

Organic Chemistry IV

Organometallic Chemistry for Organic Synthesis

Prof. Paul Knochel

LMU

2016

OCIV

Prüfung:

15. Juli 2016

9-11 Uhr

Wieland HS

Wiederholungsklausur:

5. September 2016

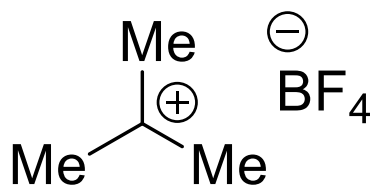
10-12 Uhr

Baeyer HS

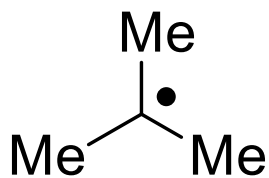
Recommended Literature

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

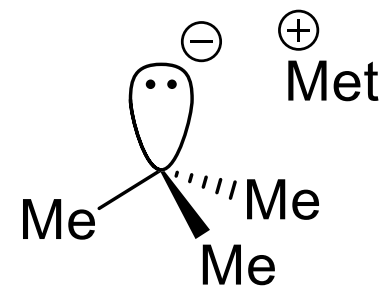
Importance of organometallics



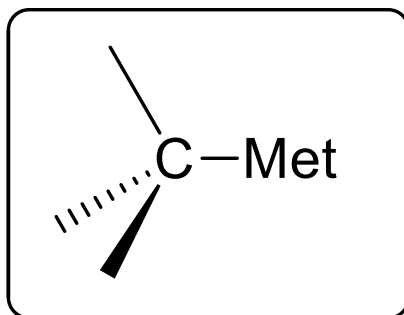
carbenium ion



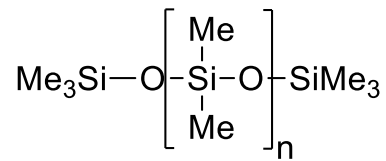
radical



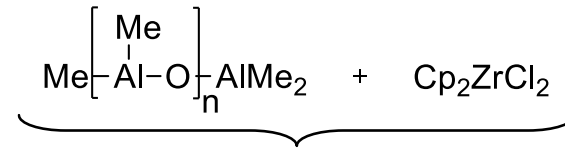
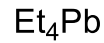
organometallic reagent



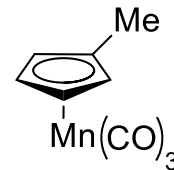
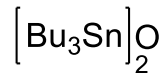
Industrial production



Silicone



Kaminsky catalyst
n=5-20 syndiotacticity of polypropylene

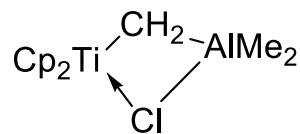
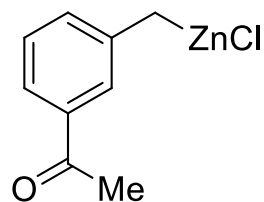
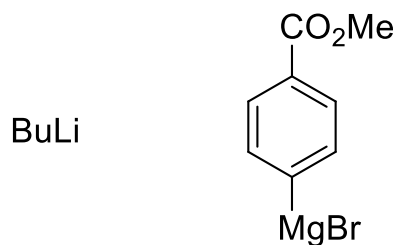


Industrial annual production of various organometallics

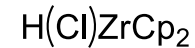
Organometallic	production [T / year]
Si	700 000
Pb	600 000
Al	50 000
Sn	35 000
Li	900

Organometallic reagents and catalysts for the organic synthesis

organometallic reagents:

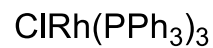
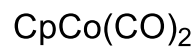


Tebbe reagent

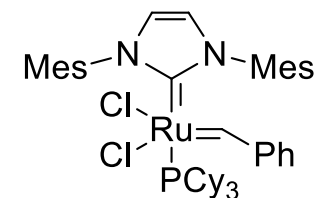


Schwarz reagent

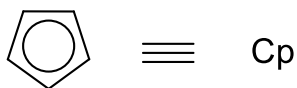
organometallic catalysts:



Wilkinson's catalyst

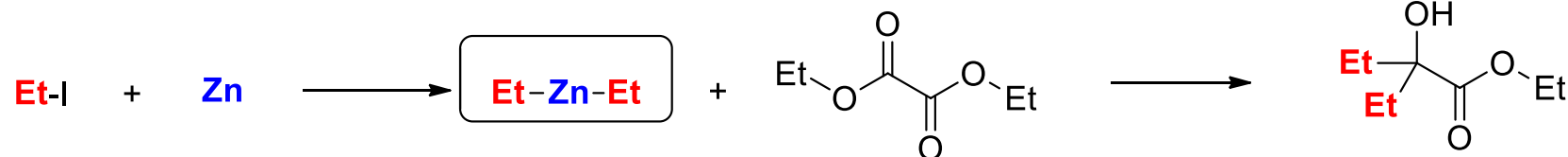


Grubbs II catalyst

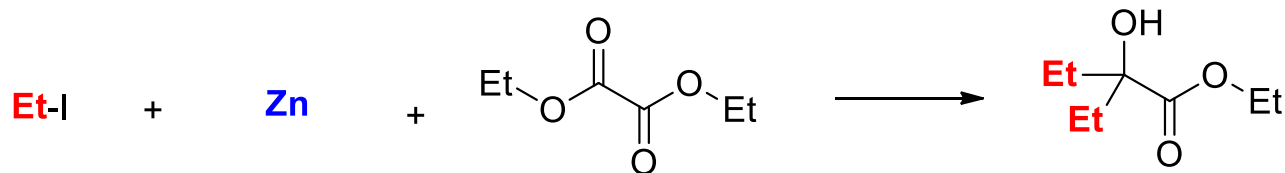


Organometallic chemistry of the XIX century

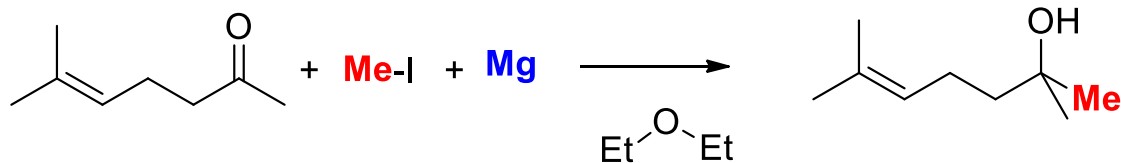
Frankland 1848, 1863



Beilstein 1862, Saytzeff 1870, Wagner 1875



Barbier 1899

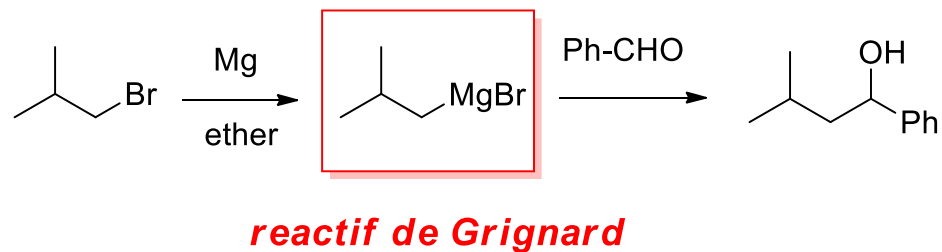
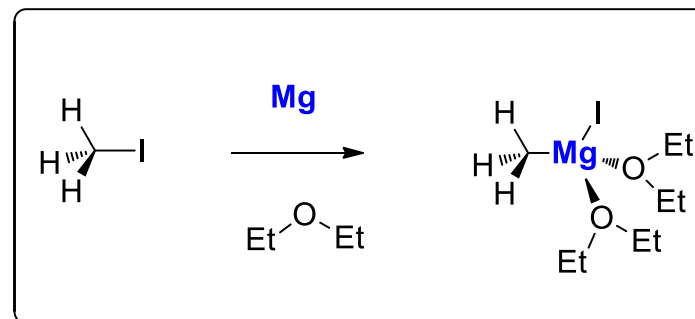


Ph. Barbier *Comptes Rendus de l'Académie des Sciences*, 1899, 128, 110

Organometallic chemistry of the XIX century



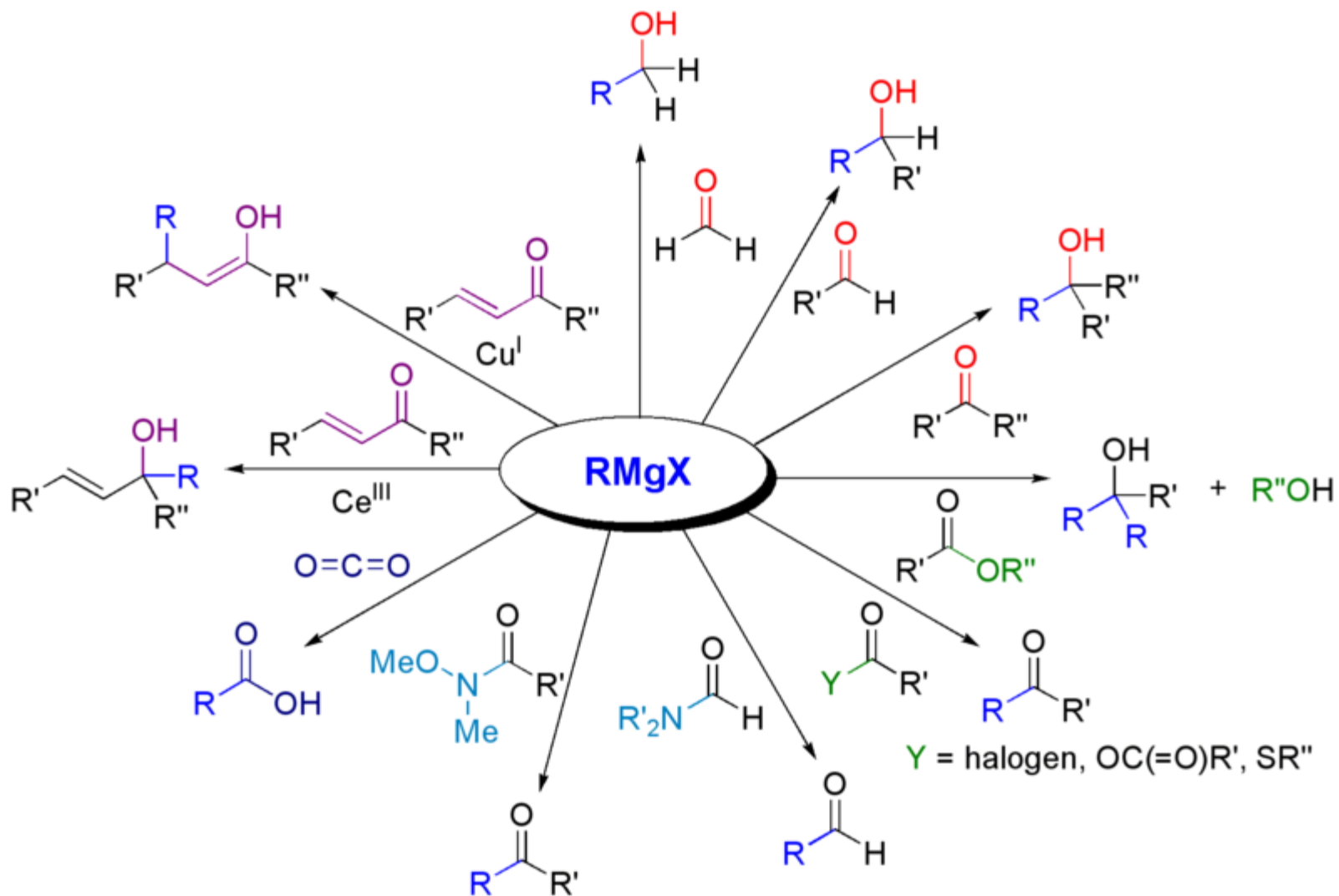
Pl. X. Victor Grignard dans son laboratoire de Nancy
1912



V. Grignard

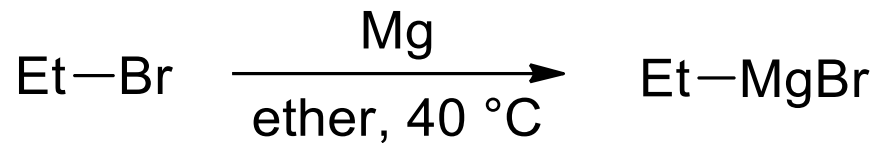
Comptes Rendus de l'Académie des Sciences, **1900**, 130, 1322

Reactivity of the Grignard reagents

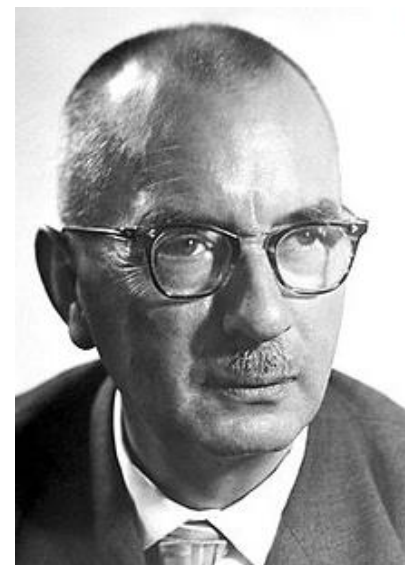


Historic point of view

Victor Grignard (1900)

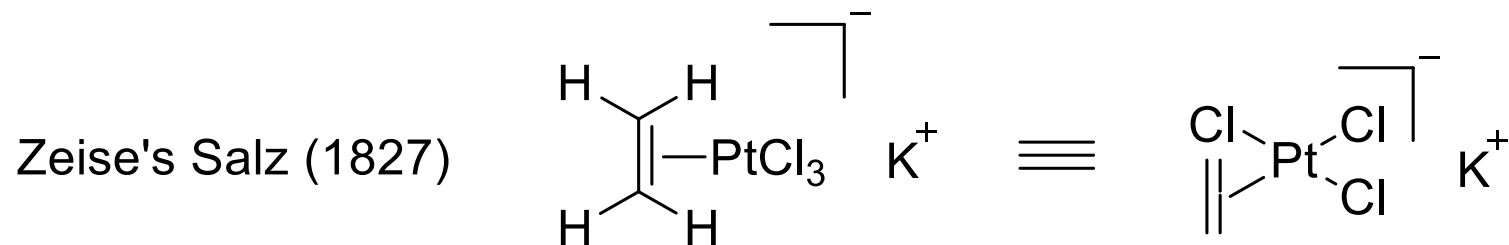


Karl Ziegler (1919)

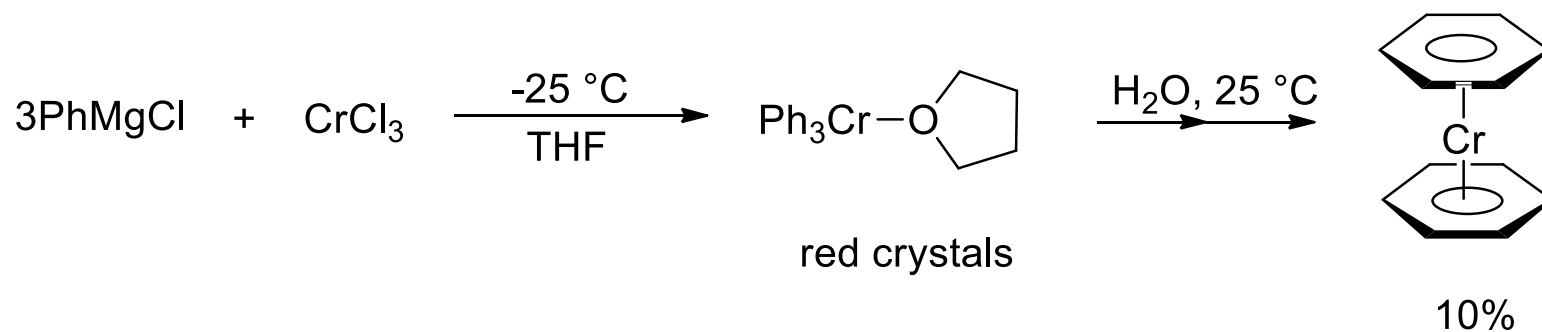


Historic point of view

first transition metal organometallics:



Hein (1919)

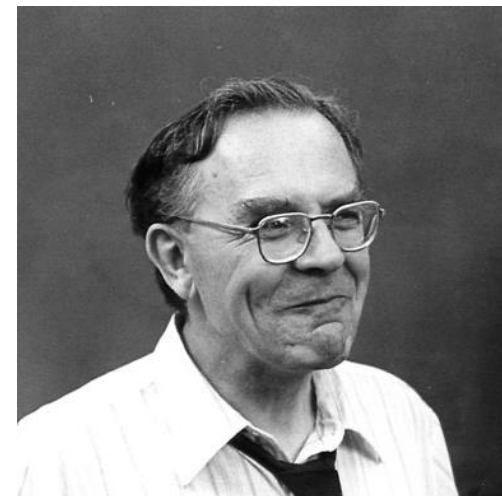
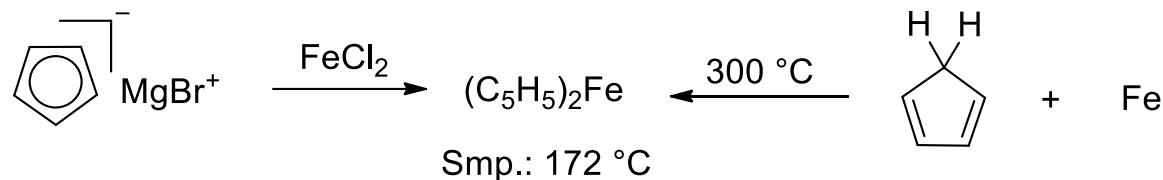


Historic point of view

1951 : synthesis of ferrocene

Pauson (Scotland) 7. August 1951

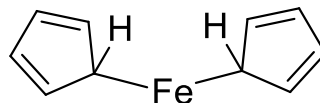
Miller 11. June 1951



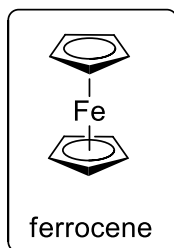
G. Wilkinson

1952

structural proposal by Pauson

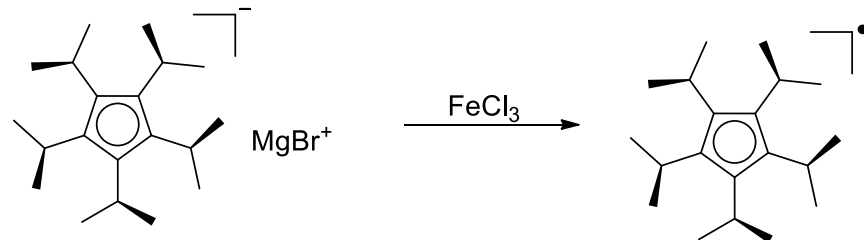


correct structure by G. Wilkinson and R. B. Woodward



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

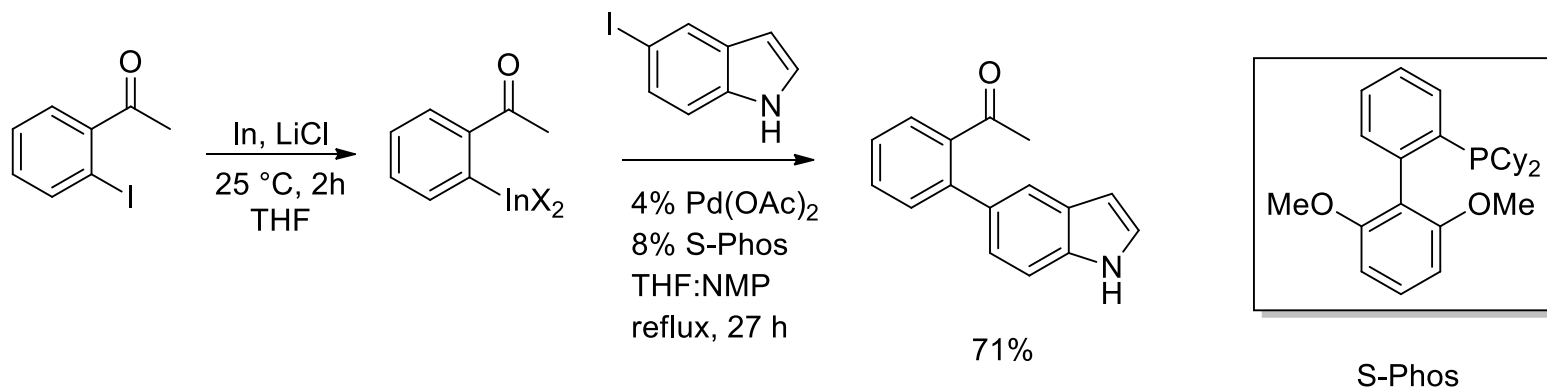
R.B. Woodward *J. Am. Chem. Soc.* **1952**, 74, 3458



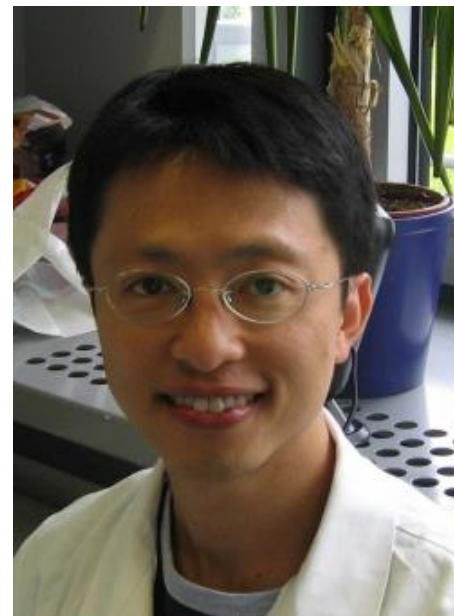
R. B. Woodward

Goal of the lecture

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



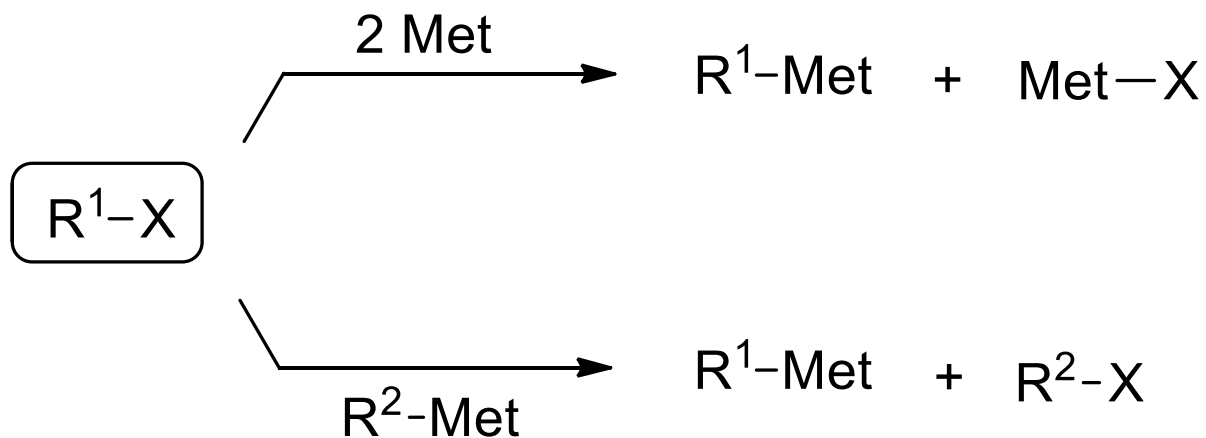
Y.-H. Chen, *Angew. Chem. Int. Ed.* **2008**, 47, 7648.



General synthetic methods for preparing organometallic reagents

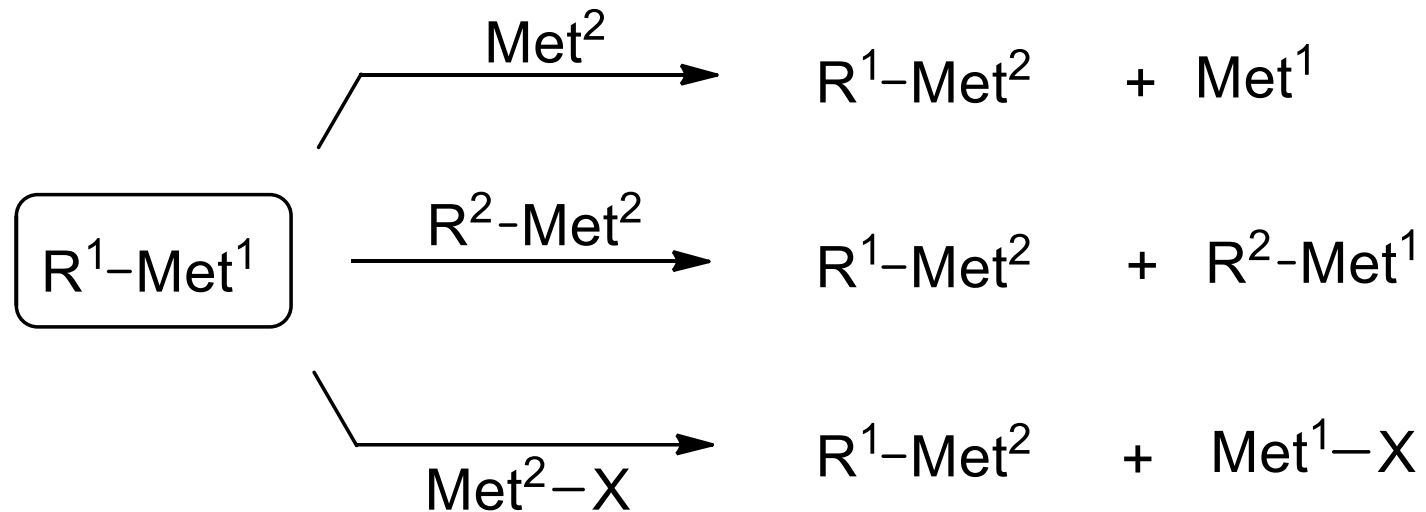
classification according to starting materials

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



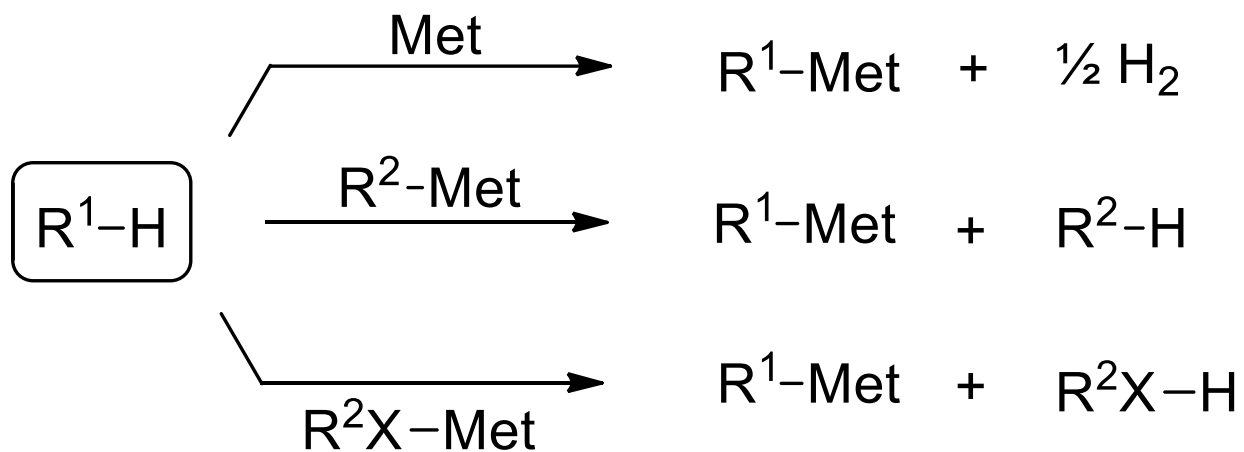
Classification according to starting materials

transmetalation



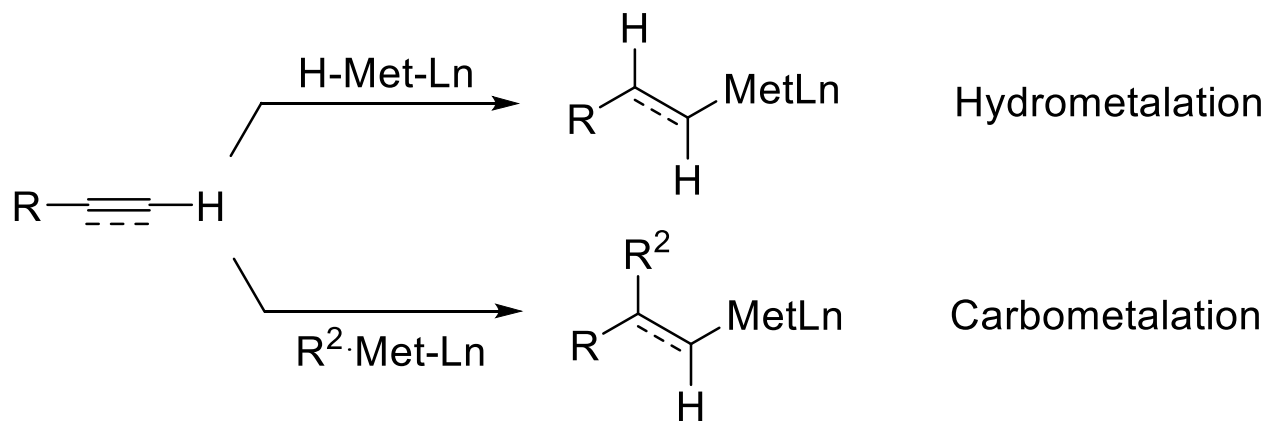
Classification according to starting materials

metalation



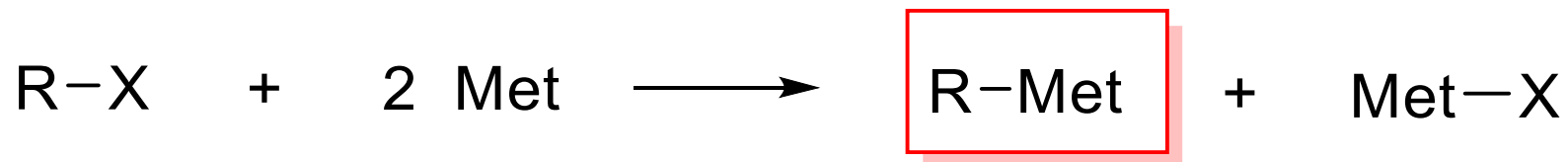
Classification according to starting materials

carbometalation and hydrometalation



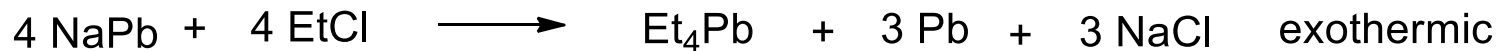
Synthesis starting from organic halides

direct synthesis - oxidative addition



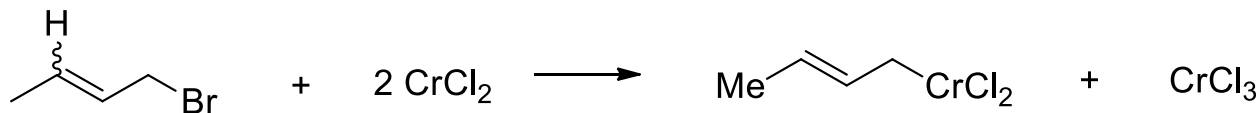
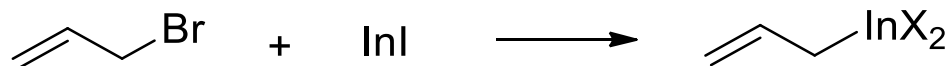
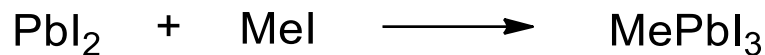
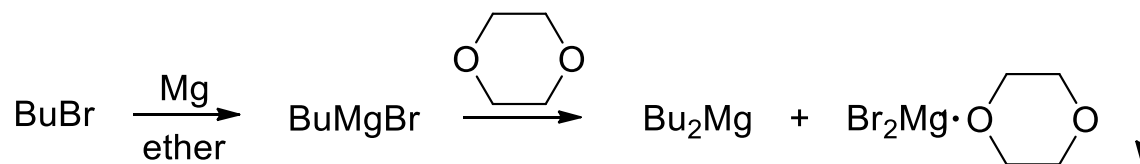
driving force of the reaction:

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



Direct Synthesis - Oxidative Addition

examples:

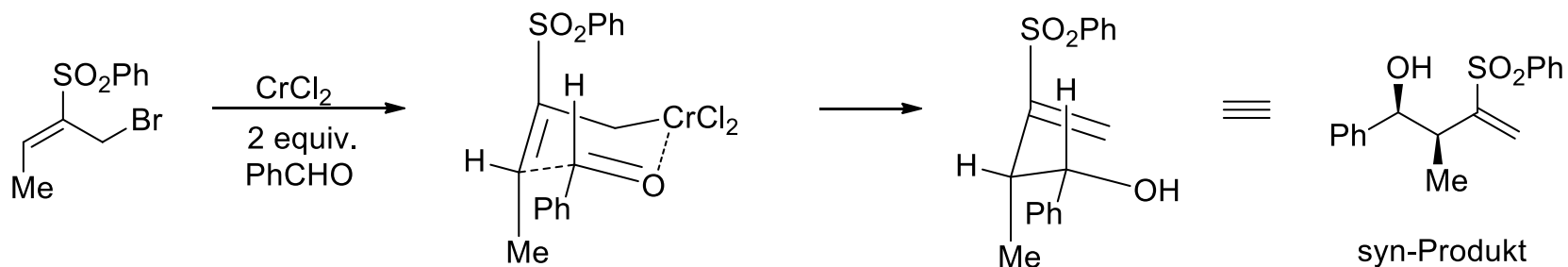
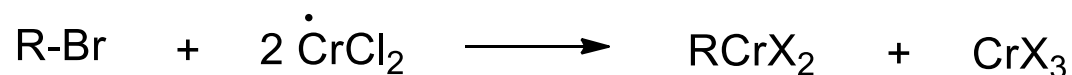
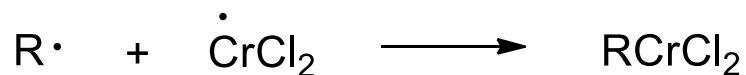
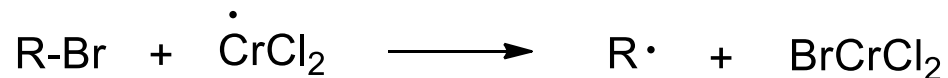


E/Z-mixture

pure E-isomer

Direct Synthesis - Oxidative Addition

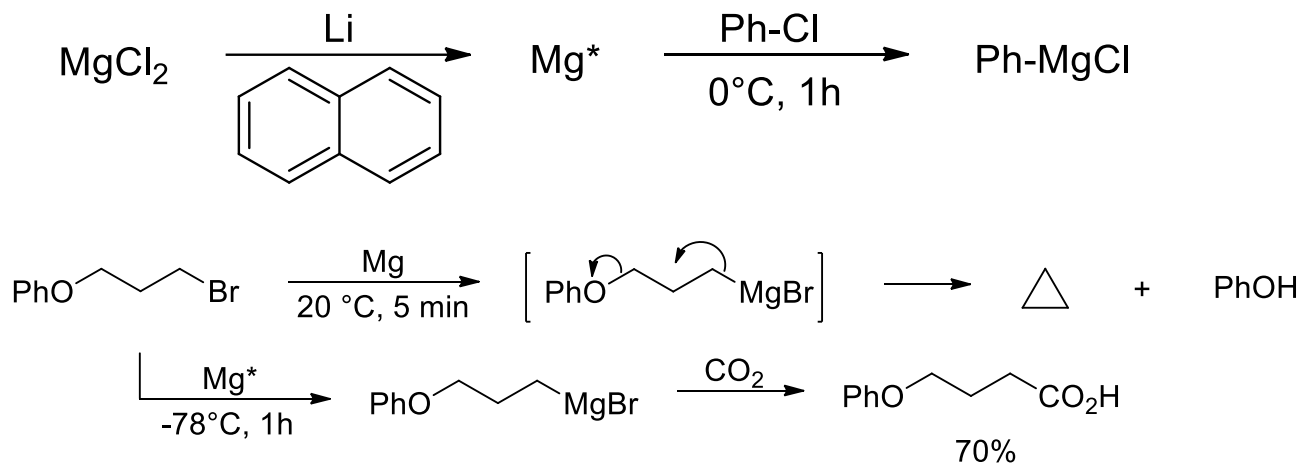
mechanism:



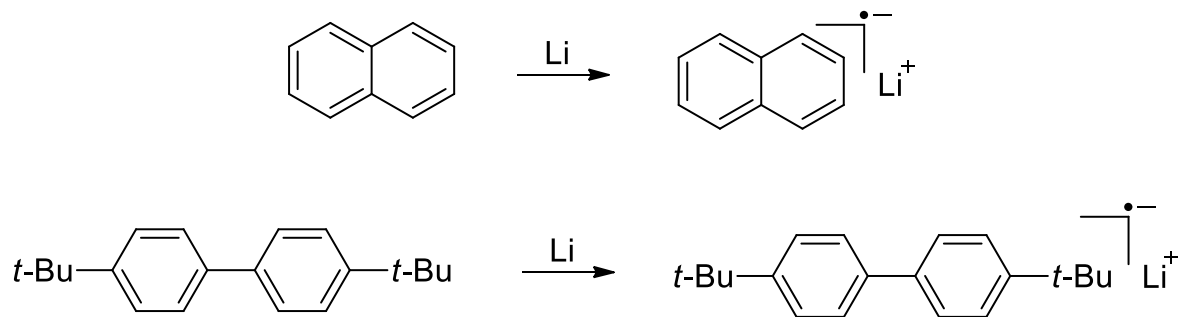
P. Knochel *Tetrahedron Lett.* **1986**, 27, 5091

Activation of the metal: the *Rieke*-approach

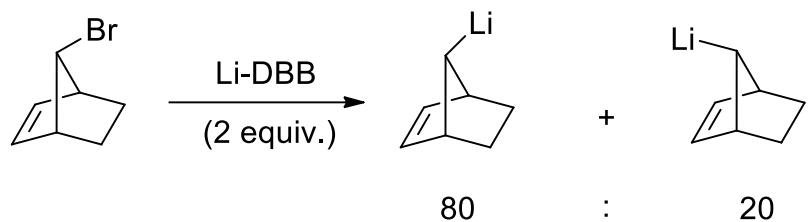
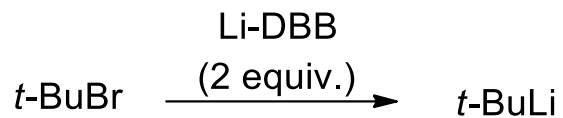
activation of the metal: R. D. Rieke, *Science* **1989**, 246, 1260



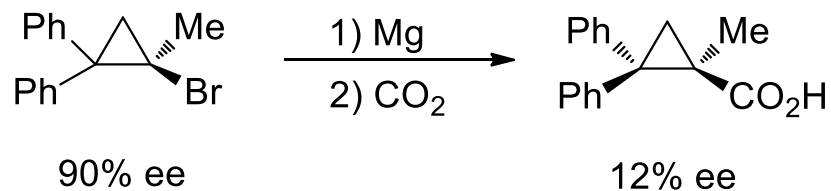
Activation of lithium: formation of soluble Li-sources:



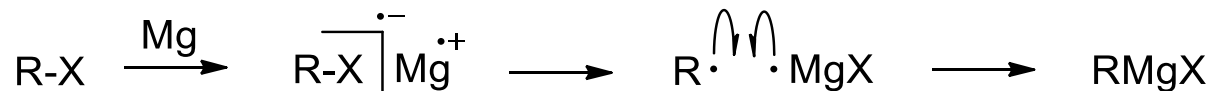
Mechanism of the metal insertion



loss stereochemical information

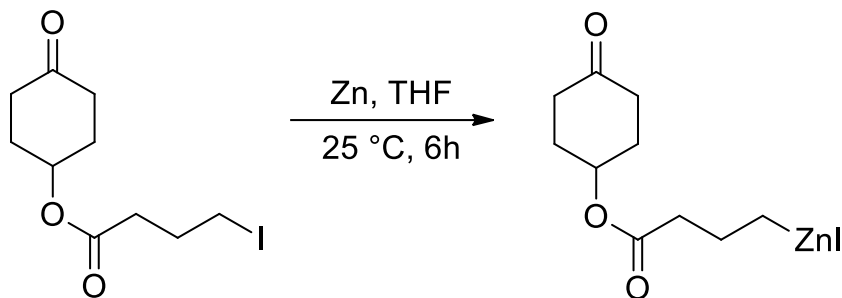
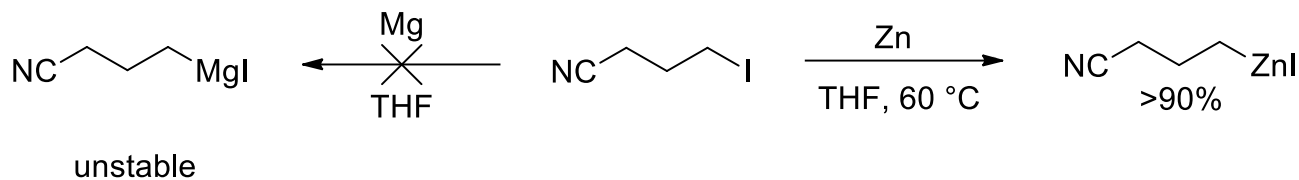


H.M. Walborsky: *J. Am. Chem. Soc.* **1989**, 11, 1896



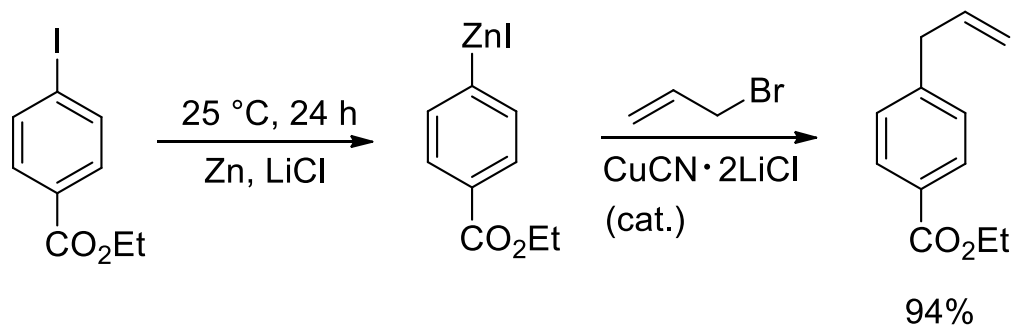
radical mechanism

Preparation of functionalized organometallics

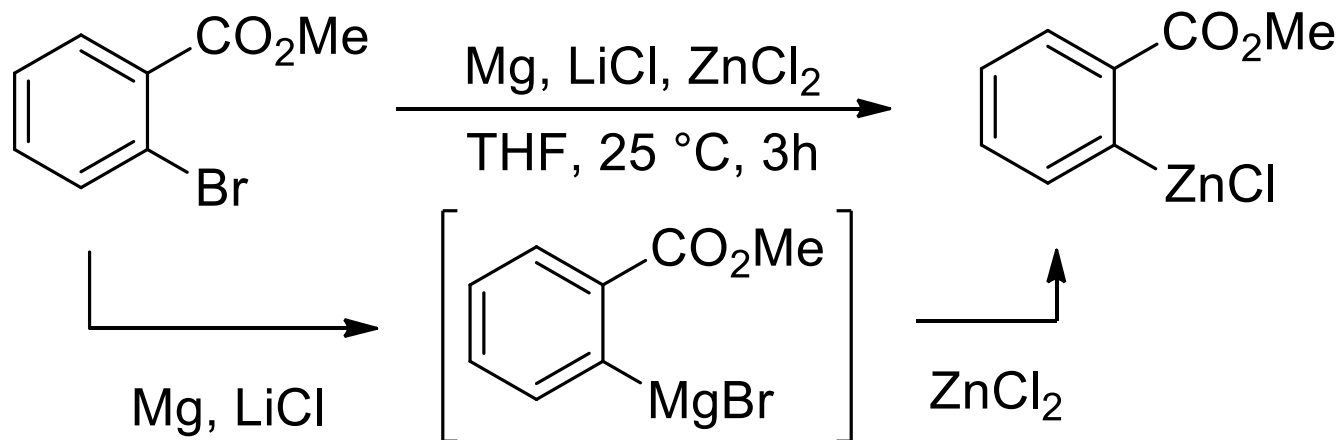
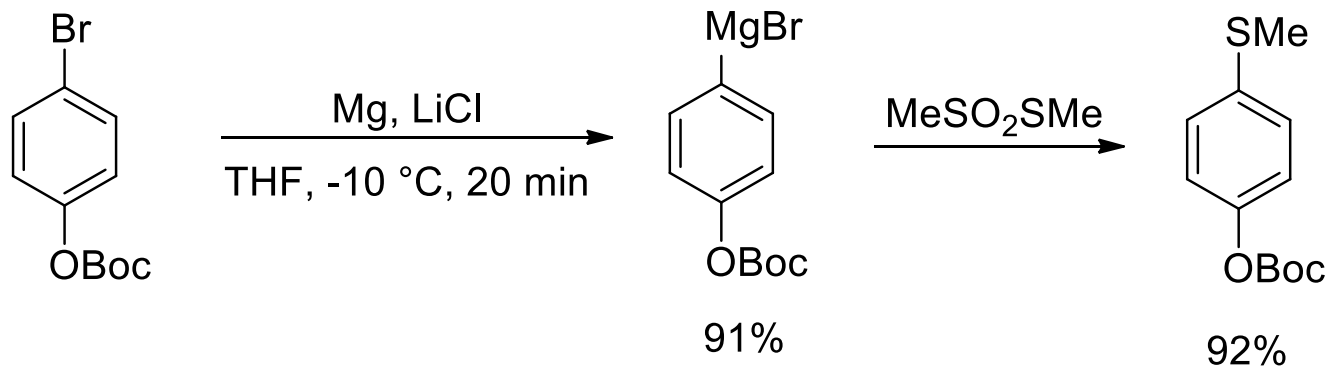


