of the TMPLi with ZnCl<sub>2</sub> or MgCl<sub>2</sub>



# Selectivity switch with (TMPLi and ZnCl<sub>2</sub>) or TMPZnCl-LiCl

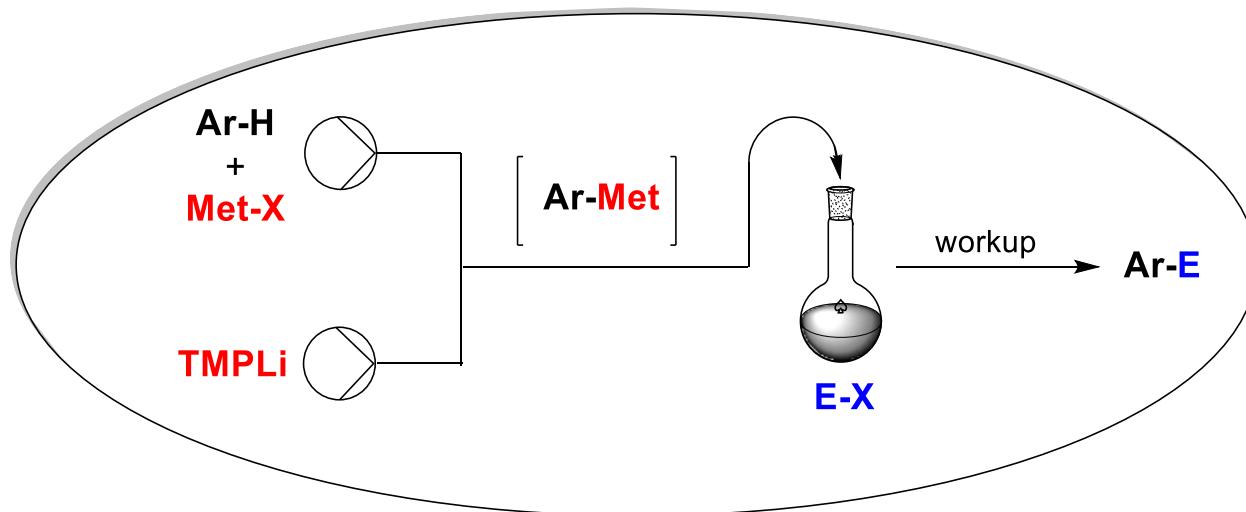


# "*in situ*"-Trapping Metalations with Metal Salts in Flow Mode

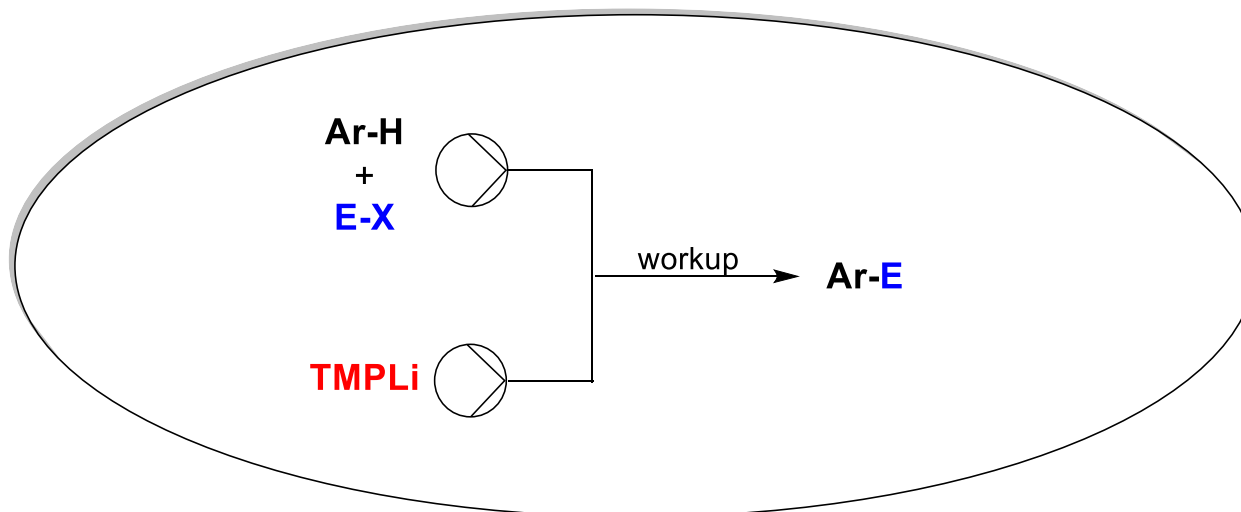


M. R. Becker, P. Knochel, *Angew.Chem.Int. Ed.* **2015**, 54, in press

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

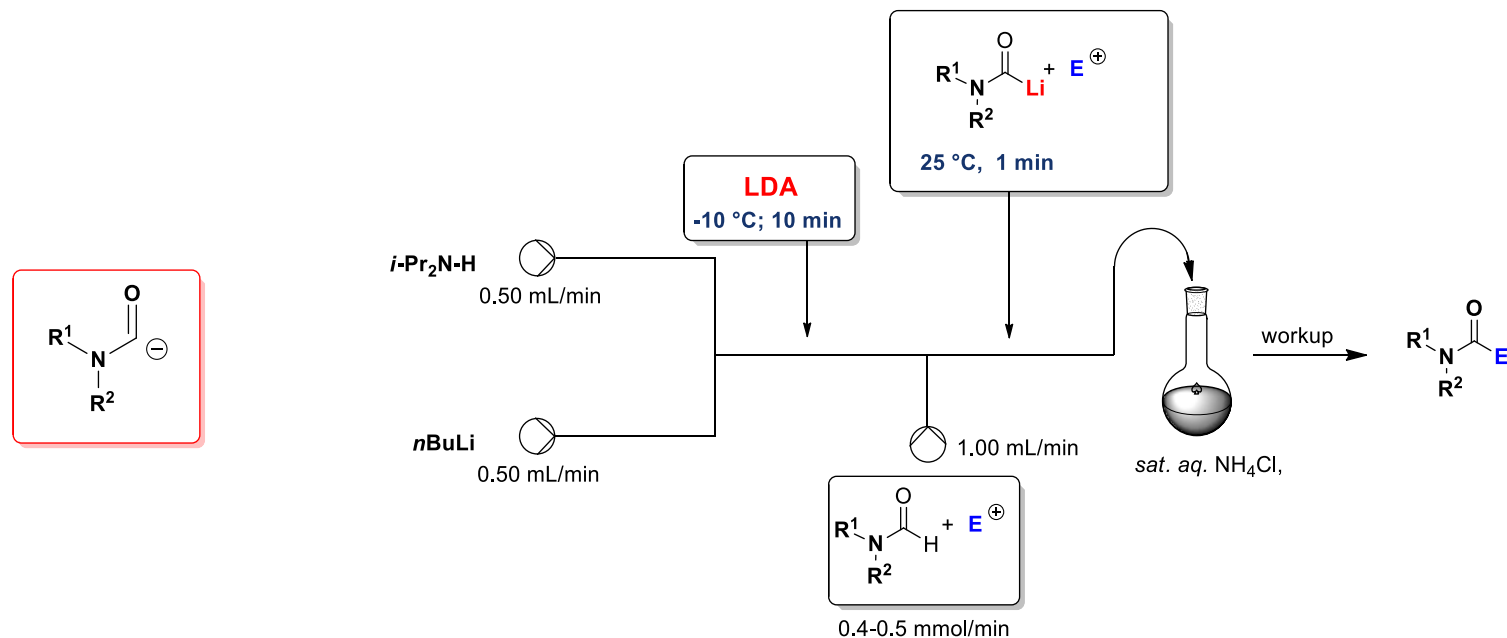


*Barbier-type conditions*

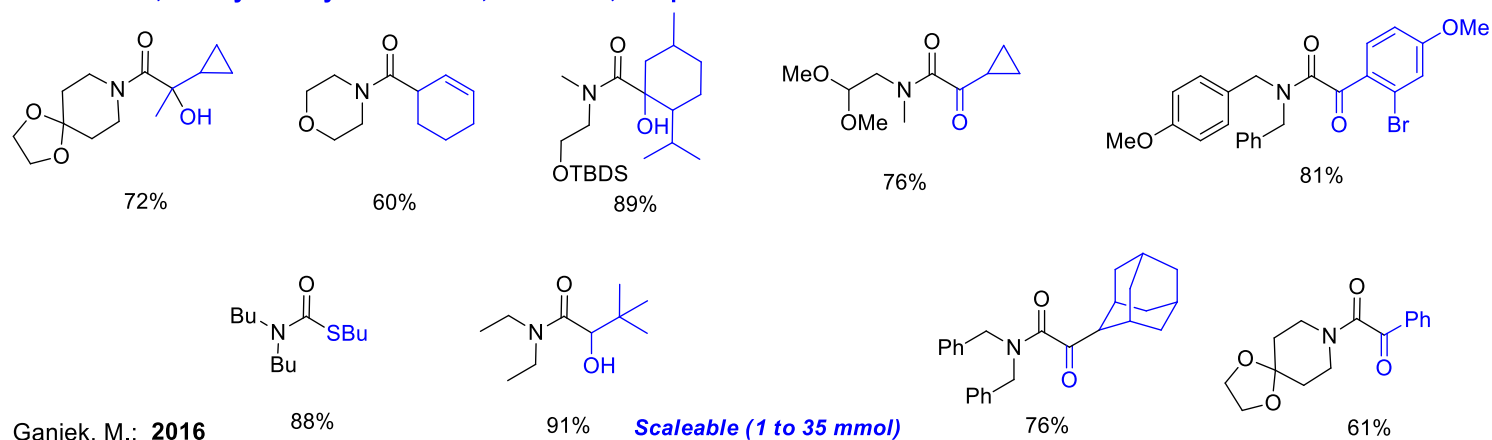




# Flow generation of carbamoyllithiums using an extended *in situ* quench

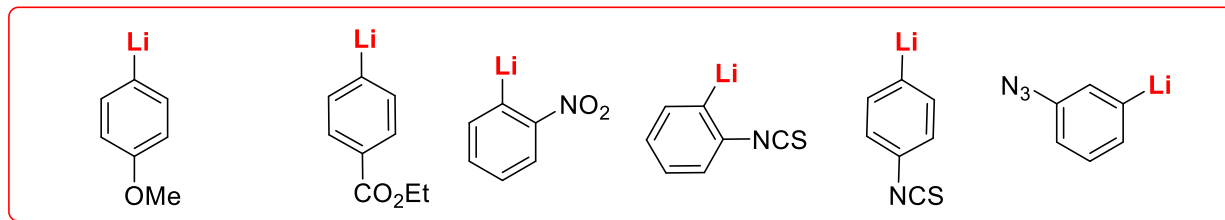
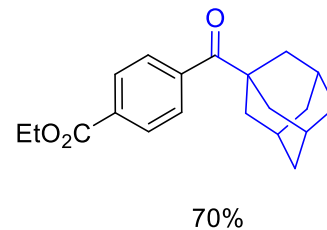
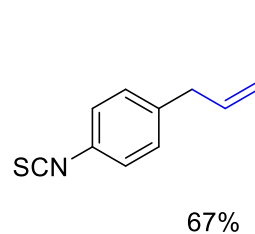
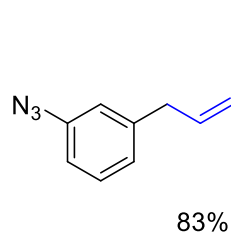
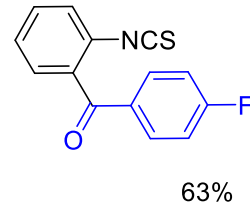
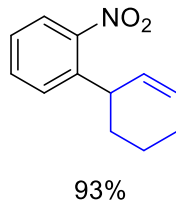
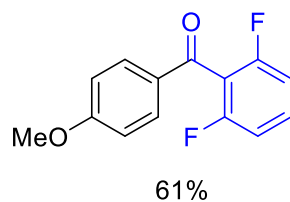
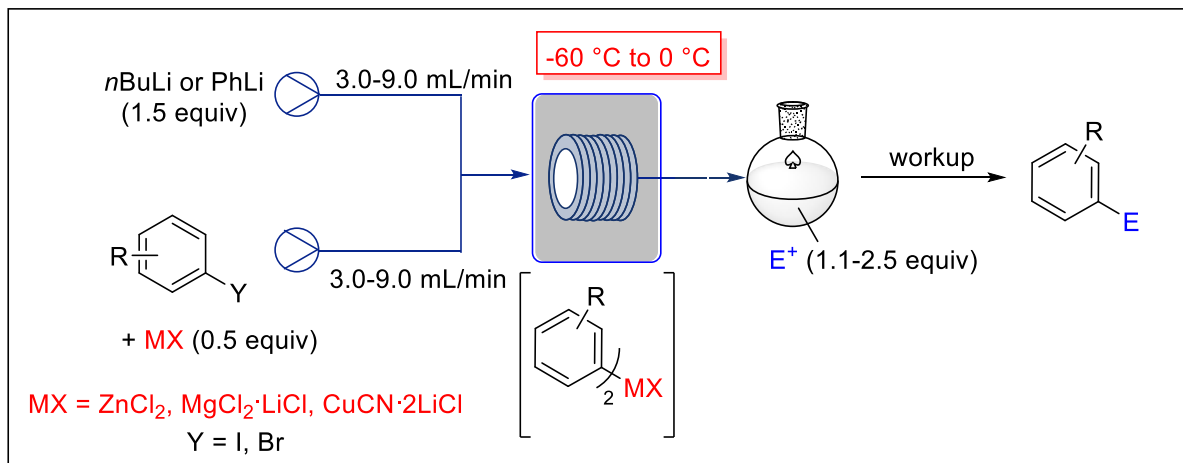


$\text{E}^+$  = ketones, aldehydes, allylic bromides, disulfides, morpholino- and Weinreb-amides

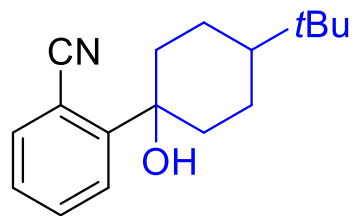
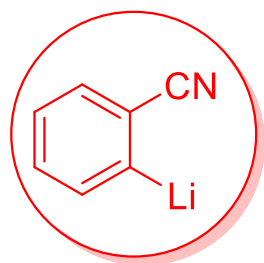
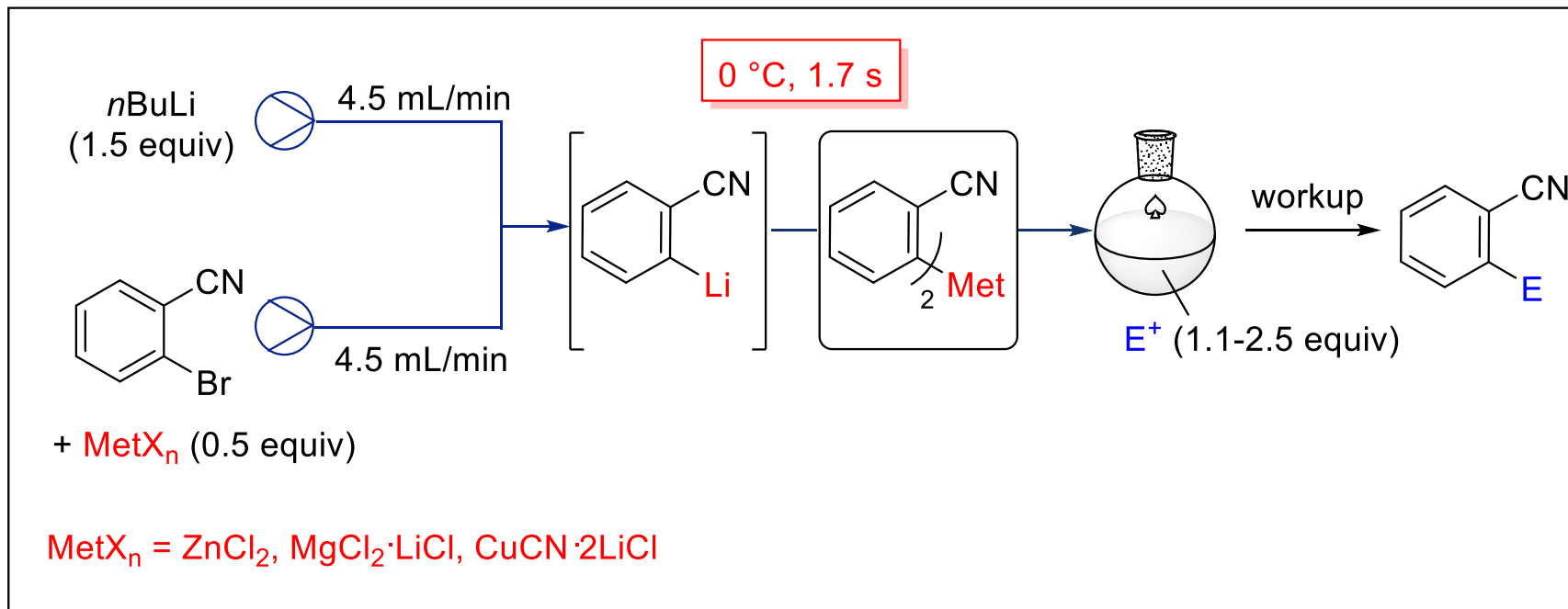


(a) B. Bahhidai, U. Schöllkopf *Angew. Chem.* **1973**, *19*, 861. (b) D. Seebach, D. Enders *Angew. Chem.* **1973**, *24*, 1104.  
 Recent flow protocol based on Li-insertion to carbamoyl chlorides: A. Nagaki, Y. Takahashi, J.-i. Yoshida *Angew. Chem. Int. Ed.* **2016**, *55*, 5327  
 Jonathan T. Reeves, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, *J. Am. Chem. Soc.* **2013**, *135*, 5565

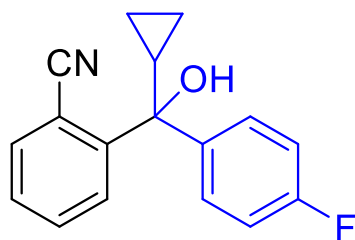
# Halogen/Lithium Exchange in Continuous Flow



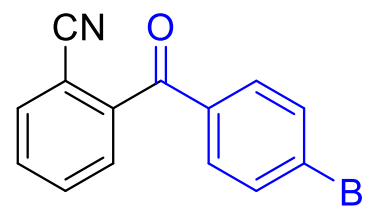
# Halogen/lithium exchange and *In Situ* trapping with a metal salt in flow



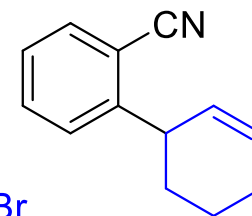
73%  
(d.r. = 84:16)



70%



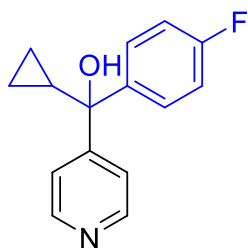
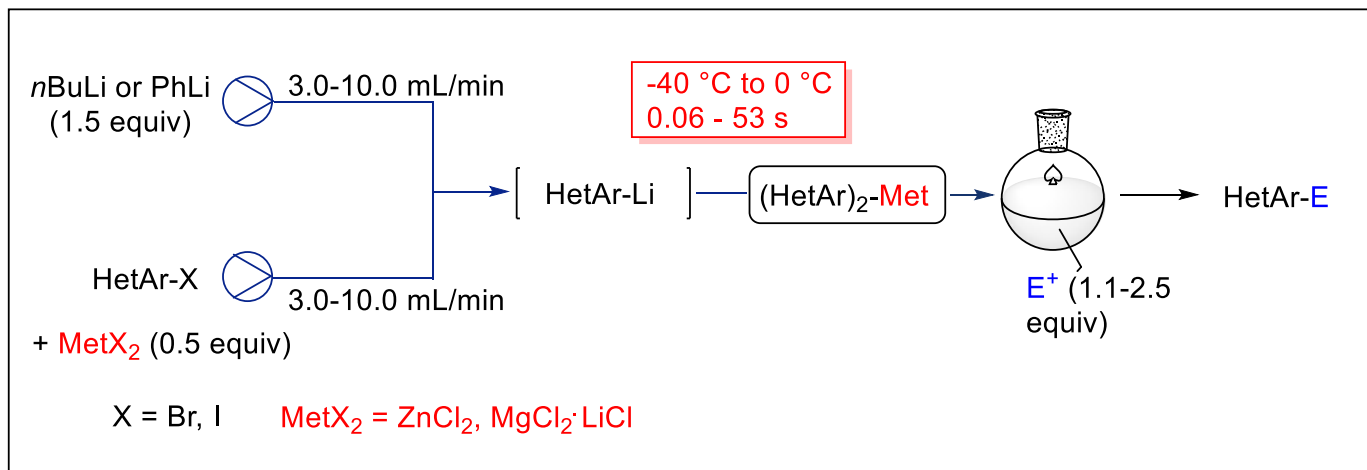
70%



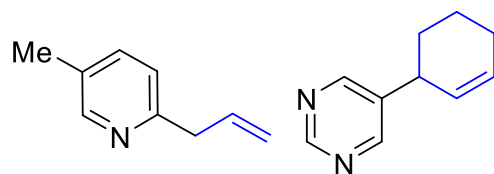
80%

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

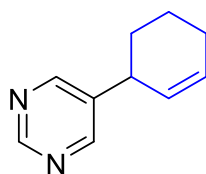
# Halogen/lithium exchange in continuous flow



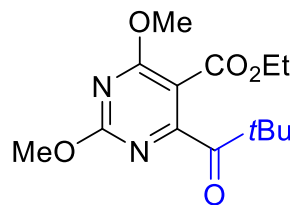
62% yield  
(X = I)



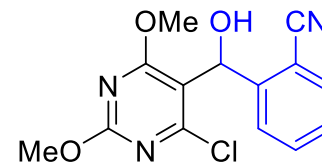
63% yield  
(X = Br)



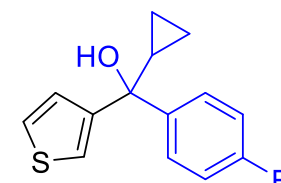
68% yield  
(X = Br)



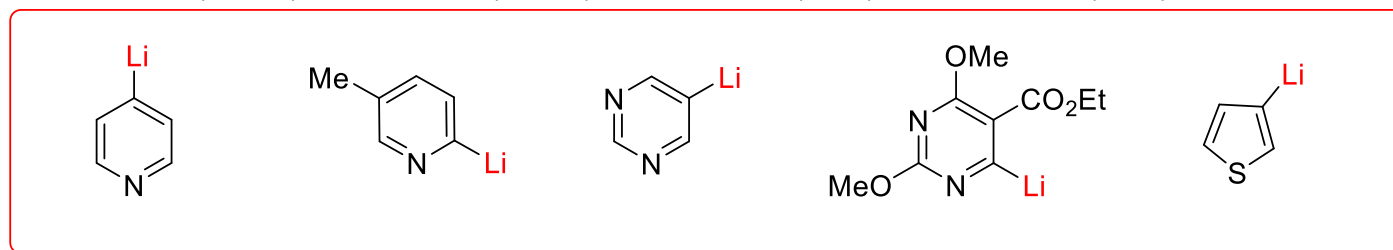
68% yield  
(X = I)



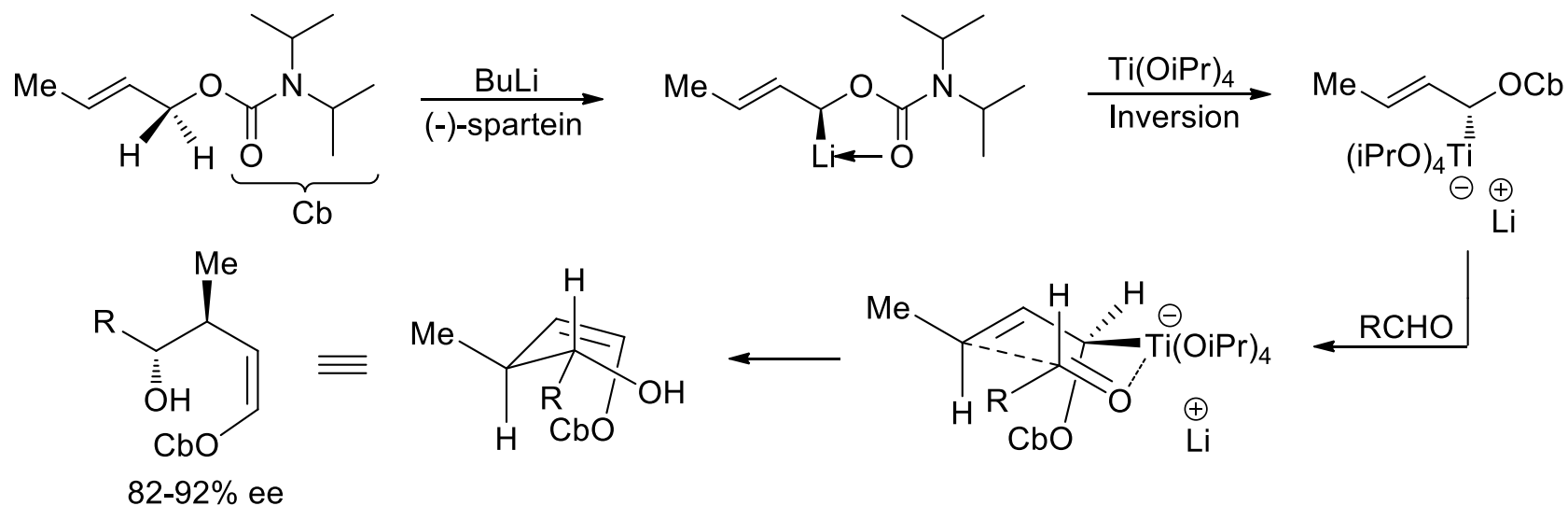
59% yield  
(X = I)



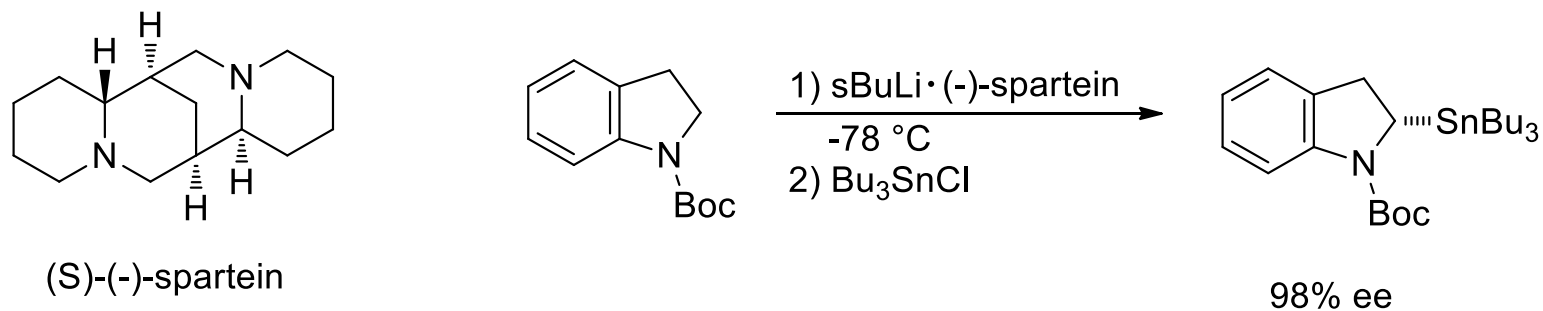
77%



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

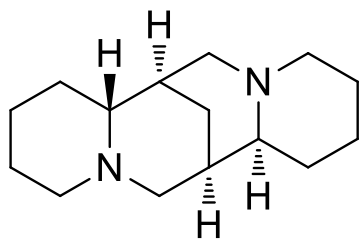
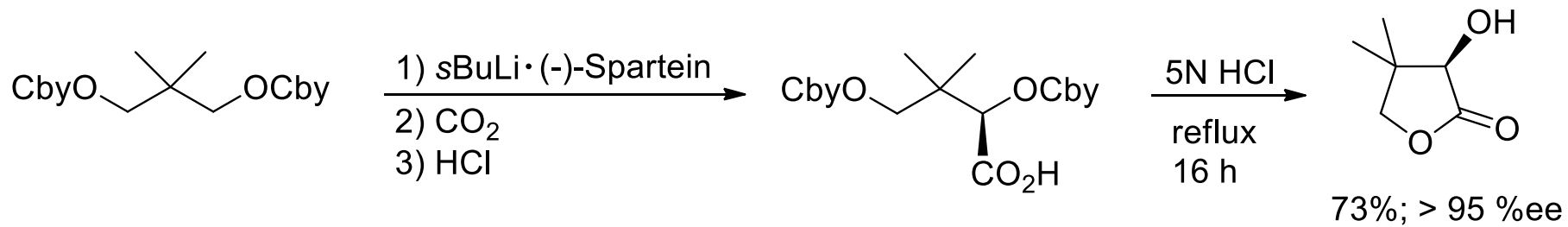


D. Hoppe, et al. *Pure Appl. Chem.* **1994**, 66, 1479.



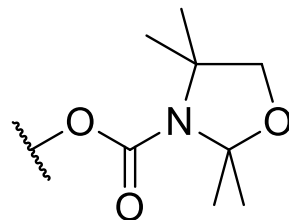
P. Beak *J. Org. Chem.* **1997**, 62, 7679