P. Knochel, *J. Org. Chem.* **1988**, 53, 2390

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

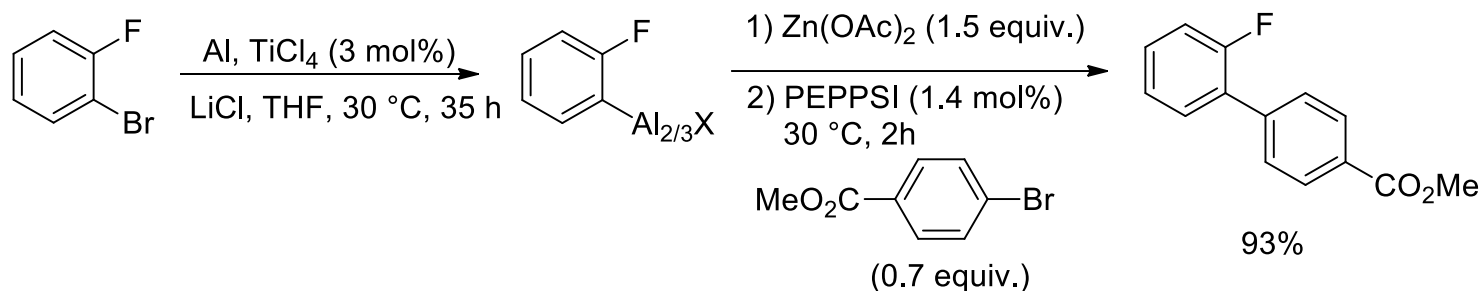


Preparation of functionalized organometallics

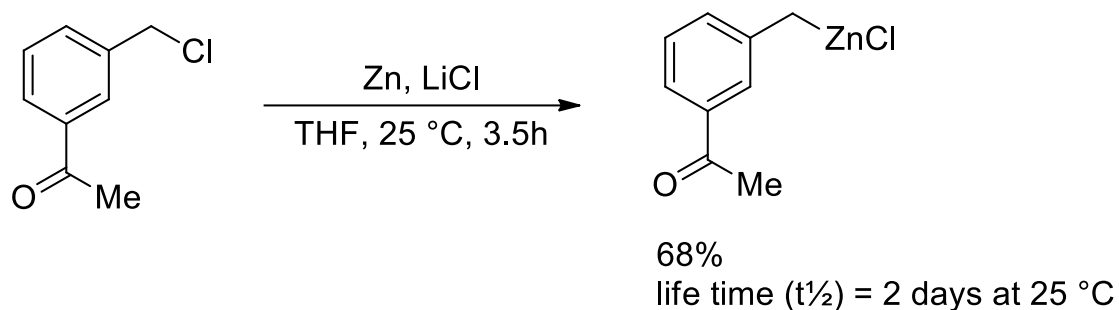


Preparation of functionalized organometallics

activation of Al using LiCl and TiCl₄, BiCl₃, PbCl₂ or InCl₃

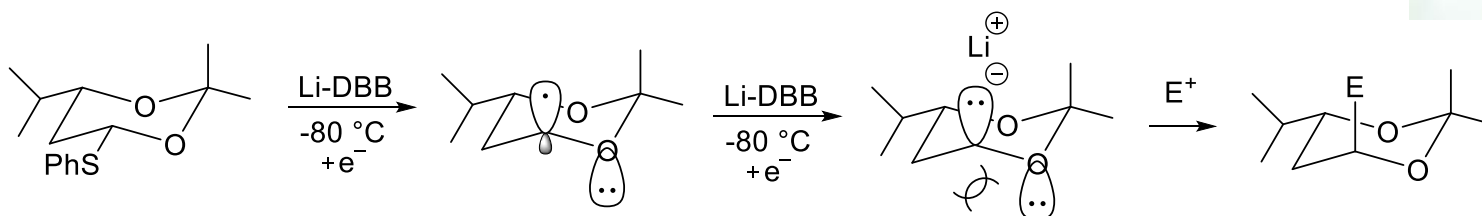
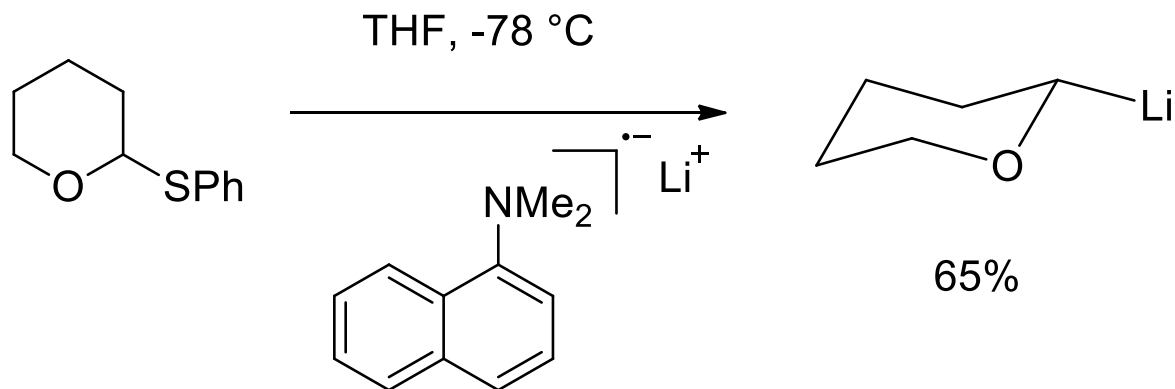


T. Blümke, Y.-H. Chen, P. Knochel *Nature Chemistry*, **2010**, 2, 313

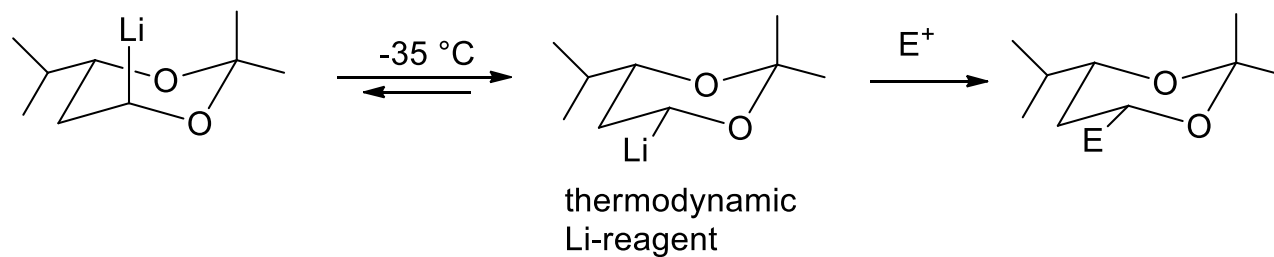


A. Metzger, P. Knochel *Org. Lett.* **2008**, 10, 1107

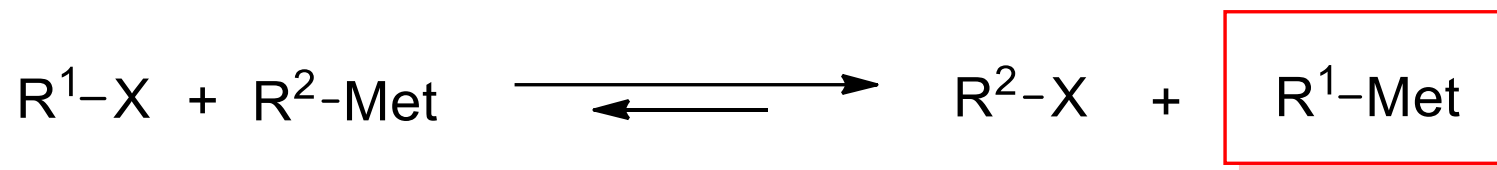
Extension to insertion reactions to C-S bonds



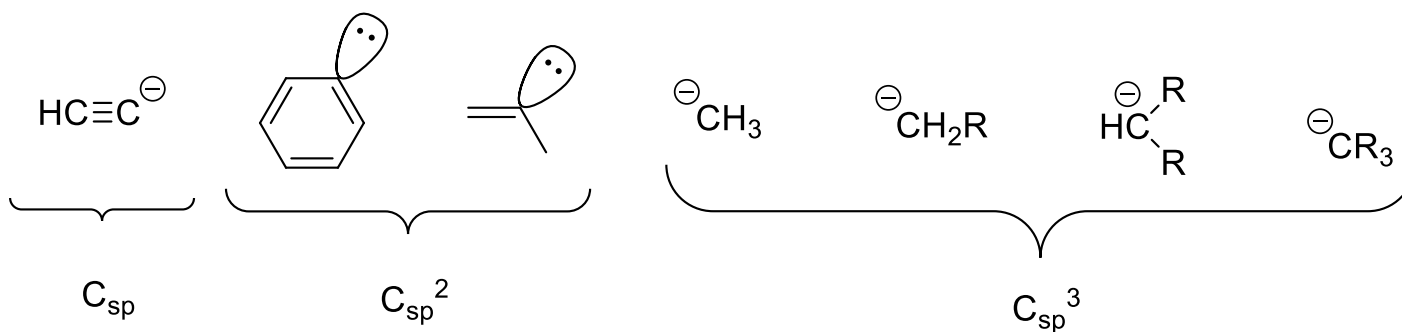
kinetic Li-reagent



The Halogen-Metal-Exchange

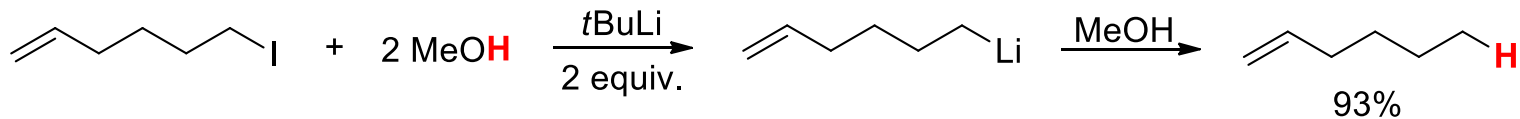
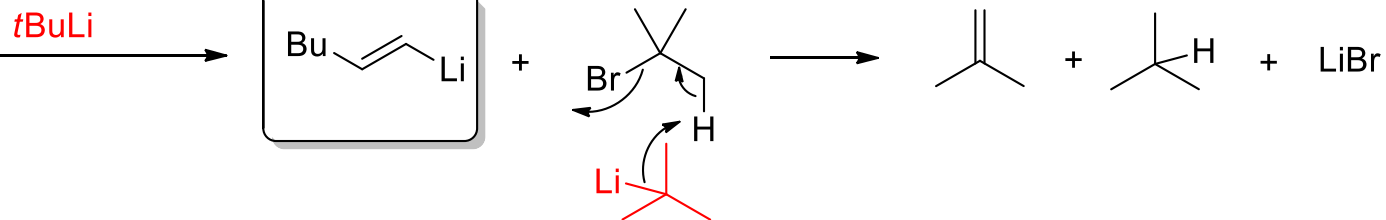
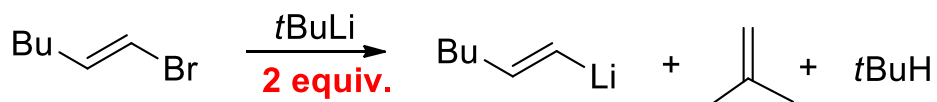
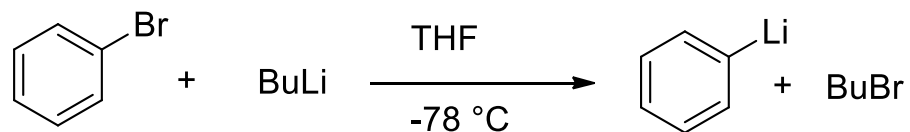


driving force: the most stable carbanion is always formed

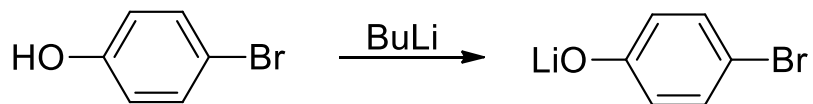


The Halogen-Metal-Exchange

1939: the Wittig-Gilman reaction



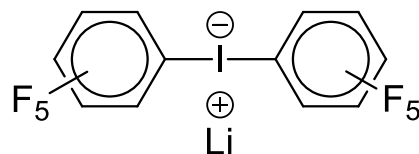
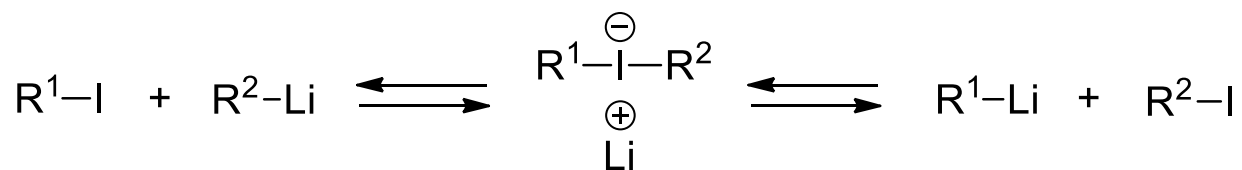
The Halogen-Metal-Exchange



I >> Br >> Cl

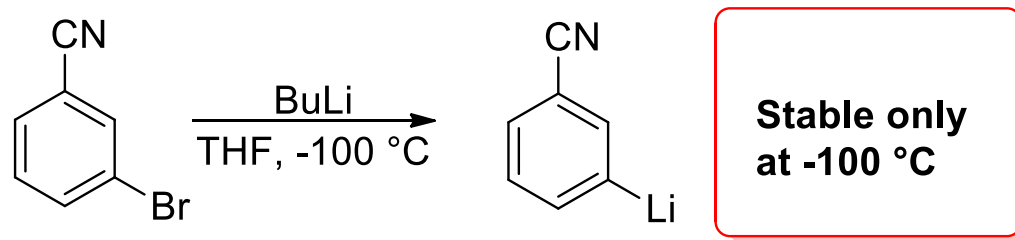
rate of the halogen/metal exchange

mechanism:

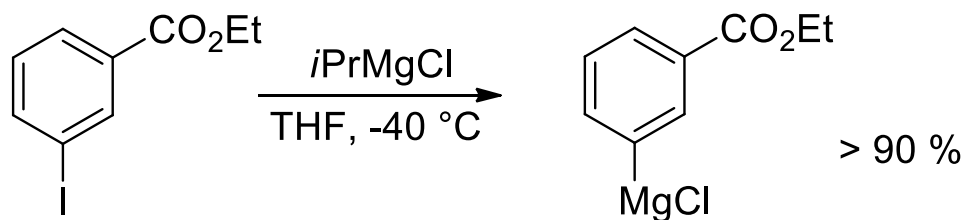


has been isolated

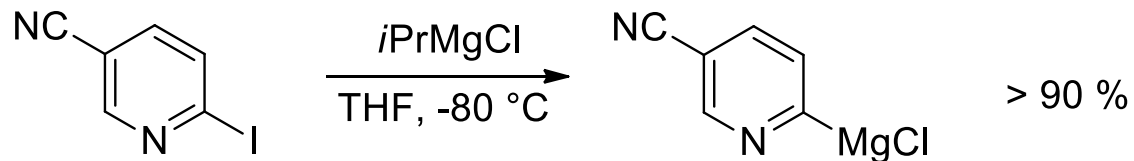
The Halogen-Metal-Exchange : tolerance of functional groups



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

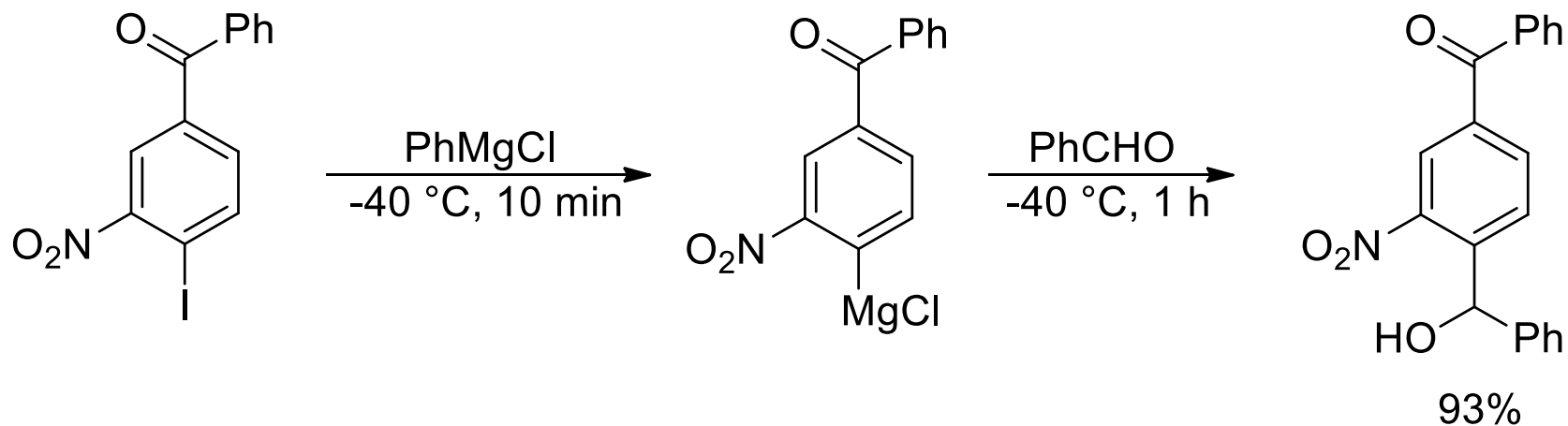


M. Rottländer, P. Knochel, Angew. Chem. Int. Ed. 1998, 40, 1801



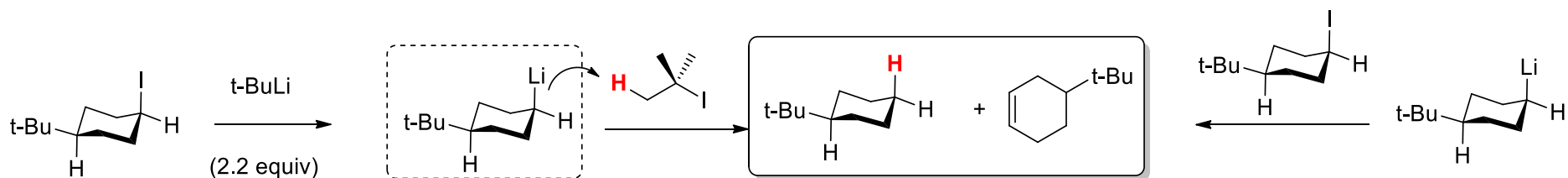
H. Ren, P. Knochel, Chem.Comm. **2006**, 726

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



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

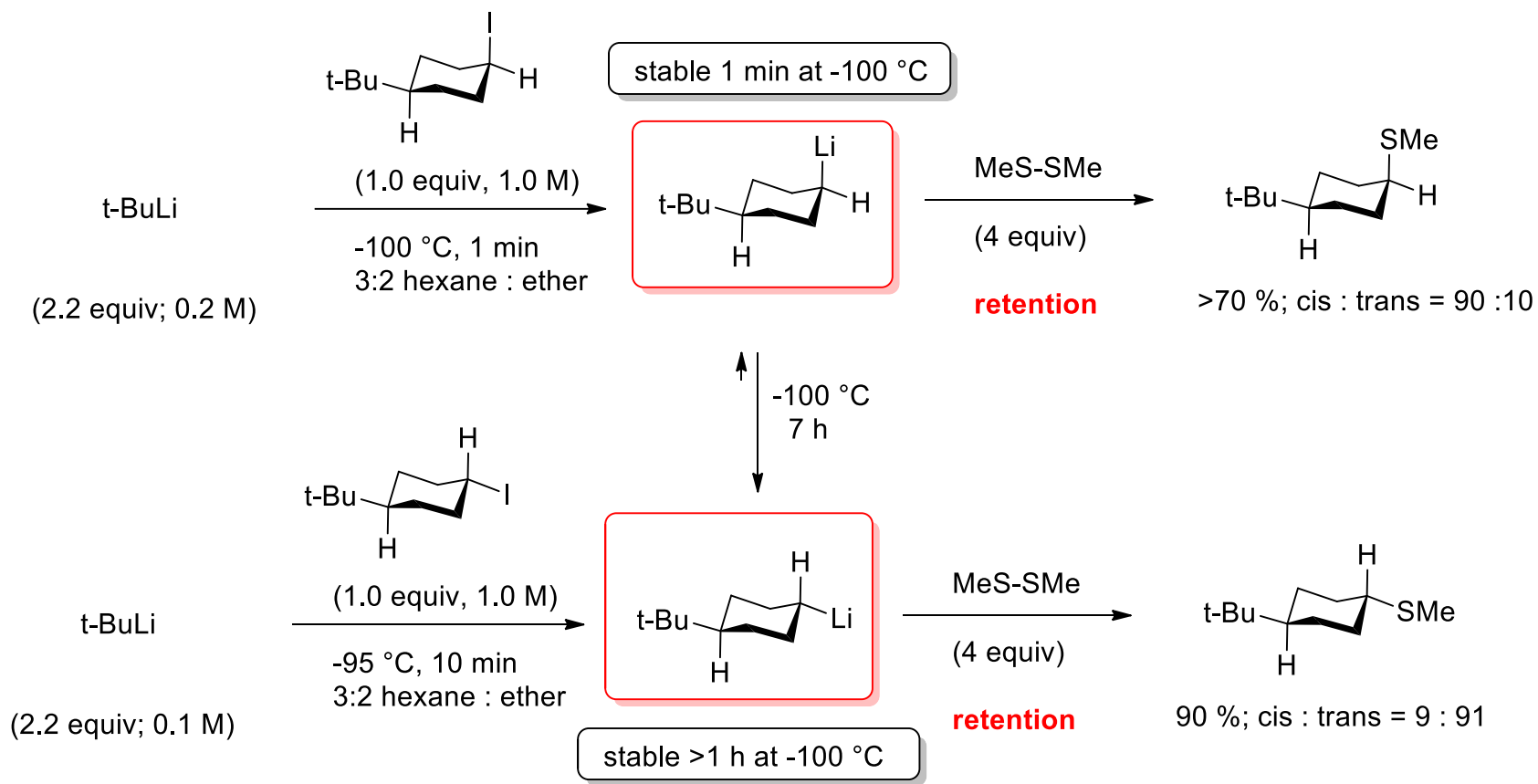
A secondary iodine/lithium exchange on cyclohexyl iodides



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

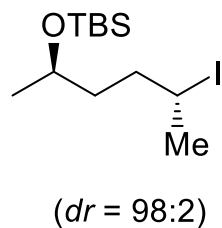
Stephanie SEEL

A secondary iodine/lithium exchange on cyclohexyl iodides

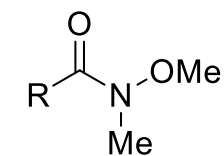
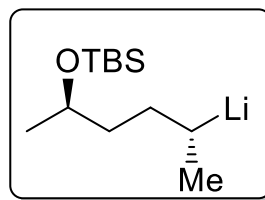
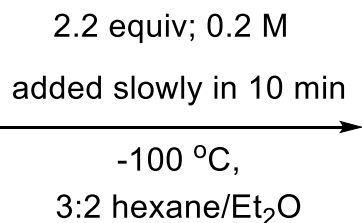


Acyclic systems: stereospecific I/Li exchange and reactions with C-electrophiles

ANTI

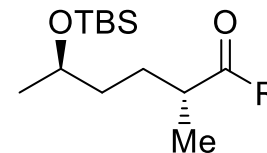


^tBuLi



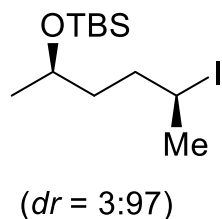
(2.5 equiv)

74%

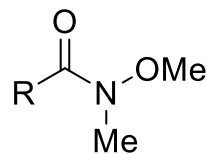
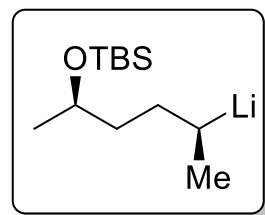
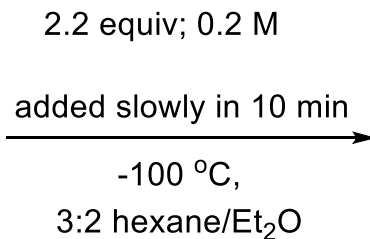


> dr = 96:4

SYN

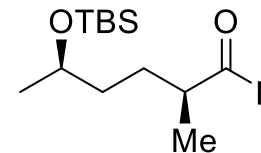


^tBuLi

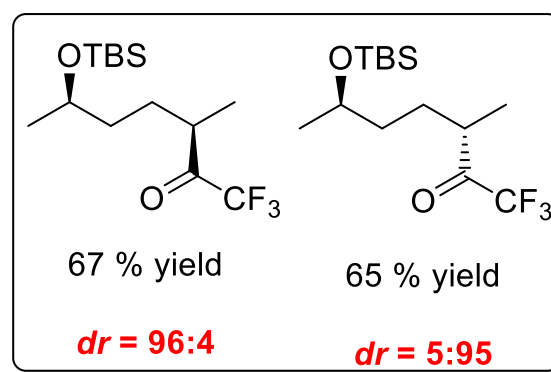
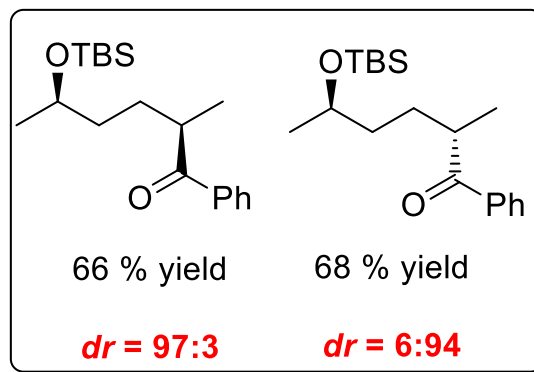
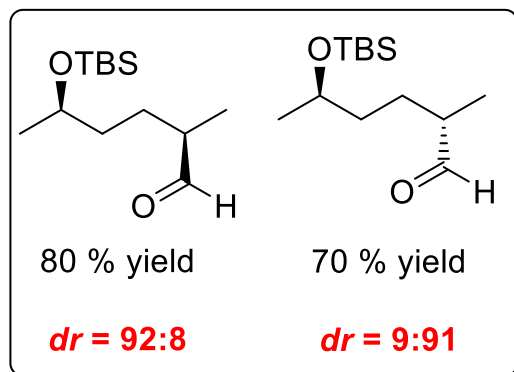


(2.5 equiv)

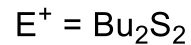
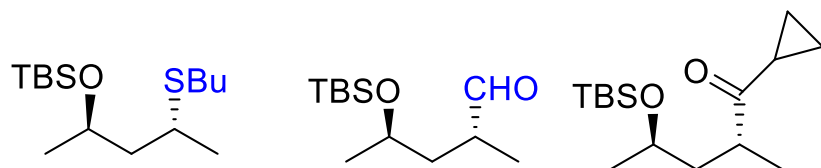
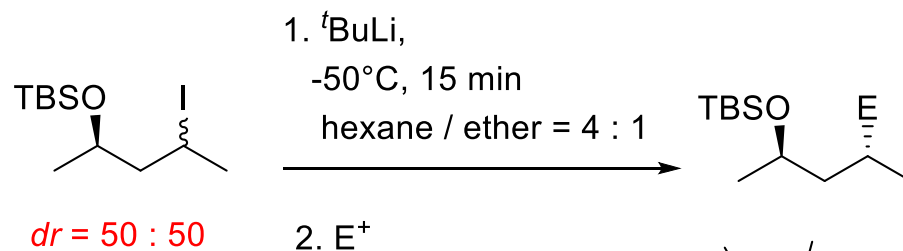
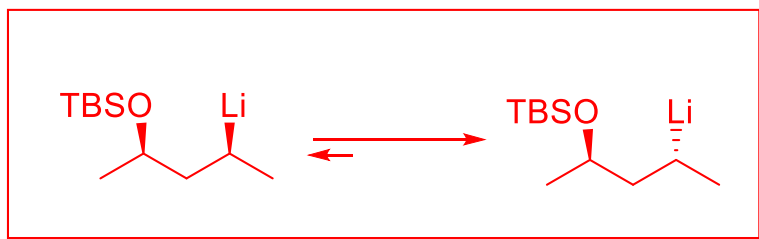
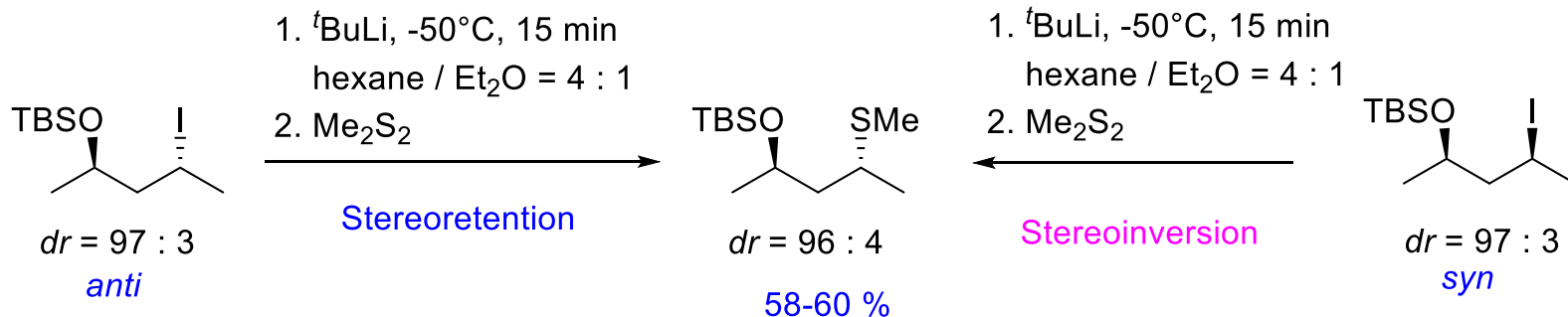
75%



> dr = 6:94

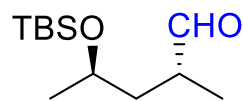


Stereoconvergent synthesis of Li-reagents



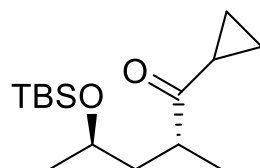
60 %

$dr = 94 : 6$



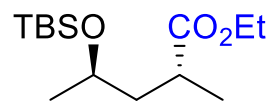
74 %

$dr = 92 : 8$



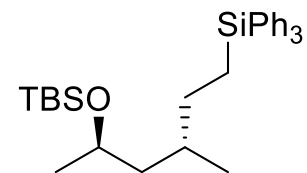
67 %

$dr = 96 : 4$



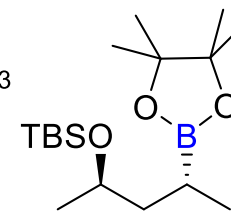
67 %

$dr = 96 : 4$



63 %

$dr = 99 : 1$

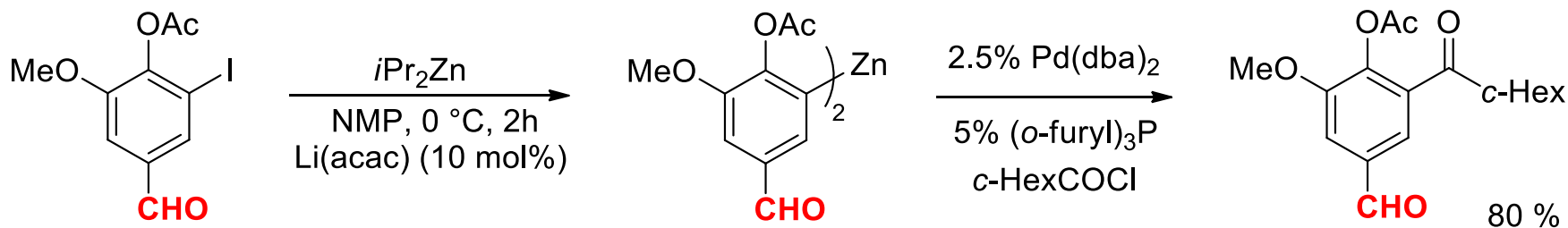
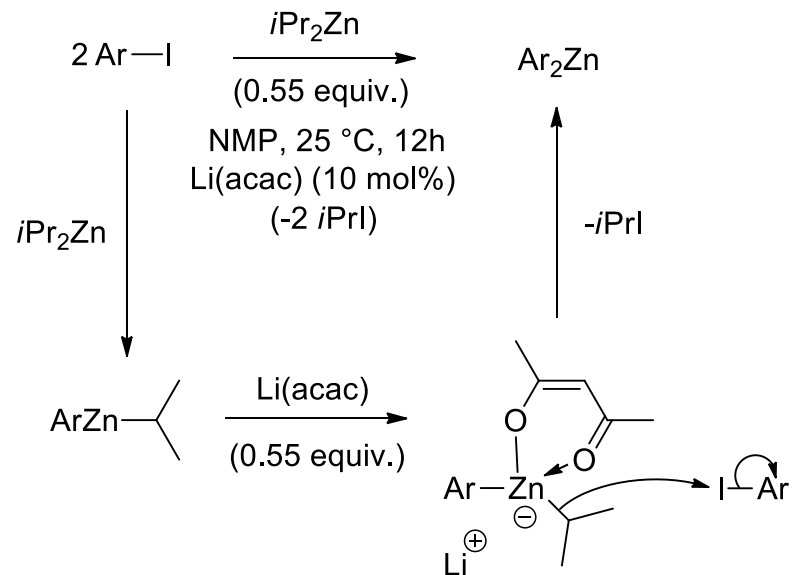


73 %

$dr = 97 : 3$

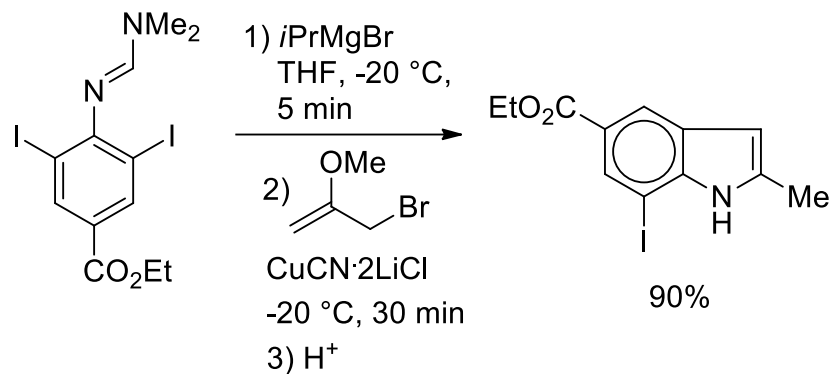
The iodine/zinc-exchange

catalysis of the halogen-metal exchange

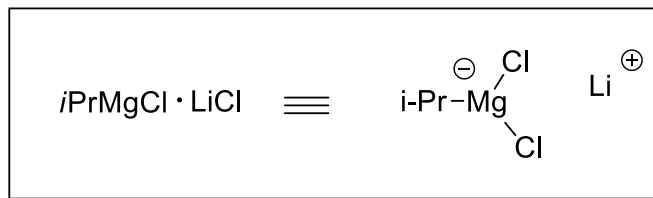
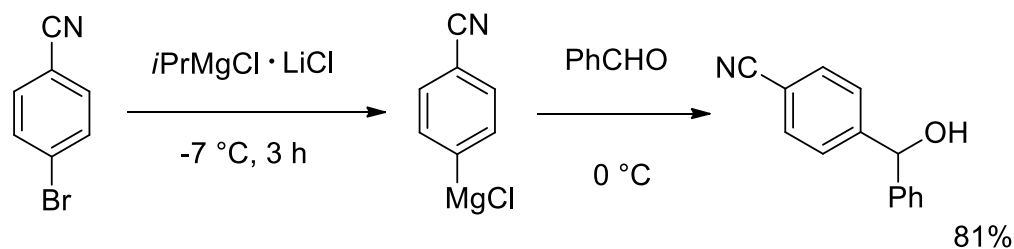


The Halogen-Metal-Exchange

indole-synthesis

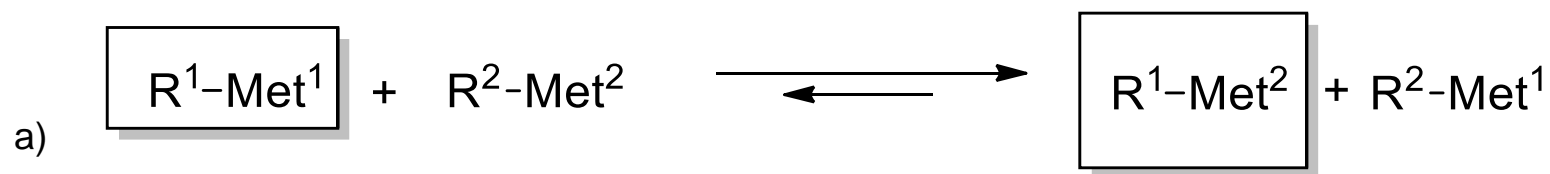


D. M. Lindsay, W. Dohle, A. E. Jensen, F. Kopp, P. Knochel *Org. Lett.*, **2002**, *4*, 1819

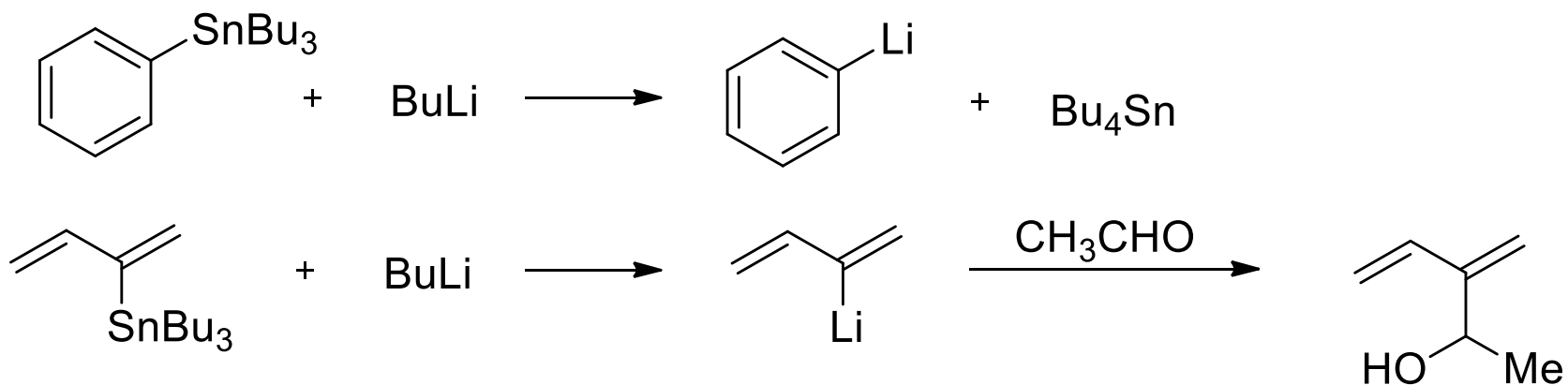


A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2004**, *43*, 3333

Transmetalation

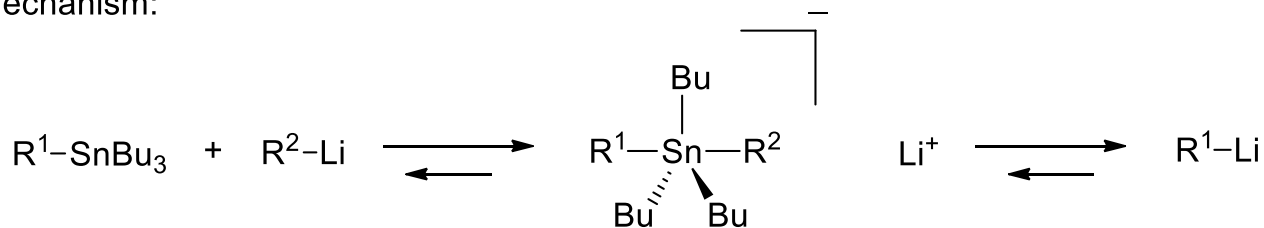


the most stable carbanion is linked to the most electropositive metal

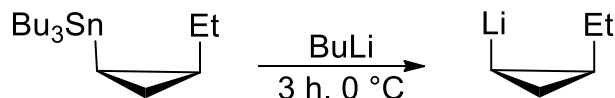


Transmetalation

mechanism:



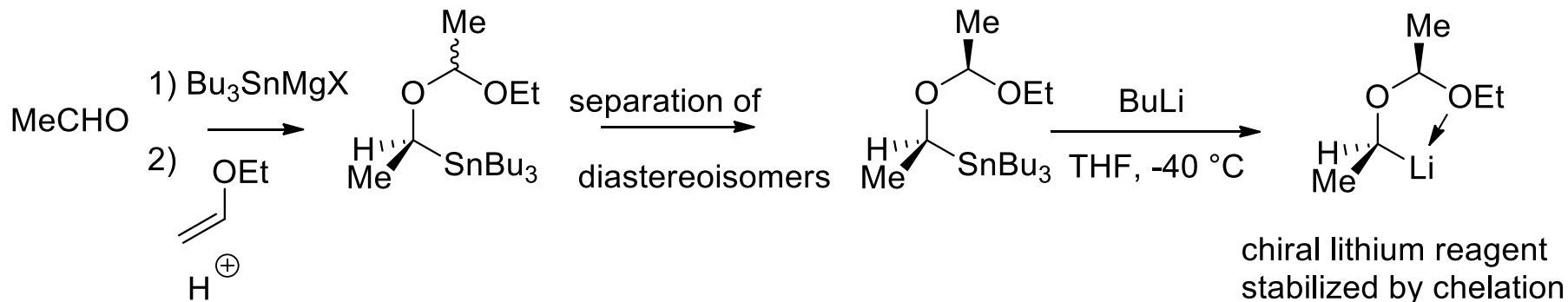
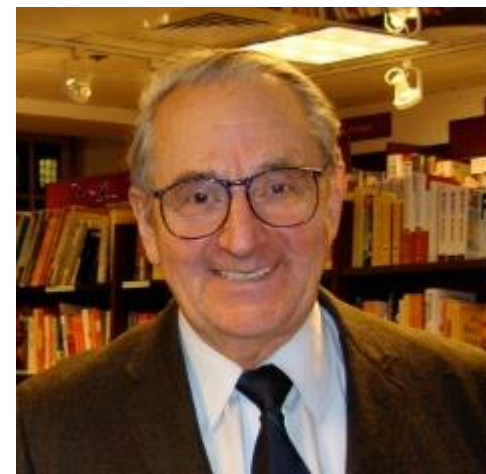
the most stable Li-organometallic is formed



configurational stable

Li-reagent due to the ring strain

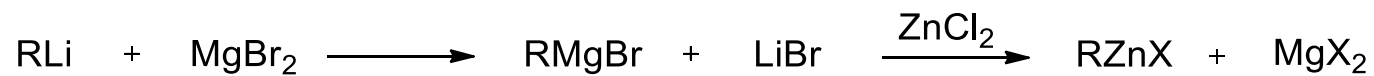
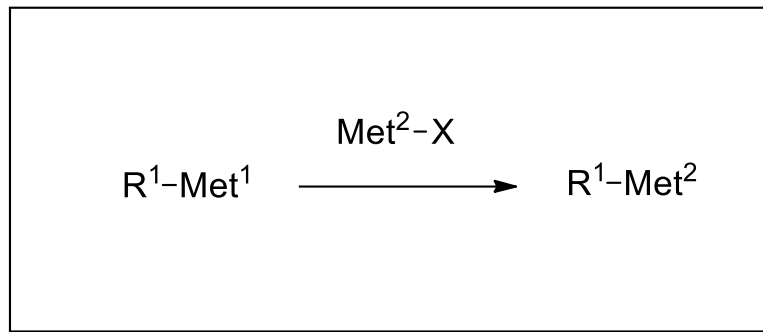
E. J. Corey Tetrahedron Lett. 1984, 25, 2415



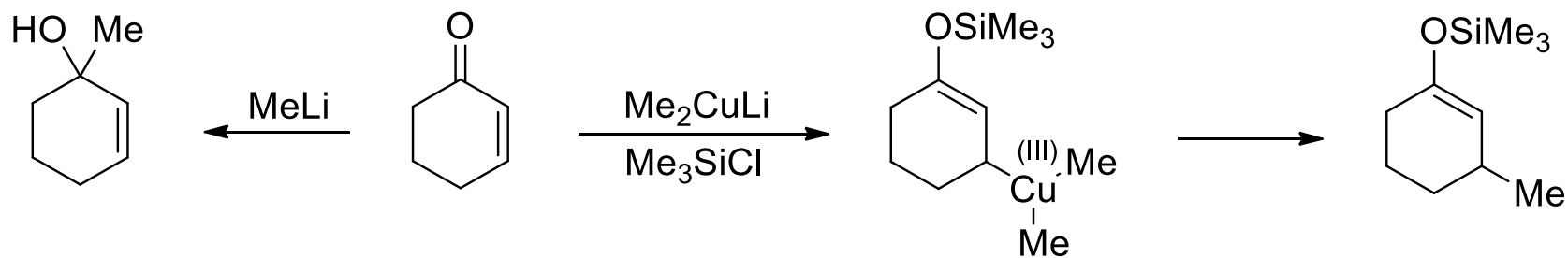
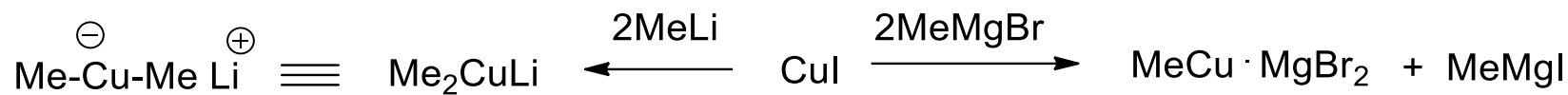
W. C. Still, *J. Am. Chem. Soc.* **1980**, 102, 1201

Transmetalation

b)

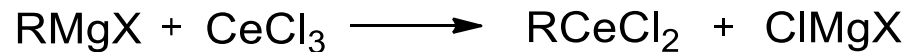


Transmetalation

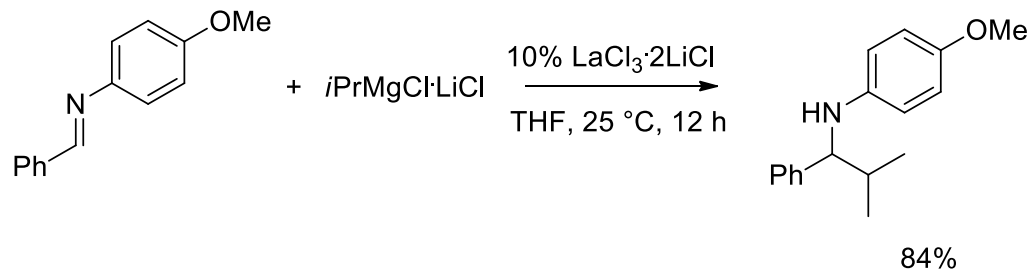
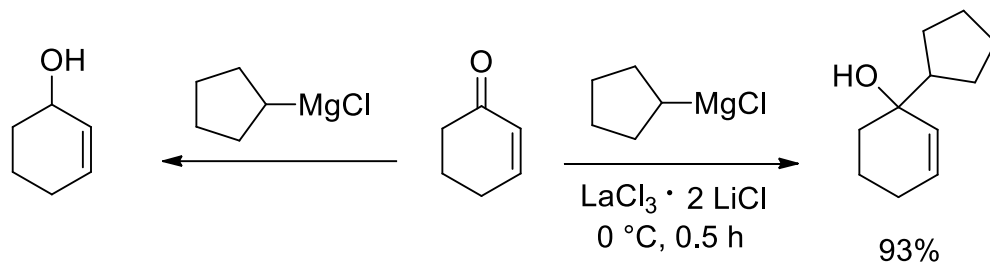
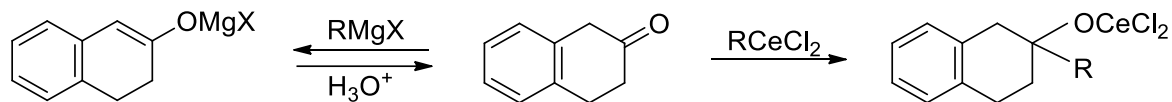


E. Nakamura, I. Kuwajima *J. Am. Chem. Soc.* **1984**, *106*, 3368

Transmetalation

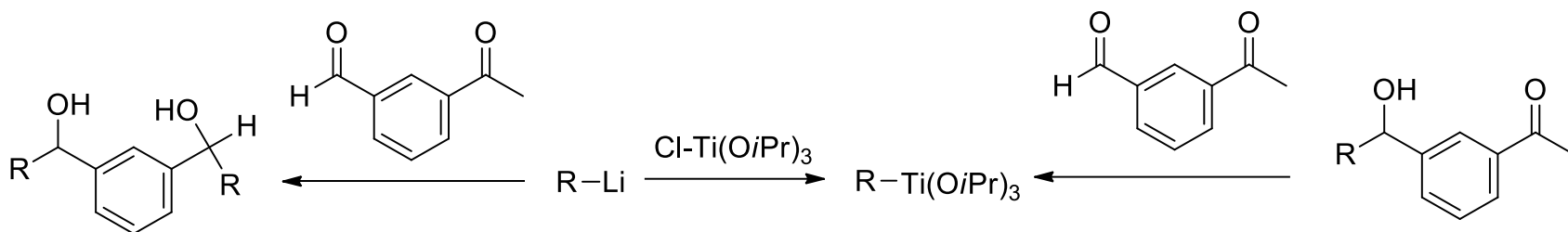


T. Imamoto, Y. Sugiyura, N. Takiyama, *Tetrahedron Lett.* **1984**, 25, 4233

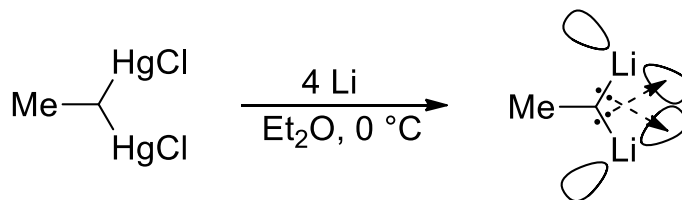


A. Krasovskiy, F. Kopp, P. Knochel *Angew. Chem. Int. Ed.* **2006**, 45, 497

Transmetalation



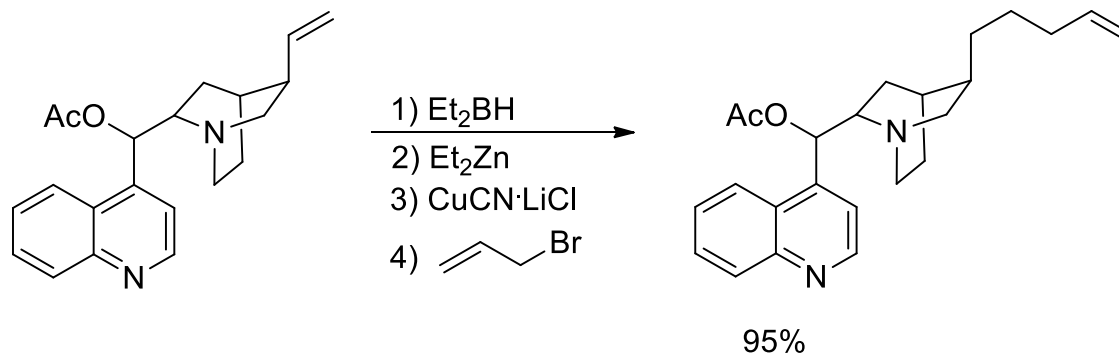
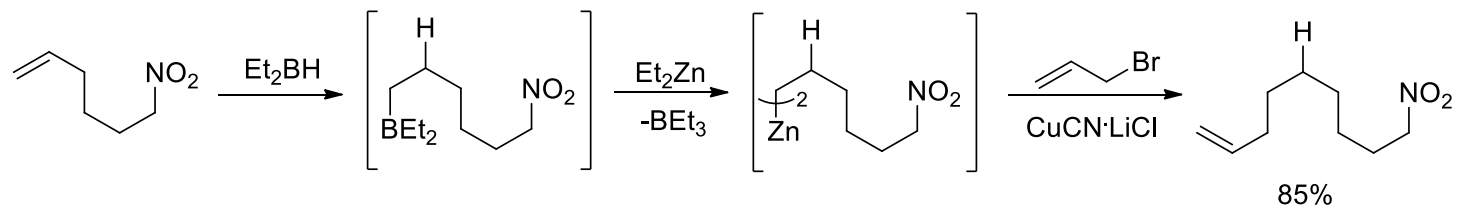
M. Reetz, D. Seebach *Angew. Chem.* **1983**, 95, 12



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

Transmetalation

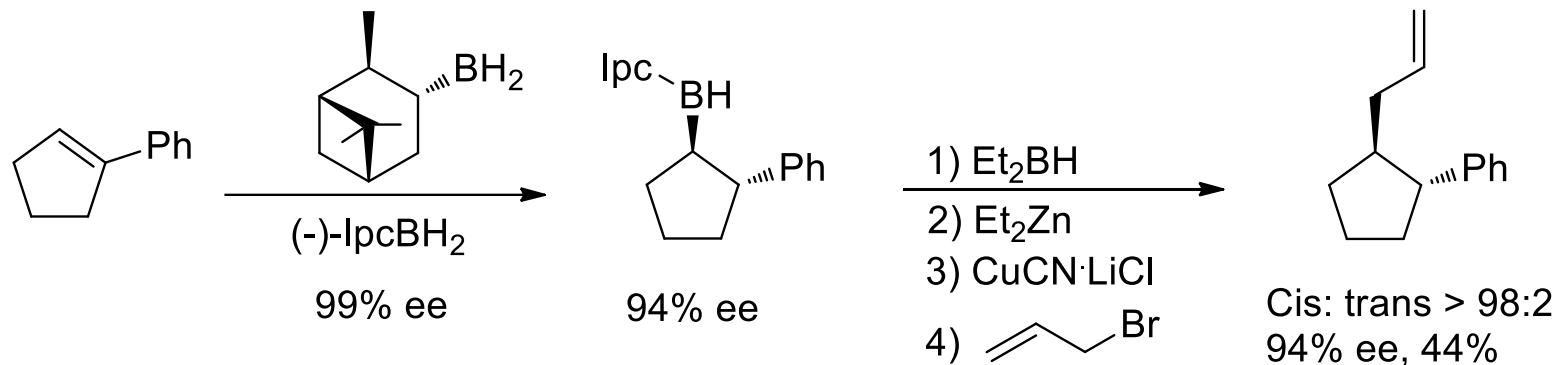
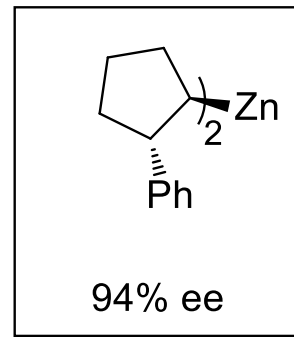
boron / zinc-exchange



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

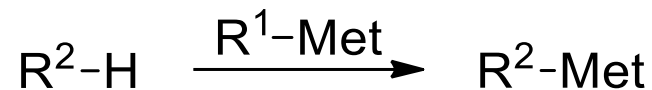
Transmetalation

boron / zinc-exchange



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

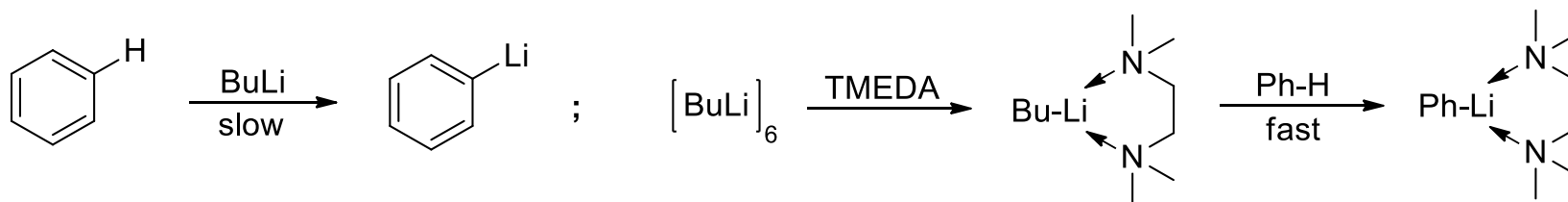
Metalation (starting from a compound with an acid proton)



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, ...

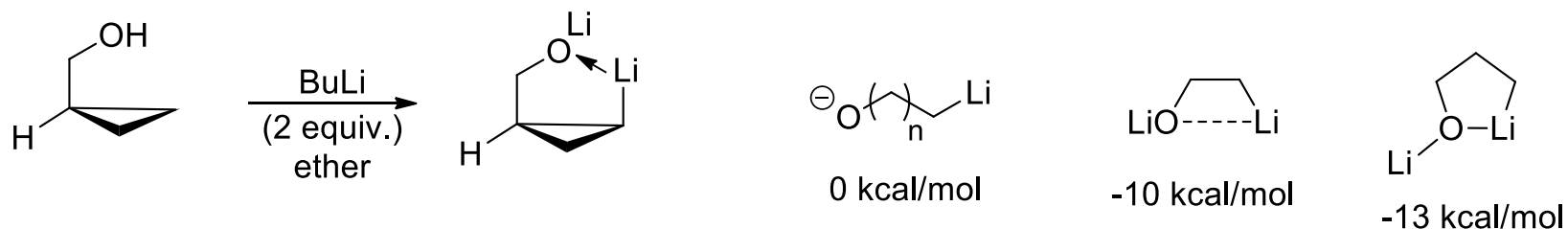
kinetic criteria (kinetic acidity)



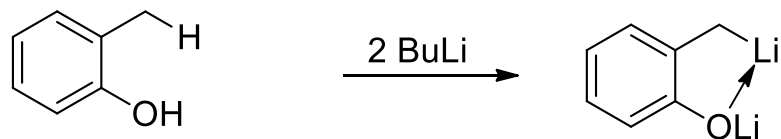
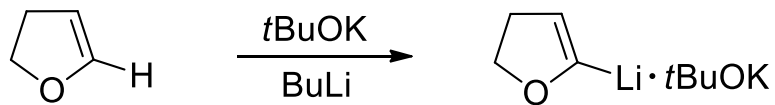
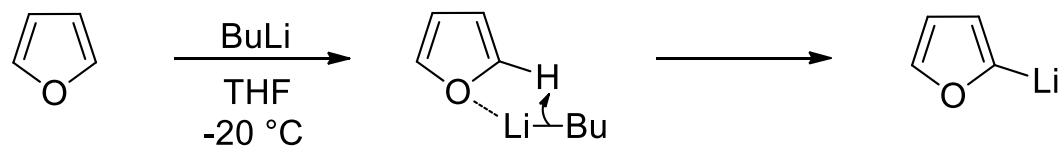
PhCH₂Li reacts with benzene 10⁴ times faster than with MeLi

PhCH₂Li is a monomer in THF, MeLi a tetramer

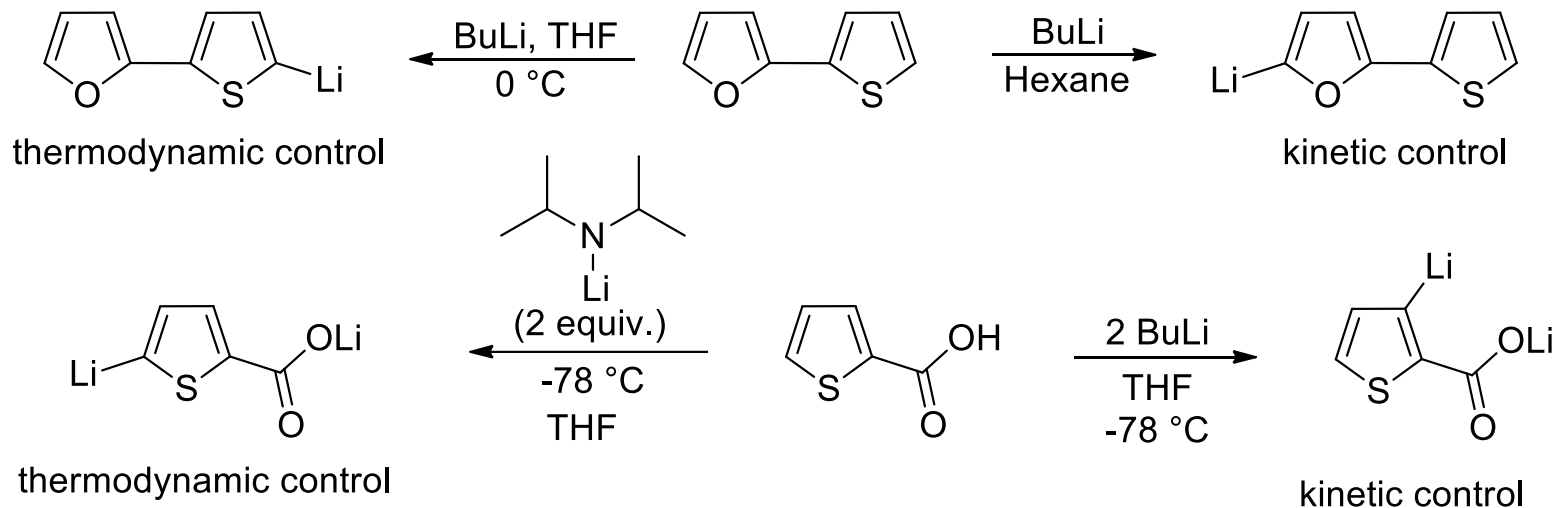
Directed metalation



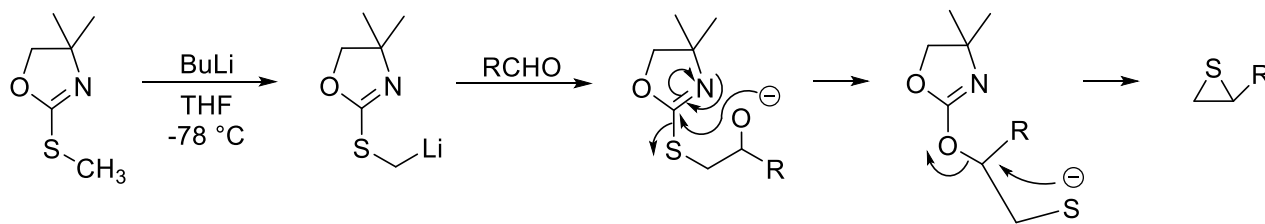
Directed metalation



Metalation

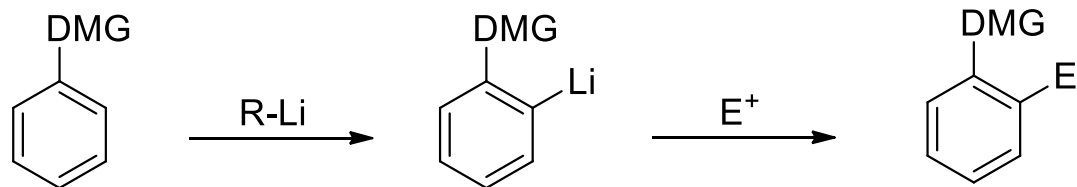


A rearrangement may occur :



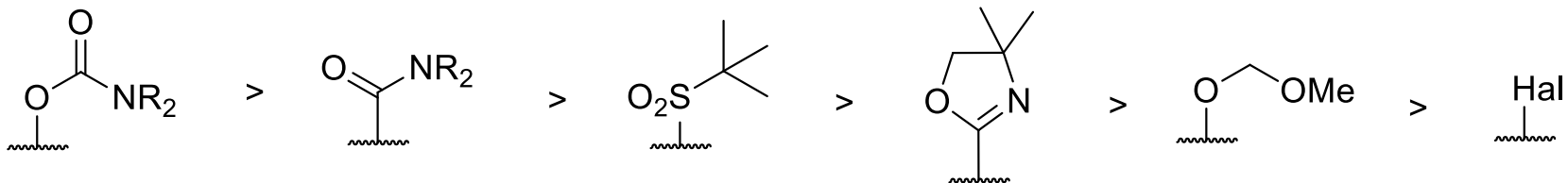
Metalation

directed lithiation



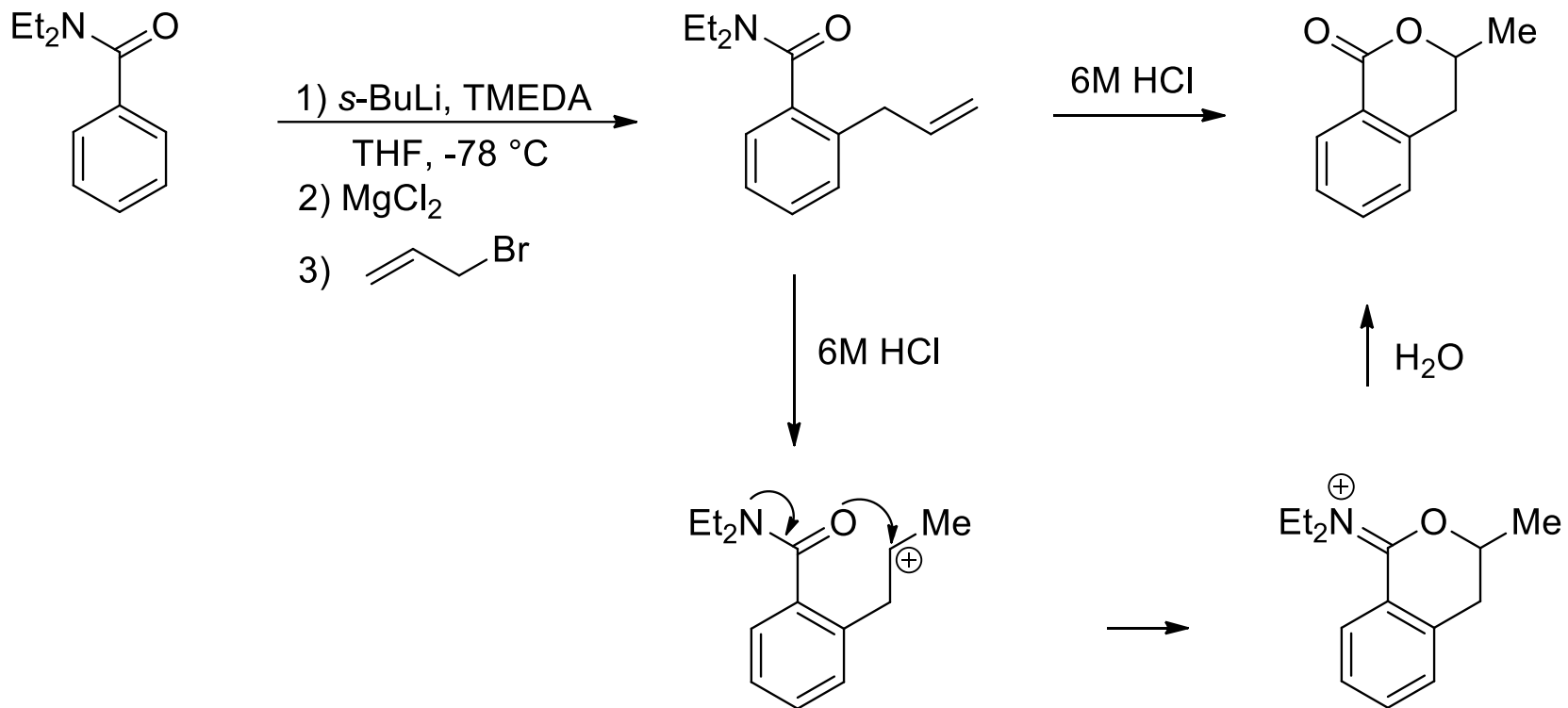
DMG = directing metalating group

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

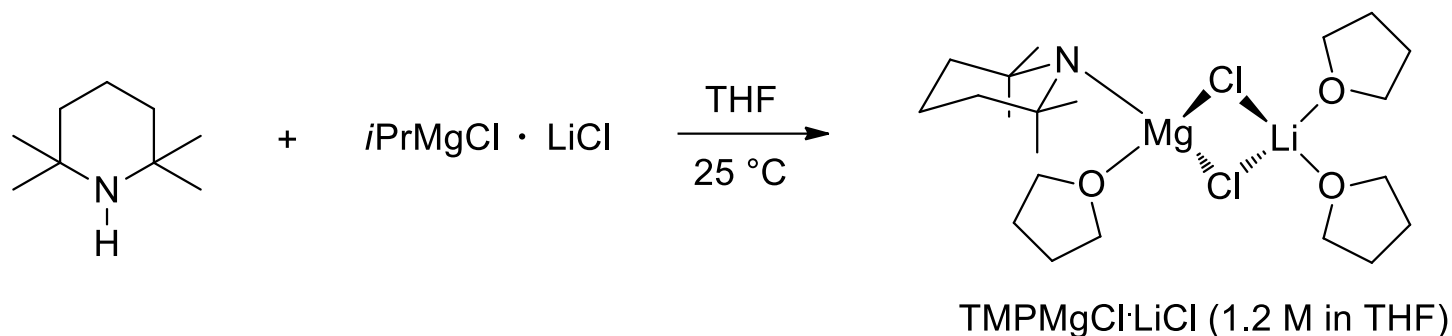


P. Beak, V. Snieckus, *Angew. Chem. Int. Ed.* **2004**, *43*, 2206

Metalation

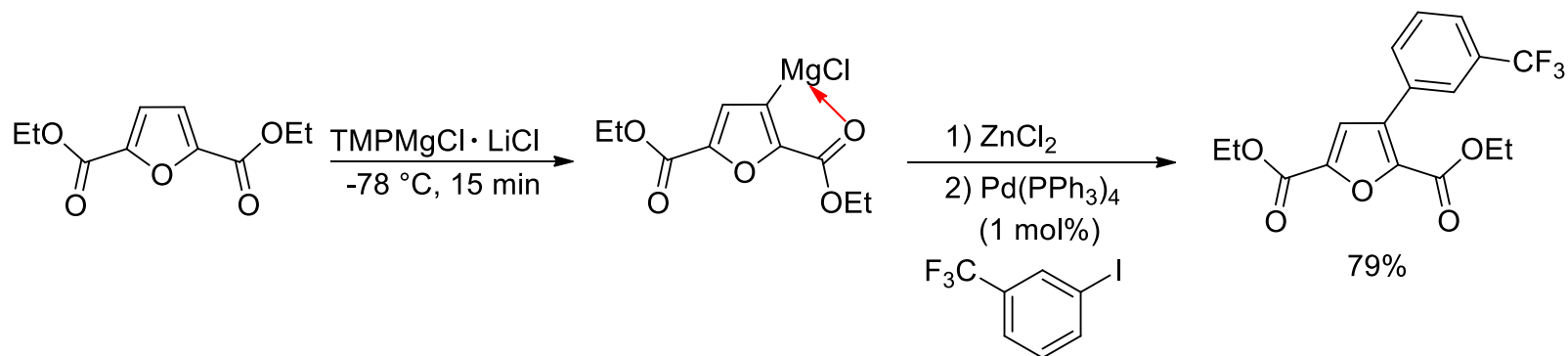


Metalation

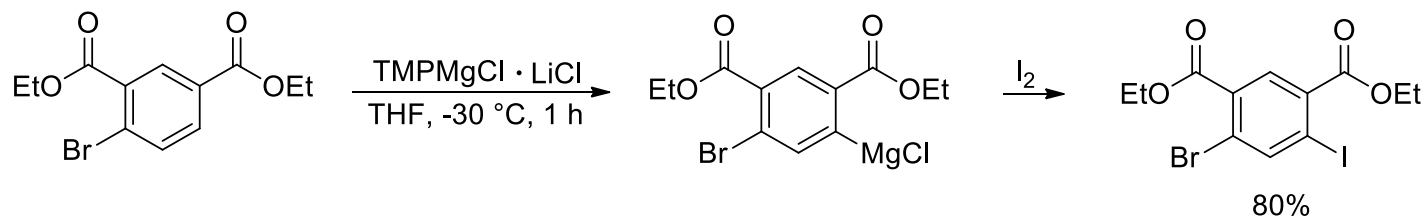


A. Krasovskiy, P. Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 2958

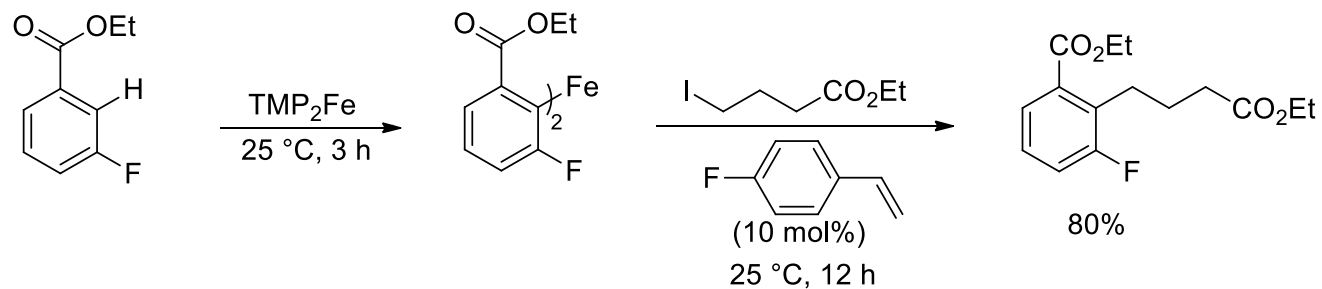
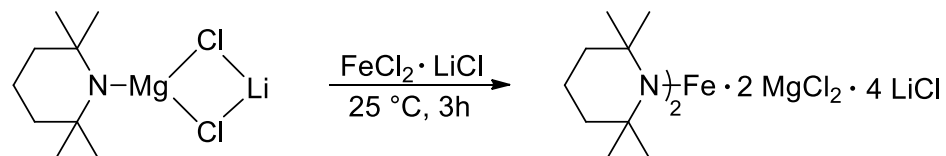
R. E. Mulvey, *Angew. Chem. Int. Ed.* **2008**, *47*, 8079



Metalation

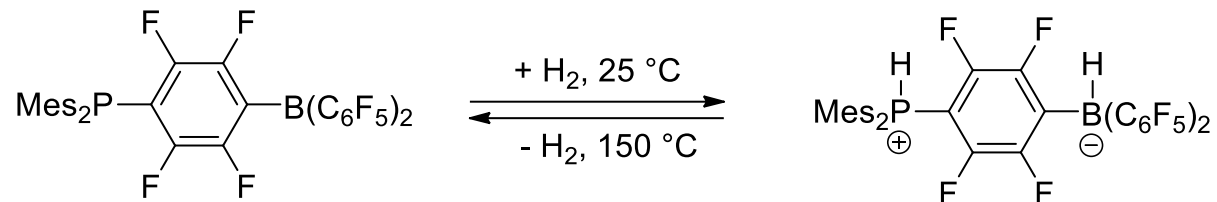


O. Baron, P. Knochel *Angew. Chem. Int. Ed.* **2006**, *45*, 2958

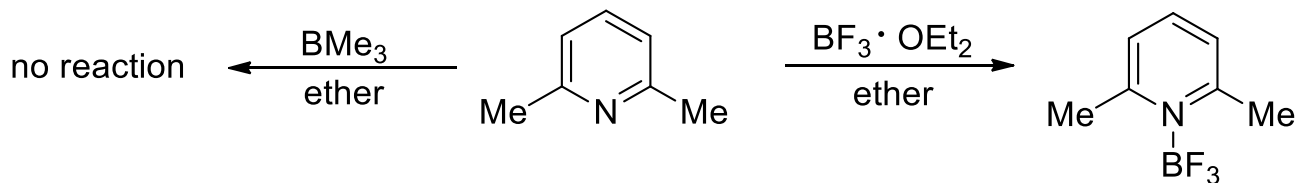


S. Wunderlich, P. Knochel *Angew. Chem. Int. Ed.* **2009**, *48*, 9717

Frustrated Lewis Pairs

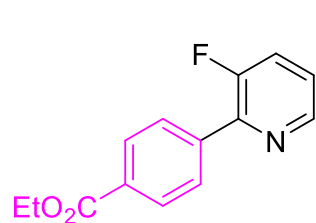
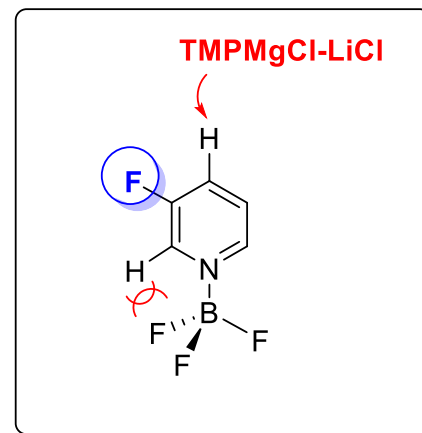
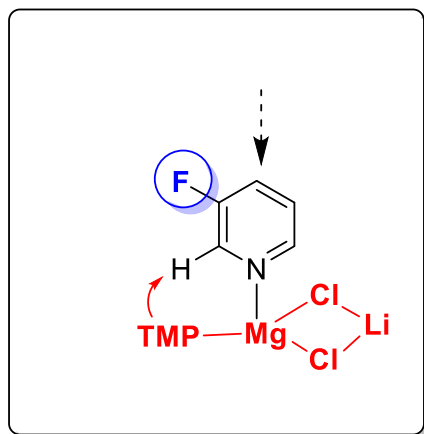
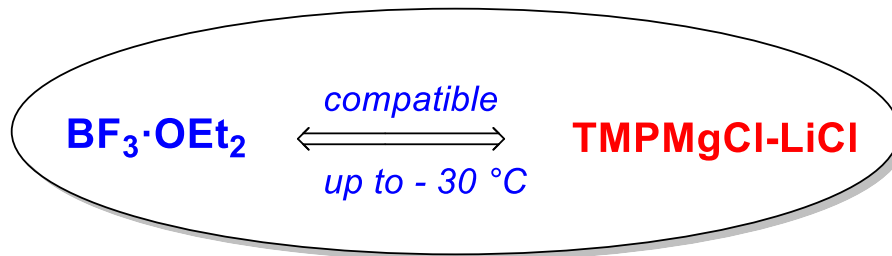


D. Stefan, G. Erker *Angew. Chem. Int. Ed.* **2010**, 49, 46



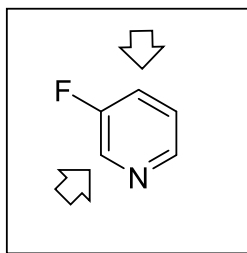
H. C. Brown *J. Am. Chem. Soc.* **1942**, 64, 325

BF₃-triggered selective metalations

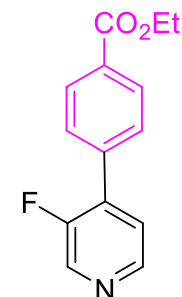


72 %

- 1) **TMPMgCl·LiCl**,
-78 °C, 30 min
- 2) ZnCl₂, **Ar-I**,
5% Pd(dba)₂,
10% P(o-furyl)₃,
25 °C, 12 h

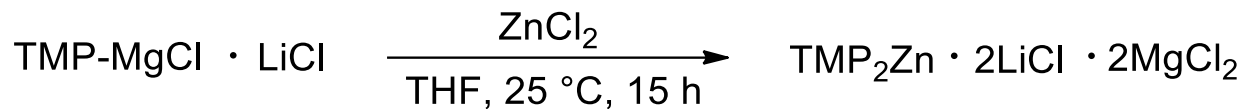


- 1) **BF₃·OEt₂**,
0 °C, 15 min
- 2) **TMPMgCl·LiCl**,
-78 °C, 30 min
- 3) ZnCl₂, **Ar-I**,
5% Pd(dba)₂,
10% P(o-furyl)₃,
25 °C, 12 h

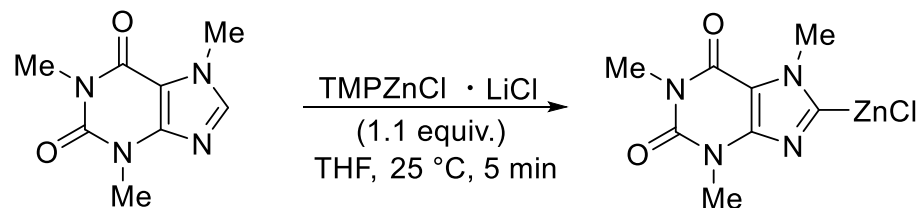
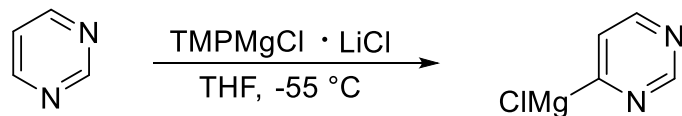
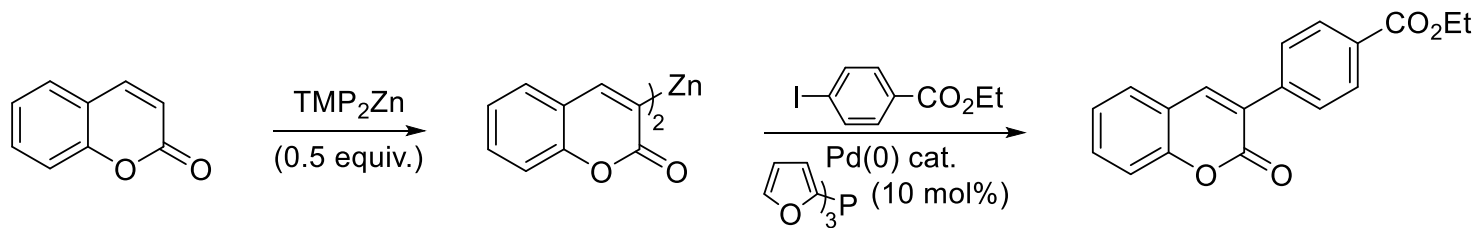


74 %

Metalation



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

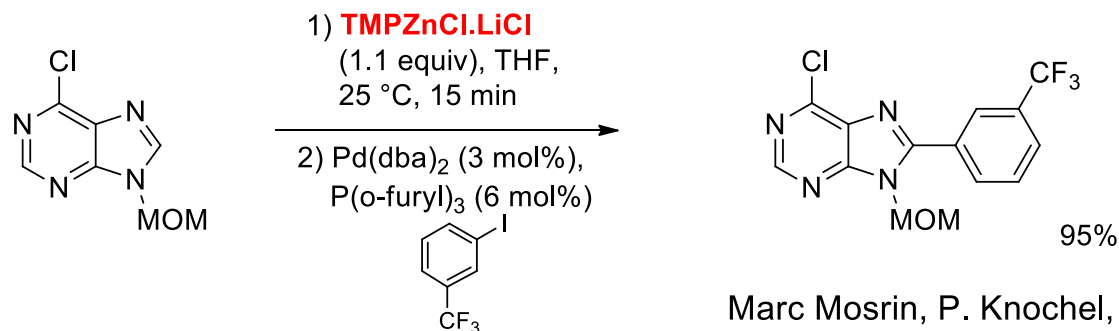
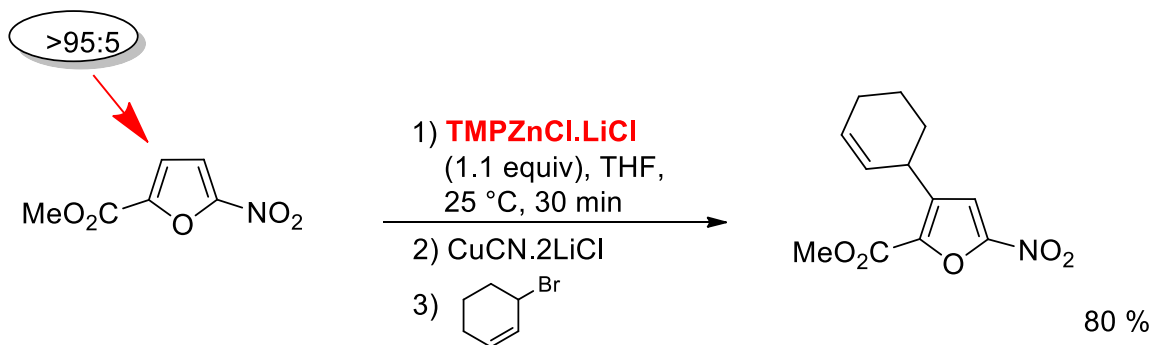


M. Mosrin, P. Knochel *Org. Lett.* **2008**, 10, 2497

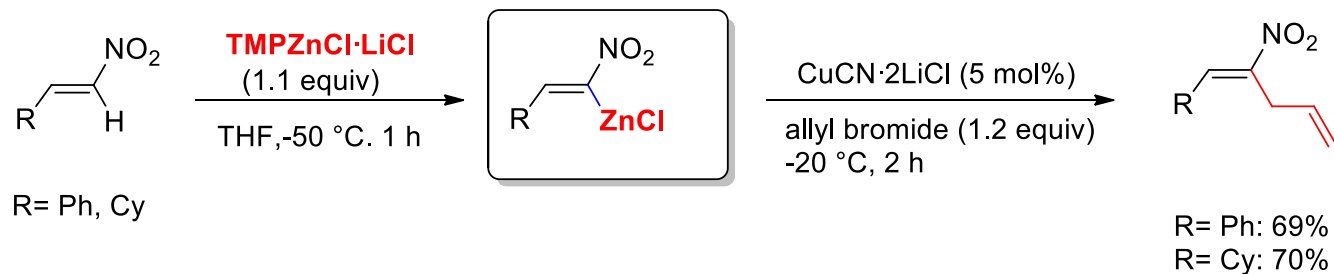
M. Mosrin, P. Knochel *Chem. Eur. J.* **2009**, 15, 1468

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

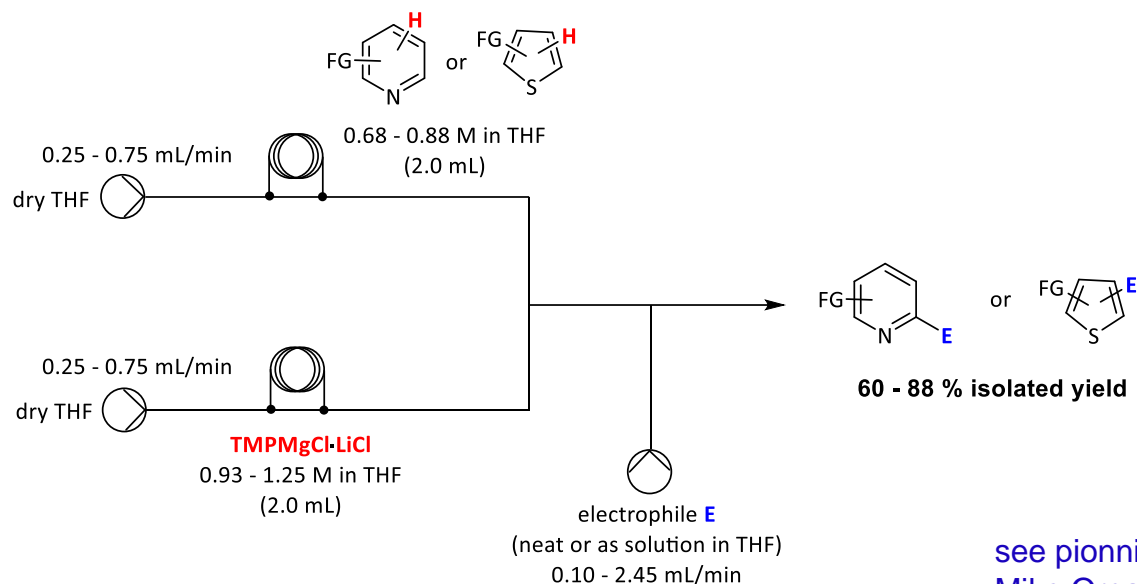
Zincations in the presence of ester and nitro groups



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



Metalations under batch and flow conditions using TMPMgCl·LiCl

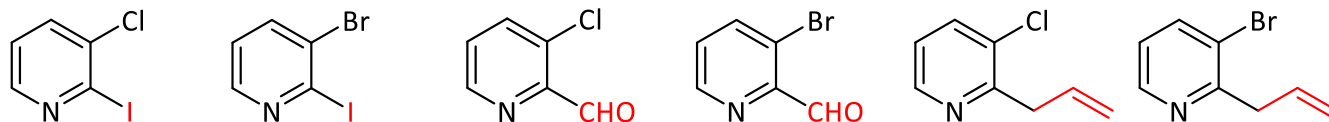


see pionnier contributions of
Mike Organ, Jun-ichi Yoshida, Steven V. Ley

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

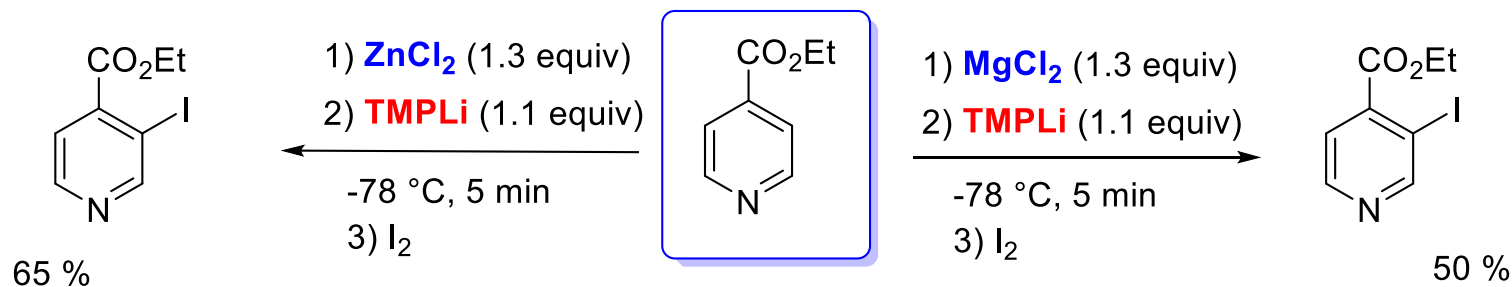
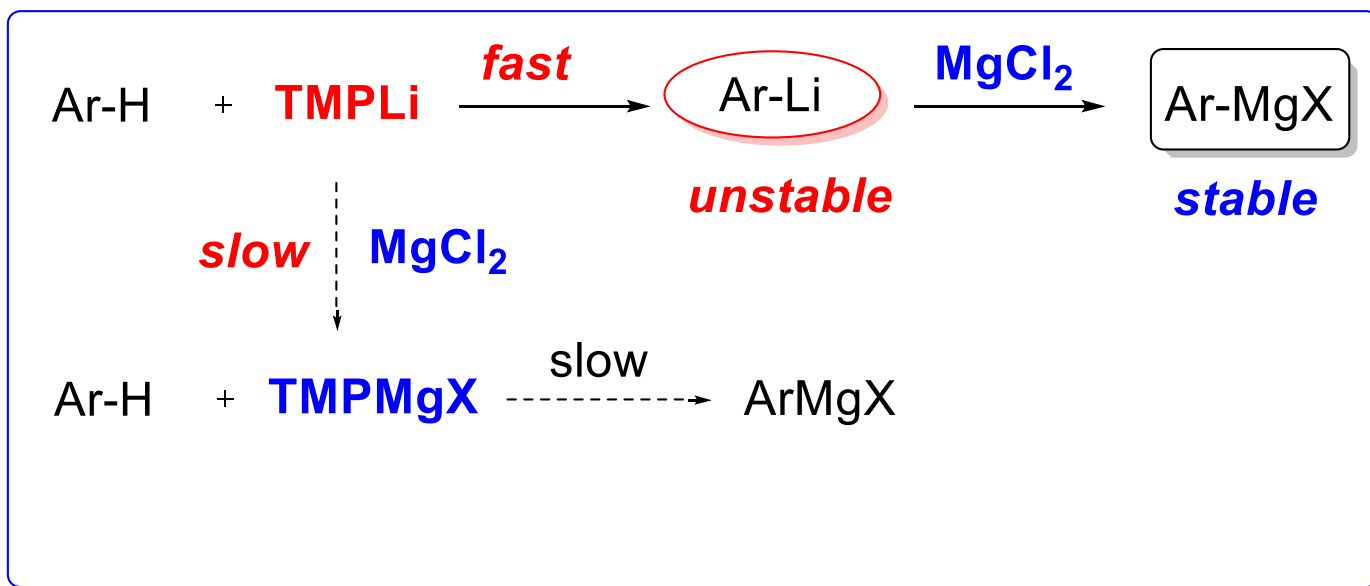
Batch conditions: Complete metalation of 3-chloropyridine after **45 min at -78 °C**

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·2LiCl
Metalation time	60 s	60 s	60 s
Isolated yield	66%	71%	78%

Compatibility of the TMPLi with ZnCl₂ or MgCl₂

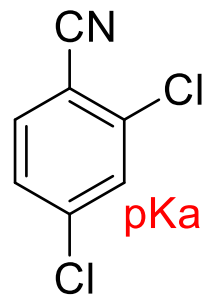


Selectivity switch with (TMPLi and ZnCl₂) or TMPZnCl-LiCl

kinetic deprotonation

pKa = 30.2

pKa = 30.1



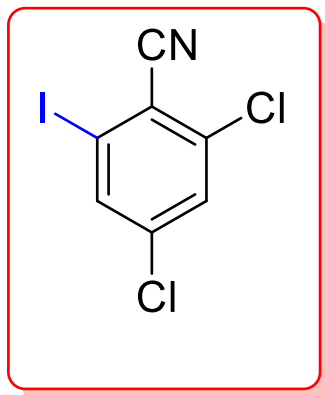
thermodynamic deprotonation

1) **ZnCl₂ · 2LiCl** (1.1 equiv)

2) **TMPLi** (1.5 equiv)

-78 °C, 5 min

3) I₂



74 %

crude selectivity

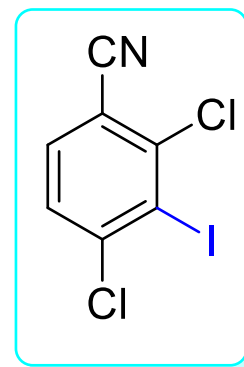
95 : 5

1) **TMPZnCl · LiCl**

(1.1 equiv.)