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



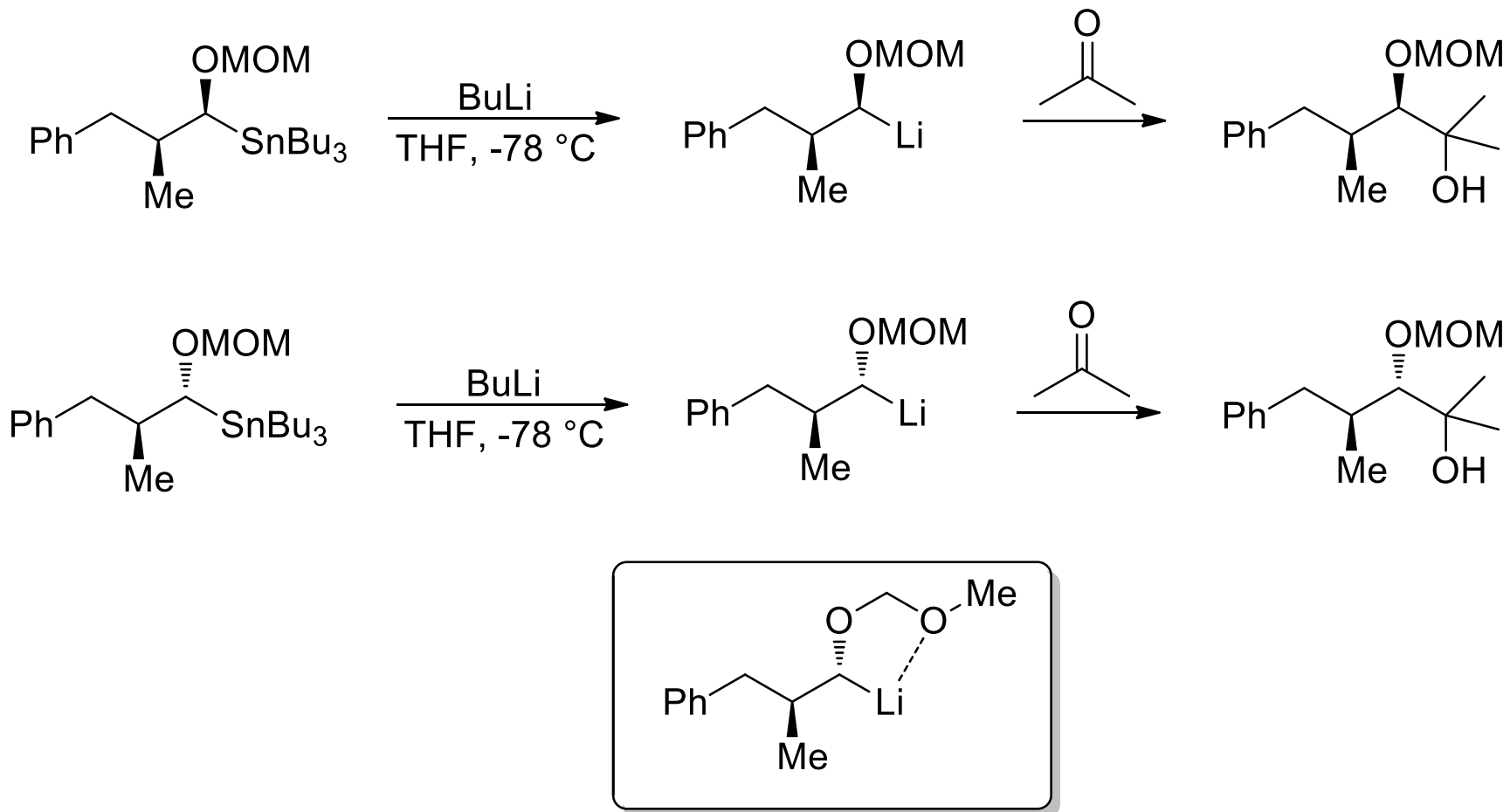
(S)-(-)-Sparteine

Cby

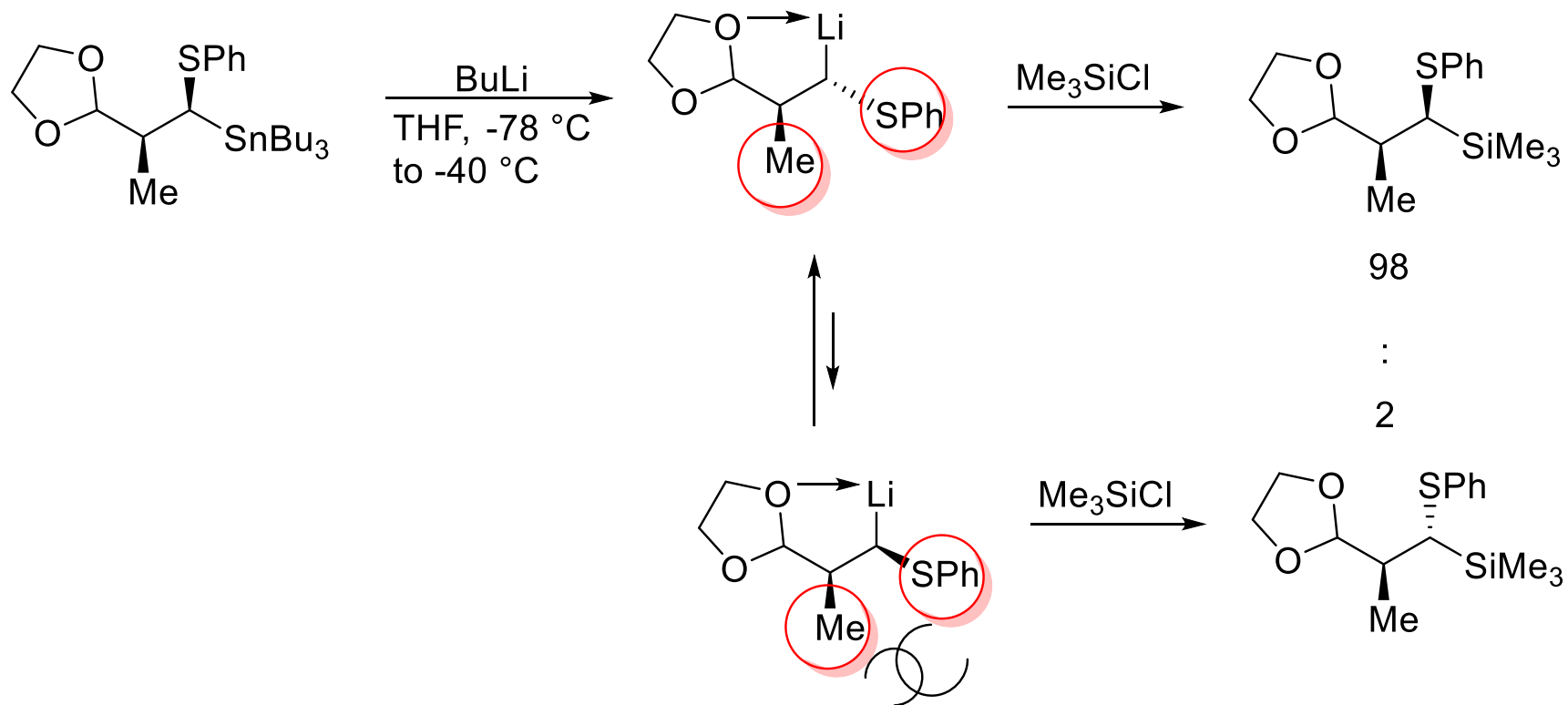


D. Hoppe *Tetrahedron Lett.* **1992**, 33, 5327

## Diastereoselective transmetalation

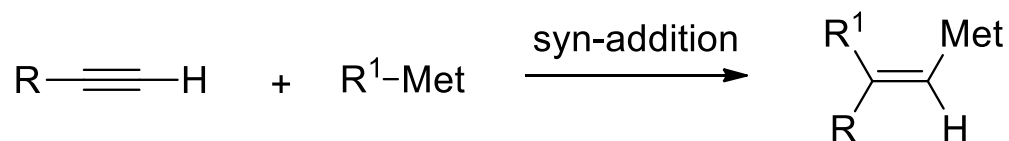


## Diastereoselective transmetalation

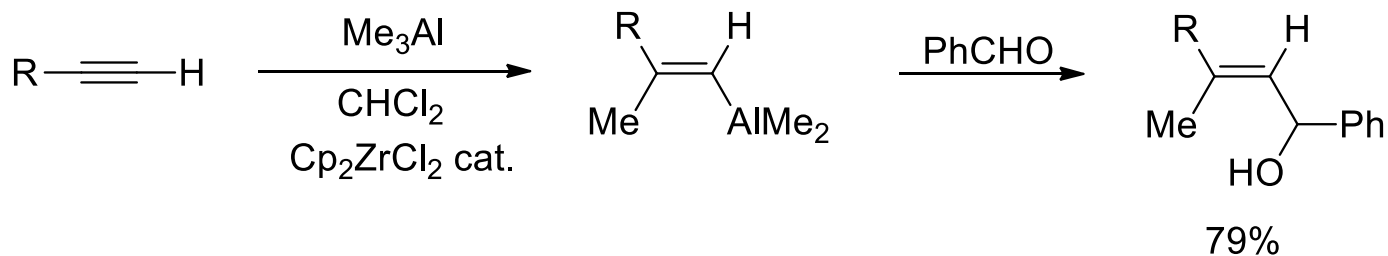




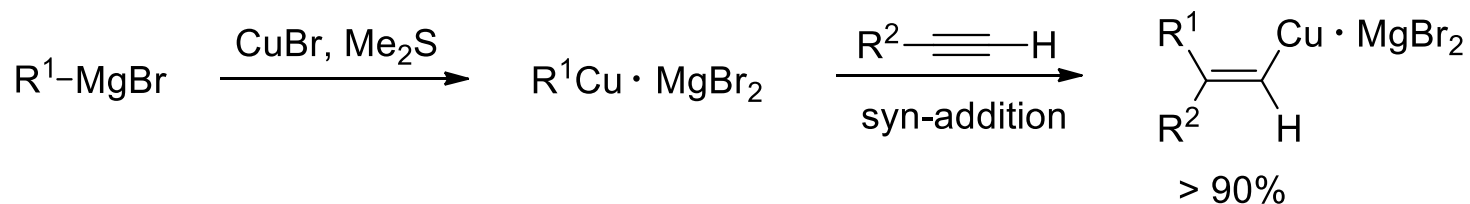
## Carbometalation



Negishi-reaction: carboalumination



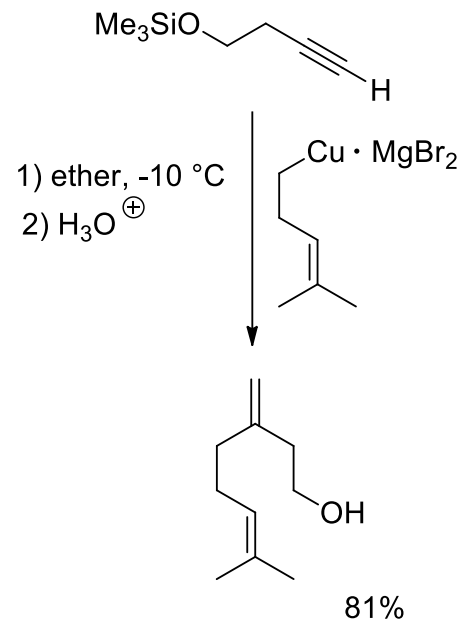
E. Negishi *J. Am. Chem. Soc.* **1976**, 98, 6729



Normant-reaction: carbocupration

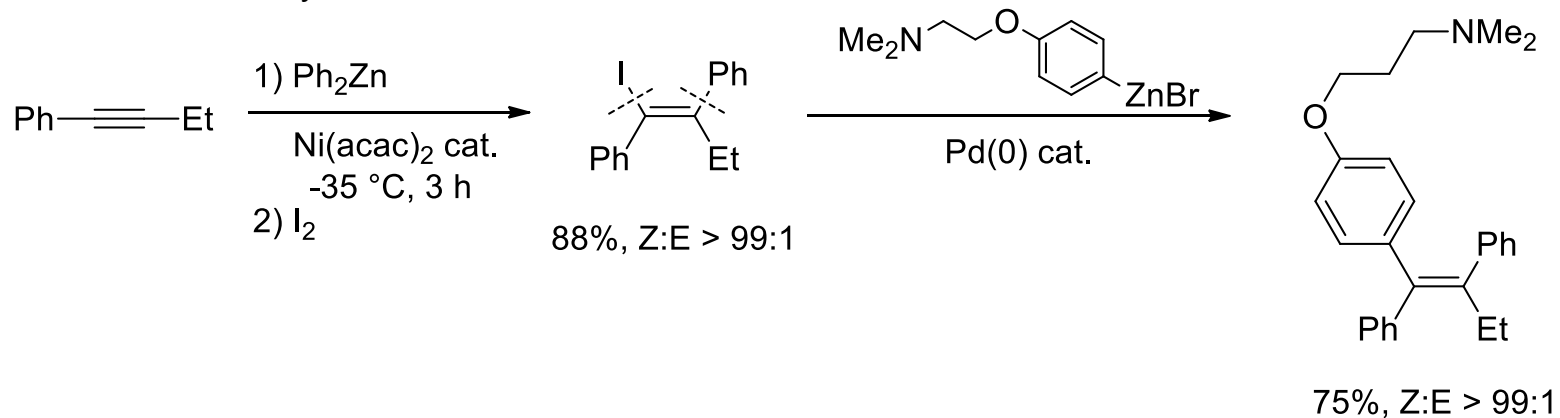
Review: A. Alexakis, J. F. Normant, *Synthesis* **1981**, 841.

# Carbometalation



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

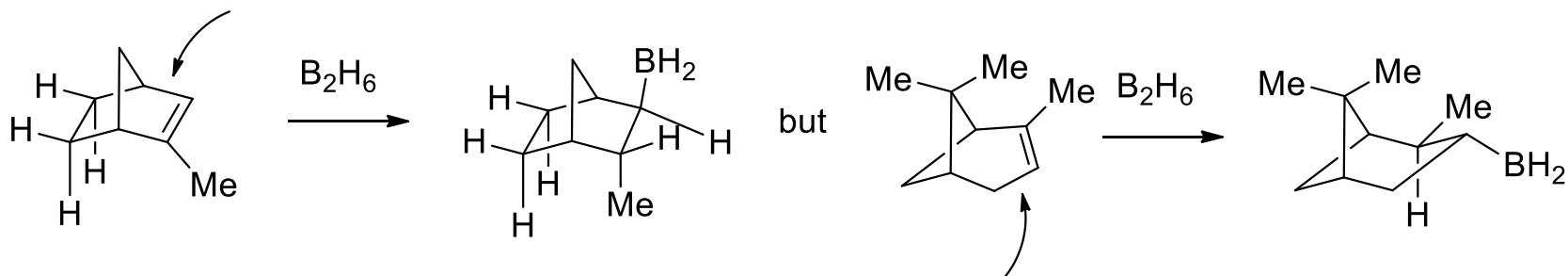
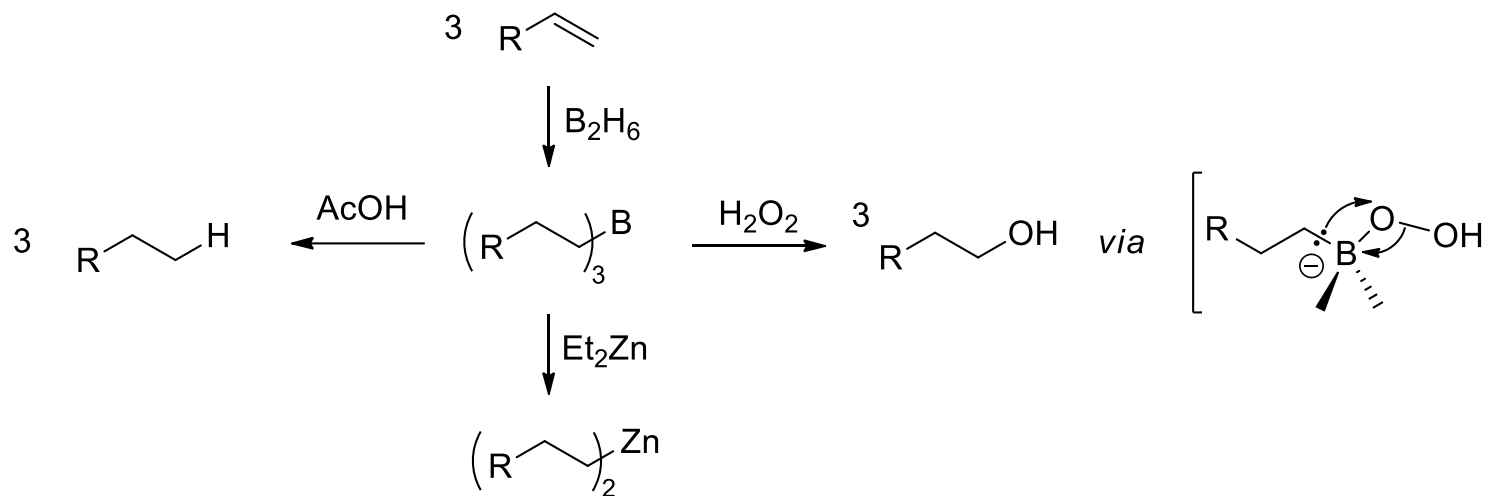
## Tamoxifen-Synthesis: Carbozincation



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

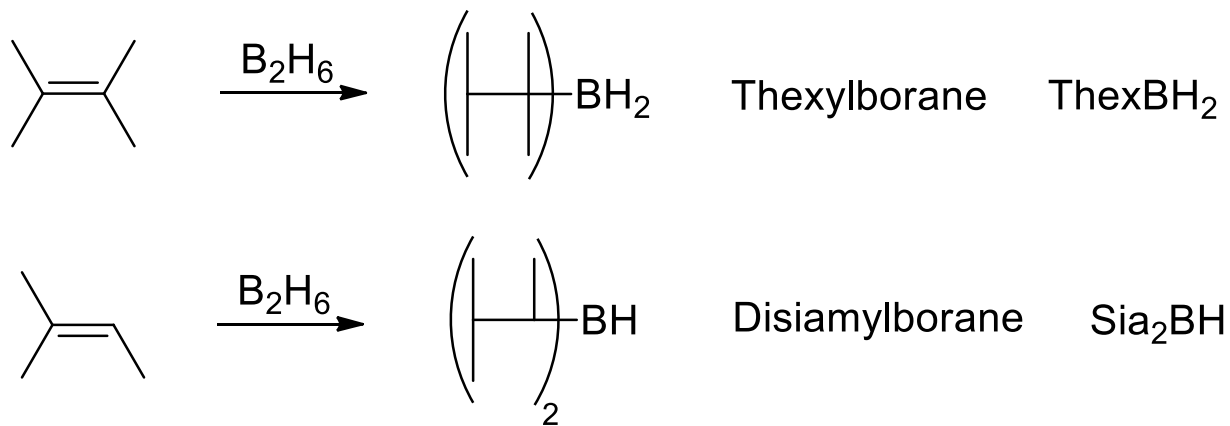
# Hydrometalation and application of organoboranes in organic chemistry

hydroboration



# Hydroboration

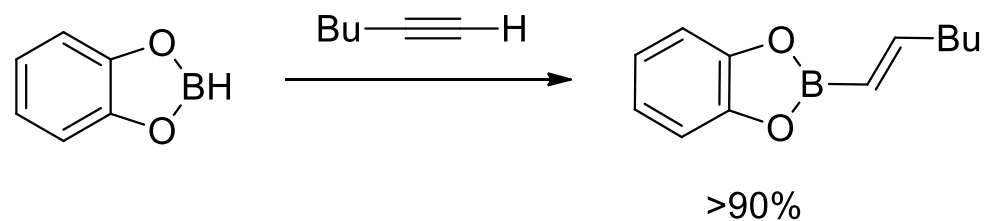
selective hydroborating reagents



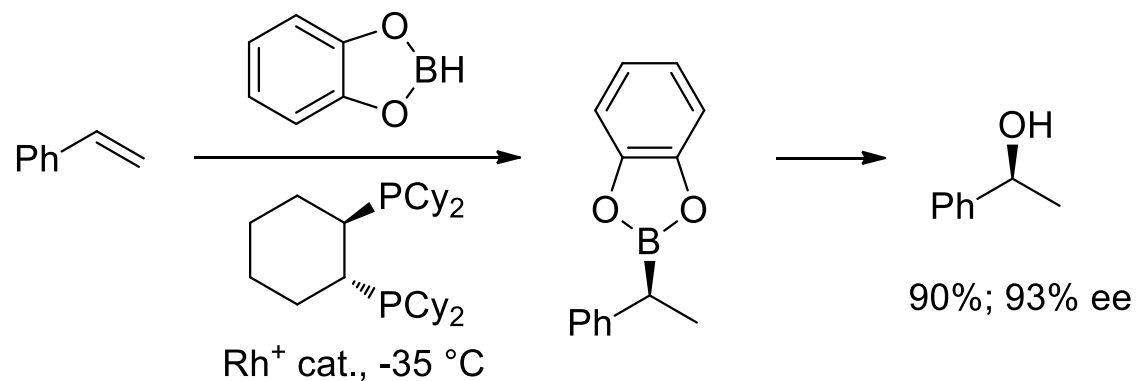
H. C. Brown, E. Negishi *J. Am. Chem. Soc.* **1975**, 97, 2799

# Hydroboration

catecholborane



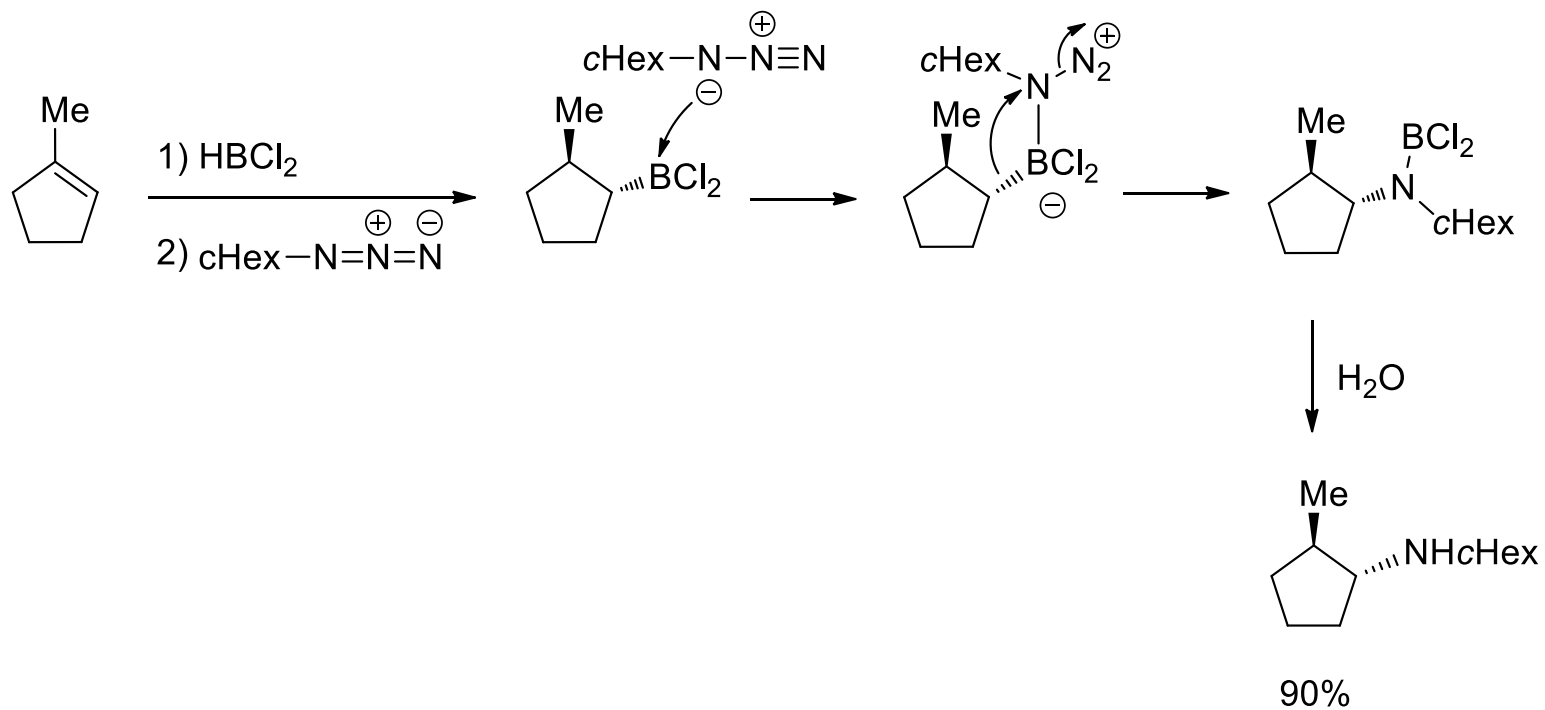
A. Arase, et al., *Synth. Comm.* **1995**, 25, 1957.



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

# Hydroboration

amination

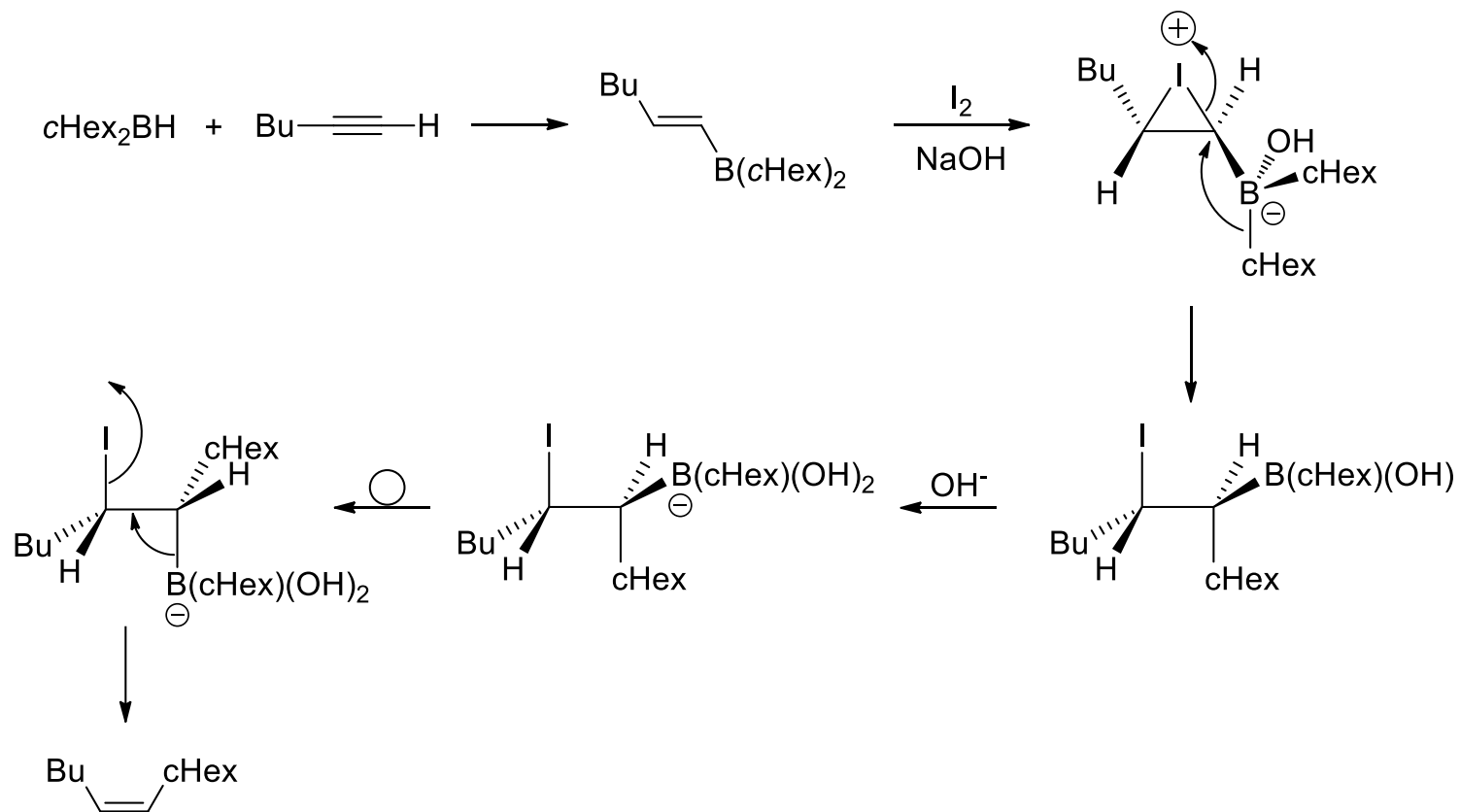


H. C. Brown, et al. *Tetrahedron* **1987**, 43, 4079

# Hydroboration

stereoselective synthesis of olefins

Z-olefins

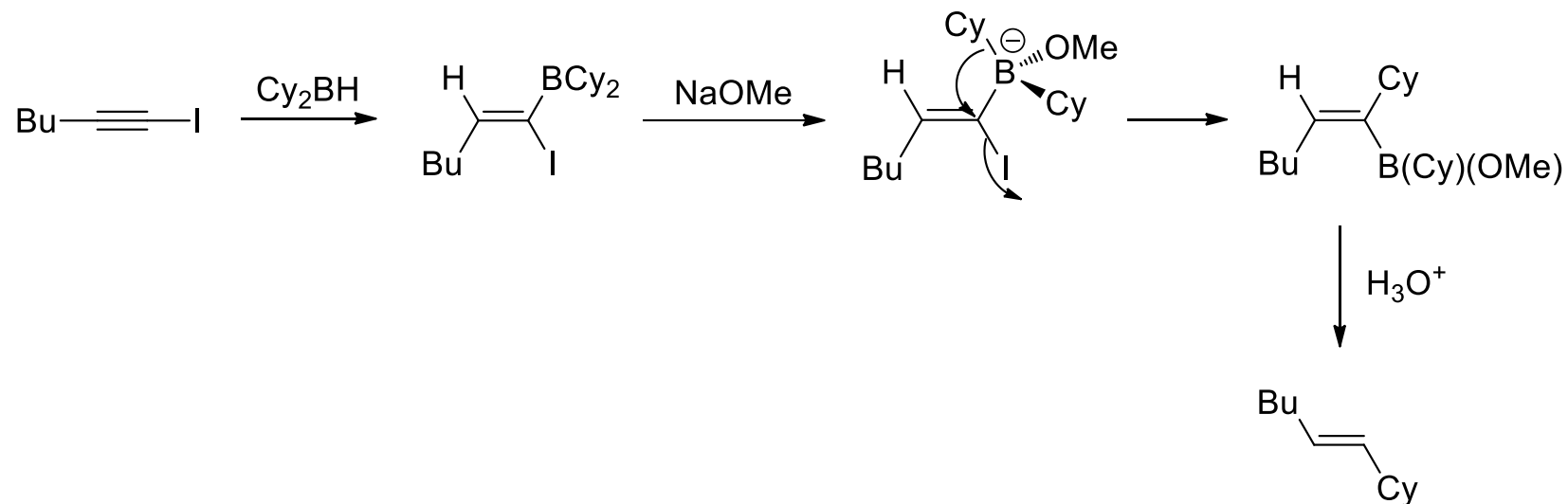


G. Zweifel, et al. *J. Am. Chem. Soc.* **1972**, *94*, 6560.

# Hydroboration

stereoselective synthesis of olefins

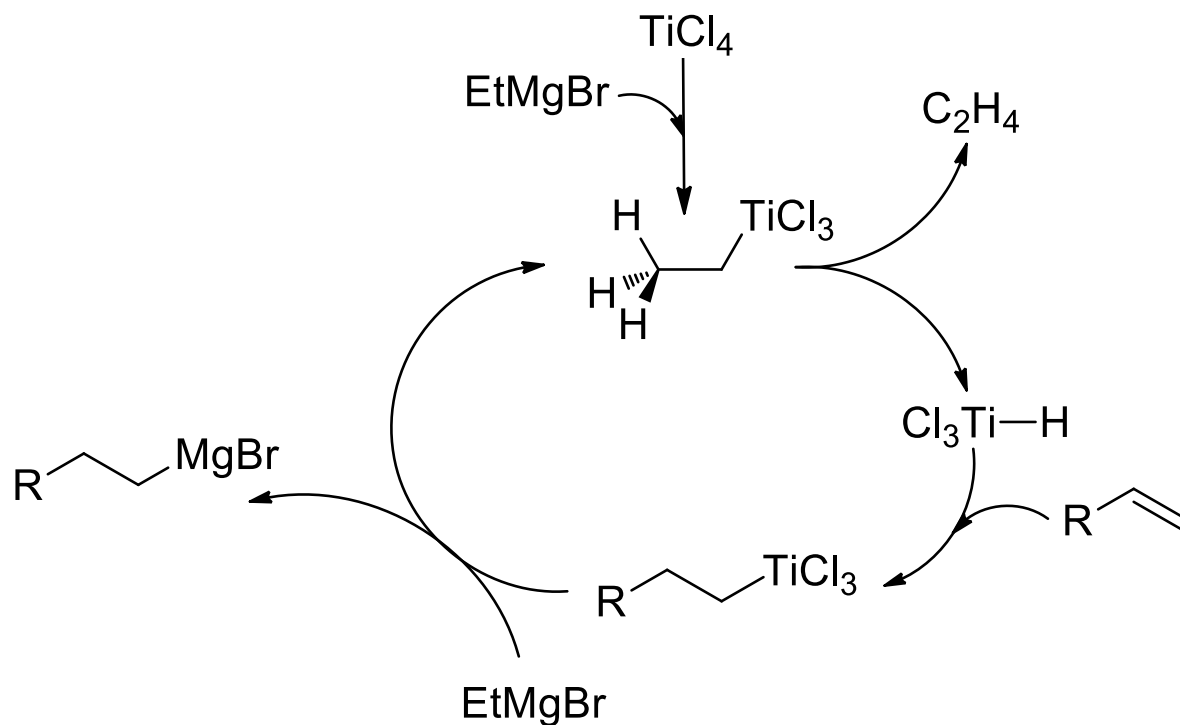
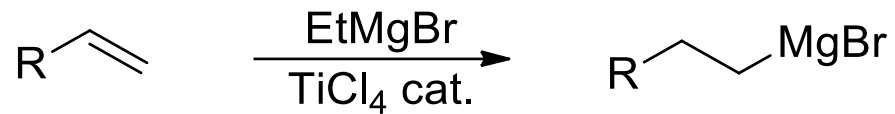
*E*-olefins



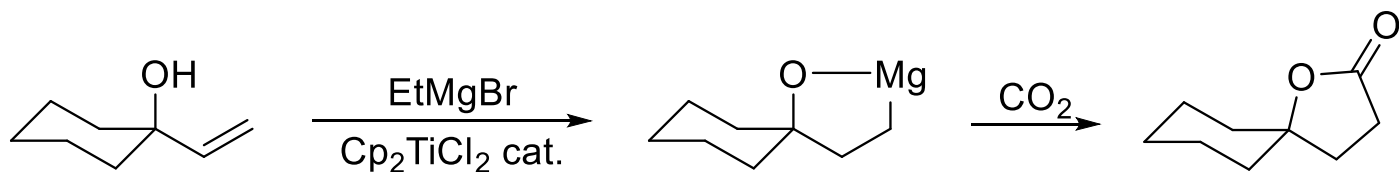
H. C. Brown, et al *J. Org. Chem.* **1989**, *54*, 6064.