60 °C, 12 h

2) I₂

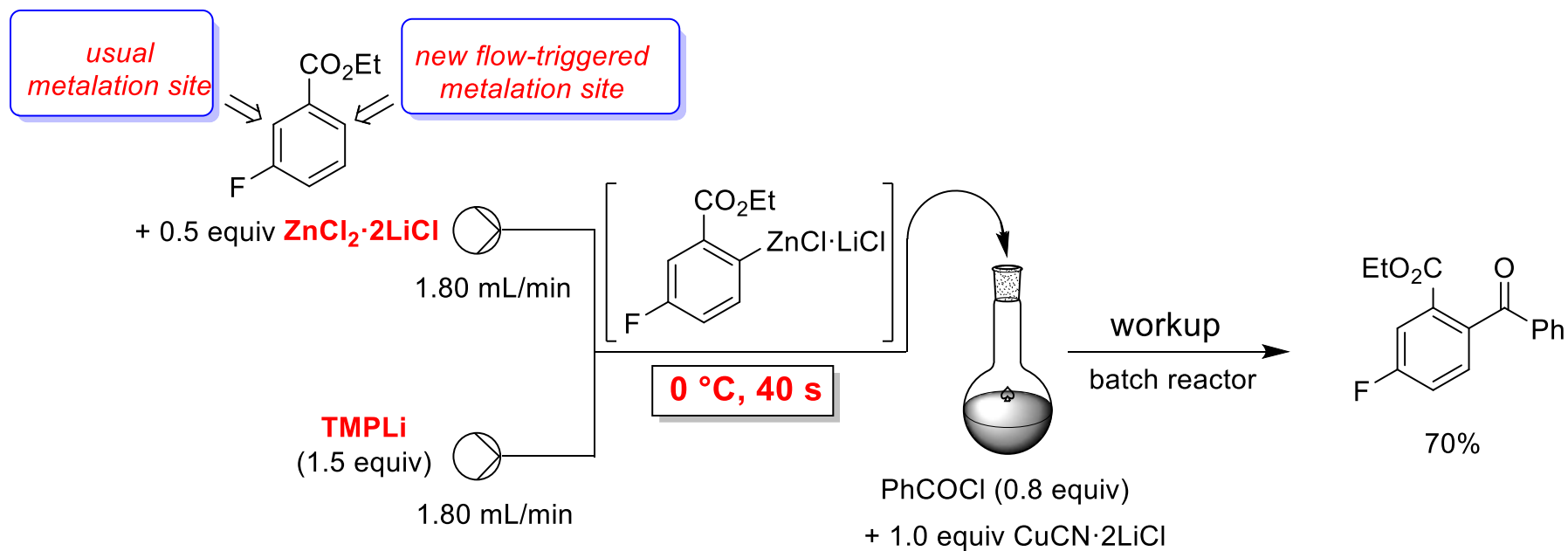


78 %

crude selectivity

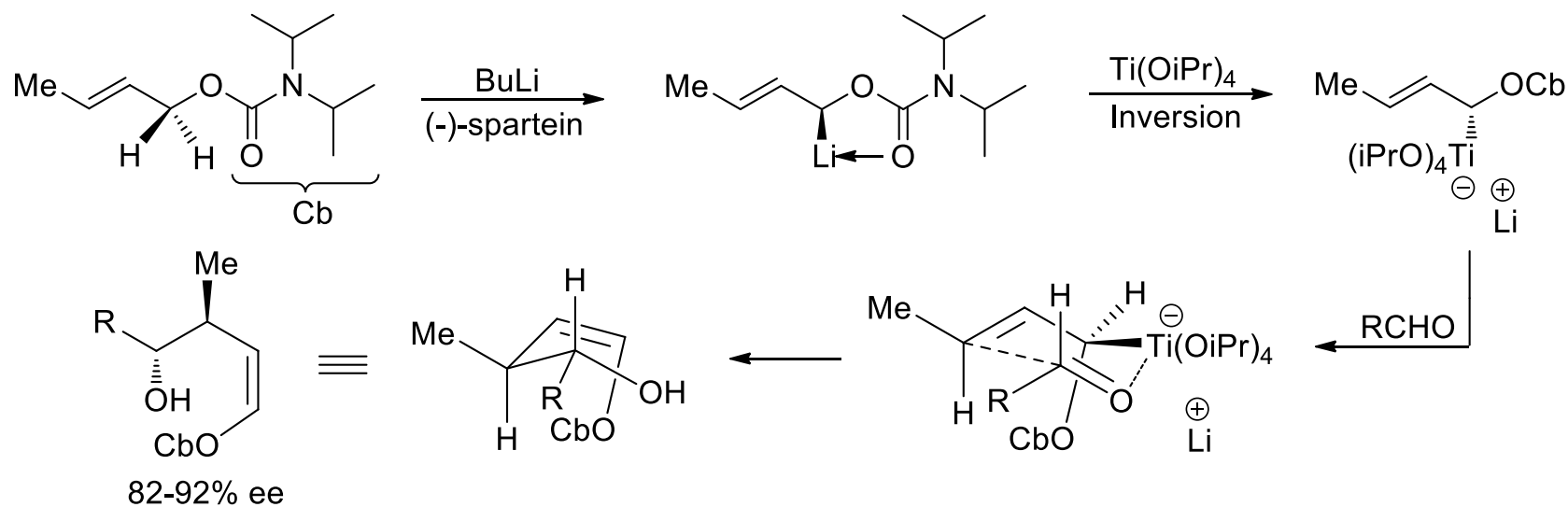
1 : 99

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

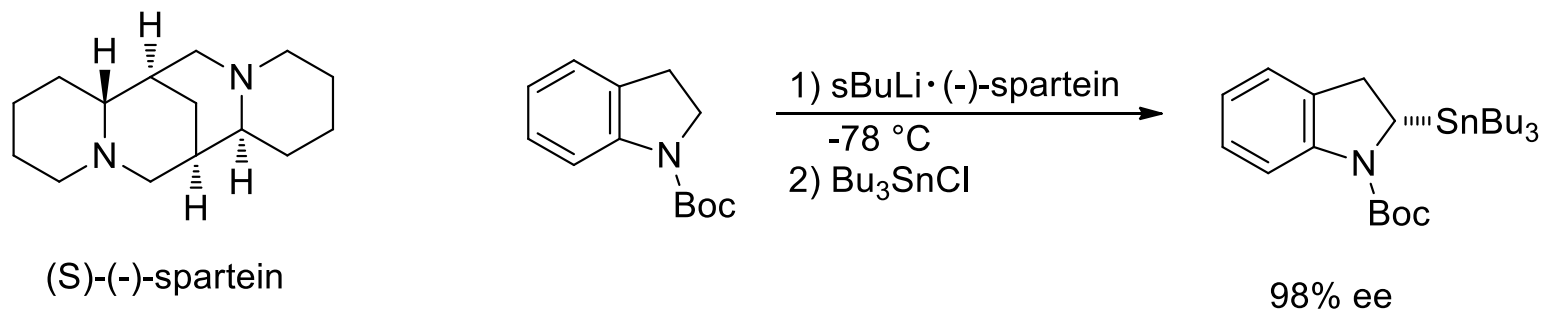


M. R. Becker, P. Knochel, *Angew.Chem.Int. Ed.* **2015**, *54*, in press

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

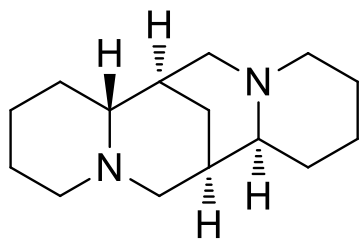
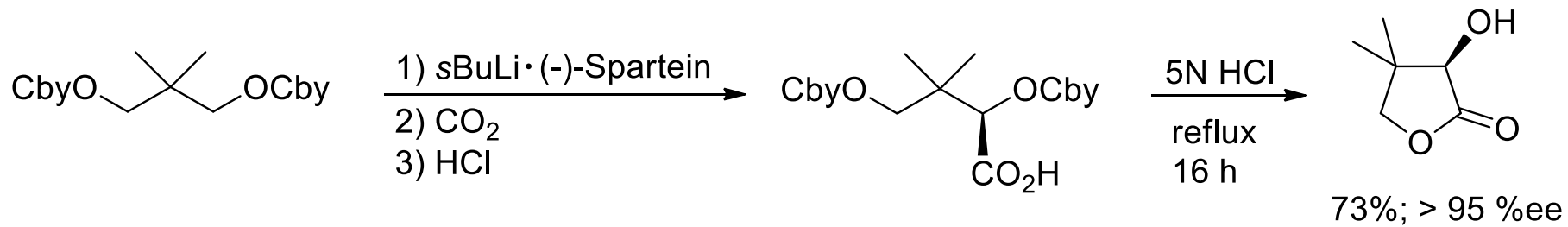


D. Hoppe, et al. *Pure Appl. Chem.* **1994**, 66, 1479.



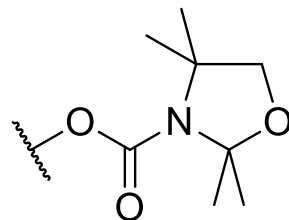
P. Beak *J. Org. Chem.* **1997**, 62, 7679

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



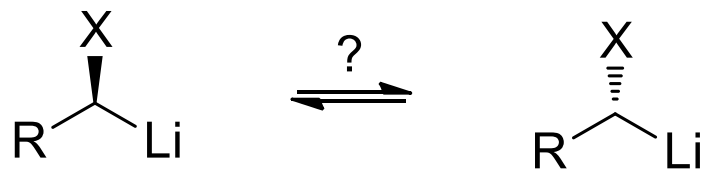
(S)-(-)-Sparteine

Cby

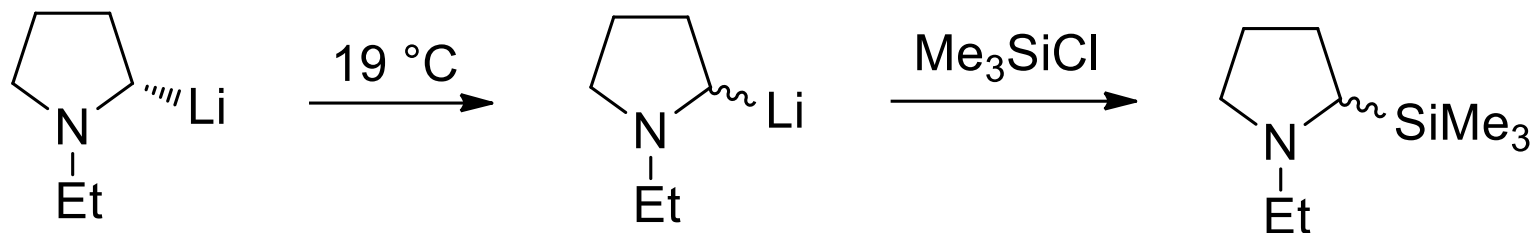


D. Hoppe *Tetrahedron Lett.* **1992**, 33, 5327

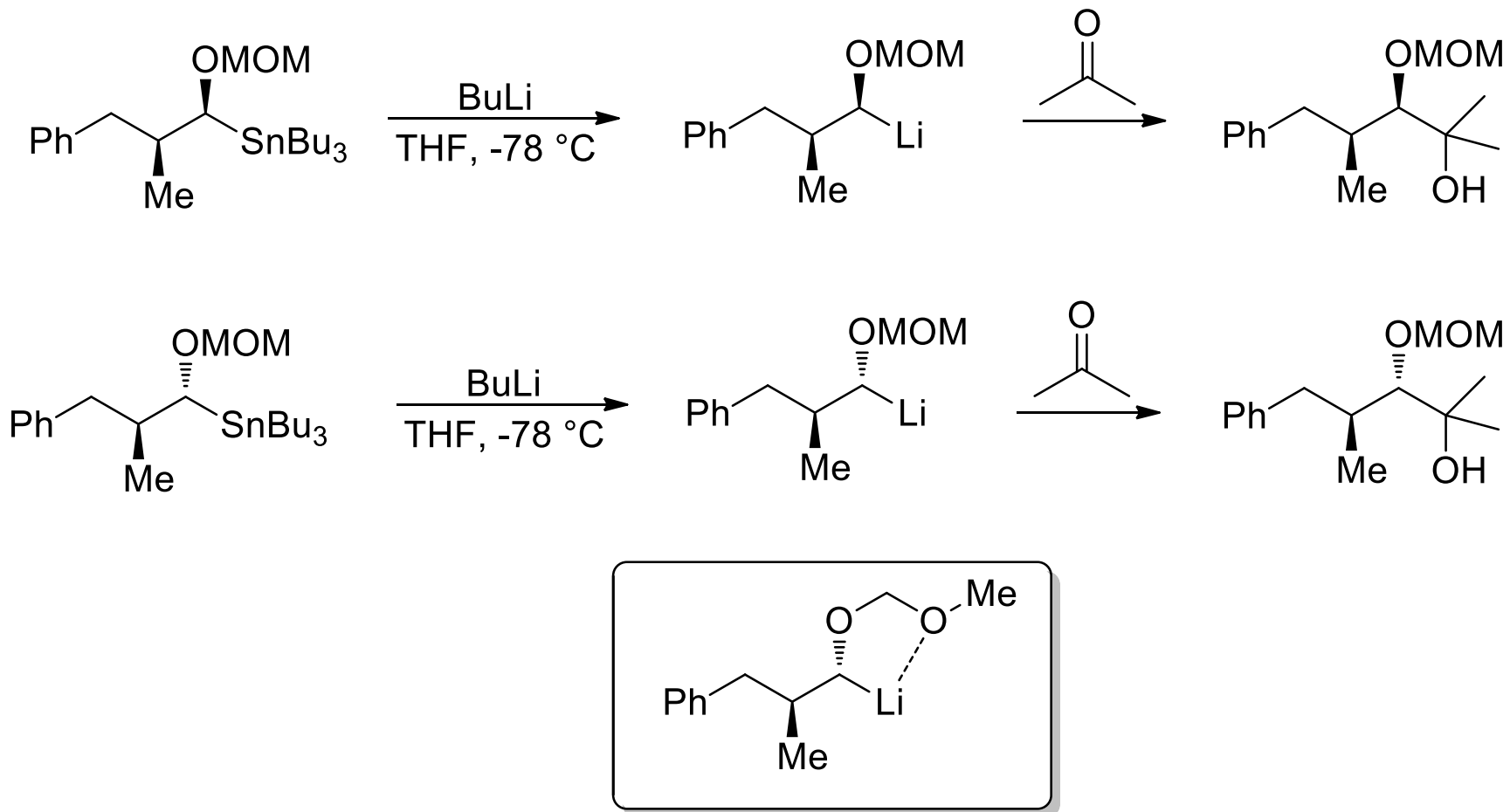
Configurational stability



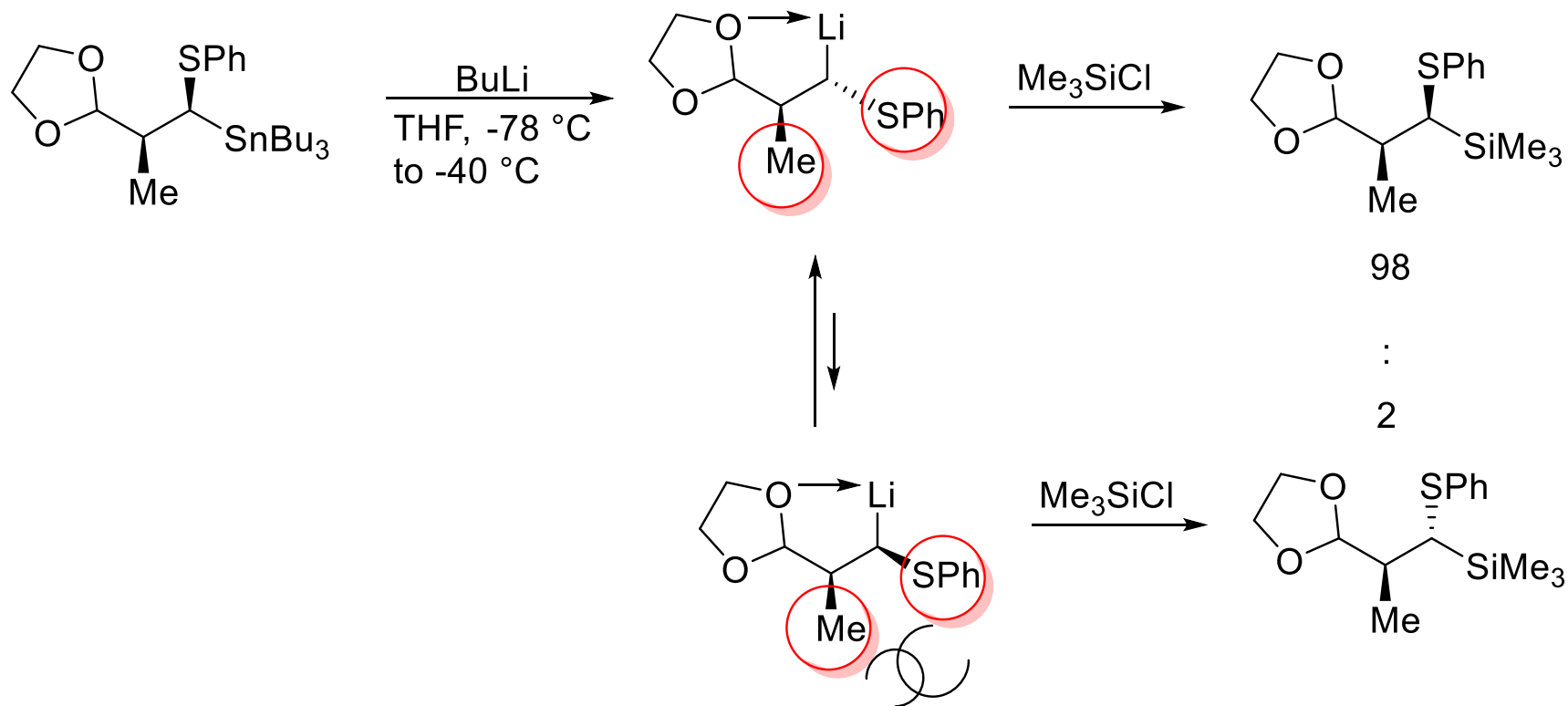
X=Br, SePh, SPh, OCH₂OMe, OCONiPr₂



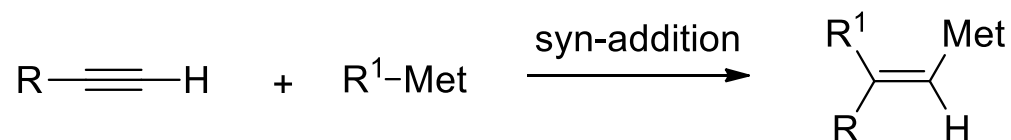
Diastereoselective transmetalation



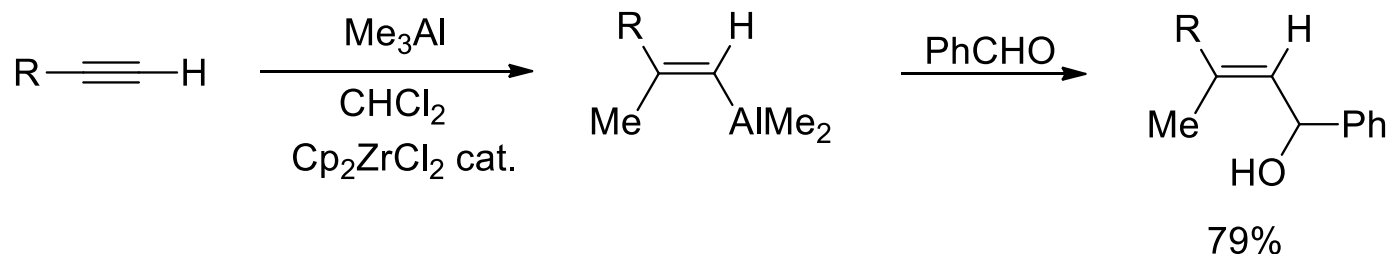
Diastereoselective transmetalation



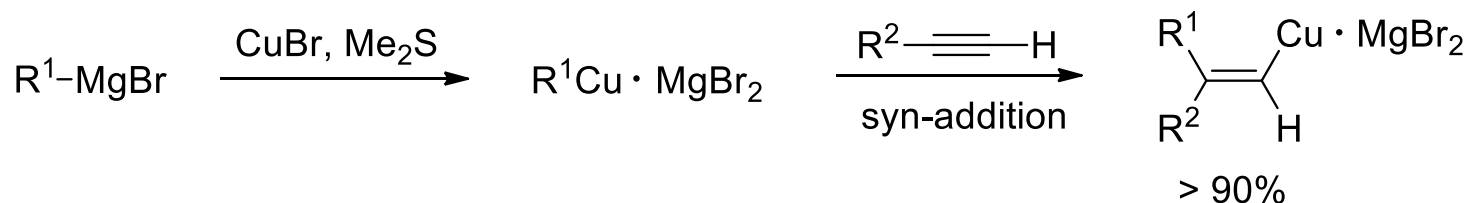
Carbometalation



Negishi-reaction: carboalumination



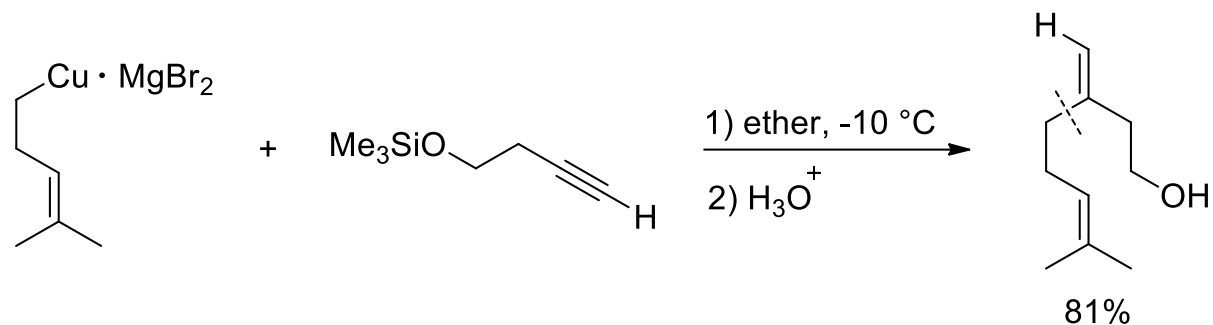
E. Negishi *J. Am. Chem. Soc.* **1976**, 98, 6729



Normant-reaction: carbocupration

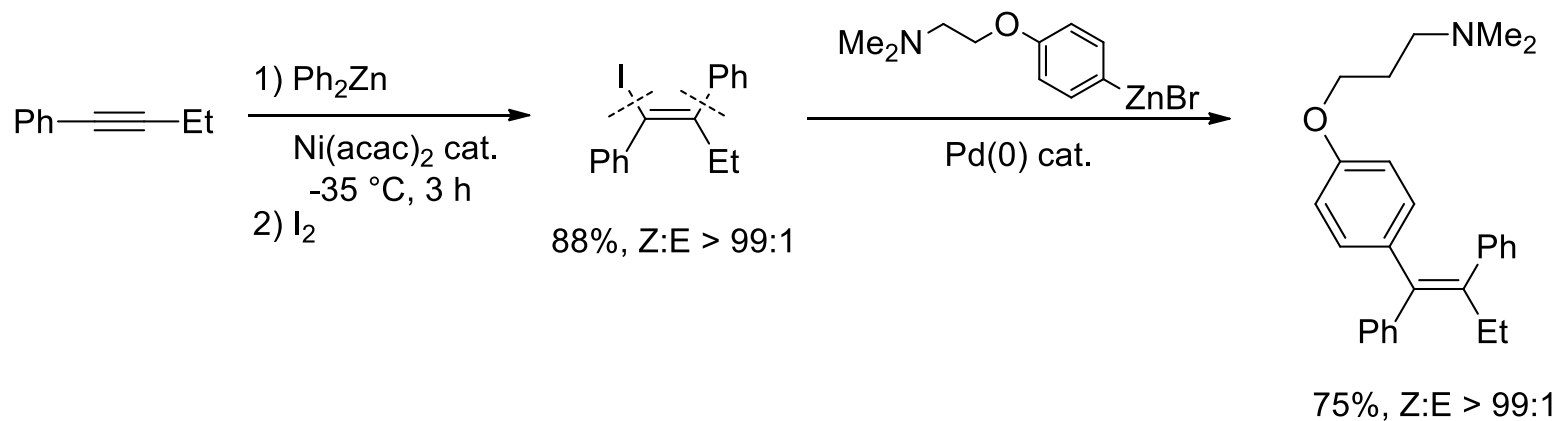
Review: A. Alexakis, J. F. Normant, *Synthesis* **1981**, 841.

Carbometalation



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

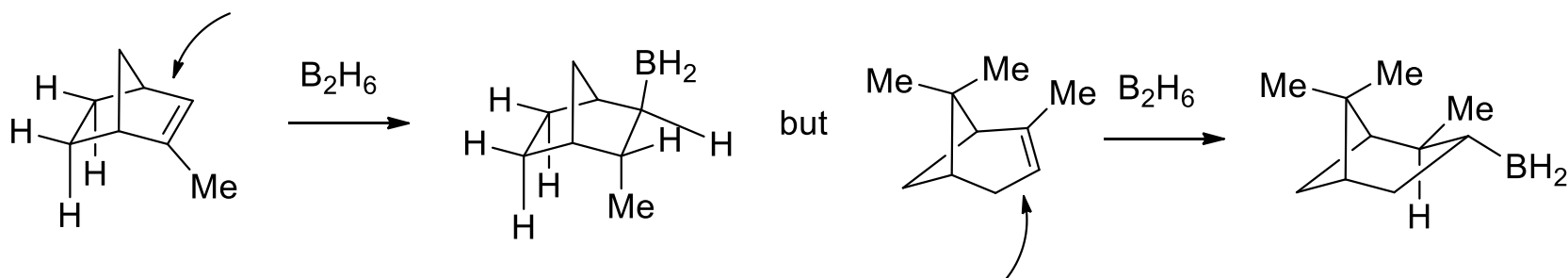
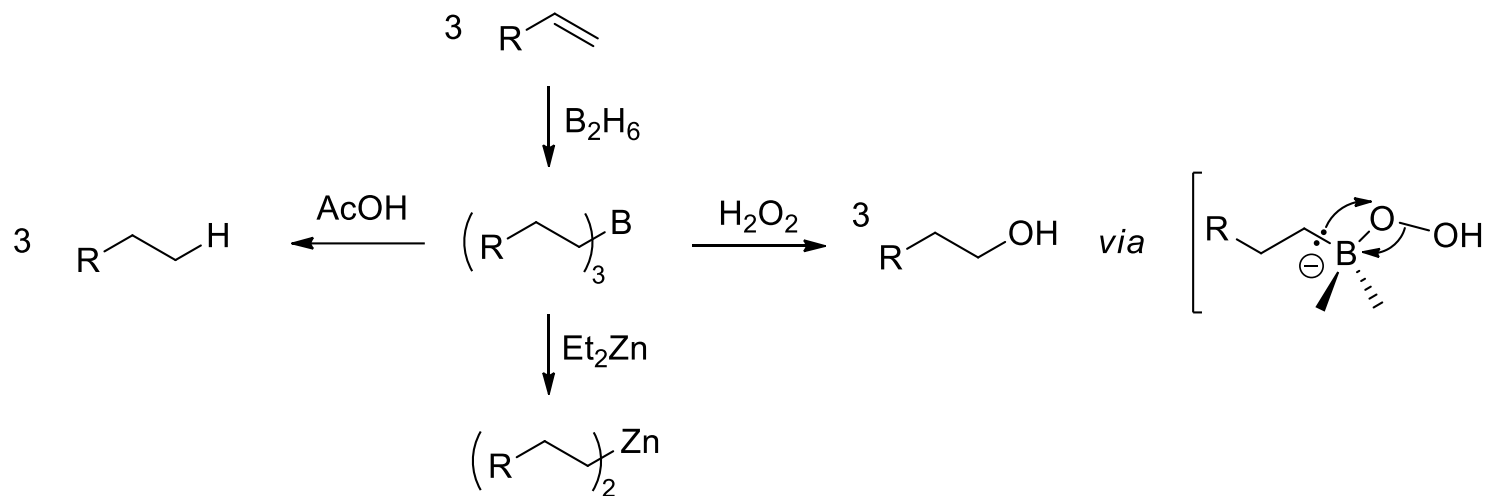
Tamoxifen-Synthesis: Carbozincation



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

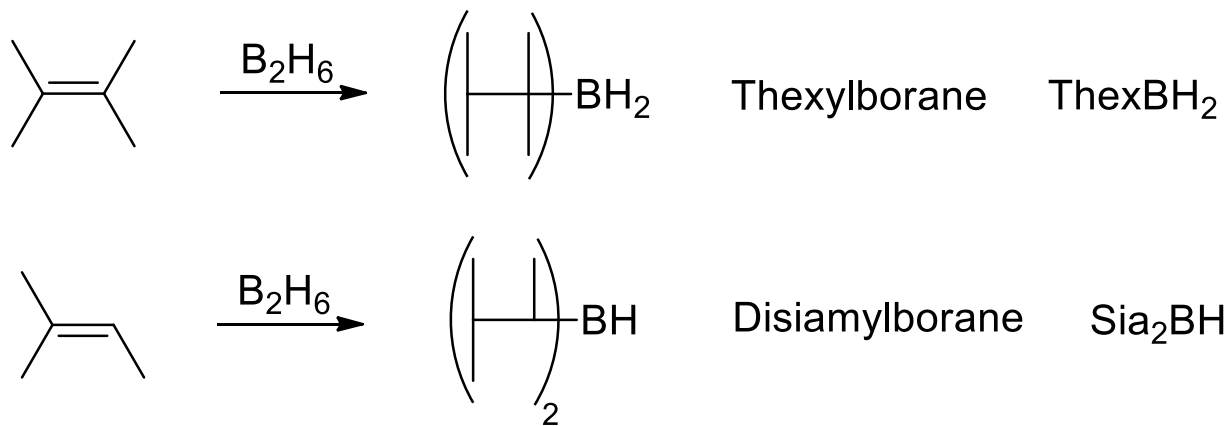
Hydrometalation and application of organoboranes in organic chemistry

hydroboration



Hydroboration

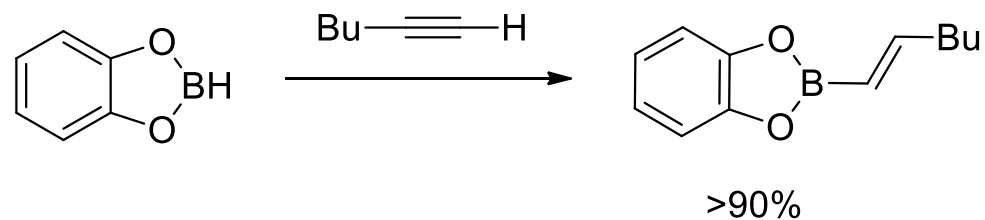
selective hydroborating reagents



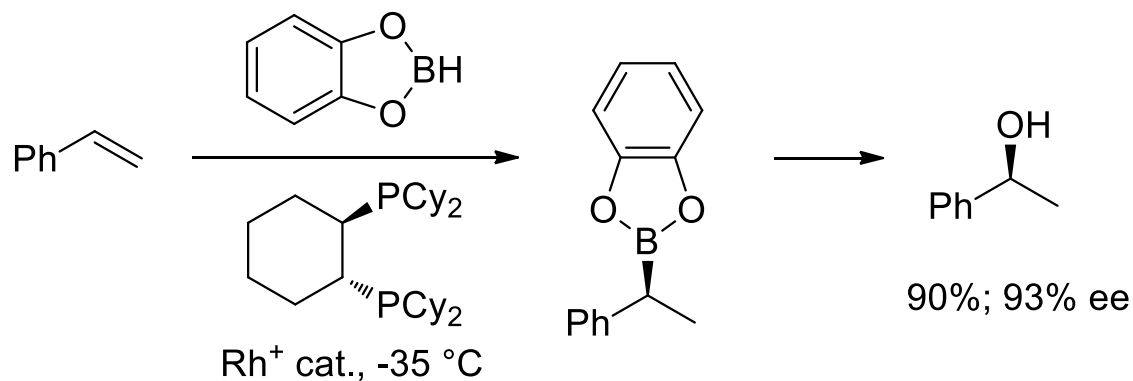
H. C. Brown, E. Negishi *J. Am. Chem. Soc.* **1975**, 97, 2799

Hydroboration

catecholborane



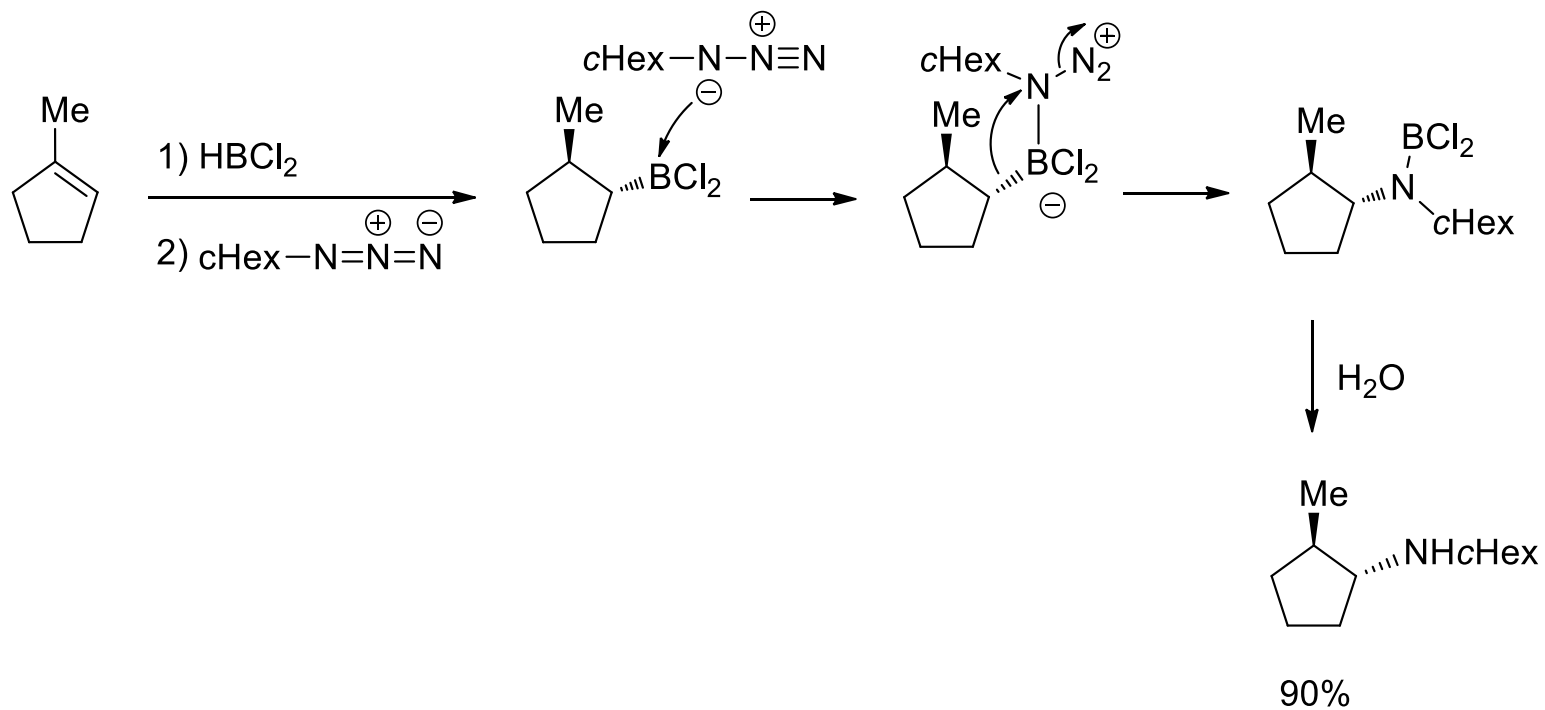
A. Arase, et al., *Synth. Comm.* **1995**, 25, 1957.



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

Hydroboration

amination

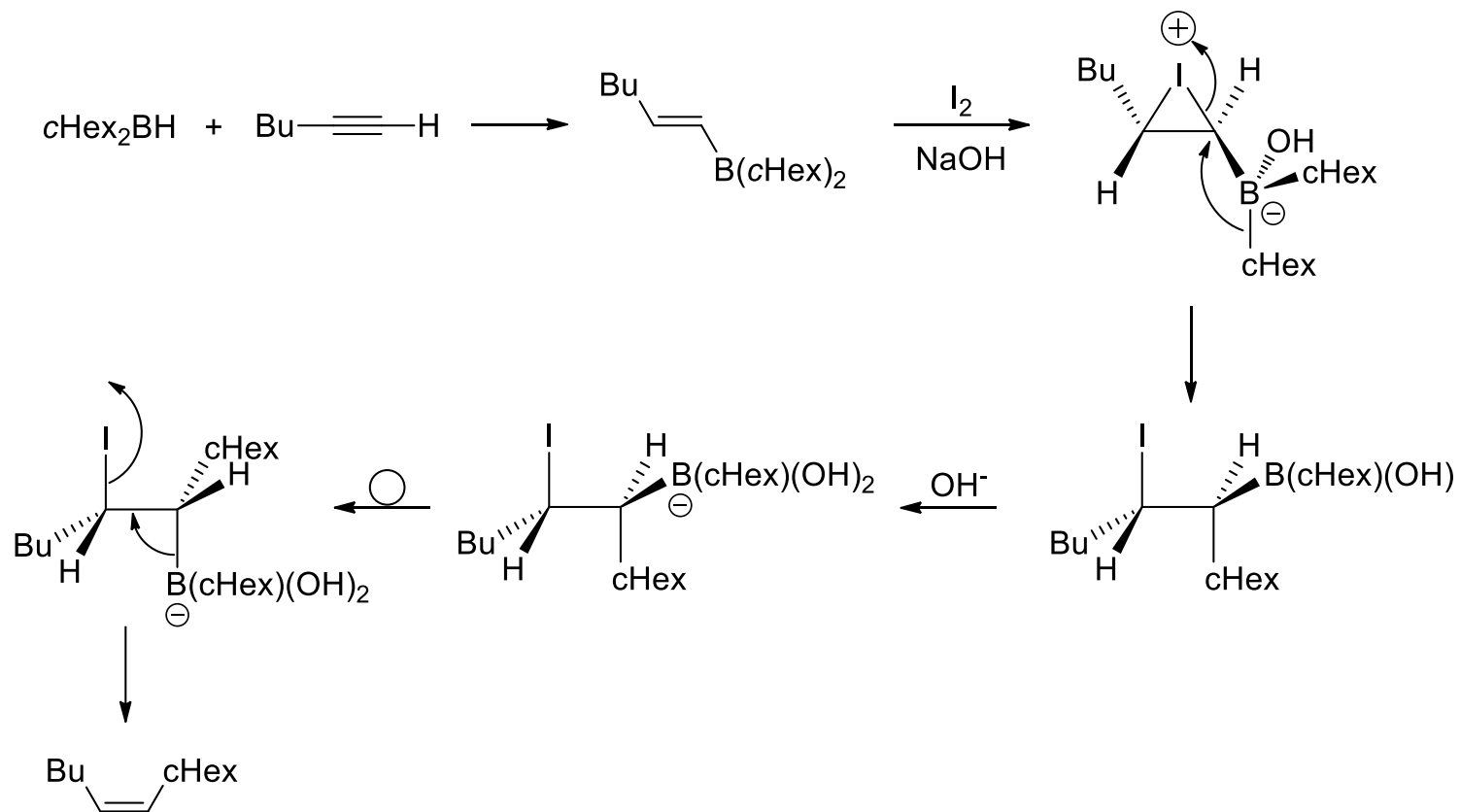


H. C. Brown, et al. *Tetrahedron* **1987**, 43, 4079

Hydroboration

stereoselective synthesis of olefins

Z-olefins

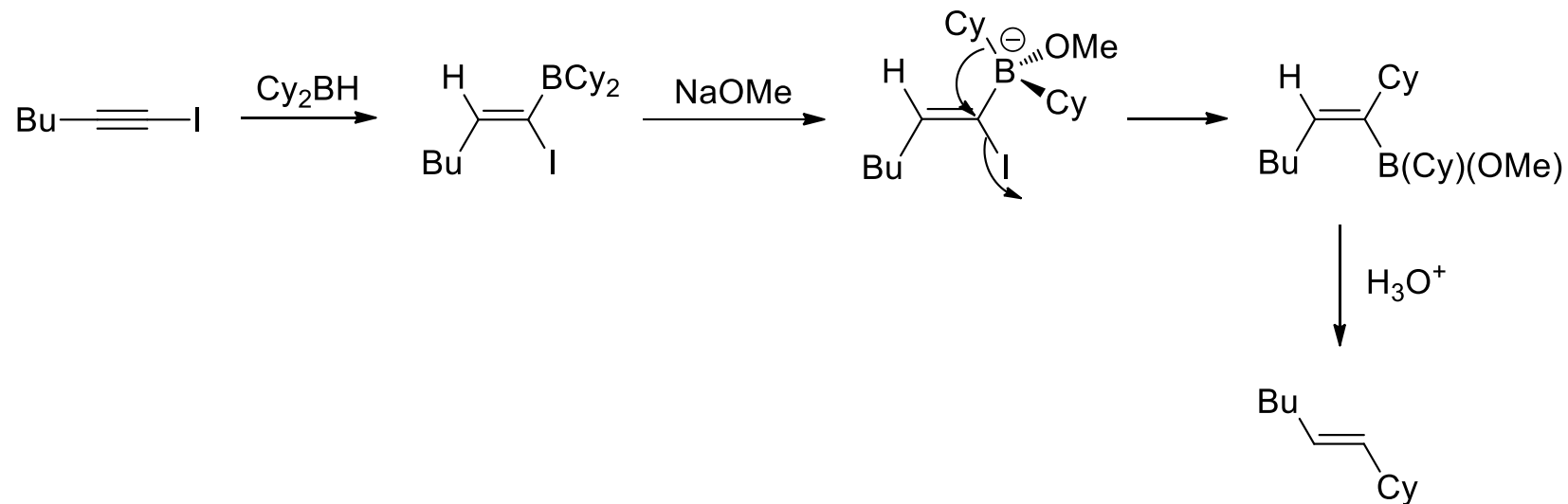


G. Zweifel, et al. *J. Am. Chem. Soc.* **1972**, *94*, 6560.

Hydroboration

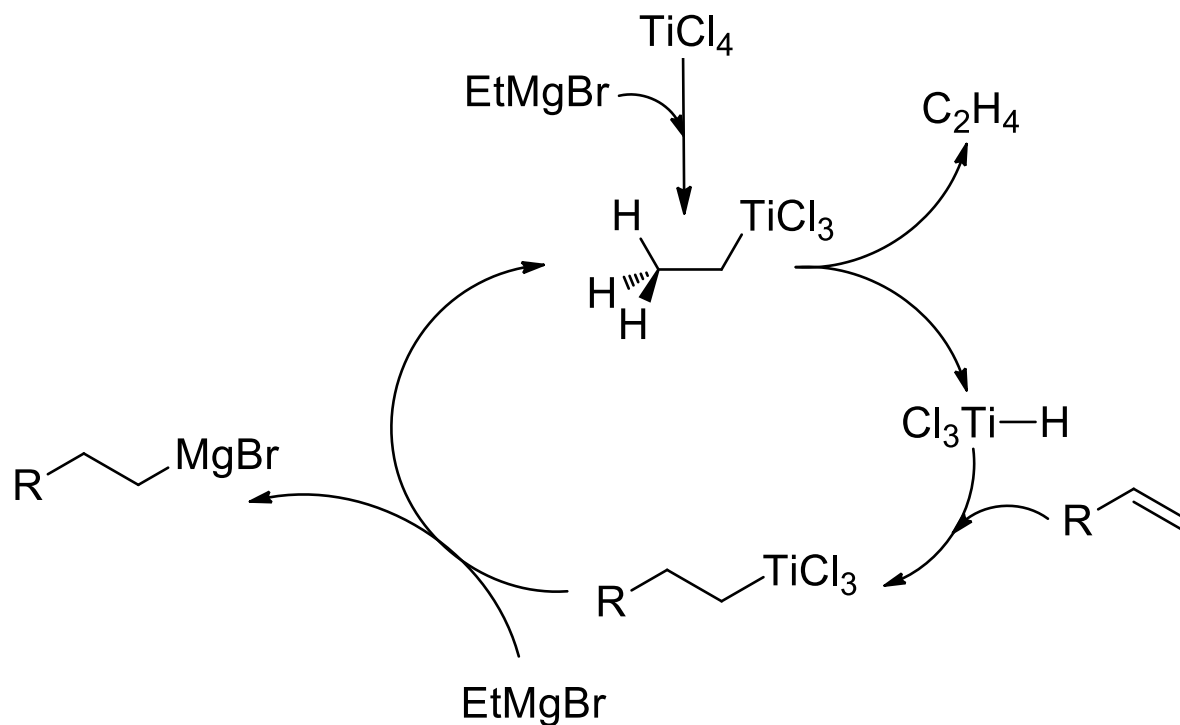
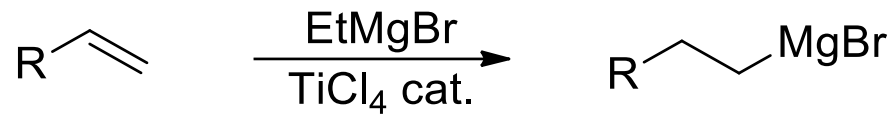
stereoselective synthesis of olefins

E-olefins

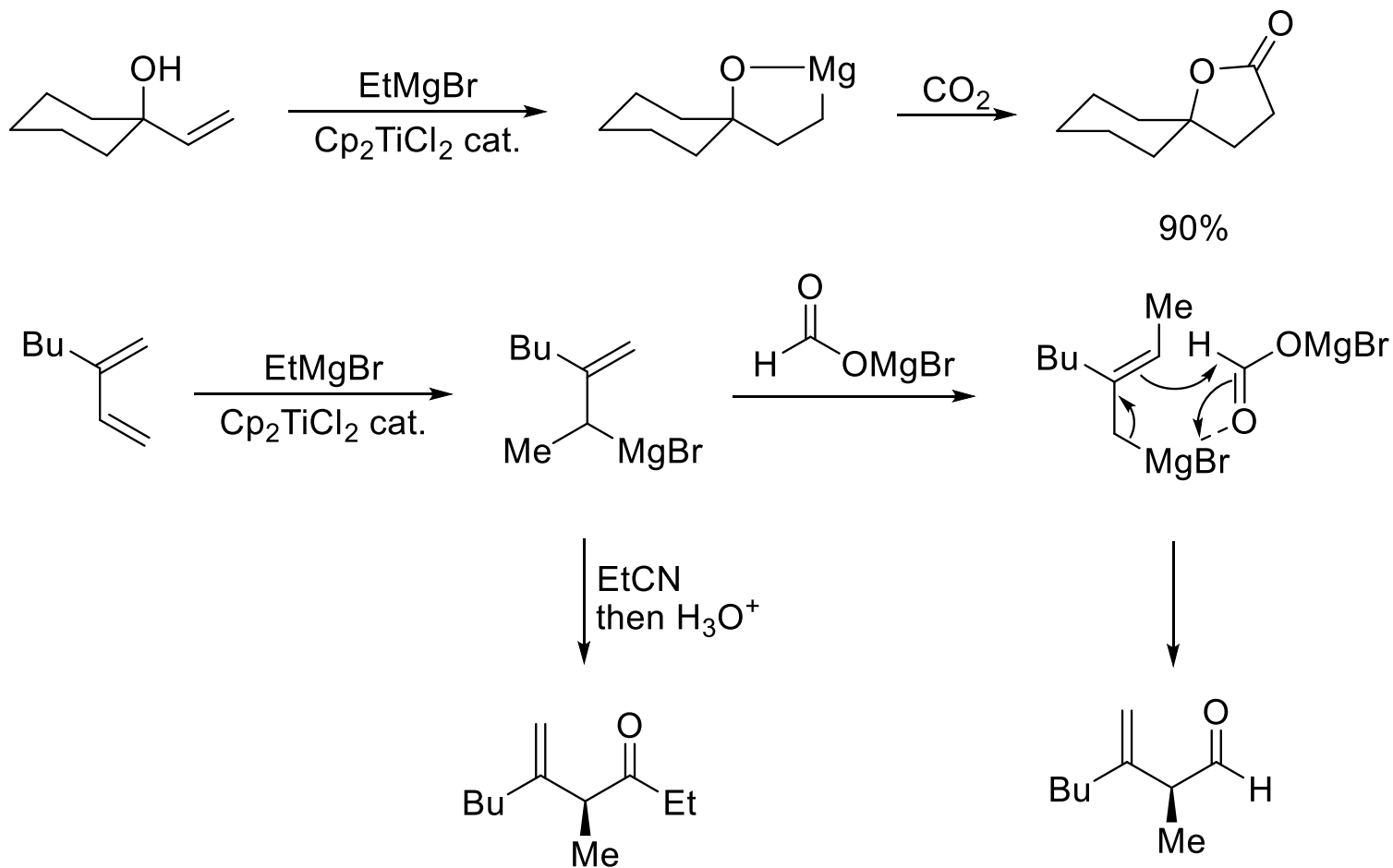


H. C. Brown, et al *J. Org. Chem.* **1989**, *54*, 6064.

Hydromagnesiation

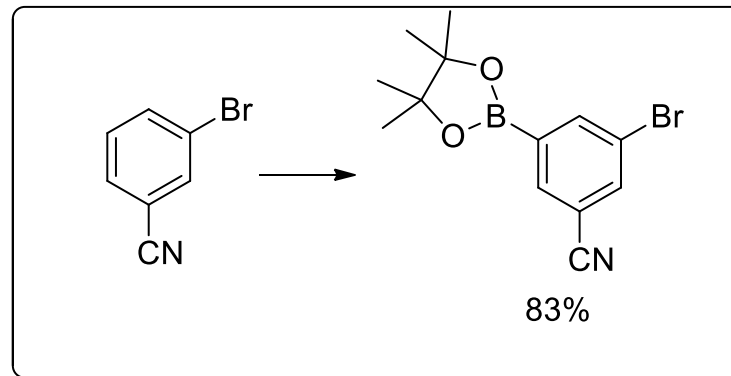
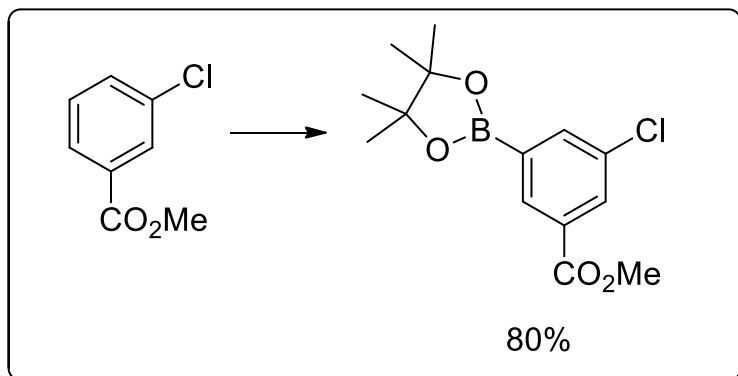
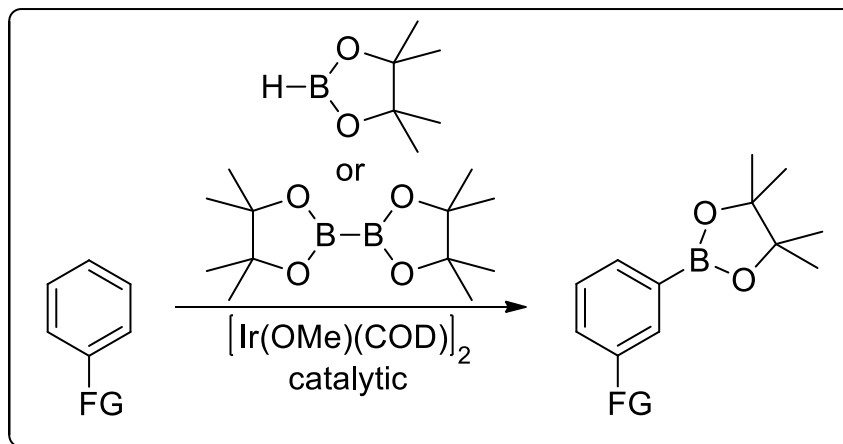


Hydromagnesiation



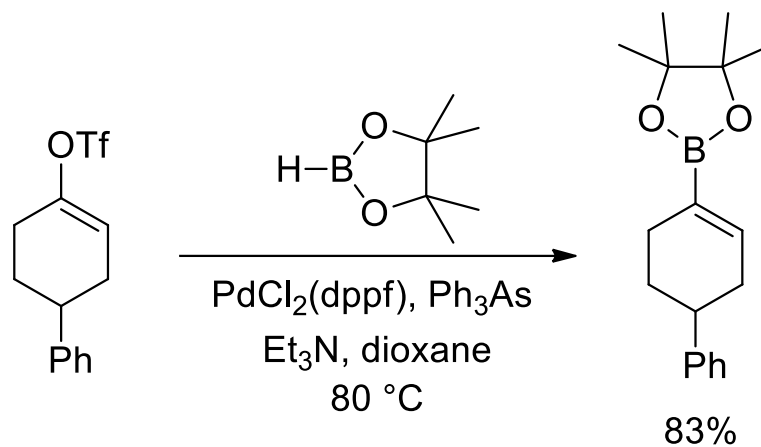
Synthesis of aryl boronic acids

transition-metal catalyzed synthesis of aryl boronic acids



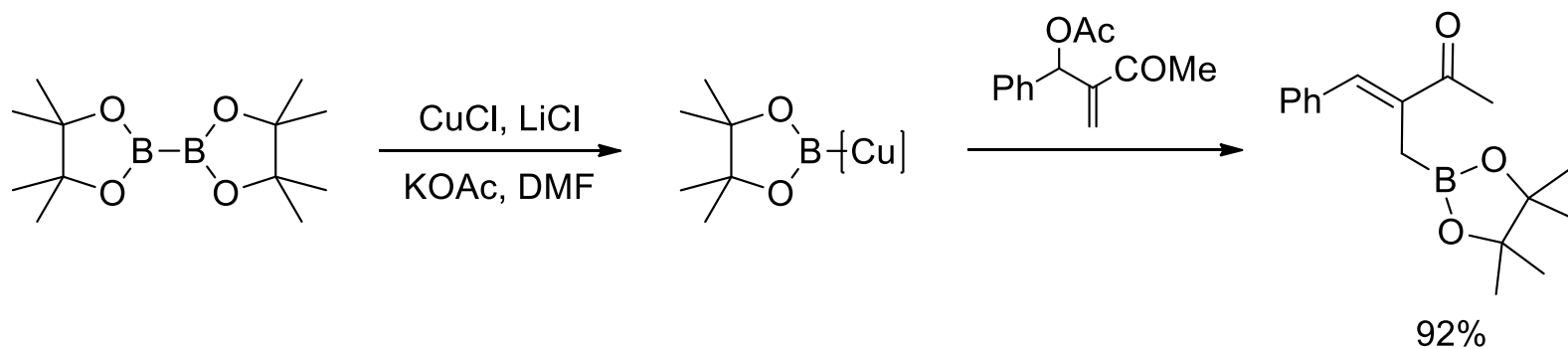
J. F. Hartwig, N. Miyaura, *Chem. Comm.* **2003**, 2924;
J. Am. Chem. Soc. **2002**, 124, 390; *Angew. Chem. Int. Ed.* **2002**, 45, 3056

Synthesis of aryl boronic acids



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

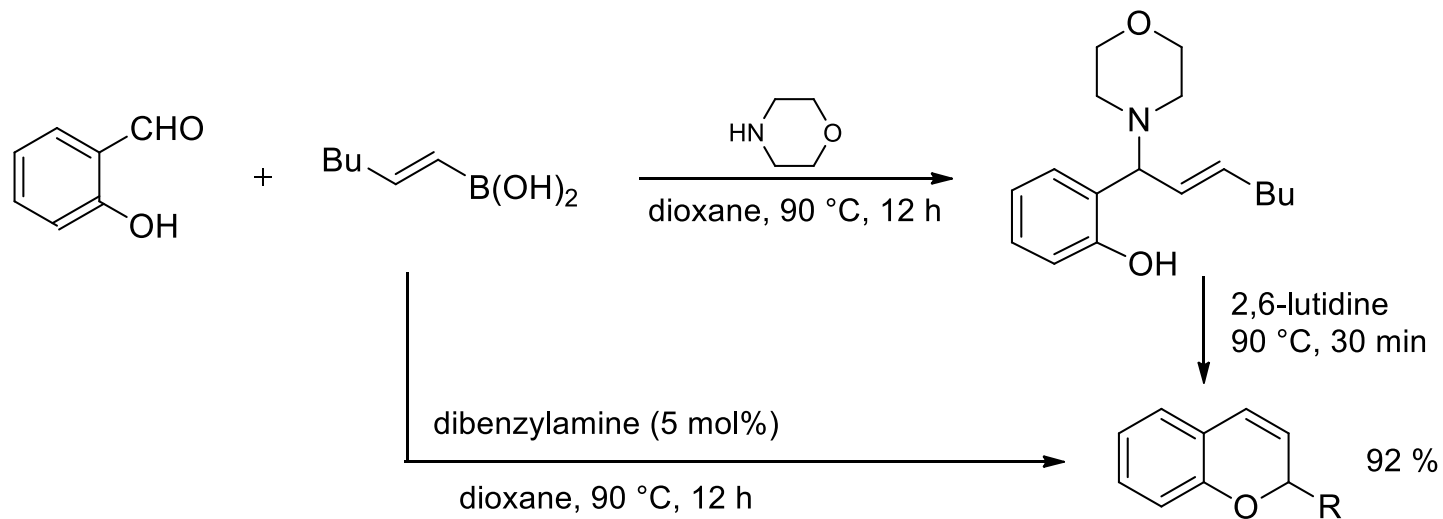
M. Murata *Synth. Comm.* **2002**, 32, 2513



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

Reactivity of unsaturated boronic derivatives

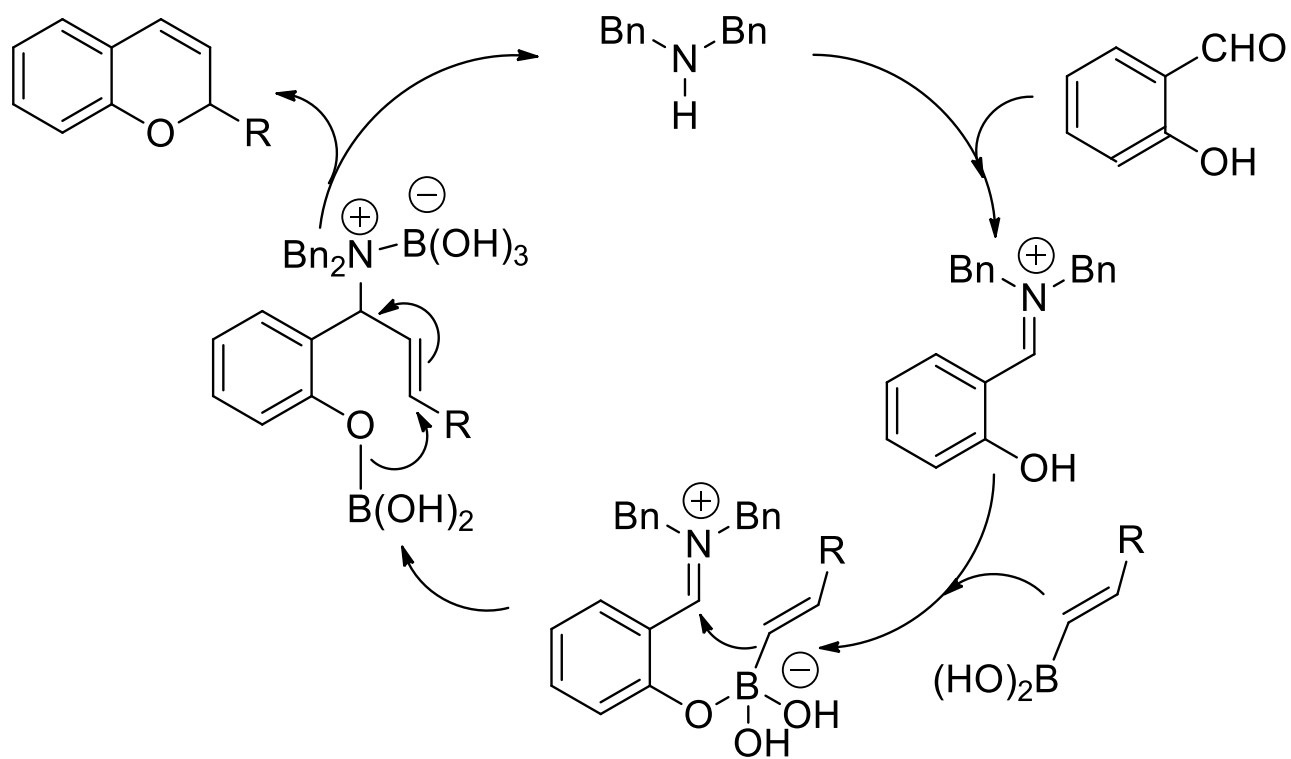
the Petasis-reaction - a short synthesis to 2H-chromenes



Reactivity of unsaturated boronic derivatives

The Petasis-reaction

mechanism

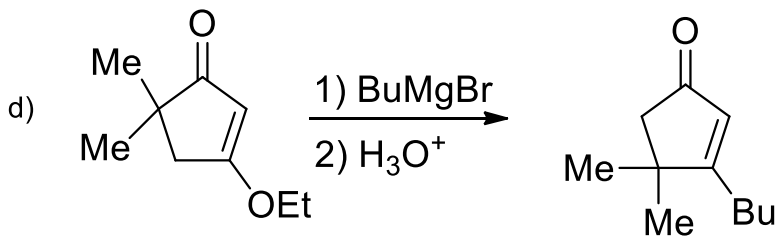
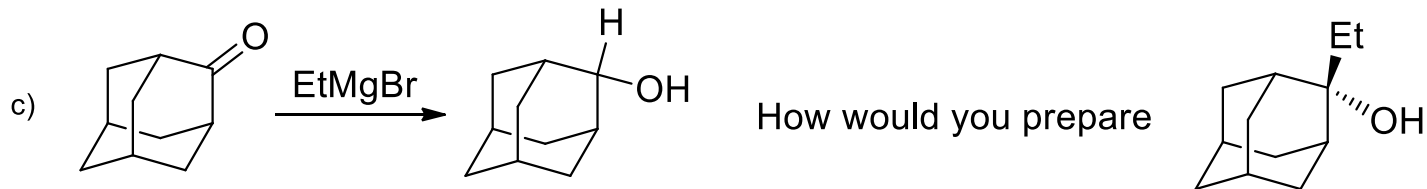
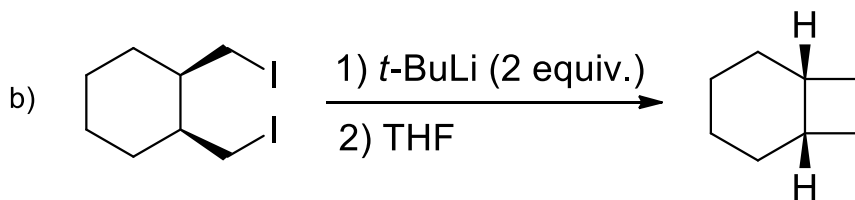
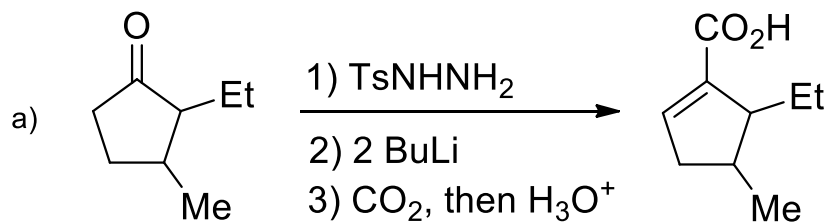


ÜBUNG

1. Problem set

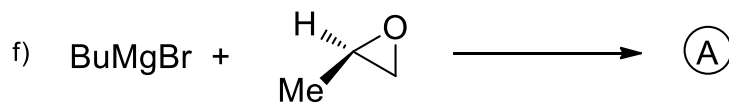
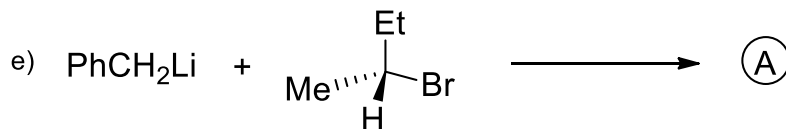
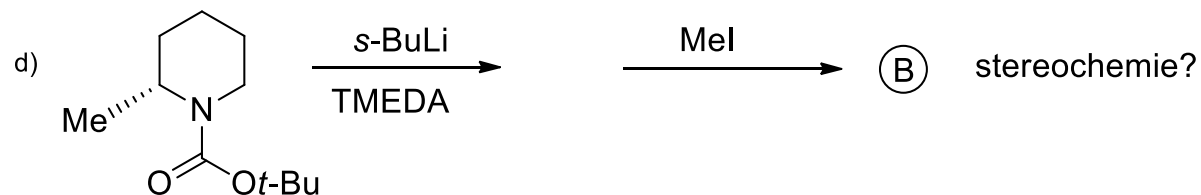
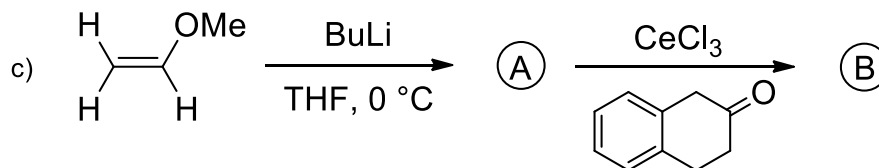
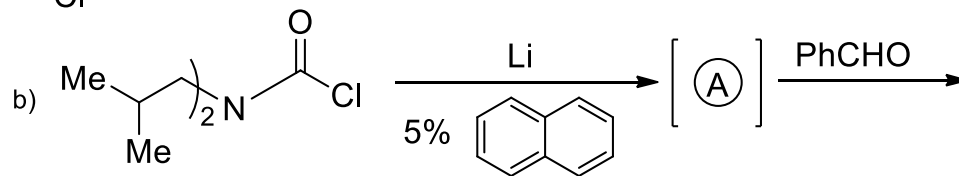
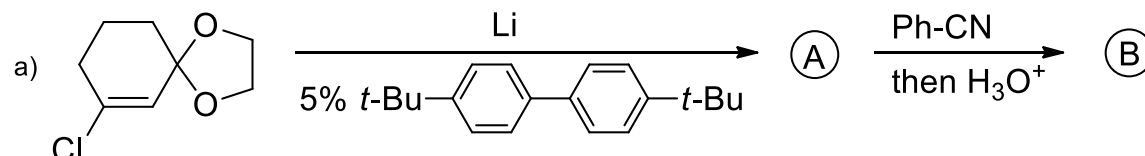
First Problem Set for OC IV

1) Give a mechanism for the following reactions:

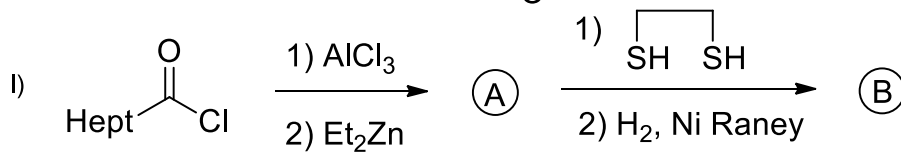
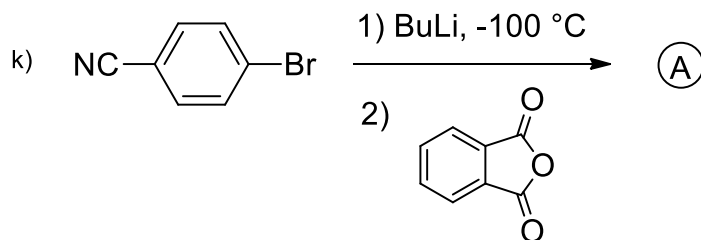
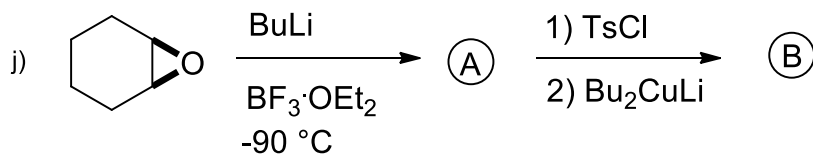
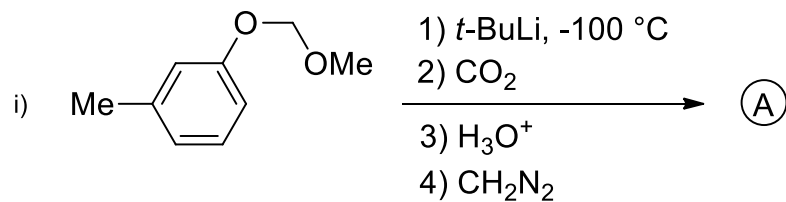
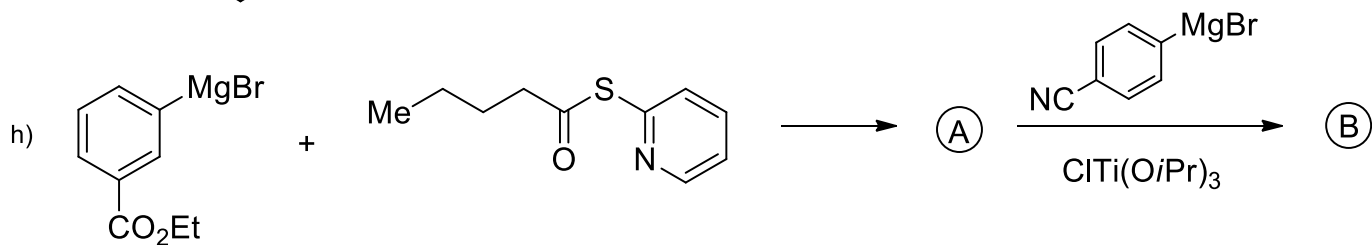
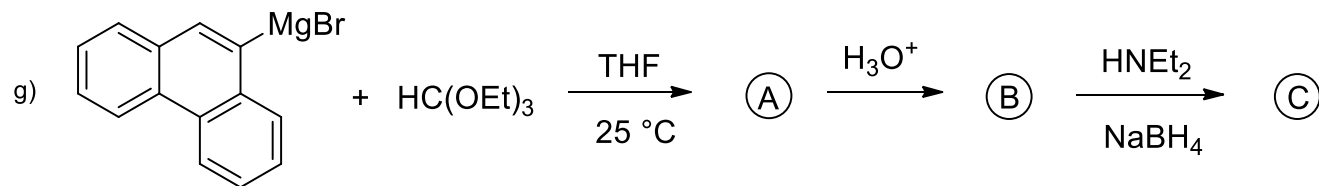


First Problem Set for OC IV

2) Give the following reaction products:

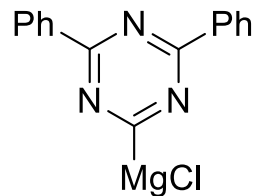
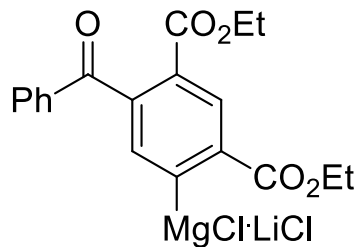
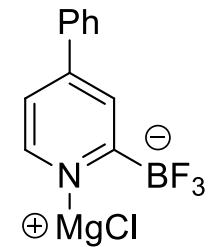
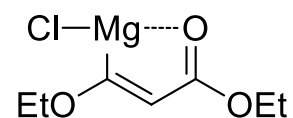
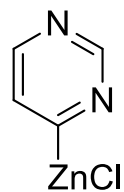
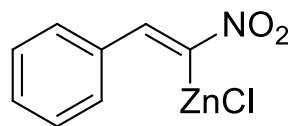
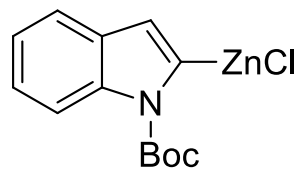
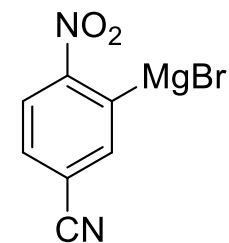
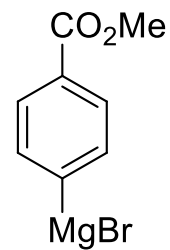
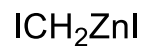
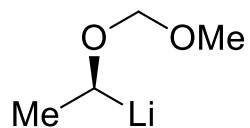
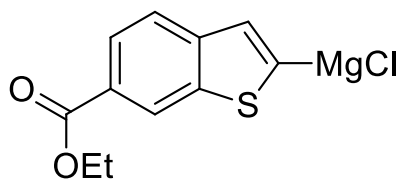


First Problem Set for OC IV

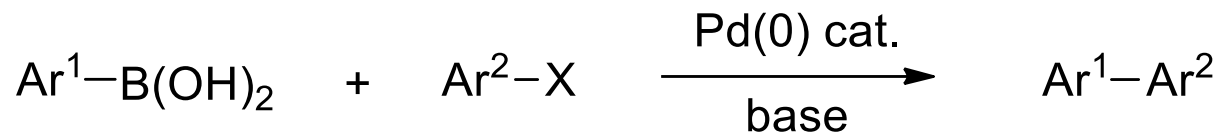


First Problem Set for OC IV

3. How you would prepare following organometallics:



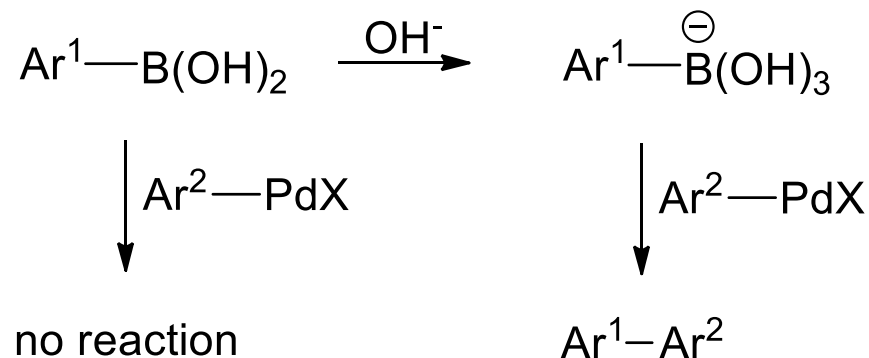
The Suzuki cross-coupling reaction



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

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

Key step

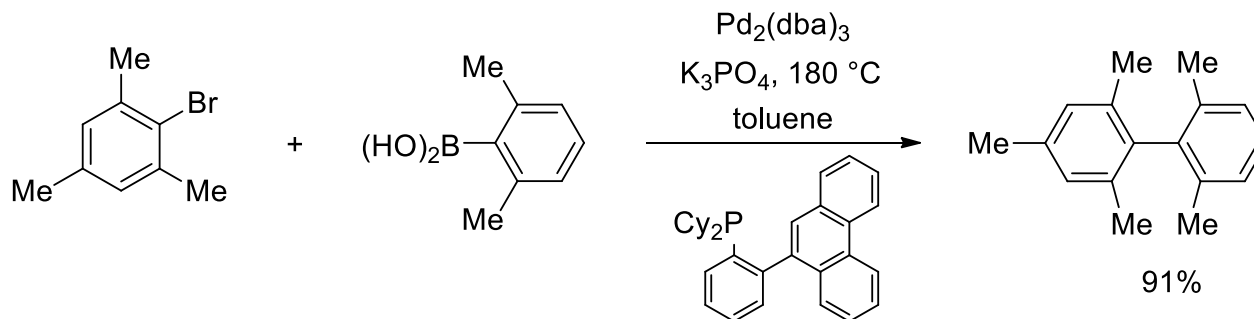


S. Buchwald, *J. Am. Chem. Soc.* **2002**, 124, 1162

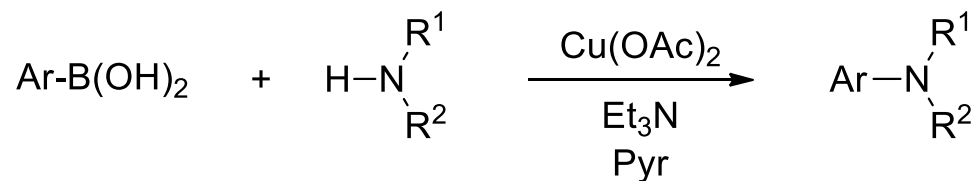
C. Amatore, A. Jutand, G. Le Duc *Chem. Eur. J.* **2011**, 17, 2492

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

The Suzuki cross-coupling reaction



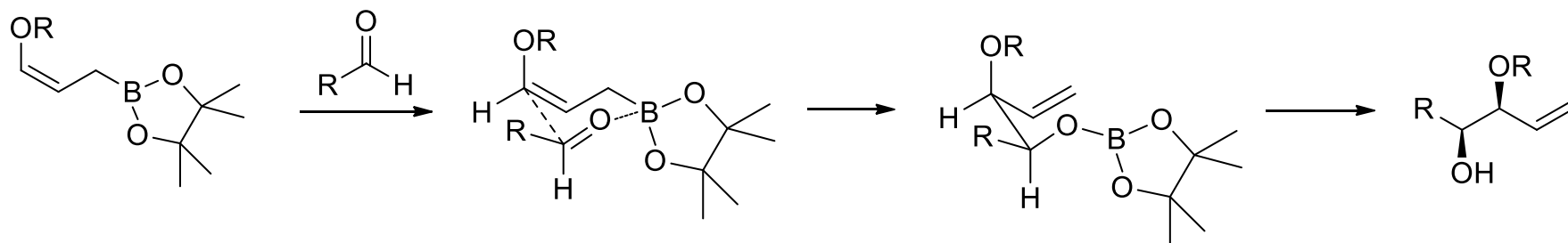
R. E. Sammelson, M. J. Kurth, *Chem. Rev.* **2001**, 101, 137



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

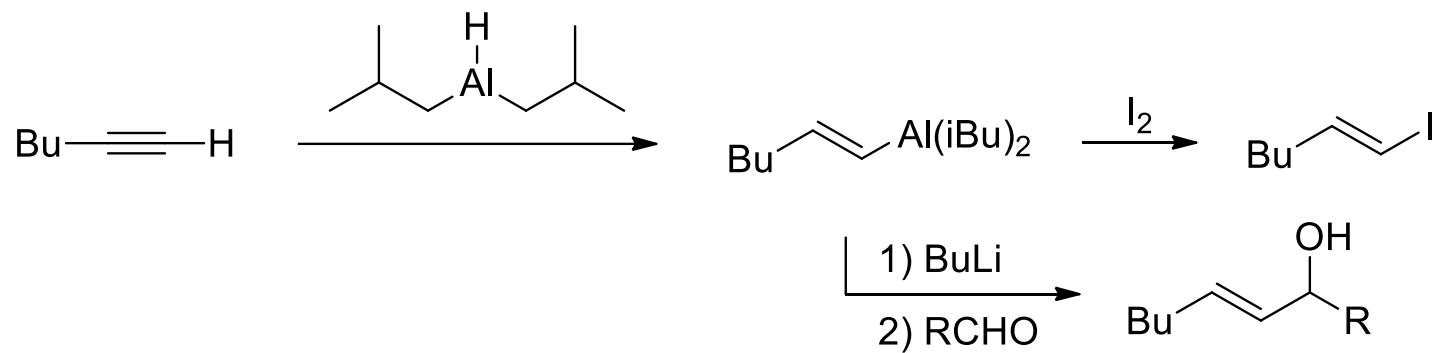
S. Ley, *Angew. Chem. Int. Ed.* **2003**, 42, 5400

Chemistry of allyl boranes



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

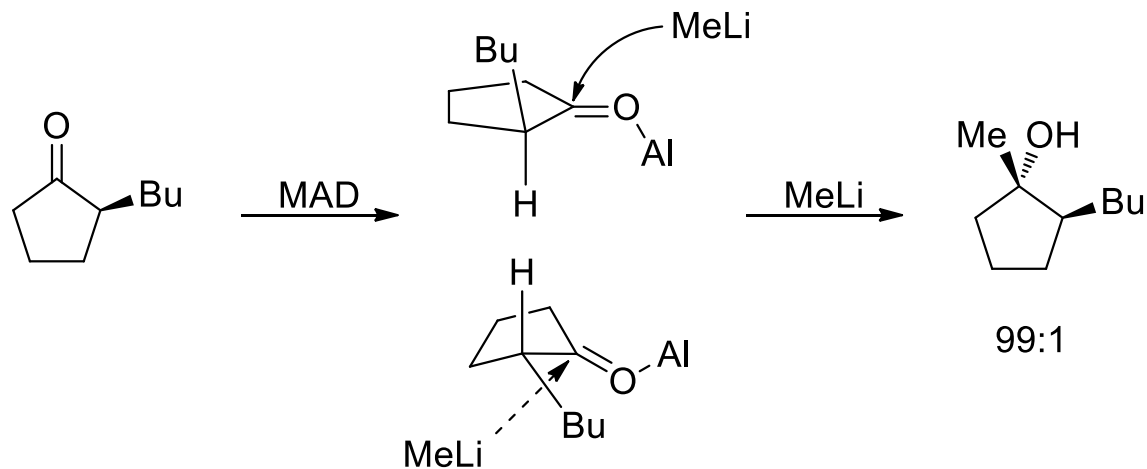
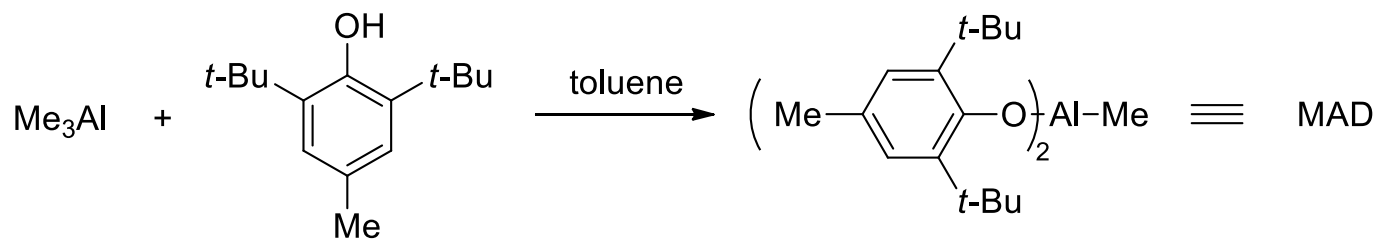
Hydroalumination



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

Hydroalumination

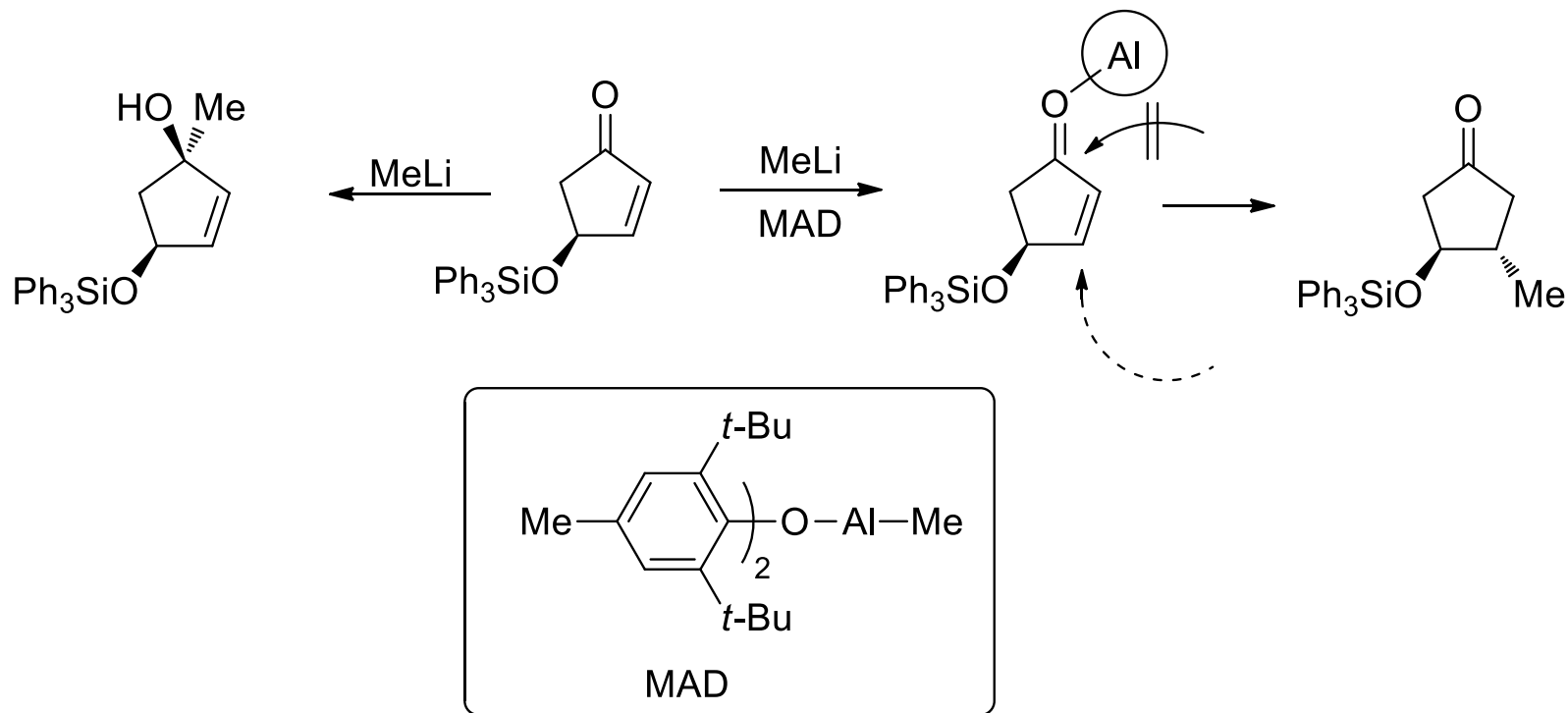
Special Al-reagents



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

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

Hydroalumination



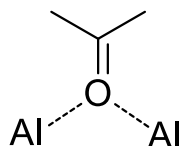
K. Maruoka, H. Yamamoto, *Kagaku, Zokan* (Kyoto, Japan) **1988**, 115, 127

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

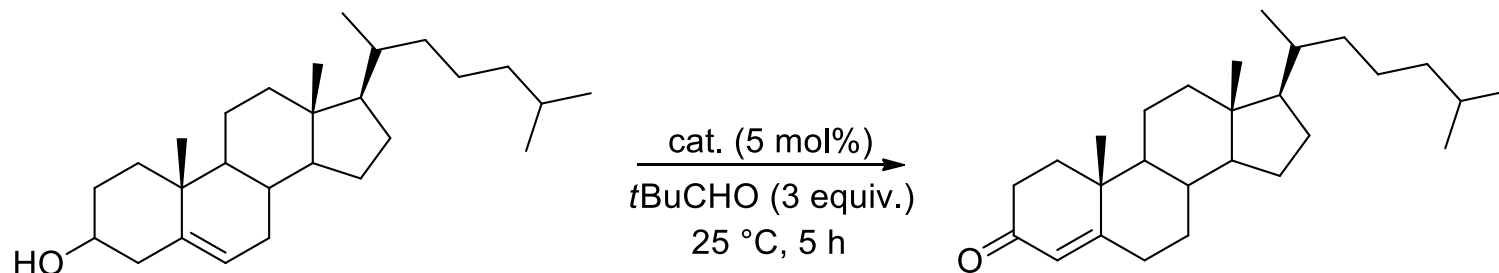
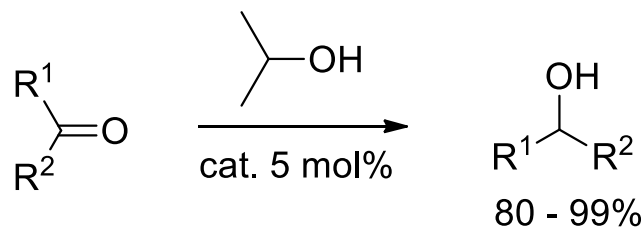
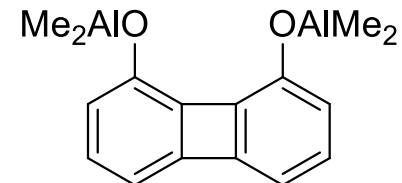
Hydroalumination

Verley-Meerwein-Ponndorf reduction

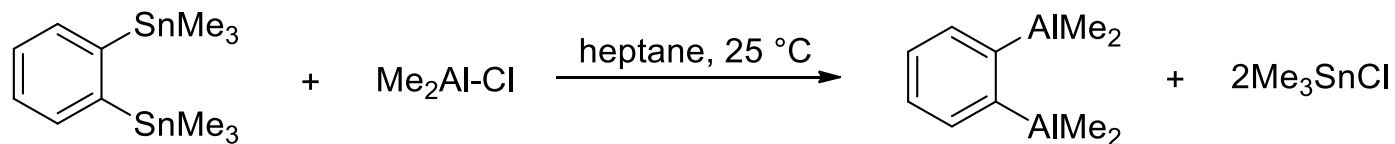
activating a carbonyl group twice



is possible using

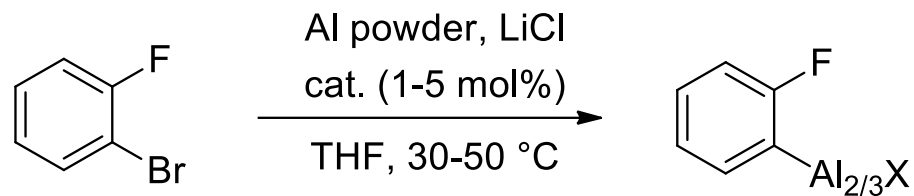


Other preparation of aluminium compounds



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

Direct synthesis of organoaluminium reagents



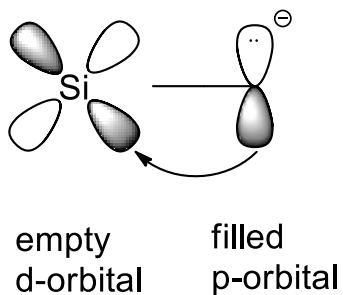
cat. = InCl₃, BiCl₃, PbCl₂, TiCl₄

The organic chemistry of main-group organometallics

Silicium

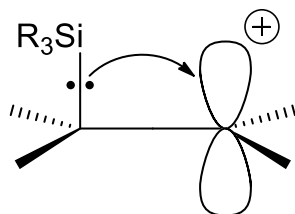
The effect of a Me_3Si -substituent:

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



stabilization of carbanions in α -position

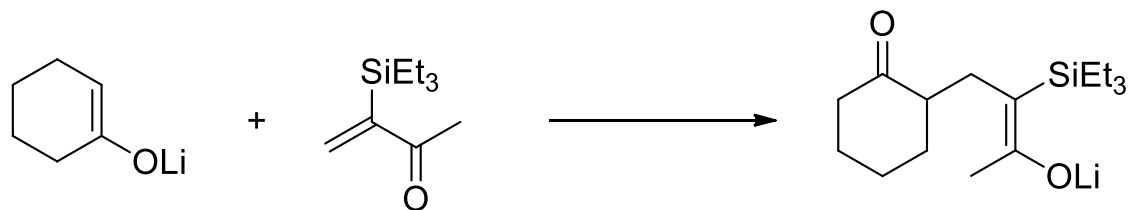
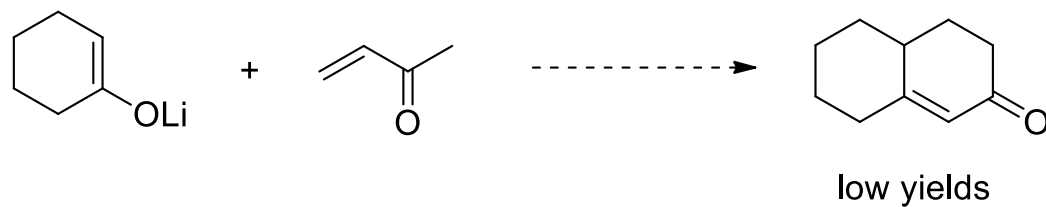
- 3) hyperconjugation: interaction of σ -framework with the π -system



stabilization of a cation in β -position

Silicium

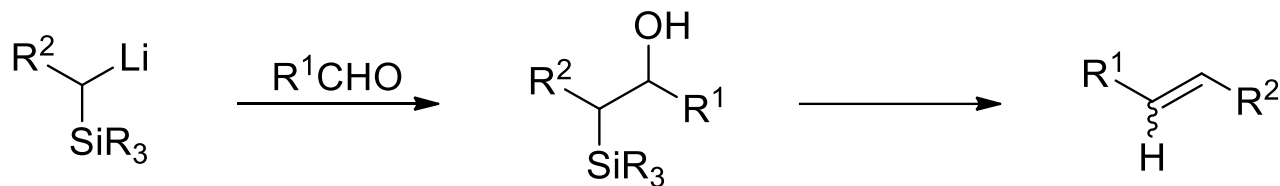
Applications:



high yield: stabilized lithium enolate
(no polymerization)

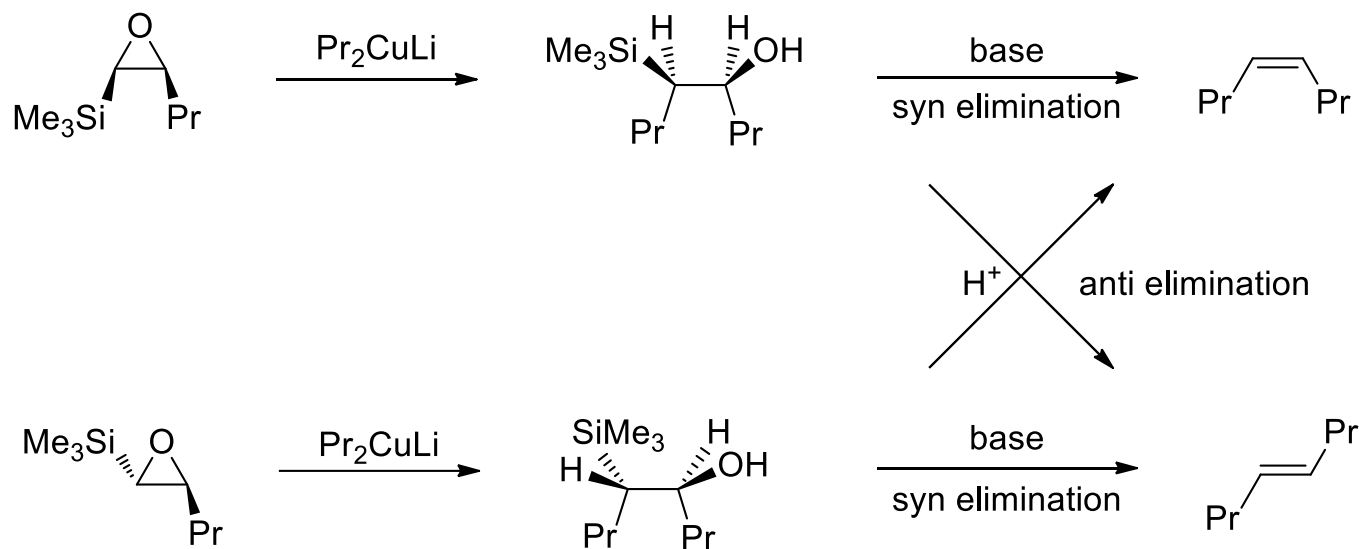
Silicium

Peterson olefination



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

Stereochemistry of the *Peterson*-elimination

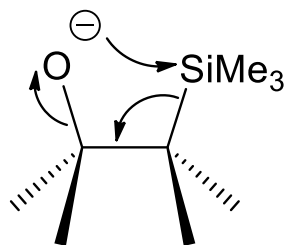


P. F. Hudrlik, D. Peterson, R. J. Rona *J. Org. Chem.* **1975**, 40, 2263

Silicium

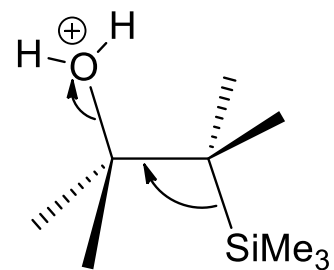
key steps:

basic
media



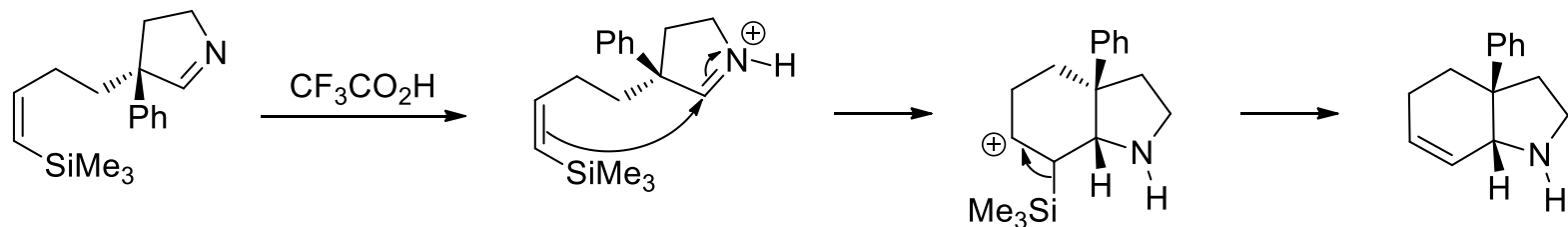
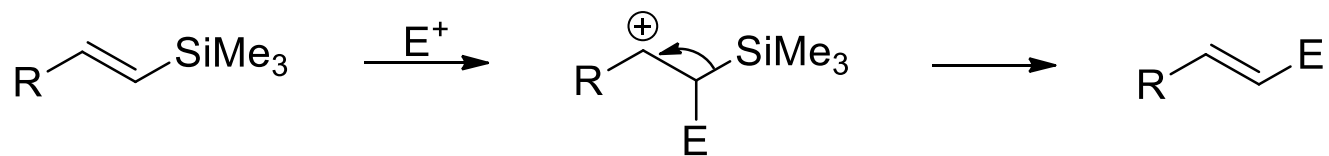
syn elimination

acidic
media



anti elimination

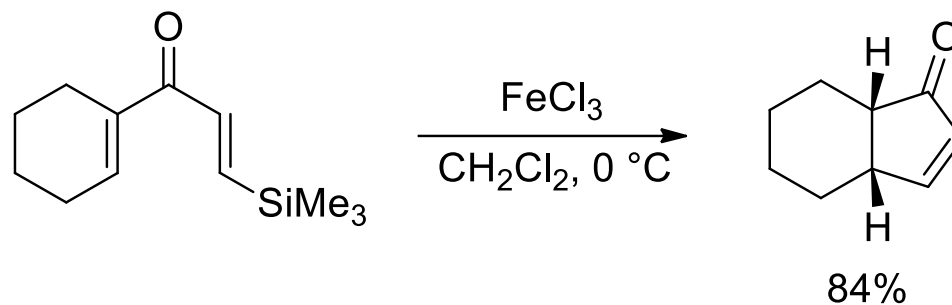
Reactivity of alkenylsilanes



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

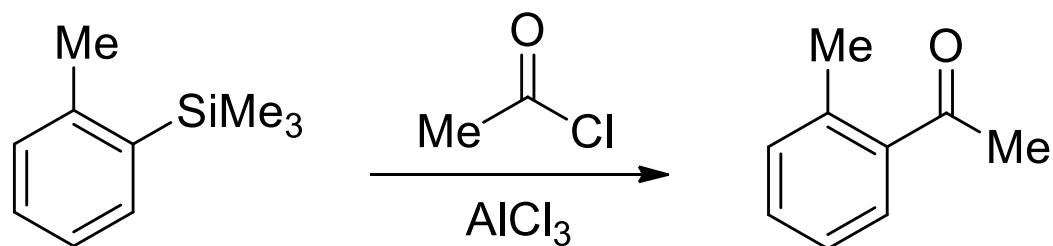
Reactivity of alkenylsilanes

Sila-Nazarov-reaction



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

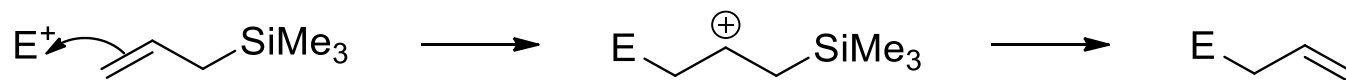
Aromatic ipso-substitution



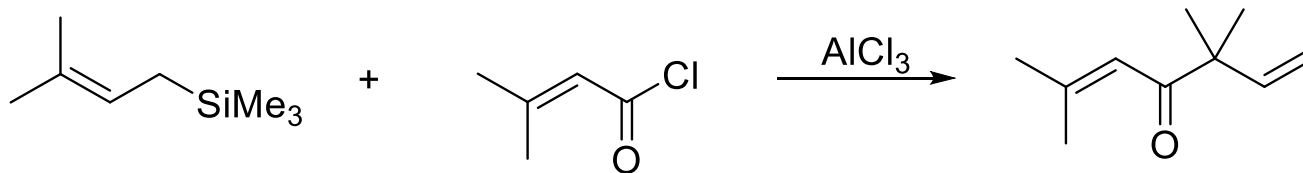
The reaction with ArSnMe_3 is 10^4 time faster

Allylic silanes in organic synthesis

General reactivity

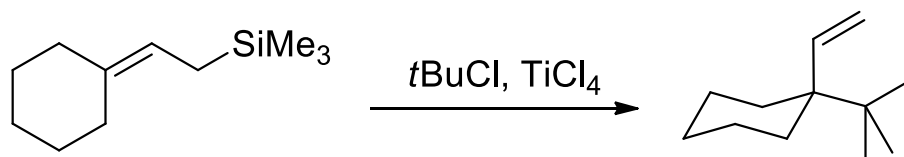


Acylation

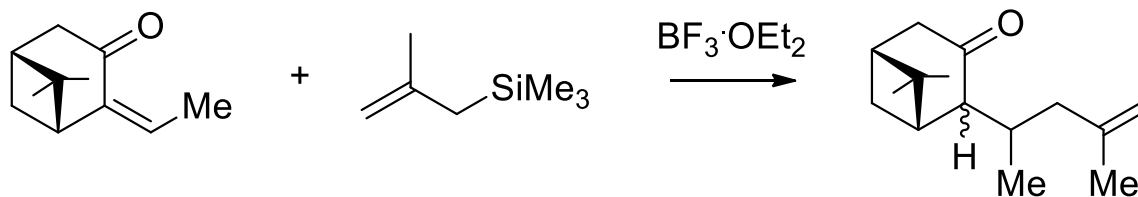


Allylic silanes in organic synthesis

Allylation



1,4-addition

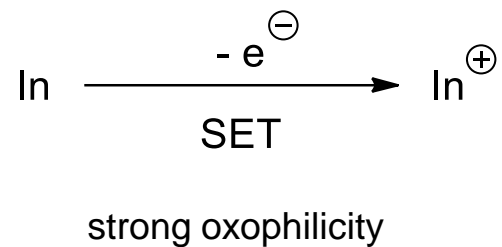


T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Chem. Soc. Chem. Commun.* **1979**, 525.