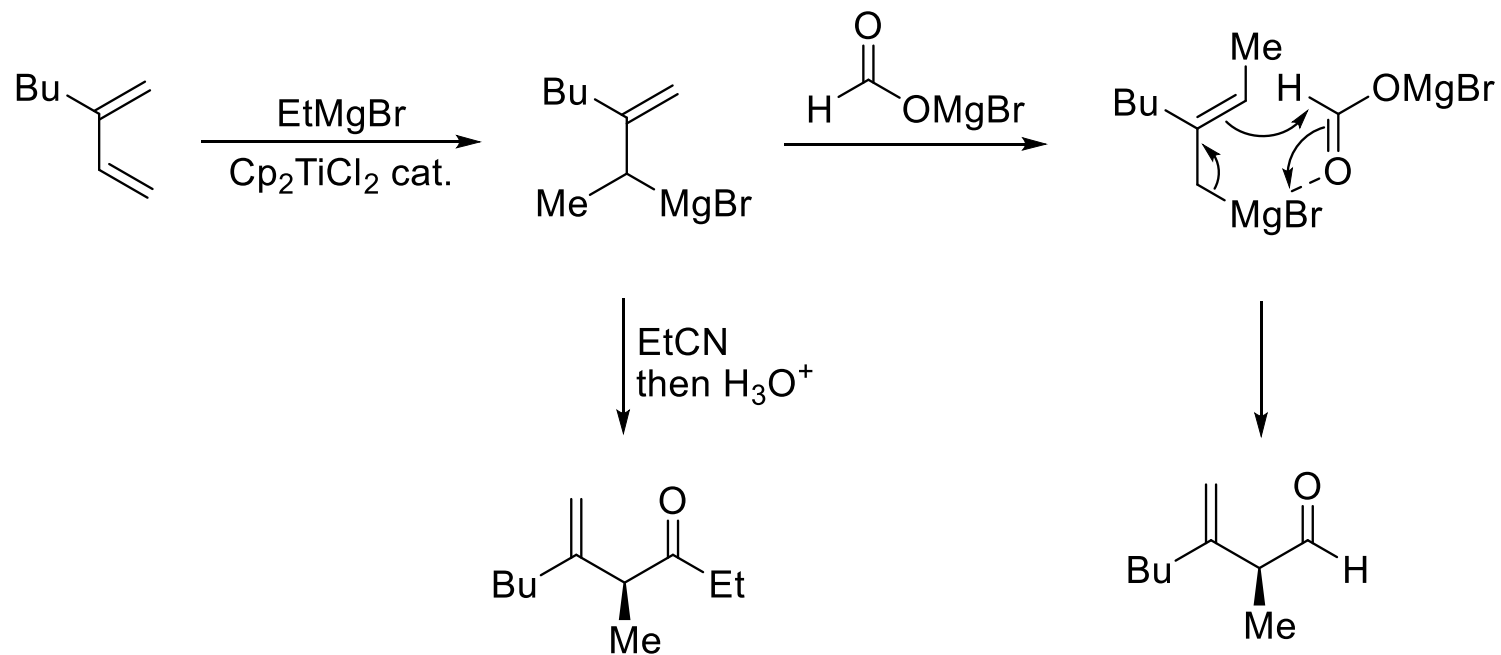
## Hydromagnesiation



## Hydromagnesiation

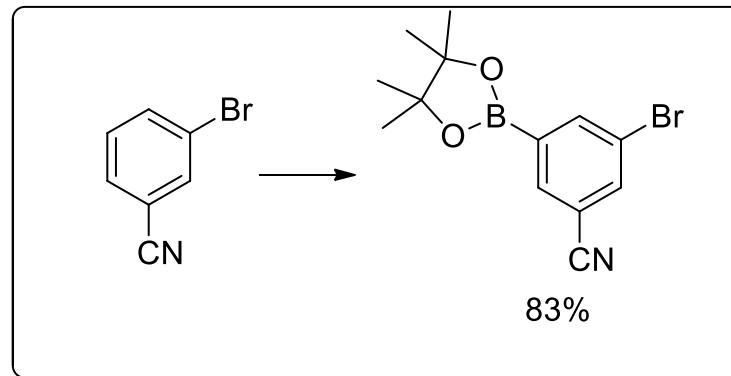
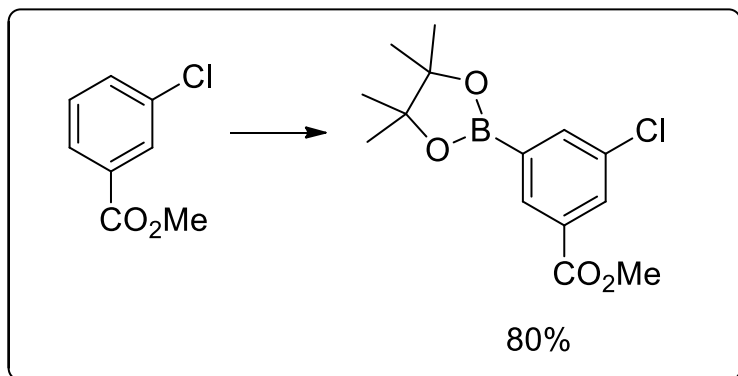
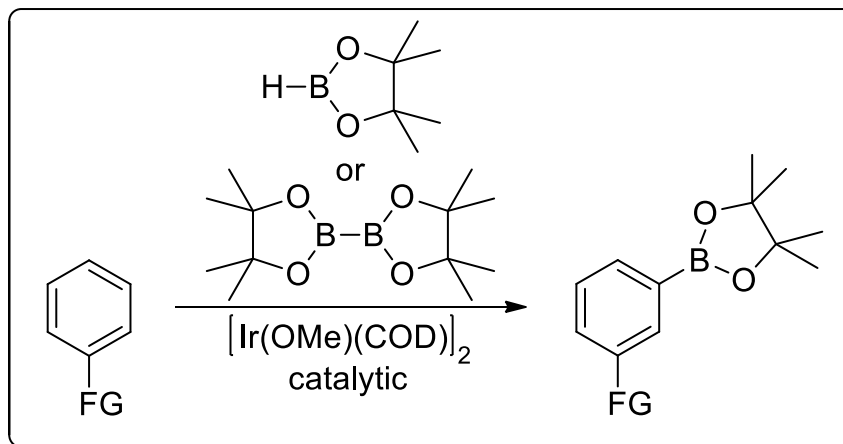


90%



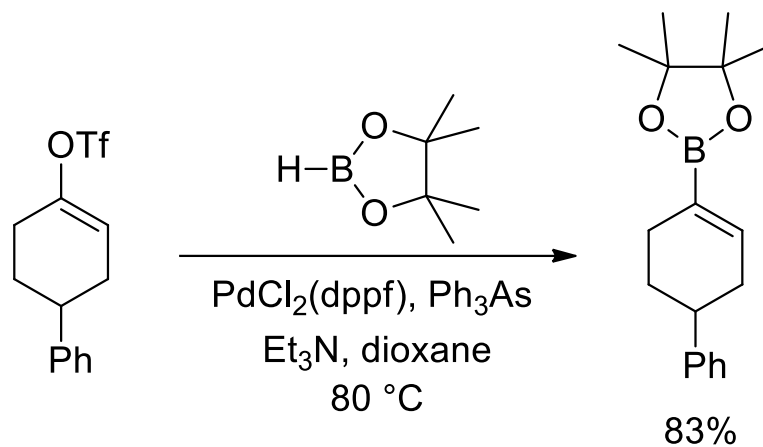
# Synthesis of aryl boronic acids

transition-metal catalyzed synthesis of aryl boronic acids



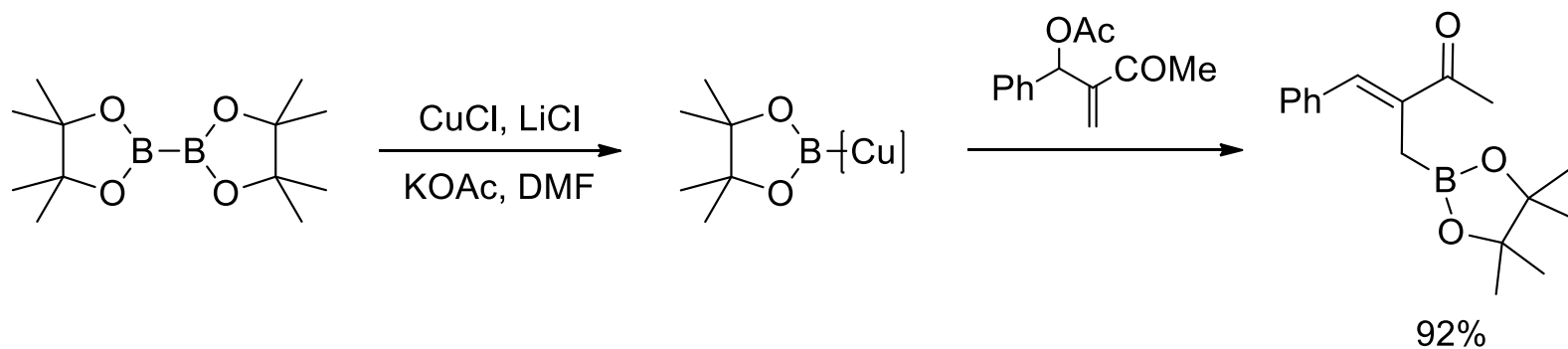
J. F. Hartwig, N. Miyaura, *Chem. Comm.* **2003**, 2924;  
*J. Am. Chem. Soc.* **2002**, 124, 390; *Angew. Chem. Int. Ed.* **2002**, 45, 3056

## Synthesis of aryl boronic acids



M. Murata *Tetrahedron Lett.* **2000**, 41, 5877

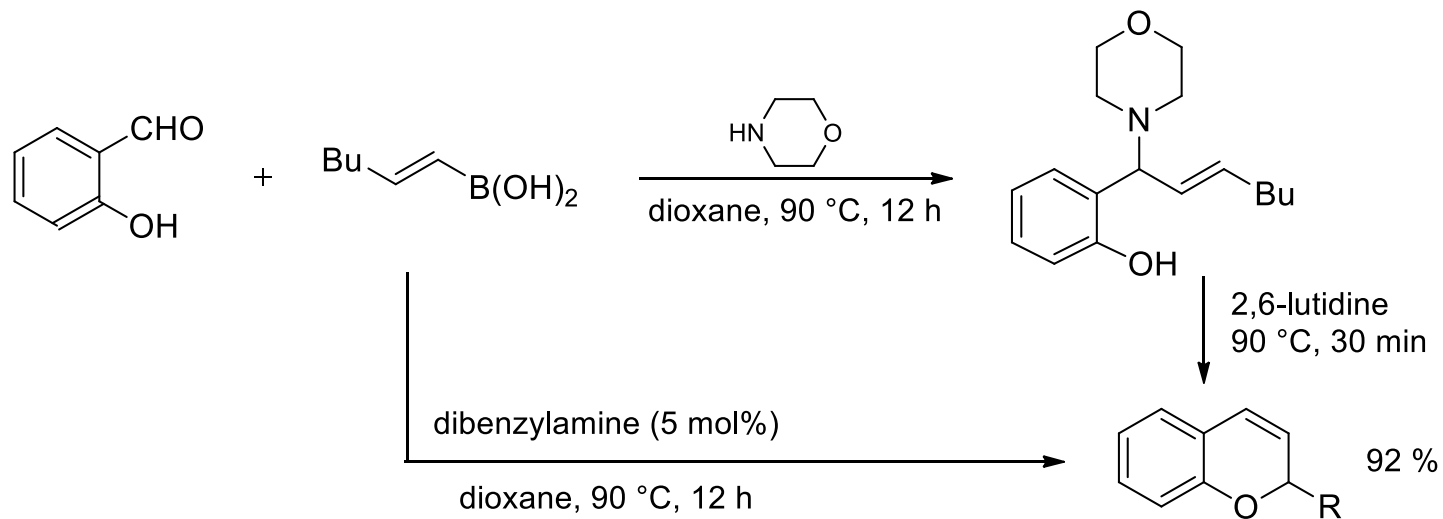
M. Murata *Synth. Comm.* **2002**, 32, 2513



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

## Reactivity of unsaturated boronic derivatives

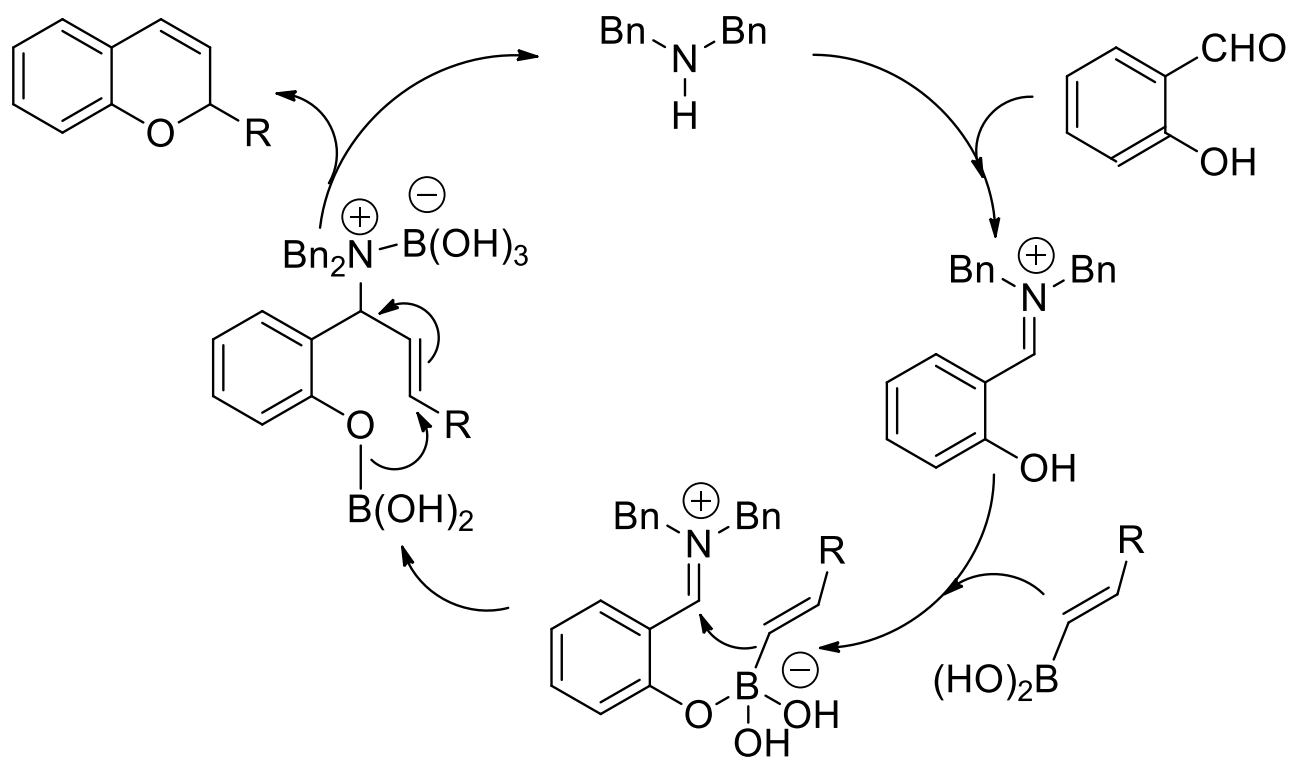
the Petasis-reaction - a short synthesis to 2H-chromenes



# Reactivity of unsaturated boronic derivatives

The Petasis-reaction

mechanism

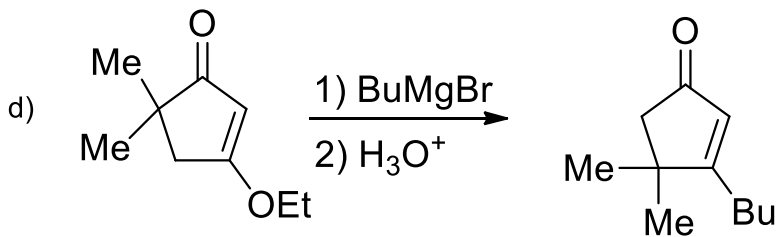
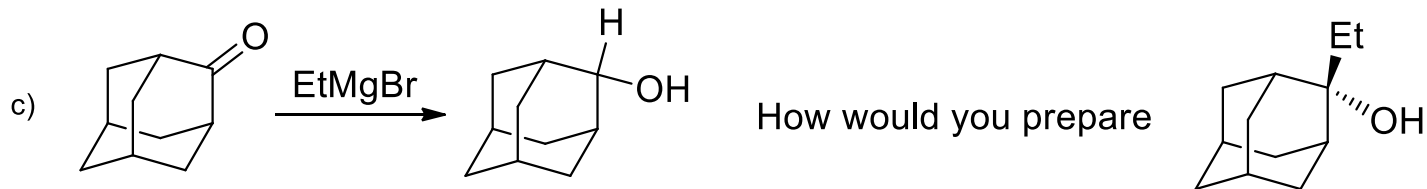
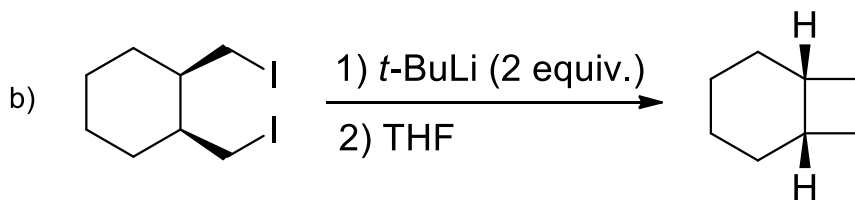
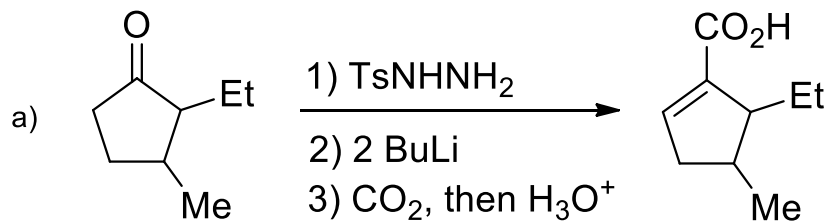


# ÜBUNG

## *1. Problem set*

# First Problem Set for OC IV

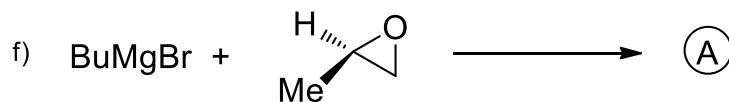
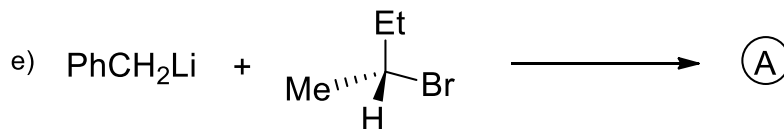
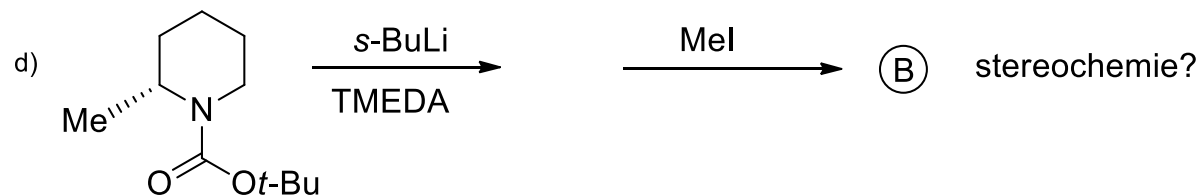
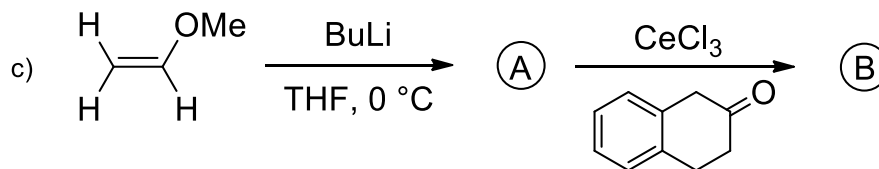
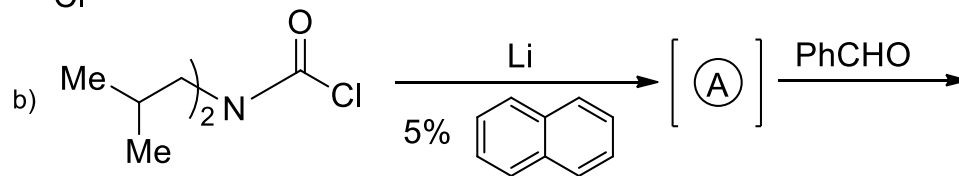
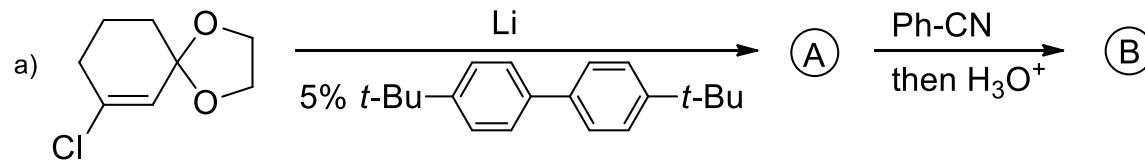
1) Give a mechanism for the following reactions:



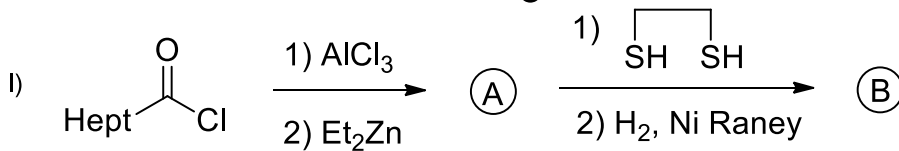
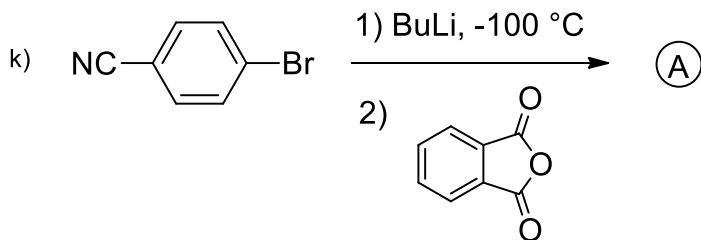
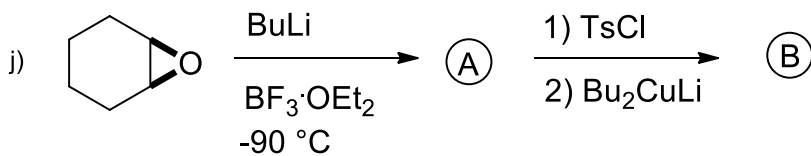
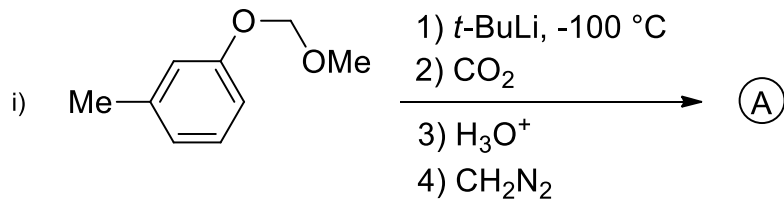
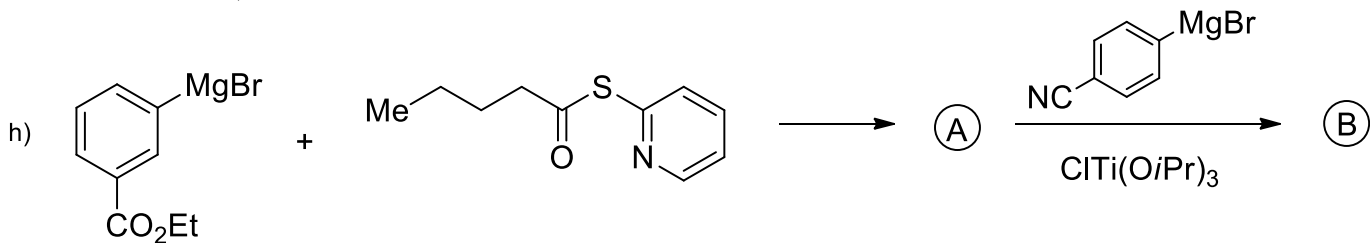
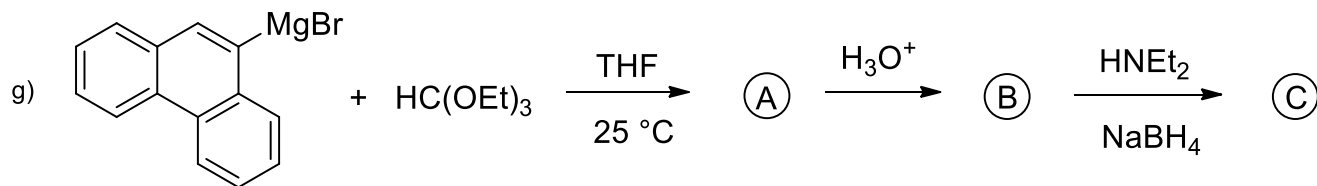


# First Problem Set for OC IV

2) Give the following reaction products:

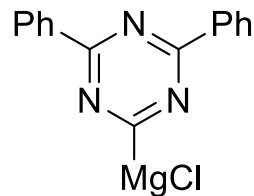
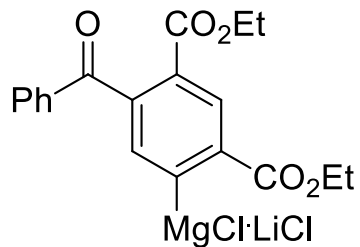
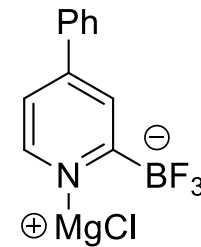
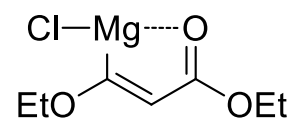
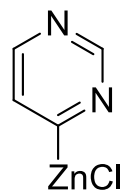
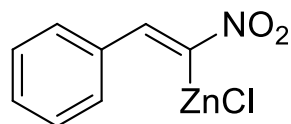
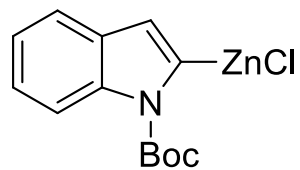
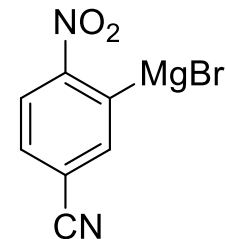
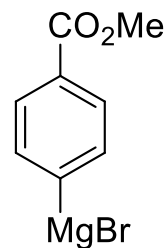
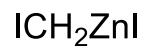
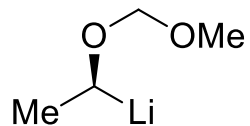
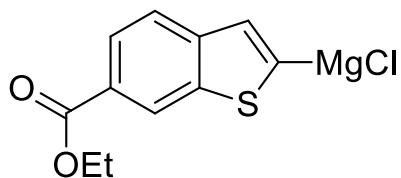


# First Problem Set for OC IV

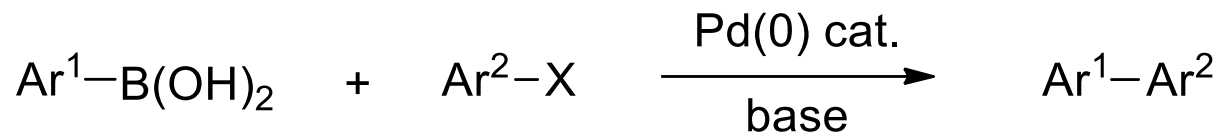


# First Problem Set for OC IV

3. How you would prepare following organometallics:



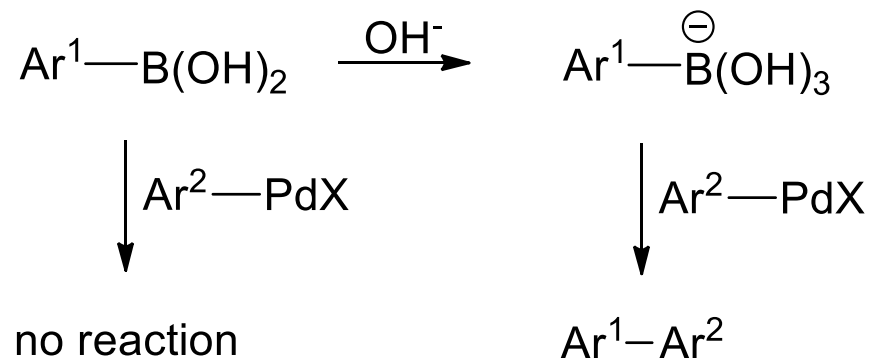
# The Suzuki cross-coupling reaction



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

Cross-Coupling Reactions. A practical guide. N. Miyaura (Ed.), Springer, **2002**