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

Indium

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



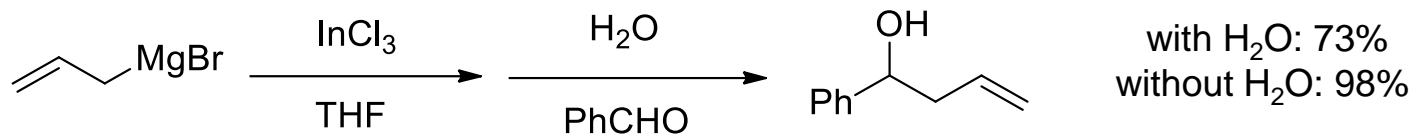
The first ionization potential of indium (5,8 eV)
is close to lithium and sodium

Key contributions:

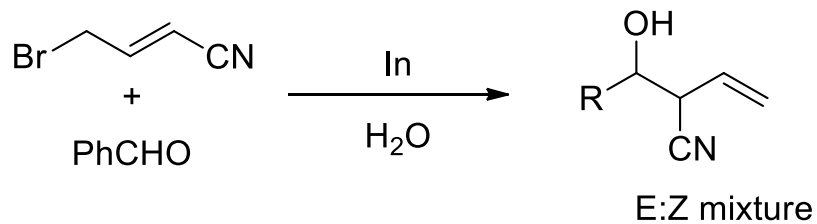
S. Araki *Main Group Metals in Organic Synthesis* **2004**, 1, 323

T.-P. Loh *Acid Catalysis in Modern Organic Synthesis* **2008**, 1, 377

Indium. Allylation reactions

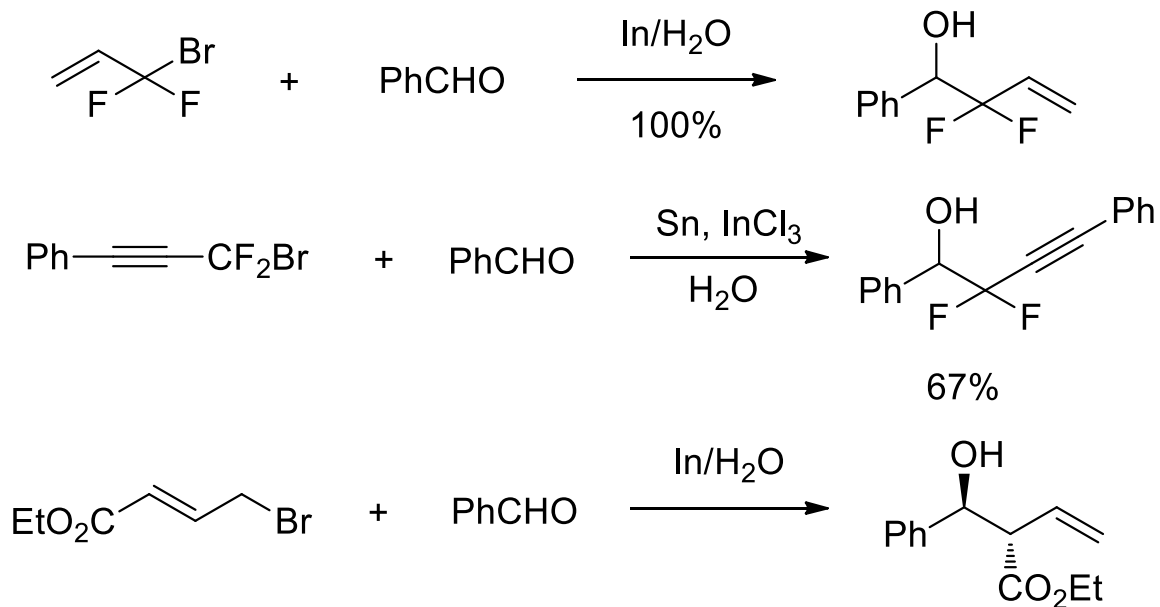


S. Akira, *J. Chem. Soc. Perkin Trans. I*, **1991**, 2395



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

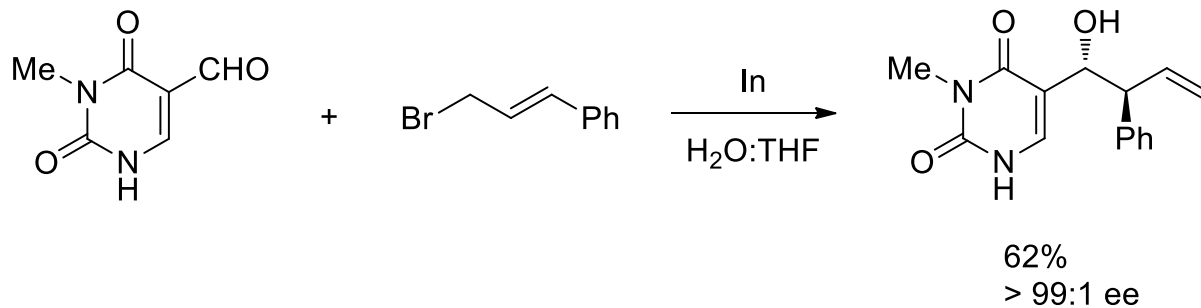
Indium



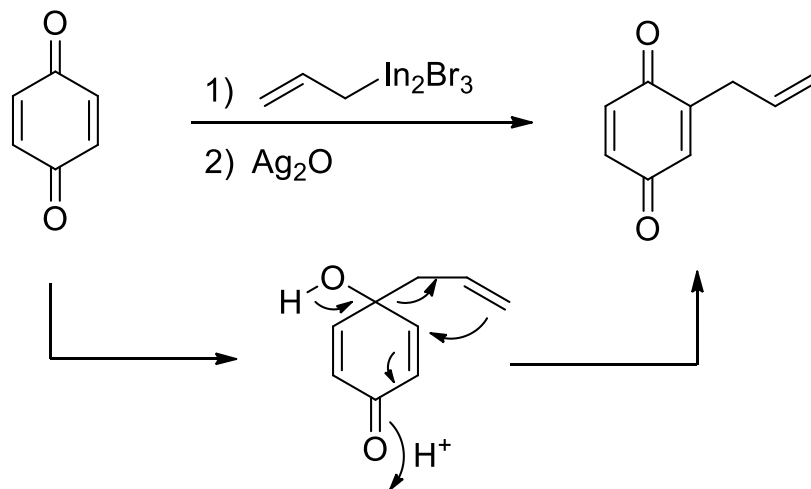
without $\text{La}(\text{OTf})_3$: 59% anti:syn = 86 : 14
with $\text{La}(\text{OTf})_3$: 99% anti:syn = 90 : 10

Indium

Applications in nucleoside chemistry:

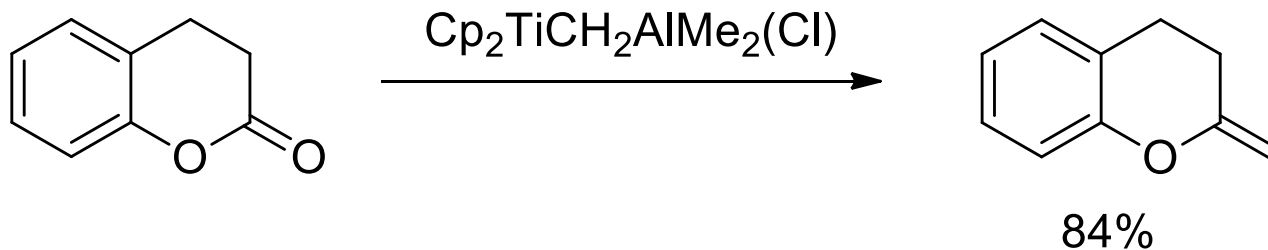
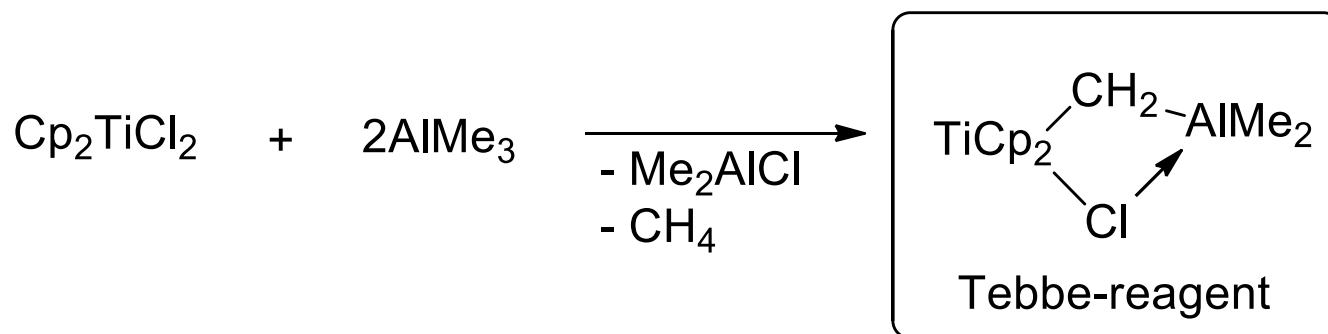
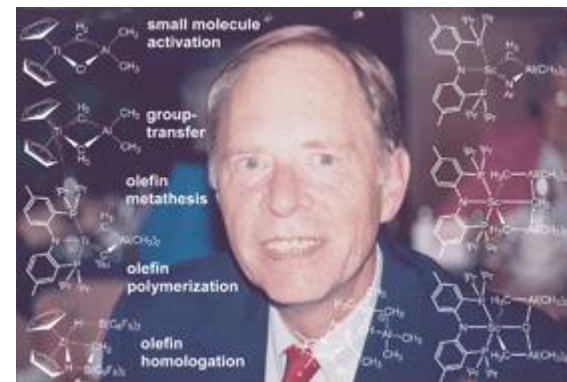


S. Kumar, *Tetrahedron Lett.* **2001**, 42, 7039



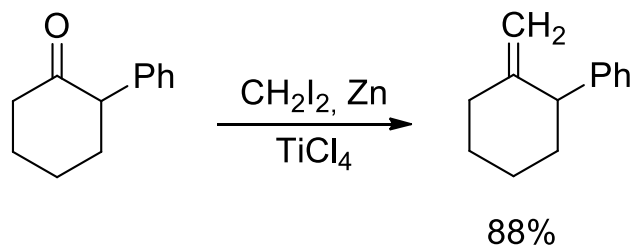
S. Akiva, *J. Organomet. Chem.* **1991**, 415, 7

Early transition metal organometallics: Titanium

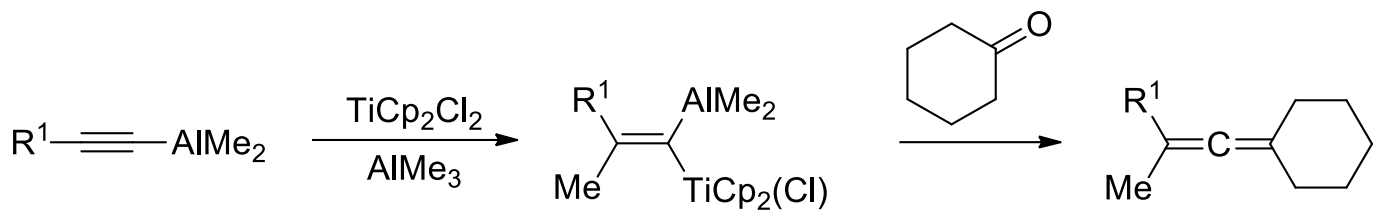
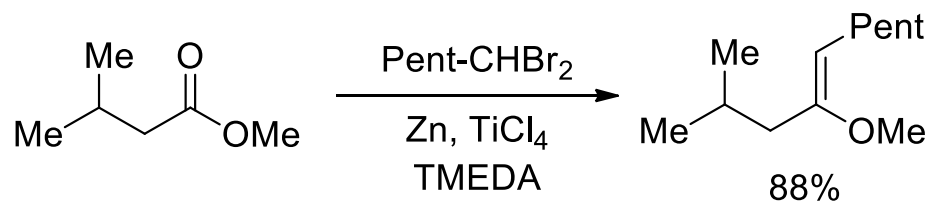


Titanium

Lombardo-reagent

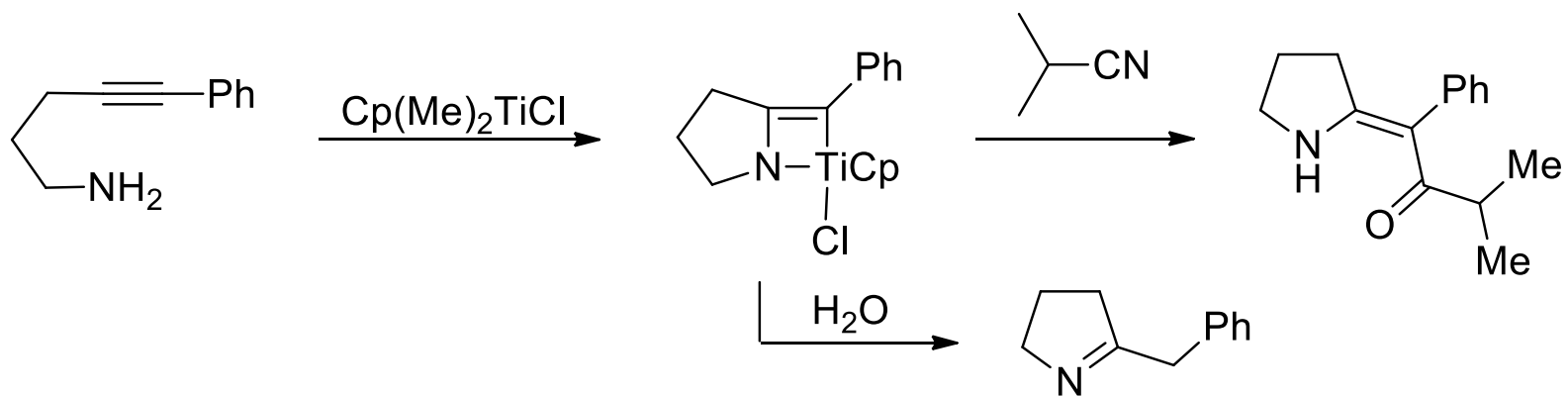


K. Takai, *J. Org. Chem.* **1994**, 59, 2668



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

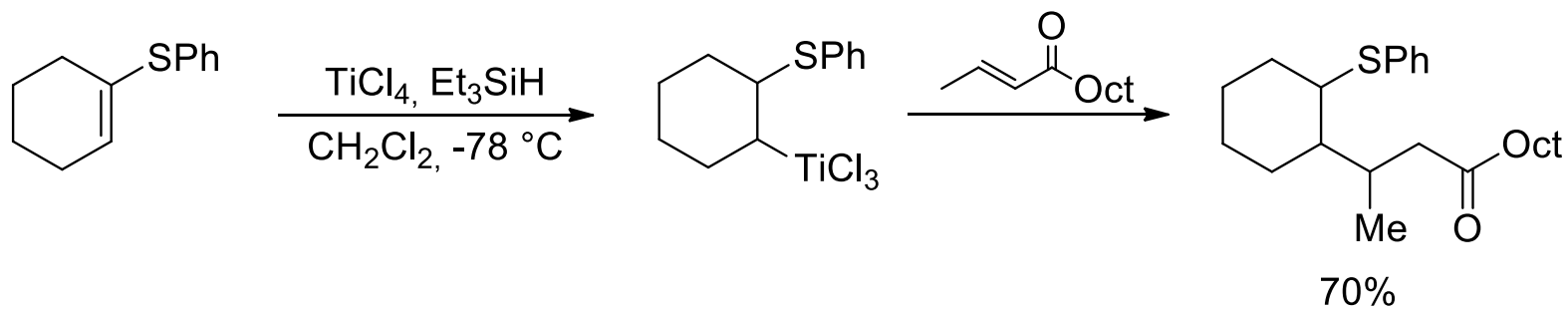
Titanium



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

Titanium

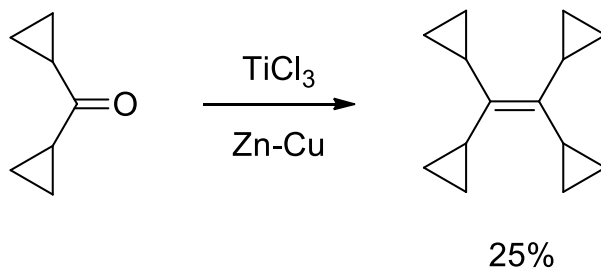
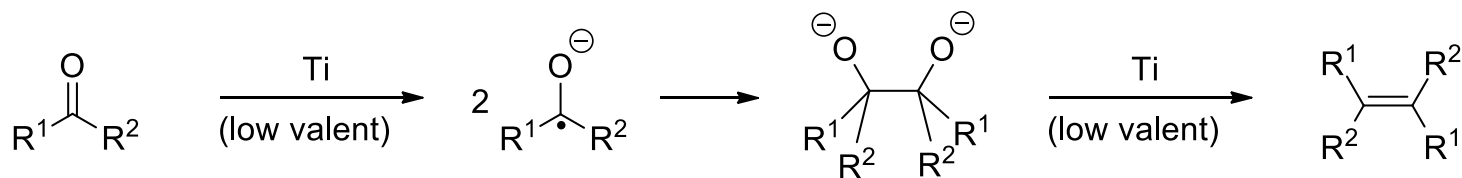
Hydrotitanation



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

Titanium

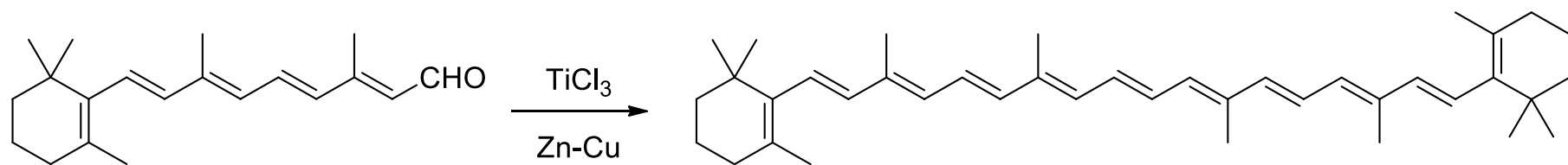
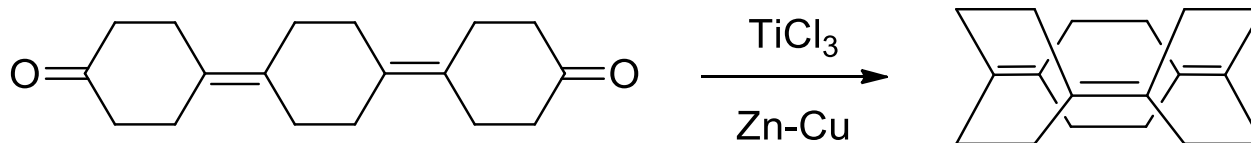
Reductive coupling: The McMurry Reaction



Review:

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

Titanium

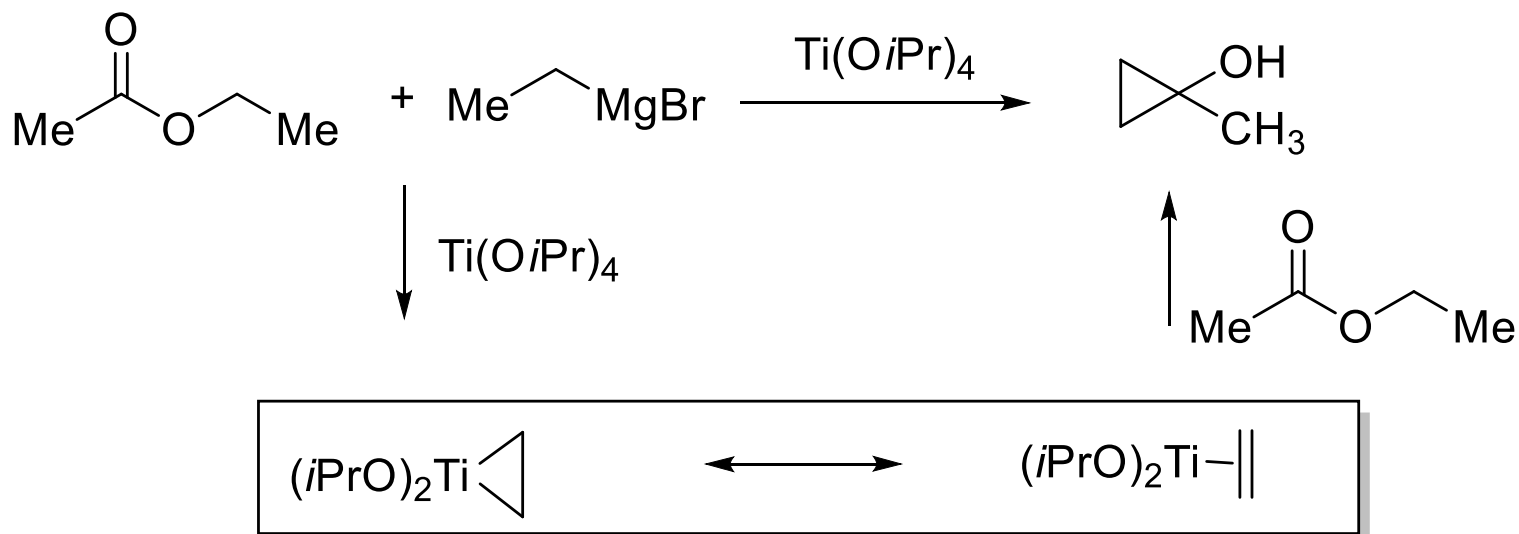


β -Caroten: 94%

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

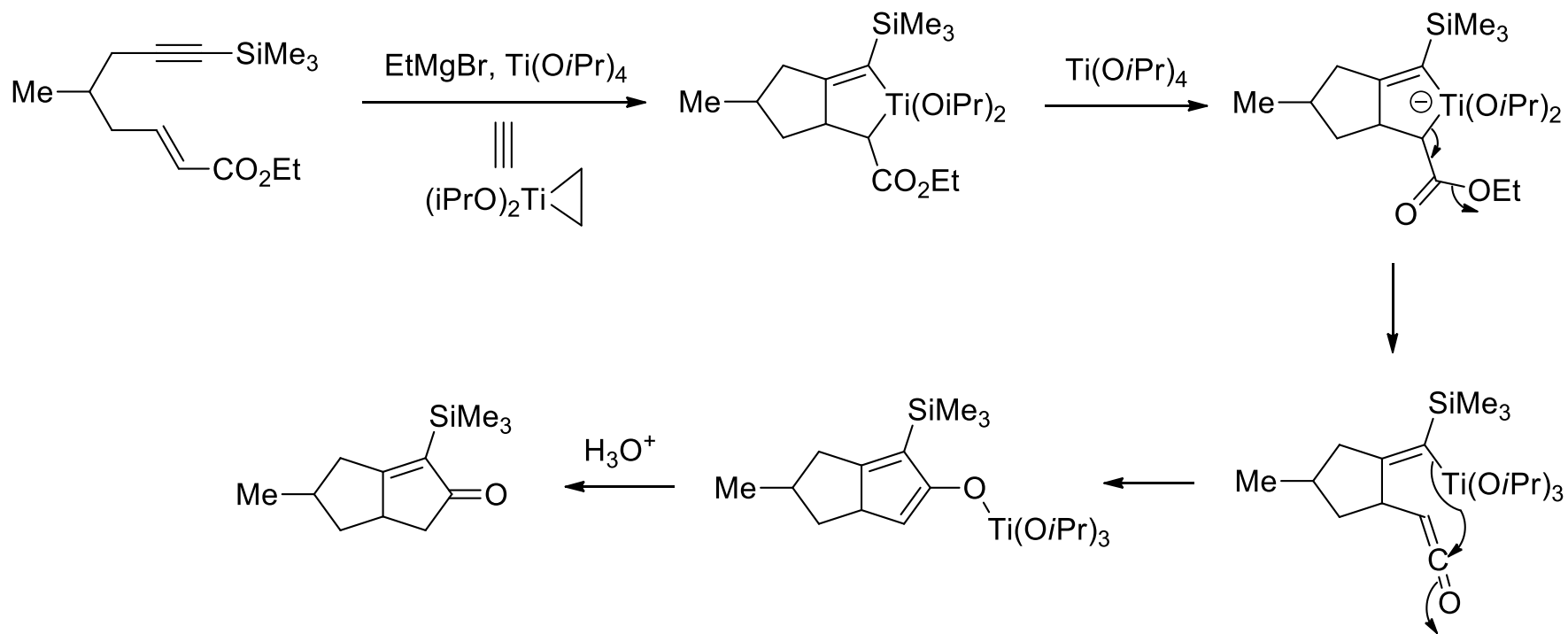
Titanium

Kulinkovich-reaction



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

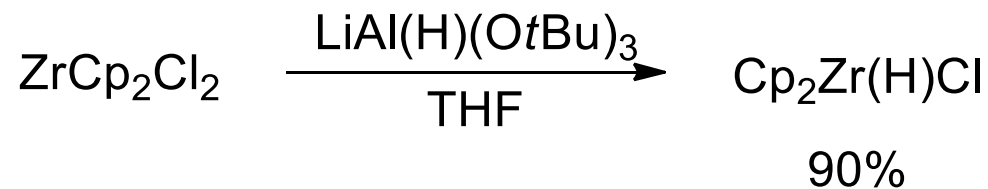
Titanium



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

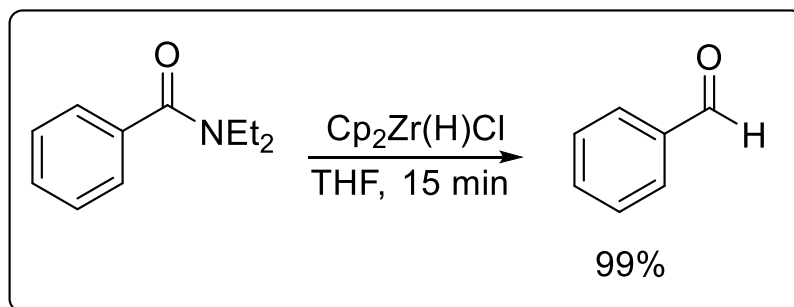
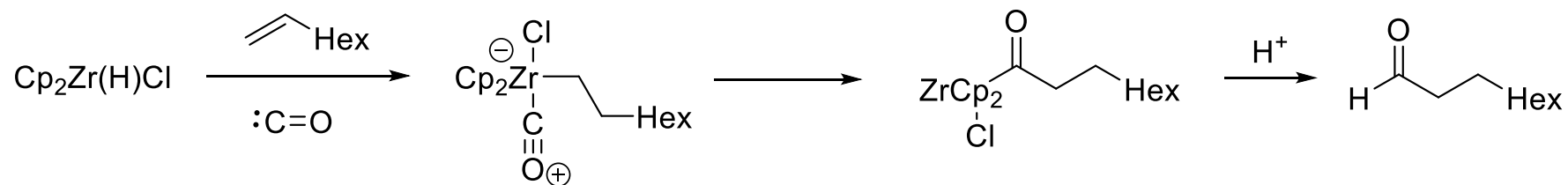
Early transition metal organometallics: Zirconium

Schwartz's reagent:



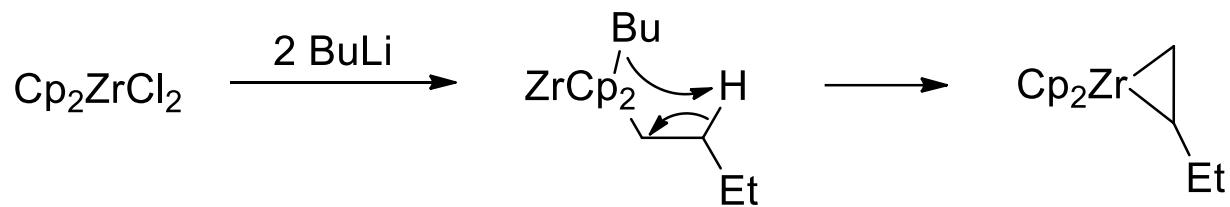
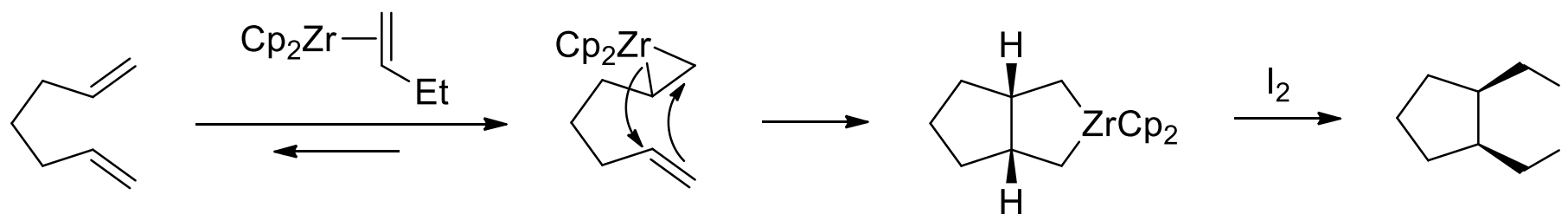
Inorg. Synth. **1979**, 19, 223

Zirconium

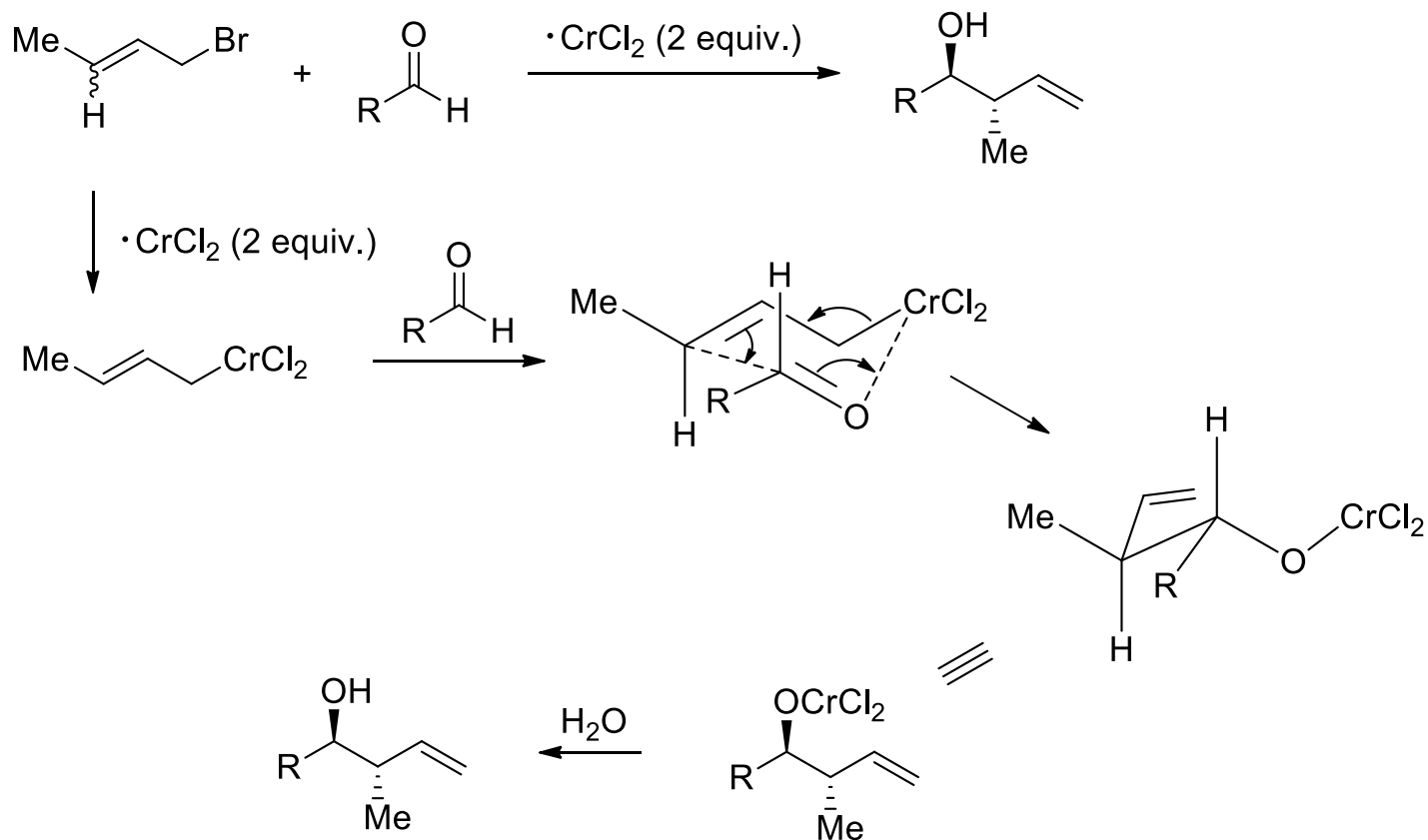


G. I. Georg *J. Am. Chem. Soc.* **2007**, 129, 3408

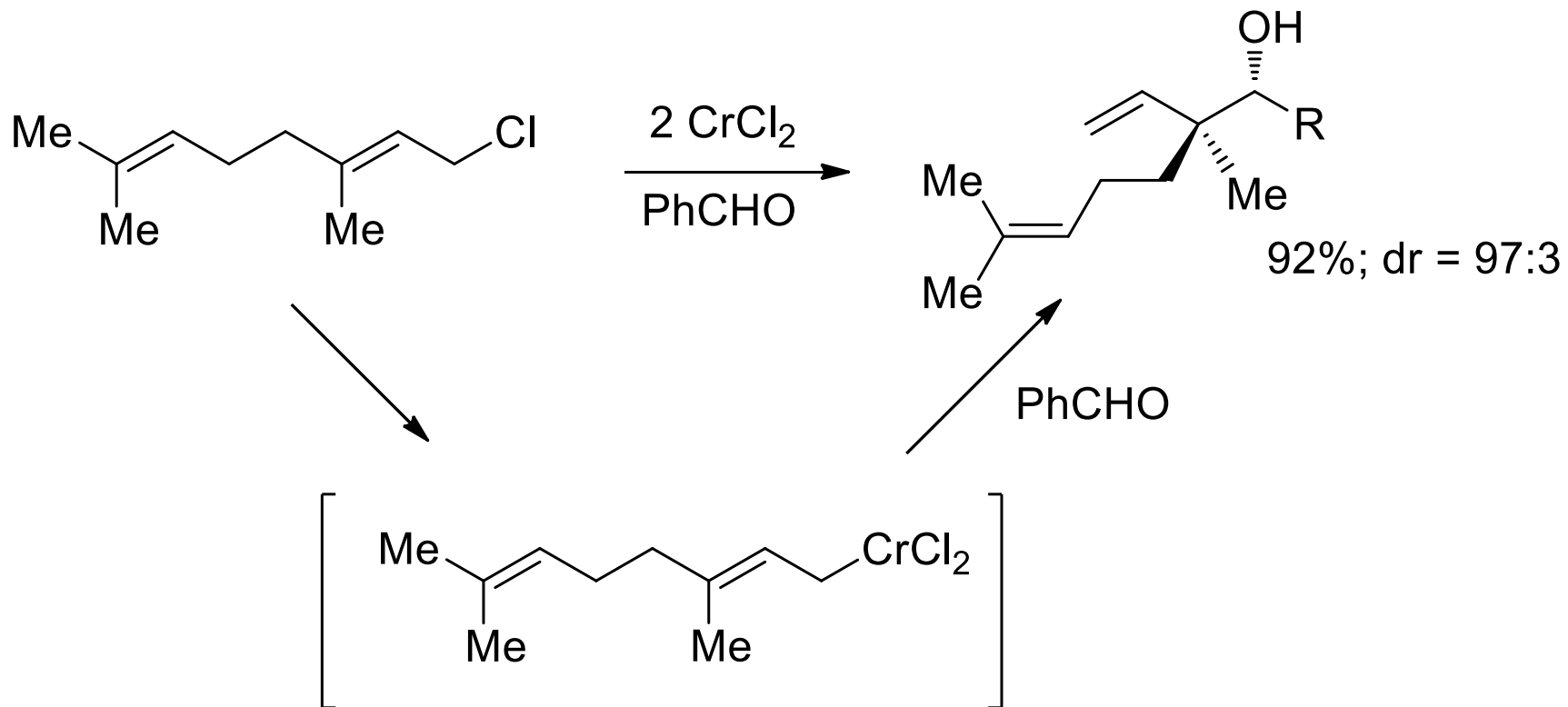
Zirconium



Early transition metal organometallics: Chromium



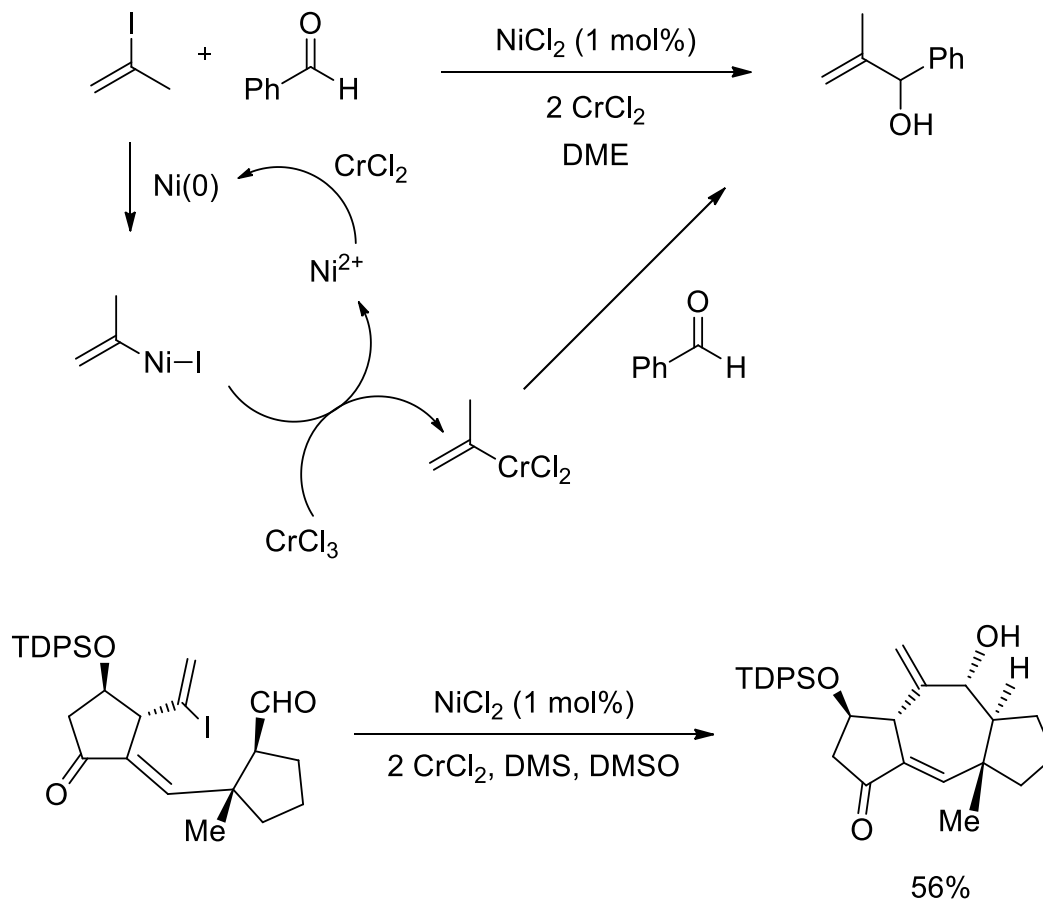
Chromium



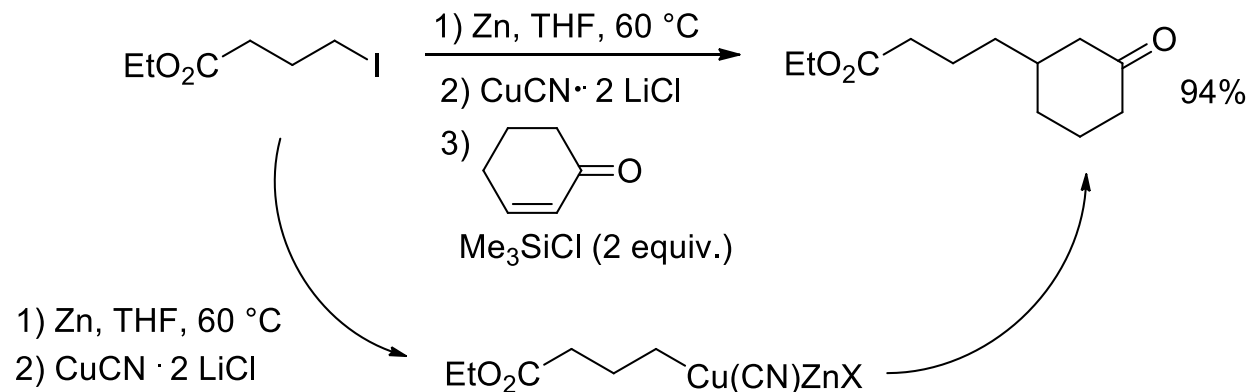
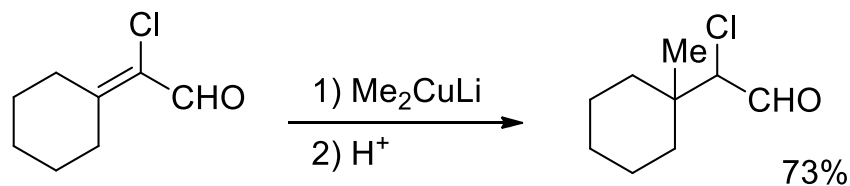
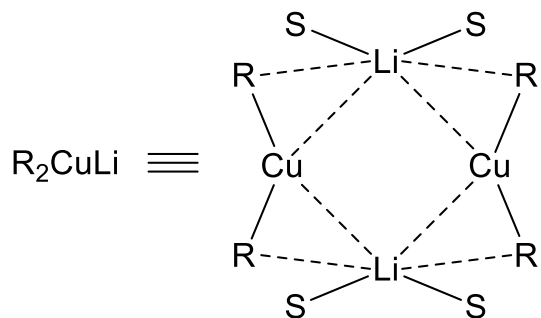
K. Belyk, M. J. Rozema, P. Knochel *J. Org. Chem.* **1992**, 57, 4070.