Key step

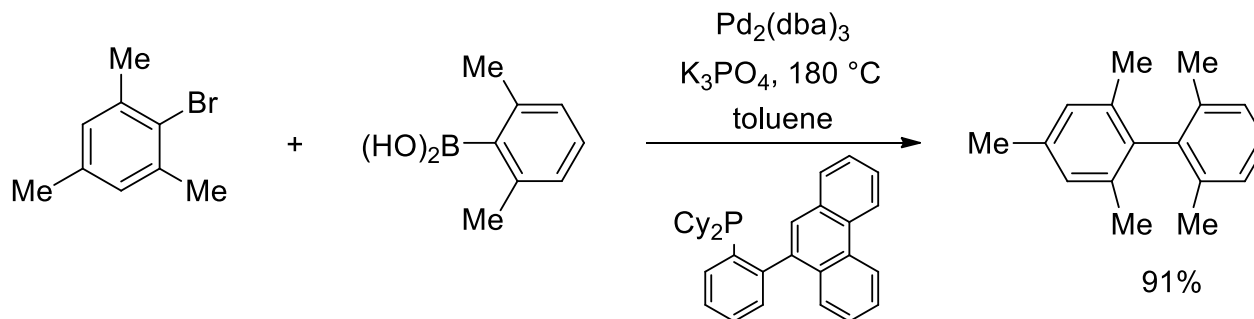


S. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162

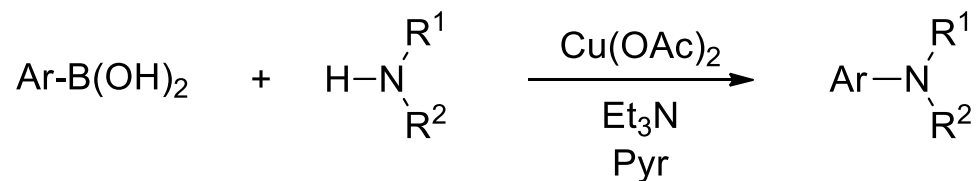
C. Amatore, A. Jutand, G. Le Duc *Chem. Eur. J.* **2011**, *17*, 2492

B. P. Carrow, J. F. Hartwig *J. Am. Chem. Soc.* **2011**, *133*, 2116

# The Suzuki cross-coupling reaction



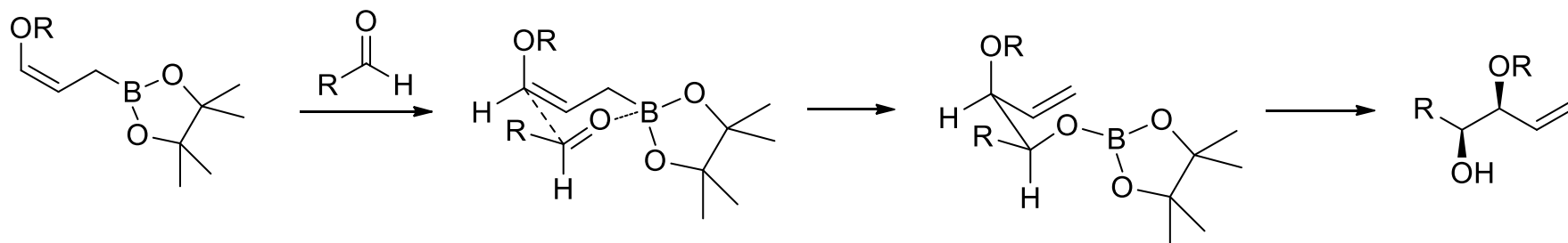
R. E. Sammelson, M. J. Kurth, *Chem. Rev.* **2001**, 101, 137



D. A. Evans, *Tetrahedron Lett.* **1998**, 39, 2937

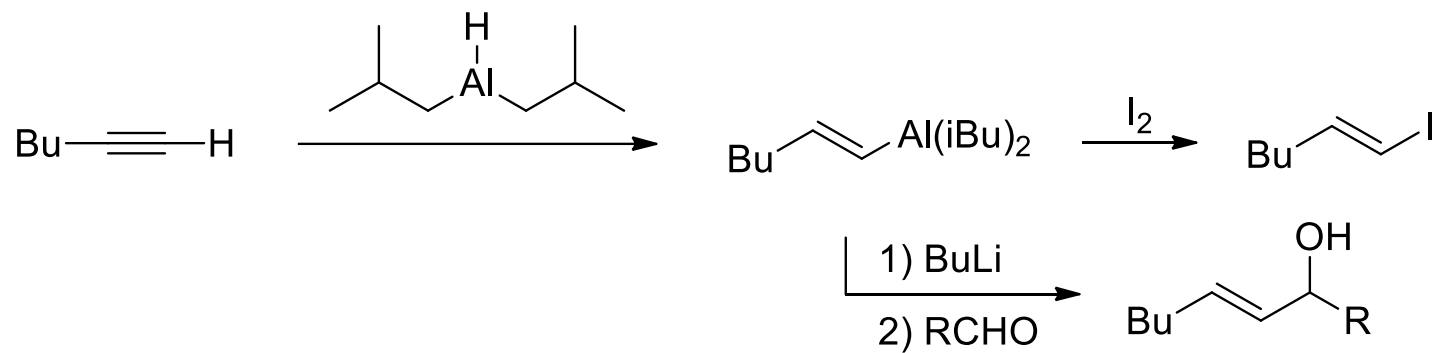
S. Ley, *Angew. Chem. Int. Ed.* **2003**, 42, 5400

## Chemistry of allyl boranes



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

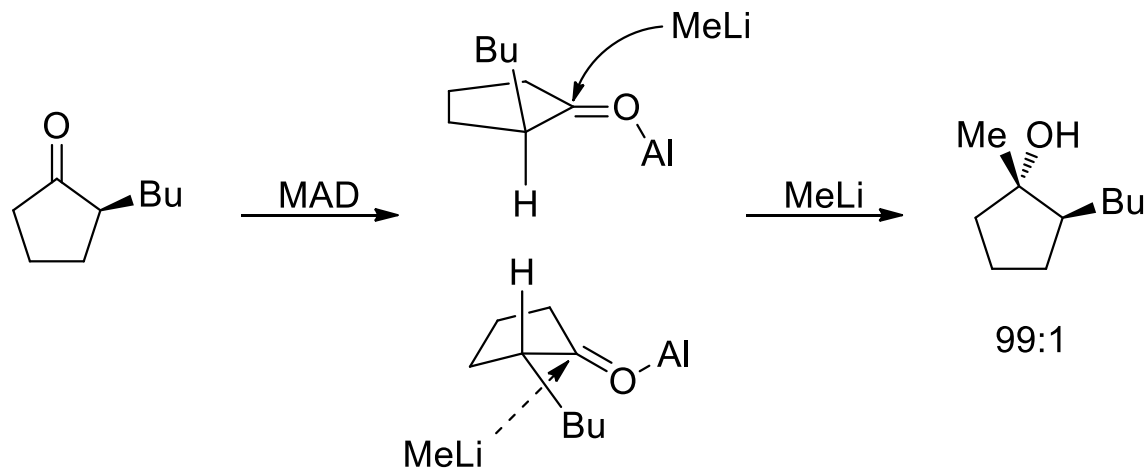
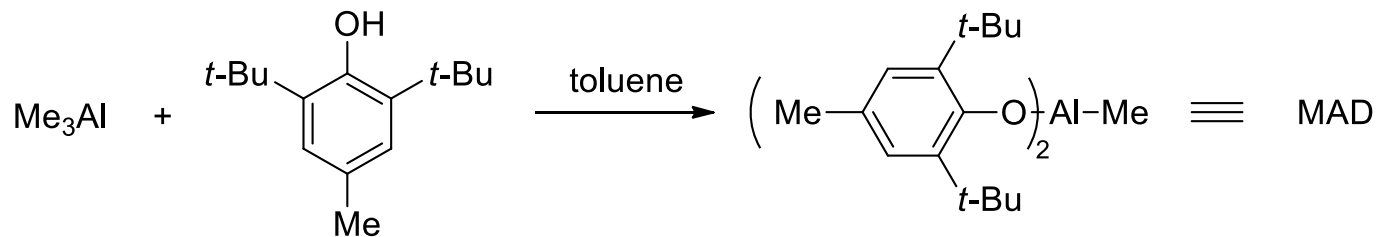
# Hydroalumination



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

# Hydroalumination

Special Al-reagents

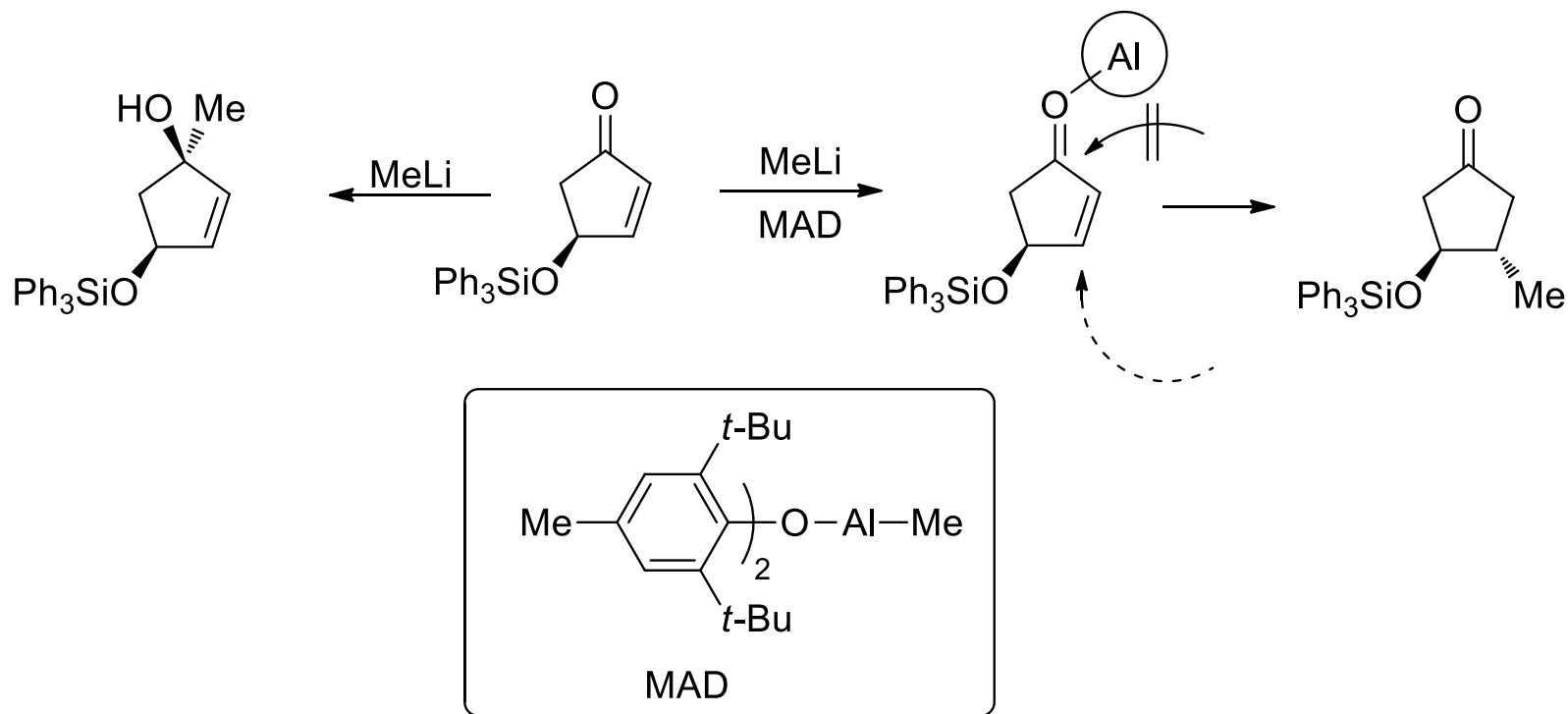


H. Yamamoto *J. Am. Chem. Soc.* **1988**, *110*, 3588

H. Yamamoto *Chem. Comm.* **1997**, 1585



# Hydroalumination



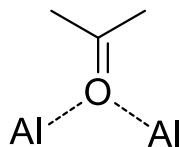
K. Maruoka, H. Yamamoto, *Kagaku, Zokan* (Kyoto, Japan) **1988**, 115, 127

S. Nagahara, K. Maruoka, H. Yamamoto, *Bull Chem Soc.* **1993**, 66, 3783

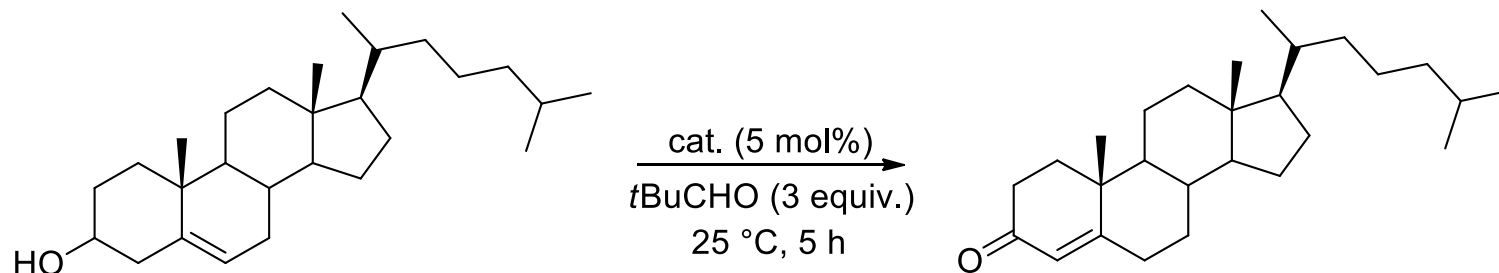
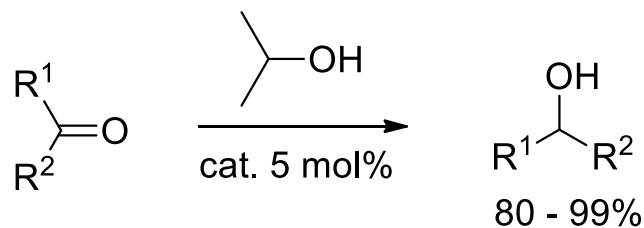
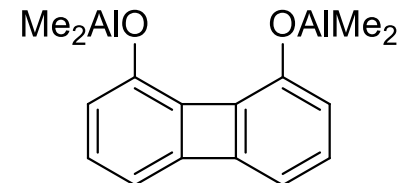
# Hydroalumination

Verley-Meerwein-Ponndorf reduction

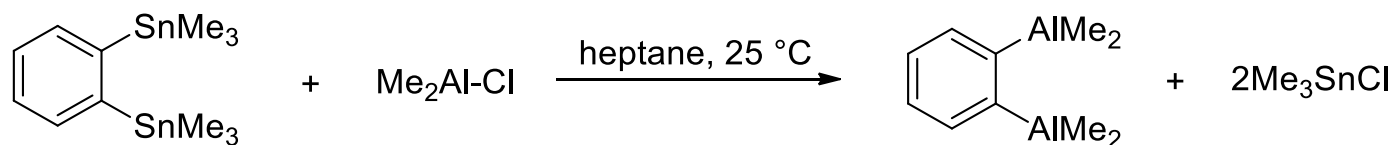
activating a carbonyl group twice



is possible using

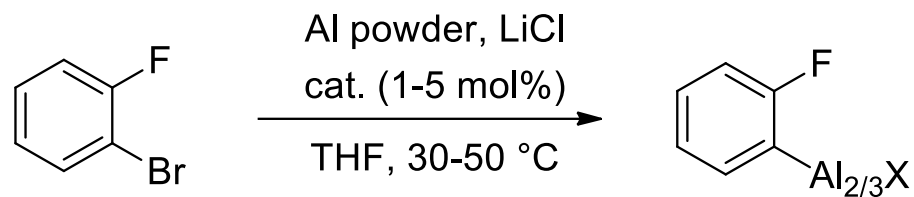


## Other preparation of aluminium compounds



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

Direct synthesis of organoaluminium reagents



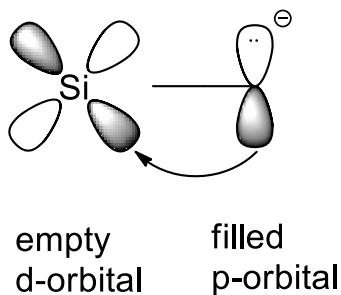
cat. = InCl<sub>3</sub>, BiCl<sub>3</sub>, PbCl<sub>2</sub>, TiCl<sub>4</sub>

# The organic chemistry of main-group organometallics

## Silicium

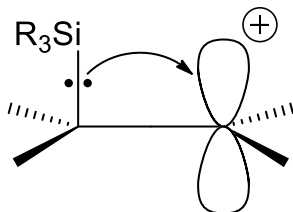
The effect of a  $\text{Me}_3\text{Si}$ -substituent:

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



stabilization of carbanions in  $\alpha$ -position

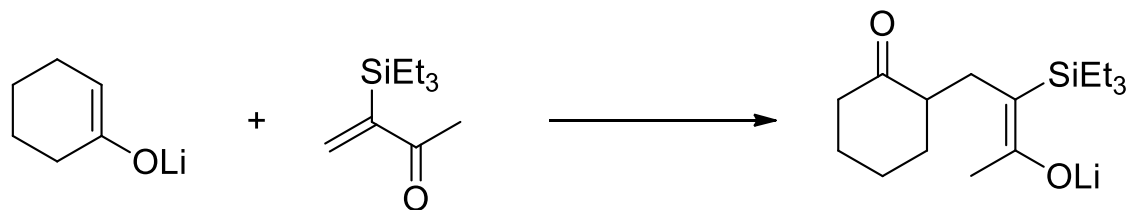
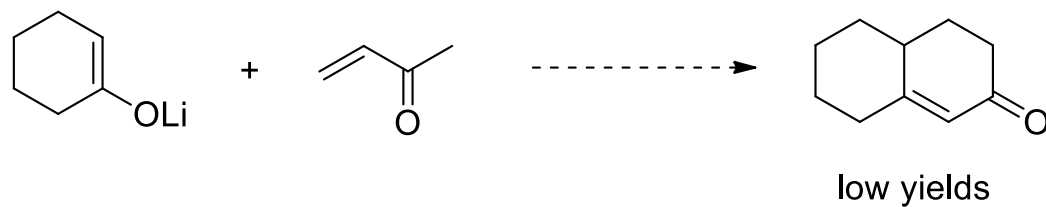
- 3) hyperconjugation: interaction of  $\sigma$ -framework with the  $\pi$ -system



stabilization of a cation in  $\beta$ -position

# Silicium

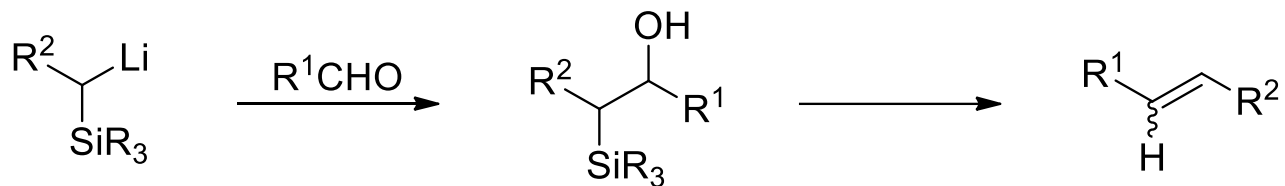
Applications:



high yield: stabilized lithium enolate  
(no polymerization)

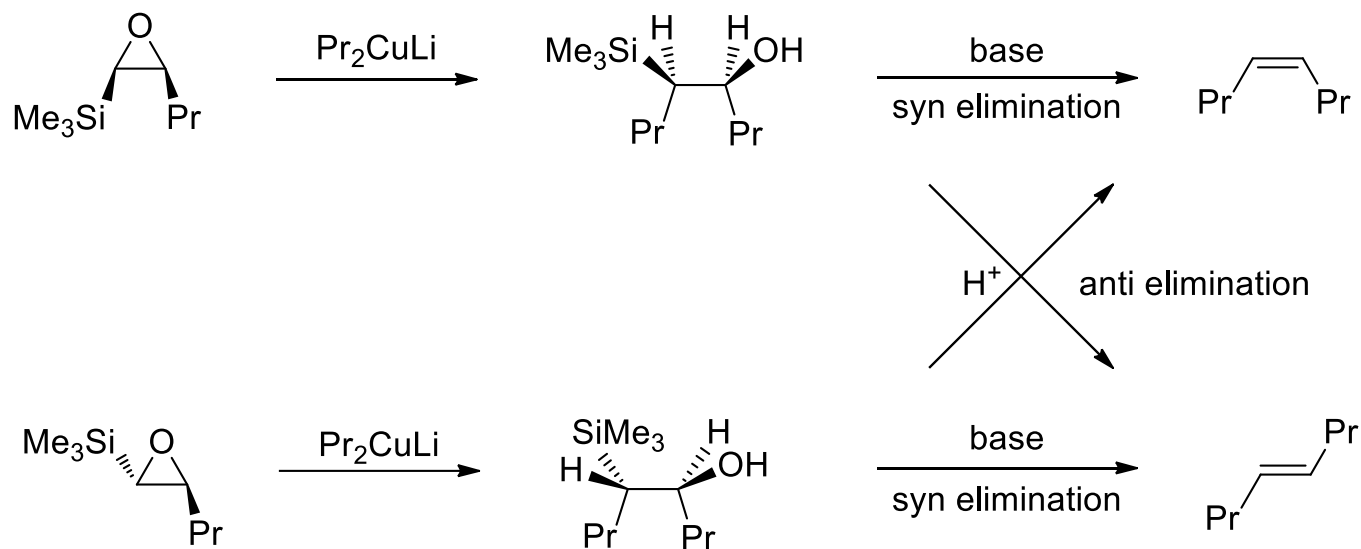
# Silicium

Peterson olefination



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

Stereochemistry of the *Peterson*-elimination

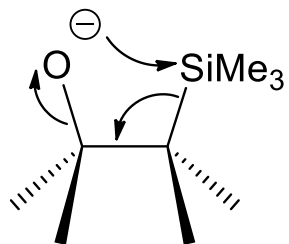


P. F. Hudrlik, D. Peterson, R. J. Rona *J. Org. Chem.* **1975**, 40, 2263

# Silicium

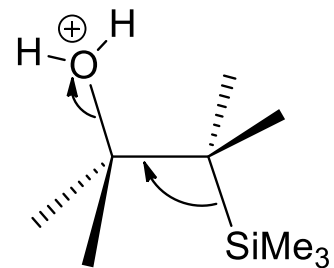
key steps:

basic  
media



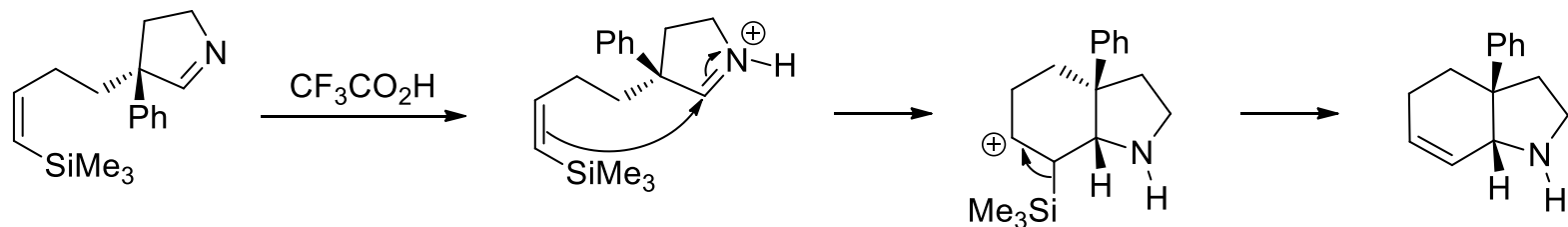
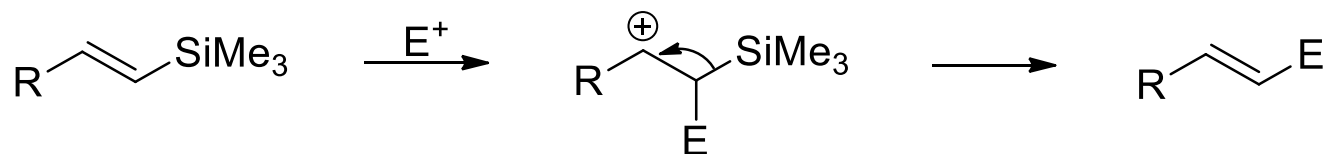
syn elimination

acidic  
media



anti elimination

## Reactivity of alkenylsilanes

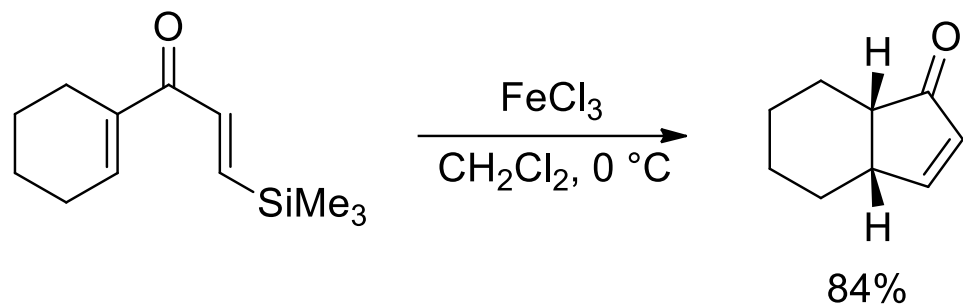


L. E. Overman, *Tetrahedron Lett.* **1984**, 25, 5739



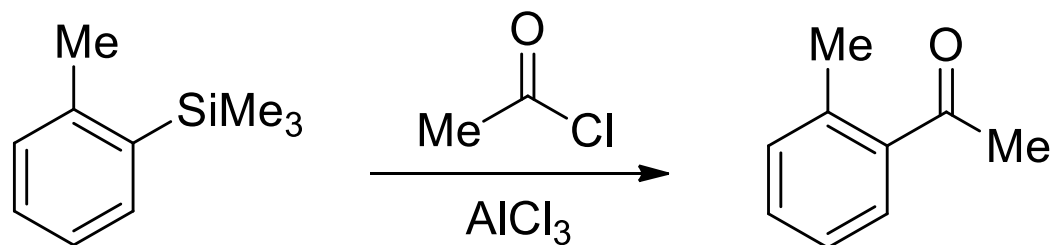
## Reactivity of alkenylsilanes

Sila-Nazarov-reaction



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

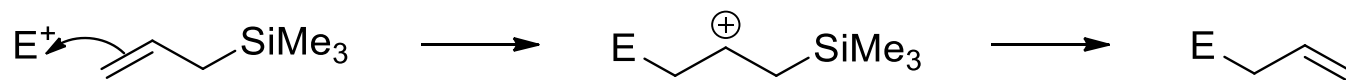
Aromatic ipso-substitution



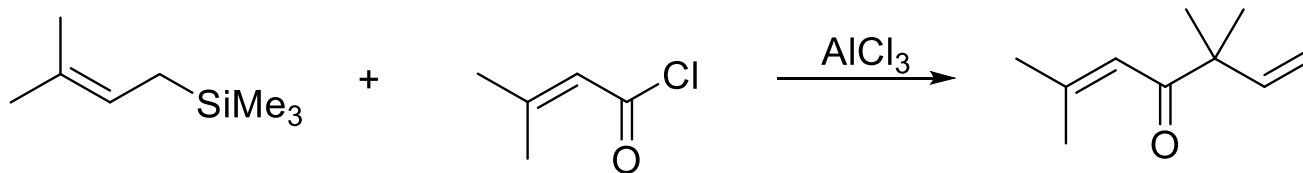
The reaction with  $\text{ArSnMe}_3$  is  $10^4$  time faster

## Allylic silanes in organic synthesis

General reactivity

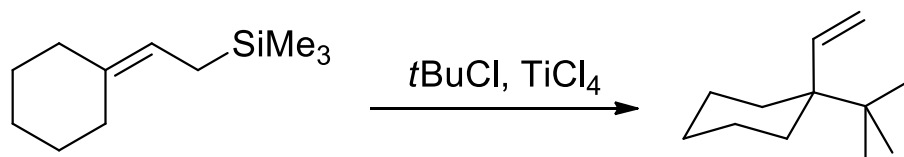


Acylation

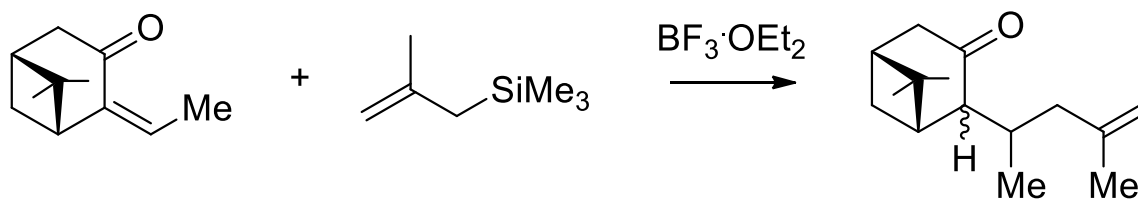


# Allylic silanes in organic synthesis

Allylation



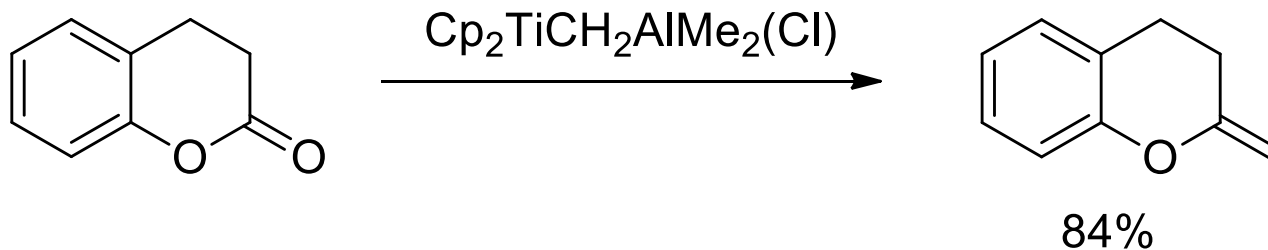
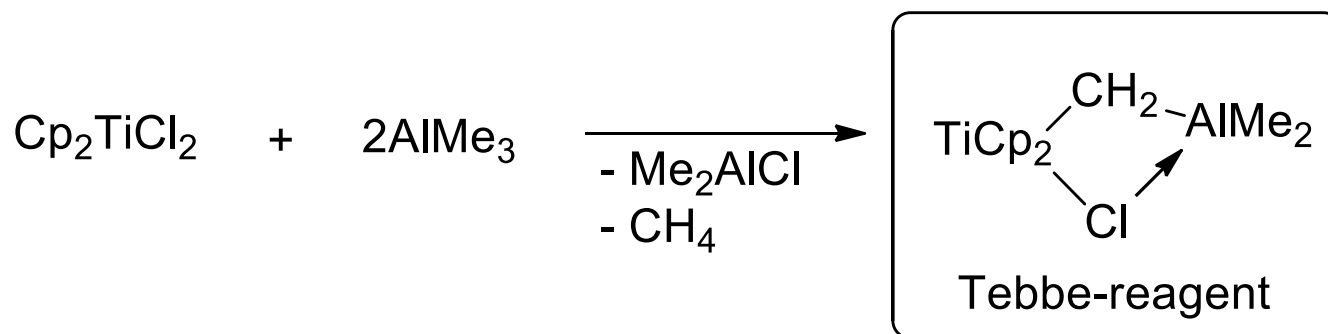
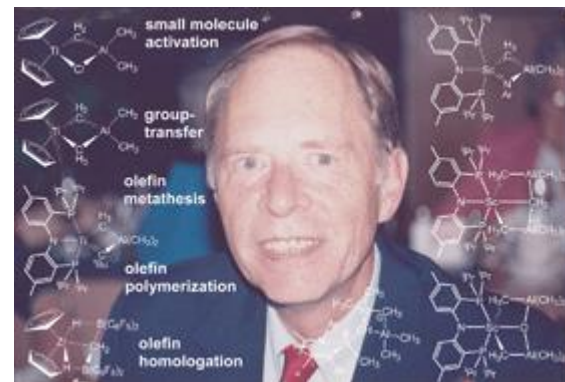
1,4-addition



T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Chem. Soc. Chem. Commun.* **1979**, 525.