Chromium

Hiyama-Kishi-reaction

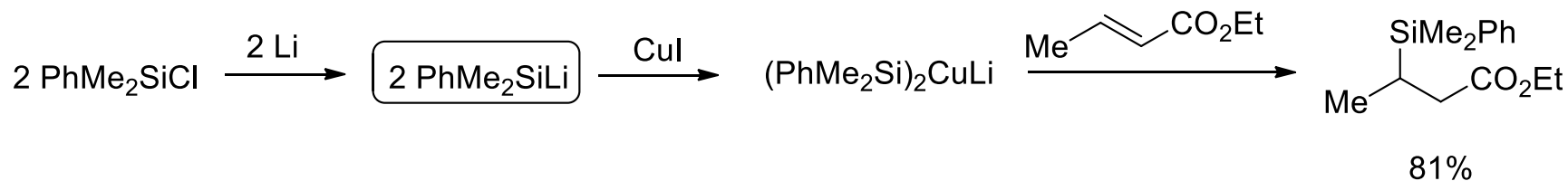


Early transition metal organometallics: Copper

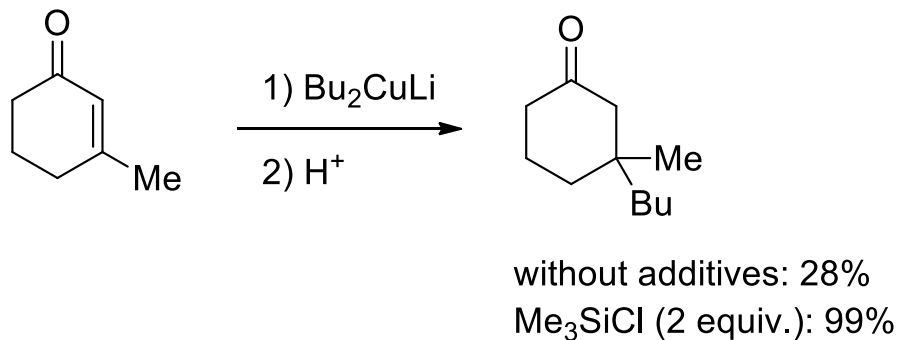


P. Knochel, et al. *J. Org. Chem.* **1988**, 53, 2390.

Copper

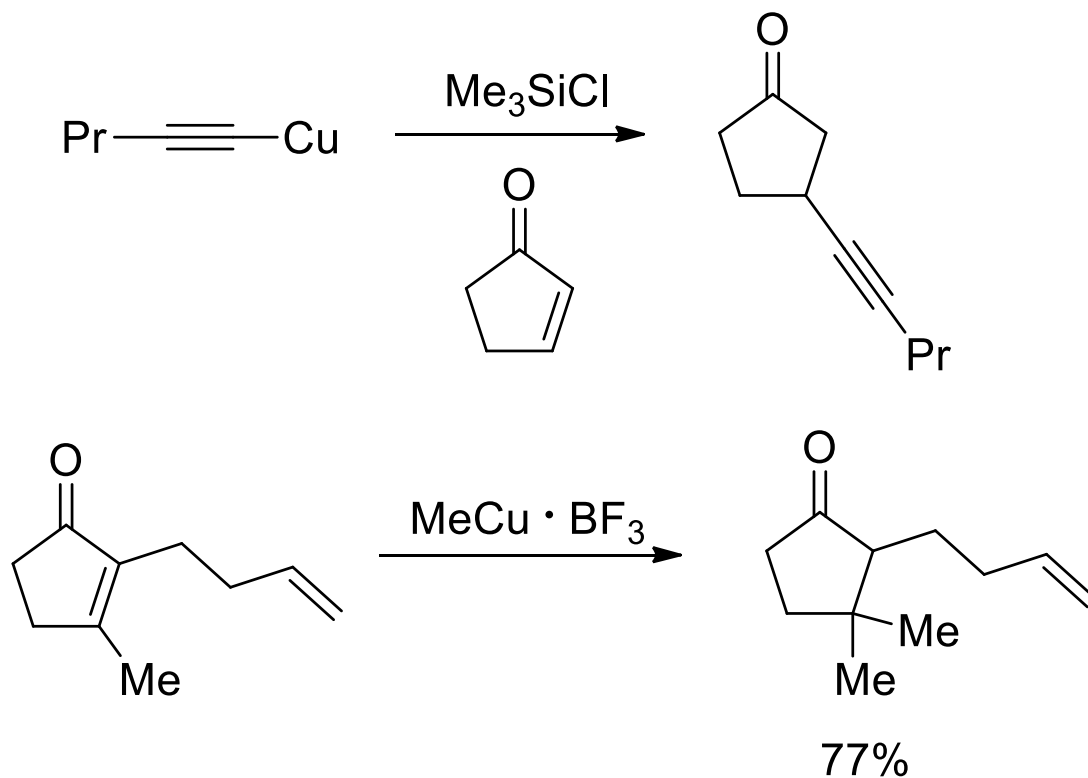


I. Fleming et al. *J. Chem. Soc., Perkin Trans.* **1998**, 1, 1209.



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

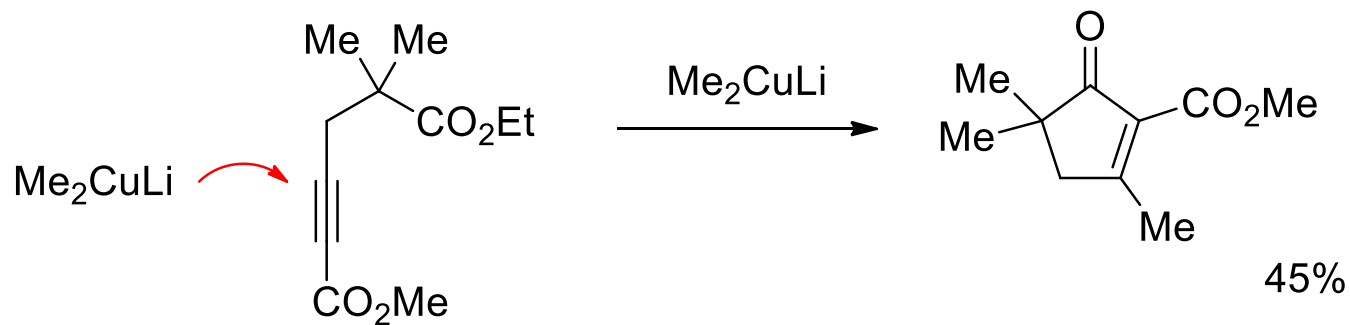
Copper-mediated 1,4-addition



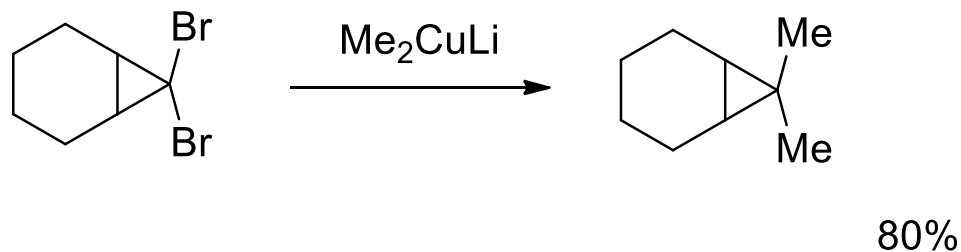
Y. Yamamoto, *Angew. Chem.* **1986**, 98, 945.

Copper-mediated reactions

Michael-addition



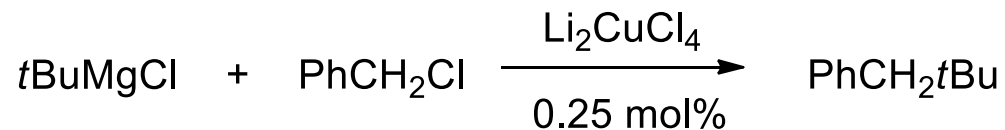
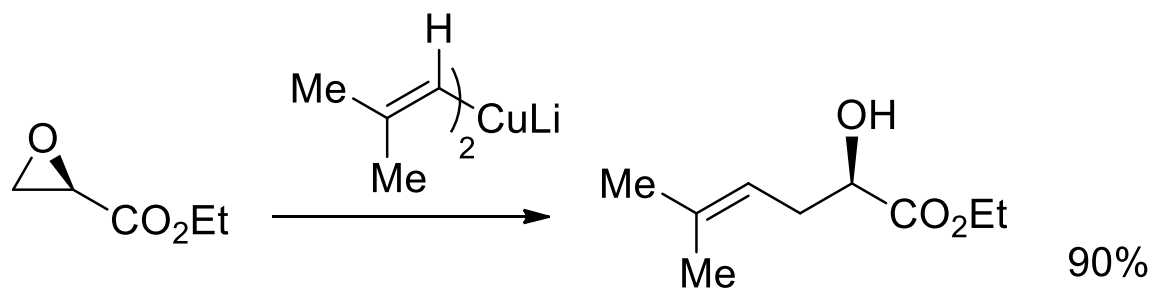
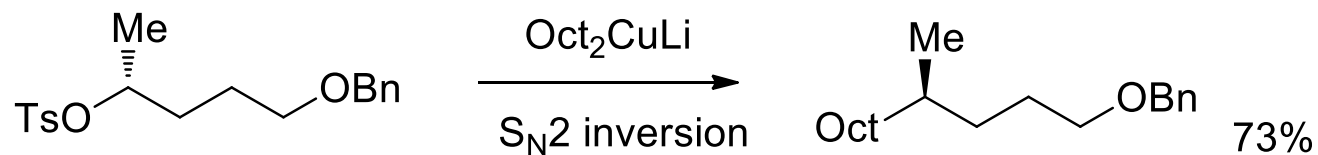
Substitution reactions



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

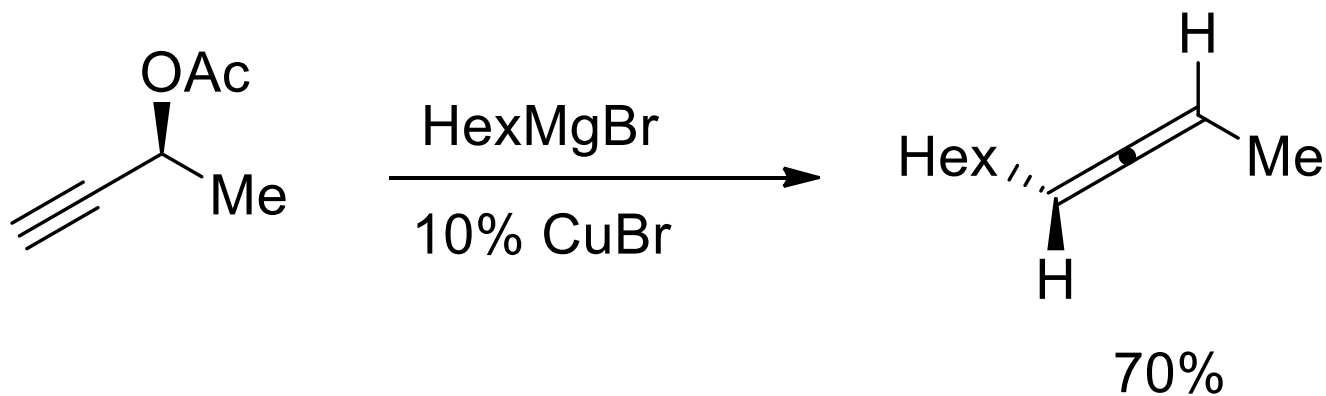
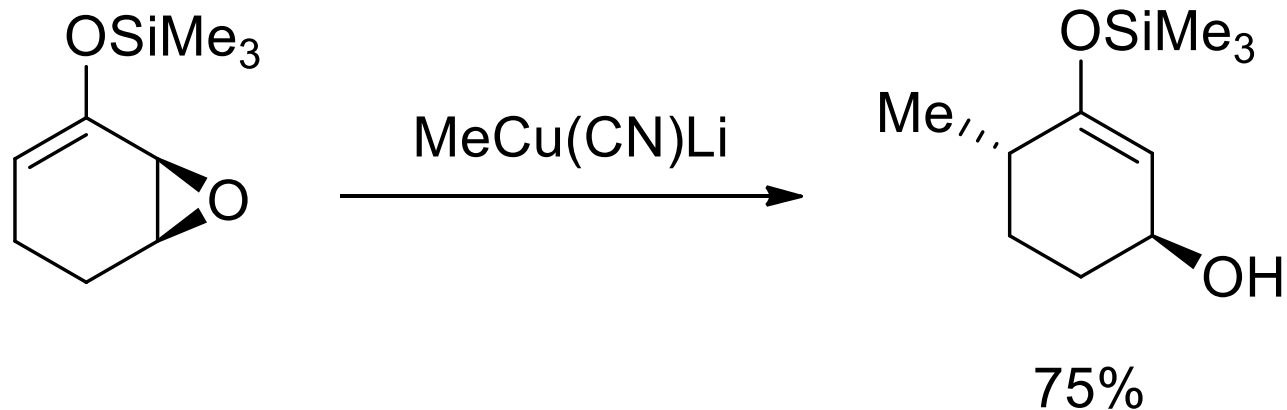
R. J. K. Taylor (Ed.), *Organocopper reagents*, Oxford University Press, Oxford, **1994**.

Copper; substitution reactions



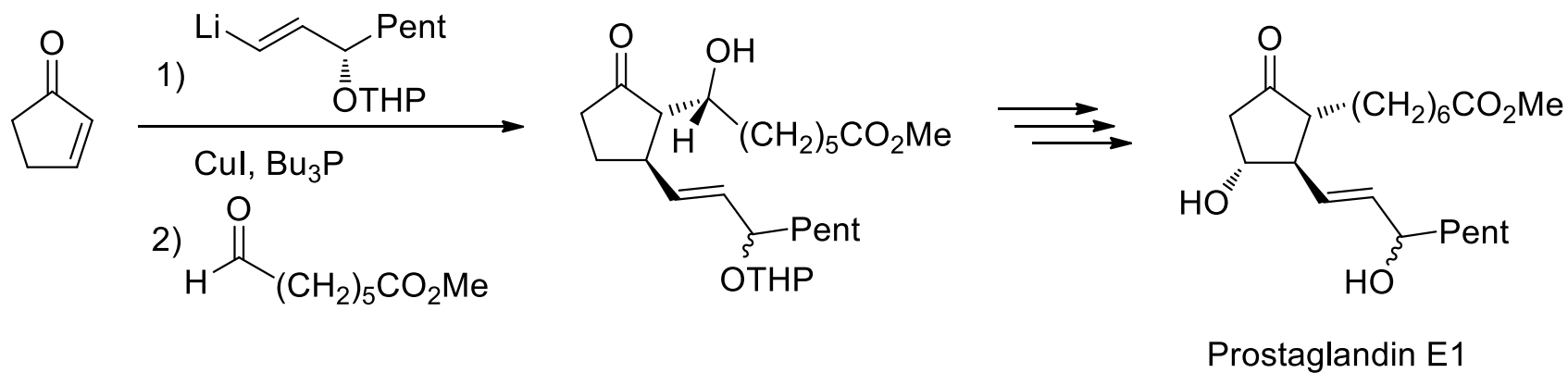
M. Larcheveque, Y. Petit, *Bull. Soc. Chim. Fr.* **1989**, 1, 130.

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**

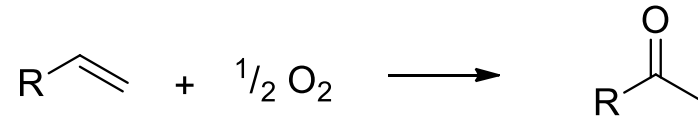
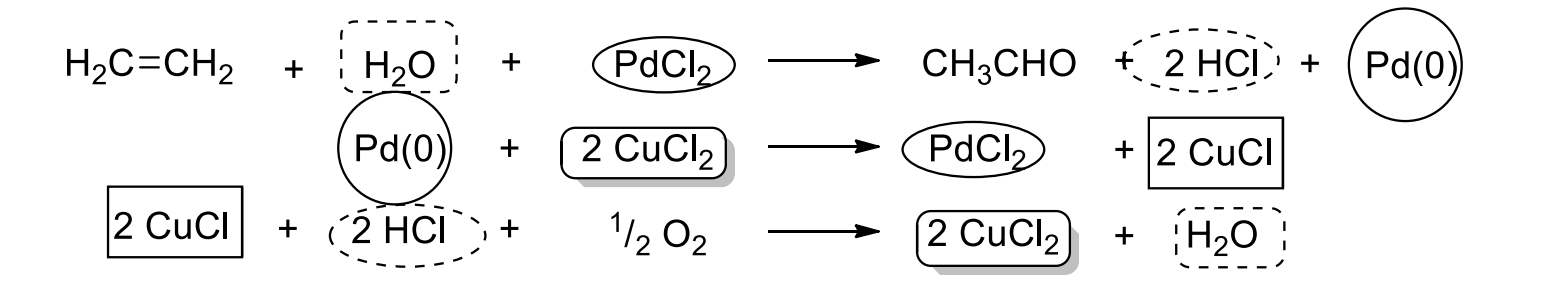
Pt: 3.3

Au: 1.9

Ru: 0.2

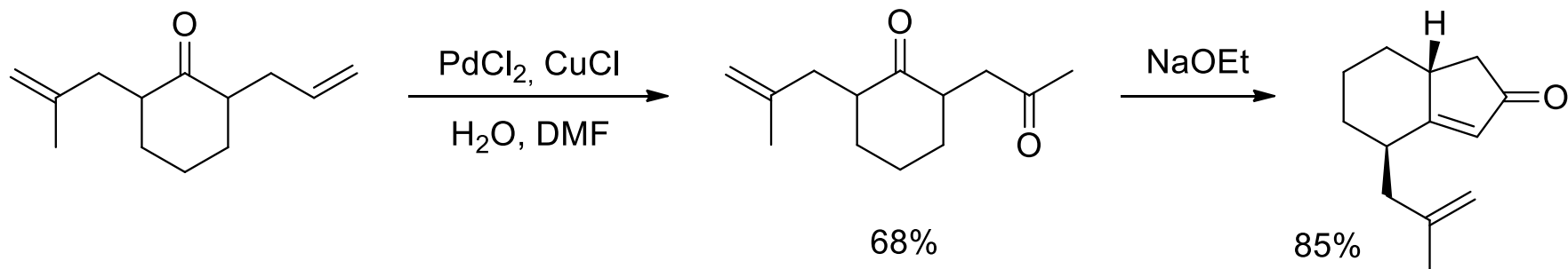
Rh: 2.8

Wacker-Reaction:



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

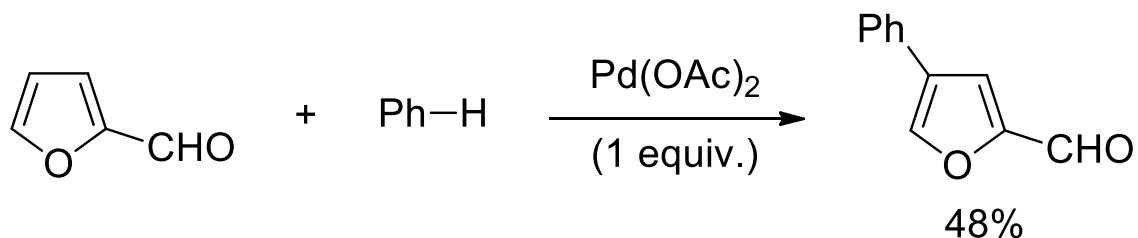
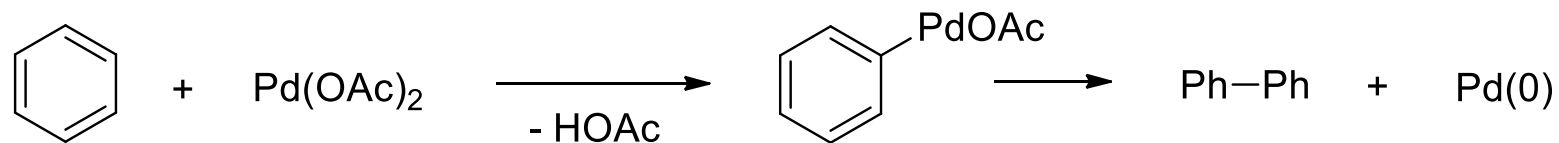
Palladium



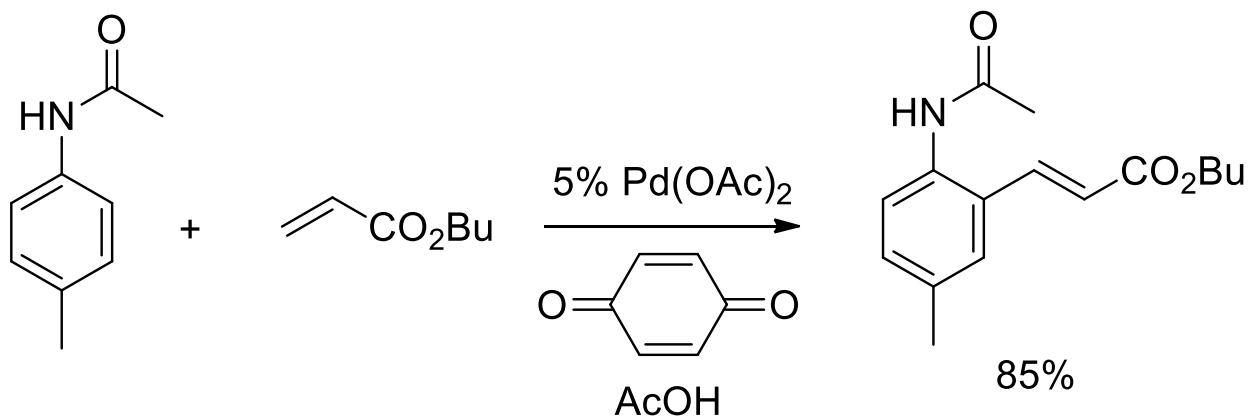
J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett.* **1976**, 34, 2975.

Palladium

C-H activation



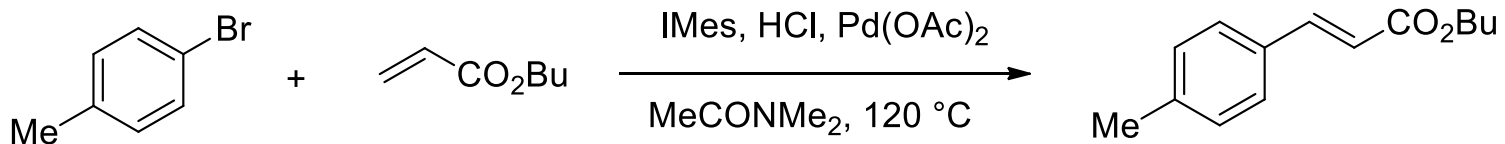
T. Itahara, *J. Org. Chem.* **1985**, 50, 5272.



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

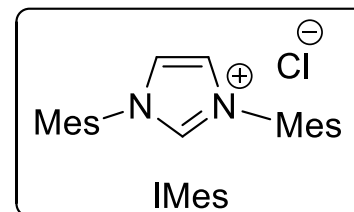
Palladium

Heck Reaction



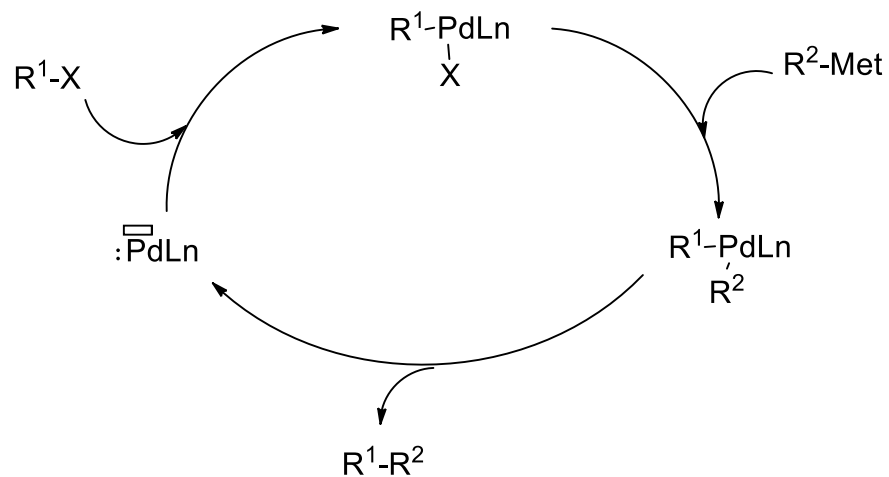
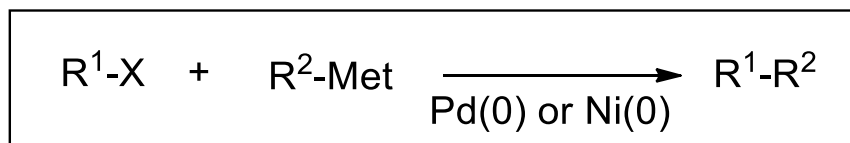
The method of T. Jeffery uses Bu₄NBr at 25 °C.

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



Palladium-catalyzed cross-coupling

Cross-coupling using Pd(0)-catalysts



Suzuki-coupling

Met = B(OH)_2

Stille-coupling

Met = SnR_3

Negishi-coupling

Met = ZnX

Kumada-coupling

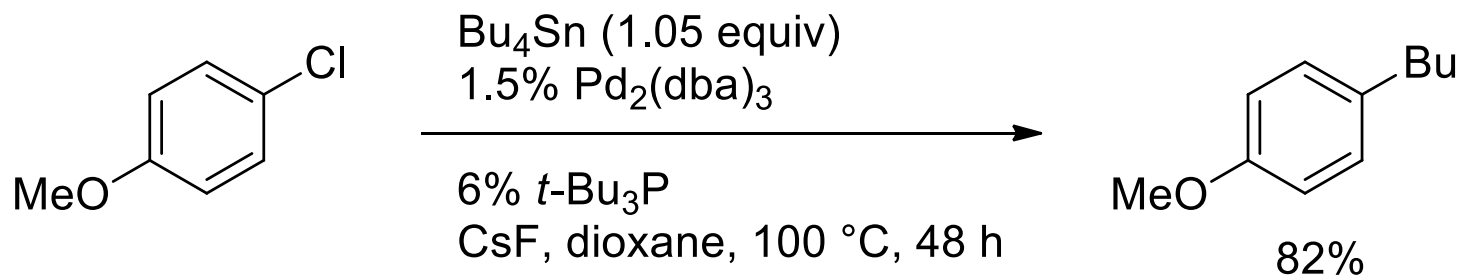
cat = Ni; Met = MgX

Sonogashira-coupling

Csp-Csp²

Palladium

Stille cross-coupling



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

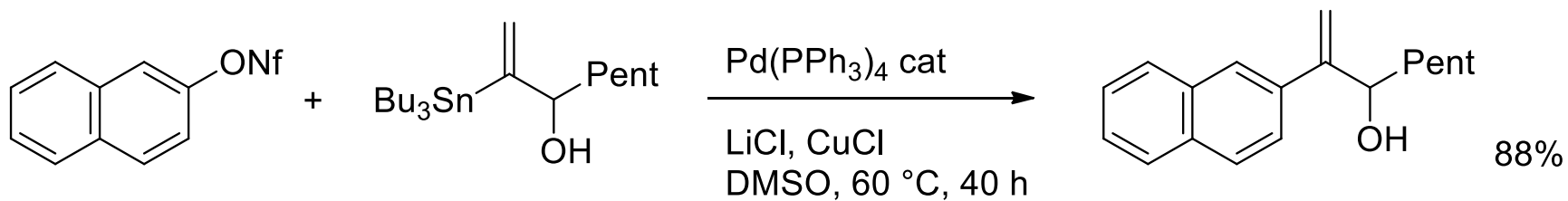
On the mechanism of the Stille cross-coupling:

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

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

Palladium

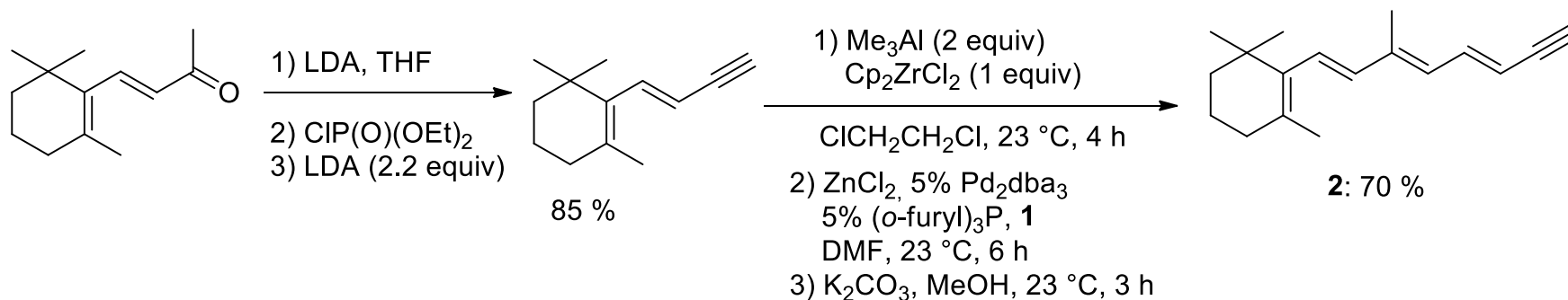
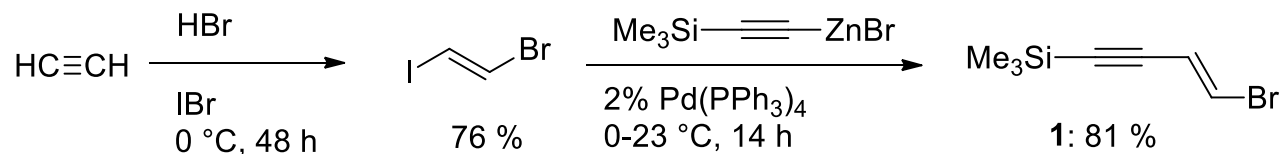
Cu-accelerated Stille-reaction



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

Negishi reactions

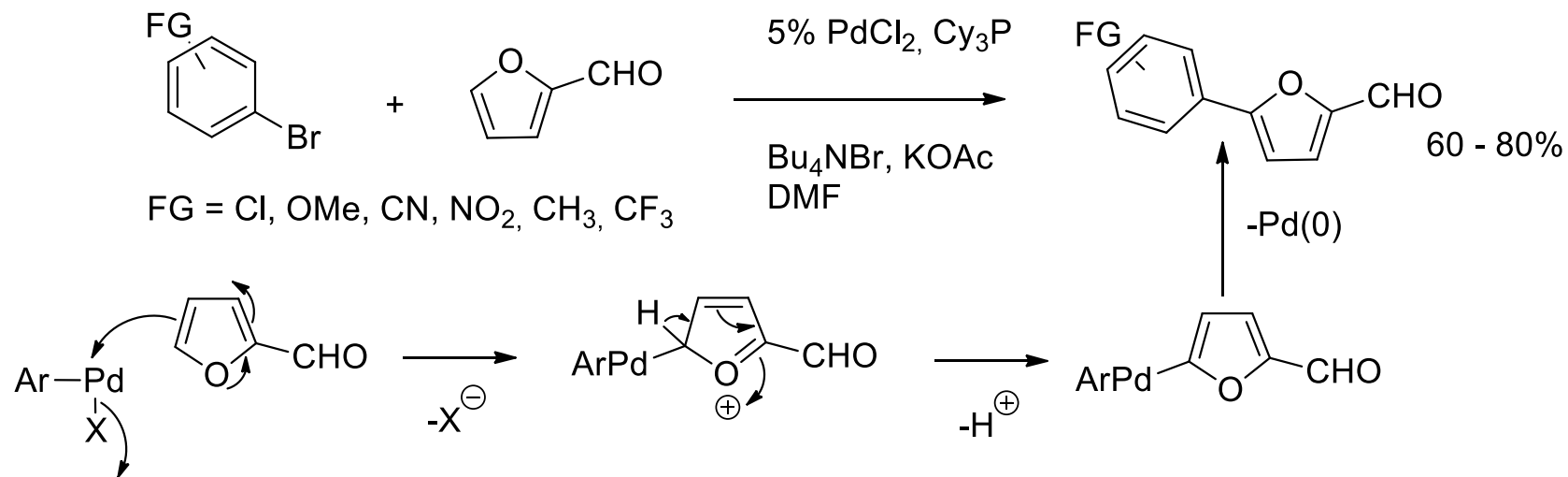
Synthesis of carotenoids *via* Zr-catalyzed carboalumination and Pd /Zn-catalyzed cross-couplings:



β -carotene: 68%; >99% isomeric purity

Palladium

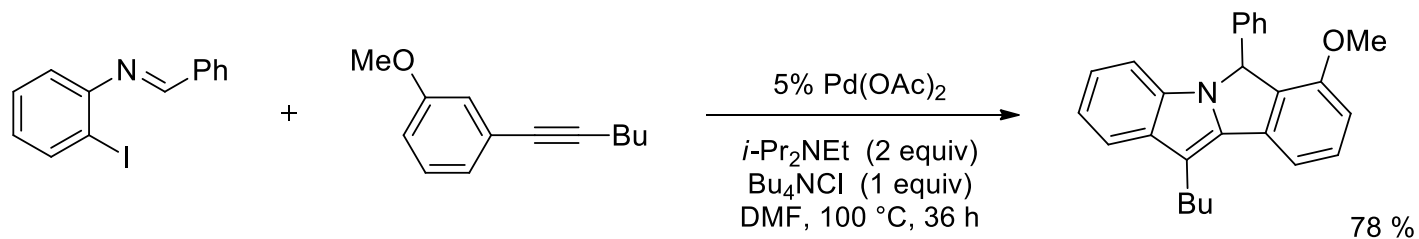
Regioselective Pd-catalyzed arylation of 2-furaldehyde using a C-H activation



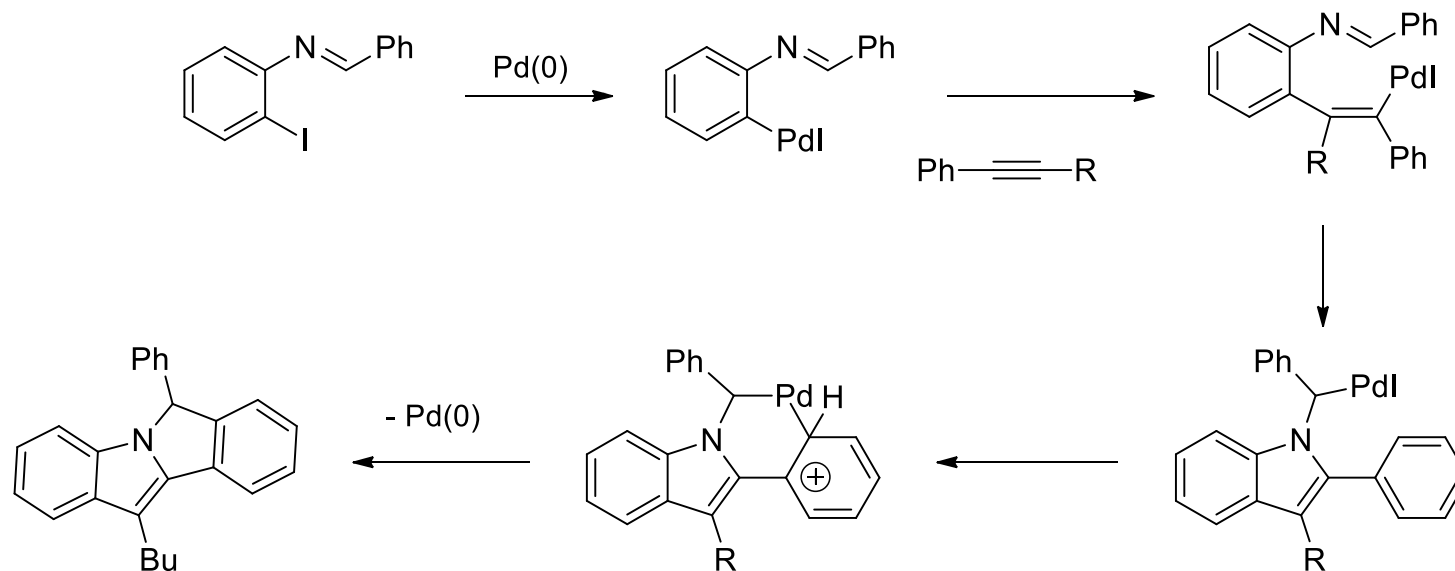
M. S. McClure, *Org. Lett.* **2001**, 3, 1677

Palladium

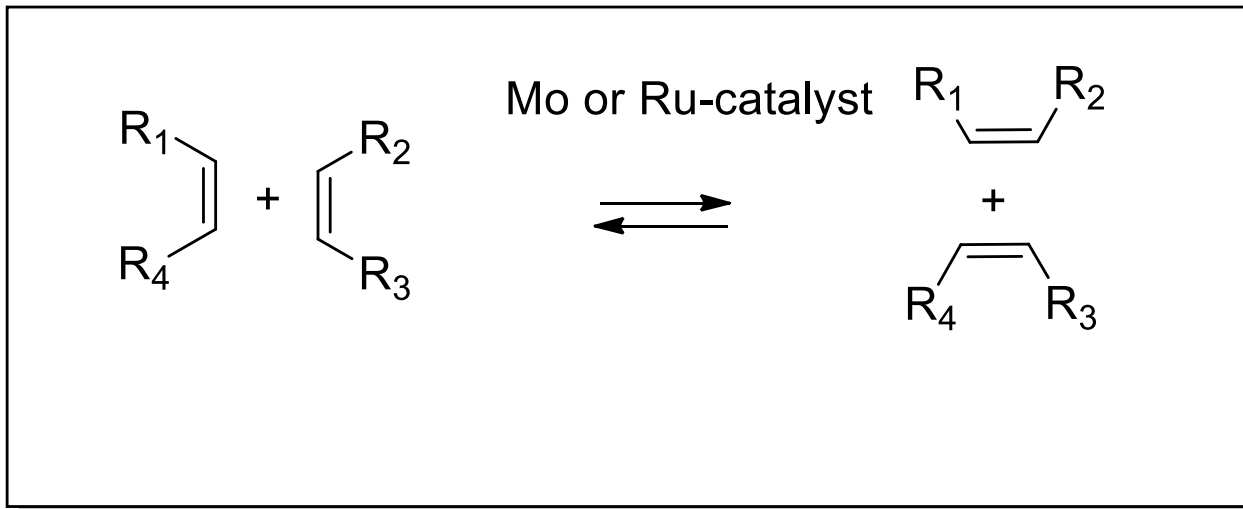
Pd-catalyzed heterocycle synthesis



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.

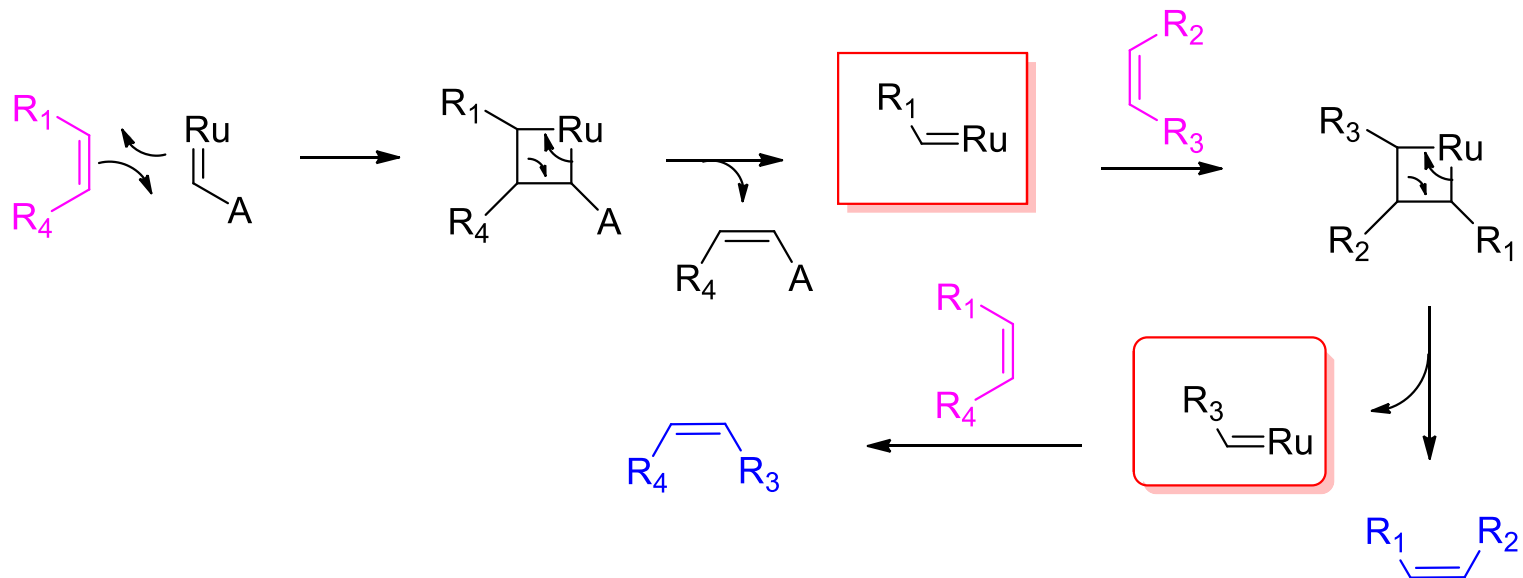
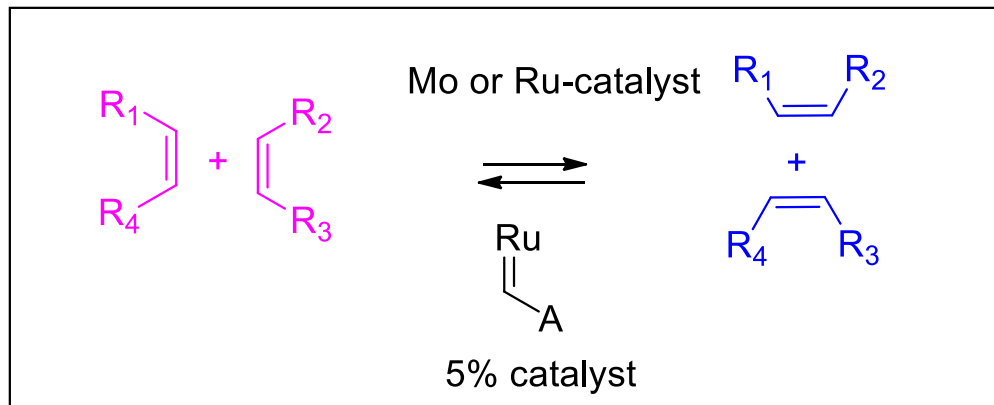
S. Blechert, *Angew. Chem.* **1997**, 109, 2124.

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

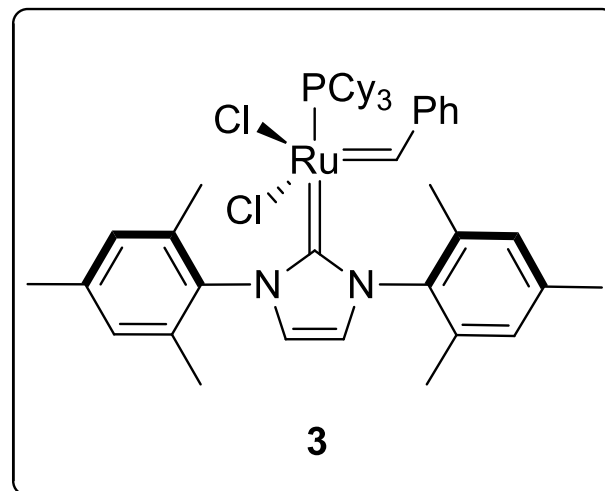
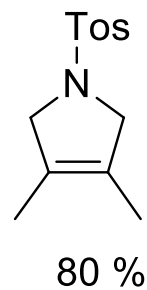
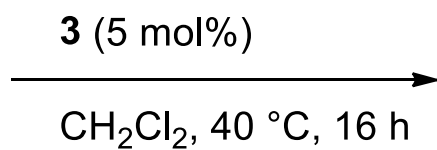
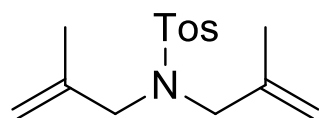
E.M. Carreira, *Synthesis* **2000**, 857.