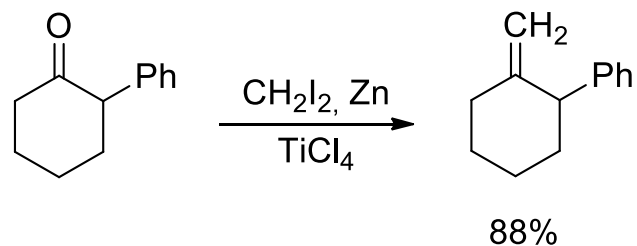
T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Org. Chem.* **1980**, 45, 607.

# Early transition metal organometallics: Titanium

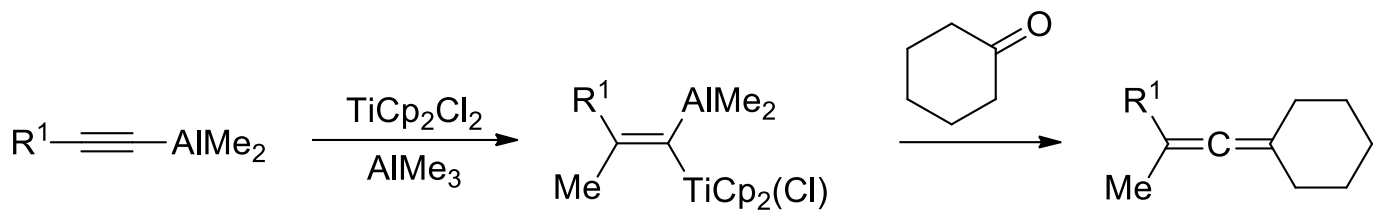
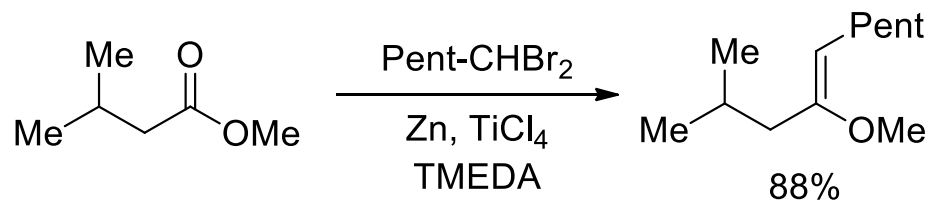


# Titanium

Lombardo-reagent



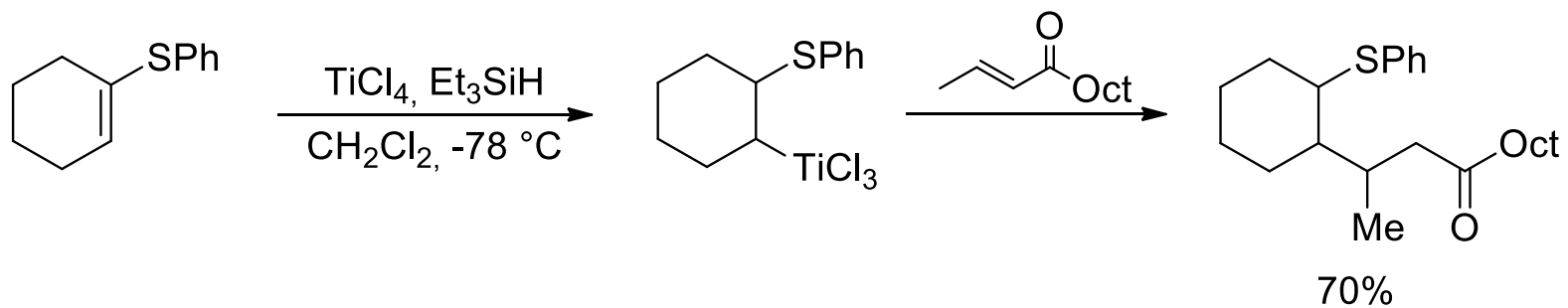
K. Takai, *J. Org. Chem.* **1994**, 59, 2668



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

# Titanium

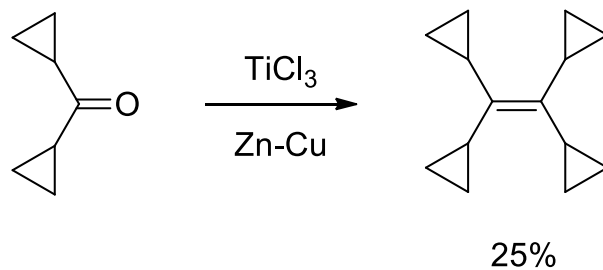
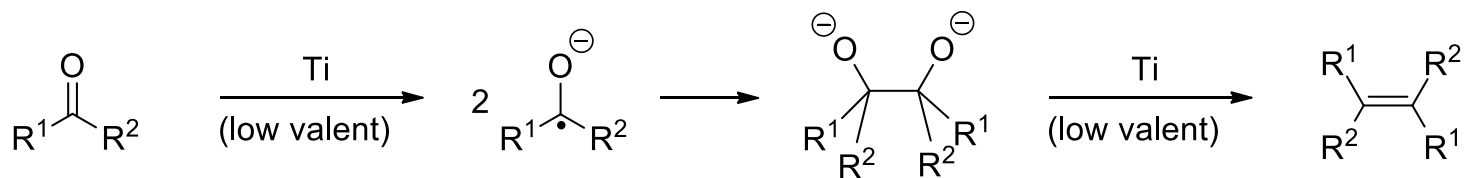
Hydrotitanation



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

# Titanium

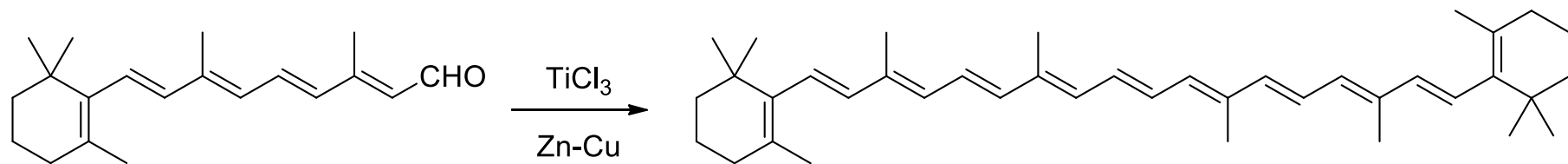
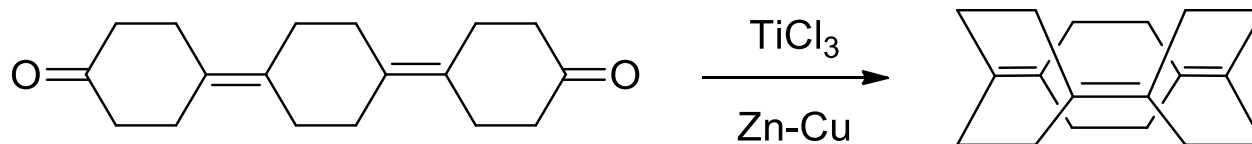
Reductive coupling: The McMurry Reaction



Review:

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

## Titanium



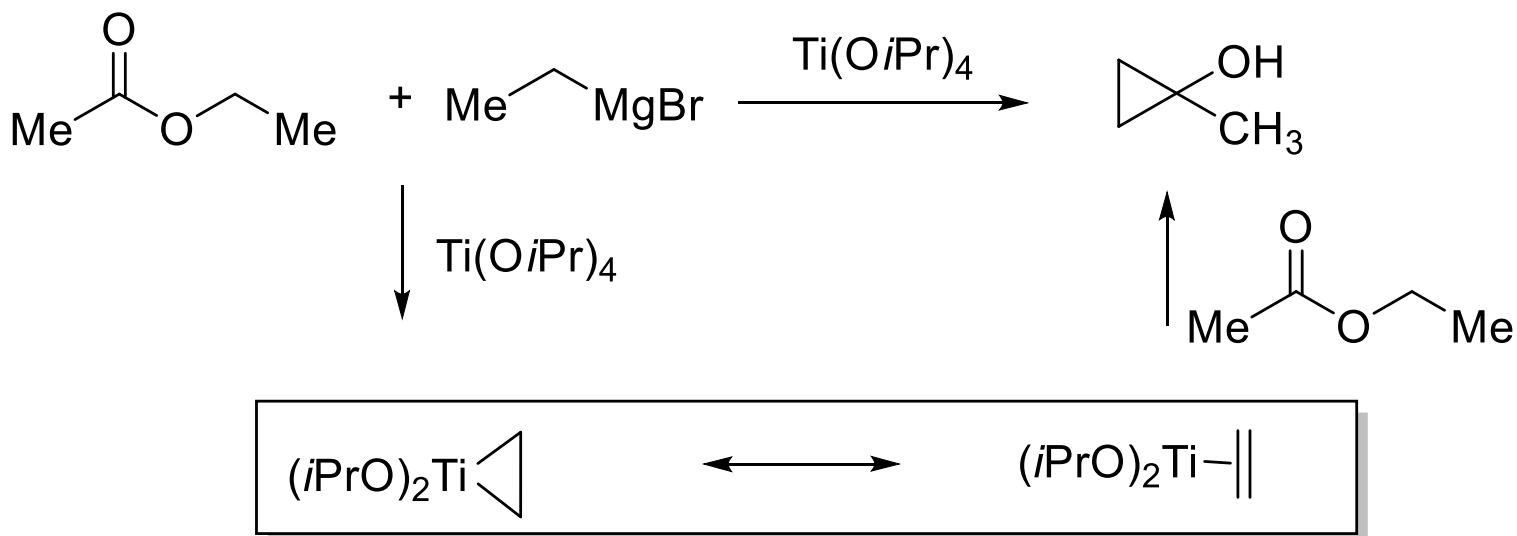
$\beta$ -Caroten: 94%

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



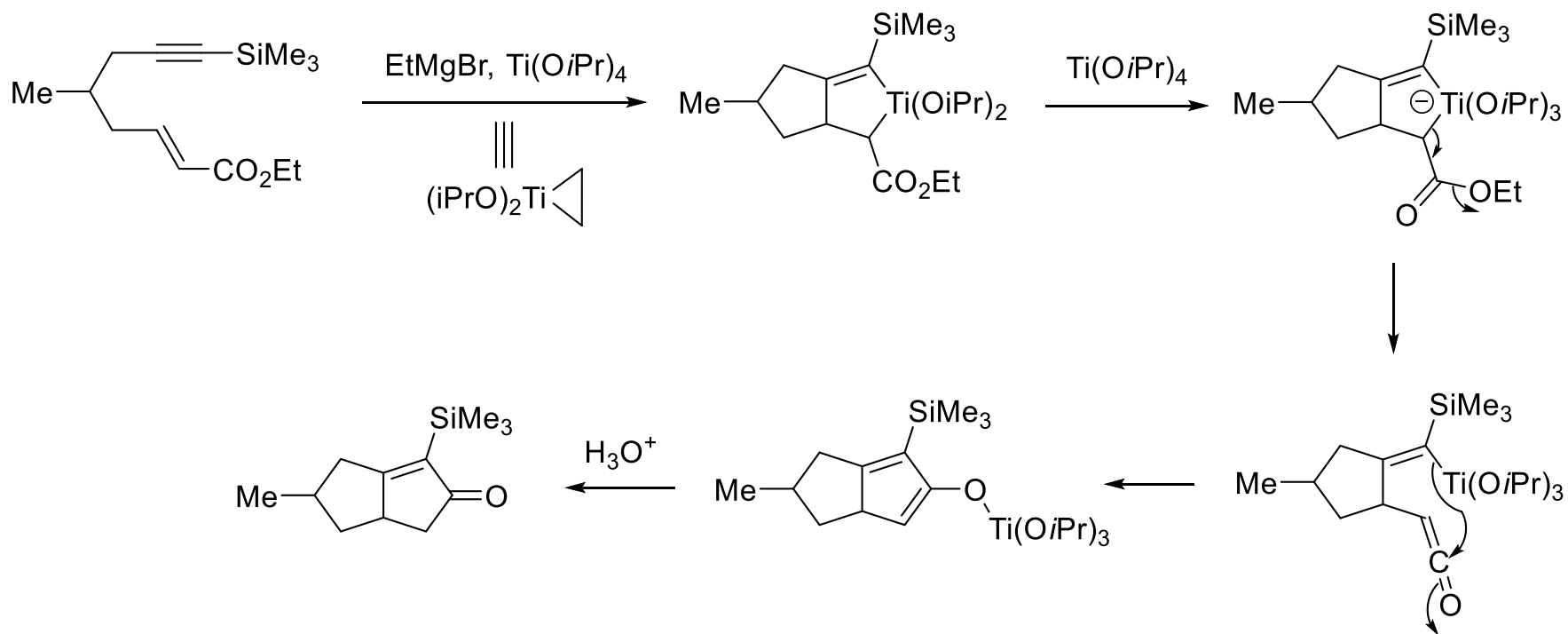
# Titanium

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.

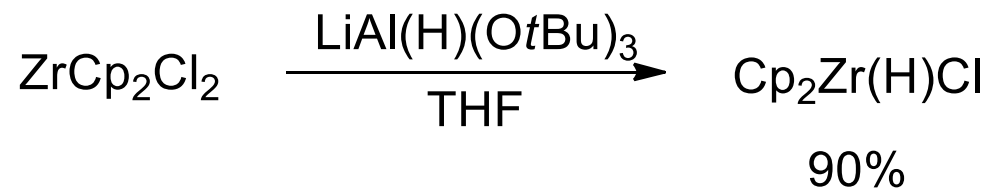
# Titanium



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

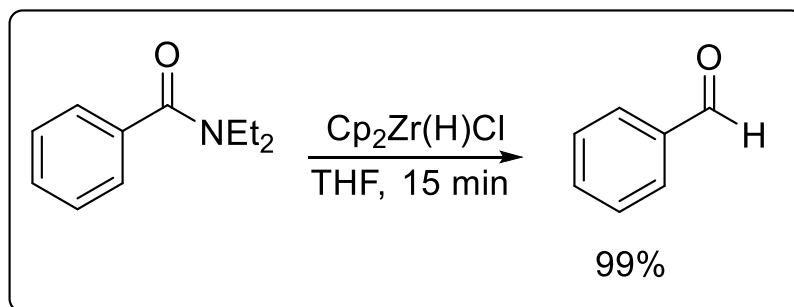
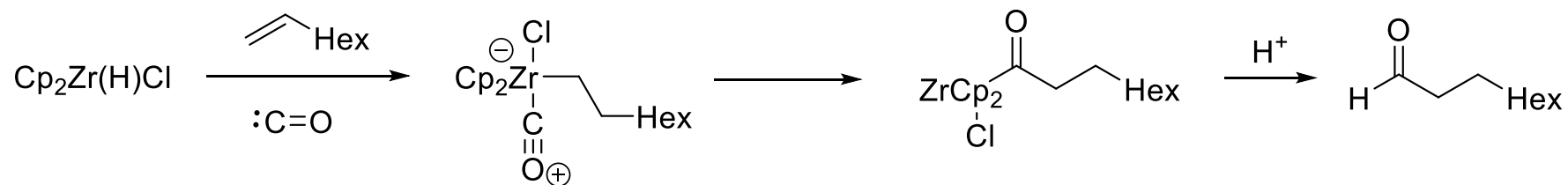
## Early transition metal organometallics: Zirconium

Schwartz's reagent:



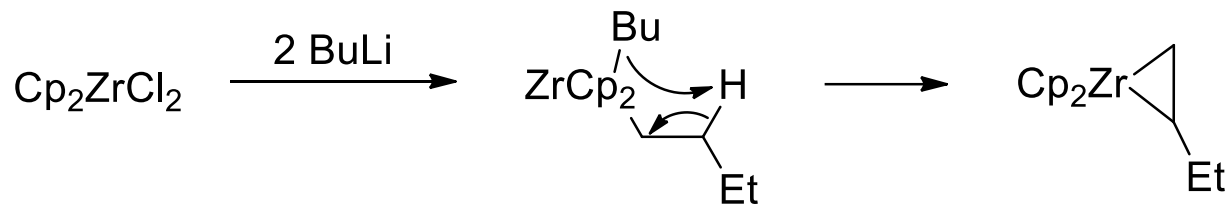
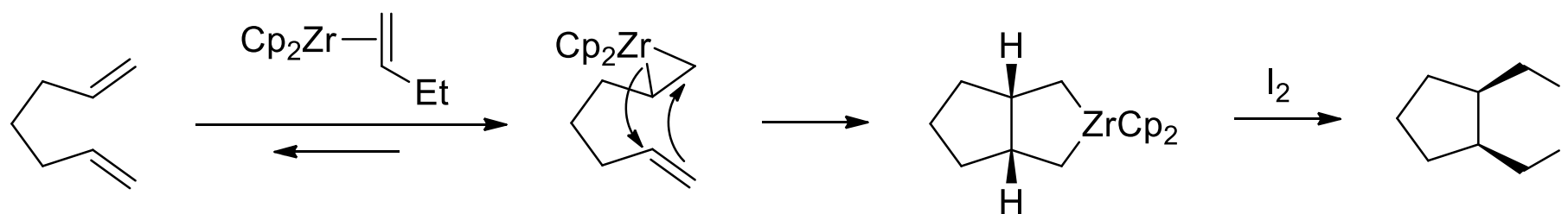
*Inorg. Synth.* **1979**, 19, 223

## Zirconium

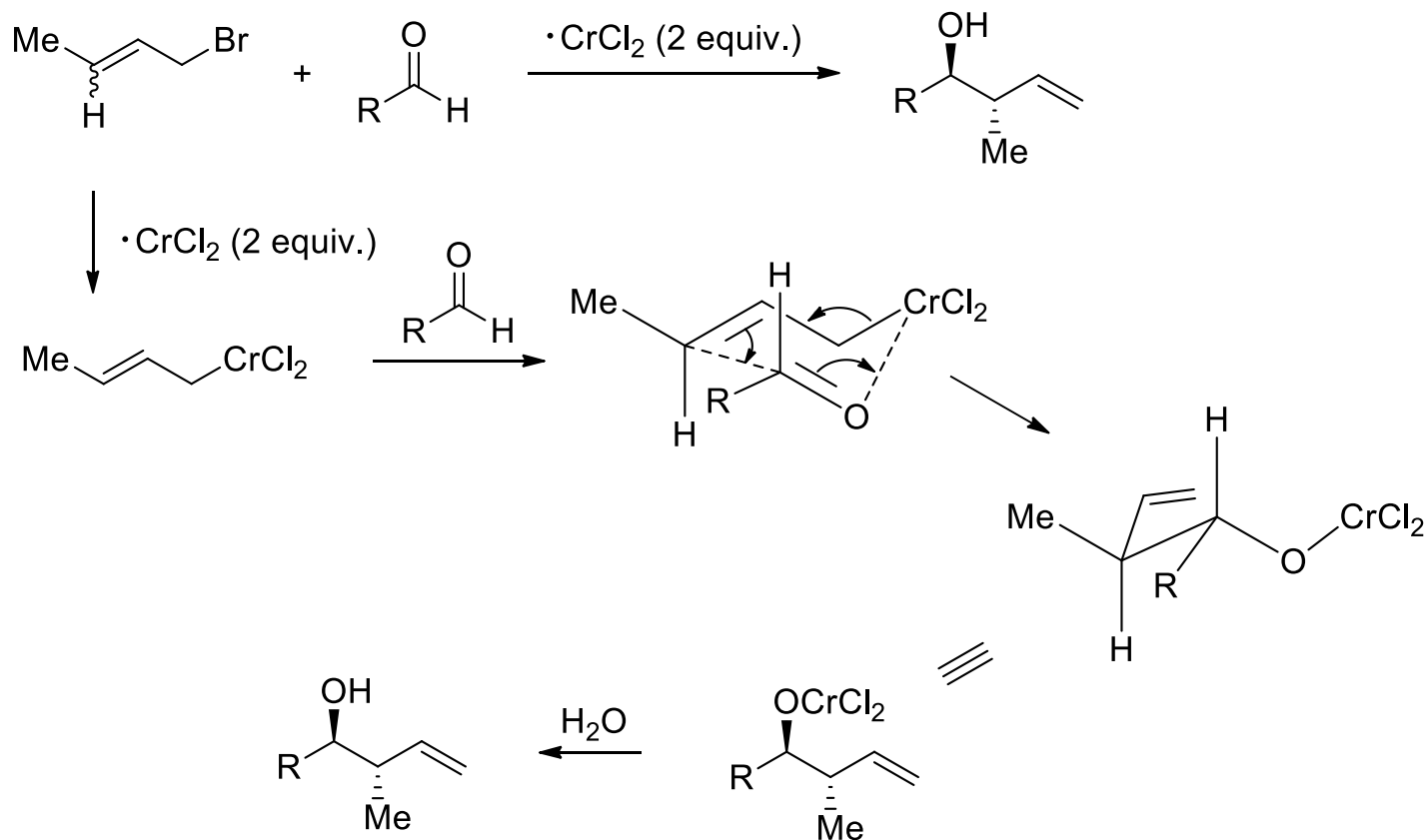


G. I. Georg *J. Am. Chem. Soc.* **2007**, 129, 3408

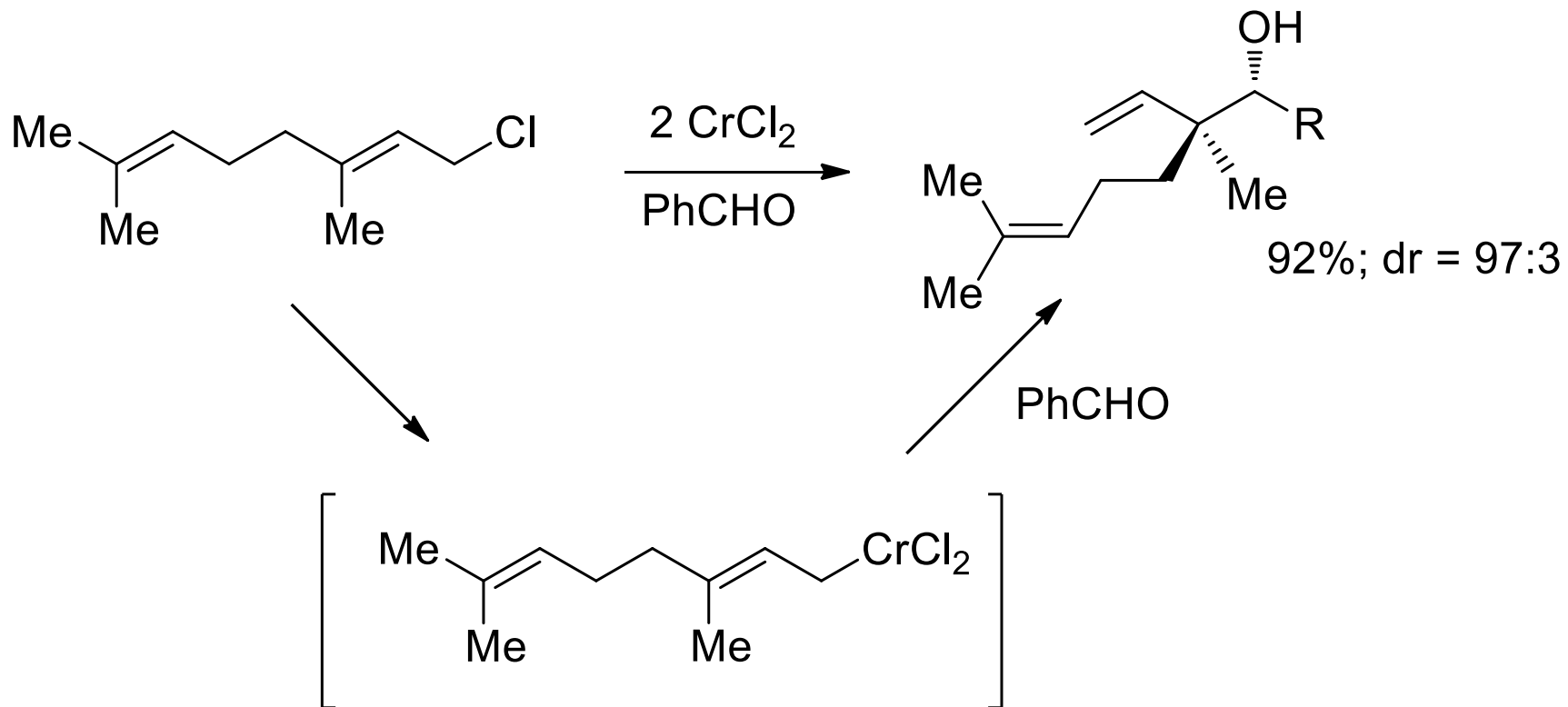
# Zirconium



# Early transition metal organometallics: Chromium



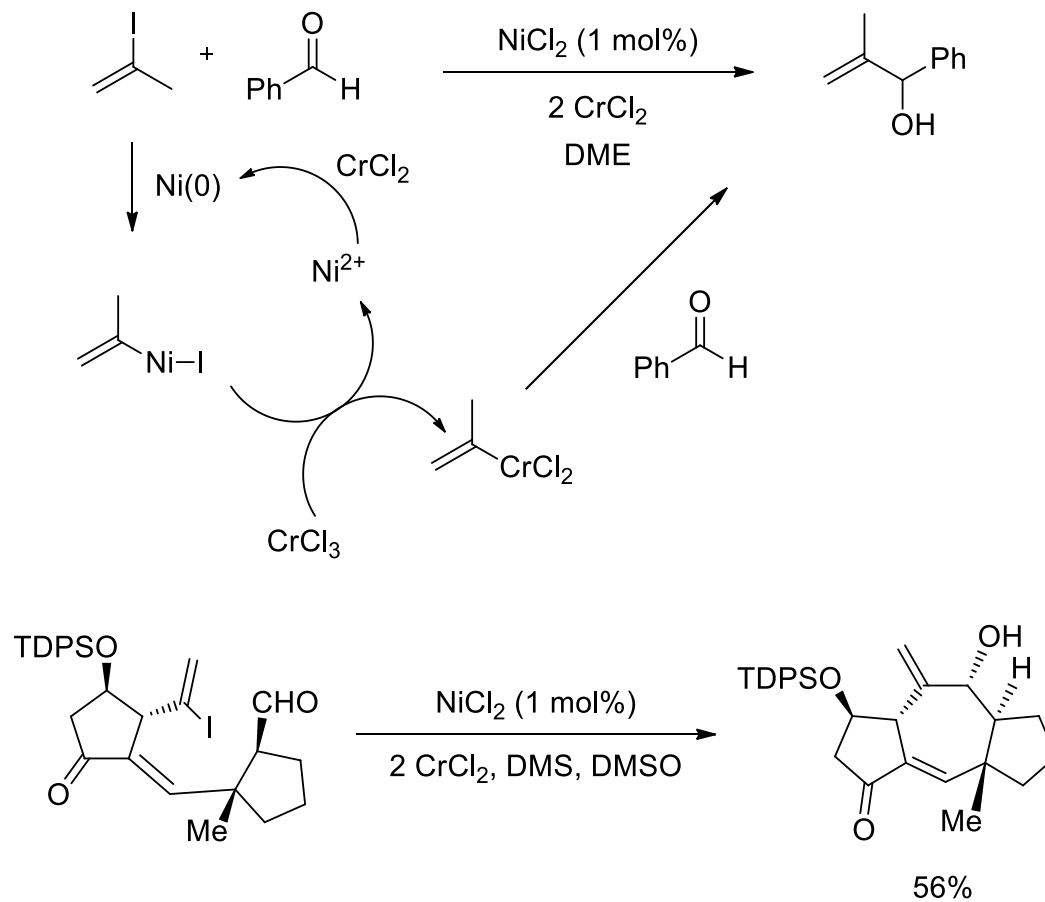
## Chromium



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

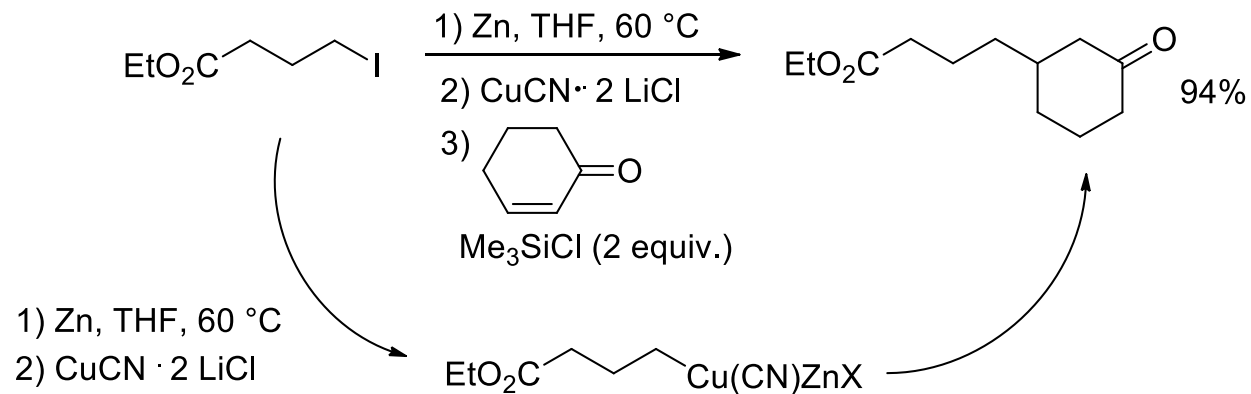
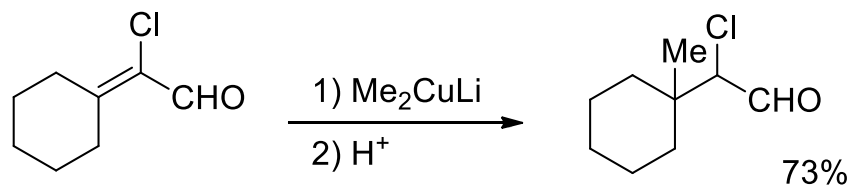
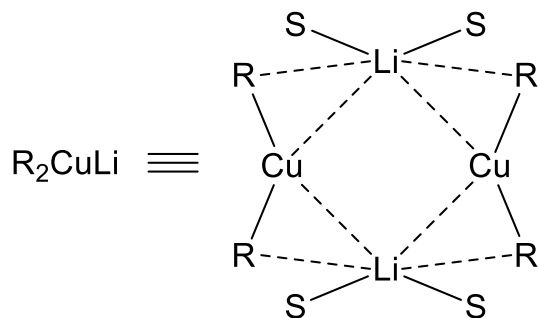
# Chromium

## Hiyama-Kishi-reaction



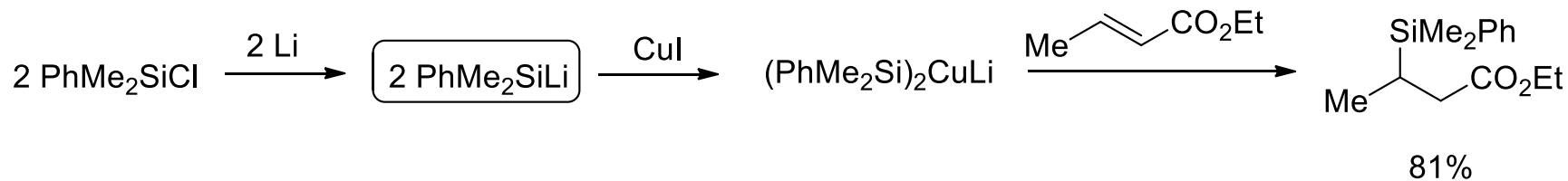


## Early transition metal organometallics: Copper

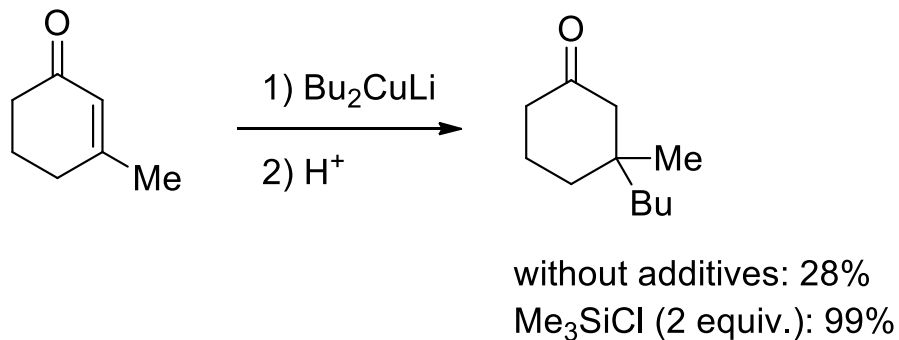


P. Knochel, et al. *J. Org. Chem.* **1988**, 53, 2390.

## Copper

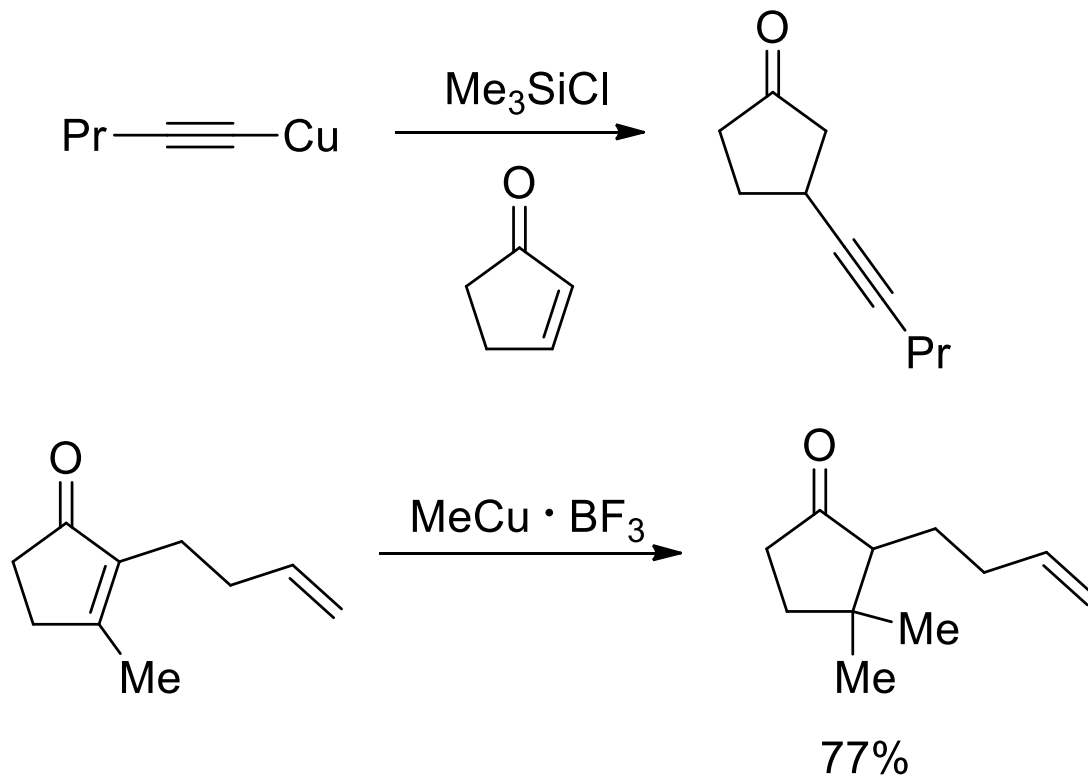


I. Fleming et al. *J. Chem. Soc., Perkin Trans.* **1998**, 1, 1209.



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

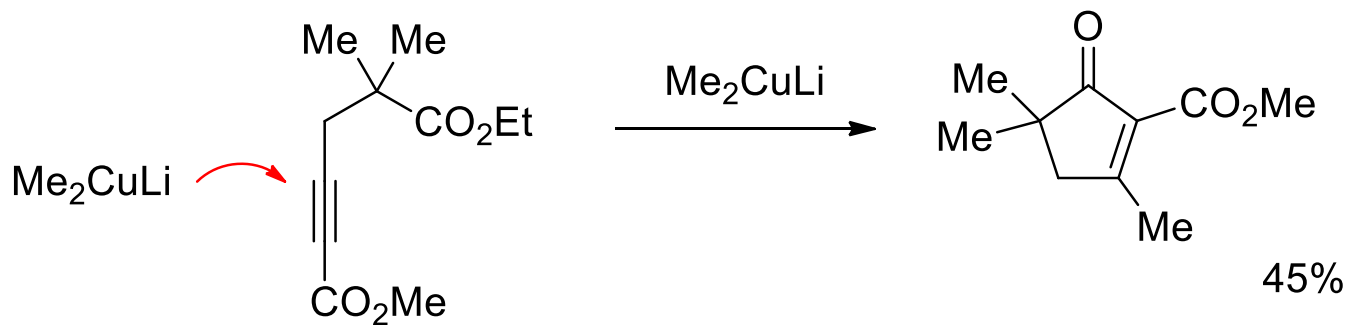
## Copper-mediated 1,4-addition



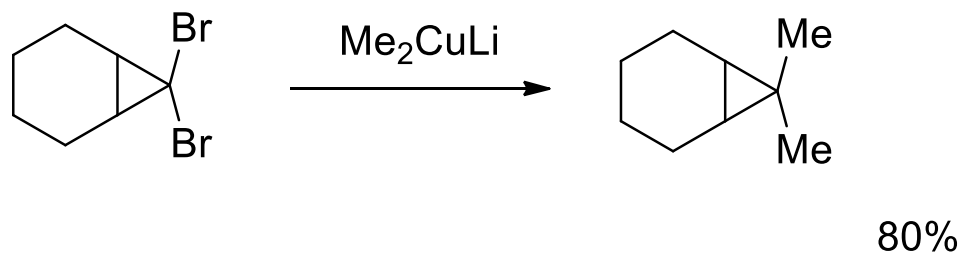
Y. Yamamoto, *Angew. Chem.* **1986**, 98, 945.

## Copper-mediated reactions

### Michael-addition



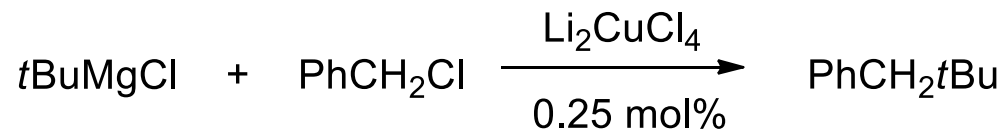
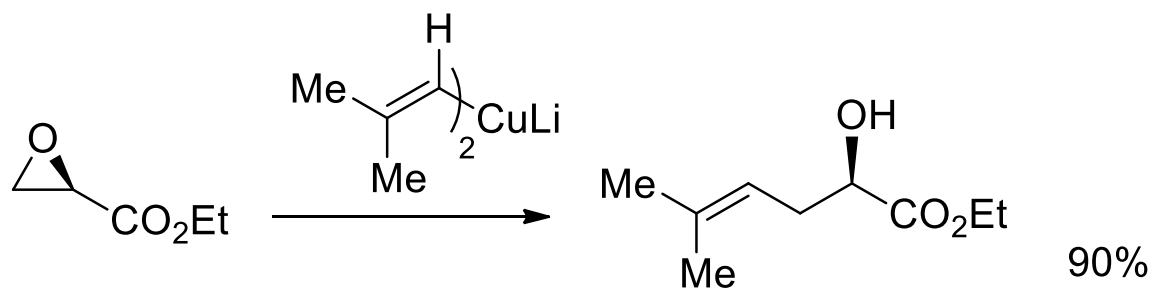
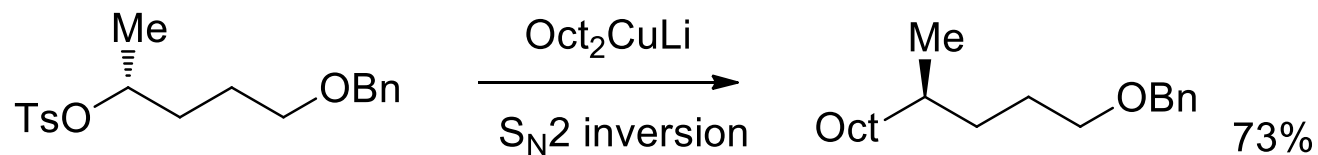
### Substitution reactions



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

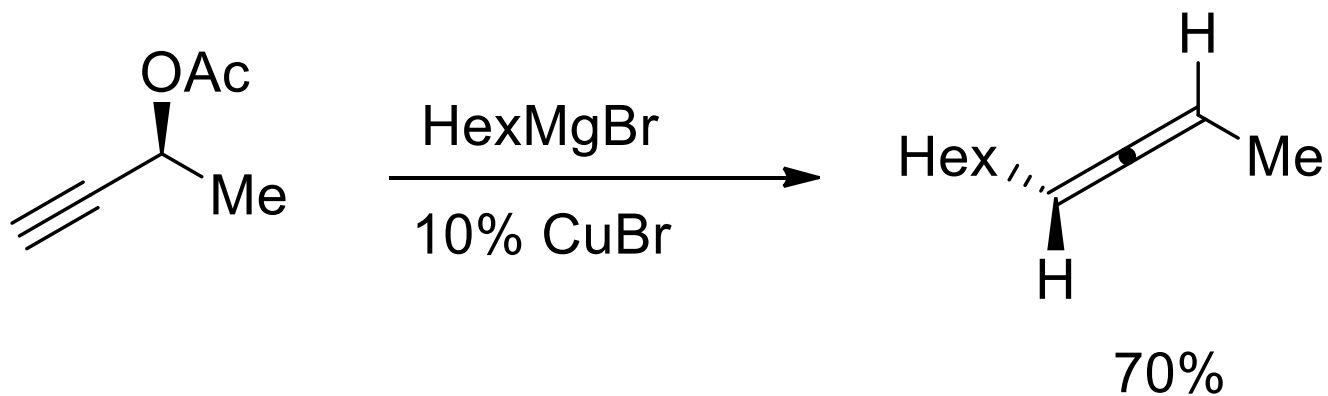
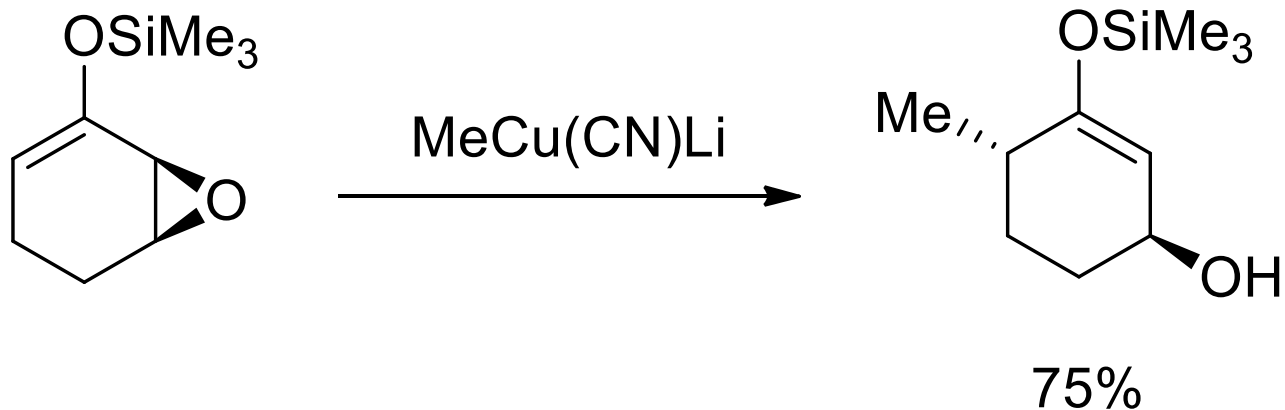
R. J. K. Taylor (Ed.), *Organocopper reagents*, Oxford University Press, Oxford, **1994**.

## Copper; substitution reactions



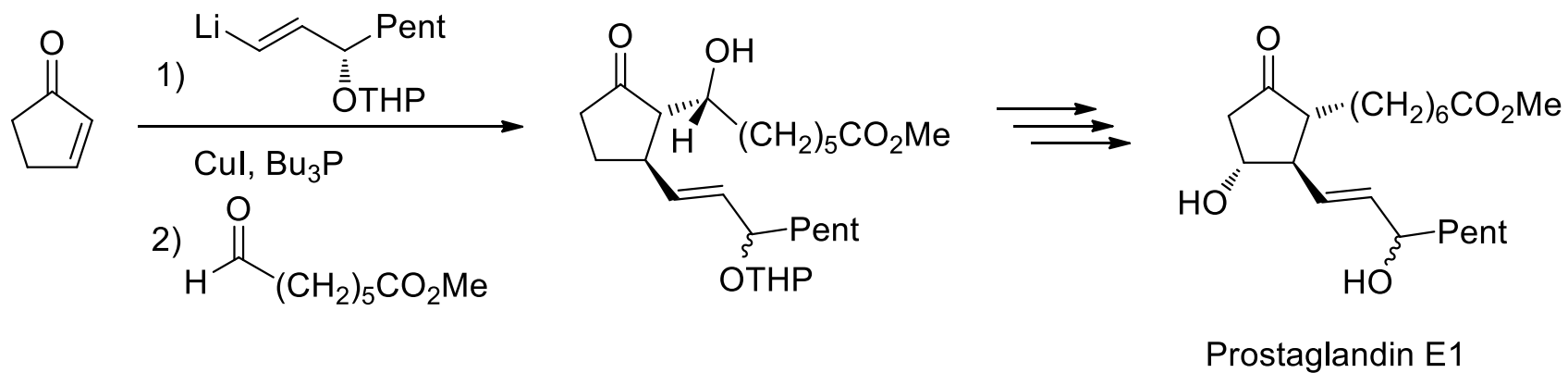
M. Larcheveque, Y. Petit, *Bull. Soc. Chim. Fr.* **1989**, 1, 130.

## Copper: allylic and propargylic substitution



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

## Copper: Prostaglandin synthesis



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

# Palladium

Price of Pd: **1.0**

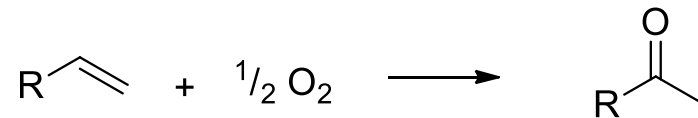
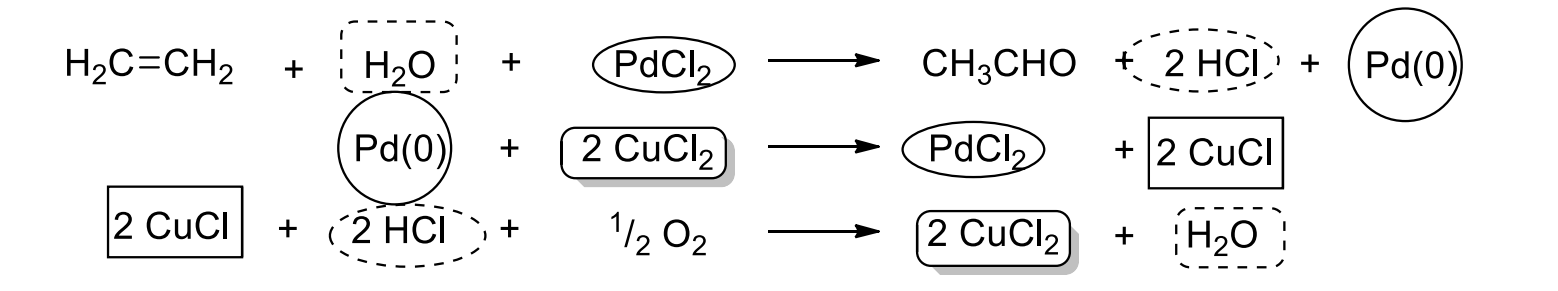
Pt: 3.3

Au: 1.9

Ru: 0.2

Rh: 2.8

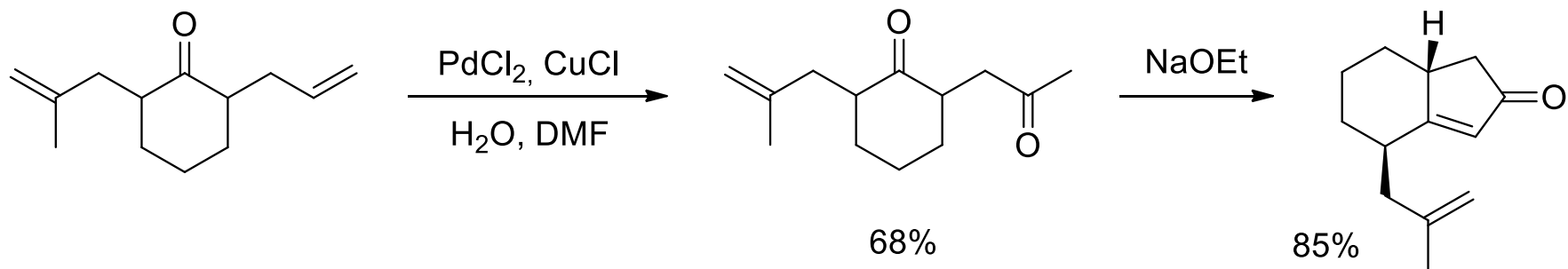
## Wacker-Reaction:



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



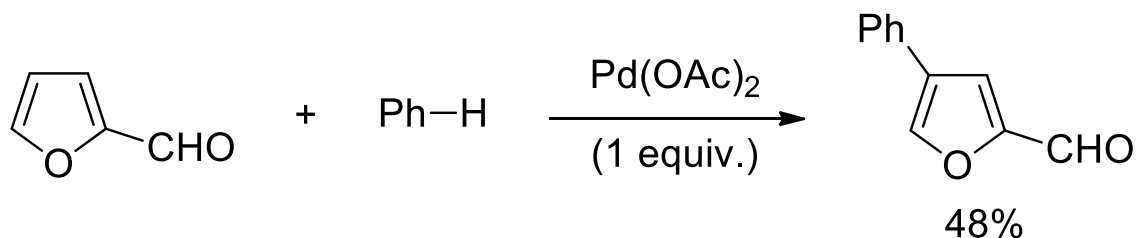
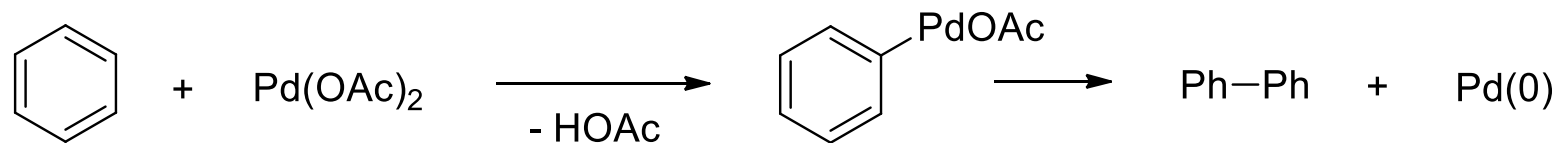
## Palladium



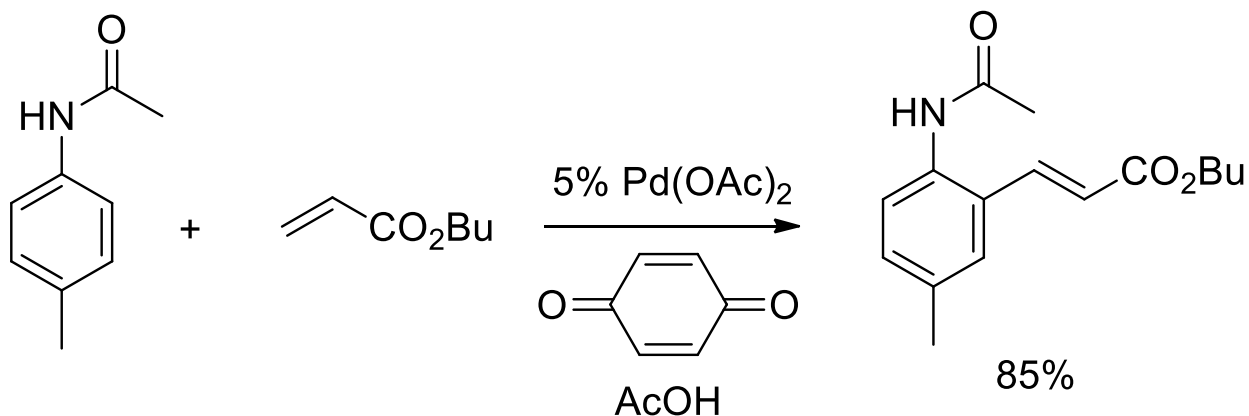
J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett.* **1976**, 34, 2975.

# Palladium

C-H activation



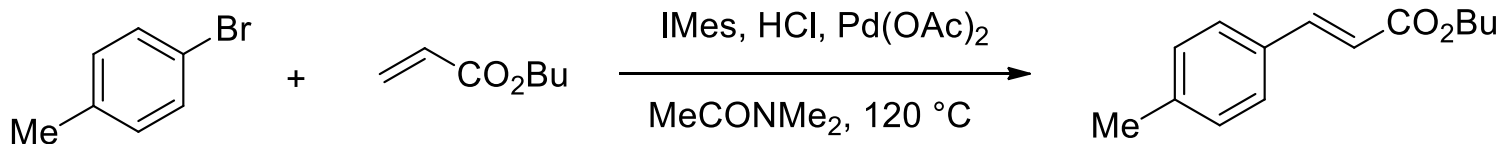
T. Itahara, *J. Org. Chem.* **1985**, 50, 5272.



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

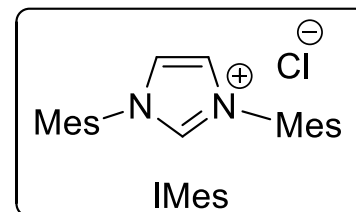
# Palladium

## Heck Reaction



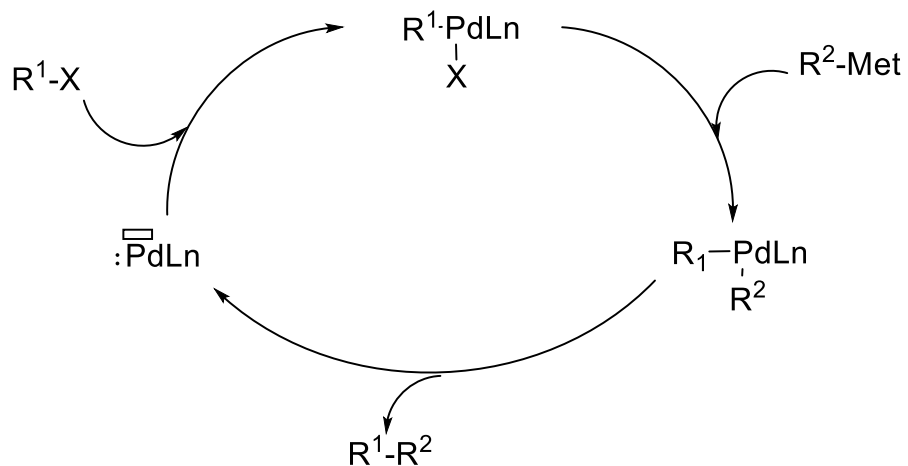
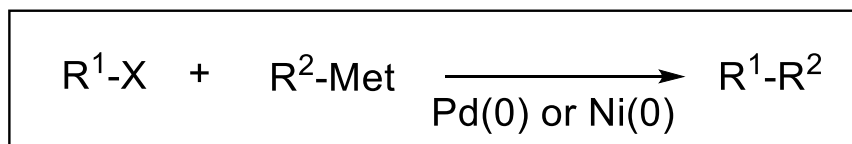
The method of T. Jeffery uses Bu<sub>4</sub>NBr at 25 °C.

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



# Palladium-catalyzed cross-coupling

Cross-coupling using Pd(0)-catalysts



Suzuki-coupling

Met =  $\text{B(OH)}_2$

Stille-coupling

Met =  $\text{SnR}_3$

Negishi-coupling

Met =  $\text{ZnX}$

Kumada-coupling

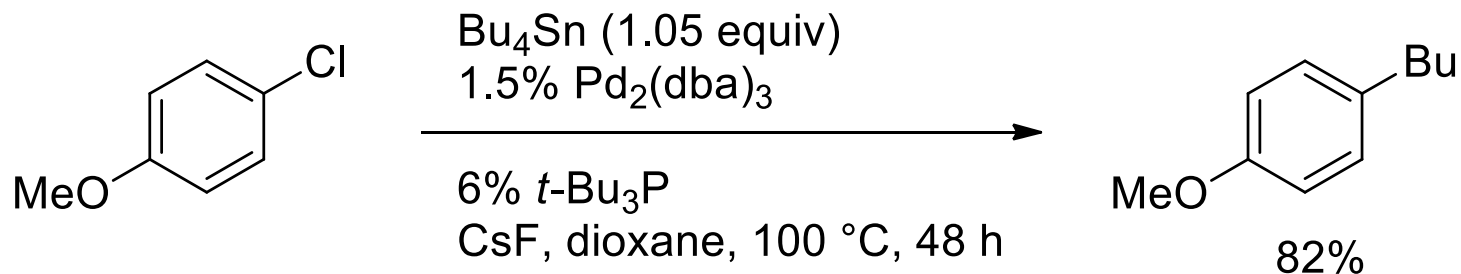
cat = Ni; Met =  $\text{MgX}$

Sonogashira-coupling

Csp-Csp<sup>2</sup>

# Palladium

## Stille cross-coupling



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

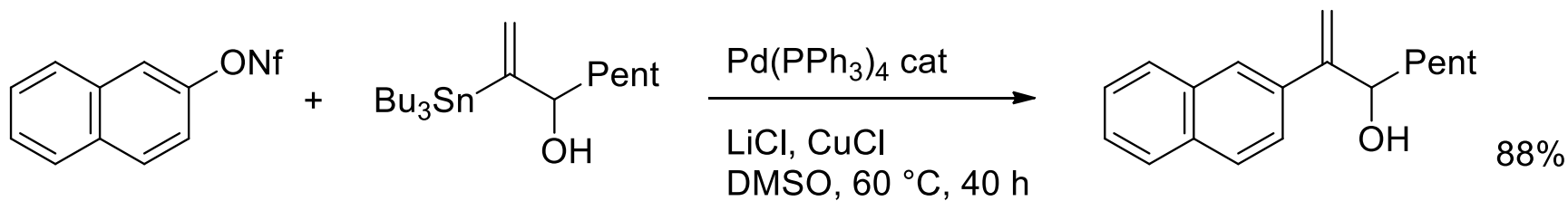
On the mechanism of the Stille cross-coupling:

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

*J. Am. Chem. Soc.* **2000**, 122, 1771.