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

Olefin metathesis mechanism



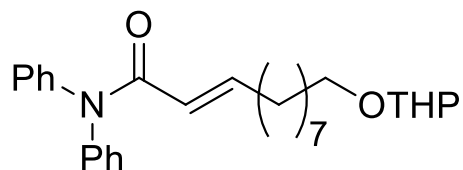
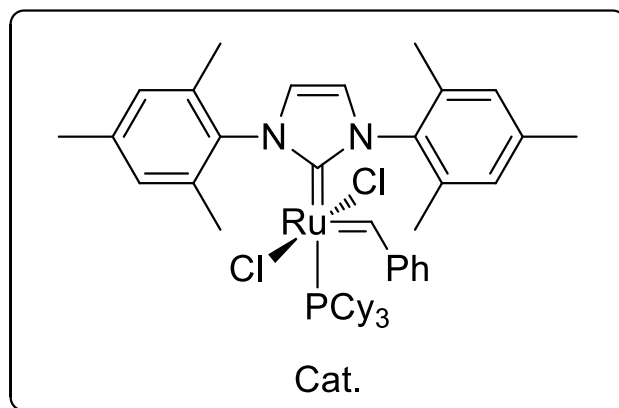
Olefin metathesis



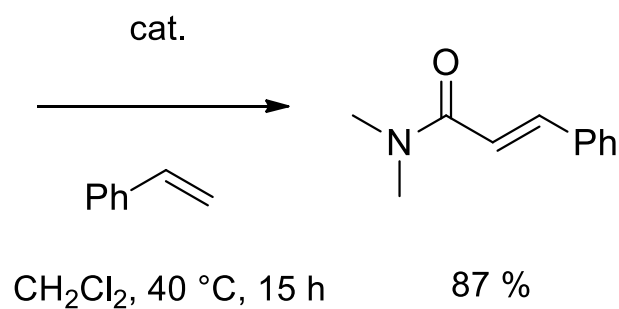
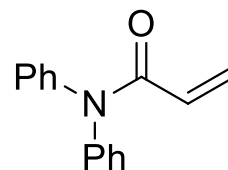
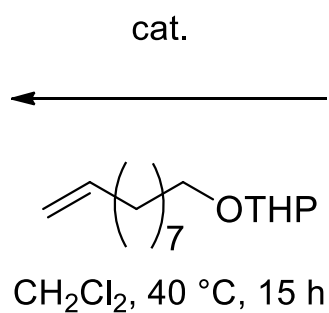
A. Fürstner, W.A. Herrmann, *Tetrahedron Lett.* **1999**, 40, 4787

Olefin metathesis

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



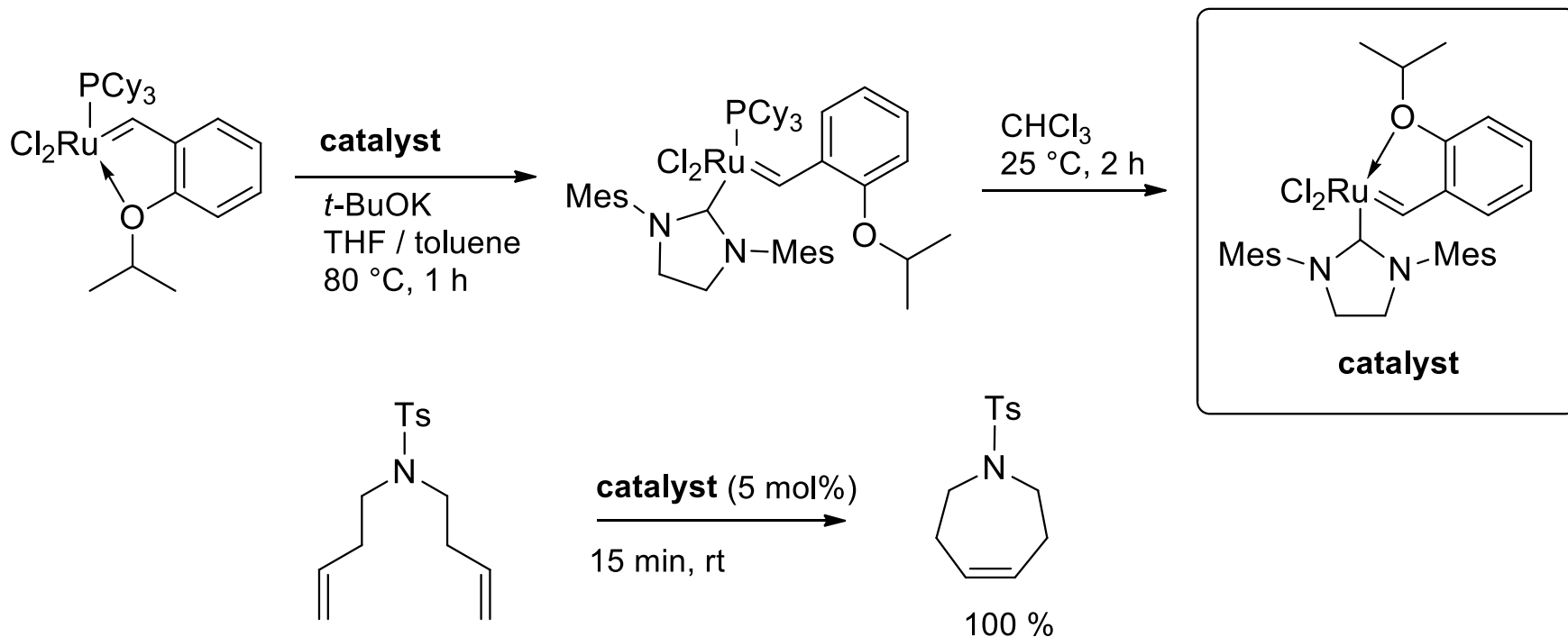
100 %



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

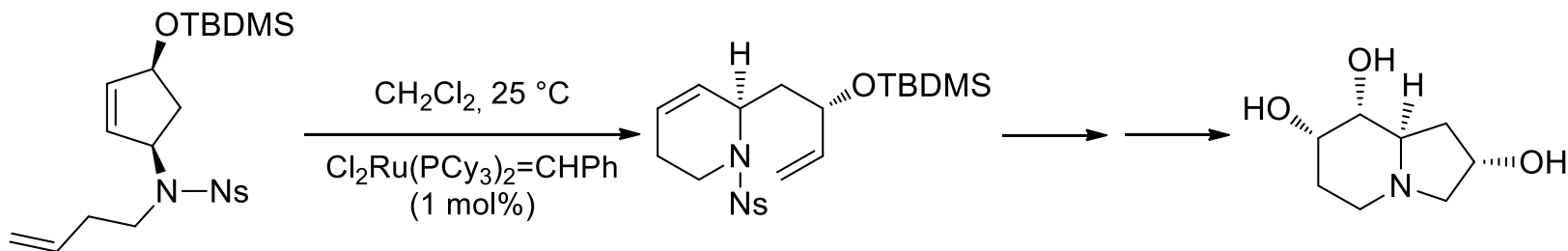
Olefin metathesis

New phosphine-free metathesis catalyst



Application to the synthesis of natural products

Synthesis of aza sugars

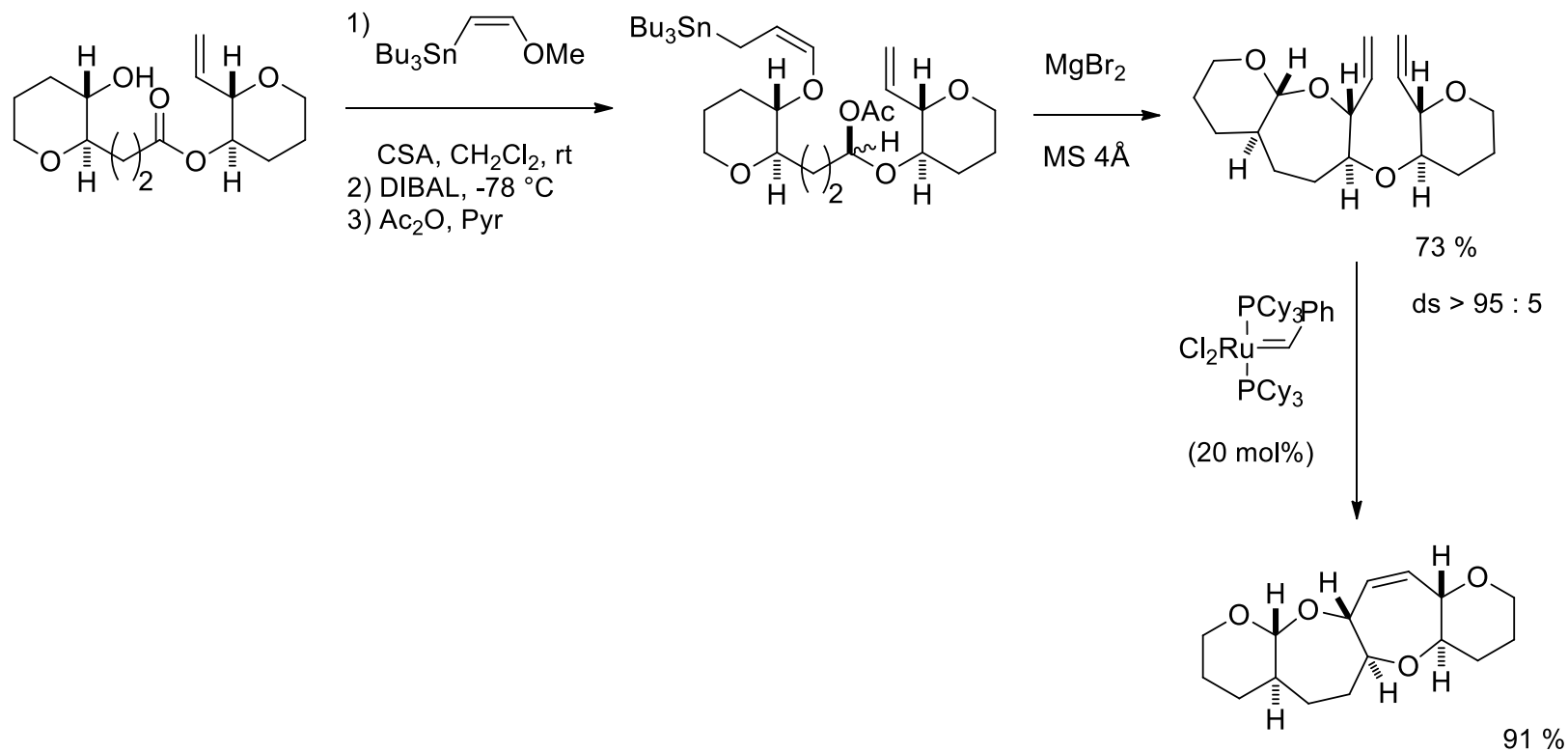


Ns = $(o\text{-NO}_2)\text{C}_6\text{H}_4\text{SO}_2^-$

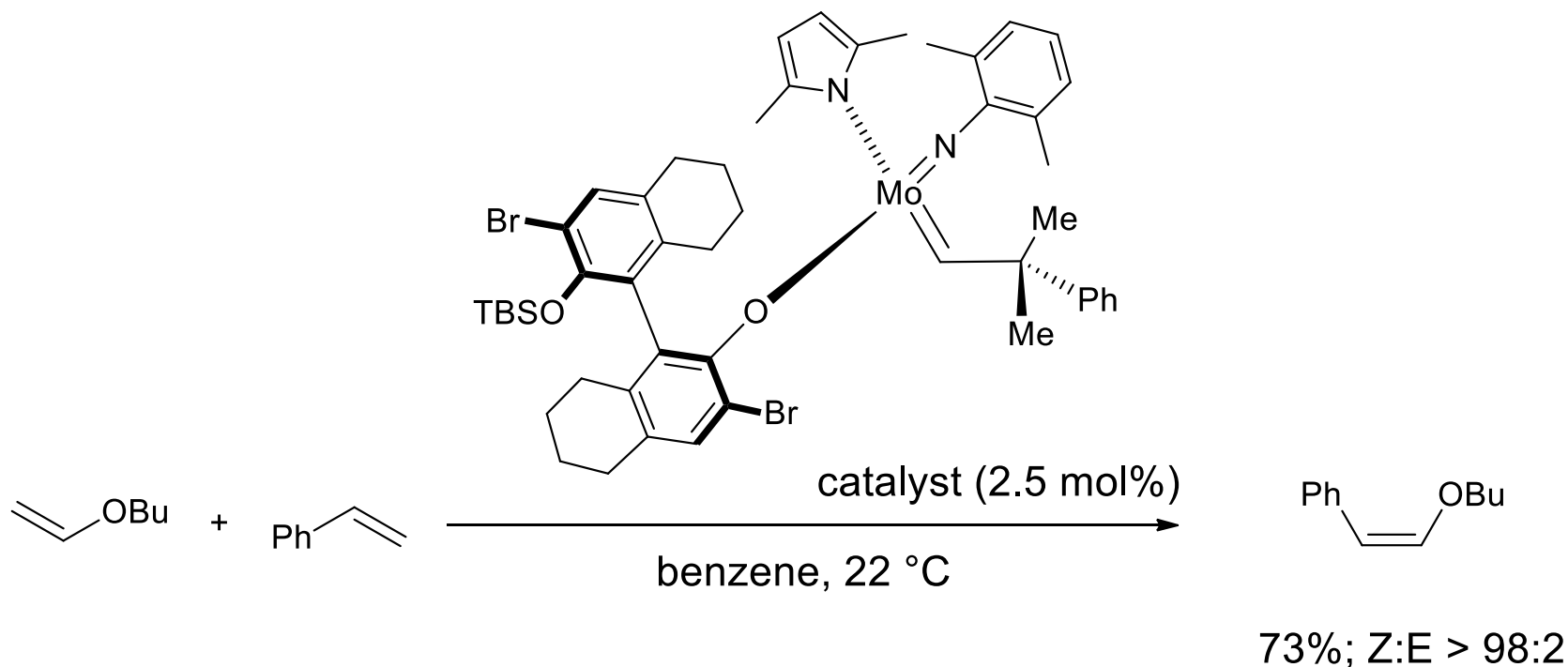
S. Blechert, *Org. Lett.* **2000**, 2, 3971

Olefin metathesis

Synthesis of complex ring-systems *via* metathesis



State of the art

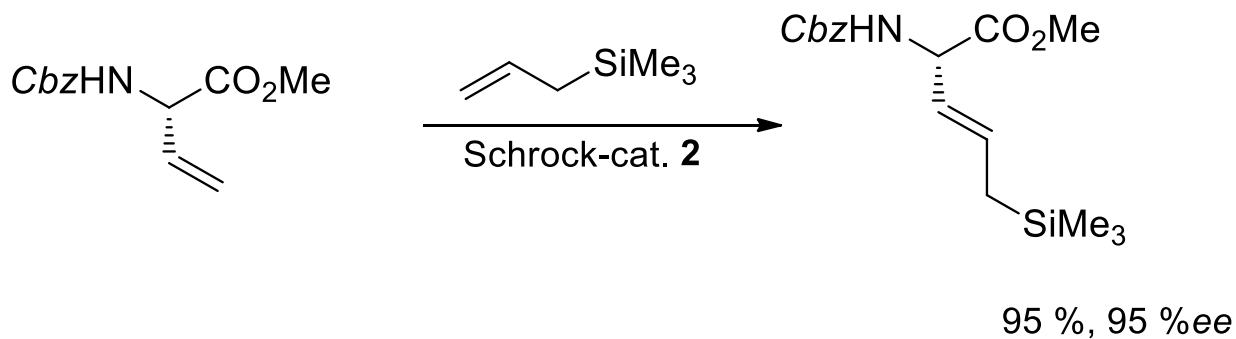
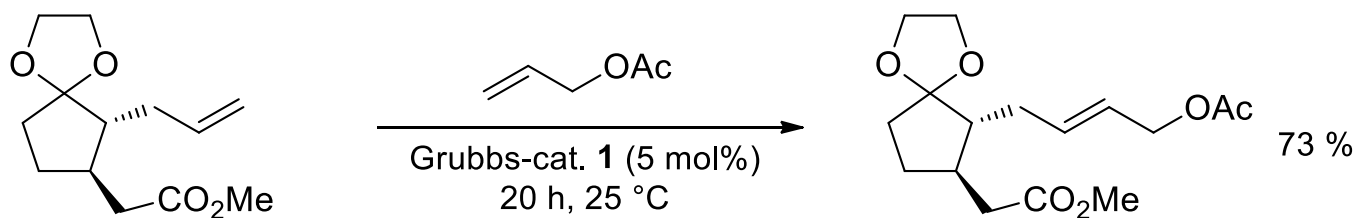


A. H. Hoveyda, *Nature* **2011**, 471, 461

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

Olefin metathesis

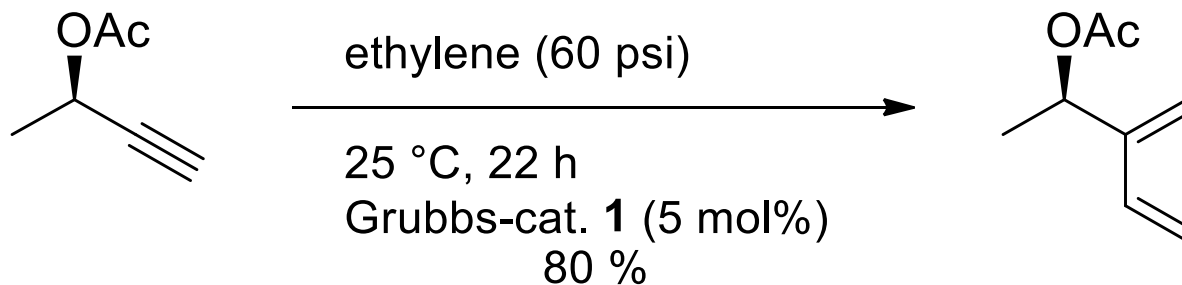
Synthesis of jasmonic acid derivatives



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

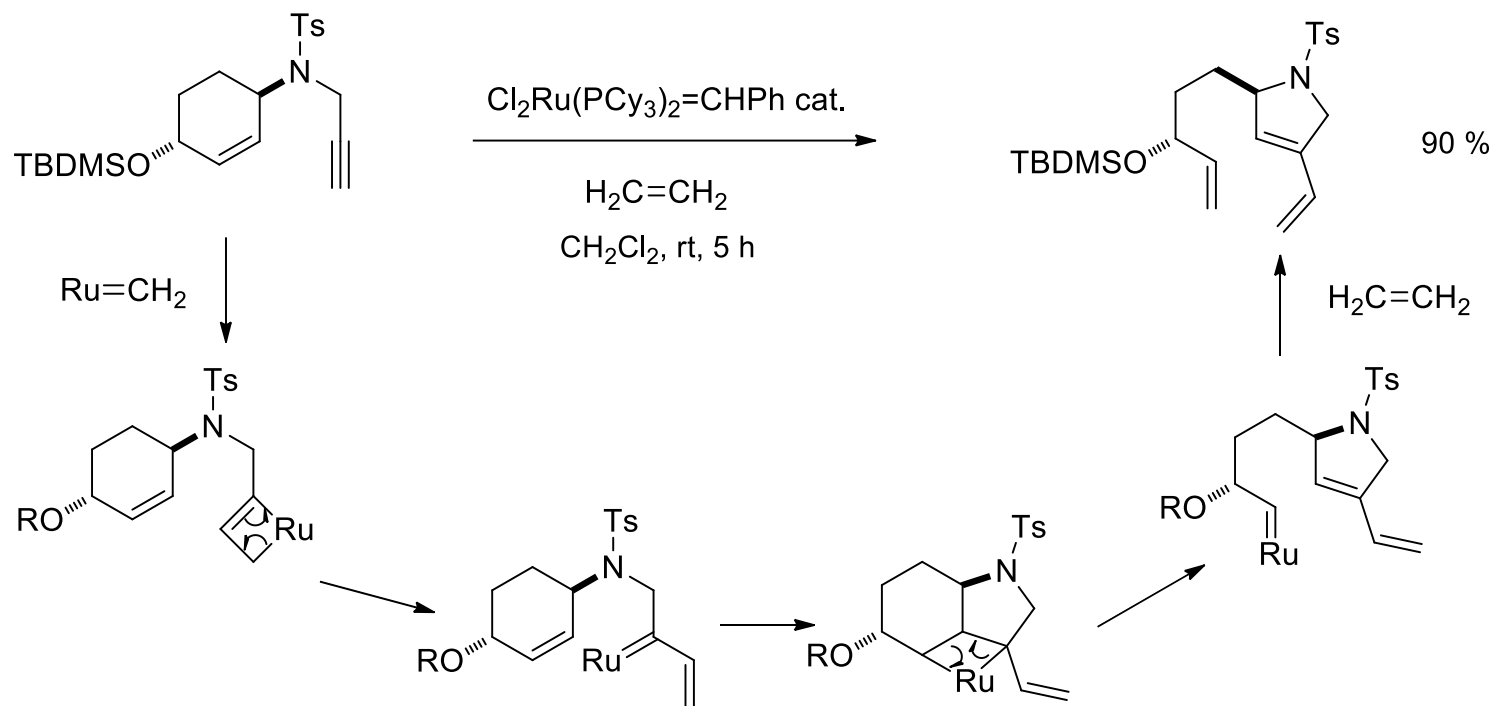
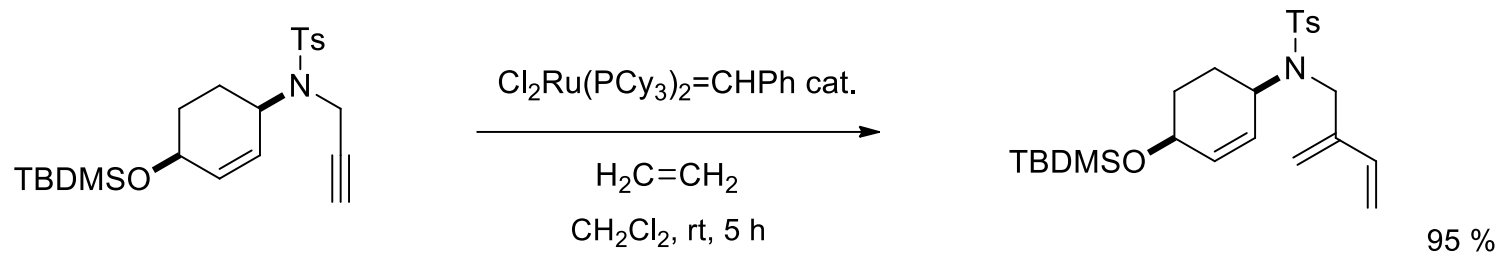
Olefin metathesis

Cross-metathesis of alkynes with ethylene



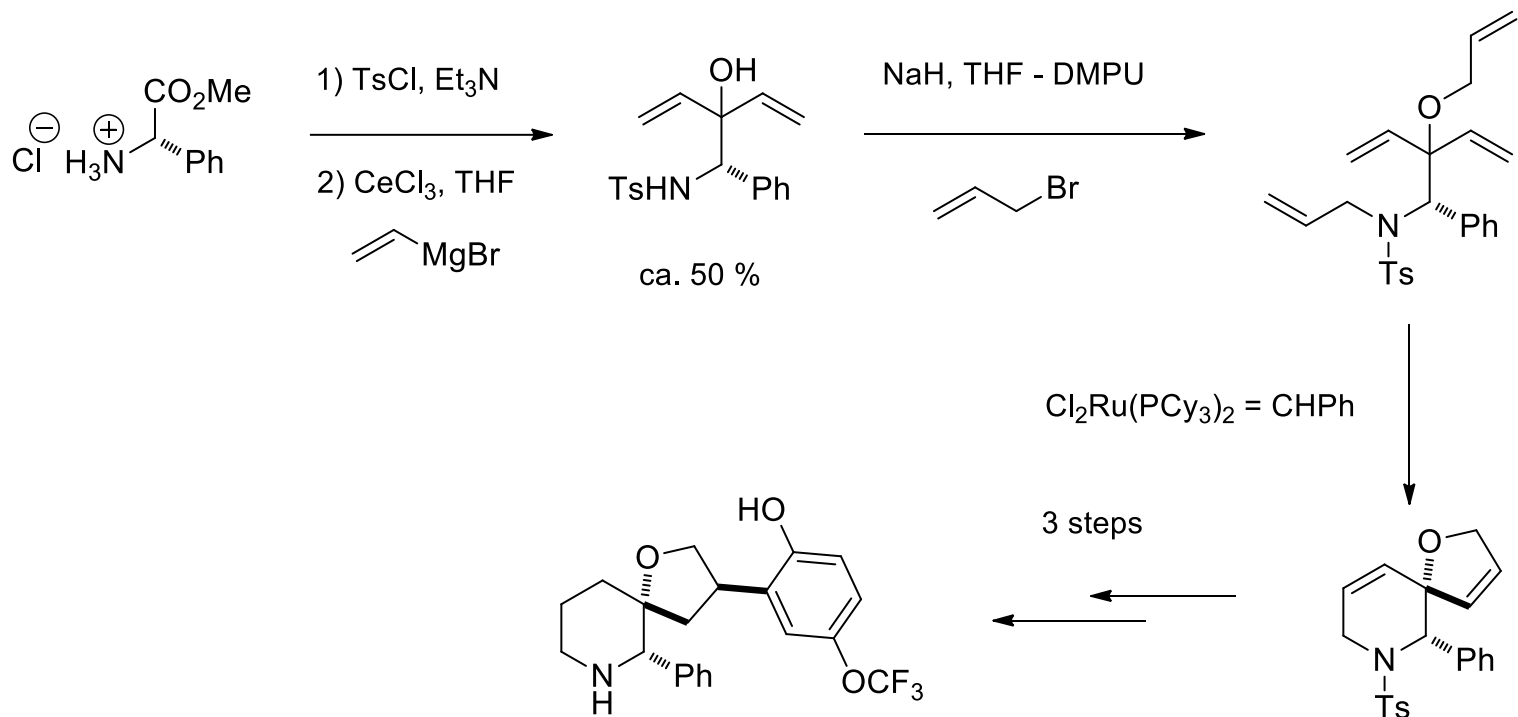
Olefin metathesis

Ru-catalyzed Ring-Opening and –Closing Enyne Metathesis

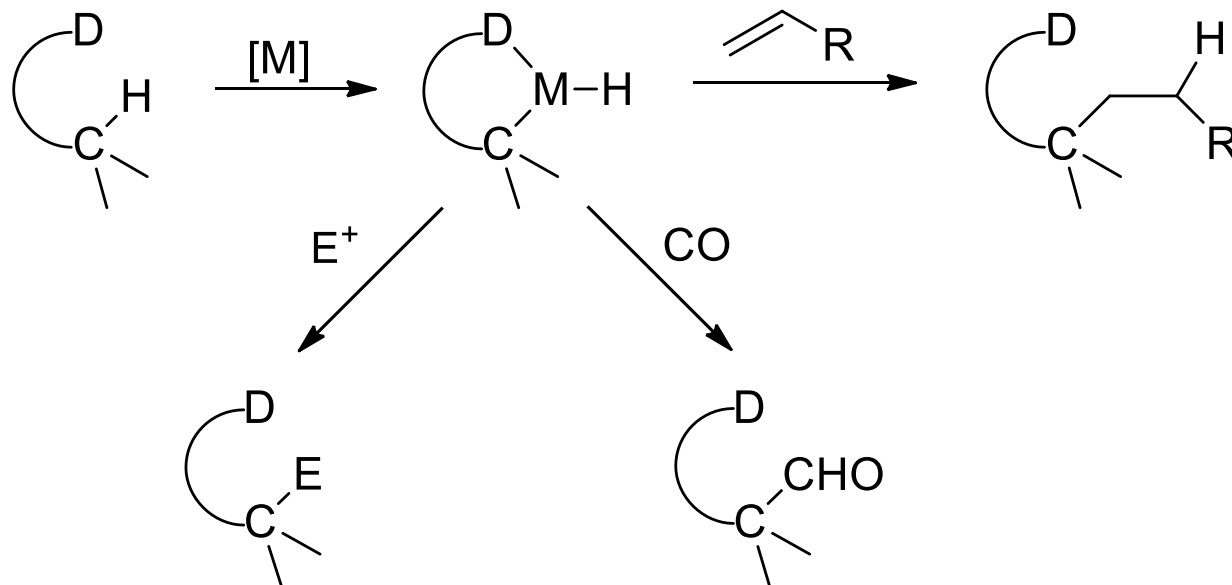


Olefin metathesis

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

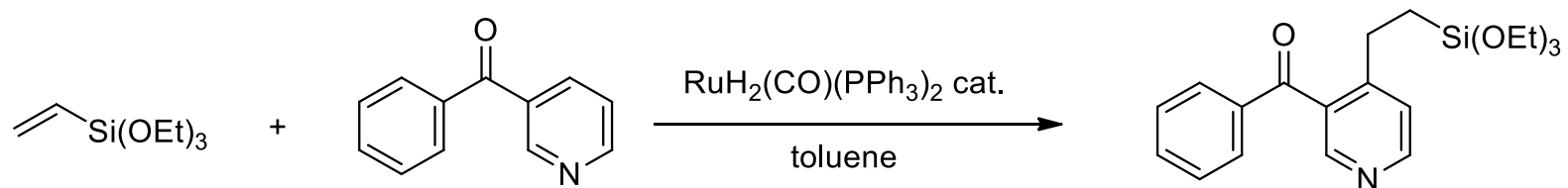
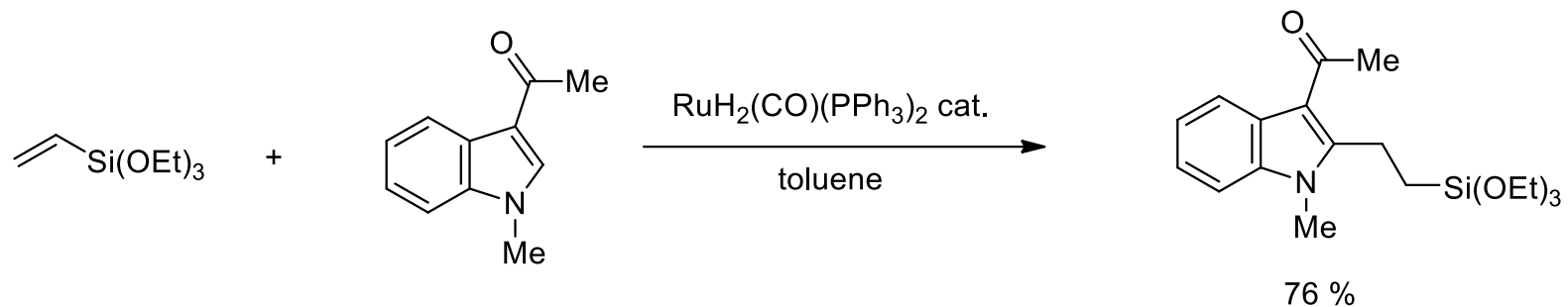


New C-H activation reactions



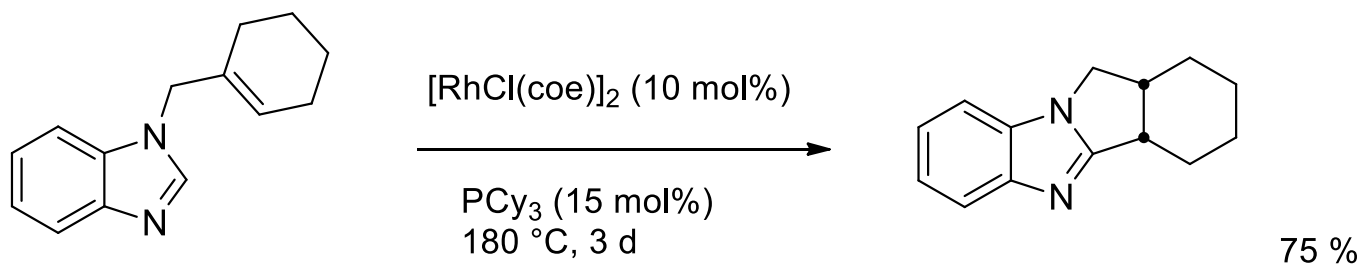
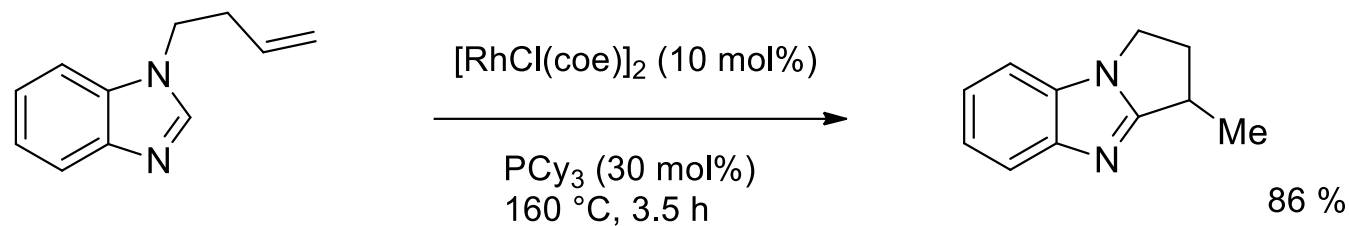
Book: S. Murai, (Ed.) Activation of Unreactive C-H Bonds in Organic Synthesis, Topics in Organometallic Chemistry, Springer, **1999**.

The Murai-reaction



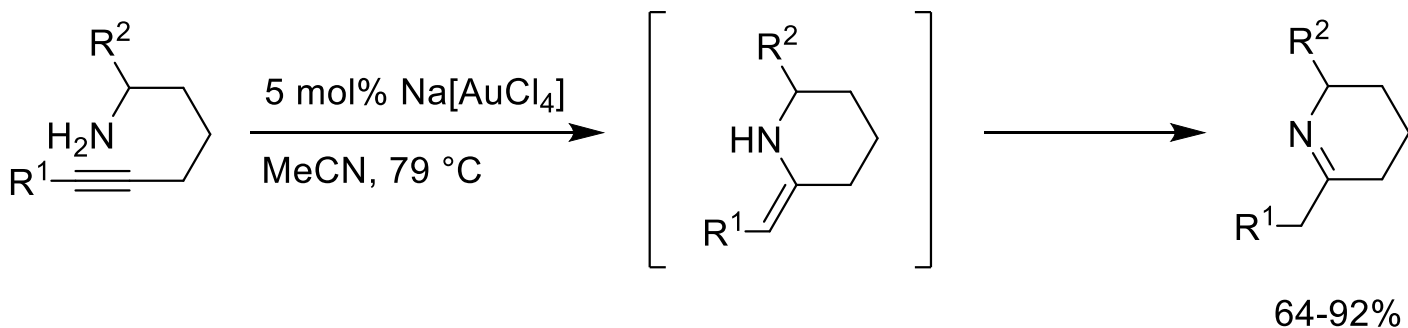
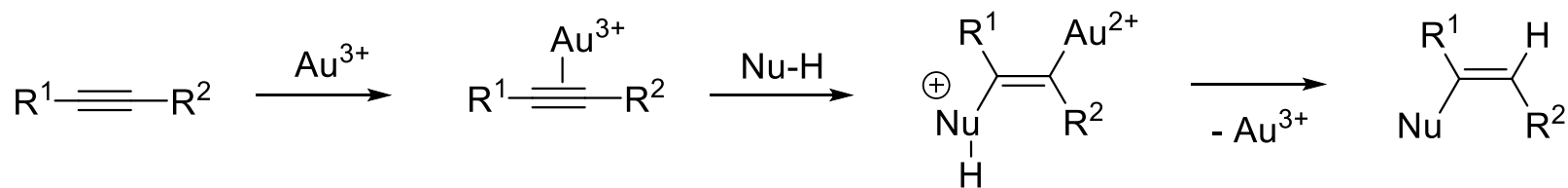
R. Grigg, *Tetrahedron Lett.* **1997**, 38, 5737
S. Murai, *Nature*, **1993**, 366, 529
S. Murai, *J. Organomet. Chem.* **1995**, 504, 151

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



Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds

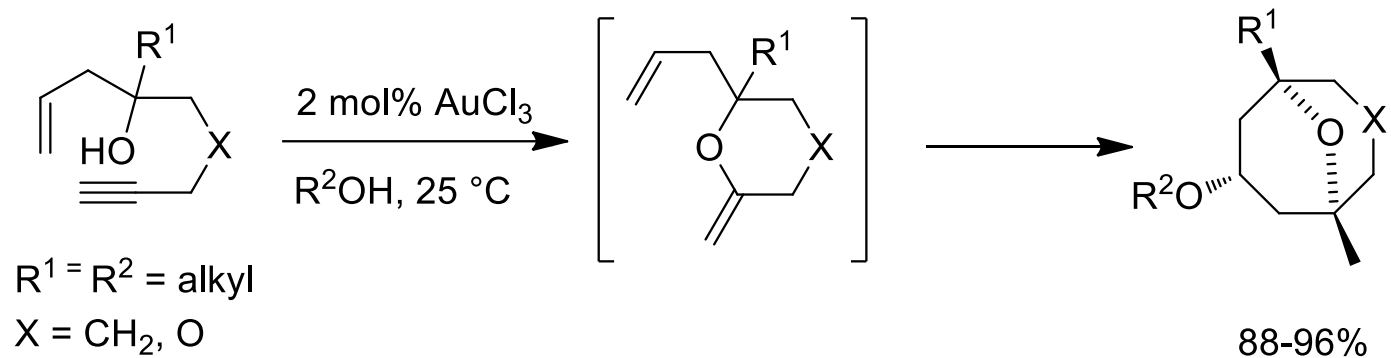


For a review see: A. S. Hashmi, *Chem. Rev.* **2007**, *107*, 3180

Gold-catalyzed organic reactions

Nucleophilic addition to C-C multiple bonds:

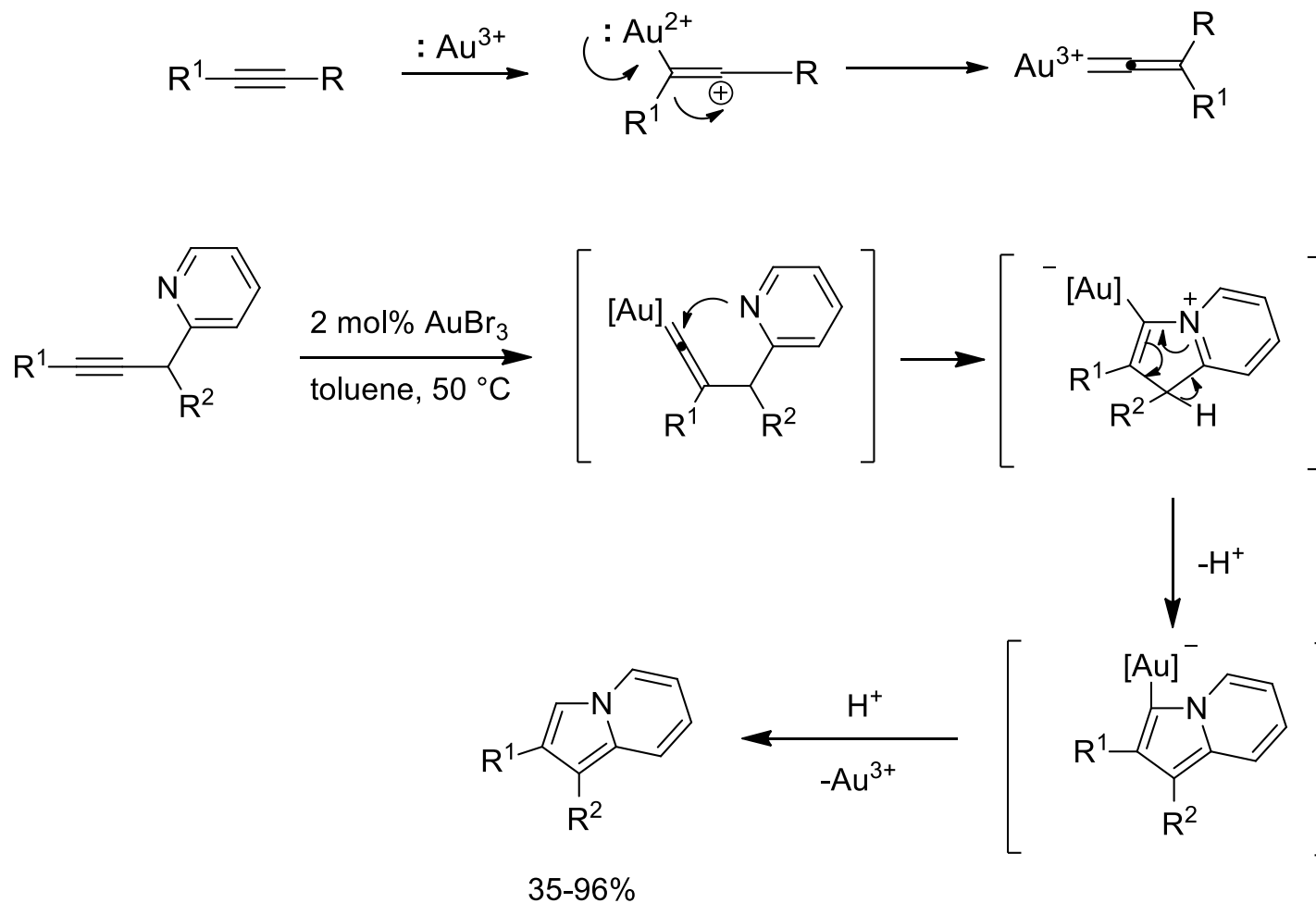
Au³⁺-catalyzed cyclization followed by a Prins type cyclization



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

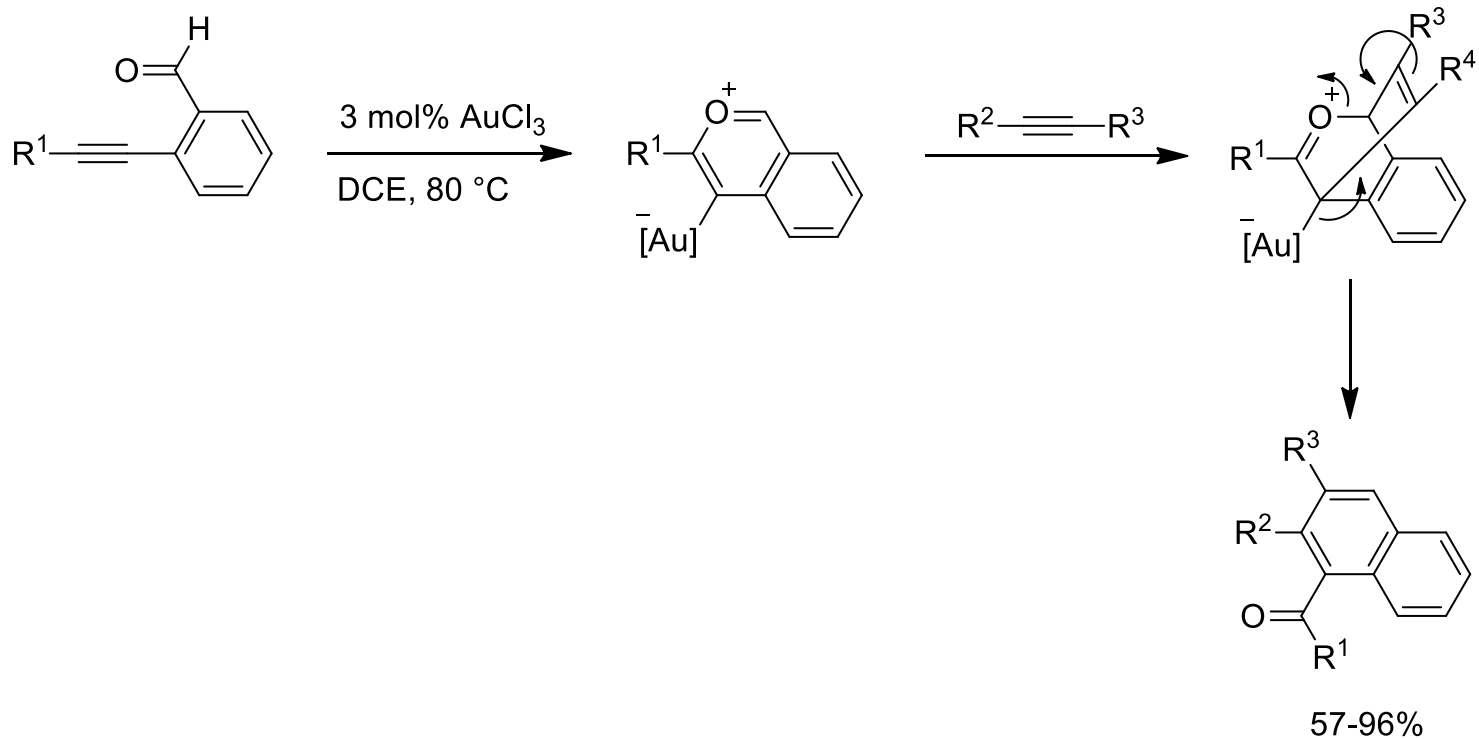
Gold-catalyzed organic reactions

Gold(III)-triggered rearrangements



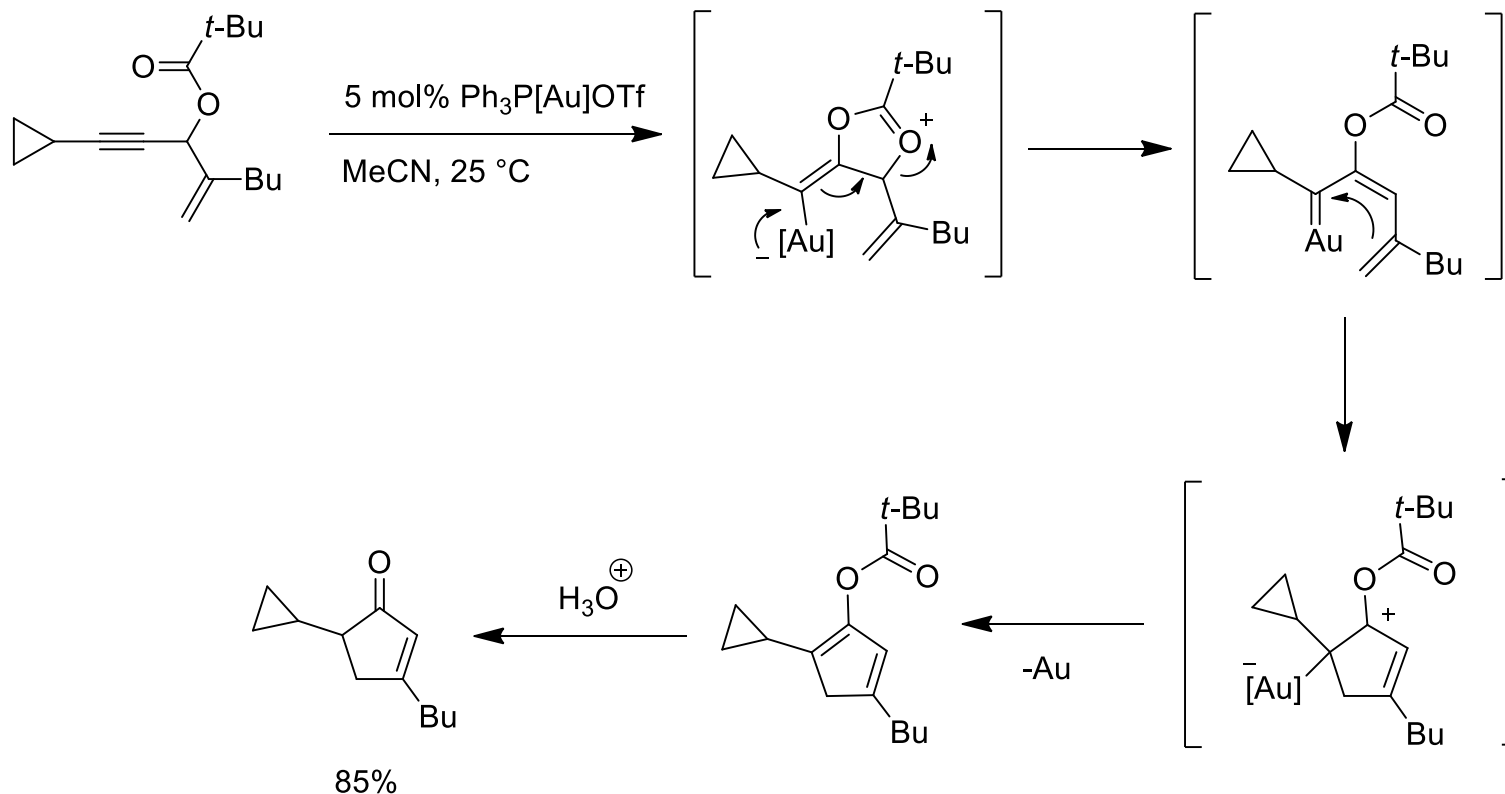
Gold-catalyzed organic reactions

Au³⁺-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