# Palladium

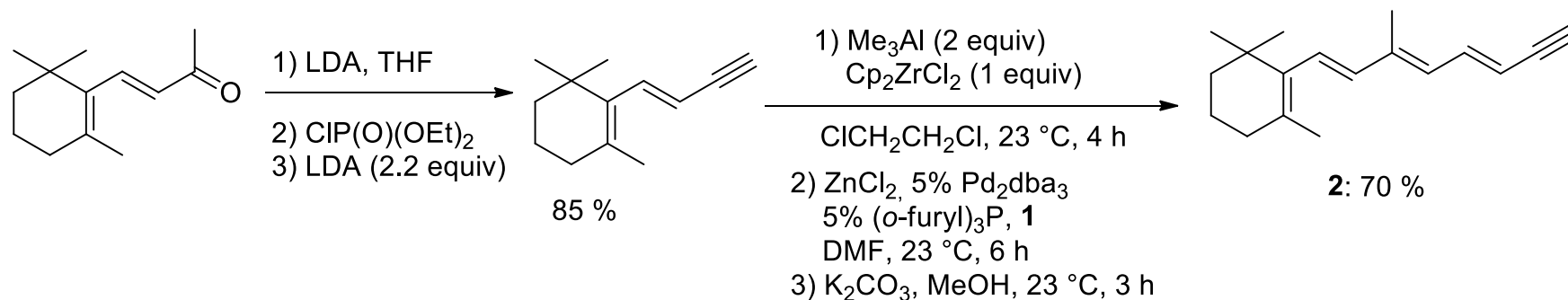
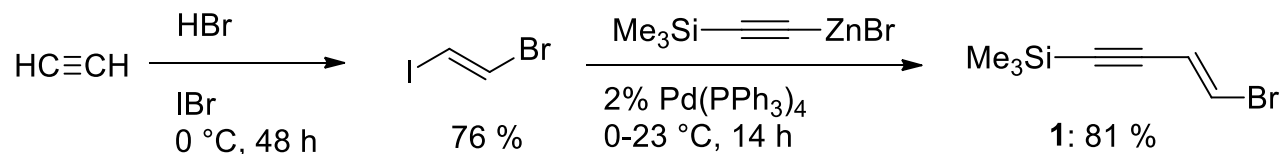
## Cu-accelerated Stille-reaction



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

# Negishi reactions

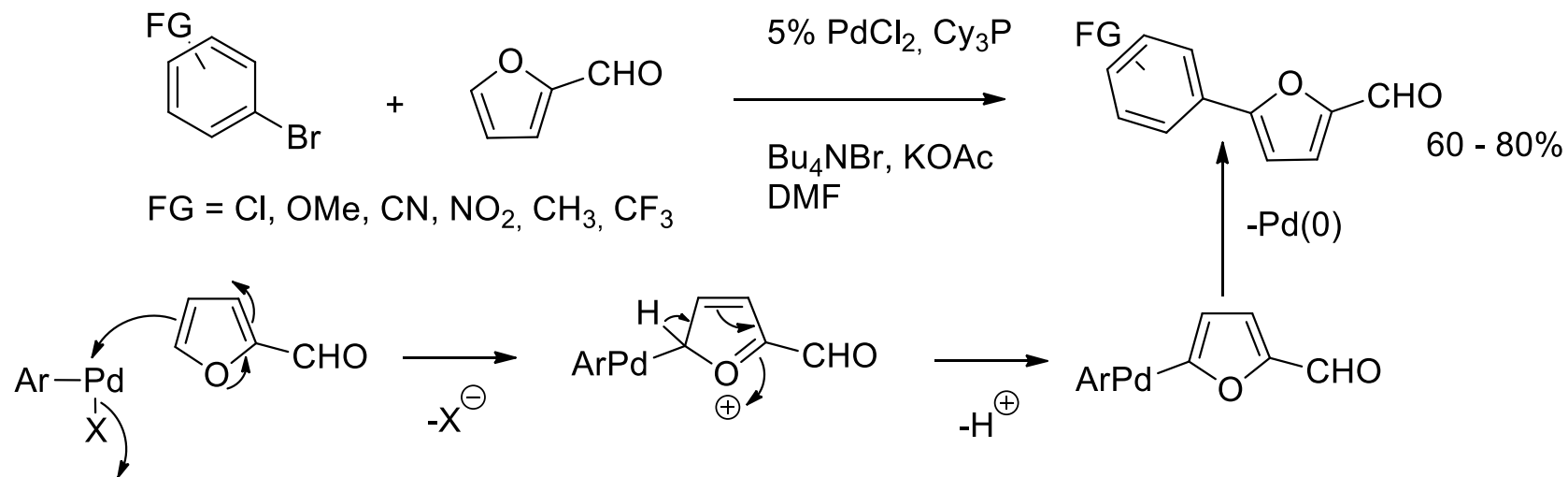
Synthesis of carotenoids *via* Zr-catalyzed carboalumination and Pd /Zn-catalyzed cross-couplings:



**$\beta$ -carotene: 68%; >99% isomeric purity**

# Palladium

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

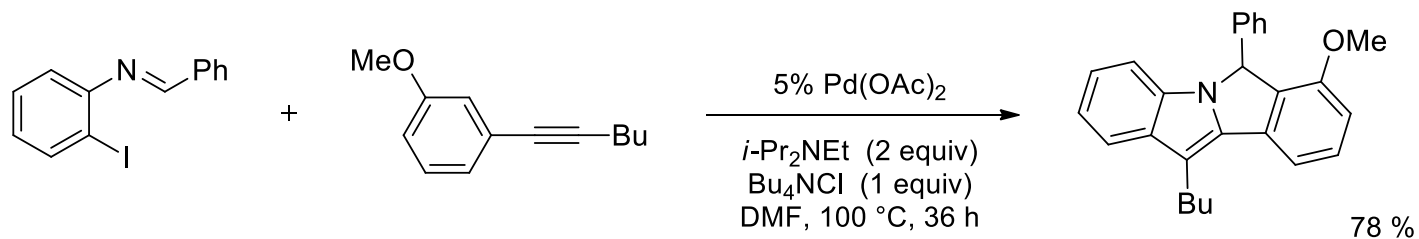


M. S. McClure, *Org. Lett.* **2001**, 3, 1677

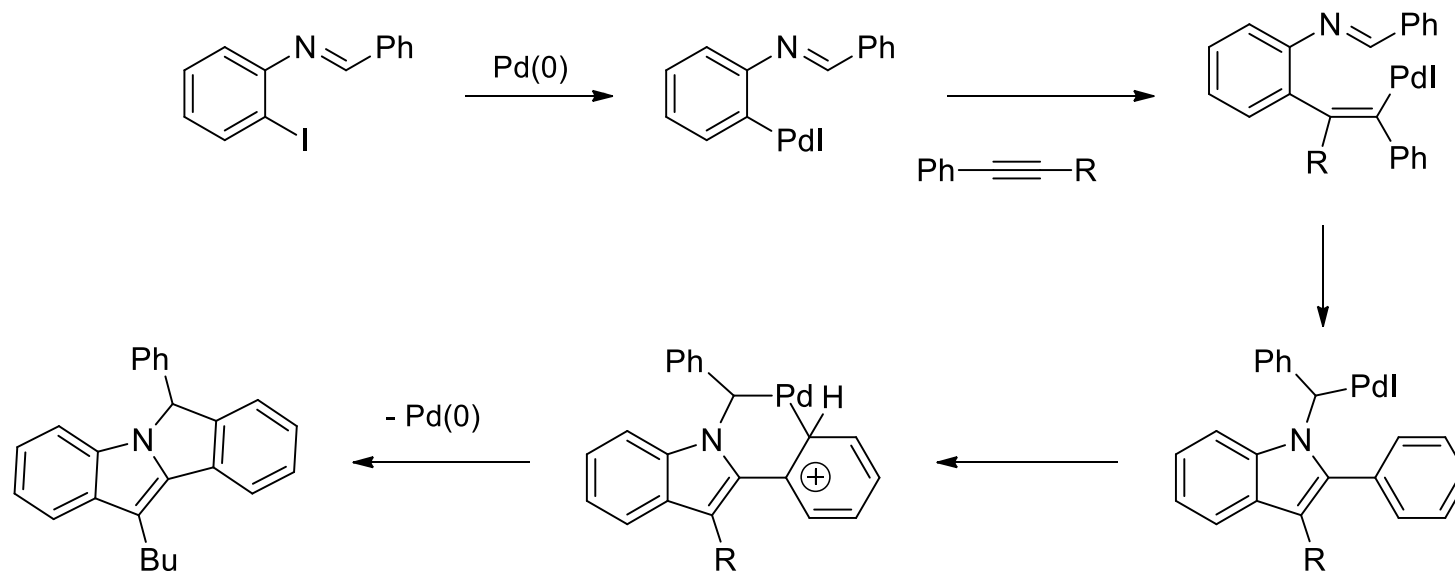


# Palladium

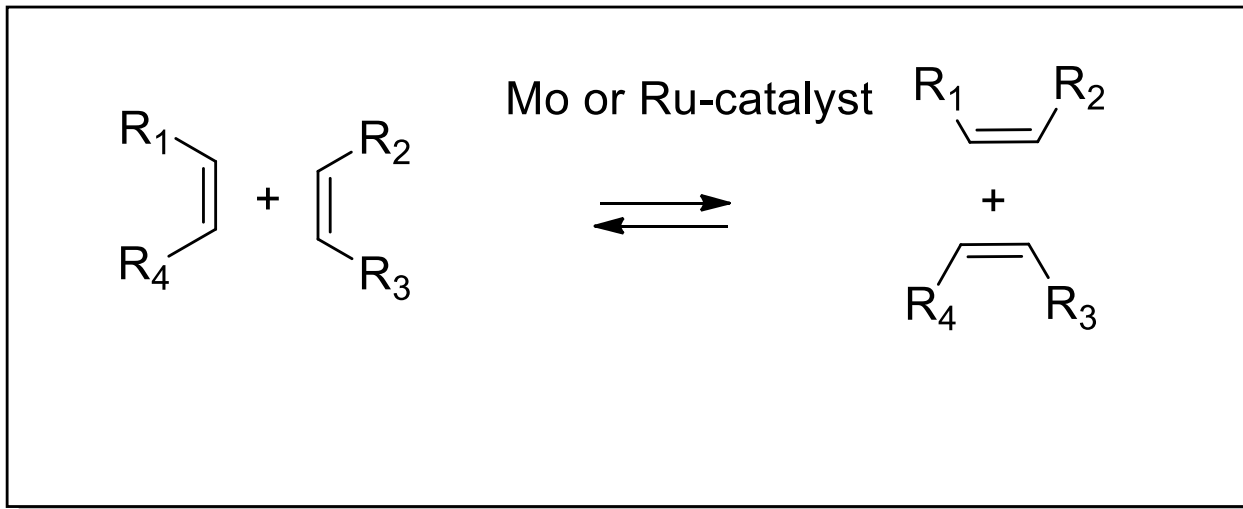
## Pd-catalyzed heterocycle synthesis



### Mechanism



## Olefin metathesis



Reviews:

R.H. Grubbs, *Tetrahedron* **1998**, 54, 4413.

A.S.K. Hashmi, *J. Prakt. Chemie* **1997**, 339, 1954.

M.E. Maier, *Angew. Chem. Int. Ed.* **2000**, 39, 2073.

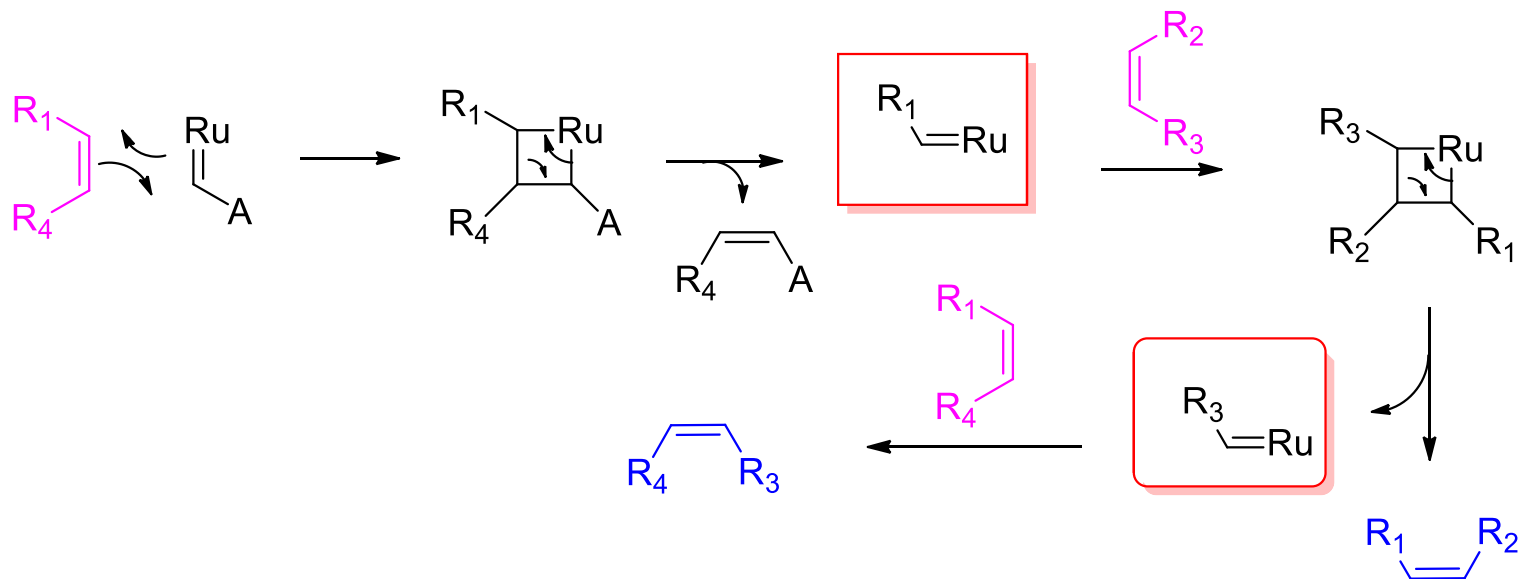
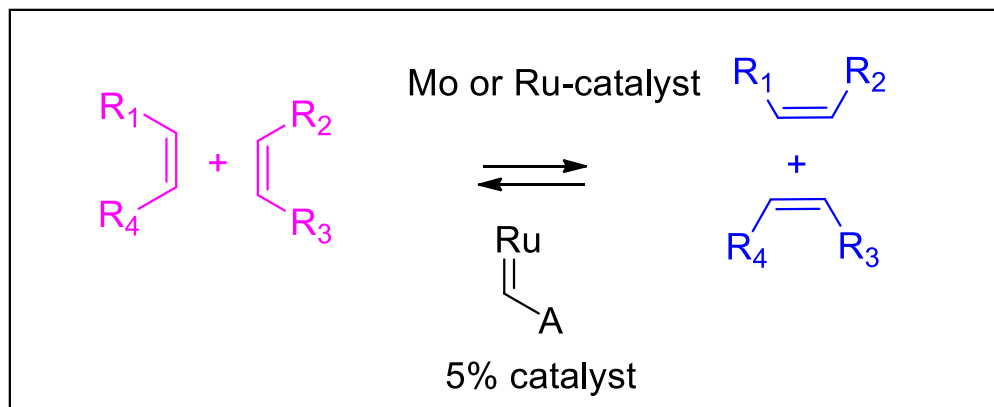
S.Blechert, *Angew. Chem.* **1997**, 109, 2124.

A.Fürstner, (Ed.) *Alkene Metathesis in Organic Synthesis*  
in *Top. Curr. Chem.*, Springer Verlag, Berlin, **1998**.

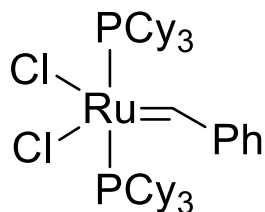
E.M. Carreira, *Synthesis* **2000**, 857.

Mechanistic study: R.H. Grubbs, *J. Am. Chem. Soc.* **2001**, 123, 749.

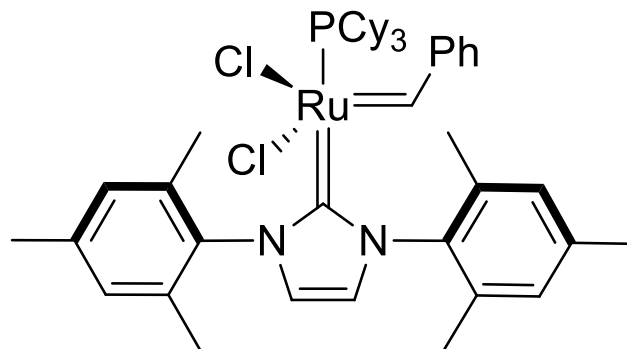
# Olefin metathesis mechanism



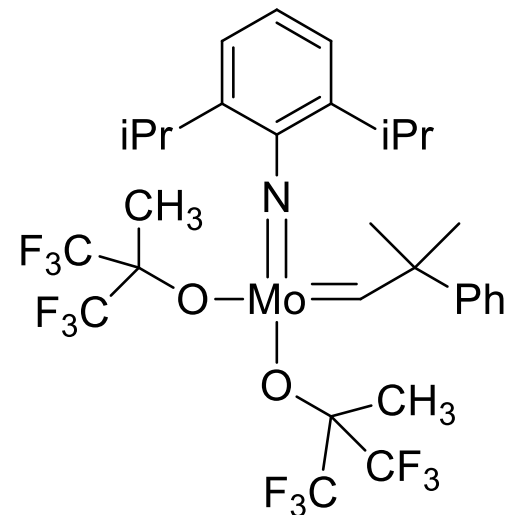
# Olefin metathesis



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

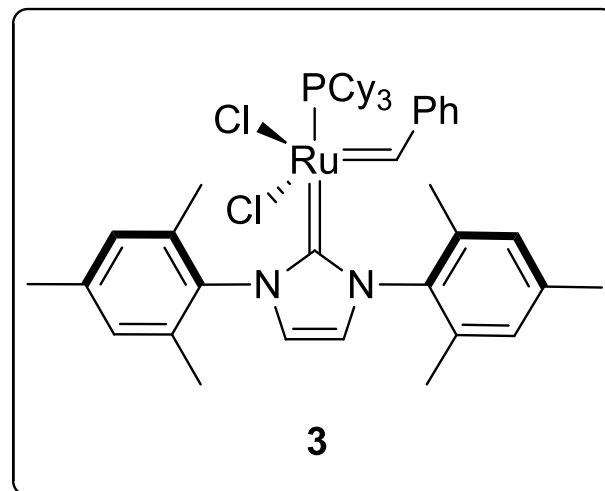
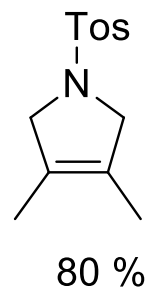
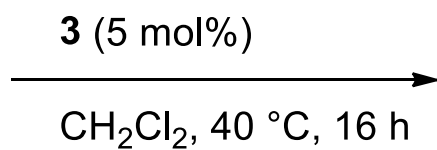
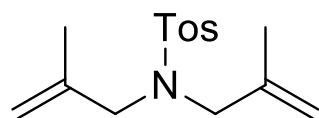


**2:** Grubbs-catalyst  
second generation  
US Patent No. 6,111,121  
and 7,329,758



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

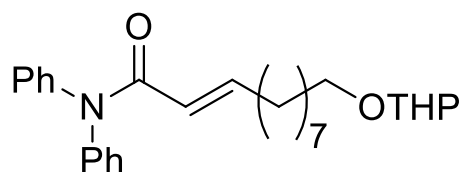
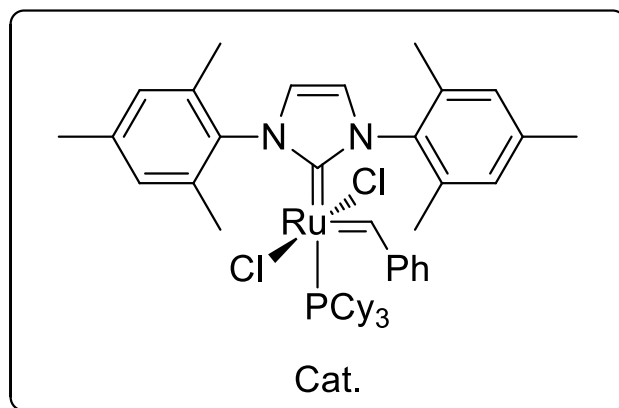
## Olefin metathesis



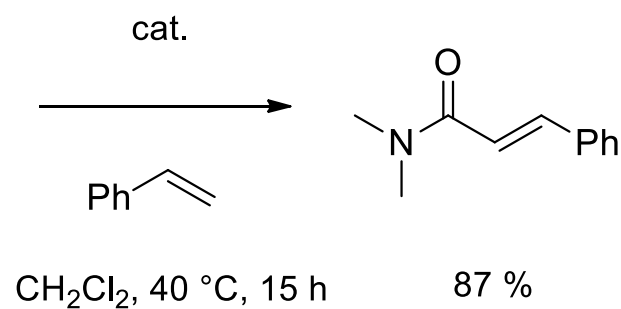
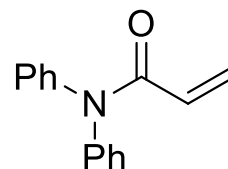
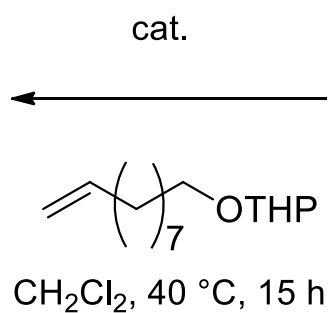
A. Fürstner, W.A. Herrmann, *Tetrahedron Lett.* **1999**, 40, 4787

# Olefin metathesis

Synthesis of  $\alpha,\beta$ -unsaturated amides by olefin cross-metathesis



100 %

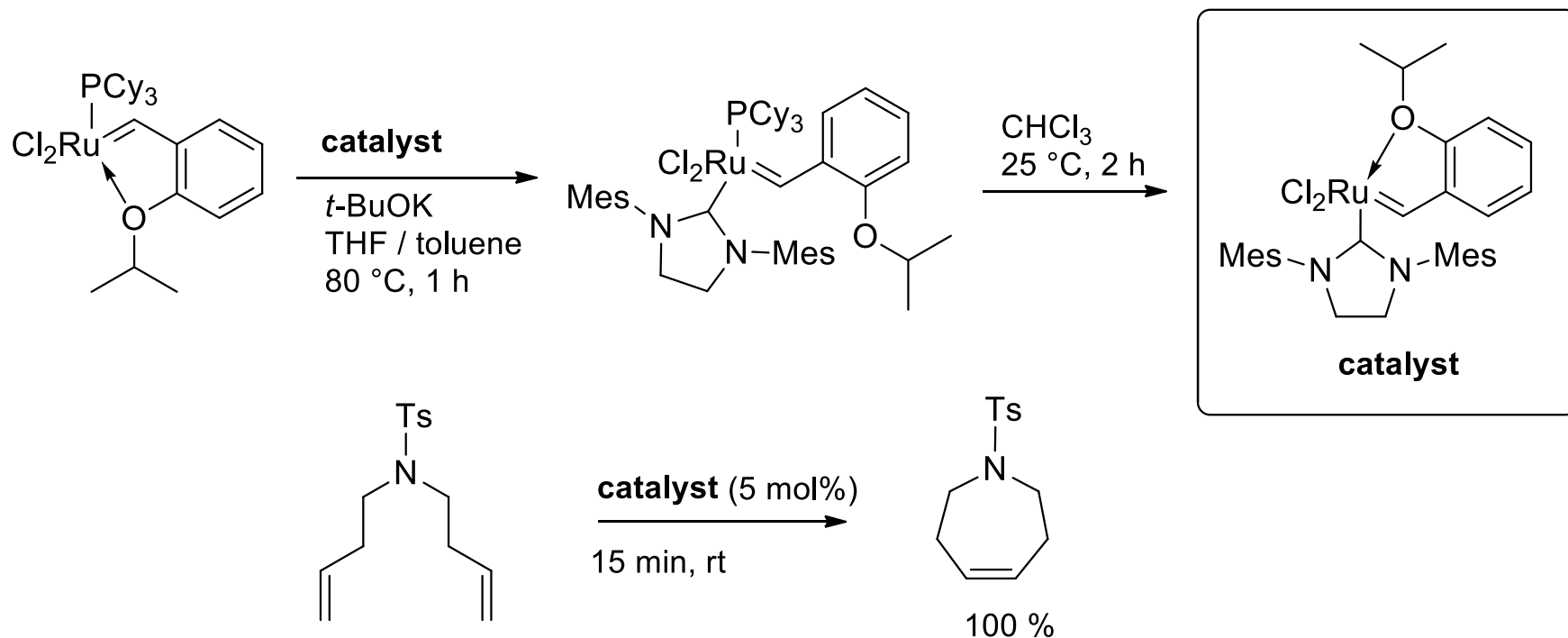


87 %

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

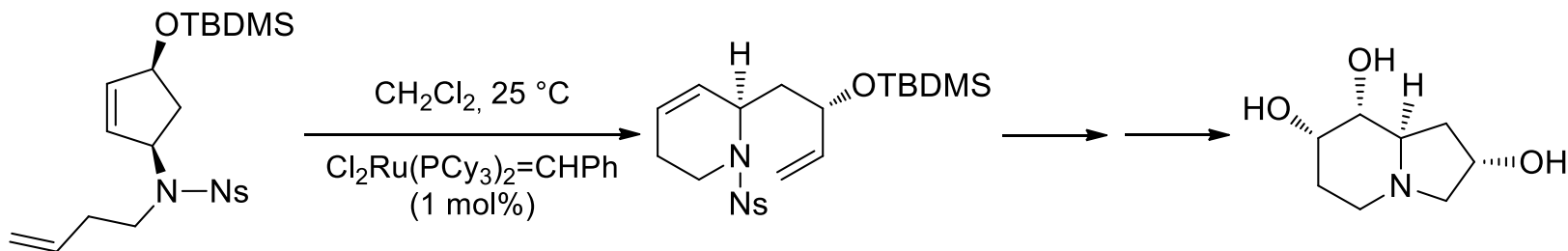
# Olefin metathesis

New phosphine-free metathesis catalyst



# Application to the synthesis of natural products

## Synthesis of aza sugars



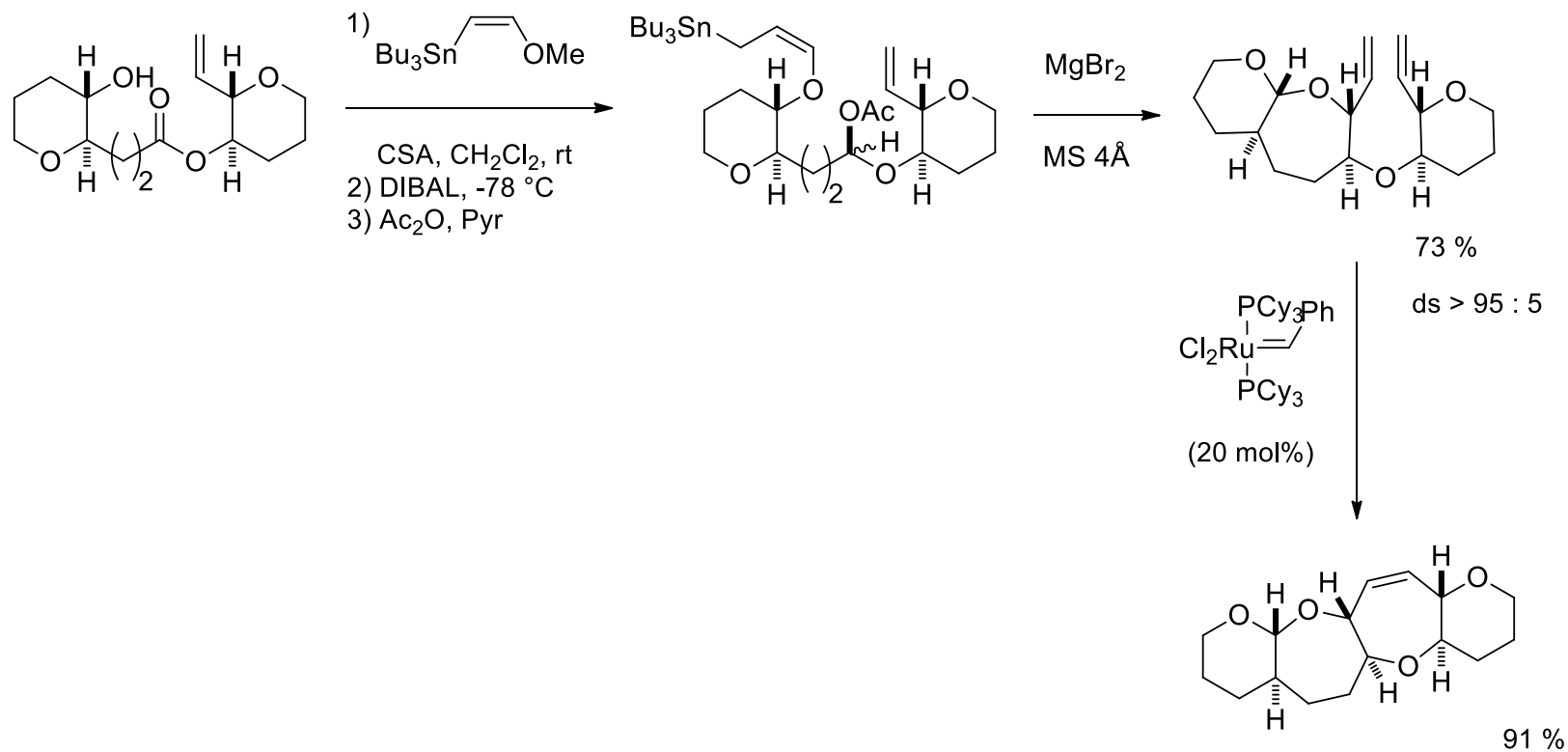
Ns =  $(o\text{-NO}_2)\text{C}_6\text{H}_4\text{SO}_2^-$

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

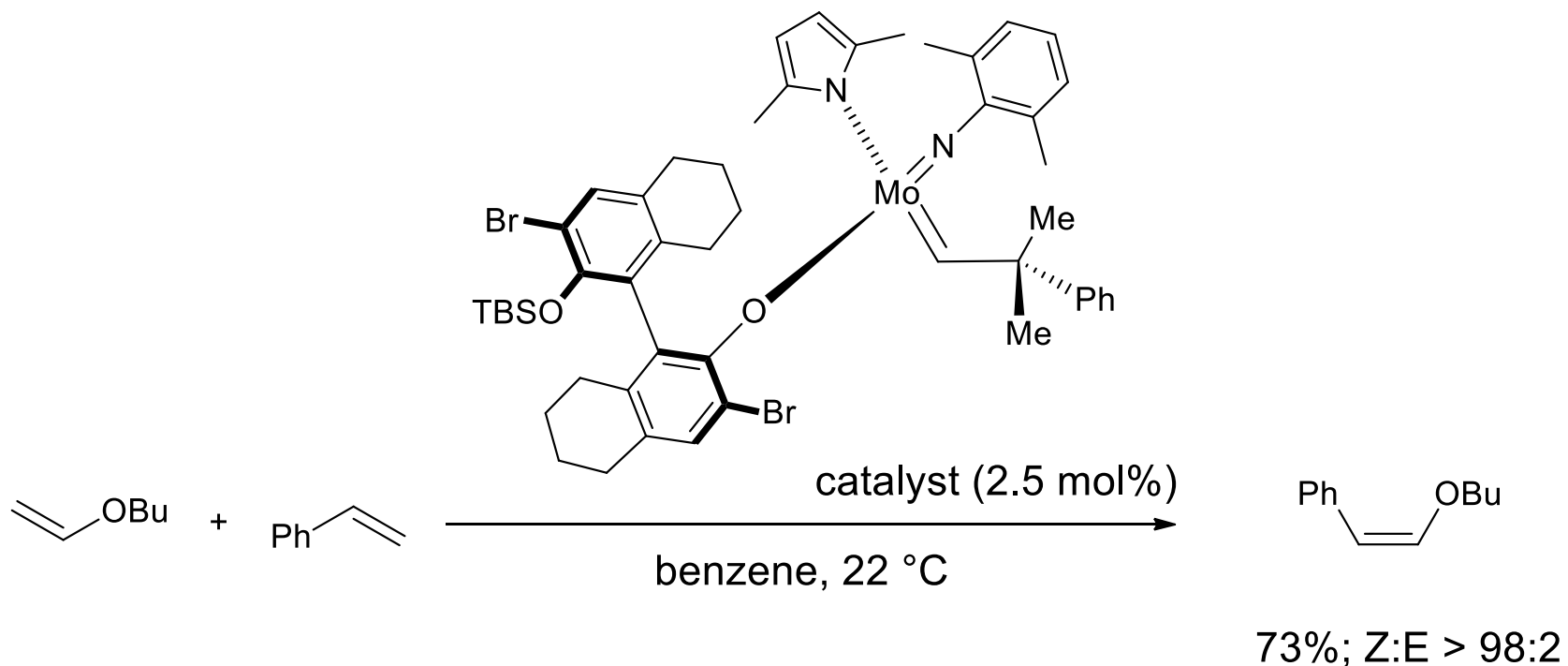


# Olefin metathesis

Synthesis of complex ring-systems *via* metathesis



## State of the art

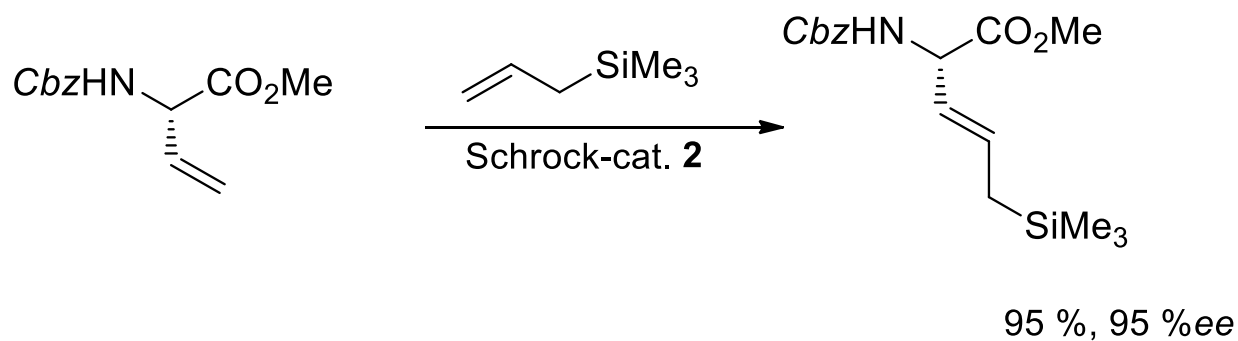
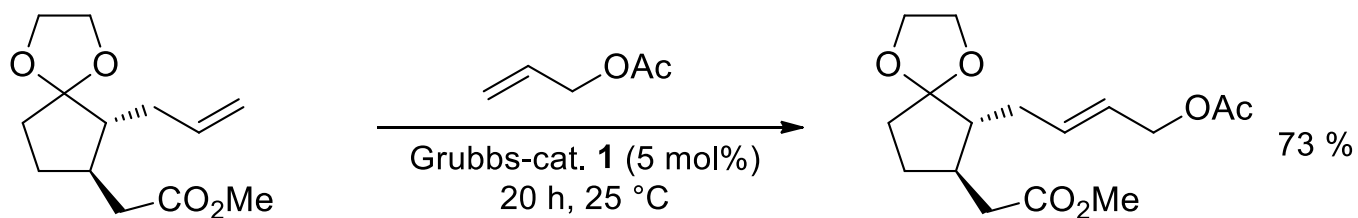


A. H. Hoveyda, *Nature* **2011**, 471, 461

A. H. Hoveyda, *Nature* **2008**, 456, 933

# Olefin metathesis

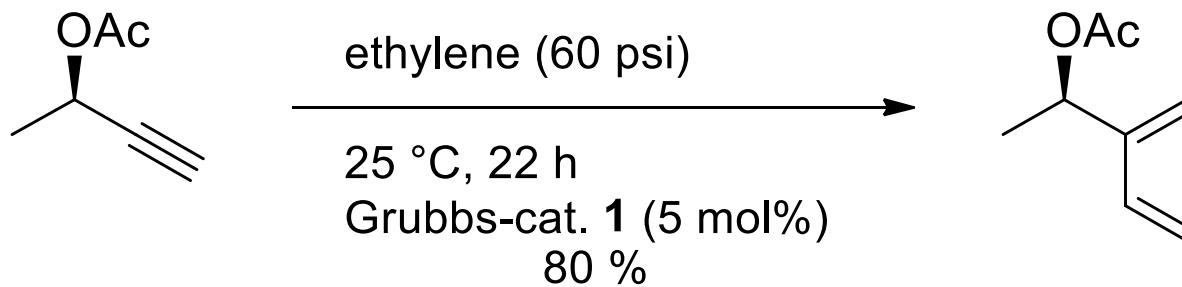
Synthesis of jasmonic acid derivatives



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

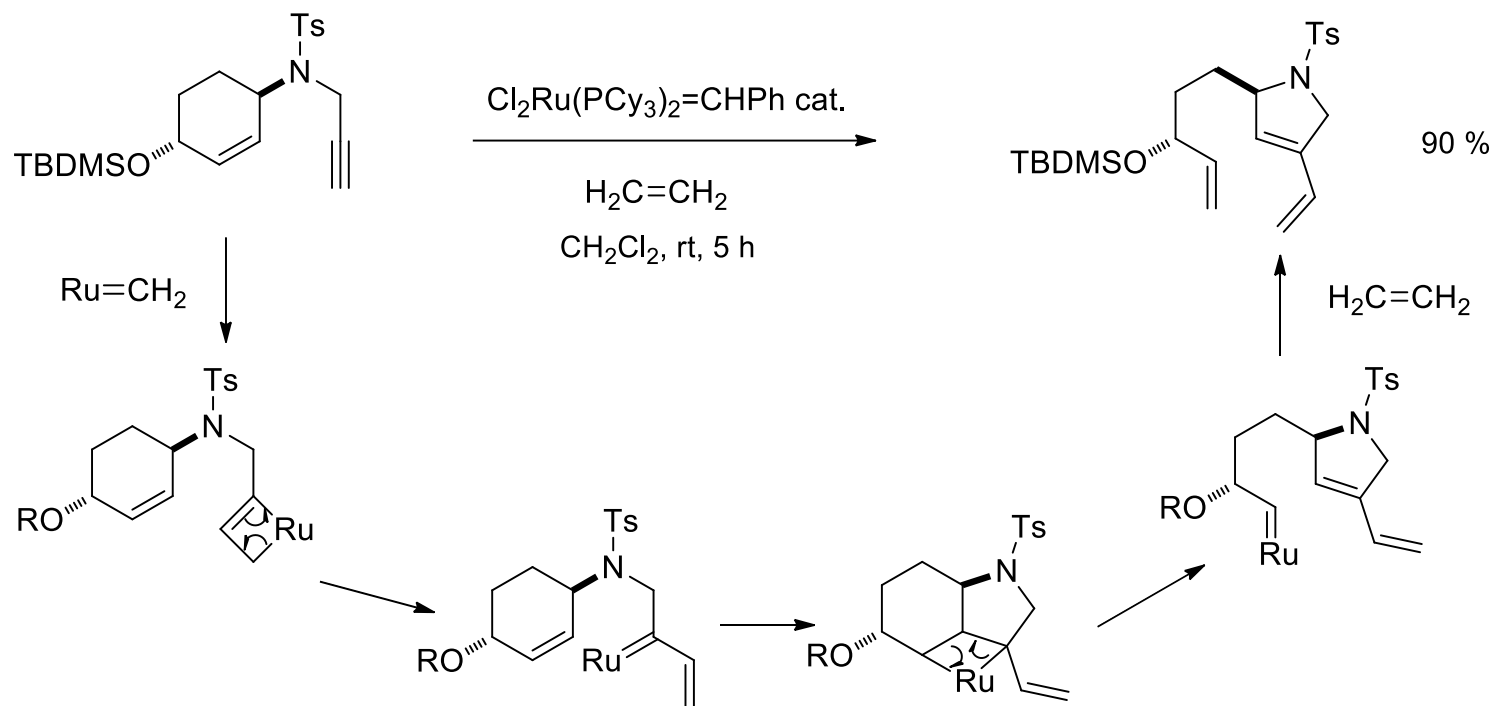
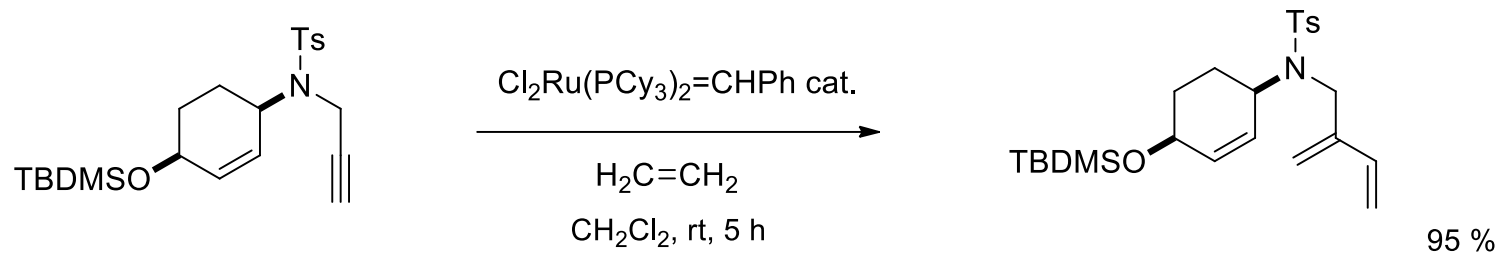
# Olefin metathesis

Cross-metathesis of alkynes with ethylene



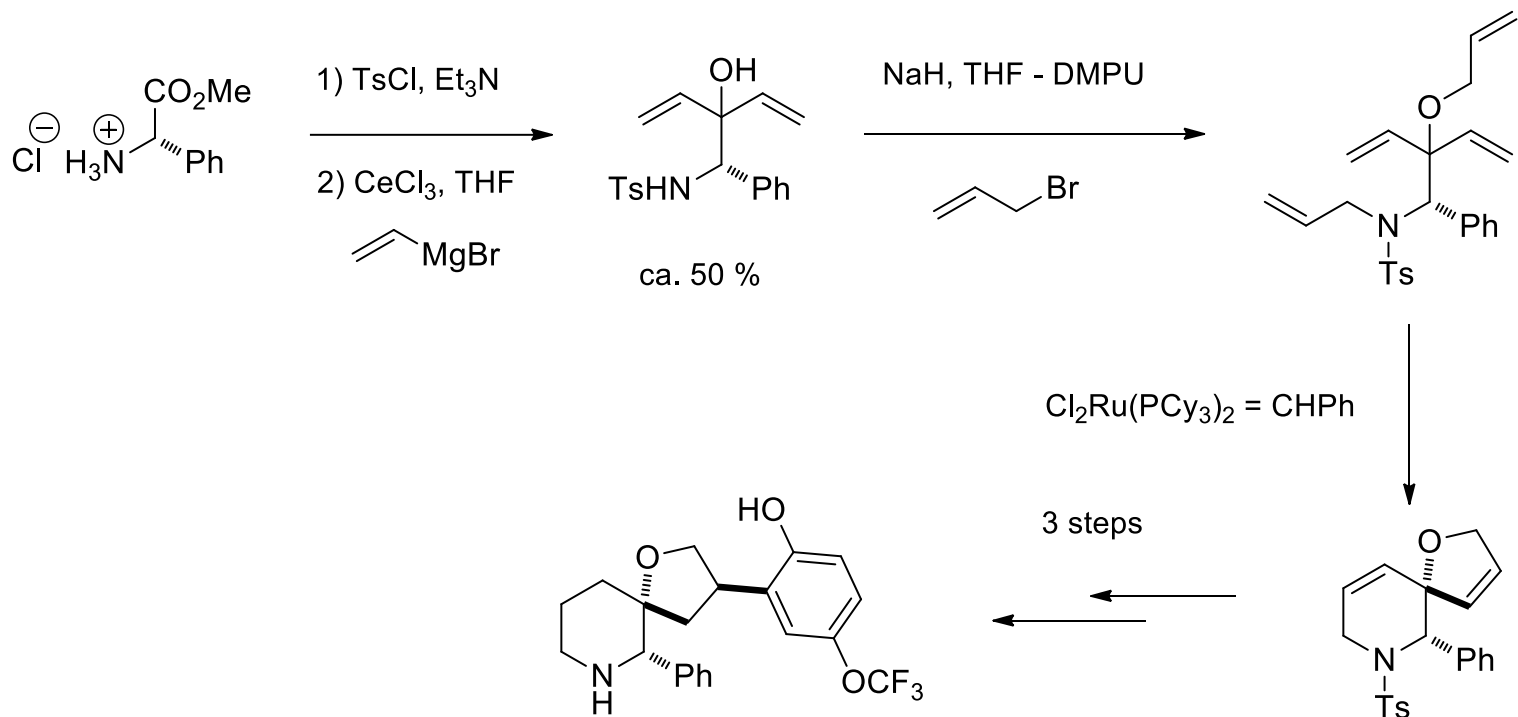
# Olefin metathesis

## Ru-catalyzed Ring-Opening and –Closing Enyne Metathesis

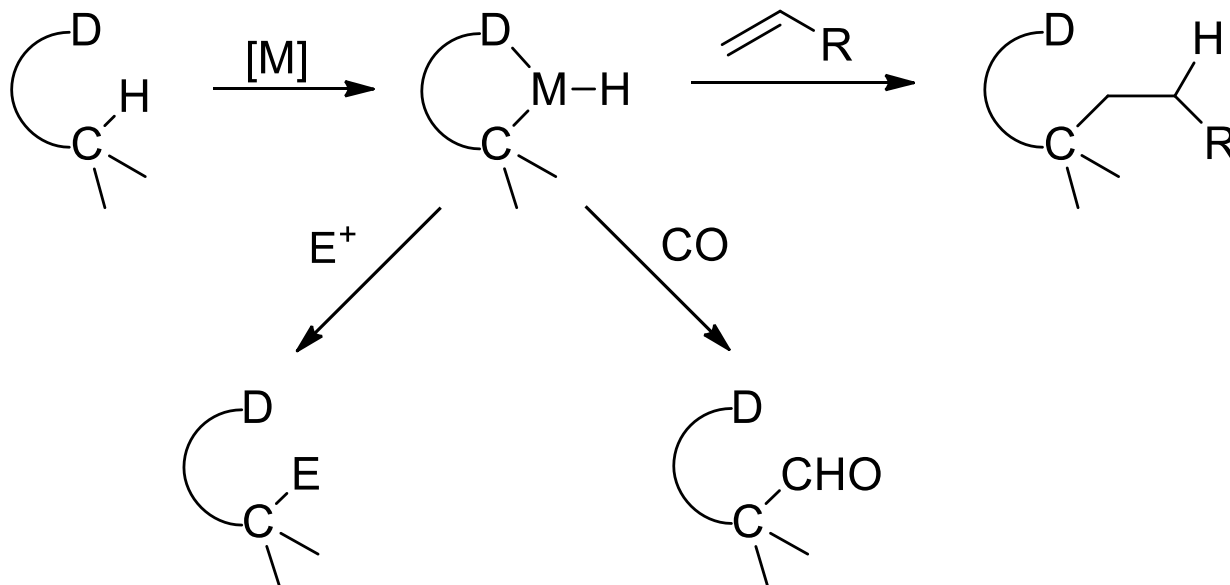


# Olefin metathesis

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

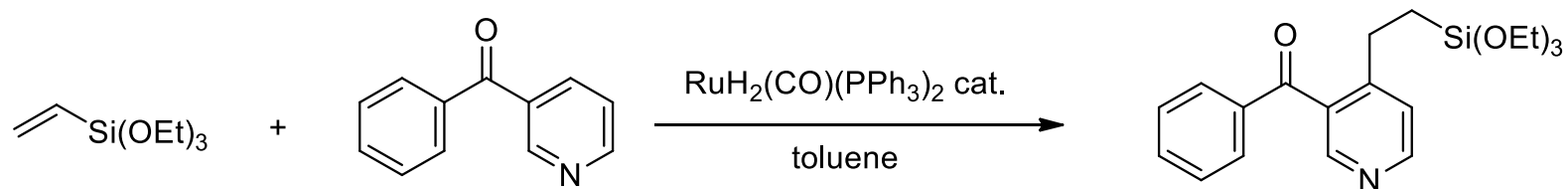
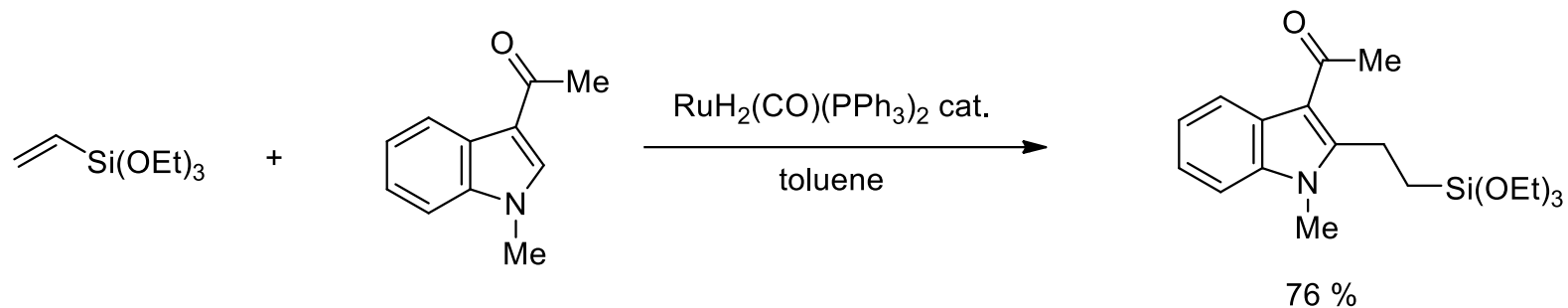


## New C-H activation reactions



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

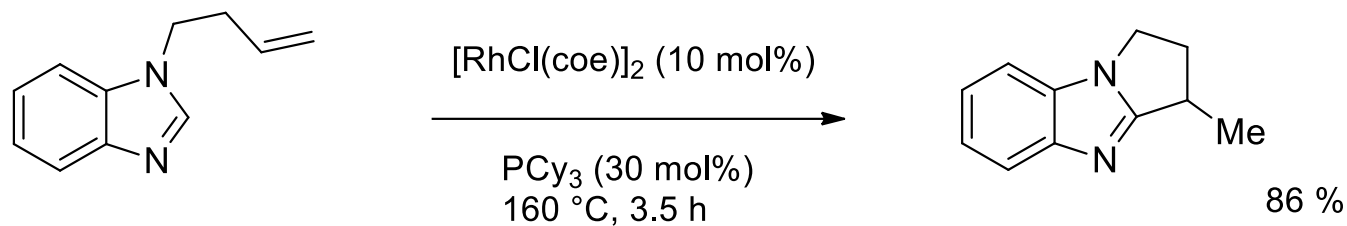
## The Murai-reaction



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

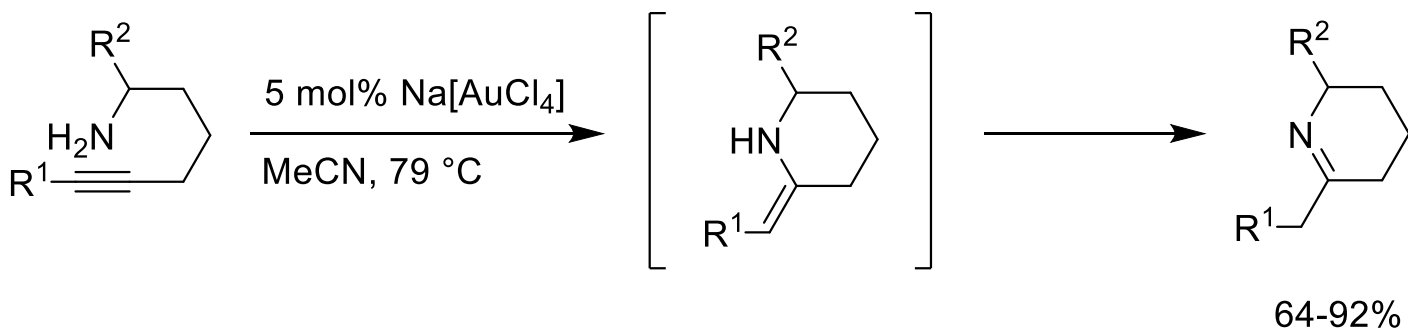
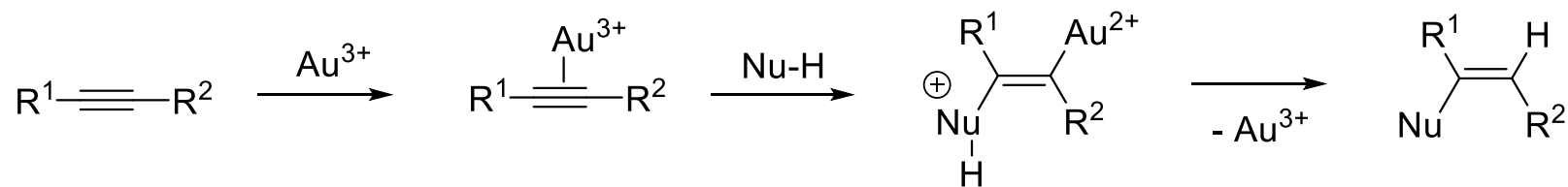


## Annulation of heterocycles *via* a Rh-catalyzed C-H-activation



# Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds

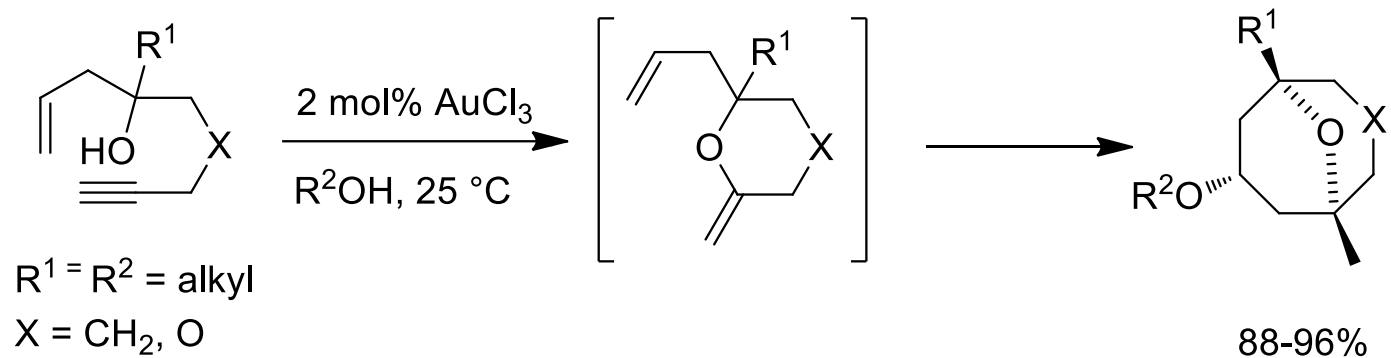


For a review see: A. S. Hashmi, *Chem. Rev.* **2007**, *107*, 3180

## Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds:

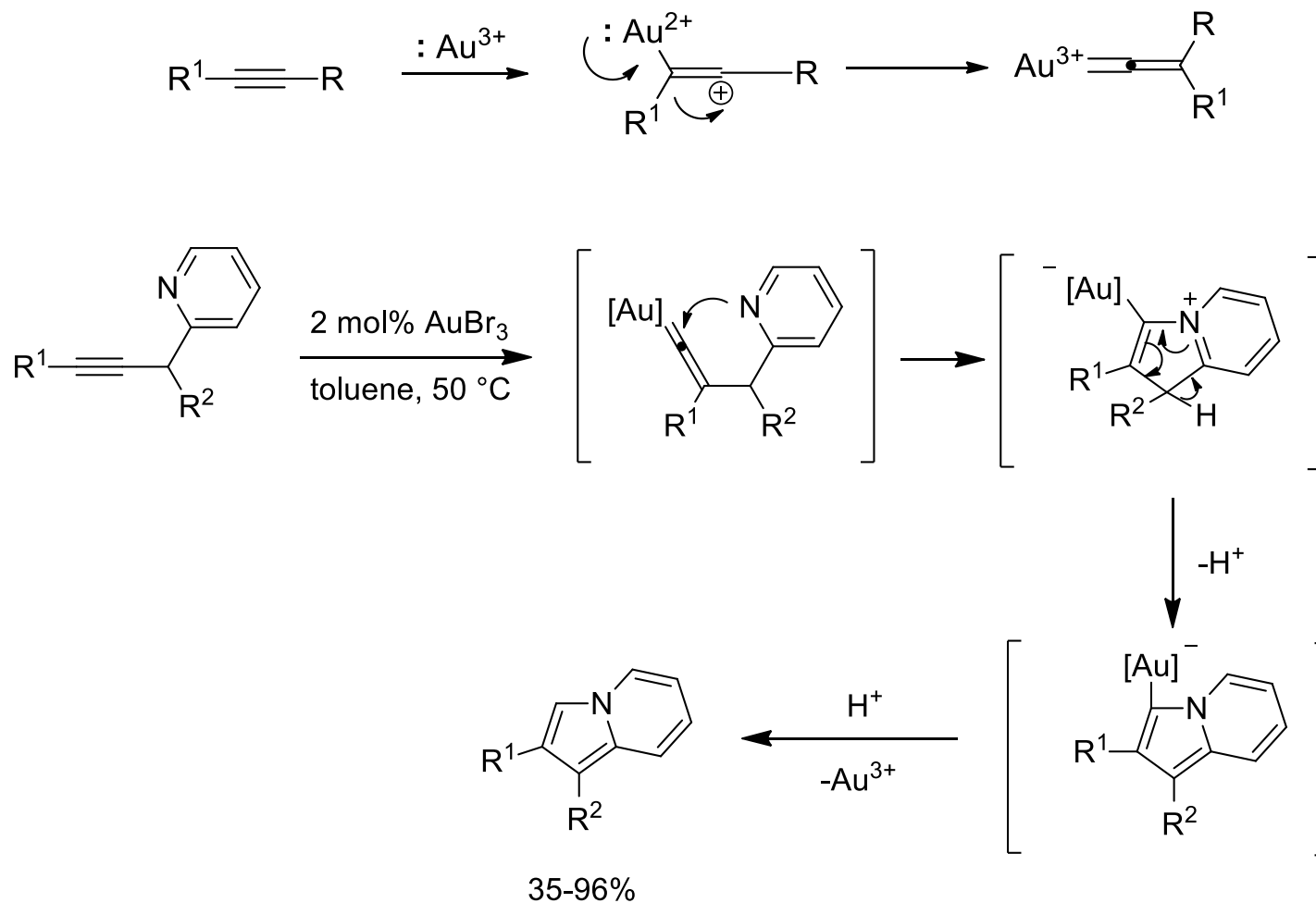
Au<sup>3+</sup>-catalyzed cyclization followed by a Prins type cyclization



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

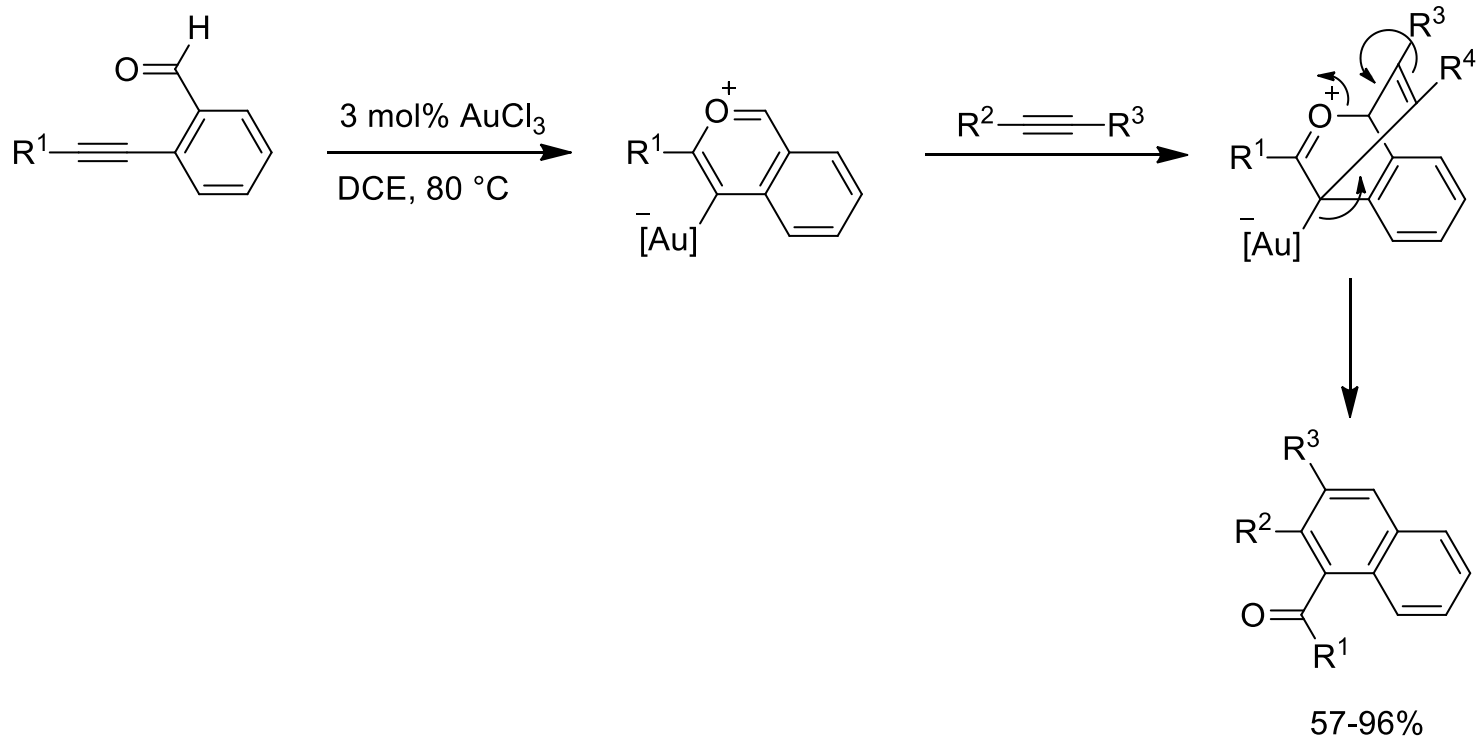
# Gold-catalyzed organic reactions

## Gold(III)-triggered rearrangements



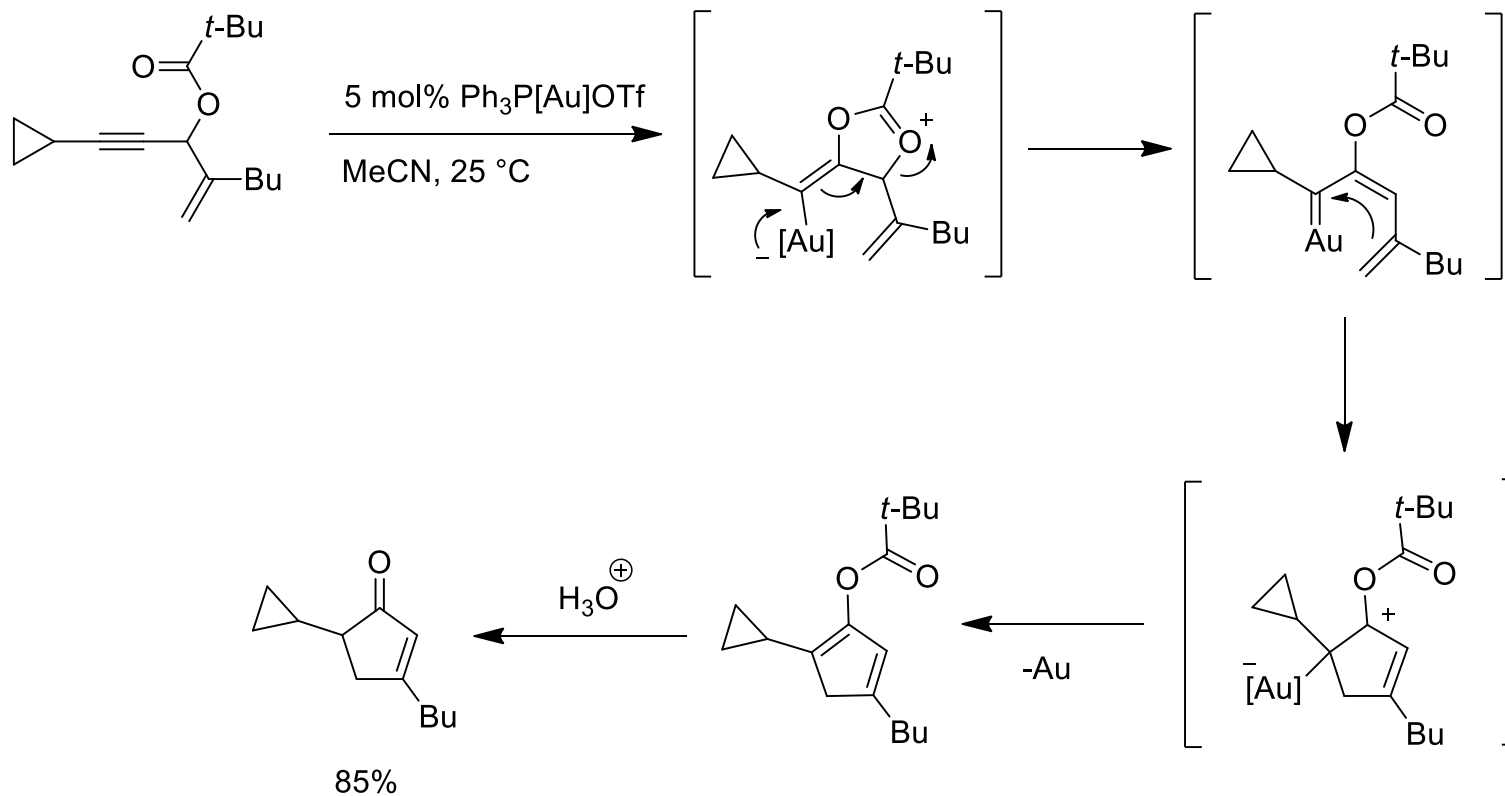
# Gold-catalyzed organic reactions

Au<sup>3+</sup>-initiated cycloadditions



# Gold-catalyzed organic reactions

Use of electrophilic Gold(I)-complexes:  $\text{Ph}_3\text{P-Au-OTf}$



# Gold-catalyzed organic reactions

## Intramolecular phenol synthesis

